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Early life stress and psychiatric disorder modulate cortical responses to affective stimuli

KATJA WEBER,[a] GREGORY A. MILLER,[b] HARALD T. SCHUPP,[a] JENS BORGELT,[a] BARBARA AWISZUS,[a] TZVETAN POPOV,[a] THOMAS ELBERT,[a] AND BRIGITTE ROCKSTROH[a]

[a]Department of Psychology, University of Konstanz, Konstanz, Germany
[b]Departments of Psychology and Psychiatry and Beckman Institute Biomedical Imaging Center, University of Illinois at Urbana Champaign, Urbana, Illinois, USA

Abstract

Altered affective processing has been proposed as mediating between early life stress (ELS) and subsequent psycho pathology. The present study examined whether ELS influences affective cortical processing differently in psychiatric patients and healthy subjects. The number of stressful experiences before onset of puberty was assessed in 50 inpatients with diagnoses of Major Depressive Disorder, schizophrenia, drug addiction, or Borderline Personality Disorder and in 20 healthy comparison subjects. Subjects monitored pleasant, neutral, and unpleasant pictures during magneto encephalographic recording. Suppression of right posterior activity 160 210 ms after stimulus onset was associated with certain diagnoses and high ELS. Results confirmed specific contributions of ELS versus adult stress, comorbid posttraumatic stress disorder, or depression.

Descriptors: Early life stress, Psychopathology, Affective modulation, IAPS, MEG

Visual stimuli with emotional content are frequent and effective prompts for cortical processing, including output systems mo tivating approach avoidance behavior (Lang, Bradley, & Cuth bert, 1998a, 1998b). The modulation of cortical processing by the salience and valence of affective pictures has been verified by neuroimaging methods such as electroencephalography (EEG), magnetoencephalography (MEG), and functional magnetic res onance imaging (fMRI; e.g., Bradley et al., 2003; Junghöfer, Bradley, Elbert, & Lang, 2001; Junghöfer, Schupp, Stark, & Vaitl, 2005, Junghöfer et al., 2006; Sabatinelli, Bradley, Fitzsim mons, & Lang, 2005; Schupp, Junghöfer, Weike, & Hamm, 2003, 2004). Event related brain potential (ERP) studies consis tently reveal that the processing of pleasant and unpleasant stimuli is associated with an enhanced posterior negativity around 120 300 ms poststimulus (early posterior negativity, EPN) compared to neutral stimuli (Junghöfer et al., 2001; Schupp et al., 2003). A recent event related magnetic field (ERF) study showed a strong and reliable magnetic counterpart to the EPN reported in ERP studies. Source analyses indicated strongly amplified processing of pleasant and unpleasant emotional pic tures compared to neutral material in occipito parieto temporal brain regions associated with visual processing (Peyk, Schupp, & Elbert, 2008). According to a bivariate motivational model of emotion (Bradley, Codispoti, Cuthbert, & Lang, 2001; Lang, Bradley, & Cuthbert, 1997), enhanced attention to emotional cues supports the organization of efficient actions (serving appetitive and defensive goals) in response to events that can sustain or threaten the life of the organism.

Normal affective processing may be modified by individual factors, among them psychopathology or early life stress (ELS), purportedly through effects on neuronal and neuroendocrine sys tems that are also involved in affect regulation (e.g., Charmandari, Kino, & Souvatzoglou, 2003). Many human studies have demon strated the impact of adverse or traumatic experiences on adult psychopathology (e.g., Heim & Nemeroff, 2002; McEwen, 2003; Nemeroff, 2004) and on risk for it, such as depression (Heim, Plotsky, & Nemeroff, 2004), schizophrenia (Thompson, Pogue Geile, & Grace, 2004), personality disorder (Goodman, New, & Siever, 2004), substance abuse (de Bellis, 2002; Sinha, 2005), and anxiety disorders, including posttraumatic stress disorder (PTSD; Scheller Gilkey, Moynes, Cooper, Kant, & Miller, 2004; van der Kolk, Roth, Pelcovitz, Sunday, & Spinazzola, 2005). Although ELS induced alterations in affective processing, neuroendocrine systems, and brain development are consistently reported as bio logical contributions to adult psychopathology, ELS may not be a differential risk factor for specific psychiatric disorders. Rather, ELS during sensitive periods of brain development is proposed to interact with genetic and/or pre or postnatal factors to influence broad vulnerability for disorder (Heim et al., 2004; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Maynard, Sikich, Lieberman, & LaMantia, 2001).

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Address reprint requests to: Prof. Dr. Brigitte Rockstroh, Depart ment of Psychology, University of Konstanz, P.O.Box D23, D 78457 Konstanz, Germany. E mail: Brigitte.rockstroh@uni konstanz.de

The impact of ELS on affective processing was exemplified in a study of 90 individuals without psychiatric diagnoses (Pole et al., 2007): The 25 subjects who reported childhood trauma also reported low positive emotion and exhibited large autonomic responses to threatening experimental stimuli compared to subjects without ELS. Similarly, Cohen et al. (2006) found adverse childhood events to be associated with depression and anxiety in over 1,500 adults without psychiatric diagnoses. A behavioral state of despair or helplessness consequent to prenatal stress or lasting, inescapable stressors (Morley et al., 2003; Porsolt, Bertin, & Jalfre, 1978) has been documented in animal studies and related to neuroendocrine alterations (Cabib & Puglisi Allegra, 1996). Lang, McTeague, and Cuthbert (2007) interpreted distress and negative affect as reflecting diminished activity of the defense system in anxious and depressive patients. They noted that defense and reward systems overlap with the function of the stress system.

In summary, studies of ELS, affective processing, psychopathology, and brain mechanisms have established many pairwise relationships. These various phenomena no doubt combine in complex, nonadditive ways. Childhood trauma may convey risk for adult psychopathology by altering emotional responses to subsequent stressors, for example. The present study explored whether retrospectively reported ELS is associated with differential cortical affective processing in patients with psychiatric disorders and healthy comparison subjects and whether this varies by specific psychiatric disorder or by emotional stimulus features. In particular, it examined attention capture by emotionally significant pictures as a function of ELS and diagnosis. Whole head MEG probed spontaneous, involuntary attention capture by emotional cues, which has been manifested in many previous studies as augmented activation over occipito parieto temporal regions from approximately 120 to 300 ms after stimulus onset. If ELS exerts long lasting effects on stress relevant systems, and if these influence cortical systems involved in affect processing and regulation (Bremner, 2002; Mayberg, 2003), high ELS may abolish or attenuate the early preferential processing of emotional cues. Hence, the prediction was reduced responses to affective stimuli and reduced modulation of cortical activity by the affective valence of stimuli in the EPN time window.

Affective modulation has also been reported for activity around 100 ms after stimulus onset (e.g., Borgelt, Odenwald, Ruf, Elbert, & Kissler, 2009; Junghöfer et al., 2003; Rockstroh, Junghöfer, Elbert, Buodo, & Miller, 2006; Smith, Cacioppo, Larsen, & Chartrand, 2003). Modulation of this effect by stress/trauma or psychopathology varies across studies in that augmented early activity relative to normal was reported for patients with PTSD (Borgelt et al., 2009; Junghöfer et al., 2003), and suppression of early activity relative to normal was reported for schizophrenia patients (Rockstroh et al., 2006). Therefore, the present study extended the search for possible effects of ELS or diagnosis to a second, earlier time window around 100 ms. At issue was the temporal specificity of ELS effects on affective processing.

Methods

Participants

Table 1 summarizes demographic and clinical data for 50 inpatients at the local Center for Psychiatry and 20 healthy comparison individuals. Patients were recruited from several wards within the center and identified by the treating psychiatrists as meeting the inclusion criteria. Patients were included if they met International Classification of Diseases, 10th Revision (ICD 10) diagnoses of Major Depressive Disorder (MDD; F31 33), schizophrenia spectrum (F20, F25), drug addiction (DA; F19, F10), or Borderline Personality Disorder (BPD; F60.31) and if they were in a sufficiently remitted state to allow data collection (interview on life stress history and MEG protocol). As the clientele of the center mainly includes long term inpatients, most were not in an acute state with severe symptoms. (This was confirmed by a global rating of symptom severity provided below.)

Table 1. *Demographic and Clinical Data*

Group: *N*	Gender (female/male)	Age ($M \pm SD$)	Years education	BDI ($M \pm SD$)	BPRS ($M \pm SD$)	Medication[a]	Secondary ICD diagnoses
Patients: 50	17/33	38.8 ± 12.5	12.2 ± 2.9	17.9 ± 11.0	52.1 ± 9.0		
MDD: 19	10/9	48.7 ± 7.4	12.5 ± 3.0	24.6 ± 10.5	51.1 ± 7.9	Mix: 7, TCA: 1, SSRI: 10, AD mix: 1	F4: 2 F10.2: 1 F6: dep: 2 other: 1 paranoid: 1 schizoid: 1 F43.2: 2 None: 9
Schizophrenia: 15	3/12	34.5 ± 10.7	13.3 ± 3.6	13.6 ± 9.9	48.2 ± 5.7	Mix: 8, AD mix: 1, atyp: 6	F12: 5 F33: 1; 20.4: 2 None: 7
Drug addiction: 10	0/10	32.3 ± 7.2	10.6 ± 1.4	10.8 ± 7.5	59.5 ± 10.4	None: 10	F60.3: 1 F61.0: 2 F12.1: 1 None: 6
Borderline Personality Disorder: 6	4/2	28.5 ± 9.4	11.2 ± 1.5	19.0 ± 9.0	50.4 ± 11.8	None: 5, Mix: 1	F10: 2, F65.4: 1 F53: 1 None: 2
Comparison subjects: 20	8/12	40.5 ± 15.2	15.3 ± 2.9	3.7 ± 4.3		None: 20	

[a]Mix: combination of antidepressants (AD) and neuroleptics (N); TCA: tricylcic AD; SSRI: selective serotonin reuptake inhibitors; AD mix: combination of TCA and SSRI; typ: typical neuroleptics; atyp: atypical neuroleptics; N mix: combination of typical and atypical neuroleptics; none: no medication.

Patients with neurological conditions, head trauma with loss of consciousness, or intellectual disability were excluded.

For analyses comparing subgroups of inpatients by diagnosis, the primary diagnosis determined the subgroup. (Secondary diagnoses, reported in Table 1, were not fully assessed for some patients.) The four diagnostic subgroups differed in gender distribution, $\chi^2(3) = 12.25$, $p < .01$, due to more male participants in the schizophrenia and DA subgroups versus balanced MDD and BPD subgroups, and in age, $F(3,46) = 10.98$, $p < .001$, MDD patients being older than the other subgroups, who did not differ (post hoc t tests evaluated significant effects as needed throughout this study). Patient subgroups did not differ in years of education, $F(3,46) = 2.2$, $p = .10$.

Severity of disorder was evaluated via the Brief Psychiatric Rating Scale (BPRS; Lukoff, Liberman, & Nuechterlein, 1986) and the Beck Depression Inventory (German version; Hautzinger, Bailer, Worall, & Keller, 1994). MDD and DA subgroups exhibited higher BPRS scores than did the other two subgroups, $F(3,42) = 3.83$, $p = .02$, and BDI scores were higher in patients with MDD than in the other subgroups, $F(3,46) = 5.86$, $p = .002$, who did not differ. Except for participants with drug addiction, most patients were on medication (see Table 1), the majority receiving combinations either of antidepressants and neuroleptics, typical and atypical neuroleptics, or tricyclic and SSRI antidepressants. Monotherapy was rare.

Healthy volunteers were recruited from hospital staff, students, and colleagues and were screened to be comparable to the patient sample in age, gender, and education. They were included if they did not meet criteria for a lifetime diagnosis (screened with the MINI interview; Ackenheil, Stotz Ingenlath, Dietz Bauer, & Vossen, 1998), did not report any history of head trauma with loss of consciousness, and were free of psychoactive medication. The patient group and the comparison group were similar in gender balance and age (Fisher's exact test $p = .8$ and $p > .6$, respectively). Comparison subjects had more years of education than did patients, $F(1,68) = 15.87$, $p < .001$.

Handedness was determined using the Edinburgh Handedness Questionnaire (Oldfield, 1970). Right handedness was confirmed for 43 patients and 16 comparison subjects. Four patients and 2 comparison subjects were ambidextrous, and 3 patients and 2 comparison subjects were left handed. All participants had normal or corrected to normal vision. The study protocol was approved by the local ethics committee. All subjects gave written informed consent.

Design and Procedure

Prior to the MEG session, prepubertal and adult stress history was assessed with the German version of the Early Trauma Inventory (ETI; Bremner, Vermetten, & Mazure, 2000; Heim, 2000).[1] Stress load was defined as the number of reported events across four domains (emotional neglect, punishment, sexual abuse, other traumatic events), separately for (a) the time before the individual onset of puberty (taken as a measure of ELS) and (b) the time between 18 years and the assessment (labeled adult stress, AS). Thus, ELS and AS were determined for each participant. In addition, PTSD was diagnosed in an interview using the Posttraumatic Stress Diagnostic Scale (PDS; Foa, 1995).

Affective modulation was evaluated via picture ratings and electromagnetic cortical responses. Affective stimuli comprised 300 colored photographs from the International Affective Picture System IAPS (Center for the Study of Emotion and Attention, 2004): 150 stimuli were high arousal, 75 pleasant and 75 unpleasant valence, according to normative valence and arousal ratings (Lang, Bradley, & Cuthbert, 1999), and 150 were low arousal, neutral valence stimuli. All pictures involved social scenes and were matched for size, contrast, and brightness. Pleasant and unpleasant pictures did not differ in rated arousal. As expected, both had significantly higher arousal scores than the neutral category.[2]

In a passive viewing task, pictures were presented for 660 ms with an offset to onset interstimulus interval of 700 to 900 ms. Each picture was presented once within each of two series of 300 pictures (600 trials in total). Pleasant, neutral, and unpleasant pictures were presented in random order. Within each affective category no more than two repetitions of the same picture category were allowed. Timing and sequence of stimulus presentation were controlled using Presentation software (Neurobehavioral Systems, Albany, CA). Participants were instructed that they would see a series of pictures with different content and that they should attend to each picture and try to avoid head and eye movements during each run, which lasted for about 15 min.

After the MEG recording, each participant was asked to rate the valence and emotional arousal of 75 representative IAPS pictures, 25 from each category. These pictures were randomly taken from the set of pictures presented during MEG recording. Picture ratings during MEG recording would have introduced an explicit evaluative task context and increased artifacts due to rating by button press. Therefore, ratings were collected following MEG recording relying on representative subsets of the pictures. The selected subsets of pleasant and unpleasant pictures were matched on arousal based on IAPS norms (Center for the Study of Emotion and Attention, 2004). Pictures were presented without time limit in randomized order, and ratings were obtained with a computerized version of the SAM (Bradley & Lang, 1994). Arousal and valence of each picture were evaluated on a 9 point scale, with higher numbers indicating evaluation as more pleasant or more arousing. Ratings were not available for 9 patients.

Data Acquisition and Analysis

MEG was recorded while subjects were in a prone position, using a 148 channel magnetometer (Magnes 2500 WH, 4D Neuroimaging, San Diego, CA). Neuromagnetic data were continuously recorded with a sampling rate of 678.17 Hz and a bandpass filter of 0.1 to 100 Hz. For artifact control, the vertical and horizontal electrooculogram (EOG; recorded from four electrodes placed near the left and right temporal canthus and above and below the right eye) and the electrocardiogram (ECG; from two electrodes attached to the right and left forearm) were recorded using a SynAmps amplifier (Neuroscan Laboratories,

[1] Psychometric properties have been confirmed for the ETI (Bremner et al., 2000; Bremner, Bolus, & Mayer, 2007), the Traumatic Antecedent Questionnaire (TAQ; van der Kolk et al., 2005), and the Childhood Trauma Questionnaire (CTQ; Paivio & Cramer, 2004). A retest of TAQ self reports after 3–6 months showed reliability of .8 (Garieballa et al., 2006). The high correlation between stressful events assessed by the ETI and traumatic events assessed by the PDS supports confidence in the retrospective self report of life events.

[2] Because the IAPS set provided only 135 appropriate low arousal neutral slides, 15 pictures were added from picture databases on the Internet. The selection of pictures thematically similar to the ones of the IAPS set was validated by ratings of 30 student subjects using the Self Assessment Manikin (SAM; Bradley & Lang, 1994) to match the normative ratings of IAPS pictures.

Sterling, VA). The subject's nasion, left and right ear canal, and head shape were digitized with a Polhemus 3Space Fasttrack prior to each session.[3]

Following noise reduction, MEG data were corrected for heartbeat related artifacts: In time segments with R wave artifact, an average magnetocardiogram was subtracted, calculated as a moving average over 20 heartbeats (4D Neuroimaging "cardiac comber" software). In addition, trials with eyeblinks were excluded from further data analyses. On average, 382 artifact free trials per subject were available for further analysis, with no differences in number of trials between patients and comparison subjects for stimulus categories (pleasant, unpleasant, neutral, all $F<1$). For artifact free trials, data epochs including 100 ms before (baseline) and 660 ms after stimulus onset were averaged and filtered with a 1 Hz (12 dB/octave, forward shift) high pass filter and a 40 Hz (24 dB/octave, zero phase shift) low pass filter. BESA software (Megis Software GmbH, Munich, Germany) was used for preprocessing.

As in previous research, the L2 Minimum Norm Pseudoinverse (L2MNP) was used for inverse modeling, providing minimum norm estimates (MNE) of cortical activity without any assumption regarding the location and/or number of current sources (Baillet, Mosher, & Leahy, 2001; Hamalainen & Ilmoniemi, 1994; Hauk, 2004; Hauk, Keil, Elbert, & Müller, 2002). Relying on EMEGS software (Junghöfer & Peyk, 2004; see www.emegs.org), a spherical shell with 2 (azimuthal and polar direction) × 350 evenly distributed dipoles served as the source model. A source shell radius of 87% of the individually fitted head radius was chosen, roughly corresponding to gray matter. A Tikhonov regularization parameter of 0.2 was applied. Magnetic field strength (independent of dipole direction) was calculated as the 3D vector length of the generator activity at each position for each subject, condition, and time point based on the averaged magnetic field distributions and the individual sensor positions.

In the source analysis, point wise analyses of variance (ANOVAs) were calculated separately for each dipole for identification of spatiotemporal modulation as a function of emotion. To avoid false positives, significant effects were considered only when they included a minimum of 21 continuous data points (32 ms) and when two adjacent representative dipoles showed emotion effects. This procedure determined a time window of differential brain activity 160 210 ms after stimulus onset for left and right occipito parieto temporal regions of interest (ROI) that were scored for average activity among 21 dipoles (Figure 1). As MEG activity in this ROI seems comparable to the early posterior negativity (EPN) described in EEG studies (Peyk et al., 2008), it will be labeled as EPN from here on for the sake of simplicity. Employing the same procedure of point wise ANOVAs, differential activity in the interval 80 115 ms after stimulus onset was used to define a ROI scored from the average of 18 dipoles each in the left and right anterior cortex (Figure 1). Referring to the time window, this component was related to a M100.

[3]The nasion and the left and right ear canal served as index points and were used to define a right handed coordinate system, called the head frame coordinate system. The positive pole of the x axis points to the front, the y axis to the left, and the z axis to the top of the head. The head shape information is used in standard analysis software for localization of activity sources (4D Neuroimaging WHS 1.2.6) by fitting a local sphere to the head shape underneath selected sets of adjacent channels. The subject's head position relative to the pickup coils of the MEG dewar was estimated before and after each session using these index points.

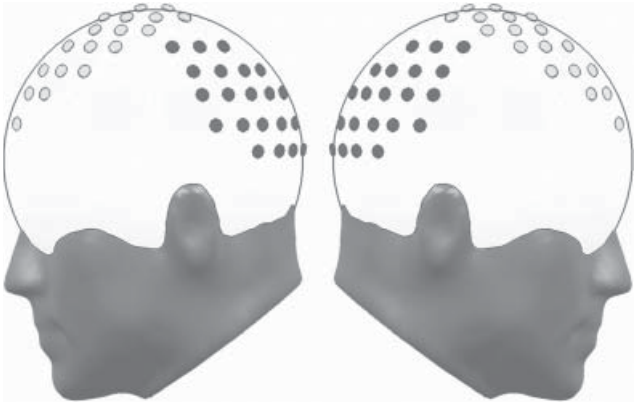

Figure 1. Schematic positions of the dipoles used for statistical analyses, displayed as left sided and right sided rendering of the spherical configuration. The dipoles forming the regions of interest (ROIs) are marked by black circles for posterior activity 160 210 ms after stimulus onset, referred to as EPN, and by gray circles for anterior activity 80 115 ms, referred to as M100.

Mean ROI activity was submitted to ANOVAs containing the within subject factors Emotion (pleasant vs. neutral vs. unpleasant), Hemisphere (left ROI vs. right ROI), and, in separate analyses, Group (patients vs. comparison subject), Diagnosis (MDD vs. BPD vs. schizophrenia vs. DA) or ELS Group (low ELS vs. high ELS; see below). Nonspecific effects of psychopathology were evaluated with Group (all patients vs. comparison subjects) × Emotion × Hemisphere (left and right occipito parieto temporal ROI) ANOVAs. In addition, patients were compared via Diagnosis (MDD, schizophrenia, DA, BPD) × Emotion × Hemisphere ANOVAs. These four group analyses were considered exploratory, given the small Ns per diagnostic subgroup. Significant main effects or interactions were explored with t tests if not already clear from orthogonal trends. The Huynh Feldt epsilon correction accounted for possible violations of the homogeneity of covariance assumption (uncorrected degrees of freedom and epsilon corrected p values are reported). The alpha level was set at .05 for each comparison.

ELS effects were first probed by Spearman rho (r_s) and Pearson (r) correlations including the entire sample. For simplicity in potential interactions with hemisphere, Group × Hemisphere ANOVAs were evaluated for ELS groups created by placing subjects with number of events above the mean+2 *SD* of the comparison group into a high ELS group and subjects with number of events below the mean of the comparison group into a low ELS group.

Ratings of the valence and arousal properties of the stimuli were examined in an ANOVA with the Emotion factor comparing 25 pleasant, 25 neutral (randomly selected from the stimulus set), and 25 unpleasant stimuli. Orthogonal trends captured valence (pleasant vs. unpleasant) as a linear trend and arousal (pleasant and unpleasant vs. neutral) as a quadratic trend. These trends reflected a priori hypotheses about critical dimensions of emotion (e.g., Lang, Bradley, & Cuthbert, 1990), so tests of the orthogonal trends did not require a significant omnibus test.

Results

Stimulus Ratings and Stress History

Valence and arousal ratings (see Table 2) showed expected patterns, primarily linear and quadratic, respectively (Bradley &

Table 2. *Ratings of Valence and Arousal*

Group: *N*	Arousal ($M \pm SD$)			Valence ($M \pm SD$)		
	Pleasant	Neutral	Unpleasant	Pleasant	Neutral	Unpleasant
Patients: 41	5.1 ± 1.5	3.2 ± 1.4	6.2 ± 1.6	6.6 ± 1.2	5.8 ± 0.9	2.1 ± 0.8
MDD: 12	4.9 ± 1.7	3.1 ± 1.3	6.5 ± 1.8	5.8 ± 1.7	5.8 ± 0.7	2.0 ± 0.7
Schizophrenia: 14	5.7 ± 1.1	3.7 ± 1.2	6.3 ± 1.0	6.8 ± 1.0	5.6 ± 0.8	2.2 ± 0.6
Drug addiction: 10	4.6 ± 1.6	2.7 ± 1.5	6.0 ± 1.6	7.2 ± 0.8	6.0 ± 1.3	2.1 ± 0.6
Borderline Personality Disorder: 5	4.8 ± 1.4	2.9 ± 1.2	5.7 ± 2.7	6.5 ± 0.9	5.5 ± 0.5	2.3 ± 1.5
Comparison subjects: 20	5.0 ± 1.3	3.2 ± 1.3	6.4 ± 0.8	6.5 ± 0.8	5.6 ± 0.6	2.2 ± 0.8

Note: Ratings were given on a 9 point scale with higher values indicating higher arousal and more pleasant rating. Ratings were not available for 9 patients (7 MDD, 1 schizophrenia, 1 BPD).

Lang, 1994). In Group (patients, comparison subjects) × Emotion analyses of valence and arousal ratings, pleasant pictures received the highest valence ratings and unpleasant the lowest, Emotion $F(2,116) = 407.50$, $p < .001$, $\varepsilon = .93$. The linear trend, reflecting valence ratings for pleasant versus unpleasant pictures, contributed 89% of the Emotion variance, $F(1,58) = 591.10$, $p < .001$, and the quadratic trend, reflecting pleasant and unpleasant versus neutral, contributed 11% of the Emotion variance, $F(1,58) = 114.29$, $p < .001$. Unpleasant pictures were rated as more arousing than pleasant ones and both as more arousing than neutral ones, Emotion $F(2,118) = 125.66$, $p < .001$, $\varepsilon = .90$. This was carried primarily by the quadratic trend, with 82% of the Emotion variance, $F(1,59) = 191.37$, $p < .001$. The linear trend added 18% of the variance, $F(1,59) = 46.76$, $p < .001$.[4] Neither Group nor Group × Emotion effects approached significance. In Diagnosis × Emotion analyses of valence and arousal ratings comparing the four patient subgroups, no effects involving diagnosis emerged. Thus, in ratings of stimuli, patients resembled comparison subjects.

Patients experienced a higher number of stressful events before onset of puberty (ELS) than did comparison subjects, $F(1,68) = 20.32$, $p < .001$ (see Table 3). Among patients, ELS was higher in BPD and MDD than in schizophrenia or DA, Diagnosis $F(3,44) = 8.88$, $p < .001$. Stimulus ratings were not associated with ELS or AS. The relationship between ELS and AS was explored before relating them to stimulus ratings. They were uncorrelated: Pearson $r(68) = .109$, $p = .37$; Spearman $r_s(68) = .178$, $p = .14$. Thus, high childhood stress load is not necessarily related to high adult stress load. Then, six hierarchical regressions were conducted with both early and adult stress predicting SAM ratings (separately for arousal and valence for each of pleasant, neutral, and unpleasant slides). None of the six omnibus tests (both life stress predictors in the model, each of the six ratings as the dependent variable) approached significance, and in only 1 of 12 possible cases did either predictor add significant variance when entered second into the model. These results indicate that, according to ratings, variations in stress history do not alter general emotional response and that ELS and AS are neither redundant measures nor confounds in relationships each may have with other variables, including MEG measures.

[4]Although the IAPS stimuli were selected to match pleasant and unpleasant pictures on arousal value based on published norms (Center for the Study of Emotion and Attention, 2004), in the present sample unpleasant stimuli received slightly higher arousal ratings than did pleasant stimuli, raising the possibility of a confound of valence and arousal. However, arousal ratings for those two high arousal categories were much closer to each other than to arousal ratings for neutral stimuli: pleasant mean, *SD* 5.05, 1.42; neutral 3.19, 1.31; unpleasant 6.29, 1.39. Because the quadratic trend among these means represented more than 4 times the variance of the linear trend, it is clear that, as intended, arousal ratings largely reflected the arousal value of the stimuli and not their valence. Furthermore, because all of the findings for the EPN analysis involved quadratic (arousal) and not linear (valence) trends, the slight (though reliable) difference in arousal ratings for pleasant and unpleasant stimuli was not judged to be a significant confound for present purposes.

EPN: ROI Activity at 160-210 ms

Diagnosis and EPN. As shown in Figure 2, pleasant and unpleasant picture processing was associated with more posterior ROI activity than was neutral picture processing. The Emotion effect, $F(2,136) = 6.33$, $p = .002$, $\varepsilon = 1$, was carried by the quadratic trend, $F(1,68) = 12.17$, $p < .001$, explaining 95% of the Emotion variance. There was more activity in the right than in the left ROI, Hemisphere $F(1,68) = 15.95$, $p < .001$. Patients showed a trend of less activity, Group $F(1,68) = 3.31$, $p = .07$. No interaction approached significance.

Activity in visual processing areas differed by diagnosis: EPN was smaller in patients with MDD and BPD than in patients with schizophrenia, Diagnosis $F(3,46) = 4.04$, $p = .01$, and Diagnosis × quadratic Emotion, $F(3,46) = 2.77$, $p = .05$, explaining 89% of the Diagnosis × Emotion variance. Post hoc tests confirmed the differences between MDD and schizophrenia (Tukey HSD,

Table 3. *Measures of Stress Load in the Different Subgroups*

Group: *N*	ELS $M \pm SD$ (range)	AS $M \pm SD$ (range)	High/low ELS	High/low AS	PTSD
Patients: 50	11.4 ± 7.1 (0 32)	2.7 ± 2.9 (0 15)			13
MDD: 19	13.9 ± 6.2 (2 32)	3.9 ± 3.7 (0 15)	14/1	4/8	9
Schizophrenia: 15	6.9 ± 5.3 (0 19)	1.8 ± 1.3 (0 4)	5/6	0/11	0
Drug addiction: 10	8.7 ± 4.0 (4 17)	2.0 ± 2.6 (0 8)	4/1	1/4	0
Borderline Personality Disorder: 6	19.3 ± 8.5 (6 28)	2.2 ± 2.8 (0 7)	5/0	1/1	4
Comparison subjects: 20	4.1 ± 2.6 (0 10)	2.6 ± 2.7 (0 10)	1/12	2/12	0

Note: ELS early life stress: number of stressful events reported for the time before the individual onset of puberty; AS adult stress: number of stressful events reported after age 18. Early Trauma Inventory scores were not available for 2 patients. PTSD: number of subjects with comorbid diagnosis of posttraumatic stress disorder based on the PDS interview. Note that the number of high and low ELS subjects does not add up to the number of studies subjects, as subjects at the extreme of the number of event dimension were assigned to the subgroups.

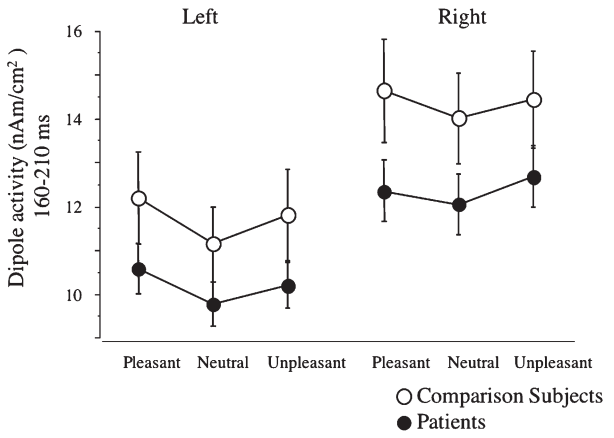

Figure 2. Modulation of posterior dipole activity at 160 210 ms by group (patients: filled black circles, comparison subjects: open circles), emotion (abscissa), and hemisphere. Ordinate: Dipole activity expressed as minimum norm estimates, mean ± standard error in nAm/cm^2.

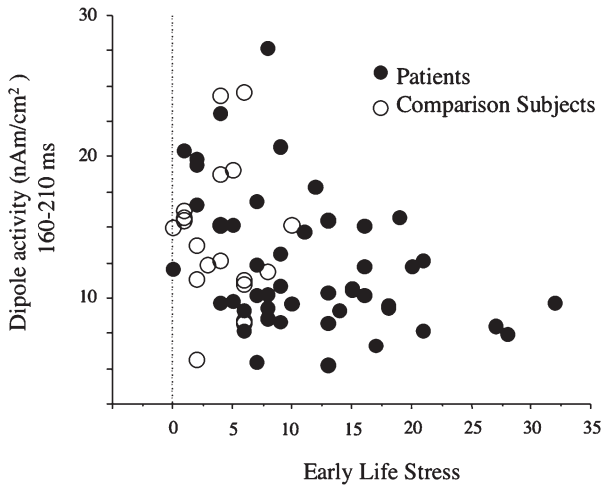

Figure 3. Relationship between stress load before puberty (ELS, abscissa: number of experienced events between birth and individual onset of puberty) and right hemisphere EPN averaged across all three levels of emotion for patients (filled black circles) and comparison subjects (open circles). Ordinate: Dipole activity expressed as minimum norm estimates, mean ± standard error in nAm/cm^2.

$p<.05$) and between BPD and schizophrenia ($p<.05$); other pairs of groups did not differ. When comparing the different diagnostic subgroups with comparison subjects, right hemi spheric EPN differences were verified between MDD patients and comparison subjects, $t(37) = 2.21$, $p = .03$, and BPD and comparison subjects, $t(24) = 2.77$, $p = .01$, but not between schizophrenia or DA patients and comparison subjects.

Pursuing the Group × quadratic Emotion interaction, visual inspection suggested that MDD and BPD patients did not show an arousal effect, compared to schizophrenia and DA patients**.** MDD and BPD patients might well be similar in emotional pro cessing abnormalities, given their frequently considerable co morbidity. Indeed, the Emotion main effect was not significant for the combined group of MDD and BPD patients, $F(2,48) < 1$, quadratic Emotion $F(1,24) < 1$, whereas it was for patients with schizophrenia and DA, $F(2,48) = 8.92$, $p<.001$, $\varepsilon = .73$, qua dratic Emotion $F(1,24) = 10.95$, $p = .003$. This suggests that, in addition to overall EPN suppression, affective modulation is impaired in patients with MDD and BPD.

ELS and EPN. As reported above, patients experienced more ELS than did comparison subjects, and among patients, ELS was higher in BPD and MDD than in schizophrenia or DA. As a consequence, it is difficult to distinguish the contributions of specific diagnosis versus ELS to electromagnetic responses. As shown in Table 4 and Figure 3, ELS score correlated negatively with EPN ROI activity elicited by pleasant, neutral, and un pleasant pictures, somewhat more pronounced for right than left ROIs. In contrast to the consistent relationship for ELS, AS did not differentiate patients and comparison subjects ($F<1$; Table 3) or diagnostic subgroups, $p = .12$. None of the six correlations between AS and EPN approached significance (Table 4).

The ELS/EPN relationship was examined further by com paring high and low ELS groups (high ELS: $N = 26$, including 25 patients; low ELS: $N = 20$, 8 patients).[5] High ELS subjects had less active visual regions, $F(1,44) = 13.14$, $p<.001$. How ever, the affective modulation of EPN, $F(2,88) = 5.55$, $p = .005$, $\varepsilon = 1.00$, was not influenced by ELS (ELS Group × Emotion interaction, $p = .14$). Activity was right lateralized, $F(1,44) = 18.58$, $p<.001$, with an ELS Group × Hemisphere interaction, $F(1,44) = 4.41$, $p = .04$, indicating less EPN lateralization for the high ELS group, Hemisphere $F(1,25) = 4.58$, $p = .04$, than in the low ELS group, $F(1,19) = 12.05$, $p = .002$, and more differenti ation between ELS groups in the right, $F(1,44) = 15.12$, $p<.001$), than in the left hemisphere, $F(1,44) = 3.62$, $p = .06$ (see Figure 4). ELS was generally related to EPN suppression, particularly in the right hemisphere (see Table 4 and Figure 3).

PTSD and EPN. There was overlap between comorbid PTSD (determined by PDS) and ELS in that the number of patients with comorbid PTSD was higher in the diagnostic sub groups with high ELS (MDD and BPD; see Table 3). An issue is the extent to which ELS effects on EPN were redundant with possible effects of PTSD on EPN. First, ELS score and PTSD (meets criteria for PTSD diagnosis or not) were indeed corre lated: Pearson $r(68) = .428$, $p<.001$; Spearman $r_s(68) = .452$,

Table 4. *Spearman Correlations between Stress Load and EPN Amplitude*

	EPN right hemisphere			EPN left hemisphere		
	Pleasant	Neutral	Unpleasant	Pleasant	Neutral	Unpleasant
ELS	– .36**	– .38**	– .40**	– .35**	– .24*	– .28*
AS	– .10	– .09	– .08	– .14	– .06	– .08

Note: N 70. ELS early life stress: number of stressful events reported for the time before the individual onset of puberty; AS adult stress: number of stressful events reported after age 18.
*$p<.05$, two tailed;
**$p<.01$ level, two tailed.

[5]High and low ELS subgroups did not differ with respect to the number of trials that entered analyses ($p>.2$). As indicated in Table 3, the assignment of patients to the high ELS and low ELS groups differed by diagnosis, χ^2 (3) 10.2, $p<.02$ (including the comparison group: χ^2[4] 26.7, $p<.001$). This was not the case for assignment to sub groups with high and low number of stressful events in adulthood, AS: χ^2 (3) 5.21, p .16; including comparison subjects, χ^2(4) 5.81, $p>.2$.

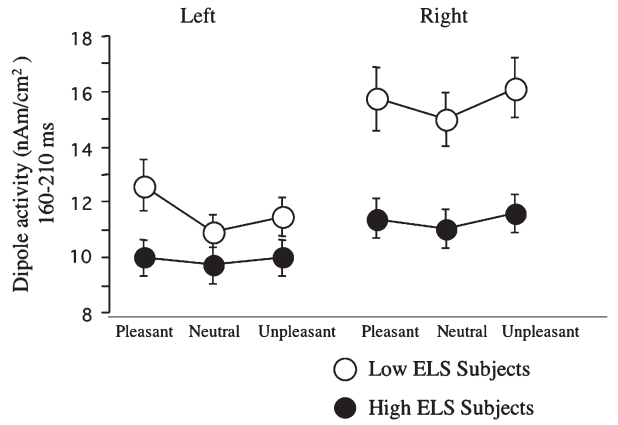

Figure 4. Modulation of dipole activity at 160 210 ms (EPN) by ELS group, emotion, and hemisphere. Filled black circles: subjects with number of stressful events more than 2 *SD* above the mean of the comparison group. Open circles: subjects with number of stressful events below the mean of the comparison group. Ordinate: Dipole activity expressed as minimum norm estimates, mean ± standard error in nAm/cm^2.

$p < .001$. However, hierarchical regression showed that high ELS was associated with EPN suppression separate from any contri bution from or redundancy with PTSD. For example, a regres sion employing ELS score and PTSD status as predictors accounted for 14% of the variance in right hemisphere EPN score for unpleasant stimuli, $F(2,67) = 5.48$, $p = .006$. Added second, PTSD diagnosis did not add variance, $p = .30$, to that accounted for by EPN, whereas EPN did add unique variance, $p = .02$. Thus, ELS related to EPN suppression above and be yond the role of PTSD diagnosis.

BDI and EPN. As a final question about the specificity of ELS/EPN effects, mood symptom severity might mediate this relationship. ELS and BDI score were correlated: Pearson $r(68) = .478$, $p < .001$; Spearman $r_s(68) = .510$, $p < .001$. Hierar chical regression showed that high ELS was associated with EPN suppression separate from any contribution from or redundancy with BDI. For example, a regression employing ELS score and BDI score as predictors accounted for 22% of the variance in right hemisphere EPN score for unpleasant slides, $F(2,67) = 8.88$, $p < .001$. Added second, both ELS, $p < .001$, and BDI, $p = .007$, added unique variance. Thus, ELS related to EPN suppression above and beyond the role of BDI.

M100: ROI Activity at 80–115 ms

It is possible that posterior brain activity in the 160 210 ms time window reflects a more general phenomenon observable earlier in the processing stream. To address this issue, activity was analyzed in left and right anterior ROI in an 80 115 ms time window. No evidence for Group ($p = .4$) or Emotion ($p = .5$) main effects emerged. A Group × Emotion interaction, $F(2,136) = 4.14$, $p = .02$, was carried by a linear trend, $F(1,68) = 5.39$, $p = .02$, explaining 64% of the variance. Inspection revealed no signifi cant Emotion effect in patients, whereas in comparison subjects Emotion approached significance, $F(2,38) = 3.12$, $p = .06$, $\varepsilon = .85$. The weakness of these effects and the absence of a Group × quadratic Emotion effect indicate that the Group × quadratic Emotion findings in the later (EPN) time window are not simply left over from early processing. The distinct effects support the specificity of findings in the EPN time window.

Discussion

The present study explored whether early life stress (ELS) influ ences brain activity during the processing of emotionally salient material and whether this influence is similar in normal subjects and in patients with psychiatric disorders. Results confirmed the reported modulation of electromagnetic activation in posterior regions 160 210 ms after stimulus onset (apparently comparable to the early posterior negativity in EEG and therefore labeled EPN in the present study) by visual stimuli as a function of emotional content (Lang et al., 1998b; Schupp et al., 2003, 2004). Using a slightly earlier time window (120 170 ms) Peyk et al. (2008) described similar modulation of posterior brain activity by stimulus valence and related it to emotional attention capture in the visual processing stream. In contrast, the present study con firmed anterior modulation around 100 ms only as a trend in healthy subjects.

As a group, present psychiatric inpatients showed normal EPN modulation as a function of stimulus arousal value, indi cating that the initial cortical analysis or "tagging" (Halgren & Marinkovic, 1995) of cues as behaviorally relevant is intact in such patients. However, both ELS and psychiatric disorder were associated with altered EPN response to emotional stimuli. Pa tients with MDD and BPD, in particular, exhibited reduced EPN and less affective modulation of EPN than did patients with schizophrenia or healthy subjects. Cortical correlates of abnor mal affective processing in psychiatric patients have been found in fMRI, EEG, and MEG studies. Schizophrenia primarily shows reduced activation by emotionally salient stimuli and re duced modulation of brain activity as a function of stimulus valence (for a review, see Rockstroh et al., 2006). In MDD, Moratti, Rubio, Campo, Keil, and Ortiz (2008) found weak arousal modulation of right temporal MEG activity by IAPS pictures. Yee and Miller (1988) observed an affective processing shutdown when dysthymic subjects anticipated such stimuli. Ev idence from fMRI suggests reduced activity in hippocampus and insula to unpleasant pictures and reduced ACC and amygdala activity to pleasant pictures in MDD (Lee et al., 2007). These examples suggest dampened rather than enhanced emotional ac tivation in some types of psychopathology. Whereas the EPN has not previously been specifically addressed in these psychiatric groups, the slow wave component of the ERP in the latency range of 300 400 ms confirmed reduced sustained activity during the processing of faces (Deldin, Keller, Gergen, & Miller, 2000;see also Kayser, Bruder, Tenke, Stewart, & Quitkin, 2000) or positive words (Shestyuk, Deldin, Brand, & Deveney, 2005), which the authors proposed as a contributing factor for cognitive deficits in MDD (see also Deveney & Deldin, 2004).

Abnormal cortical responses to affective stimuli do not nec essarily predict abnormal behavioral responses: Discrepancies between reduced affective modulation of early cortical responses but normal ratings of stimulus valence have been reported before (Rockstroh et al., 2006). In schizophrenia patients it was related to compensatory functions, which allow normal processing of emotional stimuli whenever they are presented without time constraints or workload, despite indications of abnormal auto matic processing. This explanation might hold as well for the present psychiatric sample. That measures of symptom severity (BPRS, BDI) did not vary with EPN whereas diagnosis and ELS

did suggests that present results reflect trait characteristics rather than current status of severe psychopathology.

High early life stress was also associated with EPN suppression, although specific additive versus interactive effects of ELS and psychiatric disorder cannot be fully distinguished in the present study. Indeed, because ELS contributes to psychiatric disorder and third variables promoting psychiatric disorder may also prompt ELS, a thorough differentiation, if possible, would require a much larger sample assessed for additional risk factors (e.g., genetic markers and environmental contributors). The present high ELS group comprised more MDD and BPD patients than schizophrenia and drug addiction patients and the low ELS group more patients with schizophrenia than patients with other diagnoses. This ELS/diagnosis association might be considered a confound, hampering identification of specific ELS effects. However, isolated main effects are less likely than Gene × Environment interactions, given current thinking in the psychopathology literature (e.g., Kendler, 2005; Turkheimer, 2000): Most of the variance is likely to be in the interactions, not in gene or environment main effects. The present study identified a subgroup of individuals in which ELS and other risk factors may have promoted a pattern of depressive and borderline symptoms and potentially also comorbid PTSD together with altered affective processing. Whereas both factors, ELS and affective modulation of brain responses, have not been examined within the same design, findings of high ELS in MDD (Heim & Nemeroff, 2002; Heim et al., 2004; Moratti et al., 2008) and dampened cortical responding in MDD (as described above) support the existence of such a subgroup. Moreover, comorbidity has been reported for PTSD and MDD (e.g., Breslau, 2002; Franklin & Zimmerman, 2001) and for BPD and PTSD (e.g., Clarke, Rizvi, & Resick, 2008; Heffernan & Cloitre, 2000). From this comorbidity, one might assume that the present relationship between ELS and EPN reflects the relationship between PTSD and EPN irrespective of stress load. However, the few studies that have examined affect related brain activation in patients with PTSD reported cortical hyperactivity (e.g., Attias, Bleich, Furman, & Zinger, 1996; Ehlers et al., 2006; Felmingham, Bryant, & Gordon, 2003) rather than reduced activation in the EPN latency range. Importantly, present analyses provided evidence of specificity for the ELS/EPN relationship that it is not merely a function of redundancy with adult stress, PTSD diagnosis, affective symptoms (BDI score), or responses earlier in the trial. Studies with larger psychiatric samples are needed to pursue the relationship between ELS and EPN and the role of specific types of psychopathology in that relationship.

Altered EPN has been related to brain circuits processing unpleasant or anxiety provoking stimuli (LeDoux, 2000). In healthy subjects, task irrelevant, high arousing pictures reduced N100 and EPN to subsequent task relevant stimuli (Ihssen, Heim, & Keil, 2007), indicating arousal dependent interference. It is tempting to speculate that severe stress load many years earlier can exert similar effects. In animal experiments, altered brain activity has been related to stress induced helplessness (Cabib & Puglisi Allegra, 1996; Porsolt et al., 1978), which is also relevant for altered brain activation in individuals with ELS and MDD or BPD (Lang et al., 2007; Morley et al., 2003). Stress induced hyperactivity of the stress response system (Charmandari et al., 2003) or the defense system (Lang, Davis, & Öhman, 2000) during sensitive developmental periods has been assumed to mediate changes in brain structure and function involved in affect regulation, which may be reflected in dampened cortical responses to emotional stimuli.

Methodological limitations of the present study may be noted. The null hypothesis of uniform ELS effects across diagnostic subgroups was rejected, but this involved splitting the patient sample ($n = 50$) into diagnostic subgroups of unequal size, prompting power differentials in some follow up analyses. In particular, results for BPD warrant verification in a larger sample. Moreover, a gender imbalance in diagnostic prevalence is well known, with a higher proportion of women diagnosed with MDD or BPD and a higher proportion of men diagnosed with schizophrenia or drug abuse. The present sample represented this asymmetry (association between gender and diagnostic subtype, $\chi^2[3] = 12.25$, $p = .007$). Nevertheless, when the Group (patients vs. comparison subjects) × Emotion × Hemisphere ANOVAs for EPN were repeated with Gender added as a factor, no main effect or interaction involving Gender was obtained. Thus, there was no interpretive confound with gender here. Several left handed or ambidextrous subjects were included, to preserve *N*s (especially in the diagnostic subgroups) and to avoid misrepresenting handedness in clinical samples. However, the main findings reported here did not depend on hemisphere interactions, so inclusion of such subjects does not appear to be a problem. Finally, clinical routine at the local Center for Psychiatry (which primarily treats chronic inpatients from the region) did not allow examination of nonmedicated patients or subgroups of patients with monotherapy.

In sum, exploring the relationship between ELS, psychiatric disorder, and cortical affective processing suggests that ELS interacts with type of psychiatric disorder in its effects on cortical processing. These findings suggest a dynamic relationship between vulnerability to psychopathology and an ELS induced or mediated risk for aggravation of psychopathology. Larger samples selected for high and low ELS, unconfounded with diagnostic subgroup, would be valuable to substantiate this interaction.

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