Preferential processing of phobic cues
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Spider phobic patients oft report that they see spiders everywhere. Is this due to facilitated detection? Are spiders automatically detected? ... more intensively processed? ... exaggerated in memory? Moreover, are these factors independent of the allocation of attention? In this talk, I will give an overview over our studies at the University of Würzburg, where we use binocular rivalry, eye-tracking, and fMRT to examine these questions.

New treatments for anxiety disorders
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Selective serotonin reuptake inhibitors (SSRIs) and the serotonin-norepinephrine reuptake inhibitor venlafaxine (SNRIs) are standard treatments for anxiety disorders, according to the recently published guidelines of World Federation of Societies of Biological Psychiatry for the Pharmacological Treatment of Anxiety, Obsessive-Compulsive and Post-Traumatic Stress Disorders (Bandelow et al., 2008). Recently, the SNRI duloxetine was shown to be effective in generalized anxiety disorder (GAD). The calcium modulator pregabalin is also a treatment option for GAD.

Tricyclic antidepressants (TCAs) are equally effective, but they are less well tolerated than the SSRIs. For short-term treatment an in treatment-resistant cases, benzodiazepines like alprazolam may be used when the patient does not have a history of dependency and tolerance.

Due to possible serious side effects and interactions with other drugs and food components, the irreversible mono-
amine oxidase inhibitor (MAOI) phenelzine should be used only when first-line drugs have failed.

Recently, the atypical antipsychotic was shown to be effective in GAD. According to preliminary data, agomelatine, an agonist at melatonin M1 and M2 receptors and an antagonist at 5-HT2C receptors, may be a future treatment option for patients with GAD.

Combining drug treatment with cognitive behaviour therapy is the most successful treatment strategy in anxiety disorders.


German J Psychiatry 2008; 11: S1

The role of hippocampus-dependent memory in pathogenesis and treatment of PTSD-like symptoms in mice

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The primary symptoms of Posttraumatic Stress Disorder (PTSD) were traditionally interpreted as an extraordinary strong memory of the trauma and an increased unspecific fear that grows with the passage of time (fear incubation). We would like to offer an alternative hypothesis that a time-dependent degradation and/or distortion of a trauma memory and the underlining fragility in hippocampus (HPC)-dependent performance might form the core disease phenomenology.

Employing an animal model of PTSD, which was established in our group, we investigated the role of associative fear memory and HPC in development of PTSD-like symptoms. Testing the animals at different time points after trauma, we noted a constant level of conditioned fear and hyperarousal, but a decrease in context discrimination ratio over time. In addition, the degree of hyperarousal appeared to be largely independent from the levels of conditioned fear as tested by immediate-shock deficit paradigm and therapeutic extinction training. Furthermore, we employed environmental enrichment to explore the consequences of improved memory capacity for PTSD-like symptoms. The animals that lived in the enriched environment showed lower levels of PTSD-like symptoms, in terms of both contextual fear and hyperarousal and, importantly, larger HPC volume than the standard-housed animals.
(Schneider et al.). 15% of the alcohol dependent patients suffered from PTSD, 34% of the illegal drug- and alcohol-dependent patients (N=465, Driessen et al. 2008). In the opioid-dependent patients also anxiety and affective diseases were dominating (altogether 67% of the psychiatric comorbidity). In the group of the „healthy“ smoking students (N=150) anxiety and phobic disorders were found in the group of the dependent (mostly female) smokers only. Non-dependent smokers did not show these disorders (Havemann-Reinecke et al. 2008).

Discussion and Summary: Anxiety and affective disorders are dominating the psychiatric comorbidity of alcohol-, opioid- and tobacco smoking dependent patients/probands. The data presented are discussed with respect to relapse behaviour, additional drug intake and to the relationship of (possibly common) pathophysiological mechanisms of dependence / addiction on one side and of anxiety and affective disorders on the other side.

The neural architecture of anxiety regulation

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Fear/anxiety responses need to be continuously regulated to meet the organism’s current needs and to take into account changes in stimulus properties and context. Regulation is performed on various levels, including relatively automatic, non-conscious (low-level) and more elaborate, conscious (high-level) processes. I will first summarize findings from both animal and human studies covering a range of relevant paradigms, such as extinction, reversal learning and cognitive emotion regulation (distraction, reappraisal). I will attempt to combine these results into a coherent neuroanatomical model that highlights both shared and distinct circuits for low- and high-level regulation. Recent analyses from our group which test aspects of the model will be presented. Finally, I will try to translate the insights gained from work in normal subject populations to the situation in clinical forms of anxiety.

Selective serotonin re-uptake inhibitors, such as escitalopram, are currently the pharmacological treatment of choice for patients with panic disorder. Panic response to intravenous cholecystokinin tetrapeptide (CCK-4), a potentially useful paradigm for volunteer translational studies, has so far not been characterized in healthy man after respective pre-treatment.

In a double-blind, placebo-controlled, randomized, within subject cross-over design thirty healthy young male volunteers, fifteen each with the long/long or short/short genotype for the serotonin transporter linked polymorphic region (5-HTTLPR), were pre-treated with 10 mg/d of escitalopram orally for six weeks and then challenged with 50 µg of CCK-4. The primary outcome measure was the increase of Acute Panic Inventory (API) ratings by CCK-4.

A significant pre-treatment by genotype effect on the increases of API ratings emerged. Panic induced by CCK-4 as per API was significantly more pronounced in subjects with the short/short genotype of the 5-HTTLPR under escitalopram versus placebo pre-treatment.

Contrary to our expectation, no inhibitory effect of escitalopram on panic symptoms elicited by CCK-4 could be demonstrated in healthy men. These findings do not support the potential usefulness of this experimental panic model for proof-of-concept studies. The biological underpinnings of the increased panic symptoms after escitalopram in our volunteers with short/short genotype need further research.

(Partially supported by a grant from Deutsche Forschungsgemeinschaft DFG Ko 659/7)

Onset and course of social anxiety disorder in the first three decades of life

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Background: Within the last decade, rising attention has been given to social anxiety disorder (SAD). While the symptomatology of social anxiety disorder (SAD) is comprehensively described, knowledge regarding its onset, course and outcome is still scarce. A wide range of putative factors and correlates are discussed, but it is difficult to disentangle empirically-based facts from more general or
even unproven remarks. Also, the specificity of findings for SAD is yet unknown.

Methods: Based on a representative community cohort sample of N = 1,395 adolescents and young adults, we present a data-driven overview on the natural course, predictors for onset and persistence of SAD in the first three decades of life. Information about the diagnostic status, clinical characteristics and a variety of related variables and possible familial risk factors were assessed in the prospective-longitudinal Early-Developmental Stages of Psychopathology Study.

Results: SAD is characterized by low stability on the DSM-IV threshold level, but by frequent oscillations around the diagnostic threshold, with low chance for full remission. While the onset of the disorder is predicted by common vulnerability factors such as behavioural inhibition, parental psychopathology and unfavourable family environment, the further course (e.g. persistence) of SAD is rather predicted by characteristics of early SAD expressions and family environment. Family environment (with parental rearing in particular) emerged as an important predictor for both the onset and course of the disorder. In line with the concept of a “vulnerable child”, unfavourable parental rearing was predicted by natal complications and serious health problems in the offspring. Also first evidence for specificity was found, as the pattern of parental overprotection, rejection and lack of emotional warmth only occurred in offspring SAD, but not in other offspring anxiety disorders.

Discussion: Findings characterize SAD as an early-onset disorder with a strong familial aggregation. With regard to its specificity, unfavourable family environment may serve as an indicator for an additional risk for the onset and course of SAD, and could therefore be a promising target for prevention and early intervention.

German J Psychiatry 2008; 11: S4

The neuropsychology of anxiety disorders
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Using modern neuroscientific tools, including functional magnetic resonance imaging (fMRI), it could recently be shown that anxiety disorders have organic correlates. Current data on the neuropsychology of anxiety disorders indicate specific, often only subtle abnormalities, particularly regarding a heightened sensitivity for anxiety-related stimuli in panic disorders. Furthermore, it was found that there are impairments of the explicit, verbal and visual memory as well as of the general attentiveness. Regarding social phobia and generalised anxiety disorders, the clinical picture also suggests cognitive disorders, although few systematic studies have been done on this subject so far. It is, however, known that different groups of anxiety disorder patients distort attentiveness and memories of anxiety-related stimuli to different degrees. The cause is thought to be neuropsychological disorders of the amygdala-hippocampus complex. Unfortunately, the studies published show considerable methodological differences or deficits, so that the current scientific data can only be used to generate hypotheses; e.g., the results were not always checked for potentially confounding comorbid psychological disorders or substance abuse. Furthermore, the therapeutic relevance of the results remains to be determined.

German J Psychiatry 2008; 11: S4

Workplace phobia in different professional settings
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Objective: Conditions at the workplace have an influence on the mental wellbeing of the employee. In different professional settings there are different specific demands concerning social competence, quantitative or qualitative achievements, working under pressure of time, flexibility or multi-tasking. In case the achievements cannot be fulfilled any longer, anxiety towards the work can arise, and in worst case end up in a workplace phobia with panic reactions and classical avoidance behavior which often manifests in long-term-sick-leave. The question is whether or not there are differences concerning the frequency of workplace phobias in different professional settings.

Method: 230 inpatients (71% women) from a psychosomatic rehabilitation clinic were explored concerning workplace-related anxieties and workplace phobia in a semi-structured diagnostic interview (Linden and Muschalla 2007, Muschalla 2008). It was explored whether there were differences concerning frequency and quality of workplace-related anxieties and workplace phobia in different professional groups.

Results: 58% of the interviewed were suffering from any workplace-related anxiety, 17% had a complex workplace phobia. Patients working in the domain of education were least often suffering from a workplace phobia (9%). Workplace phobia was found most frequently in employees in office and administration (22%), as well as in practical health care (21%).

In the domain of service, trade, assurances and banks 16% were suffering from workplace phobia, and 11% in the domain of building, manufacturing and industrial production.

Generalized worrying concerning the work was one of the most frequent anxieties in all professional groups. Specific social anxieties were – in contrast to the domains of health care (15%), education (14%), service and production (6%)
Conclusions: Workplace-related anxieties and workplace phobia occur with different frequencies in psychosomatic inpatients working in different professional domains. Employees in practical health care as well as in office and administration seem to be especially endangered.

Conditional analysis of concrete workplace situations should be carried out in order to identify more concretely which structural or personal workplace characteristics are related to workplace-anxieties and in which way preventive actions can be done.


German J Psychiatry 2008; 11: S5

Distinct paniogenic activity of sodium lactate and cholecystokinin tetrapeptide in patients with panic disorder (but not in control subjects)

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The validity of induced panic attacks as a model to study the pathophysiology of panic disorder has been questioned. Unspecific, unpleasant and aversive effects have been suggested, with panic disorder patients reacting only quantitatively different from healthy control subjects. We compared the two most widely studied paniogenic drugs sodium lactate and cholecystokinin tetrapeptide (CCK-4) with placebo in 25 patients with panic disorder and matched healthy control subjects. Psychopathological changes were measured using the Acute Panic Inventory (API). In patients with panic disorder 18 out of 25 experienced a sodium lactate- or a CCK-4 induced panic attack. Lactate or CCK-4-induced symptoms and induced panic attacks were only correlated in healthy control subjects, but not in patients with panic disorder. The mechanisms of lactate and CCK-4 induced panic attacks are distinct in panic disorder patients but not in healthy subjects. Different neurobiological vulnerabilities seem to be uncovered by the different challenges.

German J Psychiatry 2008; 11: S5

The Westphal Paradigm – A new paradigm to study the neuronal correlates of agoraphobia

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First described 1871 by C. Westphal, agoraphobia is a highly prevalent and disabling anxiety disorder. Disorder specific cues in fMRI studies allow to further characterize the neuronal mechanisms of the disorder but also of possible new treatment approaches. We therefore developed the first fMRI paradigm with agoraphobia specific stimuli.

More than 1000 pictures of potential agoraphobic situations were generated by the authors. Neutral pictures were collected from the International Affective Pictures System (IAPS). Two sets, each containing 48 pictures were selected on the basis of best distinguishing between patients with agoraphobia and healthy control subjects. Neutral pictures help to further elucidate the biological substrate of gender specific emotional susceptibility for anxiety disorders.
were taken from the IAPS and pictures are randomly presented in a cued and an uncued manner.

Arousal, valence and panic-inducing ratings of the agoraphobic pictures were significantly increased in patients with agoraphobia, when compared to healthy control subjects. First results of patients studied with a 3-T GE scanner suggest that anticipation of agoraphobic pictures is associated with an activation of the fear circuit including the amygdala, inferior frontal gyrus, hippocampus, anterior cingulate and insula.

We developed a first fMRI paradigm with agoraphobic stimuli. First results suggest that this paradigm can be used to further characterize the functional neuroanatomy of agoraphobia and might be sensitive to treatment.

Supported by the BMBF (01GV0612)
Results from a phase III study of once-daily extended release quetiapine fumarate (quetiapine XR) monotherapy in patients with generalised anxiety disorder

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Background: To evaluate efficacy and tolerability of once-daily quetiapine XR (extended release) in patients with generalised anxiety disorder (GAD).

Methods: 10-week (8-week active treatment, randomised phase; 2-week post-treatment drug-discontinuation/tapering phase), multicentre, double-blind, randomised, parallel-group, placebo- and active-comparator study (D1448C00011). Patients were randomised to quetiapine XR 50mg/day, 150mg/day, paroxetine 20mg/day or placebo. Primary efficacy outcome was change in HAM-A total score from baseline to Day 4, HAM-A response (≤ 50% decrease from baseline) and remission (HAM-A total score ≤ 7) at Week 8. Adverse events (AEs) were recorded throughout the study.

Results: 873 patients were randomised: 221 quetiapine XR 50mg/day; 218 quetiapine XR 150mg/day; 217 paroxetine; 217 placebo.

Mean HAM-A total score (overall baseline mean, 26.98) was significantly reduced at Week 8 in HAM-A total score. Other key outcomes included: change in HAM-A total score from baseline to Day 4, HAM-A response (≥ 50% decrease from baseline) and remission (HAM-A total score ≤ 7) at Week 8. Adverse events were recorded throughout the study.

Conclusions: Once-daily quetiapine XR 50mg/day and 150mg/day was effective and generally well tolerated for the treatment of patients with GAD, with onset of response observed as early as Day 4.
randomisation in: HAM-A total score; CGI-S score; HAM-A psychic and somatic anxiety factor scores; and Q-LES-Q% maximum score. Adverse events (AEs) were recorded throughout the study.

Results: 433 patients were randomised to quetiapine XR (n=216) or placebo (n=217). ITT population: quetiapine XR (n=216) and placebo (n=216). Mean baseline HAM-A scores (at the start of OL phase) were: quetiapine XR, 25.2; placebo, 25.1.

The risk of an event was significantly reduced for quetiapine XR vs placebo: HR=0.19 (95% CI [0.12, 0.31]; p<0.001). Fewer patients on quetiapine XR treatment (n=22, 10.2%) than placebo (n=84, 38.9%) experienced an anxiety event. Time to an anxiety event by dose at randomisation was significantly reduced by quetiapine XR 50mg (HR=0.21 [0.08, 0.51]; p<0.001), 150mg (HR 0.17 [0.08, 0.36]; p<0.001), 300mg (HR=0.22 [0.09, 0.51]; p<0.001) vs placebo.

During the maintenance phase, significant differences in mean changes were observed between quetiapine XR and placebo in: HAM-A total score (-0.14 vs 1.90, p<0.001); CGI-S score (-0.03 vs 0.26; p<0.001); HAM-A psychic (0.08 vs 1.53; p<0.001) and HAM-A somatic (-0.22 vs 0.38; p<0.001) anxiety cluster scores; Q-LES-Q% maximum score (0.22 vs -2.12; p<0.05).

The most common AEs (>5% any group) during the maintenance phase were headache, nausea, insomnia and nasopharyngitis. The incidence of serious AEs was low (<2%) in both groups.

Conclusion: Quetiapine XR monotherapy was effective at reducing the risk of recurrence of anxiety events and generally well tolerated as maintenance treatment in patients with GAD.


German J Psychiatry 2008; 11: S8

Tolerate or eliminate? Reconsidering the effects of safety behaviours in exposure therapy

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Cognitive-behavioural models of anxiety disorders consistently emphasize the decisive role played by avoidance and safety-seeking behaviours in the maintenance of anxiety. Experimental evidence for the deleterious effects of safety behaviours is less consistent, leading to a controversy about the therapeutic use of these behaviours. Whereas some authors promote abandoning all kinds of safety behaviours during therapy, recent reviews suggest that a judicious use of safety behaviours might facilitate treatment. Final conclusions are hampered by difficulties in determining whether or not a certain behaviour has to be considered as safety-seeking, the variety of concepts used to describe disorder-specific behaviours employed to prevent or reduce the risk of a feared outcome, and the methodological differences in studies examining the effects of avoidant behaviour.

Against this background, we reviewed existing evidence regarding potential contributions of safety behaviours to the onset and maintenance of anxiety as well as regarding the effects of safety behaviour use in therapy. Although the majority of studies concluded on detrimental effects of safety-seeking, there were few studies that did not support this assumption or even found beneficial effects of avoidance strategies. Inspecting these studies, it showed that neutral or positive effects of safety behaviours were most often linked to cognitive avoidance and specific phobias such as animal or blood-injury phobias; however, it might be doubted if those studies in fact examined safety behaviours when applying a functional definition of safety. Despite recent justification of a judicious use of safety behaviour in therapy, we therefore promote a more rigorous procedure of identifying individual safety behaviours and abandoning them throughout therapy.

German J Psychiatry 2008; 11: S8

Stress hormones during situationally induced panic attacks

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Objective: Data on the status of stress hormones during nonpharmacologically induced panic attacks have been inconsistent. This study examined if situationally induced panic attacks are accompanied by an increase of plasma cortisol and/or plasma ACTH.

Method: Within cognitive-behavioural therapy, 10 agoraphobic patients underwent 3 exposure training sessions to their individual phobic situations. Blood samples were taken at 7 time points before, during and up to 1h after exposure.

Results: Mostly, fear ratings were already elevated before the beginning of exposure training (anticipatory anxiety) and increased further during exposure. The release of ACTH – measured as the Area Under The Curve (AUC) - was positively correlated to the corresponding AUC of fear
ratings, despite the absence of an increase of ACTH in the group mean during exposure therapy. In contrast, cortisol release was unrelated to fear during situationaly induced panic attacks.

**Conclusions**: These findings show an involvement of ACTH rather than Cortisol in situatonally induced panic attacks. Further investigations with healthy controls are ongoing.

German J Psychiatry 2008; 11: S9

**Examining response and relapse: a continuous responder analysis from a long-term treatment trial of duloxetine for generalized anxiety disorder**

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The aim of this study was to examine the relationship between duration of a continuous therapeutic response and risk of relapse in the treatment of adults with generalized anxiety disorder (GAD). 887 patients (mean age=43.3 yrs; 61% female) with DSM-IV defined GAD entered open-label treatment with duloxetine 60–120 mg for 26 weeks. Treatment response was defined as a Hamilton Anxiety Rating Scale (HAMA) total score reduction from baseline ≥50% to a score of ≤11 and a Clinical Global Impression of Improvement (CGI-I) score of “much” or “very much improved” for the last 2 visits of open-label treatment. Patients who completed the open-label phase and met this definition were randomly assigned to either duloxetine (N=216) or placebo (N=213) for the 26-week double-blind continuation phase. Relapse was defined by an increase in GAD illness severity rating ≥ moderate or discontinuation due to loss of efficacy. Treatment groups were compared for time to relapse based on duration of weeks (6, 10, or 14) in which they continuously met the response criteria prior to randomization. The overall relapse rate was 44.5% for the placebo group (N=211) and 15.0% for duloxetine group (N=213). The rate of relapse for duloxetine-treated patients was 15.2% (28/184) for 6-week continuous responders, 14.7% (24/163) for 10-week continuous responders, and 12.8% (19/148) for 14-week continuous responders. For placebo-treated patients, the rate of relapse was 46.5% (80/172) among 10-week continuous responders, and 46.8% (72/154) among 14-week continuous responders. Time to relapse was significantly shorter with placebo than with duloxetine within each continuous responder subgroup as well as for the overall sample (P< .001 all comparisons). Increased duration of stable treatment response provided no independent protection from relapse. In conclusion, patients were at greater relapse risk, despite stability of response, when they were switched from duloxetine to placebo treatment, indicating continued protective benefit with duloxetine treatment during the study period.

German J Psychiatry 2008; 11: S9

**Comparing instructed fear and fear conditioning: Support for a high-level appraisal account of dorsomedial prefrontal function in emotion**

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Emotional reactions are shaped by both low-level (automatic, unconscious) and high-level (conscious) appraisal processes. While various subcortical areas including the amygdala have been identified as crucial for low-level appraisal, less is known about the circuitry supporting high-level evaluative processes. Recently, the rostral part of the dorsal anterior cingulate cortex (dACC) and the dorsomedial prefrontal cortex (dmPFC) has emerged as potentially pivotal in high-level appraisal. We tested this hypothesis by comparing the neural substrates of classical Pavlovian fear conditioning, which is thought to strongly rely on low-level processes, and instructed fear which has a clear high-level component. We predicted relatively more pronounced rostral dACC/dmPFC activation in instructed fear. The comparison was performed using formal quantitative meta-analysis of existing functional magnetic resonance imaging (fMRI) studies. Results confirmed our prediction. We conclude that the rostral dACC/dmPFC has a role in high-level appraisal. We discuss a model of information flow and negative feedback interactions in an amygdala – medial prefrontal – lateral prefrontal network leading from basic to successively more elaborate analysis of emotional stimulus material.

German J Psychiatry 2008; 11: S9

**Gender- and genotype-dependent differences in stress reactions in a mouse model for anxiety disorders**


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Serotonin (5-HT) is an important moderator of many physiological, behavioural and developmental processes and is discussed to play an important role in coping with stress. Anxiety disorders and depression are stress-related
disorders associated with disturbances of the serotonergic system, where the serotonin transporter (5-HTT) plays an important role. 5-Htt knockout (KO) mice represent an artificially hyperserotonergic environment and show an increased anxiety-like behaviour. Furthermore, it could be shown that female 5-Htt KO mice display exaggerated adrenomedullary responses to stress. Therefore, these mice seem to be a good model to investigate the role of the serotonergic system in the context of stress reactions and anxiety disorders.

As we recently showed acute immobilization stress resulted in significantly increased plasma corticosterone levels in mice of all 5-Htt genotypes compared to unstressed mice, and in general higher corticosterone levels were detected in females compared to males, as it is known from the literature. Interestingly, we revealed genotype-dependent differences of corticosterone levels only in stressed males but not in stressed female mice. Based on these gender- as well as genotype-dependent differences in stress reactions in the periphery we looked for possible expression differences in the brain. As synaptic proteins modulate the release of neurotransmitters into the synaptic cleft and are shown to be involved in stress reactions we studied the effects of acute immobilization stress on the expression of synaptic protein such as Synaptotagmin (Syt) I, Syt IV and Syntaxin (Stx) 1a. In addition, we studied the expression of the two immediate early genes (IEGs) FBJ osteosarcoma oncogene (c-Fos) and fos-like antigen 2 (Fra-2) as markers for neuronal activity. We performed a quantitative real-time-PCR study in five different brain regions of female/male 5-Htt KO and wildtype (WT) control mice. Acute immobilization stress primarily resulted in increased expression of Stx1a in hypothalamus of male 5-Htt KO mice and in hypothalamus and hippocampus of unstressed compared to stressed female WTs. Interestingly, Stx1a is discussed to interact with the 5-Htt and to modulate the cell-surface expression of this transporter. There were also gender-dependent differences in the expression of Stx1a and Syt IV, mainly in cortical areas. Regarding the expression of c-Fos we found stress- as well as gender-dependent differences primarily in the amygdala, hypothalamus and raphe. Gender-dependent expression of Fra2 was mainly detected in cortex and hypothalamus. In general, expression differences were mainly found in brain regions which are involved in anxiety circuits and/or emotion.

In conclusion, besides the increased anxiety-like behaviour of mice deficient for the 5-Htt, there exist not only 5-Htt-genotype-dependent differences but also gender differences regarding the responses to acute stress in the periphery (as demonstrated by plasma corticosterone levels) and in the brain (as demonstrated by altered expression levels of synaptic proteins and IEGs).

Is extinction different from habituation?

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Fear extinction is conceptualized as an associative learning process which is initiated by the relieving experience that a feared event is less aversive than expected (‘prediction error’). However, the decrease of conditioned responding during extinction might also be caused (in part) by habituation processes. We have developed a conditioning and extinction paradigm that allows us to quantify this habituation component and thus to isolate extinction proper. We derive two coefficients, extinction rate ‘r’ and short-term extinction memory ‘m’ that express the speed with which extinction learning proceeds (related to prediction error encoding) and the strength of the memory trace generated, respectively. These can be used as second-level regressors in fMRI to identify the neural substrates of both processes. Preliminary analysis suggests that the extinction learning rate relates to activity in ventral striatal areas classically associated with reward and reward learning. Our data therefore support an idea that extinction learning might be similar to an appetitive learning process, the relief experienced during punishment omission being causally involved in prediction adjustments.

German J Psychiatry 2008; 11: S10

Nocturnal urinary cortisol excretion over a randomized controlled trial with paroxetine vs. placebo combined with relaxation training or aerobic exercise in panic disorder

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Introduction: Data on basal hypothalamo-pituitary-adrenomedullary (HPA) function over controlled treatment trials with serotonergic drugs in anxiety disorders are still rare.

Methods: 29 patients with panic disorder participating in a 10 week randomized, controlled trial (paroxetine vs. placebo with exercise or relaxation; N=60) collected urine for cortisol excretion over 3 consecutive nights before start and before termination of the treatment episode. Urinary cortisol was measured by radioimmunoassay. Efficacy measures were the Clinical Global Impression Scale (CGI) and the Panic and Agoraphobia Scale (P&A). 83% were female (p<.05 vs. males). 55% received additional aerobic exercise, and 45% relaxation. 55% received paroxetine treatment, and 45% placebo. Significantly fewer males received placebo treatment (p<.05).

Results: All subjects improved significantly. Cortisol excretion did not differ between treatment groups or at pre-/post measurements. Females showed a significantly
higher variability of cortisol excretion compared to males, at pre- (p<.005) and post (p=.015) assessments. Males displayed a trend to lower basal HPA function at end of treatment (p=.08). HPA variability after treatment showed a trend to be higher in the paroxetine group (p=.052) - who clinically improved significantly better- compared to the placebo group. No relationship between HPA activity and treatment response or with exercise was detected.

Conclusion: HPA function shows significant gender differences, with females having a higher HPA function variability. Future studies on HPA function in treatment trials should address gender and medication effects.

German J Psychiatry 2008; 11: S11

A randomized, controlled trial on the effects of paroxetine versus placebo in combination with aerobic exercise or relaxation training in the treatment of panic disorder

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Introduction: To date no randomized controlled studies exist investigating combined drug and exercise treatment in panic disorder. This study was performed to compare the therapeutic effects of a drug treatment of proven efficacy (paroxetine) to placebo additionally combined with either aerobic exercise or relaxation training in panic disorder.

Methods: Randomized 10 week, controlled, double-blind drug treatment protocol. To eliminate allegiance effects, one investigator blind to the assignment to the exercise or the relaxation group did double-blind ratings. 75 outpatients aged 19-52 years (70% female) with moderate to severe panic disorder according to DSM-IV and ICD-10 were included. Patients received 40 mg paroxetine daily or placebo combined with either regular aerobic exercise or relaxation training in panic disorder.

Results: Overall dropout rate was 20% and compliance was satisfactory for all groups. All treatments showed a significant improvement on all efficacy measures over time (p<.05). Paroxetine treatment was associated with significantly better improvement compared to placebo (p<.05). On the CGI, exercise treatment resulted in a trend to better improvement over time compared to relaxation (p=.06). Response (p<.05) and remission (p=.08) rates were higher in the paroxetine compared to placebo groups. Effects sizes were large for all groups (d=1.53-3.87). Correlations between scores of blinded and non-blinded raters were high. Adverse events were reported by 30% of the patients, but none was serious.

Conclusions: While paroxetine was superior to placebo, aerobic exercise did not differ from relaxation training in most efficacy measures.

German J Psychiatry 2008; 11: S11

Serotonergic function, substance craving, and psychopathology in detoxified alcohol addicted males undergoing tryptophan depletion

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Introduction: Alcohol addiction is associated with alterations of central nervous dopaminergic and serotonergic function. A valid method to influence serotonin function as tryptophan depletion has not been applied in detoxified alcohol addicted patients in order to investigate its impact on psychopathology, psychoneuroendocrinology, and substance craving behaviour.

Methods: 25 alcohol addicted males (aged 44 ± 8.5 years) were investigated 7 to 21 days after termination of withdrawal symptoms during qualified alcohol detoxification treatment. At random, patients received either a tryptophan free or tryptophan containing amino-acid drink at 11:30 a.m. and vice versa 7 days later. On each occasion, anxiety, depression and craving were assessed by scales before and 5 hours after the drink. Tryptophan, 5-HIES, dopamine, norepinephrine, epinephrine, HVA in serum as well as serotonin transported mRNA was measured before and 5 hours after verum or placebo depletion. For two nights following the respective treatments nocturnal urinary cortisol measurements were done. Genotyping for the serotonin transporter gene was performed.

Results: Tryptophan depletion resulted in significant reduction of total and free serum levels (p<.001), whereas the tryptophan rich drink caused a significant increase in serum tryptophan (p<.001). Both modalities caused an increase of serum serotonin (verum: p<.05; sham: p<.01) levels, however serum 5HIES was decreased after depletion (p<.01) but increased after sham (p<.05). Both, dopamine (p<.01) and norepinephrine (p<.05) were elevated after verum and sham depletion, no significant changes in HVA and epinephrine were detected. Tryptophan depletion caused an increase of depression scores (MADRS, p<.01), whereas sham depletion improved anxiety ratings (STAI, p<.01) and substance craving (Visual analogue scale p<.05). Urinary cortisol excretion was not affected by both treatments, neither were correlations with depression or anxiety ratings evident. Serotonin transporter mRNA was increased after both verum and sham depletion. 80% of
subjects carried the short allele (sl-variant) of the serotonin transporter gene (SLC6A4).

Discussion: Results give evidence to an impaired serotonergic function in alcohol addicted males. Tryptophan depletion caused increased depressive pathology but not elevated substance craving, whereas elevated tryptophan and continuously elevated serotonin levels improved craving and anxiety ratings. Results may give a rationale for improving serotonergic function with serotonergic drugs in this patient group.

The Quantification Inventory for Somatoform Syndromes (QUISS)

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Introduction: To date, specific scales for the assessment of severity of somatoform disorders are still rare. Characteristic cognitive and behavioural domains, representing severity are not incorporated in the existing scales. Results with the novel Quantification Inventory for Somatoform Syndromes (QUISS) are presented in this paper.

Methods: The QUISS has been developed as a qualified severity scale for patients fulfilling diagnostic criteria according to DSM-IV or /and ICD-10. It was designed to be particularly suitable for application in clinical trials and for monitoring the efficacy of psychotherapy and pharmacotherapy. Not only number, severity and frequency of somatoform symptoms, but also common cognitive and behavioural domains of somatoform disorders have been included into this instrument. Both an 18-item patient- and observer-rated version are available taking about 20 minutes to complete. The questionnaire was applied to patients with somatoform disorder (N=96), major depression (N=24), and panic disorder (N=16).

Results: The psychometric properties of the scale are satisfactory. The QUISS showed high objectivity (Cronbach’s α = 0.90 for both versions; inter-scale correlations r = 0.64-0.88; p < 0.05), good test-retest- (r = 0.87; p < 0.05) and inter-rater-reliability (r = 0.89; p < 0.05). External validity (moderately high correlations of QUISS-T to SOMS 7T (r = 0.54), significant discrimination to major depression p < 0.05) was satisfactory. Factor structure revealed five relevant factors.

Conclusions: The QUISS could be a useful instrument in somatoform disorders for the assessment of syndrome severity and treatment outcome in scientific and clinical settings.