

IPEG



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Abstracts

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Session 1: EEG in Drug Discovery and Development: turning curses to blessings

S1.1

What can we do to unleash the potential of EEG in drug development?

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Electroencephalography has significant potential for use in drug development. However, the use of EEG for decision-making within large pharmaceutical companies is comparatively rare. This talk will highlight the points in the drug development process at which EEG could be a valuable decision-making tool, discuss why it is not being used routinely and offer some suggestions as to what needs to be done in order to unleash fully the potential of EEG in drug development.

S1.2

EEG oscillations: A pragmatic translational measure of efficacy for drugs with antipsychotic and cognitive enhancing potential

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Synchronization of rhythmic neuronal activities also termed EEG oscillations within and across the brain regions is thought to be fundamental for brain function and dysfunction. Such synchronization is evident at the levels of pairs of neurons or large neuronal populations, and reflects the exact timing of communication between distant but functionally related neurons populations. Current theories highlight impaired EEG oscillations synchrony as a putative mechanism underlying neuropsychiatric disorders. EEG oscillations abnormalities of schizophrenia symptoms and cognitive impairment in human were pharmacologically modelled in rats by using the N-methyl-D-aspartate (NMDA) receptor and the muscarinic receptor antagonists, respectively. Subsequently, we examined the efficacy of marketed antipsychotics (APs) and cognitive enhancing drugs to reverse disruptions in EEG oscillations. Administration of NMDA antagonists particularly increased EEG oscillations in gamma frequency range, whereas APs commonly decreased EEG Alpha1 and higher gamma frequency oscillations in different cortical regions. Combined treatment with APs attenuated aberrant EEG oscillations induced in NMDA-treated rats. Cholinergic drugs, which are believed to enhance cognitive performance, induced systematic “fingerprint” i.e. concomitant enhancement in EEG theta1 and gamma1 frequency oscillations. When combined with muscarinic receptor antagonist, the cognitive enhancer drugs normalized the abnormal left-ward shift towards slow EEG oscillations. The efficacy of combined antipsychotics with NMDA antagonists and cognitive enhancers with muscarinic receptor antagonist-treated rats, respectively indicate the possibly important role of the glutamatergic and cholinergic system in the action of these antipsychotics and cognitive enhancers. Statistical methods such as coherence, directed transfer function or granger causality analysis are currently explored to investigate different aspects of synchrony, connectivity and the effective direction of coupling between different cortical areas. The integration of EEG oscillations approach into system biology framework is a major advantage to investigate functional organization of neuronal circuits at different levels i.e. local neuronal populations by means of local field potential, widely distributed neuronal networks by ongoing EEG field potential in conscious animals during specific brain state, behavioral performance in cognitive test, or during information processing of external auditory event (ERP and EROS). EEG oscillations abnormalities found in psychiatric disorders involving cognitive functions and modelled in rats, makes EEG oscillations a pragmatic tool to measure neural communication on different spatial scale. The method offers valuable quantitative markers, which has

the potential to support development of effective therapeutic treatment focused on pathophysiological mechanisms and cognitive dysfunction rather than symptoms.

S1.3

A re-evaluation of construct and predictive validity for rodent counterparts to the human MMN and P300 event related potentials (ERPs)

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The human MMN and P300 assess cortical network activations underlying cognitive operations related to sensory processing and memory updating. Both ERPs reveal specific impairments in neurologic and psychiatric disorders, and have strong potential value as objective neurophysiological diagnostic and treatment biomarkers in drug development. Their translational value in animal models is of course contingent on the degree of psychophysical, mechanistic and pharmacologic homology they show to the human potentials. We performed systematic evaluations of rodent auditory MMN and P300 ERPs in behaving rats with ECoG and deep electrode recordings, and stimulus / behavioral paradigms mirroring those used to elicit the human potentials. Our findings have revealed divergent conclusions for the MMN and P300 ERPs with respect to the construct and pharmacological correspondence they show to human counterparts. With regard to MMN, auditory oddball paradigms using frequency, duration and intensity deviants all revealed field potentials and unit responses in primary auditory cortex that mimicked a stimulus specific adaptation process, but did not encode novelty in a manner analogous to the human MMN. Likewise, pharmacological studies with NMDA antagonist, MK801, failed to specifically impair these responses to oddball stimuli, contrary to known effects of similar agents on human MMN. With regard to P300, a long latency ERP (70-300 ms) emerged when rats gained an operant behavioral discrimination of oddball auditory targets. Pharmacologically, this response was specifically abolished by scopolamine, and donepezil pretreatment partially prevented this block. Results thus provide face, construct and predictive validity for existence of a P300 homolog in the behaving rat.

S1.4

Evaluating for QEEG biomarkers across preclinical and clinical studies: experience with orexin antagonists

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Objective: EEG responses to CNS specific small molecule target engagement assists drug discovery but requires managing differences in species-unique sleep and quantitative EEG (qEEG) patterns. We assembled a clinical plus basic research team to find methods for best evaluating EEG responses across species by diligently aligning recording, experimental, analytic, and reporting practices. **Methods:** EEG data was captured telemetrically from 4 animal species and humans then processed and analyzed with nearly identical methods. Different cross-species evaluative measures were assessed to determine how to track qEEG changes resulting from compound dosing in each species. Compound dose responses were assessed using polysomnography, frequency band spectral analysis, entropy, and standardized effect size analysis across circadian cycles to learn how we can best track compound CNS effects across species. **Results:** Data alignment across species for an Orexin antagonist compound found frequency by frequency standardized effect sizes (specifically Hedges 'g') to be the most valuable translational method for comparing EEG responses to small molecules across experimental species. **Conclusions:** Standardized effect sizes (SES) by frequency revealed both dose responses within species and interesting between species differences in qEEG responses to compound

target engagement. Orexin antagonists had sleep effects that were consistent between species but qEEG responses revealed fascinating species differences although the qEEG responses were also dose responsive within species. qEEG use as a drug discovery biomarker tool benefits from evaluating frequency specific SES within and across experimental species.

Session 2: Influence of comorbidity and co-medication on QEEG in neuropsychiatry

S2.1

EEG LORETA in generalized anxiety syndrome with and without non-organic insomnia

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Purpose: Comorbidity is increasingly regarded as important for both diagnosis and treatment of psychiatric disorders. The aim of the present study was to compare EEG tomographic data obtained in generalized anxiety disorder (GAD) with and without nonorganic insomnia. **Methods:** In the first study, low-resolution brain electromagnetic tomography (LORETA) was performed in 44 untreated patients (25 females) with the primary diagnosis of nonorganic insomnia (F51.0) associated with GAD (F41.1) and 44 age- and sex-matched normal controls. In the second study, 18 patients (9 females) with the primary diagnosis of GAD without mandatory insomnia were compared with 18 controls. **Results:** While patients with F51.0 and concomitant F41.1 showed an increase in LORETA power in the delta, theta, alpha-1 and alpha-2 frequencies, GAD patients without mandatory insomnia demonstrated a decrease in LORETA power – specifically in delta (more left than right hemisphere, involving occipital cortex, insula, cingulate and frontal cortex) and beta (occipital cortex), mirroring neuroimaging findings on the neural circuitry of anxiety. **Conclusion:** Different EEG LORETA findings were obtained in GAD patients, depending on the comorbidity: While in daytime recordings patients with nonorganic insomnia demonstrated increased slow activities reflecting daytime tiredness and sleepiness, GAD patients without insomnia exhibited a decrease in slow activity and thus hypervigilance. According to the key-lock principle different pharmacological strategies have to be applied, which will be demonstrated on the basis our own data sets.

S2.2

Influences of co-medication on electrophysiological neuroimaging findings in Huntington's Disease

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Objective: Huntington's disease (HD) is an inherited neuropsychiatric disease that leads to progressive motor, cognitive and behavioural symptoms. Previous studies have shown abnormal electroencephalography (EEG) in HD, but no attention has been paid on possible pharmacological influences on electrophysiological findings. We compared quantitatively analyzed EEGs of HD patients and controls by means of EEG mapping and low-resolution brain electromagnetic tomography (LORETA) in order to reveal potential medication effects on the EEG in HD. **Methods:** The vigilance-controlled EEG of 20 drug-free and 35 medicated HD patients was compared with that of age- and sex-matched controls and visualized with mapping techniques. Furthermore EEG tomography was computed by LORETA in seven frequency bands and compared between groups. **Results:** Statistical analysis demonstrated significant differences between HD patients and controls. In HD patients a general decrease in total power, alpha and beta power and an increase in delta/theta

power was found. LORETA located an increase in delta power in pre-frontal cortical areas, and found a widespread decrease in theta, alpha and beta power. Significant differences between medical treated and drug-free patients were only found in the alpha variables. HD patients with medication (predominantly antipsychotics) showed a decrease of alpha power, a slowing of the dominant frequency and a slowed alpha centroid. **Conclusions:** The slowing of the EEG seems to be the most prominent neurophysiological feature of HD. Sedative antipsychotics have an influence on the alpha variables, but EEG abnormalities in HD seem to be so strong that psychotropic drugs do not affect the overall interpretation of the quantitative EEG differences between HD patients and controls.

S2.3

LORETA, atypical antipsychotics and schizophrenia

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The aim of our study was to detect changes in the distribution of electrical brain activity in schizophrenic patients who were antipsychotic naive and those who received treatment with clozapine, olanzapine or risperidone. We included 41 subjects with schizophrenia (antipsychotic naive = 11; clozapine = 8; olanzapine = 10; risperidone = 12) and 20 healthy controls. Low-resolution brain electromagnetic tomography was computed from 19-channel EEG for the frequency bands delta, theta, alpha-1, alpha-2, beta-1, beta-2 and beta-3. We compared antipsychotic-naive subjects with healthy controls and medicated patients. (1) Comparing antipsychotic-naive and controls we found a general increase in the delta and theta over the fronto-temporo-occipital cortex, particularly in the temporolimbic structures, an increase in alpha-1 and alpha-2 in the temporal cortex and an increase in beta-1 and beta-2 in the temporo-occipital and posterior limbic structures. (2) Comparing patients who received clozapine and antipsychotic naive, we found an increase in delta and theta in the anterior cingulate and medial frontal cortex, and a decrease in alpha-1 and beta-2 in the occipital structures. (3) Comparing patients taking olanzapine with antipsychotic naive, there was an increase in theta in the anterior cingulum, a decrease in alpha-1, beta-2 and beta-3 in the occipital cortex and posterior limbic structures, and a decrease in beta-3 in the frontotemporal cortex and anterior cingulum. (4) In patients taking risperidone, we found no significant changes from antipsychotic naive. Our results in antipsychotic-naive patients are in agreement with existing functional findings. Changes in those taking clozapine and olanzapine versus those who were antipsychotic naive suggest a compensatory mechanism in the neurobiological substrate for schizophrenia. The lack of difference in risperidone patients versus antipsychotic-naive subjects may relate to its different pharmacodynamic mechanism. This research was supported by the grant NR8792 from the Grant Agency of the Ministry of Health, the Czech Republic and by projects 1M0517 and VZ 0021620816 from the Ministry of Education, Youth and Sports, the Czech Republic.

Plenary lecture 1: EEG neuroimaging: from localization to distributed patterns of function via generalized connectivity analysis

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Objective: EEG recordings contain relevant information about brain function and state. The difficulty with these measurements is that the information is not explicitly available in the scalp electric potential differences. Over the years, methods of analyses have been developed to aid in extracting essential information. For this purpose, we present a method for calculating cortical electric neuronal activity distributions from EEG measurements. This can be used for functional localization, as in classical neuroimaging; but more importantly, it provides non-invasive intracranial recordings for the assessment of dynamic functional connectivity. We present a method for assessing connectivity between pairs of brain regions, and also methods of a distributed type that uncover directional connections and generalized intra-cortical cross-frequency interactions. **Methods:** Exact low resolution brain electromagnetic tomography (eLORETA) is presented. This method is used for the calculation of the cortical current density distribution, providing intracranial signals for connectivity analysis. Two components of oscillatory connectivity are calculated: time-lagged and simultaneous. Distributed connectivity analysis is based on the singular value decomposition (SVD-link). When SVD-link is applied to time series and their lagged versions, directional connections are revealed. When applied to spectral power over the cortex (i.e. a function of space and frequency), cortico-cortical cross-frequency interactions are revealed. **Results:** Using visual, auditory, and somatosensory evoked responses obtained from different laboratories, eLORETA is shown to correctly localize function in the primary and secondary sensory cortices. In two independent data sets consisting of resting state, eyes-closed, awake EEG, a generalized distributed connectivity analysis showed that in older subjects compared to younger subjects, decreased occipital alpha activity was concurrent to increased frontal beta activity. **Conclusions:** Evidence is given here for the validation of the eLORETA method in terms of functional localization. Unfortunately, there does not exist experimental data that can be considered as a gold standard for testing connectivity. Nevertheless, the resting state comparison of older to younger subjects revealed connectivity differences that agree with current aging hypotheses.

Session 3: Oral communications 1

S3.1

Evaluation of Aripiprazole effects in schizophrenia using BRL-sLORETA norms: a preliminary study

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Objective: The aim of this study was to make an evaluation of the effects induced by the drug aripiprazole in patients suffering schizophrenia. This was based on a comparison to the normative EEG data base from the NYU Brain Research Laboratories, which has recently been extended to age-dependent “default-mode” cortical electric neuronal activity using standardized low resolution electromagnetic tomography (sLORETA). **Methods:** Resting state EEG was recorded from two schizophrenic patients before and after administration of aripiprazole. The sLORETA software from the Zurich-KEY Institute was used for analysis. The cortical distribution of the generators of oscillatory activity for classical frequency bands were computed and statistically compared to the age-corrected normal values based on 139 normal controls (NYU BRL norms). **Results:** In one patient, a significant excess of slow wave delta activity was found in right temporal-frontal areas before treatment. After three weeks treatment a trend towards normality was observed. Incidentally, this patient was at the same time being treated with benzodiazepines, showing a characteristic focus of fast beta in cingulate cortex. The second patient showed excess occipital delta and decreased parahippocampal beta generators after four weeks, Treatment produced a slight change towards normality for slow wave activity, but a very slight worsening of beta. Correspondingly, the total PANSS score for the first patient and the second patient decreased by 12.7% and 10.9%, respectively. **Conclusions:** These very preliminary results illustrate how powerful this method of analysis can be in

providing useful information that potentially has direct impact in clinical use of aripiprazole. In particular, our future goal is to routinely use these techniques and to test if the method is capable of predicting which drug therapy will be effective.

S3.2

Investigation of effects of benzylphenylpiperazine, trifluoromethylphenylpiperazine and dexamphetamine on the event-related P300 in humans

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Benzylphenylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP) are designer drugs marketed as a safe and legal alternative to MDMA and methamphetamine. Clinical studies reported humans who consumed BZP and TFMPP experienced amphetamine-like physiological (e.g. an increase in blood pressure/ heart rate) and subjective effects (e.g. increased feelings of High, Drug liking, Euphoria, and Stimulation). We investigated the effects of BZP and TFMPP on central information processing, by analysing the event-related potential P300, during an auditory odd-ball task. Healthy, right-handed males (25 ± 5.6 years old) were given an oral dose of either placebo ($n=15$), TFMPP (60mg, $n=13$), combined BZP and TFMPP (100/30mg, $n=18$) or dexamphetamine (20 mg), as a positive control ($n=16$). Subjects were tested pre- and 2 hr post-drug administration.

After administration of either TFMPP or dexamphetamine, the P300 amplitude was significantly reduced ($F(1,26) = 3.995$; $p<0.05$, $F(1, 29) = 4.881$; $p<0.05$). However placebo or combination of BZP/TFMPP did not affect the P300 amplitude. The P300 latency was not affected by all four treatments. The results demonstrate that TFMPP and dexamphetamine reduce the components involved in attention allocation and immediate memory processing.

This study demonstrates for the first time that TFMPP, but not the combination of BZP/TFMPP, reduces P300 amplitude in a manner similar to our positive control dexamphetamine. We have previously reported that BZP reduced the P300 amplitude in humans. This suggests that when BZP or TFMPP are given separately they elicit dexamphetamine-like effects on central information processing, suggesting that their effects on cognitive processes may be similar.

S3.3

Cordance as a biomarker in sleep-EEG for depression: differences in responders versus non-responders - a naturalistic study after antidepressant medication

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Objective: Cordance is a relatively new quantitative EEG-method, which has shown usability as a biomarker for depression within the resting-state in wake patients. Sleep EEG shows distinctive alterations in a depressive episode and changes after antidepressants. We wanted to test whether differences in Cordance derived from sleep EEG exist between responders and non-responders after antidepressant medication. **Methods:** 21 in-patients with a depressive episode [ICD-10 F 31.4, F 32.1-3, F 33.1-3] were treated with various antidepressants of “doctor’s choice”. The change of the Hamilton depression scores between the first and fifth week of treatment provided evidence about response. Response to treatment was defined as a $\geq 50\%$ reduction of Hamilton score. Cordance values for the prefrontal theta-EEG were calculated from sleep EEG during the first week with active medication. **Results:** Results showed significant differences: 9 responders compared to 12 non-

responders showed higher Cordance values in prefrontal EEG-sites (z -score $-1,76 \pm 0,92$ versus $-2,71 \pm 0,64$, $p = 0,023$). **Conclusion:** These results suggest that Cordance derived from sleep EEG provides a biomarker for depression.

Session 4: EEG Based Personalized Medicine

S4.1

Vigilance regulation and response to psychostimulants in affective disorders

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Major Depression as the most important unipolar depression and Bipolar Affective Disorders with manic and depressive episodes are severe and prevalent disorders. Depressive episodes are characterized by depressive mood, withdrawal, sensation avoidance and sleep disturbances. Manic episodes within bipolar affective disorder are characterised by elated mood, talkativeness, hyperactivity, sensation seeking and reduced sleep need. The vigilance model, a recently proposed theory on the pathogenesis of affective disorders (Hegerl et al., 2009), attributes an important pathogenetic role to the regulation of vigilance. Vigilance stages indicate different global functional brain states (arousal states) and can be discriminated with respect to distinct EEG features. Switches between vigilance stages are not only observable in the transition between alert wakefulness and sleep onset but happen continuously throughout wake state (Hegerl et al., 2008). The precise regulation of vigilance and its adaptation to the environment are of primary importance for all higher organisms. The proposed model takes into account that individuals can select and create more or less stimulating environments depending on their level and regulation of vigilance. An unstable vigilance regulation with rapid drops to lower vigilance stages and even microsleeps within the first minutes of resting EEG is an established finding in manic patients. Within the presented explanatory model, manic behaviour is interpreted as an autoregulatory attempt to stabilize vigilance by increasing external stimulation. This concept explains the unsatisfactory effects of sedating drugs and the paradoxical rapid antimanic effect of psychostimulants repeatedly reported in case reports (reviewed in Hegerl et al., 2009). Concerning major depression, a part of the depressive symptomatology such as withdrawal and sensation avoidance is interpreted as an autoregulatory reaction to states of tonic hyperarousal. In line with this, treatment trials with stimulants have yielded mainly negative outcomes in major depression.

References:

Hegerl U. et al. (2008): *Eur Arch Psychiatry Clin Neurosci.* 258(3): 137-143.

Hegerl U. et al. (2009): *Pharmacopsychiatry.* 42(5): 169-174.

S4.2

EEG-based assessment of vigilance regulation in major depression and cancer-related fatigue

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Background: Both, patients suffering from a major depressive episode (MDE) and patients with a cancer-related fatigue (CRF) syndrome report about increased sleepiness and tiredness. It remains unclear, however, whether such complaints are associated with neurophysiological signs of sleep proneness or, in the contrary, with a state of neurophysiological hyperarousal with difficulties to relax and to initiate sleep. A differentiation between both conditions seems useful, since a hyperstable vigilance regulation would fortify different treatment options than an unstable vigilance regulation. Therefore the goal of these two studies was to analyze the electroencephalographic (EEG)-vigilance regulation during rest in MDE and CRF in comparison to healthy controls. **Methods:** Study I included

30 unmedicated patients with MDE (19 female; mean age: 37.2 years) and 30 healthy controls (19 female; mean age: 37.3). Study II included 22 Patients (17 female, mean age 48.8 years) with CRF and 22 healthy controls (16 females, age 47.4 years). In both studies, subjects underwent a 15-minute resting-EEG with closed eyes. Consecutive 1-second EEG-segments were classified into six vigilance stages ranging from alertness after closing the eyes (stages A1, A2, A3) to drowsiness (stages B1 and B2/3) until sleep onset (stage C) using a computer-based vigilance classification algorithm (VIGALL, Vigilance Algorithm Leipzig). **Results:** Depressed patients in study I spent significantly more time in vigilance substage A1 ($p = .005$), and less time in lower substages A2, A3 and B2/3 ($p < 0.001$) than controls. Depressed patients also spent a significantly longer undisturbed time in substage A1 ($p = .001$), needed more time to achieve the substages A2, A3 and B2/3 ($p = .000$) and showed less switches between substages than controls ($p = .001$). Study II revealed that CRF patients spent significantly more time in substage A3 ($p = .004$), reached lower substages A3 ($p = .000$) and B2/3 ($p = .032$) earlier and revealed significantly increased amounts of switches between vigilance stages ($p = .003$) in comparison to healthy controls. **Conclusion:** These results support the vigilance theory of affective disorders linking a hyperstable vigilance regulation to depression. Patients with CRF, however, showed faster EEG-vigilance declines in comparison to healthy controls. These findings suggest an unstable vigilance regulation in patients with CRF and provide a physiological framework for the reported effectiveness of psychostimulants in CRF.

S4.3

The change of prefrontal QEEG cordance as a predictor of response to antidepressant treatment

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Background: A considerable body of research supports the assertion that antidepressant medication effects are physiologically detectable in the EEG. QEEG cordance is a new quantitative EEG measure that combines complementary information from absolute and relative power of EEG spectra. Previous studies of patients with unipolar depression have shown that decreases in prefrontal theta band (4-8 Hz) cordance 1 week after start of antidepressant medication have predicted clinical response with overall accuracy ranging from 72% to 88%. The aim of this study was to evaluate the efficacy of QEEG cordance in the prediction of response to various antidepressants in patients with resistant depression. **Methods:** A total of 81 inpatients (52 females) with depressive disorder (Montgomery-Åsberg Depression Rating Scale; MADRS \geq 20) who previously did not respond to at least one antidepressant treatment were treated with various antidepressants for 4 weeks. EEG data were monitored at baseline and after one week. QEEG cordance was computed at 3 frontal electrodes (Fp1, Fp2, Fz) in theta frequency band (4-8 Hz). Depressive symptoms were assessed using MADRS and response to treatment was defined as a \geq 50% reduction of MADRS score. **Results:** There were no baseline differences in demographic and clinical parameters between responders and nonresponders. 29 from 33 responders and 14 from 48 non-responders decreased prefrontal QEEG cordance value after the first week of treatment (X^2 , $p=0.0001$). There was a difference between responders and nonresponders in the change of cordance value after 1 week of treatment ($p=0.002$). Positive and negative predictive value of cordance reduction for response to treatment was 0.67 (95% CI, 0.58-0.73) and 0.90 (95%CI, 0.79-0.96), respectively. The overall accuracy of the test was 0.78 (95% CI, 0.68-0.83) and the effect size estimated from this sample ($w = 0.59$) was in large range. **Conclusion:** Early change in prefrontal theta band cordance probably reflects a common underlying mechanism of antidepressant effect, regardless of the type of treatment. Prefrontal cordance may provide a useful biomarker for the early detection of response to antidepressant therapy. **Acknowledgement:** This study was supported by projects of The Ministry of Education, Youth and Sports of the Czech Republic No.1M0517 and MSM0021620816.

S4.4

An investigation of EEG, genetic and cognitive markers of treatment response to antidepressant medication in patients with major depressive disorder: A pilot study

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In this study we investigated if biomarkers in QEEG, genetic and neuropsychological measures are suitable for the prediction of antidepressant treatment outcome in depression. Twenty-five patients diagnosed with major depressive disorder were assessed twice, pretreatment and at 8-wk follow-up, on a variety of QEEG and neuropsychological tasks. Additionally, cheek swab samples were collected to assess genetic predictors of treatment outcome. The primary outcome measure was the absolute decrease on the HAM-D rating scale. Regression models were built in order to investigate which markers contribute most to the decrease in absolute HAM-D scores. Patients who had a better clinical outcome were characterized by: 1) A decrease in the amplitude of the Auditory Oddball N1 at baseline. 2) The 'Met/Met' variant of the COMT gene. 3) Impaired verbal memory performance. 4) Raised frontal Theta power. A tentative integrative model demonstrated that a combination of N1 amplitude at Pz and verbal memory performance accounted for the largest part of the explained variance. This study demonstrated that there is added value of using an integrative approach combining measures from various domains (EEG, Neuropsychology, ERP, Genetics). These markers may serve as new biomarkers suitable for the prediction of antidepressant treatment outcome. However, replication of these results is warranted given the low sample size. Currently the largest international biomarker study in depression to date, enrolling 2000 depressed patients is collecting such integrative data to further replicate these findings (the iSPOT-D trial).

Session 5: Event-related potentials as a biomarker for cognitive deficits in schizophrenia and medication effects

S5.1

ERP studies in healthy controls and cognitive effects of antipsychotics

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Background: Event-Related Potentials (ERPs) provide a functional measure of electrical brain activity time-locked to discrete stages of information processing. They have been widely used as putative biological markers of cognitive abnormalities in schizophrenia. The N1 and P3 ERP components are of particular interest since they were found to present a double dissociation in deficit and non-deficit forms of schizophrenia, indicating different cognitive profiles in patients with and without primary and enduring negative symptoms (Mucci et al. 2007). The present study investigated the effect of risperidone and haloperidol on N1 and P3 using a randomized, placebo-controlled, cross-over design in male healthy subjects. **Methods:** ERPs were recorded from 30 unipolar leads (0.5-70 Hz bandpass, 256 Hz sampling rate), during a three-tone oddball task in which target, standard and rare-nontarget tones were randomly presented. Subjects had to press a button when hearing a target tone. Amplitude maps were compared across conditions. If a significant drug effect was obtained, changes in the cortical sources of the corresponding ERP components were analyzed using Low-Resolution Electromagnetic Tomography (LORETA). **Results:** The amplitude of N1 for attended stimuli and of P3a was significantly increased only by risperidone. No significant change was observed in overall topographic features and in LORETA cortical sources of the same components. No significant drug effect was demonstrated for the latency of all the investigated components and for P3b

amplitude. **Conclusions:** These findings suggest a favourable effect of risperidone on early attention processes and automatic attention allocation. Relevance of this findings to research in patients with schizophrenia will be discussed in the light of possible underlying neurobiological mechanisms.

Reference:

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S5.2

LORETA imaging of event-related potentials to evaluate cognitive impairments of schizophrenia and effect of psychotropic drugs

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There is considerable evidence for associations between social functioning/community outcome and cognitive function, as evaluated by neuropsychological tests, such as the MATRICS Consensus Cognitive Battery, in patients with schizophrenia [1]. Therefore, neural substrates underlying impaired cognitive performance need to be elucidated. While brain imaging methods based on blood flow, e.g. functional magnetic resonance imaging and positron emission tomography, are characterized by high spatial resolutions, their time resolutions are limited compared to neurophysiological paradigms, e.g. electroencephalography (EEG) and magnetoencephalography. Specifically, electrophysiological biomarkers, such as EEG and event-related potentials (ERPs), have been suggested to provide objective indices of cognitive dysfunction in schizophrenia, and be more sensitive to drug-induced changes compared with other functional imaging modalities [2]. Recent development of imaging technique, such as low resolution electromagnetic tomography and its modified versions, has improved the spatial resolution of ERPs, e.g. P300 and mismatch negativity (MMN), by providing three-dimensional distribution pattern of these electrophysiological activities. The speaker will present findings from electrical neuroimaging studies of schizophrenia and treatment response [3-5] and discuss: 1) neural basis for psychopathology of schizophrenia as demonstrated by current source imaging of P300; and 2) P300 and MMN indices in discrete brain areas and response to psychotropic drugs in relation to cognition and QOL. These research directions are likely to facilitate the development of novel therapeutic strategies to maximize long-term outcome in people with schizophrenia or related disorders.

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S5.3

Event-related potentials as a biomarker for cognitive deficits in schizophrenia and effects of medication

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In addition to dopaminergic hypothesis of schizophrenia, currently both GABA-ergic and glutamatergic influences are recognized as equally important in the genesis and development of this disease. This recognition changes the approach of schizophrenia treatment and suggests using add-on therapies, such as glutamate [1]. The MMN and P300 cognitive brain event-related responses are shown to be abnormal in schizophrenia [10]. Typical antipsychotics seem to have no effects on these

responses [2]. The effects of atypical antipsychotics on P300 appear to be present, however, not consistent [3,6]. No effects of antipsychotics on MMN are observed [5]. In contrast, recent studies with glutamate therapies show significant improvement in MMN parameters [9] in schizophrenia patients. We explain these findings through neurochemical modulation of MMN and P300 responses, with MMN mainly sensitive to changes in glutamate [8] and GABA [4], and with low sensitivity to dopaminergic modulation [7]. These findings imply possibility to use MMN response as a marker for cognitive changes, associated with the effect of pharmacological treatment on glutamatergic and GABA-ergic neurotransmission.

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Plenary lecture 2: QEEG Source Localization of the "Pain Matrix"

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Introduction: For many years researchers have used functional neuroimaging to study the neuronal basis of pain and pain perception and have demonstrated that painful stimulation elicits activity in extensive areas of cortical and subcortical brain regions, the "pain matrix". A meta-analysis of PET and fMRI studies report increased rCBF and metabolism consistent with increased neuronal activation in the structures comprising the "pain matrix" in chronic pain. This matrix includes the secondary somatosensory (SII), insula, anterior cingulate (ACC), posterior parietal and prefrontal cortices.

Design/Outcome Measures: EC resting EEG was recorded in 5 patients with chronic neuropathic pain at baseline in a high pain state and again after pain reduction of at least 50%. QEEG source localization was computed for estimating the mathematically most probable source generators of EEG surface potentials. **Results:** Increased neuronal activity was observed in the baseline high pain state (subjectively rated as moderate to severe) in structures of the pain matrix including somatosensory cortices, thalamus, anterior and posterior insula cortices, medial and lateral prefrontal cortices and cingulate. Significant reduction of activation in these regions was seen when pain was reduced (rated as none or mild). **Conclusions:** The areas which were activated localized to the same regions reported by other neuroimaging methods and with frequency specificity. The frequency and regionally specific activation may indicate distinctive patterns of pathophysiology underlying the pain matrix. Although in a small number of patients, this work suggests that QEEG may be useful in exploration and quantification of the pain matrix in a clinical setting.

Session 6: Oral communications 2

S6.1

On the duration and processing of pharmaco-EEG recording

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Quantitative EEG is a sensitive method used to assess the effects of pharmacological substances on the central nervous system (CNS). A standard technique is to measure the EEG under vigilance-controlled (RT) and resting (RS) conditions. The aim of the present study was to investigate the stability of 5-min EEG recordings. While the time course of the EEG was fairly stable during the RT recording sessions, systematic trends became apparent under RS condition. Pharmacology-sensitivity of the EEG and its reliability increased with the recording duration. Five minutes of EEG recording seem to be sufficient and well chosen to evaluate the influence of drugs on the EEG.

S6.2

Benzodiazepine effects on EEG connectivity: linear and nonlinear couplings

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Background: Quantitative analysis of human electroencephalogram (EEG) is a valuable tool for evaluating pharmacokinetics and pharmacodynamics CNS compounds. Although the effects of different agents on EEG spectra are quite well known, interactions between brain locations remain unclear. Objective: To evaluate the pharmacological effects of alprazolam (1mg) on brain connectivity during wakefulness in healthy volunteers (n= 9) using a cross-over, placebo-controlled design.

Methods: Eighty-five pairs of EEG leads were selected for the analysis, and connectivity was evaluated inside anterior, central, and posterior zones of the scalp. Connectivity between these zones and interhemispheric connectivity were also measured. Cross mutual information functions and appropriate surrogate data were applied to assess linear and nonlinear couplings between EEG signals.

Results: Alprazolam induced significant changes in EEG connectivity in terms of information transfer in comparison with placebo. Trends were opposite depending on the statistical characteristics: decreases in linear connectivity and increases in nonlinear couplings. These effects were generally spread over the entire scalp. Linear changes were negatively correlated ($r^2= 0.686$), and nonlinear changes were positively correlated ($r^2= 0.970$) with drug plasma concentrations. **Conclusions:** The use of both linear and nonlinear approaches revealed the importance of assessing changes in EEG connectivity as this can provide interesting information about psychopharmacological effects.

S6.3

EEG source analysis in obsessive-compulsive disorder

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Functional neuroimaging studies provide evidence for medial frontal cortical hyperactivation in obsessive-compulsive disorder (OCD). Quantitative electroencephalographic (EEG) studies confirmed abnormal activity over frontal regions in OCD, however, there is only limited knowledge about its generators. The goal of this study was to assess the activity of intracortical EEG sources in patients with OCD. We compared resting EEG from 50 OCD patients and 50 matched controls using

standardized low-resolution tomography (sLORETA) and independent component analysis (ICA). Data were analyzed with 1 Hz frequency resolution. ICA was used to separate 7 independent components from the control group data. The resulting weights and norms served to derive the same components from the OCD group and to compare their power with controls. In OCD, sLORETA indicated low-frequency power excess (2–6 Hz) in the medial frontal cortex. ICA comparison showed increased low-frequency power in a component reflecting the activity of subgenual anterior cingulate, adjacent limbic structures and to a lesser extent also of lateral frontal cortex. Both the voxel-based (sLORETA) and source separation (ICA) approach provide evidence for medial frontal hyperactivation in OCD. Our study is the first to use normative ICA in a clinical sample and indicates its potential utility as a diagnostic tool. The findings provide consistent results based on EEG source localization in OCD and are of practical interest for therapeutic interventions such as neurofeedback. Acknowledgement: This work was supported by the grant NS9751-3/2008 provided by the Ministry of Health of the Czech Republic.

Session 7: NMDA antagonists in the animal and human models of psychosis

S7.1

Comparison of animal and human EEG findings in glutamatergic models of psychosis

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Ketamine is widely used as a glutamatergic model of psychosis. In animals, ketamine induces deficits in prepulse inhibition (PPI) of acoustic startle reaction, however human data are inconsistent. The effect on EEG spectra and coherence has yet to be studied in comparable conditions in these models. Thus, we have compared EEG spectra and coherence in humans and in rats treated with NMDA antagonist ketamine and in rats treated with MK-801. Animal experiments were carried out on male Wistar rats, with ketamine 30 mg/kg i.p. or MK-801 0.3 mg/kg i.p. being used. During EEG registration (12 active electrodes) passive and active behavior was co-registered in the rats. EEG recordings in humans were obtained from 20 healthy subjects under resting conditions in a placebo/ketamine randomized design. Ketamine was applied i.v. at the dose of 0.54 mg/kg within 30 min. EEG power spectral analysis and EEG coherence from both experiments were calculated using Neuroguide Deluxe software (in rats only from parts corresponding to passive behavior). EEG spectral analysis showed an increase in absolute power in high beta and gamma bands in rats after ketamine and MK-801 and further a decrease in theta and beta power after MK-801. In humans, an increase in the power in theta, high beta and gamma, while a decrease in delta, alpha and beta bands was observed. EEG coherence was decreased throughout the spectrum in rats in both models. In humans there was a decrease in coherence in alpha and beta bands and an increase in all other bands. Our results show that glutamatergic models revealed several similarities in EEG findings both in animals and humans. These data indicate that EEG quantitative analysis of EEG epochs that corresponds to passive behavior is a relevant translational approach to studying changes in these models of psychosis. This work is supported by projects IGA MHCR NS-10374-3, NS-10375-3, CNS MEYS 1M0517 and MZ0PCP2005.

S7.2

The Ins and Outs of Ketamine Model of Schizophrenia: QEEG and fMRI Study in Healthy Volunteers

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Rationale: The glutamatergic hypothesis postulates that the N-methyl-D-aspartate (NMDA) receptor hypofunction results in the schizophrenia symptoms. With respect to this hypothesis ketamine, the non-completive antagonist of NMDA is used to model schizophrenia in animals and in humans as well. The aim of our placebo-controlled study was to detect the changes in brain electrical activity following ketamine administration to healthy volunteers by means of standardized low-resolution brain electromagnetic tomography (sLORETA) and functional magnetic resonance (fMRI). **Methods:** EEG recordings were obtained from 20 healthy subjects during resting condition in the placebo/ketamine randomized design. Ketamine was applied i.v. in the dose of 0.27 mg/kg within first 10 min, followed by a maintenance infusion of 0.27 mg/kg/h for 20 min. The intracerebral current density distribution was computed from spectrally analyzed data (at baseline and 10 and 20min after administration) by means of sLORETA. The localization of the differences in source distribution was assessed by voxel-by-voxel paired t-tests of sLORETA images of the log-transformed current density power in eight frequency bands. In the second experiment, the effect of intravenous ketamine on blood oxygenation level-dependent (BOLD) signal was measured in the group of 11 healthy volunteers. The imaging began 5 minutes before infusion and continued for a further 30 minutes (scanner: 3T Siemens Trio, ISI: 3s, isovoxel: 2 mm, smoothing: 10 mm). For the SPM5 analyses we used the „pseudoblock“ design: 5 minutes intervals before infusion were compared with 5 min. intervals throughout the infusion of ketamine or placebo. In the 2nd level analysis, the contrasts from previous steps were compared with placebo (paired t-test, $p \leq 0.01$ with FDR correction). **Results:** Significant decrease of magnitude of alpha-1 and alpha-2 sources over posterior cortical regions were observed for both time intervals after ketamine administration compared to the baseline values. Further, the decrease of magnitude of beta-1 and beta-2 sources was observed in the posterior cingulate and precuneus. Cortical beta-3 and gamma sources significantly increased mainly in the cingulate and parahippocampal structures and over the right frontotemporal cortical regions. No significant differences were found in placebo condition. In fMRI, ketamine induced increase of BOLD in a large cluster consisting of 2524 voxels in the right temporal lobe (superior temporal gyrus and insula) and in lesser extend also in the left temporal cortex. **Conclusions:** In congruence with previous studies we observed the involvement of heteromodal association cortex and limbic structures in the neurophysiological effects elicited by ketamin. We confirmed that the NMDA antagonism increases activity in temporal and cingulate regions. The alteration in temporo-cingulate network would be responsible for the deficit of information processing in schizophrenia and ketamine model of this psychosis as well. **Acknowledgement:** This work was supported by the grants IGA MZ CR No. NS9751-3/2008 and NS10379-3/2009, and project 1M0517 MSMT CR.

Session 8: New approaches in the preclinical pharmacoEEG research

S8.1

Neurophysiological signals as translational biomarkers: reverse translation of endophenotypes

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Objectives: Recent advances in neurophysiological techniques provide new opportunities to measure abnormal brain functions in patients with psychiatric disorders. These pathophysiological markers, called endophenotypes show heritability, and could be linked to genetic variants. **Methods:** Recordings were carried out in both anaesthetized and non-anaesthetized rats. Auditory sensory gating and field potential oscillations were recorded from the hippocampus, the endocrinal and medial prefrontal cortices. Auditory evoked steady state oscillations and mismatch negativity were recorded

from the temporal cortex. NMDA receptor dysfunction was induced by NMDA receptor antagonists during which cortical and hippocampal network oscillations and short-term plasticity were monitored. **Results:** NMDA receptor antagonist ketamine, GABAA receptors negative allosteric modulator FG-7142, dopamine-releaser amphetamine and cannabis-1 receptor agonist CP-55940 all disrupted auditory gating, although through different mechanisms. Furthermore, hippocampal and cortical oscillations were impacted differently: antagonism of NMDA receptors disrupted theta oscillations and induced aberrant gamma oscillations, cannabis-1 receptor agonist diminished theta and gamma oscillations, meanwhile amphetamine and FG-7142 enhanced cortical and hippocampal oscillations. NMDA receptor antagonists diminished short-term plasticity in parallel to the disruption of regular delta oscillation in anaesthetized rats. **Conclusions:** Our findings demonstrate that a diversity of psychogenic compounds disrupt auditory gating, although they induce disruption of information-processes via different mechanisms, and alter neuronal network oscillation in dissimilar ways.

S8.2

Behavioral and quantitative EEG changes in serotonergic and dopaminergic models of psychosis

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Background: To-date there is no data available on quantitative EEG from simultaneous recording of multiple cortical electrodes in rats in pharmacological models of psychosis that could be comparable to human data. Thus, we have recorded cortical EEG in freely moving rats in dopaminergic and serotonergic models of psychosis. In addition to classical EEG spectral analysis we have also concentrated on the measurement of brain functional connectivity - EEG coherences. Behavioral parameters - locomotor activity and prepulse inhibition (PPI) of acoustic startle reaction were also analyzed in these two models. **Methods:** Male Wistar rats, b.w 200 – 300g were used in all experiments. Locomotion was registered via the automatic video tracking system EthoVision Color Pro v. 3.1.1. Measurement of PPI was performed in a SR-LAB startle chamber. For the EEG study, rats were stereo-tactically implanted with 14 silver electrodes (6 pairs homolaterally). EEG was recorded using a 21-channel BrainScope amplifier system and analyzed with Neuroguide Deluxe software v. 2.3.7. Amphetamine (1 and 4 mg/kg) and 4-bromo-2,5-dimethoxyphenethylamine (2C-B) (10 and 50 mg/kg) were used in the behavioral experiments. **Results:** Both drugs were behaviorally active and produced hyperlocomotion and/or deficits in the PPI. Spectral analysis revealed an increase in theta and alpha and a decrease in beta power after amphetamine. On the contrary, 2C-B induced mainly a decrease in beta-gamma power and a slight increase in theta power. EEG coherences were mainly increased in the amphetamine model but in the 2C-B model both increases as well as decreases of coherence were observed. **Conclusions:** Both drugs in doses that are behaviorally active produced specific EEG changes in rats. The most remarkable finding was that the hyperlocomotor effects of the drugs were present along with an increase in theta power. The increase in connectivity also may have corresponded to locomotor changes induced by these drugs. **Acknowledgement:** This work is supported by projects IGA MHCR NS-10374-3, NS-10375-3, CNS MEYS 1M0517 and MZ0PCP2005.

S8.3

Orchestration of hippocampal memories by local theta oscillation

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Memories are considered to be attractor states of neuronal representations. In the hippocampus, the activity of pyramidal neurons (place cells) is strongly modulated by the subject's position, forming a spatial representation of the environment that is believed to be an element of episodic memory. We have very limited knowledge about the temporal structure of memory processing at the level of

neuronal population. In particular, detailed process of memory activation and switch between different representations is poorly described. The presented project focuses on the transitions between hippocampal memories in rats and their attractor network dynamics in high temporal resolution. Using parallel recording of large ensembles of hippocampal units, we show the basic patterns of transitions between representations on the population level - their sharp switching, transitory flashbacks from the current state into the previous one resembling the episodic recalls, and finally periods of mixed states between the distinct memories. The dominating theta oscillation in the local EEG is shown to control for separation between the competing representations suggesting to provide a temporal quantum unit for expression of the given memory state.

Poster Session

P1

Initial validation of a multiarray pain model optimizing the evaluation of analgesic drugs in healthy volunteers

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The aim of this double-blind, placebo-controlled, crossover study was to validate a cutaneous pain model combining the simple thermal pain model with UV erythema and topical capsaicin, in twenty healthy volunteers. This was conducted after optimising each of the test conditions in preliminary studies, not reported here, which compared sites on the body, concentration of capsaicin, thermal testing condition and the combination with UV-induced erythema. The primary outcome was pain detection threshold to heat (PDT). The effects of single oral doses of ibuprofen (400 mg), morphine slow release (30 mg) and pregabalin (300 mg) were assessed on normal skin and inflamed skin. Compared with placebo, both pregabalin and morphine significantly increased PDT in normal skin and both pregabalin and ibuprofen reduced primary hyperalgesia induced by UV insulation. The lack of effect of morphine in the latter condition suggests that the UV insulation condition is only sensitive to high doses of opiates. All these drugs failed to improve capsaicin-induced heat hyperalgesia as set-up here and can be explained by the fact that a specific TRPV1 mechanism mediating the primary hyperalgesia induced by capsaicin was at play. Subsequently this may be a TRPV1 selective measure while other acute and inflammatory pain conditions are sensitive to more agents. Despite some limitations, this model presents several advantages: good face validity, high within subject stability, easy and rapid to perform, possibility to test at once several hypotheses which is the concept of multiarray.

P2

A comparison of two NMDA antagonists in animal models of psychosis using behavioral and quantitative EEG measures

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Aim of the study: Schizophrenia has been associated with disrupted neural networks, which can be documented by the changes in EEG. On a molecular level, glutamate abnormalities have been suggested to underlie symptoms of schizophrenia. Ketamine and MK801, two NMDA antagonists, both induce psychosis-like symptoms in animals and humans. While ketamine binds to a number of neurotransmitter receptors in addition to NMDA, MK801 is a selective NMDA antagonist. Prepulse inhibition of acoustic startle reaction is a measure of sensorimotor gating and is often disrupted in schizophrenia. Locomotor activity reflects behavioural activity of the substance, whereas increased locomotion is considered to mimic positive symptoms of psychosis. EEG spectral analyses of NMDA

antagonists have been performed by many authors, however no EEG coherence and spectra was analyzed with higher number of cortical electrodes. The aim of this study was to compare effects of ketamine and MK801 in quantitative EEG (power spectra and coherence) and in behavioral experiments in the rat. **Methods:** In behavioral studies, male Wistar rats were treated with either ketamine (9 or 30 mg/kg) or MK801 (0.1 or 0.3 mg/kg i.p.). Sensorimotor gating was tested in the test of prepulse inhibition (PPI) of acoustic startle reaction and locomotor activity in the open field test. In EEG experiments, animals were administered with either ketamine 30 mg/kg or MK801 0.3 mg/kg. Stereotactical implantation of 14 electrodes was performed seven days before EEG recording. During EEG recording, the signal was recorded simultaneously from 12 implanted electrodes located bilaterally in frontal, parietal and temporal regions while the animal's behavior was continuously observed. Subsequent power spectral analysis and EEG coherences were assessed congruently with observed passive behaviour in order to maximize the translation of these findings to resting EEG of patients with schizophrenia. **Results:** Both doses of ketamine and MK801 caused dose-dependent deficit in PPI, the deficit was more pronounced after MK801. Acoustic startle reaction was significantly decreased only by MK801. Similarly, there was a significant dose-dependent increase in locomotion after the administration of both ketamine and MK801. In EEG spectral analysis, ketamine caused an increase of power in the gamma band. A similar increase occurred after the application of MK801; however significant power decreases in theta and beta bands were also present. In EEG coherences, decreases occurred interhemispherally in high beta and gamma bands and intrahemispherally in the delta band in both ketamine and MK801. Additionally, MK801 also showed intrahemispherical decrease in the theta, alpha and beta band. **Conclusion:** To conclude, both ketamine and MK801 produced dose-dependent changes in behavioral experiments which correlate to their schizophrenia-like potential. In quantitative EEG, both substances induced changes that were partly similar to schizophrenic patients. However, behavioral and EEG changes were more pronounced after administration of MK801. This work was supported by grants IGA MZCR NS-10374-3, NS-10375-3, CNS MSMT 1M0517 and MZOPCP2005.

P3

The effect of dizocilpine on the activity of hippocampal neurons in anesthetized rats

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Acute administration of NMDA receptors antagonists such as dizocilpine induces schizophrenia-like behavior in animals. This behavior includes impairment of spatial cognition requiring hippocampus. We studied the effect of a low dose of dizocilpine (0.1 mg/kg i.p.) on the activity of hippocampal neurons in anesthetized rats. The preliminary results indicated that the administration of the drug causes a gradual increase in the hippocampal neuronal activity and that the mutual correlation among discharges of hippocampal neurons either does not change or it decreases. The later observation points to a functional disorganization of the neuronal activity in hippocampus. We discuss the possible role of the above observations in the schizophrenia-like behavior in animals. This work was supported by grants GACR 309/09/0286, MSMT 1M0517 and MSMT LC554.

P4

Investigation of effects of benzylphenylpiperazine, trifluoromethylphenylpiperazine and dexamphetamine on the event-related P300 in humans

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Benzylphenylpiperazine (BZP) and trifluoromethylphenylpiperazine (TFMPP) are designer drugs marketed as a safe and legal alternative to MDMA and methamphetamine. Clinical studies reported humans who consumed BZP and TFMPP experienced amphetamine-like physiological (e.g. an increase in blood pressure/ heart rate) and subjective effects (e.g. increased feelings of High, Drug liking, Euphoria, and Stimulation). We investigated the effects of BZP and TFMPP on central information processing, by analysing the event-related potential P300, during an auditory odd-ball task. Healthy, right-handed males (25 ± 5.6 years old) were given an oral dose of either placebo ($n=15$), TFMPP (60mg, $n=13$), combined BZP and TFMPP (100/30mg, $n=18$) or dexamphetamine (20 mg), as a positive control ($n=16$). Subjects were tested pre- and 2 hr post-drug administration. After administration of either TFMPP or dexamphetamine, the P300 amplitude was significantly reduced ($F(1,26) = 3.995$; $p < 0.05$, $F(1, 29) = 4.881$; $p < 0.05$). However placebo or combination of BZP/TFMPP did not affect the P300 amplitude. The P300 latency was not affected by all four treatments. The results demonstrate that TFMPP and dexamphetamine reduce the components involved in attention allocation and immediate memory processing. This study demonstrates for the first time that TFMPP, but not the combination of BZP/TFMPP, reduces P300 amplitude in a manner similar to our positive control dexamphetamine. We have previously reported that BZP reduced the P300 amplitude in humans. This suggests that when BZP or TFMPP are given separately they elicit dexamphetamine-like effects on central information processing, suggesting that their effects on cognitive processes may be similar.

P5

Assessment of spontaneous and evoked gamma oscillations by quantified EEG, a potential biomarker of glutamatergic transmission: methodological issues in humans, descriptive data and test-retest reliability

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Background: The gamma band (30- 70Hz) of the EEG is a domain of growing interest for many areas, as a potential biomarker in schizophrenia or Alzheimer's disease. More generally it is a read of synchronization mechanisms (binding) between distant neuronal populations. These are involved in all sensory and cognitive tasks and could also be a potential biomarker for new chemical entities when measured either in static (resting) or dynamic (evoked or induced) conditions. Optimal setting is not known. The non-competitive NMDA antagonist ketamine in rodents produces a robust increase in resting gamma while due to the paradoxically sparse qEEG data available in humans, at subanaesthetic levels, the relative magnitude of spontaneously recorded gamma would have to be calibrated versus the more documented evoked responses triggered either by auditory or visual stimuli. Reliability of auditory stimulation has been established but since the visual modality was preferred it remained to be established. This study was therefore the first step to assess the normative values of spontaneous and visually-evoked gamma and their test-retest reliability in healthy subjects as a first validation step of a glutamatergic-sensitive biomarker. **Methods:** Quantified EEG was recorded with silver/silver electrodes: 28 on the scalp, according to the 10/20 system with linked earlobes as a reference and 4 for the purpose of electrooculogram in order to closely monitor eye movements. A Grass system with a sampling rate of 400 Hz was used. Low and high pass filters were set to 70 Hz and 0.3 Hz and a notch filter to 50 Hz. On each session there were 3 minutes of recording and eyes closed and 3 minutes eyes open, then followed by the stimuli presentation, eyes open. Evoked gamma band response was triggered by the method described by [5] with 50% of contrast between gratings of visual targets either with vertical lines (25 infrequent stimuli) or horizontal lines (100 frequent stimuli). The presentation lasted 1000 ms and the inter-stimuli interval was 1600 to 2400 ms. The visual stimuli were presented on a 22" LCD monitor using the E-prime software. After screening, the subjects were recorded on two distinct occasions separated by at least 24 hours. **Results:** Resting gamma show moderate inter-

individual variability, high test-retest reliability, but important differences between electrodes. Preliminary results indicate a good reproducibility of the evoked gamma-band responses (eGBRs) from one session to the other. Activation is mainly present in the low gamma band (<45Hz). Further statistical analyses are needed to confirm these preliminary qualitative results.

P6

Cordance as a biomarker in sleep-EEG for depression: differences in responders versus non-responders - a naturalistic study after antidepressant medication

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Objective: Cordance is a relatively new quantitative EEG-method, which has shown usability as a biomarker for depression within the resting-state in wake patients. Sleep EEG shows distinctive alterations in a depressive episode and changes after antidepressants. We wanted to test whether differences in Cordance derived from sleep EEG exist between responders and non-responders after antidepressant medication. **Methods:** 21 in-patients with a depressive episode [ICD-10 F 31.4, F 32.1-3, F 33.1-3] were treated with various antidepressants of “doctor’s choice”. The change of the Hamilton depression scores between the first and fifth week of treatment provided evidence about response. Response to treatment was defined as a $\geq 50\%$ reduction of Hamilton score. Cordance values for the prefrontal theta-EEG were calculated from sleep EEG during the first week with active medication. **Results:** Results showed significant differences: 9 responders compared to 12 non-responders showed higher Cordance values in prefrontal EEG-sites (z-score $-1,76 \pm 0,92$ versus $-2,71 \pm 0,64$, $p = 0.023$). **Conclusion:** These results suggest that Cordance derived from sleep EEG provides a biomarker for depression.

P7

Higher resting alfa-1 current density power in the anterior cingulate cortex is associated with more severe obsessive-compulsive symptoms

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Objective: Previous neuroimaging studies revealed that patients with obsessive-compulsive disorder (OCD) have hyperactivated error monitoring system which is mostly associated with dysfunction of dorsal part of anterior cingulated gyrus (ACC). The goal of this study was to assess the association of electrophysiological activity of different parts of ACC with the severity of OCD symptoms. **Methods:** We compared resting EEG of 32 OCD patients and 50 healthy controls using standardized low-resolution tomography (sLORETA). Correlation analysis between EEG activity with focus on rostral, dorsal part of ACC and entire ACC and severity of OCD symptoms as assessed by Y-BOCS were done afterwards. **Results:** OCD patients reached increased low-frequency current density power (2-6 Hz) in right dorsal part of ACC in comparison with controls. Correlation analysis of current density power at the voxel’s level with use of sLORETA did not indicate any association between EEG activity in ACC and intensity of OCD symptoms. Y-BOCS scores positively correlated with alfa-1 (8,5 – 10 Hz) current density power in entire and rostral ACC when mean current density power in regions of interest were included into the analysis. There was a trend of positive correlation of Y-BOCS and alfa-1 power in dorsal ACC which did not passed the Bonferroni correction ($r = 0,54$; $p = 0,00156$). **Conclusion:** Results confirmed that activity of ACC has specific role in pathophysiology of OCD. Further investigation of association between electrophysiological activity in the ACC and availability of serotonin reuptake inhibitors with use of PET radioligands is recommended. This research was supported by the grant NS 9752-2 IGA MZ CR.

P8

Prefrontal QEEG cordance in the prediction of ketamine hydrochloride antidepressant-like effect in depressive disorder patients - preliminary outcome of randomized double-blinded placebo-controlled trial

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Objective: Administration of subanesthetic doses of non-competitive NMDA (N-methyl-D-aspartic acid) antagonist, ketamine hydrochloride, led in numerous studies to the rapid onset (hours), but relatively shortly detectable (days) antidepressant-like effect [Berman, 2000; Zarate, 2006]. Mood improvement within the period from 2 hours to 7 days was significantly better on ketamine than on placebo. Previous studies demonstrated predictive value of prefrontal QEEG (quantitative electroencephalography) theta cordance reduction in depressive patients treated by different antidepressants [Leuchter, 1994; Cook, 2001; Bares, 2007, 2008, 2010; Hunter 2004]. In this study, we assessed the value of prefrontal QEEG theta cordance in the prediction of antidepressant response to single dose of ketamine hydrochloride. **Methods:** 15 depressive disorder patients (6 female and 9 male) diagnosed with a moderate to severe depressive episode without psychotic symptoms (F32.1, F32.2 according to ICD-10) were included. During the 2-week trial, all of the participants received successively, in the same order, the infusion with subanesthetic dose of ketamine hydrochloride (0.54mg/kg) and placebo (0.9% sodium chloride). Depressive symptoms and overall clinical state was assessed using MADRS (Montgomery-Åsberg Depression Rating Scale), BDI (Beck Depression Inventory) and CGI (Clinical Global Impression). Response to treatment was defined as equal to or more than 50% reduction of MADRS scores. Simultaneously subjects underwent 7 EEG examinations with consequent computation of prefrontal QEEG theta cordance. **Results:** 11 of 15 (73,3%) subjects responded to ketamine hydrochloride. All 11 responders decreased prefrontal QEEG theta cordance what was statistically significant in Fischer's exact test (Chi-square 6,34, df: 1 and $p < 0,01$). The positive predictive value (PPV) and negative predictive value (NPV) were 85% and 100% respectively. **Conclusions:** Our results suggest that robust and rapid antidepressant-like effect of ketamine hydrochloride could be predicted by decrease of theta prefrontal QEEG cordance. The trial contributes to the overall effort directed towards improving the therapeutic process (e.g. sequential treatment of depression) by means of quantitative electrophysiological methods. Supported by Internal Grant Agency of Ministry of Health of Czech Republic No.NS10379-3, 1M0517 (MEYS CR), MZ0PCP2005 (MH CR).

P9

Evaluation of Aripiprazole effects in schizophrenia using BRL-sLORETA norms: a preliminary study

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Objective: The aim of this study was to make an evaluation of the effects induced by the drug aripiprazole in patients suffering schizophrenia. This was based on a comparison to the normative EEG data base from the NYU Brain Research Laboratories, which has recently been extended to age-dependent "default-mode" cortical electric neuronal activity using standardized low resolution electromagnetic tomography (sLORETA). **Methods:** Resting state EEG was recorded from two schizophrenic patients before and after administration of aripiprazole. The sLORETA software from the Zurich-KEY Institute was used for analysis. The cortical distribution of the generators of oscillatory activity for classical frequency bands were computed and statistically compared to the age-corrected normal values based on 139 normal controls (NYU BRL norms). **Results:** In one patient, a

significant excess of slow wave delta activity was found in right temporal-frontal areas before treatment. After three weeks treatment a trend towards normality was observed. Incidentally, this patient was at the same time being treated with benzodiazepines, showing a characteristic focus of fast beta in cingulated cortex. The second patient showed excess occipital delta and decreased parahippocampal beta generators after four weeks, Treatment produced a slight change towards normality for slow wave activity, but a very slight worsening of beta. Correspondingly, the total PANSS score for the first patient and the second patient decreased by 12.7% and 10.9%, respectively. **Conclusions:** These very preliminary results illustrate how powerful this method of analysis can be in providing useful information that potentially has direct impact in clinical use of aripiprazole. In particular, our future goal is to routinely use these techniques and to test if the method is capable of predicting which drug therapy will be effective.