



## Adverse experiences in childhood influence brain responses to emotional stimuli in adult psychiatric patients

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### ABSTRACT

Previous results suggest that early life stress (ELS) may be related to altered cortical responses to emotional stimuli. In a previous study, we found suppressed cortical responses to emotional pictures in psychiatric patients with high-ELS. The present study explored the stability of this effect across time and stimulation conditions. In addition, the relationship between ELS and current life stress was examined, and we probed whether this current life stress was related to the cortical responses. Fifteen patients with high, 16 patients with low-ELS and 15 psychiatrically healthy subjects with low-ELS participated in two sessions 8 months apart. Subjects monitored a rapid serial presentation of pleasant, neutral and unpleasant pictures during magnetoencephalographic recording. In both sessions, estimated neural activity in occipital–parietal–temporal regions between 70 and 250 ms after picture onset was smaller in patients, particularly in those with high-ELS, compared to healthy subjects. Modulation of activity by arousing (pleasant and unpleasant) compared to neutral stimuli around 200 ms post-stimulus did not differ between groups, whereas around 300 ms, patients did not show the pronounced cortical response to pleasant stimuli exhibited by healthy subjects. Results suggest that ELS and psychiatric disorder (1) diminish early perceptual processing (<200 ms) of emotional stimuli without substantially affecting activity modulation by stimulus arousal value, (2) diminish later attention allocation processes (>300 ms), and (3) are related to more recent life stress. High intraindividual correlations of activity patterns between sessions suggest lasting effects of ELS on processing modes.

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### 1. Introduction

Automatic (involuntary) attention capture by emotional cues is supposed to support the preparation and organization of efficient appetitive and defensive actions (Lang et al., 1998). The power of emotional stimuli to attract attention is reflected in the modulation of cortical responses by the salience and valence of affective pictures, as verified in electroencephalographic (EEG; Junghöfer et al., 2001; Schupp et al., 2004), magnetoencephalographic (MEG; Peyk et al., 2008) or functional magnetic resonance imaging (fMRI) studies (Junghöfer et al., 2006; Phan et al., 2004). Activity in posterior brain regions is augmented as early as 150 ms after the onset of arousing pleasant and unpleasant pictures relative to non-arousing neutral pictures. Two components of selective emotional processing have been distinguished from opposite polarity of magnetic fields and from source analyses in an earlier time interval (120–170 ms after stimulus onset) in occipital–parietal–temporal regions and a later time interval (220–310 ms after stimulus onset) in more anterior temporal regions (Peyk et al., 2008). Both

activities have been related to automatic, perceptual attention capture by salient stimuli, but seem to reflect distinct processing states in the visual stream. The modulation of early cortical activation by stimulus content seems to be robust against stimulus duration and frequency, as it has been demonstrated for stimulus duration of 1500 ms (Schupp et al., 2003) and rapid presentation rates between 3 and 12 Hz (Junghöfer et al., 2001; Peyk et al., 2009).

The cortical responses to emotional stimuli, which characterize normal subjects, are often found to differ in individuals with a psychiatric disorder. Moratti et al. (2008) found less modulation of right-hemispheric temporo-parietal activation evoked by arousing pictures in patients with major depressive disorder (MDD) than in healthy controls. Similarly, Canli et al. (2004) reported lower response amplitude to words with happy and more activity to words with sad meaning in MDD patients compared to controls. Schizophrenia patients were found to exhibit less cortical activity modulation to arousing emotional pictures than healthy subjects (Rockstroh et al., 2006), and smaller amplitudes of the P300-event-related potential evoked by negative facial expressions (An et al., 2003). Such changes are assumed to reflect characteristics of psychopathology (like flat affect, negative symptoms) rather than consequences of dampening medication (Dichter et al., 2004; Mueser et al., 1997).

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Affective processing modes may be influenced by experiences early in life. Adverse experiences early in life have been found to influence stress-sensitive systems like the hypothalamus-pituitary-adrenal (HPA) axis and cortical systems (Charmandari et al., 2005; Sterlemann et al., 2008; Champagne et al., 2008; de Kloet et al., 2005; Plotsky et al., 2005). As a consequence, psychophysiological reactivity (e.g., Pole et al., 2007; Meyer et al., 2001) may be modified including more sensitive responses to further stressors (e.g. Hazel et al., 2008; Heim et al., 2004) and altered affective processing (Lang et al., 2007; Taylor et al., 2006). Adverse experiences early in life have also been discussed as potential factor influencing the development and course of psychiatric disorders in predisposed individuals (Andersen and Teicher, 2008, 2009; Leonardo and Hen, 2008; Walker et al., 2008; Cohen et al., 2006; Dinan, 2005; Dohrenwend, 2006; Nemeroff, 2004; Heim et al., 2004; McEwen, 2003). Heim and colleagues (Heim et al., 2003, 2004; Pace et al., 2006; Bradley et al., 2008; see also Van den Bergh et al., 2008) have demonstrated in a subtype of depression that early life stress may increase the sensitivity and reactivity of the HPA-axis, thereby affecting stress-sensitivity and stress reactivity throughout life (e.g., Graham et al., 1999). While this interaction may explain the relationship between early life stress and the course of depressive disorder later in life, it seems unclear, whether the sensitizing effect of early life stress also involves affective processing modes in the brain.

In a previous study, we examined effects of retrospectively reported adverse experiences in childhood (labeled early life stress, ELS, from here on) on cortical responses to emotional stimuli in patients with different psychiatric diagnoses (Weber et al., 2009). Adult patients who had reported a high number of stressful life events in childhood displayed reduced right-posterior activity to high-arousing pleasant and unpleasant pictures 160–210 ms after stimulus onset relative to patients with low ELS and relative to non-stressed, healthy comparison subjects. The present study explored, whether similar indications of altered cortical affective processing would be evident some 1.5 years later as a sign of lasting effects of ELS. Subjects with particularly high and with low ELS were selected from the sample recruited by Weber et al. (2009), see also Weber et al., (2008) to participate in two sessions 11 and 19 months after the previous study. Processing of emotional stimuli was examined using a rapid serial visual presentation (RSVP) protocol (Junghöfer et al., 2001). If ELS exerts lasting effects on the brain's emotional processing modes, we should expect similar cortical responses to emotional stimuli across measurements and stimulation conditions. In addition, considering Heim's model of stress-sensitization by ELS mentioned above, the present study explored, whether an increased vulnerability for stressful experiences would be evident in adult subjects with high ELS and whether cortical processing of emotional stimuli might constitute a mediator between ELS and stress reactivity in adulthood. Therefore, we examined, whether subjects differing in ELS also exhibited different experiences of current life events and whether this was related to cortical responses to emotional stimuli. Specifically, the present study examined the hypotheses that (1) the previously described differences in cortical activation by emotional stimuli between individuals with and without a psychiatric disorder could be replicated, that (2) the previously described differences in cortical activation by emotional stimuli between individuals with high and low ELS were stable across time, and that (3) differences in cortical activation by emotional stimuli between individuals with high and low ELS were related to the individuals' current life stress load.

## 2. Methods

### 2.1. Participants

The present sample comprised 31 patients (12 females, mean age  $40.0 \pm 12.6$  years) and 15 healthy subjects (7 females, mean age  $40.7 \pm 16.8$  years). Subjects were selected on the basis of their history of ELS

assessed with the Early Trauma Inventory (ETI; Bremner et al., 2000; German version by Heim, 2000) from an initial sample of 96 psychiatric inpatients and 36 healthy subjects. The ETI determines adverse experiences in the four domains of emotional neglect, physical abuse, sexual abuse and general traumatic events for different periods of life. An ELS index was defined as the sum of products of frequency and duration for each event reported before the individual onset of puberty<sup>1</sup> summed up across all domains. For the present study, the 15 patients with the highest ELS scores were selected from the original sample. They were compared to 15 subjects of the healthy comparison group, who had generally displayed low stress load scores, and 16 patients with scores within the range of the comparison group. From this sample, 23 patients and 12 healthy subjects had participated in the previous MEG-study one year earlier (Weber et al., 2009).

According to ICD-10 (International Classification of Diseases, 10th Revision), patients had been diagnosed by senior psychiatrists with Major Depressive Disorder (MDD), schizophrenia, drug addiction (DA), and Borderline Personality Disorder (BPD; see Table 1 for demographic and clinical information of the present sample). Most patients were on psychoactive medication receiving combinations of antidepressant and neuroleptic, typical and atypical neuroleptic drugs, or antidepressants of tricyclic or reuptake-inhibitor type (see Table 1). At the time of the present study, the majority of patients had been released, which indicates their clinical improvement. Exceptions were long-term admissions on the forensic ward including ten patients in the first and seven in the second session, of which 3/1 were drug addicts, 4/4 schizophrenics and 3/2 patients with BPD. As participants of the present study were not seen again by the respective hospital psychiatrists and not diagnosed again, the presently reported diagnoses refer to lifetime diagnoses.

Healthy subjects were included into the comparison group, if they had never met criteria of any psychiatric disorder according to the M.I.N.I. (Ackenheil et al., 1998) and did not take psychoactive medication. Individuals with neurological conditions, head trauma with loss of consciousness, or intellectual disability were excluded. All participants had normal or corrected to normal vision. The Edinburgh Handedness Questionnaire (Oldfield, 1970) confirmed right-handedness in 38 participants. Six participants were ambidextrous and two were left-handed. Since analyses with and without the left-handed and ambidextrous subjects did not provide different results, analyses are reported for the entire sample.

### 2.2. Design and procedure

The study protocol was approved by the ethics committee of the University of Konstanz. All participants provided written informed consent.

The present study comprised two measurement points, which were 8 months apart. Using the Münchner Ereignisliste (MEL; Maier-Diewald et al., 1983) each measurement started with the screening of life events experienced in the preceding six months. Life events were assessed in the domains of work, life, interpersonal relationships and violence. Participants were asked whether they had experienced a certain event and to rate the subjectively experienced stressfulness of this event on a 5-point-Likert scale. Thereafter, the MEG was recorded, while subjects monitored pictures in a rapid serial visual presentation (RVSP) protocol (Junghöfer et al., 2001). Based on the normative ratings of emotional valence and arousal, as well as analysis of physical picture parameters, 300 pictures from the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 2004) were selected to three categories of 100 high-arousing pleasant, 100 high-arousing unpleasant and 100 low-arousing neutral. Each stimulus was presented once within each of

<sup>1</sup> According to Heim et al. (2004), ELS accounts for the period between birth and the time of sexual maturation, the latter being determined by the onset of puberty.

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