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# Interdisciplinary

**Sunday, April 3, 2005**

## S-07. Symposium: Neuroplasticity in psychiatric diseases

*Chairperson(s):* Peter Eichhammer (Regensburg, Germany), Johannes Thome (Swansea, United Kingdom)
08.30 - 10.00, Holiday Inn - Room 8

### S-07-01

The role of genetic factors in modulating neuroplastic processes

J. Thome. *School of Medicine, Dept. of Psychiatry, University of Wales, Swansea, United Kingdom*

**Objective:** Neural plasticity represents an important factor which is most likely involved in the pathogenesis and therapy of several psychiatric disorders. The modulation of neuroplastic processes depends on a plethora of genes and their regulation via signalling cascades and transcription factors. Some gene families such as neurotrophic factors and synaptic vesicle proteins have been identified as key players in neural and synaptic plasticity. However, there is increasing evidence that neuroplastic processes result from the interaction of such genetic factors with environmental and behavioural factors.

### S-07-02

Detection of neural plasticity offered by positron emission tomography (PET)

J. Horacek, T. Novak, M. Kopecek, F. Spaniel, C. Dockery, C. Hoschl. *Prague Psychiatrc Center, Praha, Czech Republic*

**Objective:** The neuroplastic changes are supposed to be the underlying mechanism for the long lasting clinical effect of the modern neuropsychiatric treatment modalities as psychotropics, psychotherapy or repetitive transcranial magnetic stimulation (rTMS). The use of 18FDG PET in the resting state reflects the regional glutamate turnover at the synaptic level and is the probe for relative synaptic strength and consequent functional and metabolic activity of the brain regions.

**Methods:** rTMS (0.9Hz, 100% of motor threshold, 20 min.) applied to the left temporo-parietal cortex was used for ten days in treatment of medication-resistant auditory hallucinations in schizophrenia (N=11). We detected the changes in 18fluoro-deoxyglucose (18FDG) uptake (PET) followed the low frequency rTMS (SPM99).

**Results:** We found a significant improvement in the total and positive symptoms (PANSS) and in hallucinations (HCS, AHRS). The rTMS decreased the brain metabolism (18FDG PET) in the left superior temporal gyrus and effected increases in the contralateral temporal cortex and in the frontal lobes bilaterally.

**Conclusion:** Our findings confirm the effect of rTMS in this indication and the neuroplastic changes in the cortex underlying the rTMS site (inhibition). The facilitation of metabolism is likely compensatory to the rTMS induced suppression in the left temporal cortex and would be mediated by interhemispheric transcallosal connections (to the right temporal cortex) and by intrahemispheric long superior fascicule (to the frontal lobe). This research was supported by the grant NF/7578 – 3 form MZCR and the project CNS 1M0002375201 MSMT CR.

### S-07-03

Investigating subtle region-specific changes in grey and white matter by using voxel-based morphometry (VBM)

G. Hajak, P. Eichhammer, B. Langguth. *University of Regensburg, Regensburg, Germany*

Voxel-based morphometry is a sophisticated objective whole-brain technique to investigate subtle, region specific changes in gray and white matter. This method bases on high-resolution, three-dimensional magnetic-resonance imaging, registered in a common stereotactic space and is designed to find significant regional differences by applying voxel-wise statistics in the context of Gaussian random fields. Using this approach a variety of changes in grey matter could be detected in schizophrenic patients as well as in patients with affective disorder. These results point to the fact that neuropsychiatric diseases can be interpreted as a result of maladaptive neuroplasticity. These findings are supported by our own studies, demonstrating that patients with chronic tinnitus show alterations in grey matter, restricted to specific areas involved in auditory processing. Taken together, voxel-based morphometry seems to be an ideal imaging technique to detect neuroplastic processes associated with neuropsychiatric diseases. New insights into the neurobiology of these disorders may also help to develop new treatment strategies



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## S-07-04

The contribution of modern neurophysiologic methods to our understanding of cortical neuroplasticity

P. Eichhammer, B. Langguth, G. Hajak. *University of Regensburg Dep. of Psychiatry, Regensburg, Germany*

In the last decade, transcranial magnetic stimulation (TMS) has been used increasingly as a tool to explore the mechanisms and consequences of cortical plasticity in the human cortex. Depending on the stimulation frequency, TMS can induce neurobiological effects resembling those used in animal studies of neuroplasticity in which electrical stimulation was used. In rodent auditory cortex, known for learning-induced plasticity, rTMS from 1 to 10 Hz resulted in long-term potentiation (LTP)-like and more durable long-term depression (LTD)-like changes in evoked spike rate (Wang et al., 1996). In support of this study, low-frequency 1-Hz rTMS, targeting the left temporoparietal cortex, causes a remarkable and sustained reduction of auditory hallucinations in schizophrenia, which is interpreted as the result of TMS-induced lasting changes in synaptic efficacy. Based on these results, we studied whether structural neuroplasticity is involved in mediating clinical effects of low-frequency rTMS in a group of healthy volunteers by means of voxel-based morphometry, a magnetic-resonance imaging technique, which is able to detect subtle changes in cortical grey and white matter. Our results point to the fact that TMS may be able to induce regenerative neuroplastic processes in specific brain areas depending on the site of TMS stimulation. These findings are in line with current studies investigating the neurobiological effects of central acting agents like antidepressants and underscore that the induction of neuroplastic processes may be essential for a variety of different treatment strategies.

**Tuesday, April 5, 2005**

# S-03. Symposium: New aspects in therapeutic drug monitoring

*Chairperson(s):* Michael Riedel (Munich, Germany), Markus J. Schwarz (Munich, Germany)
14.15 - 15.45, Holiday Inn, Gasteig - Black Box

## S-03-01

Insights in stereopharmacology in modern antidepressant treatment

F. Bengtsson. *Dept Clin Pharmaco Uni Linköp Faculty of Health Sciences, Linköping, Sweden*

Our knowledge of the biochemical and pharmacological complexity in space, sometimes existing when a three-dimensional view is applied on such molecules, dates back a long time. This insight has prompted an awareness that both the metabolism of a molecule as well as the bioactivity of the molecule may be altered if the molecule possesses a so called chiral center. If a drug comprise a chiral center, this is made up of (at least one) carbon atom(s) that provides for different and in-exchangeable three-dimensional structures of the same molecule referred to as separate stereoisomers. Since it has been quite complicated to, at least in an industrial scale, separate the different setereoisomers of a so called racemic (i.e. 50/50 mixture of isomers) drug, many such racemates have been the only available compound for prescription on the market. However, the insight that such a chiral or racemic drug tentatively may bring about different both pharmacokinetic (PK) and pharmacodynamic (PD) activities for each stereoisomer has necessitated a deeper analysis of the problem. This in order to better understand drug dosing (e.g. linear or non-linear kinetics?) as well as drug actions (effects, side-effects and toxicity). Recently also the possibilities to separate stereoisomers from each other in a racemic preparation has advanced so that it can be done both in an experimental scale, for testing of the individual stereoisomers, as well as for production of larger quantities so that a stereochemically "pure" drugs can now be offered to the clinic. One of the worlds most commonly prescribed drug entities are the antidepressant, or thymoleptic, drugs. Interestingly, the vast majority of these thymoleptics are marketed as racemic drugs, i.e. comprising of at least two stereoisomers of the same compound. Since, inevitably, all such drugs undergo an extensive metabolism in the body the stereoisomeric outcome may be very different from drug to drug as well as for the same drug between different patients. Moreover, since this metabolism creates a number of catabolites, these metabolites will commonly bear the same stereopharmacological aspects as their parent compound, why the complexity increases even further regarding the "true" PK-outcome of such an antidepressant. Finally, since the PD-activities may vary between all these stereoisomers (parent compounds as well as metabolites), the ability to point out real causality of the outcome of any such drug exposure when viewed in the clinic of modern antidepressant treatment has to take this whole new pharmacological paradigm into consideration. The present lecture will provide information on the most common antidepressant drugs, old as well as new, in the view of their specific PK and PD-related stereopharmacological features. This will give an insight into the new pharmacological paradigm that has to be taken into account when evaluating antidepressant treatment in greater detail in the modern age.

## S-03-02

Therapeutic drug monitoring of psychotropic durgs in the era of pharmacogenetics studies

C. Eap. *Unité de Biochimie et Psychoph, Prilly-Lausanne, Switzerland*

Like for other drugs, there is a large inter-individual variability of the plasma concentrations of psychotropic drugs for a given dose, which is the main rationale for therapeutic drug monitoring. TDM is performed to avoid toxicity (due to high and poorly tolerated plasma levels) and inefficacy (due to low and ineffective plasma levels). Within the last decade, a large amount of studies in pharmacogenetics / pharmacogenomics allows us to understand the importance of genetic and environmental factors on the disposition of drugs in the organism. Thus, high and low plasma levels might concern the so-called poor and ultrarapid metabolizers, respectively, either due to a genetic basis or an environmental factor, e.g. co-administration of inhibiting or inducing drugs. Several genotyping and phenotyping methods now allow the determination of the activity of several key enzymes involved in the pharmacokinetics of drugs, in particular those of the cytochrome P450 family. Proposals of genotype specific dosages of drugs have been made (i.e. a low dose for the poor metabolizers and a high dose for the ultrarapid metabolizers), which will lead to, admittedly, equivalent plasma concentrations in all patients. Advantages and limitations of such proposals will be discussed. Finally, arguments with practical examples, clinical cases and some cost-benefit considerations, on how

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