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## Sleepless Mind. Mindless Sleep?

Bern, March 25 and 26, 2009

### Abstracts

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Chairmen (SSBP)  
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## Oral Presentations

1

**REM-sleep Increases Transfer of Executive Knowledge After Metacognitive Learning**S. Brand<sup>1</sup>, K. Opwis<sup>2</sup>, M. Hatzinger<sup>3</sup>, E. Holsboer-Trachslers<sup>1</sup><sup>1</sup>Psychiatric University Clinics Basel, Depression Research Unit, <sup>2</sup>Department of Psychology, University of Basel, <sup>3</sup>Department of Psychiatric Outpatient, University Hospital Basel, Basel, Switzerland

**Research Questions:** Sleep is crucial for memory consolidation and memory enhancement. Findings emphasize that both NREM-sleep and REM-sleep are important for specific memory consolidation; NREM-sleep rich sleep seems to particularly consolidate declarative memory; REM-sleep rich sleep seems to particularly consolidate non-declarative memory such as executive knowledge. However, the impact of sleep and sleep stages on transfer of executive knowledge is not known so far. Therefore, the present study aimed at exploring the impact of sleep on transfer of executive knowledge after metacognitive stimulation.

**Methods:** Ten female, young adults (mean age: 19.25) took part in the study. After an adaption night with sleepEEG registration, the procedure was scheduled as follows: For the learning phase, participants learned to solve the Tower of Hanoi problem (ToH; three to five disks) with or without metacognitive stimulation; then, the second sleepEEG registration followed. The post-sleep transfer phase consisted of a proximal (ToH with six disks) and two distal (Missionary and Cannibal problem; Katona's card problem) transfer tasks. **Results:** For the learning tasks, metacognitive stimulation lead to an increased acquisition of executive knowledge: metacognitively stimulated participants needed less moves to solve the ToH compared to controls. For the transfer tasks, compared to controls, the metacognitive group solved the proximal transfer task in less moves and less time. Moreover, they improved their executive knowledge for the distal transfer tasks. With regard to sleep, compared to the control group, the metacognitive group displayed decreased Stage 4 and SWS, but highly increased REM-sleep. **Conclusions:** Increased REM-sleep enhance transfer skills of complex executive knowledge after metacognitive skill acquisition ('knowing how') in young healthy women compared to age- and gender-matched controls. Most importantly, increased REM-sleep dependent transfer effects were observed for proximal and distal transfer tasks, suggesting that increased REM-sleep may be involved in consolidating non-declarative executive knowledge.

2

**Role of Prefrontal Serotonin-2A Receptors in Self-experience During Psilocybin Induced Altered States**F. Hasler<sup>1</sup>, B.B. Quednow<sup>1</sup>, V. Treyer<sup>2</sup>, P.A. Schubiger<sup>3</sup>, A. Buck<sup>2</sup>, F.X. Vollenweider<sup>1</sup><sup>1</sup>University Hospital of Psychiatry, Clinical Research & Heffter Research Center, University of Zurich, <sup>2</sup>Division of Nuclear Medicine, University Hospital Zurich, Zurich, <sup>3</sup>Swiss Federal Institute of Technology, Institute of Pharmaceutical Sciences, Zurich, Switzerland

The serotonin-2A (5-HT<sub>2A</sub>) receptor has been implicated in both the pathogenesis of schizophrenia and the psychotropic properties of serotonergic hallucinogenic drugs such as LSD and psilocybin. However, it is still unclear which brain regions are involved in altered states of consciousness during psychosis and hallucinogenic drug action. Thus, we investigated the role of 5-HT<sub>2A</sub> receptors in the hallucinogenic effects of the 5-HT<sub>2A/1A</sub> receptor agonist psilocybin with [<sup>18</sup>F]altanserin positron emission tomography (PET). Eleven healthy male subjects received placebo and a single dose of 215 µg/kg of psilocybin separated by an interval of 14 days. Seventy-five min later, 250 MBq of the 5-HT<sub>2A</sub> receptor selective PET-radiotracer [<sup>18</sup>F]altanserin were administered intravenously as a 30 sec bolus. Dynamic PET data were subsequently acquired over 90 min. Hallucinogenic drug action was assessed by the Altered States of Consciousness Rating Scale (5D-ASC). Psilocybin strongly decreased the total distribution volume (DV) of [<sup>18</sup>F]altanserin in all investigated brain regions (mean±SD 35 ± 13%), most pronounced in the insula and the frontal and anterior cingulate cortex. The increase of 5D-ASC global scores was correlated with the decrease of [<sup>18</sup>F]altanserin DV within the anterior cingulate and the medial prefrontal cortex, the insula and the superior temporal cortex. In concert with animal data, these results indicate that 5-HT<sub>2A</sub> receptor populations in the anterior cingulate and medial prefrontal cortex are involved in the development of altered states of consciousness induced by serotonin hallucinogens. Addressing the model psychosis paradigm, these receptor populations may also play a role in the development of psychotic symptoms in schizophrenia.

### Genetic Redox Dysregulation Induces Behavioural Deficits in the Adult Mouse: An Animal Model for Schizophrenia

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**Background:** Glutathione (GSH), a major cellular redox regulator and antioxidant, is decreased in cerebrospinal fluid and prefrontal cortex of schizophrenia patients. The gene of the key GSH-synthesizing enzyme, glutamate-cysteine ligase, modifier (GCLM) subunit, is associated with schizophrenia, suggesting that the deficit in the GSH system is of genetic origin. Using the GCLM knock-out (KO) mouse as model system with 60% decreased brain GSH levels and, thus, strong vulnerability to oxidative stress, we have shown that GSH dysregulation results in abnormal mouse brain morphology (e.g., reduced parvalbumin, PV, immuno-reactivity in frontal areas) and function. Additional oxidative stress, induced by GBR12909 (a dopamine re-uptake inhibitor), enhances morphological changes even further. **Aim:** In the present study we use the GCLM KO mouse model system, asking now, whether GSH dysregulation also compromises mouse behaviour and cognition. **Methods:** Male and female wildtype (WT) and GCLM-KO mice are treated with GBR12909 or phosphate buffered saline (PBS) from postnatal day (P) 5 to 10, and are behaviourally tested at P 60 and older. **Results:** In comparison to WT, KO animals of both sexes are hyperactive in the open field, display more frequent open arm entries on the elevated plus maze, longer float latencies in the Porsolt swim test, and more frequent contacts of novel and familiar objects. Contrary to other reports of animal models with reduced PV immuno-reactivity, GCLM-KO mice display normal rule learning capacity and perform normally on a spatial recognition task. GCLM-KO mice do, however, show a strong deficit in object-recognition after a 15 minutes retention delay. GBR12909 treatment exerts no additional effect. **Conclusions:** The results suggest that animals with impaired regulation of brain oxidative stress are impulsive and have reduced behavioural control in novel, unpredictable contexts. Moreover, GSH dysregulation seems to induce a selective attentional or stimulus-encoding deficit: despite intensive object exploration, GCLM-KO mice cannot discriminate between novel and familiar objects. In conclusion, the present data indicate that GSH dysregulation may contribute to the manifestation of behavioural and cognitive anomalies that are associated with schizophrenia.

## Poster Presentations

### Postnatal Migration of GABAergic Interneurons in the Developing Limbic Cortex

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Alterations in cortical interneurons are implicated in the pathogenesis of a variety of psychiatric disorders including autism, bipolar disorder and schizophrenia. Cortical interneuron migration during development has emerged a complex process that can be regulated by a variety of genes as well as classical neurotransmitters such as GABA, dopamine and serotonin. Our laboratory has focused on the migration of late-born interneurons that can be visualized using the GAD65-GFP mice. In this study we have used time-lapse videometry to monitor the migration of GAD65-GFP positive interneurons in the postnatal mouse anterior cingulate cortex at several developmental time-points. We have found that a subpopulation of cortical interneurons continue to migrate into the postnatal limbic cortex after birth. Using confocal microscopy and fluorescent immunohistochemistry we are characterizing the phenotype of this subpopulation of migrating interneurons. These data opens the possibility that interneuron cortical migration can be regulated during the postnatal period. Furthermore it is possible that this postnatal process could be altered in pathological contexts relevant for the understanding of the pathophysiology of psychiatric disorders.

### Resting State Networks: Time, Frequency and Space

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Several different functional Resting State Networks (RSNs) have been identified in fMRI studies during the past decade [1]. These RSNs are defined by synchronous BOLD signal fluctuations within their associated brain areas. More recently, simultaneous EEG-fMRI recordings demonstrated a relationship between specific RSN and EEG spectral power changes in given frequency bands [2, 3]. However, this relationship is still poorly understood. We therefore employed different analysis strategies to further characterize the relationship between RSNs and EEG spectral power fluctuations, global synchronization patterns [4] and topographic time-frequency analyses [5]. These analyses in

14 healthy subjects on the one hand confirmed the physiologically assumed close coupling of EEG power and synchronization. On the other hand, our results indicate that specific RSNs are associated with specific frequencies smaller than the regular EEG frequency bands. Furthermore, the topographic distribution of scalp fields matters and finally the RSNs show overlapping regions with BOLD correlates of specific EEG features in regions very consistent across subjects whereas regions less consistent show no concordance.

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## 6

### Anger Regulation: Childhood Abuse Interacts with COMT But Not with 5-HT Genotypes in Suicide Attempters

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**Aims:** Anger related traits are potentially regulated by genes as well as early environmental factors. Childhood maltreatment and genetic factors are well known vulnerability factors for suicidal behaviors, and they may influence the constitution of intermediate phenotypes such as anger traits. In this study we tested the interaction between susceptibility genes for suicidal behaviors and childhood trauma on anger related traits in a population of suicide attempters who are presumed to carry or express these risk factors. **Methods:** 875 suicide attempters assessed with the State-Trait Anger Expression Inventory (STAXI) were genotyped for fourteen polymorphisms in nine candidate genes previously associated with anger related traits and/or suicidal behaviors. The Childhood Trauma Questionnaire (CTQ) was used to examine the

traumatic childhood experiences. A logistic regression was used to investigate the interaction between the candidate genes and childhood maltreatment on the STAXI subscales. **Results:** The functional polymorphism of the catecholamine-O-methyl-transferase (COMT) gene Val158Met significantly modulated the association between sexual abuse and anger trait level as measured by the Trait Anger subscale ( $p = 0.001$ ). In the presence of a sexual abuse, individuals carrying the Val high activity allele displayed higher disposition toward anger than individuals homozygous for the Met allele ( $p = 0.0003$ ). **Conclusions:** The results of the present study suggest that interaction between childhood abuse and COMT modulates anger trait level. Interestingly, none of the 5-HT related genes tested interacted with childhood abuse to influence anger traits. This study was carried out in an enriched population of patients for the frequency of abuse and known to express high level of anger. These results warrant to be replicated in other populations, including healthy subjects. These findings support the hypothesis that the functional polymorphism in the COMT gene, but not 5-HT related genes, by interacting with childhood abuse, may influence the phenotype associated with anger.

## 7

### Experience in Long-term Meditation Reduces the Hypothalamic-Pituitary-Adrenocortical (HPA) Axis Activity

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**Research Questions:** There is an increasing effort in research to uncover the underlying changes in biological processes that are associated with reported changes in mental and physical health in response to meditation. Moreover, there is evidence that meditation decreases anxiety and increases positive affect. However, the impact of short- and long-term meditation on the HPA axis activity has been poorly investigated so far. To investigate the HPA axis activity is particularly important because aberrant cortisol secretion is associated with depressive disorders. The aim of the pilot study was to associate the HPA axis activity-dependent cortisol secretion with the duration of meditation in people with long-term expertise, and to compare patterns of cortisol secretion before and after training of novices in meditation. **Methods:** Eighteen people took part in the study. Nine of them (age (years):  $M = 49.8$ ,  $SD = 7.50$ ) had long-term expertise in meditation (duration (months):  $M = 264$ ;  $SD = 95.5$ ), and nine were novices (age:  $M = 40.2$ ,  $SD = 11.44$ ). Saliva samples to analyze cortisol secretion were gathered before and after the first and the last training session of an 8 week behavioral intervention termed Mindfulness Based Stress Reduction (MBSR) which includes daily meditation practice. **Results:** In people with long-term expertise, duration of meditation highly correlated with decreased cortisol secretion before ( $r = -0.69$ ,  $p = 0.04$ ; controlling for age:  $r = -0.72$ ,  $p = 0.045$ ) and after training ( $r = -0.74$ ,  $p =$

0.02; controlling for age:  $r = -0.68$ ,  $p = 0.06$ ). In novices, no statistically significant differences in mean cortisol secretions before and after the intervention could be observed, although there was a general decrease. **Conclusions:** Results suggest that long-term experience in meditation has a favorable impact on the HPA axis activity. This result may in part explain why MBSR has a favorable impact on depressive symptoms.

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### Children Suffering from Separation Anxiety Disorders (SAD) Show Increased HPA Axis Activity Compared to Healthy Controls

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**Research Questions:** The peak onset for many psychiatric disorders is adolescence, a time of remarkable physical and behavioural changes, but evidence for the beginning of psychiatric disorders already in childhood is given for ADHD, phobias, anxiety, and separation anxiety. With regard to separation anxiety disorders (SAD), little is known about the interplay between SAD and the neuroendocrine functioning. Therefore, the present study aimed at investigating the association between SAD and HPA axis activity in children suffering from separation anxiety compared to healthy controls. **Methods:** A total of 31 children with diagnosed SAD (mean age: 8.45; 17 females, 14 males) and 25 healthy controls (HC; mean age: 9.74; 12 females, 13 males) took part in the study. All participants underwent several psychological and physiological tests lasting about two hours in the afternoon. Six saliva samples to assess HPA axis related cortisol secretion were gathered in parallel. **Results:** Compared to healthy controls, children with SAD showed a highly increased HPA axis activity, as reflected by an increased cortisol secretion (always in nmol/l): AUC basal: SA: 1117.55, HC: 262.74;  $w(30.58) = 2.87$ ,  $p = 0.007$ ; AUC total: SA: 1390.85, HC: 180.14;  $w(30.10) = 2.93$ ,  $p = 0.006$ ; AUC netto: SA: 273.30, HC: -82.59;  $w(30.51) = 1.96$ ,  $p = 0.06$ . **Conclusions:** Separation anxiety disorders in children are reflected by highly increased HPA axis activity. Most importantly, compared to healthy controls, children with SAD showed increased basal cortisol values already at the beginning of and throughout the entire investigation. We hold that children suffering from SAD seem to be continuously under psychophysiological tension, which may lead to strain for social and academic performance.

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### Burnout-related Emotional and Physical Exhaustion, But Not Depressive Symptoms, Is Related to Sleep Complaints in a Non-clinical Sample

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**Research Questions:** Burnout is considered a work-related emotional and physical exhaustion, and previous studies showed that independently of gender and age, high burnout scores were related to increased sleep complaints. By contrast, people with optimistic attitude seem to be less vulnerable to stress and burnout. Therefore, assessing a non-clinical sample, the present study aimed at investigating the relation between burnout, depressive symptoms, satisfaction with life, and sleep complaints in parallel. **Methods:** A total of 2231 participants (age [years]:  $M = 40.77$ ;  $SD = 10.30$ ; 1183 females and 1048 males) took part in an internet-based study. Participants completed a series of questionnaires such as the Tedium Measure (TM; Pines, Aronson, & Kafry, 1983), the Insomnia Severity Index (ISI; Bastien et al., 2001) and the Satisfaction with Life-questionnaire (SWL; Diener et al., 1985). For statistical analyses, first, factor analyses split the TM in the dimension Depressive symptoms, Emotional and physical exhaustion, and Pessimism. Afterwards, to analyse all questionnaires in parallel, a Structural Equation Model (SEM) was applied. **Results:** Pessimism, emotional and physical exhaustion, depressive symptoms, and low satisfaction with life were highly inter-related. Emotional and physical exhaustion was highly related to sleep complaints, whereas sleep complaints were not related to depressive symptoms, satisfaction with life, and pessimism. **Conclusions:** Results suggest that among burnout symptoms the emotional and physical exhaustion is strongly related to sleep complaints and not depressive symptoms in this non-clinical sample. This is in line with the hypothesis that sleep disturbances may play a role in the development from non-clinical burnout to depression, by increasing emotional and physical exhaustion.

### Preschoolers with Behavioral and Emotional Disorders Show Increased HPA-Axis Activity Compared to Healthy Controls

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**Research Questions:** Childhood is the beginning of behavioral and emotional disorders (BED) such as phobias, anxiety, or separation anxiety. The present study aimed at investigating the association between BED and hypothalamic-pituitary-adrenocortical (HPA) axis activity in preschoolers compared to healthy controls. Moreover, gender-related issues were addressed. **Methods:** The target group was recruited from the psychiatric outpatient clinic for children and consisted of 21 preschoolers with diagnosed BED (mean age: 4.9 years; 7 females, 14 males). The control group consisted of 98 preschoolers of a non-clinical sample (mean age: 4.85; 43 females, 55 males). To assess HPA-axis activity, saliva cortisol was gathered in the morning after awakening and during a standardized psychological stress-test. **Results:** Compared to the control group, the target group showed a highly increased cortisol secretion in the morning (AUC netto:  $F(1, 115) = 71.64, p = .000$ ). Moreover, female participants showed also an increased morning cortisol secretion (AUC netto:  $F(1, 115) = 8.51, p = .00$ ), and a significant group by gender interaction was observed (AUC netto:  $F(1, 115) = 5.96, p = .016$ ), with highest cortisol values for the female target group and lowest cortisol values for male controls. Under stress conditions, the target group exhibited an increased cortisol secretion (AUC total:  $F(1, 115) = 29.43, p = .00$ ). No gender by group interaction differences were observed ( $F_s < 1.6$ ). **Conclusions:** Findings suggest that BED are reflected by increased neuroendocrine activity already in preschoolers, with a particularly high cortisol secretion in females. This finding points to the hypothesis that among young children with diagnosed psychiatric disorders, children with heightened HPA-axis activity, and especially female preschoolers may be at increased risk for developing or maintaining psychiatric disorders in follow-up.

### Long-term Treatment of Restless Legs Syndrome Does Not Improve Satisfaction with Life and Sleep Compared to Healthy Controls

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**Research Questions:** Amongst the variety of disorders affecting sleep, the Restless Legs Syndrome (RLS) demands particular attention, because of its high clinical overlap with depressive symptoms. In RLS, sleep is considered to be disrupted 'mechanically'; that is to say, sensorimotor activity leads to repeated physical arousal and awakenings. Typically, patients suffering from RLS complain about sleepiness, daytime fatigue, loss of interest, and low satisfaction with life. However, little is known about the long-term treatment outcome of patients suffering from RLS. **Methods:** Of 63 patients with diagnosed RLS, 38 (60%) could be followed-up after 34 months. An age- and gender-matched control group (HC: healthy controls) was recruited in parallel. Participants completed a series of questionnaires related to sleep, satisfaction with life, and psychological functioning. Moreover, they completed a daily sleeplog for seven consecutive days and nights. **Results:** First, results of patients with RLS did not differ with respect to age, gender, duration of disorder, and medication. Second, compared to HC, patients with RLS showed highly increased depressive symptoms, social withdrawal, and low perceived social support. Moreover, those patients with both diagnosed RLS and depressive symptoms showed higher scores of external locus of control and rumination, compared to HC and to patients with RLS. With respect to sleep, again compared to HC, patients with RLS reported a prolonged sleep onset latency, an increased sleep fragmentation, and affected mood and sleep quality. **Conclusions:** Results suggest that irrespective of age, gender, medication, and duration of treatment, compared to healthy controls, patients with RLS complain both about unfavourable satisfaction with life and psychological functioning and sleep even 34 months after onset of treatment. Thus, results may evidence the need to treat patients with RLS both with medication and psychotherapy.

## Does Age Matter? Semantic Memory in Healthy Young and Elderly Adults

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**Background:** Semantic memory processes have been well described in literature. However, the available findings are mostly based on relatively young subjects and concrete word material (e.g. tree). Comparatively little information exists about semantic memory for abstract words (e.g. mind) and possible age related changes in semantic retrieval. In this respect, we developed a paradigm that is useful to investigate the implicit (i.e. attention-independent) access to concrete and abstract semantic memory. These processes were then compared between young and elderly healthy subjects. **Methods:** A well established tool for investigating semantic memory processes is the semantic priming paradigm, which consists both of semantically unrelated and related word pairs. In our behavioral task these noun-noun word pairs were further divided into concrete, abstract and matched pronounceable non-word conditions. With this premise, the young and elderly participants performed a lexical decision task: they were asked to press a choice of two buttons as an indication for whether the word pair contained a non-word or not. In order to minimize controlled (i.e. attention-dependent) retrieval strategies, a short stimulus onset asynchrony (SOA) of 150ms was set. Reaction time (RT) changes and accuracy to related and unrelated words (priming effect) in the abstract vs. concrete condition (concreteness effect) were the dependent variables of interest. **Results and Discussion:** Statistical analysis confirmed both a significant priming effect (i.e. shorter RTs in semantically related compared to unrelated words) and a concreteness effect (i.e. RT decrease for concrete compared to abstract words) in the young and elderly subjects. There was no age difference in accuracy. The only age effect was a commonly known general slowing in RT over all conditions. In conclusion, age is not a critical factor in the implicit access to abstract and concrete semantic memory.

## EEG Global Dimensionality and Language Processing in Juveniles and Adults

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**Aims:** Complexity of brain processes increases with increasing processing demands as well as with development. This study exam-

ined whether language processing in juveniles and adults show equal demands on processing. The complexity of brain functional organization was assessed by the measure of multichannel EEG Global Dimensional Complexity (GDC) [1,2]. **Methods:** 19 electrode EEG was recorded with closed eyes; there was a 4 minutes initial rest record. Auditory language stimuli were 4 sentences consisting of correct words but in meaningless combination, presented at 1-2 min intervals. From each 'pre' and 'post' stimulus period, up to 10 2 sec epochs/subject were selected. Task was to remember the sentences for recall after recording. Recall quality was tested. Acceptable EEG data were available for analysis from 35 juveniles (21 boys; mean age 12.7 (SD = 1.3) years, range 10.5 to 14.7) and 23 adults (10 men; mean age 28.3 (SD = 5.8) years, range 18.4 to 42.3). Multichannel EEG dimensional complexity GDC was computed using 'GloDim' software (Wackermann [2]). For each subject, we computed the GDC 'response ratio' = ((postGDC-preGDC) / (postGDC+preGDC)), averaged across sentences. Non-parametric statistics were used (U-Tests, Spearman correlations). **Results:** Response ratio was significant higher in juveniles than adults (median 0.140 vs 0.050, respectively;  $p = 0.023$ ); it differed significantly from zero ( $p = 0.0007$ ) in juveniles but not in adults ( $p = 0.81$ ). There was no correlation between quality of recall and response ratio, and no correlation between GDC during rest and response ratio, neither in all 58 subjects nor separate in juveniles and adults. There was a positive correlation between GDC during rest and age in all 58 subjects ( $R = 0.27$ ,  $p = 0.040$ ). This was due to the juveniles ( $R = 0.34$ ,  $p = 0.048$ ); adults showed no correlation ( $p = 0.47$ ). There was no significant difference in recall quality between juveniles and adults. **Conclusions:** Measured with EEG global complex dimensionality, juveniles show higher processing demands than adults during language understanding and memory storage. The increase of brain functional complexity during development was confirmed; adults (age range about 22 years) showed no further increase.

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## EEG Frequency-band LORETA Distinguishes Meditation from Resting in Qigong Meditators

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**Aims:** Common across schools of meditation is the ultimate goal of calming of the mind, implying mental detachment of the self from mundane preoccupations. The question arises how brain

activity during optimal meditation differs from task-free resting. We studied this in experienced Qigong meditators. **Methods:** 19 channel EEG was recorded from eight meditators (mean age: 41.5 years, SD = 10.4; mean meditation experience: 11.5 years, SD = 8.8, range 3-30) during optimal meditation condition (10 minutes, instruction: 'thinking of nothing') and task-free eyes closed resting, i.e. 4 minutes before ('pre-rest') and 4 minutes after meditation ('post-rest'). Artifact-free EEG average/subject: meditation 355 sec (SE = 47), pre-rest 85 sec (SE = 3.9), post-rest 78 sec (SE = 4.1). LORETA tomography analysis [1] was used to compute electric source strength in 2394 cortical voxels separately for the eight independent EEG frequency bands of delta 1.5-6 Hz, theta 6.5-8 Hz, alpha1 8.5-10 Hz, alpha2 10.5-12 Hz, beta1 12.5-18 Hz, beta2 18.5-21 Hz, beta3 21.5-30 Hz and gamma 35-44 Hz for each condition and subject. Voxel-wise, 'difference C' was computed as statistical comparison of electric source strength between 'difference A' (the difference between meditation and pre-rest) and the corresponding 'difference B' (the difference between meditation and post-rest), separate for each frequency band, using t tests corrected for multiple testing. **Results:** Only the alpha 2 band yielded significant results of difference C. All significant cases involved voxels where pre-rest as well as post rest differed from meditation in the same direction. All significant voxels were in the left hemisphere. Meditation had higher power (total 12 voxels: in left temporal sup. and inf. gyrus (BAs 20, 22), left parahippocampal gyrus and hippocampus (BAs 35, 26)), and lower power in left association cortex (21 voxels in BA 7, 2 in BA 5). **Conclusions:** The results show that meditation compared to rest induces changes only in the EEG high alpha frequency band and only in left hemisphere. Accepting that increased alpha band power implies inhibition, the LORETA results during mind-calming meditation suggest reduced functioning of left hemisphere memory processes and increased functioning of association processes, conceivably reflecting decreased personalizing of fleeting associations.

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## Altered Negative BOLD Responses in the Default-Mode Network during Emotion Processing in Depressed Subjects

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Studies using functional magnetic resonance imaging (fMRI) show predominant negative blood oxygenation level-dependent (BOLD) responses (NBRs) in regions of the default-mode network such as the pregenual anterior cingulate cortex, the ventromedial

prefrontal cortex, and the posterior cingulate cortex. Patients with major depressive disorder (MDD) show emotional-cognitive disturbances, which have been associated with alterations within the default-mode network. However, it remains unclear whether these default-mode network alterations are related to abnormalities in NBRs. We therefore investigated neural activity in the default-mode network during different emotional tasks in patients with MDD in an event-related fMRI design. MDD patients showed significantly reduced NBRs in several regions of the default-mode network. Decreased NBRs in MDD patients correlated with depression severity and feelings of hopelessness. In sum, our findings demonstrate that default-mode network NBRs are reduced in MDD and modulate these patients' abnormally negative emotions.

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## Outcome of Cognitive-behavioural Therapy to Treat Tinnitus Is Related to Depressive Symptomatology

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**Research Questions:** Several studies demonstrated a significant presence of depressive symptoms in patients with tinnitus (PT). To treat tinnitus-related distress, cognitive-behavioural therapy (CBT) was found to be effective. Though, little is known about the influence of depressive symptomatology in PT on the outcome of CBT. Therefore, the present study aimed at investigating the relationship between depression scores at the beginning of the CBT and CBT outcome in PT. It was hypothesized that patients with higher BDI scores at the beginning of CBT are less responsive to CBT than patients with lower scores of BDI. **Methods:** 13 patients with tinnitus (11 males and two females; age: 52.15 years, SD = 5.73) took part in the study. Depression symptoms were measured with the Beck Depression inventory (BDI). CBT outcome was operationalized through the Tinnitus questionnaire (TF). Both measures were taken at the beginning and at the end of CBT. An ANOVA with repeated measures was conducted, with the factor Time and the factor BDI quartile groups (BDI score at the beginning of the CBT: Group 1: <10; Group 2 <20; Group 3, <27, and Group 4, >27) as between-subject factor. **Results:** BDI and TF scores correlated significantly ( $r = .74$ ). TF score did decrease significantly from beginning to the end of CBT (factor time:  $F(1, 9) = 11.76, p = 0.008$ ). No significant Time by Group interaction was observed ( $F(1, 9) = 1.70, p = 0.24$ ). TF score differed significantly between Groups ( $F(3, 9) = 6.22, p = 0.01$ ), with the first group (1st quartile) showing lowest TF scores, and with the Group 3 (3rd quartile) showing the largest decrease in TF from beginning to the end of CBT. **Conclusions:** The pattern of results suggests that self-rated depressive symptoms and rated tinnitus severity are strongly correlated. It seems that the



level of depressive symptomatology at the beginning of CBT is related to the outcome of CBT to treat tinnitus.

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### HPA Axis Activity Is Related to Sleep, But Not to Enzymatic Liver Activity or Body Fat Distribution in Adult Females Suffering from Insomnia

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**Research Questions:** Sleep is crucial for daily functioning and academic performance. By contrast, sleep complaints are related to a broad range of deficits in behavior and psychological functioning such as increased absenteeism at work and cognitive impairment. Among the variety of factors affecting sleep, both deteriorated hypothalamic-pituitary-adrenocortical (HPA) axis activity and visceral obesity are discussed. Moreover, there is growing evidence that sleep and enzymatic activity are associated. The aim of the present study was therefore to relate sleep with cortisol secretion, fat distribution, and enzymatic liver activity in adult females suffering from insomnia. **Methods:** A total of 24 adult females (age:  $M = 51.92 \pm 8.84$ ; BMI:  $M = 22.55 \pm 2.15$ ) suffering from insomnia took part in the study. Sleep was objectively assessed with polysomnographic registration. HPA axis activity was assessed by means of free salivary cortisol at midnight and immediately after awakening. Thorough lab analyses and imaging consisted of a variety of analyses such as enzymatic liver activity and distribution of visceral and intramuscular fat. Then, based on sleep efficiency, the sample was split into four subgroups differing in the degree of sleep efficiency. **Results:** The cortisol secretion at midnight differed significantly between the four subgroups ( $F(3, 20) = 3.24, p = 0.04$ ), with a higher cortisol secretion in those two subgroups with low sleep efficiency. Nor enzymatic liver activity, nor visceral and intramuscular fat distribution did differ between the four subgroups (all  $F$ 's < 1). Moreover, cortisol secretion, enzymatic liver activity, and visceral and intramuscular fat distribution did not correlate (all  $r$ 's < .2). **Conclusions:** Affected sleep and increased HPA axis activity are related. Importantly, this pattern could be observed for cortisol at midnight, where the HPA axis activity normally reaches the nadir. No associations were found between sleep, enzymatic liver activity and visceral and intramuscular fat distribution, claiming that both sample size and physiological conditions of the sample did not confer to reach statistical significance.

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### The Effects of Antipsychotics on Brain Structure – A Systematic Review

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**Aims:** Modern neuroimaging techniques have enabled us to examine the brains of patients with schizophrenia in vivo. Antipsychotics are effective in reducing the severity of positive psychotic symptoms but have limited impact on negative symptoms, cognitive impairment and produce a range of side effects. Despite a large number of neuroimaging studies in schizophrenia reporting subtle brain abnormalities, we do not know to what extent such abnormalities reflect the effects of antipsychotic treatment on brain structure. **Methods:** We systematically reviewed cross-sectional and follow-up structural brain imaging studies of patients with schizophrenia treated with antipsychotics published between 1996 and 2008. 30 magnetic resonance imaging (MRI) studies were identified, 24 of them being longitudinal and six cross-sectional structural imaging studies. Effects of typical and atypical antipsychotics are reviewed in informative table and provide an informed interpretation of the main findings. **Results:** In patients with schizophrenia treated with antipsychotics, reduced gray matter volume was described, particularly in the frontal and temporal lobes. Structural neuroimaging studies indicate that treatment with typical as well as atypical antipsychotics may affect regional gray matter volume. Results in first-episode schizophrenic patients are compatible with the trajectory of brain abnormalities observed at the very beginning of the disease in at risk mental state individuals. Studies with typical antipsychotics have reported increased gray matter in cingulate cortex, in contrast to the atypical antipsychotics with the excess more often seen in thalamus. **Conclusion:** Typical antipsychotics lead to increased gray matter volume of the basal ganglia, while atypical antipsychotics reversed this effect after switching. Atypical antipsychotics seem to have no effect on basal ganglia structure. However, despite of antipsychotic medication (both typical and atypical) there are detectable anatomical changes at the level of total and regional brain volumes. It remains unclear whether the effects of antipsychotic medication on GM volume are simply beneficial.

## Increased Self-focus in Major Depressive Disorder Is Related to Neural Abnormalities in Subcortical-cortical Midline Structures

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Patients with major depressive disorder often show a tendency to strongly introspect and reflect upon their self which has been described as increased self-focus. While subcortical-cortical midline structures have been suggested to mediate the 'core self' in healthy subjects, the neural correlates of the abnormally increased self-focus in MDD remain unclear. The aim of the study was therefore to investigate the neural correlates during judgment of self-relatedness of positive and negative emotional stimuli. Using fMRI, we investigated 27 acute MDD patients and compared them with healthy subjects employing a paradigm that focused on judgment of self-relatedness as compared to mere perception of the very same emotional stimuli. Behaviourally, MDD patients showed significantly higher degrees of self-relatedness of specifically negative emotional stimuli when compared to healthy subjects. Neurally, MDD patients showed significantly lower signal changes in various subcortical and cortical midline regions like the dorsomedial prefrontal cortex (DMPFC), supragenual anterior cingulate cortex (SACC), precuneus, ventral striatum (VS) and the dorsomedial thalamus (DMT). Signal changes in the DMPFC correlated with depression severity and hopelessness while those in the VS and the DMT were related to judgment of self-relatedness of negative emotional stimuli. In conclusion, we here present first evidence that the abnormally increased self-focus in MDD might be mediated by altered neural activity in subcortical-cortical midline structures.

## ERP Correlates of Superordinate Category Activation

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Schizophrenic patients with thought disorder exhibit difficulties in assigning objects to an abstract superordinate category. The neurobiological substrate of retrieval of categorical information has however not yet been systematically investigated. We therefore developed an ERP paradigm to examine the activation of superordinate versus otherwise related concepts: Following the presentation of a typical category member an arrow indicated whether the appropriate superordinate category had to be generated (categorization task) or an otherwise related word (relation task). To control task execution, a second word was presented for which a match-mismatch-judgment was required. The experiment was conducted in 20 healthy volunteers while 64 channel ERPs were collected. The analysis of reaction times, accuracy rates and ERPs after the second word indicated a successful access of the superordinate category name. Furthermore, verification in the categorization task was faster and easier than in the relation task. Comparing ERPs after the arrow revealed topographical, Global Field Power (GFP), and onset latency differences between the two tasks and thus indicated the involvement of at least partially different neural generators. When source localization estimates were compared between conditions, the involved brain regions were compatible to previous experiments with semantic tasks. We therefore think that the paradigm is suitable to investigate superordinate activation processes and evaluation in schizophrenic patients with thought disorders.

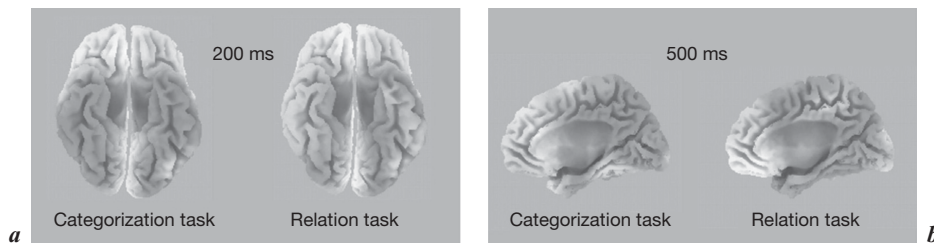


Figure for Abstract 20.

## Sleep Spindle Activity in Kindergarten Children: Is There a Link to Stress Response and Coping Strategies?

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Sleep spindles, i.e. EEG-features of Non-REM-sleep, are linked to efficient cortical-subcortical connectivity, intellectual abilities and 'off-line' memory consolidation during sleep. However, there is little knowledge concerning the relationship of spindle activity to stress response and coping strategies. In a cross-sectional study of forty one five-year old kindergarten children we examined stress-induced HPA system activity by saliva cortisol measurements and sleep regulation by sleep EEG-monitoring. Stress response was measured during application of a standardized psychological challenge appropriate at this age (McArthur Story Stem Battery, MSSB). Sleep EEG spindles were visually scored and put into relation to macrostructural sleep, coping and HPA activity parameters. Spindle density correlated with the amount of NREM-stage 4 sleep ( $p < 0.001$ ). No correlation was found between spindle density and REM-sleep variables. Stress induced HPA-activity correlated positively with coping strategies with high-ego-involvement (i.e. positive emotions;  $p < 0.001$ ); while there was no correlation with low-ego-involvement strategies like 'denial' or 'avoidance'. Though spindles were not directly associated to stress-elicited HPA-activity, spindle activity correlated with coping such as 'positive emotions' ( $p = 0.001$ ). A negative correlation was found between spindle activity and 'denial' and 'avoidant strategies' ( $p = 0.009$ ;  $p = 0.050$ ). In kindergarten children sleep spindles correlate with SWS. Spindle activity is elevated in children with coping involving positive, high ego-involvement; in contrast, low ego-involvement during stress is associated with reduced spindle activity. It seems to depend on coping strategies whether stress challenges lead to increased spindle activity during sleep.

## Modafinil Reduces Microsleep During Partial Sleep Deprivation and Improves Antidepressant Treatment Response

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**Objective:** Sleep deprivation (SD) can induce a prompt decrease in depressive symptoms within 24 hours. Following the recovery night, however, a relapse into depression occurs in most patients. Recovery sleep, naps and even very short episodes of sleep

[termed microsleep (MS)] during SD have been shown to provoke a rapid relapse into depression. This study tested the hypothesis that modafinil reduces MS during SD and augments antidepressant treatment response. **Methods:** 28 patients with a major depressive episode (13 men, 15 women) age  $45.1 \pm 12.1$  years (mean  $\pm$  SD) were investigated using a double blind placebo controlled study design. All patients were treated with a stable mirtazapine monotherapy. A partial SD (PSD) was performed after one week. Additional morning treatment with modafinil vs. placebo started during PSD and was maintained over two weeks. Sleep EEG and MS episodes were recorded with a portable EEG. Depression severity was assessed using the Hamilton Depression Rating Scale during and after PSD and at follow-ups after one and two weeks. **Results:** Modafinil treated patients showed significantly reduced microsleep during PSD ( $11.63 \pm 15.99$  min) compared to the placebo group ( $47.77 \pm 65.31$  min). This suppression of MS did not enhance the immediate antidepressive effect of PSD. After two weeks of treatment, the modafinil group showed a significant reduction in REM density, accompanied by a descriptively 3-fold increase in the antidepressive response rate. **Conclusions:** Modafinil reduces MS during PSD. Furthermore, modafinil augments the antidepressant treatment response to mirtazapine. We conclude from this study, that the augmenting effect of modafinil is not mediated by the suppression of microsleep that is thought to detriment the antidepressive effects of PSD. We assume that modafinil exhibits its augmenting effects on antidepressant treatment via modulation of monoaminergic as well as cholinergic neurotransmission as indicated by the decrease in REM density.

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## Mapping Attention-deficit/Hyperactivity Disorder (ADHD) From Childhood to Adolescence – No Neurophysiological Evidence for a Developmental Lag of Attention But Some for Inhibition

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**Aims:** Developmental lag has been implicated in the brain dysfunctions of children with ADHD, but this claim has not yet been tested in longitudinal studies. We examined the developmental trajectories of neurophysiological markers of attention (Cue P300, CNV) and inhibition (NoGo P300) in ADHD and control groups from childhood to adolescence for support of the developmental lag hypothesis of ADHD. **Methods:** ADHD (N=28) and control (N=22) subjects were assessed at baseline (time 1) and at

two follow-up examinations (time 2 after 1.2 year, time 3 after 2.5 years). Event-related potential (ERP) maps from at least 32 channels including EOG were recorded with a bandpass of 0.1-70Hz at 256Hz during a cued Continuous Performance Test (CPT) at all assessments, and analyzed using scalp and source (sLORETA) measures. **Results:** CPT performance showed common effects of ADHD and younger age, consistent with (but not specific to) developmental lag. The NoGo P300 developed earlier and became stronger in controls than in the ADHD group, which is also consistent with an initial developmental lag. In contrast, the attenuation of the Cue P300 and the CNV with ADHD at all assessments was opposite to the enhancement with younger age, and thus inconsistent with developmental lag. The sLORETA source localization also differed between ADHD and developmental effects. **Conclusions:** The results provide strong evidence for multiple and persistent neural processing deficits in ADHD. They do not support the developmental lag hypothesis for attentional dysfunction in ADHD, but they provide some evidence that developmental lag contributes to inhibitory brain dysfunction during early adolescence. Further studies should clarify how the developmental trajectories of these distinct brain function deficits continue into adulthood.

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### Association of NOS Single Nucleotide Polymorphisms and Haplotypes with Loudness Dependence of Auditory Evoked Potentials (LDAEP)

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**Aims:** The loudness dependence of auditory evoked potential (LDAEP) provides a well established and reliable measure of the central serotonergic activity (Juckel et al., 1997; Kawohl et al., 2008b). A deviant LDAEP as an epiphenomenon of serotonergic pathology has been verified in different psychiatric disorders. Thus, putative additional influencing factors on the LDAEP should be clarified as well. Nitric oxide (NO) is a gaseous molecule with neurotransmitter properties that is involved in numerous functions in the central nervous system (CNS), the vascular system and also in macrophages. The aim of this study was, additionally to another one controlling for influences of COMT-variants (Juckel et al., 2008), to clarify the relationship between genetic variants of the nitrinergic system and the LDAEP. **Methods:** 95 healthy subjects (41 males, 54 females) received electrophysiological recording and blood drawing for genotyping of SNPs and haplotypes of the NOS1 and NOS3 genes. **Results:** Two functional SNPs in both NOS1 (G-84A\_exon 1c promoter polymorphism) and NOS3 (Glu298Asp) were associated with lower LDAEP. **Conclusions:** These findings support the hypothesis that the LDAEP is also influenced by nitrinergic transmission, probably indirectly via serotonergic or dopaminergic plus serotonergic transmission

(Kawohl et al., 2008a). Further studies are needed to fully clarify the relationship between nitrinergic transmission, the LDAEP and complex disorders such as schizophrenia and affective disorders.

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### Assessment of Serotonin Release Capacity in the Human Brain Using Dexfenfluramine Challenge and [<sup>18</sup>F]altanserin PET

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Although alterations of serotonin (5-HT) system functioning have been proposed for a wide variety of neuropsychiatric disorders, a method quantitatively assessing 5-HT release capacity in the living human brain is still lacking. Therefore, we tested a novel method to assess 5-HT release capacity in the human brain using dexfenfluramine challenge and [<sup>18</sup>F]altanserin positron emission tomography (PET). Eight healthy male subjects received placebo and single oral doses of 40mg (n = 4) or 60mg (n = 4) of the potent 5-HT releaser dexfenfluramine [(+)FEN] separated by an interval of seven days. Two hours later, 250 MBq of the 5-HT<sub>2A</sub> receptor selective PET-radiotracer [<sup>18</sup>F]altanserin were administered intravenously as a 30 sec bolus. Dynamic PET data were subsequently acquired over 90 min. Moreover, in arterial blood samples drawn for measurement of total activity, (+)FEN levels as well as cortisol and prolactin plasma concentration-time profiles were quantitatively determined. Pretreatment with (+)FEN decreased the total distribution volume of [<sup>18</sup>F]altanserin in all investigated brain regions in a dose-dependent manner. Cortisol and prolactin plasma concentrations were dose-dependently increased following administration of (+)FEN. These pilot data strongly suggest that the combination of 5-HT release using (+)FEN and subsequent assessment of 5-HT<sub>2A</sub> receptor availability with [<sup>18</sup>F]altanserin PET is suitable to assess 5-HT release capacity in the healthy, as well as the psychopathologically or neurotoxically altered human brain.

## Disruption of Modal Object Completion by the 5-HT<sub>2A/1A</sub> Agonist Psilocybin Is Associated with Visual Hallucinations

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**Background:** The preferential 5-HT<sub>2A/1A</sub> agonist psilocybin is known for its ability to induce a short and transient psychotic state in normals including visual hallucinations that resembles some of the signs and symptoms of insipient and/or acute episodes of schizophrenia. In schizophrenia both reduced 5-HT<sub>2A</sub> receptor density and disturbances in visual processing such as modal object completion associated with decrements in the P1 and/or N170 component have been reported. However, whether aberrant 5-HT<sub>2A/1A</sub> receptor neurotransmission is directly linked to deficits in object completion in schizophrenia is not known. **Aim/Methods:** To further investigate the role of 5-HT<sub>2A/1A</sub> receptors in visual processing and hallucinations the effect of psilocybin (115 µg/ and 215 µg/kg vs placebo) on modal object completion has been assessed using the Kanizsa figures and high-density electrical mapping and source-analysis (LORETA) in normal volunteers (n = 17). **Results:** We found that psilocybin dose-dependently impaired modal object completion associated with a preferential reduction of the N170 amplitude to the Kanizsa relative to Non-Kanizsa stimuli in occipital cortex (LOC). This finding was supported by an additional behavioural visual detection task. Moreover, the overall reduction of the N170 amplitude in the Kanizsa and the non-Kanizsa condition correlated with the degree of psilocybin-induced visual hallucinations. **Conclusion:** These results suggest that a disruption of the serotonergic neurotransmission, particularly at the level of the 5-HT<sub>2A/1A</sub> receptor, leads to visual hallucinations and aberrant modal object completion by modulating the N170 component. Given that similar disruptions were found in schizophrenic patients the present results suggest that interferences at the level the 5-HT<sub>2A/1A</sub> receptor may underlay the aberrant object completion found in schizophrenia.

## The Factorial Structure of the Altered States of Consciousness Rating Scale (OAV)

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The OAV-Questionnaire is a visual analogue scale with 66 items that measures 3 aetiology-independent dimensions of altered states of consciousness (ASC's): 'Oceanic Boundlessness' (OSE), 'Dread of Ego Dissolution' (AIA) and 'Visual Restructuration' (VUS). It is a psychometrically improved version of the APZ-Questionnaire, which has become the international standard for the assessment of ASCs. In this study, the factorial structure and reliability of the OAV-Questionnaire was critically examined using

a large pooled dataset from a series of psychological and psychophysiological investigations between 1992 and 2008 in which ASCs were induced in healthy volunteers by either psilocybin (115-350 µg/ kg p.o.) (n = 323), ketamine (6-12 µg /kg min i.v.) (n = 162) or MDMA (1.5-1.7 mg/kg p.o.) (n = 102). Principal factor analysis with three factors and oblique rotation distributed 90% of the items to their hypothesized factor in the psilocybin and in the combined drug group. However, VUS-items measuring facilitated recollection, imagination and changed meaning of percepts loaded higher on the OAV-factor than on the VUS-factor in all drug-subgroups. Furthermore, scree-plot and parallel-analysis suggested that more than 3 factors have to be extracted to account for the variance between the items. A confirmatory factor analysis (CFA) with simple structure clearly rejected the original factorial structure and disproved unidimensionality in all scales with the strongest rejection in the VUS-scale. We developed an improved model with 9 factors measured by 47 items. Multiple Group CFA and MIMIC-Modelling demonstrated acceptable model fit and partial measurement invariance in all drug-subgroups. Satisfactory homogeneity and reliability of these newly developed scales could also be confirmed in all available data sets. We suggest to revise the existing factorial structure according to our newly developed model.

## Ageing Effects in a Homonymy Processing Paradigm: An fMRI-study

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**Aims:** Our aim was to clarify putative ageing effects in a homonymy processing paradigm (Ketteler et al., 2008). **Methods:** 10 healthy right handed individuals (55-65 years; 58,2 years mean age; dementia excluded by CERAD) underwent an ambiguity resolution task with 4 different conditions (dominant vs. non-dominant; dominant vs. distractor; non-dominant vs. distractor; distractor vs. distractor). **Results:** After subtraction of the corresponding control task (distractor vs. distractor) we found significant activation especially in the thalamus and some parts of the basal ganglia (caudate nucleus, putamen). Conjunction analysis revealed activity comparable to the data of younger subjects of the study cited above. The right inferior parietal cortex showed additional activity. **Conclusions:** The data of the former study could be replicated. Additionally, older subjects showed larger activity in the right inferior parietal cortex. This can be interpreted as a compensatory mechanism. The findings implicate a participation of the thalamus and other basal ganglia circuits in high level linguistic functions in young and older subjects and match with theoretical considerations on this highly controversial topic. Subcortical neural circuits probably become activated when the language processing system cannot rely entirely on automatic mechanisms but has to recruit controlled processes as well. Cortical circuits involved in ambiguity processing tend to extent in aging. We are currently investigating this paradigm in patients with Gilles de la Tourette-syndrome and schizophrenia.

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### Neural Correlates of Pessimism in Major Depression Compared with Healthy Subjects

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**Aims:** Pessimism is a main cognitive feature of major depression. Depressive patients are characterized by a negative attitude towards themselves, the world and the future as described in Beck's cognitive triad [1]. Our aim was to analyze the neural correlates of these features of cognitive processing in depression concerning the pessimistic attitude. We hypothesized a greater cognitive discrepancy in patients compared to healthy subjects watching a positive picture after an uncertain announcement, indicating either a positive or negative picture. The anterior cingulate cortex (ACC) is described as neural correlate of cognitive mismatch [2], so we expected particularly increased activation in the ACC in depressed patients compared to healthy subjects. **Methods:** 14 patients with a major depression and 14 healthy control subjects took part in functional magnetic resonance imaging. During fMRI, they performed a task with the cued anticipation and perception of emotional pictures of 'known' valence (positive, negative, neutral) and 'unknown' valence, that could have been either positive or negative. We computed a random effects group comparing the presentation period of positive pictures after the positive announcement with the positive pictures after the unknown announcement. **Results:** We found in patients with major depressive disorder compared to healthy control subjects increased activations in the ACC (BA 24), in the left parahippocampal area and in a left periventricular region. **Conclusion:** Our findings are consistent with the concept of pessimism as the expectation of negative events in ambiguous situations which is a cognitive feature of depression: Patients with major depressive disorder are prone to expect the worst, so the perception of a positive picture after an unknown, uncertain announcement caused a larger discrepancy compared to controls, which has its neural correlate in an increased activation in the ACC. In a similar way points the increased activation of the parahippocampus in depressed patients: Parahippocampal activations have been described to correlate to arousal. Additionally, this activation could be a correlate of negatively biased memory in depression.

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### Differential Serotonergic and Noradrenergic Modulation of Emotion Processing by Single Dose Antidepressants

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**Aims:** The anticipation of known negative and unknown (50% positive and negative) emotional stimuli revealed in previous studies a 'pessimistic' attitude towards the future in a similar pattern of brain activation, and no similarity of positive and unknown ('optimistic') in healthy subjects [1] and patients with a major depression [2]. This 'pessimism'-activity correlated with psychometric measures of depressiveness: the more depressed, the more similarity between the activation during unknown and negative expectation. The aim of this study was the differentiation and characterization of these areas concerning noradrenergic and serotonergic modulation. Thus, we used the acute application of a selective serotonin-reuptake inhibitor (SSRI) and a selective noradrenalin-reuptake inhibitor (SNRI) to achieve an acute boost of serotonergic and noradrenergic neurotransmission, respectively. **Methods:** In a single-blind pseudo-randomized crossover-study 20 healthy subjects ingested a single dose of either 40 mg citalopram (SSRI), 8 mg reboxetine (SNRI) or placebo 2-3 h prior to scanning with fMRI. During fMRI, subjects performed a task comprising the announced anticipation and delayed perception of emotional pictures of either 'known' (positive, negative, neutral) or 'unknown' valence, that could have been positive or negative. **Results:** The direct comparison of serotonergic and noradrenergic modulation during the anticipation of negative and unknown stimuli revealed increases in medial thalamic areas with reboxetine, whereas citalopram modulated more prefrontal and insular areas. Other frontal and parieto-occipital areas were modulated by both substances. **Conclusions:** We found a differential modulation of the network involved in emotional information processing by the acute application of selective noradrenergic and serotonergic drugs with a main effect in thalamic and frontal areas due to noradrenergic stimulation and a prefrontal and insular focus of serotonergic modulation. These findings could have implications for future selection criteria concerning antidepressant medication in depressed patients.

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### Bern Psychopathology Scale (BPS) – Differentiation of Psychotic Symptoms Along the Domains of Speech, Motor Behavior and Affect

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Psychopathology of schizophreniform psychoses is heterogeneous. Neurophysiological studies aiming to reveal their underlying biological mechanisms led repeatedly to inconsistent results, if the study group is not further psychopathologically differentiated. Therefore, we propose a reformulation of the psychopathology based on neurophysiological knowledge. In particular, we ordered the psychopathological symptoms according the domains of speech, motor behavior and affectivity. 52 symptoms relevant for psychoses could be mapped to the domains of speech, motor behavior and affectivity and were descriptively formulated. Each item reflects an inhibited, disinhibited or normal mode of a specific behavior in order to match the physiological state of excitation and inhibition. The severity code of inhibition or disinhibition in each of the three domains can be rated on a 7-point scale. 161 patients suffering from schizophreniform psychoses were interviewed. Interrater-reliability between 3 raters was assessed analyzing 20 video-interviews. Exploratory factor analysis was conducted to investigate the internal structure of the scale. Internal consistency was computed for the resulting subscales. 18 Items were eliminated because of low interrater-reliability or low communalities. The final factor analysis identified three consistent factors which well matched the dimensions of speech, affect and motor-behavior. The differentiation of inhibited or disinhibited psychotic symptoms seems to be reasonable. The Bern Psychopathology Scale is a tool to identify groups of schizophrenic patients who are predominantly symptomatic in the domains of speech, affectivity, or motor behavior for scientific purposes, e.g. to investigate whether these psychopathological more homogeneous groups differ in regard of their neurophysiology or in treatment response. Moreover, the scale provides information on the unaffected domains and thus the intact resources of the patients, which proved to be useful in daily contact.

### Resetting of Negatively Biased Brain Activity by Pleasant Pictures – A fMRI-study

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The emotional valence of an expected event provides the basis on which our brain develops strategies that enable us to adapt quickly and efficiently to new situations. In daily life we have to cope with upcoming potentially negative events. Therefore, we have the tendency to expect and prepare for the worst case. If so, negative stimuli after the anticipation of an event with prior unknown emotional valence should not serve as new information, whereas pleasant pictures provide ‘unexpected’ emotional input and should result in corresponding brain activity changes. 14 healthy subjects took part in functional magnetic resonance imaging. During fMRI, they performed a task with the cued anticipation and perception of emotional pictures of ‘known’ valence (positive, negative, neutral) and ‘unknown’ valence, that could have been either positive or negative. We computed a random effects analysis comparing

- a. the presentation period of positive pictures after positive announcement with positive pictures after unknown announcement
- b. the presentation period of negative pictures after negative announcement with negative pictures after unknown announcement.

During the presentation of previously unknown announced negative pictures no different activity compared to the known condition could be shown. During previously unknown announced pleasant pictures compared to correspondingly cued pleasant pictures we found activations in the superior, medial, inferior frontal gyrus, pre- and postcentral gyrus, middle temporal gyrus, right parahippocampal gyrus, cingulate cortex, precuneus and nucleus caudatus. These results show that the anticipation period has an important influence on the following perception: Although subjects regarded pictures with the same emotional content, different activation patterns were observed due to the prior unknown versus prior known emotional valence of the picture. We suggest that negative pictures after uncertain expectation do not serve as new information whereas positive pictures may falsify the negative presetting and change the negatively biased brain activity as can be seen e.g. by the cingulate cortex activation (mismatch-detection, false-belief-scenarios) and the medial frontal gyrus activation (executive functions, false-belief-scenarios). The results thus provide evidence for a ‘pessimistic’ bias when facing events of unknown emotional valence.

### Impact of Neurochemical Manipulation on Sensory Gating in Healthy Subjects with Low Gating Levels

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Deficient early information processing has been considered a central feature of schizophrenia spectrum disorders. A fundamental feature of information processing is the ability to gate extraneous stimuli and to attend to salient features of the environment. Two operational measures of gating are prepulse inhibition (PPI) and suppression of the P50 event-related potential (P50 suppression). PPI refers to the attenuation of the startle reaction elicited by an intense pulse stimulus when its presentation is preceded by a weak prepulse. Similarly, in P50 suppression the first stimulus not only produces an auditory evoked potential (AEP) but also activates gating, resulting in a suppression of the P50 AEP to the second stimulus. Patients with schizophrenia exhibit deficits in PPI and P50 suppression. Since PPI and P50 can be induced in healthy volunteers, patients and rodents, and many findings related to the neural regulation of gating in animal studies have been supported by studies in humans, these paradigms represent excellent tools for translational research. These gating measures provide a unique opportunity to characterize the neurochemical basis of information processing and might be useful for the discovery of novel compounds with antipsychotic properties. We have developed a model to investigate the possible effects of antipsychotics on PPI and P50 suppression in healthy volunteers rather than in patients. Studying healthy volunteers has the potential to overcome confounding effects of previous medication exposure in patients, the wide range in severity of psychopathology and the generally non-random allocation of patients to treatment regimens. We previously found that the antipsychotic clozapine increased PPI in subjects exhibiting low baseline sensorimotor gating. In contrast, the antipsychotic haloperidol did not increase PPI in subjects exhibiting low baseline gating levels. Furthermore, haloperidol increased P50 suppression in those subjects with low P50 suppression levels, and reduced P50 gating in individuals with high P50 gating levels. The poster summarizes the results of further psychoactive compounds, including aripiprazole, risperidone and amisulpride which have been tested on our model of gating in healthy humans exhibiting low baseline gating. The data elucidate the applicability of our translational model to serve as a useful tool for the assessment of the efficacy of novel pharmacotreatment strategies for patients with schizophrenia.

### Differences in Motor Activity Between Schizophrenia Subgroups

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**Aims:** Schizophrenia and associated psychotic disorders present with a variety of symptoms. Among them many psychopathological symptoms are shared in all groups. Of special importance are motor features. Researchers have addressed this issue by means of simple observation and description. We used wrist actigraphy during the wake hours of a day to compare motor features between three schizophrenia subtypes. **Method:** Continuous wrist actigraphy was applied for 24 hours in 57 inpatients of our hospital. Of these, 35 presented with the paranoid, 11 with the catatonic, and 11 with the hebephrenic subtype. All patients received treatment as usual and were on psychoactive medication during the study. Each participant was assessed with the Positive and Negative Syndrome Scale (PANSS). Actigraphy recorded with an interval of 2 s. For analyses, times of sleep were removed from the data. We calculated activity level (AL: mean activity counts per hour), movement index (proportion of active periods), and the mean duration of uninterrupted immobility (pauses). **Results:** No predictor but the schizophrenia subtype had an effect on motor activity in schizophrenia. A MANOVA revealed significant differences between subtypes ( $F = 3.9$ ;  $p < 0.001$ ). Subtypes differed in each of the three motor activity variables (activity level, movement index, uninterrupted immobility). Post-hoc tests demonstrated differences between the catatonic and the paranoid subtype. **Conclusion:** Groups differ in terms of quantitative motor activity. Most important was the finding that catatonic schizophrenia leads to increased duration of immobility. Motor activity was not related to age, gender, duration of illness, or antipsychotic drug use. The findings provide first objective data on the motor activity between different schizophrenia subtypes.

### Association of Objectively Measured Motor Activity and Motor Behavior Ratings in Schizophrenia – Preliminary Results

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Motor behavior is a relevant feature in psychopathology and diagnosis of schizophrenia. Observations and descriptions of motor behavior are usually limited to the diagnosis of the catatonic subtype. Moreover, rating scales have been constructed to investigate specifically motor behavior. It is unclear to which extent such scales reflect objective motor activity. The presented



study aims to detect the association between a general schizophrenia rating scale, three specific motor behavior rating scales and actigraphy in an inpatient setting. Another interest of this study is to analyze, whether motor symptoms can be found in a general schizophrenia population. Actigraphy was measured consecutively for 24 hours (2s-interval) in 23 inpatients suffering from schizophrenia. Only wakeful hours were analyzed and the following parameters were computed: Activity level (AL: mean activity counts/hour), movement index (proportion of active periods), and mean duration of uninterrupted immobility (MIP, pauses). All patients received treatment as usual and were on psychoactive medication during the study. Each patient was assessed with the Positive and Negative Syndrome Scale (PANSS), the Simpson Angus Scale (SAS), the Northhoff Catatonia Scale (NCS) and the Modified Rogers Scale (MRS). Correlation analysis showed that MI was related to the NCSIII subscale, whereas MIP was associated with the total scores of the SAS, and the subscales NCS III and PANSS Negative. A collection of a greater sample is needed to investigate catatonic symptoms, because the current sample contains only few patients who score high on the catatonia scales. Still, 52.2% and 40.9% of the patients scored with at least one symptom on the NCS total, respectively on the MRS total score. Indicating that some of the schizophrenia patients investigated show catatonic symptoms to some extent.

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### Comparison of Objectively Measured and Observed Motor Activity in Major Depression

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The use of actigraphy in depression research can help to clarify 1) the association between the observed psychopathology of depression ratings and quantitative motor activity and, 2) the impact of recurrent depression on motor activity. 59 inpatients with a diagnosis of major depression (23 with a first episode, 36 with recurrent episodes) were rated with the Hamilton depression rating scale (HAMD) and wore wrist actigraphs continuously for 24 hours. The observation of the items activities and retardation in major depression could be reflected with the objective means of actigraphy. However, agitation and HAMD total score did not meet the results of quantitative motor activity. Recurrent depressive episodes effectuates patients in having lower activity levels particularly in the afternoon ( $t = 2.15$ ,  $df 57$ ,  $p = 0.04$ ). Actigraphy should be considered as a valid instrument in clinical research to measure retardation in the course of major depression.

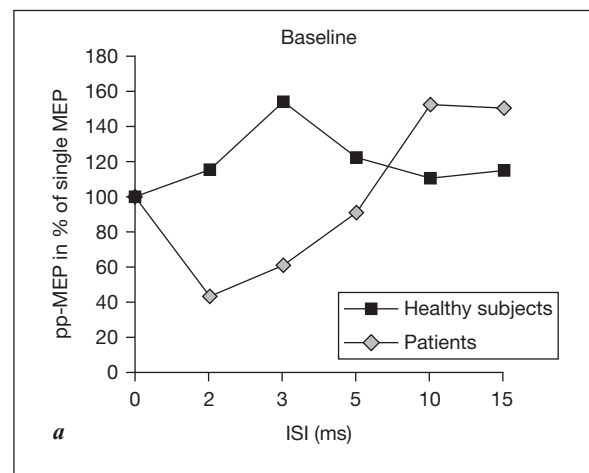
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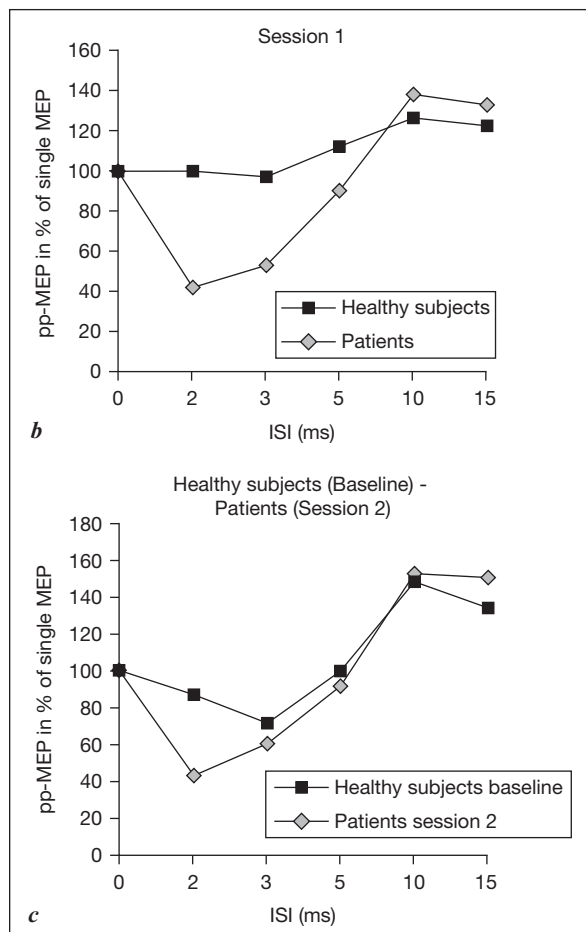
### Cortical Plasticity in Alcohol Dependence: A Double-pulse Transcranial Magnetic Stimulation Study

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**Aims:** Double-pulse transcranial magnetic stimulation (dpTMS) is a non-invasive tool for the investigation of the integrity and the excitability of inhibitory and excitatory neuronal circuits in cerebral cortex [1]. We used dpTMS to test for functional changes in the motor cortex of patients with alcohol dependence [2]. **Methods:** Participants were 11 healthy subjects ( $49 \pm 12$  years, mean  $\pm$  SE) and 10 patients ( $39 \pm 12$  years) with a DSM IV diagnosis of ethanol dependence. First, the motor threshold stimulation intensity was defined for the right abductor pollicis brevis (APB) muscle. Next, subjects underwent blocks of 10 trials delivered at short ISIs (2, 3, 5, 10 and 15 ms), 10 placebo trials and 20 single trials, conducted in random sequence at intervals of 200 ms. Patients were tested at entry, and at three and seven weeks after alcohol cessation, and control subjects were tested twice, at three weeks apart. **Results:** At baseline the patients had a significantly higher amplitude of APB response at the inhibition ISIs of 2 ms ( $p < 0.001$ ) and 3 ms ( $p < 0.001$ ), and a significantly lower motor-evoked potential (MEP) at the facilitation ISIs of 10 ms ( $p < 0.008$ ) and 15 ms compared to healthy subjects [a]. At three weeks of cessation (session 1), differences were evident at 2 ms ( $p < 0.001$ ) and 3 ms ( $p = 0.01$ ) [b], and at seven weeks (session 2) only at 2 ms ( $p = 0.003$ ) [c]. **Conclusions:** Results show that the excitability and plasticity of the motor cortex changes during alcohol withdrawal. We speculate that attenuation of glutamatergic corticofugal pathways increased sensitivity of the striatal dopaminergic system, which contributes to the phenomenology of alcohol dependence and withdrawal [3]. Perturbed cortical inhibition thus constitutes an endophenotype of altered glutamatergic transmission [4].





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## Psychosis and Treatment Resistant Pica with Bilateral Atrophy of the Hippocampus

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**Aims:** Pica is a neuropsychiatric disorder that includes ingestion of non eatable items, and it has been observed in a variety of populations such as malnourished children, patients with intellectual disability and incarcerated subjects. Pathogenesis of its origin is largely unknown. Available literature does not provide clues of a central neuropathological correlate. **Methods:** Here we report an impressive Pica patient with psychosis and ingestion of non eatable items (kitchen knife, shoe lace, batteries, spoons etc.). Occasionally, surgical interventions were necessary. During the course of the disorder, we carried out extensive laboratory analyses, EEG and anatomical magnetic resonance imaging of the brain. **Results:** Laboratory analyses revealed low normal zinc and high normal copper levels in the blood. Bilateral hippocampus sclerosis emerged as a main finding in anatomical neuroimaging. Pharmacologic treatment consisted of a combination of clozapine, carbamazepine and diazepam, including an appropriate dosage of zinc leading to better control of symptoms. Due to clozapine and carbamazepine combination treatment, monitoring of blood leukocytes was carried out once per fortnight over years. **Conclusions:** Therapeutic aspects of this case are discussed within the context of available literature. Participation of the hippocampus is a novel finding in Pica that has not been reported so far. However, it has been known that lesions of the temporolimbic lobes lead to distinct neuropsychiatric symptoms similar to pica. We propose that the hippocampal abnormality may contribute to Pica symptomatology in this patient.

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## Gender differences in rapid cerebral hemodynamic modulation during complex cognitive functions

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**Aims:** Complex cognitive functions such as planning or abstraction provoke specific alterations of cerebral hemodynamics in large basal cerebral arteries. However, no clear gender differences have been reported so far. In the following functional transcranial Doppler (fTCD) study, we introduced cerebral hemodynamic modulation, a means that assesses rapid changes of brain perfusion during two complex cognitive tasks. **Methods:** Subjects underwent the Stockings of Cambridge (SOC) and the Wisconsin Card Sorting Test (WCST) during measurements of the middle and anterior cerebral arteries in two separate experiments. Parameters of task performance and cerebral hemodynamic modulation were

examined by means of multi- and univariate analyses of variance. **Results:** Males showed significant overall differences between separate phases of SOC and WCST, whereas females changed cerebral hemodynamic modulation over time with maximum values near behaviorally relevant time points such as early planning and start of set shifting. **Conclusions:** This study provides evidence of markedly different cerebral hemodynamic modulation between males and females, or in other words, evidence of one or more gender-related time codes of brain perfusion during higher cognitive functioning. These unprecedented results suggest that a rapid cerebral hemodynamic modulation is a key parameter for the characterization of gender related differences during complex cognitive functions.

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### Resting State EEG In Auditory Verbal Hallucinations: Self Monitoring Deficit Might Be Related to Shortening of Specific Microstates

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**Aims:** All subjective experiences and eventually resulting overt behaviour result from an interaction of the subject's internal brain state with environmental stimuli. This is true in normal brain processes, but also applies to pathological processes and may be relevant to understand mental disorders. Using EEG, this study investigated whether abnormal perceptions and cognitions in schizophrenia might be related to abnormal resting states of the brain. Previous research has shown that a specific class (class D) of sub-second brain states (so-called EEG microstates) is consistently shorter in productive schizophrenic patients [1, 2, 3] and that the shortening was correlated to positive psychotic symptoms [1], suggesting that microstate class D might be a state marker specific for positive psychotic experiences. The aim of the present study was to relate microstate class D duration to spontaneous within-subject fluctuations of auditory hallucinatory experiences. The hypothesis was that state D is shorter during hallucinations than in the absence of hallucinations. **Methods:** EEGs of nine right handed schizophrenic subjects with acute auditory verbal hallucinations (AVH) were recorded. Subjects were instructed to listen and attend to their voices and to indicate the beginning and ending of them each by a button press. Off line, EEG was divided into periods with and without AVH. Microstates were analysed separately for each period. Mean microstate duration, mean number of microstates per second and percentage of total analysis time occupied in that state were computed following our standard procedure [1]. **Results:** Four microstate classes (A, B, C, and D) accounted for 79.1% of the data variance. Duration of microstate D was significantly shorter ( $p=0.046$ ) in periods with AVH compared to periods without AVH. **Conclusions:** We found a

shortening of microstate D in periods with AVH. For AVH, the common hypotheses suggested deficient self monitoring leading to a misattribution of internal and external stimuli. We hypothesize that microstate D has relevant self-monitoring functions and its premature termination may contribute to the erroneous conclusion in AVH that self-generated inner speech comes from an external source. The reduced stability of resting state networks fits well with the disconnection syndrome hypothesis of schizophrenia.

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### A Matter of Self Monitoring: Auditory Verbal Hallucinations, Thought Insertion and Thought Withdrawal

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**Aims:** Self monitoring is the ability to maintain accurate and coherent self-referential processing over time. Thus, intact self monitoring guarantees distinguishing self generated from externally perceived information. Deficits in self monitoring might lead to psychotic symptoms like auditory verbal hallucinations (AVH; voices arguing and commenting) as well as to ego disturbances (ED; audible thoughts, thought insertion and thought withdrawal). AVH consist of two components: an alien and an audible component. In ED however, the case is more sophisticated: in audible thoughts (AT), patients hear their own thoughts aloud – knowing these are their own thoughts. In thought insertion and withdrawal (TI-W), patients have the feeling of alien influence without an auditory component, indicating a deficit in self monitoring that is not the case in AT. **Methods:** In a retrospective case study all records of the year 2002 and 2007 of the university hospital of psychiatry Bern have been examined in respect of the occurrence of AVH and ED. Prevalence of AVH and ED has been evaluated in patients with acute (F23) and chronic psychosis (F20, F25). **Results:** A total of 655 records (49% women) has been examined. 424 patients suffered from chronic psychosis, 109 patients were diagnosed with acute psychosis. In the collapsed group of all patients, 37% reported AVH; 21.5% of them expressed ED. Both symptoms have been found in 12.5%. In the differential analysis of the ED we found AT in 2.1% and TI-W in 7.5%. Co-occurrence of AVH and AT was 1.2%, whereas AVH and TI-W together were found in 4.9%. **Conclusions:** Our data are in accordance with

literature in respect of epidemiology of these symptoms in psychosis. The findings suggest that psychotic symptoms that might be considered as related to a deficit in self monitoring (AVH and TI-W) occur in fact more frequently solitary (AVH or TW-I) or together (AVH and TW-I) than AT, in which self monitoring is not deficient. However, record-examination showed that often psychotic symptoms mentioned in the psychopathological status were not further distinguished by the examiner; this is exceedingly the case with ED, where a further distinction in terms of qualities was uncommon – or the examiner was unsure how to interpret them. We suggest evaluating these symptoms with the aid of reliable, differentiable and quantifiable scales, which is of special importance to identify the underlying pathophysiological mechanisms of self monitoring and the associated symptoms.

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### The Binding of Moving Facial Elements to a Single Percept Measured With EEG

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When a face is perceived, binding of neural representations of face elements into a unitary percept is taking place. This binding is assumed to be organized by the phase synchronization of EEG frequency bands measuring the synchronized activity across separate but interconnected brain areas [1]. In this study, we measured 16 healthy subjects with 74-channel EEG while they were watching continuously moving and rotating elements of a schematic face. At some instants (T<sub>0</sub>), the locations of these elements produced the perception of a face. Artefact-free 1 sec EEG epochs were selected at  $\pm$  500 ms around T<sub>0</sub> (condition ‘with face’ (WF)) and at time intervals remote from T<sub>0</sub> (condition ‘no face’ (NF)). In a first step, we analyzed the differences between these conditions concerning the event related potential (ERP) and the global field power (GFP) of the gamma frequency band known to be involved in visual binding [2]. The global field synchronization (GFS) [3] of the gamma frequency band, a measure of phase synchronization, will be analyzed in a second step. The ERPs of the two conditions differed significantly in several time-points, mainly after stimulus presentation, as shown by the TANOVA (topographic analysis of variance), the paired t-test and the ERmaps. Furthermore, a sequence of homogeneous topographies was found in WF but not in NF. The TANOVA showed no significances for any time point when looking at the GFP of the gamma frequency band. In contrast, the gamma GFS is expected to be increased in WF, presumably during the sequence of similar topographies of the ERP, differing from NF. The topography found in the sequence of similar topographies during WF resembles the facial component N170 reported in other studies [4, 5]. The finding of homogeneous topographies in WF but not in NF is consistent with the fact that in WF a face is forming, whereas NF consists only of single facial parts moving around and no unitary percept is built. The missing difference of gamma GFP between conditions was hypothesized due to the fact that all facial parts were visible at any time point and during both conditions. This

study provides new insights into the Binding Problem. For the future, we plan to measure this task by means of simultaneous EEG-fMRI to reveal binding networks for face perception.

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### Effects of Mood Stabilizers on the Akt/GSK-3 $\beta$ Signaling Pathway and on Cell Survival and Proliferation

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**Aims:** Lithium and some anticonvulsants such as valproate or lamotrigine are commonly prescribed to treat bipolar disorder. Some atypical antipsychotics are now also being considered as mood stabilizers. Some of the above mentioned drugs have been shown to affect GSK-3 beta, a serine/threonine kinase, a downstream target of protein kinase B (PKB/Akt). This Akt/GSK-3 $\beta$  pathway is a signaling cascade involved in multiple roles of cell physiology like cell cycle progression, and has previously been reported to be altered in affective disorders. In this study, we compared different classes of mood stabilizers and explored possible differences or shared mechanisms in their biochemical effects on the Akt/GSK-3 $\beta$  signaling and on phosphatidylinositol-3 kinase (PI3K). **Methods:** Dose and time course effects on the Akt/GSK-3 beta signaling pathway were investigated in human neuroblastoma SH-SY5Y cells for lithium, valproate, carbamazepine and lamotrigine, as well as for haloperidol, olanzapine and clozapine. Both immediate effects (Akt and GSK-3 beta phosphorylation) and late biochemical actions (Akt-1 and GSK-3 $\beta$  proteins and mRNA expression) were determined. Gene expression of both catalytic and regulator subunits of PI3K was also assessed in drug-activated cells. Cell proliferation and cell protection against serum deprivation-induced death, were determined along with biochemical assays. **Results:** Mood stabilizers affect differently the Akt/GSK-3 $\beta$  signaling axis, cell survival and proliferation. Strong differences among drugs in both cellular and biochemical effects were observed. Of the seven drugs, only lithium, valproate and olanzapine, enhance cell proliferation and have a protecting effect against injury. The same drugs also activate Akt-1 and GSK3 $\beta$  phosphorylation and increase Akt-1 mRNA and protein levels, as well. GSK3 $\beta$  mRNA and protein levels were not affected. More slowly, clozapine exhibits similar effects. The other drugs neither affect cellular events nor activate Akt/GSK3 $\beta$  axis. **Conclusions:** Valproate and olanzapine regulate proliferation and cell survival and activate the Akt/GSK3 $\beta$  axis, as does lithium. The other medications tested have less or no effect. These observations suggest that the Akt/GSK-3 $\beta$  axis is a target of some but not all mood stabilizers.

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