Automatic Avoidance Tendencies in Social Anxiety

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Avoidance behavior is a major factor in the maintenance of anxiety disorders. However, it sometimes is difficult to measure avoidance by directly asking anxious individuals because not all elements of fear are accessible to introspection. Recent research has shown that additional information about the more automatic processing of threatening stimuli can be gained from using indirect measures, relying on reaction time measurements. The Approach-Avoidance Task (AAT) is such an indirect measure that allows to assess automatic behavioral responses. Several studies have shown that avoidance is associated with pushing objects away from oneself, and approach is associated with pulling the objects closer. The AAT uses this association in a joystick task, in which objects on the screen are pushed or pulled.

We will report studies that used the AAT in Social Phobia (Social Anxiety Disorder, SAD), a common and debilitating disorder characterized by marked and persistent fear of social situations. In Study 1, participants were asked to evaluate “crowds” of facial stimuli (3x4 matrices of 12 individuals showing different emotional expressions), and they completed an AAT with the same crowds. Although there was no explicit bias in explicit evaluations (all participants rated the crowds in a similar way), we could show that socially anxious participants reacted increasingly avoidant to increasingly angry crowds.

In Study 2, we induced an interpretation bias in participants and studied whether this bias influences automatic avoidance behavior reflected in the AAT. We successfully induced an interpretation bias in participants with written descriptions of ambiguous social scenarios. Participants were trained to ‘develop’ a tendency to disambiguate the situation in an either benign or negative way. Most strikingly, the effects of the training transferred to completely different materials used in a different task, namely the crowds employed in the AAT. Participants trained to handle a negative interpretation bias behaved similarly to the socially anxious participants tested in Study 1. The implications for theory forming and clinical applications are discussed.
Chromosome 4q31-34 risk locus association of neuropeptide Y Y5 receptor variants with panic disorder

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There is strong evidence for a genetic contribution to the pathogenesis of panic disorder, with a recent linkage study pointing towards a risk locus on chromosome 4q31-q34 (Kaabi et al., 2006). Genes coding for neuropeptide Y (NPY) Y1, Y2 and Y5 receptors are located in the suggested risk region (4q31-q32) and the neuropeptide Y system has repeatedly been reported to be involved in the pathophysiology of anxiety (as reviewed by Heilig, 2004). Therefore, NPY receptor genes constitute most promising functional as well as positional candidate genes for association studies in panic disorder.

In the present study, tagging variants in the NPY (rs16157, rs16147, rs16139, rs9785023, rs16474), NPY Y1 (rs12507653, rs12510104, rs7687423, rs4691079), Y2 (rs11099992, rs12507396, rs1047214, rs11728843) and Y5 (rs4234955, rs11724320, rs11946004) genes were investigated for association with panic disorder in a sample of 230 German patients with panic disorder (f=135, m=95) and 230 age- and sex-matched healthy controls.

A synonymous (Gly-426-Gly) NPY Y5 coding variant (rs11946004) as well as haplotypes including rs11946004 and an intronic NPY Y5 variant (rs11724320) were significantly associated with panic disorder (p=0.027), with the effect originating from the subgroup of female patients (p=0.030), particularly with concurrent agoraphobia (p=0.002-0.019). No association was observed for any variants located in the genes coding for NPY, NPY Y1 or NPY Y2.

The present results suggest an influence of NPY Y5 receptor variants on the etiology of panic disorder in a potentially gender-specific manner and further strengthen the evidence for a risk locus on chromosome 4q31-q34 in anxiety disorders.

References:


30 young healthy male volunteers (with no history of DSM-IV axis I and axis II disorders), 15 each homozygous for the short or long allele of the 5-HTTLPR, were studied in a double-blind, placebo-controlled, cross-over design. 10 mg/d of escitalopram and placebo were given for 42 days (with three weeks of washout in between). Participants were examined on day 42 of each treatment phase.

The facial expression recognition task using the Pictures of Facial Affects featured 4 basic emotions (fear, anger, sadness, and happiness) and neutral expressions. Facial stimuli were presented and volunteers were asked to reflect the presented emotion. Pictures from the IAPS were used to elicit positive, negative, and neutral emotions. Subjects were asked to report their emotions using a visual analogue scale.

Results: We found a significant treatment effect in the homozygotes of the long allele exhibiting a decreased rating on negative emotional stimuli of the IAPS whilst positive ratings remained stable.

Secondly, subjects in this group tended to make more mistakes by confusing negative emotions in the facial recognition task and improved after escitalopram administration. Discussion: Our findings suggest that SSRIs modulate the processing of negative emotional material.

It has been controversially discussed whether social fears and Social Phobia can be described as a continuum of severity or as discrete phenomena with more or less arbitrarily derived thresholds. Research findings indicate that social fears below the diagnostic threshold are associated with substantial impairment and work disability and with an increased risk for the subsequent development for full blown DSM-IV Social Phobia and other mental disorders. Parental Social Phobia and family based developmental conditions have been suggested as important risk factors for Social Phobia. Yet, it remains unclear to what degree these known familial risk factors also play a role in the onset of social fears. The aim of this current study is therefore to confirm the importance of familial risk factors for Social Phobia and indicate, though less pronounced and less consistent, similar relationships for the onset of social fears. Given the negative outcomes associated with social fears below the diagnostic threshold in terms of disability, impairment, and malignant course, individuals with subthreshold Social Phobia should be targeted by early intervention programs. Although more research is necessary to identify their moderator and/or mediator role, parental psychopathology and negative parental styles may be used to define high-risk groups.
ment relevant variables. For the case in point, numerous levels of constructs were included ranging from genetic and physiological variables to behavioral measures and questionnaires designed to assess salient cognitive variables. Determining which variables best capture objective and subjective improvement is far from straightforward; however. Numerous complications can arise that threaten the validity of treatment results. These include various aspects of construct validity and reliability. This presentation will highlight some of these difficulties, demonstrate possible solutions, and illustrate how decisions in this domain affect both knowledge derived from the literature as well as how clinicians apply such knowledge with their patients.

The clinical meaning of job anxiety

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Objective: Anxiety disorders or trait anxiety can cause problems at the workplace. Similarly, problems at the workplace can cause anxiety reactions. Job-related anxieties pose special problems as they are always associated with problems of participation. The aim of this study is to investigate the relation between trait anxiety and job-anxiety.

Method: 90 inpatients of a psychosomatic and 100 from an orthopedic rehabilitation centre with mental and somatic disorders filled in the self-rating Job-Anxiety-Scale (JAS) and the State Trait Anxiety Scale (STAI-T) in order to explore the degrees of experienced anxiety in the workplace and general anxiety. Correlations with indicators of job participation were investigated.

Results: Highest scores of job-anxiety (Likert scale from 0-4) were found for the dimensions “job-related worries” (1,83) and “health anxieties” (1,68). Higher scores were correlated with higher self-rated anxiety (r=.687**). Job-anxiety score, in contrast to STAI-T score, was significantly related to the duration of sick leave absence from work (rJAS=.294**, rSTAI-T=.065). Women showed higher scores than men on the STAI-T but not on the JAS. Orthopedic patients had significantly lower trait-anxiety as well as job-anxiety scores than psychosomatic patients (JAS: Morth=0,99 (SD=0,68), Mpsys= 1,66 (SD=0,96)).

Conclusions: Job-anxiety is related to but not identical with trait anxiety. Job-anxiety is a special quality of anxiety which is important to understand sick leave and absenteeism. Thus it offers a better predictive value concerning socio-medical questions of job-reintegration than does a measure of general or unspecified anxiety. Job-anxiety is a multidimensional phenomenon, so that different dimensions of job-anxiety should be considered separately.

References:

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Fearless mice, ferocious men – translational phenotyping of low NOS1 expression

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In animal studies employing pharmacological techniques, nitric oxide (NO) has been suggested to play a role in depression and anxiety. To further elucidate the physiological role of NO and its downstream mechanisms, we conducted behavioral phenotyping of mice with close to none expression of the neuronal isoform of nitric oxide synthase (NOS1), the major source of NO in the central nervous system. Mice were subjected to a comprehensive battery of behavioral tests with special emphasis on anxiety and depression-like behaviors. No differences were observed in activity-related parameters; in contrast to the a priori hypothesis, depression-related tests (Forced Swim Test, Learned Helplessness) also yielded no significantly different results, yet an anxiolytic phenotype however was present in knockdown mice. As little is known about the function of NO in humans, we aimed to investigate a NOS1 promoter polymorphism, shown to result in decreased NOS1 exon 1F expression, for an association with behavioral traits. Four different samples have been ascertained: a sample of patients with adult ADHD (n=383), a sample of subjects with Cluster B and Cluster C personality disorder (n=403), a sample of criminal offenders stratified for violent and non-violent
criminality (n=233) and, finally, a control sample of 1954 subjects (total n=2973), for which NEO PIR personality assessment was available in 1099 cases. Low-expression NOS1 exon 1f alleles were significantly associated with Cluster B personality disorder, especially histrionic personality disorder, and ADHD persistence into adulthood. With regards to personality dimensions, an gene x sex x age association was observed with the NEO "Conscientiousness" scale. Finally, carriers of this allele were more prone to commit violent crime when childhood adversity was controlled for, as evidenced by multiple regression analysis. Together, NOS1 seems to balance impulsive-disinhibited and anxious behaviors which can be observed across species: while NOS1 knockdown mice display a characteristic behavioral profile consisting of reduced anxiety and impaired learning, in human personality it appears that especially interpersonal, disruptive, and goal-directed behaviors are influenced by NOS1 genotype. These findings strongly make a case for translational research in psychobiology to uncover the molecular foundations of human behaviour.

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Alcohol eliminates attentional bias in social phobics
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Background: Epidemiological studies show a substantial association of social phobia and alcoholism. However, the responsible mechanism is not well understood. According to Sayette (1993) anxiety is reduced by alcohol through disrupting initial appraisal of threatening stimuli if the cues cannot be processed automatically. We tested the effects of alcohol on primary appraisal of ambiguous and non-ambiguous faces in social phobics and controls.

Procedure: 40 participants with social phobia (DSM-IV) and 40 controls performed a visual dot probe task with either drinking alcohol (BAC 0.6 ‰) or after drinking orange juice. Expressions were happy, angry, neutral or ambiguous. Two ambiguous facial expressions were the result of mixing angry or happy with neutral faces.

Results: Without alcohol, social phobics showed an attentional bias towards explicitly angry facial expressions, indicating preferential processing of threat related stimuli (vigilance). Alcohol eliminated this attentional bias for social phobics. There were no attentional biases for other emotional face stimuli.

Discussion: The results suggest that social phobic patients show initial vigilance for angry facial expressions. This bias can be eliminated by alcohol, what may explain the increased use of alcohol in social phobics.

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Data on basal hypothalamo-pituitary-adrenomedullary (HPA) function over controlled treatment trials with serotonergic drugs in anxiety disorders are still rare. In this study, 29 patients with panic disorder participating in a randomized, controlled trial on the effects of paroxetine treatment versus placebo in combination with either aerobic exercise or relaxation over a period of 10 weeks completed a psychoendocrinological measurement protocol out a whole of 60 subjects treated in the controlled treatment trial. Nocturnal urinary cortisol excretion was measured over 3 consecutive nights before start and before termination of the treatment episode. Treatment effects were measured by changes in Clinical-Global-Impression (CGI) and the Panic and Agoraphobia scale (P&A). Urinary cortisol was measured by radioimmunoassay. 83% of the completers of the urine collection were female. 55% received additional aerobic exercise, and 45% relaxation. 55% received paroxetine treatment, and 45% placebo. Despite all patients showed significant improvement on the efficacy measures, nocturnal urinary cortisol excretion did not differ between initial and terminal assessments in the entire population. Neither did results differ between treatment modalities or were related to clinical improvement of panic disorder.

Compared to males, however, females showed a significantly higher variability of cortisol excretion before and at the end of the 10 week treatment period (p<.05). Males displayed a trend to lower basal HPA function at study termination (p=.08). The variability of urinary cortisol excretion after 10 weeks of treatment was higher in individuals receiving paroxetine (p=.052) compared to placebo. Although decrements in urinary cortisol excretion as well as paroxetine treated subjects, who clinically improved significantly better than placebo treated patients. Surprisingly we could not demonstrate a relationship of HPA-activity and treatment response, neither with the exercise condition. It could be hypothesized that HPA-activity is more like a trait parameter, showing distinct gender differences. Future studies on HPA-function in treatment trials should address gender and medication effects on results. Yet, the interpretation of this investiga-
Hypervigilance and avoidance in social anxiety: Testing gaze behavior toward faces and in virtual social interactions

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Hypervigilance to and avoidance of phobic stimuli are supposed to play a prominent role in the development and maintenance of anxiety disorders. In social anxiety, the facial expression, the gaze, or the approach of a potential interaction partner can be feared stimuli. Therefore, we investigated the attentional responding to emotional facial expressions, mutual gaze and approaching virtual characters in high and low socially anxious persons and control participants, which were pre-selected by their scores in the Brief Fear of Evaluation Scale (BFNE). Eye-tracking methodology was used to measure the overt visual attention continuously. Furthermore, virtual reality technique was used to create ecological valid situations of social interactions.

In the first study, voluntary and involuntary attention to emotional facial expressions was investigated in a free viewing task and an antisaccade task, respectively. Highly socially anxious participants showed an initial attentional hypervigilance for happy facial expressions in the passive viewing task and more errors in response to facial expressions. Thus, happy faces may attract automatically attention of socially anxious. Furthermore, social anxiety seems to be associated with a diminished ability to inhibit reflexive orienting to facial expressions. This indicates that faces per se are especially meaningful for socially anxious people.

In the second study, high and low socially anxious participants and controls were confronted with virtual characters in a virtual reality scenario while eye movements and posture of the head were recorded. In the virtual world, avatars approached the participants and stopped close (0.5 m) or far (1.5 m) in front of the participant with either direct or averted gaze. HSA showed more backward orientation of their head in response to male avatars with direct gaze, whereas no avoidance was found in LSA. Furthermore, HSA compared to LSA and controls looked less long at the male avatars with direct gaze than to male avatars with averted gaze, whereas no differences were found for the female avatars. These findings show that HSA who are confronted with social interaction of opposite sex show avoidance behaviour.

Overall, the studies showed that eye-tracking methodology is an appropriate index of attentional and avoidance processes. Furthermore, the usefulness of VR as a research tool for social interactions was demonstrated.

Possible role of repetitive transcranial magnetic stimulation (rTMS) in panic and anxiety

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Several studies suggest that treatment with repetitive transcranial magnetic stimulation has beneficial effects in patients with major depression. In contrast, so far only few studies have investigated the effects of rTMS in anxiety disorders. There are some reports that low frequency rTMS shows improvement in patients with PTSD, obsessive compulsive disorder and panic. These anxiolytic effects have been attributed to the inhibitory action of low frequency rTMS on cortical activity. Moreover, it has also been discussed whether rTMS over the prefrontal cortex might also affect other key areas of the fear-network such as the amygdala. With regard to panic disorder, only few case reports and small studies are available so far. In an experimental panic-model with cholecystokinin-tetrapeptide (CCK-4), our group investigated the effects of single-session low-frequency rTMS on panic attack severity in healthy subjects.

In a placebo-controlled cross-over design 11 healthy volunteers received a 1 Hz real or sham rTMS over the right dorsolateral prefrontal cortex (120% intensity related to the individual motor threshold, 1800 stimuli/day) on two separate days. Experimental panic induction with CCK-4 was carried out immediately after real or sham rTMS respectively. Panic symptoms were assessed using the API and PSS score. All subjects reported a marked panic response following CCK-4 administration after both active and placebo treatment. However, ANOVA revealed no significant differences of the mean API- and PSS sum scores between the active and the sham treatment condition. No differences were observed in CCK-4 induced activation of hypothalamic-pituitary-adrenal (HPA) axis activation.

Although in case reports low frequency rTMS has shown beneficial effects in panic disorder patients, the current study using an experimental panic model did not reveal therapeutic effects of a single-session rTMS in healthy subjects. This is in contrast to pharmacological studies, where significant reduction of CCK-4 induced panic has been observed after a single-dose administration of alprazolam. However, in most patient studies rTMS was applied for several days or weeks suggesting that a single rTMS session is not sufficient to counteract the strong anxiogenic action of CCK-4. Therefore, extended treatment protocols, evaluation of symptoms of panic and general anxiety, as well as modification of challenge paradigms using also models for
subthreshold panic should be considered with regard to future studies.

**Poster Presentations**

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**Does 5-HTTLPR genotype influence willingness to participate in panic challenges?**

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Several population-based association studies have reported an association between the short allele (S) of the serotonin transporter (5-HTT) gene-linked polymorphic region (5-HTTLPR) and increased anxiety related personality traits. However, so far it is unknown, how possibly aversive conditions and stressful implications of a panic challenge may influence the 5-HTTLPR genotype composition and the associated psychological traits of a study sample. We screened potential male participants for panic challenge study participation by advertisement in the general population. The 5HTTLPR genotype and different anxiety related psychometric scales (the Anxiety Sensitivity Index”, the X2 (trait)-scale of the “State–Trait Anxiety Inventory” and the neuroticism-subscale of the “NEO Five-Factor-Inventory”) were investigated in a cohort of 200 Caucasian male who applied to participate in the study. The subjects were divided into S/S and long (L) groups (L/L or L/S) according to their genotype. Psychometric scores of the two genotype groups were compared using analysis of variance. We found significantly fewer S/S carriers in our sample in comparison to previous population-based association studies with a predominantly Caucasian sample. Moreover, in contrast to previous studies, subjects with the S/S genotype scored significantly lower on the three different anxiety-related personality scales compared to those with at least one L allele. We hypothesize that the level of aversiveness to be expected in study participation, as portrayed by the advertisement, may have caused a self-selection bias. Fewer subjects with the S/S genotype may have decided to volunteer as participants for the study, and those who did volunteer are comparatively low in trait anxiety, anxiety sensitivity, and neuroticism.

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**Cannabinoid Receptor 1 (CNR1) Gene and Antidepressant Treatment Response: Modulated by anxiety?**

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The endocannabinoid system has been implicated in the pathogenesis of depression and anxiety as well as in the mediation of antidepressive pharmacological treatment efficacy, with particular, though controversial evidence for a potential utility of cannabinoid receptor 1 (CB1) receptor antagonists in the treatment of depressive as well as anxiety disorders (see Witkin et al., 2005). Thus, 256 Caucasian patients with Major Depression (f=145, m=111) were genotyped for variants rs1049353 and rs12720071 in the cannabinoid receptor 1 gene (CNR1) (6q14-15). Response to antidepressive pharmacological treatment was assessed by weekly intra-individual changes of HAM-D-21 scores over six weeks. The CNR1 rs1049353 G allele conferred an increased risk of worse response to antidepressant treatment, particularly in patients with the melancholic subtype of Major Depression and the subgroup of female patients. This effect was most pronounced, when only patients with high anxiety were considered.

This study provides preliminary support for a role of CNR1 gene variation in depression and anxiety. Provided replication in independent studies, this finding may aid in evaluating novel pharmacological treatment options for depressive and anxiety-related symptoms targeting the endocannabinoid system.

Reference:
Pathways to specialized CBT treatment in patients with panic disorder and agoraphobia: does age and previous healthcare experience play a role?

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Patients with panic disorder and agoraphobia utilize mental health services more often than patients with any other mental health disorder (Weissmann, 1991). However, these patients require on average between 7 to 10 years before they receive adequate treatment (Meyer et al., 1991). Furthermore, epidemiological studies have found that older patients access psychotherapy less often than younger patients regardless of diagnosis (Beurs et al., 1999). Given these facts about the utilization of mental health services, this study aims to analyze the various pathways patients with panic disorder and agoraphobia have taken before ending up in a specialized anxiety outpatient treatment program. This analysis will pay particular attention to possible differences between younger and older patients.

Data from 30 patients with primary panic disorder and agoraphobia are currently being collected from the outpatient psychology clinic of the Dresden Psychotherapy Institute and from the Dresden Center of “Panik-Netz” (www.paniknetz.de). To date, nineteen patients have completed the study (mean age 34.3 ± 9.7 years; 32% older than 50 years; 19% men; average disease duration = 11.2 ± 12.03 years). Diagnoses were established using a standardized clinical interview (CIDI). Patients took part in a partially-standardized interview to assess the pathways of care (e.g., number, duration, and kind of diagnostic and treatment tools encountered during in- and outpatient treatment) as well as possible influencing factors (e.g., therapy related expectations, subjective etiological concepts, response to the first panic attack, interpretation of the physician’s diagnostic and prescriptive behaviors, etc.). Results will be used to generate a taxonomy of factors that facilitate and inhibit treatment utilization.

The present study will provide an age-specific view on pathways to care in patients with panic disorder and agoraphobia and seeks to identify malleable, age-specific variables that can improve the access and utilization of specialized treatment for those who need it - especially in older patients.
a paradigm where visual abrupt-onset stimuli distract the execution of voluntary goal-directed eye movements. If phobic content would be automatically processed such distractors should have an enhanced effect in spider phobic patients. We therefore investigated with a combined reaction time and eye-tracking experiment whether threatening visual cues capture attention and distract from the execution of goal-directed task performance. Twenty one spider phobic patients and 21 control participants were instructed to search for a neutral target while ignoring task-irrelevant abrupt-onset distractors which contained either a small picture of a spider (phobic), a flower (non-phobic, but similar to spiders in shape), a mushroom (non-phobic, and not similar to spiders in shape), or no picture. Reaction times on targets and eye-movements were registered continuously. The results showed that patients' reaction times were slowed on trials with spider distractors. However, eye movement data revealed that this was not due to attentional capture by spider distractors. Instead, patients were distracted by all distractors with pictures. Furthermore, task execution was delayed by longer fixation durations on spider distractors. This data does not support automatic capture of attention by phobic cues but suggests that phobic patients fail to disengage attention from spiders.

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Social anxiety and other predictors for social anxiety

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Although a high percentage of musicians is affected by musical performance anxiety (MPA), MPA is not well understood. The literature reports mixed results on the relationship between MPA and social anxiety. The present study investigated predictors of MPA to better describe overlapping and unique features in comparison with social anxiety. 142 instrumentalists (83 female) participated in the study, half of them music students, half of them professional musicians. In addition to questionnaire measures of MPA and social anxiety we assessed perfectionism, self-focused attention, and absorption as possible predictors. The rate of returned questionnaires was 91%. Social anxiety highly correlated with MPA, but in a regression analysis only the subscale performance anxiety, not fear of social interaction or avoidance behavior, remained significant. Moreover, social anxiety only partially predicted MPA; perfectionism and public self-focus significantly increased the explained variance. We conclude that social anxiety and MPA are strongly related but that they are also unique in some ways. To find a better treatment for MPA it seems to be possible to transfer knowledge and interventions of social anxiety, but they have to be adapted to the special features of MPA. In sum, our results show that MPA may be classified as a special subtype of MPA.

Panic disorder is a common anxiety disorder often accompanied by agoraphobia with a strong genetic component and a complex mode of inheritance. The Rgs4 and Rgs7 genes, both members of the Rgs (regulator of G-protein signaling) family, are promising candidate genes via their signal transmission modulation in brain regions involved in fear and anxiety reaction [1]. Since positive association with panic disorder is already reported for Rgs2 [2], another member of the Rgs family, we hypothesized that genetic variation of the Rgs4 and Rgs7 genes might also play a role in the pathophysiology of panic disorder or panic disorder with comorbid agoraphobia.

We conducted case-control studies in patients with panic disorder diagnosed according to DSM-III-R or DSM-IV criteria (Rgs4: 160, Rgs7: 224) and age and gender matched anonymous blood-donor controls, all of German descent. Six single nucleotide polymorphisms (SNPs) covering the Rgs4 gene and seven SNPs covering the Rgs7 gene were genotyped. Hardy-Weinberg equilibrium (HWE), linkage disequilibrium and association was analyzed on single marker and haplotype level for the whole case-control samples as well as all subgroups stratified for gender and/or comorbid agoraphobia. Genotype frequencies of Rgs4-SNPs 1, 2, 4, 5 and 6 conformed to HWE, but were not found to differ between cases and controls. However, two rare haplotype alleles of SNPs 1-2-4 (rs10917670-rs951439-rs10917671), all located in the 5‘-untranslated region, were significantly overrepresented in the whole panic sample and different subgroups of the disorder compared to the control sample. Genotype frequencies of all seven Rgs7-SNPs conformed to HWE. Of
these, the rare A-allele of the intronic Rgs7-SNP3 (rs11805657) and its corresponding haplotype alleles were found to be significantly underrepresented in patients compared to controls in the whole sample and particularly in the subgroups panic with comorbid agoraphobia, with the effect originating from the female subgroup. Our results suggest a potentially risk effect of the Rgs4 variants and a potentially protective effect of the Rgs7 variants with carriers possessing a distinctly higher (Rgs4) or lower (Rgs7) risk for developing panic or panic with comorbid agoraphobia. Variants in both Rgs genes may thus play a minor role in the pathogenesis of panic disorder. In addition to independent replication studies functional studies are now warranted to identify the underlying functional mechanisms.

References:

Relevance of adenosine A2A receptor gene polymorphisms on amphetamine-induced anxiety

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Several lines of evidence point to a role of the adenosine neuromodulatory system in the pathogenesis of anxiety. The 1976C/T polymorphism of the adenosine A2A receptor gene was shown to be associated with panic disorder [1] as well as with increased anxiety after caffeine, an antagonist at the adenosine receptors, in healthy volunteers [2]. Some individuals report anxiety after amphetamine, a drug which is employed for the treatment of narcolepsy and attention deficit hyperactivity disorder. Amphetamine is thought to produce its stimulant effects mainly via the dopamine system. As dopamine D2 and adenosine A2A receptors interact antagonistically with each other via heterodimer formation, we studied the relevance of adenosine A2A receptor gene polymorphisms for the interindividual variability in amphetamine response.

A group of 99 healthy young volunteers received placebo or d-amphetamine (10 mg or 20 mg, respectively) double-blind, in randomized order and under standardized conditions. Self-report questionnaires on subjective mood states using the Profile of Mood States (POMS) were obtained. The three validated exonic A2A polymorphisms 263C/T, 1976C/T (formerly 1083C/T) and 2592T/- were genotyped by means of PCR-based RFLP- or SSCP-analysis.

All polymorphisms were in Hardy-Weinberg equilibrium and the 1976C/T and 2592T/- polymorphisms were in nearly complete linkage disequilibrium. The 263C/T polymorphism was associated to increases in vigor (at 10 mg), the 1976C/T and 2592T/- polymorphisms to increases in arousal (at 10mg) and anxiety (at 10mg and 20mg). In contrast, no significant association could be detected for the other moods. No difference in the demographic measures age, gender, race/ethnicity, BMI, education and current drug use was observed between the genotypic groups. These findings are in line with the above mentioned observations, indicating a role for A2A receptor gene polymorphisms also in amphetamine-induced anxiety [3]. In a next step, gene-environment-interactions will be investigated in a large sample of volunteers differentiated by their caffeine consumption. Future studies into the functional relevance of the associated polymorphisms will utilize positron emission tomography of cerebral adenosine receptors in the human brain [4].

References:

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Influence of adenosine A2A receptor gene variation on sympathetic indicators of anxiety-related arousal in blood-injury phobia

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Anxiety disorders have a lifetime prevalence of up to 25% and heritabilities ranging from about 30% to 67% with the exact etiology still remaining to be unraveled. Genetic variation in the catecholaminergic genes adenosine A2A receptor (A2A) and catechol-O-methyltransferase (COMT) and norepinephrine transporter (NET) has been suggested to influence vulnerability to a common anxiety disorder with
and body sway in persons with and without fear of heights. To test whether acrophobic persons indeed rely more on visual information, we investigated anxiety, dizziness, and body sway during visual stimulation consisting of misleading balance information.

Methodology: 20 persons with high fear of heights and 20 healthy controls stood on a force platform to measure body sway while being exposed binocularly to visual flow stimuli through a head mounted display. Self-report anxiety and dizziness was measured after each of nine visual conditions. The measurement took place on ground level.

Results: Acrophobic persons were more anxious and dizzy during exposure. They also showed a greater amount of body sway when receiving conflicting balance information.

Discussion: The patterns of body sway and subjective reports of dizziness can not be attributed solely to increased anxiety. Consequently, an underlying balance dysfunction in persons with fear of heights is likely.

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5-HTTLPR and anxiety- and depression-related personality traits

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The initial association study revealed that the human transporter polymorphism (5-HTTLPR) is associated with anxiety- and depression-related personality traits and accounts for 3 to 4 percent of total variation and 7 to 9 percent of inherited variance in these personality traits in individuals as well as sibships (Lesch, 1996).

Various factors might influence the inconsistency of the following association studies and meta-analyses. The methodology of these association studies exhibits differences in terms of sample size, sample consistence and assessment instruments.

A subsequent study supports the notion that there is no general association between 5-HTTLPR and anxiety- and depression-related traits and that differential gene effects and/or gene-by-environment (GxE) interactions are likely operative in distinct clinical subpopulations (Jacob, 2005). Interactions of stressful experiences and genetic variation of 5-HTTLPR that were demonstrated by Caspi et al. in depression are not accounted in anxiety- and depression-related personality traits (Caspi, 2003).

There is evidence for 5-HTTLPR gene x serotonin receptor 1A (HTR1A) gene interactions in anxiety- and depression-related personality traits. A significant effect of the HTR1A-1019 polymorphism on Neuroticism was shown in healthy controls (Strobel, 2003) and individuals affected with personality disorders (Jacob, unpublished data). The combined effect of 5-HTTLPR and HTR1A receptor genes could be
related to the clinical outcome of depressive patients treated with a selective serotonin re-uptake inhibitor (Arias, 2005). The etiology of anxiety and depression-related personality traits is influenced by complex interactions of 5-HTTLPR gene x HTR1A gene x environmental factors.

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Emotional processing and the fear circuit in the course of CBT intervention: a multicenter 3 Tesla fMRI study in panic disorder within the German “Panic Network”

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Using fMRI we want to evaluate putative neurobiological foundations of the psychotherapeutic process in panic disorder during two types of therapy (Cbt vs cBT). 60 patients with panic disorder and 60 matched healthy control subjects will be investigated twice using fMRI pre and post CBT treatment at 4 centers (interval of 8 weeks). The patients will be recruited through the BMBF funded multisite project. The following paradigms will be carried out: 1) Conditioning and habituation. The differential responses to conditioning and extinction of not-panic related stimuli will be investigated. Neutral visual stimuli will be associated with white noise as unconditional stimulus (UCS) in an aversive differential classical conditioning paradigm (Buchel et al. 1998). We expect a faster conditioning and slower extinction in patients with panic disorder. Patients will exhibit a hyper reaction during acquisition especially in the amygdale, causing hyperactivation also in the associated networks as well as a slower habituation and/or a prolonged response in the amygdale during extinction compared to healthy controls. We further expect no differences in activation in the amygdale and other areas of a subcortical fear network, i.e. the orbitofrontal cortex and the thalamus in the Cbt vs. control group after therapy. 2) Exteroception of fear related stimuli. This paradigm will focus on the conscious perception of neutral pictures taken from the IAPS picture system (Lang et al. 1999) and panic-relevant pictures which have been rated previously by patients and healthy controls using the Self-Assessment Manikin (SAM; Lang et al 1980). Pictures will be presented each for 2 sec, followed by an interval of 3.5 sec with a fixation cross and will be preceded by a 250ms lasting neutral or panic-relevant cue. We expect strongest signal changes in the amygdale in the PD patients for the panic-relevant vs. anxiety-relevant pictures before vs. after therapy. We further expect stronger changes in the cBT vs. the Cbt group. 3) Enteroception of fear related stimuli. Here we will focus on the competition of cues hypothesis by Pennebaker et al. (1981) which proposes that interoceptive cues which tend to be misinterpreted by patients with panic disorder, compete with exteroceptive cues. The task will be to attend either to tones played over headphones or to the own heartbeat and count the beats or tones. We expect strongest signal changes in the amygdale in the PD patients interoceptive task versus the enteroceptive task before vs. after therapy. We further expect stronger changes in the cBT vs. the Cbt group. Quality control of scanner and stimulation hardware will be performed according to the routines developed in the previous multicenter fMRI study (Stöcker et al 2005). This study will offer unique new insights into the neurobiology of panic disorder and effects of cognitive behavioral therapy.

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Computer-assisted cognitive training as a trauma-unspecific intervention for posttraumatic stress disorder

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Posttraumatic stress disorder (PTSD) often produces impairments of cognitive functions such as concentration and memory. In a pilot study, computer-assisted cognitive training designed to improve cognitive functioning was evaluated in 15 patients having a diagnosis of PTSD following DSM-IV criteria. Using the computer-based training program COGPACK (Marker Software) 10 sessions were arranged focusing on exercises regarding concentration and memory with gradually increasing difficulty over time. For the evaluation of possible effects of the computer-assisted cognitive training three computer tests measuring concentration (Cognitrone), memorization of graphic material (Non-Verbal Learning Test) and achievement motivation (Objective Achievement Motivation Test) were administered before and after the training. Additionally, the patients subjectively rated their concentration and memory performance on a scale ranging from zero to 100. Symptomatology was evaluated by the Symptom-Checklist-90-Revised. After the computer-assisted cognitive training with a median duration of 9.5 weeks the cognitive performance especially indicated improvements in non-verbal memory and achievement motivation. The patients’ subjective ratings of their cognitive capacity and symptomatology were significantly better at study completion. Secondary effects
observed and reported during or after the training were an increasing self-esteem, more initiative facing tasks of everyday life, less distraction by worries, more patience, and having fun doing the exercises on the computer. The evaluation of the computer-assisted cognitive training provides first indications of the applicability and the effectiveness of a trauma-unspecific intervention for patients with PTSD.

A pilot study of a combined dexamethasone/corticotropin-releasing hormone test in patients with PTSD

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Hypothalamic-pituitary-adrenocortical axis data in patients with chronic posttraumatic stress disorder (PTSD) are inconsistent and difficult to interpret. A combined dexamethasone/CRH test might help to decrease variance of findings. 14 subjects with chronic PTSD and 14 healthy controls were examined between 13:00 and 17:00 using a modified combined dexamethasone/CRH test (0.5 mg dexamethasone at 23:00, 100 µg CRH at 15:00). Plasma adrenocorticotropic hormone (ACTH), cortisol and blood pressure were measured every 15 minutes from 14:45 until 17:00. We found no significant differences between patients and controls in the analyses of ACTH and cortisol levels, but a significantly elevated systolic and diastolic blood pressure in PTSD. Severity of depressive symptoms had no influence. Explorative analyses showed that patients with a history of childhood traumatization had significantly higher post dexamethasone-ACTH levels and a significantly lower diastolic blood pressure in comparison to patients without early trauma. Maybe, childhood traumatization could influence HPA axis findings in PTSD. Further research is needed, especially dose-response studies with different doses of dexamethasone in dexamethasone/CRH tests in larger groups of patients with chronic PTSD.

The effect of acute immobilization stress on the expression of synaptic proteins in serotonin transporter deficient mice

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Anxiety disorders and depression are stress-related disorders and they are associated with disturbances of the serotonergic system, in which the serotonin transporter (5-HTT) plays an important role. As 5-Htt knockout (KO) mice represent an artificially hyperserotonergic environment, exhibit an anxious phenotype and exaggerated adrenomedullary responses to stress, they seem to be a practical model to investigate the role of the serotonergic system in the context of stress reactions and anxiety disorders. Since synaptic proteins modulate the release of neurotransmitters into the synaptic cleft and seem to be involved in stress reactions we studied the effects of acute immobilization stress on synaptic protein expression in the 5-HTT KO mouse model.

We focused our interest on the synaptic proteins Synaptotagmin (Syt) I & IV and Syntaxin (Stx) 1a. By the use of quantitative real time-PCR we previously showed differences in the expression of these synaptic proteins in different brain regions between 5-Htt KO and wildtype (WT) control mice. In the present study, we found out that exposure to acute stress primarily alters gene expression of Stx1a in hypothalamus and raphe of 5-Htt KO mice. Interestingly, Stx1a is discussed to interact with the 5-HTT and to modulate the cell-surface expression of this transporter. By measurement of plasma corticosterone levels we revealed significantly increased levels in all 5-Htt genotypes after immobilization. Furthermore, we detected significant genotype-dependent lower corticosterone levels in 5-Htt KO compared to 5-Htt heterozygous (HET) and 5-Htt WT mice in stressed males, whereas we could not find genotype-dependent differences in females and basal plasma corticosterone levels did not differ in female as well as male mice with different 5-Htt genotypes.

In conclusion, beneath exaggerated adrenomedullary responses in mice with targeted disruption of the 5-Htt gene (described by Tjurmina et al., 2002) the reduced corticosterone response to immobilization can also be discussed as an autonomic correlate of the anxiety-like behaviors in these mice. Moreover, Stx1a especially in its function to modulate 5-HT re-uptake could play an important role in stress reactions.
Westphal’s description of agoraphobia

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The term agoraphobia was introduced in 1871 by Karl Friedrich Otto Westphal (1833-1890) in “Agoraphobie - eine neuropathologische Erscheinung”. Westphal was by this time Chair of the Department of Psychiatry and Neurology at the Charité in Berlin, following Griesinger, who pioneered the integration of psychiatry and neurology into modern medicine and was a strong arguer of a biological understanding of mental diseases.

In his paper Westphal gives a detailed description of the symptomatology of three men with panic and phobia to very similar stimuli, i.e. to open places and streets, theaters, public transport. In the beginning of his report Westphal points out the limitation of the term, since it is not just a monophobia. However, the similarity of the strong fear at open places he had seen in these three patients was so striking that he named it after the Greek word for marketplace.

Interestingly also strategies to compensate, e.g. to cross the place near a wagon or things that could relieve anxiety, for example alcoholic drinks were very similar in the three men described. All these men were not considered to suffer from hypochondria, they shared to be at a loss to what was happening with them.

The characteristic summary that Westphal gave is almost identical to the diagnostic criteria for agoraphobia in today’s diagnostic classification systems DSM and ICD and is still worthwhile reading not only for historical reasons.

Westphal made also numerous other contributions to medicine, e.g. he described the association of Tabes dorsalis and paralysis. He also described hepatolenticular degeneration, the so called Westphal-Strümpell syndrome, a late form of today’s known Morbus Wilson. Together with the neurologist Ludwig Edinger (1855-1918), he is also credited for characterization of an accessory nucleus of the oculomotoric nerve, the Edinger-Westphal nucleus.

Together with the neurologist Wilhelm Heinrich Erb (1840-1921), he was the first to describe the deep tendon reflex as well as a tandon reflex anomaly in Tabes dorsalis, which later became known as the Erb-Westphal symptom.

An internet-based intervention to reduce cardiac fear in patients with implantable cardioverter defibrillator

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Implantable cardioverter defibrillators (ICD) are used for primary and secondary prevention of sudden cardiac death. After surgery, the few specialized treatment centers available in Germany typically restrict their follow-up care to ambulatory checkups with a focus on medical issues. For most patients it is complicated to get social, psychological, or peer-group support in their local area.

The internet offers unique ways for resolving these issues. In a pilot study we developed www.icd-forum.de, a 6-week on-line course specifically designed to reduce cardiac fear. The system granted anonymous access independent of time and place. Standardized information was communicated via a classic homepage. Specific topics were added weekly. These topics were linked to a complimentary discussion board. In addition, a weekly topical chat was scheduled. Both were moderated by a qualified psychologist. The study design included a pre-test followed by a 6-weeks waiting control condition, another pre-test at the beginning of the study, a post test, and a 4-week follow-up. In addition to questionnaire data gathered at these times (attitude towards internet and ICD, cardiac fear [HAF], anxiety and depression [HADS]), user behavior was accessible via the server-logs, and contributions to discussions and chats were used for text analysis in line with Pennebaker (2001).

The patients experienced the intervention as useful and positive. Avoidance of heart-beat increasing behavior (HAF-V) and anxiety (HADSA) declined during the course of the program. Frequency of contribution in discussions and chats was related to self-disclosure, emotional writing, successful contact to other patients, and positive utilization of the program.

Low availability of the internet in the typical age range of ICD-patients reduces generalizability of these results. Nonetheless the project shows that the internet can successfully fill a supply gap in the medical system.
Increased anxiety in mice lacking the cation transporter OCT3

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The organic cation transporter 3 (OCT3; synonymous: extraneuronal monoamine transporter) encodes an isoform of the organic cation transporters and is expressed widely across the whole brain. Inter alia, it accomplishes reuptake of dopamine and serotonin from the synaptic cleft which makes it an attractive candidate gene for anxiety disorders. Interestingly, OCT3 mRNA is significantly upregulated in the hippocampus of 5HTT knockout mice which alone renders examination of the behavioral phenotype of OCT3 knockouts highly interesting. While cognitive functioning, activity and aggression levels of the animals were compara-
tive to controls, OCT3 knockout animals were significantly more anxious in the elevated plus-maze test and the open field test than their respective wildtype controls. Thus, these mice appear to be a good model for anxiety or affective disorders, which is currently further investigated.