IPEG International Pharmaco-EEG Society
Association for Electrophysiological Brain Research in Preclinical and Clinical Pharmacology and Related Fields

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## Abstract Book

The "International Pharmaco-EEG Society, Association for Electrophysiological Brain Research in Preclinical and Clinical Pharmacology and Related Fields" (IPEG) is a non-profit organisation, established in 1980 and composed of scientists and researchers actively involved in electrophysiological brain research in preclinical and clinical pharmacology, neurotoxicology and related areas of interest.

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## TABLE OF CONTENTS

## EEG-BASED PERSONALIZED MEDECINE



## Dr. E. ROY JOHN MEMORIAL LECTURE





## KEYNOTES



## SYMPOSIA

## ORAL PRESENTATIONS

## POSTER PRESENTATIONS

# EEG-BASED PERSONALIZED MEDECINE





## QEEG subtyping and treatment optimization and outcome

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Historically, conventional EEG has added little to the diagnosis, treatment, or understanding of psychiatric disorders. Through the use of computerized quantitative methods of signal processing and data analysis, clinical utility has been greatly advanced. Application of such tools to the study of the heterogeneity within clinically homogeneous diagnostic categories has been demonstrated to improve treatment responsiveness.

The methodology of the studies included will be restricted to those that use eyes closed resting EEG, collected from the 19 regions of the International 10/20 System, impedances <5KOhms, referenced to linked ears, with quantitative analysis based 1-2 minutes of artifact-free data. Quantitative features include measures of power, complexity, connectivity, and source localization, in frequencies between 1.5-35Hz.

The scientific literature supports the fact that subtypes exist within categories diagnosed by symptom based systems, e.g. DSM or ICD. Some of these subtypes are recognized within this system, while others may not be recognized based on symptoms, history and presentation alone, but have been identified by use of QEEG. For example, in a population of obsessive compulsive disorder patients (OCD, n=27), two subtypes were identified using cluster analysis of a small subset of QEEG features. One subtype was characterized by increased alpha activity with decreased theta, and the other with deficit of alpha and increased theta. Considering the accuracy of classification including an independent replication, the sensitivity/specificity of treatment prediction was reported to be 88%/85%. Differences in source localization between baseline recordings and treatment condition in drug responders show clear registration with PET data in the same patients

Data will be presented that demonstrates the use of QEEG methods in subtyping of psychiatric populations, and in prediction of treatment response, recovery and outcome based on these subtypes. Such data suggests that these methods represent important translational research tools which can assist in treatment selection, outcome, and prediction of evolution of disorders.

Keywords: QEEG subtyping, source localization, psychiatric disorders, treatment outcome, biomarkers

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## A review and integration of EEG-based predictors for treatment outcome in ADHD and depression

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Personalized Medicine (PM) is a promising and well-needed development in Psychiatry, further emphasized by the results of the recent NIMH-MTA trial in ADHD and the STAR*D trial in Depression, demonstrating limited (long-term) clinical efficacy. Most recent developments investigating PM focus on pharmacogenomics. However, in psychiatry and neuropsychiatry, the use of neuroimaging methods, especially neurophysiological techniques such as the EEG, have a long and rich research history, investigating predictors or moderators of treatment outcome. In 1957 the first studies were conducted on predicting treatment outcome to ECT using barbiturate-induced changes in the EEG[1]. Several recent review articles in Nature and Science celebrated the 10th anniversary of the Human Genome project, however the contributions of genetic approaches have only been able to explain a few percent of the genetic variance[2], suggesting that a strictly genetic approach to personalized medicine for psychiatry will be not so fruitful. This presentation will further review the research on EEG Based PM in ADHD and Depression and try to integrate frequently reported and replicated findings.

Finally, ADHD will be used as an illustrative example to demonstrate how EEG based PM findings cannot only potentially improve treatment outcome, but can also lead to new insights into the underlying etiology of disorders. Such knowledge could results in
a more complete understanding of sub-groups within a disorder and potentially result in preventative strategies which could lower the prevalence of ADHD[3,4].

Keywords: ADHD, Depression, Personalized Medicine, EEG

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## Neurophysiologic predictors of treatment response in major depression

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Major Depressive Disorder (MDD) is marked by disturbances in brain functional connectivity. This connectivity is modulated by rhythmic oscillations of brain electrical activity, which enable coordinated activity across brain regions. Normal oscillatory activity plays a central role in regulating thinking and memory, mood, cerebral blood flow, and neurotransmitter levels, and restoration of normal oscillatory patterns is associated with effective treatment of MDD. Research indicates that oscillatory synchrony in the theta and alpha frequency bands may be a highly sensitive indicator of the presence of MDD, and that early changes in synchrony in these bands during antidepressant treatment may predict response and remission with a high degree of accuracy. Measurement of changes in theta and alpha power and coherence early in antidepressant treatment may be useful in guiding treatment decisions and speeding recovery from depression.

Objectives: 1) to discuss the patterns of oscillatory synchrony in normal brain function and MDD 2) to review data on the use of power and coherence measurements as predictors of treatment response in MDD

## Prefrontal EEG Cordance as a predictor of response to antidepressive treatment in patients with MDD and Bipolar depression

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**Objective:** It has been suggested that 30-40% of patients do not respond to standard antidepressive treatment and only 50% of patients achieve remission after 2trials of antidepressants. It would be clinically useful to be able to predict response to treatment at an early stage and indeed a number of potential predictors have been proposed in recent years. Cordance is a relatively new QEEG method that incorporates both absolute and relative EEG power and has demonstrated usefulness for characterizing antidepressant response. Our study aimed to evaluate the efficacy of QEEG cordance in the prediction of response to various antidepressive interventions.

**Methods:** A total of 103 inpatients with resistant depression (MADRS ≥ 20) were treated with various antidepressive interventions for 4weeks. EEG data were monitored at baseline and after 1week of treatment. QEEG cordance was computed at 3frontal electrodes in theta frequency band (4-8Hz).

**Results:** Forty-two from 46 responders (reduction of MADRS ≥ 50%) and 14 from 57 non-responders decreased prefrontal QEEG cordance after 1week of treatment. There was a significant difference between responders and nonresponders in change of cordance value after one week of treatment ($p<0.001$). Positive and negative predictive value of cordance reduction for treatment response was 0.75 and 0.92, respectively. The overall accuracy of the test was 0.83, the effect size was in large range ($w=0.67$) and the ROC analysis yielded AUC value of 0.82.

**Conclusion:** Early change in prefrontal theta 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.

Keywords: QEEG cordance, depression, prediction, treatment response

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## Resting EEG and evoked potential predictors of clinical response to antidepressants

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The resting EEG has been shown to be of value for predicting whether patients having a depressive disorder will benefit from a selective serotonin reuptake inhibitor (SSRI). In an ongoing study, we are recording resting EEG and event-related potentials (ERPs) from depressed patients prior to receiving treatment with an SSRI, an NDRI (bupropion), or dual treatment with both antidepressants or an SNRI (duloxetine). This presentation will outline these findings, with a focus on the measures of ERPs to auditory stimuli at 100-200 msec after tone onset (N1 and P2), which are indicative of early sensory/attentional processing, and on later ERPs (P3a and P3b), which are associated with cognitive processing. ERPs are measured during a novelty oddball task with three stimuli: infrequent target tones ($p=.12$), frequent nontarget tones ($p=.76$) and infrequent novel stimuli (animal or environmental sounds; $p=.12$). This paradigm provides measures of novelty P3 (P3a) and later P3b potential, which have been reported to be reduced in depressed patients. However, less is known about their association with antidepressant treatment response. Another electrophysiologic measure is the loudness dependency of the auditory evoked potential (LDAEP) to a 60-100 dB series of tones, which has shown particular promise for predicting SSRI treatment response. New findings will be presented for these paradigms using reference-free current source density (CSD) and principal components analysis (PCA) measures, taking full advantage of both the temporal resolution of ERPs and the spatial resolution of the available electrode montage.

Keywords: EEG, ERP, depression, antidepressants, clinical response

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## Can vigilance regulation be used to predict clinical response to antidepressants?

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According to the vigilance regulation model of affective disorders and ADHD an unstable vigilance ("brain arousal") with rapid declines to drowsiness and to sleep onset under quiet rest plays an important pathogenetic role in both mania and ADHD [1]. In this context an EEG-based algorithm has been developed which attributes a certain vigilance stage to every 1 second EEG segment and allows studying the transitions between different vigilance stages during a 15 minutes EEG recording under rest with eyes closed. Studies will be presented supporting the validity of VIGALL (simultaneous EEG-fMRI and EEG/FDG-PET studies [2,3]) as well as the clinical and predictive validity of the vigilance regulation model of affective disorders. Preliminary data indicate that an unstable vigilance regulation predict favourable response to psychostimulants in ADHD, mania and cancer related fatigue. The question whether methylphenidate has similar beneficial effects in mania as observed in ADHD is presently studied within an international, randomized controlled trial.

Keywords: vigilance regulation, antidepressants, HDHD

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## Biomarker Discovery – Integrative Neuroscience and EEG Biomarkers

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EEG based biomarker research undertaken with Brain Resource assessment methodology uses a standardized and integrative approach, enabling large international studies for biomarker discovery. EEG data collection and analysis is strictly standardized across identical labs in all countries, enabling quality controlled international trial design. An integrative neuroscience approach to biomarker discovery, combines EEG data with autonomic measures, cognition, genomics and MRI/DTI/fMRI. Brain Resource is currently undertaking the world's largest studies of treatment prediction in mental health using this standardized and integrated methodology approach. The International Studies to Predict Optimized Treatment (iSPOT) in both Depression and ADHD seek to improve treatment outcome by identifying objective biomarkers to predict treatment response. We provide an overview of the iSPOT studies' design, and outcomes to date using this approach to biomarker discovery. This is presented with respect to the framework of current EEG Biomarkers in the Database across disorders. The potential benefits of an open source EEG Database are also discussed, as an acceleration driver of Personalized Medicine EEG Biomarkers.

## Pharmacologic treatment of major depressive disorder guided by QEEG

Daniel A. Hoffman

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This presentation will discuss various uses of QEEG in guiding the selection of medication as well as aiding in safety of medication choices. It will concentrate on the Psychiatric EEG Evaluation Registry (PEER) Outcome Report using the Referenced EEG database. This tool offers providers shared data outcomes based on brainwave neurophysiology.

Suffin and Emory's [1] initial work showed that affective and attentional disorders had better outcomes when treated with the aid of QEEG instead of DSM nomenclature alone. DeBattista's [2] multi-site depression efficacy study demonstrated statistical significance on both primary endpoints and nine out of twelve secondary endpoints. Greenblatt [3] studied depression in Eating Disorders in which treatment options were successful on multiple measures including the HAM-D, CGI, and costs of treatment using two year pre-data and up to five years post data. In a large chart review, Hoffman [4] revealed patients reached maximum medical improvement within three to four visits in a difficult to treat population. He also looked at on and off label prescribing as well as severe adverse events and how PEER can help with patient safety as well as efficacy.

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# DR. E. ROY JOHN MEMORIAL LECTURE

Dedicated to E. Roy John, who founded a new field of science in EEG, by modeling and quantifying statistically normal electric neuronal activity, serving as a reference to advance our understanding of normal and pathological brain function. During many brain-storming sessions at his Brain Research Lab, when moving from the scalp into the brain, when focusing on brain connectivity, he was always one step ahead of us all. We would not be where we are today without his contribution and influence.

Roberto D. Pascual-Marqui



## New methods for studying localized function and distributed whole brain connectivity patterns using EEG tomographies

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Using high time resolution multichannel EEG recordings, the 3D distribution of electric neuronal activity throughout the cortex can be computed with eLORETA (exact low resolution electromagnetic tomography). This linear tomography is capable of exact localization, albeit with low spatial resolution. A straightforward application is in classical neuroimaging for functional localization. However, localization alone provides very limited information on brain function.

It is the study of brain connectivity that gives new information to better understand brain function. For this purpose, eLORETA can provide time series of activity at over 6000 cortical voxels at very high time resolution, which can then be used for quantifying functional connectivity of the brain. A “strong functional connection” between two regions corresponds to “high similarity” of the respective activity signals, typically measured as coherence and phase synchronization, which are known to be biased due to volume conduction. We introduce a new measure of physiological lagged similarity, which is not affected by such artifacts. Furthermore, in order to estimate direct connections between two areas, as opposed to connections mediated through third areas, we introduce a new method for the efficient computation of the full cortical partial connectivity field. In addition, two important extensions of network discovery methods are presented. One method allows the discovery of causal connections in the sense of Granger causality, revealing cortical regions that are senders, hubs, and receivers of information. The second family of methods allows the discovery of generalized cortical networks. Whereas a metabolic (e.g. fMRI) network consists of 3D distribution of interconnected regions, the new EEG based network consists of a spatio-frequency distribution of possibly different cortical regions that can synchronize across different frequencies. The methods presented here are illustrated with a variety of experimental data, and in many instances with the normative EEG database from the Brain Research Lab.

# KEYNOTES



## Keynote 1 –
## The science of pharmaco-EEG: a participant's recollections

Max Fink

Hans Berger's 1929 report of recording the brain's electric rhythms through the intact scalp of man established the science of electroencephalography. In his third report of 1931 Berger reported different effects induced by cocaine, morphine, scopolamine and chloroform establishing the EEG as a measure of drug effects in man. The EEG quickly became a measure of spontaneous seizures in epilepsy finding abnormal rhythms during interseizure periods. EEG measures during ECT treatment courses found increasing amplitudes, slowing of frequencies, and burst activity. When the degree of slowing was correlated with clinical outcome in 1956, a theory of the association of EEG change and behavior was formulated. The first measurements of change were hand measures but by 1958 the Grey Walter analyzer -- an electronic measure of the power in 10-second epochs -- was applied to these studies.

When chlorpromazine and then imipramine was introduced, the changes in EEG were measured and in 1958, at the CINP meetings in Rome, two reports of the differential effects in patients, one by Itil and Bente from Erlangen and Fink in New York set the stage for the science of pharmaco-EEG. By 1960, numerous EEG laboratories were examining each newly introduced agent reporting that different patterns were elicited by different drugs. Patterns for antipsychotic, antidepressant, anxiolytic, psychostimulant, deliriant, and hallucinogenic drugs were described. These established a theory of association of EEG and behavior and guidelines for evaluating putative drugs were published. The IPEG was established and annual meetings in Europe supported the science.

At the same time pharmacologists described the effects of psychoactive drugs in animals concluding that the EEG and behavior were dissociated. Dissociation was established in dogs, cats, rabbits, monkeys, mice, and rats. The ensuing controversy became a theme of IPEG meetings. By 1968, a symposium in Washington established that human studies sought correlations between EEG change and mood, thought, and vigilance while animal studies were limited to the effects on motor activity. The prediction of drug effects from human trials proceeded successfully while predictions from animal trials routinely failed. Studies in patients were complicated by the almost universal administration of drugs that affected the EEG and gradually a science developed around normal volunteers. The clinical activity of new agents was tested to predict the drug class and clinical dosage range.

Quantifying the EEG became a particular interest. The demonstration that digital computer analysis using baseline crossings (period analysis) was feasible in 1960 was

quickly followed by amplitude, period, and power spectral analysis programs based on
digital computers. The IBM 1710 digital computer was introduced in 1962 and the IBM 1800 in 1966. Specialized devices allowed the measurement of evoked potentials and programs for sleep staging were developed.

Between the mid-1960s and the 1980s an active science predicted the activity of many new drugs, showed some to be ineffective in altering the EEG and later as clinical failures. But the profession never resolved the association-dissociation controversy and industry laboratories using animals were found not to meet industry requirements for prediction of drug effects in man. Human trials became increasingly expensive and restricted by institutional review boards.

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## Keynote 2 –
## Rostral anterior cingulate function: a potential biomarker of antidepressant treatment response?

Diego A. Pizzagalli

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Increased rostral anterior cingulate cortex (rACC) activity has emerged as a promising predictor of treatment response in depression, but neither the reliability of this relationship nor the mechanisms supporting it have been thoroughly investigated. In the first part of my talk, I summarize findings from a recent meta-analysis indicating that the relationship between resting rACC activity and treatment response is robust. Specifically, at least 19 studies have found that increased pre-treatment rACC activity predicts better antidepressant response. Moreover, such relationship emerged across treatments, including various class of medications (e.g., SSRIs, atypical antidepressants, ketamine), sleep deprivation, and rTMS, and has been replicated across imaging modalities (fMRI, PET, SPECT, EEG). In the second part of the talk, I review empirical evidence suggesting that elevated resting rACC activity might confer better treatment outcomes by fostering adaptive self-referential processing and by helping to recalibrate relationships between the default network and a "task-positive network" critically implicated in cognitive control and emotion regulation. Limitations of current work and future directions are discussed.

## Keynote 3 –
## Contribution of QEEG and subtyping to outcome prediction

Leslie S. Prichep

Brain Research Laboratories, Department of Psychiatry, New York University School of Medicine, NY, NY, USA Leslie Prichep

Hans Berger's first report of human EEG recorded from the scalp was in the late 1920's, and as a psychiatrist, he hoped that EEG would pave the way for better understanding of psychiatric disorders. However, EEG added little to diagnosis and treatment for many decades. Through the use of computerized quantitative methods of signal processing and data analysis, clinical utility greatly advanced. Application of such tools to the study of the heterogeneity within clinically homogeneous diagnostic categories has been demonstrated to improve treatment responsiveness and provide important information of evolution of disorders.

The methodology of the studies included will be restricted to those that use eyes closed resting EEG, collected from the 19 regions of the International 10/20 System, impedances <5K Ohms, referenced to linked ears, with quantitative analysis based 1-2 minutes of artifact-free data. Quantitative features include measures of power, complexity, connectivity, and source localization, in frequencies between 1.5-35Hz.

Numerous studies have demonstrated the existence of distinctive profiles in abnormalities of QEEG features between different diagnostic categories and reported the relationship between degree of abnormality and severity of symptoms. With focus on specific symptom based diagnostic categories, subtypes of treatment responsive clusters have been identified using QEEG methods. Further, the sensitivity of these methods to the earliest signs of functional impairment indicates the potential of these tools to identify biomarkers predictive of the evolution of disorders.

Data from several different populations will be presented in support of the clinical utility of QEEG subtyping for optimization of treatment (e.g., Obsessive Compulsive Disorder, pain, and persistent vegetative state), prediction of evolution of disorders (e.g., longitudinal studies in normal elderly), and recovery of function/outcome (e.g., sports concussion). This data suggests that such methods represent important translational research tools which can assist in treatment selection, prediction of evolution of disorders and recovery of function.



## Keynote 4 –
## Why have sleep deprivation pro-manic and psychostimulants anti-manic effects? The wakefulness regulation model of affective disorders

Ulrich Hegerl, Peter Schönknecht, Tilman Hensch, Sebastian Olbrich, Michael Kluge, Hubertus Himmerich, Christian Sander

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According to the vigilance regulation model of affective disorders and ADHD (1) the hyperactivity and sensation seeking observed during both mania and ADHD are interpreted as an autoregulatory attempt to stabilize vigilance (central nervous arousal) by increasing external stimulation. Similar behavioural patterns are observed in overtired children. Correspondingly the withdrawal and sensation avoidance in major depression is interpreted as a reaction to a state of tonically high vigilance (1,2). Indeed, under quiet resting conditions, both patients with ADHD and mania show an unstable vigilance regulation with rapid drops to lower vigilance stages (e.g. assessed by the EEG-based Vigilance Algorithm Leipzig, VIGALL) whereas an hyperstable vigilance regulation is found in unmedicated patients with major depression. In both ADHD and mania, sleep deficits aggravate the dysregulation of vigilance as well as the symptomatology. In depression, sleep deprivation reduces the hyperstability of vigilance which explains its antidepressant effects. Theoretical and empirical arguments supporting the vigilance model will be presented. Among the far reaching consequences of this concept is the question whether psychostimulants have similar beneficial effects in mania as observed in ADHD. There is scattered but surprisingly strong evidence that psychostimulants are not detrimental in acute mania but might have similar rapid therapeutic effects as observed in ADHD (1, 4). The therapeutic role of methylphenidate in acute mania is presently studied within an international randomized controlled trial.

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## Keynote 5 –
## Relationship between ADHD and sleep problems: A new etiology perspective

Martijn Arns[1,2]

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Attention-Deficit/Hyperactivity Disorder (ADHD) is most common psychiatric disorders of childhood with average worldwide prevalence of 5.3. Heritability of ADHD has been reported as 60-70%. Pre- and perinatal factors (preterm birth, low birth weight) also play an important role in ADHD aetiology as well as other environmental factors.

Recent meta-analysis on studies in healthy children has demonstrated clear associations between sleep duration and attention, executive function, internalizing/externalizing behaviour and obesity. Furthermore sleep duration has decreased in children across the last 100 years. In a recent meta-analysis on the EEG Theta/Beta ratio we found further evidence for this, where the Theta/Beta ratio for healthy children, but not for ADHD children, increased across the last 10 years, suggestive of lower vigilance [1]. Several sleep disorders such as restless legs, sleep apnoea and sleep-onset insomnia are more prevalent in ADHD, and several studies have demonstrated that appropriate treatment of the sleep disorder also results in improvements of ADHD complaints. Sleep restriction studies in healthy children have demonstrated to result in ADHD like complaints and increased theta EEG power, further supporting an important role of sleep in the aetiology for a substantial subgroup of ADHD (for review see [2]).

We recently demonstrated in [3] independent large datasets that 34-57% of the prevalence of ADHD in both children and adults can be explained by environmental factors influencing the circadian clock. These results will be discussed in more detail related to the increased prevalence of ADHD across the last 10 years as well as implications for treatment and possibly prevention of ADHD.

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# SYMPOSIA

## Symposium 1
## Translational biomarkers in pharmaco-EEG – from bench to bed and back

NMDA antagonists like ketamine and hallucinogenic drugs like psilocybin gain attention as a model of schizophrenia as well as in the treatment of depressive symptoms. The symposium will bring recent insights in the translational research of schizophrenia with NMDA antagonists and serotonergic hallucinogens and in the use of ketamine in the treatment of unipolar depression. The symposium will focus on pharmacologically induced EEG changes and their relevance to clinical symptoms of psychosis and depression. Parallel work between human and animal models will be highlighted together with the proposal of a comprehensive statistical solution to analyze complex EEG data of various forms.

## Symposium 2
## Genetic influences on the pharmaco-EEG in psychiatric diseases and its potential for new pharmacological treatments

Pharmaco-EEG has shown great potential in clinical applications, for example in the assessment of neurophysiological correlates of psychiatric disease or in the prediction of treatment response. Neuroscience researchers have recently been making tremendous progress in understanding psychiatric disease and cognitive functioning. Accounting for interindividual differences, such as genetics and personality factors, has provided insights in mechanisms underlying disease but at the same time this has also led to the discovery of interindividual differences that interact with psychotropic medication.

In this symposium, researchers will present their work in the field of interindividual differences and psychiatry research by making use of one or more of the following approaches: human pharmaco challenge models, investigation of genetic polymorphisms, genetic animal models. The researchers will elaborate on how the investigation of genetics and other interindividual differences bears potential to yield valuable insights into the underlying mechanisms of psychiatric disease or in the development of new treatments.



## Symposium 3
## EEG-based biomarkers in diagnosis and prediction of psychopharmacological treatment in neuropsychiatric disorders

Although the EEG yields a superb sensitivity to detect intrinsic and extrinsic driven changes of brain function, its specificity for usage as diagnostic tool is rather low. Still, not only within the recent years, researchers have identified several EEG-based biomarkers that might help to delineate subgroups of patients suffering from different neuropsychiatric disorders and predict the outcome of psychopharmacological treatment.

In this symposium, researchers will present their work upon such EEG-based parameters. At first, the usage of EEG-markers assessed during the resting state (EEG-vigilance regulation and baseline EEG-alpha and theta power) and during sleep (EEG-cordance marker) for treatment prediction in major depression will be presented. Further, results of a study using event related potentials (ERPs) as markers for response prediction in attention deficit hyperactivity disorder will be shown, followed by a presentation about quantitative EEG markers that might help to optimize antiepileptic treatment.

## Symposium 4
## Pharmaco-EEG and pharmaco-sleep in drug-discovery and development

Pharmaco-EEG and pharmaco-sleep have great potential as biomarkers in drug discovery and development, where the goal is typically to make decisions on the future of a drug development project based on its likelihood of success. However, their use is not widespread, despite the urgent need to reduce attrition rates across the industry.

In this symposium, researchers and pharmaceutical industry scientists will present work on this issue, including a proposal for a framework to make greater use of the techniques, a retrospective analysis of past failures of the techniques to deliver their promise and two examples of successful application.

## Quantitative EEG in glutamatergic and serotonergic pharmacological models of schizophrenia – a translational approach

Tomáš Páleníček, Michaela Fujáková, Filip Tylš, Anna Kubešová

Psychiatric Center, Prague, Czech Republic

NMDA antagonists and serotonergic hallucinogens are widely used to model psychosis in animals. There is little information pertaining to quantitative EEG in a resting condition with translational validity in these models. Several difficulties also arise in the interpretation of EEG findings due to the lack of comparable recording conditions in humans and animals (low number of electrodes in animals, behavioral activity of animals etc.). Therefore, we used recordings from multiple electrodes located above the frontal, parietal and temporal regions of rats' brains along with registration of behavior in rats treated with various NMDA antagonists and serotonergic hallucinogens. We have concentrated on two EEG markers – EEG power spectra and coherence within the delta - gamma band.

Experiments were carried out on male Wistar rats. EEG was recorded from 12 cortical electrodes (six on each hemisphere homolaterally). NMDA antagonists (ketamine and MK-801) and hallucinogens (LSD, psilocin, 2C-B and DOB) were administered i.p. or s.c. after 10 min of baseline recording in awake freely moving rats. During EEG registration behavioral activity and inactivity was co-registered. To model the "resting condition" only EEG segments corresponding to behavioral inactivity were used for the spectral and coherence analysis. The analysis itself was performed using Neuroguide Deluxe software.

Both NMDA antagonists and serotonergic hallucinogens induced characteristic changes in EEG. While NMDA antagonists induced an increase in gamma oscillations, serotonergic hallucinogens induced a widespread decrease in the EEG power in all frequency bands. On the other hand, EEG coherence was globally decreased in both pharmacological models.

Comparison of our results with findings from clinical trials with ketamine, psilocybin and ayahuasca (studies in volunteers) and with findings from schizophrenic patients will be discussed.

Keywords: animal models, schizophrenia, NMDA antagonists, hallucinogens, EEG power spectra, EEG coherence

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## Translational validity of EEG oscillations in schizophrenia

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There is growing recognition that aberrant electroencephalographic (EEG) oscillations are core features of a wide range of neuropsychiatric and neurological disorders. Synchronous oscillatory activities in spatially distributed neural networks represent essential dynamic mechanisms for temporal coordination of multiple brain networks to coordinate higher-order cognitive functions. Electrophysiological and anatomical reports suggest that abnormalities in neuronal oscillations may play a key role in the physiopathology of schizophrenia, in which failure in gamma oscillatory synchrony seems to be a specific functional component underlying cognitive deficit and symptoms of the disorder. Clinical reports in schizophrenic patients have described complexity and opposite changes in gamma oscillatory response, which have been correlated with chronic versus psychosis state of the disease. Deficit in gamma power is generally correlated with negative symptoms, whereas increased gamma oscillation propensity is found during psychotic episode and hallucinations state.

N-methyl-D-aspartate (NMDA) receptor antagonists have utility recapitulating positive, negative and cognitive deficit in healthy man and laboratory animals. In preclinical studies, acute blockade of NMDA receptors enhances aberrant EEG gamma oscillations, thus recreates a pattern postulated to be linked to positive symptoms of the disease state. However, a major challenge remains in modeling the negative symptoms of the disease following blockade of NMDA neurotransmission. To ensure optimal translational relevance of the model in preclinical drug discovery research, repeated blockade of NMDA receptors is expected to lead to reduction in gamma oscillatory activity. This emphasizes the notion that pharmacological studies have to be conducted in ways that closely resembles acute versus chronic clinical states.

Keywords: schizophrenia, glutamate, chronic, evoked EEG oscillations, functional connectivity, cognition, translational index, rat

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## Intravenous ketamine for treatment-resistant unipolar depression: comparison of pharmaco-EEG changes in responders and non-responders

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**Objective:** Recent studies have provided evidence for shifting focus to antidepressants with primary pharmacological targets outside the monoamine system to offer more rapid activity with improved therapeutic benefit. In this context, ketamine (non-competitive antagonist of the NMDA receptor) has been repetitively studied in major depression. In the present study the time-course of effects of ketamine was assessed in depressive patients by sLORETA to elucidate changes associated with treatment response.

**Methods:** In a double-blind, cross-over, placebo-controlled study we assessed the effect of single infusion of ketamine (0.54 mg/kg within 30min) in 29 inpatients with major depressive disorder. EEG data were analysed on the day of infusion (peak at 10min; end at 30min) and 24hours, 3 and 7days after ketamine administration. Response was defined as a ≥50% reduction of MADRS score.

**Results:** In the whole group, ketamine infusion induced an acute (10min and 30min) decrease of parietooccipital alpha-1 and alpha-2 sources and increase of gamma sources. Eleven of 29 subjects who responded to medication (38%) were characterized by an excess of mediofrontal delta-and theta sources in comparison to non-responders. Moreover, only the responders showed sustained significant changes (decrease of fast activities in the left temporal lobe) 24 hours, 3 and 7 days after infusion, while no significant changes were observed in non-responders.

**Conclusion:** Our results suggest that an acute increase of mediofrontal cortical sources of slow rhythms could be potential biomarkers to differentiate responders and non-responders to ketamine in major depression.

Keywords: depression, ketamine, sLORETA, treatment response

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## A functional data analysis framework for pharmaco-EEG modeling and inference

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A comprehensive statistical solution to analyze complex EEG data of various forms is proposed in this study. Many different forms of EEG data can be naturally treated as functional data. For example, the power spectral density (PSD) of an EEG signal is a 1-dimentional function on the frequency domain, while the measurements over multiple EEG channels is a function on a spatial domain of a 3-dimentional sphere. In this study, a Functional Data Analysis (FDA) approach is proposed as a general framework to model EEG data, along with other covariates of interest (e.g. treatments). EEG data of different forms and dimensions can be uniformly modeled under this framework by selecting different basis functions and covariance matrix structures. The idea is demonstrated with two types of EEG data: the EEG PSD data represented with the B-spline basis functions, and the multichannel EEG data with the spherical harmonic basis functions. In both cases, a full profile of EEG effects of interest is estimated and naturally represented as a continuous function, and higher statistical power is achieves, comparing with conventional methods. Since representing EEG effects as a function implies that inferences are simultaneously conduced multiple times (e.g. at multiple frequencies for EEG PSD data, or at multiple channels for multichannel EEG data), the multiplicity issue arises. Thus, a multiple comparison adjustment procedure, seamlessly embedded in the proposed FDA framework, is also presented to obtain adjusted p-Values and simultaneous confidence intervals. The core R codes to implement the proposed framework are demonstrated.

Keywords: pharmaco-EEG effect estimation, functional data analysis, multiple comparisons

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## Genetic influences on the resting EEG, alcoholism and anxiety – convergent findings

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Since the resting EEG, a stable, highly heritable trait, is a dynamic index of cortical activation it may be regarded as an intermediate phenotype for arousal-related behaviors such anxiety and alcoholism. Therefore candidate genes for the resting EEG are likely to influence stress-related systems including the HPA axis and serotonergic transmission. Other candidate genes will be implicated in current flow, synchronization and rhythm generation. We performed a dense whole genome linkage scan and a genome-wide association study (GWAS) for resting EEG power in a population-isolate sample of Plains American Indians (PI) (N=328). Results were replicated in a sample of U.S. Caucasians (N=188). Genome-wide significant linkage peaks for alpha, beta and theta EEG power converged on chromosome 5q13-14, identifying a stress-related gene, CRHBP (corticotropin releasing hormone-binding protein). The same CRHBP SNPs were significantly associated with alpha power in the PI and Caucasians, anxiety disorders in the PI and alcoholism in the Caucasians. A suggestive chromosome 11 peak for alpha power identified HTR3A/HTR3B, encoding the 5-HT3 serotonin receptor. HTR3B variation was significantly associated with alpha power in the PI and Caucasians and antisocial alcoholism in Finnish Caucasians (N=518). The GWAS identified three genome-wide significant genes implicated in EEG generation: SGIP1, ST6GALNAC3 and UGDH. SGIP1 was also associated with EEG power and alcoholism in the U.S. Caucasians. Subthreshold GWAS findings identified genes previously associated with addiction. Our results indicate that the intermediate phenotype approach can identify genes that influence alcoholism and anxiety as well as genes having a specific effect on the EEG.

Keywords: alpha EEG power, alcoholism, anxiety, American Indians, intermediate phenotype, linkage scan, GWAS, CRHBP, HTR3B, SGIP1

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## A mouse model of 15q13.3 microdeletion syndrome display pre-attentive processing deficits and EEG phenotypes seen in schizophrenia

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Event-related magnetoencephalography (MEG) and electroencephalography (EEG) studies of pre-attentive processing of auditory-evoked potentials (AEP) have identified several characteristic phenotypes associated with schizophrenia. More specifically, reduced loudness dependence of AEPs, AEP amplitudes and sensory gating as well as reduced mismatch negativity (MMN) amplitude has been repeatedly reported in schizophrenia. Moreover, abnormalities in cortical gamma-band (30–80 Hz) synchrony have been observed in schizophrenia, with an increased or unchanged level of gamma during resting state, but a decreased capacity for evoked gamma oscillations e.g. when investigating auditory steady-state responses (ASSR).

The current electrophysiological characterisation of Df(h15q13)/+ microdeletion mice was designed to evaluate these specific pre-attentive processing deficits and EEG phenotypes in the auditory domain. The results demonstrated a general reduction in the processing of AEPs in Df(h15q13)/+ mice, with a decrease in the amplitude of subcomponents of AEPs. In addition, Df(h15q13)/+ mice displayed a selective deficit in evoked auditory steady-state gamma oscillations, with no change in baseline gamma oscillations. These very interesting findings suggest that this mouse model for the human 15q13.3 microdeletion syndrome recapitulates several aspects of the pre-attentive processing deficits seen in schizophrenia.

Keywords: copy number variant, CNV, schizophrenia, mouse models, EEG, auditory evoked potentials, AEP, gamma oscillations

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## Interindividual differences in the acute effects of cannabis on performance monitoring and inhibitory control

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Cannabis is the most common used drugs of abuse worldwide and is known to be associated with cognitive deterioration in a variety of neuropsychological functions, including performance monitoring and inhibitory control. It is less clear, how acute intoxication affects these functions and to what extent interindividual differences play a role. In this talk I will present a number of results obtained in a pharmacological challenge study with cannabis in healthy human volunteers, using behavioral and EEG based outcome measures such as the error related negativity (ERN) and the P300 ERP. In addition, I will present how interindividual differences account for differences in task performance. Taken together, the results of our studies suggest that already at the acute intoxication stage, we observe altered functioning in inhibitory control and performance monitoring. The implications of these findings for continued drug use and treatment of addiction will be discussed.

Keywords: EEG, error-related negativity, ERN, P300, performance monitoring, cannabis, THC, interindividual differences

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## Modulation of different EEG parameters and depressive impact mood influencing genes of COMT and BDNF

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Genetic polymorphisms of the Brain-Derived Neurotrophic Factor (Val66Met) and the Catecholamine-O-Methyltransferase (COMT Val158Met) are considered to play a role in the pathogenesis of major depressive disorder (MDD). Higher depression risks have been found for BDNF Met allele carriers [1] and COMT Val/Val genotypes [2]. The BDNF Met allele protein enhances brain plasticity and antidepressants enhance genetic BDNF transcription. The COMT enzyme degrades catecholamines in the prefrontal cortex. To investigate the genetic effects on etiology of depression, we used three different alpha frequency measurements and the P300 event related potential. Previous studies indicated that alpha frequency measures and the P300 are highly heritable EEG markers and appeared useful in genetic research [3].

In a population of 96 depressed subjects and 95 control subjects, we found that the low voltage alpha EEG and the BDNF Met allele had an accumulated risk on depression. Moreover, in 107 MDD subjects, alpha power appeared a potential mediator between the BDNF polymorphism and depression severity. Furthermore, we explored the relation between the COMT polymorphism with the P300 ERP and the alpha peak frequency in different populations. We found no significant difference between COMT genotypes for APF in 2 independent samples. When BDNF Met allele individuals show less alpha power, these individuals might are prone to develop depressive complaints. Implications for future drug research will be discussed.

Keywords: BDNF Val66Met polymorphism, COMT Val158Met polymorphism, Major Depressive Disorder, alpha peak frequency, P300, alpha power, low voltage alpha EEG

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## EEG-vigilance regulation in major depression – from theory to treatment prediction

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According to the recently presented vigilance model of affective disorders, depressive symptoms such as social withdrawal and sensation avoidance are interpreted as an autoregulatory attempt to counteract the toncially increased vigilance ("brain arousal") observed in depressed patients [1,2]. This raises the questions to what extend vigilance regulation might be useful a) as a diagnostic marker and b) as predictor of response to antidepressants.

Based on 15 minutes resting EEG-recordings and using the Vigilance Algorithm Leipzig (VIGALL [3]), the vigilance regulation of 30 unmedicated patients with MD and 30 matched HC as well as of an independent additional sample of 33 unmedicated MD patients was assessed and assigned to one of three different regulation patterns (stable, intermediate, unstable). In the second sample, depressive symptom severity was assessed using Hamilton Depression Rating Scale (HDRS) at baseline prior to antidepressant medication and two weeks later. Fisher´s Exact-Test was used to compare the EEG-vigilance regulation patterns in responders (R; >33% HDRS reduction) and non-responders (NR).

**Results:** 1) Patients with MD showed significantly more often a stable vigilance regulation pattern than HC ($p < 0.001$); 2) No differences of vigilance regulation patterns were found for NR and R ($p = 0.18$). Exploratory analyses revealed that NR differed significantly from R concerning the association between vigilance regulation and the activity of the autonomous nervous system (ANS) ($p < 0.004$). In NR high EEG-vigilance was associated with low ANS activity.

**Conclusion:** EEG-Vigilance regulation successfully separated patients with MD from HC. The exploratory finding that a stable vigilance regulation in combination with low ANS activity characterized NR to antidepressants is intriguing and requires replication.

Keywords: EEG-vigilance regulation, major depression, treatment prediction

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## Response prediction to antidepressants using alpha power and asymmetry and anterior cingulate cortex theta activity

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Electrocortical indices may be useful in predicting antidepressant treatment response. Greater pretreatment, especially posterior, alpha power tends to index favorable outcome. The predictive utility of alpha power asymmetry in antidepressant response has been under-explored even though major depressive disorder (MDD) has been linked with decreased left frontal and right posterior activity (alpha-indexed). High anterior cingulate cortex (ACC) theta activity has also been associated with positive antidepressant outcome. Baseline alpha power and asymmetry, ACC theta activity, and early (1 week) changes in these measures, were assessed in predicting response by week 12 to three antidepressant regimens [escitalopram (ESC) + bupropion (BUP), ESC or BUP] in MDD males (N=24) and females (N=29). No treatments differences in clinical response rates existed at week 12. Larger clinical ratings decreases emerged by week 1 in treatment responders. BUP responders exhibited high baseline ACC theta; non-responders had low activity. Greater early decreases in ACC $theta_{2/Total}$ activity existed in BUP responders (vs. non-responders) but greater early decreases in $theta_2$ activity emerged in ESC+BUP non-responders (vs. responders). Treatment responders exhibited high baseline $alpha_2$ power while non-responders had low power; this was also true for ESC. Greater early alpha power decreases were associated with a positive treatment response, which was also observed in ESC responders. Treatment responders had baseline $alpha_1$ asymmetry reflecting greater left frontal activity and early shifts towards this; non-responders had the opposite profile. These results indicate that baseline alpha measures and ACC theta activity and early changes in these indices are useful in predicting treatment response. These findings have implications for tailoring antidepressant treatments.

Keywords: major depressive disorder (MDD), prediction, alpha power/asymmetry, theta

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## Cordance as a biomarker in sleep-EEG for treatment response in depression – a naturalistic study after antidepressant medication

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Cordance is a new quantitative EEG-method, which has shown usability as a biomarker for depression within the waking-state. Cordance has not been tested within sleep yet, but could be a valuable biomarker, too. We tested whether differences in cordance derived from sleep EEG exist between responders and non-responders after antidepressant medication. Additionally, we compared these with healthy subjects.

20 in-patients (15 women, 5 men) with a depressive episode were treated with various antidepressants of "doctor's choice". No significant differences in age (mean 45 ± 22 y versus mean 49 ± 12 y), medication or Hamilton Depression Rating Scale (HAM-D) score (23.8 ± 4.5 p. versus 24.5 ± 7.6 p) were found between responders and non-responders at inclusion shortly before change of treatment. Response to treatment was defined as a ≥ 50% reduction of HAM-D score at the end of four weeks of active medication. Cordance values for the prefrontal theta-EEG were calculated from sleep EEG during the first week of active medication. Furthermore, to calculate and to compare the prefrontal theta cordance 7 healthy young subjects (5 women, 2 men, mean 23 ± 2 y.) were included.

Eight responders compared to 12 non-responders showed higher cordance values in prefrontal EEG-sites (z-score -1.52 ± 0.98 versus -2.52 ± 0.71; $F(1,18) = 7{,}123$, $p = 0.016$). Z-scores correlated with HAM-D scores of all patients (Spearmans Rho: $R = -0.5$; $p = 0.025$). The healthy subjects showed cordance values similar to the responders, but not to the non-responders.

These results suggest that cordance derived from sleep EEG provides a predictor for the response to antidepressant treatment in depressed patients.

Keywords: cordance, antidepressant treatment

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## ADHD – Predicting response to stimulant medication on the basis of event-related potentials

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**BACKGROUND AND PURPOSE:** To predict response to stimulants in ADHD on the basis of event related potentials (ERPs) in a cued GO/NOGO task.

**METHOD:** 19-channel EEG was recorded in 74 medication naïve ADHD patients (7 to 17 years old) as well as in 259 healthy subjects of the same age (HBImed reference database). Subjects participated in a cued GO/NOGO task. The collection of ERPs to GO and NOGO stimuli were decomposed into components by means of Independent Component Analysis. In ADHD group as a whole two types of components deviated from the norms. They were correspondingly associated with activation of 1) inferior temporal/medial parietal, and 2) supplementary motor/anterior cingulate cortical areas. Stimulant medication was evaluated after more than four weeks on the basis of ratings and reports from parents and teachers.

**RESULTS:** We found 13 NON-responder, 28 GOOD responders, and 33 moderate responders. The NON responders show decrease of the posterior components and no significant differences in the anterior components in comparison to healthy controls, whereas the GOOD responders show deficit in anterior independent components and no deviations in posterior independent components.

**DISCUSSION:** Two types of independent brain dysfunction in ADHD (frontal and temporal-parietal) were found. Only ADHD patients with frontal lobe dysfunction responded to psychostimulants. This finding corresponds to mechanisms of psychostimulant medication known to affect the dopaminergic system of the brain with higher densities of receptors in the prefrontal cortical areas.

**IMPLICATIONS:** Independent ERP components in GO/NOGO task are potentially useful predicting responses to stimulant medication in ADHD.

Keywords: ADHD, event-related potentials (ERP), stimulant medication

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## qEEG features and medicinal response in epilepsy

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More than fifty million people suffer from epilepsy worldwide. Patients with idiopathic generalized epilepsy (IGE) are at a higher risk for other somatic and neuropsychiatric disorders than the general population. The anti-epileptic drugs (AEDs) have shown efficacy in suppressing seizures in most patients, but they have a suboptimal tolerability profile and potentially life-threatening reactions. The prospect of freedom from seizures and adverse effects remains elusive for approximately 30% of patients.

We describe five young females with IGE and diverse neuropsychiatric disorders. Initial visual EEGs ranged from normal variation to markedly slow and one had sporadic spikes. Two qEEG features included: (1) low alpha mean frequencies, and (2) relative theta excess. The qEEG provided a neurophysiologic measure for medicinal treatment. First, anti-epileptic drugs (AEDs) were selected to minimize low alpha mean frequencies. Second, addition of a catecholamine up-regulator and/or agonist was combined with AEDs to reduce qEEG relative theta excess and/or accelerate low alpha mean frequencies. Positive clinical outcomes were marked by normative changes in EEG/qEEG features. All patients achieved seizure control with improved physical health and cognitive functions. The qEEG features of low alpha and excess theta indicate a priori consideration of catecholamine up-regulation after partial AED stabilization in patients with epileptic and co-morbid neuropsychiatric disorders.

Keywords: low alpha mean frequency, relative theta excess, catecholamine up-regulator, abnormal physical findings, homeostasis

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## The role of EEG and PSG in decision-making in early drug development

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The pharmaceutical industry has been suffering from low clinical success rates for new drugs for some time, with particularly high attrition in early clinical development and with drugs aimed at central targets [1,2]. In order for a drug to show efficacy it is vital that both engagement and pharmacological modulation of the intended molecular target are achieved. Indeed, a retrospective analysis has shown that when appropriate pharmacokinetic (PK) and pharmacodynamic (PD) principles are followed to confirm target exposure and pharmacological action, the likelihood of successful demonstration of efficacy in Phase 2 is increased [3].

Electroencephalography (EEG) and polysomnography (PSG) are suitable as translatable biomarkers of central pharmacological action in many cases[4,5]. However in many large pharmaceutical companies there is a feeling that the results obtained are not truly “decision-making” in terms of determining the future of the drug development programme and hence a reluctance to “slow the project down” and increase costs by including such additional biomarker work in the project plan.

This presentation will propose a framework for the use of EEG and PSG in drug development that relies on the combination of preclinical data and an understanding of translatability to generate robust hypotheses for testing in early clinical studies and is backed-up by a clear decision-making process. The areas that need further development before this framework can be put fully into practice will be discussed, along with some possible solutions.

Keywords: pharmaco-sleep, polysomnography, pharmaco-EEG, biomarker, drug development, decision making, PK-PD

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## Lost in translation

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Pharmaco-EEG has a number of properties which could make it an ideal, translatable biomarker for CNS active compounds. It is an objective, continuous, repeatable and sensitive marker, which can be recorded in many species including man, varying in a reproducible manner with states of activity of the brain. However, despite the fact that changes in EEG parameters do correlate with disease states in a number of CNS disorders, such parameters have not yet been accepted as surrogate biomarkers for the development of pharmacotherapeutics in these disorders, as their validity is still under investigation.

This presentation is not intended to hail the benefits of EEG as a drug modifiable readout of CNS activity in drug research. Instead it will focus on the pitfalls, when using EEG for translation of drug effects in the drug development process, which have affected the belief in the usefulness of EEG for psychotropic drug development in the pharmaceutical industry. A number of examples will be given in which pharmaco-EEG was considered to have failed as a translational biomarker from animal to HV or from HV to patient. Many of these translational failures are due to mistaken assumptions in the employed translational equations.

Some of these mistakes were only shown to be so with the advance in EEG science and technology. Examples include deployment of the wrong preclinical species, drug effects on structures deeper in the brain which are not “visible” in either animal or human EEG, variable results in EEG studies from different laboratories, improper matching of frequency bands across species, heterogeneity in preclinical species or patient groups, etc, etc. But the most important mistake has been the assumption that pEEG might be a surrogate marker for therapeutic effects in psychiatric conditions rather than an intermediate biomarker for altered physiological or pharmacological brain states which may correlate with improvements of pharmacotherapy.

Keywords: pharmaco-EEG, pharmaco-sleep, translation, biomarker

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## Visual scoring and computerized data processing are complementary tools – a pharmaco-sleep study investigating the effects of a new antidepressant compared to imipramine

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International Pharmaco-EEG Society – IPEG

Pharmaco-sleep research concerns the description and the quantitative analysis of the effects of drugs on the central nervous system (CNS) by means of neurophysiological methods applied to subjects during a sleep period within the framework of clinical and experimental pharmacology, neurotoxicology, drug research, and related disciplines[1]. The quantitative assessment of the biosignals recorded during polysomnography (PSG) relies on the standardised visual evaluation of sleep recordings [2] or alternatively on a computerised analysis of the sleep microstructure. The purpose of the present study is to demonstrate the complementarity of visual scoring and computerised analysis in the context of the development of a new antidepressant drug.

24 healthy male subjects participated in a double blind, placebo-controlled trial following a randomised two-factorial parallel group design with 3 treatments administered for 5 consecutive days: 6 subjects were treated with 75 mg imipramine (IMIP), 6 with placebo (PLA), and 12 with a compound under development (a phenyl substituted tetrahydro-naphtalenone derivative; DEX). The baseline night ($N_0$) was preceded by 2 adaptation nights in the sleep laboratory. Night 1 ($N_1$) and 5 ($N_5$) were the recording nights following first and last dosage.

Both IMIP and DEX suppressed REM sleep substantially after acute and repeated administration, resulting in a significant increase in Stage R latencies and affecting the sleep architecture compared to baseline. The computerised analysis of the sleep micro-structure complemented the visual scoring by quantifying additional parameters (e.g. spectral or muscle activities) thereby allowing a better understanding of the impact on PSG.

Keywords: pharmaco-sleep, imipramine, computerized sleep data processing

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## Sleep architecture as a translatable biomarker of central pharmacology in the development of PF-04457845, an inhibitor of fatty acid amide hydrolase

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Sleep changes have been proposed as translational pharmacodynamic biomarkers for a range of drug mechanisms[1,2] justified by the observation that the ultradian (REM-NREM) pattern in rodents is similar to that in humans, despite the cycles being more rapid. This study demonstrates the utility of sleep as a biomarker of central pharmacology during development of a novel inhibitor of fatty acid amide hydrolase (FAAH).

The effects of PF 04457845 on sleep were first studied in rats in four separate experiments, three in the light and one in the dark phase. PF 04457845 selectively suppressed REM sleep on the first two days of dosing in only the light phase and hence a clinical study was designed to test for a similar effect.

In the clinical study, thirty healthy male subjects participated in a double blind, placebo-controlled cross-over trial. Three nights were spent in the sleep laboratory in each period and subjects were dosed with placebo on Day 1, followed by either PF 04457845 or placebo on Days 2 and 3. The polysomnography recordings were conducted and analysed according to the recommendations of the American Academy of Sleep Medicine (AASM). PF 04457845 suppressed REM sleep on the second day of dosing (Day 3), with the lack of effect on Day 2 potentially explained by a rebound effect following the first night.

Combined with previous reports that PF 04457845 acts centrally in rodents [3], this translatable evidence of pharmacology gives strong evidence of central pharmacology in humans. This information was highly important in decision-making following the lack of analgesic effect observed in osteoarthritis patients [4].

Keywords: Pharmaco-sleep; polysomnography; biomarker; endocannabinoid

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# ORAL PRESENTATIONS





## ERPs to emotionally loaded words as an assessment tool

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***Background and purpose:*** My previous studies have shown a unique prominent neural response to personal-emotional (PE) words. The aim of the current study was to test the differential brain activity pattern to PE words in a clinical neurological group. This neural response was tested as a tool to assess the success of a new therapy approach.

***Methods:*** Healthy volunteers and people with post-stroke aphasia took part in the study. EEG was recorded while the participants listened to 20 PE and neutral words repeating in a random order. The PE value of the words was assessed in two interviews before and after the study. ERPs were averaged to each word separately and to groups of emotional vs. neutral words. Some of the participants in the aphasia group took part in a new therapy block, and their neural response to PE words was assessed before and after the therapy block.

***Findings:*** A differential pattern with higher amplitudes of ERP components was shown for the PE words. Also, a differential pattern with smaller amplitudes and delayed components was demonstrated for the aphasia group. Markers in the neural response to personal-emotional and neutral words have changed after therapy and some of those markers corrected to normal after therapy.

***Future implications:*** The ERP response to PE words was found sensitive to a clinical group and to the change after successful therapy block. A similar method can be used to assess new treatment options and to differentiate clinical groups of other neurological and psychiatric disorders.

Keywords: EEG, emotion, stroke

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## The effect of attenuating noradrenergic neurotransmission by clonidine on brain activity measures of visuospatial attention

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Bias and disengagement are central to disorders of attention. Bias refers to modulated sensory processing due to the allocation of attention. Disengagement refers to the decoupling of attention. One paradigm in which bias and disengagement have been investigated is the visuospatial cueing (VSC) task. The behavioral outcome is the validity effect, the benefit in terms of reaction time of valid cueing. Noradrenergic attenuation by clonidine has been reported to reduce the validity effect. This has been interpreted as reflecting enhanced disengagement. However, it might also be due to attenuated bias. Here, we investigated the effect of NA attenuation by clonidine (100 microgram) on EEG indices of bias (cue-locked LDAP, P1 and N1 validity effects) and disengagement (validity effect on the Late Positive Deflection, vLPD). A double-blind placebo controlled crossover design was used. Participants performed in a VSC task while EEG was recorded. Systolic blood pressure response was monitored, as a proxy of central availability. Results show that clonidine induced a general decline of speed and accuracy. It also attenuated the N1 validity effect, but not other bias related ERPs. Systolic blood pressure correlated negatively with the drug effect on the vLPD, suggestive of a positive relation between clonidine and disengagement.

Keywords: noradrenaline attention N1

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## Electrophysiological and fMRI assessments of perceptual function for use in clinical trials

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As part of the NIMH-Sponsored Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia initiative, two domains have been identified that may be useful for assessment of perceptual function in clinical trials: gain control and visual integration. Gain control refers to processes that allow sensory systems to optimize their response levels. Integration refers to processes linking the output of neurons into a global complex structure. Deficits in both domains have been linked to NMDA hypofunction. We developed several paradigms to assess gain control and integration. For example for gain control, steady-state visual evoked potentials (ssVEP) biased towards magnocellular vs parvocellular visual pathway function were utilized. Gain control is thought to be NMDA-mediated. A functional magnetic resonance imaging (fMRI) task was used in conjunction with ssVEPs to elucidate the neural underpinnings of gain control deficits. As expected, patients exhibited selective deficits under the magnocellular-biased ssVEP condition. However, occipital lobe fMRI did not differ between groups. For patients, the fMRI results showed intact recruitment of occipital areas while the ssVEP results indicated that these areas did not optimally utilize gain control. These results indicate a broad dissociation between fMRI and ssVEP measures. For integration, a contour integration task consisting of easy and difficult to integrate gabor patches was utilized. Controls showed a negative occipital component at ~280 ms that differed between easy and difficult tasks, which was impaired for patients. These types of paradigms may be very useful in clinical trials aimed at improving glutamatergic function and inhibitory/excitatory neurocircuitry.

Keywords: schizophrenia, NMDA, perception

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## Effects of the novel anxiolytic drug ABIO 08/01 on sleep and awakening quality in generalized anxiety disorder - polysomnographic and psychometric studies

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ABIO 08/01 is a new anxiolytic isoxazoline with dose-dependent activating and sedative/relaxant properties in the qEEG [1] of healthy subjects. In addition, ERP [2] and psychometry [1] showed improved P300 latency, concentration, reaction time performance and psychomotor activity, suggesting nootropic effects. Deterioration of well-being reflects sedative effects.

In the present clinical study, the acute and chronic effects (8 weeks) of ABIO 08/01 on the sleep and awakening quality of 18 drug-free generalized anxiety disorder (GAD) (ICD 10: F41.1, DSM IV-TR: 300.02) patients were investigated as compared with age- and sex-matched normal controls. After a placebo run-in period, they were split into two groups and received a 5 or 10 mg dose of ABIO 08/01. If there was no clinical improvement after two weeks, the dose could be up-titrated to a maximum of 20 or 40 mg. Evaluations included polysomnography and psychometry.

GAD patients showed reduced sleep efficiency due to increased wake after sleep onset and number of awakenings. S1 tended to increase, as did the duration of sleep cycles due to longer NREM periods. Periodic leg movement (PLM) indices were increased. ABIO 08/01 tended to improved sleep efficiency, reduced the number of awakenings, S1, stage shifts and the duration of sleep cycles by shortening NREM periods. It thus normalized the above-described aberrations from the norm (key-lock principle). There were no effects on respiratory and PLM measures. Psychometry demonstrated a significantly improved awakening quality, morning well-being, fine motor activity and attention, which reflects cognition-enhancing properties of the drug in addition to good tolerability.

Keywords: ABIO 08/01, anxiolytic, polysomnography
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## Single-blind, randomized, increasing-dose study of the novel anxiolytic drug ABIO 08/01 in generalized anxiety disorder - clinical and qEEG findings

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Phase-I topographic and tomographic pharmaco-EEG/ERP and psychometric studies with the new isoxazoline ABIO 08/01 in normal subjects on the basis of a double-blind, placebo-controlled, multiple-ascending-dose design demonstrated good tolerability and significant encephalotropic and psychotropic effects of the drug, depending on recording conditions and doses [1][2][3].

The present phase-IIa, single-center, single-blind, randomized, increasing-dose, clinical and neurophysiological proof-of-concept focused on the efficacy and tolerability of ABIO 08/01 administered to 18 drug-free generalized anxiety disorder (GAD) (ICD 10: F41.1, DSM IV-TR: 300.02) patients as compared with age- and sex-matched normal controls. The study comprised three phases: a placebo run-in, active treatment and a placebo run-out period. Clinical assessments included the Clinical Global Impression Scale as well as observer- and self-ratings of depression and anxiety.

GAD patients showed increased depression and anxiety, which significantly improved under ABIO 08/01, reaching normative values. EEG-Mapping of drug-free patients revealed reduced absolute power in delta and fast beta bands, increased relative power in slow beta and an accelerated total centroid, which reflects CNS activation. ABIO 08/01 induced significant CNS effects at all times in all recording conditions, characterized by increased absolute power in all frequency bands, increased relative theta and decreased relative alpha power (relaxation). Discontinuation of treatment did not lead to a rebound or reoccurrence of GAD symptoms, but interestingly showed optimal findings.

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## Towards a normative database for sleep macro- and microstructure

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***Introduction:*** Several prerequisites have to be fulfilled to establish a normative database for determining meaningful deviations of patients' individual sleep characteristics from normative values and for assisting in the interpretation of results of a pharmaco sleep study in patients with nonorganic insomnia in the sense of the key-lock principle (i.e. the sleep characteristics of patients with nonorganic insomnia due to psychiatric disorders are opposite to the changes induced by psychotropic drugs intended for their treatment). ***Methods:*** In addition to standard exclusion criteria for healthy volunteers, subjects included in the SIESTA normative database were screened for regularity, duration and timing of sleep (controlled by sleep diaries and actigraphy) and for sleep-related respiratory or movement disorders (controlled by a screening/adaptation night with standard polysomnography (PSG)). The database covers healthy subjects from 20 to 95 years (90 males, 99 females), nearly equally distributed in all decades. Data recording and archiving followed a standard protocol. Sleep stages according to Rechtschaffen and Kales (1968) and AASM (2007) and sleep microstructures such as arousals, sleep spindles, K complexes, rapid and slow eye movements, muscle atonia, cyclic alternating patterns (CAPs) as well as EEG power spectra were determined by means of the validated automated sleep classification system Somnolyzer 24x7, which includes a structured expert review. This review was performed by sleep experts experienced in both manual scorings and reviewing Somnolyzer scorings. ***Results:*** This semi-automatic Somnolyzer-assisted approach guarantees results that are as valid as manual scorings (agreement between Somnolyzer-assisted and manual consensus scoring: 80.4%), but have reliabilities close to 1, while inter-rater reliabilities between manual scorings in the same dataset were 77.6%. In a validation study with 6 independent manual scorings we found, for instance, that slow-wave sleep or the arousal index may vary by up to a factor of 2 between manual scorings, which voids direct comparisons between studies scored by different experts. Since we observed significant age-related changes in almost all parameters determined (e.g. sleep efficiency: -0.25%/year; arousal index: +0.2/year; spindle density: -0.1/year; K-complex amplitude: -0.7µV/year), comparisons have to be made to age- and sex-matched normative values. ***Conclusion:*** Using an analysis method that results in unbiased and reproducible scorings for both the data included in the normative dataset and the study data is an absolute requirement for the meaningful use of normative data. While the value of parameters derived from sleep stages is unequivocally accepted for describing the macrostructure of sleep, the only parameter recommended for describing the microstructure of sleep is the arousal index. Further investigations will be necessary to reveal a possible significance of additional parameters, such as CAP rates, spindle, K complex or REM characteristics.

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## Music therapy added to standard care modulates fronto-temporal activity in the rest-EEG in depressed clients with comorbid anxiety

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**Background:** Fronto-temporal areas process shared elements of speech and music. Improvisational psychodynamic music therapy (MT) utilizes verbal and musical reflection on emotions and images arising from clinical improvisation. Music listening is shifting frontal alpha asymmetries (FAA) in depression, and increases frontal midline theta (FMT). The purpose of this study is to test whether or not MT has an impact on anterior resting state alpha and theta oscillations of depressed clients with comorbid anxiety.

**Methods:** In a two-armed randomized controlled trial (RCT) with 79 clients, we compared standard care (SC) versus MT added to SC at intake and after 3 months. Correlations between anterior EEG, Montgomery-Åsberg Depression Rating Scale (MADRS) and the Hospital Anxiety and Depression Scale - Anxiety Subscale (HADS-A), power spectral analysis (topography, means, asymmetry) and normative EEG database comparisons were explored. Standard care medication was equally spread in both arms of the study.

**Results:** After 3 month of MT added to SC, MADRS and HADS-A scores were significantly decreased. Further, lasting changes in resting EEG were observed, i.e., significant absolute power increases at left fronto-temporal alpha, but most distinct for theta (also at left fronto-central and right temporoparietal leads). MT differed to SC at F7-F8 (z-scored FAA, $p<.03$) and T3-T4 (theta, $p<.005$) asymmetry scores, pointing towards decreased relative left-sided brain activity after MT; pre/post increased FMT and decreased HADS-A scores ($r = .42$, $p < .05$) indicate reduced anxiety after MT.

**Conclusion:** Verbal reflection and improvising on emotions in MT added to SC may induce neural reorganization in fronto-temporal areas. Alpha and theta changes in fronto-temporal and temporoparietal areas indicate MT action and treatment effects on cortical activity in depression, suggesting an impact of MT on anxiety reduction.

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## EEG vs. Psychometry

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Since Berger's demonstration of the electrenkephalogram (EEG) in 1929 [1], quantification of psychological variables has proceeded almost entirely on the basis of the subjective methods of psychometry. The 'window into the mind' promised by EEG had defeated all attempts at analysis, save qualitatively ('eyeballing') of coarse features such as epilepsy, tumour or coma. The complexity of the EEG remained inaccessible until the advent of greater computing power in the last quarter of the twentieth century.

Buzsáki [2] holds that the intricate phase-locking of anharmonic rhythms is the substrate of thought and reflects personality structure, if not thought content. Though intricate analysis and powerful statistical techniques make psychometry the best tool we currently have for analyzing personality, psychologists are only too aware of the problems of reliability and validity that remain. This investigation tested categories determined by EEG analysis against the best psychometry can achieve.

### Experiment

NEOAC psychometry has been measured on sixty normal controls (psychology undergraduates) and twenty patients (psychology outpatients). Each subject has also had two minutes of EEG recorded under standardized conditions using a portable, telemetric pocket electroencephalograph (the Optima-4, manufactured by Neurobit of Danzig, Poland).

Using statistical analyses and the psychometry as the independent variable, mathematical correlations were sought between the EEGs and personalities as measured by the psychometries.

Further investigations are pending into Lehmann's 'Zeitquanten' [3].

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## EEG and ERP changes following oral intake of specified oregano extracts: similarities and differences to antidepressant markers

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We have recently reported the identification of a specified oregano extract (OE) with the ability to inhibit the reuptake of the monoamine neurotransmitters, serotonin, noradrenalin and dopamine, in a dose-dependent manner. In vivo microdialysis experiments in rats revealed a significant elevation of serotonin levels in the brain. Moreover, mice treated with OE performed better in animal models broadly accepted to test the effectiveness of antidepressant and anxiolytic compounds [1]. In addition, local field potentials in rats displayed distinct dose and time patterns of alterations in global brain activity following acute oral intake of OE. Strongest effects were seen in alpha1, alpha2 and beta1 waves representing an activation of serotonergic, dopaminergic and glutamatergic neurotransmission, respectively [2]. We here present a placebo-controlled crossover study in healthy humans in which EEG changes and alteration in sleep parameters due to 3 b.i.d. regimens of OE extracts were compared to the effects of venlafaxine (37.5 mg oral b.i.d.) as initial challenge at Day1/Day2. It was hypothesized that treatments would have changes in beta activity and cordance and REM-sleep in common.

Results: In agreement to rodent data, we observed an increase in absolute energy of alpha-1 and more pronounced beta-1 frequency bands in resting condition in adult young healthy males (n=20) for the highest dose tested. Moreover, Evoked-Related Potentials (ERPs) measurements revealed a significant increase in P300 amplitude. Sleep architecture was, as expected, significantly affected for venlafaxine, and not for OE extracts.

Conclusion: These results allow the interpretation that a single dose of OE induced a state of wakeful relaxation, enhanced vigilance and improved concentration in addition to increased mental capacity. We describe here how markers for venlafaxine-action "translate" to engagement of possibly overlapping mechanisms within our test-cohort when substituting comparator by OE administration. As such this dietary supplement is potentially able to regulate mood, motivation and mental wellbeing.

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## Nicotine-related alterations of p50-indexed sensory gating in cannabis users

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Long-term cannabis use has been associated with the appearance of psychotic symptoms and schizophrenia-like cognitive impairments, however these studies may be confounded by concomitant use of tobacco by cannabis users. We aimed to determine if previously observed cannabis-associated deficits in sensory memory would be seen in users with no history of tobacco use. A secondary objective of this study was to examine the effects of acute nicotine administration on cannabis users with no tobacco history. This study examined whether the P50 event-related potential (ERP), which has been shown to be impaired in schizophrenia, is negatively influenced by acute and long-term cannabis use and is augmented with acute nicotine.

Brain electrical activity was recorded during a P50 paradigm in 34 healthy, non-tobacco smoking male volunteers between the ages of 18-30. Cannabis users (CU, n = 17) were administered nicotine (6 mg) and placebo gum within a randomized, double-blind design. Non-cannabis users (NU, n = 17) did not receive nicotine.

In CUs, attenuation of S2 P50 amplitude (compared to S1) was observed under placebo condition, but not with nicotine. When CUs were divided according to use, this effect was revealed to be only present in light, short-term users; there was no difference between S1 and S2 amplitudes in heavy long-term users in either drug condition.

These findings suggest a relationship between gating impairment and chronicity of cannabis use. Additionally, the apparent negative impact of nicotine implicates tobacco use as a potential modulator of cognitive deficits in CUs.

Keywords: nicotine, cannabis, cognitive deficits

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## Functional connectivity in schizophrenic patients who were treated with aripiprazole

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**Objective:** The EEG can be used to quantify the effect of drug-induced changes not only by frequency domain power analyses or time domain analyses but also by connectivity analysis between certain brain regions. The objective of this pilot study is to investigate the changes of brain functional connectivity in patients with schizophrenia induced by treatment with antipsychotic drug using quantitative EEG analysis.

**Methods:** We recorded resting, spontaneous EEG from 19 scalp electrodes according to the international 10/20 system before and 4 weeks after administration of aripiprazole from three drug naïve patients who suffered from schizophrenia (paranoid type) diagnosed by DSM-IV-TR. Artifact-free 40 seconds (20 epochs) EEG data applied to the quantitative analysis from each recording opportunity. Then, we calculated functional connectivity of each EEG data using sLORETA software in seven frequency bands (delta, theta, alpha1, alpha2, beta1, beta2, beta3).

**Results:** Lugged-linear connectivity tended to decrease after administration of aripiprazole in delta band compared to the lugged-linear connectivity before administration.

**Conclusion:** This study showed just a preliminary result because the number of subject was limited. However, it seems interesting that aripiprazole brought change of functional connectivity in certain frequency band. In addition, it is quite meaningful that such a change was able to be detected using quantitative EEG analysis.

Keywords: connectivity, schizophrenia, aripiprazol

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## Electroencephalographic patterns of the internal connectivity networks of the brain as revealed by simultaneous EEG/fMRI measurements

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A number of EEG/ERP studies have demonstrated how the spontaneous EEG in the pre-stimulus period determines the sensory-cognitive processes that follow the event both in behavioral and electrophysiological domains by providing endogenous or top-down constraints. However, the description of the amplitude and phase characteristics of the endogenous oscillatory activity in the spontaneous EEG, which builds the common basis of these studies, does not directly permit to anatomically describe the responsible neuronal networks. On the other side, recent fMRI studies have shown internal connectivity networks (ICN) depending on the temporal fluctuation patterns observed in the Blood-Oxygen-Level-Dependent (BOLD) signal. This study aims to characterize the interrelationship between the spontaneous "resting" EEG recorded on the scalp with the ICNs defined by their hemodynamic pattern in the BOLD signal through the analysis of simultaneous EEG/fMRI recordings of 30 healthy volunteers. To create stationary segments of spontaneous and driven EEG rhythms, a block-design has been applied with 3 blocks of 45 s of steady-state visual stimulation following 45 s of resting state for each of a series of visual stimulation frequencies between 4 and 46 Hz. The DMN, visual sensory, sensory-motor, posterior attention, left and right fronto-parietal networks were obtained through the Independent Component Analysis (ICA) of the BOLD signal. The temporal correlations between the time courses of these BOLD components with the band limited power of the scalp EEG resulted in spatio-spectral EEG patterns of ICNs that may increase the usability of the spontaneous EEG in the framework of personalized neuropsychiatry in the future.

Keywords: internal connectivity networks, simultaneous EEG/fMRI, resting state

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## The qEEG characteristics of ADHD children, responders and non-responders to long-term treatment with Atomoxetine

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Attention-deficit/hyperactivity disorder (ADHD) is the most common neurobehavioral disorder of childhood. In our ADHD Centre the effects of drug treatments are monitored with qEEG, attention tests and SNAP-IV rating scales. The aim of our study is to describe the qEEG characteristics of ADHD patients that did and didn't respond to atomoxetine treatment.

61 patients with ADHD-C were selected after a multimodal evaluation including SNAP-IV, Conners parent and teacher scales, WISC-R, a series of attention tests of the Amsterdam neuropsychological test (ANT) and qEEG (Neurometric). All the patients received atomoxetine, a SNRI. qEEG was recorded before the therapy, after one month, 3 and 6 months. After then, every 6 months. Twenty minutes of eyes closed resting EEG were recorded from 19 electrodes. A differential eye channel was used for the detection of eye movement. Data was sampled at a rate of 256 Hz with 12 bit resolution.

Furthermore, two minutes of artifact-free EEG was also submitted for computation of source localization using Variable Resolution Electrical Tomography (VARETA). Very narrow band (VNB) spectra were computed using FFT with bins 0.39 Hz wide from 1.5 to 20 Hz, for every electrode derivation. Abnormalities in these data were identified using Z-spectra computed relative to normative values. According to SNAP-IV, qEEG and VARETA results, we were able to differentiate patients into 3 groups with different characteristics: responders, non-responders and partial responders.

Based on our results, it can be concluded that a patient with alteration in alpha band at 11.7 Hz, with no evidence of alterations in the beta or theta range, might be a responder to treatment with atomoxetine. If the alteration affects the alpha band in the range 9.75 to 10.14 Hz, a partial response can be expected to treatment with atomoxetine. Finally, the alteration of the beta band at 15.21 Hz, coupled to the alteration of alpha band, seems to be related to non-responders and atomoxetine should not be the drug of first choice, especially if there is persistence of alpha and beta and an increase of theta.

Keywords: qEEG, ADHD, atomoxetine

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# POSTER PRESENTATIONS





## Brain source connectivity for visceral pain and pharmaco-EEG

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**Introduction:** Several brain structures have been consistently found to be involved in visceral pain processing. However, recent research questions the specificity of these regions and it has been suggested that it is not singular activations of brain areas, but their cross-communication that results in perception of pain. If these cross-communications are identified, then changes at any level of the pain-specific brain networks due to different analgesics could be investigated. In this test/re-test study, we identified the network of sources and their frequencies following visceral pain.

**Methods:** 62-channel evoked potentials following electrical stimulation in oesophagus were recorded in twelve healthy volunteers on two separate days. Multichannel matching pursuit (MMP) and dipolar source localization were used. Multiple sources responsible for one MMP component were considered to act synchronously as each MMP component is mono-frequency and has a single topography. We first identified components that were reproducible within subjects over recording sessions. These components were then analysed across subjects.

**Results:** MMP and source localization revealed three main brain networks; an early network at ~8.3Hz and ~3.5Hz involving brainstem, operculum, and pre-frontal cortex. This was followed by an operculum, amygdala, mid-cingulate, and anterior-cingulate network at ~4.5Hz. Finally, there was an operculum and mid-cingulate network that persisted over the entire time interval at ~2.1Hz.

**Conclusion:** This study shows the method is reliable (test/re-test) and gives evidence of operculum's central role in pain processing. This method should be used in the future pharmaco-EEG studies to observe how these networks are modified due to different analgesics.

Keywords: brain source connectivity, visceral pain, pharmaco-EEG

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## Wavelet analysis of single-sweep pharmaco-EEG: beta-band activity correlate to the analgesic effect of buprenorphine

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Pain is a widely present condition, with as many as 19 % of the European population suffering from chronic pain. In many cases pain is treated with opioids, but since little is known about the underlying mechanisms of opioid treatment, further studies are warranted.

This randomized, cross-over and double-blinded study included 22 healthy subjects to investigate the effects of buprenorphine administered through a transdermal patch.

Before and during treatment, assessments were made for bone, heat and electrical pain. Evoked brain potentials (EPs) were recorded using electrical stimulation at the median nerve.

Three different approaches to analysis of EPs were compared: 1) visual inspection of amplitude and latency of the main peaks in the average potentials; 2) spectral distribution of the average potentials; and 3) spectral distribution of the single-sweep EPs. Features which exhibited significant differences were examined for correlations to pain scores.

Visual inspection revealed no significant different between placebo and buprenorphine (all $P > 0.05$). Spectral distribution of averaged EPs showed a significant increase in the theta band for buprenorphine ($P=0.006$), which did not correlate to pain scores. Spectral distribution of single-sweep EPs revealed significant increases in the theta, alpha and beta bands (all $P<0.05$). Furthermore, changes in beta band were correlated to bone ($P=0.04$) and heat pain ($P=0.04$).

This study proved single-sweep analysis to be superior for EEG as it enabled extraction of features reflecting the analgesic effect of buprenorphine. This discovery might be useful in clinical drug trials to assess the analgesic effect.

Keywords: opioids, monitoring, wavelet

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## The analgesic effect of morphine is reflected by changes in single-sweep evoked brain potentials

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Current findings on the altered evoked brain potentials (EPs) caused by morphine are based on common alterations for a group of subjects after drug administration in comparison to pre-treatment or placebo recordings. However, the study of group alterations is a crude approximation when describing the mechanisms of action for analgesics, since it is well known that individuals display a large variation in efficacy to opioids. Therefore, we explored the individual effect of morphine in terms of altered single-sweep characteristics in the electroencephalography (EEG) in a placebo-controlled cross-over study. The EPs were recorded from 62 channels and obtained pre- and post-treatment to morphine and placebo during repeated electrical stimulations of the oesophagus in 12 healthy men. Characteristics in the sweeps were extracted by a multivariate matching pursuit (MMP) algorithm with Gabor atoms implemented with constant phase and variable amplitude across sweeps. The single-sweep amplitudes were used as input to a support vector machine (SVM), to discriminate individual responses. The grand mean multi-channel classification accuracy when discriminating pre- and post-treatment morphine responses was 85.1% ($P<0.001$). The individual classification accuracy was positively correlated to the analgesic effect of morphine ($P=0.046$). Furthermore, the two post-treatment responses were classified and validated by classification of the two pre-treatment responses ($P<0.001$). The combination of features extraction by MMP and classification by SVM on single-sweep EEG is a novel approach for monitoring individual efficacy to analgesics, which may be used in future personalized medicine for chronic pain patients.

Keywords: evoked brain potentials, analgesic effect, morphine

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## Slowed EEG rhythmicity in pharmaco-EEG spectral indices after low dose remifentanyl is correlated to the analgesic effect in healthy volunteers

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To pursuit personalized medicine, novel approaches for assessment of individual effect of opioids are warranted. This may be achieved by multivariate pattern analysis (MVPA) of the alterations in the electroencephalography (EEG) after drug administration to determine the overall alterations in several spectral indices simultaneously. To verify this approach, we recorded 62 channel resting electroencephalography (EEG) in 21 healthy males pre- and post-treatment to remifentanyl in a placebo-controlled double-blind cross-over study. EEG spectral indices were extracted by a continuous wavelet transform and normalized into spectral distribution in the delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-12 Hz), beta (12-32 Hz), and gamma (32-80 Hz) spectral indices. The alterations relative to the pre-treatment responses for all subjects were calculated for both remifentanyl and placebo and used as input to the MVPA, which was implemented as a support vector machine (SVM) applied in regression mode. Additionally, subjective pain scores immediately before the EEG recordings were obtained for bone and heat pain. Compared to placebo, remifentanyl increased the delta band and decreased the theta and alpha band oscillations as a mean over all electrodes (all $P<0.001$). The MVPA had a classification performance of 88.1% ($P<0.001$) in the F3 and F5 channels. By calculating the overall alteration of the spectral indices as the mean regression value of the SVM for these channels, the pharmaco-EEG findings were correlated to individual changes in heat pain ($P=0.03$). In conclusion, this study has shown that MVPA of pharmaco-EEG is a novel approach for monitoring the individual efficacy of opioids.

Keywords: resting EEG, remifentanyl, analgesic effect, multivariate pattern analysis

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## EEG measurement in the fentanyl/etomidate-anaesthetised beagle (FEAB) dog, a novel method for proconvulsant risk assessment

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The purpose of this study was to integrate quantitative electroencephalography (qEEG) measurements into the FEAB dog model in order to evaluate the proconvulsant risk of new medical entities (NMEs). This has the advantage of integrating cardiovascular-, respiratory- and central nervous system safety pharmacology end-points, within one large animal model. Dogs were anaesthetised and instrumented as described before [1], and three needle electrodes were placed on the cranium to measure a one lead EEG signal (Narcotrend®-Compact). The proconvulsant agents pentylenetetrazole (PTZ), bicuculline (BCC) and bupropion (BPP) were infused and qEEG was assessed visually for spikes (= spikes, polyspikes and spike & wave) and induction of seizures. Slow infusions of either: PTZ (1.5 mg/kg/min; n=6), BCC (6.25 µg/kg/min; n=6) or BPP o.5 mg/kg/min; n=6) induced a dose-dependent occurrence of spikes after 15 min in most dogs; 30±4 (6/6), 37±5 (6/6) and 27±5 (4/6) spikes/min, respectively and induced seizures (100% , 50% and 33% respectively), with a threshold of 34±2, 0.12±0.03 and 13±2 mg/kg, respectively. In another group of dogs (n=4), PTZ-induced spikes were abolished with diazepam (2 mg/kg IV) or propofol (4 mg/kg IV) and seizures were prevented. In pentobarbital or α-chloralose anaesthetised dogs, PTZ (up to 60 mg/kg i.v.; n = 4) did not induce spikes or seizures. The present study has shown that proconvulsant agents induce dose-dependent spikes and seizures on the EEG in the FEAB dog, and thus EEG measurements can be integrated into this unique risk model for NMEs in safety pharmacology.

Keywords: safety, dog and seizure

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## Monitoring cholinergic activity in the treatment progression of AD using an EEG index based on cholinergic activity

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The only medications indicated for treatment of mild AD are the cholinesterase inhibitors. The effects of the medicines are measured by cognitive tests and by caregiver reports but there are no direct biological means of evaluating treatment effects. A theoretically possible method is to measure the cholinergic response to these drugs in the brain. It has been proposed that the EEG changes seen in AD are primarily a reflection of cholinergic dysfunction. We postulate that by establishing a "cholinergic index" in EEG registration, the treatment response of cholinergic drugs could be measured.

An EEG registration was obtained from 38 elderly participants before and after a 5 mg sc administration of scopolamine. A cholinergic EEG index was created by applying statistical pattern recognition to a large set of EEG features, by considering the group before and after scopolamine administration as two distinct groups. A longitudinal study with 42 AD patients over 12 months was then performed.

A group of AD individuals has smaller index values than a group of healthy elderly controls, which means that a shift to larger index values due to treatment may be considered a favorable response. The cholinergic index of the individuals in the longitudinal study is used to group the subjects into responders and non-responders. It is better to use electrophysiology to evaluate treatment response than MMSE scores.

This approach could be valuable in following the progression of AD treatment. The underlying technology is well known, widely available and inexpensive in relation to other imaging techniques.

Keywords: EEG, cholinergic activity, treatment response

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## Evoked Potentials and Neuropsychological Tests Predict Positron Emission Topography (PET) Brain Metabolism in Cognitively Impaired Patients: Pharmacological Implications

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Fluorodeoxyglucose (FDG) Positron Emission Topography (PET) brain hypometabolism (HM) correlates with diminished cognitive capacity and risk of developing dementia. However, because clinical utility of PET is limited by cost, we sought to determine whether a less costly electrophysiological measure, the P300 evoked potential, in combination with neuropsychological test performance, would accurately predict PET HM in neuropsychiatric patients. We found that patients with amnestic and non-amnestic cognitive impairment and HM (n=43) evidenced significantly reduced P300 amplitudes, delayed latencies, and neuropsychological deficits, compared to patients with normal brain metabolism (NM; n=187). Data from patients with missing cognitive test scores (n=57) were removed from the final sample, and logistic regression modeling was performed on the modified sample (n=173). The logistic regression modeling, based on P300 and neuropsychological measures, was used to predict membership in the HM vs. NM groups. It showed classification prediction in 13/25 HM subjects (52.0%) and in 125/148 NM subjects (84.5%), correlating with total classification accuracy of 79.8%. Because abnormal P300 evoked potentials coupled with cognitive test impairment accurately predicted brain metabolism and mild/moderate cognitive impairment (MCI), we propose incorporating electrophysiological and neuropsychological assessments as cost-effective brain metabolism and MCI indicators in primary care. Pharmacological, nutraceutical, and endocrine agents in the dopamine and catecholamine class may raise voltage and agents that may improve brain processing speed should be selective and tried in these subjects more aggressively, especially those who are progressing towards dementia.

Keywords: neurophysiology, evoked potentials, dementia

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## Microstate duration and syntax in frontotemporal dementia

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Frontotemporal dementia (FTD), one of the most common forms of dementia, has pathological changes in orbitofrontal cortex, insula and anterior cingulate cortex. Some of the functional magnetic resonance imaging (fMRI) studies reported that this anterior insula and anterior cingulate network, called salience network (insular-cingulate network), is considered to be important for switching and maintaining the balance between the executive-network and the default-mode network. Interestingly, recent study combining EEG with fMRI revealed the relationship between salience network and microstate class C. We speculated that microstates class C deviates from the norm in patients with frontotemporal dementia (FTD). In this present study, we investigated microstate parameters (duration and syntax) in FTD patients (mild stage, n=18), using resting EEG recorded from 19 scalp electrodes. In FTD patients, the duration of microstate class C was significantly shorter than in age-matched controls (n=19). This result is consistent with previous studies that salience network dysfunctions to early stages of FTD. The syntax analysis showed that the sequence of activation of class C and D is reversed in FTD patients compared to healthy controls, with controls preferring transitions from C to D, and patients preferring D to C. This aberrant syntax may support that network plays a critical role in switching RSNs. These results, thus, suggest that the duration and the syntax of EEG microstates could help explain the characteristics of the alterations in pathological states.

Keywords: microstate, fronto-temporal dementia, salience network

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## The efficacy of SSRI/SNRI for Post Stroke Depression – An evaluation using event-related potentials topography

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To evaluate the efficacy of selective serotonin reuptake inhibitors (SSRI) and serotonin norepinephrine reuptake inhibitors (SNRI) for post stroke depression (PSD) we performed ERP topography. The study was carried out on 6 PSD patients without dementia. SSRI or SNRI was administered for 4 weeks. Before and after administration we have measured neuropsychological test in addition to ERP. We have done 3 kind of the ERP paradigm for measurement of the ERP.

In addition to Oddball paradigm without and with novel stimuli (novel paradigm) by auditory stimulation, continuous performance task (CPT) paradigm by visual stimulation were used in the ERP measurements. As the result, according to improvement of depressive state, data of ERP in the CPT go paradigm, P3 amplitude remarkably increased. To perform CPT paradigm needs ability for parallel or simultaneous information processing in comparison other paradigm. These data suggest that cognitive dysfunction in PSD may be caused by dysfunction of information processing system.

Keywords: SSRI, SNRI, post stroke depression

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## ADHD – Predicting response to stimulant medication on the basis of EEG spectra

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**BACKGROUND AND PURPOSE:** To predict responses to stimulants on the basis of EEG spectra in a cued GO/NOGO task.

**THEORETICAL FRAMEWORK:** Excess power in the theta band and/or a high theta/beta ratio is consistently found to be typical for a substantial part of ADHD patients. It is argued that these patients are good candidates for treatment with stimulants. However, good response to stimulants has also been reported for excess beta.

**METHODS:** 19-channel EEG was recorded in 73 medication naïve ADHD patients (7 to 17 years old) who participated in a cued GO/NOGO task. The effects of stimulant medication were evaluated after a minimum of four weeks treatment, on the basis of scores and reports from parents and teachers. Based on this information two psychologists independently rated the patients as responders (N= 56) and non-responders (N= 17) In addition the grand average files of spectra for the two groups were compared.

**FINDINGS:** Significant differences between the groups were seen only in the theta band, most pronounced in temporal and parietal areas with p-values ranging from 0.001 to 0.009. P-value at vertex (CZ) was 0.026. The effect size was moderate. There was no significant age difference between the groups.

**IMPLICATIONS:** Excess power in the theta band increases the odds for positive effects of stimulant medication in ADHD.

Keywords: ADHD, EEG spectra, stimulant medication

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## QEEG analysis in a case with difficulty making differential diagnosis between delirium and depression

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**Background:** Delirium is transient and variable consciousness disorder which induces cognitive decline and psychological symptoms such as hallucination, delusion, and so on. Manifestations of delirium imply morbidity. Therefore, early diagnosis of delirium is quite important, but particularly hypoactive delirium is difficult to be detected because it is often misdiagnosed as depression.

**Purpose:** We analyzed EEG in a case with difficulty making differential diagnosis between delirium and depression by BRL-sLORETA-norms in order to investigate whether qEEG is valuable in the differential diagnosis of delirium and depression or not.

**Methods:** Resting state EEG was recorded from one delirium patient before and after administration of trazodone. 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:** Follow on the improvement of the delirium, a significant increase of fast theta and slow alpha activity was found in frontal-occipital areas. Then a significant decrease of beta1 activity was found in posterior cingulated gyrus both before and after administration of trazodone.

**Conclusion:** EEG showed obvious changes induced by administration of trazodone. This methodology may be quite helpful for making diagnosis for delirium patients. Further consideration would be necessary.

Keywords: differential diagnosis, delirium, depression, sLORETA

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## Trait and state-based depression indicators measured using real-time sLORETA imaging and quantification

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We have been able to employ recent advances in real-time sLORETA image reconstruction and quantification to produce a real-time depression assessment method. This approach reveals characteristics of depressed mood and thinking instantaneously, with a resolution of under 1 second. It is possible to visualize chronically depressed mood as well as transient changes in mood in individuals under controlled conditions, as part of a study of ipsative assessment in relation to EEG. Published literature has established that frontal lobe activation patterns, particularly asymmetry, are relevant to emotional tone, avoidance versus approach behavior, and reactions to emotionally-charged stimuli. Studies have not, however, accessed information related to instantaneous changes in EEG activation patterns, or produced an assessment method suitable for real-time application. The system described here is capable of producing whole-brain sLORETA data at live data rates, producing a virtual “movie” of an individual’s brain activation patterns in time and space. EEG assessments are not generally controlled for immediate emotional influences, and emphasize static, or trait-based qualities. Our approach emphasizes representing and interpreting not only the static tendency in an individual, but also how that individual reacts to particular emotionally charged stimuli. This approach provides an assessment of the individual’s dynamic reaction patterns in relation to environmental factors, not simply an estimate of a resting condition. Information about individual reactions is critical in understanding how one views, reacts to, and adjusts to environmental stimuli.

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## Quantitative electrophysiology in hyperthyroidism: Polysomnographic, EEG/ERP topographic and tomographic (LORETA) Studies

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**Introduction:** In contrast to the abundance of visual qualitative EEG reports in patho-endocrinology, there is a paucity of computerized quantitative electrophysiological findings.

**Objectives:** Electrophysiology may be utilized for differential diagnosis of hypersomnolence.

**Aims:** to investigate long-term daytime sleepiness in a young female neurologist with the tentative diagnosis of narcolepsy in addition to moderate depression/anxiety and congenital thyroid hypoplasia treated with thyroxin as compared with normal controls.

**Methods:** Three-night polysomnography, multiple sleep latency test (MSLT), visual EEG/ERP-mapping, LORETA, psychometrics and blood analyses were performed.

**Results:** Polysomnography revealed normal sleep efficiency and sleep architecture, but a high arousal index of up to 63/h TST. The MSLT showed a shortened mean sleep latency of 3.7 min. without REM-sleep onsets, objectifying the high Epworth Sleepiness score of 18. Visual EEG evaluation exhibited a fast alpha rhythm with intermittent theta and delta intrusions and paroxysmal activities. EEG-mapping showed a ubiquitous increase in absolute (especially delta and beta) power, ERP revealed shortened N1 latency and very high amplitudes in N1, P2, and P300 (P300 > 5 SD). LORETA demonstrated significant regional increases in delta, alpha-2 and beta-1 power in the anterior cingulate, orbital, ventromedial, dorsolateral prefrontal cortex and temporal cortex, predominantly right hemispherically. Psychometry showed increased anxiety (SAS) and depression (SDS) and reduced quality of life. Finally, hormonal analysis pointed to thyrotoxicosis factitia (ICD-10 E05.4).

**Conclusion:** Diagnostic investigations clearly elucidated the pathogenesis of the presenting diagnosis of organic hypersomnia caused by increased sleep-microarousals due to thyrotoxicosis factitia. Discontinuation of hormone substitution led to a normalization.

Keywords: polysomnography, MSLT, EEG/ERP-mapping, LORETA

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## The effects of two GABA-enhancing drugs on a patient with Dravet's Syndrome

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Background: Dravet's Syndrome is a form of intractable epilepsy usually developing during the first year of life. Psychomotor delay and a variety of cognitive impairments typically occur, similar to Autism Spectrum Disorder. Dravet's Syndrome is linked to a mutation of the SCN1A gene that alters Nav1.1 sodium channels, resulting in impaired GABAergic inhibitory interneurons and increased seizure activity in Dravet's Syndrome. Methods: An 11/12-year-old patient with Dravet's syndrome was administered two different GABA-rewarding drugs, clonazepam and stiripentol, approximately a year apart. qEEG analysis was done before, during and after clonazepam treatment and continues to be assessed during concurrent stiripentol treatment. Results: Both drugs had a significant effect on theta absolute power, theta coherence and theta phase-lock duration and also resulted in a near of total cessation of seizures. With clonazepam, administration was stopped for ten days, resulting in a return to pre-medicine qEEG characteristics and increased seizure frequency. Clonazepam was then re-administered and the same effects on the qEEG and seizure activity were observed. Conclusions: Based on this qEEG analysis, both drugs were effective treatments for Dravet's Syndrome. These data, along with the cessation of seizures during treatment, support the hypothesis that Dravet's syndrome results from an impairment in GABA. Furthermore, the data demonstrates that GABA-enhancing drugs influence qEEG absolute power, coherence and phase reset. These results have implications for future treatment of Dravet's Syndrome as well as possible neurofeedback interventions aimed at replicating the pharmacological influence of these medicines.

Keywords: Dravet's Syndrome, qEEG, GABA

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## Comparison of EEG changes of different antipsychotics in a glutamatergic animal model of psychosis

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**Aim of the study:** Disruption of neural connectivity have been associated with schizophrenia. Most changes occurring in this disorder include a decrease in connectivity and an increase in slow activities in EEG power spectra. On the molecular level, psychotic symptoms are thought to be underlined by dysfunction of neurotransmitter systems. MK801, an NMDA antagonist, induce psychosis-like symptoms in animals and humans. Antipsychotics tend to reduce the intensity of psychotic symptoms and they produce general slowing of EEG background activity. The aim of the present study was to compare effects of haloperidol, clozapine, risperidone and 5-HT2a antagonist MDL on MK801-induced quantitative EEG changes (power spectra and coherence) in rat.

**Methods:** Stereotactical implantation of 14 electrodes was performed in male Wistar rats seven days before EEG recording. On the experimental day, rats were treated with MK801 0,3 mg/kg and one of the antipsychotic. Signal was recorded simultaneously from frontal, parietal and temporal regions bilaterally. Meanwhile animal's behavior was continuously observed. Subsequent power spectral analysis and the EEG coherences were assessed with the observed passive behaviour.

**Results:** In EEG spectral analysis, MK801 caused an increase of the power in gamma and alpha band and a decrease in slow wave bands. In EEG coherences, a decrease occurred interhemispherally in high frequency bands and intrahemispherally in slow frequency bands. Haloperidol and risperidone partially restored MK801-induced power increase, while clozapine and MDL had no effect on these changes. In EEG coherence, alpha and theta bands were completely restored by haloperidol and clozapine. Risperidone also partially normalized EEG coherence, while MDL had no effect on MK801-induced changes.

**Conclusion:** To conclude, MK801 produced EEG abnormalities similar to ones in schizophrenia. Clinically used antipsychotics tend to reduce some of spectral and coherence changes reflecting normalization of disrupted information processing.

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## Evidence-based QEEG neurofeedback therapy: Clinical outcomes in ADHD

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Neurofeedback studies to date have only used standardized protocols to try to demonstrate successful outcomes for ADHD and have often lacked the best control procedures with experimental designs. We examined patient specific protocols (non-standardized) with the use of age norm referenced performance measures along with eyes closed Z-scored QEEG variables to validate the outcomes achieved. Patient data was obtained from a private practice setting (mean age = 11.35, SD = 5.13; means FSIQ = 99.20, SD = 18.46). Derived age norm referenced EEG data and performance measures from the Integrated Visual and Auditory Continuous Performance Test (IVA/CPT) were collected at baseline and approximately every 5-10 hours in the course of therapy (Mean hours = 21.06). A t-test for dependent samples was conducted for modality specific and non-specific measures of attention and response control. Analyses were conducted on 1) patients that were off medication throughout (N= 41), 2) started on medication initially but off later off medication in the course of treatment (N=3), and 3) on medication and never off medication (N=5). All 41 cases (100%) of cases with no medication intervention showed significant improvement on all performance measures examined ($p < .0000001$ to $p < .001$) and all demonstrated improved or normalized functioning for QEEG z-scores at their respective end points of treatment. Patients engaged in medications generally showed mixed results with analyses for overall measures showing no significant improvement. The results indicate that medications obfuscate optimized individual treatment. Medication versus non-medication brain localization factors by LORETA analyses are being examined.

Keywords: neuro-feedback, QEEG, ADHD

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## Development of a mobile neurocognitive assessment to delineate CNS depressant and stimulant related deficits

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The goal of this project was to develop a mobile, neurocognitive assessment that will provide a multifactorial (i.e., neural, physiological, performance) evaluation of cognitive functioning associated with stimulant or depressant usage.

A double-blind, cross-over, within-subject assessment of neurocognitive performance (M-AMP) and driving while under the influence of either diphenhydramine (sedative, 50 mg) or caffeine (stimulant, 400 mg) in a simulator. The M-AMP consisted of two passive vigilance tasks, one auditory, one verbal; and an active vigilance task, requiring differentiation across three stimuli. Participants (n=9) completed two daytime sessions, consisting of a baseline M-AMP and driving session, followed by drug ingestion, a second M-AMP, a second driving session and final M-AMP.

The feasibility of a parametric-based multifactorial algorithm was demonstrated both through a k-NN algorithm with perfect sensitivity (100%) and specificity (100%), as well as a parametric DFA with sensitivity of 72.2% and specificity of 61.1%. Predictably, diphenhydramine also led to more performance based errors both during the driving simulation (i.e., lane departures) and the M-AMP (i.e., lapses, accuracy, reaction time) compared to caffeine, Fs $(1,17) \geq 4.95$, ps $< .05$. Central theta during the M-AMP tasks was also significantly correlated to the lane departures (r= .73), indicating that M-AMP variables may provide predictive value of impaired driving behaviors.

Future work will expand these findings to examine Marijuana, Benzodiazapines, and Amphetamines, in larger sample sizes.

Keywords: drugs, EEG, neurocognitive profile

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## The effect of noradrenergic attenuation by clonidine on inhibition in the stop signal task: performance and ERP measures

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Understanding the pharmacology of mechanisms of attention and inhibition is key to fuel optimal treatment for disorders such as Attention Deficit / Hyperactivity Disorder (ADHD). Previous studies using a NA reuptake inhibitor have suggested an inverted U curve relationship with high NA enhancement resulting in reduced inhibitory control. On the other hand, studies with a NA antagonist suggest augmented inhibitory control. Here we investigated the effect of a NA antagonist (100 microgram clonidine) on EEG (stop N2 and stop P3 effects) as well as on behavioral (stop-signal reaction time, SSRT) indices of inhibitory control. A double blind placebo controlled crossover design was implemented. EEG was recorded while healthy participants (N=21) performed the Stop Signal Task (SST). In this task go stimuli to which a response is required, are occasionally followed by a stop stimulus which prompts that the go response be withheld. Results show that clonidine had a small but significant reducing effect on the stop-P3 effect (successful minus failed stops) while the stop N2 was unaffected. Behaviorally, clonidine had a non-significant delaying effect on stop-signal reaction time and go reaction time, while clonidine did induce significantly more omissions on go trials. The results are discussed in terms of NA mechanisms in more dorsal (stop P3) versus more ventral (stop N2) inhibition systems.

Keywords: noradrenaline inhibition P3

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## CPP alters cross-frequency coupling between theta and gamma in CA1 in rats: simulation and experiment

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Non-competitive NMDA receptor (NMDAR) antagonists like ketamine are used in pharmacological models of schizophrenia. Other NMDAR antagonists (e.g. CPP), with different molecular mechanisms of action, are used to explore memory and cognition in animals and can produce psychosis. CPP, a competitive antagonist, displaces glutamate from its sites on NMDAR. We hypothesized that since competitive antagonism results in more glutamate availability, increased activity of co-localized AMPA receptors (AMPARs) would produce alterations in network dynamics. We explored this with a computer model of hippocampal CA1. We compared modeling results with data from rats.

The model consisted of 800 pyramidal cells (PYR), 200 basket cell interneurons (BAS), and 200 oriens lacunosum-moleculare interneurons (OLM), built using NEURON. Cell classes were connected with AMPA/NMDA and fast and slow GABAA synapses. We compared models to assess blockage at synapses on the different cell classes, considering differing affinities of antagonists to NMDAR. Experimental recordings were obtained from tetrode arrays implanted in CA1 of Long Evans rats trained to chase sugar pellets, both before and after 5 mg /kg of intraperitoneal CPP.

Recordings after CPP show reduced theta and increased gamma local field potential amplitude. Modeling competitive inhibition to glutamate at OLM cells alone replicated the experimental findings. This was also similar to the effect of non-competitive antagonism. Cross-frequency coupling analysis of the experimental data revealed a reduction of CFC after CPP. Our computer models replicated changes seen in-vivo and enable exploration and predictions of the effect of medications and pathology on network function and dynamics.

Keywords: NMDA receptor antagonists, hippocampus, cross-frequency coupling

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## Selective antagonism of 5HT2A receptors treated psilocin-induced disconnection in the rat brain

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**Objectives:** Our previous results showed the ability of psilocin to induce behavioral, as well as electroencephalographic changes corresponding to acute psychosis in humans. In this study, we explored the impact of the D2 receptor antagonist – haloperidol and the selective 5HT2A receptor antagonist – MDL100907 on functional connectivity using quantitative EEG. This research was performed in order to elucidate mechanisms underlying the action of psilocin and the pathophysiology of psychosis.

**Methods:** After stereotactic implantation and recovery, cortical EEG was recorded from 6 pairs of electrodes on each hemisphere in freely moving rats. EEG power spectra (local synchronization) and coherence (long projections) were subsequently analyzed in Neuroguide Deluxe v.2.6. Adopting a translational approach, only EEG traces that corresponded to behavioral inactivity (model of resting EEG) were processed so they could be compared to human recordings.

**Results:** Psilocin decreased generally both EEG spectral power (most prominently in theta band) and EEG coherences (in lower frequencies both inter- and intra-hemispherical, in higher frequencies only inter-hemispherical). Haloperidol did not impact these changes. However, MDL100907 normalized the decrement in spectral power and even induced an increase in delta and gamma band (mainly in central areas). Furthermore, MDL100907 almost completely abolished the decrement in EEG coherences (excluding few inter-hemispherical coherences).

**Conclusions:** Unlike haloperidol, the 5HT2A receptor antagonist reversed the disconnection of brain areas after psilocin. Our results confirm the crucial role of the 5HT2A receptor in the neurobiology of hallucinogenic effects and show that electrophysiological approach is a useful method in the research of altered states of consciousness.

Keywords: psilocin, quantitative EEG

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## Gamma: Separating signal from noise

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Gamma oscillations (>30 Hz) have been found to be important in processes of attention and conscious perception. In animals they have been shown to be altered by neuropharmaceuticals as well as in animal models of psychiatric disease. However, due to the existence of electrical artefacts in the gamma band, studies of gamma in the scalp EEG of humans have to be interpreted with caution. Recently, we have been developing methods which reduce the effect of these artefacts, in order to uncover the true neuronal signal. These consist of: firstly a noise cancellation technique to remove any power-line noise, secondly a regression technique to reduce the micro-saccade associated artefact, and thirdly a mathematical modeling technique, using Gabor functions, which reduces the effect of scalp and neck EMG contamination. These techniques have been applied to clean induced gamma from visual and motor tasks, and the results indicate that it is possible to separate neuronal gamma from artefactual signals. For example, in a self-paced motor task the algorithms significantly reduce the baseline high frequency signal, which is a mixture of true neuronal gamma and scalp EMG. The specificity of this reduction to EMG is confirmed by the increase in signal to noise ratio of the expected high gamma event related synchronization over contralateral motor areas during the task. The application of new methods of artefact reduction enables gamma band changes induced by neuropharmaceuticals to be detected more effectively in the scalp EEG.

Keywords: gamma, artefact, muscle

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