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Electrophysiological Evidence Reveals Affective Evaluation Deficits Early in Stimulus Processing in Patients With Panic Disorder

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Cognitive and neurobiological accounts of clinical anxiety and depression were examined via event-related brain potentials (ERPs) recorded from patients with panic disorder and healthy controls as they performed an old/new recognition memory task with emotionally negative and neutral words. The emotive connotation of words systematically influenced control subjects'—but not patients'—ERP effects at prefrontal sites in a latency range (~300–500 ms) generally assumed to reflect greater contribution of automatic than controlled memory processes. This provides evidence for dysfunctional inhibitory modulation of affective information processing in panic disorder. The ERP effects after 700 ms, however, suggest that some patients may adopt conscious strategies to minimize the impact of these early processing abnormalities on overt behaviors.

The Cognitive And Neural Basis of Anxiety and Depression

The development and maintenance of clinical anxiety and depression—mood disorders characterized by a tendency toward avoidance and withdrawal (Davidson, 1998; Wiedemann et al., 1999)—have been linked to abnormal cognitive processes, on the one hand, and to dysfunctional brain processes on the other. Cognitive models propose that although anxiety and depression disorders differ in the specific contents of their accompanying cognitive schemas (Beck & Clark, 1991), both are characterized by a bias to expect negative consequences from external events as well as from internal processes, that is, one's own behaviors and physiological reactions (Beck & Clark, 1997; D. A. Clark, Beck, & Alford, 1999; D. M. Clark, 1986; Mogg & Bradley, 1998; Windmann, 1998). In other words, such patients tend to overevaluate and overgeneralize the negative implications of sensations and events, thereby treating stimuli and events of varying emotional significance as if they all had negative consequences. Patients with panic disorder, in particular, have been characterized as prone to misinterpret harmless internal (bodily) and external (environmental) stimuli as dangerous and catastrophic (D. M. Clark, 1986; Ehlers, 1988), presumably as part of a failure to inhibit automatically evoked fear responses or to modulate them through more sophisticated, consciously controlled higher order processes (Beck & Clark, 1997; Windmann, 1998).

At the same time, neurobiological researchers have attributed anxiety and depression to a dysfunctional interaction between prefrontal cortex (PFC) and the limbic system (Coplan & Lydiard, 1998; Drevets, 1998; Gorman, Kent, Sullivan, & Coplan, 2000). The ventromedial or orbital part of the PFC is known to be crucially involved in emotion regulation and the prediction of behavioral outcomes and to cooperate closely with the dorsal and lateral parts of the PFC required for executive functions, problem solving, complex behavior planning, and attentional control (Bechara, Tranel, & Damasio, 2000; Damasio, 1994; Dias, Robbins, & Roberts, 1996; Rolls, 1999). The limbic system—in particular the amygdala complex with its direct bilateral connections to the PFC—is known to mediate fear conditioning, unconscious threat-detection, and arousal-related memory consolidation processes (A. K. Anderson & Phelps, 2001; LeDoux, 1996; McGaugh, 2000). Failure of prefrontal regions to flexibly modulate and inhibit emotional reactions and evaluations engendered by these limbic structures thus may underlie the affective biases and cognitive abnormalities that have been described for patients with anxiety and depression (Dias et al., 1996; Drevets, 1998; Gorman et al., 2000; LeDoux, 1996; Quirk, Russo, Barron, & Lebron, 1998; Windmann, 1998; Windmann & Kutas, 2001).

Studies examining this presumed neural circuitry with brain imaging techniques have yielded a largely consistent picture (for reviews, see Davidson, 1998; Drevets, 1998; Reiman, 1997). Neural activity in inferior regions, and sometimes also dorsal prefrontal regions, is typically reduced in patients with anxiety and depression compared with healthy control subjects and is often characterized by a larger right-to-left ratio in these regions as well as in the temporal lobes (Davidson, Abercrombie, Nitschke, & Putnam, 1999; Drevets, 1998; Martinot et al., 1990; Nordahl et al., 1998; Reiman, 1997). Using single photon emission computer tomography (SPECT), Kuikka et al. (1995) observed reduced benzodiazepine receptor uptake in the right inferior prefrontal

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cortex in patients with panic disorder (see also Kaschka, Feistel, & Ebert, 1995; Malizia et al., 1998). This finding suggests that the specific contribution of inferior frontal cortex regions to the development of clinical anxiety may involve a deficit in inhibitory neural activity (see also Crestani et al., 1999).

To understand the cognitive implications of these abnormal patterns of neural activity in patients with anxiety and depression, we believe that it is essential to link the activity to the dynamic processing of stimuli of varying emotional significance. Event-related potentials (ERPs) are a method of choice for this purpose because their high temporal resolution allows for real-time observation of activity changes in neural circuits during the processing of the relevant information. Although ERP waveforms do not index the loci of the brain generators of the associated cognitive processes, they do provide a direct measure of brain activity that is a sensitive index of sensory, emotional, and cognitive manipulations. This dual role of ERPs affords a natural convergence between psychological and neural perspectives on any domain, such as anxiety disorders in the present case, for which there exist theories at both levels.

Three specific predictions can be derived from the cognitive and the neurobiological theories outlined above: First, if panic and anxiety disorders are yoked to abnormalities in the early, preattentive affective appraisal of stimuli, as proposed by cognitive models (e.g., Beck & Clark, 1997; Windmann, 1998), this should be reflected in abnormal patterns of relatively early ERP effects of the type that has been related more to automatic, unconscious processes than to controlled, conscious processes. Second, if these disorders are linked to dysfunctions of inferior/medial prefrontal cortex, as suggested by the neurobiological studies, then one would expect to see variation in ERP components and effects that are typically thought to index some aspect of prefrontal functioning. Last but not least, we can predict the direction of the activity difference between patients and control participants. One corollary of the assumption, that patients with anxiety and depression are deficient in the processes that normally inhibit fear or other negative emotions and evaluations, is that they should be more likely (than individuals who do not experience panic or anxiety) to show evidence of negative affective appraisal in situations in which this is inappropriate. This means that they should tend to show affective information-processing patterns not just in response to actually aversive or threatening stimuli but also in response to harmless stimuli and events. If this characterization is apt, then we expect these patients' ERP responses to neutral (i.e., harmless) stimuli to resemble those shown by healthy individuals in response to emotionally negative stimuli (and not those shown by healthy individuals in response to emotionally neutral stimuli). In other words, although control subjects will show some signs of affective inhibition to emotionally neutral stimuli and a selective withdrawal of these inhibitory processes to emotionally negative stimuli, we expect the patients to show little affective inhibition regardless of the actual emotional value of the stimulus. In short, patients and control participants should differ more in their processing of emotionally neutral stimuli than in their processing of actually negative stimuli (cf. Mogg & Bradley, 1998; Windmann, 1998; Windmann & Krüger, 1998). In fact, the results of several studies examining ERPs to emotionally neutral stimuli seem to be consistent with this latter hypothesis (C. R. Clark, McFarlane, Weber, & Battersby, 1996; Korunka, Wenzel, & Bauer, 1993; Proulx & Picton, 1984; Tecce, 1971). Patients with panic disorder and anxious individuals have been observed, through ERP indices, to allocate processing resources to irrelevant and insignificant stimuli and to be unable to generate appropriate predictions. None of these studies, however, included a direct comparison with emotionally negative stimuli.

The Emotion-Induced Recognition Bias

To experimentally investigate the mechanism(s) of the hypothesized stimulus evaluation processes that are presumably deficient in patients with negative affect, we needed a task that combines incidental processing of emotional information with the executive control functions mediated by the prefrontal cortex. A task in which we have observed an *emotion-induced recognition bias* (Windmann & Krüger, 1998; Windmann & Kutas, 2001) seemed ideal for this purpose. This refers to the well-established (but rarely discussed) observation that healthy participants tend to classify words in a recognition memory task as "old" more often when these words have an emotionally negative connotation (i.e., unpleasant or threat-related) as opposed to emotionally neutral ones, whether the words are in fact old or new (Cross, 1999; Ehlers, Margraf, Davies, & Roth, 1988; Leiphart, Rosenfeld, & Gabrieli, 1993; Maratos, Allan, & Rugg, 2000; Windmann, Daum, & Güntürkün, in press; Windmann & Krüger, 1998; Windmann & Kutas, 2001). Apparently, participants adopt a more "liberal" response bias to the emotional words than to the neutral ones (Windmann & Krüger, 1998; Windmann & Kutas, 2001). As the words are presented in a quasi-randomized order during the test phase, this finding implies that participants shift their decision criterion in a flexible manner on a trial-to-trial basis, depending on the emotional meaning of each test item. Although this response pattern does not improve participants' accuracy scores, it does ensure that memories for events with a high survival value (i.e., emotional memories) are not as readily missed, that is, erroneously considered irrelevant (cf. A. K. Anderson & Phelps, 2001; Gunther, Ferraro, & Kirchner, 1996; LeDoux, 1996; Schnider & Ptak, 1999; Windmann & Krüger, 1998).

Windmann and Kutas (2001; cf. also Maratos et al., 2000) reported that this emotion-induced shift in the bias to respond "old" is accompanied by reduced ERP old/new effects at (pre)frontal recording sites between 300 and 500 ms poststimulus. When participants responded "old" (hits and false alarms), ERPs to neutral items showed reliable differences between old and new items over frontal sites (i.e., frontal old/new effects) that were not present in the ERPs to negative items. In general, ERP old/new effects refer to a generally greater positivity for stimuli that were presented in a prior study phase (old items) relative to stimuli that were not presented before (new items). These effects have been hypothesized to reflect the contribution of several different memory-related processes. "Early" old/new effects (between 300 and 500 ms), for example, seem, in large part, to index unconscious memory and automatic familiarity processes, whereas "later" old/new effects (500 ms and beyond) have been found to be more sensitive to consciously controlled episodic memory processes (Allan, Wilding, & Rugg, 1998; Curran, 2000; Düzel, Vargha-Khadem, Heinze, & Mishkin, 2001; Düzel, Yonelinas, Mangun, Heinze, & Tulving, 1997; Mecklinger, 2000; Nessler, Mecklinger, & Penney, 2001; Paller, 2000; Paller & Kutas, 1992;

Paller, Kutas, & McIsaac, 1995; Rugg et al., 1998). Moreover, ERP old/new effects over frontal sites have been linked to functions of the prefrontal cortex during memory retrieval, in particular to criterion-setting and monitoring functions (Allan et al., 1998; Maratos et al., 2000; Swick & Knight, 1999; Windmann, Urbach, & Kutas, in press).

As the ERP old/new effects associated with the emotion-induced recognition bias were maximal over prefrontal sites, Windmann and Kutas (2001) suggested that they might reflect the automatic withdrawal of inhibitory control normally exerted by the prefrontal cortex over limbic structures during memory retrieval (M. C. Anderson & Green, 2001; Schacter, Norman, & Koutstaal, 1998; Schnider & Ptak, 1999; Tomita, Ohbayashi, Nakahara, Hasegawa, & Miyashita, 1999) due to the impact of negative emotions. This interpretation is further supported by other lines of evidence. First, imaging studies have implicated the orbitofrontal cortex in guessing and response bias shifts in recognition memory tasks (Elliott & Dolan, 1998; Elliott, Rees, & Dolan, 1999; Miller, Handy, Cutler, Inati, & Wolford, 2001). Second, neuropsychological work suggests that the ventromedial prefrontal cortex mediates decision making on the basis of unconscious anticipation of emotional states (Bechara, Damasio, Tranel, & Damasio, 1997; Bechara et al., 2000). Third, other studies have implicated the amygdala in unconscious semantic analysis of emotional words (A. K. Anderson & Phelps, 2001). Finally, single-unit recordings in humans have revealed that neurons in the medial prefrontal cortex are informed about the aversive content of complex visual stimuli (pictures) within the first 200 ms post-stimulus onset (Kawasaki et al., 2001). Taken together, it seems highly likely that an intact interplay of the prefrontal cortex with limbic structures is crucial for the emotion-induced recognition bias as well as for the early ERP effects reported by Windmann and Kutas (2001).

Aims and Scope of the Present Study

The present study was aimed at finding out whether patients with panic disorder, who were also moderately depressed, would show abnormalities in the cognitive and neural processes intrinsic to the emotion-induced recognition bias. To these ends, behavioral speed-and-accuracy measures as well as scalp-recorded electrical brain activity were recorded as participants performed a recognition memory task with emotionally negative and neutral words. In contrast to the majority of previous studies on emotional memory in patients with panic disorder, we (a) used emotional stimuli that had no specific relationship to panic symptomatology but were generally negative in connotation (this was done to minimize potentially confounding effects of familiarity) and (b) investigated not only correct recognition (e.g., hits and correct rejections) but also measures of false recognition and recognition bias.

Based on the results of two previous studies (Maratos et al., 2000; Windmann & Kutas, 2001) and the other evidence illustrated above, we expected the ERP old/new effects over frontal sites to distinguish the patients from the control participants in a latency range that numerous laboratories have noted as especially sensitive to automatic (as opposed to controlled) memory processes. Specifically, we predicted that ERP old/new effects at frontal sites would show less emotion-related modulation of ERP old/new effects in the patients than in the control participants, particularly between 300 and 500 ms post-stimulus onset.

Inconsistencies between the findings of Windmann and Kutas (2001) and Maratos et al. (2000) prevented us from specifying a priori whether the effects of negative affect on the ERP old/new effect would be largest in the hits versus false alarms comparison, as suggested by Windmann and Kutas (2001), or in the hits versus correct rejections comparison, as suggested by Maratos et al. (2000). Preliminary visual inspection of the data indicated that the effect went in a similar direction for both of these types of comparisons (shown later in Figure 3), albeit slightly more strongly and more reliably for the comparison of hits versus correct rejections. As the ERPs associated with false alarms were quite noisy (due to low trial counts, especially for the neutral items in the patient sample), our main inferential analyses were restricted to the traditional ERP old/new effect involving hits and correct rejections.

Method

Participants

The study was carried out at the Department of Cognitive Science, University of California, San Diego. Participants[1] were 17 healthy adults (16 women, 1 man; mean age = 22.00 years, *SD* = 7.96) with no history of psychiatric or neurological disorders and 17 adults (16 women, 1 man; mean age = 24.05 years, *SD* = 6.91) with panic disorder according to criteria set forth in the *Diagnostic and Statistical Manual of Mental Disorders* (4th edition; *DSM–IV*; American Psychiatric Association, 1994) participated in the study. Participants were recruited through campus flyers, local psychotherapists, and support groups. Diagnosis of panic disorder was made by an experienced psychologist (Sabine Windmann) using the Structured Clinical Interview for *DSM–IV* Axis I Disorders, Clinician version (SCID–CV; First, Spitzer, Gibbon, & Williams, 1996) and additional questionnaires. A total of 15 participants in the clinical sample (88%) also had indicated that they had been diagnosed with panic disorder previously by a medical doctor or clinical psychologist and/or had undergone treatment or psychological counseling for that reason. Individuals with a secondary diagnosis (e.g., of generalized anxiety disorder) were excluded from the sample (see below regarding depression). The median duration of the disorder was 5 years (minimum = 1 year). Most patients had never received any drug treatment (82%) and even of those who had, all were free of psychoactive medication for at least 5 months at the time of their participation in this study. Data of two patients with a history of alcohol abuse were excluded from the analyses.[2] Six patients (35%) indicated the presence of only mild agoraphobic avoidance tendencies according to *DSM–IV* criteria. Eight patients (47%), but none of the control participants, had a Beck Depression Inventory (BDI; Beck, Steer, & Brown, 1996) score of 12 or more, the cutoff score for mild depression. Only two patients had a BDI score higher than 30.

Patients and controls were native English speakers matched in age, handedness (one left-handed female participant in each group), gender, and

[1] A total of 7 participants of the control group were selected (on a strictly random basis) from the data set of the earlier study (Windmann & Kutas, 2001). The procedures of that study were identical to those of the present study, except that participants had not filled out the clinical questionnaires and the stimulus ratings after the session in the earlier study. The behavioral as well as the ERP data of these 7 participants were representative of those data for all of the control participants.

[2] On average, the pattern of ERP effects for the 5 patients (who were excluded because of a history of alcohol abuse and/or because they had dropped out of college) looked practically identical to the average of the other patients, but their old/new recognition accuracies were somewhat lower.

years of education. All participants either had a college degree (but no additional education) or were currently enrolled in college. All were paid $8/hr for 3–4 hr of participation.

Stimuli

The complete stimulus lists are given in Windmann and Kutas (2001). A sample is shown in the Appendix. A total of 70 negative items and 70 neutral items (including approximately 10% slightly positive items) were randomly assigned to Lists A and B. Either List A or List B was presented at study, counterbalanced across participants. For participants who studied List A, List B items served as distractor items at test, and vice versa. A total of 32 additional distractor items—16 negative and 16 neutral—were presented to all participants. In addition, all studied items were presented as target items at test. Hence, all participants saw 140 items at study and 316 items at test (140 old, 176 new). All negative and neutral words were relatively infrequent verbs matched to each other on average on frequency, length, semantic interrelatedness (using the Hyperspace Analogue to Language [Burgess & Lund, 1997] and the Latent Semantic Analysis [Landauer, Foltz, & Laham, 1998]) and, as far as possible, abstractness (using the MRC Psycholinguistic Database, http://www.psy.uwa.edu.au/MRCDataBase/uwa_mrc.htm).

Procedure

Participants' consent was obtained in writing. All procedures were approved by the Human Subjects Committee of the University of California, San Diego. Participants were seated in a comfortable chair approximately 1.5 m in front of a 21-inch (53.34-cm) computer screen. The experimental stimuli were presented for a duration of 400 ms each at a fixed rate (once every 2,600 ms) in the middle of the screen in the center of a yellow frame to help participants maintain visual focus. In the study phase, participants were instructed to memorize the words displayed for a subsequent recognition memory test. (Note, however, that the emotion-related recognition bias does not depend on intentional encoding; see Windmann & Krüger, 1998.) During a retention interval of approximately 30 min, participants were engaged by a lexical decision task (with different stimuli). For the recognition test, participants were asked to indicate with a button press whether each word that was flashed on the screen had been presented during the study phase (*old*) or not (*new*), guessing as needed. At an interval of 1,600 ms after a response was given, the next test item appeared on the screen. After the experimental session, participants were asked to fill out the State–Trait Anxiety Inventory (STAI; Spielberger, Gorsuch, & Lushene, 1970) and the BDI and were asked some further questions about the experiment and their well-being.

ERP Recordings

The electroencephalogram (EEG) was recorded using 26 tin electrodes embedded in an elastic cap and 2 additional ones placed at 'ventromedial' prefrontal sites (starting from the nasion, moving 5% of the sagittal midline in the dorsal direction and 10% of the interaural distance in the lateral direction; see Figure 1). Electrode impedances were below 5 kΩ. Recordings were referenced to the left mastoid, and re-referenced offline to the average of the right and left mastoids. The horizontal and vertical electrooculograms (EOG) were also recorded. All signals were amplified with a Nicolet SM2000 amplifier (Nicolet Instrument Technologies, Madison, WI) with a bandpass filter of 0.016 to 100 Hz at 12 dB/octave and digitized at 250 Hz for offline storage. Digitized EEG data were scanned manually for electrical and biological artifacts; contaminated trials (~15%) were excluded from further analyses. The resulting average trial counts were as follows: for the control participants: 44 hits negative, 37 hits neutral, 39 correct responses (CR) negative, and 47 CR neutral; for the patients: 41 hits negative, 34 hits neutral, 37 CR negative, and 44 CR neutral. The minimal trial count was 15 trials. Eyeblinks were corrected using an adaptive spatial filter procedure developed by Professor Anders Dale (Massachusetts General Hospital NMR Center). For plotting purposes only, ERPs were filtered with a low-pass of 8 Hz.

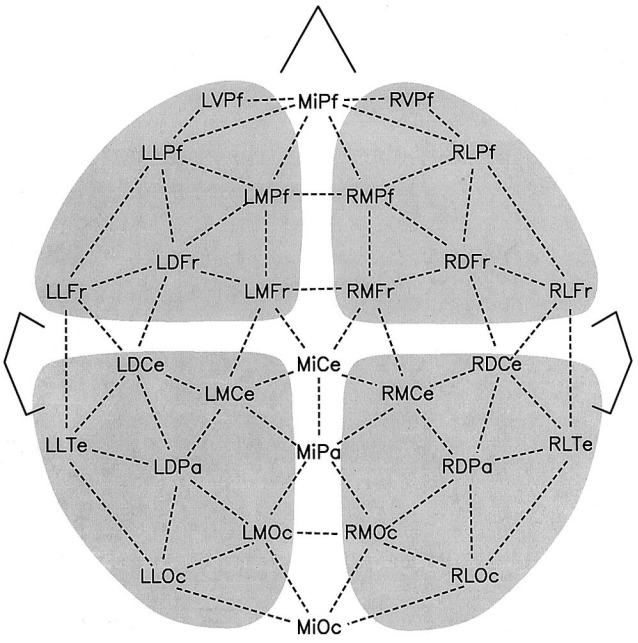

Figure 1. Positioning of the 28 electroencephalogram (EEG) electrodes over the scalp. LVPf and RVPf were loose electrodes (not embedded in the cap) placed ventromedial to LLPf and RLPf. Event-related brain potential amplitudes taken at 24 electrode sites were analyzed to examine effects of hemisphere (left/right) and anteriority (frontal/posterior) as follows: *left frontal*: left ventromedial prefrontal (LVPf), left lower prefrontal (LLPf), left medial prefrontal (LMPf), left dorsal frontal (LDFr), left lower frontal (LLFr), left medial frontal (LMFr); *left posterior:* left dorsal central (LDCe), left medial central (LMCe), left lower temporal (LLTe), left dorsal parietal (LDPa), left medial occipital (LMOc), left lower occipital (LLOc); and the same on the right side, respectively: *right frontal* (RVPf, RLPf, RMPf, RDFr, RLFr, RMFr) and *right posterior* (RDCe, RMCe, RLTe, RDPa, RMOc, RLOc).

Data Analyses

We computed behavioral measures of old/new recognition accuracy (Pr = Hit − FA) and response bias, Br = FA/(1 − Pr), from the hit rates, Hit = *p*("old"/old), and false alarm rates, FA = *p*("old"/new), according to two-high-threshold theory (Snodgrass & Corwin, 1988).

Inferential statistical analyses on behavioral and ERP data were performed using repeated measures analyses of variance (ANOVAs). Following our previous work (Windmann & Kutas, 2001) as well as other related ERP studies (e.g., Maratos et al., 2000; Rugg et al., 1998), mean ERP amplitudes were taken in an early time-window (300–500 ms), a late time-window (300–500 ms), and a very late time-window (800–1,100 ms). These were then collapsed across six electrode sites (four midline sites were dropped), as indicated in Figure 1, to constitute the two within-subjects factors: hemisphere (left/right) and anteriority (anterior/posterior) for the comparison of hits (old items) versus correct rejections (new items). Thus, the ANOVAs of the ERP data included the between-subjects factor of group (patients/control participants) and the within-subjects factors of study status (old/new), valence (negative/neutral), hemisphere (left/right), and anteriority (anterior/posterior). Only results involving effects of group

and/or experimental manipulations are reported. For post hoc tests, Bonferroni–Holm corrections were applied in determining significance, but uncorrected *p* values are reported.

Correlational analyses were performed to explore the relationship between dependent variables. Spearman correlation coefficients (r_s) were used whenever correlations were computed for the two groups separately to deal with potential outliers and small sample sizes. (As noted previously, clinical questionnaire data were available for only 10 of the 17 control participants.)

Results

Questionnaires

Patients had significantly higher scores than control participants on the BDI, $t(25) = 3.82$, $p < .005$, the STAI-State form, $t(25) = 3.54$, $p < .005$, and the STAI-Trait form, $t(25) = 4.03$, $p < .001$. Means and standard deviations are shown in Table 1.

Patients and control participants, however, did not differ in the stimulus ratings that they provided after the experiment. Negative items ($M = 3.43$, $SD = 0.84$) were evaluated as significantly more negative than neutral items ($M = 0.67$, $SD = 0.69$), $F(1, 32) = 289.72$, $p < .0001$. Group and Group × Valence interaction effects were both associated with *F* values of less than 0.5.

Behavioral Results

As can be seen in the top panel of Figure 2, both hit rates and false alarm rates were higher for negative items than for neutral items, as expected. Figure 2 (center panel) shows that this pattern resulted in a difference between negative and neutral items in the response bias measure Br, $F(1, 32) = 17.18$, $p < .001$, reflecting the expected emotion-induced recognition bias. By contrast, the accuracy measure Pr did not show any significant effects of emotional connotation ($F = 0.01$). The pattern of results was essentially the same in the patients and control participants for both variables (all Fs < 1.5).

There was no significant correlation between overall recognition accuracy (i.e., Pr collapsed across negative and neutral items) and overall response bias (i.e., Br collapsed across negative and neutral items) or between overall accuracy and the emotion-induced recognition bias (i.e., Br for negative items minus Br for neutral items). All Pearson product–moment correlations were smaller than .10 (with practically no differences between the two groups), suggesting that both overall Br and the emotion-related shift in Br were independent of accurate recognition memory.

Table 1 shows the correlations of the behavioral performance measures with the clinical depression and anxiety scores. The emotion-induced recognition bias (Br negative minus Br neutral) correlated significantly with BDI scores as well as with trait

Table 1
Scores on Clinical Questionnaires

Measure	Patients		Control participants	
	M	*SD*	*M*	*SD*
Clinical questionnaire scores				
Beck Depression Inventory	12.7	10.4	2.6	2.4
STAI Trait Anxiety	46.3	11.3	30.6	8.7
STAI State Anxiety	36.6	10.6	25.3	6.0
Correlation of scores with EIRB				
Beck Depression Inventory	.544		.150	
STAI Trait Anxiety	.449		−.006	
STAI State Anxiety	.325		−.081	

Note. Values are means (standard deviations) for patients with panic disorder and control participants on clinical questionnaire scores, and Spearman's rank-order correlation coefficients of the clinical scores with the EIRB (Br negative − Br neutral). STAI = State–Trait Anxiety Inventory; EIRB = emotion-induced recognition bias.

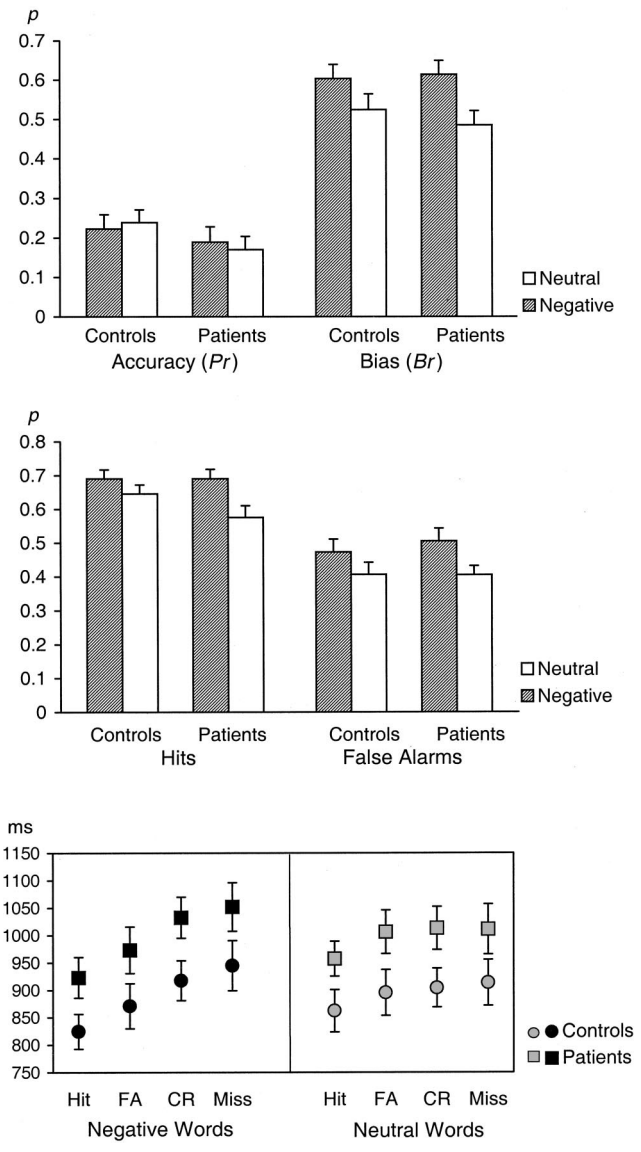

Figure 2. Behavioral results. Top panel: Response bias (*Br*) and old/new discrimination performance (*Pr*) of patients and control participants for emotionally negative and neutral items. Center panel: Hit rates and false alarm rates of patients and control participants for emotionally negative and neutral items. Bottom panel: Reaction times associated with correct responses of "old" (hits), incorrect responses of "old" (false alarms, FA), correct responses of "new" (correct rejections, CR), and incorrect responses of "new" (misses) of patients and control participants.

anxiety scores in the patient sample, but not in the control sample. The correlation with state anxiety scores was marginally significant in the patient sample ($p < .10$). For the entire group (patients and control participants), the correlations were as follows: BDI = .45 ($p < .02$), trait anxiety = .33 ($p < .10$), and state anxiety = .35 ($p < .10$).

An ANOVA on the reaction time data involving the between-subjects factor, group, and the three repeated measures factors—valence (negative/neutral), response type (old/new), and correctness of response (correct/incorrect)—revealed a marginally significant group effect, $F(1, 32) = 3.88$, $p < .06$, as the patients' responses were on average about 100 ms slower than those of the control participants (see Figure 2, bottom panel). The main effect of response type was significant, $F(1, 32) = 24.33$, $p < .0001$, as responses of "old" were overall much faster than responses of "new." The main effect for correctness of response was also significant, $F(1, 32) = 12.71$, $p < .001$, as correct responses were made faster than incorrect responses. The interaction effect of correctness of response and response type was also significant, $F(1, 32) = 10.007$, $p < .005$. Post hoc tests indicated that for responses of "old," correct responses (hits) were made faster than incorrect responses (false alarms), $F(1, 33) = 22.34$, $p < .001$, whereas this pattern did not hold for responses of "old" (i.e., correct rejections and misses ($F = 2.63$, $p = .11$; see Figure 2).

ANOVA Results of the ERP Data

Figure 3 shows the grand average of the ERPs recorded at parasagittal midline sites of the right hemisphere of the control participants ($N = 17$) and the patients ($N = 17$) for correctly recognized old items (hits) as compared with correctly recognized new items (correct rejections: CR) and incorrectly recognized new items (false alarms: FA). Figure 4 shows the mean values submitted to the ANOVA.

In the *early time-window* (300–500 ms), the ANOVA yielded a significant old/new main effect, $F(1, 32) = 13.63$, $p < .001$, indicating overall more positive ERP amplitudes for old items relative to new items. The Group × Old/New interaction was also

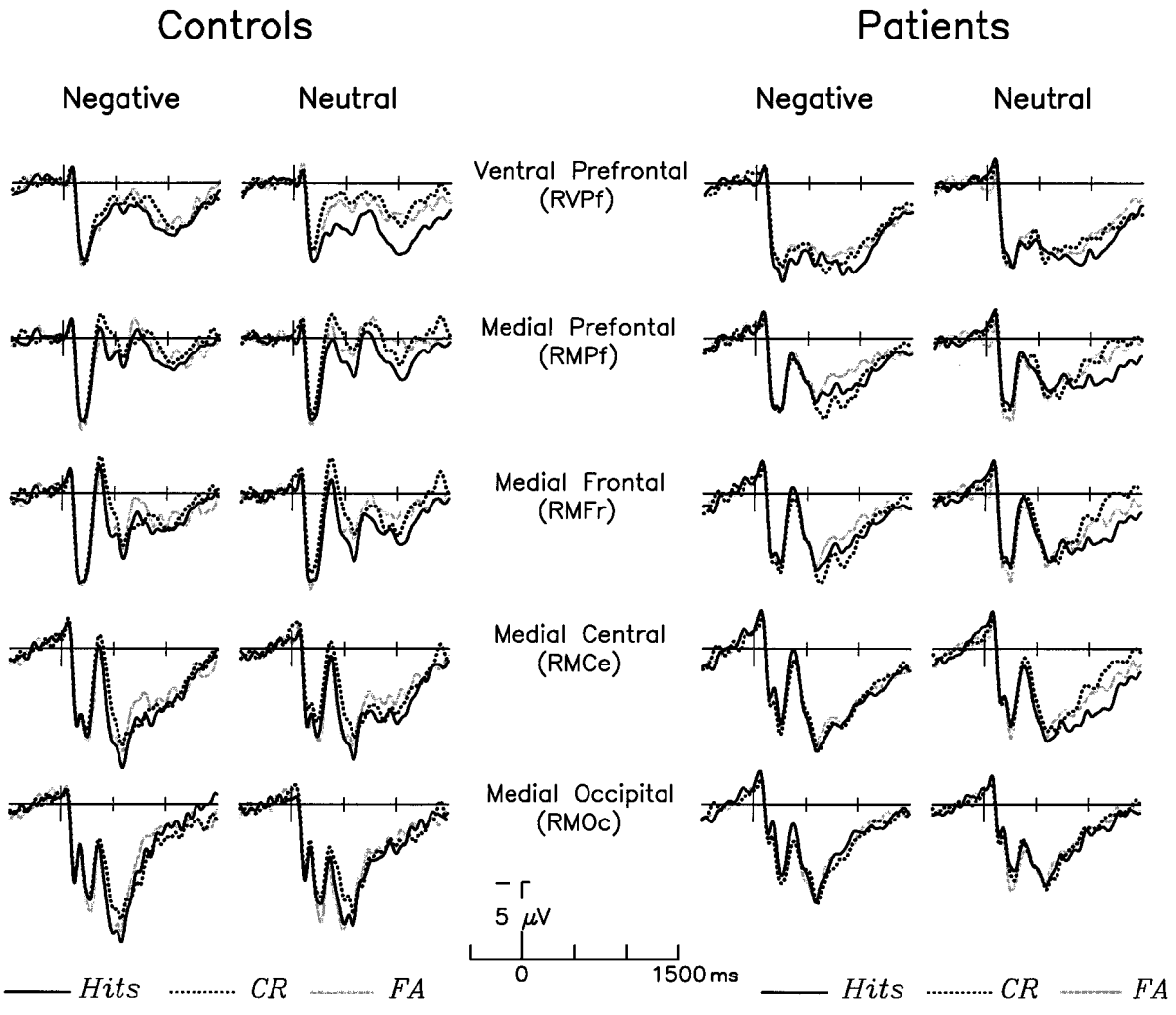

Figure 3. Grand average event-related brain potentials (ERPs) associated with hits, correct rejections (CR), and false alarms (FA) of negative and neutral items, for patients and control participants. A subset of sites at the right medial parasagittal line is shown (cf. Figure 1).

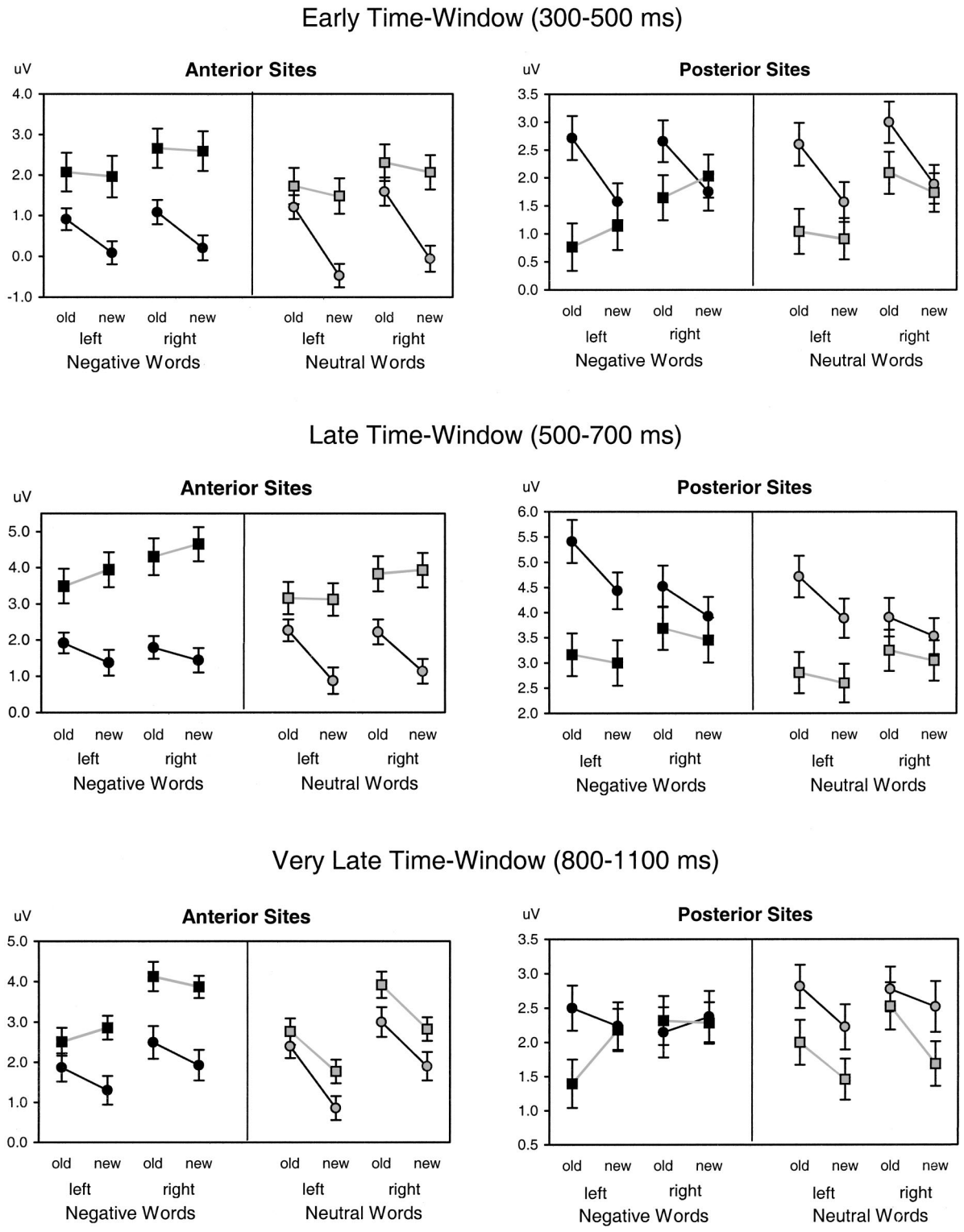

Figure 4. Mean amplitudes of event-related brain potentials (ERPs) at anterior and posterior sites to negative and neutral items associated with hits and correct rejections (CR) for patients and control participants. Negative slopes of the lines indicate the typical ERP old/new effect (with old items eliciting more positive potentials than new items). Note the different scales for the data from anterior and posterior sites. Squares represent patients; circles represent control participants.

significant, $F(1, 32) = 11.46$, $p < .005$, as was the Group × Anteriority interaction, $F(1, 32) = 4.36$, $p < .05$. In addition, there was a significant Group × Old/New × Valence × Anteriority interaction, $F(1, 32) = 4.45$, $p < .05$.

Post hoc tests were performed to elucidate the nature of this pattern of results. In the control sample, there was a significant old/new effect, $F(1, 16) = 25.78$, $p < .0001$, accompanied by a significant Old/New × Valence × Anteriority interaction, $F(1, 16) = 7.24$, $p < .01$. By contrast, there were no such effects in the panic patient group (Fs < 1). To further elucidate the Old/New × Valence × Anteriority interaction in the control sample, separate analyses were performed for the negative and neutral items. For neutral items, a significant old/new effect, $F(1, 16) = 14.22$, $p < .001$, and a significant Old/New × Anteriority interaction, $F(1, 16) = 10.49$, $p < .005$, were found. The interaction reflected that the old/new difference was larger over anterior sites, $F(1, 16) = 17.50$, $p < .001$, than over posterior sites, $F(1, 16) = 9.43$, $p < .01$. For negative items, the old/new main effect was significant, $F(1, 16) = 11.36$, $p < .005$, but the Old/New × Anteriority interaction was not ($F = 0.40$).

No other significant differences between the two groups were observed. However, there was a significant Old/New × Valence × Hemisphere × Anteriority interaction, $F(1, 32) = 4.27$, $p < .05$, and a marginally significant Valence × Anteriority interaction, $F(1, 32) = p < .07$. Both of these effects seem to reflect a larger anterior–posterior amplitude gradient for negative than for neutral words, especially for ERPs to old items recorded over the right hemisphere. As can be seen from Figure 4, negative old items tended to elicit larger N400 amplitudes over right hemisphere sites than did neutral old items (cf. Windmann & Kutas, 2001).

In the *later time-window* (500–700 ms), the Group × Anteriority interaction continued to be significant, $F(1, 32) = 8.89$, $p < .01$. The old/new main effect remained marginally significant, $F(1, 32) = 3.34$, $p < .08$, as did the Group × Old/New interaction effect, $F(1, 32) = 3.55$, $p < .07$. These effects were accompanied by a significant Old/New × Valence × Anteriority interaction, $F(1, 32) = 4.38$, $p < .05$. As in the previous analysis, post hoc tests demonstrated that healthy control participants produced relatively typical ERP old/new effects, $F(1, 16) = 6.54$, $p < .025$, whereas the patients did not ($F < .01$). Additional analyses were performed on the data from the two groups separately. In the patient sample, there were no interactions involving the old/new factor (all Fs < 1). In the control group, there was an Old/New × Valence × Anteriority interaction, $F(1, 16) = 8.70$; $p < .01$, reflecting the larger old/new effect for neutral items, $F(1, 16) = 4.89$, $p < .05$, than for negative items ($F = 2.83$, *ns*)—a difference which was particularly pronounced at anterior sites: neutral, $F(1, 16) = 6.17$, $p < .025$, versus negative ($F < 1.2$).

The omnibus ANOVA for this time-window also revealed a significant Group × Valence × Anteriority interaction, $F(1, 32) = 4.13$, $p < .05$. Unlike in the earlier time-window, negative items tended to elicit more positivity at posterior sites compared with neutral items in the control sample (as part of a late positive complex amplitude modulation, consistent with previous observations; Naumann, Maier, Diedrich, Becker, & Bartussek, 1997; Schupp et al., 2000), whereas this difference was less than 0.1 μV at anterior sites. The patient data showed the opposite pattern: ERPs to words with negative emotive connotations were more positive than those to neutral words, especially over frontal as compared with posterior sites (see Figure 4).

Finally, there was a significant Group × Hemisphere interaction, $F(1, 32) = 4.72$, $p < .05$, as the overall right–left difference of the ERPs was negative in the controls (~−.31 μV) but positive in the patients (~.61 μV).

In the *very late time-window* (800–1,100 ms), the Group × Anteriority interaction effect present in the two previous time-windows just missed statistical significance, $F(1, 32) = 4.09$, $p < .052$; however, the old/new main effect remained significant, $F(1, 32) = 4.37$, $p < .05$. The old/new effect was marginally larger for the neutral words than for the negative ones, Old/New × Valence interaction effect, $F(1, 32) = 3.06$, $p < .09$, and was larger over anterior sites than over posterior sites, Old/New × Anteriority interaction effect, $F(1, 32) = 4.70$, $p < .05$ (see Figure 4). No clear differences between the groups emerged in this analysis. Only two marginally significant effects including group were found: (a) a Group × Old/New × Hemisphere interaction, $F(1, 32) = 3.88$, $p < .058$, reflecting a larger old/new difference over the left than right hemisphere in controls and the reverse pattern in the panic patients; and (b) a Group × Valence × Hemisphere interaction, $F(1, 32) = 3.20$, $p < .09$, reflecting group differences in the pattern of ERP asymmetries for neutral and negative stimuli. In the controls, ERPs to neutral items tended to be more positive than those to negative items over the right hemisphere (0.3) and more negative over the left (~ −0.1), whereas in the patients, ERPs to neutral items were *less* positive than those to negative items over both hemispheres (−0.24 and −0.40, respectively).

In summary, the group differences with respect to the emotion-dependent old/new effects were maximal, as predicted, in a relatively early time-window (300–500 ms) at the prefrontal sites (Figure 3). Frontal old/new effects were reliably modulated by the emotive connotation of the eliciting words in the controls but not in the patients. The patients not only showed the same ERP old/new effect for negative and neutral words but this pattern resembled the one generated by controls in response to emotionally *negative* words. That is, panic patients showed virtually no sign of the anterior old/new effects that characterized the ERPs of the controls to emotionally neutral items.

Visual inspection (Figure 3), however, suggested that the patients did show emotion-dependent old/new effects much later in their ERPs, namely post–1000 ms, albeit with a somewhat different distribution than the earlier effect seen in the controls. We performed an additional, exploratory analysis to test the statistical reliability of this observation. An ANOVA of the mean ERP amplitudes between 1,100 and 1,500 ms at the five sites depicted in Figure 3 revealed a significant old/new main effect, $F(1, 16) = 9.70$, $p < .005$, a significant Old/New × Valence interaction effect, $F(1, 16) = 9.00$, $p < .006$, and a significant Old/New × Site interaction effect, $F(4, 128) = 5.57$, $p < .006$ (Huynh-Feldt corrected). Most importantly, for present purposes, there was a significant Group × Old/New × Valence × Site interaction effect, $F(4, 128) = 2.62$, $p < .05$ (Huynh–Feldt corrected). Post hoc tests in the controls yielded no significant old/new effects nor any significant interactions involving valence; there was only a reliable Old/New × Site interaction, $F(4, 64) = 6.53$, $p < .05$ (Huynh–Feldt corrected). In contrast, the patients' ERPs did show a significant old/new main effect, $F(1, 16) = 7.74$, $p < .015$, as well as an Old/New × Valence interaction effect, $F(1, 16) = 7.84$, $p <$

.015, reflecting a significant old/new effect in response to neutral words, $F(1, 16) = 12.17$, $p < .005$, but not in response to emotionally negative words ($F = 1.20$). Morever, the old/new effect for neutral words was not evenly distributed across the five sites included in the analysis as reflected in an Old/New × Site interaction, $F(4, 64) = 2.86$, $p < .05$ (Huynh-Feldt corrected). As can be seen in Figure 3, this very late ERP old/new effect was largest at frontocentral sites, falling off somewhat at the occipital and the ventral prefrontal sites. Post hoc tests confirmed that the old/new difference over the medial frontal site (RMFr) was larger than over both the medial occipital site, $F(1, 16) = 4.86$, $p < .05$, and the ventral prefrontal site, $F(1, 16) = 6.60$, $p < .025$, but not significantly different from either of the two sites directly adjacent to it (medial prefrontal and medial central).

Correlations of Clinical Scores With ERP Amplitudes

Both visual inspection (Figures 3 and 4) and the ANOVA results point to a different spatial distribution of the overall ERP amplitudes in the patients and the controls. The patients' potentials are larger than those of the controls over prefrontal sites (but smaller over posterior sites). The two groups also differ in the laterality of their ERP amplitudes. To further examine the potential clinical relevance of these ERP differences, we correlated amplitude measures with clinical scores for all the participants in whom both were available. Mean amplitudes were taken between 300 and 700 ms, collapsed across all item- and response types.

For the entire sample (patients and controls), ERP amplitudes at frontal sites were significantly correlated with BDI (.481) and trait anxiety scores (.466) but not with state anxiety scores (.301). This pattern of correlations was even more pronounced in the patient sample alone (BDI = .566; trait = .490; state = .126). The right–left asymmetry of the ERP amplitudes correlated significantly only with state anxiety scores (.516); correlations with BDI (.313), and trait anxiety scores (.329) were not significant. In the patient sample alone, these correlations were .510, .156, and −.136, respectively. None of these correlations was significant in the control sample alone (however, note the limited variance in all variables).

Possible Role of Different Response Times in Accounting for Control/Patient ERP Differences

We examined the possibility that either the reduced overall old/new differences or the absence of the emotion-related effects in the patients' ERP data before 700 ms was due solely to their slower response times relative to the controls. We first divided the patient sample into two groups based on their median reaction times. Patients with relatively short reaction times ($N = 8$) had an overall mean reaction time of 894 ms, similar to that of the controls (892 ms). Nonetheless, they differed from the controls in the timing of their ERP old/new effects: The earliest signs of frontal old/new effects in the patients' ERPs to neutral items occurred about 400ms later than in the control group. An ANOVA of mean ERP amplitudes taken in the early time-window at the frontal sites contrasting the two subgroups of the patients with fast (892 ms) vs. slow (1,097 ms) response times revealed no significant interaction of speed with either the valence or the old/new factors (all Fs < 1). Most importantly, the effect size of the relevant Speed × Old/New × Valence interaction was close to zero ($F = 0.01$). These results indicate that the overall difference between patients and controls in mean reaction times cannot account for the observed differences in their old/new effects before 500 ms post-stimulus onset.

Discussion

We investigated the mechanisms involved in recognition of words with negative and relatively neutral connotations in patients with panic disorder (and some mild depression) and in healthy control individuals. Our experiment was aimed at using a combination of behavioral and scalp recorded electrical activity measures to arrive at a better understanding of whether the emotive content of the stimulus words affected the cognitive and neural processes involved in old/new recognition memory decisions differentially in the two groups. We expected the controls to show clear behavioral and electrophysiological signs of (presumably prefrontally mediated) top-down inhibition on the retrieval of emotionally neutral words but not on the retrieval of negative words, resulting in (a) a tendency to classify the negative words as "old" more often than neutral ones, and (b) a differential pattern of ERP old/new effects for negative and neutral words over frontal sites, as previously reported (Maratos et al., 2000; Windmann & Kutas, 2001). We predicted that these emotion-induced effects would be reduced or even absent in the patients in a latency range that has previously been argued to reflect a greater contribution from early, automatic memory processes than from conscious or controlled processes. Under the assumption that these patients were inclined to treat all stimuli, regardless of their actual content, as if they were menacing, we predicted further that the pattern of their ERP old/new effects should resemble that shown by controls in response to negative words (rather than that shown to neutral words).

The results, in large part, confirmed our predictions, some unanticipated results notwithstanding. As predicted, there was a reliable group difference in the pattern of ERPs over frontal sites early during stimulus processing: The control group showed valence-dependent modulations of their frontally distributed ERP old/new effects starting around 300 ms post-word onset, whereas the patient group did not. In line with previous findings, for words with emotionally neutral connotations, the controls' ERPs to correctly recognized old items (hits) were reliably more positive than those to new items (correct rejections) for almost one second, presumably until the recognition response was given. Words with negative connotations, by contrast, were associated with significantly smaller, if any, ERP old/new effects at frontal sites across the entire recording epoch.

By contrast, the patients responded uniformly to negative and neutral items in this early time-window. The earliest sign of effects of emotion on the patients' ERP old/new effects appeared after 700 ms when the patients started to show ERP effects similar to those in the controls. This means that the old/new divergence in response to neutral items was delayed by about 400 ms in the patient sample compared to that in the control sample. These electrophysiological differences between the patients and the controls cannot be explained by group differences in accuracy or speed of processing. Differences in accuracy were small and negligible; and speed of response did not have any significant impact on the pattern of ERP

results. Though the patients were in fact somewhat slower in rendering recognition decisions than the controls (about 100 ms on average), an analysis of a subset of patients with reaction times equal to that of the control participants indicated that there were virtually no ERP old/new effects for neutral items in these patients in the early time-window (300–500 ms) and a somewhat reduced effect in the later time-window (500–700 ms).

In the very late time-window (800 and 1,100 ms poststimulus), valence effects on the ERP measures of the patients and the controls seemed to be fairly equivalent, although differences in the laterality pattern remained. It is surprising, however, that the patients showed an even greater valence-dependent modulation of their ERP old/new effects than the controls *after 1,100 ms.* Notably, the distribution of these very late old/new effects in the patient sample was different than it had been in the control sample in the early and the late time-windows: They peaked at frontocentral rather than prefrontal sites. This finding points to the engagement of different mechanisms in the patient and the control subjects as they performed this recognition memory task with emotionally negative and neutral words.

The timing of the early ERP differences between the two groups (between 300 and 500 ms) suggests that they are related to automatic memory and familiarity processes more than to consciously controlled memory (Allan et al., 1998; Curran, 2000; Düzel et al., 2001; Paller, 2000; Paller et al., 1995; Rugg et al., 1998). Qualitatively, the pattern confirmed our expectations: There is virtually no frontal ERP old/new effect in the patient sample for neutral words, just as there is none in the control group for negative words. Thus, the patients seem to treat neutral words at this early processing stage the same way control subjects treat negative words; that is, the patients respond as if they associated negative implications or consequences with the neutral words. This interpretation is consistent with a number of theoretical assumptions linking pathological anxiety to implicit affective biases and overreactive automatic threat-detection systems (Beck & Clark, 1997; G. Matthews & Wells, 2000; McNally, 1995; Mogg & Bradley, 1998; Williams, Watts, MacLeod, & Mathews, 1997; Windmann, 1998). More specifically, it has been suggested that the recurrent irrational fears of panic/anxiety patients might arise from deficits in the conceptual verification and inhibition of preattentively triggered alarm signals ascending from diencephalic structures within the limbic system (Beck & Clark, 1997; C. R. Clark et al., 1996; Gorman et al., 2000; LeDoux, 1996; Quirk et al., 2000; Windmann, 1998). Intact communicative interchange between ventromedial prefrontal cortex areas and the amygdala complex has been shown to be crucial for this type of regulation of affect (Dias et al., 1996; Gorman et al., 2000; LeDoux, 1996; Quirk et al., 2000; Schoenbaum, Chiba, & Gallagher, 2000; Windmann, 1998). Insofar as the early anterior ERP old/new effects observed in a recognition memory task with emotional stimuli index the engagement of such higher order control functions by the prefrontal cortex, the present data provide empirical support for these proposals.

We suggest further that the lack of modulation of the early ERP old/new effects in the patient sample according to the actual emotional salience of the word stimuli may be causally related to other group differences seen in the ERP data before 700 ms poststimulus. The spatial distribution of the patients' ERPs (collapsed across all conditions) differed from that of the controls, particularly during that early half of the recording epoch in which the stimuli are usually analyzed and response decisions are generated: Patients' ERPs were characterized by more positivity anteriorly (and more negativity posteriorly) than those of the controls and by a positive right > left difference compared to a negative one for controls. Remarkably, these abnormal distributions of the ERP amplitudes across the scalp correlated significantly with clinical scores. ERP amplitudes over frontal sites in the patients correlated significantly with their depression and trait anxiety scores, and the right–left asymmetry correlated significantly with their state anxiety scores. Apparently, the topography of the brain potentials in the patients reflect their *internal states* typified by negative affect and/or negative expectations rather than the emotive content of the external input (words) presented.

These findings may be related to the type of functional neuroanatomical abnormalities that have been described for anxiety and depression on the basis of other dependent measures (Davidson, 1998; Davidson et al., 1999; Drevets, 1998; Heller, Nitschke, & Miller, 1998; Javanmard et al., 1999; Reiman, 1997; Wiedemann et al., 1999). Particularly dysfunctions of the orbital part of the prefrontal cortex can give rise to an inflexible, perseverative form of affective reaction to events of varying emotional significance (Dias et al., 1996; Hauser, 1999; Quirk et al., 2000). Hence, patients with panic disorder might habitually engage a processing mode wherein prefrontally mediated top-down control over limbic and other posterior cortex areas is *dis*inhibited. This interpretation corresponds with SPECT findings of decreased prefrontal benzodiazepine receptor reuptake in these individuals (Kaschka et al., 1995; Kuikka et al., 1995; Malizia et al., 1998), as well as with those of a recent animal study demonstrating that dysfunctions of the inhibitory $GABA_A$ receptor induces anxiety, avoidance behavior, and a bias for emotionally negative associations (Crestani et al., 1999).

Turning to our less expected findings we note that the pattern of the behavioral results in the patients is completely normal with regards to both old/new recognition accuracy and response bias. More surprisingly, their emotion-induced recognition bias is *positively* correlated with their depression and trait anxiety scores. While this result underscores the importance of this bias in the development and maintenance of affective disorders, it appears to contradict the logic of our argument as outlined above. If anxiety and depression were truly based on a diminished capacity for successfully discriminating negative from neutral items (as the patients' ERP data suggest), and for selectively modulating inhibitory brain functions accordingly, then the emotion-related recognition bias should have been *smaller* for the patients with panic disorder relative to controls, as was found previously (Windmann & Krüger, 1998). In addition, the emotion-induced shift in the bias should correlate *negatively,* not positively, with the severity of the affective symptoms (cf. Brébion, Smith, Amador, Malaspina, & Gorman, 1997). Also obscure is the apparent dissociation between patients' recognition performance and the associated electrophysiological modulations, that is, the finding that patients' old/new discrimination performance is normal for both neutral and emotionally negative words, even though they showed markedly diminished, if any, ERP old/new effects prior to 700 ms. Finally, we had not anticipated the significantly *enhanced* valence-dependent old/new divergence seen in the ERPs of the patients after 1,100 ms—an effect peaking over frontocentral sites and not over the

'ventromedial' prefrontal scalp sites where the earlier old/new effect was localized in the control participants.

Perhaps the patients with panic disorder, or at least some of them, have learned to compensate for their automatic processing deficits with slow, capacity-limited, and consciously controlled strategies, which are reflected in the very late part of the ERP waveform. On this hypothesis, the patients invoke higher order processes to perform the emotional memory task, and the bias shift that it requires, in lieu of the customary reliance on presumably deficient automatic stimulus appraisal processes. The neural circuitry sustaining these compensatory operations apparently differs, at least to some extent, from that habitually engaged by the control individuals. This is suggested not only by the huge timing difference but also by the different spatial scalp distributions of the early emotion-related bias effects in the control group compared to the very late (~1,100 ms) effect in the patients. The very long latency at which these processes are manifest in the patients' ERPs is remarkable and unusual for a simple old/new recognition memory task with speeded instructions. It is noteworthy that at least half of the recognition decisions had already been rendered by the time these late old/new ERP effects became statistically significant. Naturally, we must be mindful that any ERP divergence only provides an upper bound on the onset of the processes of interest, and that our interpretation is only a post hoc explanation of the unanticipated effects we observed.

Given that our patient group had mild depression together with the more prominent panic/anxiety symptoms, it is possible that the pattern of ERP effects reported herein reflect the influence of both these disorders and not just panic disorder per se. For example, deficits related to panic/anxiety may be the cause of the early differences while depression may relate more to the very late differences between the two groups. On this hypothesis, panic/anxiety symptoms may be relatively more related to the proposed deficits in automatic processes while depressive symptoms may be more closely linked to abnormal conscious evaluation processes. This interpretation is in line with suggested distinctions between panic/anxiety and depression in the cognitive literature (Mathews & MacLeod, 1994; Mogg & Bradley, 1998; Williams et al., 1997). Although the comorbidity of anxiety and depression, especially in advanced stages of panic disorder, will make it empirically very hard to tease apart the neural and cognitive processes sustaining these two disorders, certainly this will be an important next step (Beck & Clark, 1991; Keller et al., 2000; Mogg & Bradley, 1998; Williams et al., 1997). Likewise, we remain cautious about generalizing these results (and their interpretation) to individuals with other forms of anxiety.

In conclusion, our data suggest that it may be possible to ameliorate if not counteract the consequences of chronic dysfunctioning in early affective stimulus evaluation processing on overt behaviors so that patients with mood disorders characterized by a tendency towards behavioral withdrawal and avoidance may function relatively normally in many everyday life situations (C. R. Clark et al., 1996). Naturally, these "compensatory" higher order processes may provide a possible target for the cognitive–behavioral therapeutic approach (Beck & Clark, 1997; Gorman et al., 2000; LeDoux, 1996; Windmann, 1998). This may be particularly important for individuals with a longer history of anxiety disorders who also tend to be more depressed. In the present study, the only behavioral remnant of the dramatic abnormalities observed in the patients' ERP data is a slowing of about 100 ms in mean reaction times (relative to age- and education-matched controls).

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Appendix

Stimulus Examples

Neutral words			Negative words		
protract	paraphrase	revise	wreck	stagger	degrade
designate	allegorize	refine	destroy	slander	shame
denominate	describe	actualize	damage	batter	punch
persuade	accentuate	qualify	crush	strike	insult
convince	elucidate	renew	ruin	hit	enrage
discuss	signalize	verify	demolish	stab	humiliate
negotiate	delineate	modulate	mutilate	harm	intimidate
interpret	verbalize	draft	disturb	spank	demoralize
inform	explicate	illustrate	eliminate	torment	fight
formulate	illuminate	sketch	extinguish	strangle	provoke
tabulate	articulate	doodle	deprive	murder	conquer
enunciate	intone	compose	exterminate	rape	criticize
emblazon	display	outline	cease	execute	disappoint

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