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Abstracts

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Oral Presentations

1

A Longitudinal Study Investigating Cognitive Performance in First-Episode Patients Before and After Antipsychotic Treatment

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Cognitive dysfunctions are core symptoms of schizophrenia. It is not clear whether deficits in sustained attention, executive functions and planning abilities are stable or if they fluctuate in response to medication. Thus, the purpose of this study was to evaluate the cognitive performance in first-episode schizophrenia patients before and after medication. We hypothesized, that drug-naïve patients perform worse than controls and that they can improve their performance following medication. Matched controls and patients were asked to perform four computerized neuropsychological tests of the Cambridge Neuropsychological Test Automated Battery (CANTAB) at baseline, after one month and after two months. Sustained attention (RVIP) was assessed at all times; planning abilities (SOC) and executive functions (IDED) were assessed at baseline and after two months, and spatial working memory (SWM) was measured only after one month. The patients were drug-naïve at baseline ($n = 40$: 32 men/8 women) and then received antipsychotic medication for one month ($n = 25$: 18 atypical/1 typical/6 combination) and two months ($n = 9$: 8 atypical/1 typical). 34 controls (25 men/9 women) participated at baseline, 32 after one month and 16 after two months. The patients' psychopathology was assessed using the PANNS. Drug-naïve, first-episode patients exhibited significant impairments ($p < 0.05$) in sustaining attention and planning. Their performance on the IDED was partly similar (ED errors and pre-ED errors) and partly worse (stages completed) relative to the controls. Patients' performance on the SWM was inferior. Two months after the start of medication, the patients did not improve their performance in the RVIP and IDED, whereas some measures (4-moves-task) of the planning task (SOC) were performed better. Cognitive deficits in attentional (RVIP) and planning tasks (SOC) already seem to be present at early stages of the development of schizophrenia and might point at dysfunctional neural circuits including the frontal lobe. The SOC and RVIP are the tasks that differentiate best between drug-naïve first-episode schizophrenia patients and healthy controls, whereas the IDED seems to be less

potent. A positive overall effect of a two-months antipsychotic treatment is not evident in the present schizophrenics due to the controls' better performance on all three tests after two months. A difference between type of medication could not be observed.

2

Structural and Perfusion MRI in Schizophrenic Patients with and without Delusional Misidentification Syndrome

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Neuropsychological investigations in patients with prosopagnosia have given evidence of specific anatomical loci of face processing in temporo-occipital brain areas. Electrophysiological investigations showed face specific activation at about 170 ms after stimuli at vertex. At least, a large number of neuroimaging studies currently address their focus on clarifying how the brain processes face stimuli. In this context, the so-called fusiform-face area (FFA) has been found to be in centre of the face processing system. Impaired processing of faces is known as an additional symptom in schizophrenia. This leads to social isolation by inadequate behaviour in everyday life. In a subgroup of acute schizophrenics, delusional misidentification is a prominent symptom (DMS). Patients mistake people or they believe to know people who they actually cannot know. **Methods:** Functional magnetic resonance imaging (fMRI) was applied in 19 healthy subjects, 9 schizophrenics with and 7 without DMS during a face recognition paradigm (data still under process). Furthermore we obtained the brain perfusion as measured by arterial spin labelling at rest and during a checkerboard task. **Results and Discussion:** Test performance during fMRI revealed that controls correctly recognized stimuli in 66%, patients with PMS in 45% and without in 55%. Additionally, the regional cerebral blood flow of the right fusiform face area (FFA) at rest in patients with PMS was reduced to 42 ml/100 g grey matter substance/min, in patients without to 47, whereas controls showed 61 ml/100 g grey matter substance/min (significant as compared to controls). On the other hand no differences were found in the primary visual cortex. This data give evidence of a functional impairment of the FFA in patients with schizophrenia, especially with DMS. Data from fMRI will add valuable informations to these findings.

Phenomenology of Mixed States: A Principal Component Analysis Study

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Background: Defining the external and internal limits of mixed states remains an open question. **Method:** 165 in-patients with a major mood episode were diagnosed as presenting either pure depression ($n = 62$), mixed depression (depression plus at least 3 manic symptoms, $n = 28$), full mixed state (full depression and full mania, $n = 15$), mixed mania (mania plus at least three depressive symptoms, $n = 20$) or pure mania ($n = 40$), using an adapted version of the Mini International Neuropsychiatric Interview (DSM IV version). They were evaluated using a 33 items inventory of depressive, manic and mixed affective signs and symptoms. **Results:** Principal component analysis without rotation yielded three factors that explained together 43.6% of the variance. The first factor (24.3% of the variance) had a bimodal distribution ranging from typical depressive symptoms to typical euphoric, manic symptoms. The second (13.8%) factor 'dysphoria' had strong positive loadings for irritability, distressing sensitivity to light and noise, impulsivity and inner tension. The third (5.5%) factors included symptoms of insomnia. Median scores for the first factor significantly decreased from the pure depression group to the pure mania group (test for trend, $p < 0.001$). For the dysphoria factor, scores were highest among patients with full mixed state and decreased towards both pure depression and pure mania ($p < 0.001$). **Conclusions:** Factor analysis revealed that dysphoria, a cluster of symptoms such as irritability, impulsivity, inner tension and distressing sensitivity to light and noise represents an important dimension of mixed states.

Glutathione (GSH) Deficit in Schizophrenia: Dysfunction of NMDA Receptors and Alteration of Dopamine Modulation of NMDA Responses

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Synthesis of glutathione (GSH), an antioxidant, is compromised in schizophrenia. Patients show a GSH deficit in cerebrospinal fluid and prefrontal cortex, and a decrease in gene expression of the modulatory subunit of glutamate-cysteine ligase, the rate limiting enzyme of GSH synthesis. A polymorphism of this gene is also associated with the illness. Since hypofunction of NMDA receptors has been implicated in schizophrenia, we studied the effects of GSH deficit on NMDA receptor function. GSH deficit was induced by L-buthionine-(S,R)-sulfoximine (BSO), an inhibitor of the glutamate-cysteine ligase. In hippocampal slices, a GSH deficit caused decrease in NMDA receptor-mediated fEPSPs. This hypofunction of NMDA receptors was due in part to oxidation of extracellular redox-sites on NMDA receptors.

Using cultured cortical neurons, we also investigated if a deficit in [GSH] could affect intracellular signalling pathways which could in turn dysregulate NMDA-mediated responses. We found that low micromolar dopamine depressed NMDA-mediated calcium responses in GSH-depleted but not in control neurons. This depression of NMDA responses was abolished when intracellular [GSH] was replenished with GSH-ethyl-ester. Antagonist for D2 receptors, but not for D1 receptors, prevented the dopamine-induced depression of NMDA responses in GSH-depleted neurons. In addition, dopamine-induced depression of NMDA responses was not observed when GSH-depleted neurons were incubated in dantrolene. Caffeine, but also dopamine, evoked more calcium release from internal stores in GSH-depleted than in control neurons. Altogether, these results indicate that GSH deficit leads to hypofunction of NMDA receptors and suggest that GSH deficit alters dopamine-dependent intracellular signalling pathways, involving D2-type receptor activation and ryanodine receptors and leading to a decrease in NMDA responses.

The First Episode Psychosis Outcome Study (FEPOS): Pre-morbid and Baseline Characteristics of 704 First Episode Psychosis Patients Treated in EPPIC between 1998 and 2000

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Background: Study of psychotic disorders is hampered by many potential biases that can be avoided in first episode psychosis (FEP) studies. However, very few studies are based on epidemiological samples. **Aims:** Description of pre-morbid and baseline clinical and socio-demographic characteristics of a large epidemiological sample of FEP. **Methods:** Medical records review of patients treated at EPPIC between 1998 and 2000. **Results:** 704 files were assessed. Pre-morbid evaluation revealed high rates of substance use disorder (74%), history of psychiatric disorder (46%), traumatic events (68%), suicide attempts (14%) and family history of psychiatric illness (55%). Baseline characteristics revealed high intensity of illness, high prevalence of lack of insight and high rate of co-morbidity. **Conclusion:** Majority of subjects have gone either through traumatic events or episodes of mental illness before treatment for FEP. Such elements must be considered when designing treatment approach since a too narrow focus on positive psychotic symptoms will inevitably lead to incomplete treatment. Additionally, early intervention programs need sufficient range of resources to address the multiple challenges presented by FEP patients such as co-morbidities and high severity of illness. Finally, observation that patients in this cohort developed important level of functional impairment before FEP treatment despite a relatively short duration of untreated psychosis suggests that while early detection of FEP is a necessary step in early intervention, it may not be a sufficient strategy to limit functional impairment and that efforts aimed at identifying people during the prodromal phase of psychotic disorders should be pursued. In this context, the identification of valid biological markers is critical in order to improve the specificity of current early diagnosis strategies.

6

Identification of a Genetic Cluster Influencing Memory Performance and Hippocampal Activity in Humans

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Experimental work in animals has shown that memory formation depends on a cascade of molecular events. By using a linkage disequilibrium-based behavioral genetics approach we observed that variability of human memory performance is related to variability in genes encoding proteins of this signaling cascade, including NMDA receptor, metabotropic glutamate receptor, adenylyl cyclase, CAMKII, PKA and PKC. The individual profile of genetic variability in these signaling molecules correlates significantly with episodic memory performance ($p < 0.00001$). Moreover, functional magnetic resonance imaging during memory formation reveals that this genetic profile correlates with activations in memory-related brain regions, including the hippocampus and parahippocampal gyrus. We conclude that genetic variability in the human homologues of memory-related signaling molecules contributes to inter-individual differences in human memory performance and memory-related brain activations.

Posters

7

Monitoring with Real-Time Imaging the Migration and Differentiation of Cortical Interneurons

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Converging experimental and clinical evidence suggests that altered cortical interneuron development may underlie part of the pathophysiological processes involved in psychiatric disorders such as schizophrenia and bipolar disorder. To have an easy access to these complex developmental processes and understand their molecular mechanisms, we have developed a model allowing us to study in real time the migration and integration of cortical interneurons in the early postnatal cortex. Neural precursor cells (NPC) were isolated from the subventricular zone (SVZ) of postnatal day 0 (P0) pups, expanded in the presence of FGF-2, transduced with a GFP lentivirus, transplanted in the SVZ of P0 pups and monitored on sagittal slices cultured at P3. Time-lapse recordings revealed that after 1 day in vitro (DIV) a large number of GFP+ cells displayed the morphology of interneurons and migrated directionally into cortical regions. These cells had a mean migration speed of 70.1 $\mu\text{m/h}$ and displayed high directional persistence

(0.86). At 3 DIV, the speed of migration was reduced to 20.8 $\mu\text{m/h}$ and GFP+ cells extended and retracted branched processes, suggesting that they were actively searching for positional cues. Posthoc confocal analysis of triple-labeled cells at DIV3 showed that 91.6% of GFP+ cells expressed the immature neuronal marker doublecortin and 55% expressed the calcium binding protein calretinin. At 7 DIV the vast majority of GFP+ cells expressed NeuN, calretinin, and GAD67, indicating a process of differentiation into interneurons. At 14 DIV many cells extended a fine ramified process resembling an axon-like process. This cortical slice model represents a promising tool not only for analyzing the migration and integration of cortical interneurons but also for identifying candidate molecules that regulate these processes.

8

The Frontal Cortex may be the Site of Synaptic and Cytoskeleton Reorganization in Alzheimer's Disease

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As executive and attention deficits may be linked to damage of the frontal cortex in the evolution of Alzheimer's disease (AD), we studied in frontal area 9 of 4 AD and 4 control patients, the variations in neuropile intensity of several synaptic and cytoskeletal markers and compared them with beta-amyloid deposits (Zeiss KS400 image analysis system). While the distribution of the presynaptic protein synaptophysin, linking to small synaptic vesicles, was unchanged in AD patients, that of alpha-synuclein, another presynaptic protein and component of Lewy bodies, was significantly increased, as well as that of MAP2, a cytoskeletal protein associated to the somatodendritic part of neurons and to spines. GAP43, a growth-associated protein synthesized in neurons and primarily localized to axons, was on the contrary significantly decreased. These results may indicate an increased remodeling activity in dendrites and spines, as well as a decreased axonal activity and/or connectivity in AD frontal cortex. The latter point was further confirmed by a significant decrease in the staining of non-phosphorylated neurofilament protein with the SMI32 antibody, representing normal cells and dendrites. On the contrary, the SMI31 antibody, reacting with a pathologically phosphorylated epitope in axons, was increased in AD. Phosphorylated protein tau, as detected with the AD2 antibody, was increased as well. In 2 severe AD cases, SMI31 and AD2 stained also a small number of neuronal cell bodies, not reactive in control samples and correlating with neurofibrillary tangles labeled by the Gallyas silver impregnation. The amount of beta-amyloid within senile plaques was significantly higher in AD than in controls, and a correlation was found with the density of AD2, alpha-synuclein and MAP2 staining. These data indicate a clear involvement of the frontal cortex in AD, damaged by beta amyloid deposition and abnormal phosphorylation, but suggest also some attempt to synaptic reorganization.

A Prefrontal Cortex Defect of Glutamate Release Capacity in the Phencyclidine (PCP) Model of Schizophrenia

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Subchronic administration of PCP, a psychotomimetic agent acting as an NMDAR channel blocker, produces in rodents a syndrome that models some aspects of schizophrenia. Our research investigates the consequences of PCP administration on glutamatergic functionality in rodents' prefrontal cortex (PFC). Rats were treated once daily for 7 or 14 days with either PCP (5 mg/kg) or saline. 24 h after the last treatment, glutamatergic functionality is evaluated in terms of glutamate release capacity in acute PFC slices stimulated with high KCl (60 mM). Slices from rats pre-exposed to PCP released less glutamate than slices from saline-treated animals. Such a defect persisted 72 h after the last treatment and was not observed in a different cortical area, the visual cortex. For 14 days treatments, the adaptive changes are extinguished 7 days after the last exposure to PCP. These findings were then reproduced in mice. Furthermore, we tested the effect of antipsychotics (haloperidol and olanzapine) in PCP-treated animals. PCP treatment lasted 14 days, antipsychotics were administered in parallel starting from the 8th day (when the glutamate release defect is already established). Both antipsychotics reversed the PCP-induced defect, restoring a normal glutamate release capacity. The plastic modifications apparently occur at the level of glutamatergic terminals, as synaptosomes prepared from the PFC of PCP-treated animals showed defective glutamate release in comparison to control animals. In this preparation we are now studying the molecular target of PCP action, focusing our attention on a likely presynaptic NMDAR and the regulation of Ca⁺⁺ increases leading to neurotransmitter release. Preliminary data demonstrated that NMDA administration on PFC synaptosomes increases the glutamate release induced by 8 mM KCl, while a pre-incubation with PCP fully blocks this effect. In parallel, we are interested in assessing the effects of PCP treatment on PFC functionality, in order to establish a possible link between glutamatergic function, performance in behavioural tests involving this region and its metabolic activity during the test determined by 2-deoxyglucose quantitative autoradiography. Thus, the 'PCP model' highlights functional anomalies that could underlie aspects of the psychopathology of schizophrenia (glutamatergic hypofunction).

Genetic Vulnerability Factor for Schizophrenia: Association with Glutamate Cysteine Ligase Modifier Gene and Abnormal Enzyme Activity

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We previously reported in schizophrenia patients a decreased level of glutathione ([GSH]), the principal non-protein antioxidant and redox regulator, both in cerebrospinal-fluid and prefrontal cortex. To identify possible genetic causation, we studied genes involved in GSH metabolism. Case-control association study of single nucleotide polymorphisms (SNP) from the GSH key synthesizing enzyme glutamate-cysteine-ligase (GCL) modifier subunit (GCLM) was performed in two populations: Swiss (patients/controls: 40/31) and Danish (349/348). We found a strong association of SNP rs2301022 in GCLM gene (Danish: $c2 = 3.2$; $p = 0.001$ after correction for multiple testing). Evidence for GCLM as a risk factor was confirmed in linkage study of NIMH families. All the subjects were genotypes using sequencing or mass spectrometry analysis of polymerase chain reaction (PCR) amplified DNA fragments purified from peripheral blood. Moreover, we observed a decrease in GCLM mRNA levels in patient fibroblasts, consistently with the association study. The gene expression was estimated by measuring specific mRNA steady state levels. Real-time PCR was done with total RNA isolated from fibroblast cultures derived from skin of patients (DSM-IV) and healthy controls (DIGS). Interestingly, Dalton and collaborators reported in GCLM knock-out mice an increased feedback inhibition of GCL activity, resulting in 60% decrease of brain [GSH], a situation analogous to patients. These mice also exhibited an increased sensitivity to oxidative stress. Similarly, under oxidative stress conditions, GCL enzymatic activity was also decreased in patient fibroblasts. These results at the genetic and functional levels, combined with observations that GSH deficient models reveal morphological, electrophysiological, and behavioral anomalies analogous to those observed in patients, suggest that GCLM allelic variant is a vulnerability factor for schizophrenia.

Dysregulation of Glutathione Metabolism: A Risk Factor for Schizophrenia

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Schizophrenia is a complex multi-factorial psychiatric brain disorder. It affects individuals at the centre of their personality and concerns about 1% of the world population. Both environmental and genetic factors are implicated in the vulnerability to develop this disease. Previous studies showed reduced levels of glutathione (GSH), the main non protein cellular redox regulator, both in cerebrospinal fluid and prefrontal cortex of schizophrenia patients (Do et al. 2000). In case-control association studies for candidate genes of GSH metabolism we found a strong association between schizophrenia and single nucleotide polymorphisms in the GSH key synthesizing enzyme glutamate-cysteine-ligase (GCL) modifier subunit (GCLM) gene (Tosic et al. submitted). In this study we investigated if these genetic anomalies led to functional consequences at the protein expression, as well as at the enzyme activity levels. Since GSH is ubiquitously present in cells, these parameters of the GCL regulation were determined in fibroblasts derived from skin biopsies. Moreover, in the GCLM knock-out mouse model it was observed that the lack of GCLM led to an increased sensitivity to oxidative stress (Yang et al. 2002). We thus compared between patients and controls the functional parameters at baseline, as well as under oxidative stress induced conditions by treating cells with tert-butylhydroquinone, a substance known to produce reactive oxygen species. In the presented study we observed that compared to controls schizophrenia patients had a reduced GCL activity under oxidative stress conditions, a reduced protein expression of GCLC under baseline, as well as under oxidative stress conditions, and an uncoupling of GCLM and GCLC protein expression in response to oxidative stress. Finally, in the group of patients we observed an inverse correlation between the levels of GSH increase under oxidative stress conditions and the severity of positive symptoms of the disease.

Glutathione Deficit During Development Induces Anomalies in the Rat Anterior Cingulate GABAergic Neurons: Relevance to Schizophrenia

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A series of studies in schizophrenic patients report a decrease of glutathione (GSH) in prefrontal cortex (PFC) and cerebrospinal fluid, a decrease in mRNA levels for two GSH synthesizing enzymes and a

deficit in parvalbumin (PV) expression in a subclass of GABA neurons in PFC. GSH is an important redox regulator, and its deficit could be responsible for cortical anomalies, particularly in regions rich in dopamine innervation. We tested in an animal model if redox imbalance (GSH deficit and excess extracellular dopamine) during postnatal development would affect PV-expressing neurons. Three populations of interneurons immunolabelled for calcium binding proteins were analyzed quantitatively in 16 day-old rat brain sections. Treated rats showed specific reduction in parvalbumin immunoreactivity in the anterior cingulate cortex, but not for calbindin and calretinin. These results provide experimental evidence for the critical role of redox regulation in cortical development and validate this animal model used in schizophrenia research.

Glutathione Deficit in Schizophrenia: Replenishment of Glutathione Levels in Neurons and Astrocytes Models

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In schizophrenia patients, a decrease in glutathione levels ([GSH]) in cerebrospinal fluid and prefrontal cortex was observed, as well as a decrease in the expression of a gene coding for glutamyl-cysteine ligase (GCL), the limiting enzyme of GSH synthesis. As a redox regulator, GSH plays an important role in protecting cells against oxidative stress. In rat models with a GSH deficit, anomalies analogous to those of patients were observed, such as a decrease in spine number in prefrontal cortex and an alteration of NMDA responses. We aim to find substances that could increase [GSH] in cortical cells and to study the underlying mechanisms. GSH-ethyl-ester (GSHEE) succeeded in replenishing [GSH] in cultured neurons and astrocytes depleted in GSH by BSO, an inhibitor of GCL. GSHEE also abolished dopamine-induced decrease of NMDA-mediated calcium response observed in BSO-treated neurons. Gamma-glutamyl-cysteine-ethyl-ester (GCEE) increased [GSH] mostly in astrocytes. These results show that GSHEE and GCEE re-establish physiological [GSH] in brain cells by bypassing the limiting step of GSH synthesis. Curcumin (polyphenol), tert-butylhydroquinone (tBHQ; quinone), quercetin (flavonoid) and FK506 (immunosuppressant) were tested for their capacity to boost GSH synthesis. Curcumin was the most efficient. It increased [GSH] by 50 and 100% in non BSO-treated neurons and astrocytes, respectively, and increased GCL activity by more than 100% in astrocytes. In neurons, low concentrations of tBHQ (10–20 μ M) increased [GSH] by 20% while high [tBHQ] and quercetin led to cell death. In astrocytes, both substances increased [GSH] and GCL activity at rather high concentrations (100 μ M). FK506 was inefficient in both cell types. These results indicate that neurons and astrocytes are not responding similarly to some of the tested substances, suggesting that the mechanisms regulating GSH synthesis and the susceptibility to oxidative stress might differ in the two cell types.

Elevated Plasma Leptin Levels and Sympathetic Arousal may Promote Eating Behaviour in Obese Patients

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Introduction: Distinct abnormalities in autonomic functions and elevated plasma leptin levels (PLL) are well known in obese patients. Therein, the link between emotional upsets and eating behavior remains one of the major bones of contention. Up to date, underlying neurophysiological mechanisms are only marginally understood. **Aim:** To identify the relationship between mental stress, sympathetic activation, eating specific vulnerabilities, coping strategies, and psychophysiological and neuroendocrine factors. **Patients and Methods:** A total sample of 198 patients (42 male/136 female, aged 42.7 ± 12.7 years; BMI $38.4 \pm 6.7 \text{ kg/m}^2$ (mean $\pm$ SD)) participated in this comprehensive rehabilitation program. At baseline, a blood draw was taken, and psychological questionnaires had to be filled out to measure eating habits and coping behavior. Moreover, autonomic functions were assessed using standardized non-invasive technique (TFM-systems, Graz). Ln-transformed power values were used for total heart rate variability and mid- and high-frequency (HFHR) heart rate bands. **Results:** Controlling for BMI, comorbidities, and waist circumference significant correlations were found between PLL, and eating specific vulnerability ($r = 0.57$; $p < 0.01$), feelings of hunger ($r = 0.61$; $p < 0.01$), and the tendency to eat in stressful situations ($r = 0.46$; $p < 0.01$). An inverse relationship resulted between PLL and psychological resource potential ($r = -0.50$; $p < 0.01$). Correlation of PLL and HFHR under mental stress conditions was not significant ($r = -0.48$, $p = \text{ns}$). **Conclusion:** Our study revealed a correlation of general and eating specific psychological factors and neurophysiological arousal in obese patients. These findings could help to understand the difficulties to change eating behavior.

Synchronized Brain Activity during Schizophrenia

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Introduction: Many parts of human cognition are covered, i.e. they are not driven by direct external input and don't produce immediate overt responses. The covert cognitive state is however relevant for the appropriate evaluation of the environment and the selection of behavioral responses. Abnormal internal states may therefore be priors to abnormal perceptions and behavior observed in schizophrenics.

Methods: Spontaneous brain activity can be measured and quantified by EEG. Physically, changes of EEG topography indicate changes of active brain regions and therefore assumingly a change of momentary cognitive state. When studying changes of EEG topography, one finds that these changes are discontinuous and separated by periods of quasi-stable topography of about 100 ms durations. These periods (microstates) assumingly represent basic steps of information processing and correspond to transient, highly synchronized global brain events. **Results:** In never medicated schizophrenic patients, the duration of EEG microstates was reduced across three independent studies. The reduction predominantly affected microstates with specific topographies. When using measures of synchronization between different brain regions, schizophrenics showed less synchronized activity. This reduction was most prominent in the θ band that has been associated with working memory functions in awake subjects. **Discussion:** We conclude that we observe a reduced and abnormal synchronization between brain regions in patients with schizophrenia.

Increase of P300-NoGo-Anteriorisation in First-Episode Schizophrenia Patients during Continuous Performance Test

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Objectives: It was found that in chronic schizophrenia patients the NoGo anteriorisation (NGA) in a cued Continuous Performance Test (CPT) was markedly reduced [1]. Our study was performed to reproduce this result in first-episode schizophrenic patients by microstate (MS) analysis [2]. **Methods:** 18 schizophrenic patients and 18 healthy subjects matched for gender and age were investigated with a cued CPT. Event-related potentials (ERP) were recorded with 21 EEG-channels. Go trials must be answered by pressing a button. In each subject the resulting 150 instantaneous topographical maps of the analyzed 600 ms-interval of the Go- and NoGo-average ERP were clustered into 5 topographical classes. MS were defined as continuous time periods belonging to the same class. During the P300 the maximal amplitude and the respective latency within the corresponding MS as well as its start, end and duration were determined. At MS-maximum the positive centroids of the Go- and NoGo-maps and their distance, the NGA, were determined. **Results:** In schizophrenia patients the following significant effects were found: increase of NGA, reaction time and NoGo-latency as well as decrease of Go- and NoGo-amplitudes and NoGo-MS-duration. Beginning of NoGo-MS was retarded. **Conclusions:** Whereas most of the P300-parameters reflecting attention are typically decreased already in first-episode schizophrenia patients, frontal function represented by the increase of NGA seems to be intact in first-episode but decreases during chronicification of schizophrenia.

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Dissociated Time Representation in Neural Networks of Valence and Arousal Indexing Processing of Emotional Stimuli

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The two experiments investigated the time course of brain electric representation of affective valence and arousal during perception of emotional stimuli. In experiment 1, the stimuli were selected from a standardized picture set (International Affective Picture System, IAPS) that allowed control over arousal as well as affective valence. Used pictures represented: high-arousal positive-valence ($n = 20$), high-arousal negative-valence ($n = 24$), low-arousal positive-valence (25), low-arousal negative-valence (21). Each picture was presented for 600 ms ($ISI = 1,000$ ms) 3 times in pseudo random sequences. In experiment 2, the stimuli were selected from words used previously (e.g. Gianotti et al., Chaos and Complexity Letter, in press). Used words were: high-arousal positive-valence (11), high-arousal negative-valence (8), low-arousal positive-valence words (9), low-arousal negative-valence (12). Each word was visually presented for 450 ms ($ISI = 1,550$ ms) 6 times in pseudo random sequences. Fifty-eight-channel event-related potentials (ERPs) were recorded from 32 healthy students viewing the pictures (experiment 1) and silently reading the words (experiment 2). ERPs were recomputed into map series, averaged across subjects and conditions and segmented into microstates (i.e. steps of information processing; e.g. Koenig et al., *Electroencephalogr Clin Neurophysiol* 1998). Fifteen microstates were identified for experiment 1, eleven for experiment 2. Experiment 1: Testing microstate maps for significance between positive and negative valence pictures (matched for arousal), five microstates qualified: #5 (142–178 ms), #6 (178–226 ms), #7 (226–246 ms), #9 (262–302 ms), and #10 (302–330 ms); whereas between high and low arousal pictures (matched for valence), two microstates qualified: #10 (302–330 ms) and #15 (562–600 ms). Experiment 2: Testing microstate maps for significance between positive and negative valence words (matched for arousal), four microstates qualified: #3 (116–160 ms), #6 (212–236 ms), #7 (236–264 ms), and #8 (264–292 ms), whereas between high and low arousal words (matched for valence), two microstates qualified: #8 (264–292 ms) and #9 (292–344 ms). In sum, a similar pattern appeared in both experiments: during processing of emotional stimuli, cortical activity first extracts information about affective valence and thereafter information about arousal, with a common, overlapping step in the sequence of steps of information processing (i.e. microstates) where information about valence and arousal is extracted simultaneously.

Dimensionality of Multichannel and Single-Channel EEG in First-Episode, Productive, Medication-Naïve Schizophrenics

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Background: Hypotheses about the brain mechanisms that underlie schizophrenic symptomatology prominently included functional dissociation since the conceptualization of the disease. Measuring the ‘dimensionality’ of the behavior of a complex system can assess the degree of non-cooperativity or functional dissociation of the processes that generate the system’s behavior. The dimensionality of the resting EEG of acute, first-episode, productive, medication-naïve schizophrenics measured as Omega Complexity or Global Dimensional Complexity (GDC) or correlation dimension (D2) was reported by us to show increased values compared to controls. Others also reported increased dimensionality in the resting EEG of chronic schizophrenics on and off medication. But, opposite findings were also published, i.e. decrease of Omega, GDC or D2 in schizophrenia; however, diagnostics and medication information in the decrease reports often was incomplete. **Aim:** To analyze EEG of another, independent cohort of acute, first-episode, productive, medication-naïve schizophrenics with the three dimensionality analyses Omega, GDC, and D2 and thereby contribute to a clarification of the controversy. **Methods:** Resting EEG of above-defined patients ($n = 9$) and their age-, gender-, and education-matched controls ($n = 18$) was analyzed with spatial embedding multichannel Omega Complexity and with multichannel Global Dimensional Complexity (GDC) of the whole head and four separate head regions, and with temporal embedding channel-wise correlation dimension (D2), following the methods used by Saito et al. (*Biol Psychiatry* 1998). **Results:** Wilcoxon statistics of the differences between patients and controls showed that using spatial embedding (Omega and GDC), 5 of the 10 possible tests yielded $p < 0.001$ to $p < 0.20$; using temporal embedding (D2), 1 of the 12 possible tests yielded a p -value of < 0.20 . All these six differences involved higher mean values of the EEG dimensionality measures in patients than controls. **Conclusion:** The present findings support our earlier reports on increased EEG dimensionality in acute, first-episode, productive, medication-naïve schizophrenics (Koukkou et al., *Biol Psychiatry* 1993; Saito et al., *Biol Psychiatry* 1998). The contrary reports of decreased EEG dimensionality in schizophrenics might concern other classes of patients, or might reflect medication effects. Further studies with well-documented chronic and medicated patients are required for a deeper elucidation of the controversy.

EEG Microstate Analysis in Obsessive Compulsive Disorder

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Purpose of the Study: To determine the pattern of the brain electrical activity in obsessive compulsive disorder (OCD) compared to healthy volunteers. **Method:** Nine OCD subjects and 14 healthy volunteers participated in this study. Nineteen-channel spontaneous EEG was recorded during resting. We applied EEG microstate analysis: EEG data can be represented as a temporal sequence of topographies that are stable for subsecond periods. These periods of stable topography are called microstates, and they can be identified by spatial clustering procedures. We obtained four microstate topographic classes from all EEG data. The topographical configurations of all classes were similar to previous studies. For statistics, we calculated three microstate parameters, mean microstates duration (duration), mean number of microstates per second (occurrence) and percent total time covered (contribution) for each microstate class. **Results:** We found significantly decreased mean duration and significantly increased mean occurrence for all microstate classes in patients with OCD compared to healthy volunteers. There was no difference in configuration of microstates between patients with OCD and healthy volunteers. **Conclusion:** The decrease of duration has been assumed to correspond to shortening of basic building blocks of human information processing. Therefore, the result of this study suggests that there are some disturbances of cerebral information processing in patients with OCD. In our previous study about symptom provocation in patients with OCD, symptom provocation did not changed microstate parameters, but it significantly changed configurations of some microstates. This phenomenon indicates that microstate values are trait dependent, and on the other hand, microstate configuration is state dependent.

Differences between Schizophrenia and Transient Psychotic Disorders in the Event-Related Potential P300

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Studies on P300 in schizophrenics have shown reduced amplitudes and altered scalp topography. However, inconsistent results have been reported, which may be due to heterogeneity of patient samples. A more differentiated subclassification of schizophrenic patients increases

homogeneity of groups and should lead to more consistent results. In the present study we compared the P300 of patients with schizophrenia and transient psychotic disorders. We investigated the auditory P300 in 24 schizophrenics (F20; 15 males, 9 females; mean age: 36.0 ± 12.9 years) and 11 patients with transient psychotic disorders (F23; 6 males, 5 females; mean age 29.8 ± 6.7 years) classified according to the ICD-10. 21-channel (10/20-system) eyes-closed EEG was recorded during an auditory odd-ball paradigm in which randomly presented rare tones interspersed among frequent tones had to be counted (presentation rate 1:5). After averaging epochs following the rare stimuli and recomputation against average reference, P300 was determined individually at the point of maximal global field power (GFP) within 270–470 ms after stimulus presentation. Locations of the maxima and minima of the electrical field map at P300 were used as topographic field descriptors. The resulting parameters were compared between groups by Mann-Whitney U-tests. Schizophrenics differed from patients with transient psychotic disorders by revealing lower GFP and a shift of the maximum to the right. In contrast, the minimum was dislocated to the left in the schizophrenic patients. These findings are in line with studies comparing core schizophrenics with cycloid psychosis.

Preliminary Results of the Influence of Sensation Seeking on Multistable Perception as Obtained with High-Resolution EEG

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This study was performed to clarify the influence of sensation seeking on the time course of multistable events and the effect of possible vigilance changes during the EEG. The ability to maintain the vigilance performance is assumed to depend on individual personality traits. People with high sensation seeking may not maintain their vigilance on monotonous stimuli but are looking for new, intensive stimuli. Both, people with extraordinary personality traits and high versus low sensation seeking are often found in personality disorders, particularly in Cluster B and C according DSM-IV. 9 subjects with a Cluster B personality disorder (32.6 ± 11.3 years, 1 male, 8 female) and 5 subjects with Cluster C personality disorder (33.6 ± 6.8 , 3 male, 4 female) were instructed to answer the Sensation Seeking questionnaire. Later they were recorded with a 76-channel digital EEG during a stroboscopic alternative motion paradigm implying illusionary motion with ambiguous direction. We found no significant results but some moderate effects, which indicate that the frequency of flips and the vigilance changes in the second trial are associated with sensation seeking. These are preliminary results and need further investigations.

Semantic Processing Deficits in Schizophrenia

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In this study we investigated semantic processing deficits in schizophrenia. 17 schizophrenic patients and 20 healthy controls were measured with a 74 channel EEG. For stimulation we applied a silent reading task consisting of German noun-noun word pairs. The word pairs varied in their degree of semantic relation; related (house-building) vs. unrelated (house-shoe). The N400, an electrical negative component of the ERP, was recorded around 400 ms after the onset of the first (index) and second (terminal) word. In ERP research it has been repeatedly shown that the N400 sensitively indexes semantic relation: the N400 amplitude of a terminal word is reduced in case it is preceded by semantically related context. This so called semantic N400 effect led to the interpretation that the N400 reflects aspects of contextual integration. The semantic N400 effect was found to be abnormally reduced in schizophrenia. However little is known about the N400 component in schizophrenic patients compared to healthy controls. Therefore we analyzed the ERP of both words with Global Field Power (GFP) and topographic analyses. Besides the well established reduction in neural signal strength, a topographic difference was revealed in the N400 component of schizophrenic patients compared to healthy controls for index and terminal word. The results suggest that a specific language related dysfunction in neural networks underlying the N400 component might lead to poor use of semantic context in schizophrenia.

An ERP-Investigation of 2nd Language Word Learning

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The present study aims at determining changes in brain activity related to second language learning. Brain electrical activity evoked by visually presented language stimuli was measured before (day 1) and after (day 2) 5 months of intense language learning in 12 exchange students in Switzerland. Stimulus material consisted of nouns in the participant's native language (English), her/his second language (German) and an unknown language (Rumantsch). After each word, subjects indicated whether the meaning of the noun was known to them. Brain activity was measured with 74-channel-EEG. Additionally, subjects participated in a German language tests on both examination days. We will present result of the comparison between day 1 and day 2 with a special interest on changes observed in the

evoked potentials to German words. Topographical changes in the German-ERPs were observed between 396 and 540 ms. English- and Rumantsch-evoked potentials showed no topographical differences between day 1 and day 2. Amplitude differences between day 1 and day 2 were observed in the English-evoked potentials between 470 and 570 ms. Neither the German- nor the Rumantsch-evoked potentials showed significant changes in amplitude. This indicates that with growing 2nd language proficiency the pattern of neuronal activity change in a specific time window during word processing.

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Characterization of Hypnotic States in Subjects with Dissociative Symptomatology: An EEG Study

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A possible explanation for the mechanisms underlying dissociations is that subjects that are prone to dissociative symptoms develop autohypnotic states. This could mean that subjects showing dissociative symptoms are more hypnotizable. Taking into account these assumptions we concluded that hypnosis under continuous EEG registration could represent an EEG model for dissociation. Our study sample consisted of 30 subjects in three groups: 10 subjects with psychiatric diagnosis showing significant values in the dissociative experiences scale (DES), 10 subjects with psychiatric diagnosis and without dissociative symptoms and a control group of 10 healthy subjects without dissociative symptoms. We performed continuous 76 electrode EEG (10/20 Positions) with 15-min resting EEG as a baseline measure and EEG during performance of 20-min hypnosis following a standardized instruction. Subjects were also tested with the Eysenck Personality Questionnaire Revised (EPQ-R) and the Test d2 testing attention. Preliminary results show significant differences between the two groups with psychiatric diagnosis and the control group and between the group with and without dissociative symptoms: (a) The DES score in subjects with dissociative symptoms correlates significantly with the dimension neuroticism of the EPQ-R. (b) There are significant differences in all groups between single phases of hypnosis in FFT measures over the entire EEG frequency spectrum. (c) There are significant differences in several frequency bands under hypnosis between subjects with and without dissociative symptoms. These results indicate that specific psychological and EEG factors of subjects with dissociative symptoms can be described forming the basis for an EEG model for dissociation.

Preattentive Auditory Processing in Professional Musicians versus Non-Musicians a fMRI-Study

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Introduction: The brain of musicians represents an interesting experimental model to investigate neuroplasticity. We investigated professional musicians using a mismatch paradigm measuring automatic encoding of deviant rhythms. The aims of this pilot-study are: Which are the most usable stimuli to examine the temporal precision of acoustic perception using fMRI? Which brain areas are involved in the automatic detection of acoustic deviants? Do music experts show differences in preattentive auditory processing compared to musical laypersons?

Methods: We recruited 7 professional musicians with experiences in ear training and 7 non-musicians, matched by age, gender, and handedness. In the fMRI-scanner, the participants were exposed to an acoustic temporal mismatch paradigm: Sine tones were presented with a standard stimulus onset asynchrony (SOA) of 150 ms. Every 16–20 s sine tones occurred after a shorter deviant interval. Three different levels of deviance consisted of SOAs of 142, 130, 100 ms. Each deviant condition was repeated 12 times in a pseudorandomized order. Subjects were instructed to watch a silent movie and to ignore the presented sounds. The fMRI data were acquired on a 1.5-T standard clinical MRI scanner (Siemens). The variance of all image time series was estimated voxel-wise according to a random effects convolution-based general linear model analysis. **Results:** The occurrence of sine tones presented with shorter SOAs (142, 130, 100 ms) compared to the standard SOA (150 ms) elicited a mismatch response in the planum temporale of the right hemisphere (rPT). This region is considered as a computational interface, which is mandatory for segregating spectrotemporal sound patterns and matching them with stored representations (Griffiths, 2002). Additionally, we showed that in both musicians and non-musicians, BOLD activity in the right temporale plane induced by a mismatch embedded in the otherwise regular temporal pattern depends on the level of deviance, i.e. the greater the deviance in the SOA the more neural activation. However, the activation induced by deviant SOAs did not differ between groups in auditory cortex. Contrasting neural activity evoked by the deviant SOA of 150 ms in musicians versus non-musicians revealed a significant difference in the neural response to temporal mismatch: in musicians the deviant event induces BOLD activity in left anterior hippocampus whereas non-musicians do not show a mismatch response in this region. **Conclusion:** Our data suggest that superiority in preattentive auditory processing of musicians is based on differences in second-order mismatch detection represented by differential activation of left anterior hippocampus (Strange, 2001) and not due to discriminative temporal mismatch representation in auditory cortices. Mismatch responses in the hippocampus may therefore be linked with associative hippocampal functions and enhanced by learning processes.

Brain Magnetic Resonance Imaging Findings in Individuals at-Risk for Schizophrenia

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Objective: The aim of this study was to investigate norm variants and pathological brain abnormalities in individuals at-risk for schizophrenia compared to patients with first-episode schizophrenia, healthy and depressive controls, using structural MRI with T1 and T2 contrasts. **Methods:** At the Psychiatric University Outpatient Department Basel a clinic for early detection of psychosis has been established. In a screening procedure, indicators and risk factors for schizophrenia (e.g. psychopathology, psychosocial factors and genetic risk) were assessed, then a comprehensive investigation was done (extensive early recognition interview, neuropsychological tests, EEG and MRI brain scan). For this study MRI scans were performed routinely in individuals at high risk for schizophrenia (IR; n = 52) and compared to those patients with first-episode psychosis (FE; n = 30), depressive controls (DC; n = 17), and healthy controls (HC; n = 26). There was no significant difference in sex ratio and educational level between the groups. **Results:** MRI scans showed a significantly higher proportion of brain abnormalities (norm variants and pathological abnormalities) in individuals at-risk for schizophrenia and patients with first-episode psychosis as compared to depressive and healthy controls. **Conclusion:** Whereas the high amount of pathological abnormalities underlines the importance of brain imaging in an early detection clinic for clinical reasons, the high proportion of norm variants could provide further evidence for the neurodevelopmental hypothesis of schizophrenia.

These results were first presented at the 13th AEP congress, Munich, April 2005.

Schizophrenia Connectivity: Correlation Between Cognitive Deficits and Reduced Thalamo-Cortical Fibers

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Introduction: Schizophrenia is associated with multiple neuropsychological dysfunctions, such as disturbances of attention, memory, perceptual functioning, concept formation and executive processes. These cognitive functions are reported to depend on the integrity of the prefrontal and thalamo-prefrontal circuits. Multiple lines of evidence suggest that schizophrenia is related to abnormalities in neural circuitry and impaired structural connectivity. Here, we

report a preliminary case-control study that showed a correlation between thalamo-frontal connections and several cognitive functions known to be impaired in schizophrenia. **Materials and Methods:** We investigated 9 schizophrenic patients (DSM IV criteria, Diagnostic Interview for Genetic Studies) and 9 age and sex matched control subjects. We obtained from each volunteer a DT-MRI dataset (3 T, $\beta = 1,000$ s/mm²), and a high resolution anatomic T1. The thalamo-frontal tracts are simulated with DTI tractography on these dataset, a method allowing inference of the main neural fiber tracks from Diffusion MRI data. In order to see an eventual correlation with the thalamo-frontal connections, every subject performs a battery of neuropsychological tests including computerized tests of attention (sustained attention, selective attention and reaction time), working memory tests (Plane test and the working memory sub-tests of the Wechsler Adult Intelligence Scale), a executive functioning task (Tower of Hanoi) and a test of visual binding abilities. **Results:** In a pilot case-control study (patients: $n = 9$; controls: $n = 9$), we showed that this methodology is appropriate and giving results in the expected range. Considering the relation of the connectivity density and the neuropsychological data, a correlation between the number of thalamo-frontal fibers and the performance in the Tower of Hanoi was observed in the patients (Pearson correlation, $r = 0.76$, $p < 0.05$) but not in control subjects. In the most difficult item of the test, the least number of fibers corresponds to the worst performance of the test (fig. 2, number of supplementary movements of the elements necessary to realize the right configuration). It's interesting to note here that in an independent study, we showed that schizophrenia patients ($n = 32$) perform in the most difficult item of the Tower of Hanoi (Mann-Whitney, $p = 0.005$) significantly worse than control subjects ($n = 29$). This has been observed in several others neuropsychological studies. **Discussion:** This pilot study of schizophrenia patients shows a correlation between the number of thalam-frontal fibers and the performance in the Tower of Hanoi, which is a planning and goal oriented actions task known to be associated with frontal dysfunction. This observation is consistent with the proposed impaired connectivity in schizophrenia. We aim to pursue the study with a larger sample in order to determine if other neuropsychological tests may be associated with the connectivity density.

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Safety and Efficacy of Repetitive Transcranial Magnetic Stimulation Applied to a Specific Area of the Left Dorsolateral Prefrontal Cortex in Treatment

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Background: Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique of selective stimulation of the cortex which is showing promise as a treatment for depression while the clinical significance of its antidepressant effects are still being debated. **Methods:** In an open trial, we aimed at assessing the safety and efficacy of high-frequency rTMS applied to a specific area of the left dorsolateral prefrontal cortex (Brodmann area 46) in the treatment of depression. Nine medication-resistant depressed patients

completed 10 sessions (2 weeks) of 20 Hz rTMS at 90% motor threshold. The primary efficacy measure was treatment response defined as a 50% reduction in Montgomery-Asberg Depression Rating Scale (MADRS) score immediately after and two weeks following the last rTMS session. Remission was defined as a MADRS score < 7 . **Results:** The response rate was 44.4% (4/9) and the remission rate was 11.1% (1/9). The MADRS scores showed a significant decrease over time, particularly within the two weeks following rTMS. Treatment was well tolerated without major adverse effects. **Conclusion:** Statistically significant antidepressant effects were found with rTMS targeted at Brodmann area 46 (left hemisphere) and compare favorably with other open studies using similar stimulation parameters. Comparison studies with a larger number of sessions and more stringent parameters should be considered.

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Spectroscopy of Speech-Related Brain Areas: fMRI Guided Evaluation

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The evaluation of MR spectroscopic imaging (MRSI) of the human brain suffers from two main limitations: (1) Intrinsic field inhomogeneities may obscure certain brain regions when covering the whole brain with MRS. To obtain optimal results the regions of interest (ROI) should be targeted by smaller MRS-volumes, each optimized individually. (2) In many neuropsychiatric disorders where the target of metabolic inquiry is defined by functionality, the ROI cannot be defined reliably from morphological MRI. Instead the target ROI must be defined by fMRI in a previous or preferably the same MR session. Aiming to study metabolic alterations associated with auditory hallucinations, we developed a comprehensive fMRI-guided MRS protocol to target MRS to functionally defined areas of the brain. Target regions were the main cortical speech-related areas: Broca in the left hemisphere and its homologous area in the right hemisphere, Heschl's gyrus and Wernicke's area. 6 subjects were measured on a 3 Tesla MR scanner. Based on structural and functional (fMRI) measurements the ROI's were identified. After detecting the main speech related areas the spectroscopy was performed using two single voxel spectra for left and right Broca and one MRSI scan for Wernicke and both Heschl's gyri. The acquisition of structural MRI, fMRI, two single voxel spectra (to cover Broca), and one MRSI scan (to cover Heschl and Wernicke bilateral) could be completed in a single session of less than one hour. Spectral quality was good, even when Broca was located very peripherally. A comprehensive protocol for fMRI-guided MRS in neuropsychiatric disorders was established, with tolerable acquisition time of 1 h. Acquisition of optimized short TE MRS data from the main speech-related brain regions is possible in a single MR session, if MRS acquisition is divided into SV acquisitions for 'difficult' brain regions and a MRSI scan for central locations, and if the placement of the ROIs is guided by fMRI data that

can be obtained in the same session. The exact determination of functional active areas, as well as individual optimization of spectral quality is fundamental in order to avoid miss-localization and to detect localized and potentially subtle metabolic changes.

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Abnormalities of Temporal Lobe Function in Formal Thought Disorder

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Abnormalities of the temporal lobe and especially the superior temporal gyrus in schizophrenia are a well known fact. The symptom of formal thought disorder is strong connected to the volume loss of the left superior temporal gyrus (STG). Until now the pathophysiological foundations of this symptom are unknown. **Method:** We investigated 18 schizophrenic patients. Psychopathology was measured by the PANSS; additionally the degree of formal thought disorder was quantified by the scale for the assessment of thought, language and communication. A structural MRI was recorded for the volumetric measurements of the STG. Additionally we measured the regional cerebral blood flow by perfusion MRI (arterial spin labelling) as an index for the basic metabolism. **Results:** Patients with formal thought disorder showed a volume reduction of the left STG. This was combined with a significant hyperperfusion in Wernickes Area and hypoperfusion in the right STG in the formal thought disordered group. **Conclusion:** Exceeding neurodegeneration in the left STG measured by volume loss in the formal thought disordered patients is accompanied by higher rCBF in Wernickes Area as an insufficient attempt for functional compensation.

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Brain Regional Alpha-[11C]Methyl-L-Tryptophan Trapping in Medication-Free Patients with Obsessive Compulsive Disorder

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Background: The hypothesis of a central serotonin (5HT) dysfunction in Obsessive Compulsive Disorder (OCD) stems largely from pharmacological treatment studies, where enhancement of 5HT neurotransmission is thought to be critical for treatment efficacy. Direct measures of central 5HT metabolism has recently been possible through Positron Emission Tomography (PET) coupled with the α -[11C]-methyl-L-tryptophan (11C- α Mtrp) tracer, believed to provide an index of the brain regional rates of 5-HT synthesis, through the measure of 11C- α Mtrp brain trapping constant K^* . **Method:** In this study the 11C- α Mtrp method was applied to compare medication-free

patients with current OCD ($n = 21$) to normal controls ($n = 21$) matched for age and gender. The functional PET data were analyzed with Statistical parametric mapping (SPM99). Pairwise t-statistical maps were obtained comparing OCD patients to controls; the regions considered statistically significant had an extended threshold of 100 voxels with a peak threshold of $p = 0.005$. **Results:** 21 OCD patients and 21 controls participated in the study. There was no significant group effect in the whole sample, or in either sex analysed separately for global K^* values ($p = 0.66$). In the sample as a whole, α -[11C]Mtrp trapping was significantly higher for subjects with OCD in the right hippocampus and the Left Temporal Gyrus (BA 20). A region of interest (ROI) based analysis confirmed the SPM findings. In addition the ROI analysis conducted in males ($n = 15$) revealed a main group effect in the caudate nucleus, with significantly higher regional trapping ($p < 0.05$) in OCD subjects. No volumetric differences were found for any of the ROI between OCD subjects and healthy controls. In the sample as a whole YBOCS total score correlated positively with α -[11C]Mtrp trapping in the right middle and superior Temporal Gyrus (BAs 21, 38) and in the left inferior and middle Temporal Gyrus (BAs 20, 21). **Conclusion:** These findings add to the cumulative evidence supporting serotonergic dysfunction in OCD, and more specifically a possible increase in brain regional 5HT in the hippocampus, the Temporal Gyrus and the Caudate nucleus.

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Deficits in Attention and Executive Functions in Individuals at Risk for Schizophrenia

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Objective: To investigate the cognitive capacity of individuals at risk for schizophrenia (IR) compared to healthy controls (HC) and to determine a subset of cognitive functions which enables a non-redundant discrimination between the two groups. **Methods:** $n = 40$ IR and $n = 42$ HC were matched for age, sex and handedness and assessed with a neuropsychological test battery. Five tests, providing nine measures were administered to assess attentional (CPT, TAP-Working Memory, TAP-Go/NoGo) and executive functions (WCST, ToH). These measures were adjusted for intelligence, education, and use of cannabis by means of multiple linear regression and z-transformed. Groups were compared using (M)ANOVA. A LOGIT regression procedure with backward stepwise elimination was then carried out in order to detect the subset of measures which best discriminate IR from HC. **Results:** With these standardized measures a MANOVA yielded a general difference between IR and HC. In six of nine measures statistically significant differences were found. HC always performed better than IR. By means of LOGIT regression, four variables were identified as the best discriminators. These were CPT false alarms, TAP-Go/NoGo false alarms, TAP-Working Memory missings, and TAP-Go/NoGo missings. **Conclusion:** Both executive and attentional functions are impaired in IR. The best discrimination of IR from HC is achieved by assessing certain aspects of attention such as working memory and disinhibition.

Learned Irrelevance is Disrupted in First-Episode but not in Chronic Schizophrenia

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Learned irrelevance (LIrr) refers to the retardation of classical conditioning if the conditioned stimulus (CS) and the unconditioned stimulus (US) are preexposed in an explicitly unpaired manner. LIrr is closely related to latent inhibition (LI) which is thought to be a measure of the ability to filter out irrelevant stimuli protecting normal individuals from stimulus overload. These filter mechanisms as well as LI are deficient in first-episode and acute schizophrenia. In contrast, the LI effect has been shown to be reinstated in chronic schizophrenia patients. In a former study we used a recently developed computerized within-subject, target-recognition LIrr paradigm and showed that also LIrr is disrupted in first-episode schizophrenia. The LIrr test involves a reaction time task consisting of different stimulus conditions encompassing novel non-preexposed (NPE) and preexposed (PE) CS. A LIrr effect is obtained, if reaction times after the PE-CS are significantly slower than after the NPE-CS. Using the same LIrr paradigm, we aimed to investigate if chronic schizophrenia patients exhibit intact LIrr. Moreover, we examined the impact of typical and atypical antipsychotic drugs on the LIrr effect. The performance of 20 chronic schizophrenia patients (5 with typical, 15 with atypical antipsychotics) was compared to that of 15 healthy controls matched for age and gender. Patients showed significantly slower reaction times than controls which might be a general effect of antipsychotic medication. Healthy controls showed a clear LIrr effect, but chronic schizophrenics did not, regardless of medication type. More thorough analysis revealed that chronic schizophrenia patients initially tended to respond faster after PE-CS than after NPE-CS, but there was no significant effect of reversed LIrr. Indeed, patients started to learn about the NPE-CS towards the end of the test. Therefore, we assume that consistent with the results obtained in LI studies, LIrr is also reinstated in chronic schizophrenia. These results indicate that, besides LI, LIrr might serve as a state marker of acute schizophrenia.

Working Memory in Schizophrenia: Dynamic Visuo-Spatial Information Processing

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Working memory, commonly defined as the ability to hold mental representations on line transiently and to manipulate these

representations, is known to be a core deficit in schizophrenia. The aim of the present study was to investigate the visuo-spatial component of the working memory in schizophrenia, and more precisely to what extent the dynamic visuo-spatial information processing is impaired in schizophrenia patients. For this purpose we used a computerized paradigm in which 29 patients with schizophrenia (DSM-IV, Diagnostic Interview for Genetic Studies) and 29 age and sex matched control subjects (DIGS) had to memorize a plane moving across the computer screen and to identify the observed trajectory among 9 plots proposed together. Each trajectory could be seen max. 3 times if needed. The results showed no difference between schizophrenia patients and controls regarding the number of correct trajectory identified after the first presentation. However, when we determine the mean number of correct trajectories on the basis of 3 trials, we observed that schizophrenia patients are significantly less performant than controls (Mann-Whitney, $p = 0.002$). These findings suggest that, although schizophrenia patients are able to memorize some dynamic trajectories as well as controls, they do not profit from the repetition of the trajectory presentation. These findings are congruent with the hypothesis that schizophrenia could induce an unbalance between local and global information processing: the patients may be able to focus on details of the trajectory which could allow them to find the right target (bottom-up processes), but may show difficulty to refer to previous experience in order to filter incoming information (top-down processes) and enhance their visuo-spatial working memory abilities.

Allostatic Working Memory Processing in Schizophrenia: Human and Animal Model Coherence

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The most evident symptoms of schizophrenia are severe impairment of cognitive functions like attention, abstract reasoning and working memory. The latter has been defined as the ability to maintain and manipulate on-line a limited amount of information. Whereas several studies show that working memory processes are impaired in schizophrenia, the specificity of this deficit is still unclear. Results obtained with a new paradigm, involving visuospatial, dynamic and static working memory processing, suggest that schizophrenic patients rely on a specific compensatory strategy. An animal model of schizophrenia with a transient deficit in glutathione during the development reveals similar substitutive processing, masking the impairment in working memory functions in specific test conditions only. Taken together, these results show coherence between working memory deficits in schizophrenic patients and in animal models. More generally, it is possible to consider that the pathological state may be interpreted as a reduced homeostatic reserve. However, this may be balanced in specific situations by efficient allostatic strategies. Thus, the pathological condition

would remain latent in several situations, due to such allostatic regulations. However, to maintain a performance based on highly specific strategies requires in turn specific conditions, limiting adaptive resources in humans and in animals. In summary, we suggest that the psychological and physical load to maintain this rigid allostatic state is very high in patients and animal subjects.

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Early Recognition of Psychosis, the Basel FEPSY Study: An Update

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Objectives: The study aims to establish a scientific basis for the early detection of schizophrenic psychosis and to develop a 'risk index'. The approach is a prospective and multilevel assessment of individuals at risk, and, after transition to psychosis, a post-hoc validation of the risk factors assumed a priori. Here, we describe the recruitment of the at-risk sample, the psychopathological features, and the transition to psychosis. **Methods:** We established a specialised early recognition clinic at our psychiatric outpatient department. All referrals, suspected to be at risk for psychosis, were screened consecutively. Our specifically developed screening instrument ('Basel FEPSY Screening Instrument') assesses prodromal signs (DSM III-R), as well as other indicators of the beginning disease and known risk factors. Transition to psychosis was assessed with the BPRS and defined according to Yung et al. 1998. **Results:** From 01.03.2000-02.2004, we screened 234 individuals. 91 were already psychotic. In 37, no risk for psychosis was found. 106 were identified as being 'at risk', n = 65 consented to participate, mean age 26.43 (SD 8.57), 39 (60%) male, 26 (40%) female. Of 53 remaining in follow-up up to September 2004, 18 have made the transition to clear cut psychosis. **Conclusions:** Many of the referred patients were already psychotic and in need of neuroleptic treatment, which underlines the necessity of specialised clinics. The amount of transitions to psychosis of at-risk individuals shows that our screening instrument is a useful tool for the identification of individuals at risk.

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Stress and Sleep in Pre-Schoolers

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Profound alterations in sleep and hypothalamic-pituitary-adrenocortical (HPA) system regulation were described in psychiatric disorders like depression. If these abnormalities precede the development of psychiatric disorders and may contribute to the identification of high-risk subjects early in life still warrants clarification. In order to assess HPA system functioning and sleep regulation as possible candidates for

prediction of psychiatric disorders a cross-sectional and longitudinal study was started in children during the developmental period at the turn from a home-based context to a peer-dominated environment. Here, we report the first cross-sectional investigation's results. 91 children (age 4.91 ± 0.44 years, 55 boys, 36 girls) at the beginning of Kindergarten assessed by a comprehensive psychological/behavioral test battery were enrolled in a first cross-sectional examination of (1) basal and stress-challenged HPA system activity by the use of saliva cortisol measurements and (2) sleep regulation investigated by actigraphy over 7 days. Basal HPA axis regulation was assessed by morning cortisol after awakening, whereas stress-elicited hormonal responses were measured during the application of a standardized psychological stress test appropriate at this age (McArthur Story Stem Battery, MSSB). Baseline HPA system activity was significantly increased in girls when compared to boys ($p < 0.001$). Furthermore, high morning cortisol secretors predicted a high hormonal release during the MSSB with – again – females showing higher hormonal responses than males ($p < 0.01$). Additionally, heightened HPA system activity was related to psychological values in a gender specific manner: whereas boys had an increased hyperactivity/impulsivity and more emotional problems ($p < 0.05$), girls experienced more positive emotions ($p < 0.05$). Sleep recordings revealed severe disturbances in up to 15% of the investigated children with no gender difference. Particularly these subjects had significantly increased morning cortisol values when compared to good sleepers ($p < 0.05$). Moreover, they showed significantly elevated scores of dysregulated aggression and of a worse family climate ($p < 0.05$). The present results in children point to a possible occurrence of neurobiological abnormalities early in development. These alterations may be gender specific already at the age of 5 years. Prospective long-term follow up of these identified subjects will clarify if these markers are predictive for the onset of psychiatric disorders.

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Sleep Behavior in the Swiss Population: The First Results of a Survey Study

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High prevalence of sleep disturbances and particularly their chronic course are a recognized medical and socio-economic problem. Insomnia impairs working capacities and the life-quality. It is frequently associated with other psychiatric diseases but despite these facts in the practice it is an underestimated problem. A survey study of the sleep behavior was therefore performed with the aim to provide a background for specific programmes which would improve the diagnostics and the treatment. We report here the first results of the analysis of this study. **Method:** A specially constructed questionnaire was addressed to a random sample of 1,002 male and female subjects (18–74 years old). The interviews were carried out by telephone (computerized CATI system) by a specialized institution (LINK, Institute de Recherche). No incentives were given to the interviewed subjects. Data were analysed descriptively. **Results:** In the total sample of 1,002 subjects men were represented by 47.6% and women by 57.4%. The mean age in the sample was 39.5 years. The analysis of data according to the pre-defined criteria of insomnia and its severity showed

that about 1/3rd (31.5%) of the Swiss population suffers from some degree of insomnia. The incidence was slightly higher in females than in men, but with a significant trend ($p < 0.05$) to more severe disturbances. Likewise there was a significant trend to increased severity of insomnia with increasing age. Professional activity influenced the incidence of insomnia in that the lowest incidence was found in the free-lanced and the highest in employees and retired ($>30\%$). The highest incidence of the more severe degree of insomnia was found in subjects without profession and unemployed. **Conclusion:** These first results already indicate that insomnia in the Swiss population is not rare and a medical problem which needs attention.

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Adolescents' Self-Reported Sleep Quantity and Sleep-Related Personality Traits

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Objectives: The aim of this study was to assess adolescents' self-reported sleep quantity and personality traits in order to describe typical personality patterns related to sleep and characteristics which distinguish between good and poor sleepers. **Participants and Methods:** 134 adolescents (age 18–60; 74 females and 60 males) completed a single sleep-related personality traits questionnaire (FEPS-I) and daily sleep logs for seven consecutive days. All participants were attending the 7th grade at high school in Basel (Switzerland). Data were collected during school term; students went to school from Monday to Saturday. The daily logs data were used to cluster participants in three subgroups of poor, normal and good sleep quality. **Results:** Up to 25% of the adolescents could be considered 'poor' sleepers and displayed personality traits such as decreased self-confidence, increased mental arousal and self perception of body sensations. Female adolescents were at high risk of being 'poor' sleepers (OR 4.8, $p < 0.05$). Furthermore, female participants showed significantly increased values for mental and physical arousal and body self-perception. Additionally, they complained more about daily sleepiness, bad mood and lowered concentration. Up to 20% of the adolescents could be described as 'good' sleepers. Noteworthy, during week days, 'good' sleepers went to bed always before midnight. Fifty-five percent of the adolescents could be considered 'normal' sleepers without appropriate sleep-related personality traits or sleeping habits. Irrespective of the sleep group, adolescents showed altered sleep patterns at weekend, that is, from Saturday to Sunday they went to bed much later and slept significantly longer. **Conclusions:** The investigation, using exclusively self-reported sleep data, showed that about three quarters of adolescents displayed sleeping patterns without particular findings. Though, a quarter of adolescents were considered 'poor' sleepers with specific sleep-related personality traits. Female adolescents were at risk of reporting irregular sleep patterns and of complaining about increased daily sleepiness and increased bad mood. Further investigations using objective data collection such as actigraphy are needed to support these results and to allow possible preventive interventions.

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A Key Role for Hypocretin in Regulating Brain Reward Function and Reinstatement for Drug Seeking Behaviour in Rats

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The hypocretins, also known as orexins, are neuropeptides produced in a few thousand neurons in the lateral hypothalamus (LH). Hypocretin-containing neurons project throughout the brain, with a prominent input to basal forebrain structures involved in motivation, reward and stress. In addition to being key regulators of arousal, these peptides have been shown to influence many diverse functions and consummatory behaviors. They have recently been described as a component of the circuitries that mediate the hypothalamic response to acute stress, notably by connecting to the extended amygdala that includes the bed nucleus of the stria terminalis (BNST) and the central nucleus of the amygdala, but their role in addiction-related behaviors remains largely unexplored. In the present study, we show that intracerebroventricular (ICV) infusions of hypocretin-1 (1, 2.5 and 5) leads to a dose-dependent reinstatement of previously extinguished cocaine-seeking behavior without, however, altering cocaine intake (0.25 mg/infusion) in rats. In parallel, hypocretin-1 (5, ICV) dramatically elevated intracranial self-stimulation (ICSS) thresholds, indicating that hypocretin-1 negatively regulates the activity of brain reward circuitries. Hypocretin-induced reinstatement of cocaine-seeking was prevented by simultaneous blockade of noradrenergic and corticotropin releasing factor systems, but not by blockade of either system alone, suggesting that Hcr-1 reinstated drug seeking through induction of a stress-like state. Consistent with this interpretation, the selective Hcr-1 receptor antagonist, SB 334867, blocked footshock-induced reinstatement of previously extinguished cocaine seeking behavior. Overall, these data suggest that Hypocretin-1 does not regulate the primary reinforcing effects of cocaine but may play a key role in the circuitry that underlies vulnerability to relapse, probably by driving drug-seeking through induction of a negative affective state due to the activation of stress pathways in the brain. This system may therefore represent a new target to prevent relapse for drug-seeking during protracted abstinence.

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Cannabis Using Schizophrenia Patients Treated with Atypical Neuroleptics: Do Their Symptoms Differ from That of Cannabis Abstainers?

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Purpose: Most studies investigating the influence of cannabis use on schizophrenia symptom patterns have been performed in

patients treated with high D2 receptor blocking typical neuroleptics (TN). Since a cannabis-TN combination might be particularly disadvantageous, this study examined schizophrenia symptoms in a group of cannabis using schizophrenia outpatients treated with atypical neuroleptics (AN) blocking less on D2 blockade. **Sample:** Forty-three schizophrenia patients treated with AN on an outpatient basis. Patients were divided into three groups: Cannabis abstainers, moderate users, and daily users. **Methods:** All patients completed a questionnaire assessing demographic and drug use characteristics. Next, patients were interviewed by the semi-standardized Positive and Negative Syndrome Scale (PANSS). Cannabis use was assessed by self-declaration. **Results:** No differences were found between the abstainers, the moderately, and the daily cannabis using schizophrenia patients on the PANSS scores. **Conclusion:** Cannabis use had no influence on symptom patterns in schizophrenia patients treated with AN blocking less on D2 blockade.

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Highly Increased Smoking Rates in Adults Diagnosed with Attention-Deficit/Hyperactivity Disorder

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Purpose: Despite prior expectations, experts have assumed for some years that attention-deficit/hyperactivity disorder (ADHD) in childhood can persist into adulthood. The special neurobiological characteristics of ADHD lead us to presume that individuals with ADHD are at special risk concerning substance abuse, particularly cigarette smoking. Although current research in the United States has demonstrated numerous associations between adult ADHD and smoking behaviour, no specific work in this topic has been done in Switzerland. The aim of the present study is to generate new knowledge of the associations between adult ADHD symptoms and smoking patterns in a Swiss sample of adult ADHD patients. **Methods:** The population of this study were adult out-patients diagnosed with DSM-IV confirmed ADHD who have been treated in a special ADHD clinic of the Psychiatric University Hospital Zurich from September 2000 to January 2006 (N = 148). A sample of 101 adult ADHD patients (58 males, 43 females; age: M = 36.71, SD = 11.32) completed a questionnaire about smoking behaviour. Detailed measures of comorbidity, substance use, and medication were obtained from the patient's therapists. **Results:** 54% of the patients were current smokers (47% daily, 7% occasionally), 25% ex-smokers, and 21% have never smoked. Compared to the Swiss general population, smoking rates were significantly elevated, χ^2 (3, N = 101) = 45.05, $p = 0.001$. Furthermore, daily smokers in the ADHD sample smoked significantly more cigarettes per day (M = 21.00, SD = 9.85) than those in the general population (M = 16.2), $t(47) = 3.37$, $p = 0.001$ (one-tailed). A majority of the daily smokers intend to stop smoking within the next six months (50%) and 30 days (8%). Associations between smoking status and ADHD symptoms could not be statistically confirmed, neither for ADHD subtype diagnosis, nor for the self-rating instruments ADHS-SB and WURS-k. **Conclusion:** The results of this Swiss study concerning adult ADHD patients are consistent with previous research in the United States. Particularly outstanding

findings are the high rate of daily smokers, the small number of never smokers, and the high number of smokers who want to quit.

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Prescribing of Benzodiazepines Among the Swiss Adult Population: Results from a National Survey of Community Pharmacies

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Objective: This study investigated prescription benzodiazepine medications among the Swiss general population. **Methods:** We calculated the prevalence, incidence, the amount and duration of benzodiazepine use from pharmacy dispensing databases for persons aged 15 years and older (n = 520,000). **Study Design:** A retrospective, six-months population-based cross-sectional study using databases from community pharmacies (January 2002–June 2002). **Results:** Of 45,309 adults 9.2% had at least one benzodiazepine prescription in a 6-month period (one-year prevalence; 14.5%). The 6-month incidence of benzodiazepines was estimated at 5.3% (one-year incidence; 10.3%). Most persons with benzodiazepine prescriptions were women (67%), and half of all patients were aged 65 or older. 42.5% of all patients had a single benzodiazepine prescription for a short period (>90 days), and in low therapeutic doses, 57.5% had repeated benzodiazepine prescriptions in low therapeutic doses. Only 1.6% used benzodiazepines in very high doses. **Conclusion:** To our knowledge, this is the first pharmacoepidemiologic study assessing the prevalence and incidence of benzodiazepine prescribing patterns in Switzerland; showing that most patients (86.6%) used benzodiazepines in an appropriate way, thus over a short period and in low therapeutic doses, as indicated in the treatment guidelines.

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Circadian Rest Activity Cycles in Antepartum Depression during Light Therapy

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Purpose of the Study: Affective disorder during pregnancy is a difficult situation that requires careful judgment for treating the depression without harm to the fetus. Preliminary trials of light therapy have shown promising results, prompting a randomized controlled trial with larger sample size. **Methods:** Pregnant women who fulfilled DSM-IV criteria for major depressive disorder without seasonal pattern were

randomly assigned either to 7,000 lux fluorescent bright white light therapy or 70 lux dim red light as a placebo control, administered in the morning upon awakening for 1 h/day in a 5-week trial. Clinical state was monitored weekly by a validated German version of the 25-item SIGH-ADS interview with a rater blind to conditions. The circadian rest-activity cycle was monitored by an actigraph/lux meter device worn throughout the five weeks. **Results:** Ten patients have completed the trial and eight completed actigraphic recordings. SIGH-ADS scores declined significantly from 26.7–4.1 (mean SD) at baseline to 16.6–13.2 ($p = 0.03$) after 5 weeks (blind data, placebo dim and bright light combined; 5 full remission, 1 responder). Average activity per hour showed highly interindividual differences in activity levels and distribution. Phase was in stable alignment with time of day (activity onset 7–8 h, activity offset more variable 23–2 h). Preliminary analyses of the circadian measures of relative amplitude, interdaily stability and intradaily variability in the rest-activity cycle showed similar estimates before and after treatment. **Conclusions:** In this ongoing controlled double-blind trial of light therapy for antepartum depression, clinical improvement occurred in 60% of the patients, but this did not appear to be mirrored in changes in the circadian rest-activity cycle.

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Is There a Place for Tricyclics and Subsequent Augmentation Strategies in Obtaining Complete Remission for Patients Suffering

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In the field of mood disorders, complete remission and the management of treatment resistant depression are major challenges. Our group conducted an observational study including 131 patients on the outpatient treatment of depression. We took a closer look at the pathways and the characteristics of twenty patients presenting a treatment resistant depression and who received, at the last steps of the observational study, a tricyclic trial (clomipramine for one month) and, if necessary, two sequential augmentations: lithium and triiodothyronine (each for one month). Twenty patients (14 women and 6 men) acceded to the last steps. They had a median MADRS score of 29 (max: 43, min: 8) before receiving clomipramine. One patient suffered from bipolar disorder type II. Eighteen patients (80%) entering the clomipramine step presented a comorbid anxiety disorder, no patient had a comorbid borderline personality disorder, 4 patients presented alcohol substance abuse. All had failure to an adequate trial in time and dosage of SSRI (paroxetine 30 mg/j) plus a failure either to venlafaxine 300 mg/j or to an augmentation strategy with lithium salts. Among the 20 patients, 14 had previous depressive episodes. The median was 2 (min: 0; max: 4). If we look at the best response rate they obtained in term of reduction on the MADRS scale, we have five complete remissions, three responses and three partial responses with clomipramine alone. The lithium augmentation allowed to add one complete remission and one partial response. The adjunction of triiodothyronine allowed only two patients to achieve a partial response.

Our study seems to point out that there is a specific place for this antidepressant and the subsequent augmentation strategies. Nevertheless our sample is small and only further study on larger samples could confirm this first impression.

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Are There Neurogenic-Inflammatory Psychiatric Phenotypes Mediated by a BBB-Disturbance from Oro-Nasal-Infections via the Sphenopalatine Ganglion (SPG)

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Data points to neuro-vascular ante- and/or postnatal disruption of the BBB and the neuro-glial-endothelial triad as an important gateway to pathology. Therapeutic and self-regulated opening of the BBB is at center stage. Stimulation of the SPG has been successful at this. The SPG supplies nasal mucosal vessels and glands as well as cerebral blood vessels and has been associated with somatoform disturbances. We review the putative influence of systemic para-infectious neurogenic inflammation induced by parodontal pathogens via SPG and parasympathetic and other perivascular nerves on the BBB. We started from exploring discrete rheumatic inflammation (remembering Victorian outy maniatreated with lithium) in mostly bipolar II patients and the caseomorphine breach of BBB into dysmorphic nuclei in SIDS after pharyngeal infections. Extra-intracranial perivascular nerves (trigeminal, sympathetic, parasympathetic) and the induction of neurogenic inflammation by nerves from the SPG are reviewed considering lipid metabolism. In rat SPG sensory SP-fibres from the trigeminal ganglion make contact with such parasympathetic tonic vasodilatory efferents to ACA and PCA. The etiology of the migraines, which are comorbid with BPAD-II, includes extra-cranial inflammatory vascular causes disturbing the posterior cerebral vasculature, which seems reached by SPG perivascular nerves maybe carrying endothelin-1. Geneticists ask for an inflammatory-vascular synthesis and look beyond the CNS searching for microbes. The evidence for streptococcal PANDAS attracted strong criticism. But microbes remain prime targets of inflammation and act to their advantage: superantigens distract antibody-responses via dendritic cell-activation both in skin (neurodermitis) and oral mucosa. Ocus theory (F. Billing) is not popular since the unrewarding vascular dissemination experiments and the induction of serious crimes (H. Cotton, 1907–33). Parodontosis nevertheless produces cytokines endangering health: a specific oral carrier state parallels carotid atherothrombosis. Oral infections should influence the fenestrated SPG and paranasal sinuses could be amplifiers for nitrergic signals. Psychosomatics: Parodontal infections are stress-sensitive and crevicular cellular defences are early victims of depression (possibly from submissive biting inhibition).

Synaptic Changes in the Lateral Amygdala as an Underlying Factor for the High Concordance Rate of Anxiety Disorders and Temporal Lobe Epilepsy

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Epilepsy is a chronic disorder characterized by spontaneously recurrent seizures. Its most prevalent form, temporal lobe epilepsy (TLE), often originates in the hippocampus and/or amygdala and is frequently associated with profound fear and anxiety disorders. Also, a panic attack and an epileptic seizure can share many of the same symptoms. Recently, it has been shown that fear conditioned learning potentiates synaptic transmission in the lateral amygdala of rodents. Furthermore, we have found that hippocampal epileptic activity can also cause potentiation of synaptic transmission between CA3 pyramidal cells. From these findings we hypothesize that TLE causes fear and anxiety disorders through long-lasting changes in synaptic transmission in the lateral amygdala (LA). To test our hypothesis, we used a horizontal slice preparation of the rodent brain which includes the hippocampus and amygdala as well as preserved interconnections. Within this preparation we studied the spreading of epileptic bursts by means of c-fos expression as well as multiple extracellular and whole-cell patch-clamp recordings. We found spreading of epileptic activity between hippocampus, perirhinal cortex and lateral and basolateral amygdala with varying delay times in between burst-onsets. This suggests the existence of a number of different networks underlying the spreading of bursts. We also looked at the long term effects of this epileptic activity on cellular excitability and synaptic transmission in the LA, and found significant differences in the amplitudes of excitatory postsynaptic currents. Interestingly, the nature of these changes depended on the cell type from which the measurements were made. Thus, pyramidal cells with so-called 'highly adapting' spiking patterns underwent a decrease in amplitude, while pyramidal cells with 'little adapting' spiking patterns showed increases in amplitudes. These different spiking patterns, thought to be caused by the absence or presence of a slow after hyperpolarizing current, thus seem to have a differential effect on the induction of changes in synaptic strength.

Neuropeptidergic Modulation of Brain Stem Projections from the Central Amygdala: An in vitro and in vivo Study

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The emotional expression of anxiety and fear involves changes in physiological parameters, among which heart rate, blood pressure, respiration and temperature. These parameters are under the control of

brainstem nuclei that are modulated by the central amygdala (CeA). Anxiety responses can be highly individual in that they consist of a unique combination of changes in these physiological responses. The CeA expresses a large number of neuropeptide receptors and we have recently shown how two of these, oxytocin and vasopressin, oppositely affect fear reactions through an inhibitory circuit in the CeA (Huber et al., Science 2005;308:245). We now hypothesize that this unique combination results from endogenous differences in neuropeptidergic signaling at the level of the CeA. To test this, we are using a combined in vitro and in vivo approach. The in vitro part includes electrophysiological techniques to study neuropeptidergic modulation of cells in the CeA with brainstem projections identified by fluorescent retrograde tracing. The in vivo part combines behavioral tests with telemetry recordings of above mentioned parameters after neuropeptide injections in the CeA in freely moving rats. The combined approach of retrograde tracing with whole-cell patch-clamp recordings has already revealed the presence of neurons in the CeA with direct projections to brainstem nuclei that can be oppositely modulated by vasopressin and oxytocin. The co-application of a series of different neuropeptides now seems to demonstrate the presence of at least two distinct subpopulations in the CeA. We are currently testing the involvement of these populations in their specific modulation of physiological parameters. This combination of in vitro and in vivo approaches should allow us to determine whether a basis for an individualized autonomic fear response can be found at the level of the central amygdala.

Neural Activity in Prefrontal Cortex and Cognitive Symptoms in Depression

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Major depression can be characterized by co-occurrence of emotional and cognitive symptoms. We investigated patterns of neural activity in ventral prefrontal cortex during emotional and cognitive stimulation in 29 healthy and 20 depressive subjects using functional magnetic resonance imaging (fMRI) and carried out an extensive neuropsychological battery (CANTAB). Prefrontal concentrations of GABA were measured using magnetic resonance imaging (MRS). Analysis focused on patterns of hyper- and hypoactivation in ventral prefrontal cortex including VMPFC and VLPFC and the correlation between psychopathological symptoms, neuropsychological symptoms and neural activity. Data shows attentional modulation of neural activity in ventral prefrontal cortex in healthy subjects and specific cognitive deficits as well as abnormal patterns of neural activity in ventral prefrontal cortex in depressive subjects. Abnormal activity in the ventral prefrontal cortex correlated with GABA concentrations within the group of depressive subjects.

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