Frontal Brain Asymmetry as a Biological Substrate of Emotions in Patients With Panic Disorders

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Background: Right frontal hemisphere activation, as indicated by reduced frontal alpha amplitude, seems to represent activation of an avoidance-withdrawal system and seems to be associated with negative emotions. Since patients with panic disorder are characterized by both negative emotions and avoidance-withdrawal behavior, we expected them to show greater right than left frontal hemisphere activation.

Methods: Spontaneous electroencephalography was recorded from the left and right frontal and parietal scalp regions of 23 patients with panic disorder patients without a diagnosis of depression and from 25 healthy control participants during the following conditions: rest, confrontation with neutral, panic-relevant, anxiety-relevant but panic-irrelevant, or anxiety-irrelevant but emotionally relevant stimuli, and performance of a motor task. Their emotional state during these conditions was assessed by the Self-Assessment Manikin.

Results: In patients with panic disorders, there were asymmetries in frontal hemisphere activation during resting phases and when confronted with anxiety-relevant stimuli. Their right frontal alpha power was significantly decreased compared with the left, while control participants did not show frontal brain asymmetry during these phases. There was no frontal brain asymmetry when patients observed an emotionally neutral picture or performed a motor task. Under these conditions, left and right frontal hemisphere alpha activation of patients with panic disorder and healthy participants were comparable.

Conclusions: These data support the hypothesis that patients with panic disorder are characterized by greater activation of a right frontal avoidance-withdrawal system in negatively valenced situations. The findings are interpreted as biological evidence for a disturbed cortical processing in patients with panic disorder.

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PARTICIPANTS AND METHODS

PATIENTS AND CONTROL PARTICIPANTS

Twenty-three patients with panic disorder were compared with 25 healthy control participants. Diagnoses were made by 2 independent, experienced psychiatrists according to the DSM-III-R on the basis of the Diagnostisches Interview bei psychischen Störungen. The Diagnostisches Interview bei psychischen Störungen represents an extended modification of the American Anxiety Disorder Interview Schedule-Revised.

All patients met DSM-III-R criteria for panic disorder with or without agoraphobia. Fourteen reported a history of depressive symptoms, but none fulfilled diagnostic criteria for an affective disorder. Patients with and without a history of depressive symptoms did not differ in subjective or electrophysiological measures. Two patients had histories of alcohol abuse and 2 of benzodiazepine abuse. Additional diagnoses were generalized anxiety disorder (2 patients), past generalized anxiety disorder (1 patient), mild social phobia (1 patient), and past social phobia (1 patient). No patient had a specific phobia according to DSM-III-R criteria. No other current or past Axis I or II disorder (including dysthymia) was detected. With the exception of 3 patients who each received a very low dose of medication, all others had not received any psychoactive medication for at least 4 weeks and no neuroleptic medication for at least 6 months. All participants were physically healthy as confirmed by history, physical examination, and screening laboratory tests. The control participants had no history of Axis I disorder and reported no such disorder in first-degree relatives. All participants were right-handed as assessed by the Edinburgh Inventory.

should be associated with a relatively increased left parietal activation.

Several observations suggest that panic disorder should be characterized by right frontal hyperactivation: (1) The right hemisphere predominantly controls processes that are not at rest. 15 Both important factors in the development and maintenance of panic disorder. 16-18 (2) Most patients with panic disorder are characterized by avoidance-withdrawal behavior, 19 which seems to be controlled by right frontal brain regions.

This study is the first to examine FBA in patients with panic disorder. In contrast to prior studies, patients with anxiety disorder without comorbidity of depression were examined to separate effects of anxiety and depression on FBA. Stimulus-specific FBA effects were examined by the comparison of panic-relevant and panic-irrelevant stimuli conditions. The main hypothesis of this study was that patients with panic disorder exhibit a dispositional FBA with emotionally neutral stimuli (emergency situations), but not when confronted with emotionally neutral stimuli (mushroom picture). Second, no FBA should be elicited in patients with panic disorder by anxiety-relevant but panic-irrelevant stimuli (spider picture), by emotionally relevant but anxiety-relevant stimuli (erotic picture), or by a concentration-consuming but emotionally neutral task (motor task).

DESIGN AND PROCEDURES

Stimuli

The erotic, spider, and mushroom pictures were taken from the International Affective Picture System, the emergency picture from Pauli et al. During the standardized motor performance task, participants had to track a line with a pencil on a sheet of paper along a labyrinth as quickly as possible and without touching the margins.

Self-report Instruments

All participants completed a psychometric test battery (Table 1) including the Agoraphobic Cognition and Body Sensation Questionnaires, the State (STAI-S) and Trait (STAI-T) versions of the Spielberger Anxiety Inventory, the Beck Depression Inventory (BDI), and the Symptom Checklist 90-Revised (SCL-90-R). The participants’ acute affective states in the experimental situations were measured by the Self-Assessment Manikin (SAM). The SAM assesses arousal, valence, and dominance on 9-point rating scales. Each dimension is depicted by a graphic figure on a continuously varying scale. When representing the valence dimension, the SAM ranges from a smiling, happy figure to a frowning, unhappy figure. For the arousal dimension, the SAM ranges from an excited, wide-eyed figure to a relaxed, sleepy figure. For the dominance dimension, the size of the manikin changes from a relatively small to a relatively big figure. High values represent negative valence, high arousal, or high dominance.

Physiological Recording

Brain electrical activity was recorded continuously during the whole session with an electroencephalography amplifier.

RESULTS

Affective Judgments

Patients with panic disorders reported a significantly more negative valence than control participants (t = 3.0, P = .005) (Table 2). No other significant differences were found.

Electroencephalograph Alpha Power

For frontal electrodes (F3 and F4), there was a significant Group × Hemisphere interaction (F1,46 = 5.8, P = .02).
Patients with panic disorders showed significantly less right than left frontal alpha power (t2 = 2.3, P = .03), while control participants did not show any FBA. Neither Group nor Hemisphere main effects reached statistical significance. For parietal electrodes (P3 and P4), a significant Group × Hemisphere interaction (F1,46 = 5.7, P = .02) was found. Post hoc tests revealed no posterior brain asymmetry for patients with panic disorders. However, for control participants, the right parietal alpha power was enhanced compared with the left (t2 = 2.7, P = .01). No significant main effects were obtained.

An overall ANOVA including frontal and parietal electrodes revealed no Group × Hemisphere × Region interaction (F1,46 = 0.81, P = .37).

Correlational Analysis

Similar to Schaffer et al6 and Jacobs and Snyder,12 Pearson correlations were computed between the frontal or parietal right minus left alpha power difference ([P4 − F3], or [P4 − P3]) and the BDI, the SCL-90-R depression and anxiety score, the STAI-S and STAI-T. For all participants, significant negative correlations were found between the FBA and BDI (r = −0.39, df = 48, P = .007), SCL-90-R depression (r = −0.34, df = 48, P = .02), SCL-90-R anxiety (r = −0.52, df = 48, P = .001), STAI-S (r = −0.41, df = 47, P = .004), and STAI-T (r = −0.27, df = 48, P = .07, trend only), whereby negative correlations indicated that high questionnaire scores were associated with a relatively reduced right frontal alpha power. For parietal electrodes, no significant correlations were found.

However, correlational analysis within control participants only revealed a trend for a negative correlation between FBA and BDI (r = −0.39, df = 25, P = .06), but not for the SCL-90-R or the STAI-S or STAI-T. By controlling for the BDI, the partial correlation coefficient of all anxiety measures remained nonsignificant.

Correlational analysis within the patients with panic disorders indicated for FBA a significant negative relationship with SCL-90-R anxiety (r = −0.50, df = 23, P = .02) and a trend for a negative relationship with STAI-S (r = −0.40, df = 23, P = .06), but no significant correlation with the BDI (r = −0.17, df = 23, P = .43). No correlations were found for parietal asymmetry (SCL-90-R anxiety, r = −0.01, STAI-S r = 0.01).
By controlling for the BDI, the partial correlation coefficient between FBA and SCL-90-R ($r = -0.50, df = 20, P = .01$) or STAI-S ($r = -0.36, df = 20, P = .05$) remained significant. Comparable results were found by using the SCL-90-R depression score as a covariate.

**STIMULUS PHASES—PANIC-RELEVANT**

Affective Judgments

The ANOVA for valence ratings revealed significant main effects for the factors Group ($F_{1,46} = 13.9, P < .001$) and Picture Category ($F_{1,46} = 64.1, P < .001$). Furthermore, there was a significant Group × Picture Category interaction ($F_{1,46} = 3.9, P < .05$). Patients with panic disorders and control participants rated the valence of the mushroom picture similarly ($t_{46} = 1.3, P = .19$), while the emergency picture was rated significantly more negative by patients than by controls ($t_{46} = 4.2, P < .001$). Similar ANOVAs for arousal and dominance ratings revealed only significant main Picture Category effects (both $F_{1,46} > 30.0, P < .001$). The emergency picture elicited more arousal and less dominance than the mushroom picture in both groups (Table 3).

Electroencephalograph Alpha Power

For frontal electrodes, the ANOVA revealed a significant Picture Category main effect ($F_{1,46} = 7.6, P = .008$), indicating that the emergency picture elicited a generally lowered alpha power compared with the mushroom picture. Likewise, there were significant Hemisphere × Group ($F_{1,46} = 4.6, P = .04$) and Hemisphere × Group × Picture Category ($F_{1,46} = 4.8, P = .03$) interactions.

Post hoc analyses in the control group revealed neither significant main effects of Picture Category or Hemisphere nor a significant Hemisphere × Picture Category interaction. Hence, there is no indication of any asymmetry in frontal alpha power in control participants during viewing of mushroom or emergency pictures.

In patients with panic disorders, however, the ANOVA revealed a significant main effect of Picture Category ($F_{1,22} = 4.4, P = .05$) and a significant Hemisphere × Picture Category interaction ($F_{1,22} = 9.7, P < .005$). While looking at the emergency picture, patients with panic disorders showed a significantly reduced right frontal alpha power compared with left frontal alpha power ($t_{22} = 2.7, P = .01$). For the mushroom picture, this FBA did not emerge. These findings indicate that a panic-related stimulus induced a reduced right frontal alpha power in patients with panic disorder only.

For parietal electrodes, the ANOVA revealed a significant Picture Category main effect ($F_{1,46} = 5.8, P = .02$) and a significant Picture Category × Group interaction ($F_{1,46} = 4.2, P = .05$). A post hoc analysis for patients with panic disorders showed a significant main effect of Picture Category ($F_{1,46} = 8.2, P = .009$), indicating that their parietal alpha power was generally lower while looking at the emergency than the mushroom picture. A corresponding post hoc analysis for control participants revealed no significant effects. No parietal asymmetry effects were found for either patients or controls.

An overall ANOVA including frontal and parietal electrodes revealed no significant Group × Hemisphere × Region interaction ($F_{1,46} = 0.52, P = .48$).

**STIMULUS PHASES—PANIC-IRRELEVANT**

Affective Judgments

Patients with panic disorders reported a significantly more negative valence than control participants during inspection of the spider picture ($t_{46} = 3.3, P = .002$) (Table 4). No other group differences reached statistical significance.
Electroencephalograph Alpha Power

Frontal power during the execution of the motor task was virtually identical for left and right electrodes and for patients with panic disorders and control participants (Table 4).

The ANOVAs on frontal alpha power for the spider and erotic picture revealed no significant main effects of Group or Hemisphere, but significant Hemisphere x Group interactions: spider picture ($F_{1,46} = 6.4$, $P = .02$); erotic picture ($F_{1,46} = 4.6$, $P = .04$). Post hoc analyses revealed that patients with panic disorders showed significantly lower alpha power at the right compared with the left frontal electrode while looking at the spider ($t_{22} = 2.1$, $P = .05$) or erotic picture ($t_{22} = 2.3$, $P = .03$). The same analysis for control participants revealed no FBA.

For parietal electrodes, the ANOVAs for the motor task, the spider picture or the erotic picture revealed no significant main or interaction effects. Overall, ANOVAs, including frontal and parietal electrodes, revealed no Group x Hemisphere x Region interaction for the spider ($F_{1,46} = 1.88$, $P = .18$) or the erotic ($F_{1,46} = 1.33$, $P = .25$) picture. As sex is suspected to be correlated with hemispheric differences, especially concerning the response to erotic pictures, we additionally ran the analyses for the erotic pictures for women only. The reported difference was still present.

These data are the first to provide evidence that patients with panic disorders are characterized by an FBA with a relatively reduced right alpha power during rest and when confronted with anxiety-relevant stimuli. No FBA was found in the control participants. According to Davidson et al., these findings indicate an enhanced activa-
tion of the right frontal avoidance-withdrawal system in patients with panic disorders.

The FBA found in patients with panic disorders was not caused by symptoms of depression. First, patients with panic disorders were selected to have no depression co-morbidity. Second, as in previous studies, FBA was correlated with a psychometric measure of depression (ie, BDI)\(^3,12\) in the healthy controls, while in patients with panic disorders FBA was not correlated with the BDI, but with anxiety measures. Third, the data of Davidson et al\(^9\) showed that FBA in depression is more supportive of decreased left frontal hemisphere activation, while the FBA of patients with panic disorders seems to be caused by increased right frontal hemisphere activation.

Increased right frontal hemisphere activation may reflect an acute emotional reaction,\(^9\) indicating the prevalence of negative emotions and an acute activation of the avoidance-withdrawal system. The correlation between the FBA of patients with panic disorders during rest and STAI-S, but not the STAI-T indicates that FBA is a state rather than a trait marker. The affective judgments during the rest phase also indicated that the patients with panic disorders experienced this situation as more aversive than the healthy controls. Rumulative thoughts related to the illness during the rest phase might be among the reasons for the more negative valence ratings. Previous studies showed that patients with panic disorders experience baseline or rest phases as more aversive\(^42-44\) and periods of relative relaxation as anxiety-inducing\(^45,46\).

The interpretation of FBA in patients with panic disorders as a state marker is also in line with our additional findings that patients with panic disorders show FBA while confronted with anxiety-relevant stimuli (emergency situation, spider). In both situations, negative valence ratings were observed in patients with panic disorders than in healthy controls, and patients with panic disorders exhibited FBA. On the other hand, both groups showed comparable valence ratings and no FBA for the mushroom picture or for the motor task. Therefore, the FBA of patients with panic disorders may reflect negative emotional reactions elicited by these situations.

However, the finding that an anxiety-irrelevant erotic picture also induced an FBA in patients with panic disorders seems to be inconsistent with this interpretation. Erotic stimuli are arousing, and patients with panic disorders may exhibit FBA in all arousing situations, irrespective of their positive or negative valence. Arousal may induce bodily reactions (ie, heart rate acceleration) that are known to be important triggers of panic attacks.\(^10,32,45\) This explanation is supported by the fact that patients with panic disorders showed a tendency to more negative valence ratings for the erotic picture than control participants.

However, a more detailed analysis of the data suggests another interpretation. While looking at the erotic picture, the FBA of patients with panic disorders did not derive from a reduction of right frontal alpha power, but instead from an increase in left frontal alpha power. This distinguished the reactions of patients with panic disorders to anxiety-irrelevant erotic pictures from those to anxiety-relevant emergency or spider pictures. To what extent frontal asymmetry from either a decrease of right frontal alpha power or an increase of left frontal alpha power reflects functional differences cannot be solved with our data. It might be assumed, however, that an increase in left frontal alpha power is associated with the inhibition of the approach system and a decrease of right frontal alpha power with the selective activation of the avoidance-withdrawal system.

Another way of interpreting our findings is to assume that patients with panic disorders are characterized by generally negative emotions and a tonically over-activated withdrawal-avoidance system. This disposition causes FBA in most situations, except when patients with panic disorders are occupied with explicitly neutral stimuli. Neutrally valenced and unarousing stimuli may ameliorate the tonic right frontal overactivation. Consequently, no FBA is observable. It is well known by clinicians that many patients with panic disorders try (and often succeed) to cope with their symptoms with distractions. Findings in depression showing that negatively valenced thoughts are significantly reduced if patients engage in some form of distraction also support this notion. Finally, the frequent observation that patients with panic disorders feel safe at home might be explained. The home presumably is an explicitly neutral stimulus that reduces right frontal overactivation.

Although recorded frontal alpha levels consistently have been shown to be associated with phenomena interpreted as right or left frontal hemisphere activation, the possible neurobiological mechanism by which such measures are associated with frontal activation are unclear. To date, no data are available that suggest frontal cortex alpha generators. But recent neuroimaging studies show a reverse relationship between the activation of prefrontal cortex and amygdala.\(^48,49\) These data suggest that the frontal cortex regulates and restrains subcortical structures related to affect (see also references 50-53). Weakening of these influences can facilitate activity of the amygdala, which, in turn, can release uncontrolled affect such as anxiety and panic. Nevertheless, further research is warranted to elucidate what brain processes underlie changes in recorded frontal alpha levels.

While our data clearly support the hypothesis that patients with panic disorders are characterized by FBA, our findings on parietal brain asymmetries (PBA) are equivocal. All specific tests for PBA in patients with panic disorders failed to reach significance, and significant correlations between asymmetry measures and psychopathology were restricted to frontal areas exclusively. However, the overall tests, which included frontal and parietal electrodes, failed to confirm that the FBA in patients with panic disorders was restricted to frontal brain areas. Although we cannot draw clear-cut conclusions about PBA, these findings can be viewed as consistent with an overall favoring of right over left frontal hemisphere activation in patients with panic disorders. Also, the finding during the resting phase that the control participants showed a greater parietal asymmetry favoring the right over the left side in alpha power could be viewed as con-
consistent with this overall favoring of right over left. Other recent studies\textsuperscript{13,14} also found a relatively enhanced right parietal brain activation in anxious participants during rest. Together, these findings support the model of Heller et al\textsuperscript{10} that anxious arousal is associated with a relatively enhanced right parietal activation.

In summary, patients with panic disorders are characterized by an asymmetry in frontal activation, which can be taken as evidence for an overactive avoidance-withdrawal system. The asymmetry was independent of symptoms of depression but was influenced by situational information.

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