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Free Communication 1

Telestroke in Eastern Switzerland – preliminary experience of a pilot project

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Introduction: The establishment of stroke networks is an approach to forward guideline-driven stroke care to hospitals without full-time neurological service. Telestroke networks are evidence based for remote neurological support of acute stroke patients, administration of thrombolysis safely as well as increasing thrombolysis rates. Thus, aim of our efforts is the dissemination of high-quality stroke care to rural areas.
Methods: In a pilot project we linked the district hospital in Grabs to the stroke center at the cantonal hospital St. Gallen and provided teleconsultations with full-scale audiovisual communication and access to brain images 24 hours per day 7 days per week. This telestroke concept was embedded in an acute stroke care concept and included mobile as well as hospital-based teleconsulting. We prospectively recorded parameters for quality control before and after implementation of the telestroke project in February 2011.
Results: In a cohort of 57 acute stroke patients, 49 teleconsultations were conducted between end of February and July 2011, 10 patients received systemic thrombolysis, one patient was selected for bridging-therapy, initiated by the systemic application of rt-PA in the district hospital and accomplishment of treatment at the stroke center. Compared to 33 patients treated with systemic thrombolysis before implementation of telestroke, symptom-onset-to-door times (84 ± 47 vs. 97 ± 68 minutes) and door-to-CT times (23 ± 6 vs. 22 ± 9 minutes) were similar whereas door-to-needle times dropped markedly (45 ± 12 vs. 71 ± 29 minutes). Regarding safety issues using the telestroke network no intracerebral hemorrhage or in-hospital mortality occurred in the 11 patients mentioned above. The patients were older and had more severe deficits than patients treated before (mean age 78.9 vs. 69.9 years and median NIHSS 9 vs. 7).
Conclusion: The preliminary data of our telestroke network are promising regarding quality and safety issues. This includes the selection of patients for appropriate treatment with allocation to systemic thrombolysis or bridging-therapy. As perspective it may definitely contribute to better supply of rural areas with acute stroke therapy.

Free Communication 2

Factors associated with efficacy and side effects of botulinum toxin A injections in focal hand dystonia

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Introduction: Intramuscular botulinum toxin injections are an established treatment for focal hand dystonia such as writer's cramp. However, lack of efficacy and side effects such as paresis are more frequent than in other dystonias treated with botulinum toxin. It is still unclear which factors may be used to predict the outcome of the therapy.
Methods: In this cohort study, we investigated 246 consecutive single consultations for botulinum toxin treatment in 25 patients with writer's cramp or musician's dystonia treated in our Movement Disorders Center. We correlated the outcome (efficacy, side effects) with demographic factors as well as with the characteristics of the injections. Statistical analysis was performed mainly by using Spearman correlation tests.
Results: Similar to previous studies, we found a marked improvement in focal hand dystonia in 73% of all sessions in spite of the frequent occurrence of side effects (48%). Paresis was the most common side effect. We found no correlation between age, gender, total dose, and the improvement of dystonia. Efficacy did not correlate with the number of muscles but weakly with the mean dose/muscle. In contrast there was a signifcant correlation ($p < 0.01$) between the number of injected muscles and the severity of side effects.
Conclusions: Our data suggest that the number of injected muscles and not the total dose is an important predictor of side effects such as paresis. In contrast the lack of correlation between improvement and the number of injected muscles or the total dose emphasizes the complex interplay between voluntary hand function and botulinum toxin treatment in focal hand dystonia.

Free Communication 3

Phenotypes in Swiss patients with familial ALS carrying TARDP mutations

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Background: Recently mutations in the TARDP gene which codes for the TAR DNA binding protein 43 (TDP43) have been identified in familial (FALS) and sporadic ALS (SALS) patients. The phenotype and frequency of TARDP mutations seems different in various European populations.
Objective: To further define the phenotypic spectrum of TARDP mutations and their frequency in a Swiss population.
Methods: A total of 225 patients diagnosed with ALS (182 sporadic cases, 43 familial cases) were screened for TARDP mutations. Except for one patient who was followed at the University of Geneva all patients were followed at the Kantonsspital St.Gallen.
Results: In 4 patients with a family history of ALS TARDBP mutations were indentified. TARDBP mutations were not found in SALS. The frequency o TARDP mutations amongst FALS patients was 9.3%. Two female ALS patients carried the N352S mutation. Both had limb onset and a slowly progressive course of the disease. In a 44-year old female patient a novel mutation (G376D) was identified. Survival amongst affected family members varied between 6 and 18 months. The patient and also the other siblings affected with ALS had an accessory nipple. A 4th male patient carried the A90V mutation. None of the patients had cognitive impairment.
Conclusion: In this Swiss population the novel G376D mutation is associated with rapid disease progression and an accessory nipple while the N352S mutation is associated with slow disease progression. The frequency of TARDP mutations in the FALS cases in the Swiss population seems to be higher than in other European populations.

Free Communication 4

Spike triggered reaction-time-EEG as a possible assessment tool for driving ability

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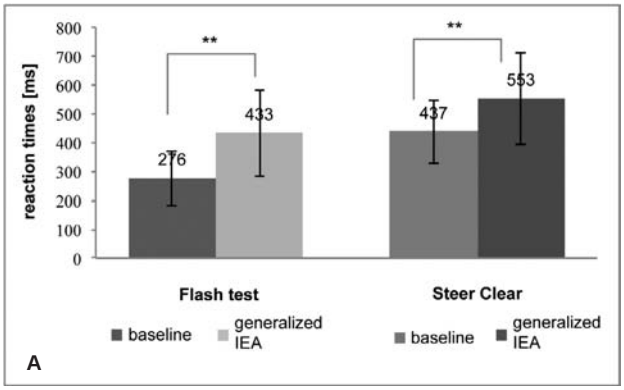
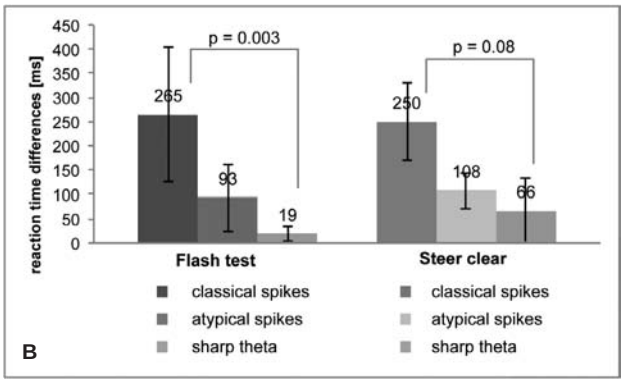
Introduction: The impact of interictal epileptic activity (IEA) on driving is a rarely investigated issue. We analyzed the impact of IEA on reaction time in a pilot study (Krestel et al., Epilepsia 2011).
Methods: Reactions to simple visual stimuli (light flash) in the Flash test or complex visual stimuli (obstacle on a road) in a modified car driving computer game, the Steer Clear, were measured during IEA bursts and unremarkable EEG periods.
Results: Individual epilepsy patients showed slower reaction times (RT) during generalized IEA compared to RT during unremarkable EEG. RT differences were ~300 ms ($p < 0.001$) in the Flash test and ~200 ms ($p < 0.001$) in the Steer Clear. Prior work suggested that RT differences >100 ms may become clinically relevant. This occurred in 40% of patients in the Flash test and in up to 50% in the Steer Clear. When RT were pooled, mean RT differences were 157ms in the Flash test ($p < 0.0001$) and 116 ms in the Steer Clear ($p < 0.0001$) (fig. 1A). When RT differences were grouped according to EEG morphology, we could show that they were significantly longer during IEA bursts with classical spike waves than with atypical spikes or sharp theta activity (fig. 1B).
Conclusions: Generalized IEA of short duration seems to impair brain function i.e. the ability to react. Our results extend previous findings insofar that an impact on performance during generalized IEA is observed down to two seconds duration in simulated driving ability. The reaction-time-EEG could be used routinely to assess driving ability.

Figure 1
Reaction times in the Flash test and in the Steer Clear.



Reaction time differences, according to EEG morphology



References: KRESTEL H.E., NIRKKO A., von ALLMEN A., LIECHTI C., WETTSTEIN J., MOSBACHER A. & MATHIS J. 2011. Spike triggered reaction-time-EEG as possible assessment tool for driving ability. Epilepsia, in press.

Free Communication 5

Successful deep brain stimulation in a patient with severe automutilations

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Introduction: Deep brain stimulation (DBS) has been reported to improve self-injurious behaviour in patients who underwent neurosurgery for Gilles de la Tourette-Syndrome and dystonia in Lesch-Nyhan-Syndrome. We report the case of a patient with automutilations who was treated with DBS.
Methods: A 30 year old female patient with mental retardation after encephalitis during infancy and consecutive severe self-injurious behaviour was assessed for DBS. Written informed consent was obtained of the patients' mother and siblings following several consultations in which detailed and repeated information about the risks and possible benefits was provided. The information process was extended over more than one year to allow for sufficient time of reflection. Based on the published and preliminary personal experience in patients with automutilations in the context of other diagnoses, DBS of the anterior pallidum was planned and carried out in general anaesthesia Correct electrode location was confirmed with postoperative imaging.
Results: Self-injurious behaviour including hitting herself, banging her head, and biting had resulted in injuries with loss of teeth and blindness before surgery. The patient had to remain all time with her hands tied on her back to prevent constant violent self-injurious behaviour. After surgery, the automutilations had at first completely disappeared and recurred gradually and only partially after several weeks. Stimulation was tested and programmed progressively over the following months, giving special attention to the close observation of possible side effects the patient could not express verbally. After one year, the patient's self-injurious behaviour continues to be much improved so that she does not have to be tied up for most of the time.
Conclusions: As ultima ratio, DBS of the anterior pallidum can be an effective treatment of severe self-injurious behaviour. The process to obtain informed consent for invasive treatment in patients with mental retardation is particularly delicate and requires strict ethical standards including particularly thorough information of the caregivers and legal guardians with repeated consultations and sufficiently long time for reflection. The testing and setting of DBS parameters in a patient who cannot communicate verbally rely on observation. Adjustment of stimulation parameters in the ventral pallidum is a complicated process over several months.
key words: deep brain stimulation, self-injurious behaviour, automutilations, globus pallidus, mental retardation preferred means of presentation: oral; audiovisual equipment required: computer projection.

Free Communication 6

Morning light as a countermeasure to sleep-loss related decrements in cognitive performance and well being

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Introduction: Light exposure elicits numerous effects on human physiology and behaviour. However, it remains inconclusive whether morning light exposure has beneficial effects on cognitive performance, mood and circadian physiology following sleep restriction (SR). Here we investigated the role of morning light exposure as a countermeasure for impaired cognitive performance and mood during SR.
Methods: Seventeen participants were studied during 42h in the laboratory in a balanced cross-over design where 3 different light settings were administered each morning after SR (6h): blue light (BL) (20 min exposure 2h after wake-up; 200 lux of light at 470 nm), dawn simulating light (DsL) (blue-enriched polychromatic light gradually increasing from 0 to 250 lux during 30 min before wake-up time, with light around 250 lux for 20 min after wake-up time) and Dim light (DL) (<8 lux). Cognitive tests were performed every 2h during the wake episode and questionnaires were hourly completed to assess subjective mood and well-being. Salivary melatonin and cortisol were collected during wake episode in regular intervals.
Results: Analysis of cognitive performance yielded a significant main effect of "light condition" ($p < 0.01$), such that during the first day following SR, performance was significantly deteriorated during DL, while it maintained stable during BL and significantly improved with DsL. After the second SR night, these differences on cognitive performance did not further reveal significances between DsL and DL. Analysis of well-being revealed a significant main effect of "light condition", such that morning DsL improves levels of well-being, and even more after the second SR night, as compared to DL and BL ($p < 0.001$). Exposure to morning DsL did not significantly affect circadian melatonin phase, while, after morning BL, melatonin onset was significantly earlier as compared to DsL and DL. Furthermore, after DsL, salivary cortisol levels were significantly higher at wake-time as compared to BL and DL.
Conclusion: Our data indicate that exposure to morning light after the first and second day of SR alleviate decrements in cognitive performance under conditions of mild SR. This effect was more pronounced after dawn simulation, since the DsL was able to maintain higher well-being levels and did not affect circadian melatonin phase, whereas morning blue-light induced a phase advance of melatonin, and therefore impacted on the circadian system.

Free Communication 7

Long-term follow-up of the pregnancy related restless legs syndrome

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Introduction: Pregnancy is a significant risk factor for transient form of restless legs syndrome, which usually recovers during the post-delivery puerperal period. The goal of the present survey is to investigate whether transient restless legs syndrome during pregnancy represents a risk factor for later developing restless legs syndrome.
Methods: A long-term follow-up study, planned as an extension of a previous epidemiological survey was carried out. After a mean interval of 6,5 years, parous women were newly contacted to compare the incidence of restless legs syndrome between subjects who never experienced the symptoms to those who reported restless legs syndrome during the previous investigated pregnancy.
Results: A total of 207 women previously admitted at the Unit of Obstetric and Gynecology. Seventy four women who experienced restless legs syndrome during the previous pregnancy, and 133 ones who did not. The incidence of restless legs syndrome was 56‰ person/year in women who experienced the transient pregnancy restless legs syndrome form, and 12.6‰ person/year in subjects who did not, with a significant four-fold increased risk of developing a chronic restless legs syndrome in women who presented restless legs in the previous pregnancy. Considering further new pregnancies during the follow-up period, the restless symptoms reappeared in 58% of the cases, while they emerged for the first time only in 3% of women who never experienced restless legs syndrome.
Conclusion: The transient pregnancy restless legs syndrome form is a significant risk factor for the developing of a future chronic idiopathic restless legs syndrome form, and for a new transient symptomatology in a further pregnancy.

Free Communication 8

Long-term follow-up in patients with deep brain stimulation for cervical dystonia

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Introduction: High frequency stimulation of the internal pallidum (GPi) is an effective treatment of generalized and segmental dystonia. Several prospective studies have reported short term and up to five year follow-up results. We here report the outcome of deep brain stimulation in five patients with cervical dystonia (CD) after more than a decade.
Methods: The five patients (2 men) were treated at the Departments of Neurology and Neurosurgery of the University Hospital in Bern. Their age of onset of CD was 39 [21–48] years, and they were operated for deep brain stimulation (DBS) after 5 [2–7] years. They have previously been treated with botulinum toxin for 20 [2–60] months with an unsatisfactory result. CD was predominantly phasic in three and tonic in two patients. Patients were videotaped and assessed using the Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS) before surgery and annually thereafter. All ratings have been done from the videotapes in randomized order by the same physician. All patients were implanted bilaterally with quadripolar electrodes (Medtronic, model 3389) into the posteroventral GPi, if possible in local anaesthesia. Position of two electrodes was revised after postoperative imaging. Final location of the electrodes in the GPi was confirmed by imaging.
Results: Mean TWSTRS severity score improved significantly (Friedmann test, Chi2 = 7.68, p <0.05) by 54.1%, corresponding to an improvement from a mean score of 23.8 (SD 3.3) before surgery to 10 (7.3) at last follow-up. Individual responses were, however, variable: three patients clearly responded to stimulation with a pronounced motor improvement of >80%, whereas two patients had a poor response (5% and 19.1%). These two patients were those whose dystonia was tonic. The mean TWSTRS disability score dropped by 70.4% from baseline to last follow-up corresponding to 24.3 points before DBS to 7.6 at last follow-up. Two patients did not report any disability at last follow-up. In contrast, there was no significant improvement of the mean pain TWSTRS subscore.
Conclusions: Pallidal stimulation is an effective treatment of CD, but the responses vary from one individual to another in spite of correct electrode placement. Beneficial effects on disability are more pronounced than those on motor scoring and last over more than a decade without wearing off.

Free Communication 9

Which receptor subtype is the target of dopamine-agonists in restless legs syndrome?

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Introduction: Dopamine agonists (DA) are the first line treatment in restless legs syndrome (RLS) and periodic leg movements during sleep (PLMS). In order to understand which DA receptor subtype plays the main role in the treatment of RLS with PLMS, we compareed the efficacy of equivalent low dosages of the dopamine D3 receptor subtype preferring agonist pramipexole (PRA) with the D2 receptor subtype preferring agonist bromocriptine (BRO) on RLS and PLMS.
Methods: A placebo-controlled, prospective single-blind investigation was carried out on 45 drug naïve patients with idiopathic RLS. Each patient underwent two consecutive full night polysomnographic studies. The first night was performed without pre-medication. Prior to the second night, one group received a single oral dose of 0.25 mg PRA while a second group received a single oral dose of 2.5 mg BRO, and the remaining patients received placebo. After each polysomnography, additional subjective evaluation of the severity of RLS symptoms was also assessed in the morning.
Results: Subjective symptoms improved with both PRA and BRO, however the amelioration after PRA medication was considered more notable, where as side effects were preponderant after BRO. Only PRA induced an improvement of the sleep efficiency and a reduction of the wakefulness after sleep onset. Further, PRA was more effective than BRO in reducing PLMS in patients with a high level of PLMS index at baseline. Typical leg movements, with an inter-leg movements intervals ranging between 10 and 40 s disappeared completely after PRA treatment but persisted, even if reduced, after BRO treatment.
Conclusions: This study demonstrates that a drug targeting the dopamine D3 receptor subtypes has a higher efficacy on PLMS and RLS symptoms than a drug that preferentially targets the D2 receptor subtype. It also suggests that DA has a specific role in RLS, with scientific relevance and important clinical implications.

P01

18F-FDG PET/CT findings in the Kleine-Levin syndrome

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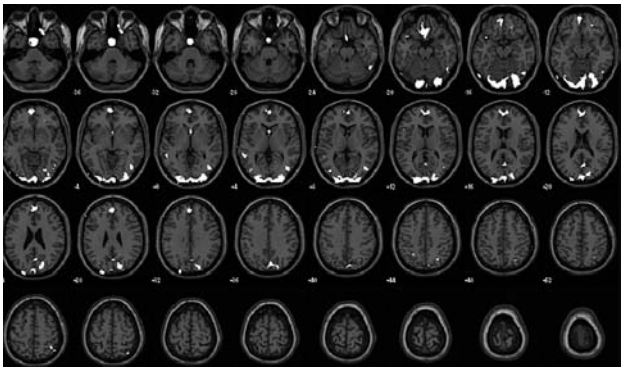
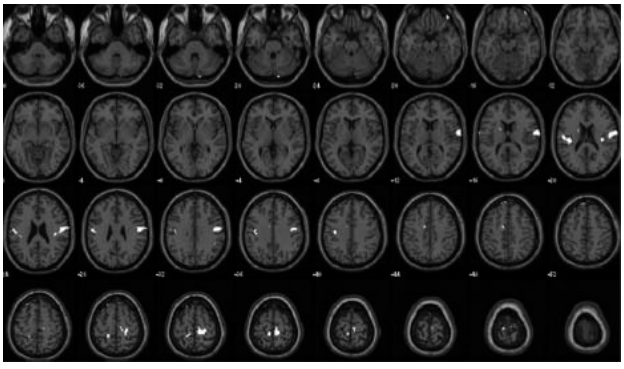
Introduction: Kleine–Levin syndrome (KLS) is a rare disorder characterized by recurrent episodes of hypersomnia, cognitive and behavioral disturbances. While etiology and pathogenesis underlying KLS remains enigmatic, functional imaging studies have been inconsistently reported.
Methods: We performed 18F-FDG PET/CT in two patients (a 17 years-old man and a 18 years-old woman, right-handed, with typical clinical presentation, fulfilling the International Classification of Sleep Disorders II criteria of KLS), while symptom free and during an acute KLS episode. All scans were performed during quiet wakefulness, under EEG monitoring. Increases and decreases in brain glucose metabolism were determined during symptomatic periods, in comparison to asymptomatic periods, using a 5%-threshold. Concordant changes found in each patient are presented.
Results: While symptomatic, patients exhibited significant decreases in metabolism in orbitofrontal, frontal parasagittal, and occipital areas. Increase in metabolic activity was observed in the premotor cortex, particularly on the dominant side, as compared to the asymptomatic period. Striatal and diencephalic areas showed unchanged metabolic rates.
Conclusions: This is, to the best of our knowledge, the first 18F-FDG PET study in KLS investigating variations in cerebral glucose metabolism according to the presence of symptoms. During the symptomatic period, focal brain metabolic changes were observed in frontal, occipital and left premotor cortex, but no variations were seen in diencephalic regions. Areas of decreased metabolism may correlate with motivational and perceptive symptoms, while regions of increased metabolism could reflect a tentative of recruitment of compensatory mechanisms. Further studies are necessary to confirm these hypotheses.



Decrease in metabolism



Increase in metabolism

P02

Acute stroke treatment in the regional hospital

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Introduction: Treatment of acute ischemic stroke with intravenous rt-PA still is the only officially approved pharmacological therapy. Its application is bound to strict treatment criteria and to a narrow time window of actually 0 to 4.5 hours after symptom onset. The regional hospital in Grabs is situated in a distance of 1 hour from the next comprehensive stroke unit. To save time for treatment systemic thrombolysis was introduced in the hospital of Grabs under neurological guidance in 2007. A database study was conducted to assess the quality of thrombolytic treatment in the regional hospital.
Methods: All patients with suspected acute stroke were prospectively recorded in a database. We documented age, sex, time of stroke onset, admission to hospital, start of imaging and start of thrombolysis. Additionally, the NIH-stroke scale was recorded on arrival at the hospital. Patients treated with rt-PA were followed up at 3 months after stroke onset with NIH-SS, mRS (modified Rankin Scale) and Barthel Index being recorded. Endpoints of the study were the proportion of patients with a favorable outcome (mRS <2) at 3 months, mortality at 3 months and the proportion of patients with intracerebral hemorrhage. We compared the data with the results from the SITS-MOST register. For statistical comparison we used the Wilcoxon rank test and the chi-square test.
Results: In the study period 274 patients were assigned as acute stroke at the age of 69.4 (16-92) years. The time from symptom onset to admission was 128 min (± 76), the NIH-SS was median 2 (IRQ1-3), this included 51 patients with TIA. 43 patients were treated systemically with rt-PA. Time of symptom onset to admission was 101 min (± 61), time from admission to imaging was 22 min (± 9), admission until treatment was 75 min (± 56). The NIH-SS at admission was 7 (IQR 2-12). The proportion of patients with a favorable outcome at 3 months was 55% (CI 54.7–55.7) in our study compared to 54.8% (CI 53.5–56.0) in the SITS-MOST register. 2% (1.7–2.7) (Grabs) versus 1.7% (CI 1.4–2.0) (SITS-MOST) had an intracerebral hemorrhage. The mortality rate was 11% (10.4–11.6) versus 11.3% (CI 10.5–12.1) (SITS-MOST). The differences are not statistically significant.
Conclusions: The results of the acute stroke treatment in the regional hospital correspond to those of the large SITS-MOST register. Strict application of international treatment guidelines for stroke therapy allows a safe and effective treatment of stroke patients even in a regional hospital.

P03

Benefits of cognitive training in MS patients treated with INFB-1b

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Introduction: Cognitive problems are observed across different MS disease courses, including patients at the earliest stages and may have detrimental effects on working capacity and social integration. In most patients with cognitive deficits, working memory, cognitive flexibility and mental speed are affected. Treating these deficits early in the disease course is of high relevance. A re-analysis of the BENEFIT data has recently indicated that IFNB-1b has favourable effects on both short and longterm cognitive outcomes in patients with clinically isolated syndrome (CIS). In this study we explore the added value of cognitive training.
Methods: After informed consent 40 patients with CIS or early MS under treatment with IFNB-1b will be included and monitored over 1 year. Patients will be randomly assigned to either the training group (TG), receiving IFNB-1b and cognitive training, or the control group (CG), receiving IFNB-1b only. The training consists of three different modules, which are applied for 15 minutes each in a 45 minutes session. The whole training consists of 16 sessions within four weeks. A neuropsychological test battery and self-reported outcomes for depression, fatigue and quality of life are applied at baseline (T1), immediately after the training (T2), after 3 months (T3) and after 6 months (T4). In addition, treatment effects on cerebral function and structure are

investigated using MRI (fMRI, resting state fMRI, DTI, conventional MRI) performed at T1, T2 and T4.
Results: Currently, nine patients have been included in the study. The study is still recruiting. Results of a planned first interim analysis will be presented.
Conclusion: Initial experience with the training indicates a high acceptance by the participating patients and indicates improved performance in both behavioural measures and neuropsychological test performance.

P04

Brain Cell Autotransplantation reverses Enkephalin increase in MPTP-treated Monkeys

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Parkinson's disease (PD) is caused by a degeneration of dopaminergic cells in the Substantia Nigra (SN). PD symptoms, like bradykinesia, only appear after a large striatal dopamine depletion. Compensatory mechanisms are probably responsible for this delay in symptoms appearance and may also play a role in new therapies such as stem cell transplantation. In a previous study, we have observed in PD rats that enkephalin (ENK) mRNA striatal expression is modulated even in asymptomatic animals. ENK seems to play a role in the pre-clinical stage of the disease. Our hypothesis was that ENK should be increased in the pre-symptomatic PD phase also in 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridin (MPTP) monkeys and that an autologous brain cell transplantation would modulate ENK expression.
Eight St. Kitts green monkeys were used for this study and separated into three groups: two normal controls without any intervention, two MPTP controls and four MPTP animals implanted with autologous cultured cells from cortical biopsy. All MPTP monkeys were asymptomatic. Four months after reimplantation, monkeys were sacrificed. TH-immunopositive cells were counted in SN and ENK mRNA expression was measured by in situ hybridization in caudate nucleus and putamen.
Preliminary results showed that even in asymptomatic MPTP monkeys, ENK mRNA expression was increased in both caudate nucleus and putamen. Implanted animals presented a decrease of ENK mRNA expression in both caudate and putamen, compared to the normal controls.
Our results indicate that there is an ENK increase already in the pre-symptomatic phase. This increase is reversed by an autologous graft, where nigral TH protein expression is back to normal. We suggest that ENK plays a role in the pre-clinical stage of PD. Stem cell transplantation may possibly act by modulating such plastic mechanisms.

P05

Case of reading epilepsy influenced by nutrition

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Introduction: Reading epilepsy is a well-known type of reflex epilepsy, in which seizures are provoked by reading. After initiation of reading typically sudden jerks of the jaw and – to a variable extent – upper limbs appear, sometimes progressing into generalized tonic-clonic convulsions. Treatment consists of clonazepam/carbamazepine.
Methods: Case Report.
Results: We report a case of a 45 year-old right-handed male teacher with a ten-year history of nocturnal limb jerks responsive to night-time clonazepam, diagnosed as essential myoklonus. Over the last 5 years, he presented with progressing reading difficulties and associated twitching of the arms. He described consistently that symptom intensity varied from very disturbing to barely existing depending on the content of carbohydrates in his diet. Routine neurological examination – with the exception of occasional, subtle twitching of the arms – proved normal. Seconds after starting to read, a stuttering articulation and impaired text comprehension appeared together with jerks of the jaw and upper limbs, ceasing again with discontinuation of reading. No known previous medical history was given. His grandmother (father's side) and father had a lifelong tremor, his father also intermittent muscle twitching of the arms – a brother of similar age has no speech or movement impediment. Levetiracetam and baclofenum were not beneficial. A cranial MRI scan and routine blood tests were normal. Repeated EEG recordings were consistent with the diagnosis of primary non-convulsive reading epilepsy: Resting EEG showed occasional fronto-temporal sharp waves, predominantly on the right with a progression to a generalized, midline-dominant spike-slow-wave pattern upon reading. Parallel metabolic screenings showed increased blood levels of ammonia and several aminoacids after 3 weeks of decreased carbohydrate intake in comparison to 3 weeks of regular diet – clinically and electroencephalographically, this resulted in a more severe epileptic reading impairment.
Conclusions: We report a case of non-convulsive reading epilepsy with a possible family history, influenced by the content of carbohydrates in the daily diet. Further metabolic studies are currently pending to delineate the exact link between carbohydrate intake and ammonia / amino acid levels in this case.

P06

Case report: A case of ALS with paraneoplastic Anti-Ma2 antibodies

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Objectives: Anti-Ma2 antibodies are well characterized onconeural antibodies causing paraneoplastic neurological syndromes like limbic and brainstem encephalitis. They are highly specific for the presence of germ-cell tumours of the testis and lung carcinoma [1]. There are few reports of other neurological syndromes associated with anti-Ma2 antibodies including one case with encephalitis and progressive muscular atrophy (PMA).
We report a patient with anti-Ma2 antibodies without evidence of carcinoma who presented with clinical signs of motor neuron disease without evidence of encephalitis.
Methods: A 64-year-old Caucasian man presented with progressive muscular weakness of the lower extremities and continued weight loss for approximately one year. In addition to distally pronounced tetraparesis he showed severe muscular atrophy of all extremities, widespread fasciculations and increased reflexes in the upper extremities. At follow up the patient developed dysphagia. The diagnostic workup consisted of a detailed blood and cerebrospinal fluid analysis including routine blood tests, serologies of HIV, hepatitis, borrelia and syphilis as well as vasculitis markers and paraneoplastic antibodies. We also conducted extensive electrophysiological studies. For differential diagnosis magnetic resonance (MR) scans of brain and spine were performed. Furthermore we did an extensive tumour screening including sonography of the testis, chest and abdominal radiography as well as a positron emission tomography (PET) scan.
Results: Clinical examination and electrophysiological studies revealed signs of upper motor neuron involvement in two regions and signs of lower motor neuron involvement in four regions of the body. Thus, probable ALS was diagnosed. MR imaging of the brain and spine were normal apart from moderate degenerative changes of the cervical and lumbar spine without myelopathy. CSF analysis revealed mild pleocytosis, other parameters within normal limits. The detection of increased anti-Ma2 antibodies originated the intensive search for a tumour (e.g. testicular germ-cell tumour), which could not be detected so far.
Conclusion: This is the first report of a clinically typical motor neuron disease associated with anti-Ma2 paraneoplastic antibodies. In consideration of a high specificity of anti-Ma2 antibodies in view of a paraneoplastic neurological disease, the clinical presentation of motor neuron disease should be considered in differential diagnosis and might be a paraneoplastic syndrome of these antibodies.

P07

Chronic alcohol abuse and reversible cerebral vasoconstriction disorder: case report

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Introduction: Reversible cerebral vasoconstriction syndrome (RCVS) describes a group of disorders with severe headaches (thunderclap-type), reversible segmental and multifocal vasoconstriction of cerebral arteries, with or without focal

neurological deficits or seizures. Several conditions are related to RCVS, but alcohol consumption has only been considered in the context of acute intoxication. Ischemic stroke has been reported as a complication of RCVS. Heavy alcohol consumption (>60 gr/j) is a well-studied risk factor for ischemic brain injury. We describe a case suggesting an association between RCVS, ischemic stroke and daily heavy alcohol abuse.
Case presentation: A 39-year-old man with residual schizophrenia presented with impaired consciousness and athetosic movements; no headache was mentioned. This occurred after 10 days of fatigue, dizziness, apathy and behavioural changes including cessation of his usual beer consumption (3-4 litres/day). Cerebral-MRI indicated multiple acute ischemic lesions. MRI-angiography revealed multiple bilateral areas of tapered arterial narrowing ("beading"), especially on the anterior and medial cerebral arteries. Cerebral arterial vasoconstriction was confirmed by transcranial Doppler ultrasonography (TDU). Cerebrospinal fluid indicated minimal and non-significant abnormalities. Toxicologic screens of urine and a hair sample covering a period of 4 month prior to admission were negative. Total-body PET-CT-scan showed no tumoral lesions. Treatment with Nimodipine was started. Two weeks after admission the patient presented a generalized tonic-clonic seizure, followed by severe aphasia, apraxia, ataxia, rightside neglect and hemiparesia. MRI showed a large sub-acute ischemic stroke in the territory of the left medial cerebral artery. Three weeks later TDU showed normalized arterial blood-flow.
Discussion: Clinical course and radiological evidence are consistent with the criteria of RCVS. Thunderclap-type headaches were not reported but the reliability of history was very poor. Common conditions related to RCVS were ruled out. It seems, therefore, possible that the RCVS of this patient was caused by heavy chronic alcohol abuse.

P08

Comorbidities in patients with status epilepticus: which role for prognosis?

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Purpose: Status epilepticus (SE) is a condition related to significant mortality and morbidity; knowledge about prognostic factors is important to orient medical resources and treatment strategies. Some independent predictors of dismal outcome after SE have been identified in previous studies, such as acute (or potentially fatal) etiology, advanced age, de novo presentation, and severe consciousness impairment before treatment. However, these variables encompass only a limited aspect of the clinical background: in fact, previously existing medical problems (comorbidities) have received little attention in this setting.
Methods: We studied 280 adult incident SE episodes prospectively collected in our tertiary care hospital over 55 months, excluding patients with post-anoxic encephalopathy. Prediction for mortality and return to clinical baseline at hospital discharge was assessed using demographics, SE etiology, a validated clinical SE severity score (STESS, including age, seizure type, consciousness, history of previous seizures), and comorbidities (assessed with the Charlson Comorbidity Index, CCI); the models were compared using the ROC statistics.
Results: The overall short-term mortality was 14%, and only half of patients returned to their clinical baseline. About one third of patients did not have any comorbidity, one third had a moderate CCI, and the last third presented a high comorbidities' load. Before correction for confounding factors, age, SE severity score, potentially fatal etiologies, and number of pre-existing comorbidities were significant predictors of both mortality and return to clinical baseline. As compared to the simplest predictive model (including age and deadly etiology), more complexes models comprising additionally SE severity and comorbidities were only marginally better in their predictive performance for mortality (ROC 0.77 vs. 0.84 for mortality, P = 0.0158; ROC 0.82 vs. 0.86 for return to baseline; P = 0.0043).
Conclusions: Pre-existent comorbidities and clinical presentation in patients with incident SE seem to affect the outcome only by a relatively marginal degree, while age and etiology are confirmed as robust and widely applicable predictors. This finding emphasizes the importance of a thorough search for etiology in this clinical setting.

P09

Comparison of quantitative EEG (qEEG) parameters in patients with mild cognitive impairment in Alzheimer's (AD-MCI) and Parkinson's Disease (PD-MCI)

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Introduction: Differential diagnosis of cognitive decline in beginning neurodegenerative disorders is difficult to classify. Recent publications showed that qEEG measures have the potential to separate between different diseases. The actual study compares spectral parameters in a group of patients with mild cognitive impairment in Alzheimer's and Parkinson's Disease.
Methods: 12 Patients with AD-MCI and 14 patients with PD-MCI were included in the study. Mean education and MMSE score differed not between groups. The PD-MCI group was significantly younger than the AD-MCI group. EEG was recorded with 257 electrodes and analysed using automated Matlab®-routines. Relative Power was determined in the delta- (0.5–4 Hz), theta- (4–8 Hz), alpha1- (8–10 Hz), alpha2- (10–13 Hz) and beta- (13–30 Hz) bands in 11 brain regions. In addition, the occipital Peak and Median Frequency were analysed.
Results: Analyses showed significantly reduced relative alpha1 power in all regions for patients with PD-MCI (grand avg: 12.3 ± 5.3%) compared to AD-MCI (grand avg: 20.0 ± 14.8%). No significant differences were found for the Peak and Median Frequency.
Conclusions: qEEG measures could be helpful to distinguish between AD and PD in very early stages of cognitive decline. To determine the cut-off for relative alpha1 power reduction a larger study group is needed.

P10

Deep brain stimulation in patients with mental disorders – practical and ethical issues; the Bern experience

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Introduction: DBS is a hopeful therapeutic last resort in patients with severe treatment-resistant psychiatric diseases and is currently used – often in therapeutic trials – in Gilles de la Tourette syndrome, obsessive compulsive disorder, depression, automutilations, and addiction. Neurosurgery in psychiatric patients poses particular practical and ethical challenges.
Objective and methods: Presentation of case reports from the University Hospital in Bern to illustrate practical challenges and problems in the recruitment process, documentation of informed consent, surgical treatment, logistics of in- and out-patient care, and parameter programming of DBS in patients with psychiatric disorders. Special ethical aspects must be taken into account.
Results: In addition to usual approach to DBS patients and the standards defined by the Ethics Committees, 5 points are particular in DBS-treatment in patients with psychiatric disorders: 1. DBS for psychiatric disorders aims to therapeutically alter the patients' psychological condition. The claim of some ethicists that neurosurgery must not affect psychological features does thus not apply here. 2. The process of obtaining informed consent must be multi-stage with repeated consultations over several months including caregivers, significant ones, and legal guardians. The indication for DBS must rely on a consensus of a multidisciplinary team. 3. The modifications of behaviour and mood brought about by DBS programming are gradual, reversible and often not immediate after parameter setting. Close and repeated observation must be guaranteed. A consensus must be found among the patients, their surrounding and the responsible clinicians about which psychological effects are considered therapeutic (i.e. desired) and which effects are to be considered adverse effects requiring modification of the stimulation parameters. 4. The programming expert's responsibility is considerable and needs to be shared with a multidisciplinary team. A practical approach to parameter testing will be presented. 5. The senior DBS expert must be within reach

24/7 as stimulation effects may occur with a delay of several hours to days.
Conclusions: DBS in psychiatry is a formidable challenge but a great hope for patients with certain treatment-resistant severe psychiatric diseases. The unethical use of psychosurgery in the 1950s must not prevent the successful use of DBS meeting the highest ethical standards.

P11

Deep brain stimulation of the STN in a patient suffering from Parkinson's disease and Turner syndrome

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We present a 45-year old woman suffering from juvenile Parkinson's disease (PD) that was diagnosed January 2004. Despite different regimes of dopaminergic drugs she developed severe and disabling motor fluctuations and dyskinesias even with low doses of L-Dopa and dopaminagonists. The DATScan SPECT showed markedly symmetrical presynaptic dopaminergic deficiency. The family history for PD or other movement disorders is negative. Genetic testing concerning a herditary parkinson syndrome has not been performed so far.
In addition to the Parkinson Syndrome the patient suffers from a genetically assured Turner syndrome. To our knowledge this is the first description of a patient suffering at the same time from these two diseases. In November 2011 Deep Brain Stimulation (DBS) of the nucleus subthalamicus (STN) was successfully performed bilaterally with good post interventional result. Because of persisting and disabling dystonic movement of the left foot a dopaminergic therapy with pramipexol was readministered.

P12

Dementia in cerebellar ataxia associated with anti-GAD-antibodies

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Introduction: It is known that in subjects with antibodies to glutamic acid decarboxylase (GAD-ab) the spectrum of neurological symptoms comprises stiff-person-syndrome (SPS), cerebellar ataxia and limbic encephalitis as well as some less common conditions. However, dementia has only rarely been described in association with GAD-ab.
Case report: A 60-year old Swiss female was referred for diagnostic work-up of gait disturbances and cognitive impairment. Gait disturbances had evolved within several days, thereafter the progression had slowed down; however, at the time of referral she was already severely impaired by her gait disorder. Furthermore she complained about increasing cognitive disturbances particularly in visually estimating distances and about an increased error rate during writing despite proof reading.
Results: On clinical examination she disclosed marked cerebellar ataxia, gaze evoked nystagmus, positive frontal release signs, torticollis, slightly increased muscle tone, exaggerated tendon reflexes on her lower limbs and a positive Babinski sign. Neuropsychological examination revealed severe deficits in attention, visuospatial function and short-term memory. Moreover, behavior was disinhibited. MR scan of the brain showed supra- and infratentorial atrophy without any evidence for focal lesions. Screening for vasculitis, putative infectious diseases, prion diseases and several degenerative and metabolic forms of ataxia or dementia remained negative. Due to the clinical presentation with a subacute cerebellar ataxia, GAD-ab testing was considered. Testing showed very high levels of serum GAD-ab, thus leading to the diagnosis of GAD antibody-associated ataxia and dementia.
Conclusion: Several neurological symptoms including SPS and cerebellar ataxia were found to be associated with elevated GAD-ab titers, suggesting an immune-mediated process in these conditions. The clinical presentation of a subacute cerebellar ataxia encouraged us to test for GAD-ab in this patient. Rapidly progressive dementia can be caused by autoimmune diseases, namely in conjunction with voltage-gated potassium channel (VGKC) and GAD autoimmunity. Actually, the clinical picture of the presented patient would have fit well with CJD. As we excluded numerous putative etiologies of dementia or ataxia including prion diseases, we conclude that raised GAD-ab levels are likely to be causative for the neurological symptoms including dementia in this case.

P13

Eating disorders in anti-NMDAR encephalitis: a case report indicating the glutamatergic control of food intake

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Introduction: Feeding and satiety centers are located in various hypothalamic and brainstem nuclei. Recent animal data demonstrate that N-Methyl-D-aspartate (NMDA) glutamate receptors in these centers are implicated in the control of food intake. Apart from some clinical trials showing the efficacy of NMDA antagonists in treating eating disorders, no other human studies have supported this implication to our knowledge.
Case report: We describe the case of a 22-year-old girl who presented with anti-NMDAR encephalitis, a newly described autoimmune encephalitis, where antibodies target NMDA glutamate receptors. The encephalitis followed the classic course of symptom presentation, with memory deficits, psychotic symptoms, and alternating mood states. First-line and second-line immunotherapy was used. For about one month, the patient refused to take food in the mouth and reported both dysgeusia and fear of gaining weight. She expectorated every food she was given and often talked about calories and fat content. She progressively began to eat, and in a few days, she entered a hyperphagic phase, the severity of which could not be explained solely by corticoid treatment, due to its compulsive character. She was eating hypercaloric food, demanded the double or triple quantity of a normal meal portion and tried to eat from other patients' plates. Her premorbid BMI was at 21, two months later at 27 and five months later at 31.
Discussion: We propose that this case report indicates the glutamatergic control of food take in humans. The blockade of NMDA receptors in the hypothalamus and potentially the brainstem could explain the eating disorders of our patient. Temporal succession of hyperphagic and anorexic behaviors suggests a successive blockade and release of NMDA receptors in different brain structures regulating food intake during different stages of illness. Based on these findings, future pharmaceutical roads can be opened in treating eating disorders like anorexia nervosa or bulimia nervosa, by modifying NMDA transmission.

P14

Effect of transnasal insufflation on sleep disordered breathing in acute stroke

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Introduction: Sleep disordered breathing (SDB) is frequent in acute stroke patients and is associated with early neurologic worsening and poor outcome. Although continuous positive airway pressure (CPAP) effectively treats SDB, compliance is low. The objective of the present study was to assess the tolerance and the efficacy of transnasal insufflation (TNI), a less intrusive method, to treat SDB in acute stroke patients.
Methods: Ten patients (age, 56.8 ± 10.7 yr), with SDB ranging from moderate to severe (apnea-hypopnea index [AHI] >15 /hour of sleep) on a standard sleep study at a mean of 4.8 ± 3.7 days after ischemic stroke (range: 1–15 days) were selected. The night after, they underwent a second sleep studies while receiving TNI (18 L/min).
Results: TNI was well tolerated by all patients. For the entire group, TNI decreased the AHI from 40.4 ± 25.7 to 30.8 ± 25.7 /h ($p = 0.001$) and the oxygen desaturation index >3% from 40.7 ± 28.4 to 31 ± 22.5 /h ($p = 0.02$). All participants except one showed a decrease in AHI. The % of slow wave sleep (SWS) significantly increased with TNI from 16.7 ± 8.2 to 22.3 ± 7.4 % ($p = 0.01$). There was also a trend toward a reduction in markers of sleep disruption (number of awakenings, arousal index).
Conclusions: TNI improves SDB indices, and possibly sleep parameters in stroke patients. Although these changes are

modest, our findings suggest that TNI is a viable treatment alternative to CPAP in patients with SDB in the acute phase of ischemic stroke.

P15

Effects of subthalamic nucleus stimulation on cognition and mood in Parkinson's disease (PD)

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Objective: To assess the neuropsychological outcome as a safety measure and quality control in patients with subthalamic nucleus (STN) stimulation for PD.
Background: Deep brain stimulation (DBS) is considered a relatively safe treatment used in patients with movement disorders. However, neuropsychological alterations have been reported in patients with STN DBS for PD. Cognition and mood are important determinants of quality of life in PD patients and must be assessed for safety control.
Methods: Seventeen consecutive patients (8 women) who underwent STN DBS for PD have been assessed before and 4 months after surgery. Besides motor symptoms (UPDRS-III), mood (Beck Depression Inventory, Hamilton Depression Rating Scale) and neuropsychological aspects, mainly executive functions, have been assessed (mini mental state examination, semantic and phonematic verbal fluency, go-no go test, stroop test, trail making test, tests of alertness and attention, digit span, wordlist learning, praxia, Boston naming test, figure drawing, visual perception). Paired t-tests were used for comparisons before and after surgery.
Results: Patients were 61.6 ± 7.8 years old at baseline assessment. All surgeries were performed without major adverse events. Motor symptoms "on" medication remained stable whereas they improved in the "off" condition ($p < 0.001$). Mood was not depressed before surgery and remained unchanged at follow-up. All neuropsychological assessment outcome measures remained stable at follow-up with the exception of semantic verbal fluency and wordlist learning. Semantic verbal fluency decreased by 21 ± 16% ($p < 0.001$) and there was a trend to worse phonematic verbal fluency after surgery ($p = 0.06$). Recall of a list of 10 words was worse after surgery only for the third attempt of recall (13%, $p < 0.005$).
Conclusion: Verbal fluency decreased in our patients after STN DBS, as previously reported. The procedure was otherwise safe and did not lead to deterioration of mood.

P16

Endothelial dysfunction in stroke: the role of sleep disordered breathing (SDB)

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Objectives: To analyze the endothelial function in patients with acute ischemic events (stroke or TIA, AIE), its relationship with sleep disordered breathing (SDB) as well as its evolution in the subacute phase (3 months).
Patients and methods: We studied 39 consecutive patients from the SAS CARE study (26 m, 13 w, 62.7 ± 9.7 yrs) referred to our Stroke Unit. 25 patients also underwent a second analysis in the subacute phase. The endothelial function was assessed by peripheral arterial tonometry by ENDOPAT 2000, Itamar (Israel) measuring the reactive hyperemia index (RHI) and the augmentation index (AIx), in the fasting morning after Polysomnography (PSG); Both parameters were compared/correlated with clinical, principal PSG and blood parameters. In addition, an analysis of patients with endothelial dysfunction (def. RHI ≤1.67) and of patients with increased arterial stiffness (Aix ≥30%) was conducted.
Results: In the acute phase RHI was 2.0 ± 0.4 and the augmentation index 29.3% ± 22.6%. In the acute phase 6 patients presented endothelial dysfunction (1.44 ± 0.24 vs 2.10 ± 0.37). Endothelial dysfunction was associated with a lower level of HDL (1.0 ± 0.2 against 1.5 ± 0.7, $p = 0.02$) and the total level of cholesterol (Spearman: $r = 0.410$, $p = 0.012$). The outcome of patients with endothelial dysfunction in the acute phase tended to be less favorable. In particular, there was a trend showing that the frequency of non-independent patients (mRankin ≥2) was higher in patiens with RHI ≤1.67 (60% against 19.2%, $p = 0.09$ NS). This trend was confirmed in the subacute phase with 50% against 9% ($p = 0.1$, NS). A correlation between AIx and Saturation Time<90% (ST90) was found (Pearson: $r = 0.491$, $p = 0.042$). In the acute phase, 15 patients had increased arterial stiffness (AIx 51.6% ± 19.0% vs 14.1 ± 6.8) and the frequency of patients with extreme high ST90 (over 50 min) was significantly higher for patients with Aix ≥30 (28.7% vs 0%, $p = 0.022$ Fisher test). AIx in acute phase is also found to correlate with the mean O2 saturation at 3 months (Pearson: $r = –0.776$, $p = 0.025$) and the augmentation index correlates with the arousal index in the subacute phase (Spearman: $r = 0.436$, $p = 0.042$).
Conclusion: Preliminary data if this ongoing study suggests that endothelial dysfunction in acute and subacute stroke is correlated with cardiovascular risk factors profile (e.x: cholesterol and HDL blood levels), with oxidative stress, arousals and may be associated with a less favourable outcome. This preliminary data suggest a relationship between endothelial dysfunction and SDB in patients with AIE, but this should be confirmed by further analysis.

P17

Frontotemporal Lobar Degeneration (FTLD) and Amyotrophic Lateral Sclerosis (ALS): Two diseases linked by TDP-43 Pathology

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Introduction: A subset of Frontotemporal Lobar Degeneration (FTLD) patients develops signs of Amyotrophic Lateral Sclerosis (ALS) during the course of the disease and – vice versa – some patients with ALS show features of frontotemporal dementia. Thus, a common pathological cause of these neurodegenerative diseases has been subject of intensive research. Recently, TDP-43 and FUS (Fused in Sarcoma Protein) have been identified as disease proteins in both conditions confirming that they belong to a clinico-pathological spectrum of diseases.
Case presentation: We report the case of a 53-year-old man who developed behavioural changes over a course of approximately 6 months, leading to massive problems at work as a bank employee. Additionally, he showed changed sexual behaviour and became unable to manage his finances. According to history, clinical and neuropsychological features, a diagnosis of behavioural variant of frontotemporal dementia was established. Shortly after, the patient developed fasciculations of both arms, followed by mild pareses mainly of the right arm. During further follow-up, signs of motor neuron disease deteriorated rapidly and ALS was diagnosed. Even though the patient received best supportive treatment including early PEG placement, he died one year after the diagnosis of ALS and two years after the first symptoms of FTD.
Results: Pathological examinations revealed aspiration pneumonia as cause of death. Besides a predominant frontotemporal atrophy of the cortex, pathological features of ALS including atrophy of lower motor neurons as well as Bunina bodies were present. Immunohistochemical analysis revealed widespread TDP-43-positive inclusions in the brain and spinal cord, while stainings for Tau- and Beta-Amyloid rendered negative results. Thus, the pathological diagnosis of FTLD-TDP (subtype 2) was made.
Conclusion: This case highlights the common pathological cause of FTLD and ALS at least in a subgroup of patients. Pathological examination of these diseases should include search for TDP-43 and FUS (Fused in Sarcoma Protein) pathology. Autopsy of deceased FTLD or ALS patients is helpful in our understanding of these diseases and should be discussed with patients and caregivers.

P18

Functional outcome of severe dysphagia in neurorehabilitation – a series

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Introduction: Dysphagia requiring nasogastral or FGT (feeding gastrostomy tube) in the early neurorehabilitation phase is not a rare condition. Frequently causing bronchopulmonal infections,

dysphagia is a critical factor of life-threatening complications. Hence, a successful rehabilitation of dysphagia is of high prognostic relevance quo ad vitam as well as for qualitiy of life in survivors. Our aim was to compare localisation and etiology of central nervous system lesions in FGT-patients admitted to our acute neurorehabilitation center as determining factors for functional recovery (removal of FGT, oral food intake).
Methods: In our acute neurorehabilitation center we retrospectively analysed the functional outcome of 26 consecutive (01/2010 – 06/2011) patients with severe dysphagia and FGT in respect to swallowing and eating orally as rated by the Functional Oral Intake Scale for Dysphagia (FOIS, Crary M et al., Arch Phys Med Rehabil Vol 86, August 2005). Patients participated at least twice daily in an individually adapted neurorehabilitative therapy program including FOTT (facio-oral-tract therapy), meals supervised by therapists and self-training instruction. Our interdisciplinary neurorehabilitation team assessed patients clinically at admission, regularly during the hospitalisation and before discharge. If indicated, additional fiberendoscopic exploration was performed.
Results: Of 26 Patients admitted with FGT, 7 (27%) presented with nuclear or peripheral nervous (bulbar) and 19 (73%) with supranuclear lesions. Etiologies of dysphagia were ischemic stroke (62%), cerebral bleeding (19%), cerebral (4%) and craniopharyngeal (11%) neoplasms and neurodegenerative disease (4%). Of 19 patients with supranuclear lesions, it was possible to remove the FGT in 15 (79%) by the end of stationary neurorehabilitation. This goal was not achieved by 71% of patients with nuclear or peripheral nerve lesions.
Conclusion: In our FGT patient collective, the vast majority of patients with supranuclear lesions (pseudobulbar syndrome) achieved a sufficient oral food intake (FOIS level 4–7) by the end of their neurorehabilitation stay. Only a minority of patients with nuclear or peripheral lesions (bulbar syndrome) were discharged without a FGT. In respect to the functional outcome in the rehabilitation of dysphagia, the location of the nervous system lesion appears to be more determinant than the etiology.

P19

Ictal dystonia and non versive early head turns – Clinical significance

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Introduction: We evaluated the laterizing value and performed a subtype analysis of unilateral dystonic posturing (UDP) and non versive early head turns (NVEHT) in temporal lobe epilepsy. While UDP is a reliable ictal laterizing sign, there is conflicting evidence on the significance of NVEHT. The relevance of different subtypes of these clinical signs remains unclear. Prior research indicates that laterizing semiology predicts favourable seizure outcome after epilepsy surgery.
Methods: Retrospective analysis of 311 seizures in 126 patients with unilateral temporal lobe epilepsy verified by comprehensive preoperative evaluation.
Results: UDP was observed in 16% of seizures and was contralateral to the epileptogenic focus in 95% ($p < 0.001$). A subtype-analysis demonstrated that only UDP with evident forced and rotatory elements was of laterizing significance. NVEHT occurred in 39% of seizures and were ipsilateral in 67% ($p < 0.05$). Ipsilateral and contralateral NVEHT had a mean duration of 24.1s and 12.8s respectively ($p < 0.05$), the mean latencies were 20.3s and 27.4s. The positive predictive value of NVEHT was higher in seizures without generalization than in secondary generalized seizures (70% vs. 47%; $p = 0.074$). NVEHT were associated with UDP in 60% of patients and were ipsilateral in 73% of these. In comparison, UDP was observed in only 2% of seizures in a group of 17 patients (47 seizures) without verified temporal lobe focus.
Conclusions: UDP is a reliable lateralizing sign in temporal lobe seizures but only when forced and rotatory components are apparent. NVEHT are ipsilateral to seizure onset in approximately two-thirds of cases, a higher positive predictive value is associated with longer duration, absence of secondary generalization and concomitant UDP.

P20

Infectious complications in status epilepticus: evidence of a five-year observational cohort study

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Introduction: Infectious complications in status epilepticus (SE) are frequent and may worsen course and outcome, requiring additional treatment on an ICU. The aim of this study was to determine the incidence and time of onset of infections during SE, as well as their association with SE course, length of hospitalization, ICU stay, and outcome.
Methods: Records of patients hospitalized from 2005 to 2009 due to SE were selected from a prospectively collected EEG database and included into the study. Microbiological data were extracted from an established database and cross-checked with clinical data and medical records. Refractory SE (RSE), SE duration and type, days on the ICU, as well as all infectious complications, comorbidities, and outcome were assessed.
Results: 22.5% of 160 patients had infections during SE. Almost all infections during SE (94.4%) were respiratory tract infections, 29.4% were ventilator-associated pneumonias. Patients with infections during SE had longer mean course of SE (6.37 vs. 1.82 days; $p < 0.0001$), longer mean ICU stay (11.09 vs. 6,00 days; $p = 0.0041$), higher risk of RSE (OR: 4.8, $p = 0.0002$), and higher mortality (OR: 5.2, $p = 0.0003$) than those without infections. Infections occurring in the first three days of SE were significantly associated with longer SE duration, higher RSE, and higher mortality in contrast to infections detected before SE onset.
Conclusions: Nosocomial infections during the first three days of SE are frequent, associated with higher mortality, prolonged ICU stay, and higher rate of RSE. Therefore, patients with SE should undergo intensive supportive care including intensified EEG-monitoring and antiepileptic treatment to prevent and comprehensively lower the burden of infectious complications.

P21

Lesions to primary sensory and posterior parietal cortices impair recovery from hand paresis after stroke

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Introduction: Neuroanatomical determinants of motor skill recovery after stroke are still poorly understood. Although lesion load onto the corticospinal tract is known to affect recovery, less is known about the effect of injury to cortical sensorimotor areas. Here, we test the hypothesis that lesions of somatosensory cortices leading to somatosensory dysfunction interfere with the capacity to recover motor skills after stroke.
Methods: Standardized test of motor skill (Jebsen Taylor Test, JTT) and tactile somatosensory function were acquired longitudinally over nine months in 29 consecutive patients suffering from first-ever stroke affecting the pre – and/or postcentral gyrus and to varying degrees the adjacent higher order sensorimotor areas of the frontal, parietal and insular cortex. Five JTT subtests were analyzed separately using response feature analysis: first, individual recovery trajectories of all subtests were derived for each patient using least-squares curve fitting and objective model selection procedures. Second, essential features of each recovery trajectory, i.e. model structure and derived model parameters, were used to classify and compare subgroups with different recovery trajectories. Acute lesions were mapped onto diffusion weighted imaging scans and normalized into stereotaxic space using cost-function masking. Voxel-wise lesion subtractions were calculated between trajectory subgroups. Finally, a probabilistic cyto- and myeloarchitectonic atlas was used for neuroanatomical

identification and quantification of lesion extent and topographical distribution.
Results: JTT subtests differed in their recovery profiles: tasks that relied on distal movements showed a higher proportion of patients with exponential recovery trajectories and more patients with incomplete recovery than tasks that relied on proximal movements. In a precision grip task, a majority of patients (23/29) showed exponential recovery trajectories. Of this group, 17 patients regained normal motor performance, whereas 6 did not. Lesion subtraction analysis and cytoarchitectonic mapping revealed that this group had a higher load and a more central location of ischemic lesions in the sensorimotor cortex (area 2), the posterior parietal cortex (intraparietal sulcus areas hIP1 and hIP2) and the superior longitudinal fascicle. Lesion volumes of these areas correlated with impaired somatosensory performance and chronic motor deficit. We did not find differences in injury to areas of the motor system or the corticospinal tract.
Conclusions: Our findings support a critical role of uni- and multimodal somatosensory cortices in the recovery of skilled hand function after stroke.

P22

NREM sleep increase and memory decline after mild traumatic brain injury in rats

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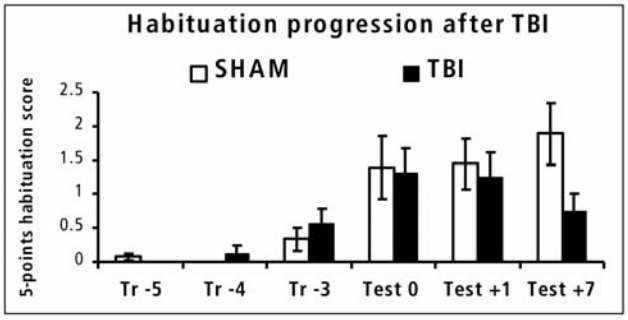
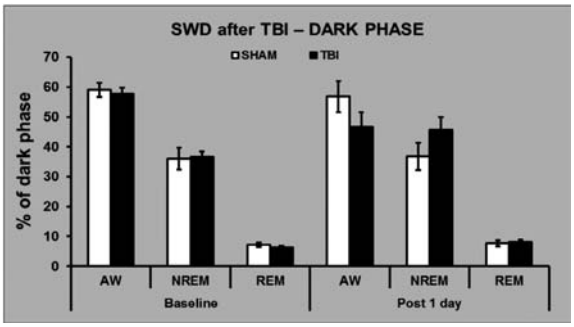
Introduction: Traumatic brain injury (TBI) is a major cause of disability world-wide, often leaving surviving patients with persistent neurological deficits including sleep-wake disturbances (SWD) and cognitive impairment which impair daytime functioning and quality of life. Clinical studies of posttraumatic SWD, however, are hampered by the fact that TBI is a most heterogeneous entity in respect to localization and severity. Therefore, the neurobiological processes underlying SWD after TBI remain unclear. We aimed at developing the first animal model of posttraumatic SWD to provide better insights into the mechanisms, consequences and possible treatments for sleep-wake sequelae after TBI.
Methods: We developed a new closed acceleration-deceleration TBI model in which infliction of brain injury and recording of vigilance states are compatible. After implantation of electroencephalography-myography (EEG/EMG) electrodes for recording of vigilance states, an incision was made in the scalp over the midline in the prefrontocortical area of 9 adult male Sprague-Dawley rats. Rats were fixed on a foam platform, allowing the head to incline during trauma induction. A 0.5 kg metal rod with a silicon tip of 5 mm was placed over the selected injury point, elevated 12 cm with an angle of 65° and released over the exposed skull to induce trauma. 24h EEG/EMG recordings were performed before (baseline) and 1 day after TBI. Acquired habituation after exposure to a repetitive task was also evaluated, using a 5-points scoring method. In 9 sham controls, the same procedures were performed, except for trauma induction.
Results: Our preliminary findings show non significant habituation scores 7 days after injury in TBI rats, while sham controls acquire significant habituation scores compared to training (TBI (n = 8): Tr-5: 0 ± 0; Test 7 days: 0.75 ± 0.25 vs. Sham (n = 9): Tr-5: 0.07 ± 0.05; Test 7 days: 1.88 ± 0.45. Repeated measures ANOVA (RMA), Tukey's post hoc comparisons, *P <0.05).



One day after TBI, the EEG/EMG recording revealed that NREM sleep is increased during the dark phase in TBI rats compared to sham controls (TBI (n = 4): Baseline: 36.6 ± 1.8%; Post 1 day: 44.3 ± 4.2% vs. Sham (n = 5): Baseline: 36.0 ± 3.7; Post 1 day: 36.8 ± 4.6. RMA, Tukey's post hoc comparisons, *P <0.005).



Conclusions: Our preliminary study revealed a decline in memory and increased need of sleep per 24h in TBI rats, i.e. posttraumatic hypersomnia. The latter result is in line with our previous findings in humans, suggesting that hypersomnia is a cardinal finding after TBI and might be important for neuroplasticity and recovery. Whether cognitive impairment is linked to reduced vigilance or to neuronal damage remains unclear at this point. We conclude that our TBI model will constitute a valuable biological tool in the study of SWD and other sequelae after TBI.

P23

Postpartal onset of Amyotrophic Lateral Sclerosis (ALS): A case report

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Introduction: ALS is a rare neurological disorder leading to degeneration of upper and lower motor neurons. Mean age of onset ranges from 45 to 65 years and males are affected more often than females. There are only a few reports of ALS presenting during pregnancy. We report the case of a 25-year-old woman who developed first symptoms of ALS in childbed immediately after delivery of her second child.
Case presentation: One day after uncomplicated spontaneous vaginal delivery of her second child the 25-year-old woman noticed muscle weakness of her right hand. The weakness eventually spread to the right foot and finally to the left hand within four months. Moreover, the patient developed dysphagia, dysarthria and forced laughing and crying.
Results: Neurological examination five months after symptom onset revealed tetraspasticity with hyperreflexia in all limbs, atrophy of the small hand and foot muscles, fibrillation of the tongue as well as severe dysarthrophonia. Electromyography showed signs of widespread denervation in three out of four regions of the body. Motor evoked potentials (MEP) showed signs of pyramidal tract lesions to all limbs, whereas somatosensory evoked potentials (SEP) and sensory nerve conduction studies revealed normal results. Further examinations including MRI of brain and spine and extensive laboratory and CSF testing were performed to rule out other causes of motor neuron degeneration, all with negative results. Particular attention was given to exclude immune-mediated diseases like paraneoplastic disorders. At last, the diagnosis of ALS was definite according to El Escorial and Awaji criteria. Treatment with riluzole was started.
Conclusion: To our knowledge, this is the first report of ALS onset in childbed. Whether this coincidence is a matter of chance or does reflect a causal link remains unclear to date. It might be possible that the disease already began during pregnancy without overt clinical signs. As mentioned above, some reports of ALS onset in pregnancy exist. Thus, a relationship between hormonal changes during pregnancy and an increased susceptibility to ALS may be discussed. Finally, the number of patients with ALS onset during pregnancy or in childbed is too small to draw definite conclusions.

P24

Primary diffuse leptomeningeal gliomatosis: A case report

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Introduction: Primary diffuse leptomeningeal gliomatosis (PDLG) is a rare disorder which has been described in only about 50 patients up to now. The clinical course may be variable but is fatal within months in most patients. Here we report on a case who was treated with radiotherapy and temozolomide chemotherapy.
Clinical case: The 42year old female patient presented with headache and epileptic seizures arising from the left temporo-lateral region. On MRI (fig. 1a) a left-sided temporoparietal and cerebellar leptomeningeal enhancement with diffuse parenchymal edema was seen. Cerebral angiography (fig. 1 bled to the diagnosis of leptomeningeal angiomatosis. Further examinations including CSF and ophthalmologic examination were unreveiling. The patient was discharged on antiepileptic treatment without any symptoms. Three weeks later she developed again severe headaches, seizures and a mild hemiparesis on the right side. MRI (fig. 2) showed a substantial lesion enlargement rendering the diagnosis of leptomeningeal angiomatosis unlikely. Leptomeningeal biopsy then established the diagnosis of PDLG. In spite of high-dose steroids, fractioned whole-brain radiatiotherapy (50 Gy) and concomitant chemotherapy with temozolomide the patient status deterioriated rapidly. Six weeks after symptom onset hemicranectomy due to massive swelling was performed. After surgery, the patient recovered partially and was able to walk again. However, over the course of three weeks the clinical state deteriorated. On MRI 13 weeks after symptom onset (fig. 3) further tumor growth was seen. Therefore treatment was stopped and the patient was discharged for palliative therapy. Her clinical state than worsened gradually. She died seven month after disease onset.
Conclusion: In the here presented setting rapid meningeal biopsy appears mandatory. As some patients may achieve lasting responses early cytotxic treatment must be initiated in view of this highly malignant tumor.

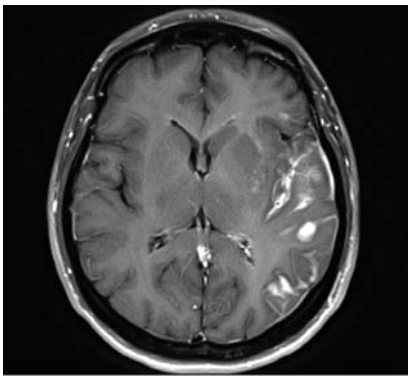

Figure 1a

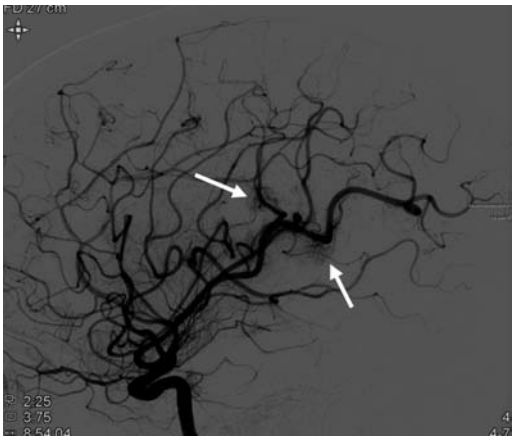

Figure1b

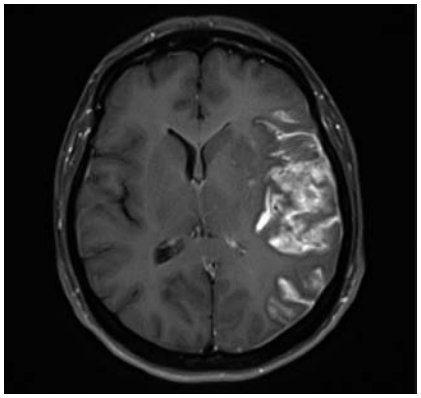

Figure 2

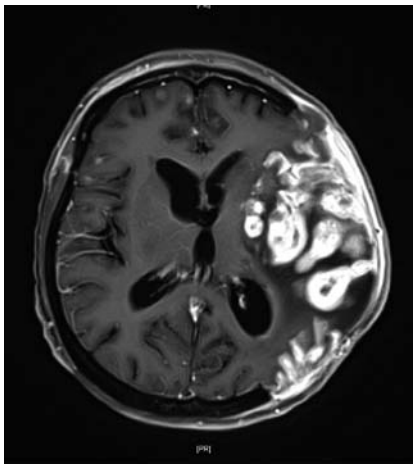

Figure 3

P25

Radiation- induced de novo Cavernoma after Treatment of Acute Myeloid Leukemia

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Introduction: Cavernomas are vascular lesions composed of thin-walled, dilated capillary spaces. Formation of cavernomas after radiation therapy has been suspected since 1994. The causative mechanisms are far from being understood. Vulnerability of the pediatric brain obviously accounts for the age preponderance. Blood vessel necrosis as well as connective tissue changes leading to increased VEGF expression may account for the development of vascular malformations. Radiation-induced cavernomas are mostly seen after the treatment of medulloblastomas, gliomas and acute lymphatic leukemia. De novo cavernomas in adults commonly occur ten years after higher radiation dosage (>30 Gy).
Case Report: We report a 45-year-old man who was admitted to our hospital following a first epileptic seizure. He demonstrated a tongue bite and a mild left hemiparesis. Laboratory results including CSF analysis were normal. CT scan of the brain showed a hemorrhagic lesion in the right parietal lobe as the potential cause of the seizure. Initial and more evident serial follow up MRI brain scans showed the typical appearance of a cavernoma. Of note, a cerebral MRI scan in 2006 showed no corresponding lesion. The patient suffered from an acute myeloid leukemia 11 years ago treated by allogenic stem cell transplantation. As a part of this procedure whole body radiation with 12 Gray was administered. According to the data from the literature, a typical delay from irradiation and a former normal MRI scan of the brain we assume that our patient suffers from a

radiation-induced de novo cavernoma. The patient remains free of seizures with anticonvulsive therapy (levetiracetam).
Conclusion: Radiation-induced cavernomas are eventually seen in children. It is speculated that radiation dose and fraction as well as predisposing factors of the developing brain cause de novo formation of cavernomas. To the best of our knowledge, we report the first patient with a radiation-induced cerebral cavernoma treated with whole body radiation for stem cell transplantation suffering from an AML so far. Evidence for this correlation is high as a former MRI scan was normal. Interestingly, compared to the reported adult cases in the literature, radiation dose in our patient was considerably low. Therefore, cavernomas should be considered in the differential diagnosis of hemorrhagic lesions in any patient with previous brain irradiation.

P26

Readily accessible acute phase proteins CRP and albumin predicting outcome in status epilepticus: an observational cohort study

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Introduction: Status epilepticus (SE) is a neurological emergency requiring intensive care. Numerous studies have tried to identify prognostic factors for refractory SE (RSE) and death. Changes of cytokine levels during SE have been demonstrated. Therefore, acute phase proteins, such as C-reactive protein (CRP) and albumin may be useful to predict SE course and outcome. The aim of this study was to determine the association and predictive value of CRP and albumin regarding course and outcome of SE.
Methods: Records of patients with SE from 2005 to 2010 were selected from a prospectively collected EEG database. CRP and albumin were measured during three days after SE onset. RSE, SE duration, days on ICU, comorbidities, and outcome were assessed. We further compared the overall predictive value of albumin and CRP, as well as their ratio (CRP at SE onset to albumin on admission) for the outcomes death and RSE by calculating receiver operating characteristic (ROC) analysis with and without adjustment for age, gender, and number of comorbidities.
Results: 160 consecutive SE patients were identified. Higher levels of albumin at SE onset were associated with lower rates of RSE, death, and shorter ICU stay ($p = 0.0017$, $p < 0.0001$, $p < 0.0001$). Increasing risk for RSE, death, and longer ICU stay was observed for elevated CRP ($p = 0.0202$, $p = 0.0005$, $p = 0.0007$). Hazard ratios for death increased significantly for both, higher CRP levels at SE onset and lower albumin levels at admission. The negative predictive value (NPV) of albumin >26 g/l at SE onset was 85% for RSE and death. According to the ROC-analysis, a value below the cutoff of 0.2208 of the ratio of CRP at SE onset to albumin on admission had a NPV of 90% for death.
Conclusions: CRP and albumin at SE onset are readily accessible biomarkers allowing for predicting SE course and outcome. These laboratory parameters may help to identify patients early in the course of SE, who would profit from intensified and comprehensive SE management

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P27

Resting tremor in Parkinson disease is a negative predictor of Levodopa-induced Dyskinesia

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Background: It is unclear whether patients with different clinical subtypes of Parkinson disease (PD) differ in their risk of developing levodopa-induced dyskinesia (LID) and whether resting tremor is negatively correlated with this risk.
Objectives: To determine whether resting tremor as an initial manifestation of PD negatively correlated with subsequent occurrence and severity of LID and to study the correlations between LID and other epidemiological factors (eg, age at onset of PD and duration of PD).
Design: Logistic regression analysis was used to determine predictive factors of LID. Spearman rank correlations between LID and epidemiological factors and motor signs (including tremor) were calculated.
Setting: Institutional tertiary referral center for movement disorders.
Patients: Cohort of 85 patients with PD.
Main Outcome Measure: Occurrence of LID according to the Unified Parkinson Disease Rating Scale part IV.
Results: Resting tremor as an initial manifestation of PD was associated with reduced risk of developing LID in- dependent of other predictors of LID (duration of PD, axial signs, and levodopa dose).
Conclusion: Resting tremor as an initial manifestation of PD predicts lower probability of developing LID under levodopa treatment.

P28

Risk factors for conversion of acute ischaemic brain lesions into persisting tissue defects among patients randomly allocated to stenting or endarterectomy for symptomatic carotid stenosis in the ICSS-MRI substudy

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Background: The MRI-substudy of the International Carotid Stenting Study (ICSS) found a higher incidence of acute ischemic brain lesions on diffusion-weighted imaging (DWI) after stenting (CAS) than after endarterectomy (CEA). However, only a minority of DWI lesions were visible on fluid-attenuated inversion recovery (FLAIR) sequences 1 month after treatment. Among patients with new DWI lesions after treatment, we aimed to determine patient-related and lesion-related predictors for conversion into permanent lesions on FLAIR.
Methods: In ICSS, patients with recently symptomatic carotid stenosis ≥50% were randomly assigned to CAS or CEA. In the ICSS-MRI substudy, 161 patients who underwent either CAS (n = 85) or CEA (n = 75) received 3 MRI scans (1–7 days pre-treatment, 1–3 days post-treatment and at 1 month follow-up). A persisting lesion was defined by a hyperintense signal on FLAIR sequences at follow-up at the site of a post-treatment hyperintense DWI lesion. At the patient level, the association between age, sex, hypertension, diabetes, systolic blood pressure, qualifying event, white matter disease measured by the ARWMC score, and the number of persistent lesions was analysed using negative binomial regression models. At the lesion level, the association between location and volume of post-treatment DWI lesions and lesion persistence was analysed using generalised linear mixed effects models with binomial error distribution.
Findings: 44 of 86 patients (51%) in the CAS group and 10 of 75 (13%) patients in the CEA group had new DWI lesions on post treatment scans and were included in the analysis. Persistent lesions on FLAIR at 1 month follow-up were detected in 28 (33%) and 6 patients (8%), respectively. Among patient-related varialbes, increasing age (risk ratio [RR] 1.87, 95% CI 1.07–3.26 per decade; $p = 0.028$), hemispheric stroke as qualifying event (RR 3.07, 95% CI 1.29–7.28; $p = 0.011$) and ARWMC (RR 1.12, 95% CI 1.02–1.23; $p = 0.014$) were significantly associated with a higher number of persistent lesions. Volume but not location of post-treatment DWI lesions predicted persistence at 1 month (Odds ratio [OR] 1.74, 95% CI 1.47–2.06; $p = <0.001$).
Conclusion: The rate of acute ischaemic brain lesions after treatment converting into persistent tissue defects increased with

age and severity of white matter disease, which might suggest increased vulnerability towards peri-procedural embolism. Larger lesions were more likely to persist.

P29

SAS CARE 1 study: Short term evolution of sleep disordered breathing (SDB), blood pressure (BP) profile and clinical outcome in transient ischemic attacks (TIA)/ischemic stroke patients

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Introduction: SAS CARE 1 is a multicentric swiss-italian study assessing the short term and long term cardiovascular impact of SDB in patients with transient ischemic attacks (TIA) and acute ischemic events (AIE). SAS CARE 1 specifically addresses the natural evolution of an AIE/TIA in the first 3 months.
Patients and methods: We prospectively recruit patients within the first 7 days after AIE or TIA onset (acute phase). Stroke severity on admission (National Institutes of Health Stroke Scale [NIHSS]) and stroke outcome at discharge (modified Rankin Disability Scale [mRS]) are estimated. Independency is defined by a mRS<=2. Video-polysomnography (V-PSG) is performed in the acute phase and subsequently after 3 months (stable phase). Severity of SDB is defined by apnea–hypopnea index (AHI). Blood pressure (BP) monitoring is performed during 24 hours in the acute and stable phase. A non-dipping status (NDS) is defined by a ratio >0.9 of mean systolic BP during the night/ mean systolic BP during the day; Plasma glucose, fibrinogen, lipids, and specific vascular markers are measured in the acute and stable phase.
Results: So-far 41 patients (mean age = 62 ± 10 years; 13 females [32%], mean NIHSS = 5 ± 6; TIA [10%]) were fully recruited in 3 centers, of whom 22 were already retested after 3 months. During the acute phase, 19/41 (46%) had an AHI>=20. SDB was obstructive in 11 (27%), central in 7 (17%) and mixed in 1 (2%). In the stable phase 9/22 patients (41%) had an AHI>=20. SDB was obstructive in all cases (100%). A significant reduction of the central apnea index (p = 0.001) was found. A NDS was observed in 26/41 patients (64%) in the acute phase and in 6/22 patients (27%) in the stable phase. No significant changes were found in mean AHI values in patients with/without a NDS, neither in the acute phase nor in the stable phase. We found higher fibrinogen levels in patients with NDS in the acute phase (NDS 3.5 ± 1.1 g/L; DS 3.1 ± 0.1 g/L; [p = 0.002]) but not in the stable phase. Fibrinogen levels showed a near to significant decrease in the stable phase in patients with AHI <20 (acute 3.6 ± 0.8 g/L; stable 3.1 ± 0.6 g/l; N = 12; [p = 0.11]). No reduction was found in patients with AHI> = 20. The mRS at 3 months was <=2 in all patients with AHI<=10 (n = 8) and in 5/11 patients (45%) with AHI>=20.
Preliminary results of this ongoing trial suggest the following:
1) we confirm the previously reported high frequency of SDB in the acute phase of TIA/AIE, 2) our data supports the notion that central SBD improves in the first three months after TIA/AIE, 3) NDS is frequent in patients with TIA/AIE in the acute and stable phase, 4) fibrinogen levels are elevated in the acute phase in patients with a NDS and remain elevated in the stable phase in patients with AHI>=20, and 5) SDB patients may have a poorer outcome at three months.

P30

Secondary Moyamoya syndrome with multiple ischemic strokes in a 10-year old child from Central Africa with sickle cell disease

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An unresolved issue in sickle cell disease is treatment in the presence of Moyamoya syndrome.
Case report: We present a 10 year old child from Central Africa who suffers from homozygous sickle cell disease (SCD). Cerebral MRI showed multiple, clinically silent ischemic infarctions while diffusion weighted imaging (DWI) was negative for acute lesions. The neurological examination revealed normal clinical findings without an evident neurological deficit. In colour-coded duplex sonography high peak flow velocities in the left middle cerebral artery up to 300 cm/s and in the right posterior cerebral artery up to 200 cm/s could be detected. Peak flow velocities in the extracranial internal carotid arteries were slightly elevated. MR angiography showed high grade stenosis of the middle cerebral artery on both sides, of the right posterior cerebral artery and middle grade stenosis of the left posterior cerebral artery and of the anterior cerebral artery on both sides. MR angiography showed a secondary moyamoya syndrome with collateralisation via the leptomeningeal vessels.
Discussion: Children with SCD are at a high risk for ischemic strokes. In essence, the strokes are the result of large-vessel occlusive disease. Moyamoya disease is described as an angiographic pattern which is due to large-vessel occlusions resulting in progressive development of collaterals. As moyamoya collaterals reflect the degree of large vessel occlusive disease, it is a surrogate marker for higher risk of recurrent strokes in these subjects similarly as elevated peak flow velocities (>200 cm/s) in the terminal segment of internal carotid artery or proximal middle cerebral artery as measured with duplex sonography. Chronic transfusion therapy that is administered to keep HbS levels below 30% has been thought to reduce the risk of recurrent stroke, but there are studies which showed progression of the disease despite chronic transfusions in the presence of collaterals. Prevention of collaterals by chronic transfusion therapy and the effect of bone marrow transplantation are other unresolved issues. Therefore, regular monitoring by MRA and colour-coded duplex sonography may help to indentify subjects at high risk for stroke and evaluate treatment regimes.

P31

Sleep deprivation prior to stroke reduces infarction and increases expression of inflammatory genes TNFa and IL-1b in the rat

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Introduction: Sleep-wake disturbances are frequent in stroke patients and linked with a poorer functional outcome. We have recently provided direct evidence in a rat model of focal cerebral ischemia that sleep disruption shortly after stroke onset aggravates brain damage and impairs long-term stroke recovery. However, sleep deprivation (SD) prior to stroke was reported to be neuroprotective and beneficial for functional recovery in rodents. The aim of this study was to investigate potential mechanisms for the preconditioning-like effect induced by prestroke SD.
Methods: Focal cerebral ischemia was induced by permanent occlusion of distal branches of the middle cerebral artery in Sprague Dawly rats. SD for 6h was performed by gentle handling before ischemia, as reported. Brains were collected at 3 or 7 days after surgery. Control experiments included ischemia without SD (nSD), sham surgery with SD or nSD. Each experiment group included 6 rats. Tape removal and cylinder tests were used for assessing sensorimotor function; Nissl staining was for the infarct size; Quantitative PCR (Taqman assay) for gene expression and histochemical staining with several cell-type markers for neuron (NeuN) survival, neutrophil (myelopexidase, MPO) infiltration, microglia (Isolectin-B4) reactivation and capillary endothelium (von Willebran Factor, vWF) generation.

Results: When compared with the ischemia/nSD group, rats subjected to ischemia/SD showed a decrease (by 50%) in the infarct size (57.4 + 16.2 vs. 28.8 + 10.4 mm^3, p = 0.0047) on poststroke day 7, although not on day 3; a significant increase in brain swelling (13.5+3.2 vs. 20.7+6.8%, p = 0.038) on day 3; and an increase ($p < 0.05$) in expression of inflammatory genes TNFa (on day 3) and IL-1b (on days 3 and 7), but not the glial marker GFAP on both time points. Type removal and cylinder tests revealed deficits in sensorimotor function after ischemia, but there was no difference between the SD and nSD group on any time point evaluated (days 1, 3 and 7). There was no difference in the number of cells positive for NeuN, MPO, Isolectin-B4 and vWF between the ischemia/nSD and ischemia/SD group in both the infarct core and periinfarct area.
Conclusion: SD6h prior stroke indeed resulted in reduction in the infarct size. Current experiment is undertaken to determine whether the neuroprotective effect is related to the SD-induced increase in TNFa and IL1b by pharmacological inhibition of their expression.

P32

Subthalamic deep brain stimulation appears to be superior to best medical therapy for L-dopa responsive pain in Parkinson's disease

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Background: Pain is common in Parkinson's disease (PD), can be more disturbing than motor symptoms, and in some patients fluctuates in parallel to motor symptoms. Recent studies with follow-up times up to 6 months revealed that deep brain stimulation (DBS) in the subthalamic nucleus (STN) may improve pain in PD.
Case reports: In all patients, DBS was performed because of motor fluctuations. The first and the second patient suffered from severe neck pain without radicular neurological deficits. The third and the fourth patient suffered from extreme abdominal pain. In these patients, examinations of the gastrointestinal system and the heart were normal. In terms of impairment of quality of life, all patients described their pain as the worst symptom of all. Before STN-DBS, we performed an L-dopa challenge test in all patients. Besides motor symptoms, we assessed intensity of pain, and in all patients, L-dopa led to a significant yet incomplete relief of pain. After STN-DBS, all patients were completely pain-free. The follow-up intervals ranged from 2 to 24 months.
Conclusion: Our cases show that STN-DBS can produce complete remission of severe PD-related pain. This response to surgery may be predicted by L-dopa challenge tests assessing pain severity, but high-dose L-dopa appears to be inferior to STN-DBS for the treatment of PD-related pain. Different characters of pain are treatment-responsive, including pain with a distinctly visceral character which occasionally occurs in PD.

P33

Supplementary motor cortex and alien hand syndrome – an intriguing association after anterior cerebral artery ischemia

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Introduction: Pre-SMA and SMA are part of the so-called supplementary motor complex (SMC) and of particular importance for planning of complex motor sequences and inhibition of inappropriate, externally triggered movements. The SMC is located in the dorso-medial frontal cortex and supplied by the anterior cerebral artery (ACA). Lesions at this location interfere heavily with motor control. The full-blown clinical picture of pre-SMA and SMA damage may evoke an alien-hand syndrome (AHS) in its extreme form. From a theoretical point of view the pre-SMA is suggested to represent the critical site for generation of the Bereitschaftspotential.
Case reports: Both cases, case 1 (an 81-year old male) and case 2 (an 83-year old female), were referred to our hospital due to a sudden speech arrest and right-sided hemiparesis. Neuroimaging revealed an extensive left-sided ACA infarction in both cases. It should be noted that primary motor cortex of the hand area was not affected by ischemia in either case.
Behavioral observations: In the the acute stage both cases did not show any spontaneous hand movements. In case 1 not-perceived grasping exaggerated by unspecific triggers such like slight touch occurred one week after admission. Nonetheless, at that time he had difficulty in initiating elementary movements which were associated by co-activation of the contralateral hand. Imitating complex motor sequences was not possible. Case 2 still suffered from a lack of spontaneous, internally cued movements at discharge from the clinic after 14 days. At follow up two months later, she showed an exaggerated grasp reflex, severe impairment in performing complex motor tasks, intermanual conflicts and involuntary, disturbing movements of the implicated limb.
Conclusion: These two cases, both suffering from left-sided ACA infarction, showed a severe and persisting AHS after lesion of the pre-SMA and SMA. The observed motor behavior was initially characterized by the inability to carry out internally cued movements while externally cued movements were not suppressed and perceived by the subject. These non-specifically triggered finger movements persisted during recovery in the chronic stage and became disturbing as they were more and more perceived. An additional aspect of the AHS was intermanual conflict in one case. In sum, AHS is a challenge for motor rehabilitation due to inadvertent motor activity and the deficient voluntary control.

P34

The clinical spectrum of ataxia with oculomotor apraxia type 2

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Background: AOA2 is an autosomal recessively inherited disorder caused by mutations of the senataxin gene (9q34). Clinical spectrum comprises neuropathy, oculomotor apraxia, gait ataxia and choreatic or dystonic movements. First symptoms are usually noticed between the ages of 10 and 25. Alpha-fetoprotein (AFP) is nearly always elevated.
Methods: Case 1 is a 56-year old female with disease onset around 35 years who came to medical attention with involuntary head movements which were interpreted as cervical dystonia. At that time a CT scan of the brain was normal. After another 10 years she was referred due to progressive gait difficulties and problems with her eyes which had developed over the past years. Case 2 is a 35-year old man who was referred due to mild gait ataxia. In childhood and early adulthood he experienced difficulties in doing sports. Dysarthria and gait ataxia developed in the third decade and remained mild until referral.
Results: Current clinical examination of patient 1 reveals abnormal eye movements with impaired initiation of saccades and insuppressible vestibulo-ocular reflex, right-sided hemidystonia and gait ataxia. Clinical examination of patient 2 shows a mild phenotype with gait ataxia, cerebellar ocular signs without oculomotor apraxia and right-sided akinesia during walking. Electroneurography has revealed pathologically low amplitude of the sensory potentials of the sural nerve, however, sensory neuropathy remains subclinical. In both patients serum levels of AFP are moderately elevated and the MRI shows cerebellar atrophy. In patient 1 a DAT-scan was normal. Genetic testing has confirmed the diagnosis in both patients and has revealed a novel homozygous missense mutation (I1942T) of the senataxin gene in patient 1.
Conclusions: These two cases highlight the broad clinical spectrum of AOA2. While patient 2 represents a case of young onset cerebellar ataxia without ocular apraxia, patient 1 with a novel missense mutation in the senataxin gene has a late disease onset far beyond the age of 30 with cerebellar ataxia, dystonia and severe oculomotor apraxia but without evidence for neuropathy. We conclude that allelic genetic heterogeneity might be responsible for the broad spectrum of clinical presentation.

P35

Valid, sensitive, interpretable: A novel approach to EEG analysis

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Introduction: Recent advances in the capabilities of EEG recordings have made the issue of how to statistically tackle the large datasets unavoidable. Several attempts have been made to reduce the data's complexity however we argue that this inevitably introduces user-biases and unjustified assumptions.
Methods: Threshold-free cluster enhancement (TFCE) has recently been shown to be a superior technique in the analysis of fMRI datasets. Combined with non-parametric permutation based statistics, we show that TFCE can also be applied to analyse EEG datasets. TFCE essentially finds clusters in the data over multiple thresholds and combines the information with the strength of the signals in that cluster, enhancing weak but clustered signals to a level directly comparable to strong focal signals. We show that the method is both statistically valid, sensitive to the wide range of signal types commonly found in EEG, and results in an openly interpretable result structure, while only requiring the data and the electrode coordinates as inputs. The method is proposed in detail, along with a user-independent algorithm to calculate neighbouring channels in space. We then compare the method to previously used permutation approached using the maximum-statistic, cluster size and cluster mass, as well as the parametric approach used in SPM.
Results: For single subject time-channel analyses over different SNR, frequency analysis or multi-subject data, the TFCE approach outperformed the other approaches in terms of sensitivity and false-alarm rate and was able to provide specific information about the localisation and statistical strength unavailable in the contrasting methods.
Conclusion: Using only the original ERP waveforms and information about electrode location as input parameters we show that TFCE approach combined with non-parametric statistics is not only a statistically valid method of analysis with little room for user-biases or tweaking options, but also a highly sensitive method for the variety of signal differences possible in EEG experimentation. With the results providing a unique p-value for each channel and time point, interpretability is maintained as flexible as before the analysis but with the confidence that results can be relied upon.

P36

Validation of a semi-automatic cerebellar segmentation method in patients with multiple sclerosis and healthy controls

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Introduction: Despite the well-known importance of cerebellar dysfunction as a significant contributor to disability in patients with multiple sclerosis (MS), there are only few magnetic resonance imaging (MRI) and neuropathological studies focusing on cerebellar white (WM) or grey matter (GM) loss so far. This relates to technical challenges regarding the correct segmentation and extraction of the cerebellar tissue from nearby structures such as the peduncles, brainstem as well as spinal cord and venous sinuses. Furthermore, the thin cerebellar gyri and sulci are difficult to segment. In this study, we validated the semi-automatic ECCET software for performing a volumetric analysis of cerebellar atrophy using high-resolution 3D-T1-MR scans.
Material/Methods: Test-retest (TR-R) and inter-observer reliability (IO-R) of ECCET and a comparison to the fully automatic segmentation program FreeSurfer was performed using high resolution T1 weighted MPRAGE scans (Siemens Avanto 1.5T) in a group of 15 MS patients. After the validation of the method, we conducted a pilot study investigating the total normalized cerebellar (nCV) and cerebellar GM (nCGMV) volume of another 15 relapsing-remitting MS patients (mean age 35 yrs (range 21–62), mean EDSS 2.7 (1–4.5) and 15 age-matched healthy controls (HC). High resolution T1 weighted MPRAGE scans (Siemens Verio 3T) were used for this purpose. The normalized total brain volume (nBV) was generated using SIENAX. PD-weighted images were used to determine the total WM lesion load.
Results: For both TR-R and IO-R, there was a strong intraclass correlation (ICC) in terms of nCV (TR-R $\rho = 0.99$, 95%-CI = 0.98–0.99; IO-R $\rho = 0.98$, 95%-CI = 0.74–0.99) as well as nCGMV (TR-R $\rho = 0.99$, 95%-CI = 0.97–0.99; IO-R $\rho = 0.96$, 95%-CI = 0.85–0.98). Cross-validation between ECCET and FreeSurfer yielded likewise a good ICC ($\rho = 0.86$, 95%-CI = 0.58–0.95). Compared to HC, MS patients had significantly reduced nBV and nCV (both $p < 0.05$). Mean total WM lesion volume was 9.35 cm3 (range 0.09–30.5 cm^3). No correlation was found between nCV and clinical measures, such as EDSS, cerebellar FSS or disease duration.
Conclusions: ECCET is a useful tool for cerebellar segmentation in MS with excellent test-retest and inter-observer reliability as well as good intraclass correlation with FreeSurfer. Using this software, we were able to confirm a reduced cerebellar volume in MS patients compared to healthy controls. These results provide the basis for a larger study on longitudinal changes of cerebellar volume in MS patients.

Free communication 1

Prolonged wakefulness increases metabotropic glutamate receptor 5 density in human brain

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Introduction: Recent research suggests that Homer 1a, brain-derived neurotrophic factor, adenosine deaminase, adenosine A2A receptor, and other molecular markers of synaptic plasticity, play an important role in sleep homeostasis. All these molecules interact either directly or indirectly with metabotropic glutamate receptor 5 (mGluR5). To investigate whether mGluR5 is involved in sleep homeostasis, mGluR5 density was quantified in human brain after normal sleep and after sleep deprivation.
Methods: Twenty one male volunteers completed this randomized, cross-over study, consisting of a sleep control and a sleep deprivation (SD) condition separated by one week. Subjects performed at regular intervals cognitive tasks and waking-EEG recordings, and rated their subjective state. A positron emission tomography (PET) scan with the highly selective tracer, 11C ABP688, to quantify mGluR5 density was performed roughly 8 (control) and 32 (SD) hours after wakening from baseline sleep. PMOD® software was used for image analyses. Eleven regions of interest with reported high mGluR5 density and presumed involvement in sleep regulation were analyzed with mixed-model analyses of variance (ANOVA).

Results: Prolonged wakefulness enhanced subjective sleepiness (Karolinska sleepiness scale) and state anxiety, and reduced sustained attention and memory performance. Moreover, sleep deprivation induced a global increase of 3.3 ± 1.1% in normalized distribution volume of 11C ABP688 when compared to control ($p < 0.006$). The mGluR5 density was increased in 16 out of the 21 subjects. Four brain regions including anterior cingulate cortex, insula, parahippocampal gyrus, and striatum stood up against Bonferroni correction for multiple testing ($p_{all} < 0.001$). The changes in left and right insula were significantly correlated with sleep deprivation-induced changes in subjective sleepiness ($r_{all} > 0.49$, $p_{all} < 0.023$).
Conclusions: This molecular imaging study provides the first in vivo evidence for increased mGluR5 density after prolonged wakefulness, indicating that mGluR5 are involved in sleep homeostasis. Given the role for mGluR5 in synaptic long-term depression and long-term potentiation, these findings are consistent with the hypothesized occurrence of plastic synaptic changes across the sleep-wake cycle in humans.
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Free communication 2

Non-visual effects of light on EEG correlates of human alertness and melatonin: Effects of a PER3 polymorphism

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Introduction: Light exposure, particularly at the short-wavelength range, prompts several effects on human circadian physiology via the non-imaging forming system. However, the extent to which this light-induced response differs between individuals remains unknown. Here we investigated if blue-enriched polychromatic light differentially impacts on melatonin, and subjective and objective alertness.
Methods: Eighteen healthy young male participants genotyped for the PERIOD3 (PER3) variable-number tandem-repeat (VNTR) polymorphism (PER35/5 and PER34/4) were investigated in a balanced cross-over design carried out during the winter season. Three different light settings were carried out: compact fluorescent lamps with light of 40 lux at 6500 K and at 2500 K and incandescent lamps of 40 lux at 3000 K, during 2h in the evening. Artefact-free wake electroencephalographic (EEG) samples were subjected to spectral analysis. Ratings of sleepiness levels and salivary melatonin measurements were collected every 40 minutes.
Results: In comparison to the light at 2500K and 3000K, exposure to blue-enriched light at 6500K induced a significant suppression of the evening rise in endogenous melatonin levels in PER35/5 individuals but not in PER34/4 volunteers. Likewise, PER35/5 individuals showed a significantly more pronounced alerting response to light at 6500K than PER34/4 volunteers. Waking EEG activity in the theta range (5–7 Hz), a correlate of subjective sleepiness, was significantly attenuated during light exposure at 6500K in PER35/5 individuals as compared to PER34/4.
Conclusions: We have first preliminary evidence that inter-individual differences in the alerting and melatonin response to blue-enriched light may be modulated by a clock gene polymorphism, which is known to be implicated in human sleep-wake regulation. These findings may help to unravel the inter-individual differences in the spectral sensitivity of non-image forming responses to light.

Free communication 3

The functional Val66Met polymorphism of brain-derived neurotrophic factor (BDNF) modulates sleep intensity

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Introduction: Electroencephalographic (EEG) slow waves are the hallmark of deep non-rapid-eye-movement (NREM) sleep and may reflect the restorative functions of sleep. Evidence suggests that increased sleep slow waves after sleep deprivation reflect plastic synaptic processes, and that brain-derived neurotrophic factor (BDNF) is causally involved in their homeostatic regulation. The functional Val66Met polymorphism of the gene encoding pro-BDNF causes impaired activity-dependent secretion of mature BDNF protein. We investigated whether this polymorphism contributes to the pronounced inter-individual variation in sleep slow-wave activity (SWA) in healthy humans.
Methods: Eleven heterozygous Met allele carriers (7 men, 4 women; mean age: 23.7 ± 0.6 years) and 11 individually, sex- and age-matched Val/Val homozygotes (mean age: 24.0 ± 0.8 years) participated in this case-control study. Women participants were matched with respect to the phase of their menstrual cycle, and the two groups did not differ in view of body-mass index, habitual sleep duration, diurnal preference, subjective sleepiness (Epworth sleepiness scale), trait anxiety (Spielberger State Trait Anxiety Inventory), and consumption of alcohol and caffeine. Cognitive performance, subjective state, and waking and sleep EEG in baseline, as well as during and after 40 hours prolonged wakefulness were studied in the sleep laboratory. The data were analyzed with mixed-effect analyses of variance (ANOVA) models and Tukey's HSD tests.
Results: Val/Val homozygotes showed better response accuracy than Met allele carriers on a verbal 2-back working memory task. This difference did not reflect genotype-dependent differences in sleepiness, well-being, or sustained attention. In baseline and recovery nights, deep stage 4 sleep and NREM sleep intensity as quantified by EEG SWA (0.75–4.5 Hz) were higher in Val/Val compared to Val/Met genotype. Similar to sleep deprivation, the difference was most pronounced in the first NREM sleep episode. By contrast, increased activity in higher EEG frequencies (> 6 Hz) in wakefulness and REM sleep was distinct from the effects of prolonged wakefulness.
Conclusions: BDNF contributes to the regulation of sleep slow wave oscillations, suggesting that genetically determined variation in neuronal plasticity modulates NREM sleep intensity in humans.

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Free communication 4

Effects of PERIOD3 polymorphism on circadian rhythmicity and sleep homeostasis in healthy older individuals

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Aging is associated with a decrease in non-rapid eye movement (non-REM) sleep consolidation and circadian phase advance, which can reflect changes in the sleep homeostatic and/or circadian drive. In young subjects, a polymorphism of the clock gene PERIOD3 (PER3) can predict inter-individual sleep differences, such as slow EEG oscillations during NREM sleep, REM sleep and wakefulness, with no changes in circadian rhythmicity. Predictors of these inter-individual differences insleep in older people are still unknown. Here we investigated circadian rhythms and sleep EEG characteristics in older participants homozygous for the longer (PER35/5) and for the shorter (PER34/4) allele of the clock gene PER3.
Healthy older volunteers were selected exclusively on the basis of their PER3 genotype, andPER3 polymorphism was determined in 133 participants (55–75 years). Twenty-one PER35/5 and 16 PER34/4 participants completed the 3-week field segment of the study, which comprised actigraphy monitoring and sleep diaries to characterize habitual sleep and wake times. Wake-up times from sleep diaries indicated a tendency for earlier timing for PER35/5 participants. Similarly, actiwatch analysis revealed significant earlier timing of the rest-activity cycle in PER35/5 participants. For the laboratory study, 13 PER35/5 (5 men, 8 women, 62.23 ± 1.01 years) and 13 PER34/4 (5 men, 8 women, 62.38 ± 1.39 years) participants were selected and matched by age, gender, body mass index and ethnicity. Following a baseline night, all volunteers underwent approximately 40 hours of extended wakefulness

under constant routine conditions (CR), to assess endogenous circadian phase and amplitude in the absence of the confounding effects of light-dark and behavioural cycles. The CR was followed by a recovery sleep.
Circadian rhythms of core body temperature and cortisol did not differ between genotypes. Interestingly, melatonin profile across extended wakefulness revealed that PER35/5 subjects had a phase-advance of fitted melatonin maximum compared to PER34/4 subjects. Sleep structure and consolidation differed between genotypes: Homozygosity for the longer allele (PER35/5) had a significant effect on baseline sleep structure, with lower total sleep time, sleep efficiency, shorter non-REM sleep stage-2 duration, and more wakefulness. Spectral analysis of baseline and recovery sleep EEG activity further indicated differences between the genotypes: EEG delta activity (0.75–1.75 Hz) in non-REM sleep was significantly higher (increase of 39.7% for the entire night) and spindle activity (11–13.5 Hz) was significantly lower (decrease of 31.9% for all night) in PER35/5 compared to PER34/4 individuals ($p < 0.05$).
Within the framework of the circadian and homeostatic regulation of sleep, our data imply for the first time that the interaction of aging and the PER3 VNTR polymorphism affects both the circadian and the homeostatic aspects of sleep regulation. These data have implications for our understanding of the basis of inter-individual differences in age-related changes in circadian rhythmicity and sleep.

Free communication 5

The effect of simulated obstructive apnea and hypopnea on heart rhythm

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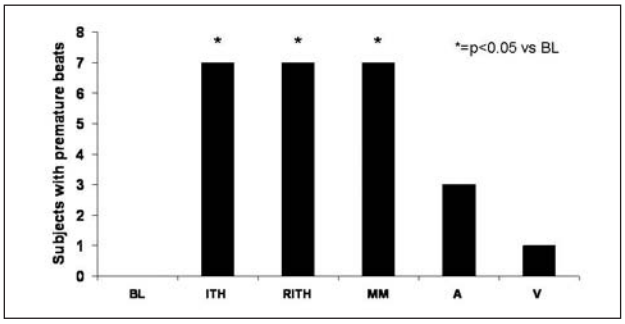
Background: Preliminary evidence supports an association between obstructive sleep apnea (OSA) and cardiac arrhythmias. The mechanisms through which OSA may promote cardiac arrhythmias are insufficiently understood. Data from animal models suggest that excessive negative intrapleural pressure, as occurring during OSA, may provoke cardiac arrhythmias. Therefore, we studied the acute effects of experimentally induced intrapleural pressure changes on heart rhythm in humans.
Methods: In 41 healthy volunteers ECG was continuously recorded prior, during and immediately after experimentally induced negative intrathoracic pressure (inspiration through a threshold load, repetitive inspiration through a threshold load, Mueller manoeuvre), positive intrathoracic pressure (Valsalva manoeuvre), end-expiratory central apnea and normal breathing in randomized order. The number of subjects with arrhythmias and the total number of events during breathing manoeuvres was compared by Chi2 –and Wilcoxon-tests, respectively.
Results: The characteristics of the studied population are shown in table 1. The number of subjects with supraventricular and ventricular premature beats was significantly higher during inspiration through a threshold load (n = 7), during repetitive inspiration through a threshold load (n = 7) and during the Mueller manoeuvre (n = 7) compared to normal breathing (n = 0) ($p = 0.006$ for all comparisons), but not during the Valsalva manoeuvre (n = 1, $p = 0.314$) or end-expiratory central apnea (n = 3, $p = 0.078$). The total number of observed premature beats was significantly higher during inspiration through a threshold load, repetitive inspiration through a threshold load and Mueller manoeuvre compared to normal breathing, but not during the Valsalva manoeuvre or end-expiratory central apnea (fig. 1). No other arrhythmias than premature beats were observed.



Conclusions: Simulated obstructive apnea and hypopnea are both associated with an increase of premature supraventricular and ventricular beats. Therefore, negative intrapleural pressure change may be an important mechanism underpinning the association between OSA and cardiac arrhythmias.

Free communication 6

The effects of transcranial magnetic stimulation and inhibition on vigilance

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Introduction: Previous animal and human research has shown that cortical stimulation using transcranial magnetic and electrical stimulation can affect vigilance levels. Both stimulation and inhibition of the prefrontal cortex using transcranial magnetic stimulation (TMS) have a significant effect on subcortical dopamine levels. Studies have shown that the levels of dopamine released upon TMS stimulation are similar to those released with substantial doses of modafinil, d-amphetamine, and caffeine; all substances with a profound effect on our level of vigilance. In this experiment we examined whether TMS stimulation, and cortical inhibition of the dorso-lateral prefrontal cortex (DLPFC) could have opposing modulatory effects on vigilance levels compared to control stimulation of the occipital cortex.
Methods: 24 participants (17 male), with no prior history of sleep disorders, restricted a night of sleep to a maximum of 4 hours prior to the experimental day. We used a a combined MSLT/MWT variant to measure the participants ability to fall asleep or to stay awake , consisting of four naps in which for the first 15 minutes participants were required to stay awake in a dark, silent room, while in the following 15 minutes participants were allowed to sleep. After each nap participants performed a Psychomotor Vigilance Test (PVT) to assess sustained vigilance performance. Prior to each nap, continuous or intermittent theta-burst TMS was used to either hyper-excite (10 participants) or inhibit (14 participants), the activity of either the DLPFC or a control region of the occipital cortex (OC). Optimal stimulation site was controlled by neuronavigation.
Result: Data from each participant was normalised by subtracting the average values of TMS over the OC by DLPFC. Thus for each measure, participants' difference scores were taken for the analysis of variance controlled by the order of whether the DLPFC or OC were targeted first. A significant effect was found for participants sleep latency to stage N1 ($F = 4.59$, $p = 0.045$), with stimulation being associated with longer latencies (mean: 1.42 minutes) and inhibition showing shorter latencies (mean; –1.14 minutes). TMS also significantly affected total sleep duration ($F = 10.25$, $p = 0.005$) with stimulation showing shorter sleep times (mean: –12.8%) and inhibition longer sleep times (mean: +11.1%). PVT mean/median (?) reaction times were also affected ($F = 5.55$, $p = 0.029$) with DLPFC-stimulated participants gaining 27 ms and DLPFC-inhibited participants losing 8ms compared to OC stimulation.
Conclusion: Targeted TMS stimulation and inhibition on the DLPFC can have significant opposing effects on participants' ability to fall and remain asleep during a daytime nap test and modulate gainson participants' post nap performance speed during a sustained vigilance test. These effects may be mediated by TMS induced subcortical dopamine release.

Free communication 7

Differential effects of Sodium Oxybate and Baclofen on EEG, sleep, neurobehavioral performance, and memory in young healthy volunteers

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Introduction: Sodium oxybate (SO, sodium salt of gamma-hydroxybutyric acid) is a GABAB agonist registered for the treatment of the sleep disorder, narcolepsy. SO was shown to increase slow-wave sleep (SWS) and EEG delta power (0.75–4.5 Hz), both indexes of non-rapid eye movement sleep (NREMS) intensity and depth, suggesting that SO enhances NREMS's

recuperative function. We investigated whether SO affects the homeostatic regulation of sleep and thus induces physiological sleep. We also compared the effects of SO with those of baclofen (BAC), another GABAB receptor agonist, to assess the role of GABAB receptors in the response to SO.
Methods: In this randomized double-blind crossover study, SO (30 mg/kg) and BAC (0.35 mg/kg) were administered before an afternoon nap or before the subsequent, experimental night in 13 young healthy volunteers. Sleep and the electroencephalogram (EEG) of each subject were analyzed. Neurobehavioral performance, subjective sleepiness and memory consolidation were also assessed.
Results: As expected, under placebo condition a nap significantly decreased sleep need and intensity the subsequent night. Both drugs, given prior to the experimental night, reversed this nap effect by decreasing sleep latency and increasing total sleep time, SWS during the first NREMS episode, and EEG delta and theta (0.75–7.25 Hz) power during NREMS. The SO-induced increase in EEG delta and theta power was, however, not specific to NREMS and was also observed during REMS and to some extent during wakefulness. Moreover, the high levels of delta power reached during a nap following SO administration, did not affect delta power during the following night. Overall, both SO and BAC administrated before the nap did not affect subsequent psychomotor performance and subjective alertness or memory consolidation compared to placebo treatment. Finally, SO and BAC induced sleep onset REM periods.
Conclusion: Our results strongly suggest that SO-induced EEG slow waves are not functionally similar to physiological slow waves. Also, cognitive performance was generally not affected by SO, although SO induced higher EEG delta power during the naptime sleep.

Free communication 8

STOP-BANG questionnaire as a screening tool for obstructive sleep apnea in the general population

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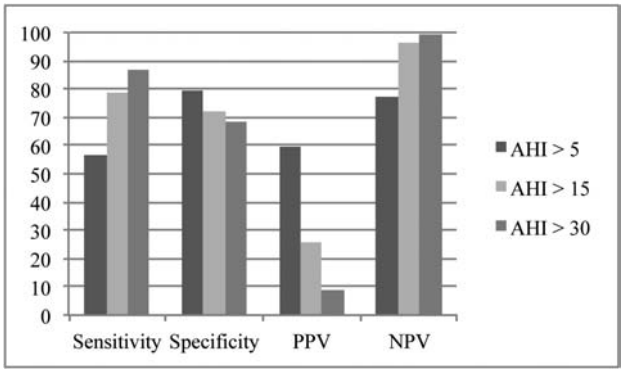
Introduction: STOP-BANG (Snoring, Tiredness during daytime, Observed apnea, High blood Pressure, Body mass index >35, Age >50, Neck circumference >40 cm, Male Gender) questionnaire has been shown to be a useful tool to screen for obstructive sleep apnea (OSA) during preoperative evaluation. The aim of our study is to evaluate the sensitivity and specificity of this questionnaire for screening for OSA in a large sample of middle-aged general population.
Methods: 922 subjects (49.2% male, 50.2 ± 5.7 years old, BMI 25.7 ± 4.2 kg/m^2) participating in an ongoing population-based cohort study (HypnoLaus, Lausanne, Switzerland) underwent complete polysomnographic recordings at home and had an extensive cardiovascular, metabolic, genetic and psychiatric workup including STOP BANG parameters. A score of 3 or more out of a possible 8 was considered suggestive of OSA. This score was compared to apnea-hyponea index (AHI) determined by PSG. AHI was scored according to 2007 American Academy of Sleep Medicine (AASM) recommended criteria .



Results: Mean AHI was 9.03 ± 11.8/h in men and 3.3 ± 4.9/h in women. Prevalence of OSA defined as an AHI >5/h, 15/h and 30/h was 49.2.0%, 17.5% and 6.2%, respectively in men and 20.7, 4.0 and 0.4 in women. Mean STOP-BANG score was 2.9 ± 1.3 in men and 1.3 ± 0.9 in women. 56.6 % of the men and 9.7% of women had a score ≥3. To detect OSA with AHI thresholds of 5/h, 15/h and 30/h, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were respectively 56.8%, 79.1%, 59.5 % and 77.2% for an AHI >5/h; 79.0%, 72.0%, 25.6% and 96.6% for an AHI >15; 87.1%, 68.4%, 8.7% and 99.7% for an AHI >30/h. The area under the ROC curve for whole STOP-BANG score was 0.741 for an AHI >5/h, 0.806 for an AHI >15/h and 0.841 for an AHI >30/h.
Conclusions: STOP-BANG questionnaire appears to be a useful clinical tool to rule out moderate to severe OSA with a high negative predictive value. However, it is not an adequate screening tool for OSA in the general population due to its poor sensitivity.

Free communication 9

Long-term adherence to CPAP in sleep apnea patients

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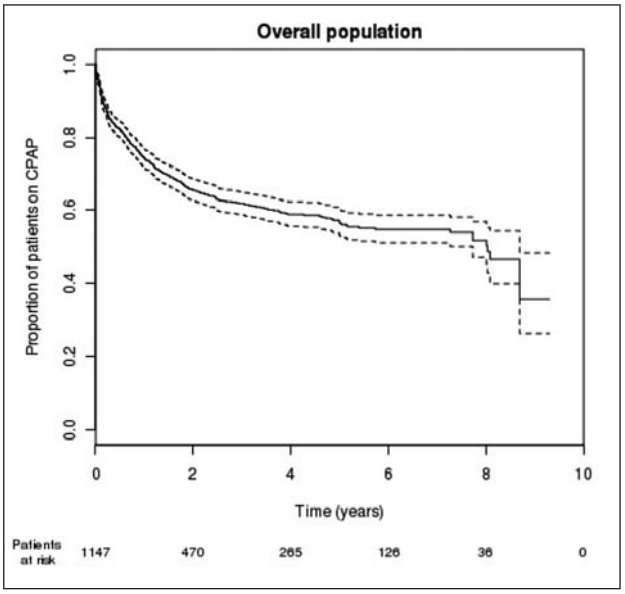
Introduction: Continuous positive airway pressure (CPAP) is the standard lifetime treatment for sleep apnea syndromes (OSAS). Few studies have assessed long-term CPAP adherence and its predictors in large cohorts. The aim of this retrospective study is therefore to determine adherence and to investigate its potential predictors.
Methods: All patients treated at the St.Gallen sleep centre between November 2001 and April 2011 were included in the study. Baseline data and follow-up information of the last yearly CPAP control were analysed, using the R statistical software (version 2.9.0). The primary dependent variable of interest was continued use of CPAP. Kaplan-Meier estimates as well as Cox-proportional hazards regression were used to model the risk of loss of adherence in patients on CPAP. Data are represented in the quartiles of their distribution, where appropriate.
Results: Data of 1492 OSAS patients started on CPAP were available. 18 died while using CPAP, 65 no longer needed CPAP after weight reduction or other alternative treatment modalities and 262 (17.6%) were lost to follow up. The percentage of patients adherent to CPAP therapy after 1 year was 74% (95% CI: 71–77), after 5 years 56% (95% CI: 53–60), and after 8 years 50% (95% CI: 45–56) (fig. 1).



A univariate analysis for potential predictors of CPAP adherence is presented in table 1.

	n = 1147		**HR“**	**SE**	**p**	**Lower 95% CI**	**Upper 95% CI**
Gender	n = 1141						
	male	929	–				
	female	212	1.16	0.13	0.23	0.91	1.49
Age [years]	n = 1147						
	<46.3	290	–				
	46.3; 54.2	296	0.95	0.14	0.72	0.72	1.25
	54.2; 61.4	277	1.08	0.14	0.58	0.82	1.42
	>61.4	284	0.99	0.14	0.96	0.75	1.31
Country of origin	n = 1112						
	Switzerland	912	–				
	Northern / Western Europe	107	1.35	0.16	0.06	0.99	1.86
	Eastern Europe	93	1.75	0.16	0.0005*	1.27	2.36
Education	n = 947						
	Primary	126	–				
	Secondary	62	0.63	0.27	0.09	0.37	1.07
	Professional education	453	0.9	0.16	0.52	0.66	1.24
	High school	68	1.34	0.22	0.18	0.87	2.06
	Higher professional education	164	0.59	0.21	0.009*	0.39	0.88
	University	74	0.86	0.23	0.54	0.55	1.37
CPAP start date	n = 1147						
	5 Nov 2001 to 17 April 2005	353	–				
	18 April 2005 to 13 Jan 2008	353	1.02	0.12	0.85	0.8	1.31
	14 Jan 2008 to 8 Oct 2009	351	1.02	0.14	0.86	0.86	1.34
	after 9 Oct 2009	352	1.1	0.19	0.62	0.76	1.59
ESS [points]	n = 1009						
	<7	260	–				
	7;11	293	0.89	0.14	0.39	0.68	1.16
	11;14	213	0.67	0.16	0.01*	0.49	0.91
	>14	243	0.84	0.14	0.23	0.64	1.11
BMI [kg/m^2]	n = 982						
	<27.2	249	–				
	27.2;30.7	256	0.68	0.15	0.01*	0.51	0.91
	30.7;35.3	246	0.89	0.14	0.41	0.67	1.18
	>35.3	231	0.8	0.15	0.14	0.6	1.07
ODI [events/h]	n = 1104						
	<11.6	281	–				
	11.6; 25.3	271	0.66	0.13	0.002*	0.51	0.87
	25.3; 51.7	281	0.65	0.13	0.001*	0.5	0.84
	>51.7	271	0.43	0.15	<0.0001*	0.32	0.58
AHI [events/h]	n = 1106						
	<22.8	277	–				
	22.8;39.7	277	0.87	0.13	0.26	0.67	1.11
	39.7;67.6	273	0.6	0.14	0.0002*	0.45	0.78
	>67.6	279	0.47	0.15	<0.0001*	0.36	0.63
“A higher hazard ratio (HR) denotes a higher likelihood to stop CPAP treatment.							

A higher ODI and a higher AHI were associated with a higher adherence. Over the 10-year period, no change in adherence rates was found. Among the socio-cultural factors tested, a country of origin in South-Eastern Europe was associated with lower CPAP adherence. BMI and ESS were not significantly associated with adherence, but the quartile of patients with an ESS score between 11 and 14 points were more likely to adhere. With regards to educational level (taking the lowest level as reference), patients with a higher professional school degree had a higher adherence (HR: 0.59, 95% CI: [0.39–0.88], p = 0.009), whereas university graduates had not.

Conclusion: With the analysis of our notably large cohort of CPAP treated OSAS patients, we were able to determine both clinical and socio-cultural factors significantly influencing treatment adherence. Technical progress achieved over the last 10 years does not seem to have increased adherence significantly. To improve long term results with CPAP, novel approaches, targeted to subgroups with low adherence, like intensified educational programs or telemedicine tools to detect non-adherence early, should be investigated.

P37

A need for sleep to facilitate the development of skills?

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Slow wave activity (SWA, 1–4.5 Hz) is the main electrophysiological marker of sleep depth (Borbély & Achermann, 2005). Evidence is increasing that SWA plays a crucial role in synaptic plasticity (Tononi & Cirelli, 2006). During development, SWA undergoes prominent changes that parallel the structural and behavioural maturation of the cortex (Kurth et al., 2010).
We used high-density sleep electroencephalography to map age-related SWA changes in subjects of different ages (n = 63, 2-26y). Based on magnetic resonance imaging co-registration, electrodes were assigned to Brodmann areas and related to different skills.
During development SWA topography changed in a meaningful way: The chronology of regions showing maximal SWA was 1) vision 2) visuomotor 3) simple motor 4) complex motor 5) language 6) cognitive control, in accordance with the maturation of skills associated with these regions. Behavioural data allowed a direct comparison between the maturational state of a skill and SWA. We found a positive relationship between SWA topography and skill maturation (e.g. "complex motor": R = 0.42 p = 0.001; "pooled skills": R = 0.48, p = 0.0002; Pearson correlations). This relationship indicates that individuals with more "mature" SWA topography showed better performance. Finally, we observed that the maturation of SWA topography preceded the maturation of skills.
In line with increasing evidence for SWA being actively involved in plastic processes, it is possible that SWA not only mirrors, but even contributes to maturational processes of the cortex, resulting in improved skills.

P38

Autonomic dysfunction in restless legs syndrome with periodic leg movements are normalized by dopamine-agonist treatment

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Introduction: Restless legs syndrome (RLS) is a common sleep-related movement disorder characterized by a disagreeable sensation in the limbs which worsens at night and in rest condition and is improved by movement. The majority of patients with RLS present periodic leg movements during sleep (PLMS) which are coupled with cortical and autonomic activations. Dopamine agonists are the first-line treatment in RLS.
Methods: A prospective, polysomnographic, single-blind, placebo-controlled study was performed in 23 patients with RLS and 10 healthy subjects. Basal spectral analysis of heart rate variability (HRV) and phasic heart rate (HR) during periodic leg movements during sleep (PLMS) were compared between the two groups and, within the RLS group, before and after treatment with placebo or pramipexole (dopamine D3 receptor agonist).
Results: No differences were found in the basal sympathovagal balance outside of PLMS between RLS and controls and, in the RLS group, before and after treatment. The amplitude of PLMS-related HR changes resulted higher in patients than in controls. Treatment with pramipexole decreased the number of PLMS and normalized the HR PLMS-related response in RLS subjects.
Conclusions: The repetitive abnormal autonomic response to PLMS might play a role in the increased cardiovascular risk observed in RLS patients. Pramipexole reduced the number of PLMS and the autonomic response to the residual PLMS, without effects on the tonic sympathovagal regulation. This suggests that D3 receptors in the sympathetic pre-ganglionic neurons of the spinal intermediolateral columns, which represent the final common output of the sympathetic nervous system, might be a target of pramipexole. The normalization of the HR reaction to PLMS may be relevant in reducing the risk of cardiovascular diseases and associated autonomic dysfunctions in patients with RLS.

P39

Behaviourally induced insufficient sleep syndrome

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Introduction: Behaviourally induced insufficient sleep syndrome (BIISS) occurs when an individual chronically fails to obtain the amount of sleep required to maintain normal levels of alertness and wakefulness. Its significance is mostly unappreciated by the patient. Some patients may develop secondary symptoms which may even become the main focus of the patients, serving to obscure the primary cause of the difficulties.
Methods: This study presents the results of the post hoc evaluation of 47 consecutive patients who received the diagnosis of BIISS in our Centre of Sleep Disorders.
Results: Mean age of the BIISS patient was 40 ± 12 years (mean ± SD). Only 30% were females. Patients mostly complain symptoms of hypersomnia with excessive daytime sleepiness, however, many individuals reported other symptoms as sleep attacks without general daytime sleepiness, fatigue, sleep drunkenness, concentration and attention deficits or cognitive impairment. Mean ESS was 14.1 ± 3.6. Time in bed (TIB) estimation based on the SQ revealed TIB of 7:10 h ± 1:03 h during weekdays and 8:29 h ± 1:16 h on weekend. TIB estimation based on actigraphy recordings revealed significantly shorter TIB on weekdays and on weekends (weekday: 6:25 h ± 0:57 h, weekend: 7:56 h ± 1:13 h) compared to TIB taken from the SQ. In this population the PSG recording revealed short sleep latency 8.4 ± 7.9 minutes and high sleep efficiency (91.5 ± 16.7%). Mean sleep latency of MSLT was 5.5 ± 3.3 minutes. Sleep onset REM (SOREM) episodes with 2 and more SOREM were present in 8 patients. Mean sleep latency of MWT was very variable. A clear reduced ability to maintain wakefulness (sleep latency <12 min) was present in 34% of patients.
Conclusion: The results of this case series indicate that there are a noticeable large number of patients who were not aware that their sleep duration was insufficient and that there is a substantial clinical overlap between BIISS, narcolepsy without cataplexy and idiopatic hypersomnia without long sleep.
A positive response to increased sleep time is diagnostic of BIISS and an important feature to differentiate between these three entities.

P40

Berlin questionnaire performance for detecting sleep apnea in the general population

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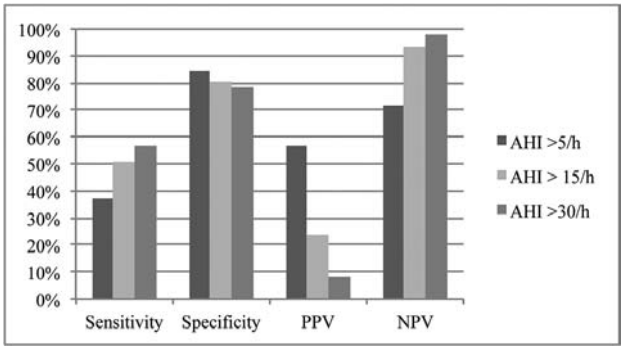
Introduction: Berlin questionnaire (BQ) has been proposed as a screening tool for identifying patients at risk for obstructive sleep apnea (OSA). The aim of our study is to evaluate the performance of this questionnaire for detecting OSA in a large sample of middle-aged general population.
Methods: 922 subjects (49.2% men, 50.2 ± 5.7 years old, BMI 25.7 ± 4.2 kg/m^2) participating in an ongoing population-based cohort study (HypnoLaus, Lausanne, Switzerland) underwent a complete polysomnographic recording at home and an extensive clinical workup including BQ. This instrument includes 3 categories: 1) witnessed apnea and snoring behavior 2) waketime sleepiness and fatigue and 3) history of obesity and hypertension. A positive score in two or more categories was considered suggestive for OSA. This score was compared to apnea-hypopnea index (AHI) and 4% oxygen desaturation index (ODI) determined by PSG. AHI was scored according to 2007 AASM criteria.
Results: Mean AHI was 6.3 ± 10.6/h. Mean 4%ODI was 5.8 ± 10.0/h. Prevalence of OSA defined as an AHI >5/h, >15/h and >30/h was 33.3%, 10.3% and 3.8%, respectively in our population. Prevalence of positive BQ score was 24.4% (29.2 in men, 18.81 in women). BQ sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) to detect OSA were 36.1%, 82.4%, 51.8% and 72.9% respectively for an AHI >5/h; 52.1%, 78.8%, 21.9% and 93.5% for an AHI>15; and 72.2%, 77.6%, 11.4% and 98.6% for an AHI >30/h. Positive

BQ was associated with higher 4% ODI (10.8/h vs 4.2/h p <0.001), higher Epworth score (8.3 vs 6.2 p <0.0001) and broader neck circumference (38.6 vs 35.7 cm p <0.0001).



Conclusions: BQ questionnaire performance for identifying OSA is lower in a middle-aged general population than initially reported in a clinical population. Our results do not support its use as a screening tool for OSA in an unselected population.

P41

Challenging the sleep homeostat in young depressed and healthy older women: sleep in depression is not premature aging

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Introduction: Major depression and sleep disturbances are closely related and often occur concomitantly. This led to the hypothesis of a deficiency in homeostatic sleep pressure in depression (S-deficiency hypothesis). Many of the observed changes of sleep characteristics in depression are also present in healthy aging, which led to the premise that sleep in depression resembles premature aging. Here, we aimed at quantifying the homeostatic and circadian sleep-wake regulatory components in young women suffering from major depression disorder and healthy young and older control women during 40 hours of sustained wakefulness.
Methods: After an 8-h baseline night 9 depressed women, 8 healthy young and 8 healthy older women underwent a 40-hour sustained wakefulness protocol followed by a recovery night under constant environmental conditions. Polysomnographic recordings were carried out continuously and subjective sleepiness was assessed half-hourly along with salivary melatonin. Sleep parameters as well as NREM sleep EEG spectra in the frequency range of 0.75–25 Hz along the anterio-posterior axis were analyzed during the night sleep episodes. In particular, the time course of EEG slow-wave activity (SWA) (EEG spectra range: 0.75–4.5 Hz), as a marker of homeostatic sleep pressure, was analyzed during the recovery night.
Results: Young depressed women exhibited higher absolute mean SWA levels and a stronger response to sleep deprivation in the delta frequency range compared to healthy young and healthy older women, particularly in frontal brain regions. In contrast, healthy older women exhibited not only attenuated SWA values compared to the other two groups but also an absence of the frontal predominance of mean SWA during the recovery night. Relative EEG spectra also showed higher homeostatic response to sleep deprivation in young depressed compared to the healthy volunteers, particularly in the first sleep cycle. Furthermore, nighttime melatonin secretion was reduced in depressed and older women compared to young women.
Conclusions: Our data clearly show that homeostatic sleep regulation as well as sleep architecture in young depressed women is not equal to premature aging. Moreover, our findings demonstrate that young depressed women exhibit no deficiency in the sleep homeostatic process S but rather live on an elevated level of homeostatic sleep pressure. We hypothesize that a reduced circadian arousal signal during wakefulness may contribute to this homeostatic overexpression.

P42

Changes in the sleep EEG at moderate altitude

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Introduction: Based on visually scored sleep stages, several studies have reported a shift towards lighter sleep with an ascent to high altitudes. Changes in sleep resulting from exposure to moderate altitude, however, are difficult to detect. The aim of the current study was to examine whether there are differences in the sleep EEG spectra at three different altitudes and whether altitude-related changes occur in a 'dose-dependent' manner.
Methods: In a randomized cross-over design, 44 healthy young men spent one baseline night at 490 m and two consecutive nights at two higher altitudes (1630 m and 2590 m). Polysomnographic recordings including frontal and central EEG derivations were conducted on all five nights with time in bed restricted to 7 hours. Power density spectra were calculated for 30-s epochs (FFT; average of six 5-s epochs; frequency resolution 0.2 Hz) and averaged over the minimal common length of non-REM sleep within individuals.
Results: Exposure to hypobaric hypoxia decreased slow wave activity (SWA, 0.8–4.6 Hz) in an 'altitude-dependent' manner. SWA was reduced by ~15% in both nights at 2590 m and 4.4% in the first night at 1630 m (frontal derivation only). At the highest altitude the decrease in spectral power extended to theta activity (4.6–8 Hz), where a ~10% reduction in power was observed. SWA was negatively correlated with the apnea/hypopnea index and oxygen desaturation index (range r = –0.31 to –0.52), while theta activity was positively correlated with mean oxygen saturation during non-REM sleep (range r = 0.32 to 0.41). Therefore, the decrease in SWA and theta activity may be due to impairment of sleep through breathing disturbance. In addition spindle power increased at higher altitudes. Sleep spindles have been proposed to have a sleep protecting function, therefore this increase may reflect an attempt to preserve sleep at altitude.
Conclusion: Delta activity – a marker of sleep intensity and homeostasis – was reduced at altitude perhaps leading to increased sleep propensity during the day, and increasing sleep intensity on the following night.
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P43

Circadian sleep-wake cycles, well-being and light therapy in borderline personality disorder

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Objectives: Patients with borderline personality disorder (BPD) frequently suffer from emotional instability, daytime fatigue and sleep disturbances. Since circadian sleep-wake and light-dark cycles are implicated in affect regulation, we investigated circadian rhythms, sleep and well-being in women with BPD under their habitual life conditions with light treatment (LT) and without LT (oLT).
Methods: Fourteen women diagnosed with BPD according to DSM-IV criteria were investigated during 3 weeks without and 3 weeks with morning LT. Rest-activity cycles were continuously measured using wrist actimetry, together with measuring proximal skin temperature. Saliva samples were weekly collected to determine the diurnal melatonin rhythm. Self-ratings and questionnaires were used to assess depression and clinical state throughout the 6-week protocol. The control group comprised ten healthy women, who followed the same 6-week protocol without light treatment.
Results: Women with BPD had significantly worse subjective sleep quality, reduced daytime alertness, and higher scores in anxiety, anger and depression than controls (p <0.003). Rest-activity cycles ranged from highly disturbed to extremely regular patterns in women with BPD and their sleep-wake rhythm, as indexed by the relative amplitude of day:night activity, had a significantly higher variance than controls (p = 0.007). Morning

LT significantly phase advanced the five hours with least activity in BPD as compared to oLT (L5 onset: p = 0.019), with a tendency for an advanced dim light melatonin onset (p = 0.092). During morning LT, BPD women slept shorter (p = 0.019), nocturnal movement time was decreased (p = 0.019) and proximal skin temperature was increased (p = 0.029) as compared to oLT. Daytime alertness improved significantly with morning LT (p = 0.010) and atypical depression scores were significantly attenuated (p = 0.024), whereas general depression scores and borderline symptoms showed no improvement.
Conclusions: Circadian sleep-wake disruptions, daytime alertness and atypical depression symptoms improved with morning LT. Thus, light therapy may be a useful adjunct treatment for patients with BPD.

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Comparison of polysomnographic variables and their relationship to cognitive impairment in patients with Alzheimer's disease and frontotemporal dementia

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Polysomnograhic studies in Alzheimer's disease (AD) show REM sleep abnormalities, which may be indicative for the deterioration of cholinergic pathways and probably closely linked to declarative memory impairment. To clarify the specificity of the association between sleep and cognitive impairment in dementia, we compared AD patients with patients suffering from frontotemporal dementia (FTD) with regard to PSG and neuropsychological variables. 15 AD and 6 FTD patients underwent polysomonography and a neuropsychological battery (CERAD-NB). Group differences (age: AD>FTD; education level: AD<FTD) were considered as covariates. Polysomnography revealed a trend towards increased REM latency and reduced REM sleep in AD, as well as a decrease of stage 2 sleep, however, at least partly due to effects of age. Declarative memory was more impaired in AD than in FTD, but this difference disappeared when adjusted for covariates. While no relationship was found between REM sleep and CERAD-NB parameters, strong positive correlations between stage 2 sleep and declarative memory measures were observed, which were also detectable when analyzing both groups separately. Based on these results we conclude that REM sleep alterations may be specific for AD, distinguishable from other dementia diagnoses, whereas NonREM stage 2 sleep may be related to declarative memory formation in dementia independent of subtype.

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Differential effects of GABA(B) receptor subtypes, Gamma-Hydroxybutyric Acid, and Baclofen on EEG activity and sleep regulation in mice

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Introduction: The role of GABAB receptors in sleep is still poorly understood. Gamma-hydroxybutyric acid (GHB) targets these receptors and is the only drug approved to treat the sleep disorder narcolepsy. GABAB receptors are obligate dimers comprised of the GABA(B2) subunit and either one of the two GABA(B1) subunit isoforms GABA(B1a) and GABA(B1b). The aim of this study was to better understand the role of GABAB receptors in sleep regulation and the mechanism of action of GHB.
Methods: Electroencephalographic (EEG) and electromyographic (EMG) recordings were performed in adult male mice devoid of functional GABA(B) receptors (1-/- and 2-/-) or lacking one of the subunit 1 isoforms (1a-/- and 1b-/-). The effects of the GHB-prodrug gamma-butyrolactone (GBL) and baclofen (BAC), a high-affinity GABAB receptor agonist were also evaluated.
Results and conclusions: The distribution of sleep over the day was profoundly altered in 1-/- and 2-/- mice suggesting a role for GABA(B) receptors in the circadian organization of sleep. Several other sleep and EEG phenotypes pointed to a more prominent role for GABA(B1a) as compared to the GABA(B1b) isoform. Moreover, we found that GABA(B1a) protects against the spontaneous seizure activity observed in 1-/- and 2-/- mice. Both GBL and BAC induced a state distinct from physiological sleep that was not observed in 1-/-and 2-/- mice. Subsequent sleep was not affected by GBL while BAC was followed by a delayed hypersomnia even in 1-/-and 2-/- mice. The differential effects of GBL and BAC might be attributed to differences in GABAB-receptor affinity. These results also indicate that all GBL effects are mediated through GABAB receptors while these receptors seem not to be involved in mediating the delayed BAC-induced hypersomnia.

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Effects of daytime light exposure on early evening performance, subjective sleepiness and hormonal secretion

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Introduction: In sighted humans, light intensity, timing, exposure duration and spectral composition of light are important to entrain the endogenous circadian pacemaker to the 24-h day-night cycle. We tested the impact of two realistic office lighting conditions during the afternoon on subjective alertness, hormonal secretion and cognitive performance in the early evening hours.
Methods: Twenty-nine young subjects (12 f) came twice and spent 8 h (12:00–20:00) in our laboratory, where they were exposed for 6 h to either artificial light (AL) or to mainly daylight (DL). In the early evening between 18:00 and 20:00 we assessed their salivary cortisol and melatonin secretion, subjective sleepiness and cognitive performance (n-back test) under dim light conditions.
Results: Subjects felt significantly more alert at the beginning of the evening after the DL condition, and they became significantly sleepier at the end of the evening after the AL condition. For cognitive performance we found a significant interaction between light conditions, mental load (2- or 3-back task) and the order of light administration. On their first evening, subjects performed with similar accuracy after both light conditions, but on their second evening, subjects performed significantly more accurately after the DL in both n-back versions and had fewer false alarms after the 2-back task compared to the AL group. Greater alertness in the evening was significantly correlated with better cognitive performance ($p < 0.05$).
Conclusion: Even short-term changes of lighting conditions during the afternoon can impact on alertness and on cognitive task performance in the evening.

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Effects of exposure to moderate altitude on slow wave sleep characteristics

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Travelling to higher altitudes causes changes in sleep architecture (e.g. Weil, 2004). Still, little is known about the effects of moderate altitude on the major EEG characteristic of deep sleep – the slow waves (SW; 1–4.5 Hz). Such SW are thought to be involved in memory consolidation and synaptic downscaling (Steriade et al., 2003, Tononi and Cirelli., 2006). Changes in the slopes of SW represent an indirect but reliable electrophysiological marker of synaptic strength. Vyazovskiy et al. (2007) showed that the slopes of SW decrease with diminishing homeostatic sleep pressure, they are usually steeper at the beginning of the night and after sleep deprivation and decrease in the course of sleep.
The aim of our study was to investigate the effects of acute altitude exposure on the overnight time course of SW, in particular their slope, amplitude and incidence. To control for amplitude differences between the first and last hour of sleep we calculated the slope of SW at a fixed amplitude of 75 mV for both time points (linear regression between slope and amplitude). The

slope difference between the first and last hour of NREM sleep represents a measure of synaptic downscaling. In a randomized cross-over design, 51 healthy young men spent one baseline night in Zurich (ZH) at 490 m and two consecutive nights at each higher altitude Davos Wolfgang (WO) and Jakobshorn (JH) (1630 m and 2590 m) (3 subjects had to be excluded from the analysis due to missing data). Polysomnographic recordings including central EEG derivations were conducted with time in bed restricted to 7h.
We found that the slope and amplitude of the overnight time course of SW were significantly lower in JH day 1 (JH1) and day 2 (JH2) compared to ZH, WO day 1 (WO1) and day 2 (WO2) ($p < 0.001$) whereas ZH, WO1 and WO2 showed similar results. The number of SW did not change. The slope difference between the first and last hour of NREM sleep showed a continuous reduction from ZH, WO1 and WO2 to JH1 and JH2 ($p < 0.05$) while ZH, WO1 and WO2 showed similar results. This reduced difference is mainly due to lower SW slopes in the first hour of NREM sleep in JH1 and JH2 compared to ZH and WO ($p < 0.05$).
The ascent to moderate altitude seems to affect slow wave sleep characteristics. The mechanisms underlying the reduction of our marker of synaptic strength are unknown, possibly involving any acute physiological effect of moderate altitude.
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Effects of sleep deprivation and functional polymorphisms of DAT and COMT on EEG slow wave characteristics in NREM sleep

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Introduction: Prolonged wakefulness increases slow wave sleep (SWS) and EEG slow-wave activity (SWA) in non-rapid eye movement (NREM) sleep. The role for dopamine in modulating these changes is unknown. We investigated whether functional single nucleotide polymorphisms (SNP) of the genes encoding dopamine transporter (DAT; variable-number-of-tandem-repeats (VNTR) in 3'-untranslated region of DAT gene) and catechol-O-methyltransferase (COMT; Val158Met polymorphism; SNP identification number: rs4680) affect the response to sleep deprivation. In particular, we focused on the characteristics of individual slow wave oscillations in NREM sleep.
Methods: Polysomnographic recordings of sleep and the sleep EEG in baseline and recovery nights after 40 hours prolonged waking were analyzed in 57 healthy adults (mean age; 24.67 ± 3.31 years). Sleep stages were visually scored in 20-s epochs according to Rechtschaffen and Kales, and artifact-free 4-s EEG epochs were subjected to Fast-Fourier Transformation (0.25-Hz resolution; 0.5–20 Hz). Furthermore, period-amplitude analysis of narrowly band-pass filtered EEG was applied, to specifically detect sleep slow oscillations between 0.5–2 Hz (method described by Bersagliere et al., J Sleep Res, 2010). Statistical analyses were carried out in SAS 9.1 (SAS Institute). Two-way mixed-model ANOVA with the between-subject factor "genotype" and the within-subject factor "condition" was used. Genotypes were analyzed separately, unless an interaction was found. Results were considered significant for $p < 0.05$. To minimize false positive findings, changes were only considered significant when they included two or more neighboring frequency bins.
Results: Sleep deprivation induced a SWS/SWA rebound in recovery sleep in all genotypes. Nevertheless, both polymorphisms modulated the increase in SWS/SWA from baseline. The differences occurred in the 3rd NREM sleep episode, and consisted of a relatively larger SWA rebound in DAT10/10 and COMT Val/Met genotypes compared to the other genotype groups. Sleep deprivation also induced major changes in slow-wave characteristics in all of the first four NREM episodes. These effects included decreased number of peaks per wave, as well as increased wave amplitude, wave density and average wave slope. DAT genotypes modulated the density of slow waves, whereas the Val158Met polymorphism of COMT affected the number of wave peaks, both in the 3rd NREM sleep episode.
Conclusion: These preliminary results suggest that genetically altered dopaminergic neurotransmission influences homeostatically regulated EEG slow waves in NREM sleep.
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Effects of sleep deprivation on performance on an emotional stop-signal task

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Introduction: Sleep deprivation affects a wide range of cognitive and emotional processes. Based on previous research, we hypothesized that sleep deprivation impairs response inhibition, i.e., the rapid interruption of an ongoing motor action. Moreover, we investigated whether this impairment may be modulated by simultaneous emotional processing.
Methods: Performance on a modified stop-signal task including an emotional component (Sagaspe et al., NeuroImage, 2011) was studied in 11 healthy men (age range: 20–23 years) after 8 and 32 hours of wakefulness. Each subjects completed a randomized, cross-over, 2 x 2 factorial study. Eighteen images of faces with fearful (n = 9) and happy (n = 9) expression from the Ekman's series were presented for 1000 ms on a computer screen. Subjects were instructed to discriminate as quickly and as accurately as possible the gender of each face by button press. Importantly, when a tone was present during image presentation, participants were asked to immediately withhold their initiated response. The data were analyzed with two-way within-subjects ANOVA with the factors 'time awake' (8 h, 32 h) and 'emotional expression' (fearful, happy).
Results: Reaction times (RT) of correct Go responses were significantly slower to fearful faces than to happy faces (468.7 ± 10.8 vs. 462.8 ± 9.5 ms, $F1, 10 = 8.0$, $p = <0.02$). Prolonged wakefulness increased the percentage of gender discrimination errors (6.8 ± 0.7 vs. 10.5 ± 1.5, $F1,10 = 11.1$, $p < 0.01$) and the number of response lapses (no response and RT >1000 ms) (1.5 ± 0.4 vs. 6.4 ± 1.5, $F1, 10 = 14.0$, $p < 0.005$). By contrast, while sleep deprivation slowed down mean RT, the effect did not reach significance. Similarly, the latency of the inhibition process was unaffected by sleep deprivation. No interaction between time awake and facial expressions was found for any dependent variable.
Conclusions: Consistent with previous studies, our findings show that RT on an emotional stop-signal task were prolonged by the presence of fearful incidental threat information. Sleep deprivation increased gender discrimination errors and lapses, whereas it had no effect on the latency to the stop signal. These findings suggest that response inhibition and emotional processing may be less vulnerable to acute sleep deprivation than simple RTs, which are consistently impaired after one night without sleep.
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Electrical imaging of sleep deprivation and sleep slow waves

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Introduction: The electroencephalogram (EEG) during non-rapid eye movement (non-REM) sleep is characterized by high amplitude, low frequency waves. On a neuronal level, these waves originate from the synchronous activity of large populations of cortical neurons, alternating between a depolarized (ON) state and a hyperpolarized (OFF) state, with a frequency around 1 Hz. The functional significance of this activity is still under investigation, although it is believed to underlie the restorative function of sleep. In our study we assessed the topographic distribution of sleep EEG power and examined the electrical sources of slow waves in baseline sleep and in sleep after 40 hours of sustained wakefulness.
Methods: We analyzed EEG traces during baseline sleep and recovery sleep after 40 h of sustained wakefulness in 8 healthy young men (27 channels). Power maps (average reference) of the first non-REM sleep episode (where sleep pressure is highest) were estimated in baseline and recovery sleep, at frequencies between 0.5 and 2 Hz (0.25 Hz resolution). Electrical sources within the cortex of very-low-delta (0.5–2 Hz) and low-delta activity (1.25–2 Hz) were estimated using the software LORETA.

Results: Power maps of all frequencies between 0.5 and 2 Hz in baseline and recovery sleep showed a frontal predominance; below 1 Hz, an occipital focus of activity was also observed. No change in power maps was observed as a consequence of sleep deprivation below 1 Hz, whereas a significant increase in power was found at 1.25 Hz and above. Electrical sources were predominantly distributed in prefrontal regions. Sleep deprivation resulted in an increase in source strength only for low-delta activity, mainly in parietal and frontal regions. Comparing the electrical sources of the two bands revealed that very-low delta dominated in occipital and temporal regions and low-delta activity in limbic and frontal regions, independent of the level of sleep pressure. Moreover, power maps and electrical sources displayed trait-like features.
Conclusions: Our analysis revealed differential response to sleep deprivation in the 0.5 to 2 Hz range. Furthermore, the topographic distribution of power and sources were trait-like.

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Manipulating the regulation of cortical excitability during sleep by electromagnetic fields

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Introduction: Recent evidence suggests that pulsed radiofrequency electromagnetic fields (RF EMF) are capable of modifying cortical excitability. Slow wave activity (SWA) during non-rapid eye movement (NREM) sleep seems to be critically involved in the regulation of cortical excitability across 24 h. Thus, the reduction of SWA across the night is accompanied by a reduction of cortical excitability during sleep, normalizing the increase in excitability observed during the day. We examined whether pulsed RF EMF exposure during sleep interacts with this regulation of excitability and possible behavioural consequences.
Methods: 16 male adolescents underwent two experimental nights, one of them with all-night 0.25-0.8Hz pulsed RF EMF exposure. All-night electroencephalography (EEG) was recorded and SWA (EEG power band 0.75–4.5Hz) during NREM sleep was calculated for 4 sleep episodes. Additionally, we analysed event related spectral power (ERSP) of single RF EMF pulses in the SWA frequency range. Changes in overnight performance improvement were assessed with a motor sequence finger tapping task (training in the evening, retest next morning) for both nights.
Results: We found increased SWA in the 4th NREM sleep episode during the exposed compared to the sham night (+44.0 ± 17.9%, $p < 0.04$). The decrease of SWA across the sham night was significantly correlated with the corresponding overnight performance improvement ($r = 0.63$, $p < 0.01$). No such correlation was found for the exposed night ($r = 0.15$, $p < 0.59$). Subjects responding strongest to RF EMF exposure (n = 8, median split) showed a SWA increase in the 2nd (+61.6 ± 33.2%, $p < 0.07$) and 4th NREM sleep episode (+94.4 ± 24.4%, $p < 0.01$). This group of subjects showed increased ERSP after single RF EMF compared to sham pulses.
Conclusions: The changes in SWA during the exposed night may reflect an interaction of RF EMF with the normalization of cortical excitability during sleep, with a possible negative impact on sleep dependent performance improvement. There is evidence that applied weak electrical fields can entrain spiking activity of neurons and synchronize them. Thus, our RF EMF may also entrain and synchronize neuronal activity in the SWA range. Individual differences may be explained by the fact that such external fields cooperate with or compete against synaptically mediated network activity.

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Morning blue light exposure affects facial emotion processing under sleep restricted conditions

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Introduction: Both light treatment and sleep deprivation have repercussions on well-being including mood and are often used in the treatment of mood disorders such as seasonal affective disorder (Terman & Terman, 2005). Sleep deprivation has been recently shown to alter the judgement of human facial emotions (Van der Helm, Gujar & Walker, 2009). Here we investigated whether blue light exposure affects the rating of facial emotions under sleep restricted conditions.
Methods: Sixteen healthy male (22.8 ± 3.5 years) performed a facial emotion rating task at different times during a sleep restriction (SR) protocol (6h of sleep for two consecutive nights) under different morning light conditions [blue light: 20 min exposure 200 lux of 470nm, 2h after wake up vs. dim light (<8 lux)]. Here, we focus on the results of the three evening sessions [(1. well-rested baseline (BL; no light exposure), 2. after the first (S1) and 3. the second (S2) SR night; each time of testing approx. 14h after wake up]. Pictures of facial expressions ranging in a 10-steps gradient from neutral to increasingly happy were rated on a scale from 1–4 (entirely neutral to entirely happy). The gradients were presented in a randomized order. Subjective sleepiness (KSS) and mood (VAS) was assessed prior to testing.
Results: In the dim light condition participants tended to rate the faces more happy at S1 and S2 as compared to BL (main effect of session for gradient 4, 5 & 8: $p = 0.08$; $p = 0.09$; $p = 0.07$). Comparison of the time course of ratings between both light conditions showed that blue light exposure dampened the rating of happy faces in higher emotional gradients as compared to the dim light condition (tendency for condition x timepoint-interaction in gradient 7 & 10; $p = 0.05$; $p = 0.09$; significant condition x timepoint-interaction in gradient 8 & 9; $p = 0.04$; $p = 0.03$). The light condition did not significantly affect subjective measures of mood and sleepiness collected prior task administrations ($p = 0.69$; $p = 0.76$).
Conclusion: Our data indicate that accumulated sleep restriction alters the rating of emotional faces in healthy young male. Interestingly, morning blue light exposure counteracts this effect as indexed by lower ratings of happy faces. The underlying mechanisms of this light-modulated effect remain to be determined but do not seem to be a simple by-product of alterations in subjective sleepiness and mood as both these values did not significantly differ between light conditions.

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Piezoelectric system as an alternative for electroencephalography in animal sleep experiments: an example of a large-scale study in CFW outbred mice

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Introduction: Non-invasive methods to record sleep in animals are being developed as an alternative to electroencephalography (EEG) and electromyography (EMG). The 'piezo' system uses piezoelectric films placed on the bottom of a cage to detect animal's movements with high sensitivity. The resulting signal can be used to automatically distinguish sleep from wakefulness. During wakefulness, locomotor activity and even small movements result in a high frequency, erratic, and irregular signal while during Non Rapid Eye Movement Sleep (NREMS) the principal movements are respiration-related chest-wall movements, producing a ca. 2 Hz rhythmic signal. We are currently validating this technique in a cohort of CFW outbred mice by comparing EEG/EMG-determined sleep to piezo-determined sleep within individual mice. The piezo-system is part of a phenotyping pipeline in CFW mice for an ongoing Genome-Wide-Association study at MRC Harwell run by Jérome Nicod.
Methods: Eleven male and 10 female Swiss Webster CFW mice (Charles River, USA), 18–20 weeks old were used. Mice were maintained under standard housing condition, with food and water ad lib, in a temperature controlled room (25 °C) and a 12h:12h light/dark cycle. Mice were implanted with EEG/EMG electrodes under deep anesthesia. After surgery, mice were singly housed and connected to recording cables. A minimum of 13 days for recovery and habituation were allowed prior to the experiments. For the EEG/EMG-piezo comparison mice were transferred to recording cages each of which contained a piezoelectric film, covered with some litter. EEG/EMG (EMBLA and Somnologica, ResMed) and piezo (MouseRec, Signal Solutions LLC) signals were recorded continuously for 3 consecutive days.
Results: Comparison from EEG/EMG recordings and piezoelectric data showed that the distribution of sleep and wake over the day, as well as the amount of time spent in NREMS is consistent with both techniques. With both techniques, we observed that CFW mice have a different sleep/wake pattern than common used inbred strains; the amount of sleep during the

dark period is significantly higher than in inbred mice, close to the amount of sleep observed during the light period.
Conclusion: Although EEG activity and Rapid eye movement sleep cannot be measured with this technique, piezoelectric system is an interesting alternative to EEG/EMG experiments in mice that can be used for large-scale sleep studies and rapid screening of sleep/wake promoting drugs.

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Regional association between sleep spindle activity and fluid intelligence

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Introduction: In adults, sleep spindles seem to be a marker for intelligence. Recently, those findings were replicated in children and adolescents: sleep spindle frequency activity (SFA, EEG spectral power from 10 to 16 Hz) positively correlated with standardized intelligence quotient (IQ) test performance. Using high-density (hd) EEG we aimed to investigate regional aspects of the relationship between sleep spindling and IQ. We hypothesized that local sleep SFA is linked to specific IQ sub-test scores.
Methods: We recorded sleep during two nights separated by three weeks using hd EEG (128 electrodes) in young subjects (12–16 years). Before each night, the subject's fluid intelligence was assessed with a standardized matrices test (TONI-IV, 2-versioned test of non-verbal intelligence).
Results: First results indicate that sleep SFA over parietal and prefrontal areas correlated with fluid intelligence test performance (e.g. Brodmann area 40: $r = 0.89$, $p < 0.05$, $n = 3$, 2 nights each). Both areas are associated with fluid intelligence in the awake condition.
Conclusion: With these preliminary data, we show regional aspects of the known relation between SFA and fluid intelligence. In a next step, we will manipulate performance in several IQ sub-tests by cognitive training and investigate related regional changes in sleep SFA.

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Responses in a monetary incentive task do not differ between narcolepsy patients and healthy controls

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Introduction and Objectives: Hypocretin (orexin) deficiency in narcolepsy –cataplexy patients has been linked to disturbed emotional processing, especially reward. We aimed at assessing reaction time (RT) of successful trials in narcolepsy patients and healthy controls in an incentive monetary task, and at comparing the outcomes to those in healthy controls.
Materials and Methods: Twelve HLA positive, hypocretin-deficient (8/8 tested) unmedicated (8/12) narcolepsy patients with cataplexy (mean age 40 ± 10 years) and nine healthy controls (mean age 31 ± 10 years) performed an incentive monetary task using different value and valence cues. The participants had to press a button as fast as possible while a picture of a landscape was presented on the screen in order to gain or not lose money. On each trial, the picture was preceded by one of four possible cues: potential gains (+1/+5 points) or losses (-1/-5 points). The duration of the target presentation was adapted online based on the participant's performance on the previous trials to ensure a balanced amount of won and lost trials in each participant. We analyzed RT using repeated measures ANOVA (with group as a between subject factor and valence – positive versus negative, and value – small versus big cues, as within subject factors).
Results: Reaction time for successful trials did not differ between patients (mean ± SD, 310 ms ± 59 ms) and controls (277 ± 61) in general. There were no differences in reaction times neither for small versus large cues nor for positive versus negative cues. Conclusion: Patients with narcolepsy-cataplexy achieve normal performance in highly motivational game-like tasks and are able to compensate hypocretin related dysfunctional reward behavior.
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Sleep homeostasis and adolescent development

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Introduction: Two independent processes influence the timing and duration of sleep: a homeostatic (Process S) and a circadian (Process C) process. Cross-sectional and longitudinal studies of Process S in adolescent humans have shown that the rate of dissipation of sleep pressure across the night does not change between pre- and post-pubertal adolescents. The aim of the current study was to examine sleep homeostasis across adolescent development with longitudinal data.
Methods: Twenty children and twenty-five teens underwent polysomnographic recordings when they were ages 9/10 and 15/16 years and again 1.5 to 3 years later. Sleep EEG was recorded from C3/A2. Parameters pertaining to the dissipation of slow wave activity (SWA) across the night (time constant of the decay or τd, lower asymptote and S at sleep onset) were estimated for each individual at both assessments using the method of Rusterholz et al., 2010. Statistical analysis was performed within a cohort using a paired t-test.
Results: In the children and teen cohorts there was no change in any of the parameters of Process S (τd, LA, or SSO) from the initial to the follow-up session.
Conclusion: These results suggest that the dissipation of sleep pressure does not change across adolescent development indicating that sleep need does not change across this period.
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Sleep loss alters DNA-binding activity of circadian transcription factors

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We have previously shown that sleep deprivation (SD) alters the expression of clock genes in the forebrain suggesting that clock genes are not only involved in circadian rhythms, but also in sleep homeostasis [Franken P & Dijk DJ, Eur.J.Neurosci.2009]. Here, we test the hypothesis that SD alters clock genes expression by modifying the specific DNA-binding of the three core-clock transcription factors BMAL1, CLOCK, and NPAS2 to E-box or E'-box containing sequences of their target clock genes Per1, Per2, Cry1, and Dbp.
First, we verified if the DNA-binding of BMAL1 and CLOCK to targeted clock genes varied in function of time-of-day in the cerebral cortex of C57BL/6J mice using chromatin immunoprecipitation (ChIP) at ZT0, -6, -12, and -18 (ZT0 = light onset). DNA enrichment of sequences was measured by qPCR. We observed that BMAL1 and CLOCK binding to Per1, Per2, Cry1, and Dbp genes varied with time-of-day with maximal binding reached around ZT6-12. We then sleep deprived mice from ZT0 to ZT6 to assess the effects of sleep loss. We found that SD significantly and specifically decreased DNA-binding of CLOCK to Dbp, of NPAS2 to Per2, and of BMAL1 to both these target genes.
Our results show that the changes in the expression of specific clock genes with sleep pressure, notably that of Dbp and Per2, could result, at least in part, from changes in the DNA-binding activity of the core clock proteins BMAL1, CLOCK, and NPAS2.

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The maturation of sleep SWA in juvenile rats predicts their behavioural development

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Human studies show a remarkable decline of sleep EEG slow wave activity (SWA) during puberty and adolescence, which is thought to reflect cortical maturation, i.e. pruning, the reduction of synaptic density (Campbell and Feinberg, 2009). This developmental change in SWA across age has never been explored in the rat. Our studies aim at exploring causality in the relationship between cortical maturation and sleep SWA. To do so, in a first step, we longitudinally recorded SWA in the rat and assessed cortical maturation on the structural and behavioural level.
13 male Sprague Dawley rats were recorded for three weeks starting form postnatal day 25 (P25). The rats were individually housed and maintained on a 12hr:12 hr light-dark cycle. Food and water was given ad libitum. EEG signals were subjected to a fast Fourier transform for 4-s epochs. Vigilance states were visually scored. For the analysis of maturational changes in behaviour video was recorded in their home cage twice during free exploration on P28 and P42 in a subgroup of animals (n = 7).
Our data shows a similar time course of SWA during non-rapid eye movement sleep in the juvenile rat as found in human studies: in early days, SWA significantly increased up to the age of P30, which was followed by a steady decrease until the rat entered adulthood (SWA in % of P30 ± SE; P26: 77.9 ± 6.7, P30: 100.0 ± 0, P42: 60.3 ± 15.2; t-tests p(26/30) <0.01, p(30/42) <0.01, p(26/42) <0.05). During the same time the amount of object exploration (in % of 60 min) increased from 9.5 (± 2.0) to 22.9 (±3.7) % (p(28/42) <0.01). Moreover, we found a negative correlation between the increase in exploration and the reduction of SWA across age (r = 0.8, p <0.01).
Thus, the maturation of SWA parallels behavioural maturation. Histological analysis will provide us insights into age dependent cellular differences accompanying the changes in SWA.

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The role of sigma activity for the localization of the epileptogenic zone in drug-resistant nocturnal frontal lobe epilepsy patients with hypermotor seizures

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Introduction: Nocturnal frontal lobe epilepsy (NFLE) is a disease characterized by sleep-related paroxysmal motor attacks that occur during non-REM sleep. In case of drug-resistance, surgical treatment can be a valid therapeutic option. The identification of the epileptogenic zone (EZ), the cortical area where seizures initiate and whose removal leads to the disappearance of seizures, is frequently a challenging issue in patients with NFLE. This is due to the absence of anatomo-clinical lateralizing and localizing information and the lack of informative inter-ictal and ictal EEG correlates. The aim of our analysis was to find asymmetries in the ictal activity that could provide information on the lateralization of the EZ.
Methods: The electroencephalogram (EEG) recorded during pre-surgical investigation was analyzed retrospectively in a group of patients (n = 4) who underwent successful surgery after bilateral intracerebral stereo-EEG investigation. Therefore the location of the EZ was known. Sleep EEG (19 derivations) during the ictal phase was compared to sleep EEG during the pre-ictal phase. Electrical sources were estimated using the software LORETA.
Results: The scalp distribution of EEG power in the delta (1–4 Hz) and sigma (12-16 Hz) band during the pre-ictal and ictal phase was compatible with maps of physiological sleep. In all patients, electrical sources of delta and sigma activity increased in strength during the ictal phase. The increase in sigma activity was larger in the hemisphere containing the EZ, whereas that of delta activity was larger contralateral to the EZ (in 3 of 4 patients, 75%).
Conclusions: Sigma activity may predict the lateralization of the EZ and thus has potential as a clinical tool for the pre-surgical evaluation of NFLE patients with uninformative EEG and clinical data.

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Time dependency of motor sequence learning – time alive, time awake and time of day

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Introduction: Procedural learning refers to acquisition and consolidation of perceptual-motor skills affecting behaviour without necessarily requiring conscious recollection. The effects of aging on the ability to form procedural memories are controversial. In young adults, circadian and sleep-wake dependent modulations have been reported for motor skill learning. Since aging is characterized by changes in sleep-wake regulation, it can be assumed that circadian phase and sleep pressure affects procedural memories differentially in older people.
Methods: Eight older (61 ± 4 years) and 12 young adults (25 ± 4 years) completed a motor sequence learning task throughout a 40 h sleep deprivation (SD) protocol under controlled laboratory conditions. Procedural memory performance was assessed by contrasting reaction times (RTs) between sequenced (S) and random (R) trials [(S-R)/R]. Performance was tested at 3 mornings (9 am after baseline and SD night, 8 am after recovery night) and 3 evenings (10 pm before baseline, SD and recovery night). Subjective sleepiness was assessed on the Karolinska Sleepiness Scale (KSS) 10 min. after the motor sequence task.
Results: Learning occurred in both age groups as indicated by faster RTs in S compared to R trials (p <.001). However, a main effect of age was observed, indicating better overall performance in young relative to older subjects (p <.05). Importantly, procedural memory yielded a time of day modulation (p <.05). Data inspection revealed that performance levels remained fairly stable throughout the protocol in the older while young adults were able to improve their performance, particularly in the evening after 36 h of wakefulness (p <.01) despite of similarly rising levels of subjective sleepiness in both age groups in the course of SD (effect of time: p <.001, KSS values of young: 4.3 to 8.0 and old: 2.5 to 7.3; no interaction of time and group).
Conclusions: Our results are in line with prior studies showing that procedural learning is still possible with advanced age. However, motor slowing in the older cohort may have contributed to the observed overall attenuation in procedural performance. We have evidence that young adults profit from a circadian alerting signal, which allows further improvement of motor performance in the evening even under high sleep pressure. In contrast, older people do not seem to benefit from this circadian signal, probably due to its weakening or a stronger negative impact of elevated sleep pressure.

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Time perception in narcolepsy patients and healthy controls

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Introduction and Objectives: Prefrontal cortex plays an important role in cognitive time processing, and time perception depends on sustained attention. Narcolepsy-cataplexy patients are unable to maintain sustained attention, probably due to deficient hypocretin (orexin) signaling. We aimed at assessing time perception in patients with narcolepsy-cataplexy and compare the outcome with that of healthy control subjects.
Materials and Methods: Twelve HLA positive, hypocretin-deficient (8/8 tested) unmedicated (8/12) narcolepsy patients with cataplexy (mean age 40 ± 10 years) and nine healthy controls (mean age 31 ± 10 years) performed a time estimation task, where they had to estimate one, two or five seconds.
A picture was presented on the screen and the participants had to press a button after the above mentioned time periods. Feedback was provided for correct time estimations, in that the initial picture turned funny, if not a mirror image of the initial picture was presented. Accuracy of time estimates (real time estimation minus time to be estimated) and its variability (presented as standard deviations ((SD)) were analyzed using repeated measures ANOVA with group (patients versus controls) as a between subject factor and accuracy (three levels) and variability (three levels) as within subject factors.

Results: No significant differences were observed in accuracy of time estimation for different periods to be estimated and between patients and controls. There was a trend for higher variability of responses in narcolepsy patients (main effect for group, $F(1) = 3.99$, $p = 0.06$). In both groups the responses varied significantly more for longer periods to be estimated (main effect for variability, $F(2) = 13.6$, $p < 0.001$). There was no interaction between group and variability.
Conclusion: Time perception appears to be intact in narcolepsy patients but tend to be more variable as compared to healthy controls.
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Topographical distribution of theta activity in the waking EEG during development

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Slow wave activity (SWA, 1–4.5 Hz) during non-rapid eye-movement (NREM) sleep is homeostatically regulated and mirrors sleep pressure (Borbély et al., 2000). The topography of SWA shows regional changes during development, in that the predominance of SWA shifts from back to front (Kurth et al., 2010). A similar trajectory is found for anatomical and functional maturation. In the waking EEG, theta activity was proposed as a marker of increased sleep pressure (Cajochen et al., 1995). Moreover, in adults, the topographic distribution of the theta activity rise rate during prolonged wakefulness shows a frontal predominance as found for SWA (Finelli et al., 2000). Our aim was to investigate whether the topographical distribution of theta activity shows maturational changes as found for SWA.
In our preliminary analysis we included all-night high density (hd) EEG (128 channels) and 4 minutes of waking hd EEG during an attention task in the evening and morning, right before and after sleep, in 12 healthy children (9.5–11.8 years). Artifacts were rejected based on EEG activity in two frequency bands (0.75–4.5 Hz, 20–30 Hz).
When comparing the waking EEG in the morning to the evening we found a significant increase of activity ($p < 0.05$, all channel mean) in the theta frequency band (6.25–7.75 Hz). The topographical distribution of theta activity in the evening and morning showed maximal values over the occipital cortex. The rise rate of theta activity was fastest over frontal and occipital regions (see fig. 1). A similar topographical pattern was observed when comparing sleep SWA of the first to the second half of the night.

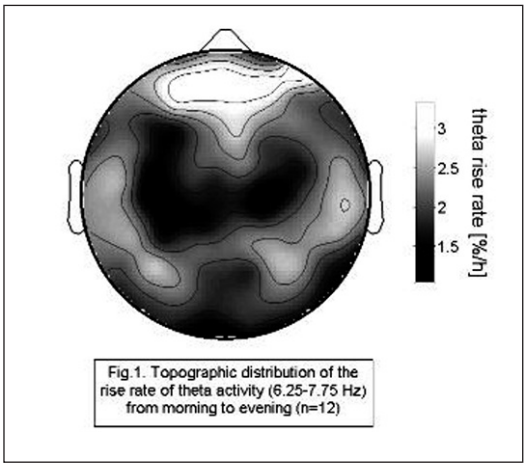

Fig.1. Topographic distribution of the rise rate of theta activity (6.25-7.75 Hz) from morning to evening (n=12)

We found in our children a close correspondence of the topography of theta activity in the waking EEG and SWA during sleep, as previously found for adults. However, in contrast to the frontal predominance of theta activity and SWA in adults, children showed for both activities secondary maxima over occipital cortex. Thus, as proposed for sleep SWA, theta activity in the waking EEG may represent an electrophysiological marker of cortical maturation. Mechanistically, this similarity of theta activity and SWA is in line with recent data showing that theta activity in awake rats may represent local populations of neurons falling asleep (Vyazovskiy et al., 2011). These offline periods during wakefulness are, on the electrophysiological level, similar to the off periods underlying slow waves during NREM sleep.
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P63

Topography of sleep slow wave activity in children with attention deficit hyperactivity disorder

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Introduction: Attention deficit hyperactivity disorder (ADHD) is the most common disorder in childhood (Olfson, 1992), whose genesis is still discussed. Supporting the idea that ADHD may be the result of a maturational delay (e.g. Gustafsson et al., 2010) it was shown that in children with ADHD gray matter maturation lagged behind that of typically developing children (Shaw et al., 2011). Recently, the topography of sleep slow wave activity (SWA), the major characteristics of non-rapid eye movement (NREM) sleep, was shown to mirror the actual state of cortical maturation and functioning during development (Kurth et al., 2010). We therefore investigated the sleep EEG of children with ADHD and age-matched healthy controls, asking, if a maturational delay would be reflected in the SWA topography.
Methods: All-night high density EEG (128 electrodes) was recorded in nine children with ADHD and nine age- and sex-matched healthy controls (ADHD: mean age 11.8 ± 0.4 years; controls: 11.6 ± 0.5). EEG recordings were sleep staged, subjected to semi-automatic artefact removal and processed using power spectral analysis. Mean SWA (1–4.5 Hz) was calculated for the first hour of NREM sleep. For statistical analysis mean SWA was calculated in a frontal and central cluster of 8–9 electrodes (fig. 1).

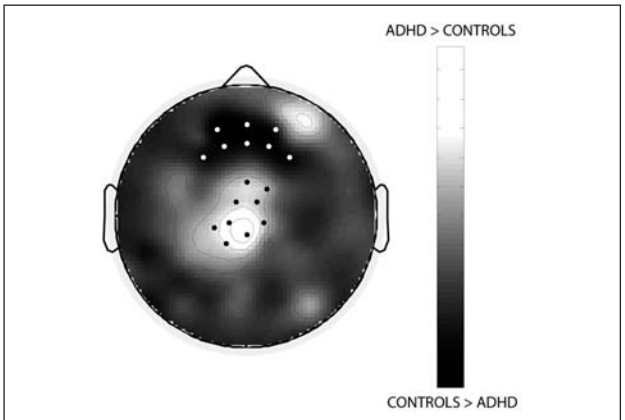

Fig 1: Differences in SWA topography between children with ADHD and healthy controls. Compared to controls children with ADHD showed higher SWA over central (mean ± SE: +12% ± 4%) and lower SWA (mean ± SE: -22% ± 7%) over frontal derivations.

Results: A comparison of the SWA topography of the first 60 minutes of NREM sleep revealed differences between the two groups: Compared to healthy controls children with ADHD showed more SWA over the central region (+12% ± 4%, $p = 0.004$) and less SWA over the frontal cortex (–22% ± 7%, $p = 0.02$) (fig. 1). No other area showed significant group differences.
Discussion: During cortical maturation maximal SWA shifts along the posterior-anterior-axis (Kurth et al., 2010). Thus, the major differences in SWA topography found in ADHD children depict a pattern typically seen in children of younger age. This pattern may well be due to a maturational delay. However, as major symptoms of ADHD include deficits in inhibitory control and motor hyperactivity the observed differences in topography could also reflect functional differences in the underlying areas.

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Transcriptional correlates of an in vitro model of sleep

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Introduction: Sleep is a vital function. However, the functions of sleep remain elusive. Although many theories have been proposed, none is accepted with large consensus.
Methods: To study and understand the function of sleep, we developed a model of sleep in vitro. In this study we investigated the molecular correlates of sleep: the transcriptional marker of sleep in vitro. For this purpose, we used dissociated cortical cultures harvested for 12–14 days in vitro until they matured in a sleep-like firing state. To mimic wakefulness, we used a physiological cocktail of excitatory neurotransmitters and analysed the transcriptome of waking-neurons versus sleeping neurons.
Results: Microarray data showed that stimulated cortical cultures have a highly similar gene expression pattern to that of the cortex of sleep deprived living animals. We also demonstrated that the homeostatic process of sleep can be reproduce in culture by a dose-response experiment.
Conclusion: In conclusion, we have shown that an in vitro neuronal assembly can nicely mimic sleep and wakefulness. Therefore, a major advantage of this in vitro model is to open up new avenues in investigating sleep at cellular and molecular levels.

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Vigilant attention in sleep-wake disorders measured with the psychomotor vigilance test

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Introduction: The Psychomotor Vigilance Test (PVT) is widely used in sleep research. However, little is known about PVT performance in patients suffering from sleep-wake disorders. We aimed at evaluating PVT as a clinical routine diagnostic tool in a sleep laboratory.
Methods: We analyzed PVT data of 356 patients and 67 healthy controls. Patients were diagnosed with one of the following sleep-wake disorders: narcolepsy with cataplexy (n = 14), behaviorally induced insufficient sleep syndrome (BIISS) (n = 69), hypersomnia (n = 61), fatigue (n = 38), sleep related movement disorder (SRMD) (n = 23), central and obstructive sleep apnea (n = 84), REM-sleep parasomnia (n = 33) and insomnia (n = 34). Every patient underwent a diagnostic work-up including polysomnography, actimetry, multiple sleep latency test (MSLT), Steer Clear and questionnaires. Control subjects were examined with PVT and questionnaires only. The following PVT outcomes were analysed: median reaction time, lapses (>500 ms), false starts (<100 ms) and variability (range between 10th and 90th percentile). We compared PVT results to standardized clinical tests of sleep and wakefulness, analyzed to which extent the influence of age, gender, major depression (n = 43) and Parkinson's disease (n = 30) is relevant on PVT results and whether PVT can be used to evaluate treatment effects (n = 26).
Results: We found highly significant differences in PVT results between patients and controls (table 1). We suggest the following cut-offs: 270 ms for median reaction time (sensitivity = 69%, specificity = 94%), 1 for lapses (sensitivity = 72%, specificity = 93%) and 120 ms for variability (sensitivity = 67%, specificity = 91%). There are significant influences of age, sex, major depression and Parkinson's disease on PVT. Women, older people and patients with comorbidities have worse PVT results. There was a correlation between PVT and Steer Clear, whereas correlations between PVT and MSLT/MWT were weak or absent. PVT might be used to elevate treatment effects, though measures a different aspect of vigilance than MWT.
Conclusion: We showed that PVT may be helpful in the diagnostic process of sleep disorders. This study is the first attempt to publish cut-offs for the distinction between normal and impaired vigilant attention measured with PVT. However, PVT results always must be interpreted in combination with other clinical findings and sleepiness tests and influences of gender, age and comorbidities must be taken into account.