

Event-related potentials (ERPs) to hemifield presentations of emotional stimuli: differences between depressed patients and healthy adults in P3 amplitude and asymmetry

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Abstract

Depression may involve dysfunction of right parietotemporal cortex, a region activated during perception of affective stimuli. To further test this hypothesis, event-related brain potentials (ERPs) were measured in a paradigm previously shown to produce ERP asymmetries to affective stimuli over parietal sites in healthy adults. Pictures of patients with dermatological diseases showing disordered or healed facial areas before (negative) or after (neutral) surgical treatment were briefly exposed for 250 ms to either the left or right hemifield. ERPs of 30 unmedicated, unipolar depressed patients and 16 healthy adults, all right-handed, were recorded from 30 electrodes. A principal components analysis extracted factors which closely corresponded to distinctive ERP components previously reported for this task (N1, N2, early P3, late P3, slow wave). Significant effects of emotional content, i.e. enhanced amplitudes to negative than neutral stimuli, were found for early and late P3. Control subjects showed significant hemispheric asymmetries of emotional processing for late P3 (peak latency 460 ms), with the largest emotional content effects over the right parietal region. In striking contrast to control subjects, depressed patients did not show an increase in late P3 for negative compared to neutral stimuli over either hemisphere and had smaller late P3 amplitude than control subjects. Patients did, however, show larger early P3 (peak latency 330 ms) to negative than neutral stimuli.

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Results suggest intact early discrimination but abnormal late appraisal of affective content in depression, which may arise from selective inhibition of right parietal regions integral for perceiving and evaluating emotional stimuli. © 2000 Elsevier Science B.V. All rights reserved.

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1. Introduction

Several lines of evidence suggest that mood disorders are associated with specific patterns of regional hemispheric activation, which may reflect dysfunctions of left frontal and/or right parietal-temporal cortical regions (e.g. see reviews by Kinsbourne, 1988; Tucker, 1988; Henriques and Davidson, 1989; Heller, 1990; Bruder, 1995). Neurophysiological and neuropsychological findings implicate left frontal hypoactivation in depression, as revealed by quantitative electroencephalogram (EEG) alpha asymmetry, functional imaging, and neuropsychological test profiles (e.g. Henriques and Davidson, 1991; Allen et al., 1993; George et al., 1994; see reviews by Goodwin, 1997; Rogers et al., 1998). On the other hand, behavioral and neuropsychological evidence, including the performance of depressed patients on neuropsychological tests (e.g. Flor-Henry, 1976; Abrams and Taylor, 1987; Miller et al., 1995), and on behavioral laterality tasks using either visuospatial (e.g. Jaeger et al., 1987; Liotti et al., 1991; David, 1993; Heller et al., 1995) or auditory stimuli (e.g. Bruder et al., 1989, 1992; Overby et al., 1989; Yovell et al., 1995), also suggest a right posterior deficit in depression.

This evidence parallels findings from patients with unilateral brain lesions. Lesions close to the left frontal pole have been found to be correlated with dysphoric symptoms, whereas emotional indifference was common with right-hemispheric lesions (see reviews by Gainotti, 1983, 1989; Silberman and Weingartner, 1986; Starkstein and Robinson, 1988). Extending these findings, Shimoda and Robinson (1999) reported that the anatomical correlates of post-stroke depression change over time, observing short-term effects of left anterior lesions and long-term effects of right posterior lesions. Damage to the right hemi-

sphere, particularly to right parietal areas, also interferes with processes required for the perception and evaluation of emotional stimuli (e.g. Silberman and Weingartner, 1986; Etcoff, 1989; Heller, 1990). Furthermore, there is ample evidence that right parietal lesions are also often associated with reduced autonomic arousal (e.g. Heilman et al., 1978; Tranel and Damasio, 1994; see reviews by Gainotti, 1987, 1989), and autonomic arousal usually accompanies emotional processing. Several authors have argued that the mood changes observed after unilateral brain damage are characterized by qualitatively different types of depressive reaction: *cognitive-anxious* after left frontal lesions, and *anhedonic-detached* after right posterior lesions (e.g. Kinsbourne, 1988; Gainotti, 1989). Heller (1990, 1993) has proposed a model which links one neural system located in the frontal lobes to emotional valence (pleasant–unpleasant is determined by the ratio of left–right hemispheric activation), and another neural system located in the right parietotemporal region to emotional responsivity, affective perception, and related autonomic nervous system responses. According to Heller (1990), emotional state is determined by the relative activation of both neural systems, so that depression is characterized by a right-greater-than-left frontal activation and a relative hypoactivation of right parietotemporal regions. A direct prediction from this model is that depressed patients should show reduced cortical responses to emotional stimuli, particularly over right parietal regions that are thought to mediate affective perception.

Until recently, few studies had recorded event-related brain potential (ERP) measures as concomitants of emotional processing (for a review, see Kayser et al., 1997), but their number is growing. Although these ERP studies differ widely

in methodology, a relatively consistent finding has been that the late positive P3 component is enhanced for positive and negative stimuli when compared with neutral stimuli (e.g. Johnston et al., 1986; Naumann et al., 1992; Palomba et al., 1997), and this enhancement is greatest over the right parietotemporal region (Cacioppo et al., 1993, 1996; Kayser et al., 1997). This lateralization of cortical activity related to emotional processing has also been confirmed by functional imaging data (Lang et al., 1998). Studying a homogenous sample of young, right-handed women (Kayser et al., 1997), we found enhanced amplitudes for negative compared to neutral stimuli for several ERP components (i.e. N2, P3, and slow wave). Hemispheric asymmetries in emotional processing were restricted to subcomponents of the N2–P3 complex, with maximal effects over the right parietal region. Given hypotheses of right parietotemporal hypoactivation in depression (Heller, 1990), we would predict that during processing of emotional stimuli depressed patients would show anomalies in these ERP components recorded over this cortical region.

So far, there has been little ERP research on emotional processing in clinically depressed patients. However, one recent study (Deldin et al., in press; see also Miller, 1996) found reduced N2 amplitude to emotional face stimuli in depressed patients, with largest reductions over the right parietal cortex. ERP measures in depressed patients have typically been used as an electrophysiological index of cognitive information processing deficits (Yee, 1995; Miller, 1996). Some ERP studies have reported deficits or anomalies in depression for early sensory and attentional processes, as reflected by ERP components such as P1 and N1 (e.g. el Massioui and Lesevre, 1988; Pierson et al., 1996), for automatic stimulus processing, as reflected by mismatch negativity or N2a (e.g. el Massioui and Lesevre, 1988; Ogura et al., 1993), for initial allocation of conceptual resources, as reflected by N2b (e.g. Bruder et al., 1998b), and for effortful stimulus evaluation, as reflected by late ERP components such as P3 (e.g. Bruder et al., 1995, 1998b; Pierson et al., 1996). Other studies comparing healthy individuals and moderately depressed patients have found

no group differences in N1 (e.g. Bruder et al., 1995, 1998b), N2b (e.g. Ogura et al., 1993), or P3 amplitude (e.g. Sara et al., 1994; Bange and Bathien, 1998). A defining feature of functional deficits seen in depression may be the differential involvement of various brain regions during specific forms of cognitive processing, but few studies with clinically depressed patients have tried to exploit the topographic information potentially provided by ERP measures.

The experimental paradigm used in a prior study of healthy adults (Kayser et al., 1997) appeared to be a good starting point for investigating ERP topography in depressed patients during processing of emotional stimuli. This paradigm controls for several potentially confounding variables. First, emotional content is manipulated using negative and neutral pictures that are highly similar in physical characteristics so as to reduce the contribution of visual–spatial stimulus characteristic, which may impact on functional hemispheric asymmetries (e.g. Young, 1983). Second, pictures are presented to one hemifield, directly stimulating the contralateral hemisphere (e.g. McKeever, 1986), and thereby controlling for asymmetries arising from exogenous stimulus processing. Third, participants are instructed to attend to the pictures, but no overt response is required so as to enhance inherent affective reactions to these stimuli rather than cognitive information processing, and also to minimize motor-related artifacts (e.g. Kayser et al., 1998; Tenke et al., 1998). Lastly, the use of a 30-electrode recording montage to cover the scalp provides more adequate topographies of regional hemispheric activation during emotional processing.

Given the specific findings of the Kayser et al. study, the immediate goal of the present study was to probe right parietal functioning during the perception of emotional stimuli in healthy adults and clinically depressed outpatients, and further explore hemispheric asymmetries for emotional processing in these groups by using a more dense electrode array. For healthy participants, we expected to find greater amplitudes of late ERP components (N2, P3, slow wave) to negative than neutral stimuli over posterior brain regions, and that these differences would be greatest over right

parietal-temporal regions for subcomponents of the N2–P3 complex. We further hypothesized that depressed patients would show reduced amplitudes of components of the N2–P3 complex, particularly over the right parietal region, and less increase in late positivity to emotional stimuli. By analyzing the time course of ERPs with adequate spatial resolution, we hoped to gain further insight into the temporal characteristics of regional hemispheric abnormalities during emotional processing in mood disorders.

2. Methods

2.1. Participants

Thirty depressed outpatients (14 male) were recruited from a university-affiliated depression research clinic at New York State Psychiatric Institute. All aspects of the diagnostic assessment of the depressed individuals were carried out by research psychiatrists in the clinic. All depressed participants were diagnosed with unipolar depressive disorder, meeting DSM-IV criteria for either major depressive disorder ($n = 13$), dysthymic disorder ($n = 7$), or both ($n = 10$). The depressed patients were tested after a minimum drug-free period of 1 week, with most participants being drug-free for a considerably longer period. Depressed patients were compared with 16 healthy adults (seven male) recruited from the New York City metropolitan area through newspaper advertising and local postings. Control participants were screened using a modified version of the Schedule for Affective Disorders and Schizophrenia-Lifetime Version (Spitzer and Endicott, 1975) to exclude those with current or past psychopathology.

All participants were right-handed as indicated by the Edinburgh Handedness Inventory (Oldfield, 1971), and all had normal or corrected-to-normal vision. Prior to the session, participants were given a baseline questionnaire to verify that they were not on the test day taking any medication, alcohol, caffeine, or nicotine, and were not distressed by mental (e.g. academic tests) or physical (e.g. exercise) demands. Individuals were only included in the study if they had no history of any

neurological or substance abuse disorder, and if they yielded at least 50% valid trials (see below). All participants were paid approximately US\$30 for participation.

Table 1 summarizes relevant characteristics of depressed patients and control participants. As expected, depressed persons had considerably higher scores on the Beck Depression Inventory (Beck et al., 1961), $F_{1,30} = 18.8$, $P < 0.0001$. There were no group differences in gender, mean education level, and handedness. Individuals in the patient group were 22–55 years old, and those in the control group were 20–48 years old. Although comparable in age range, groups differed significantly in mean age ($F_{1,42} = 15.3$, $P < 0.001$). Since age is known to affect latency, amplitude, and topography of exogenous and endogenous ERP components, particularly P300 latency (e.g. Hilliard and Picton, 1987; Gilmore, 1995), the 16 youngest depressed patients were compared with the 16 healthy control subjects on all ERP components using repeated measures ANOVA (see ERP component evaluation and statistical analysis below). There was no significant group difference in age for this data subset, but all effects were comparable to those reported below for the total sample of depressed patients. Most importantly, essential group effects involving hemisphere and emotional content found for late P3 were maintained at an even stronger significance level for this subgroup of younger depressed patients.

2.2. Stimuli and procedure

The general experimental procedure, i.e. selection of stimuli and stimulus presentation, closely followed that of former studies (Kayser, 1995; Kayser et al., 1997). Thirty-two pictures depicting patients with dermatological diseases served as stimuli, one half displaying disordered facial areas *before* or immediately after surgical treatment (negative), the other half showing the same facial areas a few years *after* the operation (neutral), i.e. healthy skin or a healed scar. The major advantage of this stimulus set is that, within each picture pair, neutral stimuli differ from negative stimuli only in the emotionally relevant feature

Table 1
Participant characteristics

Variable	Patients	Controls
Gender (<i>n</i>)		
Female	16	9
Male	14	7
Age (years)		
Mean	39.5 ^a	27.4
S.D.	10.7	8.6
Education (years)		
Mean	15.0 ^b	15.8
S.D.	2.3	1.3
Handedness (LQ) ^c		
Mean	87.3	83.9
S.D.	19.5	17.3
Beck Depression Inventory		
Mean	23.4 ^a	1.1 ^d
S.D.	9.7	1.7

^a Patients differ significantly from healthy control subjects ($P < 0.001$).

^b $n = 27$.

^c Laterality quotient (range -100 to 100 ; see Oldfield, 1971).

^d $n = 10$.

but are identical in all other aspects (e.g. their general physical characteristics). As intended, self-report ratings for pleasantness and skin conductance responses to these stimuli had revealed a robust distinction between negative and neutral stimuli (Kayser, 1995; see Kayser et al., 1997).

Stimuli were presented on a 15-inch monitor (resolution 800×600 pixel) located behind a window outside an IAC sound-attenuated booth. Using a chin rest, participants were positioned with their eyes at a constant 52 cm to the surface of the screen. The stimuli were digitized images (resolution 182×137 pixel, 256 colors) exposed to the left or right hemifield on dark background. A small white cross (20×20 pixel) in the middle of the screen served as fixation. Stimulus presentation subtended visual angles of 6.58° (6.0 cm) horizontally, with the outer borders at 1.65° (1.5 cm) and 8.21° (7.5 cm) from fixation in each visual field, and 4.95° (4.5 cm) vertically, centered along the fixation horizon. Stimulus exposure time was 250 ms. Rapid and predictable stimulus onsets and offsets were coordinated by STIM software (NeuroScan, Inc., 1994), and verified by direct

measurement with a photo resistor attached to the surface of the screen.

Each stimulus was exposed to each visual field (64 trials) in a block-randomized fashion, distributed over two blocks of 32 trials. However, the important conditions were equally distributed, i.e. within every four consecutive trials of the 32-trial sequence each combination of *emotional content* (negative/neutral) and *visual field* (left/right) occurred exactly once. Within each group, each participant received a different stimulus sequence. Because the affective feature of a particular stimulus was not necessarily in the center of the picture, stimuli were mirrored for half of the participants (see Bryson et al., 1991, for a related issue). Stimuli were presented with variable inter-trial intervals (ITI) of 12, 14, 16, or 18 s (mean = 15 s) to allow concurrent recordings of phasic skin conductance responses. Trials were separated by the temporary disappearance of the fixation cross (3 s after stimulus offset). Participants were instructed and trained to attend to the stimulus presentations while maintaining fixation (for details, see Kayser et al., 1997), and to relax between trials. No manual response was required. At the end of the experiment, participants were debriefed to verify that they were aware of the stimulus content.

2.3. Data acquisition and recording procedures

Using an electrode cap (Electro Cap International, Inc.), electroencephalograms (EEGs) were collected from 30 scalp locations (10–20 system) that included four midline (Fz, Cz, Pz, Oz) and 13 homologous placements over both hemispheres (Fp1/2, F3/4, F7/8, FT9/10, FC5/6, C3/4, T7/8, TP9/10, CP5/6, P3/4, P7/8, P9/10, O1/2; for nomenclature, see Pivik et al., 1993). The nose tip was used as reference, and Fpz as ground. Horizontal electrooculograms (EOGs) were recorded differentially from the outer canthi of each eye (horizontal bipolar) and from supra- and infraorbital sites (vertical bipolar). Horizontal eye movements were calibrated by asking participants to focus on the fixation cross which was shifted between different horizontal screen locations. All impedances were maintained at 5 k Ω

or less. EEG gain was 10000 (5000 for eye channels) using a 0.01–30-Hz band pass (-6 dB/octave). Data were continuously sampled at 100 Hz. Recording epochs of 1280 ms (200 ms pre-stimulus baseline) were extracted off-line and digitally low pass filtered at 20 Hz (-24 dB/octave). Statistical analyses were based on an effective sampling epoch of 1100 ms (100 ms baseline).

2.4. Data reduction and ERP component evaluation

Trials contaminated by artifacts were eliminated when EEG and horizontal EOG data exceeded ± 100 μ V following vertical EOG reduction (Semlitsch et al., 1986), or when horizontal eye movements occurred during stimulus exposure.¹ For equivalence, the matched stimulus presentations of a rejected trial were also excluded (i.e. all four trials of a particular negative/neutral stimulus pair). However, a minimum of 50% valid trials (eight trials/condition) was required to include participants in the statistical analyses, which resulted in a mean of 13.2 (S.D. = 2.5, median = 14) trials per condition and participant. There were no significant differences between control subjects (mean = 12.8, S.D. = 2.6, median = 13) and patients (mean = 13.4, S.D. = 2.3, median = 14) in the number of valid trials per condition, both groups ranging from 8 to 16 trials. These means closely matched the respective mean values reported for our previous sample of healthy adults (mean = 13.0, S.D. = 2.7, median = 14; Kayser et al., 1997). Despite this rather small number of trials per condition, visual inspections of individual ERP waveforms for each condition confirmed a distinct ERP component structure in all instances and indicated a sufficient signal-to-noise ratio. It is also important to keep in mind

that comparisons for emotional content (across levels of visual field) or visual field (across levels of emotional content) are based on twice this number of trials. Average ERP waveforms were computed from these valid trials.

In order to determine the sources of variance in the ERP waveforms, the averaged ERP waveforms were submitted to a Principal Components Analysis (PCA) derived from the covariance matrix, followed by a Varimax rotation (Chapman and McCrary, 1995; Achim and Marcantoni, 1997; Kayser et al., 1997, 1998). The factor analysis was computed using BMDP statistical software (BMDP-4M; Dixon, 1992). Columns of the data matrix represented time (110 sample points from -100 ms to 1000 ms), and rows consisted of subjects (46), conditions (four), and electrode sites (30). The number of orthogonal factors extracted and rotated by the PCA was not limited in order to maximize the capacity of the PCA to remove 'noise' or 'error' variance from meaningful components. Peak latencies of factor loadings and topographies of factor scores were used to describe the PCA factors in terms of ERP components. The first five principal components, which accounted for 85.0% of the total variance after Varimax rotation, closely corresponded to N1, N2, early P3, late P3, and slow wave, and matched exactly those PCA factors previously reported for this paradigm (Kayser et al., 1997).

To better understand the topographies of the PCA factor scores, a surface Laplacian (second spatial derivative; see Nunez, 1981) was computed using a local Hjorth method (Hjorth, 1980) based on 3–5 neighbors (Tenke et al., 1998). This transformation preserves localized changes, but eliminates activity that varies linearly across the scalp (e.g. volume conducted activity from other regions), producing more sharply localized topographies. Since each PCA factor is a concise summary of sequential ERP activity, the application of the local Hjorth transformation to the PCA factor scores provides a quasi-stationary representation of the current generators underlying the observed topographies. A detailed description of the specific local Hjorth transformation is reported in Tenke et al. (1998), and will not be repeated here. However, it should be noted that

¹Because individuals differ largely in the size of the electrical eye dipole, μ V equivalents corresponding to horizontal eye movements of approximately 2° visual angle from fixation were calculated from the data of an eye movement calibration procedure taken immediately before the experiment (e.g. Kayser, 1995). When each trial was visually inspected off-line, these values served as individual reference points to determine whether or not a saccade occurred during stimulus exposure.

the second spatial derivative is formally undefined at the edges of the recording montage (i.e. for this specific Hjorth transformation at electrode sites Fp1/2, FT9/10, TP9/10, and P9/10). Therefore, local Hjorth estimates were evaluated only for the remaining 22 electrode sites.

2.5. Statistical analysis

PCA factor scores were submitted to repeated measures ANOVA with group (patient/control) and gender (male/female) as between-subjects factors, and emotional content (negative/neutral) and visual field (left/right) as within-subjects factors. Separate analyses were computed for four midline and 26 lateral recording sites (13 homologous placements over both hemispheres). For midline sites, an additional within-subjects factor site (Fz, Cz, Pz, Oz) was included in the ANOVA design. As the midline ANOVA simply confirmed the analyses for lateral locations, only ANOVA results for lateral sites are reported. For lateral sites, hemisphere (left/right) and site (three electrode pairs) were added as within-subject factors to the ANOVA design. To increase statistical power for testing a priori hypotheses, repeated measures ANOVA were conducted with three lateral pairs of electrodes for each PCA factor. The selected electrode sites were at symmetric electrode placements where: (1) PCA factor scores were largest; and (2) corresponded to areas of maximal radial current flow (as determined by local Hjorth estimates). However, exploratory analyses in which all 13 lateral electrode pairs entered into the variable site were also computed. Greenhouse–Geisser epsilon (ϵ) correction (sphericity assumption) was used to evaluate F -ratios for within-subject effects where appropriate (Vasey and Thayer, 1987). Significant interactions were examined through simple effects to locate

²Significant topographic effects involving emotional content and hemisphere were also evaluated after scaling the amplitudes for each condition by the vector amplitude measured across electrodes (hemisphere and site) in each participant (McCarthy and Wood, 1985). Although weaker, ANOVA effects computed for the scaled data were comparable to those of the unscaled data reported below.

the source of the interaction (BMDP-4V; Dixon, 1992).² Our a priori hypotheses focused on ERP measures of the N2–P3 complex over lateral-parietal sites (Kayser et al., 1997), and predicted group differences involving emotional content and hemisphere at these sites. For these reasons, follow-up analyses of simple effects were planned for effects and sites of interest, particularly locations P7 and P8 (see Kayser et al., 1997), and were calculated at those sites for PCA factors corresponding to subcomponents of the N2–P3 complex.

3. Results

3.1. ERP component structure and PCA factors

Grand average ERP waveforms for emotional content, averaged across visual field, are shown for all recording sites for healthy control subjects in Fig. 1, and for depressed patients in Fig. 2. In both groups, ERPs were characterized by a sharp negative component (N2) that was most prominent over the right parietal region (see site P8 in Figs. 1 and 2), followed by a late positive complex with a parietal-maximum (P3, slow wave) that was clearly larger for negative than neutral stimuli. This differentiation of emotional content was more evident in control participants than in depressed patients, particularly over right parietal sites (e.g. see sites P4 and P8 in Figs. 1 and 2).

PCA factor loadings were included in Figs. 1 and 2 at representative sites (see thin solid lines at Fz, Cz, Pz, P4, and TP10) to indicate their time

³Multiple factor loading peaks at different latencies or significant inverse (negative) factor loadings over its time course may make a factor (and its scores) uninterpretable. For the present data, however, the time course of factor loadings indicated for most factors a very narrow, coherent time interval in which common ERP variance was explained, with the maximum loading centered in this narrow time range. The adjacent data points still showed considerably high loadings, but loadings decreased sharply for more remote data points. In other words, the PCA factors represent a measure of weighted time window amplitude, a very favorable characteristic to comprehend the meaning of an extracted PCA component.

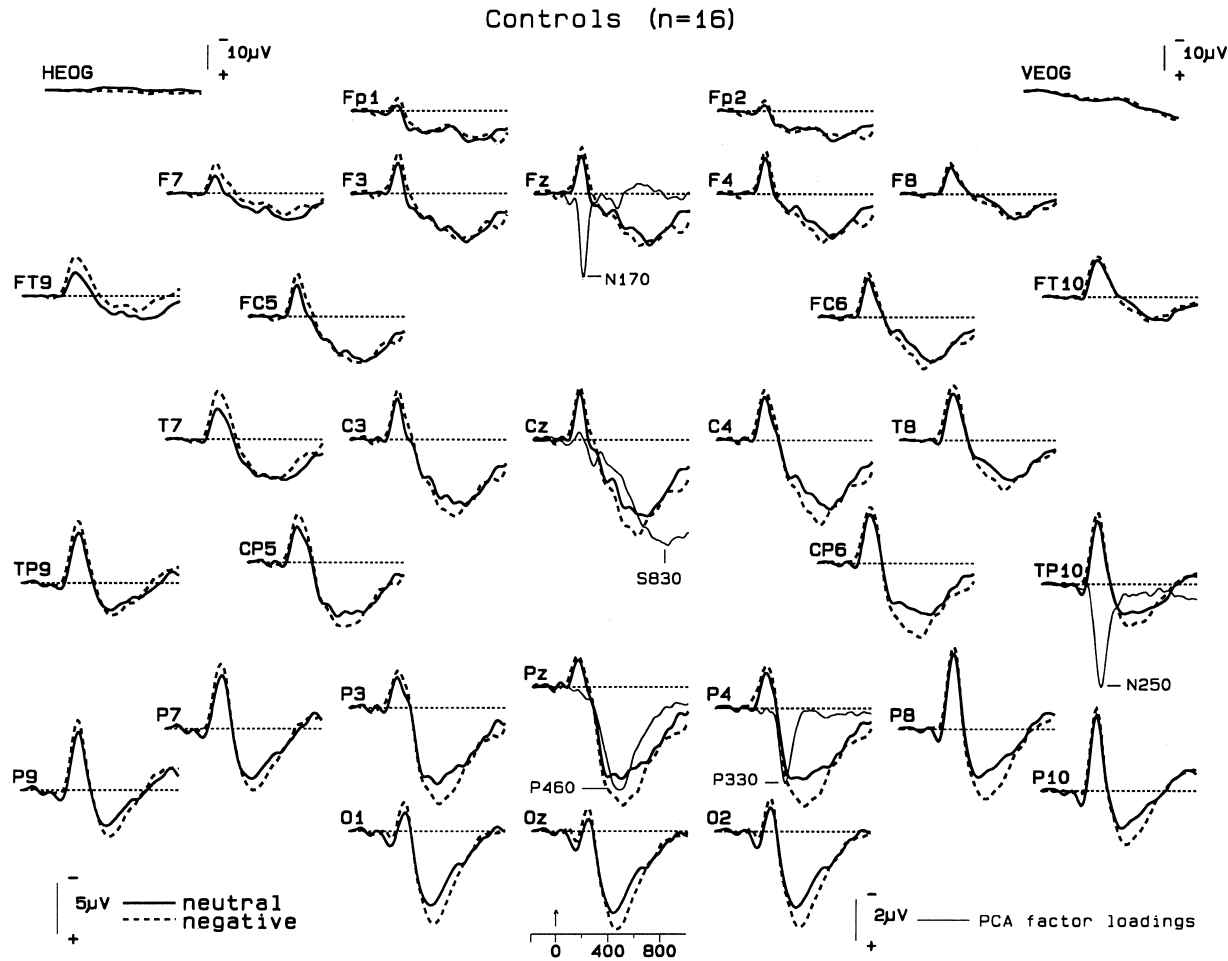


Fig. 1. Grand average event-related potentials (ERPs) for 16 healthy control participants for neutral (solid line) and negative (dashed line) stimuli at all recording sites, averaged across hemifield. Distinct ERP components closely corresponded to the extracted PCA factors, as it is evident from the time course of the PCA factor loadings (thin solid lines at sites Fz, Cz, Pz, P4, and TP10). Note the different scale for electrooculogram (EOG) channels, showing horizontal (HEOG) and vertical (VEOG) EOG averages before eye blink correction. For display purposes, grand average waveforms were smoothed using a two-pass digital low pass filter at 12.5 Hz (Ruchkin and Glaser, 1978).

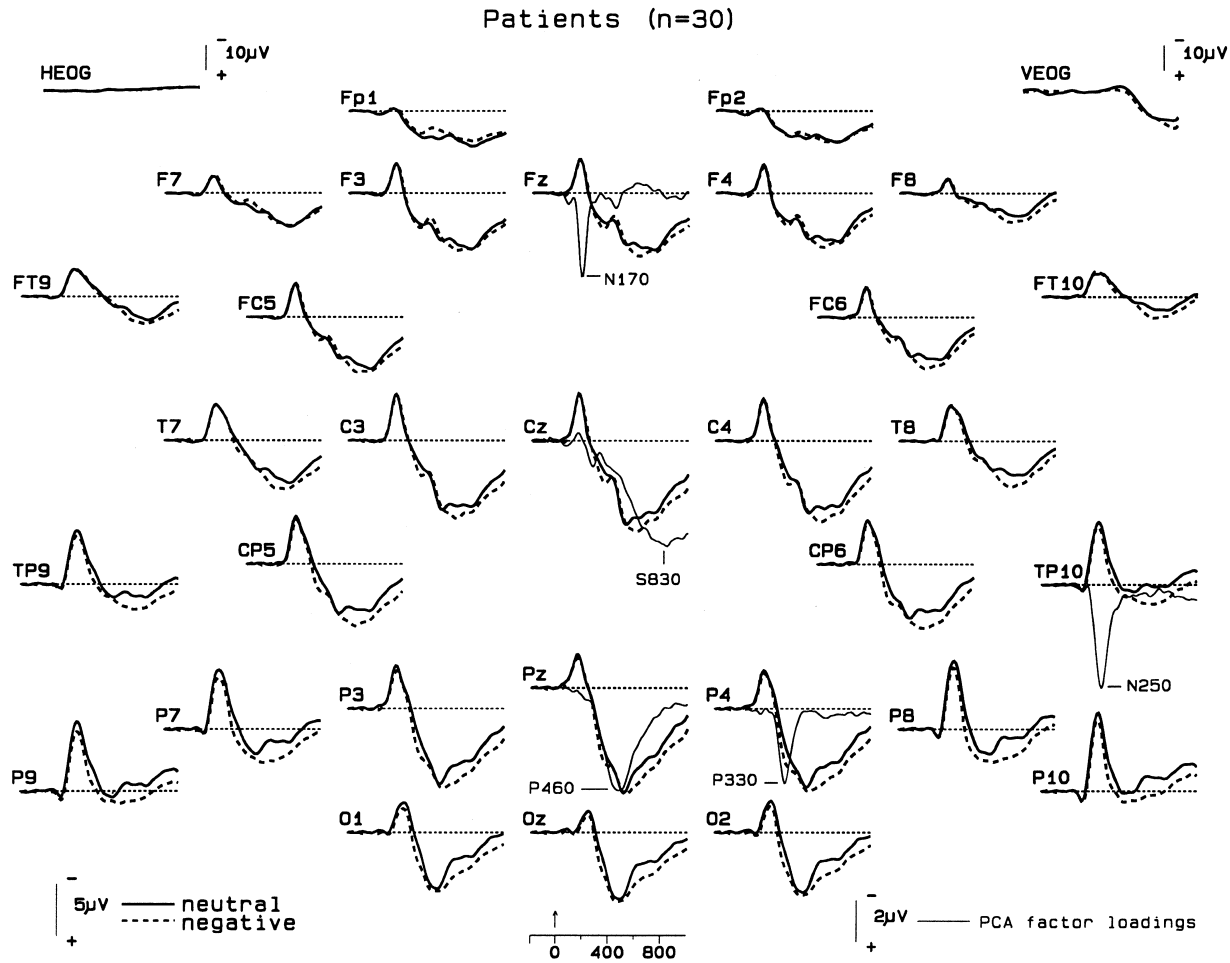


Fig. 2. Grand average event-related potentials (ERPs) for 30 depressed patients for neutral (solid line) and negative (dashed line) stimuli at all recording sites, averaged across hemifield. Time courses of the PCA factor loadings (thin solid lines) are shown at the same electrode sites as in Fig. 1. Eye movement channels (HEOG, VEOG) are scaled as in Fig. 1.

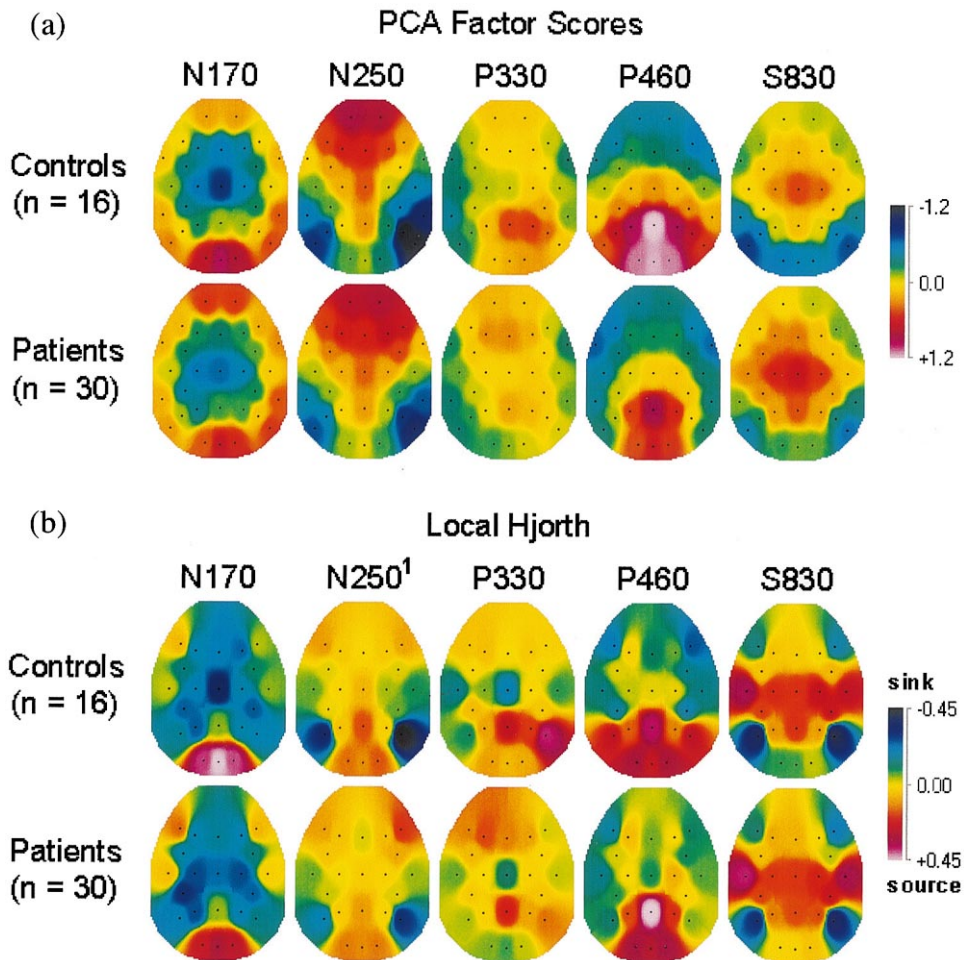


Fig. 3. (a) Topographies of principal components analysis (PCA) factor scores at 30 electrode sites (top view, nose upwards) for 16 healthy adults (top row) and 30 depressed patients (bottom row), averaged across emotional content and hemifield. PCA factor amplitudes (from left to right) closely corresponded to ERP amplitudes of N1 (Factor N170), N2 (N250), early P3 (P330), late P3 (P460), and slow wave (S830). Maps represent the degree of association of each region with each factor. The sign of the factor scores reflects the polarity of the underlying event-related potential (ERP) component (warm colors are associated with positive ERP components, cold colors with negative ERP components). Note that the weights of each component (i.e. the factor scores) reflect the removal of the grand mean ERP waveform for a covariance based PCA (e.g. see Achim and Marcantoni, 1997). (b) Laplacian (local Hjorth) estimates derived from PCA factor scores yielding data for 22 electrode sites (for computation details, see Tenke et al., 1998). ¹Note. Scale range is -0.85 to $+0.85$ for the local Hjorth topographies of factor N250 to avoid amplitude saturation over the right parietal region.

course and their correspondence with components in the ERP waveforms. A non-inverting, triangular morphology was a characteristic feature for most PCA components, which, in combination with their topographies, allowed a straightforward interpretation of each PCA factor.³ The topographies of PCA factor scores for both patient

and control groups (see Fig. 3a) reveal the regions of ERP activity associated with each factor.

Both ERP waveforms and PCA factors closely matched those previously reported for this paradigm (Kayser et al., 1997). An early negativity (N1), most prominent over central and frontal sites, corresponded largely to a distinct PCA fac-

tor labeled 'N170' (peak latency 170 ms, 3.8% explained variance; see location Fz in Figs. 1 and 2, and blue areas in column 1 of Fig. 3a). Analogously, factor 'N250' (250 ms, 9.5%; see TP10 in Figs. 1 and 2) overlapped a second negative ERP component (N2), which was most marked at posterior-lateral sites, especially over the right parietal region (blue areas in column 2 of Fig. 3a). A late positive complex (P3 and slow wave) was represented by three PCA factors (red areas in columns 3–5 of Fig. 3a). Factor 'P330' (330 ms, 4.4%; see P4 in Figs. 1 and 2) corresponded to the early phase of the P3 component, and its amplitude was most positive over right posterior regions. Factor 'P460' (460 ms, 24.2%; see Pz in Figs. 1 and 2) corresponded to the prominent mid-parietal maximum of P3. Factor 'S830' (830 ms, 43.2%; see Cz in Figs. 1 and 2) had a broad distribution with a central maximum and corresponded to a long-lasting positive slow wave.⁴

Additional PCAs were computed separately for control and patient groups. The overall PCA component structure for the five factors was preserved in these separate PCAs: factor loadings had matching peak latencies and shapes, and factors explained similar proportions of variance. It was concluded that the extracted factors were not unique to one group, and did not result from temporal latency 'jitter' (e.g. Dien, 1998) between groups. Exactly the same PCA components have been previously observed for this paradigm (Kayser et al., 1997), and similar PCA components have been found to correspond to known ERP components across different modalities,

tasks, and subject populations (Bruder et al., 1998a, 1999; Kayser et al., 1998, 1999), which supports the assertion that these PCA components reflect and clarify the conventionally defined ERP component structure.

3.2. Surface Laplacian (local Hjorth) estimates

The local Hjorth topographies derived from PCA factor scores for each factor and each group revealed distinct sinks and sources that overlapped regions where factor amplitudes were most prominent (see Fig. 3b). The interpretability of Hjorth topographies was simplified by virtue of the non-inverting, triangular morphology typical of most PCA components. For factor 'N170', a broadly distributed sink with a vertex maximum was paralleled by a focal source over occipital sites (note that the color yellow indicates a value of zero in Fig. 3). Factor 'N250' was characterized by large inferior-parietal sinks, with a clear maximum over the right hemisphere (i.e. at site P8). Factor 'P330' featured a posterior, predominantly right parietal source. Factor 'P460' had a broad posterior source with a Pz maximum. For factor 'S830', lateral sources over temporal areas extended toward the vertex region.

The considerable overlap between local Hjorth and PCA factor score topographies confirmed that the N2 and late positive components elicited in this paradigm indeed activated the targeted right parietal areas. This provided a rationale to reduce the number of recording sites entering into a particular analysis from 13 to three symmetric electrode pairs so as to increase statistical power for evaluating the predicted interactions. The most representative lateral electrode pairs characterizing the topography of each PCA factor were as follows: a sink for factor 'N170' (C3/4, CP5/6, FC5/6), and sources for factors 'P330' (P7/8, P3/4, O1/2), 'P460' (O1/2, P3/4, P7/8), and 'S830' (T7/8, C3/4, CP5/6). As factor 'N250' was characterized by a very focal sink over the lateral-parietal region (local Hjorth estimates are formally undefined at electrodes locations P9/10 and TP9/10; see method), all sites covering the lateral-parietal region (P7/8, P9/10, TP9/10) were selected for factor 'N250'. Midline sites were

⁴It should be noted that in physiological data sets, such as ERPs, the variance is not evenly distributed across sample points (the variables), and is more likely to be large at ERP component peaks. Moreover, the variance of individual sample points (across cases) should be comparably small at the beginning of the recording interval, because baseline offsets are removed by averaging the ERP baseline activity, but the variance should be higher for sample points near the end of the recording epoch, particularly in association with large ERP deflections. It is therefore possible that for factor 'S830', the first factor extracted by the PCA, a large portion of its variance is related to the grand mean waveform, irrespective of the removal of the grand mean waveform in a covariance-based PCA.

Table 2
Summary of *F*-ratios (and ϵ corrections) from repeated measures ANOVA performed on PCA factor scores at most representative sites^a

Variable	d.f.	Factor (and electrode sites included in analysis)				
		N170 (FC5/6, C3/4, CP5/6)	N250 (P7/8, P9/10, TP9/10)	P330 (P7/8, P3/4, O1/2)	P460 (P7/8, P3/4, O1/2)	S830 (T7/8, C3/4, CP5/6)
SITE	2,84	20.01*** (0.74)	15.88*** (0.97)	4.54* (0.97)	35.48*** (0.89)	31.65*** (0.81)
EMOT	1,42			4.20*	4.70*	
HEMI	1,42		23.48***	25.93***		
SITE × EMOT	2,84					3.60* (0.70)
SITE × HEMI	2,84			15.87*** (0.89)		3.44* (0.84)
EMOT × HEMI	1,42			4.62*	5.91*	
SITE × EMOT × HEMI	2,84			5.99** (0.79)	8.12*** (0.91)	
SITE × VF	2,84			3.47* (0.86)		
HEMI × VF	1,42	8.01**		16.66***	74.42***	68.35***
EMOT × HEMI × VF	1,42			4.08*		
SITE × HEMI × VF	2,84	17.60*** (0.70)	22.70*** (0.62)	14.29*** (0.92)	31.78*** (0.88)	22.18*** (0.84)
SITE × EMOT × HEMI × VF	2,84	5.20** (0.99)		4.63* (0.99)		
GRP	1,42				5.10*	
SITE × GRP	2,84				3.75* (0.89)	
EMOT × GRP	1,42				6.80*	
HEMI × GRP	1,42					4.10*
EMOT × HEMI × GRP	1,42				6.59*	
SITE × HEMI × GRP	2,84			3.28* (0.89)		
SITE × EMOT × HEMI × GRP	2,84				5.39** (0.91)	
SITE × VF × GRP	2,84				3.73* (0.93)	
SITE × HEMI × VF × GRP	2,84				4.97* (0.88)	
SITE × EMOT × HEMI × VF × GRP	2,84		4.20* (0.98)			3.34* (0.89)

^aNote: SITE = electrode site (see sites listed above under each factor name); EMOT = emotional content (negative, neutral); HEMI = hemisphere (left, right); VF = visual field (left, right); GRP = group (depressed patients, healthy control subjects). Only *F*-ratios with $P < 0.05$ are reported. Effects involving gender are omitted. * $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$.

also characteristic for the sink of factor ‘N170’ (Cz) and the sources of factors ‘P330’ (Pz), ‘P460’ (Pz, Cz), and ‘S830’ (Cz, Pz).

3.3. ANOVA findings for PCA factor scores at targeted sites

Results of the repeated measures ANOVA performed on the factor scores at the most representative lateral sites (see local Hjorth estimates above) are summarized in Table 2. Effects involving group are presented in the lower half of the table. Despite restricting the number of recording locations, the distinct topography of each factor (see Fig. 3a) was nevertheless evident in significant site main effects for all factors, and several higher order interactions involving site. Replicating our previous findings (Kayser et al., 1997), significant Hemisphere \times Visual Field interactions for most factors, and significant Hemisphere \times Visual Field \times Site interactions for all factors, demonstrated a strong influence of visual half-field presentations on these ERP components. Visual half-field presentations affected ERP components in two ways: (1) early ERP components were relatively enhanced with direct (i.e. contralateral) hemifield stimulation, that is, N1 amplitudes were relatively larger over the right posterior region with left than right visual field input, and relatively larger over the left posterior region with right than left visual field input; (2) late ERP components were more negative (less positive) with direct (i.e. contralateral) hemifield stimulation, that is, early P3, late P3, and slow wave amplitudes were less positive over the right hemisphere with left compared with right visual field input, and vice versa. The later effect, labeled ‘hemifield-dependent negativity’ (Schweinberger and Sommer, 1991), has been interpreted as attention-related processes induced by the visual half-field stimulation. As these effects have been reported and discussed elsewhere (e.g. Schweinberger and Sommer, 1991; Kayser et al., 1997), no further descriptions of these visual field effects will be given.

3.3.1. Factor ‘N170’

A significant site main effect indicated that

‘N170’ amplitude was greater at site C3/4 (mean = -0.58 , S.D. = 1.09) compared to sites CP5/6 (mean = -0.34 , S.D. = 1.06) and FC5/6 (mean = -0.27 , S.D. = 0.80 ; for both contrasts, $F_{1,42} > 33.2$, $P < 0.0001$). Besides highly significant Hemisphere \times Visual Field and Hemisphere \times Visual Field \times Site interactions, there was also a Hemisphere \times Visual Field \times Site \times Emotional Content interaction, which stemmed from modifications of the Hemisphere \times Visual Field effects already summarized above. Systematic exploration of the four-way interaction by means of simple effects revealed that ‘N170’ amplitude was enhanced with contralateral visual field stimulation at centroparietal sites (CP5/6) for both negative and neutral stimuli (simple Hemisphere \times Visual Field interactions; at negative, $F_{1,42} = 9.38$, $P = 0.004$; at neutral, $F_{1,42} = 11.9$, $P = 0.001$), but there was only a tendency for this pattern at central sites (C3/4) for neutral but not negative stimuli, and at frontocentral sites (FC5/6) for negative but not neutral stimuli.

3.3.2. Factor ‘N250’

A site main effect stemmed from greater ‘N250’ amplitude at sites P9/10 (mean = -0.89 , S.D. = 1.05) compared to P7/8 (mean = -0.77 , S.D. = 1.06), which in turn was greater than TP9/10 (mean = -0.65 , S.D. = 0.85 ; for all contrasts, $F_{1,42} > 6.56$, $P < 0.05$). A highly significant hemisphere main effect confirmed that ‘N250’ amplitude was greater over the right than left hemisphere (right hemisphere, mean = -0.92 , S.D. = 1.03 ; left hemisphere, mean = -0.62 , S.D. = 0.94). This asymmetry was present for each group and each temporal-parietal site (simple main effects of hemisphere, all $F_{1,42} > 10.5$, all $P < 0.01$; see column 2 of Fig. 3). Although there was a significant five-way interaction involving emotional content and group (see Table 2), systematic follow-up analyses did not reveal a meaningful source for this higher-order interaction. No other effects for emotional content or group were observed for ‘N250’ amplitude at temporal-parietal sites.

3.3.3. Factor ‘P330’

Like factor ‘N250’, highly significant effects of hemisphere and Hemisphere \times Site (see Table 2)

confirmed that ‘P330’ amplitude was larger over the right than left hemisphere, particularly for sites P7/8 (simple hemisphere effect, $F_{1,42} = 29.4$, $P < 0.0001$; see column 3 of Fig. 3). A significant interaction of Hemisphere \times Site \times Group revealed that this site-dependent ‘P330’ asymmetry was more prominent for control subjects than patients (simple Hemisphere \times Site interactions, for control subjects, $F_{2,84} = 12.7$, $P < 0.0001$, $\epsilon = 0.89$; for patients, $F_{2,84} = 3.42$, $P = 0.04$, $\epsilon = 0.89$).

Negative stimuli produced a significantly larger ‘P330’ amplitude than neutral stimuli (negative, mean = 0.20, S.D. = 1.26; neutral, mean = -0.10, S.D. = 1.13). Significant interactions of Emotional Content \times Hemisphere and Site \times Emotional Content \times Hemisphere (see Table 2) indicated that this ‘P330’ difference of emotional content was asymmetric and site-dependent. Simple effects revealed that differences for emotional content were significant for right hemisphere sites ($F_{1,42} = 5.76$, $P = 0.02$), but not for left hemisphere sites ($F_{1,42} = 2.72$, $P = 0.11$). Testing the

Emotional Content \times Hemisphere interaction at each site revealed significance at lateral-parietal sites (at P7/8, $F_{1,42} = 7.02$, $P = 0.01$), but not at mid-parietal or occipital sites (at P3/4 and O1/2, $F_{1,42} < 2.06$, $P > 0.15$).

Fig. 4 shows the interaction Emotional Content \times Hemisphere for ‘P330’ amplitude separately for each group. The obvious differences in ‘P330’ amplitude for negative and neutral stimuli for depressed patients, but not for control subjects, were supported by a marginally significant Emotional Content \times Group interaction ($F_{1,42} = 3.93$, $P = 0.05$; not listed in Table 2), and a significant simple main effect of emotional content for patients ($F_{1,42} = 11.8$, $P = 0.001$), but not for control subjects ($F_{1,42} < 1.0$, n.s.). It is, however, important to note that there were no significant Emotional Content \times Hemisphere \times Group interactions, including simple interactions effects at each site (all $F_{1,42} \leq 1.51$, $P > 0.22$).

Significant Emotional Content \times Hemisphere \times Visual Field and Emotional Content \times

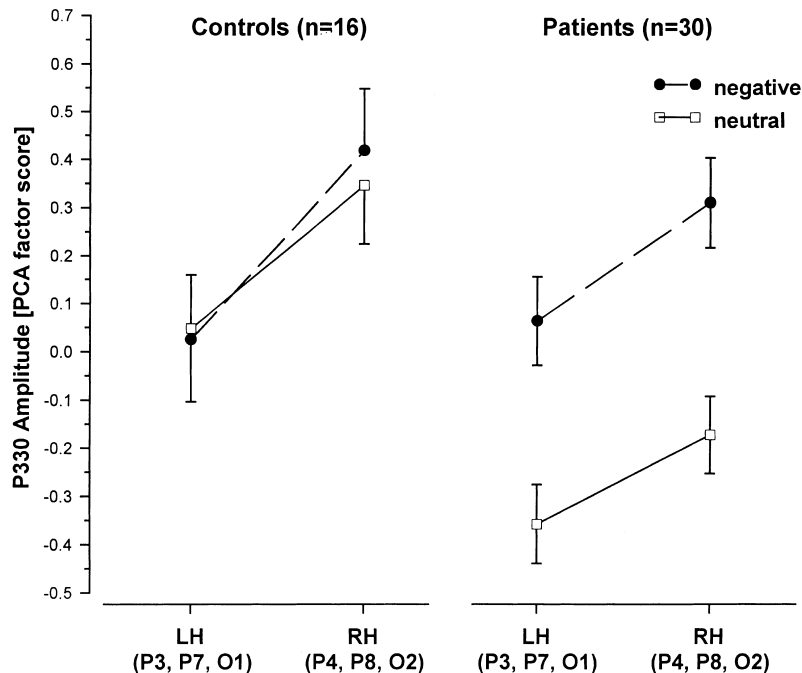


Fig. 4. Mean ‘P330’ amplitude (and standard error of the mean) for negative and neutral stimuli across posterior sites of the left (LH: P3, P7, O1) and right hemisphere (RH: P4, P8, O2), plotted separately for 16 healthy control subjects and 30 depressed patients.

Hemisphere \times Visual Field \times Site interactions across groups (see Table 2) emanated from lateral-parietal sites (P7/8), where a simple Emotional Content \times Hemisphere \times Visual Field interaction ($F_{1,42} = 6.44$, $P = 0.02$) was observed. Simple Emotional Content \times Hemisphere interactions tested for each visual field at site P7/8 revealed that larger 'P330' amplitudes for negative compared with neutral stimuli were more prominent over the right than left hemisphere only for left visual field stimuli ($F_{1,42} = 11.3$, $P = 0.002$), but not for right visual field stimuli ($F_{1,42} < 1.0$, n.s.).

3.3.4. Factor 'P460'

The topography of factor 'P460' had a parietal maximum resembling a classical P3b component (see column 4 of Fig. 3a). Analogous to factor 'P330', 'P460' amplitude was significantly larger to negative stimuli compared with neutral stimuli (negative, mean = 0.58, S.D. = 1.18; neutral, mean = 0.46, S.D. = 1.06), and significant interactions of Emotional Content \times Hemisphere and Site \times Emotional Content \times Hemisphere indicated that the negative-larger-than-neutral 'P460' amplitudes were asymmetric and dependent on site. Again, like the former 'P330' factor, simple effects revealed that 'P460' amplitude was significantly larger for negative compared with neutral stimuli over the right hemisphere ($F_{1,42} = 6.42$, $P = 0.02$), but not over the left ($F_{1,42} = 3.15$, $P = 0.08$). The Emotional Content \times Hemisphere interaction was significant at parietal sites (at P7/8, $F_{1,42} = 8.83$, $P = 0.005$; at P3/4, $F_{1,42} = 5.46$, $P = 0.02$), but not at occipital sites (at O1/2, $F_{1,42} < 1.0$, n.s.).

There were several significant group effects for factor 'P460' (see Table 2). A group main effect and a Site \times Group interaction indicated that depressed patients had a reduced 'P460' amplitude (see column 4 of Fig. 3a), but only at lateral-parietal and occipital sites (simple group effects at P7/8, $F_{1,42} = 8.00$, $P = 0.007$; at O1/2, $F_{1,42} = 4.94$, $P = 0.03$); no group differences were found at mid-parietal sites (at P3/4, $F_{1,42} = 2.44$, $P = 0.13$). A significant Emotional Content \times Group interaction indicated that control subjects showed

greater 'P460' amplitude to negative than neutral stimuli, whereas patients did not (simple effects of emotional content for control subjects, $F_{1,42} = 8.71$, $P = 0.005$; for patients, $F_{1,42} < 1.0$, n.s.). This effect is illustrated in Fig. 5, which shows the topographies of 'P460' amplitude (and, for comparison, of 'P330' amplitude) for negative and neutral stimuli, and the amplitude difference between negative and neutral stimuli, that is, the topography of the emotional content effect. This emotional content effect for factor 'P460' was salient for control subjects, and most prominent over right parietal sites (see Fig. 5d); for depressed patients, there were no differences in 'P460' amplitude between negative and neutral stimuli over this right parietal region (see Fig. 5d).

The means for the significant three-way interaction Emotional Content \times Hemisphere \times Group are shown in Fig. 6. Simple effects of Emotional Content \times Hemisphere calculated for each group found that the negative-larger-than-neutral 'P460' amplitudes were asymmetric for control subjects ($F_{1,42} = 9.54$, $P = 0.004$), but there was no interaction for patients ($F_{1,42} < 1.0$, n.s.). This effect was most prominent at lateral-parietal sites (at P7/8, $F_{1,42} = 13.5$, $P < 0.001$), but also significant at mid-parietal sites (at P3/4, $F_{1,42} = 7.26$, $P = 0.01$) for control subjects. Depressed patients failed to show hemispheric asymmetries of 'P460' amplitude related to emotional content at any site (all $F_{1,42} < 1.0$, n.s.).

Table 2 also lists two significant higher-order interactions involving group, visual field, and site. However, there were no significant simple interactions effects of Visual Field \times Group or Hemisphere \times Visual Field \times Group at any site, and the higher-order interactions were not further resolved.

3.3.5. Factor 'S830'

A site main effect stemmed from larger 'S830' amplitudes at central sites C3/4 compared with sites T7/8 and CP5/6 (for both contrasts, $F_{1,42} > 35.3$, $P < 0.0001$; see column 5 of Fig. 3). Although there were significant interactions of Site \times Emotional Content and Site \times Hemisphere (see

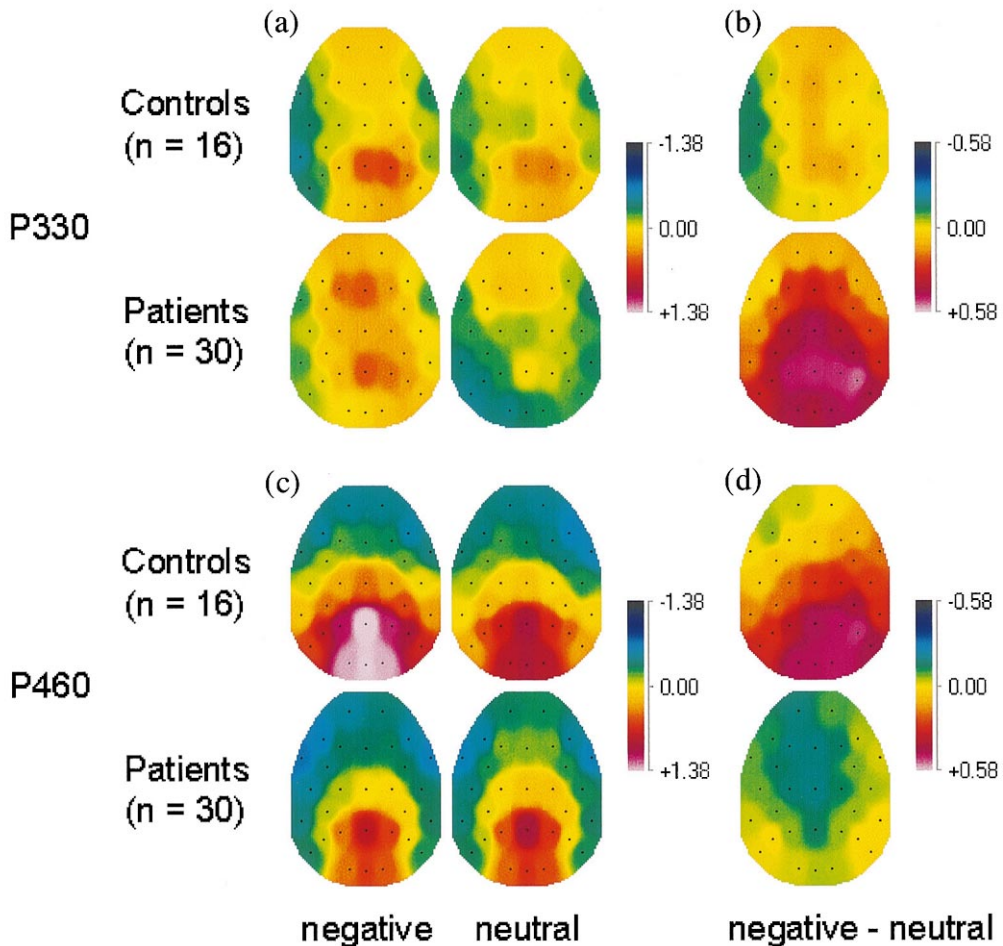


Fig. 5. Topographies of (a,b) 'P330' amplitude and (c,d) 'P460' amplitude derived from principal components analysis (PCA) factor scores at 30 electrode sites (top view, nose upwards) for 16 healthy adults and 30 depressed patients. Maps were calculated for (a,c) negative and neutral stimuli (averaged across hemifield), and (b,d) the corresponding difference map for negative-minus-neutral stimuli.

Table 2), none of the simple main effects of Emotional Content or Hemisphere were significant at any site (all $F_{1,42} < 2.18$, all $P > 0.14$), and these interactions were not further resolved. Simple hemisphere effects for each group revealed that the Hemisphere \times Group interaction resulted from a larger 'S830' amplitude over the left than right hemisphere for patients ($F_{1,42} = 5.02$, $P = 0.03$), whereas control subjects did not show asymmetric amplitudes ($F_{1,42} < 1.0$, n.s.). Finally, although the analyses for factor 'S830' revealed a significant higher-order interaction involving

group, there were no significant simple effects of Emotional Content \times Hemisphere \times Visual Field \times Group at each site, and the source of the five-way interaction was not further explored.

3.4. Supplemental ANOVA findings for PCA factor scores

To limit the possibility of overlooking potentially interesting effects at sites not included in the targeted analyses, exploratory ANOVA across all 13 lateral electrode pairs were also calculated.

In view of the increased risk of committing a Type I error, only the more compelling and theoretically meaningful findings are reported.

The extended analyses for factor ‘N170’ yielded a hemisphere main effect ($F_{1,42} = 4.35, P = 0.04$) stemming from a larger ‘N170’ amplitude over the left than right hemisphere. A Hemisphere \times Site interaction ($F_{12,504} = 2.80, P = 0.03, \epsilon = 0.29$), and simple main effects of hemisphere at each site revealed that this left-larger-than-right asymmetry was particularly evident at inferior-lateral sites, where ‘N170’ amplitude was low (at TP9/10, $F_{1,42} = 10.5, P = 0.002$; at FT9/10 and P9/10, $F_{1,42} \geq 5.52$, both $P = 0.02$; see Fig. 3). Although Figs. 1 and 2 seem to indicate that healthy adults, but not depressed patients, show greater N1 amplitude to negative than neutral stimuli at several fronto-temporal sites, there was only a tendency for interactions of Emotional Content \times Group ($F_{1,42} = 3.57, P = 0.07$) and Emotional Content \times Site ($F_{12,504} = 2.43, P = 0.05, \epsilon = 0.20$), and no significant Emotional Content \times Group \times Site effect ($F_{12,504} < 1.0, n.s.$).⁵

In contrast, the respective ANOVA for factor ‘N250’ across all sites yielded an emotional content main effect ($F_{1,42} = 4.10, P < 0.05$), but no other effect involving emotional content was significant in this analyses. Simple main effects for emotional content at each site revealed that ‘N250’ amplitude was greater for negative than neutral stimuli at fronto-central and temporal sites across groups (i.e. at C3/4, F3/4, FC5/6, T7/8, FT9/10, and CP5/6, all $F_{1,42} \geq 4.20$, all

⁵Despite the lack of statistical support, simple effects for emotional content and group were nevertheless calculated at each site in view of evidence that depression may be linked to a dysfunction of frontal regions. These analyses revealed significant Emotional Content \times Group interactions at lateral frontal and lateral temporal sites, strongest at FT9/10 ($F_{1,42} = 10.4, P = 0.003$), but also present at F7/8 ($F_{1,42} = 6.89, P = 0.01$), T7/8 ($F_{1,42} = 5.21, P = 0.03$), Fp1/2 ($F_{1,42} = 4.72, P = 0.04$), and TP9/10 ($F_{1,42} = 4.12, P < 0.05$). Simple main effects for emotional content computed for each group and each site were only significant for healthy adults at sites FT9/10 ($F_{1,42} = 10.4, P = 0.003$), F7/8 ($F_{1,42} = 7.12, P = 0.01$), and Fp1/2 ($F_{1,42} = 4.30, P = 0.04$).

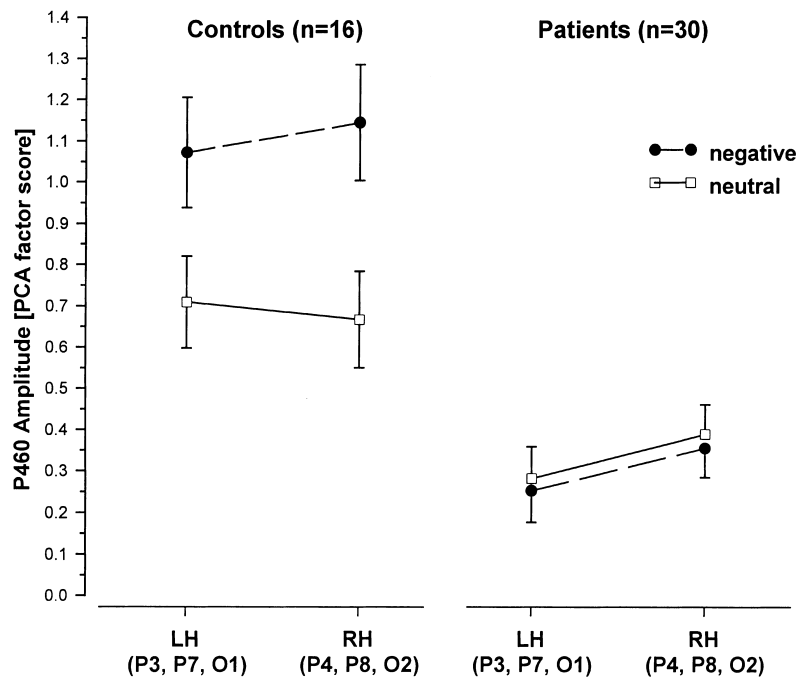


Fig. 6. Mean ‘P460’ amplitude (and standard error of the mean) for negative and neutral stimuli across posterior sites of the left (LH: P3, P7, O1) and right hemisphere (RH: P4, P8, O2), plotted separately for 16 healthy control subjects and 30 depressed patients.

$P < 0.05$). There were also significant interactions of Hemisphere \times Group ($F_{1,42} = 6.75$, $P = 0.01$) and Hemisphere \times Site \times Group ($F_{12,504} = 2.81$, $P = 0.03$, $\varepsilon = 0.29$). Simple Hemisphere \times Group effects were significant at anterior sites where 'N250' amplitude was low (i.e. at F7/8, F3/4, FT9/10, FC5/6, T7/8, and C3/4, all $F_{1,42} \geq 7.28$, all $P \leq 0.01$; at Fp1/2 and CP5/6, both $F_{1,42} \geq 5.09$, both $P < 0.03$). For healthy adults, 'N250' amplitude was greater over the right than left hemisphere at all sites, whereas depressed patients showed this hemispheric asymmetry only at posterior sites where 'N250' was large.

The ANOVA across all sites for factor 'P330' did not reveal any additional significant results. However, as there were suggested interactions of Emotional Content \times Group ($F_{1,42} = 2.99$, $P = 0.09$) and Emotional Content \times Group \times Site ($F_{12,504} = 2.42$, $P = 0.08$, $\varepsilon = 0.22$), simple effects were computed at each site. Significant Emotional Content \times Group interactions were only found at lateral temporal-parietal sites (i.e. at P9/10, P7/8, and TP9/10, all $F_{1,42} \geq 4.29$, all $P < 0.05$), stemming from greater 'P330' amplitudes for negative than neutral stimuli for depressed patients but not for healthy control subjects (see Fig. 5b). Simple emotional content main effects for each group at each site were significant for patients over posterior regions (i.e. at P7/8 and P9/10, $F_{1,42} > 12.4$, both $P \leq 0.001$; at P3/4, O1/2, and CP5/6, $F_{1,42} \geq 9.49$, all $P \leq 0.01$; at TP9/10, C3/4, and T7/8, $F_{1,42} \geq 5.14$, all $P \leq 0.05$), but insignificant for healthy adults at all sites (all $F_{1,42} < 1.0$, n.s.).

Lastly, the ANOVA across all sites for factors 'P460' and 'S830' did not reveal any additional effects to those reported for the targeted analyses.

3.5. Confirmatory ANOVA findings for time window amplitudes

A number of caveats have been raised concerning the interpretation of PCA based ERP analyses, most notably misallocation of variance and latency jitter (e.g. Wood and McCarthy, 1984; Chapman and McCrary, 1995; Dien, 1998). At the same time, these authors underline that these

problems are inherent to any technique for component identification, including measures of peak amplitude, peak latency, or time window amplitude. Notwithstanding, to address this concern, we confirmed the prominent PCA findings by submitting mean amplitudes of the average waveforms calculated for time windows of 140–200 ms (N1), 210–280 ms (N2), 290–370 ms (early P3), 380–540 ms (late P3), and 550–1000 ms (slow wave) to repeated measures ANOVA as described above (i.e. using the same electrode sites listed in Table 2). Time windows were determined by the time course of PCA factor loadings. In summary, results of the time window analyses were largely in accordance with the PCA results for corresponding factors, and no additional effect involving group and emotional content emerged from these analyses.

When compared to healthy control subjects, depressed patients tended to have reduced late P3 amplitude, as indicated by a suggested group main effect ($F_{1,42} = 3.34$, $P = 0.07$) and, although the Emotional Content \times Group interaction did not reach statistical significance ($F_{1,42} = 2.20$, $P = 0.15$), control subjects showed larger P3 amplitude for negative than neutral stimuli ($F_{1,42} = 5.77$, $P = 0.02$), but patients did not ($F_{1,42} < 1.0$, n.s.). Most importantly, patients failed to show the asymmetric effect of emotional content for late P3 seen for healthy adults, as indicated by a significant Emotional Content \times Hemisphere \times Group interaction ($F_{1,42} = 5.01$, $P = 0.03$) and a significant Emotional Content \times Hemisphere interaction for control subjects ($F_{1,42} = 7.88$, $P = 0.007$), but not for patients ($F_{1,42} < 1.0$, n.s.). Follow-up tests of the significant Site \times Emotional Content \times Hemisphere \times Group interaction ($F_{2,84} = 4.25$, $P = 0.02$, $\varepsilon = 0.86$) revealed that the Emotional Content \times Hemisphere \times Group interaction was most prominent at site P7/8 ($F_{1,42} = 7.26$, $P = 0.01$), which was also the site with the most robust Emotional Content \times Hemisphere interaction for control subjects ($F_{1,42} = 12.6$, $P = 0.001$). This interaction was insignificant for patients at any site (all $F_{1,42} < 1.0$, n.s.).

The analyses for the early P3 time window confirmed all relevant effects for factor 'P330' listed in Table 2. To summarize the effects for

emotional content, there was a significant main effect of emotional content ($F_{1,42} = 4.43$, $P = 0.04$), and significant interactions of Emotional Content \times Hemisphere ($F_{1,42} = 4.89$, $P = 0.03$) and Emotional Content \times Hemisphere \times Site ($F_{2,84} = 7.35$, $P = 0.004$, $\epsilon = 0.74$). None of these effects interacted with group. It is also noteworthy that there was a tendency towards a group main effect ($F_{1,42} = 3.12$, $P = 0.08$), stemming from a greater early P3 amplitude in healthy adults (mean = 3.46 μ V, S.D. = 5.39) than depressed patients (mean = 1.47 μ V, S.D. = 4.94).

The ANOVA effects of the other time windows supported the PCA findings in a similar fashion. However, effect sizes were generally smaller for the time window analyses, which is in accord with our previous comparisons between conventional and PCA-based ERP measures (e.g. Kayser et al., 1997, 1998). By more efficiently disentangling temporally and spatially overlapping ERP components, the PCA approach not only enhanced statistical power, but also revealed additional early P3 effects, which may have been overlooked with traditional ERP measures.

4. Discussion

4.1. P3 amplitude and asymmetry during emotional processing in healthy adults

The results for healthy adults confirmed previous research (e.g. Johnston et al., 1986; Johnston and Wang, 1991; Naumann et al., 1992; Kayser et al., 1997; Palomba et al., 1997; Oliver-Rodriguez et al., 1999), indicating that the perception of affective stimulus value is reflected in greater late ERP positivity. Compared with neutral control pictures, stimuli of negative valence elicited greater amplitudes of late P3 at posterior scalp locations. In further agreement with previous studies (Cacioppo et al., 1993, 1996; Kayser et al., 1997), the greatest relative enhancement of this late positivity for negative compared with neutral stimuli was observed over the right parietotemporal region. This is consistent with the hypothesis that right parietal brain regions are normally required for the perception and evaluation of

emotional stimuli (e.g. Silberman and Weingartner, 1986; Etcoff, 1989; Heller, 1990). Similar topographic effects for emotional content were also evident for early P3, with asymmetric right-greater-than-left enhancement of positivity to negative compared with neutral stimuli over posterior brain regions.

Although latency and topography of these late positive ERP components, particularly factor 'P460', are consonant with those of the classical P3b component (e.g. Picton, 1992), the meaning of these ERP components in a passive viewing paradigm, which features equal condition probabilities and lacks response selection, is not easily understood in terms of the classical P3 model. The observed P3 effects could be parsimoniously attributed to the intended stimulus manipulation, i.e. a difference in affective significance. Johnston et al. (1986) indicated that their ERP findings paralleled self-reported pleasantness ratings of the stimuli, and two recent ERP studies also found positive correlations between preference ratings for faces and P300 measures for these face stimuli (Pizzagalli et al., 1998; Oliver-Rodriguez et al., 1999). We have found that greater P300 amplitudes to negative than neutral stimuli, particularly over the right hemisphere, are paralleled by larger skin conductance responses to negative than neutral stimuli (Kayser and Tenke, 1996). Along with this evidence, we conclude that the late positivity in these paradigms, without a cognitive task, reflects processing of affective stimulus significance, which is an important mechanism for survival. The enhancement of late positivity to emotionally significant stimuli may function as a somatic marker, required to guide an individual in response selection and decision making by signaling stimulus significance to the body (e.g. Damasio et al., 1991; Damasio, 1994).

4.2. Reduced P3 amplitude and asymmetry during emotional processing in depression

As the most prominent finding, depressed patients had a marked reduction of late P3 amplitude, and, in striking contrast to healthy control participants, showed no enhancement of late P3

amplitude to negative compared with neutral stimuli. In as much as the enhancement of late positivity indexes a central arousal to affective stimuli, such a selective arousal was absent in depressed patients. Moreover, there was no evidence of greater late P3 over right than left lateral-parietal sites, which appears to be a characteristic topographic feature of late P3 in healthy control subjects. In addition to supporting previous reports of reduced P3 amplitude and asymmetry in depressed patients during cognitive challenge (Bruder et al., 1995, 1998b; Pierson et al., 1996), our findings are consistent with the hypothesis of impaired activation of the right parietal region during emotional processing in depressed patients (Heller, 1990, 1993).

In contrast to the findings for the late P3 component, depressed patients showed a transitory difference in early P3 amplitude to negative and neutral stimuli over posterior, particularly right parietal regions. This finding parallels the debriefing reports, which indicated that depressed participants were aware of the affective stimulus content, as were healthy control subjects. Whereas healthy control subjects did not show the overall enhancement of early P3 to negative stimuli at posterior sites, both groups had an asymmetric right-greater-than-left early P3 amplitude over parietal sites, and this hemispheric asymmetry interacted equally in both groups with emotional content (see Fig. 5b). Moreover, depressed patients showed the same distinct N2 topography as control participants, which revealed a maximum over right lateral-parietal sites. The enhancement of early P3 to negative as compared with neutral stimuli in depressed patients and the subsequent absence of this enhancement in late P3 raises the possibility that early stimulus classification in depressed patients was followed by an active inhibition of later affective processing. A similar mechanism may be at work during cognitive tasks and may account for reports of enhanced N2b but reduced P3 amplitude in anhedonic individuals 'at-risk' for depression (e.g. Giese-Davis et al., 1993; see Miller, 1996) and in depressed patients (e.g. Bruder et al., 1998b). An alternate possibility is that depressed patients may have been quicker to discriminate negative from

neutral stimuli resulting in an enhancement of early P3 to negative stimuli that was not seen in control participants. While this could very well be the case, it is important to stress that this affective discrimination activity in depressed patients was very transitory (lasting less than 100 ms) in comparison to the extended duration of a central activation to affective stimuli seen for healthy adults.

4.3. Earlier negative ERP components during emotional processing

In further agreement with our previous study are the findings for N2 amplitude, which was greater for negative than neutral stimuli only at fronto-central and temporal sites where N2 amplitude was low, but not at parietal sites, where N2 amplitude was most prominent. Although the replication of this difference in emotional content is noteworthy, its exact meaning is unclear at the present time, but it may imply an involvement of fronto-temporal brain regions in discriminating affective stimulus content.

In this study, we did not find any difference in N2 amplitude between depressed patients and healthy control subjects. One other study of ERPs to affective stimuli in depressed patients (Deldin et al., in press; see also Miller, 1996) reported a reduction of N2 amplitude, maximum over right parietal sites, during recognition of emotional words and faces. While the topographic anomaly of depressed patients matches the present findings, the ERP component that showed the effect does not. This discrepancy raises important questions about the significance of N2 and P3 during different ERP paradigms, that need to be reconciled in future studies. The Deldin et al. study used a recognition memory task that entails greater cognitive and response requirements when compared to our paradigm in which the subject passively views affective pictures. We have previously argued that the typical task and response requirements of ERP studies blend emotional processing with cognitive operations (Kayser et al., 1997). This argument could provide a basis for resolving these issues.

Finally, depressed patients also did not differ

from control subjects in overall N1 amplitude and topography, confirming earlier evidence that early sensory/attentional processes are intact in moderately depressed outpatients (Bruder et al., 1995, 1998b). These findings argue against the idea of a general sensory or cognitive processing deficit in these depressed patients. N1 amplitude was, however, greater to negative than neutral stimuli at fronto-temporal sites for control participants but not for depressed patients. The study design targeted posterior brain regions known to be primarily involved in emotional *perception*, and it is unknown whether this fronto-temporal effect truly reflects an early differentiation of emotional content in healthy adults. This exploratory finding will need replication and should be regarded with extreme caution because: (1) based on the findings of our previous study with healthy adults, we had no a priori hypotheses for any effects of emotional content for N1 amplitude; and (2) effects were observed at electrode sites where N1 amplitude and its error variance was low, which raises questions about the reliability and meaning of these effects.

4.4. *Issues for further study*

The similarity of the results with those of our prior study (Kayser et al., 1997) deserves comment. Besides a close match of the PCA component structure, the findings generally replicated effects involving emotional content and hemisphere for most ERP components. A strongly lateralized N2 component was prominent over right lateral-parietal sites, presumably indicating that this region was highly activated during stimulus classification (Hillyard and Picton, 1987). As in our previous study, no emotion-related effects for N2 were found at sites where N2 amplitude was largest, but effects of emotional content were evident for N2 at frontal and central sites. The overall N2 asymmetry was independent of a parietal N2 enhancement to contralateral hemifield stimulation, labeled N2pc (N2 parietal contralateral), which has been linked to attentional filtering processes during visual search tasks (Luck and Hillyard, 1994; Eimer, 1996). Therefore, it is most likely that N2 amplitude and asymmetry observed

for this task represents an electrophysiological correlate of an intermediate information processing stage required for appropriate stimulus classification.

In contrast to our prior study (Kayser et al., 1997), we did not find significant effects of emotional content on positive slow wave, although mean amplitudes tended to be larger for negative than neutral stimuli over the medial-central region. Also, the lateralization of ERPs related to emotional content was primarily associated with late P3 in this study, but was confined to the N2–P3 complex in our previous study. Irrespective of the similarities, important methodological differences between these studies should not be overlooked, including differences in number of recording sites, location of EEG reference (linked ear lobes instead nose tip), and, most importantly, the homogeneity, size, and demographics of the sample. In particular, the younger age of the sample of healthy women in the prior study is reflected in their larger ERP amplitudes and shorter latencies. Moreover, the heterogeneity of the sample of healthy men and women used in the present study may have weakened statistical support for ERP components that are more subject to inter-individual variability, such as positive slow wave.

Previous research has shown that the issue of heterogeneity is also important to take into account in studies of depression (e.g. Bruder et al., 1989). We have found that depressed patients scoring high on the Revised Physical Anhedonia Scale (Chapman and Chapman, 1978) failed to show right-greater-than-left hemisphere P3 seen for healthy adults during a pitch discrimination task (Bruder et al., 1998b). However, patients with low anhedonia scores showed an intermediate P3 asymmetry, supporting the notion that dysfunctions of right posterior regions are characterized by anhedonic-detached mood changes (e.g. Kinsbourne, 1988; Gainotti, 1989). Although preliminary analyses of the current data suggested an influence of anhedonia, the sample sizes were too small to draw any further conclusions at this point. However, it will be important to address the issue of diagnostic subtypes with larger samples.

Another issue to be considered in future research concerns the distinction between affective valence and arousal (e.g. Lang et al., 1990, 1993). The prime goal of the present study was to address hypotheses about the lateralization of emotional perception in depression. The one point of agreement among different theories about how emotional processing is lateralized is the role of the right hemisphere in processing negative emotions (e.g. Silberman and Weingartner, 1986). Therefore, at this initial research stage, it was advisable to focus on ERPs to stimuli with clearly negative valence and control stimuli that would not elicit negative emotional reactions. The negative stimuli used here also have the advantage of being relatively well matched to neutral stimuli in their perceptual content (Kayser et al., 1997). Therefore, for the benefit of maintaining the ability to test an emotion effect per se and concomitantly control for important potential confounds, we deliberately selected stimuli that differed not only in valence but also in the arousal dimension. Subsequent studies will need to develop stimuli to elicit positive emotions and 'neutral' stimuli matched for stimulus content, a criterion not met by stimuli from the International Affective Picture System (Lang et al., 1997). This is an important aspect when studying hemispheric asymmetries, because general physical stimulus characteristics may contribute to laterality effects, such as the well-known right hemispheric advantage for visual-spatial processing. Although it was not our intention at this stage to differentiate between valence and arousal effects, the concurrent recording of autonomic measures could provide some indication of the physiologic arousal evoked by these stimuli.

5. Conclusions

The findings of the present study provide further support for a differential hemispheric contribution to affective processing in healthy adults. In accordance with the hypothesis of a right hemisphere superiority for the perception of affect (e.g. Silberman and Weingartner, 1986; Tucker, 1988; Heller, 1990, 1993), a differential

ERP response to affective stimulus features was most prominent for late P3 amplitude over right parietal regions. In addition, this study provides electrophysiological evidence for abnormal evaluation of affective stimuli in depression, in that a difference in late P3 to affective stimulus features was absent over right parietal regions in clinically depressed patients. At the same time, however, affective stimulus discrimination was evident in depressed patients at approximately 330 ms post-stimulus in early P3, which also appeared to involve primarily right parietal regions. Taken together, these findings suggest intact or even heightened initial classification of affective stimuli in depression, initiated by right parietal cortical regions that are activated during emotional perception; however, this is not followed by a deeper evaluation of the emotional content of the stimuli, as evidenced by a lack of late P3 effects seen in healthy adults. This may arise from actively inhibiting exactly the same right parietal regions normally involved in the evaluation of emotional stimuli. This difference in affective stimulus processing in depressed patients is unlikely to result from reduced involvement of the right hemisphere for visuo-spatial perceptual processing, because negative and neutral stimuli were nearly identical in stimulus content (see discussion by Kayser et al., 1997), and depressed patients, like healthy control subjects, showed strongly right-lateralized amplitudes of N2 and early P3 for both negative and neutral stimuli. Rather, our interpretation of these findings is that depression is associated with a deficit in a late stage of affective appraisal that involves functions of the right parietal region. If the enhancement of late positivity to affective stimuli serves as a somatic marker to signal stimulus significance and to guide behavior (e.g. Damasio et al., 1991), we may postulate that one feature of depression is a defect in the activation of somatic markers that commonly accompany processes of affective stimulus evaluation and involve activity of right parietal regions.

Future studies should include stimuli of positive valence in a comparable paradigm, as the present results cannot be generalized beyond the processing of negative affective stimuli. Studying

the differences in ERP topography to positive and matched 'neutral' control stimuli would be a particularly promising endeavor in depression, given the postulate that loss of pleasure is a distinct feature of depression (e.g. Watson et al., 1988). Also, concurrent measures of autonomic activity should be added to multichannel ERP recordings for two reasons: first, the right parietal region has been closely linked to autonomic arousal (e.g. Heilman et al., 1978; Gainotti, 1987; Tranel and Damasio, 1994), and, second, evidence of vegetative hypoarousal has also been found in mood disorders (e.g. Henriques and Davidson, 1989; Sponheim et al., 1995).

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