LONG-TERM EFFECTS

OF EARLY LIFE STRESS

ON PSYCHO-PHYSIOLOGICAL FUNCTIONS

IN PSYCHIATRIC PATIENTS

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List of abbreviations

ACTH	adrenocorticotropin hormone
AVP	arginine vasopressin
BDNF	brain-derived neurotrophic factor
BDI	Beck Depression Inventory
BPD	borderline personality disorder
CNS	central nervous system
CRF	corticotropin-releasing factor
DA	drug addiction
EEG	electroencephalography
ELS	early life stress
EOG	electrooculogram
EPN	early posterior negativity
ERF	event related magnetic field
ERP	event related potential
ETI	Early Trauma Inventory
fMRI	functional magnetic resonance imaging
GR	glucocorticoid receptor
HHN-Achse	Hypothalamus-Hypophysen-Nebennierenrinden Achse
HPA-axis	hypothalamus-pituitary-adrenal axis
IAPS	International Affective Picture System
IFTL	Inventar früher traumatischer Lebensereignisse
ISI	inter stimulus interval
LE	life event
MDD	major depressive disorder
MEG	magnetoencephalography
MEL	Münchner Ereignisliste
M.I.N.I.	Mini International Neuropsychiatric Interview
MNE	minimum norm estimate
MR	mineralocorticoid receptor
NA	negative affect
PANAS	Positive and Negative Affect Schedule
PDS	Posttraumatic Stress Diagnostic Scale
PTBS	Posttraumatische Belastungsstörung
PTSD	posttraumatic stress disorder
PVN	paraventricular nucleus
ROI	region of interest
RSVP	rapid serial visual presentation
11β-HSD-2	11β-hydroxysteroid dehydrogenase type 2

Summary

Over the past decades, the link between childhood adversities, brain development and various forms of psychopathology has been well established in the literature. This dissertation aims at identifying psychological functions that are altered as a consequence of early life stress (ELS) and may play a mediating role in the development of a psychiatric disorder. In a quasi-longitudinal design, the present project examined a sample of psychiatric patients that reported a particularly high or a particularly low amount of childhood adversities.

Across a 1.5 years period, two groups of patients with high and low ELS as well as a low stress healthy control group were examined three times in order to assess measures of stress sensitivity (number of life events and their subjectively experienced stressfulness), negative affect and psychopathology. Moreover, cortical processing of affective pictures was evaluated with magnetoencephalographic recordings. Patients that had experienced a high amount of ELS reported the most stressful life events in the six month prior to the assessments and experienced them as more stressful than patients without a history of ELS and healthy control subjects. Moreover, they exhibited a stable disposition to high levels of negative affect and had more comorbid diagnoses. Overall cortical responses to affective stimuli were dampened in patients as compared to controls while modulation by stimulus content did not seem to be crucially affected. Dampening of cortical responses was more pronounced in high ELS patients than in low ELS patients. Effects remained stable across a period of altogheter 1.5 years.

Results indicate lasting effects of ELS on psychological functions in psychiatric patients despite of clinical improvement. Findings are discussed on the basis of the current literature concerning the mediating pathways between ELS and psychopathology.

Zusammenfassung

In den vergangenen Jahrzehnten hat sich in der Literatur die Auffassung durchgesetzt, dass zwischen belastenden Erfahrungen in der Kindheit, Hirnentwicklung und verschiedenen Formen der Psychopathologie ein Zusammenhang besteht. Diese Dissertation hat das Ziel, psychische Funktionen zu identifizieren, die durch die Auswirkungen kindlicher Stressbelastung verändert sind und möglicherweise eine Mediatorfunktion bei der Entstehung psychiatrischer Krankheiten einnehmen. Mit einem längsschnittlichen Design untersuchte das vorliegende Projekt eine Stichprobe psychiatrischer Patient/innen, die eine besonders hohe bzw. besonders geringe kindliche Stressbelastung aufwiesen.

Über einen Zeitraum von 1.5 Jahren wurden zwei Patientengruppen mit hoher und geringer kindlicher Stressbelastung sowie eine wenig belastete gesunde Kontrollgruppe dreimalig zu Maßen der Stresssensititität (Anzahl kritischer Lebensereignisse und deren subjektiv erlebte Belastung), negativem Affekt und Psychopathologie befragt. Außerdem wurde die kortikale Verarbeitung affektiver Bilder mittels Magnetenzephalographie untersucht. Patient/innen mit hoher kindlicher Stessbelastung berichteten die meisten Lebensereignisse in den sechs Montaten vor den Erhebungen und erlebten diese subjektiv belastender als wenig belastete Patient/innen und Kontrollpersonen. Darüber hinaus zeigten sie eine dauerhafte Tendenz zu erhöhter negativer Grundstimmung und wiesen eine höhere Anzahl komorbider Diagnosen auf. Kortikale Reaktionen auf affektive Reize waren in der Patientengruppe im Vergleich zur Kontrollgruppe reduziert, wobei die Modulation durch den Reizinhalt nicht wesentlich beeinträchtig schien. In der hoch belasteten Patientengruppe waren die kortikalen Reaktionen noch stärker gedämpft als in der wenig belasteten Patientengruppe. Die Effekte blieben über einen Zeitraum von insgesamt 1.5 Jahren stabil.

Die Ergebnisse weisen auf einen auch bei günstigen Krankheitsverläufen anhaltenden Einfluss kindlicher Stressbelastung auf psychische Funktionen bei psychiatrischen Patienten hin. Die Befunde werden auf Grundlage der aktuellen Literatur, die sich mit den vermittelnden Pfaden zwischen kindlicher Stressbelastung und Psychopathologie beschäftigt, diskutiert.

1 Introduction

Which factors contribute to the development of psychopathology? This question has concerned researchers for decades but still the mechanisms are not fully understood. Heritability studies based on prevalence rates of psychopathology in monozygotic vs. dizygotic twins led to an estimated genetic contribution of 40-50 % in the development of a psychiatric disorder. However, family as well as twin and adoption studies have been criticized on methodological grounds. Recently, modern genome-wide association scans allow the identification of genetic variants that increase an individual's risk for certain diseases. Nevertheless, all attempts to trace psychiatric disorders back to single genes have failed. This encourages the search for further mediating factors that contribute to the development of a psychiatric disorder. Stress in sensitive developmental periods has been discussed as one potential environmental mediator. An increasing number of studies has demonstrated the deleterious effects of adverse experiences early in life (and prenatally) on the psychological and physiological health in adulthood. Moreover, as part of the gene-environment interaction research, epigenetic approaches suggest effects on gene expression through early life programming and indicate a complex interaction between genetic vulnerability and environmental factors influencing the development and course of psychiatric disorders.

It is undoubted that adverse experiences early in life affect brain development. But what changes in brain development are associated with repeated or chronic stress and how do they contribute to psychopathology? The present thesis addressed this question with a specific perspective: would early life stress (ELS) effects become manifest in brain activity patterns in adult patients suffering from psychiatric disorders? In order to explain how this overall perspective was translated into a study design, I will first give an overview on (1) stress and the concept of allostatic load, (2) the empirical

evidence on the relationship between psychopathology and stress experienced in prenatal life and in childhood (i.e. before sexual maturation), and (3) findings from gene-environment and epigenetic approaches that seek to disentangle the complex relationship between genotype, environmental factors, brain development and psychopathology. I will then introduce psychological functions that may constitute mediating factors between alterations in brain development due to ELS and psychopathology such as negative affect, stress sensitivity, and cortical affect processing.

Based on this framework, I will outline the hypotheses and rationale of the empirical part of this thesis: a longitudinal study examining the effects of early life stress (ELS) on sensitivity for further stress and negative affect, and on cortical affect processing in a sample of psychiatric patients. Whether and how ELS affected processing modes in adulthood and whether these influences remained stable across time (altogether 1.5 years) was the focus of the present project. Lasting effects of ELS would point to its impact on psychological and physiological development, hence, to its etiological role in the development of psychiatric disorders with potential consequences also for treatment and prevention.

1.1 Stress and the concept of allostatic load

According to McEwen (2000), stress can be defined as a real or perceived threat to the physical or psychological integrity of an individual, which is accompanied by a physiological and/or behavioral response. Any threat disturbs homeostasis and triggers a stress response starting with the release of corticotropin-releasing factor (CRF) and arginine vasopressin (AVP) from the parvocellular neurons of the hypothalamic paraventricular nucleus (PVN). This activates the autonomic nervous system and the hypothalamus-pituitary-adrenal (HPA) axis and prepares the organism against the stressor (‘fight or flight’). Activation of the autonomic nervous system results in the

release of epinephrine and norepinephrine (catecholamines) from the adrenal medulla allowing the control of cardiovascular, respiratory, gastrointestinal and other functions. Activation of the HPA-axis causes the release of adrenocorticotropin hormone (ACTH) produced by the pituitary gland, which in turn triggers the release of cortisol and corticosteron (glucocorticoids) from the adrenal cortex. Circulating glucocorticoids bind to two different corticosteroid receptors, the glucocorticoid- (GR) and the mineralocorticoid receptor (MR), which allows them to counter-balance the secretion of CRF and ACTH and to modulate a variety of metabolic and immune processes. When the stressor is no longer present, feedback loops at each level of the system are initiated to shut down the activation of the HPA-axis (for more detailed descriptions of the stress reponse see e.g. Heim & Nemeroff, 2001; de Kloet & Derijk, 2004; Charmandari, Tsigos, & Chrousos, 2005; Lupien, McEwen, Gunnar, & Heim, 2009). The physiological stress response allows the organism to retain equilibrium and can be seen as a certain form of allostasis (Kollack-Walker, Day, & Akil, 2000). Allostasis is defined as the ability of an organism to maintain stability through change, that is the re-establishment process of homeostasis as a response to external or internal challenges (McEwen, 2000). Systems that contribute to allostasis are not only the autonomic nervous system and the HPA-axis, but also the cardiovascular, metabolic, and immune system, all of which are interacting in response to a stressor. In general, mediators of allostasis – like catecholamines and glucocorticoids – are beneficial and promote adaptation. However, a frequent or prolonged activation of these mediators as a result of chronic or cumulative stress may lead to negative consequences like receptor desensitization and tissue damage (McEwen, 2003a). This “wear and tear on the body and brain” promotes damage rather than protection and has thus been labeled “allostatic load” (McEwen, 2003b).

1.2 How can stress affect the brain? Early life programming before and after birth

Studies on the relationship between stress and psychopathology suggest developmental periods, which are particularly sensitive to the effects of stress exposure. Stress in these periods causes structural and functional changes that may persist throughout life (Seckl, 2004). Recent research has aimed at clarifying these so-called 'programming effects' of environmental factors with increasing attention directed to the pre- and perinatal period and to childhood (defined as the time before the onset of puberty).

Consequences of pre- and perinatal stress

Pre- and perinatal conditions that have been demonstrated to affect development include malnutrition, psychosocial stressors or traumatic events experienced by the mother and also maternal psychopathology. Evidence from epidemiological studies indicates that prenatal stress and/or maternal psychopathology influence physiological and psychological functioning in newborns, lasting into adolescence and adulthood.

Physical and psychological stress has been related to low birth weight and decelerated early life growth, which is in turn associated with increased vulnerability for various physiological and psychological disorders (Barker et al., 1993; Smits, Krabbendam, De Bie, Essed, & Van Os, 2006). Infants of depressed or anxious mothers have been found to be less responsive to faces and voices in the neonatal period and to show neurophysiological abnormalities in attention allocation to voices (Field, Diego, & Hernandez-Reif, 2009; Harvison, Molfese, Woodruff-Borden, & Weigel, 2009). Moreover, high maternal anxiety levels in late pregnancy have been related to emotional and behavioral problems at 47 and 81 month of age (O'Connor, Heron, Golding, & Glover, 2003) and to HPA-axis alterations and depressive symptoms at 14-15 years of age (Van

den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 2008). Exposure to traumatic stress during pregnancy has been related to increased risk for psychiatric disorders like schizophrenia (Van Os & Selten, 1998). In rodents, prenatal stress has been associated with reduced hippocampal cell proliferation and a reduced number and differentiation of immature neurons (Lemaire, Lamarque, Le Moal, Piazza, & Abrous, 2006). In sum, findings from animal and human studies suggest a general susceptibility to psychopathology due to prenatal stress exposure (Huizink, Mulder, & Buitelaar, 2004).

Consequences of early life stress

ELS concerns stressful experiences in childhood, including sexual, physical and emotional abuse, as well as parental loss and other traumatic events like accidents, illness, natural disasters or war. Other forms of ELS concern instable families, poor parental care due to physical or mental illness, dysfunctional relationships, and poverty (Heim, Plotsky, & Nemeroff, 2004). According to Heim and colleagues (2004) every such stressor that is experienced before the onset of sexual maturation may be referred to as ELS. Sexual maturation as a convenient cut-off is supported by animal studies focusing on the juvenile stage, which is assumed to correspond to human childhood (Heim et al., 2004). For example, Avital & Richter-Levin (2005) found that exposure to a combination of juvenile and adult stress in rats (platform and acute swim stress) had a greater effect on anxiety than exposure to stress twice in adulthood. Retrospectively, ELS can be assessed by structured interviews or self-report questionnaires, both yielding sufficient inter-rater reliability, test-retest reliability and internal consistency (Bremner, Vermetten, & Mazure, 2000; Bremner, Bolus, & Mayer, 2007; Durrett, Trull, & Silk, 2004).

Different forms of ELS often accumulate and constitute ongoing or chronic adversities. ELS is assumed to be a major risk factor for the development of depression

and anxiety later in life. Physical, emotional or sexual abuse in childhood is associated with more symptoms of depression (McCauley et al., 1997), a higher risk to develop full syndromal major depression (Mullen, Martin, Anderson, Romans, & Herbison, 1996), and earlier onset as well as higher chronicity (Heim & Nemeroff, 2001; Jaffee et al., 2002). Other forms of psychopathology like substance related disorders and personality disorders, especially borderline personality disorder (BPD), have also been linked to ELS (De Bellis, 2002; Teicher, Andersen, Polcari, Anderson, & Navalta, 2002; van der Vegt et al., 2009). The high prevalence of ELS in patients diagnosed with BPD (e.g. Bradley, Jenei, & Westen, 2005; Crawford, Cohen, Chen, Anglin, & Ehrensaft, 2009; Golier et al., 2003) and the substantial overlap of BPD symptomatology with PTSD have even caused a discussion on redefining BPD as a trauma spectrum variant (Lewis & Grenyer, 2009). In schizophrenia, a dose-effect for psychotic symptoms, higher levels of overall symptom severity and a higher number of comorbid disorders have been reported for patients that had experienced abuse and neglect in childhood (Lysaker, Beattie, Strasburger, & Davis, 2005; Read, van Os, Morrison, & Ross, 2005; Read & Ross, 2003; Scheller-Gilkey, Moynes, Cooper, Kant, & Miller, 2004). Taken together, a relationship between ELS and psychopathology seems to be evident across diagnostic categories.

Early life stress, environmental programming and brain development

There are competing, yet complementary, hypotheses about the mechanisms that lead to alterations in brain development as a consequence of stress. The *glucocorticoid cascade hypothesis* of stress and aging states that prolonged stress causes an overexposure of glucocorticoids (=hypercorticism), which accelerates hippocampal and thus cognitive aging (Sapolsky, 1992; Oitzl, Champagne, van der Veen, & de Kloet, 2009). In rodents and nonhuman primates, alterations in HPA-axis responsiveness, such as hypercorticism or reduced ACTH responses to CRF stimulation, as well as behavioral changes have been

demonstrated as a permanent consequence of stress (for review see Heim & Nemeroff, 2001). Glucocorticoids operate in those brain circuits that are initially activated by the stressor. Hence, MR and GR are distributed throughout the so-called "stress centers" of the brain – hippocampus, amygdala and prefrontal cortex (de Kloet & Derijk, 2004). While MR-mediated effects prepare the organism to defend against the stressor, binding of glucocorticoids to GR promotes processing and storage of the stressful event into memory. According to the *balance hypothesis*, a balanced function of GR and MR is crucial for effective stress responding and thus mental health (Oitzl et al., 2009). There is some evidence that gene variants, stressors during adult life in predisposed individuals, and early life or prenatal stress disturb this balance resulting in a delayed onset and/or termination of the stress response. As activation of MR and GR results in up- and down-regulation of gene expression patterns in the involved brain areas, an imbalance caused by severe stress might have long-lasting consequences on their function and structure and thus on the organism's stress-responsiveness, cognitive performance and emotional arousal later in life (Oitzl et al., 2009).

This line of research has been recently complemented by approaches studying epigenetic mechanisms involved in prenatal programming. Epigenetic mechanisms cause changes in gene expression without altering the primary DNA sequence. It is assumed that through epigenetic modification of gene promoters, the epigenome builds a crossing point between the inherited genome and the dynamic adaptation to the environment (Weaver, 2009). Epigenetic mechanisms may result in lasting pathogenetic alterations of various physiological systems including the HPA axis (Schwab, 2009). Maternal nutrition and maternal stress experience have been proposed as important factors involved in prenatal programming of the HPA axis by affecting fetal glucocorticoid levels. Although important for normal maturation of the central nervous

system (CNS), glucocorticoids may have damaging effects, depending on the timing and amount of exposure (Seckl, 2004). Maternal glucocorticoid levels are much higher than those of the fetus. To protect the vulnerable developing systems from premature glucocorticoid exposure, most maternal cortisol is converted to inert cortisone by 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD-2) when it crosses the placenta. Maternal malnutrition during pregnancy has been shown to selectively diminish this enzyme, affecting in turn fetal glucocorticoid exposure (Bertram, Trowern, Copin, Jackson, & Whorwood, 2001). High concentration of glucocorticoids results in saturation of MR and a stronger activation of GR. During early CNS development, this stronger activation of GR may lead to reduced expression of neurotrophic factors and to inhibition of neurogenesis, neuronal differentiation and myelinization (Antonow-Schlorke, Schwab, Li, & Nathanielsz, 2003; Schwab, 2009; Uno et al., 1994). In late pregnancy, 11β-HSD-2 activity attenuates thereby increasing the exposure to circulating glucocorticoids allowing maturation of the developing brain regions. Disturbances in the timing of 11β-HSD-2 silencing, subtle changes in 11β-HSD-2 activity as well as extensive maternal glucocorticoid exposure due to stress, psychopathology or prenatal corticosteroid therapy apparently reduce expression of GR and MR receptors in the hippocampus resulting in permanently decreased HPA axis feedback sensitivity and elevated plasma glucocorticoid levels throughout life (Seckl, 2004).

Environmental programming occurs not only in prenatal but also in postnatal life. Recent findings suggest that besides undernutrition and exposure to chemical toxins also psychosocial factors like maternal care may result in epigenetic modifications (for review see Szyf, Weaver, & Meaney, 2007). In rodents, DNA methylation patterns differ between pups receiving high and low maternal care. As DNA methylation alters expression of the GR gene in the hippocampus, maternal behavior is apparently causally

related to alterations in the offspring's stress regulating systems (Meaney & Szyf, 2005).

In a review integrating results from animal and human studies on the effects of stress throughout the life span, Lupien and colleagues (2009) propose a life cycle model of stress. According to this model, stress at different periods of life exerts its effects on those brain areas that are developing at the time of the exposure. While brain regions involved in HPA-axis regulation are affected by stress in the prenatal period in an unspecific manner, stress in early childhood seems to affect predominantly the hippocampus, which is rapidly developing in the first two years of life. In adolescence, stress has major effects on the development of the frontal cortex. The amygdala is developing throughout childhood and adolescence and may thus be affected by stress exposure from birth until late childhood. Changes in these regions might be adaptive at the time the adversity occurs but may have negative long-term effects. Results provided by Andersen and colleagues (2008) suggest that childhood sexual abuse differentially affects hippocampal, frontal cortex and corpus callosum volume depending on the age when the abuse occurred. Similarly, Carpenter and colleagues (2004) found that the timing of stress exposure in patients with depression predicted either increased or decreased corticotropin-releasing factor concentrations in the cerebrospinal fluid. Sexual abuse before the age of 12 has also been associated with reduced gray matter volume in primary and secondary visual cortices in young women (Tomoda, Navalta, Polcari, Sadato, & Teicher, 2009) and white matter tract abnormalities have been observed in young adults with a history of exposure to parental verbal abuse (Choi, Jeong, Rohan, Polcari, & Teicher, 2009). Thus, ELS seems to exert its effects on brain development not only in terms of gray matter volume loss or gain but also influences neural pathways between different brain regions.

In sum, there is accumulating evidence that stress during critical developmental periods has lasting effects on the organization of the brain and the organism's stress regulating systems. However, it remains unclear to what extent changes in psychological functions reported for different populations of adult psychiatric patients might be related to lasting effects of these structural alterations due to ELS.

1.3 Stress sensitivity, negative affect and cortical affect processing as potential mediators between changes in brain development and psychopathology

Despite the broad range of studies linking ELS to alterations in brain development, the mediating factors promoting the development of a psychiatric disorder remain unclear. As a linear causal relationship seems unlikely, we may ask which psychological functions might be altered as a consequence of ELS-induced changes in brain development, thereby fostering the development of psychiatric disorders. Alterations in the stress systems and thus in the stress response may vulnerabilize an individual for further life stress and increase the risk to develop a psychiatric disorder (Charmandari, Kino, Souvatzoglou, & Chrousos, 2003; Lupien, McEwen, Gunnar & Heim, 2009). Accumulation of life events (LE) has been reported to precede relapse or exacerbation of psychiatric symptoms indicating an increased sensitivity to current life stress that may affect the course of a psychiatric disorder (Brown, Harris, & Hepworth, 1994; Kessler, 1997; Mueser, Rosenberg, Goodman, & Trumbetta, 2002; Nuechterlein et al., 1992; Read & Ross, 2003; Sigmon et al., 2007; Myin-Germeys, Krabbendam, Delespaul, & Os, 2003). Moreover, studies in community samples revealing associations between ELS and depressive symptoms or anxiety have identified negative affect (NA) as a potential mediating factor (Allen, 2008; Bergdahl & Bergdahl, 2002; Cohen et al., 2006; Wright, Crawford, & Castillo, 2009).

If NA constitutes a mediating factor between ELS and psychopathology, it might also become manifest in the cortical processing of affective stimuli. As it will be a major concern of the present thesis, I will give an overview on the principles of (visual) cortical affect processing and on some methodological issues of psychophysiological measurements.

As various stimuli compete for attentional resources in most environments, survival and reproductive success depends on a fast and reliable detection of appetitive and aversive cues facilitating and fastening adaptive behavior (Lang, Bradley, & Cuthbert, 1998; LeDoux, 2000). Processing of visual stimuli involves the thalamus that projects perceptual information to the visual cortex, from where it is carried forward along the dorsal (object location) and the ventral stream (object recognition) to the parietal and temporal cortices, respectively. From there, projections to the pre-frontal cortex allow a representation of the stimulus in working memory. From the late stages of sensory cortical processing, projections to the amygdala allow to determine whether the perceived stimulus indicates danger. As the amygdala projects back even to the earliest stages of cortical processing, its activation directly enhances cortical processing of a stimulus (LeDoux, 2000). Amygdala responses to visual emotional stimuli in patients who are blind due to lesions in the visual cortex (Morris, DeGelder, Weiskrantz, & Dolan, 2001; Pegna, Khateb, Lazeyras, & Seghier, 2005), suggest that a raw representation of the stimulus is directly projected from the thalamus to the amygdala allowing the organism to respond very fast to potentially dangerous situations (Vuilleumier, 2005).

In passive viewing tasks, simple qualities of a stimulus such as intensity, suddenness of onset, novelty or emotional salience cause immediate attention capture (Ohman, Flykt, & Esteves, 2001; Schupp et al., 2004). As organisms respond to

environmental cues according to their emotional/motivational significance, Lang and colleagues (1998) proposed a bivariate motivational model of emotion. According to this model, emotions functionally reflect action dispositions to either approach or withdrawal/defense and can be basically described in terms of valence (appetetive vs. aversive) and arousal (intensity of activation). Hence, emotional stimuli can be arranged in a two-dimensional affective space of co-varying pleasure and arousal ratings, resulting in a boomerang-shaped distribution with a high arousing pleasant and a high arousing unpleasant arm extending from a calm, non-affective center. The International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008) provides a large set of color photographs that includes a wide range of emotionally evocative contents. Normative valence and arousal ratings are available for each picture.

One approach to examine the function of the supposedly overlapping reward and defense systems (Lang, McTeague, & Cuthbert, 2007) is electroencephalographic recording (EEG) of event related potentials (ERPs). ERPs allow the measurement of neural responses to affective stimuli with high temporal resolution and are thus useful in characterizing the time course of distinct processing stages. One ERP component, the early posterior negativity (EPN), has received particular interest. The EPN is believed to be the first component that reflects differential processing of emotional compared to neutral stimuli. In EEG, the difference between stimulus categories appears as a negative deflection over occipito-parietal sensor sites that develops around 150 ms and is most pronounced around 250-300 ms after stimulus onset (Schupp, Flaisch, Stockburger, & Junghöfer, 2006). Modulation of this component by the valence and arousal of stimulus material has been consistently reported confirming the bimotivational model of emotion (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Junghöfer, Bradley, Elbert, & Lang, 2001; Peyk, Schupp, Keil, Elbert, & Junghöfer, 2009; Schupp et al., 2000, 2004; Schupp,

Junghöfer, Weike, & Hamm, 2003). An alternative tool for evaluating brain psychophysiology associated with affective processing stages is whole head magnetoencephalography (MEG), which provides neuromagnetic fields with as high temporal resolution as EEG. Neuromagnetic fields pass the skull and scalp without significant distortion resulting in a better spatial resolution than derived from EEG data. They mostly reflect the dendritic current flow of pyramidal cells oriented parallel to the surface of the skull. Pyramidal cells with this orientation are mainly located in the sulci of the neocortex. The neuronal currents of about one million synchronously active synapses (corresponding approximately to one square millimeter of cortex) generate an extracranial recordable signal. They involve intracellular and transmembrane currents as well as extracellular volume currents and can be modulated as a current dipole. Inverse source modeling allows estimating the location of the neural generators of neuromagnetic fields, but bears the problem of an infinite number of inverse solutions that can explain the recorded field pattern (inverse problem). Thus, the accuracy of the solution depends on the validity of the modeling assumptions. For example, the volume conductor model plays a critical role: on a spherical surface, only open-field configured cells like the pyramidal cells that are arranged into cortical columns can produce a magnetic field, whereas subcortical structures that are often characterized by closed-field cell assemblies fail to produce an external magnetic field (Lewine & Orrison, 1995). In visual processing, even the earliest components of an event related neuromagnetic field (ERF) involve activation of both primary and secondary visual cortical areas (Kaneoke, Watanabe, & Kakigi, 2005). Thus, EPN equivalent ERF components assumably reflect activity of distributed neural generators. Neural activity that is not localized in one small area (or several separate areas) requires distributed source modeling. The L2-Minimum-Norm-Pseudoinverse provides minimum norm estimates (MNEs) for the

source-current distribution with minimal a priori assumptions (Hamalainen & Ilmoniemi, 1994; Hauk, 2004; Hauk, Keil, Elbert, & Muller, 2002). This procedure calculates the shortest vector in the source-current space that can explain the measurements. The source-current space is modeled as a spherical configuration of evenly distributed dipoles. MNEs were used in the present project to evaluate cortical activation patterns in response to affective visual stimuli.

1.4 The present project

The present thesis is part of a project on the influences of ELS in psychiatric patients. As ELS has been reported in patient groups with different diagnoses, the initial focus of the project was to identify a stress-related phenotype in psychiatric patients across the boundaries of diagnostic categories. Effects of childhood stress load on severity of psychopathology and cortical processing of affective stimuli were evident in addition and beyond effects of diagnosis (for further aspects see Weber et al., 2008; Weber et al., 2009). For the present thesis a subsample of patients with particularly high and particularly low ELS was examined three times across a period of 1.5 years in order to evaluate ELS-effects on (a) reactivity to current life stress as well as measures of affect and psychopathology and on (b) cortical processing of affective pictures. The major focus of this longitudinal study was on the (c) stability of ELS-effects. Lasting effects of ELS on stress sensitivity and cortical processing modes are discussed as potential mediating factors in the development of psychiatric disorders.

(a) Stress reactivity, negative affect and psychopathology

As mentioned above, there are associations between ELS and psychopathology on the one hand and between psychopathology and sensitivity to current life stress on the other hand. Studies on the relationship between ELS, stress sensitivity and psychiatric

disorders are rare. In depression, effects of additional stressful experiences later in life on the relationship between childhood stress and adult psychopathology have been reported (e.g. Hazel et al., 2008). On that background, this study assesses sensitivity to current life stress and measures of affect and psychopathology in patients with high and low ELS.

(A) In Study 1, the present thesis addressed the hypothesis that psychiatric patients with high ELS exhibit more current life stress and perceive stress events as subjectively more stressful than patients with low ELS and healthy comparison subjects.

(B) Moreover, patients with high ELS were expected to show higher ratings of NA and depressive symptoms and to be at higher risk to experience relapse or exacerbation of symptoms than patients with low ELS.

(b) Cortical processing of affective visual stimuli

As described above, stress in sensitive periods of brain development affects cortical and subcortical regions that are crucial in the processing of threat or reward related information. To evaluate the effects of ELS on the function of these motivational systems, neuromagnetic event-related fields were recorded in response to emotional visual stimuli from the International Affective Picture System with two stimulation conditions differing in presentation rates. Cortical activation was modeled with minimum norm estimates.

(C) Based on the findings of the initial MEG study by Weber et al. (2009), study 2 and 3 of the present thesis addressed the hypothesis that patients with high ELS exhibit dampened cortical activation in response to affective visual stimuli around 200 ms after stimulus onset (EPN equivalent time window) in occipital-parietal-temporal cortical areas across stimulation conditions.

(c) Stability of early life stress effects

The literature on ELS and brain development cited above suggests a lasting impact of early adverse experiences that might persist into adulthood. In animal studies, life long effects of ELS on physiological and psychological functions have been verified (e.g. Plotsky et al., 2005; Spinelli et al., 2009). Longitudinal or prospective studies in humans are rare but confirm effects of early abuse on lasting psychological distress (Lindhorst, Beadnell, Jackson, Fieland, & Lee, 2009) increasing the risk for various psychological and physiological disorders in genetically predisposed individuals (e.g. Afifi, Boman, Fleisher, & Sareen, 2009; Danese, Moffitt, Pariante, Ambler, Poulton & Caspi, 2008).

To evaluate lasting effects of ELS, the present study comprised three measurement points, which were 11 and 8 months apart, respectively. At the first assessment, all patients were treated at the local center of psychiatry, whereas upon re-assessments, most patients had been released and were in a remitted state. Thus, stability of group effects between high- and low-ELS patients would indicate lasting effects of ELS independent of clinical improvement. The first assessment corresponds to the initial study by Weber et al. (2008) and both re-assessments include subgroups of this initial sample. As illustrated in Figure 1, measures of current life stress and each of two visual affective stimulation conditions were assessed twice across a period of altogether 1.5 years. Ratings of NA and depressive symptoms were obtained at all three assessments. The MEG protocols and questionnaires are described in the respective sections.

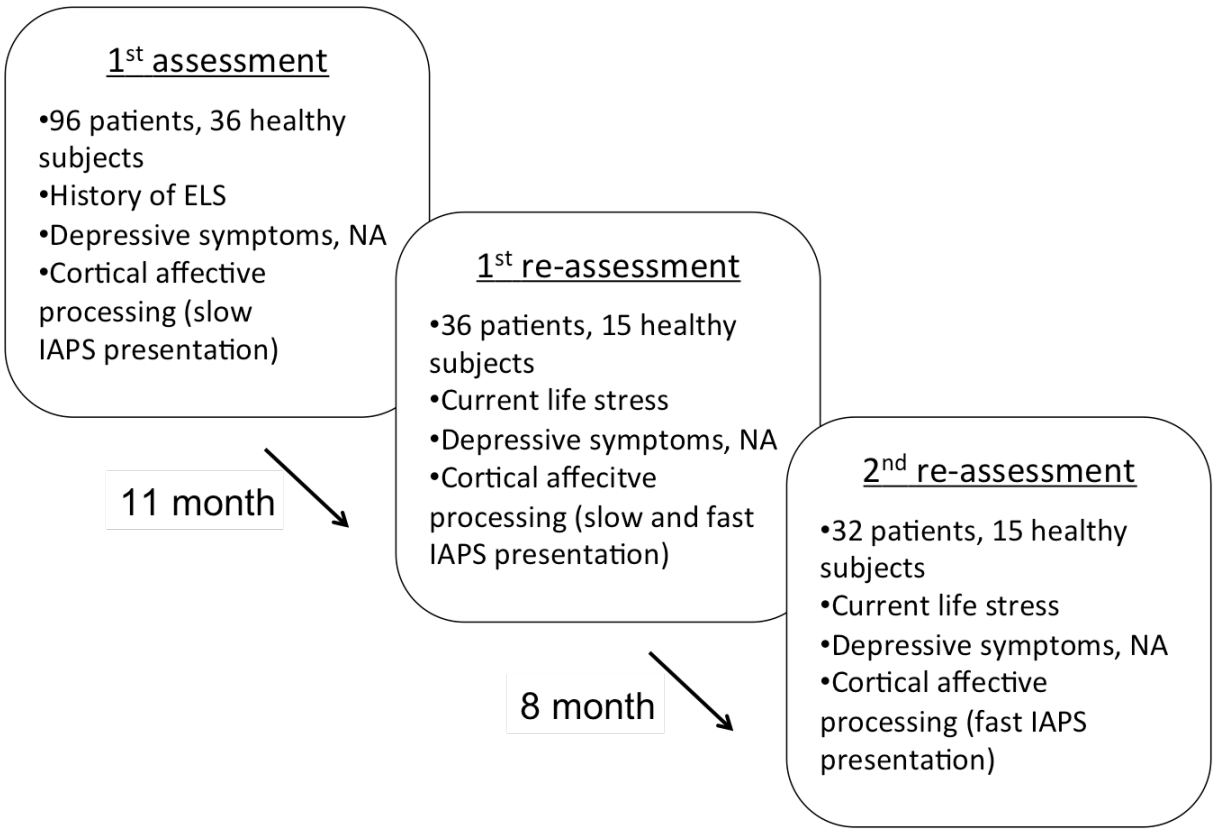

Figure 1. Overview on the three time points of assessments.

(D) All three studies reported in this thesis addressed the hypothesis that ELS effects are stable across time. In particular, (1) elevations in stress reactivity, negative affect and measures of psychopathology, and (2) alterations in cortical activation patterns in response to visual affective stimuli were expected to be stable across at least a period of 1.5 years despite of clinical improvement.

2 Studies on the stability of ELS effects

2.1 Stress in der Kindheit sensitiviert für Stress im Erwachsenenalter – eine Studie mit psychiatrischen Patienten

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Zusammenfassung

Theoretischer Hintergrund: Verschiedene Studien weisen darauf hin, dass Stress in der Kindheit dauerhaft für weitere Stresserfahrungen sensitiviert. **Fragestellung**: Besteht bei Patient/innen mit psychischen Erkrankungen ein Zusammenhang zwischen kindlicher Stressbelastung und Belastung durch Stress im Erwachsenenalter und gilt dieser unabhängig von der Diagnose? **Methode**: Basierend auf einem Interview zu kindlicher Stressbelastung wurden 16 Patient/innen mit besonders hoher und 20 Patient/innen bzw. 15 Kontrollen mit niedriger Belastung zweimalig zu aktuellen Lebensereignissen und deren subjektiv erlebter Belastung, sowie zum Erleben sozialer Stressoren befragt. **Ergebnisse**: Hoch-belastete Patient/innen wiesen mehr Lebensereignisse auf als wenig-belastete Patient/innen und Kontrollpersonen, erlebten diese subjektiv als belastender und zeigten eine höhere Belastung durch soziale Stressoren. **Schlussfolgerung**: Die Ergebnisse stützen die Hypothese einer dauerhaft erhöhten Empfindlichkeit für Stress durch kindliche Belastung.

Schlüsselwörter: kindlicher Stress, Stress-Sensitivierung, Lebensereignisse, Psychopathologie

Abstract

Background: Various studies suggest that early life stress (ELS) sensitizes for stressful life events throughout life. **Objective**: Aim of this study was to demonstrate a relationship between ELS and stress experiences in adult psychiatric patients across diagnostic categories. **Methods**: Patients were interviewed for adverse experiences in childhood. 16 patients with high and 20 patients and 15 controls with low ELS were recruited twice for assessment of life events, subjective strain induced by these events, and social stress. **Results:** High-ELS patients exhibited more life events, experienced them as more stressful, and were more sensitive for social stressors than low-ELS patients and controls. **Conclusions**: Results support the hypothesis that ELS increases the vulnerability for further stress later in life.

Key words: Early life stress, sensitization, life events, psychopathology

Einführung

Belastende Erfahrungen in der Kindheit, von emotionaler Vernachlässigung über physischen und emotionalen Missbrauch bis hin zu sexuellem Missbrauch und Traumata, werden weltweit häufig berichtet. In den USA z.B. schätzt man die Zahl traumatisierter oder misshandelter Kinder auf 1.5 Millionen pro Jahr (Sedlack & Broadhurst, 1996). Für Deutschland ergab die retrospektive Erhebung einer repräsentativen Stichprobe von 3241 Personen, dass 10.6% der Befragten als Kinder physischen Misshandlungen durch ihre Eltern ausgesetzt waren, sexuellen Missbrauch vor dem 16. Lebensjahr gaben 8.6% der weiblichen und 2.8% der männlichen Befragten an (Wetzels, 1997).

Die klinisch-psychologische und epigenetische Forschung konzentriert sich zunehmend auf die Folgen solcher Erfahrungen, wie etwa erhöhte Vulnerabilität für physische und psychische Erkrankungen oder eine dauerhafte Sensitivierung für weitere Stresserfahrungen. Neuere Langzeituntersuchungen an repräsentativen Stichproben legen nahe, dass Stresserfahrungen in der Kindheit eine erhöhte Vulnerabilität für verschiedene körperliche und psychische Erkrankungen zur Folge haben (z.B. Afifi, Boman, Fleisher, & Sareen, 2009; Danese, Moffitt, Pariante, Ambler, Poulton & Caspi, 2008). Es wird angenommen, dass Stress in der Kindheit zu langfristigen Veränderungen in stressverarbeitenden Systemen (wie der Hypothalamus-Hypophysen-Nebennierenrinden-(HHN)-Achse) führt und dadurch die Reaktions-bereitschaft auf Stress dauerhaft verändert wird (Charmandari, Kino, Souvatzoglou, & Chrousos, 2003; Lupien, McEwen, Gunnar & Heim, 2009). Heim und Kollegen (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008; siehe auch Nemeroff, 2004; Bradley et al., 2008) beschreiben diese Vulnerabilisierung insbesondere für eine Subgruppe

depressiver Patient/innen, welche auf eine Interaktion zwischen genetischer Prädisposition und dem Einfluss (früh)kindlicher Traumata hinweist.

Bei erwachsenen Patient/innen mit psychischen Störungen (Depressionen, Schizophrenien, Angststörungen, Posttraumatische Belastungsstörung (PTBS), Substanzabhängigkeit sowie Persönlichkeitsstörungen) wird gegenüber dem Bevölkerungsdurchschnitt eine erhöhte Rate sexuellen und physischen Missbrauchs in der Kindheit berichtet (Bradley, Jenei, & Westen, 2005; Bremner, Southwick, Johnson, & Yehuda, 1993; de Bellis, 2002; Kendler, Kuhn, & Prescott, 2004; McCauley et al., 1997; Mueser, Rosenberg, Goodman, & Trumbetta, 2002; Widom, 1999). Auch dieser Befund stützt die Hypothese, dass traumatische Erfahrungen den Verlauf einer psychischen Störung beeinflussen können.

Stress wurde bei Patient/innen mit psychischen Erkrankungen aber nicht nur im Zusammenhang mit Belastung in der Kindheit thematisiert: Studien ergaben bei depressiven und schizophrenen Patient/innen eine vergleichsweise erhöhte Anzahl kritischer Lebensereignisse (LE, *life events*) im Zeitraum von 6-12 Monaten vor Exazerbation oder Rückfall (Brown, Harris, & Hepworth, 1994; Kessler, 1997; Mueser et al., 2002; Nuechterlein at al., 1992; Read & Ross, 2003; Sigmon et al., 2007). Experimentelle Ansätze haben zudem gezeigt, dass insbesondere depressives Verhalten Zurückweisung im sozialen Umfeld auslösen kann (z.B. Gurtman, 1987; Stephens, Hokanson, & Welker, 1987). Ähnlich berichtet Hammen (2006), dass Personen mit depressiver Erkrankung in der Vorgeschichte durch bestimmte Charakteristika und Verhaltensweisen stressreiche Erfahrungen provozieren können. Ferner stellen negative soziale Interaktionen eher einen Stressor dar als beispielsweise soziale Isolation (Ruehlman & Karoly, 1991), so dass Empfindlichkeit für Stress auch über negativ erlebten sozialen Austausch operationalisiert werden kann. Da auch bei

gesunden Personen ein Zusammenhang zwischen Stress in der Kindheit und dem Ausmaß von Depressivität und Ängstlichkeit im Erwachsenenalter berichtet wurde (Allen, 2008; Bergdahl & Bergdahl, 2002; Cohen et al., 2006; Wright, Crawford, & Castillo, 2009), wird negativer Affekt als möglicher Faktor diskutiert, der in der Folge kindlicher Stressbelastung fortbesteht (Lang et al., 2007) und damit die Empfindlichkeit für und Reaktivität auf LE dauerhaft beeinflusst.

Die vorliegende Studie untersuchte, inwieweit Stresserfahrungen in der Kindheit mit dem Ausmaß und der subjektiv erlebten Belastung aktueller Lebensereignisse bei erwachsenen Patient/innen mit psychischen Erkrankungen zusammenhängen. Spezifisch wurde die Hypothese geprüft, dass Patient/innen mit hoher Stressbelastung in der Kindheit mehr belastende LE erfahren und diese subjektiv als belastender erleben als Patient/innen mit geringer kindlicher Stressbelastung. Ein solcher korrelativer Zusammenhang sollte als Hinweis auf eine anhaltend erhöhte Empfindlichkeit für Stresserfahrungen in der Folge früher belastender Lebenserfahrungen gewertet werden. Gleichzeitig wurde die Bedeutung einer bestehenden psychischen Erkrankung für die aktuelle Stressbelastung berücksichtigt: Wenn psychische Erkrankungen per se für kritische LE und das Erleben von Stress vulnerabilisieren, dann sollten Patient/innen unabhängig von ihrer in der Kindheit erfahrenen Belastung eine höhere Anzahl kritischer LE berichten als Kontrollpersonen. Um aufzuzeigen, inwieweit sich diese Vulnerabilität für Stresserfahrungen unabhängig von den Charakteristika der spezifischen Erkrankung manifestiert, wurden Patient/innen mit verschiedenen Diagnosen einbezogen. Bisherige Studien konzentrierten sich entweder auf kindlichen Stress oder auf aktuelle kritische Lebensereignisse bei Patienten mit psychischen Störungen. Die vorliegende Studie prüfte darüber hinausgehend die Hypothese eines vulnerabilisierenden Einflusses kindlicher Stresserfahrungen auf das Erleben aktueller

Belastungen bei Patienten mit psychischen Störungen. Schließlich wurde die Hypothese untersucht, dass sich Patient/innen mit hoher Stressbelastung in der Kindheit durch ausgeprägtere negative Affektivität, depressive Symptomatik oder Kennzeichen eines ungünstigeren Krankheitsverlaufs (Exazerbation oder Rückfall) auszeichnen.

Methode

Die Studie ist Teil eines Projektes, das den Einfluss von Stressbelastung in der Kindheit bei Patient/innen mit psychischen Störungen anhand verschiedener psychopathologischer und psychophysiologischer Maße untersucht (weitere Aspekte des Projektes werden in Weber et al., 2008 und Weber et al., 2009 vorgestellt). Das Projektdesign wurde von der Ethikkommission der Universität Konstanz genehmigt. Datenerhebung und die Untersuchung von Patient/innen folgten den Richtlinien des Helsinki-Protokolls.

Stichprobe und Studiendesign

An der vorliegenden Studie nahmen 36 Patient/innen (15 Frauen, Alter 37.6, *SD*= 12.4 Jahre) und 15 psychisch gesunde Personen (7 Frauen, Alter 39.9, *SD*= 17.0 Jahre) teil. Die Gruppen unterschieden sich nicht signifikant in Geschlechts- ($\chi^2(1)< 1$, $p> .6$) und Altersverteilung ($F< 1$). Die hier untersuchte Stichprobe wurde aus einer Population von 96 Patient/innen und 36 psychisch gesunden Kontrollpersonen ausgewählt, die zu belastenden Erfahrungen während verschiedener Lebensphasen befragt worden waren (siehe Weber et al., 2008). Hierzu diente das *Inventar zur Erfassung früher traumatischer Lebensereignisse* (IFTL; deutsche Version des *Early Trauma Inventory* von Heim, 2000; Bremner et al., 2000), das für verschiedene Lebensphasen physischen, emotionalen und sexuellen Missbrauch und traumatische Erlebnisse erfragt. Der Definition von *‚early life stress'* als Belastungen vor Erreichen der sexuellen Reifung folgend (Heim et al., 2004),

wurden als kindliche Belastung die in den erfragten Bereichen genannten Erfahrungen bis zum individuellen Beginn der Pubertät bewertet und als Kennwert der gesamten Belastung die Produkte aus Frequenz und Dauer dieser Erfahrungen aufsummiert. Der individuelle Beginn der Pubertät wurde bei Frauen über den Zeitpunkt der Menarche, bei Männern über den Zeitpunkt von Stimmbruch und/oder Beginn des Bartwuchses bestimmt. Für die vorliegende Studie wurden diejenigen Patient/innen als ‚hoch-belastet' ausgewählt, deren Belastungswerte deutlich über dem Streuungsbereich der gesunden Kontrollgruppe lagen. Als cut-off wurden dabei Werte 2 Standard-abweichungen über dem Mittelwert der Kontrollgruppe festgelegt. Als ‚wenig-belastet' galten Patient/innen mit Belastungswerten innerhalb des Streuungsbereichs der Kontrollgruppe (siehe Abbildung 2). Die Kontaktaufnahme zur Rekrutierung der vorliegenden Stichprobe erfolgte postalisch oder telefonisch. Insgesamt wurden 32 hoch-belastete, 43 wenig-belastete Patient/innen und 20 Kontrollpersonen kontaktiert, von denen 16, 20 und 15 Personen zur Teilnahme gewonnen werden konnten. Drop-out Gründe waren Nicht-Erreichbarkeit wegen Umzug oder Haftstrafe, keine Antwort und Ablehnung der Teilnahme. Die Teilnehmer/innen und Drop-outs unterschieden sich nicht in der kindlichen Stressbelastung (Kontrollpersonen: $U= 26$, $p> .6$; wenig-belastete Patient/innen: $U= 189$, $p> .3$; hoch-belastete Patient/innen: $U= 107$, $p> .4$). Die Ausgangspopulation schloss Patient/innen mit verschiedenen ICD-Diagnosen ein (MDD, F32/33; Schizophrenie, F20.0; Drogenabhängigkeit, F10,19; Borderline Persönlichkeits-störung, BPS, F63.01; siehe Weber et al., 2008 zu Diagnostik und Ein/ Ausschlusskriterien). Tabelle 1 fasst die Verteilung der Diagnosen für die Stichprobe der vorliegenden Studie zusammen.

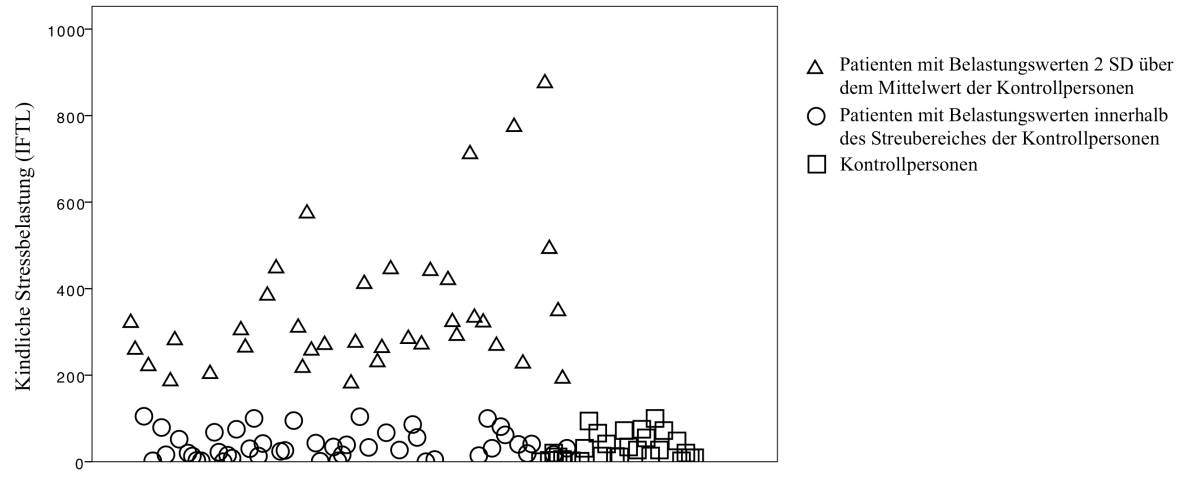

Abbildung 2. Verteilung der Werte kindlicher Stressbelastung (gemessen mit dem IFTL) in der Ausgangsstichprobe.

Diese Stichprobe wurde 11.1 (*SD*= 2.8) Monate nach dem Interview zu belastenden Erfahrungen während verschiedener Lebensphasen sowie nach weiteren 8.3 (*SD*= 1.3) Monaten untersucht, wobei für die 2. Untersuchung jeweils 2 hoch- und 2 wenig-belastete Patient/innen nicht mehr zur Verfügung standen. Die drei Untersuchungsgruppen (2 Patientengruppen, 1 Kontrollgruppe) unterschieden sich zu keinem Erhebungszeitpunkt hinsichtlich Geschlechts- ($\chi^2(2)$= 2.61 bzw. 2.93, p> .2) und Altersverteilung (F< 1). Während sich hoch- und wenig-belastete Patient/innen bei der 1. Untersuchung hinsichtlich der Verteilung der Diagnosen unterschieden ($\chi^2(3)$= 8.16, p< .05), traf dies bei der 2. Untersuchung nicht zu ($\chi^2(3)$= 5.85, p= .12). Jede Datenerhebung dauerte etwa 30-90 Minuten. Alle Studienteilnehmer wurden über Ziele und Vorgehensweisen schriftlich und mündlich aufgeklärt und gaben ihr schriftliches Einverständnis zur Datenerhebung und –auswertung.

Tabelle 1. Anzahl der Patient/innen mit der jeweiligen ICD-10-Diagnose, die den Gruppen mit hoher und geringer Stressbelastung in der Kindheit zugewiesen waren.

	Patienten hoch-belastet		Patienten wenig-belastet	
Diagnose	1. Erhebung	2. Erhebung	1. Erhebung	2. Erhebung
MDD	8	7	3	3
Schizophrenie	2	2	11	9
Drogenabhängigkeit	3	2	3	3
BPD	3	3	3	3
Gesamt	16	14	20	18

Bemerkung: Der Unterschied zwischen der 1. und der 2. Datenerhebung resultiert aus Drop-out nach der 1. Datenerhebung.

Diagnostische Instrumente und Kennwerte

Folgende Kennwerte wurden zu beiden Untersuchungszeitpunkten erfasst:

(1) Kritische LE wurden anhand der Münchner Ereignisliste (MEL; Maier-Diewald et al., 1983) als stresshaft erlebte Probleme, die die normale Lebensführung unterbrechen, für die der jeweiligen Untersuchung vorausgehenden 6 Monate erhoben. Dabei wurden LE in den Bereichen Arbeit (z.B. Arbeitsplatzverlust), allgemeine Lebensbedingungen (z.B. Umzug), interpersonale Probleme (z.B. Trennung vom Partner), sowie Gewalt- und sexuelle Gewalterfahrungen erfragt. (2) Zu jedem LE wurde die subjektiv erlebte Belastungsintensität auf einer 5-Punkte Skala eingeschätzt. (3) Erhöhte Empfindlichkeit gegenüber sozialen Stressoren wurde mit dem Fragebogen zu negativen sozialen Interaktionen (*Test of negative social exchange,* TENSE; Ruehlman & Karoly, 1991) gemessen. Für die der Erhebung vorausgehenden 4 Wochen bewerten die Probanden hierbei auf einer 5-Punkte Skala, wie häufig sie sich negativen Verhaltensweisen von

Personen in ihrem näheren Umfeld ausgesetzt gefühlt hatten[1]. (4) Funktionsbeeinträchtigungen in Lebensbereichen wie Arbeit, Beziehungen zu Familie und Freunden und allgemeine Leistungsfähigkeit wurden jeweils für die 4 Wochen vor den Datenerhebungen erfasst. Die Liste der erfragten Bereiche wurde der deutschen Version der *Posttraumatic Stress Disorder Diagnostic Scale* (PDS; Ehlers et al., 1996; Foa, 1995) entnommen. Als Kennwert für die Funktionsbeeinträchtigung galt die Anzahl der Bereiche, für die der/die Proband/in eine schwerwiegende Beeinträchtigung durch aktuelle Stressbelastungen angab. (5) Affektive Symptomatik wurde mit dem Beck Depressionsinventar (BDI; Hautzinger et al., 1995) sowie mit der deutschen Version des *Positive and Negative Affect Schedule* (PANAS; Krohne et al., 1996; Watson et al., 1988) erfasst, der die Grundstimmung in den letzten 4 Wochen erfragt. (6) Als Kennwert für den Krankheitsverlauf galt die Zahl stationärer Wiederaufnahmen.

Auswertung

Da sich für die meisten Kennwerte keine Normalverteilung absichern ließ, wurden Gruppenunterschiede und Unterschiede zwischen den beiden Datenerhebungen mittels nicht-parametrischer Verfahren geprüft: Für Vergleiche zwischen Gruppen dienten der Kruskal-Wallis-Test (*H*, Vergleiche zwischen drei unabhängigen Stichproben) bzw. der Mann-Whitney-Test (*U*, Vergleiche zwischen zwei unabhängigen Stichproben und post hoc Gruppenvergleiche); für Vergleiche zwischen den Datenerhebungen wurde der Wilcoxon-Vorzeichen-Rang-Test (*T*, für Vergleiche zwischen zwei abhängigen Stichproben) bzw. der Friedman-Test (χ^2, für Vergleiche zwischen drei abhängigen Stichproben) herangezogen. Bei Mann-Whitney-Tests und Wilcoxon-Vorzeichen-Rang-Tests sind die Effektstärken als Bravais-Pearson Korrelation (*r*) angegeben. Der Einfluss

[1] Die zu bewertenden Aussagen lauteten beispielsweise: „Personen in meiner näheren Umgebung waren ungeduldig mit mir", „…ignorierten meine Wünsche und Bedürfnisse", „…machten sich lustig über mich".

von Diagnose und Stressbelastung in der Kindheit auf aktuelle Lebensereignisse und deren Erleben als stresshaft wurde mittels hierarchischer Regressionsanalysen untersucht. Dabei gingen die Diagnose (mit Hilfe von vier Dummy-Variablen kodiert) und der Belastungswert abwechselnd nacheinander als Prädiktoren in das Regressionsmodell ein, um zusätzliche Varianzaufklärung durch den jeweils anderen Prädiktor zu erkunden.

Ergebnisse

Aktuelle Belastung variiert nicht überzufällig über 6 Monate hinweg

Vergleiche mit dem Wilcoxon-Vorzeichen-Rang-Test ergaben für keinen Kennwert signifikante Unterschiede zwischen den beiden Messzeitpunkten (Tabelle 2), was auf eine gewisse zeitliche Stabilität der erfassten Belastungen hinweist. Daher wurde die Hypothesenprüfung für beide Untersuchungen gemeinsam vorgenommen, indem für jeden Kennwert der Mittelwert über beide Zeitpunkte gebildet wurde. Die Mittelwerte und Standardabweichungen (ergänzend auch aufgeteilt nach Ereignistypen) sind für beide Zeitpunkte getrennt in Tabelle 2 dargestellt.

Aktuelle Belastung variiert zwischen Patient/innen und Kontrollpersonen

Im Vergleich zwischen Patient/innen und gesunden Kontrollpersonen berichteten Patient/innen eine signifikant höhere Anzahl LE als Kontrollpersonen *(U*= 108.5, *p*< .01, *r*= -.44*).* Auch erlebten die Patient/innen LE als belastender als Kontrollpersonen (*U*= 79.5, *p*< .001, *r*= -.53). Trotz insgesamt gering ausgeprägter Belastung durch negative soziale Interaktionen (TENSE; Mittel der gesamten Stichprobe 14.0, *SD*= 11.8 von maximal 72 Punkten) ergab sich eine Tendenz zu stärkerer Belastung der Patienten- gegenüber der Kontrollgruppe (*U*= 161.0, *p*= .07, *r*= -.26). Schließlich erlebten Patient/innen in einer höheren Anzahl der mittels des PDS erhobenen

Funktionsbereiche eine ‚schwerwiegende Beeinträchtigung' als Kontrollpersonen (U= 77.0, p< .001, r= -.52).

Aktuelle Belastung variiert zwischen Patient/innen mit hoher und niedriger Belastung in der Kindheit

Hoch-belastete Patient/innen wiesen die höchste Anzahl LE auf, während wenig-belastete Patient/innen etwas weniger LE berichteten (siehe Tabelle 2). Der Haupteffekt Gruppe (H(2)= 9.85, p< .01) ließ sich über die Unterschiede zwischen hoch-belasteten Patient/innen und Kontrollpersonen (U= 45.0, p< .01, r= -.49) und zwischen wenig-belasteten Patient/innen und Kontrollpersonen (U= 63.5, p< .01, r= -.45) aufklären, während sich die beiden Patientengruppen nicht signifikant unterschieden (U= 94.5, p> .2, r= -.21). Subjektiv erlebten Patient/innen mit hoher Belastung in der Kindheit aktuelle LE als deutlich belastender als wenig-belastete Patient/innen (U= 73.0, p< .05, r= -.36) und Kontrollpersonen (U= 26.0, p< .001, r= -.64). Das subjektive Belastungserleben lag auch bei wenig-belasteten Patient/innen über dem der Kontrollpersonen (U= 53.5, p< .01, r= -.51; Haupteffekt Gruppe: H(2)= 16.0, p< .001). Hoch-belastete Patient/innen berichteten eine stärkere Belastung durch negative soziale Interaktionen als Kontrollpersonen (U= 56.0, p< .05, r= -.40), während sich die Patientengruppen nicht signifikant unterschieden (U= 88.5, p= .15, r= -.25; Haupteffekt Gruppe H(2)= 5.08, p= .08). Die Anzahl der beeinträchtigten Funktionsbereiche unterschied sich signifikant zwischen den drei Gruppen (H(2)= 15.38, p< .001): Hoch-belastete Patient/innen berichteten mehr Funktionsbeeinträchtigungen als Kontrollpersonen (U= 22.0, p< .001, r= -.67) und als wenig-belastete Patient/innen (U= 76.0, p= .06, r=- .34), obwohl auch wenig-belastete Patient/innen mehr Funktionsbeeinträchtigungen angaben als Kontrollpersonen (U= 55.0, p< .01, r= -.49).

Tabelle 2. Mittelwerte und Standardabweichungen für die Kennwerte der Stresssensitivität[a], getrennt für die Gruppen hoch-belasteter, wenig-belasteter Patient/innen und Kontrollpersonen und für die 1. und 2. Datenerhebung.

	Patienten hoch-belastet			Patienten wenig-belastet			Kontrollen			Gesamtstichprobe		
	1. Erhebung	2. Erhebung	T[b]	1. Erhebung	2. Erhebung	T[b]	1. Erhebung	2. Erhebung	T[b]	1. Erhebung	2. Erhebung	T[b]
LE-Anzahl gesamt	6.9 (3.2)	6.7 (3.1)	45.5, r=0	6.3 (2.9)	5.5 (2.6)	46.5, r=-.29	3.9 (2.3)	4.3 (1.9)	52, r=-.08	5.8 (3.0)	5.5 (2.7)	456, r= -.10
Arbeit	2.1 (1.1)	2.5 (1.6)		2.3 (1.2)	2.4 (1.2)		1.9 (0.9)	1.9 (1.0)		2.1 (1.1)	2.3 (1.3)	
Lebensbedingungen	1.3 (0.9)	1.0 (0.8)		1.4 (1.1)	0.9 (0.8)		0.6 (0.6)	0.7 (0.8)		1.1 (1.0)	0.9 (0.8)	
Interpersonell	2.9 (2.4)	2.6 (2.0)		2.2 (1.9)	1.6 (1.7)		1.4 (1.7)	1.3 (1.2)		2.2 (2.1)	1.8 (1.7)	
Gewalt	0.3 (0.4)	0.1 (0.4)		0.2 (0.5)	0.2 (0.4)		0	0.3 (0.5)		0.1 (0.4)	0.2 (0.4)	
sexuelle Gewalt	0.1 (0.3)	0		0	0		0	0		0.1 (0.2)	0	
Sonstige	0.3 (0.6)	0.5 (0.7)		0.4 (0.7)	0.4 (0.7)		0	0.1 (0.4)		0.2 (0.6)	0.4 (0.6)	
LE-Belastung gesamt	2.8 (0.9)	2.7 (1.0)	33, r=-.17	2.5 (0.6)	2.3 (0.8)	66, r=-.08	1.5 (0.9)	1.9 (0.7)	37.5, r=-.23	2.3 (0.9)	2.3 (0.9)	501.5, r= -.02
Arbeit	2.0 (1.4)	1.6 (1.6)		1.6 (1.1)	1.8 (1.0)		1.2 (0.9)	1.2 (1.1)		1.6 (1.2)	1.6 (1.3)	
Lebensbedingungen	2.1 (1.5)	1.5 (1.6)		1.6 (1.3)	1.4 (1.4)		0.7 (1.0)	0.8 (1.2)		1.5 (1.4)	1.2 (1.4)	
Interpersonell	2.6 (1.3)	2.4 (1.3)		2.5 (1.0)	1.7 (1.2)		1.1 (1.2)	1.3 (1.2)		2.2 (1.3)	1.8 (1.3)	
Gewalt/sex. Gewalt	1.4 (1.9)	0.6 (1.5)		0.2 (0.9)	0.4 (1.0)		0	0.7 (1.2)		0.5 (1.3)	0.6 (1.2)	
Sonstige	0.7 (1.5)	1.1 (1.6)		0.8 (1.5)	1.1 (1.6)		0	0.3 (0.7)		0.5 (1.3)	0.8 (1.4)	
TENSE	19.4 (16.4)	21.6 (17.3)	32, r=-.10	13.2 (9.8)	10.8 (7.9)	57.5, r=-.20	8.3 (8.0)	10.5 (9.6)	36, r=-.18	13.7 (12.4)	14.0 (12.7)	487.5, r=-.09
Beeinträchtigte Funktionsbereiche	2.9 (2.0)	2.4 (2.1)	30, r=-.21	1.7 (1.5)	1.3 (1.6)	16, r=-.20	0.1 (0.4)	0.7 (1.1)	1.5, r=-.31	1.6 (1.8)	1.5 (1.7)	175, r=-.07
IFTL[c]	312.8 (67.8)			42.1 (33.3)			32.0 (34.7)					

[a] Kennwerte der Stresssensitivität: LE nach MEL und subjektive Einschätzung der LE-Belastungsintensitität getrennt nach Ereignistypen, soziale Stresssensitivität nach TENSE, Zahl der Funktionsbereiche mit schwerwiegender Beeinträchtigung nach PDS

[b] Wilcoxon-Vorzeichen-Rang-Test zur Veränderung der Kennwerte über die Zeit, alle $p > .05$

[c] Summenwert der zu einem früheren Zeitpunkt mit dem IFTL erhobenen Stressbelastung in der Kindheit

Über die gesamte Stichprobe hinweg korrelierte kindliche Stressbelastung mit der Empfindlichkeit gegenüber negativer sozialer Interaktion (TENSE), der Anzahl der Funktionsbeeinträchtigungen und der subjektiv erlebten Belastung durch LE (siehe Tabelle 3). Dieser Zusammenhang blieb auch bestehen, wenn die Anzahl erlebter LE als Kontrollvariable in eine partielle Korrelation aufgenommen wurde. Unter Berücksichtigung des jeweiligen Ereignistyps blieb der Zusammenhang zwischen kindlicher Stressbelastung und der aktuellen Belastung durch Stressereignisse in den Ereigniskategorien allgemeine Lebensbedingungen, interpersonelle Probleme und Gewalterfahrungen bestehen (siehe Tabelle 3).

Tabelle 3. Partielle Korrelationen zwischen kindlicher Stressbelastung (IFTL) und Kennwerten der aktuellen Belastung.

Kontrollvariable	TENSE	Funktions-bereiche	Belastung					
			gesamt	Arbeit	Lebens-bedingungen	Inter-personell	Gewalt	Sonstige
ohne Kontrollvariable	.40**	.54***	.67***	.28^{+}	.37*	.55**	.23, n.s.	.28^{+}
LE gesamt	.37*	.44**	.35*					
Arbeit				.12, n.s.				
Lebensbedingungen					.30*			
Interpersonell						.31*		
Gewalt							.49***	
Sonstige								.01, n.s.

$^{+}$ p<.10. * p<.05. ** p<.01. ***p<.001

Sowohl psychische Erkrankung als auch Belastung in der Kindheit beeinflussen die Vulnerabilität gegenüber aktuellen Lebensereignissen

Innerhalb der untersuchten Patientenstichprobe waren Patient/innen mit MDD und Schizophrenien in der Mehrheit; auch spiegelte sich der wiederholt berichtete Befund vermehrter kindlicher Stressbelastung bei MDD in der Zusammensetzung der hoch-belasteten Patientengruppe wieder (siehe Tabelle 1). Daher wurde explorativ der

Einfluss der beiden Variablen (Diagnose und Stress in der Kindheit) auf die Anzahl berichteter LE und deren Erleben als belastend analysiert (siehe Tabelle 4). Für alle Kennwerte der Belastung ergab sich das gleiche Muster: gleichzeitig in ein Regressions-

Tabelle 4. Regressionsmodelle für die Kennwerte der Stresssensitivität, getrennt für die 1. und die 2. Datenerhebung.

Kennwert	Modell	1. Datenerhebung (N=51)		2. Datenerhebung (N=47)	
		$R^2/\Delta R^2$	$F/\Delta F$	$R^2/\Delta R^2$	$F/\Delta F$
LE Anzahl (MEL)	(1) Diagnose allein	**27.1**	**4.23****	11.0	1.30
	Stress zusätzlich	4.5	2.98+	**9.9**	**5.14***
	(2) Stress allein	13.0	7.31**	**17.1**	**9.30****
	Diagnose zusätzlich	**18.7**	**3.07***	3.8	0.49
	(3) Gleichzeitig	31.6	4.17**	20.9	2.17+
LE Belastung (MEL)	(1) Diagnose allein	**39.3**	**7.45*****	23.4	3.20*
	Stress zusätzlich	0.7	0.55	**6.6**	**3.86+**
	(2) Stress allein	19.4	11.76***	**21.2**	**12.08*****
	Diagnose zusätzlich	**20.7**	**3.88****	8.8	1.27
	(3) Gleichzeitig	40.0	6.01***	30.0	3.51**
TENSE	(1) Diagnose allein	**31.5**	**5.29*****	14.0	1.71
	Stress zusätzlich	3.1	2.16	**10.4**	**5.64***
	(2) Stress allein	15.6	9.07**	**19.4**	**10.86****
	Diagnose zusätzlich	**19.6**	**3.28***	4.9	0.67
	(3) Gleichzeitig	34.6	4.78***	24.3	2.64*
Funktions-beeinträchtigung	(1) Diagnose allein	**34.0**	**5.79*****	23.2	3.12*
	Stress zusätzlich	4.0	2.81+	**12.1**	**7.66****
	(2) Stress allein	22.5	13.93***	**19.8**	**11.12****
	Diagnose zusätzlich	**15.4**	**2.74***	15.5	2.46+
	(3) Gleichzeitig	37.9	5.34***	35.3	4.48**

Modelle: (1) Diagnose als 1. Faktor eingegeben, durch Faktor Stress in der Kindheit zusätzlich erklärte Varianz; (2) Faktor Stress in der Kindheit als 1. Faktor eingegeben, durch Faktor Diagnose zusätzlich erklärte Varianz; (3) Faktoren Diagnose und Stress in der Kindheit gleichzeitig eingegeben. F: F-Statistik für R^2 bzw. ΔR^2. + p<.10. * p<.05. ** p<.01. ***p<.001.

modell eingegeben klärten Diagnose und Stress in der Kindheit signifikant Varianz des jeweiligen Kennwertes auf. Nacheinander in das Modell eingegeben, erwies sich bei der ersten Untersuchung die Diagnose allein als signifikanter Prädiktor, während die

kindliche Stressbelastung keine zusätzliche Varianz aufklärte. Bei der zweiten Untersuchung jedoch war die kindliche Stressbelastung allein signifikanter Prädiktor, während die Diagnose keine zusätzliche Varianz aufklärte.

Belastung in der Kindheit und Verlauf der Erkrankung

Während sich alle 36 Patient/innen zum Zeitpunkt des Interviews zur Stressbelastung in der Kindheit in stationärer Behandlung befanden, traf dies für die beiden Messzeitpunkte der vorliegenden Studie nur für die 10 bzw. 7 Patient/innen zu, die in der forensischen Abteilung behandelt wurden (davon 3 bzw. 1 Patient/innen mit Drogenabhängigkeit, 4/4 mit Schizophrenie und 3/2 mit BPS). Die anderen Patient/innen waren mediziert mit Erhaltungsdosis entlassen worden und befanden sich in regulärer nervenärztlicher Nachbetreuung. Rückfälle im Sinne einer Rehospitalisierung wurden innerhalb der etwa 18 Monate zwischen dem Interview zur Stressbelastung in der Kindheit und dem 2. Messzeitpunkt der vorliegenden Studie bei 5 (von 14) hoch- und bei 6 (von 18) wenig-belasteten Patient/innen (χ^2 (1)= 0.02, p> .8) notiert.

Berücksichtigt man für den Verlauf der Symptomatik drei Messzeitpunkte über insgesamt etwa 18 Monate hinweg (Zeitpunkt des Interviews zur Stressbelastung in der Kindheit, 1. und 2. Zeitpunkt der vorliegenden Studie), so nahm die Depressivität über den gesamten Zeitraum vor allem in der wenig-belasteten Patientengruppe ab (χ^2(2)= 15.6, p< .001), die beiden anderen Gruppen zeigten keine signifikante Veränderung im BDI (hoch-belastete Patient/innen: χ^2(2)= 2.07, p> .3; Kontrollpersonen: χ^2(2)= 3.21, p> .2). Eine signifikante Veränderung der negativen Grundstimmung ließ sich für keine Gruppe nachweisen (gesamte Stichprobe: χ^2(2)= 2.01, p> .3; hoch-belastete Patient/innen: χ^2(2)= 1.96, p> .3; wenig-belastete Patient/innen: χ^2(2)= 2.55, p> .2; Kontrollpersonen: χ^2(2)= 0.46, p> .7). Eine Zunahme positiver Grundstimmung über die

Tabelle 5. Mittelwerte und Standardabweichungen für Kennwerte affektiver Symptomatik getrennt für die Stichproben hoch-belasteter, wenig-belasteter Patient/innen und Kontrollpersonen für 3 Messzeitpunkte.

	Patienten hoch-belastet			Patienten wenig belastet			Kontrollen			Gesamtstichprobe		
	Stress-interview	1. Erhebung	2. Erhebung	Stress-interview	1. Erhebung	2. Erhebung	Stress-interview	1. Erhebung	2. Erhebung	Stress-interview	1. Erhebung	2. Erhebung
BDI	22.4 (13.3)	19.6 (14.5)	17.9 (15.4)	16.0 (8.8)	10.5 (5.6)	7.6 (6.1)	1.8 (2.5)	1.8 (1.9)	2.4 (3.0)	13.2 (12.0)	10.9 (11.7)	9.1 (11.3)
PANAS												
PA	26.6 (8.8)	29.6 (8.5)	32.7 (8.2)	28.9 (5.0)	29.4 (6.8)	32.8 (6.0)	36.9 (5.3)	38.0 (4.6)	39.2 (4.2)	30.5 (8.0)	32.3 (7.7)	34.8 (6.9)
NA	32.2 (8.4)	28.1 (9.7)	27.7 (9.3)	24.9 (5.9)	23.2 (6.2)	21.2 (6.8)	17.2 (4.7)	17.5 (5.3)	17.9 (6.2)	24.3 (8.6)	23.0 (8.6)	21.8 (8.3)

Bemerkung: Stressinterview: IFTL-Interview zur Erhebung der Belastung in der Kindheit; 1. und 2. Datenerhebung: Erhebung der Kennwerte aktueller Belastung.

Zeit hinweg ($\chi^2(2)= 12.34$, $p< .01$) war vor allem auf die Kontrollgruppe ($\chi^2(2)= 6.36$, $p< .05$) zurückzuführen, obwohl auch hoch-belastete Patient/innen tendenziell eine Zunahme in der positiven Grundstimmung zeigten ($\chi^2(2)= 5.78$, $p< .1$; siehe Tabelle 5 für Mittelwerte und Standardabweichungen).

Diskussion

Die vorliegende Studie untersuchte den Zusammenhang zwischen retrospektiv berichteter Belastung in der Kindheit und Kennwerten aktueller Belastung bei Patient/innen mit psychischen Erkrankungen im Vergleich zu gesunden Personen. Dabei wurden sowohl Befunde zu vergleichsweise erhöhter Stressbelastung im Kindesalter als auch Befunde zu vergleichsweise vermehrt im Vorfeld von Rückfällen auftretenden kritischen LE bei Patient/innen mit psychischen Erkrankungen berücksichtigt. Die Vulnerabilität für potentiell belastende Faktoren des täglichen Lebens und deren Erleben als belastend wurde in der vorliegenden Studie operationalisiert über die Häufigkeit von kritischen LE und deren subjektive Bewertung als belastend, über die Empfindlichkeit gegenüber sozialen Stressoren und die Anzahl von Lebensbereichen, in denen gravierende Einschränkungen erlebt wurden.

Die vorliegende Studie bestätigt für die untersuchte Stichprobe den vielfach berichteten Befund einer erhöhten Zahl belastender LE bei Patienten mit psychischen Erkrankungen. Dieser Befund wird ergänzt durch weitere Indikatoren aktueller Belastung (subjektives Belastungserleben, Sensitivität für negative soziale Interaktion, Funktionseinschränkung in verschiedenen Lebensbereichen). Für einen zusätzlichen Einfluss der in der Kindheit erfahrenen Stressbelastung sprechen sowohl das erhöhte subjektive Belastungserleben als auch die Funktionseinschränkungen in verschiedenen Lebensbereichen insbesondere bei Patient/innen, die in der Kindheit extreme

Stressbelastung erfahren hatten. Zusammen mit den Ergebnissen der hierarchischen Regressionsanalysen, in denen sich kindliche Stressbelastung nur auf Dauer (hier zum 2. Untersuchungstermin) als allein signifikanter Prädiktor der Sensitivität für aktuelle Belastung erwies, weisen die vorliegenden Befunde auf einen Einfluss früher Stressbelastung auf aktuelle Belastung und Belastungserleben hin – dies jedoch in Kombination mit Einflüssen der Erkrankung selbst. Studiendesign und Ergebnisse erlauben nicht, einen Einfluss der Kindheitsbelastung von dem der psychischen Störung zu trennen. Unter anderem stellt die ungleiche Verteilung der Diagnosen in den Gruppen mit hoher und niedriger Stressbelastung in der Kindheit ein methodisches Problem dar, das eine Differenzierung des Einflusses der beiden Faktoren Stress und Krankheit auf die Vulnerabilität für Stress nicht erlaubte. Andererseits weist diese Koinzidenz auf die angenommene Wechselwirkung von Vulnerabilitätsfaktoren hin. Für Depressionen haben Heim und Nemeroff (Heim et al., 2004, 2008; Nemeroff, 2004) den Einfluss von Belastungen und Traumata in der Kindheit auf Entwicklung und Verlauf psychischer Störungen modelliert. Insbesondere bei einem (genetisch-biologisch prädisponierten) Subtyp von Depressionen erklären sie eine Vulnerabilisierung durch frühe Stress-Effekte mit einer dauerhaften Veränderung stress-verarbeitender Systeme. Diese vermittelt sowohl eine erhöhte Reaktivität auf spätere LE als auch erhöhte Sensitivität für weitere Belastungen. Der Befund einer Häufung von Patient/innen mit Depressionen in der Gruppe hoch-belasteter Patient/innen in der vorliegenden Studie (für die Ausgangspopulation siehe auch Weber et al., 2008) weist in diese Richtung. Ferner steht die Koinzidenz von hoher Stressbelastung in der Kindheit und Depression in Einklang mit Befunden eines Zusammenhanges von Trauma oder Misshandlung im Kindesalter und depressiven Erkrankungen im Erwachsenenalter (Mello, Mello, Carpenter, & Price, 2003). Während in der Ausgangspopulation (von 96) Patient/innen mit Borderline

Persönlichkeitsstörung ähnlich hohe Belastung in der Kindheit aufwiesen wie depressive Patient/innen, trat auffällige Belastung bei (den ursprünglich 32) Patient/innen mit Schizophrenien erst mit der Pubertät und in der späten Adoleszenz hervor (siehe Weber et al., 2008). Die in dieser Studie vorgenommene Gruppenzuweisung aufgrund extremer bzw. geringer kindlicher Stressbelastung mag den Eindruck einer im Vergleich zu Berichten in der Literatur (z.B. Read, Van Os, Morrison, & Ross, 2005) eher niedrigen Belastung bei schizophrenen Patient/innen entstehen lassen. Nicht auszuschließen ist, dass dieser diagnosespezifische Effekt mit der vergleichsweise kleinen Stichprobe und einer speziellen Klientel des hiesigen Psychiatrischen Zentrums zusammen hängt. Krankheitsspezifische Zusammenhänge zwischen Kennwerten aktueller Belastung und Stresserfahrungen in unterschiedlichen Lebensphasen wären zukünftig für größere Stichproben zu klären, um die krankheitsspezifische Vulnerabilisierung durch kindliche Belastung zu präzisieren.

Bedeutsam erscheint, dass die beobachtete Empfindlichkeit gegenüber aktuellen Belastungen, die unabhängig von einem bei den meisten Patient/innen günstigen Krankheitsverlauf auftrat, mit einer dauerhaften Tendenz zu eher negativer Grundstimmung einherging. Dies traf besonders auf Patient/innen mit hoher Belastung in der Kindheit zu und stützt die Hypothese, dass negative Grundstimmung eine Mediatorfunktion zwischen kindlicher Stresserfahrung und Merkmalen späterer psychischer Störungen darstellt (Charmandari et al., 2003; Lang et al., 2007). Hierarchische Regressionsanalysen deuteten auf einen geringeren Einfluss der Diagnose auf die Kennwerte der Stress-Sensitivität zum 2. Messzeitpunkt hin. Dies könnte darauf hinweisen, dass mit Besserung des Zustands die Langzeitfolgen kindlicher Stressbelastung deutlicher werden. Eine Prüfung dieser Hypothese würde allerdings längsschnittliche Erhebungen über einen längeren Zeitraum voraussetzen, in denen der

Krankheitsverlauf spezifischer erfasst würde als es in der vorliegenden Studie möglich war, und in denen auch eine potentielle Wirkung protektiver Faktoren wie z.B. spezifischer therapeutischer Maßnahmen zu berücksichtigen wären.

Die vorliegende Studie kann aufgrund des begrenzten Stichprobenumfangs nur erste Hinweise auf die lebenslangen Konsequenzen von Belastung in der Kindheit liefern. Von den ursprünglich fast 100 untersuchten Patient/innen wurde etwa ein Drittel als ‚hoch-belastet' eingestuft, bei etwa einem weiteren Drittel entsprachen die Belastungswerte denen der gesunden Vergleichsgruppe (Weber et al., 2008). Diese Verteilung weist auf die interindividuelle Variabilität des Zusammenhanges zwischen kindlicher Belastung und psychischer Erkrankung im Erwachsenenalter hin, die in jüngerer Zeit über die Interaktion von Genetik und Umwelt bzw. epigenetischen Einflüssen aufzuklären versucht wird (z.B. Bradley et al., 2008; Caspi & Moffitt, 2006; McGowan et al., 2009). Eine psychisch gesunde Kontrollgruppe mit hoher Stress-belastung in der Kindheit könnte dazu beitragen, Einflüsse der Störung einerseits und kindlicher Belastung andererseits genauer zu prüfen. Längsschnittliche Studien mit Patient/innen sind besonders anfällig für drop outs. Dies bestätigte sich auch in der vorliegenden Studie, in der nur 50% der geplanten Stichprobe für beide Nachuntersuchungen gewonnen werden konnten. Entsprechend müssen die Ergebnisse der vorliegenden Studie als vorläufig betrachtet und in Nachfolgestudien mit ausreichend großen und balancierten Patientenstichproben erhärtet werden. Als weitere Einschränkung der vorliegenden Studie könnte die mangelnde Zuverlässigkeit retrospektiver Selbstberichte betrachtet werden (Reimer, 2001). Die Reliabilität retrospektiv erfasster autobiographischer Details könnte besonders bei Personen eingeschränkt sein, die störungsbedingt kognitive Beeinträchtigungen aufweisen. Andererseits liegen Befunde zur Validität von Selbstberichten bei Patient/innen vor (z.B.

Goodman et al., 1999; Herman & Schatzow, 1987; Margo & McLees, 1991). Darüber hinaus legt eine hohe Re-Test-Reliabilität für ein ähnliches Instrument zur Erfassung von Erfahrungen in verschiedenen Lebensphasen (Traumatic Antecedents Questionnaire; Van der Kolk, 2001) die Zuverlässigkeit der Angaben nahe (Garieballa et al., 2006). Alle Patient/innen waren in ausreichend remittierten Zustand, um das etwa 1-3-stündige Interview absolvieren zu können, was gravierende Verzerrungen z.B. durch akute psychotische Symptomatik möglicherweise kompensieren konnte.

Zusammenfassend stützen die vorliegenden Ergebnisse die Hypothese, dass die (wiederholt berichtete) erhöhte Vulnerabilität für kritische Lebensereignisse bzw. für erhöhte Belastung durch Lebensereignisse bei Personen mit psychischen Störungen durch kindliche Stresserfahrungen beeinflusst werden kann. Sie lassen sich damit mit Modellannahmen vereinbaren, dass Belastungen in der Kindheit stress-verarbeitende Systeme modulieren und darüber anhaltend die Verarbeitung weiterer potentiell belastender Lebensereignisse beeinflussen. Dies sollte bei der weiteren Aufklärung von Faktoren, die Entwicklung und Verlauf einer psychischen Störung beeinflussen, berücksichtigt werden.

2.2 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 magneto-encephalographic 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.

Keywords: early life stress, affective pictures, mental disorder, magneto-encephalography, RSVP

Introduction

Automatic (involuntary) attention capture by emotional cues is supposed to support the preparation and organization of efficient appetitive and defensive actions (Lang, Bradley, & Cuthbert, 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, Bradley, Elbert, & Lang, 2001; Schupp, Junghöfer, Weike, & Hamm, 2004), magnetoencephalographic (MEG; Peyk, Schupp, Elbert, & Junghöfer, 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, Junghöfer, Weike, & Hamm, 2003) and rapid presentation rates between 3 and 12 Hz (Junghöfer et al., 2001; Peyk, Schupp, Keil, Elbert, & Junghöfer, 2009).

The cortical responses to emotional stimuli, which characterize normal subjects, are often found to differ in individuals with a psychiatric disorder. Moratti, Rubio, Campo, Keil, & Ortiz (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 and colleagues (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, Junghöfer, Elbert, Buodo, & Miller, 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, Tomarken, Shelton, & Sutton, 2004; Mueser, Penn, Blanchard, & Bellack, 1997).

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 (Champagne et al., 2008; Charmandari et al., 2005; de Kloet, Sibug, Helmerhorst, & Schmidt, 2005; Plotsky et al., 2005; Sterlemann et al., 2008). As a consequence, psychophysiological reactivity may be modified (e.g. Meyer, Chrousos, & Gold, 2001; Pole et al., 2007) including more sensitive responses to further stressors (e.g. Hazel, Hammen, Brennan, & Najman, 2008; Heim et al., 2004) and altered affective processing (Lang et al., 2007; Taylor, Eisenberger, Saxbe, Lehman, & Lieberman, 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 & Teicher, 2008, 2009; Cohen, et al., 2006; Dinan, 2005; Dohrenwend, 2006; Heim et al., 2004; Leonardo & Hen, 2008; McEwen, 2003b; Nemeroff, 2004; Walker, Mittal, & Tessner, 2008). Heim and colleagues (Bradley et al., 2008; Heim et al., 2003, 2004; Pace et al., 2006; see also Van den Bergh, Van Calster, Smits, Van Huffel, & Lagae, 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, Heim, Goodman, Miller, & Nemeroff, 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 hereon) 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.

Methods

Participants

The present sample comprised 31 patients (12 female, mean age 40.0 ± 12.6 years) and 15 healthy subjects (7 female, mean age 40.7 ± 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[2] 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

[2] 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.

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 6 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 6). 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 diagnosed with substance related disorders, 4/4 with schizophrenia 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, Stotz-Ingenlath, Dietz-Bauer, & Vossen, 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.

Table 6. Demographic and clinical data for the three ELS-groups at both assessments

	1st session			2nd session		
	High-ELS patients	Low-ELS patients	Healthy subjects	High-ELS patients	Low-ELS patients	Healthy subjects
Number of subjects	15	16	15	13	15	15
Gender (female/male)	8/7	4/12	7/8	7/6	4/11	7/8
Group comparison	$chi^2(2)=2.83$, $p=.24$			$chi^2(2)=2.33$, $p=.31$		
Age (M±SD)	42.7±12.3	37.5±12.9	40.7±16.7	44.5±12.7	38.9±13.2	41.6±16.9
Group comparison	$F(2,43)=0.53$, $p=.59$			$F(2,40)=0.52$, $p=.60$		
Diagnosis[a]						
MDD	8	3		7	3	
Schizophrenia	2	8		2	7	
DA	3	3		2	3	
BPD	2	2		2	2	
Group comparison (High- vs. low-ELS)	$chi^2(3)=5.85$, $p=.12$			$chi^2(3)=4.46$, $p=.22$		
Comorbid diagnoses (M±SD)	1.5 ± 0.8	0.5 ± 0.6		1.5 ± 0.9	0.5 ± 0.7	
Hospitalizations (M±SD)	6.5 ± 6.2	4.5 ± 3.3		7.7 ± 6.7	4.3 ± 3.6	
Medication[b]	No med: 3 AD&N: 4 Ntyp: 1 Natyp: 1 AD: 2 RI:2 Missing: 2	No med: 4 AD&N: 2 Natyp: 4 AD: 2 AD:1 RI:2 TCA: 1	No med: 15	No med: 3 AD&N: 3 Ntyp: 1 Natyp: 1 AD: 2 RI: 2 Missing:1	No med: 4 AD&N: 1 Natyp: 4 AD: 2 AD:1 RI:2 TCA: 1	No med: 15
Early life stress (M±SD total score)	311.5±70.0	42.6±36.0	32.0±34.7			

a: Diagnoses: MDD: Major depressive disorder; DA: Drug addiction; BPD: Borderline personality disorder.
b: Medication: AD&N: combination of antidepressants and neuroleptics; Ntyp: typical neuroleptics; Natyp: atypical neuroleptics; AD: combination of tricyclics and serotonin/NA reuptake inhibitors; RI: selective serotonine reuptake inhibitor or serotonine-NA-reuptake inhibitors; TCA: tricyclic antidepressives.

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; Lang et al., 2008) 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 two series of 300 pictures (total 600 stimuli). Pictures were presented without perceivable gap for 349 ms each (2.86 Hz, 60Hz refresh rate) in a pseudorandom sequence. Presentation order was controlled for transition probabilities between the three stimulus categories. Physical picture parameters (brightness, contrast, color distribution, complexity) did not differ between stimulus categories. Timing and sequence of stimulus presentation were controlled using PRESENTATION software (Neurobehavioral Systems®, Albany, CA, USA). Participants were asked to keep their eyes focused on a small central fixation cross overlaying each picture and to attend to the picture series carefully without any additional task. The two picture series were

presented without a break. Presentation of the total 600 stimuli lasted for about 4 minutes.

Data Acquisition and Analysis

The MEG was recorded while subjects were in a prone position using a 148-channel magnetometer (MAGNES™ 2500 WH, 4D Neuroimaging, San Diego, USA). Neuromagnetic data were continuously recorded with a sampling rate of 678.17 Hz and a bandpass filter of 0.1 to 200 Hz. For artifact control, the vertical and horizontal electrooculogram (EOG from four electrodes placed near the left and right temporal canthus and above and below the right eye) and the electrocardiogram from two electrodes attached to the right and left forearm were recorded using a SynAmps amplifier (NEUROSCAN Laboratories, Sterling, VA, USA). The subject's nasion, left and right ear canal, and head shape were digitized with a Polhemus 3Space® Fasttrack prior to each session.

Following noise reduction based on distant reference sensors, 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). Further preprocessing was accomplished with BESA® software (MEGIS Software GmbH, Munich, Germany) and included filtering of continuous data with a 0.5 Hz (6 dB/octave, forward-shift) high-pass and a 40 Hz (48 dB/octave, zero-phase-shift) low-pass filter, and rejection of epochs containing eye blinks. Data of one MDD patient from the low-ELS group had to be excluded from analyses of the first session because of too many artifact-contaminated trials.

Following preprocessing, event-related fields were averaged across trials separately for each subject and stimulus category. Of the 200 trials of each stimulus

category 188 artifact-free trials were available on average for low-ELS patients, 188 trials for high-ELS patients and 197 trials for healthy subjects in the 1st session (group difference n.s.). A similar number of trials was available in the 2nd session (185 trials for low-ELS patients, 175 trials for high-ELS patients and 198 trials for healthy subjects (difference n.s.). Each trial was referenced to the preceding trial as a baseline. Averaged across trials, baselines represented an average over the three stimulus categories. The L2-Minimum-Norm-Pseudoinverse was used for inverse modeling, providing minimum norm estimates (MNE; Hamalainen & Ilmoniemi, 1994; Hauk, 2004; Hauk et al., 2002). Relying on EMEGS© 2.4 custom software (Junghöfer & Peyk, 2004) written in Matlab® (MathWorks Inc., MA, USA), a spherical shell with 2 x 350 evenly distributed dipoles (azimuthal and polar direction, radial dipoles do not generate magnetic fields outside of a sphere) served as the source model. A source shell radius of 87% of the individually fitted head radius was chosen, roughly corresponding to grey matter. A Tikhonov regularization parameter of 0.2 was applied. Independent of dipole direction, source strength was calculated as the vector length of the generator activity at each position for each subject, condition and time point based on the averaged magnetic field distributions and individual sensor positions.

The course of global power of estimated neural activity, illustrated in Figure 3 for the 1st session, indicates two activity peaks around 100 ms and 200-250 ms after stimulus onset, followed by a general decline in activity. Whereas activity differs between patients and healthy subjects around 100 ms, differences between high- and low-ELS subjects emerge at around 200 ms and later. For statistical evaluation of group and stimulus effects, two sets of point-wise repeated measures analysis of variance (ANOVA) were accomplished separately for each estimated source and time point: one ANOVA, carried out with healthy subjects only, included the within-subjects factor

Emotion (comparing pleasant, unpleasant and neutral stimuli). This ANOVA served to verify the modulation of cortical activation by emotional stimulus content as described, for instance, by Peyk et al. (2008; see also Schupp et al., 2006). The second ANOVA included the between-subjects factor ELS (comparing the three groups). To avoid false positives, significant effects were only considered when they included a minimum of 21 continuous data points (32 ms) and when at least two adjacent representative dipoles showed the effect. The first set of ANOVAs determined two time windows with prominent effects of stimulus content, 120-170 ms and 250-349 ms after stimulus onset. The second set of ANOVAs determined group differences for the time windows 70-120 ms, and 170-250 ms after stimulus onset. In the next step, cortical regions (regions of interest, ROI), in which the differences between groups or stimulus conditions were prominent, were determined by plotting the statistical measures of activity differences (F-ratios) onto a spherical configuration of dipoles. Figure 4 illustrates the ROIs defined as dipole groups with highly significant F-ratios for each time window.

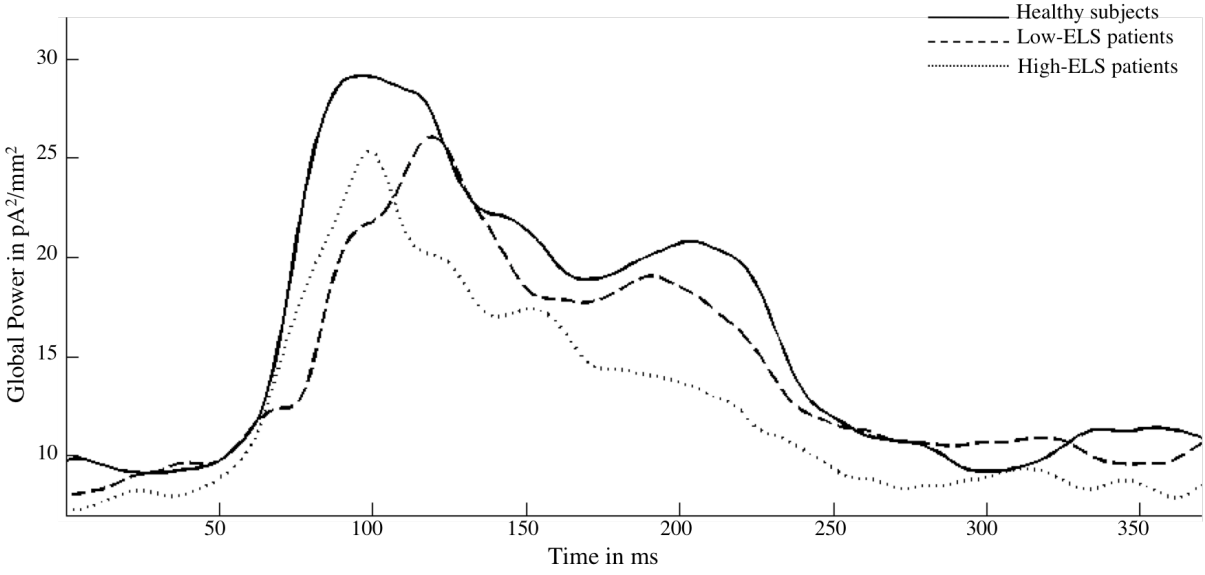

Figure 3. Time course of overall estimated source activity (global power in pA²/mm²) in the first session, averaged across stimulus categories separately for patients with high ELS (dotted line), patients with low ELS (dashed line) and healthy comparison subjects (solid line).

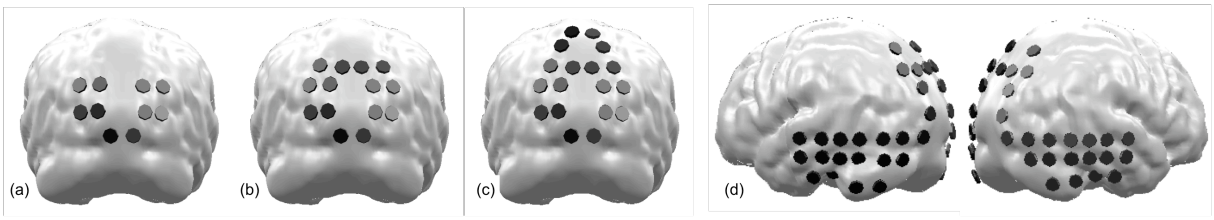

Figure 4. Schematic positions of modeling sources used for statistical analyses. For illustrative purposes, the dipoles forming the regions of interest (ROIs) are superimposed on the back view of a schematic cortical surface for activity (a) 70-120 ms, (b) 120-170 ms, (c) 170-250 ms, and (d) on left- and right-sided view for activity 250-349 ms after stimulus onset. Optimizing tests for laterality central model sources belonging to both groups have not been considered.

Effects of psychiatric disorder and ELS on dipole activity in the four time windows were verified by two repeated-measures analyses of variance (ANOVA), one with the between-subjects factor Group (comparing patients and healthy subjects), the other with the between-subjects factor ELS (comparing high-ELS, low-ELS patients and healthy subjects). In both ANOVAs the effect of emotional stimulus content was evaluated by the within-subjects factor Emotion (comparing pleasant, unpleasant, and neutral stimuli), and in both ANOVAs, differences of dipole activity between left and right ROI were tested with the additional within-subjects factor Hemisphere. Main effects of Group or ELS should reflect overall differences in cortical responses across stimulus categories, whereas interactions between Group or ELS and Emotion should reflect group-dependent differential processing of stimulus content. Post-hoc analyses decomposed significant main effects or interactions with orthogonal polynominal contrasts and follow-up pair-wise comparisons corrected with Bonferroni, with polynominal contrasts capturing the effect of stimulus valence (pleasant vs. unpleasant) as a linear trend and the effect of stimulus arousal (pleasant and unpleasant vs. neutral) as a quadratic trend. These trends reflect a priori hypotheses about critical dimensions of emotion (e.g. Lang et al., 1998). Effects of ELS (ELS-score as a measure of severity and age at the first reported event as a measure of ELS-onset) on dipole activity were probed by intraindividual partial correlations (*r*) using the number of reported life events as a

control variable. In addition, effects of disorder-severity on dipole activity were probed by non-parametric spearman correlations with the number of hospitalizations and the number of comorbid diagnoses. In order to control for potential gender effects on cortical activity (Sabatinelli, Flaisch, Bradley, Fitzsimmons, & Lang, 2004), an additional ANOVA with the between-subjects factor Gender and the within-subjects factors Emotion and Hemisphere was accomplished. A main effect Gender only emerged in the 120-170ms interval in the 1st session ($F(1,43)= 8.12$, $p< .01$) with men displaying stronger cortical responses than women irrespective of stimulus valence. Since there were no interactions with Emotion or Hemisphere in any of the four components, results are reported for men and women together. Temporal stability of cortical activity across sessions was explored using Pearson correlations (r) and an additional exploratory ANOVA including the within-subjects factor Time (comparing dipole activities of the 1st and the 2nd session).

Finally, as interview data were not distributed normally, group differences and variations across the two sessions regarding current life stress were evaluated with non-parametric tests (Kruskal-Wallis (chi^2) and Mann-Whitney-U (U) for independent, Wilcoxon signed-rank test (T) for dependent measures). The relationship between current life stress and cortical responses was probed by non-parametric Spearman correlations.

For all analyses statistical significance was evaluated at the .05 level. Possible violations of the homogeneity of covariance assumption were corrected with the Huynh-Feldt epsilon (statistical reports include uncorrected degrees of freedom and epsilon-corrected p-values).

Results

Processing of emotional stimuli is modified by psychiatric disorder

Lower dipole activity in patients as opposed to healthy subjects, as illustrated in Figure 3 for the 1st session, was statistically confirmed for the 70-120 ms and the 170-250 ms interval (main effect Group, $p< .05$; see also Table 7). In the 2nd session, group differences were verified for all three latency windows between 70 and 250 ms.

In patients and controls, modulation of occipital-parietal dipole activity by high-arousing pleasant and unpleasant relative to low-arousing neutral stimuli was evident 120-170 ms following stimulus onset (Emotion, 1st session, $F(2,86)= 10.94$, $p< .0001$, $\varepsilon= 1.0$; linear trend explaining 19% of the variance, $F(1,43)= 4.16$, $p< .05$; quadratic trend explaining 81% of the variance, $F(1,43)= 17.97$, $p< .001$). In the 2nd session, the Emotion effect ($F(2,82)= 4.62$, $p< .05$, $\varepsilon= 1.0$) was carried by a linear trend indicating the largest responses to unpleasant stimuli (linear trend explaining 85% of the variance, $F(1,41)= 8.90$, $p< .01$, quadratic trend explaining 15%, $F(1,41)= 1.15$, $p> .2$). At 250 - 349 ms, groups differed in the modulation of dipole activity by emotional content (Group x Emotion, 1st session, $F(2,86)= 5.97$, $p< .01$, 2nd session, $F(2,82)= 6.52$, $p< .01$): healthy subjects exhibited most pronounced parietal-temporal dipole activity in response to pleasant stimuli (linear trend explaining 72% of the variance in the 1st session, $F(1,14)= 18.67$, $p< .001$, and 67% in the 2nd session, $F(1,14)= 10.41$, $p< .01$), whereas modulation by arousal prevailed in patients (1st session, quadratic trend explaining 60% of the variance, $F(1,29)= 4.95$, $p< .05$; 2nd session, 97%, $F(1,29)= 3.90$, $p= .06$).

Processing of emotional stimuli is modified by ELS

If ELS was related to lasting changes in cortical affective processing, we might expect a relationship between ELS and present estimated neural activity. Across all subjects, correlation coefficients indicated that higher ELS was moderately related to lower

overall dipole activity (all components, all stimulus categories, both hemispheres; 1st session: r= -.31, p< .05; 2nd session: r= -.36, p< .05).

Table 7. Statistical effects of Group (patient vs comparison), Emotion (pleasant vs unpleasant vs neutral stimuli) and Hemisphere (left vs right) on dipole activity in the four latency windows, separately for the two sessions.

	1st session			
	70-120ms	120-170ms	170-250ms	250-349ms
Group	$F(1,43)=4.48$*	$F(1,43)=1.50$	$F(1,43)=4.56$*	$F(1,43)=1.96$
Emotion	$F(2,86)=1.43$	$F(2,86)=10.94$***	$F(2,86)=2.45^{+}$	$F(2,86)=20.27$***
Hemisphere	$F(1,43)=1.64$	$F(1,43)=3.28^{+}$	$F(1,43)=8.43$**	$F(1,43)=1.21$
Group x Emotion	F<1	$F(2,86)=1.66$	$F(2,86)=1.61$	$F(2,86)=5.97$**
Group x Hemisphere	F<1	$F(1,43)=3.24^{+}$	$F(1,43)=1.55$	F<1
Emotion x Hemisphere	F<1	$F(2,86)=1.66$	$F(2,86)=4.66$*	$F(2,86)=2.01$
Group x Emotion x Hemisphere	$F(2,86)=1.41$	F<1	$F(2,86)=2.18$	$F(2,86)=2.80^{+}$
	2nd session			
	70-120ms	120-170ms	170-250ms	250-349ms
Group	$F(1,41)=6.31$*	$F(1,41)=4.05$*	$F(1,41)=10.75$**	$F(1,41)=2.53$
Emotion	$F(2,82)=7.58$**	$F(2,82)=4.62$*	$F(2,82)=1.32$	$F(2,82)=12.53$***
Hemisphere	F<1	$F(1,41)=2.96^{+}$	$F(1,41)=4.88$*	$F(1,41)=3.91^{+}$
Group x Emotion	$F(2,82)=6.34$**	$F(2,82)=1.32$	F<1	$F(2,82)=6.52$**
Group x Hemisphere	F<1	$F(1,41)=1.44$	F<1	$F(1,41)=2.44$
Emotion x Hemisphere	F<1	$F(2,82)=4.09$*	$F(2,82)=3.60$*	F<1
Group x Emotion x Hemisphere	F<1	$F(2,82)=2.39^{+}$	$F(2,82)=2.87^{+}$	$F(2,82)=4.71$*

*: p< .05, **: p< .01; ***: p< .001; $^{+}$: p< .1, F-ratios without superscript: p> .1

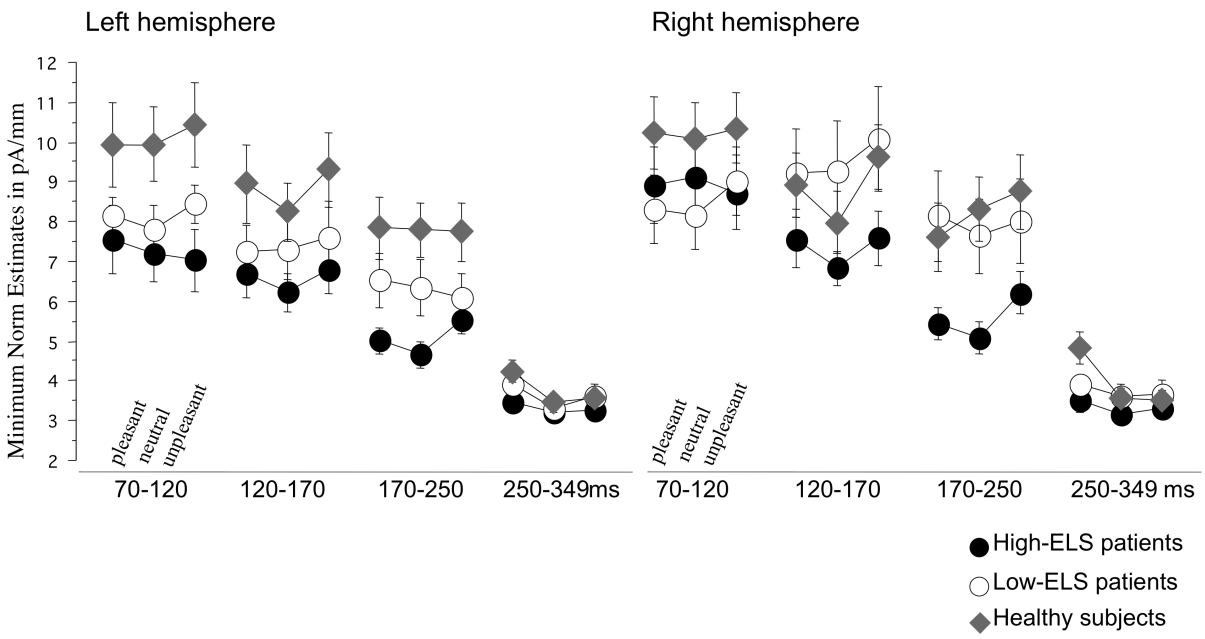

Figure 5a. Estimated source activities in the 1st session are plotted for four latency windows (abscissa: 70-120 ms, 120-170 ms, 170-250 ms, 250-349 ms after stimulus onset) separately for emotional stimulus content (pleasant – neutral – unpleasant), group (filled circles: high-ELS patients, open circles: low-ELS patients, grey squares: healthy subjects) and left and right hemisphere. Ordinate: Dipole activity expressed as minimum norm estimates, Mean ± Standard Error in pA/mm.

Figures 3, 5a and 5b[3] indicate lower estimated source activity in high-ELS patients compared to low-ELS patients and healthy subjects around 200 ms and thereafter. This was confirmed in the repeated measure ANOVA for the 170-250 ms component (ELS 1st session: $F(2,42)= 4.29$, $p< .05$; 2nd session: $F(2,40)= 5.70$, $p< .01$). Bonferroni post hoc tests verified significant differences between high-ELS and healthy subjects (1st session, $p< .05$, 2nd session, $p< .01$), whereas low-ELS patients did not differ significantly from the other two groups. Correlations between higher ELS-scores and lower neural activity across subjects were also confirmed for this time window (1st session: $r= -.40$, 2nd session: $r= -.40$, $p< .01$). ELS-onset (measured by the age at the first reported event) and dipole activity at 170-250 ms were significantly correlated across subjects in the first (r= .34, p< .05) but not in the second session. Neither within the patient group nor within the diagnostic subgroups, relationships between dipole

[3] *Note.* Figure 5b has been added for illustrative purposes and is not included in the published manuscript.

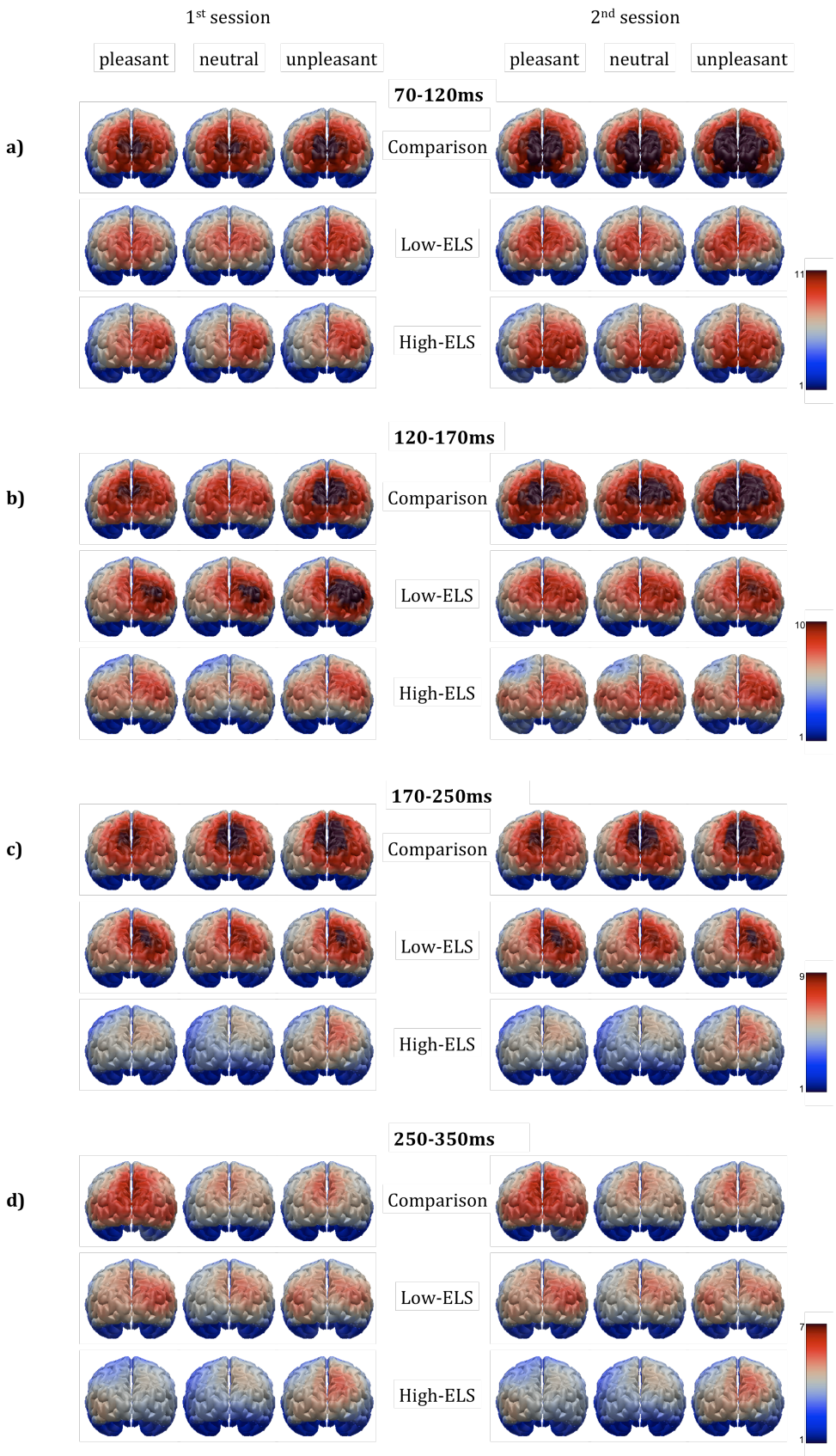

Figure 5b. Estimated source activities in the 1st and 2nd session superimposed on the back view of a schematic cortical surface for a) 70-120 ms, b) 120-170 ms, c) 170-250 ms, d) 250-349 ms after stimulus onset separately for emotional stimulus content (pleasant – neutral – unpleasant) and group (high-ELS patients, low-ELS patients, healthy subjects). Dipole activity expressed as minimum norm estimates in pA/mm.

activity and severity of illness (measured by the number of hospitalizations and the number of comorbid diagnoses) were significant.

All subjects showed modulation by arousal between 120-170 ms, which persisted in high-ELS patients in the subsequent 170-250 ms window (1st session, ELS x Emotion, ($F(4,84)= 2.44$, $p= .05$; main effect Emotion for high-ELS patients $F(2,28)= 4.92$, $p<.05$, quadratic trend explaining 52% of the variance, $F(1,14)= 6.39$, $p< .05$). In the later 250-349 ms time interval an interaction ELS x Emotion (1st session, $F(2,84)= 3.02$, $p< .05$; 2nd session: $F(4,80)= 3.20$, $p< .05$; main effects Emotion, 1st session, $F(2,84)= 15.22$, $p< .001$; 2nd session, $F(2,80)= 8.14$, $p< .001$) resulted from pronounced activation by pleasant stimuli in healthy subjects (linear trend, $F(1,14)= 18.67$, $p< .001$) compared to low-ELS patients, who tended to show a dominant modulation by arousal (quadratic trend, $F(1,14)= 2.97$, $p= .1$), and high-ELS patients, who exhibited neither arousal nor valence modulation (quadratic trend, $F(1,14)= 1.91$, $p= .19$; linear trend, $F< 1$). Stronger activation by pleasant stimuli in this time interval was related to later ELS-onset across subjects in both sessions (1st session: $r= .37$, 2nd session: $r= .34$, $p< .05$), but there were no significant correlations with ELS-severity. Neither within the patient group nor within the diagnostic subgroups, relationships between cortical responses to pleasant stimuli and severity of illness were significant.

Right-hemispheric dominance of dipole activity was verified for all subjects around 200 ms (120-170 ms or 170-250 ms, see Tables 7 and 8 for Hemisphere effects). For the 170-250 ms component, an Emotion x Hemisphere interaction (1st session, $F(2,86)= 4.66$, $p< .05$, $\varepsilon= .93$; 2nd session, 120-170 ms, $F(2,82)= 4.09$, $p< .05$; 170-250 ms, $F(2,82)= 3.60$, $p< .05$) confirmed that the described modulation of estimated neural activity by emotional stimulus content was confined to the right hemisphere.

Table 8. Statistical effects of ELS (high-ELS vs low-ELS patients vs comparison), Emotion (pleasant vs unpleasant vs neutral stimuli) and Hemisphere (left vs right) on dipole activity in the four latency windows, separately for the two sessions.

	1st session			
	70-120ms	120-170ms	170-250ms	250-349ms
ELS	$F(2,42)=2.22$	$F(2,42)=1.79$	$F(2,42)=4.29$*	$F(2,42)=1.66$
Emotion	$F(2,84)=1.40$	$F(2,84)=9.39$***	$F(2,84)=3.13$*	$F(2,84)=15.22$***
Hemisphere	$F(1,42)=2.98^{+}$	$F(1,42)=6.72$*	$F(1,42)=13.16$***	$F<1$
ELS x Emotion	$F(4,84)=1.98$	$F(4,84)=1.34$	$F(4,8)=2.44$*	$F(4,84)=3.02$*
ELS x Hemisphere	$F(2,42)=1.36$	$F(2,42)=2.78^{+}$	$F(2,42)=2.65^{+}$	$F<1$
Emotion x Hemisphere	$F<1$	$F(2,84)=1.59$	$F(2,84)=3.45$*	$F<1$
ELS x Emotion x Hemisphere	$F<1$	$F<1$	$F(4,84)=1.84$	$F(4,84)=1.77$
	2nd session			
	70-120ms	120-170ms	170-250ms	250-349ms
ELS	$F(2,40)=3.14$*	$F(2,40)=2.30$	$F(2,40)=5.70$**	$F(2,40)=1.23$
Emotion	$F(2,80)=5.00$**	$F(2,80)=3.23$*	$F(2,80)=1.33$	$F(2,80)=8.14$**
Hemisphere	$F<1$	$F(1,40)=4.88$*	$F(1,40)=5.18$*	$F(1,40)=2.19$
ELS x Emotion	$F(4,80)=3.14$*	$F<1$	$F<1$	$F(4,80)=3.20$*
ELS x Hemisphere	$F<1$	$F<1$	$F<1$	$F(2,40)=1.34$
Emotion x Hemisphere	$F(2,80)=1.10$	$F(2,80)=4.15$*	$F(2,80)=1.89$	$F(2,80)=1.32$
ELS x Emotion x Hemisphere	$F<1$	$F(4,80)=1.35$	$F(4,80)=1.60$	$F(4,80)=2.38^{+}$

*: $p<.05$, **: $p<.01$; ***: $p<.001$; $^{+}$: $p<.1$, F-ratios without superscript: $p>.1$

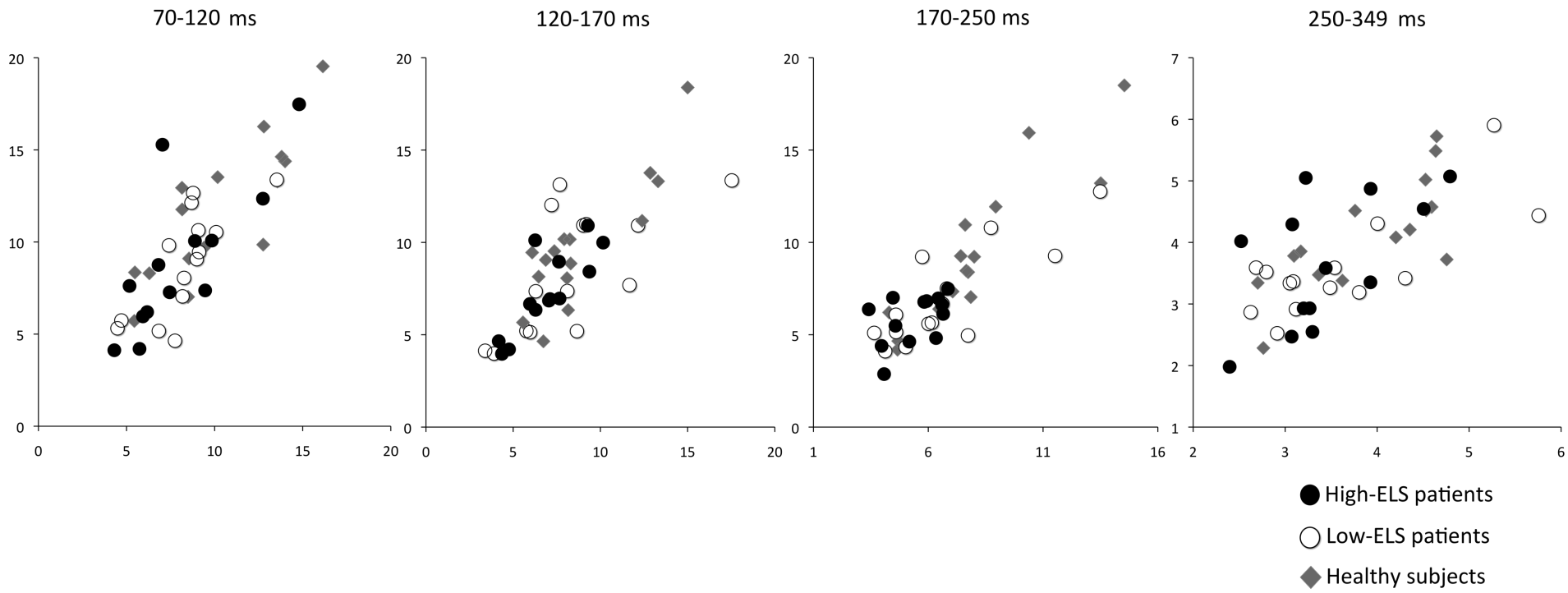

Figure 6. Mean estimated source activity in pA/mm (across stimulus categories and hemisphere) in the 1st session (ordinate) is plotted against mean activity in the 2nd session (abscissa) for each subject separately for the four components (filled circles: high-ELS patients, open circles: low-ELS patients, grey squares: healthy subjects).

Stability of ELS effects

Figure 6 illustrates high intraindividual correlation, that is, stability of cortical responses to emotional stimuli across the two measurements. Pearson correlation coefficients were significant for the four components and the three stimulus categories (70-120 ms: r= .70 to r= .86; 120-170 ms: r=.67 to r= .81; 170-250 ms: r= .76 to r= .85; 250-349 ms: r= .36 (p< .05) to r= .73, all p< .01), indicating similarity of response patterns across time. The ANOVA including the within-subjects factor Time disclosed larger early (70-120 ms) dipole activity in the 2nd compared to the 1st session in all subjects (F(1,40)= 9.23, p< .01, ε= 1.0). In healthy subjects, larger activity in the 2nd session was also found at 170-250 ms (Time x Group, F(1,40)= 4.26, p< .05; Time, F(1,40)= 10.82, p< .01; ε= 1.0). Stability of ELS effects across time can be taken also from similarity of effects across the two sessions, as summarized in Tables 7 and 8. Exceptions from similarity have to be noted: (1) in the 2nd session dampened dipole activity and group-specific emotional modulation of dipole activity in high-ELS patients became prominent already in the earliest time window 70-120 ms after stimulus onset, which was not the case in the 1st session (see Table 8, 2nd session: main effect ELS, F(2,40)= 3.14, p< .05, ELS x Emotion, F(4,80)= 3.14, p< .05, Emotion, F(2,80)= 5.0, p< .01). The arousal modulation was most pronounced in high-ELS patients (quadratic trend (F(1,12)= 5.27, p< .05). Low-ELS patients did not show any modulation by stimulus content (quadratic trend F(1,14)= 1.78, p= .20). The interaction Group x Emotion in Table 7 (F(2,82)= 6.34, p< .05; Emotion, F(2,82)= 7.58, p< .01, ε= 0.97) may be explained as a related effect. (2) In contrast – or as a consequence – emotional modulation at 170-250 ms was weaker in the 2nd compared to the 1st session, so that interactions of Emotion with ELS or Hemisphere were no longer significant (see Table 8). Since the Emotion x Hemisphere effect, which was significant at 170-250 ms in the 1st session, became significant for the

earlier 120-170 ms window in the 2nd session (see Table 8), one may again speculate that modulation started slightly earlier in the 2nd compared to the 1st session. (3) Emotional modulation in the two patient groups (high- and low-ELS) at 250-349 ms were reverse in the 2nd relative to the 1st session: high-ELS patients displayed an arousal effect (quadratic trend $F(1,12)= 5.07$, $p< .05$), whereas low-ELS patients did not show any modulation (quadratic trend $F(1,14)= 1.13$, $p= .31$) in the 2nd session.

ELS, current life stress and cortical activity

Subjects reported 5.3±2.9 life events on average for the preceding six months in the 1st and 5.2±2.4 life events in the 2nd session (see Table 9). High-ELS patients reported a higher number of life events than low-ELS patients and healthy subjects. The number of reported life events did not differ across the 8 months that separated the two sessions

Table 9. Life events and their experienced strain during the six month preceding the 1st and 2nd session.

	1st session			2nd session		
	High-ELS patients	Low-ELS patients	Healthy subjects	High-ELS patients	Low-ELS patients	Healthy subjects
Number life events (M±SD)	6.67±3.06	5.37±2.75	3.87±2.33	6.38±2.96	5.13±2.00	4.27±1.94
Group comparison	$chi^2(2)=7.19$, $p<.05$			$chi^2(2)=4.67$, $p<.10$		
high-ELS vs healthy Ss	$U=51.5$, $p<.05$			$U=53.5$, $p<.05$		
low-ELS vs healthy Ss	$U=78.5$, $p<.10$			$U=82.0$, $p=.22$		
high- vs low-ELS	$U=88.5$, $p=.21$			$U=74.5$, $p=.28$		
Subjective strain (M±SD)	2.77±0.92	2.45±0.65	1.51±0.87	2.58±1.01	2.28±0.85	1.89±0.70
Group comparison	$chi^2(2)=16.84$, $p<.001$			$chi^2(2)=6.89$, $p<.05$		
high-ELS vs healthy Ss	$U=24.0$, $p<.001$			$U=46.5$, $p<.05$		
low-ELS vs healthy Ss	$U=47.5$, $p<.01$			$U=68.5$, $p<.10$		
high- vs low-ELS	$U=72.0$, $p<.10$			$U=71.0$, $p=.22$		

(total sample: Wilcoxon $T= 447$, $p= .75$; high-ELS patients, $T= 45.5$, $p= 1.0$; low-ELS patients, $T= 47$, $p= .46$; healthy subjects, $T= 52$, $p= .65$). Participants subjectively experienced life events as only mildly stressful (M±SD 2.2±1.0 on the 5-point Likert scale). Still, high-ELS patients perceived the experienced events as more stressful than

low-ELS patients and healthy subjects. Within the eight month, subjective experience of life events as more stressful did not change (total sample: T= 396.5, p= .66; high-ELS patients: T= 25, p= .27, low-ELS patients: T= 49.5, p= .85, healthy subjects T= 37.5, p= .20). Across subjects, lower dipole activity was not related to the number of stressful events but to the subjective experience of life events as more stressful at 170-250 ms (1st session, r_s= -.37, 2nd session, r_s= -.28, p= .07) and at 250-349 ms (1st session, r_s= -.36, p< .05).

Discussion

The present study explored long-term effects of early life stress on cortical affective processing modes, the stability of these effects across an eight-month interval, and their relation to current life stress in psychiatric patients. Life long effects of early life experiences on physiological and psychological functions have been verified in animal studies (Plotsky et al., 2005; Spinelli et al., 2009). In humans, they have been inferred from the relationship between early life stress, abnormal HPA-axis functioning, and severity of disorder in a subgroup of depressive patients (Bradley et al., 2008; Heim et al., 2003; 2008). Longitudinal or prospective studies in humans (e.g. Landrigan et al., 2008) disclosed an effect of additional stressful experiences later in development on the relationship between childhood stress and adult depression (e.g. Hazel et al., 2008) and effects of early abuse on lasting psychological distress (Lindhorst et al., 2009).

Comparing subgroups of patients with high and low ELS, present results confirmed a relationship between early life stress and abnormal cortical activity to affective pictorial stimuli. As reported for a slightly different stimulation design (Weber et al., 2009), higher ELS varied with dampened cortical responses to emotional stimuli. Lasting effects of childhood experiences were further suggested by the temporal

stability of altered cortical affective processing over about eight months. Temporal stability of cortical responses to affective visual stimuli has been documented across a period of ten days (Codispoti, Ferrari, & Bradley, 2007). We are not aware of other studies examining stability of cortical responses and their relationship to events earlier in life across a similar period of time. The present results suggest the challenging hypothesis that the stability of ELS effects on cortical processing modes may be considered parallel to the lifelong effects reported in animal studies. This needs to be substantiated in further studies.

Dampened cortical responses to emotional stimuli seem intriguing, as one might expect more pronounced responses to emotionally arousing stimuli as a consequence of a sensitizing effect of ELS. Stress sensitization as a result of ELS has been demonstrated for endocrinological responses (e.g. Charmandari et al., 2003; Danese et al., 2008; Heim et al., 2008) and sensitivity to further life stress (e.g. Espejo et al., 2007; Matz, Pietrek, & Rockstroh, 2009; Wright et al., 2009). In patients suffering from PTSD, early enhanced frontal activation in response to emotional stimuli has been found in MEG studies (Borgelt, Odenwald, Ruf, Elbert, & Kissler, 2009; Junghöfer et al., 2003). Functional MRI studies found augmented subcortical activity in the amygdala and insula (e.g. Etkin & Wager, 2007; Morey, Petty, Cooper, Labar, & McCarthy, 2008). On the other hand, PTSD patients also exhibited reduced activation in other regions associated with the experience and regulation of emotion like anterior cingulate and prefrontal structures (Etkin & Wager, 2007). However, these patients experienced traumatic stress in late adolescence or adulthood and intensity as well as timing of stress may modulate cortical affective processing in different ways (Lupien et al., 2009). It seems also possible that dampened cortical activation reflects stress-related functional brain changes, as Tomoda and colleagues (2009) found reduced gray matter volume in primary and secondary

visual cortices in subjects with a history of childhood sexual abuse. Moreover, white matter tract abnormalities indicating alterations in neural pathways have been associated with parental verbal abuse (Choi et al., 2009). While cortical activity can be reliably determined with the localization methods used in the present study, it is difficult to draw conclusions on (possibly enhanced) subcortical activation and on alterations in neuroanatomical pathways that might be related to dampened activation in the visual cortex. Finally, dampened cortical responses to emotional stimuli (Moratti et al., 2008) and delayed and reduced P300 responses to target stimuli (Kemp et al., 2009) have been reported for depressive patients. These results have been interpreted as an impairment of attention allocation. As depressive patients with high ELS constituted a substantial subgroup of the present sample, diagnosis-specific or –related clinical aspects might have resulted in the dampened response to pleasant stimuli around 300 ms. Although available clinical variables (number of hospitalizations and number of comorbid diagnoses, which may roughly point to severity and duration of illness) were not related to the reported cortical activity, we cannot rule out the impact of disorder-specific aspects. The present sample may also reflect the effects of ELS on vulnerability for and course of MDD in a subgroup of (genetically) predisposed individuals, as modeled by Heim and colleagues (2008). Specification of the distinct effects of the two factors, depression and ELS, requires larger and more balanced samples than available for the present study. However, in the light of assumptions of gene x environment interactions, isolated main effects of either ELS or diagnosis seem unlikely (e.g. Bradley et al., 2008; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005; Turkheimer, 2000).

The hypotheses, that ELS influences vulnerability for and reactivity to current stressors in adulthood, and that emotional processing might contribute to this lasting

stress-sensitivity was partly supported: ELS predicted the perception of current life events as more stressful in the present adult sample. Cortical responses to emotional stimuli were related to ELS, but less prominent to current stress-sensitivity. Thus, although present results may be considered a preliminary indication that affective cortical processing modes may constitute a mediating factor between ELS and psychological dysfunctions in adulthood, the mediating pathway remain to be specified in future studies for larger samples. Moreover, it should be emphasized that the reported correlations do not bear causal relationships.

The present design addressed specific aspects of cortical affective processing modes. Posterior activity in the latency range 150 – 300 ms after stimulus onset has been related to automatic perceptual processing and attention capture by emotional stimuli (Codispoti et al., 2007; Junghöfer et al., 2006; Lang et al., 1998; LeDoux, 2000; Schupp et al., 2003-2006). Despite of an overall reduced response, ELS did not substantially influence the modulation of activity by the arousal and valence of stimuli around 200 ms. Around 300 ms, high-ELS patients did not show the 'normal' response to pleasant stimuli in the first assessment, whereas arousal modulation was found in the second assessment. This suggests reduced modulation by stimulus valence. Taken together, ELS differentially affected activity in early and late time intervals that are assumed to reflect distinct states in visual emotional processing (Peyk et al., 2008). Results suggest a dampened though still sufficiently functioning automatic attention capture by emotional stimuli.

The small and unbalanced samples of the present study are certainly a major methodological shortcoming and limit the conclusions. Longitudinal studies bear the problem of drop outs and the repeated study of selected samples even amplified this problem, resulting in subsamples too small to adequately evaluate the interaction of ELS

and disorder-specific influences on brain activation. Moreover, modulation of cortical responses by emotional arousal of stimulus content in healthy subjects of the present study was confined to an earlier and smaller latency window (120-170 ms) compared to results reported in the literature for normal subjects (e.g. Peyk et al., 2008, 2009). The present healthy sample differed from those 'normal' subject groups with respect to age, as subjects were recruited to be comparable to the patient samples. Moreover, the small sample size may have increased variability, and thereby reduced significant effects.

Despite of these limitations, the present results point to lasting effects of adverse childhood experiences on cortical processing modes and stress-sensitivity. Further validation of a potential specific impairment of evaluation of the intrinsic significance of emotional stimuli should improve our understanding of the relationship between adverse experiences early in life and the course of mental illness.

2.3 Early life stress and psychiatric disorder modulate cortical responses to affective stimuli – a replication

The cortical manifestation of affective processing was examined in two protocols, one using a slow (660 ms with a 700 to 900 inter stimulus interval (ISI)) and the other a fast (349 ms without ISI) presentation rate of affective stimuli. First results obtained with the slow presentation protocol have been published in Weber et al. (2009). The present report includes data of the subsample of subjects who participated in the longitudinal study of this thesis. Again, patients with high ELS were expected to exhibit dampened cortical activation in response to affective visual stimuli in occipital-parietal-temporal cortical areas around 200 ms after stimulus onset.

Methods

Participants

MEG recordings of the first and second session were available from 15 high ELS patients (8 female, mean age 41.6 ± 12.2), 15 low-ELS patients (3 female, mean age 36.3 ± 13.1) and 15 healthy subjects (7 female, mean age 39.9 ± 17.0 years; see Table 10 for demographic and clinical information). 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. At the time of the first session of the present study, all patients were inpatients at the local center of psychiatry, whereas at the time of the second session the majority of patients had been released. Thus, most of them showed improvement of their clinical status. Exceptions were long-term admissions of 10 patients on the forensic ward (3 with diagnoses of drug addiction, 4 with schizophrenia and 3 patients with BPD-diagnosis). As participants

of the present study were not diagnosed again in the second session, the presently reported diagnoses refer to lifetime diagnoses. Within the patient sample, ELS was related to the number of comorbid diagnoses (r_s= .65, p< .0001), which served as a measure of severity of disorder.

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 37 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.

Design and Procedure

Processing of the affective stimuli was evaluated via picture ratings and electromagnetic cortical responses. Based on the normative ratings of emotional valence and arousal, as well as analysis of physical picture parameters, 300 colored photographs from the International Affective Picture System (IAPS; Center for the Study of Emotion and Attention, 2004) were selected and assigned to three categories of 75 high-arousing pleasant, 75 high-arousing unpleasant and 150 low-arousing neutral stimuli. Neutral pictures were represented twice as often as pleasant and unpleasant pictures to allow comparisons between affective (pleasant and unpleasant together) and neutral stimuli. For comparisons between the three valence categories, selection of the odd 'neutral' trials served to balance trial numbers. All pictures involved social scenes and were

matched for size, contrast, and brightness. Pleasant and unpleasant pictures did not differ in rated arousal[4].

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 a pseudorandom order. Presentation order was controlled for transition probabilities between the three stimulus categories and no more than two

Table 10. Demographic and clinical data for the three ELS-groups at both sessions.

	1st session			2nd session		
	High-ELS patients	Low-ELS patients	Healthy subjects	High-ELS patients	Low-ELS patients	Healthy subjects
Number of subjects	15	15	15	15	15	15
Gender (female/male)	8/7	3/12	7/8	8/7	3/12	7/8
Group comparison	$chi^2(2)=3.89$, $p=.14$			$chi^2(2)=3.89$, $p=.14$		
Age (M±SD)	41.6±12.2	36.3±13.1	39.9±17.0	42.7±12.3	37.1±13.2	40.7±16.7
Group comparison	$F(2,42)=0.55$, $p=.58$			$F(2,42)=0.59$, $p=.56$		
Diagnosis+						
MDD	8	3		8	3	
Schizophrenia	2	7		2	7	
DA	3	3		3	3	
BPD	2	2		2	2	
Group comparison (High- vs. low-ELS)	$chi^2(3)=5.05$, $p=.17$			$chi^2(3)= 5.05$, $p=.17$		
Comorbid diagnoses (M±SD)	1.5 ± 0.8	0.5 ± 0.6		1.5 ± 0.8	0.5 ± 0.6	
Hospitalizations (M±SD)	6.5 ± 6.2	3.9 ± 2.5		6.5 ± 6.2	3.9 ± 2.5	
Early life stress (M±SD total score)	311.5±70.0	44.5±36.3	32.0±34.7			

+: Diagnoses: MDD: Major depressive disorder; DA: Drug addiction; BPD: Borderline personality disorder.

[4] 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 was validated by valence and arousal ratings of 30 students using the Self Assessment Manikin (Bradley & Lang, 1994).

repetitions of the same picture category were allowed. Timing and sequence of stimulus presentation were controlled using Presentation software (Neuro-behavioral Systems, Albany®, CA, USA). Participants were asked to keep their eyes focused on a small central fixation cross preceding each picture and to attend to the picture series carefully without any additional task. The two picture series were presented without break. Presentation of the total 600 stimuli lasted for about 15 minutes.

After the MEG recording, each participant evaluated the valence and emotional arousal of 75 IAPS pictures, 25 from each category, taken from the set of pictures presented during the MEG recording. Pictures were presented without time limit in a randomized order, and ratings were obtained with a computerized version of the Self Assessment Manikin (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, respectively. Ratings were not available for one low-ELS patient and one healthy subject.

Data Acquisition and Analysis

Data acquisition and preprocessing was identical to the procedure used for the data obtained with the fast presentation protocol (see 2.2). Following preprocessing, event-related fields were averaged across trials separately for each subject and stimulus category. Of the 150 trials of each stimulus category, 141 artifact-free trials were available on average for low-ELS patients, 140 trials for high-ELS patients and 146 trials for healthy subjects in the 1st session (group difference n.s.). A similar number of trials was available in the 2nd session (141 trials for low-ELS patients, 141 trials for high-ELS patients and 145 trials for healthy subjects (difference n.s.)). Each trial was referenced to a 100 ms baseline before stimulus onset. Again, the L2-Minimum-Norm-Pseudoinverse was used for inverse modeling, providing minimum norm estimates

(MNE) of cortical activity (Hamalainen & Ilmoniemi, 1994; Hauk, 2004; Hauk, Keil, Elbert, & Müller,2002).

In order to replicate findings from the initial sample and to probe temporal stability, statistical evaluation of group and stimulus effects followed the procedure reported in Weber et al. (2009). For the sake of clarity, this description will be repeated here: A point-wise repeated measures analysis of variance (ANOVA) with the within-subjects factor Emotion (comparing pleasant, unpleasant and neutral stimuli) carried out with healthy subjects only had determined a time window of differential brain activity 160-210 ms after stimulus onset for left and right occipital-parietal-temporal regions (Figure 7). To avoid false positives, significant effects had been considered only when they included a minimum of 21 continuous data points (32 ms) and when two adjacent representative dipoles had shown the effect. As MEG activity in this ROI seemed comparable to the early posterior negativity (EPN) described in EEG studies (Peyk et al., 2008), it was labeled as EPN for the sake of simplicity. The same ROI and time window was used in the present longitudinal study.

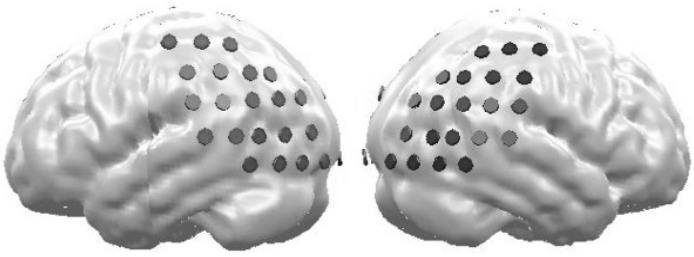

Figure 7. Schematic positions of modeling sources used for statistical analyses. For illustrative purposes, the dipoles forming the regions of interest (ROIs) are superimposed on the left- and right-sided view of a schematic cortical surface for activity 160-210 ms after stimulus onset. Optimizing tests for laterality central model sources belonging to both groups have not been considered.

Mean ROI activity was submitted to ANOVAs containing the within-subjects factors Emotion (pleasant vs. neutral vs. unpleasant), Hemisphere (left ROI vs. right ROI), and, in separate analyses, Group (patients vs. comparison subject) or ELS-Group

(low ELS vs. high ELS vs. healthy subjects). Significant main effects or interactions were gradually decomposed with orthogonal polynomial contrasts and follow-up pair-wise comparisons corrected with Bonferroni. Statistical significance for all tests was evaluated at the .05 level. Possible violations of the homogeneity of covariance assumption were corrected with the Huynh-Feldt epsilon (statistical reports include uncorrected degrees of freedom and epsilon-corrected p-values). In order to control for potential gender effects on cortical activity (Sabatinelli et al., 2004), an additional ANOVA with the within-subjects factors Emotion and Hemisphere and the between-subjects factor Gender was accomplished. Neither in the first nor in the second session significant main effects of Gender or interactions with Emotion or Hemisphere were found. Thus, results will be reported for men and women together. Temporal stability of cortical activity across assessments was explored using Pearson correlations (r) and an additional exploratory ANOVA including the within-subjects factor Time (comparing dipole activities of the 1st and the 2nd session). Effects of ELS and current life stress on cortical activity were probed with Spearman correlations (r_s).

Ratings of the valence and arousal of the stimuli were examined in two repeated-measures ANOVAs with the within factor Valence or Arousal, respectively, comparing pleasant, neutral and unpleasant stimuli. Orthogonal trends captured valence (pleasant vs. unpleasant) as a linear trend and arousal (pleasant and unpleasant vs. neutral) as a quadratic trend, reflecting a priori hypotheses about critical dimensions of emotion (e.g., Lang, Bradley, & Cuthbert, 1990).

Results

Processing of emotional stimuli is modified by psychiatric disorder and ELS

Across stimulus categories and assessments, cortical activity was smaller in patients than in healthy subjects (Group: 1st session: $F(1,43)= 2.92$, $p< .1$; 2nd session: $F(1,43)= 11.87$, $p< .01$; see Table 11 and Figures 8a and 8b). Within the patient sample, patients with high ELS displayed smaller amplitudes than those with low ELS (ELS-group 1st session: $F(2,42)= 3.00$, $p< .1$; 2nd session: $F(2,42)= 8.11$, $p< .01$). Higher ELS-scores were related to lower mean EPN activity (across stimulus conditions and hemispheres; 1st session: $r_s= -.53$. $p< .001$; 2nd session $r_s= -.60$, $p< .0001$). Within patients, mean EPN activity seemed to be related to severity of disorder, as indicated by the relationship to the number of comorbid diagnoses (1st session: $r_s= -.43$, $p< .05$; 2nd session: $r_s= -.50$, $p< .01$). Mean EPN amplitude and number of hospitalizations were not significantly correlated.

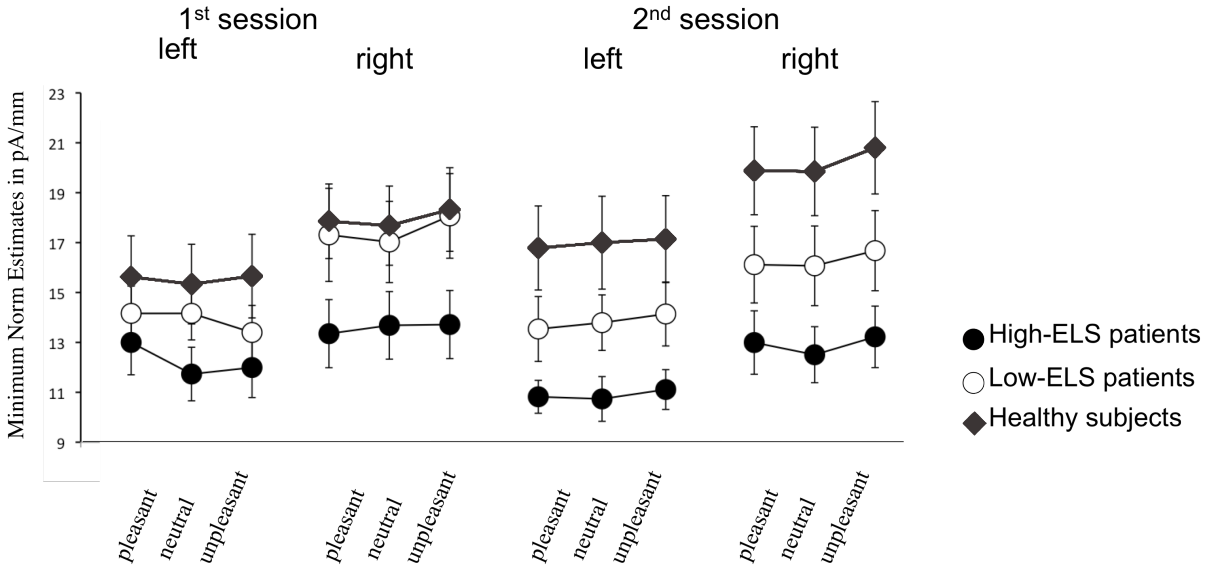

Figure 8a. Estimated source activities in both sessions are plotted separately for emotional stimulus content (pleasant – neutral – unpleasant), group (filled circles: high-ELS patients, open circles: low-ELS patients, grey squares: healthy subjects) and left and right hemisphere. Dipole activity expressed as minimum norm estimates, Mean ± Standard Error in pA/mm.

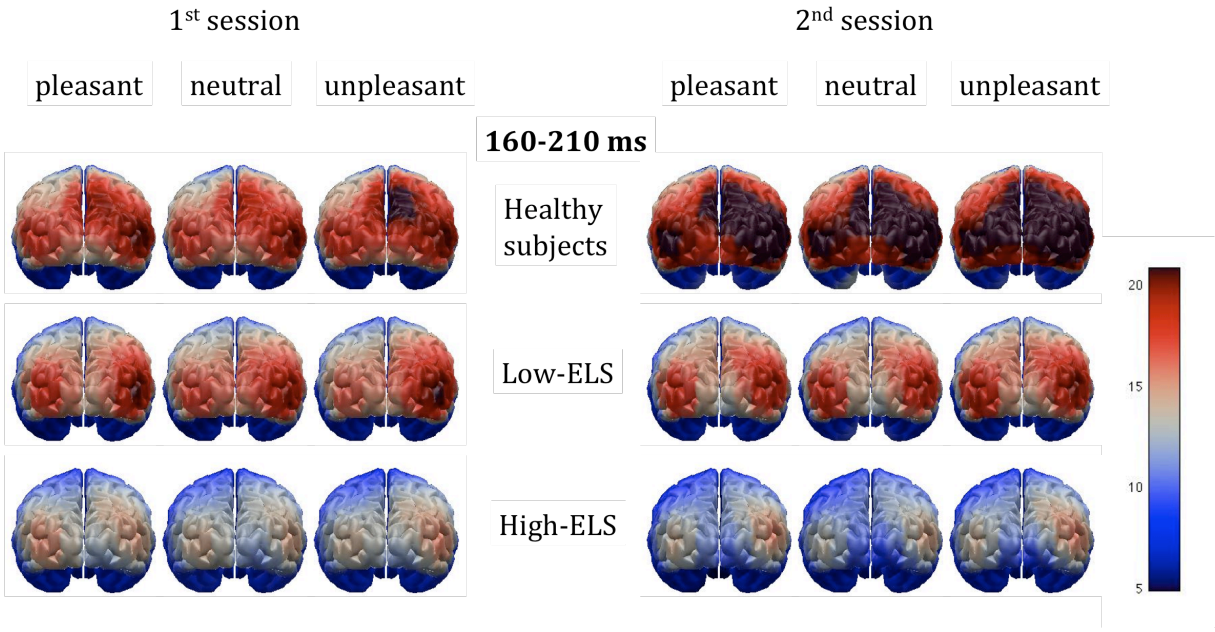

Figure 8b. Estimated source activities in the 1st and 2nd session superimposed on the back view of a schematic cortical surface for 160-210 ms after stimulus onset separately for emotional stimulus content (pleasant – neutral – unpleasant) and group (high-ELS patients, low-ELS patients, healthy subjects). Dipole activity expressed as minimum norm estimates in pA/mm.

In the first session, cortical activity was not significantly modulated by the emotional stimulus content (Emotion: $F(2,84)= 1.25$, $p= .29$, $\varepsilon= 1.0$; Emotion x Hemisphere: $F(2,84)= 3.83$, $p< .05$, $\varepsilon= 1.0$; Emotion right Hemisphere: $F(2,84)= 2.28$, $p= .11$, $\varepsilon= 1.0$). However, a marginal quadratic trend suggested modulation by stimulus arousal ($F(1,42)= 2.83$, $p=.1$; explaining 99% of the variance). In the second session a significant main effect Emotion confirmed affective modulation by stimulus valence ($F(2,84)= 3.68$, $p< .05$, $\varepsilon= 1.0$). A linear trend explaining 70% of the variance ($F(1,42)= 5.92$, $p< .05$) indicated that activity was most pronounced in response to unpleasant stimuli.

Affective modulation was similar across groups (patients vs. controls, Emotion x Group: $F<1$) and ELS-groups (Emotion x ELS-group: $F<1$) in both sessions. In both sessions and across subjects, activity was stronger in the right compared to the left

hemisphere (1st session: $F(1,42)= 6.17$, $p< .05$, $\varepsilon= 1.0$; 2nd session: $F(1,42)= 8.17$, $p< .01$, $\varepsilon= 1.0$).

ELS effects are stable across time

Stability of cortical responses to emotional stimuli across the two sessions was evaluated by Pearson correlations. Coefficients were significant for the three stimulus categories across all subjects (pleasant: r= .80; neutral: r= .81; unpleasant: r= 1.0; all p< .001), indicating similarity of response patterns across time. The ANOVA including the within-subjects factor Time disclosed a significant Time x ELS-group ($F(2,42)= 4.27$, p< .05) and a significant Time x Group ($F(1,43)= 8.55$, p< .01) interaction: Healthy subjects exhibited more pronounced overall activation in the second compared to the first session ($F(1,14)= 9.74$, p< .01, $\varepsilon= 1.0$), whereas both patient groups showed similar activation across sessions (low-ELS: F< 1; high-ELS: $F(1,14)= 1.60$, p= .23, $\varepsilon= 1.0$).

Table 11. Statistical effects of Group (patient vs comparison) and ELS (high-ELS vs low-ELS patients vs comparison), Emotion (pleasant vs unpleasant vs neutral stimuli) and Hemisphere (left vs right) on dipole activity, separately for the two sessions.

	1st session	2nd session		1st session	2nd session
Group	$F(1,43)=2.92^{+}$	$F(1,43)=11.87$**	ELS	$F(2,42)=3.00^{+}$	$F(2,42)=8.11$**
Emotion	$F(2,86)=1.34$	$F(2,86)=3.60$*	Emotion	$F(2,84)=1.25$	$F(2,84)=3.68$*
Hemisphere	$F(1,43)=5.48$*	$F(1,43)=8.38$**	Hemisphere	$F(1,42)=6.17$*	$F(2,42)=8.17$**
Group x Emotion	$F<1$	$F<1$	ELS x Emotion	$F<1$	$F<1$
Group x Hemisphere	$F<1$	$F<1$	ELS x Hemisphere	$F<1$	$F<1$
Emotion x Hemisphere	$F(2,86)=2.36^{+}$	$F<1$	Emotion x Hemisphere	$F(2,84)=3.83$*	$F<1$
Group x Emotion x Hemisphere	$F<1$	$F<1$	ELS x Emotion x Hemisphere	$F(2,84)=1.69$	$F<1$

*: $p< .05$, **: $p< .01$; ***: $p< .001$; $^{+}$: $p< .1$, F-ratios without superscript: $p> .1$

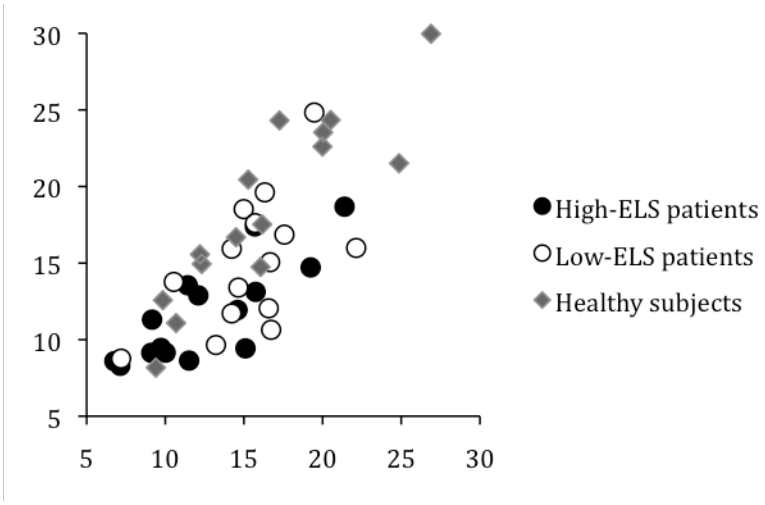

Figure 9. Mean estimated source activity in pA/mm (across stimulus categories and hemisphere) in the 1st session (ordinate) is plotted against mean activity in the 2nd session (abscissa) for each subject separately (filled circles: high-ELS patients, open circles: low-ELS patients, grey squares: healthy subjects).

Valence and Arousal Ratings

Means and standard deviations of value and arousal ratings are summerizd in Table 12. Two repeated-measures ANOVAs with the within-subjects factors Valence and Arousal, respectively, and the between-subjects factor ELS-Group yielded a significant main effect Valence ($F(2,82)= 280.7$, $p< .001$, $\varepsilon= 1.0$), which was carried by a linear trend explaining 89% of the variance ($F(1,41)= 419.0$, $p< .001$; quadratic trend $F(1,41)= 77.7$, $p< .001$). Pleasant stimuli received the highest, unpleasant stimuli the lowest ratings on the 9-point likert-scale. This pattern did not differ between ELS groups (main effect ELS-group and interaction ELS-group x Valence $F< 1$). Arousal ratings were carried by a quadratic trend explaining 86% of the variance ($F(1,41)= 163.2$, $p< .001$; linear trend $F(1,41)= 21.8$, $p< .001$; main effect Arousal $F(2,82)= 85.2$, $p< .001$, $\varepsilon= .94$) with pleasant and unpleasant stimuli receiving higher ratings than neutral stimuli. Again, ELS-groups did not differ (interaction ELS-group x Arousal $F< 1$).

Table 12. Mean and standard deviation of valence and arousal ratings for each ELS group

Group (N)	Valence			Arousal		
	pleasant	neutral	unpleasant	pleasant	neutral	unpleasant
healthy subjects (14)	5.2 (1.2)	3.7 (1.3)	6.6 (0.8)	6.5 (0.7)	5.6 (0.6)	2.4 (0.7)
low ELS patients (15)	4.6 (1.7)	2.7 (1.2)	5.8 (1.6)	6.8 (1.0)	5.8 (1.0)	2.3 (0.8)
high ELS patients (15)	5.5 (1.1)	3.1 (1.1)	6.4 (1.8)	6.3 (1.7)	5.8 (0.7)	2.3 (1.1)
total (44)	5.1 (1.4)	3.1 (1.3)	6.3 (1.5)	6.6 (1.2)	5.7 (0.8)	2.3 (0.9)

Discussion

The present study evaluated long-term effects of ELS on the cortical processing modes of affective stimuli and their stability across an 11-month interval. As reported by Weber and colleagues (2009) for the original sample, higher ELS varied with dampened cortical responses to emotional stimuli. Stability of results across a period of 11 month suggests lasting effects of ELS on cortical affect processing. Stability of effects was further indicated by the lack of Emotion x Group or Emotion x ELS-group interaction across the assessments. Thus, in patients with a psychiatric disorder ELS seems to affect overall cortical responses to pictorial stimuli that vary in their emotional content, rather than modulation of cortical activity by the arousal or valence content of the stimuli.

However, present results for healthy subjects differed from the literature (e.g. Peyk et al., 2008, 2009) where modulation of cortical responses by emotional arousal of stimulus content has been reported. In the first session of the present study, cortical responses to emotional stimuli were only marginally modulated by arousal. In the second session, no modulation by arousal but modulation by valence was evident. Potential reasons may be found in sample characteristics, as healthy subjects in the

present study differed from 'normal' subject groups with respect to age. However, normative studies have to evaluate, whether age constitutes a crucial variable affecting EPN amplitude. Another reason for divergent effects may be the smaller size of the reanalyzed sample, which might have increased variability, thereby reducing the significance of effects. Data analysis was identical to the study by Weber et al. (2009), which found significant arousal modulation of cortical responses in a sample of 50 patients and 20 healthy subjects.

Valence and arousal ratings of the present sample correspond to normative data available for the IAPS (Lang et al., 2008) and are in line with the literature on the bivariate motivational model of emotion (Lang et al., 1998). Patients and healthy subjects similarly rated stimuli as pleasant or unpleasant. Thus, abnormal cortical responses to affective stimuli do not necessarily predict abnormal behavioral responses. Discrepancies between reduced affective modulation of early cortical responses and normal ratings of stimulus valence have been reported before (Rockstroh et al., 2006). In schizophrenia patients this has been attributed to compensatory functions, which allow normal processing of emotional stimuli whenever they are presented without time constraints or workload, despite indications of abnormal automatic processing. This explanation might hold as well for the present sample.

Present results further substantiate findings from the RSVP protocol (see 2.2), again demonstrating a dampened though still sufficiently functioning automatic attention capture by emotional stimuli in psychiatric patients with high ELS.

3 General discussion

The present thesis examined the hypotheses that stress sensitivity, negative affect and cortical processing of affective stimuli vary as a function of adverse childhood experiences in psychiatric patients. Therefore, patients were assigned to a high- and a low-stress group based on their retrospectively reported childhood stress load. In a quasi-longitudinal design, sensitivity for current stress, stability of negative affect and cortical affect processing were examined in three assessments across a period of about 1.5 years. Based on animal and human studies that have suggested life-long effects of early life stress, we expected more pronounced stress sensitivity and higher ratings of negative affect in those patients who had suffered from early life stress. According to findings from Weber and colleagues (2009), we further expected dampened cortical activation in response to visual stimuli varying in their emotional content. Confirming these hypotheses would indicate that childhood stress load modulates vulnerability of psychiatric patients for further stressful experiences, or even the course of the disorder itself. The stability of early life stress effects on the reactivity to current life stress, on measures of affect and psychopathology and on cortical processing of affective pictures across a period of altogether 1.5 years was considered as supporting the assumption of long lasting effects of childhood experiences.

Supplementary, the present thesis aimed at identifying potential mediating factors that may contribute to explain the frequently reported link between ELS and psychopathology. In addition to early life stress itself, negative affect and cortical information processing (in particular of emotional information) have been discussed as potential mediators of stress effects on the course of illness in (genetically or otherwise) vulnerable individuals. Assuming that early life stress alters affect and affective processing (cortical and behavioral) throughout life, changes in negative affect and

measures of cortical affect processing should be visible across time despite of changes in clinical status in the course of treatment. Although the present quasi-longitudinal design did not allow to satisfactorily demonstrate a mediating pathway, confirming a stable relationship between ELS and the proposed factors would justify a more elaborate evaluation of their mediating role for the development of psychopathology.

Present results showed a lasting impact of early life stress on the *subjective experience of current life stress* in psychiatric patients. High-ELS patients experienced the most subjective strain in response to current life events and ELS scores were strongly correlated with stress experience (Hypothesis A). Over time and despite of clinical improvement, ELS became a stronger predictor of subjective strain experienced by current life events and other measures of stress sensitivity than diagnosis. This suggests a persistently elevated reactivity to current life stress that might affect the course of a psychiatric disorder (Hypothesis D). This corresponds to findings by Heim and colleagues (2008) that demonstrated effects of ELS on the vulnerability for and course of major depressive disorder in a subgroup of (genetically) predisposed individuals and also supports the assumption that early life stress constitutes a mediating factor for stress vulnerability in psychiatric disorders.

Negative affect was elevated in patients with high ELS throughout the three assessments (Hypothesis B; Weber et al., 2008; 2009; Matz et al., 2010). In line with the literature (Krohne et al., 1996; Watson et al., 1988), negative affect seems to reflect a stable disposition, as scores did not change significantly across the three measurement points in none of the subject groups. From the additional fact that early life stress correlated with negative affect, which in turn correlated with current stress sensitivity, we may conclude that negative affect can be considered as a mediator of early life stress effects on lasting stress sensitivity. Negative affect might reflect a trait programmed by

effects of stress exposure early in life that possibly influences the course of a psychiatric disorder in otherwise predisposed individuals.

Cortical processing of affective pictures was dampened in patients with high ELS across assessments and across slightly varying stimulation conditions (Hypothesis C and D). General response strength was weak, although the differential response to high-arousing pleasant and unpleasant stimuli (i.e. stronger cortical activation as compared to low arousing neutral stimuli) did not seem crucially affected. Animal studies on the influences of environmental factors on brain development (Champagne et al., 2008; Meaney & Szyf, 2005) suggest that the brain's information processing modes may be shaped by early experiences. Although we can hardly demonstrate structural changes in brain development as a consequence of ELS in humans, we might hypothesize that the processing of affective stimuli acts as a mediator between ELS and the vulnerability for or course of a psychiatric disorder. Assuming such a mediating role, which has to be clarified in further, more specific research, present results suggest a generally reduced responsiveness to affective stimuli rather than an impaired discrimination of relevant (arousing, pleasant and unpleasant) information. Specifying this mediator might be of interest, because responses to affective stimuli are associated with action dispositions to either approach an appetitive cue or withdraw from an aversive cue (Lang et al., 1998) and might reflect functionality of the reward and defense system.

Statistical confirmation of potential mediating effects requires, first of all, significant relationships between the independent and the dependent variable (ELS and psychopathology), between the independent and the proposed mediator variable (ELS and stress sensitivity, NA or cortical affect processing), as well as between the dependent and the proposed mediator variable (psychopathology and stress sensitivity, NA or cortical affect processing). As stated above, ELS was strongly correlated with

measures of stress sensitivity, negative affect and cortical affect processing. Measures of stress sensitivity and negative affect and cortical responses to affective stimuli in the slow presentation design were also related to measures of psychopathology, such as number of hospitalizations and comorbid disorders, thereby satisfying the precondition for assuming a mediating effect. In a second step, the proposed mediator variable has to be added as a second factor (the first factor would be ELS) into a hierarchical regression analysis. If this variable bears a mediating effect, it will explain additional variance of the dependent variable and will diminish the predictive power of the independent variable (Baron & Kenny, 1986). Although ELS itself was a significant predictor of available measures of psychopathology, hierarchical regression analyses did not consistently reveal significant mediating effects of measures of stress sensitivity or negative affect. However, statistical evaluation of mediating effects was limited because of the lack of diagnosis-specific measures of psychopathology and too small diagnostic subgroups. Therefore, we can only speculate whether these psychological functions actually reflect mediating factors.

Hypotheses based on the retrospective assessment of ELS might be questioned. It has been argued that they bear the problem of inaccurate recall and classification of abusive experiences (Loftus, 1993) and may be biased by current psychopathology (Burbach & Borduin, 1986). Theoretically, objective measures of stress, brain processing modes, mood, and coping behavior, etc. could be assessed in prospective longitudinal studies. Such studies on large birth cohorts, ideally starting during pregnancy with repeated re-assessments during childhood, adolescence and adulthood could substantiate findings on lasting impacts of ELS, differentiate effects in distinct sensitive periods of development, and verify mediating factors. Based on the present results, the

following hypotheses about potential mediators of ELS effects on adult psychopathology could be scrutinized in future studies:

(a) In terms of a gene x environment interaction, ELS itself might induce the manifestation of a genetic vulnerability, thereby influencing the course and/or the severity of a psychiatric disorder. In the present study, ELS was unevenly distributed across diagnostic subgroups, which indicates that ELS is not related to psychopathology per se but might interact with disorder-specific vulnerability factors. This view has been supported by gene x environment approaches studying genetic polymorphisms e.g. within the corticotropin-releasing hormone type 1 receptor gene that seems to mediate the effects of child abuse on adult depressive symptoms (Bradley et al., 2008). However, various polymorphisms have been proposed as mediators between ELS and adult psychopathology (Enoch et al., 2010; Kendler, Kuhn, Vittum, Prescott, & Riley, 2005). Whether there are interactions between specific genetic polymorphisms and ELS that may help to explain the development of a particular psychiatric disorder has to be substantiated in future studies.

(b) As the timing of development differs between brain regions, only ELS in certain critical developmental periods might mediate the development of psychopathology. For example, hippocampal volume reduction was associated with sexual abuse at ages 3-5 years and ages 11-13 years but not in the period in-between. Moreover, frontal cortex reduction was related to sexual abuse at ages 14-16 years (Andersen et al., 2008). Although structural alterations in other brain areas like the amygdala and the prefrontal cortex as a consequence of ELS (Tomoda et al., 2009) have been reported, specific effects of ELS in unique sensitive time windows as described by Andersen and colleagues (2008) have not been replicated so far. To further evaluate this hypothesis, a prospective, longitudinal and objective assessment of both stress exposure and brain

development would be necessary, which seems hardly possible. Nevertheless, if we consider brain processing modes as a mediating factor between ELS and adult stress sensitivity or psychopathology, then it might be interesting to specify whether ELS exerts these effects only when present in distinct sensitive periods.

(c) Another way to 'quasi-experimentally' examine the function of ELS as a mediator concerns the treatment of psychiatric disorders. Diversity in the etiology of a psychiatric disorder implies distinctive effectiveness of different treatments. This has been confirmed for the treatment of depressive patients (Nemeroff et al., 2003): patients with a history of ELS treated with psychotherapy alone showed significantly more improvement as under antidepressant pharmacotherapy and a combination of both was only marginally superior to psychotherapy alone. Conversely, across all patients irrespective of ELS, psychotherapy and antidepressant medication were equally effective and a combination of both was significantly superior over either one alone. This result suggests that ELS mediates a certain type of depression, and, hence, emphasizes the gene x environment interaction.

With an etiological perspective, the present thesis sought to create hypotheses to specify ELS effects on psychopathology. The preceding discussion related findings from the empirical parts of this project to implications for future research. As an even more far-reaching perspective, all this research should lead to conclusions for treatment and prevention. As accumulating evidence points to the long-term effects of ELS, the importance of early and preventive interventions becomes increasingly obvious. In rodents, increased maternal care permanently reduces neuroendocrine and behavioral responses to stress through epigenetic programming, thereby decreasing the risk for depressive behavior and cognitive deficits (Korosi et al., 2010). Increased maternal care may even attenuate or reverse the deleterious effects on brain development associated

with prenatal adversity (Brabham et al., 2000; Lemaire et al., 2006). In humans, friendship social support has been associated with decreased risk for depression in women with a history of childhood emotional abuse and neglect (Powers, Ressler, & Bradley, 2009) and cognitive deficits of abandoned children seemed to be diminished by moving them from institutional care to foster care (Nelson et al., 2007). These results indicate that providing a reliable supportive relationship outside of adverse family environments may constitute a protective factor against the development of psychopathology. Further research is needed to evaluate effectiveness and feasibility of such early interventions.

Although one could consider several aspects of the conducted studies as constraints or limitations, I am not aware of the ideal design that would allow to define causal effects of ELS and to specify mediators between ELS and adult psychopathology. Studies such as the present one provide hypotheses to be examined in other designs. In sum, results indicate that ELS persistently affects reactivity to current life stress, negative affect and altered cortical processing of reward and defence related stimuli in psychiatric patients. Stability of the results points to a lasting impact of ELS on the development and course of psychiatric disorders. Whether the psychological functions examined in the present project actually constitute mediating factors between ELS and psychopathology has to be confirmed in future studies with larger samples and more specific measures of psychopathology than available in this project.

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