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Long-term effects of Cognitive Behavior Therapy on pathological worrying in Generalized Anxiety Disorders

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Background: Generalized Anxiety Disorders (GAD) are defined by “excessive” worrying, which means a tendency to worry frequently with difficulties to control the worries. Few studies report effects of Cognitive Behavior therapy (CBT) on pathological worrying in GAD. The worry-measures used in these studies do not differentiate between frequency, controllability, or other formal aspects of pathological worrying. Following the tradition in psychopathology to differentiate between formal thought disorders and disorders of content, the Formal Aspects of Worry-Rating-Scale (FAS-Rating) was developed.

Method: Results of the FAS-Rating, which was given to a subsample (n=25) of patients in the Berlin CBT-GAD trial (Linden et al. 2002, Verhaltenstherapie 12, 173-182) will be presented. This questionnaire measures formal aspects of everyday-worry (frequency, intensity, controllability, worry-chains, perception as reasonable, internal and external attributions) in five standardized situations.

Results: CBT had significant effects on worry-frequency, -strength, -controllability, worry-chains, and internal attribution of everyday-worrying as compared to a contact control group. The results remained stable at 8 months follow up. Multivariate analyses showed that the most significant pre-post-differences could be found in worry-controllability.

Conclusions: CBT is effective in reducing pathological worrying in GAD. The results are stable for a period of 8 months. Worry controllability is of special importance for the treatment of GAD.

The Depression Anxiety Differentiation Test (DANDTE) - Results with a new patient screening instrument for recognizing and measurement clinically relevant depressive and/or anxious symptoms

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Introduction: Most patients with depressive and anxiety disorders were not recognized in the primary care health system. Screening instruments can be helpful for early identifying relevant clinical symptoms. Traditional scales like BAI or SCL - 90 - R are not helpful for diagnosing these patients according the ICD - 10 or DSM - 4 System. The Bandelow Panic and Agoraphobia Scale provides good psychometric properties, but need patients with a specific diagnosis. The DANDTE is a new patient questionnaire with 18 psychopathological items (7 depressive and 9 anxious symptoms) according the German AMDP - System, the ICD - 10 and the DSM - 4 diagnostic criteria. The DANDTE allows a different measurement of relevant symptoms and their extent. This instrument can be used as a screening instrument as well as for controlling the therapy success.

In the first study we examined inpatients of our psychiatric hospital for the psychometric properties of the DANDTE and the acceptance. In a second study we examined the DANDTE in a setting of a medication study for patients...
with a diagnosis of a GAD or anxious symptoms in the general practice care.

**Methods:** In the first study all inpatients at one unit of our clinic, independent of their diagnoses, get the DANDTE within the first three days after hospitalization. The patients judge the DANDTE for several aspects as economy, distinctness and stimulation of the questionnaire. The judgement of these patients were performed by clinical experienced psychiatrists and include the diagnosis, HAMA, HAMD, the new BOEAS - scale for anxiety symptoms and the CGI. In the second study the DANDTE were performed in a setting of a medication study by general practitioners and was compared with HAMA and BOEAS.

**Results:** In the first study we assessed 78 inpatients; 48.7% with a F 30 diagnosis, 14.1% with a F40 diagnosis. The middle range of the CGI was 6.3. These very ill psychiatric inpatients judge the psychological properties between 1.7 and 2.3 (school notes), so we find a high acceptance for this new instrument in this setting. The retet -reliability for the two parts was between 0.5 and 0.67 (1% significance). The validity score with the new BOEAS scale was 0.5, with the HAMA 0.68 and with the HAMD 0.627 (1% Significance). In a discriminance - analysis 59% of the patients with anxiety disorders and 76% with depressive disorders could be correctly diagnosed. In the second study with 270 outpatients the high validity and reliability of the DANDTE could be confirmed, the DANDTE was established as a good follow - up parameter.

**Summary:** The DANDTE is a new instrument for recognizing and measurement of anxiety and depressive symptoms according with a ICD – 10 or DSM 4 diagnosis, provides good psychometric properties, a high acceptance by patients, was well -tried in the primary care health system and can be used as a follow - up measurement.

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**German J Psychiatry 2002; 5: S2**

**Six-Month-Follow-Up of Patients with Panic Disorder following Treatment with aerobic exercise, clomipramine or placebo**

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**Objective:** Aerobic exercise has been reported to be effective in the treatment of panic disorder. In comparison to a placebo condition, both aerobic exercise and clomipramine lead to significant improvements within ten weeks. However, no follow-up studies have been performed for these treatment conditions.

**Method:** In order to document the stability of treatment effects, a naturalistic follow-up examination was performed six month after the end of the study treatment. At the end of the original study, patients had been informed about other available treatment options.

**Results:** 80% of the patients in the exercise and in the clomipramine group continued the original treatment, but the majority of patients decided to try additional treatment options. The improvement of anxiety and depressive symptoms remained stable during the follow up period. In the original placebo group, the majority of the patients (73%) decided to start a behavioral therapy, antidepressant medication (45%) and aerobic exercise (19%) were less popular. During the six month follow-up period, patients from the original placebo group reached the same degree of improvement as the patients from the other two treatment groups.

**Conclusion:** Stable and comparable improvements were observed after treatment with different approaches (antidepressants, exercise, behavioral therapy). The value of naturalistic follow-up studies will be discussed.

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**German J Psychiatry 2002; 5: S2**

**Genetic findings in panic disorder: Linkage disequilibrium or clinically relevant polymorphisms?**

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Over the last 5 years several association findings have been reported in panic disorder. They include associations with genes of the adenosine A2A receptor, the monoamine oxidase A, cholezystokinin and cholezystokinin receptor B, the catechol-O-methyltransferase and the transcription factor CREM. Replications though have been inconsistent. One possible explanation for this may be that the associated polymorphism is not the clinically relevant polymorphism, but in population-specific linkage disequilibrium with a second, clinically relevant polymorphism.

There are several strategies to differentiate between association with a clinically relevant and clinically irrelevant polymorphism. One is to define a functional relevance for the polymorphism either in vitro in a cell culture system via a reporter assay or in vivo in an animal model. A second approach is to type several polymorphisms in a given gene and to perform a haplotype analysis. A third finally is to type the polymorphism in independent samples. These three approaches have to be considered complementary. Examples for all three will be presented, e.g. the monoamine oxidase gene as an example for a functional characterization (1), the catechol-O-methyltransferase gene as an example for a haplotype analysis (2) and finally the cholezystokinin receptor B gene as an example for investigation of independent samples (3).
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MAO-A and COMT gene polymorphisms: Evidence for increased catecholamine metabolism as a risk factor for panic disorder

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Several lines of evidence suggest that genes coding for the catechol-O-methyltransferase (COMT) and the monoamine oxidase A (MAO-A) are relevant for the pathogenesis of panic disorder. In patients with anxiety states, significantly elevated levels of erythrocyte COMT activity and platelet MAO-A were observed (1, 2). Additionally, MAO-A inhibitors are effectively used in the pharmacological treatment of panic disorder (3).

In the present study, we genotyped in parallel a functional 30 bp repeat polymorphism (30 bp VNTR) in the MAO-A promoter and a single nucleotide polymorphism (472G/A-Val158Met) in the coding region of COMT in a sample of 90 patients with panic disorder (DSM-III-R) and 90 age- and sex-matched controls. Allele frequencies were determined by means of PCR-based gel electrophoresis for the 30 bp VNTR and a restriction fragment length polymorphism (RFLP) assay for Val158Met. In accordance with our previous findings (4), we observed the more active longer alleles of the VNTR to be highly significantly associated with panic disorder in the female subgroup of patients (p<0.005). The more active valine allele of the Val158Met polymorphism was weakly associated with the disorder in female panic patients.

Our data support a role of the MAO-A 30bp VNTR and the V158M COMT polymorphism in the pathogenesis of panic disorder in women. They are consistent with the notion that increased catecholamine metabolism constitutes a risk factor for the development of panic disorder in women, but not in men. Analysis of possible synergistic or epistatic effects of these two polymorphisms is in process.


Effects of alcohol on social phobia patients’ responses to social-anxiety related stimuli

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Background: Epidemiological studies show that social phobics are at a higher risk to abuse alcohol or develop an alcohol dependency. It has been suggested that socially anxious people use alcohol to better cope with social situations. According to Sayette (1993) alcohol disrupts appraisal of danger stimuli and consequently leads to less anxiety if alcohol was drunk before entering an anxiety-eliciting situation. We employed the emotional-stroop-test to investigate whether social phobic patients indeed showed such appraisal disruption after ingestion of alcohol.

Procedure: 32 social phobic women (DSM-IV) and 32 female controls participated in our study. Half of each group completed an emotional stroop test after drinking alcohol resulting in 0.7% BAC, the other half of each group completed the test after drinking a non-alcoholic beverage. The emotional stroop test contained social anxiety related primes. According to Sayette (1993) alcohol disrupts appraisal of danger stimuli and consequently leads to less anxiety if alcohol was drunk before entering an anxiety-eliciting situation. We employed the emotional-stroop-test to investigate whether social phobic patients indeed showed such appraisal disruption after ingestion of alcohol.

Results: Both controls and social phobic participants showed increased reaction times to socially relevant compared to neutral stimuli if not exposed to alcohol. Contrary to our expectations only controls showed leveling of reactions to social-anxiety related stimuli compared to neutral stimuli after drinking alcohol. Alcohol had no such effect on our socially phobic participants, they reacted slower to alcohol.
social anxiety related stimuli regardless of blood-alcohol levels.

Discussion: The results of our study suggest that alcohol does not disrupt appraisal of social-anxiety related stimuli in social phobics. Other mechanisms explaining the higher risk of alcohol abuse in social phobia need to be explored.

Reference

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Self- and observer-ratings of anxiety, fear, phobia, and obsession-compulsion

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Objective: Seven scales designed to assess anxiety, fear, phobia, and obsession-compulsion (Brief Symptom Inventory, Hamburger Zwangsinvventar - Kurzform, Hamilton Anxiety Scale, Liebowitz Social Anxiety Scale, Pani- und Agoraphobie-Skala, State-Trait-Anxiety Inventory, and Yale-Brown Obsessive Compulsive Scale) published in the most recent edition of Collegium Internationale Psychiatriae Scalarum (2003) were evaluated regarding their feasibility as reliable measures of the underlying constructs.

Method: The scales were evaluated with regard to their respective potential to assess the stability aspect of the phenomenon (trait-state differentiation), the component structure of the phenomenon (worry, emotionality, bodily symptoms, fear, fright) and their sensitivity toward artifacts (aquisience, social desirability, tendency toward the mean for self-ratings and degree of standardization of the interview procedure, degree of experience of the interviewer, and suggestive influence by the interviewer for observer-ratings). In addition, the scales are evaluated with regard to the logical consistency of items and response categories and the implementation of the concept of item-intensity specificity.

Results: The analysis reveals that most of the seven scales show deficits with regard to the variables under scrutiny that limit their applicability as diagnostical and research tools.

Conclusions: Specific suggestions to remedy the situation are proposed, such as the limitation to certain areas of measurement and with regard to the interpretation of the scores.

CCK induces panic attacks in patients with panic disorder. Reports on associations of CCK neurotransmitter system gene polymorphisms with panic disorder have been inconsistent. In the present study, we therefore analyzed genetic variation of CCK and the CCK B receptor gene polymorphisms in panic disorder.

We determined allele and genotype frequencies first in a German DSM-IIIR sample (n=87) and subsequently in a second German DSM-IV sample (n=84) in comparison with gender- and age-matched control samples using RFLP (BSL I and Hin6 I) and fragment analysis of two SNP and one VNTR polymorphisms of the CCK gene and one VNTR polymorphism of the choleystokinin-B receptor gene. Association analysis in the German DSM-IIIR sample showed a highly significant excess of the VNTR CCKR-B allele in panic disorder (p=0.0007). While in the clinical DSM-IV sample this excess was not observed at all (p>0.99), in the combined sample still a significant association (p=0.008) was seen.

Our results are in contrast with those reported by Hattori et al. (1) and Wang et al. (2), but partly consistent with those reported by Kennedy et al. (3). They add to the inconsistent association findings in the CCK and CCKR-B genes by individual groups. One possible explanation obviously is population-specific linkage disequilibrium with another, clinically relevant polymorphism, another population-specific effects of individual polymorphisms. Further studies at the genetic and functional level are necessary to probe the latter possibility.

Modulation of neuropeptidergic neuronal circuits (AVP, CRH) as a novel therapeutic strategy in anxiety disorders

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To date, it is still unclear by which pharmacological mode of action currently available antidepressants exert their clinical effects in depression and anxiety disorders. In recent years neuropeptidergic circuits known to be dysregulated in major depression and anxiety disorders like corticotropin-releasing hormone (CRH) and vasopressin (AVP) neuronal systems have attracted attention as potential therapeutic targets. Accordingly, hyperactivity of central neuropeptidergic circuits such as CRH and AVP neuronal systems is thought to play a causal role in the etiology and symptomatology of affective disorders. In support of this, after prolonged stress and in human depression, AVP and CRH are increasingly expressed and released from hypothalamic neurons in both humans and rodents. To obtain predictions about the clinical condition in human psychiatric disorders, appropriate animal models that reflect both significant psychopathological and neuroendocrine features of human depression with face, predictive and construct validity should be used. The present series of experiments was conducted to investigate the neuroendocrine and behavioral impact of both the high-affinity non-peptide CRH1 receptor antagonist R121919 and the well-established antidepressant paroxetine. Experiments were conducted in inbred mice strains and in two Wistar rat lines selectively bred for either high (HAB) or low (LAB) anxiety-related behavior. Interestingly, the high emotionality of HAB rats is accompanied by an aberrant outcome of the DEX/CRH test. This phenomenon could be shown to be related to a hypothalamic AVP hyperdrive thus confirming an early clinical postulate. Therefore, HAB rats, reflecting cardinal signs and symptoms prevalent in human anxiety disorders and depression, provide a tool to identify neuroendocrine and behavioral alterations associated with clinically efficacious antidepressant drug treatment.

In vivo stress-induced ACTH release was significantly inhibited by R121919 in both HAB and LAB rats, whereas robust anxiolytic effects could be obtained in HAB rats only which was reflected by CRH1 receptor blockade. Chronic paroxetine treatment induced a more active coping strategy in the forced swim test in HAB rats but not in LAB rats. In HAB rats, these paroxetine-induced behavioral changes towards more active stress coping were accompanied by a normalization of the CRH-stimulated increase in corticotropin (ACTH) and corticosterone secretion in the DEX/CRH test. Concomitantly, the hypothalamic vasopressinergic hyperdrive was found to be reduced in HAB but not LAB rats, as indicated by a decrease in vasopressin mRNA expression, whereas vasopressin 1a receptor binding was unaffected.

These findings provide first direct evidence that modulation of the vasopressinergic and CRH systems is likely to be critically involved in the behavioral and neuroendocrine effects of antidepressant drugs. Moreover, the novel mechanism of action of paroxetine on vasopressin gene regulation render vasopressinergic neuronal circuits a promising target for the development of more causal antidepressant treatment strategies.

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tive MR changes in the patient group. Further investigation of MR function in PTSD may be indicated, since MR modulates pertinent cognitive and behavioral effects.

This study was supported by Deutsche Forschungsgemeinschaft (grant Ke 595/5-1).

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Is there a difference in overt behaviors of panic patients depending on catastrophic cognitions? A study on the development of agoraphobic vs. hypochondriacal behavior

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Background: Earlier studies have shown that panic disorder and hypochondriasis show an overlap concerning symptoms and anxiety reducing behaviours. It was the aim of this study to find out in how far specific catastrophic misinterpretations correlate with agoraphobic or hypochondriacal behavioral styles.

Methods: 42 patients with a diagnosis of panic disorder participated in the study. They were administered structured and semistructured interviews, diaries and self report questionnaires on hypochondriacal and agoraphobic behaviours.

Results: Patients with the catastrophic misinterpretation „I will die” somatized more, were more hypochondriacal, and used safety signals more often than patients without this specific cognition.

Conclusions: The results of this study suggest that a subgroup of panic patients also show hypochondriacal besides their agoraphobic behaviors in correlation with specific catastrophic misinterpretations of bodily symptoms. It is suggested that these data may, to a certain extent, explain the overlap between panic disorder and hypochondriasis which was found in earlier studies. Finally consequences of our results concerning therapeutical strategies will be discussed.

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Postpartum anxiety disorder: specific avoidance as expressed by premature termination of family planning

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Any psychiatric disorder is common during the postpartum period. Although this is a well-known fact, puerperal psychiatric illnesses are often overlooked or treated insufficiently.

While the syndromes described are predominantly affective, studies also showed a prevalence of new onset panic disorder in the puerperium of up to 17% (1). For therapeutic interventions it is important to establish the precise symptoms relating to panic disorder. Panic attacks and agoraphobic symptoms are much more obvious than avoidance. The latter, however, is responsible for chronification. In the case of postpartum panic disorder women may decide not to have another baby or interrupt a new pregnancy, because they are frightened that in the puerperium panic disorder may reoccur.

In our opinion this is a form of avoidance specific for postpartum panic disorder. We describe two cases and discuss therapeutic interventions.


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The combination of psycho- and pharmacotherapy in panic disorder and agoraphobia: Potentiation or inhibition of the effects?

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Objective: Both (cognitive) behaviour therapy (BT) and pharmacotherapy are considered to be effective treatments for panic disorder and agoraphobia. The combination of these approaches may lead to both advantages and disadvantages in theory. Method: After a comprehensive literature search the results of 18 studies comparing combination therapy with (cognitive) BT were integrated in a meta-analysis. Mostly antidepressants were investigated. The computation of the effect sizes was done with Hedges g between groups (Cooper & Hedges, 1994) across means with standard deviations, frequencies, gain scores and significance levels. We present the results of both random and fixed effects model. The random effects model is to prefer in the context of therapy research because of the generalizability of the effects, but results are possibly only an approximate estimate by including a small number of studies.

Results: For quality of life there was no significant difference between the approaches neither for post or follow up (mostly six months). For anxiety in all and for depression a significant better outcome of the combination treatment at post could be demonstrated. Investigating the clinical significance (responder and endstate functioning) there was the highest significant positive effect size for the combination treatment in both statistical models. However the differences didn’t remain stable at follow up. The extent of drop-outs was not significantly different between the treatments, so a hypothetical increased compliance for exposure by medication could not be established. The influence of
other variables was investigated. **Conclusions:** Although there are advantages of the cost intensive combination treatment at post the previous results don’t support an increased efficacy in long-term. Moreover possible disadvantages of the integrative approach could not be investigated because of design and result presentation of the included studies. These aspects will be discussed.

**References:**

Hypophosphataemia correlates with clinical course in a patient with panic disorder: a case report

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Hypophosphataemia has been described in experimentally induced panic attacks (1). It correlates with the severity of the symptomatology (2). One clinical case has been reported in which extensive diagnostic procedures failed to provide evidence for a parathyroid disorder in a patient with panic disorder and a catamnestic exploration demonstrated a remission of the anxiety symptoms as well as a normalization of serum phosphate (3).

In our patient panic symptoms occurred in April 2002 following a symptom-free interval after previous episodes. Under a combined treatment with mirtazapine (60mg) and citalopram (20mg) remission developed until Mid-July with a short relapse after returning to the workplace at the end of July. Since August 2002 the patient is free of panic attacks.

On routine laboratory testing a hypophosphataemia with values as low as 1.3mg/dl (2.5 - 4.5 mg/dl) was observed in May and June 2002. Parathormone was measured normal with 31.6 pg/ml (12-72 pg/ml). Phosphate normalized in early July 2002, only to fall below the lower limit at the end of July. At the last control in September 2002 phosphate again had returned to normal. Phosphate levels during these four months thus ran in parallel with the severity of the panic symptoms. This obviously is not a common observation in panic disorder and not reported as a symptom in clinical textbooks. The possible explanation for its occurrence in our patient is that the panic attacks were extremely severe with a panic state over hours per day in May and June. This state was characterized by continuous hick-ups and paraesthesia indicative of hyperventilation. The hypophosphataemia may best be explained as a secondary metabolic acidosis to compensate for a primary respiratory alkalosis.

Our case supports the notion that hypophosphataemia can be observed as a symptom not only directly after experimental attacks, but also in the clinical course of severe clinical panic disorder. It appears to mirror the clinical course of the disorder.


Anxiety and alexithymia in the long-term course of obsessive-compulsive disorder treated with cognitive behaviour therapy

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**Introduction:** Cognitive Behaviour therapy (CBT) has been shown to be effective in the treatment of obsessive-compulsive disorder (OCD). However, not all patients do benefit from this treatment. In order to develop more effective interventions it is essential to examine potential predictors of treatment outcome.

**Method:** Of an initial group of 55 patients suffering from chronic and severe obsessive-compulsive disorder, 44 (80%) were included in a follow-up (FU) study 3-8 years after inpatient treatment. The following measurements were employed: Y-BOCS; HAMD; FSS-P; FSS-S; TAS-20.

**Results:** Highly significant improvement at the end of treatment was maintained at follow-up. Patients with higher pre-treatment blood/injury phobia scores showed less improvement at post-treatment and FU. At pre-treatment, scores for alexithymia were higher compared to normals, but this did not predict treatment-nonresponse.

**Conclusion:** Most patients received further pharmacological or psychotherapeutic treatment during FU. In almost half the patients, alexithymia appeared to be a state rather than a trait variable. The high incidence of positive blood/injury phobia ratings may have been a result of a misinterpretation of these items in the FSS by “contamination-phobic” washers and cleaners in the OCD sample.
“Anxietas Tibiarum” - Depression and Anxiety Disorders in Patients with Restless Legs Syndrome

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Various studies have observed increased levels of anxiety and depression among patients with restless legs syndrome (RLS). However, it remains unclear whether rates of threshold mood and anxiety disorders according to DSM-IV in such patients are elevated as well. 130 RLS patients were assessed with a standardized diagnostic interview (Munich-Composite International Diagnostic Interview for DSM-IV). Rates of anxiety and depressive disorders were compared between RLS patients and community respondents from a nationally representative sample with somatic morbidity of other type. RLS patients revealed an increased risk of having 12-month anxiety and depressive disorders with particularly strong associations for panic disorder (OR=4.7; 95% CI=2.1-10.1), generalized anxiety disorder (OR=3.5; 95% CI=1.7-7.1), and major depression (OR=2.6; 95% CI=1.5-4.4). Further, lifetime rates of most anxiety and depressive disorders as well as comorbid depression and anxiety disorders were considerably increased among RLS patients as well. The results suggest that RLS patients are at increased risk for having specific anxiety and depressive disorders. Causal attributions of patients suggest that a considerable proportion of the excess morbidity might be due to RLS symptomatology.

Reduced temporal lobe volume in patients with panic disorder – a quantitative morphometric study

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Introduction: Previous studies demonstrated functional and morphometric changes of the temporal lobe in patients with panic disorder. Up to now only one quantitative volumetric study was performed demonstrating a reduction of temporal lobe volume in this patient group [Vythilingam et al. 2000].

Methods: In a group of 16 in-patients with panic disorder and a control group matched for age and gender structural magnetic resonance imaging (MRI) scans were performed. Volumetric analyses of regions of interest were made semi-automatically by two raters who were unaware of identifying subject data. The following structures were measured: whole brain volume, frontal lobe, temporal lobe, amygdala-hippocampus complex and brain ventricles. The differences between groups were tested with MANCOVA with covariates gender and brain volume.

Results: Patients with panic disorder had a significantly smaller temporal lobe size on both sides and the volume of the left lateral ventricle was reduced. The amygdala-hippocampus complexes of the patients and healthy control subjects did not differ.

Conclusions: The results of Vythilingam et al. [2000] are confirmed by our findings and the hypothesis of a pathogenetic involvement of temporal lobe in panic disorder is supported. At present it can not be decided whether the volume reduction observed represents a primary phenomenon or a secondary alteration in the later course of the disease.