

IPEG



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

PROCEEDINGS OF THE 13th BIENNIAL IPEG MEETING

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Antwerp, Belgium

IPEG2004 LOCAL ORGANISING COMMITTEE

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IPEG Meeting History

1980 – Berlin, Germany

1982 – Hanover, Germany

1984 – Vienna, Austria

1986 – Santa Margherita, Italy

1988 – Kobe, Japan

1990 – Göteborg, Sweden

1992 – Boca Raton, USA

1994 – Berlin, Germany

1996 – Prague, Czech Republic

1998 – Milan, Italy

2000 – Vienna, Austria

2002 – Barcelona, Spain

2004 – Antwerp, Belgium

Preface

Electrophysiological brain research has a long tradition going back as far as 1875 when the first report on the animal electroencephalogram (EEG) was published by Caton. Consequentially, the first recordings from the human skull were reported by Berger in the early '20s of the last century. Not long thereafter the intriguing world of the effects of drugs on the EEG opened up, a scientific area now known as pharmaco-EEG research.

To date, the impressive progress in knowledge and methodology in pharmaco-EEG research still enjoys the advantageous exchange of empirical findings and insights between animal and human research. This interdependence is also reflected by the different abstracts of presentations at the occasion of the IPEG2004 Scientific Meeting that was held on September 10-12 in Antwerp, Belgium. The proceedings consist of abstracts of keynote lecture, symposia, oral sessions, and poster sessions.

The last decade has brought many attempts to improve understanding and tools for sophisticated analysis of the electrophysiological brain as a three-dimensional organ: functional 3D tomography. Combined application with for example imaging techniques such as fMRI or novel (non-linear) analysis methodology shows that the pharmaco-EEG, with its outstanding temporal characteristics and its unique applicability in man and animal alike, still has the powerful potential to help us to further understand the brain and its pathology, and to help (e.g., as a biomarker or in clinical application) to discover and to develop new drugs to treat CNS disorders.

It is therefore not so surprising that a small but dedicated society as the IPEG manages to successfully organise a series of biennial meetings on electrophysiological brain research in preclinical and clinical pharmacology and related fields. Progress in pharmaco-EEG research relies on the continuing input from a broad range of experts such as preclinical and clinical pharmacologists, psychiatrists, (neuro-) psychologists, neurologists, biologists, bio-statisticians, and computer scientists. The IPEG scientific meetings aim to bring these experts together in a colourful palette of symposia on pharmaco-EEG research of which the proceedings can be found on the following pages.

As with any scientific abstract, its contents are bound to age, and in this case we expect and like it to age rapidly as that would indicate that the pharmaco-EEG field is continuing to develop successfully. Nonetheless, we hope and trust that in the meantime these proceedings will be of help to those of you, who want to accept the challenge to use the opportunities that pharmaco-EEG research brings.

Pim Drinkenburg
chair IPEG2004

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K1 A theory of consciousness and psychiatric disordersE.R. John^{1,2}

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This theory is based upon a body of experimental evidence, partially cited in the attached set of references that supports the following propositions:

1. Consciousness combines information about elements of the complex multimodal stimuli present in the environment with memories of relevant elements of the past experience of the individual, constructing perception of what has been termed the "remembered present" (Tononi and Edelman 2000).
2. Complex stimuli are transmitted by the exogenous system via sensory specific pathways to relay nuclei in the thalamus and propagated to synapses of pyramidal neurons in lower cortical layers, continuously distributed among ensembles of neurons relatively specialized for extracting distinct preferred "features", or attributes of complex stimuli.
3. Feature extracting neurons are unreliable and noisy, sometimes firing when the preferred feature is present, firing when it is absent, failing to fire when it is present, altering its preference, or firing to a non-preferred event. Information about the presence of an attribute in the stimulus is reliably and rapidly represented by the departure from randomness in the average behavior of the ensemble (Burns 1968).
4. These features constitute fragments of sensations, encoded in parallel as time series of firing that cause nonrandom spatiotemporal patterns of synchronization in spatially dispersed cell assemblies, increasing voltages of local field potentials (LFPs) in local cortical regions that may be spatially coherent (Fox and O'Brien 1965, Herculano-Houzel et al. 1999, Rager and Singer 1998) (nonrandom levels of synchronization among the ensembles receiving this input, particularly in the anterior cingulate, supplementary motor area (SMA) and primary visual cortex, may play an important role in working memory).
5. Collateral inputs from the exogenous system reach the limbic system via the inferotemporal and entorhinal cortex, impinging as a time series of synchronized discharges upon pyramidal cells in the hippocampus and distributed as "readin" to other limbic regions such as the amygdala, septum, nucleus accumbens, and the basal ganglia (John and Morgades 1969) (storage of these correlated but spatially dispersed temporally patterned synchronous activations establishes a neural representational assembly (NRA) based on these temporal relationships, which will serve for the consolidation of episodic memory, with associated context and emotional valence).
6. Subsequent synchronized collateral input to separate components of this spatially dispersed NRA, with sufficient similarity with particular portions or the totality of this distinctive spatiotemporal pattern, activates the most relevant memories by associative mechanisms, sending feedback "readout" to the hippocampal pyramidal neurons (John 1972, John and Kleinman 1975) (this constitutes "activation" of an episodic memory).
7. Coincidence detection between readin and readout spatiotemporal firing patterns activates a highly synchronized temporal pattern of output from the limbic system (the "weights" of the relative contributions of different portions of the NRA may vary depending upon the momentary state, e.g., drive levels, arousal level, etc.).
8. These endogenous readouts from representational systems encoding memories in a mesolimbic system (NRAs) are transmitted *via* components of the basal ganglia, medialis dorsalis, the non-specific diffuse projection nuclei of the thalamus and the anterior cingulate cortex to synapses of the pyramidal neurons in upper cortical layers.
9. Excitability of spatially dispersed ensembles of pyramidal neurons receiving convergent temporally synchronized patterns of coinciding exogenous and endogenous inputs is enhanced, converting fragments of sensations to fragments of perception and creating islands of non-random synchrony (Larkum et al. 1999, Llinas and Ribary 1998) (regions of Local Negative Entropy) with increased local field potentials (LFP).
10. "Spontaneous" interactions between large populations of neurons in spatially dispersed but weakly interconnected ensembles of a self-organizing thalamo-cortical-cortical network produce widespread oscillations. In the short term, these oscillations establish a transient random noise environment of the ambient local field potential environment of the ensembles.
11. The effect of the environmental noise on the activated ensembles is to enhance their excitability and to produce large-scale synchronization among remote ensembles of neural oscillators (perhaps by stochastic resonance, linking them into a more globally synchronized system (Kitajo et al. 2004).
12. Abundant normative data indicates that LFP oscillations are regulated in the brain by a homeostatic system involving many brain regions, whose local and long-range interactions are mediated by a variety of neurotransmitters, including but not limited to acetylcholine, dopamine, gamma-aminobutyric acid (GABA), glutamate, N-methyl-D-aspartate (NMDA), norepinephrine, and serotonin.
13. This regulation is evident from the facts that: (i) relatively long term samples of these oscillations reproducibly converge to regionally predictable power spectra of the EEG activity recorded from any brain region (Hughes and John 1999, John and Prichep 1993, Kondacs and Szabo 1999); (ii) the spatiotemporal interactions among all brain regions can be decomposed into a small number of spatial principal components that account for essentially all of the variance of the EEG (Duffy et al. 1992); and (iii) the global field power maps that describe the overall topography of the scalp potential field have been segmented into a small number of microstates that have a mean duration of 80 ± 2 ms from age 6-80 (Koenig et al. 2002). It is noteworthy that psychophysical evidence indicates that perception is actually discontinuous, with the average duration of a "perceptual frame" being about 80 ms (Efron 1970).
The brain mechanisms that underlie these regularities and dynamics of local field potentials (LFP) impose dynamically maintained local voltage thresholds that reliably define the "ground state" of the brain of any healthy, normally functioning individual, independent of ethnic background.
14. As the membranes of neurons in dispersed brain regions are modulated by these regulated ambient local field potentials, summation with those pyramidal neurons whose excitability has been enhanced by convergent exogenous and endogenous influences causes their membrane potentials to become suprathreshold. This action facilitates coherent cortico-thalamic (C-T) volleys, binding together the local perturbations of entropy which are dispersed fragments of perception (Larkum et al. 1999, Llinas and Ribary 1998).

15. The thalamic cells from which afferent input to the cortex resulted in convergence respond to these C-T volleys by coherent T-C-T-C reverberating spatiotemporal patterns in the gamma frequency range (Llinas and Ribary 1998).
16. Substantial evidence exists of zero phase-locking of electrical activity in remote brain regions during human as well as animal performance of cognitive or perceptual tasks (Desmedt and Tomberg 1944, Francis et al.2003). These and numerous other reports of zero phase lag between multiunit activity and LFPs in remote but synchronized neuronal ensembles cannot be reconciled with conventional ideas of information transfer only by synaptic transactions. Such evidence can be explained as the result of a transition from reverberation to resonance.
17. Spatially extensive sustained T-C-T-C reverberations establish a spatiotemporally fluctuating resonating electromagnetic field of information, the physical vehicle sustaining unified perception.
18. This resonating field of information is an improbable distribution of energy in time and space that constitutes global negative entropy and generates the content of consciousness (John 2001).
19. Blockade of the coincidence detection between the exogenous and endogenous inputs to the pyramidal cells of the limbic system will cause failure of episodic memories.
20. Blockade of the coincidence detection between the exogenous and endogenous inputs to the neocortex results in loss of consciousness, blockade of awareness as in coma or anesthesia (Hassler 1979, John et al. 2001).
21. Perturbation of the thresholds of local brain regions or changes in the level of interactions between any region and all other brain regions can result from anatomical damage or by excesses or deficits of the neurotransmitters mediating those transactions. Such perturbations of homeostasis will change the threshold defining the corresponding local negative entropy and thereby alter the contribution of that portion of the self-organizing system to the unified global negative entropy. This may result in alterations of particular dimensions of perception, may bias activated NRA toward distorted values or emotions, change the contextual perspective of subjective experiences and is a major factor contributing to psychiatric illness (Hughes and John 1999, John and Prichep 1993).
22. The contribution of psychopharmacology as guided by pharmac-EEG lies in restoring the perturbed system to its natural Ground State, thereby enabling restoration of normal adaptive behavior and interpretation of subjective experiences (Saletu et al. 2000).

Key words: consciousness, binding, ground state, local negative entropy, global negative entropy, pyramidal neurons, local field potentials, LFPs, QEEG

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K2 Adenosine, sleep loss, and the EEG

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This talk will address three principal questions about adenosine and sleep-wake regulation: (i) is adenosine an endogenous sleep factor; (ii) are there specific brain regions/neuroanatomical targets and receptor subtypes through which adenosine mediates sleepiness; (iii) what are the molecular mechanisms by which adenosine may mediate the long-term effects of sleep loss? Data suggest that adenosine is indeed an important endogenous, homeostatic sleep factor, likely mediating the sleepiness that follows prolonged wakefulness. The cholinergic basal forebrain is reviewed in detail as an essential area for mediating the sleep-inducing effects of adenosine by inhibition of wake-promoting neurons *via* the A₁ receptor. The A_{2a} receptor in the subarachnoid space below the rostral forebrain may play a role in the prostaglandin D₂-mediated somnogenic ef-

fects of adenosine. Recent evidence indicates that a cascade of signal transduction induced by basal forebrain adenosine A₁ receptor activation in cholinergic neurons leads to increased transcription of the A₁ receptor; this may play a role in mediating the longer-term effects of sleep deprivation, often called sleep debt. New behavioral experiments shows that the cognitive effects of sleep deprivation in humans can be modeled in rodents, with the 5 choice serial reaction time test showing a reduction of vigilance following sleep deprivation. A recent review article will provide a detailed account of the main points in this talk: Basheer R, Strecker RE, Thakkar MM, McCarley RW (2004) Adenosine and sleep-wake regulation. *Progress in Neurobiology* 73: 379-396.

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K3 From single-lead analysis to LORETA: the successful development of QEEG in neuropsychiatry and neuropsychopharmacology

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While Hans Berger was of the opinion that the EEG would represent a breakthrough in the diagnosis and treatment of psychiatric disorders, visual evaluation turned out to be mainly of help in neurological disorders, especially epilepsy, and thus initially the method gained more momentum in neurology than in psychiatry. Only with the advent of computer-assisted quantitative analyses was the EEG rediscovered for psychiatry *via* psychopharmacology. Utilizing in the '60s and '70s single-lead and from the '80s onwards multi-lead analyses and subsequent mapping techniques, it became possible to classify psychotropic substances and objectively evaluate their bioavailability at the target organ, the human brain. Pharmacology-EEG profiles and maps of neuroleptics, antidepressants, tranquilizers, hypnotics, psychostimulants and nootropics/cognition-enhancing drugs were presented. Specifically, it could be determined at an early stage of drug development whether a drug was effective on the central nervous system (CNS) compared with placebo, what its clinical efficacy would be like, at which dosage it acted, when it acted and which were the equipotent dosages of different galenic formulations. In the past decade, the development of 3-dimensional EEG tomography such as low-resolution brain electromagnetic tomography (LORETA) made it possible to determine where a drug worked within the brain. In analogy to the above-described development, several research centers also applied these techniques in clinically well-defined diagnostic subgroups of mental disorders, such as schizophrenia with predominantly plus and minus symptomatology, major depression, generalized anxiety disorder, agoraphobia, social phobia, obsessive-compulsive disorder, age-associated memory impairment, multi-infarct dementia, senile dementia of the Alzheimer's type and alcohol dependence. It turned out that EEG maps of different nosological groups differed both from each other and from normal controls, although overlaps may be seen, which reflect the clinical situation. Interestingly, the differences to normal controls were in many variables found to be opposite to the differences observed between psychotropic drugs and placebo. Thus, by considering these differences between psychopharmacological agents and placebo in normals as well as between mental disorder patients and normal controls, it may be possible to choose the optimum drug for a specific patient according to a key-lock prin-

ciple, since the drug should normalize the deviant brain function. Low-resolution brain electromagnetic tomography (LORETA), which identifies brain regions affected by psychiatric disorders and psychotropic drugs, will provide further knowledge on the utilization of the QEEG in diagnosis and treatment of neuropsychiatric disorders.

S1.1 Post-training sleep enhances precise timing of the MMN: a neural correlate of memory consolidation

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Psychophysical and neurophysiological evidence confers diurnal and nocturnal sleep a crucial role in memory consolidation. As a result of posttraining sleep, performance on perceptual and motor tasks becomes more automatic – that is, less dependent on voluntary attention. We have recently shown that sleep, regardless of behavioral benefits, is critical for enhancing automaticity in the absence of attention. In the two, three days following training on an auditory discrimination task, subjects who were allowed to sleep the night after training, contrary to those who were sleep deprived, could not avoid switching their attention toward the unexpected task-irrelevant (distracting) sound while reading a book (Atienza et al. 2004). In response to task-irrelevant sound changes 48 h after training, sleep-deprived subjects neither showed the significant increase in the MMN amplitude as controls did at frontal derivations, nor the enhanced MMN was followed by the P3a component of event-related potentials (ERPs), signalling involuntary switch of attention towards the previously unattended sound. Sleep deprivation, however, did not prevent improved behavioral performance. We conclude from these results that sleep might reduce the voluntary attentional effort required to be aware of potentially meaningful events that are out of one's focus attention.

We have now investigated whether sleep-based consolidation of sensory memories, as revealed by delayed increases in the MMN amplitude, stems from a decrease in the latency variability (latency-jitter) of event-related neural responses elicited by unexpected infrequent (deviant) sounds over trials. In other words, the present study aims at determining whether post training sleep enhances consistency with which neural assemblies in the auditory cortex respond to unexpected changes in previously registered regularities. To obtain the event-related neural response over trials eliminating contribution of the EEG background, a denoising implementation based on the wavelet transform was applied to each single trial. Subjects who slept the night following training showed a significant decrease in the latency variability of the deviant-related negativity within the MMN time window at 48 and 72 h post-training sessions as compared with the sleep-deprived group. After correcting the latency-jitter in the two groups, differences in the amplitude of brain responses disappeared. This finding was not observed for the standard sound. No sleep-dependent effect was either observed on the amplitude-jitter. All together, these results suggest that post-training sleep enhances automaticity by improving the precise response timing of neuronal populations in the auditory cortex to unexpected changes in the environment, rather than changing the synchrony or the number of neurons that represent auditory scene.

Reference

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S1.2 Determinants of stimulus repetition and deviance on cortical potentials

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While repetition of stimuli leads mostly to a response decrement of event-related potentials (ERPs), stimulus deviance in a repetitive auditory stimulation elicits an additional activation in form of a mismatch negativity (MMN). The MMN was found to be reduced in schizophrenia in several studies, most consistently and pronounced for deviance in tone duration. A reduced MMN can functionally be taken as an indicator for an impaired auditory discrimination process, but it remains unclear whether it is associated to anatomical and/or neurotransmitter deficits. One problem with respect to anatomical correlates of MMN generation is their exact determination. In a recent study of our group, the MMN could be recorded intracranially from the lateral inferior frontal cortex and the anterior gyrus cinguli. Besides, neuromagnetic recordings of the MMN revealed that the source within temporal lobe depends on the kind of deviance. The N-methyl-D-aspartate (NMDA) antagonist ketamine induces psychotic behaviour in healthy subjects and reduces the MMN, possibly indicating an involvement of this neurotransmitter in the deficient MMN generation in schizophrenics. However, also lorazepam as gamma-aminobutyric acid (GABA) agonist led to a reduction of MMN and both drug-induced reductions were found for several kinds of deviance in similar degree. Future studies will target the MMN and response decrements of other ERP components by repeated stimulation, as both are processes in close association to the formation of an echoic memory trace. So far, the differential impact of drugs on MMN and sensory gating (as one aspect of response decrement by repeated stimulation) possibly indicate two on the neuronal basis distinct processes.

S1.3 Mismatch negativity in schizophrenia and Alzheimer's disease

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Mismatch negativity was studied in 49 schizophrenic patients, 49 healthy controls, 25 bipolar affective disorder patients, and 13 Alzheimer's patients. Only the schizophrenics exhibited reduction in mismatch amplitudes. A measure called the "memory trace effect" was developed using the length of the pre-train of standard tones, which correlated with the magnitude of the mismatch negativity potential. This measure was used to show that the encoding of auditory signals is weekend in proportion to the severity of cognitive deficits in the schizophrenic group, but not other groups, and reveals a specific deficit of basic auditory encoding specific to schizophrenics with cognitive deficits which is very probably based on a deficit of NMDA-NR1 and 2 receptor functioning, as indicated by deficits of NR1 and 2-gene expression which correlated highly with cognitive deficit in schizophrenia (Humphries et al. 1996).

S1.4 Target detection in patients with schizophrenia: a simultaneous EEG/fMRI-study

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Introduction. The P300 component of the event-related potential is thought to reflect various cognitive processes including the allocation of attentional resources to incoming stimuli. Reduction of the auditory P300 amplitude is constantly found in schizophrenic patients. Besides it could be shown that the P300 amplitude correlated negatively with the severity of thought disorders. Thus the P300 appears to be a suitable functional parameter of thought disorders in schizophrenic patients. We combined ERP and simultaneously acquired functional MRI data as suggested earlier (Mulert et al. 2004) to examine discrepancies in brain regions involved in information processing as well as in the time course of neural generators of the event-related potential between schizophrenics and normal controls.

Methods. So far the study comprises nine patients with schizophrenia and six age matched controls with no known history of neurological or psychiatric disorder. The subjects performed an auditive oddball task requiring responses to infrequent tones presented in a series of frequent tones of a different pitch. MR imaging was performed at 1.5 T Siemens Sonata scanner (EPI sequence; 12 slices; TR/TE: 3 000/53 ms). EEG signals were recorded with an amplifier that cannot be saturated by MR activity (61 channels according to the international 10/10 system; Cz reference).

Results and Discussion. The EEG recordings showed the expected positive deflection about 400 ms after the presentation of infrequent stimuli in normal controls and a reduced P300 component in schizophrenics. In addition we could replicate findings of previous P300-/fMRI studies revealing BOLD activations mainly in frontal, especially anterior cingulate cortex, SMA, insula, inferior and middle frontal gyrus as well as thalamus, temporal and parietal brain structures in healthy subjects. The functional MRI data of schizophrenic patients showed a reduced BOLD response in a widespread network of cerebral areas involved in task execution. There was a modest negative correlation between the extent of functional activation in the ACC/SMA region and thought disorders as well as negative symptoms (PANSS). Our findings suggest widespread abnormal brain functioning in patients with schizophrenia during information processing. The relationship between psychopathology and BOLD-activation pattern underlines that beside the well known genetically determined trait character of the P300 potential additional relations to present symptoms can be detected and attributed to the activity of distinct brain regions.

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S2.1 Drug related electrical fingerprints: the importance of specially defined frequency ranges leading from preclinical experiments to successful clinical trials

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Quantitative evaluation of EEG recordings is usually based on frequency analysis according to Fast Fourier Transformation. In or-

der to interpret the resulting power spectrum four or more frequency ranges are defined for further analysis and documentation. For historical reasons ranges were called delta, theta, alpha, and beta bands. But there has been no common agreement on exact definitions. Since the final goal of the definitions was to search for correlations with other biological parameters numerous approaches exist with as many band definitions as research groups are working on the problem.

In 1987 we used a definition of ranges for the first time where frequency bands changed independently from each other accordingly to the presence of different drugs (Dimpfel et al. 1987). The basic idea behind this approach was to use receptor specific compounds in order to selectively change neurotransmission aiming at the correlation of frequency changes with neurotransmitter activity. From the results of this kind of preclinical studies the idea emerged that cholinergic transmission was mainly reflected in delta band activity (0.86-4.5 Hz). Pharmacological interference with the norepinephrine alpha2 receptor led to selective changes in theta band activity (4.75-6.75 Hz). Application of compounds changing serotonergic activity led to changes in alpha 1 band activity (7-9.5 Hz) whereas changes in dopaminergic activity seemed to be reflected in alpha 2 band activity (9.75-12.5 Hz).

With respect to clinical research correlates between these same frequency bands (which also change independently from each other in humans) and behavioral parameters have been found. For example theta activity transiently increased in response to mental concentration at frontal electrode positions (Schober et al. 1995). Alpha 1 activity could be related to changes in attention at parietal electrode positions. Decreases in alpha 2 activity have been related to activation of working memory by Stipacek and coauthors (2003). Increases in beta 1 activity (12.75-18.5 Hz) have been seen in the presence of minor and major tranquillizers probably reflecting sedation and anxiolysis. Furthermore evidence emerged that the electrical fingerprints as produced from these data allowed to construct algorithms related to depth of sleep or changes in behavioral mood scales (i.e., Hamilton depression scale). Thus, changes in these defined frequency ranges now allow for better interpretation of the EEG in terms of biochemical and psychophysiological consequences in preclinical and clinical drug trials.

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S2.2 PK-PD modeling of human pharmaco-EEG data reveals information otherwise unseen

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Descriptive data analysis applied to topographic brain maps is the analysis strategy most frequently used when dealing with human pharmaco-EEG data, however in some circumstances this approach

can become unsatisfactory. An example is presented where the application of PK-PD modelling to human pharmaco-EEG led to conclusions otherwise unachieved. Specifically, the use of the population approach to PK-PD modelling has shown the possibility to assess different *in vivo* properties of GABA_A receptor through 16-leads relative alpha activity after iv and oral lorazepam administrations as a function of psychometric anxiety differences in healthy volunteers (12 for each anxiety group: high, normal and low) together with evidencing acute tolerance development after oral benzodiazepine intake.

S2.3 Localization of electrical sources of event-related brain activity in menopausal women with age-related cognitive decline before and after hormone replacement therapy with a conjugated estrogens/medrogeston combination

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Objective. Although epidemiological and clinical studies suggest that hormone replacement therapy (HRT) may protect against cognitive and neurodegenerative disorders, the relation between estrogen and cognition in postmenopausal women remains controversial.

Methods. In a double-blind, placebo-controlled, parallel-group-design study, the effects of HRT with the estrogen-progestogen combination Presomen 1.25 compositum[®] (1.25 mg equine conjugated estrogens administered for 21 days plus the progestogen 5 mg medrogeston given for eleven days) on the electrical sources of event-related potentials (ERPs) were investigated in postmenopausal patients with age-related cognitive decline (DSM-IV code 780.9, ICD-10 code R 41.8). After a pre-drug comparison with age-matched normal healthy postmenopausal controls, 48 patients aged 60 ± 6 years and free of psychotropic drugs were randomized to receive either placebo or verum for 3 months. ERPs were recorded before as well as on the 91st and 92nd day of the study, which thus fell into the estrogen phase of the treatment during the 4th cycle.

Results. Concerning latencies, patients showed a lengthening of P300 latency as compared with normal controls. After HRT with Presomen, a significant shortening of P300 latency as compared with placebo was observed. Concerning LORETA source strength, untreated patients showed changes in structural and energetic processes related to task-irrelevant stimuli and reduced task-related brain activation in the precuneus and the anterior cingulate cortex (ACC) for the N2 component as well as increased brain activation in the occipital lobe for the P300 component. After HRT with Presomen, as compared to placebo, a significantly decreased activation in brain regions that were not task-specific was observed.

Conclusions. The baseline LORETA-ERP differences between patients and normal controls suggest that in the patient group the aging process was advanced. After HRT with Presomen a significant improvement and a normalization of information processing and attentional processes were observed.

S2.4 Towards rational polytherapy: interactions within the GABA-A receptor complex

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Abstract not available

S3.1 Discovery and integrative neuroscience using neuroinformatics approaches

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<http://www.nimh.nih.gov/neuroinformatics/index.cfm>

Contemporary technologies used to understand brain structure and function break new ground in terms of our ability to collect data at high levels of granularity from the level of the gene to the intact functioning brain in living, behaving subjects. While there are many challenges in this exciting research area, two of the greatest are the: (i) creative design and completion of appropriate experiments revealing new data; and (ii) integration of data from the genomic and molecular to the structural and functional data obtained from, for example, an fMRI experiment. Success in the first requires a creative mind, intellect and knowledge of current data and our understanding of brain structure/function. The second, in my opinion requires the creation of a new neuroscience infrastructure and the sharing of primary data (Koslow 2000, Koslow and Hyman 2000). The creation of a data infrastructure will also facilitate the challenge (1 above), by providing immediate and easy access to primary data. The ever-increasing quantity and types of data being produced further complicate the data integration issue. The infrastructure required to solve this problem is similar to that created for genome projects. The creation of databases, analytical tools and models has greatly enabled this field. A similar system for neuroscience should also enable our efforts to understand the nervous system across the life span in health and disease and create a new field of discovery neuroscience. The field of informatics provides the knowledge and ability to build this capacity. Informatics offers us the ability to store, retrieve, access, visualize, analyze, integrate, electronic collaboration and share data. Neuroscience informatics will be different than bioinformatics in that there will probably be distributed federations of databases and not one central database. Similar to bioinformatics, we will need to create unique databases and tools to capture the diverse data types and data forms. To create this ability requires a focused effort to ensure that databases and tools are interoperable, that is that "computers can interact" with each other. Using current technology, this would require the use of a standard terminology, developing an ontology for all data types and experimental conditions, with the ability to continually add and update terms. Also requiring unique attention are quality assurance, metadata, analytical and modeling tools and most important, the cultural, legal and ethical issues. This presentation will discuss these issues in depth; provide examples of existing database and analytical tools that are under development (Koslow 2002), as well as global efforts that are underway in this area (Neuroinformatics Working Group 2002).

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S3.2 Integrative neuroscience in pharmaceutical trials

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In neuroscience alone, more than 60 000 neuroscientists and 300 specialist journals generate a plethora of poorly related datasets. In psychiatry, there are hundreds of studies showing possible distinctive patterns of brain dysfunction, but they have been undertaken in relatively small datasets (sample sizes of less than 30). Such small subject numbers preclude proper account being taken of the inherent inter-subject variability in human brain function and behaviour. It may be myopic to continue to generate large numbers of such small study outcomes, without some commensurate evaluation of the relative amount of variance explained by the different measures, as well as the sensitivity and specificity of these findings across different psychiatric disorders. The lack of integration across studies also means there is no consistent and widespread platform from which to evaluate the efficacy of medication in these disorders. This talk focuses on the potential use of neuroimaging-psychometrics-genetics databases in pharmaceutical trials in psychiatry. In addition to outlining the extraordinarily systematic nature of many variables that have been found in the database, key multimodal interrelationships are provided. For example: subjects with the met allele for BDNF were found to have fMRI underactivity of the hippocampus, intrusion memory disturbances in neuropsychological tests and delayed P300 latency in the auditory oddball paradigm. The implications for Alzheimer's trials are explored. A second example concerns ADHD: the numerical simulation shows that EEG theta activity reflects activity of the reticular nucleus of the thalamus and its propensity to inhibit networks not required for adaptive sensory processing. The links of this finding with neuropsychological tests of executive function are examined with respect to "Personalised Medicine" predictive validity of Ritalin and Strattera. The specific benefits of a standardised methodology at multiple sites and a multimodal database are examined with respect to pharmaceutical trials from proof of concept stage to phase IV.

S3.3 Sex specific differences in EEG/ERPS relevant to depression, psychosis and pharmacotherapy: evidence from an international database

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Demographic variables including sex, age, life-trauma, drug-use, and socio-economic status impact on the prevalence and manifestation of psychiatric illness. In understanding aetiology and treatment, potentially confounding variables cannot simply be controlled for by matching. Rather, complex interactions must be examined which require large sample sizes of patient and healthy populations. Studies of subclinical populations offer opportunity to observe both vulnerability and compensatory mechanisms. Both of which might be used as targets for development of novel treatments that improve debilitating symptoms, while maintaining potentially beneficial traits. Again, the interaction between these mechanisms can only be studied if power is provided by large datasets. Evidence is presented from an international database supporting demographic (e.g., sex, age, life-trauma, handedness)-specific changes in event-related potentials relevant to psychiatric illness. Particular focus is given to sexual dimorphism in schizophrenia and depression. Results suggest sex-specific changes in brain function found in psychiatric illness

are similar to those seen in healthy, but at risk groups. Underlying mechanisms reflect changes in brain structure, and hormonal fluctuations. Analysis of sex-diagnosis interactions will lead to better understanding of the aetiology of psychiatric illness and has implications for effective treatment of men and women. Other demographic variables are likely to be of equal importance. Discussion will involve the value of databases in providing the large sample sizes required for integrating information from multiple variables. The use of subclinical models in identifying biomarkers for prediction of treatment outcome and assessment of drug efficacy is also discussed.

S3.4 Working memory effects of methylphenidate in attention deficit/hyperactivity disorder

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Rationale: AD/HD is associated with deficits in verbal learning and memory. It is unclear however, whether these deficits in learning and memory are due to difficulties registering and updating new information within working memory (WM), or with the retrieval of such information once learnt. The current study assessed (i) whether learning difficulties in AD/HD are associated with the registration of content within working memory and (ii) the effects of methylphenidate (MPH) treatment on this relationship. Working memory registration was assessed using event-related potential (ERP) components shown previously to reflect working memory updating processes. Learning and memory capacity was assessed using well-established neuropsychological testing.

Method. Participants were 40 adolescents diagnosed with AD/HD (combined and inattentive subtypes) and 160 age- and sex-matched healthy controls. AD/HD participants were unmedicated during their first session and had been on a minimum of one month's treatment with MPH prior to their second session. All participants completed two tasks during each session. A working memory task (WMT) involved monitoring a sequence of letters presented one at a time and detecting occasional letter repeats (targets). An ERP component (P372) specifically associated with working memory updating was obtained to non-target letters in this task. A learning and memory task (LMT) was used to provide behavioural assessment of verbal learning and recall capability.

Results. Prior to medication, the AD/HD group showed significantly smaller P372 amplitude relative to Controls. They also demonstrated significantly poorer recall of words on the LMT. Post medication, there was significant improvement in word recall but no change in the amplitude of the P372, though the latency of this component was significantly decreased.

Summary and conclusion. This study replicates previous findings of verbal learning and memory deficits in AD/HD and finds that there are concurrent abnormalities in the updating of verbal content in working memory. MPH treatment improved both the recall of newly learned verbal material and the speed of registration of new information in working memory. However, the specific pre-treatment abnormalities observed in working memory updating were not ameliorated, suggesting that MPH achieved improvements in memory recall *via* alternative working memory mechanisms.

S4.1 Transcranial magnetic stimulation combined with EEG in pharmacological brain research

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Transcranial magnetic stimulation (TMS) is a direct, non-invasive tool to study neurophysiological properties of the human brain (Barker 1991). In TMS, a time-varying magnetic field is generated by driving current pulses through a stimulator coil placed above the head. This induces an electric field in the brain, resulting in membrane depolarization and neuronal activation. TMS has been used widely in pharmacological studies for studying effects of different drugs on motor cortex with simultaneous recording of motor evoked potentials (Kähkönen and Ilmoniemi 2004)

Recently, TMS has been combined with EEG, which allows one to obtain direct evidence about the TMS-evoked transient changes of neuronal activation in millisecond time resolution in different conditions (Ilmoniemi et al. 1997, Kähkönen et al. 2001, 2003, Paus et al. 2001). For example, stimulation of the left sensorimotor hand area elicited an immediate intensity-dependent response at the stimulated site and a subsequent spread of activation about 20 ms after stimulation to the contralateral hemisphere (Ilmoniemi et al. 1997, Komssi et al. 2004). TMS combined with EEG has also been applied to non-motor cortical areas, such as the prefrontal cortex. Prefrontal TMS caused an intensity-dependent increase in EEG responses, but the extent of activation varied in different intervals after stimulation (Kähkönen, submitted). TMS/EEG allows one to study differences in excitability between cortical areas. Cortical reactivity after prefrontal TMS was lower compared with that after motor cortex TMS. However, reactivities after prefrontal TMS and motor cortex TMS correlated positively (Kähkönen et al. 2004).

We studied the effects of alcohol on EEG responses evoked by magnetic stimulation, demonstrating the potential of combined TMS and EEG in neuropsychopharmacological studies. A dose of 0.8 g/kg ethanol was given to healthy subjects; EEG responses to left motor cortex TMS were recorded before and after the ethanol challenge (Kähkönen et al. 2001). Ethanol changed the EEG responses mainly at 45 ms after stimulation at the site of stimulation and the right frontal areas. Minimum-norm estimation was used to locate the effects more precisely. Activation of the right prefrontal area seemed to be most clearly affected, meaning that alcohol would have changed the functional connectivity between the left motor cortex and the right prefrontal cortex. In another study, EEG responses after left prefrontal TMS were measured before and after ethanol intake (Kähkönen et al. 2003). Alcohol decreased global mean field amplitude (GMFA), the effect being largest in the anterior EEG electrodes. These studies provide direct evidence that ethanol could change local cortical excitability and functional connectivity to remote sites.

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S4.2 Combined fMRI and MEG studies on P50-suppression and mismatch negativity in schizophrenia

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In schizophrenia, various measures of stimulus adaptation are known to be impaired. These deficits were suggested to be causal for the attention deficit and hallucinations due to impaired suppression of irrelevant or self-induced sensory stimuli. Disturbed connectivity with reduced synchronization of neuronal networks might contribute to these phenomena. Magnetoencephalography (MEG) captures synchronized stimulus evoked activity and induced oscillation. Functional magnetic resonance imaging (fMRI) relies on metabolic processes and reflects neuronal events irrespectively of synchronization.

We assessed mismatch responses and stimulus suppression by means of fMRI and whole-head MEG. Thus, we could assess hemodynamic and electrical activation at both auditory cortices. To allow for similar stimulation in both modalities, we modified the P50 suppression paradigm and tested 12 patients and matched controls with pairs of tones. Suppression after a short stimulus onset asynchrony (SOA = 500 ms) was compared with the effect of a long pause (SOA = 1 500 ms).

Patients exhibited a reduction of the suppression of P50m (evoked field 50 ms after stimulus onset), N100m (100 ms), and hemodynamic responses (%-BOLD in primary and secondary auditory cortex). In general, group effects were more consistent at the left hemisphere. Temporal-spatial analysis of the induced components revealed pre- and post-stimulus alterations in the high alpha range. The expectancy of stimuli reduced this component; however, 250 ms after stimulus onset a relative increase of this band was found in the patients only. Regression of the evoked components with induced suppression revealed associations of the P50m with pre-stimulus suppression and of the N100m component with post-stimulus enhancement. The hemodynamic analogue correlated with early (<200 ms) induced oscillations and inter-hemispheric covariance.

In schizophrenia, stimulus adaptation is disturbed on multiple levels. We described changes in the neuronal processing of repeated auditory stimuli by means of whole-head MEG and fMRI. Across these measures reduced adaptation was found in schizophrenic patients. Moreover, temporo-spectral analysis revealed late post-stimulus enhanced oscillatory activation and anticipated alpha suppression. Whereas these alterations in different modalities seem to be associated to a large degree, early and late induced components can be assigned differentially to P50m, N100m, and BOLD re-

sponses. We suggest that schizophrenia is characterized by a combination of various processing deficits rather than an alteration in a unique system. Some of these changes are reflected in evoked and induced components during automatic sensory processing. Changes in the auditory system are associated with formal thought disorder in schizophrenia. The delineation of specific neuronal mechanisms involved in the processing of automatic adaptation processes and pharmacological changes of them might help to understand further the basis of the disorder.

S4.3 Uridine is a novel putative neuromodulator in the nervous system

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There are sporadic data on uridine-induced changes in the nervous functions. Uridine promotes sleep in rats and uridine diet decreases seizure incidence in epileptic patients. Consequently, uridine might be an interesting compound for modulation of neuronal functions without influencing too many traditional receptors inducing side effects. Before our studies, no direct evidences were available about the cellular targets and mechanisms of uridine activation. The series of experiments reported here on uridine induced neuromodulation is a good example of combination of classical EEG, other electrophysiology methods, and neurochemical techniques. Application of 40 mM uridine *via* a dialysis probe inhibited the firing rate of hippocampal CA1 pyramidal cells. However, rapid application of uridine by iontophoresis using multi-barrel electrodes (40-100 nA, 5 s) was both excitatory and inhibitory in the thalamic, hippocampal, and cortical neuronal networks. Excitation was more frequently recorded than inhibition in the thalamus and hippocampus. There was no specificity in distribution of the uridine sensitive cells. Effect of uridine on neuronal firing was different from the effect of adenosine and it was not blocked by P1 receptor antagonists. Sustained depolarization of thalamic and hippocampal neurons induced by ouabain, high potassium and kainate resulted in release of adenosine, inosine, guanosine, and uridine as measured by microdialysis. Placing AP4 crystal to the surface of the cortex in rats induces epileptic seizures in Halothane anaesthetized rats. There is no detectable cell loss in AP4 treated rats but the calcium binding proteins in hippocampal interneurons disappear after the seizure induction. Extracellular concentration of uridine increases during epileptic activity but not in the interictal periods as measured by microdialysis combined with EEG recording. The search for uridine target protein(s) was initiated using photoligand assay detecting H3 azido-uridin in 2D electrophoresis gels of the hippocampus. We demonstrated that Br-uridine and azido uridine develop the same electrophysiological effect as uridine so the binding proteins of azido uridine is probably the same as uridine binding proteins. We have some promising data but actually we also have too many uridine binding protein candidates. On the basis of our findings about uridine, we can conclude that depolarization releases uridine; uridine is able to modulate neuronal firing; uridine is released under epileptic seizures. These data are matching the criteria of a neuromodulator. Thus we claim that uridine is a putative neuromodulator, which could be involved in the pathogenesis of diseases in which sustained depolarization kills the cell. We can but speculate about the physiological role of uridine because actually available data suggest that uridine is released perhaps in pathological conditions rather than in physiological procedures.

S4.4 Unraveling the pathophysiology of obstructive sleep apnea: EEG, microdialysis, *in vitro* electrophysiology, and behavioral techniques in an animal model

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Obstructive sleep apnea (OSA) is a common sleep disorder, affecting 2-4 % of the general adult population, and a higher percent of the elderly. OSA is characterized by a collapse of the upper airway during sleep, which leads to periods of hypoxemia, as well as brief arousals from sleep, which terminates the apneic episodes and re-establishes a patent airway. The frequency of apneas and subsequent arousals is typically 20 to 40 per hour. The interruption of the normal sleep cycle due to frequent arousals results in a reduction in stages 3-4 sleep (delta sleep), while stages 1-2 are increased. OSA produces daytime hypersomnolence and neurocognitive deficits. We are using behavioral, microdialysis and EEG techniques to understand the relative role of intermittent hypoxia (IH) *versus* sleep interruption (SI) in producing the effects of OSA. We specifically hypothesize that the SI associated with OSA, but not the IH, is primarily responsible for the symptom of daytime sleepiness seen in OSA, and for certain neurocognitive effects, and that these SI effects are due to an increase in extracellular adenosine, which we hypothesize to be a mediator of the homeostatic sleep drive.

To model SI in the rat, we used 30 s of a moving treadmill followed by 90 s of no movement. EEG analysis indicates this SI selectively deprived the animal of delta sleep (analogous to stages 3-4 in humans), while not markedly affecting the percent of wake, nonREM and REM stages. Extracellular adenosine levels in the basal forebrain continued to rise during 2 days of SI, but did not rise in exercise control animals (30 min of treadmill movement, and 90 min no movement), nor in animals treated with IH, supporting the hypothesis that an adenosine increase may mediate at least some of the daytime sleepiness in humans with OSA, who have a marked reduction in delta sleep. We hypothesized that sleep fragmentation-induced changes in hippocampal plasticity could underlie some of the impairments in cognition/memory performance observed in humans with OSA, since activity-dependent hippocampal synaptic plasticity plays a vital role in declarative, working, and spatial memory. Using *in vitro* hippocampal slices, SI was compared with exercise controls in effects on long-term potentiation (LTP), a measure of synaptic plasticity. Slices prepared from rats subjected to 24 h or 72 h of SI showed an impairment of LTP, an impairment that was reversed by adenosine blockade with CPT and mimicked by adenosine in untreated animals. We are also investigating the behavioral effects of SI, such as an impairment of extradimensional learning (analogous to set-shifting in the human Wisconsin card sorting task), as well as vigilance effects.

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S5.1 First-night effects on visually and automatically determined measures of sleep in a large database of healthy controls and sleep-disturbed patients

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Introduction. The first-night effect (FNE) is a well-reported phenomenon in sleep research. It is considered to result from the subject's adaptation to the unfamiliar environment of the sleep laboratory. The aim of the present paper was to study FNEs on sleep measures based on visual classification according to Rechtschaffen and Kales (R&K) and on automatically evaluated sleep spindle data, utilizing the Siesta database.

Methods and Results. In 189 healthy controls (90 males, 99 females, 20-95 years) as well as 48 patients with sleep apnea (41 males, 7 females, aged 29-73 years) and 17 patients with insomnia related to generalized anxiety disorder (GAD) (9 males, 8 females, 21-66 years), two consecutive nights in the sleep laboratory were recorded. For sleep parameters based on R&K the most pronounced FNEs were reduced stage REM sleep and increased REM latency as well as reduced total sleep time and sleep efficiency due to increased sleep latency and prolonged wake within the total sleep period. These FNEs were predominantly observed in the first, less pronounced in the middle and completely absent in the last sleep cycles. While in apnea patients and controls similar FNEs were observed, no significant FNEs were found in GAD patients. However, of greater relevance than the effects on group means were the significantly increased variances observed in all groups in the first as compared to the second night. In contrast to clear FNEs on R&K variables, the characteristics of automatically evaluated sleep spindles were not influenced by adaptation phenomena.

Discussion. Generally, subjects' sleep in the first night was lighter and more fragmented, specifically in the first half of the night. The main FNE, however, concerned parameters related to REM sleep: increased REM latency and reduced REM stage. Thus, the partial REM sleep deprivation in the first night most likely has consequences for the second night (REM rebound). In statistical tests for significant differences between patients and controls, pre- and post-drug or drug-induced and placebo-induced changes, the observed differences are related to the observed variances and thus the pronounced FNE on group variances might lead to falsified results in studies without an adaptation night. On the other hand, sleep spindle density, intensity, frequency and episode duration showed a strikingly distinctive and reproducible pattern for each individual in the first and the second night, proving the high retest reliability of the automatic detection method.

Conclusion. In order to obtain reliable and valid measures of sleep, the recording of an adaptation night is absolutely necessary, independent of the subjects' sex, age and diagnosis.

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S5.2 On the relationship between the number of sleep cycles and delta power

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It is a common practice in nowadays sleep research to compare delta power as computed by ultradian cycles. First cycles are compared between controls and studied patients, first cycles are compared to second cycles; other comparisons are performed on the first four cycles, for instance comparing the habituation effect.

One of the assumptions in doing so is that the number of sleep cycles in a night does not interfere with the spectral power per cycle. Yet this number has been shown repeatedly to vary substantially in controls. Two to seven cycles have as such been described in healthy subjects.

Furthermore, one study on healthy controls (Preud'homme et al. 2000) has shown that the total delta spectral power per night did not differ significantly between nights including four, five or six non-rapid eye movement (NREMS) cycles. It was thus interesting to measure the relationship between the delta power per cycle and the number of these cycles, the hypothesis being that the delta power per cycle would not be related to the this number.

Twenty-six healthy controls were carefully selected and were recorded at home. Negative correlations were observed between the delta power in the first, second and third cycle and the number of cycles by night. Thus, the delta power in a cycle is dependent on the number of cycles in that night.

To avoid potential bias, future cycle-by-cycle comparisons should compare cycles in nights with the same number of cycles.

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S5.3 Differential effect of fast and slow sleep spindles on overnight improvement in an explicit memory task

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Recent studies suggest a connection between explicit memory tasks and the activity of sleep spindles in the night following learning. The present study explored whether the overnight improvement in a word-pair association task is differentially correlated to characteristics of fast (>13 Hz) or slow (<13 Hz) sleep spindles. Twenty four healthy volunteers between 20 and 29 years spent 3 nights in the sleep-lab. The first night served for adaptation purposes, while the second and third nights were randomly assigned either to a control condition without intentional learning or to an experimental condition in which subjects had to perform a declarative memory task (paired-associate word list) approximately 2.5 hours before sleep. A set of 160 word pairs was presented twice in randomized order. Subjects performed a cued recall task after the encoding session in the evening and after sleep in the morning. Spindles were detected automatically in channel C3-A1 using a recently developed step-wise

procedure with bandpass filtering and subsequent linear discriminant analysis. Spindle density (number/minute S2) and intensity (sum of discriminant scores/minute S2) were determined for all spindle events as well as for fast and slow spindles for the entire night and for five 1.5-hours parts of the night. Subjects correctly retrieved 62.6% of all word-pairs in the evening and 63.7% in the morning after the experimental night. This slight improvement between evening and morning recall was not significant. Moreover, there were no significant differences regarding sleep efficiency and sleep architecture as well as spindle density and spindle intensity between experimental and control night. However, there was a significant correlation between changes in spindle density and intensity (experimental minus control night) and overnight changes in memory performance ($r=0.44$, $P<0.05$ and $r=0.52$, $P<0.01$ for density and intensity, respectively). These correlations were most prominent in the first three 1.5-hours parts of the night. Interestingly, changes in memory performance correlated significantly only with fast but not with slow spindle measures. In summary, we found a relationship between changes in the density and intensity of fast spindles during S2 sleep (experimental minus control night) and changes in declarative memory performance (morning minus evening recall). Significant correlations were observed in the first parts of the night, which is in line with the hypothesis that sleep in the first part of the night is critical for consolidation of declarative memory. The differential effect on fast and slow spindles provide further evidence for differential functional significances of slow (probably frontally generated) and fast (probably parietally generated) spindles. Thus, the present study directly proves the involvement of sleep spindle activity in the consolidation of explicit memory.

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S5.4 Sleep as a tool to investigate psychotropic drug effects in proof-of-concept studies

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Sleep EEG recordings are an unique non-invasive tool to analyse brain functioning. Even in the very early phase of development in man, these investigations are mandatory in a developmental plan of a new sleep acting compound, such as hypnotic drugs. Sleep may also be an interesting tool for the development of other CNS acting drugs. Indeed, the central effects of a psychoactive compound could be objectively demonstrated at a functional level through its characteristics sleep EEG profile. These changes are specific to the way the drug is acting on the brain neurotransmitters systems.

Moreover, new compounds can be compared with reference drugs in terms of the sleep EEG profile they induce. For instance, cognitive enhancers involving cholinergic mechanism have consistently demonstrated to increase rapid eye movement (REM) sleep pressure and studying drug-induced slow wave sleep (SWS) alteration is a particular useful tool for the development of CNS compounds acting at the level of the 5-HT_{2a/c} receptor, such as most atypical antipsychotics and some antidepressant drugs. The sleep EEG profile of antidepressants, and particularly, the effects on REM

sleep are specific to their ability to enhance noradrenergic or serotonergic transmission. It is suggested that the respective effects of noradrenergic *versus* serotonergic reuptake inhibition could be disentangle using specific monoamine depletion tests and by studying drug effects on sleep microstructure.

S6.1 Non-linear analysis of functional connectivity in EEG and MEG

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One of the central questions of neuroscience is how the activity of multiple widely distributed systems in the brain is integrated into a functional whole. Functional integration is crucial for higher brain functions such as consciousness, attention, memory and reasoning. Disturbances in functional integration may give rise to epileptic seizures, but also to cognitive dysfunction in neurological disorders such as Alzheimer's disease, Parkinson's disease and multiple sclerosis. Measures of interdependencies between EEG and MEG signal recorded over different brain regions can be used to characterize the functional interactions of the underlying brain regions ("functional connectivity"). The synchronization likelihood (SL) is a general measure of such interdependencies, which can characterize linear as well as non-linear correlations between time series with a high time resolution (Stam and van Dijk 2002). Using synchronization likelihood we could demonstrate that interdependencies in EEG and MEG recordings in healthy subjects are non stationary and non-linear, and that MEG is superior in characterizing these interactions. In healthy subjects, performance of cognitive tasks results in specific changes in functional connectivity: working memory is associated with an increase in theta synchronization, and a decrease in lower alpha band synchronization. Mental arithmetic changes gamma band synchronization. In Alzheimer's disease a loss of synchronization in upper alpha, beta bands has been found with EEG and MEG. Fluctuations of mean SL levels can be characterized with detrended fluctuation analysis (DFA), and this shows significant correlations in the synchronization level on long time scales. These spontaneous fluctuations in synchronization level are disturbed in Alzheimer patients. In patients with multiple sclerosis a strong decrease of synchronization in the alpha band was found with MEG. Preliminary results of MEG recordings in Parkinson patients suggest that Parkinson dementia is characterized by a loss of alpha band connectivity in the parieto temporal regions; compared to healthy controls Parkinson patients show an increase of frontal connectivity in the delta band.

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S6.2 Correlation dimension of the human EEG under anaesthesia

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Background: Because of the inter-individual variability in sensitivity to anesthetics and the dependence of depth of anaesthesia

(DOA) to the strength of surgical stimulation, the need for an individualized dosage scheme with constant readjustment of DOA is evident. The electroencephalogram (EEG) reflects the overall activity of the central nervous system (CNS) and is influenced by anesthetic drugs. At present, the usefulness of new measures originating from nonlinear dynamics to characterize the EEG is frequently studied. Here, an adapted algorithm to compute the correlation dimension (CD) was used. The hypothesis that CD of the EEG relates to DOA is object of the present study.

Methods. One hour before elective surgery patients received propofol by target controlled infusion with a stepwise deepening of anaesthesia. DOA was assessed by an extended version of the Observer's Assessment of Alertness and Anaesthesia and therefore termed Observer's Assessment of Sedation and Anaesthesia (OASA) scale to enable DOA assessment at deep anaesthesia levels. With approval of the local ethics committee, twenty ASA 1,2 patients undergoing surgery (age>18 years) were selected for the study. The EEG was recorded continuously, filtered (analogue BP: 0.16-250 Hz and digital LP: 40 Hz) and digitized at a rate of 1 000 Hz. At 5 to 7 steady state propofol levels, CD of 9 EEG-leads was computed. The results of CD were related to the OASA-score and BIS.

Results. When DOA was becoming deeper (decrease of OASA score) CD decreased. A sharp decrease of CD was found between OASA=4 and OASA=3. There were no significant differences for CD among the EEG-leads. BIS showed no sharp decrease between OASA=4 and OASA=3. However, at deeper levels of DOA (OASA<=3), BIS at OASA=0 was not significantly different from BIS at OASA=3. To compare CD and BIS as anesthetic depth indicators, the prediction probability P_k was calculated. Results showed a higher P_k for BIS (0.9) compared to CD (0.7). If P_k is calculated without the awake levels (OASA-score 7, 6, 5), results of P_k change to or remain at 0.7 for BIS respectively CD.

Conclusions. During propofol administration CD is especially sensitive to DOA changes at the transition from awake or light anaesthesia to deep anaesthesia. At the deeper DOA levels CD and BIS perform equal as indicators of anesthetic depth. Differences between CD and BIS in recorded time tracings show that CD can provide information not supplied by the BIS. As CD can be calculated online it might be useful for monitoring purposes.

S6.3 Increased synchronization between central EEG derivations with depth of anaesthesia

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The multivariate nonlinear analysis of biological time series has received great attention in the last ten years. Several theoretical advances in the field have boosted the application of nonlinear dynamical system theory to the study of physiological signals. Broadly speaking, three different kinds of methods can be applied to this aim: (i) information theory-based indexes, such as the mutual information of the transfer entropy, which however need a lot of data to give reliable results; (ii) phase synchronization analysis, which has the advantage of been applicable to both linear and nonlinear time series but requires the signals to be narrow band ones; (iii) the study of the existence of generalized synchronization between the reconstructed state spaces of the signals.

This latter approach, despite the difficulties that might present when the analysed signals are of different complexity (Pereda et al. 2001), has recently shown to excel the other two methods, when applied to broadband EEG signals (David et al. 2004, Quiroga et al. 2002). Additionally, the latest development in this field suggests that it is possible to overcome the aforementioned limitation regarding its application to signals of different dynamics (Hu and Nenov 2004). In this work we present the current state of this methodology for the assessment of the interdependence between EEG channels by mean of a case study, in which we analyse the changes in the functional connectivity of the C3 and C4 channels in human subjects undergoing anaesthesia with different doses of propofol. After reviewing the basic theory underlying this methodology, we show that this approach is in fact very useful in assessing not only the extent but also the possible asymmetry in the interdependence among different brain areas. We also show how the surrogate data method can be extended to produce multivariate surrogates, which may give further insight about the nature of the interdependence (Pereda et al. 2001).

Finally, we present some recent applications to the analysis of multichannel EEGs in the context of cognitive and functional neuroscience and suggest future lines of research.

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S6.4 Nonlinear and fractal analysis applied to characterization of the vigilance states

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The continuous record of the electrical activity of the brain is one of the non-invasive methods used for studying the human brain function. The usefulness of the EEG as both a diagnostic and a research tool has been recently backed by the appearance of new time-series analysis methods stemming from the field of dynamical systems, contributing to a better characterization of the integrative brain operation.

The two nonlinear measures most generally analysed are the correlation dimension (D_2), as a measure of the EEG complexity that estimates its degrees of freedom and the largest Lyapunov exponent (λ_1), an index of the sensitive dependence of the temporal evolution of the system on initial conditions.

Another way to characterize the complexity of a time series is the determination of its fractal dimension. A procedure for this purpose is called the coarse graining spectral analysis (CGSA), which is based in the calculation of the fractal exponent from the power spectral density (PSD) function of signals that exhibit frequency power-law dependence of the type $1/f^\beta$. In addition, this algorithm

allows us to split the total PSD in two components: harmonic and fractal.

This presentation aims at showing some basic aspects of the non-linear analysis and its applications to physiological temporal signals such as the EEG, ECG, temperature, respiration, etc. As an example, this set of tools has been used to analyse the EEG in different vigilance states under different drugs (midazolam, pilocarpine) in rats, and to compare vigilance states in different taxonomic groups (humans *versus* reptiles). In all these cases, the new time series analysed methods show a higher resolution power and clear evidences for the convenience of its application to clinical aspects.

S7.1 Spatial temporal EEG changes after a single dose of atypical antipsychotics

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The principle of EEG-based drug classification is that single doses of therapeutically equivalent psychotropics cause similar EEG changes, while therapeutically different psychotropics produce different changes. However, traditional EEG frequency analysis has generally been restricted to a phenomenological description of local effects within the electrode array without direct use of the spatial information. The present study applied for spatial analyses of multi-channels that estimate temporal brain information processing.

Effect of four novel atypical antipsychotic drugs (olanzapine, perospirone, quetiapine, and risperidone) on scalp-recorded multi-channel EEGs were compared with two conventional typical antipsychotic drugs (chlorpromazine and haloperidol) and placebo in fourteen healthy male volunteers. All subjects went through seven sessions. In each session, EEGs were recorded before and 2, 4, and 6 hours after drug administration.

Global Field Power (GFP) in delta frequency band (1.5-6 Hz) increased around the time of peak serum concentration of quetiapine and risperidone compared to baseline. The increase of GFP in delta activity after quetiapine was significantly prominent in comparison to two other atypical antipsychotic drugs, perospirone and olanzapine, as well as to typical antipsychotic drugs, chlorpromazine and haloperidol ($P < 0.05$). The increase in GFP of delta after risperidone was more prominent in comparison to after haloperidol ($P < 0.05$). The greater sedative effects after quetiapine and risperidone may reflect the high affinity to A_1 and H_1 receptor bindings of these drugs. According to LORETA, olanzapine increased the delta in the posterior region indicating a frontal shift of brain activity (frontal activation), suggesting that olanzapine might be useful against negative symptoms in schizophrenics. In addition, Global Dimensional Complexity (GDC) was higher after risperidone than after quetiapine ($P < 0.05$); also GDC was higher after perospirone than quetiapine and chlorpromazine ($P < 0.05$). These GDC results suggest that so-called SDA such as risperidone and perospirone may function without decreasing vigilance level compared to so-called MARTA such as quetiapine and conventional antipsychotics such as chlorpromazine.

S7.2 Influence of neuroleptic drugs on EEG and evoked potentials

W. Strik

Abstract not received

S7.3 Influence of L-dopa on executive dysfunction in Parkinson's disease: an evaluation using ERP topography

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We investigated the efficacy of the levodopa (L-dopa) on executive dysfunction in patients with de novo Parkinson's disease (PD) using the event-related potential (ERP) measure and neuropsychological test batteries. We studied 20 PD patients who had never received anti Parkinson medications. The ERP with auditory oddball P3 paradigm and neuropsychological tests such as Mini-Mental State Examination (MMSE), New Modified Wisconsin Card Sorting Test (WCST) and Trail Making Test were repeated in the patients before and after administration of levodopa plus benserazide daily 300 mg. For the ERP's components, reference-independent measures (global field power = GFP) were determined, and P3 GFP peak, peak latency and topography were assessed. After administration of levodopa, the patients revealed significant increase of the achieved categories and decrease of preservation errors in the WCST, shortening of time in Trail Making Test although MMSE score showed no significant difference. The P3 GFP peak attenuated although there were no differences in peak latency or on scalp topography. These findings suggest that levodopa affect to the neural circuit connect frontal cortex with the striatum and normalize its function, and it causes decrease of P3 GFP peak reflecting appropriate resource allocation. In addition, P3 GFP might be more appropriate indicator rather than psychological test.

S7.4 Topographic and tomographic EEG changes induced by antipsychotic drugs

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Antipsychotic drugs have characteristic effects on the quantitative electroencephalogram. For standard neuroleptics two different patterns of changes have been described: (i) the sedative low-potency neuroleptic profile, characterized by increases in delta and theta, as well as by a decrease of the alpha band; and (ii) the high potency non-sedative neuroleptics, characterized by an increase of theta and slow alpha activity, and a decrease of the fast alpha band. Few studies have explored quantitative EEG changes induced by novel antipsychotics. A multilead pharmaco-EEG study, carried out in our department to characterize the EEG profile of clozapine in healthy subjects, showed an increase of delta, theta and alpha1, and a decrease of alpha2 and beta activities. At the present time, in our department a pharmaco-EEG study is being carried out, in which topographic and tomographic EEG changes induced by haloperidol and risperidone versus placebo are investigated in young healthy male subjects. Preliminary findings from this study show that both drugs increase delta and theta2 absolute power, while only haloperidol produces a significant increase of the alpha1 and beta activity. Delta increase is significant only in posterior regions for risperidone, while for haloperidol frontal and central regions are also involved. Also the theta2 increase appears more diffuse for haloperidol. The alpha1 increase induced by haloperidol is significant in the right hemisphere fronto-central regions only. LORETA analyses reveal significant differences in cortical generators activity between placebo and antipsychotic drugs, which involve limbic and neocortical regions for the alpha1 and theta2, and are limited to neocortical regions for beta activity.

O1.1 Spatio-temporal dynamics of epileptogenesis in kainic acid-treated rats

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Various aspects of the spatiotemporal dynamics of kainic acid (KA) induced *status epilepticus* (SE) in rats are presented. The primary objective was to increase our understanding of the epileptogenic process, and to develop EEG-biomarkers for epileptogenicity in this rat model of epilepsy. Fifteen rats were i.p. injected with KA ($n=8$) until a SE occurred, or saline ($n=7$) as a control. The EEG was recorded from 2 bipolar derivations, 1 on each hemisphere for 24 hours. Events were defined as local maxima in the EEG, including spikes. Event rate (ER), event synchronization (Q, scaled 0-1), and event interval (EI) distributions were used to quantify the induced changes in the EEG by KA. In all 8 KA-rats, we observe a significant increase in the ER for each bipolar recording from baseline (BL) values of ER_BL $\sim 0.37/s$ to ER_KA $\sim 3.11/s$. Events started either unilaterally, or bilaterally asynchronous, and became highly synchronized after minutes to hours (Q_BL ~ 0.24 , Q_KA > 0.90). This was typically accompanied by a decrease in the event rate. The spatiotemporal dynamics, as quantified by the time course of the EI distributions, showed a similar behaviour in most rats, with a global maximum at EI ~ 100 ms during 6-8 hours. All KA-rats show a biphasic response to KA. The first phase is characterized by a relatively high ER, and intermediate interhemispheric synchronization. The second phase is characterized by a decrease in ER and a further increase in synchronization between the two hemispheres, to values near 1, indicating a very strong interhemispheric coupling. The spatiotemporal dynamics, as quantified by the EI distributions, shows a characteristic time course in most KA treated rats. The presented analysis may further serve as a possible EEG biomarker for epileptogenicity.

O1.2 Frontal EEG biomarker measures effect of antidepressant treatment in major depressive disorder

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Background. Prior work demonstrated that frontal theta (4-8 Hz) EEG activity changes after venlafaxine administration in normal subjects, and predicts clinical response in patients with major depressive disorder (MDD) treated using SSRI, NRI, and SNRI antidepressants. Also, frontal asymmetry (i.e., left-right asymmetry of theta+alpha (4-12 Hz) power) and EEG bispectrum have been reported to reflect depressive mood and to predict treatment response. This study evaluated a novel EEG index (BIS-D) based upon these 3 parameters. BIS-D was designed to measure the effect of antidepressant treatment and to predict clinical response.

Methods. MDD patients in 5 prior studies ($n=109$) were treated with fluoxetine, reboxetine, venlafaxine, duloxetine or physician-selected SSRI antidepressants. The HAM-D was administered at baseline, and at weeks 1 and 8 during treatment. Response and re-

mission were defined as HAM-D at week 8 \leq 10 and 7, respectively. Previously identified EEG features were extracted from 4-channel, 2-min recordings made each visit (F7-Fpz, F8-Fpz, A1-Fpz, A2-Fpz). Logistic regression was used to select and combine features measured at baseline and week 1 to create an index (BIS-D) to predict response.

Results. At week 1, BIS-D achieved 72% accuracy (72% sensitivity, 71% specificity) in predicting response, 67% accuracy (71% sensitivity, 64% specificity) in predicting remission, and correlated with final HAM-D ($r = -0.365$, $P < 0.001$.)

Conclusions. These results demonstrate that frontal EEG provides a quantitative, pharmacodynamic measure of antidepressant treatment effectiveness (i.e., a biomarker). It may be possible to develop an easy-to-use, clinical assessment tool using frontal EEG to predict treatment efficacy early in the course of antidepressant treatment.

O1.3 Single channel frontal EEG evaluated by neuro and fuzzy methods to estimate the depth of anaesthesia and the sleep profile

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A monitor showing the actual anaesthetic depth and the further trend would be very useful to supervise out- and inpatients during surgery. In our paper hard- and software solutions based on microcontroller platforms will be presented. Real time processing of EEG is necessary to estimate and to predict anaesthetic depth or awareness. The classifier should be robust to cope with patient's variability according to different drug tolerance and more or less serious illnesses. Features of the frontal bipolar EEG and auditory evoked potentials (AEP) have been extracted in time and frequency range for 10 s segments. The original sampling rate of the EEG was 504 Hz. According to the used sigma delta converter the upper critical frequency was 126 Hz. The EEG of more than 50 patients was manually scored by means of clinical signs, the time course of the surgical procedure and the anaesthetic technique (drug administration) registered in the protocol of anaesthesia.

The falling depth of anaesthesia is mapped to the four classes A1, A2, A3 and A4.

Including awareness or awaking a 5-class problem has to be solved. The class A2 indicates the depths called stage of surgical tolerance. The burst suppression EEG appears in A4. The transient from wake to A2 is labeled by A1. Different approaches originally developed for the one channel sleep analysis were applied. The first results were obtained by populations of neural networks topologically optimized by genetic and evolutionary procedures. The cooperation of neural networks was optimized by genetic programming. The classification could be partially improved by the post processing procedure, which base on fuzzy rules. A continuous indicator of depths and a certainty indicator could be derived too.

In a third approach the classification task has been separately solved by a set of fuzzy rules.

The following preliminary state dependent results could be obtained by the neuro approach and the neuro fuzzy approach. The val-

ues in the table are percentages in the correspondence between the manually scored and the automatically classified 10 EEG segments:

Manually scored:	Wake	A1	A2	A3	A4
Neuro approach:	50%	30%	96%	76%	23%
Neuro Fuzzy approach:	72%	22%	88%	68%	71%

Table rates of agreement between manual and automatic classification for 15 patients which were not included in the training set.

The post processing raised the wake and A4 values at the expense of A2, which is the dominant state in the profile of depths of anaesthesia.

Further improvements are expected by the inclusion of additional features, which base on the bispectral analysis and the approximate entropy.

The approaches are evaluated and compared on basis of sleep and anaesthesia profiles.

O1.4 EEG oscillations in the brain: selective and local effects of noradrenergic system

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Thalamo-cortical oscillations, i.e., sleep spindles and spike-wave discharges (SWD), are influenced by alpha2-noradrenergic drugs (Kleinlogel 1985). These oscillations are generated in a loop between the neocortex, specific thalamus and reticular thalamic nuclei (Steriade and Deschenes 1984). Rats of the WAG/Rij strain have, next to sleep spindles and generalized SWD (Coenen and van Luijtelaaar 2003), also a second type of SWD, which could be recorded in the posterior cortex (Midzianovskaia et al. 2001). Whether the RTN is also involved in these oscillations, is not known. In the present experiment it is investigated whether clonidine, an alpha2-noradrenergic agonist would affect the EEG during both types of SWD in the thalamus equally as in the cortex.

EEG recordings were made in the frontal and occipital cortical areas, in the ventroposteromedial (VPM) and reticular thalamic nuclei (RTN) of adult male WAG/Rij rats. Positioning of the thalamic electrodes was verified by post mortem histological control. Clonidine (dose 0.00625 mg/kg, i.p.) was administered and EEG recordings were performed in free moving rats. Number and mean duration of both types of SWDs and FFT's using 1-s EEG epochs containing SWD and epochs during non-REM sleep were analysed.

After injections of clonidine animals seemed drowsy, wakefulness significantly decreased. Both type of SWD were present in cortex and thalamus. Clonidine increased the number and mean duration of SWD type I. Expression of SWD II was not changed after injections of clonidine. The total power of the EEG during SWD I, II and sleep was either not changed after clonidine, an exception was the RTN, which showed more power during SWD I, not during SWD type II.

It can be concluded that SWD type I is under the control of clonidine, in contrast to SWD type II. Therefore it seems that the noradrenergic system might selectively control SWD I. The selective effects on FFT obtained at the RTN do suggest that the increase in SWD I is due to the action of clonidine in the RTN.

O2.1 Prefrontal and hippocampic EEG changes and their relationships during an acute stress in adult and aged rats

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Synopsis. Statement of the study: EEG power changes induced by stress in prefrontal and hippocampic cortices were evaluated in adults (8 months) and aged (22 months) Wistar rats, untreated or, pre-treated with diazepam (1 mg/kg i.p.). The relationships between both cortices EEG were evaluated by their coherence.

Methods. Transcortical electrodes were chronically implanted in the different cortices. After surgery, recuperation, and, habituation to the recording condition (Sebban et al. 2002) the effects of acute stress were evaluated in conscious animals by placing the rats on a platform positioned 30 cm up the ground level.

Summary of result. In adult rats stress produces in the prefrontal cortex a sharp increase in the 9-10 Hz power which exhibits a nearly total coherence with hippocampic EEG activity.

In aged rats, stress was followed by a decrease in power concerning all the frequencies of the prefrontal cortex EEG spectrum. However, if only the prefrontal cortex activities coherent with hippocampic EEG are studied, there was in aged rats the same increase in 9-10 Hz power as observed in adult rats.

The large decrease in power observed on prefrontal cortex EEG of stressed aged rats was totally independent of hippocampic EEG activities. In fact, in adult rats, when only the prefrontal cortex activities non-coherent with hippocampic EEG were studied, a slight decrease was also present.

Diazepam induced only slight changes in EEG reaction of adult rats to stress, but cancelled nearly all the power decrement observed in aged rats. In both groups diazepam did not change the stress related EEG synchronisation on 9-10 Hz frequencies.

Conclusion. Acute stress produces two EEG changes in prefrontal cortex:

A synchronisation on 9-10 Hz frequencies, highly dependent on hippocampus, of the same magnitude in adult and aged rats, and, unchanged by diazepam;

A desynchronisation on a large frequency band, totally independent from hippocampus, by far greater in aged rats, and, blocked by diazepam pre-treatment

Key words: benzodiazepines, electrophysiology, stress, aging, EEG coherence

Reference

Sebban C, Tesolin-Decros B, Ciprian-Ollivier J, Perret L, Spedding M (2002) Effects of phencyclidine (PCP) and MK801 on the EEGq in the prefrontal cortex of conscious rats antagonism by clozapine, and antagonists of AMPA-, alpha1 - and 5-HT2A-receptors. *Br J Pharmacol* 135: 65-78.

O2.2 Effect of DHEA on the neural correlates of episodic memory

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Rationale. Dehydroepiandrosterone (DHEA), a functional cortisol antagonist has been shown to improve memory in rodents. However, there are inconsistent findings of DHEA effects on memory in humans. Cortisol impairs episodic memory and increases the voltage of event-related potentials (ERPs) related to episodic mem-

ory recollection. The aim of this study was to investigate the effect of DHEA on episodic memory and its neural correlates in normal young men using an ERP technique.

Methods. Twenty-four right-handed healthy men took part in a double blind, placebo-controlled, crossover study. ERPs were recorded during an episodic memory test following a seven-day course of oral DHEA (300 mg) or placebo. During a study phase, subjects heard words spoken in a male or female voice. Old and new words were presented visually during a test phase; subjects were requested to identify words as old or new (recognition) and if old the gender of the voice at study (recollection). ERPs associated with correctly identified new words (correct rejections: CR) and successfully recollected old words (Hit/hits: HH) were compared, with the difference believed to reflect the neural activity underlying memory retrieval.

Results. DHEA improved recollection as measured by percentage accurate recollection given recognition of an old item ($P < 0.01$); however, it had no significant effect on recognition ($P > 0.1$). DHEA had a robust effect on ERPs, decreasing mean voltage from 1.2 to 0.5 μV ($P = 0.005$) for the period 800-1400 ms post-stimulus with a significant drug by response interaction ($P < 0.05$). This interaction was due to a specific effect of DHEA on ERPs associated with HH responses and located over the right temporo-parietal scalp.

Conclusions. DHEA enhanced recollection, though not the less effortful task of recognition. This effect was associated with a modification of the electrophysiological correlates of recollection in the right temporo-parietal region, which may reflect neuronal involvement of the right hippocampus. These data demonstrate beneficial effects of DHEA on episodic memory in healthy young men.

O2.3 Subjective sleepiness and its associated current density changes of alpha and theta frequency sources during quiet wake

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Subjective sleepiness is associated with changes in wake EEG. With eyes closed, high sleepiness coincides with low alpha power and high theta power. Source locations of EEG generators can be assessed with multi-channel EEGs using LORETA (low resolution electromagnetic tomography (Pascual-Marqui et al. 1994). Sleepiness associated changes in current density of alpha and theta frequency generators were assessed in EEG traces of 10 quiet waking subjects sitting upright with eyes closed during 21 EEG recording sessions evenly spaced in a 40 h wake period (see Strijkstra et al. 2003). During the first 16 h of waking (low sleepiness) LORETA found sources for alpha activity in the occipital/parietal lobe, and for theta activity in the parietal lobe and in the frontal lobe (anterior cingulate cortex). During the last 16 h of waking (after a sleepless night) alpha activity was reduced (as expected) over most of the LORETA brain space, except in the frontal lobe. Theta was (not significantly) lower, thus (unexpectedly) not enhanced. The association between subjective sleepiness and alpha and theta frequency current density was assessed by making within individual correlations per LORETA brain space voxel over the 21 recording sessions, and combining individual correlations between subjects using meta-analysis statistics (see Strijkstra et al. 2003). Significant correlations were mapped in LORETA brain space. Subjective sleepiness correlated negatively with alpha frequency current density in the en-

tire LORETA brain space. Subjective sleepiness correlated positively with theta frequency current density in the frontal lobe, and negatively in parietal/occipital lobes. In conclusion, enhanced subjective sleepiness seems to be based on a general reduction in alpha and theta source current density, with the exception of the frontal theta current density source.

O2.4 An N400 LORETA study

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Three-word German sentences beginning with personal pronouns *Ich* (I), *Er* (he), or *Sie* (she), followed by a verb, and ending with a semantically congruous or incongruous noun, were visually presented, word by word, to 15 healthy, right handed volunteers (9F, 6M). Subjects were required to discriminate if the last word of the sentence was congruent or incongruent. Continuous EEG was recorded from 30 electrodes, off-line filtered from 1-30 Hz, and re-referenced to average reference. Evoked potentials were calculated for each subject from artifact free segments of 700 ms duration following each word. In a separate session, checkerboard pattern reversal visual ERPs were also obtained for each subject.

In a first analysis step, the imaging method LORETA was validated. LORETA images corresponding to the checkerboard N70/P100 complex demonstrated activation of primary and secondary visual cortices.

In a second analysis step, full ERPs corresponding to "sentence-ending" were compared for the contrast "incongruent-congruent". This test compared scalp electric potential differences at 30 electrodes, and at 350 discrete time samples. Exact non-parametric randomization statistics with correction for multiple testing was used. Significant differences for the ERPs occurred in the time windows corresponding to the N400 (370-390 ms), and to a late positive complex at 530-550 ms.

In a final step, LORETA images in these significant time windows were compared for the contrast "incongruent-congruent". The N400 generators were located left parahippocampal gyrus, hippocampus, and amygdala. These results are in agreement with a number of previous studies that used intracranial recordings to localize the sources of the N400. At the P600-type latencies, a significant decrease in activation for the incongruent ending as compared to the congruent ending was observed in left fusiform and parahippocampal gyri.

P1.01 Comparative PK/PD analysis of high and low efficacy agonists for the mu-opioid receptor

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Opioids play an important role in anaesthesia, analgesia and treatment of drug abuse. However, different applications require different properties and therefore the pharmacokinetic/pharmacodynamic (PK/PD) relationships of opioids should be investigated. Previously, the effects of alfentanil, fentanyl and sufentanil have

been studied with a rat EEG model. The data were analyzed with the operational model of agonism, but inconsistencies were found between the *in vitro* and *in vivo* results. A possible explanation is that the tested opioids all behaved as high efficacy agonists. Thus, the aim of the present study was to investigate the PK/PD relationships of low efficacy agonists and to compare them with the high efficacy agonists.

Male Wistar rats received 2.5, 5 or 10 mg/kg butorphanol, 5, 10 or 15 mg/kg nalbuphine or 4, 10 or 40 mg/kg morphine in a 10-min infusion. The EEG (0.5-4.5 Hz) was recorded continuously from -45 min to a maximum of 360 min after infusion and analyzed off-line. Serial blood samples were drawn to determine opioid concentrations.

The pharmacokinetics of butorphanol, nalbuphine and morphine were best described with a 2-compartment model. For all three opioids, hysteresis was observed between the blood concentrations and the EEG effect. In addition, a decrease in maximum effect (E_{max}) was observed for the low efficacy agonists. Fentanyl had an E_{max} of 100 μV whereas for nalbuphine, butorphanol and morphine the E_{max} values were 30, 40 and 70 μV , respectively.

In conclusion, butorphanol, nalbuphine and morphine behave as low efficacy agonists *in vivo*. In combination with the high efficacy agonists, a mechanism-based PK/PD model can be developed that is able to describe and predict the concentration-effect relationships of a wide range of opioids.

P1.02 Chronic i.p. cannula in rat for undisturbed pharmaco-EEG studies

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In order to determine the hypnotic effects of a drug in undisturbed rats, with a correct measure of its latency, we have performed i.p. injections through a chronically implanted cannula during three weeks. Rats, ca. 225 g at the time of surgery, were anaesthetized with isoflurane and surgically prepared with a cranial implant for chronic EEG/EMG recordings. Temporal muscle EMG was recorded with two 0.5 mm \times 1 mm silver plates cemented to the skull. Stainless steel screws served for grounding/anchoring. Leads were crimped into miniature pins prior to surgery and, after electrode placement, were inserted into a plastic socket. The chronic i.p. cannula (IITC, S25B) was aseptically implanted as follows: a 15 mm skin incision was made on the right side of the abdominal wall, below the costal ridge, and the 180 mm long end of the polyethylene catheter (PE20, 140 mm; PE10, 40 mm) was tunnelled under the skin from that point until the posterior end of the exposed skull, where it protruded several centimeters to be cemented, pointing up, together with the cited electrical connector. Connection tubing was later fixed to the recording cable and threaded thru the swivel. The other end of the cannula, 25 mm of 0.025" OD silastic tubing, was inserted in the abdominal cavity through an incision across its wall; this was sutured after injection of 1 ml of Earle's balanced salt solution (EBSS, Sigma E2888) added with antibiotics (cloxacillin 10 mg/kg and gentamicin 0.16 mg/kg). This was repeated daily during the one week recovery period allowed before drug testing. It is important to note that 0.1 ml of distilled water and 0.05 ml of air followed injections, to maintain the catheter patency.

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P1.03 Brain function, paranormal ideation, mysticism and risk for psychosis

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Reduced P300 amplitude is robustly seen in schizophrenia and may represent an extreme of a continuum of risk. Neural generators of P300 include the temporoparietal junction (TPJ). Left hemisphere P300 amplitude reduction and reduced TPJ volume is associated with psychotic symptoms. In healthy controls, stronger right TPJ function is associated with mystical sensations and may lead to loose semantic connections involved in creativity. The current study explored mysticism in relation to creativity, schizotypal personality and changes in P300 amplitude. Forty-two healthy controls completed tests of paranormal ideation (PNI), mysticism (ME), schizotypal personality and creativity. EEG was recorded during an auditory oddball task and scored for P300 amplitude. Pearson tests explored the relationship between psychometric scores. PNI but not ME scores correlated with schizotypal personality, and ME, but not PNI scores correlated with creativity measures. Subjects were grouped based on PNI and ME scores. ANOVA was performed to test between group differences with hemisphere (left, right) and coronal (anterior, central, posterior) electrode sites as within group variables. High PNI scorers had lower P300 amplitude at anterior sites than low PNI scorers. High ME scorers had lower P300 amplitude than low ME scorers at left central and temporal sites. Results suggest separate risk factors for psychosis respectively involving frontal and left temporal function. Developments in pharmacotherapy have seen reduction in adverse side effects. The next challenge is to treat symptoms of psychosis that disable patients, while maintaining those that are potentially beneficial such as creativity and mysticism. Further studies of mechanisms underlying these functions would facilitate this.

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P1.04 Prediction of response to drug treatment in major depression with electrophysiological approaches using LORETA

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Two major approaches which have been introduced for the prediction of treatment response in major depression could be replicated by several groups independently. An unspecific way of prediction is based on the activity/metabolic rate in the ventral anterior cingulate. Subjects with higher metabolic rates respond better to antidepressive medication with paroxetine. These findings could be replicated with resting EEG-data. A more specific approach is the investigation of the loudness dependence of the auditory evoked potential (LDAEP). Here, a high LDAEP is supposed to reflect low central serotonergic activity and is associated with good response to selective serotonin reuptake inhibitors like citalopram, but not to noradrenergic drugs. We present the first study comparing both approaches in the same group of depressive patients: twenty-six depressed inpatients. In the analysis of the resting EEG, we found significant differences between responders and non-responders in the anterior cingulate cortex (ACC) not only in the theta-frequency

range ($P < 0.05$). Responders showed significant increased current source density in the ACC in comparison to healthy controls. There was no significant difference in the ACC activity between healthy controls and non-responders. In the subgroup of patients, treated with citalopram, we found a significant difference between responders and non-responders with both the LDAEP ($P = 0.003$) and in the resting activity of the anterior cingulate cortex ($P = 0.034$). Both with the LDAEP and the resting activity in the anterior cingulate cortex a prediction of treatment response was successful. The methods pick up different neurophysiological aspects and do not correlate.

P1.05 Changes in EEG parameters as biomarker for development of epilepsy

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The relation between kainic acid (KA) induced status epilepticus (SE) in rats, and the subsequently developing epilepsy was investigated using different EEG-parameters.

Eight rats were treated with KA, and 7 rats with saline as control. During treatment EEG was recorded for 24 hours. From 1 KA-rat and 1 control rat EEG was measured continuously for 28 days. From the EEG the event rate (ER) and interhemispheric synchronization (Q, scaled between 0-1) were calculated. An event was defined as a local maximum in the EEG. During 28 days, the convulsive threshold (TLS) was measured as a biomarker of excitability of the brain, and at 28 days after KA-treatment EEG was recorded for 1 hour. Neuronal cell death was measured *ex vivo* with NeuN as a neuronal marker.

All rats showed similar EEG-behavior during SE: both Q and ER were strongly increased ($Q > 0.9$) during 8-10 hours. In the continuously measured KA-rat, Q decreased to almost basal levels ($Q \sim 0.1$) after the increased level during SE. Five-six days later, Q slowly increased again to $Q \sim 0.2$ at 28 days. The control rat had a constant level ($Q \sim 0.1$) during 28 days. The mean level of Q at day 28 for all KA-rats was higher than for control rats (0.22 vs. 0.07, respectively). In KA-rats the TLS was higher, and they showed more neuronal cell death. However in the KA-rats, no significant correlations were found between these parameters and any EEG-parameter during SE. Possibly this can be explained by low variability in KA-induced SE and subsequently developing epilepsy in this study, and consequently low variability in EEG changes and neuronal death.

In conclusion, this study illustrates the feasibility of studying epileptogenesis with EEG-parameters, like Q. Correlation to other biomarkers for epilepsy has to be studied further.

P1.06 Changes of electroencephalographic coherence and candance in Alzheimer's disease after the rivastigmine therapy

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Background. Previous research has shown altered EEG coherence in AD compared to normal elderly controls as a marker of im-

paired functional and/or anatomical connectivity. While coherence allows one to observe the integrity of connections between two brain regions, the new EEG method – cordance (Leuchter et al.) permits an assessment of the afferent input into a single cortical region and thus it is more sensitive in the detection of deviation from normal patterns over cortical regions with abnormal afferent inputs, such as deafferented cortex in AD (discordance over the parietal regions).

Methods. Twenty AD patients meeting the NINCDS-ADRDA criteria for mild to moderate AD were examined before and after the treatment with rivastigmine (6-9 mg daily after titration). Twenty age and sex-matched healthy subjects were recruited as controls. Measures included clinical and neuropsychological assessment (Mini-Mental State Examination – MMSE) and EEG recordings at baseline and after 12 weeks of the rivastigmine treatment. Analyses of QEEG data (spectral data, coherence and cordance) were performed using ANOVA (healthy controls vs. AD patients at the baseline) and Wilcoxon signed-rank test (AD patients at baseline vs. after 12 weeks treatment).

Results. In the spectral data AD patients at baseline presented significant power modifications compared to healthy subjects, in particular a significant decrease of alpha power, an increase of theta power in posterior regions and a diffuse increase of delta activity. After the 12 weeks rivastigmine therapy, there was significant decrease of delta power ($P < 0.01$), which correlated with improvement on MMSE. In the coherence analysis, differences were only found regarding the intrahemispheric coherences in delta and alpha bands (AD patients at baseline vs. healthy controls; $P < 0.01$). While the delta coherences after the rivastigmine therapy sign. Increased (normalization), the coherences in the alpha band persisted impaired. Before the treatment, the AD patients had significantly lower EEG cordance values than gender- and age-matched control subjects in the theta and beta-1 frequency bands over the bilateral parietal and temporal regions. After the rivastigmine treatment there was significant increase of EEG cordance in the theta band, reaching the positive values (i.e., normalization from discordant to concordant state), which correlated with clinical improvement on MMSE scale.

Conclusion. These findings suggest that in comparison to elderly healthy subjects have AD patients an impairment of intrahemispheric functional connectivity as well as impairment of cortical metabolism/perfusion over temporoparietal regions (assessed by means of EEG cordance method). This study also shows that the cholinesterase inhibitor treatment exerts different effects on neurophysiological indicators for AD.

P1.07 Topographic EEG changes after single oral doses of atypical neuroleptics with different pharmacological profile in healthy young subjects

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Background. It is widely reported that representatives of the main psychotropic drug groups induce reliable EEG changes. This holds true for "traditional" drugs but there are still scarce data regarding the behavior of the newer developed compounds, generally involving different biochemical mechanisms of action, as is the case for the neuroleptic agents.

Objective. To assess the EEG changes of atypical neuroleptics with different pharmacological profile in healthy subjects under the same experimental procedures.

Methods. Twenty subjects participated in a phase I, crossover, double blind, placebo-controlled study receiving at weekly intervals single oral doses of: (i) placebo (P); (ii) risperidone 1 mg (R); (iii) olanzapine 5 mg (O); (iv) haloperidol 3 mg (H). Topographic pharmaco-EEG mapping (3 minutes: 19 EEG, vertical and horizontal EOG with eyes closed) was performed before and after 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 hours. Plasma levels of R, 9-OH-R, O, and H were assessed through LC-MS/MS methods.

Results. Mean peak plasma concentration was attained round +4 h for O and H while for R was round +1 h and for 9-OH-R round +5 h. Pharmaco-EEG changes obtained at +4 h consistently differ between R and O while H changes resemble those obtained after O but at a lower extent. R showed increases in total absolute power while O decreased it, inducing both compounds decreases in its centroid. Most relevant changes after R were observed in absolute power while after O were in relative power variables. R induced increases in delta, theta, alfa-1 and beta but decreases in alfa-2. O induced increases in delta, theta but decreases in alfa-1, alfa-2 and beta activities.

Conclusions. Although some pharmaco-EEG similarities can be observed after atypical neuroleptics different pattern of changes follows the acute administration of compounds with different pharmacological profile.

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P1.08 The effects of stimulating and sedative drugs on error monitoring

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Action monitoring has been studied extensively by means of measuring the error-related negativity (ERN). The ERN is an event-related potential (ERP) elicited immediately after an erroneous response and is thought to originate in the anterior cingulate cortex (ACC). Although the ACC has a central role in the brain, only a few studies have been performed to directly investigate the effects of drugs on action monitoring. A recent theory by Holroyd and Coles (2002) argues that the mesencephalic dopamine system carries an error signal to the ACC, where it generates the ERN. ERPs and behavioral measurements were obtained from twelve healthy volunteers performing an Eriksen-Flankers task. On each of the four test days, the stimulant d-amphetamine, the sedative lorazepam, the antidepressant mirtazapine, or a placebo was orally administered in a double blind, four-way crossover design. The indirect dopamine agonist amphetamine led to a strong enlargement of ERN amplitudes without affecting reaction times. Lorazepam and mirtazapine both showed slowing of responses, but only lorazepam led to reduce ERN amplitudes. Administration of amphetamine leads to stimulated action monitoring, reflected in increased ERN amplitudes. This result provides evidence for dopaminergic involvement in action monitoring.

ing and is in line with distortions in ERN amplitude found in neuropsychiatric disorders also suggesting dopaminergic involvement. The different effects for lorazepam and mirtazapine are probably caused by the neurobiological characteristics of these two types of sedation. Action monitoring is suppressed after administration of lorazepam, because the GABAergic pathways directly inhibit ACC functioning, whereas the histaminergic pathways of mirtazapine do not innervate the ACC directly.

P1.09 EEG effects of diazepam and zolpidem are behaviour-specific in rats

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A pharmacological dissociation of the normal relation between electroencephalographic (EEG) brain activity and behavior has been described for the benzodiazepines. In drug-free conditions, a decrease in EEG beta frequency activity is associated with a decrease in arousal. However, benzodiazepines increase beta activity, although they are sedative. Most studies on the EEG effects of benzodiazepines measure at induced behavioral activity. In this study EEG effects were measured under non-forced vigilance conditions in the open field in rats, where behavioral activity and inactivity spontaneously alternate. Thus, it was studied whether EEG activity is affected differentially with regard to the type of behavior in diazepam (2.5 mg/kg) and zolpidem (2.5 mg/kg). Behavior was analyzed in detail. The EEG was segmented according to the behavioral scoring and for each behavioral element a power spectrum was calculated. Both diazepam and zolpidem showed an increase in EEG beta activity, characteristic for the benzodiazepines. However, this increase was specific for active behavior. During inactivity in the open field, this increase was much less pronounced in diazepam and absent in zolpidem. Thus, drug effects on the EEG differed between active behaviors and sitting behavior. Moreover, this could implicate that, while under influence of diazepam and zolpidem, even higher levels of EEG beta activity are necessary for active behavior to occur. Furthermore, this suggests that the pharmacological dissociation of the relation between behavior and beta activity for benzodiazepines is only apparent. Rather, high levels of beta activity are necessary for behavioral activity to occur under sedative conditions induced by diazepam and zolpidem.

P1.10 Opposite effects of GABA enhancement on the power of the beta band of the EEG during sleep and during active behavior of rats

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Introduction. It is stated that the increase in the power of the beta frequency can be used as a biomarker for a GABA agonistic mechanism of action. However, all these reported biomarker effects of GABA agonists have been measured during only one behavioral state, namely during active behavior. Aim of the present study was to investigate the effects of the GABAergic drug vigabatrin on the power of the beta frequency during both sleep and active behavior of

rats. Vigabatrin enhances the concentration of endogenous GABA by inhibiting GABA-transaminase.

Methods. Male WAG/Rij rats were used ($n=20$). A cortical tripolar electrode was implanted, co-ordinates related to bregma: A: 2.0, L: 3.5; -6.0, L: 4.0; ref. above the cerebellum. Doses ranged between 15 and 500 mg/kg vigabatrin i.p. In the dark period, at 6 hours following the vigabatrin injection the EEG and behavior were recorded during 30 minutes. Active behavior was defined as: locomotion, rearing, digging and sniffing. Sleeping behavior was defined as: immobile, curled up or lying straight with their eyes closed. Behavior was scored independent of the EEG. The EEG signal was sampled with 512 Hz and filtered between 1 and 100 Hz. The power spectrum of the EEG was calculated, using a FFT procedure. The beta frequency range was defined as 13-30 Hz.

Results. During active behavior vigabatrin increased the power in the beta frequency band with an ED ($2 \times$ baseline) of 499 mg/kg; S.E. 49 mg/kg. During sleep vigabatrin decreased the beta power with an ED ($0.5 \times$ baseline) of 270 mg/kg; S.E.= 54 mg/kg).

Discussion. When looking at the beta power it appears that this biomarker is not independent of the behavior. Indeed, both the increase of beta power during active behavior and the decrease during sleep after vigabatrin show a strengthening of the normal relationship between behavior and the EEG, in contrast to diazepam after which a behavior independent beta increase is found. In conclusion we recommend that whenever there is referred to a biomarker effect, it should be mentioned during which behavioral state the measurements were obtained.

P1.11 Effects of GABA enhancement on the relationship of behaviour and auditory evoked potentials of rats

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Introduction. Aim of the present study was to investigate the effects of the GABAergic drug vigabatrin on the relation of behavior and the auditory evoked potentials of rats. Vigabatrin enhances the concentration of endogenous GABA by inhibiting GABA-transaminase.

Methods. Male Wistar rats were used ($n=20$). A tripolar electrode was implanted, co-ordinates related to bregma: A: 2.0, L: 3.5; -6.0, L: 4.0; ref. above the cerebellum. Vigabatrin, 500-mg/kg i.p. or saline controls was used. In the dark period, 7 hours following the vigabatrin, behavior and auditory evoked potentials (AEPs) were recorded. Behavior was scored in: sleep (passive with sleep-EEG), passive behavior (sitting or lying motionless with wake-EEG), automatic behavior (eating, drinking and grooming) and explorative behavior (sniffing, rearing, locomotor activity). Auditory evoked potentials were elicited by presentation of sound stimuli (8 kHz, 80 dB) with random duration of 1.5 to 5 seconds with an inter stimulus interval of a similar random duration. The EEG signal was sampled with 512 Hz and filtered between 1 and 100 Hz.

Results. An increase in time spent on sleeping and a decrease in time of automatic and exploratory behaviors was observed. From the grand average AEP analysis it appeared that in the vigabatrin condition the N61, a marked component, had significantly larger amplitude than the saline controls. However, when analyzing the sub averages per behavioral category no difference between the vigabatrin – and saline treated groups could be observed.

Discussion. Vigabatrin has an effect on behavior, the changes observed in the amplitude of the N61 of the AEP might be secondary to

the behavioral changes. Therefore we recommend, when investigating drug effects on evoked potentials, to sub-average the AEPs per behavioral state.

P1.12 AEP and BIS monitoring during the induction of anaesthesia

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Background. The AEP 2 monitor was developed to calculate an index (ARX AEP index; AAI) by automatically using the amplitudes and latencies of the AEP.

We investigated 100 patients before laparoscopic abdominal surgery.

Methods. AAI; BIS index; relative (%) delta, theta, alpha, and beta; spectral edge frequency; median frequency; mean arterial blood pressure; heart rate; and oxygen saturation were obtained simultaneously during stepwise (1.0-2.0 µg/ml) induction of target-controlled TCI propofol concentration until 6.0-8.0 µg/ml, followed by an infusion of 1.0-0.1 µg/kg/min of TIVA remifentanyl. Every 20 seconds, the patients were asked to squeeze the observer's hand. Prediction probability (PK), receiver operating characteristic, and logistic regression were used to calculate the probability to predict the conditions awake, unconsciousness (first loss of hand squeeze), and steady-state anesthesia (6.0 µg/ml of propofol and 0.1 µg/kg/min of remifentanyl).

Results. Although a statistically significant difference among the conditions was observed for AAI, BIS, mean arterial blood pressure, median frequency, and % alpha, only AAI and BIS were able to distinguish unconsciousness *versus* awake and anesthesia *versus* awake with better than PK = 0.98. The EEG variables AAI and BIS were superior to the classic EEG and hemodynamic variables to distinguish the observed anesthetic conditions.

Conclusions. The modern electroencephalographic EEG ARX-derived auditory evoked potential index and the bispectral index were superior to the classic electroencephalographic EEG and hemodynamic variables for predicting anesthetic conditions.

Variables derived from the auditory evoked potential did provide an advantage over variables derived from spontaneous electroencephalogram.

P1.13 Polygraphic study of the effects of biperiden administration on behavioral changes in rats

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In order to elucidate the neurological mechanisms of delirium, we administered the anticholinergic drug biperiden (40 mg/kg i.p.) to 10 adult male Wistar rats and examined the resulting polygraphic recordings (EEG, EMG, and EOG) for 2 h following injection. Treated rats alternately demonstrated two types of behavioral change: hyperactive and hypoactive states. In the hyperactive state, rapid walking, excessive random searching, rearing at walls and retropulsion were observed, with marked rapid eye movements, and increased delta and alpha-1 band EEG activity. In the hypoactive state, motor arrest and drowsiness were observed, with mild rapid eye movements, increased delta band and decreased alpha-1 and theta-2 band EEG activity, and mild EMG activity. Ten rats receiving saline (i.p.) did not demonstrate any behavioral or polygraphic changes. These results suggest that the behavioral and polygraphic

changes induced by biperiden administration in rats are similar to those of delirium in humans.

P2.01 Differential event-related potential abnormalities in men and women with subclinical depression

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Abnormalities in amplitude, latency and asymmetry have been reported in event-related potential studies of depression. Some of these effects have also been observed in subclinical forms of depression. The current study employs a large international database of 276 healthy, right-handed participants (aged 20-60 years) to investigate gender and laterality effects on alterations in P300 and N200 ERP components in subclinical depression. Participants completed the depression anxiety and stress scale (DASS) and an auditory oddball task. Latency and amplitude of ERPs were measured from midline, medial and lateral electrode sites. Repeated measures techniques tested for differences between groups differentiated by gender and depression, while covarying for age, stress and anxiety. Subjects with higher depression scores showed shorter P300 latencies, and loss of asymmetry in lateral P300 amplitude. The later was more evident in women. Depressed women also demonstrated an increase in P300 amplitude at posterior temporal sites. Depressed men had reduced right N200 amplitude compared with non-depressed men. Changes in P300 and N200 asymmetry and increased posterior temporal P300 amplitude may reflect trait characteristics. Latency delays found previously in clinical groups are likely to be state dependent. Gender differences suggest distinct aetiologies for men and women may exist for subclinical depression. Such differences should be explored in clinical populations and specifically with regard to response to pharmacotherapy.

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P2.02 Mismatch negativity is related to thought disorder in schizophrenia

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Mismatch negativity (MMN) is an auditory ERP generated mainly in the superior temporal lobe. In addition, the generation of MMN critically depends on NMDA receptor functioning. MMN impairment is well documented in schizophrenia. However, it is still uncertain if this impairment is related to any clinical features of schizophrenia.

Previously, we demonstrated that MMN reduction is related to cognitive deficits in schizophrenia (Baldeweg 2004). In order to further understand this deficit the present study was set to investigate the clinical correlates of MMN dysfunction in schizophrenia.

49 patients with schizophrenia and 49 age-matched controls participated in the study. MMN was obtained for frequency and duration deviants. Ratings with the Positive and Negative Syndrome Scale (PANSS) were obtained within 7 days as well as duration of illness, number of admissions, and chlorpromazine equivalents.

Exploratory correlation analysis showed that only the positive symptom sub-scale of PANSS was significantly associated with MMN amplitudes. Following, stepwise regression analysis was performed in order to evaluate the relative weight of different positive symptoms on MMN. Results showed that only conceptual disorganization scores were predictive of MMN amplitude ($b=0.73$ $P<0.0001$).

These findings are in the line with previous studies showing that superior temporal pathology and NMDA changes are associated with thought disorder in schizophrenia (Adler 1999, Rajarethinam 2000, Shenton 1992). Our findings suggest that NMDA receptor functioning in STL may be crucial to pathogenesis of thought disorder in schizophrenia.

P2.03 How actions and errors are monitored under the influence of antipsychotic and antidepressant drugs

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Monitoring our daily actions plays an important role in successful human behavior. It is in this process of action monitoring that effects of psychopharmacology are often clearly evident as, for instance, state of arousal is degraded by a sedative drug and, consequently, human performance is decreased. State of arousal is known to affect information processing and error monitoring. However, little is known about how the underlying neurobiology of different types of drugs affects the precise process of action and error monitoring. When we make an error, a sharp negative peak can be seen in the event-related potential (ERP) measured from response onset. This error-related negativity (ERN) peaks around 50-100 ms after the erroneous response is made. Twelve healthy subjects participated in a double blind four-way cross-over study involving haloperidol, a classic conventional antipsychotic drug, olanzapine, an atypical antipsychotic drug, paroxetine, a selective serotonin reuptake inhibitor mainly used in the treatment of depression, and a placebo control condition. Subjects performed a standard Eriksen-Flankers task in which they had to press a button with either their left or right index finger depending on the central letter of a target string (HHHHH, SSSSS, SSHSS or HSSH). Next to reaction times (RTs), ERPs were measured from 27 electrode sites. In a previous study involving d-amphetamine, lorazepam and mirtazapine, clear differential effects on RTs and ERN amplitude were present for the different types of drugs. In this poster we will discuss the current RTs, ERN amplitudes, and other ERP results in detail and also relate them to the results from our previous work.

P2.04 R278995/CRA0450, a novel selective CRF₁ receptor antagonist modulates REM sleep in rats: implications for therapeutic indication

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Evidence exists that deregulation of the hypothalamic-pituitary-adrenal axis plays a critical role in the development and the course of major depression. In depressed patients, sleep quality is typically found disturbed and depression is associated with strong changes in sleep EEG. Consequently, changed sleep-wake architecture is considered a potential predictor or surrogate marker of response to treatment in affective spectrum disorders. The aim of this study is to investigate the effects of the novel CRF₁ receptor antagonist R278995, also known as CRA0450 on sleep wake organization and pharmacoeEG (pEEG) in rats, and to determine whether the observed changes in the sleep and EEG patterns resemble those seen with reference antidepressants. Effects of oral administration of R278995 (at 3 and 10 mg/kg) or vehicle on sleep-wake organization and on pEEG were investigated after the acrophase of sleep. Sleep polygraphic variables and pEEG were measured during 8 hours in male Sprague-Dawley rats, which were chronically implanted with electrodes. When administered at 3 mg/kg, R278995 produced major changes in sleep behavior during the first 2 hours of the recording session. The time spent in wakefulness was decreased (-27%) while the amounts of both deep sleep and REM sleep were increased (+62%, +288%, respectively). An overall reduction in power spectra was observed during deep sleep. At 10 mg/kg waking as well as light and deep sleep were slightly affected over the recording session. However, a pronounced reduction of REM sleep (-50%) was found in the first 4 hours following the administration and the REM sleep latency was significantly increased by 64% (85.8 ± 6.2 minutes for vehicle *versus* 140.9 ± 25 minutes for R278995 in the absence of systematic changes in power EEG frequency bands, which are characteristic anti-depressant-like effects. Hence these findings in rats show that this novel CRF₁ specific antagonist R278995 exerts central activity as it promotes wakefulness and inhibits REM sleep. Despite the compound's antagonistic activity on the σ_1 receptor, the characteristic changes in sleep variables as found in the present study suggest a non-sedative, antidepressant-like action of R278995 based primarily on CRF₁ receptor blockade.

P2.05 Activation of 5-HT_{1A} receptors prolongs REM latency and inhibits REM sleep in the rat

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Introduction. 5-HT_{1A} receptors are believed to be involved in the regulation of REM sleep (Boutrel et al. 2002, Gillin et al. 1994, Monti and Jantos 2004). Buspirone, a 5-HT_{1A} receptor agonist; WAY100635 (WAY), a selective 5-HT_{1A} receptor antagonist and a combination of buspirone and WAY were tested to investigate the involvement of 5-HT_{1A} receptors in the generation of REM sleep in the rat.

Methods. EEG, EMG and movement signals were used to classify sleep/wake states for every 2-second epoch into active waking,

passive waking, light sleep, deep sleep, intermediate sleep or REM sleep. Two 14.5 h recording sessions were performed over two successive days. The first recording provided a baseline. The second recording measured the effect of placebo, WAY (1 mg/kg), buspirone (3.2 mg/kg) or both WAY and buspirone. Drugs were administered i.p. at the start of the 14.5 h recording period 2.5 to 3.0 hours after lights-on. Significance was calculated by means of the Mann-Whitney U test ($\alpha < 0.05$).

Results. REM latency following drug treatment was increased from 56 minutes in controls to 251 minutes in the buspirone treated group, however, co-administering WAY with buspirone reversed this effect (REM latency = 87 minutes). Similarly the percentage of REM sleep occurring over a 6 hour period was significantly decreased by buspirone (3.1%) compared to controls (8.1%), but this effect was prevented by co-administering WAY with buspirone (8.0%).

Conclusion. The decreases in REM sleep observed following administration of buspirone can be blocked by the 5-HT_{1A} antagonist WAY. The results suggest that the effects of buspirone on REM sleep are mediated by 5-HT_{1A} receptors.

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P2.06 The effects of subtype selective 5-HT₂ antagonists on rat sleep-wake behaviour

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Introduction. 5-HT₂ receptors are believed to be involved in the regulation of Slow Wave Sleep (SWS) in both humans and animals (Dugovic et al. 1992, Kantor et al. 2002, Sharpley et al. 1994). The aim of this study was to investigate the role of the 5-HT_{2A} and 5-HT_{2C} receptors in light and deep sleep (SWS) by comparing the effects of the 5-HT₂ antagonists SB242084 (5-HT_{2C} selective), MDL 100907 (5-HT_{2A} selective), ketanserin (mixed 5-HT_{2A/2C}; 2A>2C) and ritanserin (mixed 5-HT_{2A/2C}; 2C>2A) in rats.

Methods. Each compound was administered i.p. at the start of a 14.5 hours recording period. Recording started 2.5-3 hours into the light period of the 12h-12h light-dark cycle. EEG, EMG and movement were recorded. On the basis of these signals every 2-second epoch was classified into active waking, passive waking, light sleep, deep sleep, intermediate sleep or REM sleep. Significance was calculated by means of the two-sided rank sum test (Mann-Whitney U test; $\alpha < 0.05$).

Results. The 5-HT_{2A} antagonist MDL100907 (0.01-0.1 mg/kg) elicited a pronounced and dose dependent increase in deep sleep that was accompanied by a decrease in light sleep. In contrast the 5-HT_{2C} antagonist SB242084 (1-10 mg/kg) did not increase deep sleep or change the occurrence of light sleep. Ketanserin increased deep sleep at 1 mg/kg and 3 mg/kg. Ritanserin (0.1-3 mg/kg) increased

SWS at 1 and 3 mg/kg but did not specifically alter the occurrence of deep sleep.

Conclusion. Increases in deep sleep occurred after administration of 5-HT_{2A} selective and not the 5-HT_{2C} selective antagonists. We suggest that the occurrence of deep sleep in the rat is restrained by 5-HT acting *via* 5-HT_{2A} rather than 5-HT_{2C} receptors.

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P2.07 Effects of selective activation or inhibition of the 5-HT₇ receptor on sleep EEG and concomitant physiological variables

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Growing evidence points towards a role of 5-HT₇ receptors in a number of common CNS disorders. Availability of specific 5-HT₇ agonists and antagonists provides a springboard for new investigations into the function of this latest member of the serotonergic subreceptor family. Our objective was to determine the effects of selective activation (BASF agonist) or inhibition (SB269970; DR4004) of 5-HT₇ receptors on peripheral physiological and sleep EEG variables *via* telemetric assessment in freely moving rats. Effects of drugs administered intraperitoneally at 1, 10, and 30 mg/kg were evaluated on body temperature (BT), blood pressure (BP), heart rate (HR), locomotor activity (Act), and sleep-wake organization in rats implanted with EEG/EMG electrodes.

Increased HR was observed during one hour after administration of SB269970 at 30 mg/kg. Otherwise, no significant changes were observed in BT, BP, HR or Act after administration of either 5-HT₇ antagonists at any of the doses tested. However, both antagonists changed sleep-wake organization, especially in reducing time spent in Rapid Eye Movement sleep (REM) as well as in increasing REM latency. This REM inhibition lasted for two hours after SB269970 (30 mg/kg) but up to eight hours after DR4004 administration (10 mg/kg).

In contrast, the 5-HT₇ agonist induced a significant decrease in BT during the first four post-administration hours, followed by an increase in BP (30 mg/kg). Moreover, it induced a biphasic effect on sleep-wake organization: REM decreased at the expense of wakefulness during two hours after administration, followed by a decrease in waking in favor of REM during the following three hours. In sum, the earlier reported involvement of 5-HT₇ in mechanism underlying both temperature and REM sleep regulating was confirmed. The sleep-wake architecture after 5-HT₇ receptor activation most closely resembles stimulant-like changes while antagonizing induces a more antidepressant-like pattern. Ongoing analysis of power spectra in different frequency ranges aim to reveal alterations of certain EEG oscillations during wakefulness and non-REM sleep. Evidence exists that such variables derived from sleep and quantified EEG analysis can predict therapeutic efficacy to different 5-HT₇ ligands and have potential use as biomarkers.

P2.08 Sleep and sleep EEG spectra in marmoset monkeys: effects of late afternoon temazepam treatment

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Sleep is a common feature in all mammals, serving maintenance of behavioural function during waking. For addressing invasive aspects of sleep concerning research questions on typical human behaviours or diseases, sleep in a model organism similar to humans may be preferred over rodents. Marmoset monkeys are small (300-500 g) primates. They sleep mono-phasically, spending 93.1% (SE 0.8%) of a 12 h dark phase in sleep, of which 13.8% (SE 1.4%) in REM sleep. EEG sleep spectra mimic human sleep EEG spectra. Slow wave activity in the NREM sleep EEG shows a gradual decrease in the course of the night. For investigating effects of temazepam used at an irregular sleep time on subsequent sleep induction and after-effects on sleep and sleep spectra, 15 mg/kg temazepam was applied orally to 6 Marmoset monkeys in the late afternoon 2 h before lights off. Temazepam treatment induced more sleep (61%, SE 3%) compared to baseline (37%, SE 11%, paired *t*-test: $P < 0.05$) in the 2 h before lights off. During the 12 h dark phase following temazepam treatment, total sleep time increased to 94.5% compared to baseline (paired *t*-test: $P < 0.05$) of which 13.0% was REM sleep. All night sleep EEG spectra and sleep architecture were not significantly affected.

P2.09 Liver transplantation in cirrhotic patients significantly ameliorates severe sleep deficiencies

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Sleep disturbances are early clinical signs of hepatic encephalopathy (HE). Twenty cirrhotic patients included in the protocol of liver transplantation of our hospital, and without overt HE, were studied by polysomnography during nocturnal sleep. Seven of them were also recorded after transplantation, to determine whether or not sleep alterations present at this stage of the illness would be lessened after liver transplantation. Patient recordings were compared with those obtained from twenty age matched healthy volunteers. Artefacts were suppressed and sleep stages were determined by two expert staggers. Sleep was characterised by total sleep time (TST), sleep efficiency, sleep latency, number of sleep cycles, number of awakenings after sleep onset and percentage of sleep stages. Also, REM latency, and REM periods and REM episodes duration were determined. Pretransplanted patients showed lower TST and sleep efficiency than controls, with an increase in sleep and REM latencies and in the number of intra sleep awakenings, corresponding to considerable sleep fragmentation. They also showed lower number of REM periods and episodes, and percentage of REM sleep, and significant increases in the percentages of wakefulness and stage1, compared with healthy subjects. Corresponding values obtained from post-transplanted patients, showed a tendency to reach values similar to those presented by control subjects. In fact, liver transplantation introduced significant changes in the patients TST, sleep efficiency and morning wake duration. In conclusion, liver transplantation reverses partially important alterations in sleep onset, maintenance and structure present in cirrhotic patients.

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P2.10 Clustering of EEG paroxysms in a genetic rat model of pyknolepsy: effects of drug administration and hormonal fluctuations

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Rationale. Spike-wave discharges (SWDs) of absence epilepsy are known to appear in clusters. To elucidate the mechanisms of such clustering, long-term sequences of SWDs were analyzed.

Methods. WAG/Rij rats served as a model for absence epilepsy (pyknolepsy). Clustering was assessed by the autocorrelation function's half-decay time (τ) calculated for long sequences of SWDs. Sequences of SWDs were obtained in drug-naive male ($n=8$) and female ($n=6$) rats; the latter were recorded during the whole estrous cycle. Also, SWDs sequences from male rats injected with vigabatrin (125, 250 or 500 mg/kg; $n=8$ rats per dose) and haloperidol (0.5 mg/kg; $n=5$ rats) were checked.

Results. Drug-naive male and female WAG/Rij rats had similar τ values (about 2.4 minutes). Female rats showed significantly higher number of SWDs on the proestrous day, without any corresponding changes in τ . Vigabatrin (an inhibitor of GABA-transaminase) increased τ only in the highest dose, whereas smaller doses affected number of SWDs without any detectable effects on τ . However, haloperidol (a mixed D1/D2 dopamine antagonist) induced an increase in SWDs, which was accompanied by prolongation of τ up to about 4.4 minutes. Also, the light-dark shifts effectively modulated τ : it was larger during the dark, than in light periods.

Conclusions. not all factors, capable to increase the amount of spike-wave activity, can also affect the clustering of SWDs, as measured by τ . Ovarian hormones and modulation of GABA levels within a physiological range do not alter τ . However, the brain aminergic neurotransmission can be a putative candidate for modulation of τ and, consequently, be responsible for arrangement of SWDs in time clusters.

P2.11 GABAergic manipulation in absence epilepsy: WAG/Rij rats and a computational model

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In this study we analyzed the influence of vigabatrin on spike and wave discharges (SWDs) in the EEG of WAG/Rij rats, an animal model for absence seizures. The *in vivo* data were compared to a computational model (Suffczynski et al. 2004) in which we studied the influence of modulating GABAergic neurotransmission in the thalamocortical loop. The parameter changes needed to obtain model behavior similar to the *in vivo* SWD data were linked to the mechanism of action of vigabatrin. More specifically, the model output was used to predict whether the increase of GABAergic neurotransmission after vigabatrin is either homogeneous or heterogeneous throughout the brain.

In vivo, vigabatrin dose dependently increased the incidence of SWDs. Also, the SWD peak frequency was decreased. Model simulations of manipulation with GABAergic neurotransmission in the whole network, or only part of the network, showed that the effects of vigabatrin are reproduced best by a relative increase of GABAergic neurotransmission at the level of the thalamic relay nucleus. We conclude that vigabatrin most likely affects in homogeneously different parts of the thalamocortical circuitry. We hypothesise that an increase of GABAergic neurotransmission by vigabatrin is most pronounced at the level of the thalamic relay nuclei.

P2.12 Effects of lorazepam, mirtazapine, and d-amphetamine on EEG, saccadic eye movements, psychomotor performance, and subjective experience

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The hypnotic/sedative effects of two hypnotics – lorazepam and mirtazapine – were compared with placebo, with each other and with the central stimulant d-amphetamine. The hypnotic/sedative and activating effects were evaluated with the EEG power spectrum during the waking state (eyes open, eyes closed), saccadic eye movements

(SEM); peak saccadic velocity (PSV), reaction time (RT) and accuracy (ACC), psychomotor tasks (Fitts-variant and Pursuit) and subjective ratings. It was expected that lorazepam and mirtazapine yield a similar, hypnotic EEG profile with similar effects on SEM, subjective state and motor slowness while amphetamine would show a more active profile.

A single oral dose of lorazepam (2.5 mg), mirtazapine (5 mg) and amphetamine (15 mg) was administered to 16 healthy volunteers in a double blind, crossover study. The order of the drug administration was counterbalanced.

The spectral analyses of the EEG showed an increase of high delta after mirtazapine and lorazepam, while both drugs reduced alpha2. Different effects emerged in the theta, alpha1, beta and gamma bands: lorazepam reduced theta and alpha1 and enhanced beta, mirtazapine decreased gamma, and amphetamine increased alpha1, beta and gamma. The PSV and ACC of the SEM were reduced by both lorazepam and mirtazapine, the RT's were increased. Amphetamine, on the contrary, accelerated PSV and improved ACC. Fitts- and Pursuit-task showed more slowing after lorazepam than after mirtazapine. Amphetamine improved performance on only the Pursuit. Lorazepam and mirtazapine impaired, amphetamine increased subjective alertness.

It can be concluded that, in contrast to the expectations, the spectral profile of mirtazapine differs from that of lorazepam. This differentiation was related to distinctions between the two drugs on psychomotor performance, with mirtazapine showing smaller effects than lorazepam. The EEG profiles of the two hypnotic drugs and the opposite effects of amphetamine were also in accord with the findings on SEM. The different types of drug-induced-hypnosis merit further investigation.

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