Universität Trier

Pre-, peri-, and postnatal Risk Factors in Borderline Personality Disorder

Dissertation

Dipl.-Psych. Cornelia E. Schwarze

Mainz, Oktober 2011

Gutachter:

Prof. Dr. Dirk H. Hellhammer
Prof. Dr. Klaus Lieb

TABLE OF CONTENTS

ABBREVIATIONS

AAS	Adult Attachment Scale
ACC	Anterior Cingulate Cortex
ACTH	Adrenocorticotropic Hormone
ADHD	Attention Deficit Hyperactivity Disorder
ALS	Affective Lability Scale
ANCOVA	Analysis of Variance
BMI	Body Mass Index
BOLD	Blood-Oxygen-Level dependent
BPD	Borderline Personality Disorder
BPDSI	Borderline Personality Disorder Severity Index
BSL	Borderline Symptom List
CG	Control Group
CNS	Central Nervous System
CRH	Corticotrophin Releasing Hormone
CTQ	Childhood Trauma Questionnaire
DAT	Dopamine Transporter
DNA	Deoxyribonucleic Acid
DSM	Diagnostic and Statistical Manual for Mental Disorders
FDS/DES	Dissociative Experience Scale
fMRI	Functional Magnetic Resonance Imaging
HPA	Hypothalamic Pituitary Adrenal
IDQ	Identity Distortion Questionnaire
GR	Glucocorticoid Receptor
MAO	Monoamine Oxydase
MANCOVA	Multivariate Analyisis of Variance
MR	Mineralocorticoid Receptor
NE	Norepinephrine
NPQ-A	Neuropattern Questionnaire A
NPQ-PSQ	Pre/Peri/Postnatal Stress Questionnaire
OR	Odds Ratio
PBI	Parental Bonding Inventory
pCRH	Placental Corticotrophin Releasing Hormone
PEPCK	Phosphoenolpyruvate Carboxykinase
PET	Position Emission Tomography
PTSD	Post Traumatic Stress Disorder

SCID	Structured Clinical Interview for DSM-IV
SPSS	Statistical Package for Social Science
SSS	Sensation Seeking Scale
TSST	Trier Social Stress Test
UPPS	Impulsive Behavior Scale
11β HSD	11β-Hydroxysteroid Dehydrogenase

INDEX OF TABLES AND FIGURES

Tables

Figures

Chapter 1

INTRODUCTION AND OBJECTIVE OF THE THESIS

1.1 Introduction

In addition to the well-recognised effects of both, genes and adult environment, it is now broadly accepted that adverse conditions during pregnancy contribute to the development of mental and somatic disorders in the offspring, such as cardiovascular disorders, endocrinological disorders, metabolic disorders, schizophrenia, anxious and depressive behaviour and attention deficit hyperactivity disorder (ADHD)[1-3]. Early life events may have long lasting impact on tissue structure and function and these effects appear to underlie the developmental origins of vulnerability to chronic diseases[4].

The assumption that prenatal adversity, such as maternal emotional states during pregnancy, may have adverse effects on the developing infant is not new. Accordant references can be found in an ancient Indian text (ca. 1050 before Christ), in biblical texts and in documents originating during the Middle Ages[5]. Even Hippocrates stated possible effects of maternal emotional states on the developing fetus.

Since the mid-1950s, research examining the effects of maternal psychosocial stress during pregnancy appeared in the literature. Extensive research in this field has been conducted since the early 1990s. Thus, the relationship between early life events and long-term health outcomes was already postulated over 20 years ago. David Barker and colleagues demonstrated that children of lower birth weight - which represents a crude marker of an adverse intrauterine environment - were at increased risk of high blood pressure, cardiovascular disorders, and type-2 diabetes later in life[6-8]. These provocative findings led to a large amount of subsequent research, initially focussing on the role of undernutrition in determining fetal outcomes. The phenomenon of prenatal influences that determine in part the risk of suffering from chronic disease later in life has been named the “fetal origins of health and disease” paradigm[8]. The concept of “prenatal programming” has now been extended to many other domains, such as the effects of prenatal maternal stress, prenatal tobacco exposure, alcohol intake, medication, toxins, as well as maternal infection and diseases. During the process of prenatal programming, environmental agents are transmitted across the placenta and act on specific fetal tissues during sensitive periods of development. Thus, developmental trajectories are changed and the organisation and function of tissue structure and organ system is altered[9].

The biological purpose of those ‘early life programming’ may consist in evolutionary advantages. The offspring adapts its development to the expected extrauterine environment which is forecast by the clues available during fetal life[10]. If the fetus receives signals of a challenging environment, e.g. due to maternal stress hormones or maternal undernutrition, its survival may be promoted due to developmental adaptation processes. However, if the

expected environment does not match with the real environment, maladapation and later disease risk may result[11, 12].

For example, a possible indicator of a "response ready" trait, such as hyperactivity/inattention may have been advantageous in an adverse ancient environment. However, it is of disadvantage when the postnatal environment demands oppositional skills, such as attention and concentration – e.g. in the classroom, at school, to achieve academic success[2].

Borderline personality disorder (BPD) is a prevalent psychiatric disorder, characterized by impulsivity, affective instability, dysfunctional interpersonal relationships and identity disturbance[13]. Although many studies report different risk factors, the exact etiologic mechanisms are not yet understood. In addition to the well-recognised effects of genetic components and adverse childhood experiences, BPD may potentially be co-determined by further environmental influences, acting very early in life: during pre- and perinatal period. There are several hints that may suggest possible prenatal programming processes in BPD. For example, patients with BPD are characterized by elevated stress sensitivity and reactivity and dysfunctions of the neuroendocrine stress system, such as the hypothalamic pituitary adrenal (HPA) axis. Furthermore, patients with BPD show a broad range of somatic comorbidities[14] – especially those disorders for which prenatal programming processes have been described[1]. During infancy and childhood, BPD patients already show behavioural and emotional abnormalities as well as pronounced temperamental traits, such as impulsivity, emotional dysregulation and inattention[15, 16] that may potentially be co-determined by prenatal programming processes. Such temperamental traits - similar to those, seen in patients with ADHD - have been described to be associated with low birthweight which indicates a suboptimal intrauterine environment[2]. Moreover, the functional and structural alterations in the central nervous system (CNS) in patients with BPD[17, 18] might also be mediated in part by prenatal agents, such as prenatal tobacco exposure.

Prenatal adversity may thus consist a further, additional component in the multifactorial genesis of BPD. The association between BPD and prenatal risk factors has not yet been studied in such detail. We are not aware of any further study that assessed pre- and perinatal risk factors, such as maternal psychoscocial stress, smoking, alcohol intake, obstetric complications and lack of breastfeeding in patients with BPD.

1.2 Objective and Outline of the Thesis

The major objective of the present study was to examine a potential association between pre-/perinatal risk factors and the diagnosis of BPD. Furthermore, we aimed to determine whether early risk factors act as possible predictors for the borderline diagnosis and its associated features, such as impulsivity, affective instability, attachment/bonding, and

somatic comorbidities.

After a short introduction and the outline of the thesis in chapter 1, a theoretical background about the diagnosis of BPD and early life programming is provided in chapter 2. Chapter 2 deals with the prevalence, symptomatology, comorbidities and etiological aspects of BPD, such as genetic, neurobiological and psychosocial factors. Furthermore, a short overview of attachment-related problems in BPD is provided.

The second focus of chapter 2 is a theoretical background as well as an overview of the literature about early life programming. Here, factors and mechanisms of prenatal programming are provided, such as prenatal maternal stress, prenatal tobacco exposure, maternal infection and prenatal exposure to toxins. Furthermore, chapter 2 deals with prenatal programming of physical and mental health, temperamental traits and behaviour.

The chapters 3, 4 and 5 present findings from our own study focussing on prenatal adversity as a potential risk factor in BPD (Chapter 3), physical health conditions in association with prenatal adversity (Chapter 4) as well as lack of breastfeeding in BPD and bonding/attachment-related problems (Chapter 5).

Patients with BPD show a high prevalence of early adversity, such as childhood trauma. However, prenatal risk factors have never been assessed in detail in association with the BPD diagnosis. Thus, the main focus of the study in chapter 3 was to assess the prevalence of prenatal risk factors in borderline patients compared to healthy controls and to test if prenatal risk factors act as potential predictors for the borderline diagnosis and associated sub-domains. Subsequently, we assessed the prevalence of lifetime somatic comorbidities in borderline patients compared to controls, such as cardiovascular disorders, gastrointestinal disorders, disorders of hormone system and metabolism, sensory and neurological disorders, skin disorders, urogenital symptoms, pain disorders and musculoskeletal disorders. For the first time, an association of somatic disorders in BPD and prenatal risk factors, such as prenatal maternal stress, was assessed (Chapter 4).

Finally, we aimed to assess if bonding/attachment-related problems in BPD – as well as the BPD diagnosis itself - may be associated with early life risk factors, such as lack of breastfeeding. The study, presented in chapter 5, provides first evidence of an association between lack of breastfeeding and the diagnosis of BPD as well as impairment in perceived maternal bonding.

In the last chapter (Chapter 6), the findings from chapter 3, 4 and 5 are summarized, followed by a general discussion. An outlook of future research directions as well as options for a possible transfer into the praxis is provided in the end of chapter 6.

Chapter 2

THEORETICAL BACKGROUND

2.1 Borderline Personality Disorder

Borderline personality disorder (BPD) is a common psychiatric disorder, characterised by a pervasive pattern of instability in affect regulation, impulse control, identity distortion and interpersonal relationships[19]. BPD is associated with high rates of mortality due to suicide, severe impairments in psychosocial function[20-22] and a high prevalence of comorbid somatic and mental disorders.

2.1.1. Epidemiology

The prevalence of BPD in epidemiological studies ranges between 0.5% and 5.9% in the general population [13, 23]. A median prevalence of 1.35% has been reported [24]. In clinical settings, BPD is the most common personality disorder with up to 25% of psychiatric inpatients and about 10% of psychiatric outpatients [13]. In primary care, the prevalence of BPD is even four times higher than in the general population[25].

Earlier studies reported a higher proportion of women with BPD (about 70%) whereas the prevalence rate in men has been reported to be about 30% [23]. Current studies report no differences of BPD rates between female and male individuals [20, 26]. In a community-based sample of children and adolescents, the prevalence rates of BPD have been reported to be 11% in individuals aged 9 to 19 years and 7.8% in individuals aged 11 to 21 years [13, 27].

2.1.2. Symptomatology

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)[19], BPD is characterised by a pervasive pattern of instability in interpersonal relationships, identity, impulsivity, and affect regulation. At least five of nine diagnostic criteria must be met to confirm the diagnosis of BPD.

DSM-IV Criteria of BPD:

1.) Frantic efforts to avoid real or imagined abandonment
2.) A pattern of unstable and intense interpersonal relationships characterised by alternating between extremes of idealisation and devaluation
3.) Identity disturbance: notably and persistently unstable self-image or sense of self
4.) Impulsivity in at least two areas that are potentially self-damaging (eg, spending, sex, substance misuse, reckless driving, binge eating)
5.) Recurrent suicidal gestures, or threats or self-mutilating behaviour

6.) Affective instability caused by a distinct reactivity of mood (eg, intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days)
7.) Chronic feelings of emptiness
8.) Inappropriate intense anger or difficulty controlling anger (eg, frequent displays of temper, constant anger, recurrent physical fights)
9.) Transient, stress-related paranoid ideation or severe dissociative symptoms

BPD is characterised by a pronounced affective reactivity[28], manifesting in rapid switches from one affective state to another. Mood changes in borderline patients may occur rapidly and repeatedly over the course of one day. Emotional qualities such as rage, anxiety, desperation, feelings of emptiness, euthymia or shame are often experienced by patients with BPD and may change within several minutes[13]. Furthermore, a characteristic feature of BPD is the perception of intense and aversive tension that sometimes results in self-mutilating behaviour.

Borderline patients also show other potentially self-harming and impulsive behaviours such as high risk behaviour, substance abuse, promiscuity, binge eating or reckless driving. High rates of suicide attempts are common in patients with BPD[29] [30]. 8% to 10% of borderline patients commit suicide. Thus, the rate of death due to suicide is 50-times higher, compared to the general population[29] [30]. Suicidal tendency or self-injurious behaviour have been described as the most useful indicators for a correct diagnosis [31], whereas suicidal tendency, self-injury or unstable interpersonal relationships were reported to be the most predictive features in follow-up studies [32].

Another feature, typical for BPD, is a pattern of intense but unstable interpersonal relationships with frequent alterations between idealization and devaluation and repeated break ups. Borderline patients show intense fear of being unloved or abandoned by others. This may lead to desperate efforts to avoid being left alone.

Furthermore, patients with BPD show a pronounced instability in identity and self-perception[13]. The unstable sense of self sometimes manifests in rapid switches from the perception of being a totally good to being a totally bad person. Many borderline patients show instability in education or professional life with repeated changes of employments and sudden break-ups of educational training. Disoriented behaviour in terms of sexual orientation, persuation, friendships, life's goals or religious orientation is typically seen in BPD. During disstress, borderline patients sometimes experience alterations of consciousness, such as phenomena of derealisation and depersonalisation, pronounced suspiciousness or quasi-psychotic symptoms, such as transitory delusions or hallucinations[13].

Taken together, the diagnosis of BPD seems to be a quite heterogeneous syndrome. But statistical models revealed that the nine DSM-IV criteria of BPD indicate a statistically coherent construct[33]. Alternatively, factor analyses revealed a three-factor model, consisting of 'disturbed relatedness', 'behavioural dysregulation' and 'affective dysregulation' which may indicate an underlying multidimensional structure of the borderline diagnosis [33, 34].

2.1.3. Comorbidities

2.1.3.1 Mental Disorders

Patients with BPD show high rates of comorbid mental disorders[20, 21, 34]. Thus, 84.5% of borderline patients meet the diagnostic criteria for at least one other axis I disorder and 73.9% meet the diagnostic criteria for at least one or more comorbid lifetime axis II disorders[20, 21]. In terms of axis I disorders, BPD is most frequently associated with major depression, substance abuse disorders, post-traumatic stress disorder (PTSD) and other anxiety disorders, as well as eating disorders[35-38 20, 21, 34]. 41–83% of borderline patients report a history of major depression[35, 37, 38]. The lifetime prevalence of other axis I disorders has been reported to be 12–39% for dysthymia, 10–20% for bipolar disorders, 64–66% for substance abuse disorders, 23–56% for PTSD, 23–47% for social phobia, 16–25% for obsessive-compulsive disorder, 31–48% for panic disorder, and 29–53% for any eating disorder[13]. The most frequently diagnosed comorbid axis II disorders are avoidant personality disorder with 43–47%, dependent personality disorder with 16–51%, and paranoid personality disorder with 14–30%[13, 35-37].

With respect to comorbid axis I disorders, differences between female and male borderline patients have been reported. Thus, eating disorders were more prevalent in female patients whereas substance abuse disorders were more prevalent in male patients[20].

2.1.3.2 Somatic Disorders

It has been reported that the diagnosis of BPD is related to a high number of somatic comorbidities, such as cardiovascular disorders, metabolic disorders, neuroendocrine disorders and musculoskeletal disorders. A recent population-based study (The National Epidemiologic Survey on Alcohol and Related Conditions, NESARC, Wave 2, n=34.653) found high rates of arteriosclerosis and hypertension, cardiovascular diseases, stroke, diabetes, gastrointestinal diseases, arthritis, venereal diseases, and hepatic diseases in 2231 patients with a diagnosis of BPD[39].

Another study found high rates of medical problems in patients with a current borderline diagnosis compared to those with remitted borderline diagnoses[14]. Nonremitted borderline patients were found to be significantly more likely to show a history of hypertension, diabetes, osteoarthritis, chronic back pain, urinary incontinence and syndrome-like

conditions, such as chronic fatigue syndrome, fibromyalgia and temporomandibular joint syndrome[14]. Moreover, BPD has been repeatedly associated with an elevated body mass index (BMI) and obesity[14, 40, 41].

2.1.4. Etiology of Borderline Personality Disorder

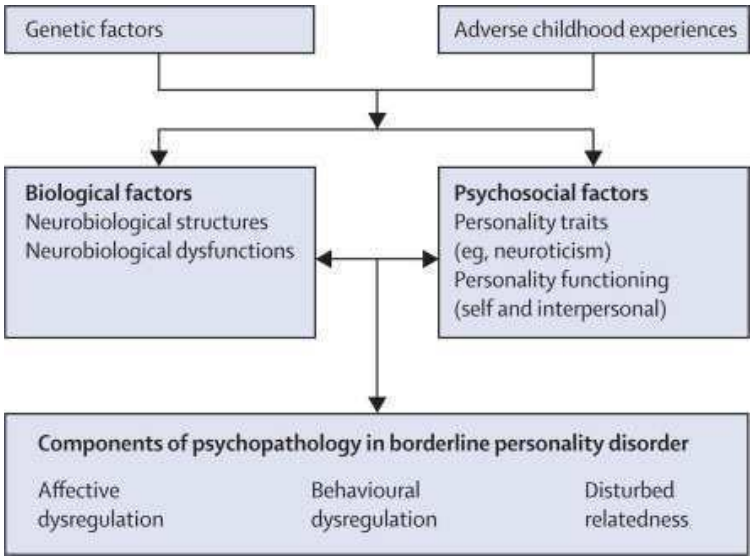
2.1.4.1 Etiological Model

The etiology of BPD is complex and the pathogenetic factors are only partly known. Several studies recognized a range of possible determinants, including genetic, neurobiological, and psychosocial factors that interact at various levels[13]. Genetic factors and prenatal risk factors may act as an early vulnerability for affective dysregulation, impulsivity and difficult temperament. These characteristics may lead to dysfunctional behaviour and to psychosocial conflicts across individual's development. Adverse childhood experiences may in turn aggravate the individuals' emotional, behavioural and cognitive dysgregulation later in life[42, 43]. It has been reported that a high percentage of borderline patients were exposed to severe trauma during childhood, such as sexual abuse, physical maltreatment and emotional neglect[44]. A history of childhood trauma may act as an important risk factor for the development of BPD.

One of the most thoroughly delineated etiological models of borderline pathology is Linehan's biosocial theory of BPD[45] (for other models, see Fonagy et al. [46]; Judd & McGlashan[47], Kernberg[48-50]. According to Linehan, BPD is primarily a disorder of emotional dysregulation and emerges from transactions between individuals in association with biological vulnerabilities and specific environmental risk factors. The dysfunction proposed by Linehan manifests in a broad dysregulation across all aspects of emotional responding. Subsequently, individuals with BPD show heightened emotional sensitivity, inability to regulate intense emotional responses, and slow return to emotional baseline[42].

An extension of Linehan's model proposes pronounced impulsivity, followed by heightened emotional sensitivity. These vulnerabilities are potentiated across development by environmental risk factors that may aggravate the emotional, behavioral, and cognitive dysregulations[42]. During the past decades, research focussed more and more on neurobiological correlates of BPD. Thus, an increasing number of studies identified neurobiological alterations in BPD, such as structural or functional brain abnormalities, alterations in neurotransmitter systems, stress reactivity and endocrinological functions. Figure 2.1 shows the possible etiologic mechanisms of BPD.

Figure 2.1. Etiological Model of BPD (Leichsenring et al., 2011)



2.1.4.2 Neurobiological Correlates of BPD

Research on biological dysfunction in BPD has focused on the genetic, neurochemical, and structural correlates of the disorder. Several neurotransmitter systems, including serotonin, dopamine, noradrenaline, acetylcholine, vasopressin, and gamma-aminobutyric acid, have recently received attention in the literature. Researchers have also identified relations between borderline pathology and dysfunction of the peripheral nervous system and the neurobiological stress system. Furthermore, evidence suggests that BPD has a profound heritable component[51, 52].

Genetic Factors

Evidence emerged that genetic factors contribute to the development of BPD[43, 51, 53]. However, no specific genes have yet clearly been identified, which suggests complex underlying genetic mechansims.

For the diagnosis of BPD, twin studies revealed a heritability of 0.65 to 0.75[54]. These scores are consistent with the reported heritability for personality disorders in general (40% to 60%)[55].

One of the largest and methodologically well-founded twin studies identified a concordance rate of 38% for the BPD diagnosis among monozygotic twins and 11% among dizygotic twins[52]. These results suggest a strong genetic influence. In general, 69% of the variance in BPD symptoms was attributable to additive genetic effects, whereas 31% of the variance was attributed to non-shared environmental factors[52].

In a separate family study[56], it has been reported that the risk for affective instability and impulsivity was greater in relatives of individuals, diagnosed with BPD compared to relatives

of individuals with other personality disorders or schizophrenia[42]. A moderate heritability of 35% has been reported for dimensional representations of BPD traits, such as their quantitative intensity, e.g. the number of diagnostic criteria[51].

Neurotransmitter Systems

Serotonin

Empirical research supports an association between borderline pathology and deficits within the central serotonin system. This assumption has been derived from studies that found associations of deficits in serotonin functioning and borderline-related symptoms, such as mood disturbance, self injurious behaviour, suicidality, and aggression[57]. Pharmacologic challenge tests have been conducted in samples with personality disorders, including individuals with BPD that suggest a reduction in central serotonergic activity[58-61]. Furthermore, impulsive aggression and affective instability are associated with specific genetic polymorphisms and functional impairments in the central serotonin system[42].

Dopamine

There is an emerging consensus that dopamine dysfunction contributes to the affective, cognitive, and behavioural traits seen in BPD[43, 62]. However, the specific mechanisms of dopaminergic dysfunction still remain unclear (hypo- versus hyperfunctioning). One study implies that the genetic variations associated with the dopamine transporter *(*DAT1) in BPD result in hyperdopaminergic functioning which may lead to the psychotic-like features of BPD[63]. However, the same dopamine transporter abnormalities have been associated more consistently with trait impulsivity, resulting from hypodopaminergic states[64]. In fact, findings from several research groups indicate that the same polymorphism of the dopamine transporter gene (i.e., the 9-repeat allele) is linked to the diagnosis of ADHD[65] and other externalizing behaviours, such as conduct disorders[66] and alcohol abuse[67]. These findings suggest that impulsivity and negative affectivity in BPD may be related more likely to hypodopaminergic functioning[42].

Vasopressin and Monoamine Oxidase

Vasopressin is a neurotransmitter that is on one hand involved in aggressive behaviour and on the other hand in pair bonding. Thus, increased levels of vasopressin have been reported to correlate with higher levels of aggressive behaviour in animals[68]. Furthermore, high levels of vasopressin correlate negatively with serotonin functioning in personality disorders[69]. Based on these findings, it is assumed that both, the vasopressin and the serotonin system interact in promoting aggressive behaviour[70]. Thus, some investigators hypothesized that vasopressin may be associated with borderline symptomatology[42, 71, 72].

Monoamine oxidase (MAO) is an enzyme that is involved in the breakdown of monoamine neurotransmitters. It has been hypothesized that MAO may be involved in borderline pathology too. There are two forms of MAO: MAOA and MAOB.

Brunner et al.[73] reported of a point mutation in the MAOA gene that may be related to violent behaviour and to increased risk for suicide[73]. Similarly, polymorphisms in the MAOA gene appear to interact with adverse environmental influences to potentiate impulsive and aggressive behaviour. Thus, the high-risk allele of the MAOA gene seems to result in high levels of aggression only in combination with early child maltreatment[74] which may have implications for the emergence of BPD. Platelet studies of MAOB found negative correlations between peripheral MAOB and impulse control disorders, including BPD, ADHD, antisocial personality disorder, criminality, pathological gambling as well as alcohol and drug abuse[42, 75].

Acetylcholine

Brain structures that are involved in emotion regulation, such as the amygdala, hippocampus, and dorsal tegmental cortex, portions of the striatum and the cingulate cortex are innervated by cholinergic neurons. Acetylcholine binds to nicotinic acetylcholine receptors which contribute to the regulation of several mood-related processes and physiological functions, such as sleep, arousal, fatigue, anxiety, pain processing, food intake, and cognitive functions[76]. It is assumed that complex interactions between the cholinergic and the adrenergic system lead to some depressive features in mood disorders[77]. A prolonged exposure to stress may result in an imbalance of the cholinergic versus the adrenergic system. Thus, the central acetylcholine turnover may be elevated as a consequence of the stress response, and may lead to chronic increases in heart rate, blood pressure, dysphoria, depression, anxiety, irritability, aggression, and hostility. These features all are traits associated with BPD[42].

Norepinephrine

It is assumed that the noradrenergic (NE) system is associated with individual differences in mood regulation, affect, social affiliation, irritability, and reactivity to the environment [43, 71, 78].

Thus, elevated NE activity (e.g. due to administration of reboxetine) may be associated with increased social engagement and cooperation and with reduced self-focus[79]. For example, NE depletion that occurs as a result of the exposure to chronic stress may lead to an up-regulation of tyrosine hydroxylase proteins in rats[80]. Furthermore, some forms of depression, in particular melancholic depression, appear to be treated effectively by drugs that affect the NE system[81]. However, further studies of noradrenergic mechanisms in BPD are needed[82].

Hyothalamic Pituitary Adrenal Axis

There is evidence of abnormal HPA axis function in patients with BPD[83, 84]. Some studies suggest a hyperactive HPA axis in borderline patients, characterized by excessive release of cortisol [85, 86] whereas other studies described a hypoactive stress axis in BPD patients[83]. These mixed results may occur due to different subgroups of borderline patients – characterized by different comorbidities, such as depression, PTSD or dissociative symptoms[83]. A recent review has shown that comorbid mental disorders may in fact modulate HPA axis function in borderline patients[83]. Wingenfeld et al.[87] reported a positive association between urinary cortisol release and depression scores whereas low cortisol release was associated with a high number of PTSD symptoms. One study used a novel approach to assess basic parameters of the HPA axis in borderline patients, by means of portable mini computers in an ambulatory setting[84]. Lieb et al.[84] found significantly higher daily salivary cortisol levels and higher cortisol awakening response in BPD patients compared to healthy controls. Another study however, found no increase in overall cortisol levels in BPD - when controlled for comorbid disorders, such as PTSD and depression[88].

The HPA reactivity in response to an acute psychosocial stressor (Trier Social Stress Test [89]; TSST) was particularly pronounced in borderline patients that showed high levels of dissociative symptoms[90]. Conversely, patients with a history of childhood trauma showed low basal levels of urinary cortisol[90].

Nater et al.[91] reported a substantial hyporeactivity of cortisol and alpha-amylase in BPD patients compared to healthy controls – in response to a standardised psychosocial stress protocol. Similarly, studies on HPA feedback after administration of Dexamethasone showed various results. Carrasco et al.[92] found an increased HPA feedback inhibition after administration of 0.25 mg dexamethasone in patients with BPD. However, these findings could also be mediated by comorbid diagnoses of PTSD, because Wingenfeld et al.[87] reported more pronounced cortisol suppression in BPD patients with comorbid PTSD compared to patients without comorbid PTSD. However, non-suppression of cortisol after dexamethasone suppression test has also been reported[84, 93, 94].

Summarized, these findings suggest that alterations in cortisol release in BPD are strongly associated with the existence and severity of comorbid psychopathologies as well as clinical features such as trauma history and dissociative symptoms.

Structural Neuroanatomy

Empirical evidence suggests structural brain abnormalities in borderline patients[95, 96]. Findings from structural brain imaging studies suggest volume reductions of several CNS structures, such as amygdala, hippocampus, cingulate gyrus as well as parietal, dorsolateral and orbitofrontal cortices[13, 24, 96-99]. The most consistent finding is a volume reduction of the

amygdala which has been described in several studies and which was recently confirmed in a meta-analysis. A possible causative factor of the reduced amygdala volumes in BPD may be excitotoxic processes during the course of the disorder[24].

Furthermore, structural imaging studies also indicated reduced hippocampal volumes in patients with BPD[17, 96-98, 100]. However, reduced hippocampal volumes[101] but no reductions in the amygdala volume, were also observed in patients with PTSD[102]. Thus, eventually, borderline patients without comorbid PTSD might not have reduced amygdala volumes[103]. These data highlight the importance of taking into account possible confounding effects of comorbid mental disorders on brain structure in patients with BPD.

A reduction in grey matter volume has been reported for several other brain structures such as the anterior and posterior cingulate gyrus[104], the right parietal cortex[98], the dorsolateral cortex, the left orbitofrontal cortex[105], as well as size abnormalities of the superior parietal cortices[99]. However, most of these findings are not specific to the diagnosis of BPD.

Functional Neuroanatomy

The most consistent finding from functional magnetic resonance imaging (fMRI) studies in patients with BPD is a bilaterally increased amygdala activity. The amygdala is considered as a key structure in processing of affective states, such as anxiety. Furthermore, the amygdala is part of a fronto-limbic network that seems to mediate aspects of the BPD symptomatology[13]. This network includes the anterior cingulate cortex (ACC), the orbitofrontal and dorsolateral prefrontal cortices, the hippocampus and seems to be dysfunctional in patients with BPD[13]. The increased amygdala activation has been described as particularly pronounced during tasks that induce negative emotions, such as viewing aversive emotion-inducing pictures[106], pictures of negative human facial expressions[107] or the recall of a personal unresolved life event[108].

Further findings from fMRI studies indicate less blood-oxygen-level dependent (BOLD) signal changes in the anterior cingulate in patients with BPD compared to controls[106] as well as greater activation of the superior temporal sulcus and the superior frontal gyrus. These patterns of brain activity have been described to appear when participants were asked to use a cognitive strategy to control the emotional responses to unpleasant pictures[106]. It thus implies less pronounced cognitive control functions in borderline patients compared to healthy controls. Furthermore, it is supposed that this kind of dysregulation may contribute to the affective instability of BPD[106].

Different neuronal patterns of traumatic memory in patients with and without comorbid diagnosis of PTSD have been reported[109]. During thermic pain-induction, decreased amygdala activation has been described only in those patients with a comorbid diagnosis of PTSD[110]. These findings may indicate different neuronal networks in subgroups of borderline patients. Altogether, the described results from fMRI studies support the assumption of a

dysfunctional frontolimbic network in BPD[13]. However, future studies are needed to investigate the specificity of those findings.

Findings from PET studies

The assumption of a frontolimbic dysfunction in patients with BPD lends further support from findings of Positron Emission Tomography (PET) studies that detected changes in frontal glucose metabolism, mostly characterized by a prefrontal hypometabolism[111].

During an aggression provocation task in a recent PET study, controls showed a more pronounced activation of prefrontal cortex regions compared to patients with BPD[112]. These prefrontal cortex regions are known to be associated with processes of emotion control, which lends further support to the assumption of abnormal prefrontal brain functions in BPD. These alterations seem to be associated with emotional dyscontrol in borderline patients.

2.1.4.3. Psychosocial and environmental factors in BPD

In addition to the biological risk factors, stressful environmental factors play a crucial role in the multifactorial genesis of BPD. Numerous studies identified a variety of adverse childhood experiences in borderline patients, such as sexual abuse, physical maltreatment or emotional neglect[113-122]. However, also other forms of childhood adversity are common in borderline patients, such as experiences of early separation, parental divorce, parental mental illness and violence within the family [123]. Therefore, it may be the experience of cumulative early trauma and adversity that is characteristic for BPD and that seems to contribute to the pathogenetic development.

Several studies found an association between a history of childhood abuse and neglect and later mental health morbidity[116, 124, 125]. For instance, Tyrka et al. [126] confirmed an association between different forms of childhood abuse with axis II personality disorders in adulthood. A long-term study has shown that individuals, that experienced abuse or neglect during childhood, were four times more likely to develop a personality disorder in early adulthood, compared to individuals without such traumatic experiences.

In a longitudinal study, Yen et al.[127] showed that borderline patients exhibit the highest rates of childhood trauma compared to all other personality disorders.

In a review of studies, published between 1995 and 2007, Ball et al.[113] found indicators of a causal relationship between childhood trauma and BPD. Also Bandelow[123] reported that borderline patients were exposed to multiple unfavourable conditions during childhood. He compared borderline patients and healthy controls and found that only 6.1% of borderline patients, compared to 61.5% of the control group, did not report adverse childhood events[123]. Abuse and neglect in several forms, including experiences of inconsistency, early separation from parents and domestic violence, were reported more often by patients with BPD[123].

A recent study by Loebbestal et al. [116] recognized different forms of child maltreatment such as sexual abuse, physical abuse, emotional abuse and emotional and physical neglect in patients of various personality disorders. They identified sexual abuse, emotional abuse and emotional neglect as significant risk factors for the development of BPD[116].

Sexual abuse

One form of interpersonal trauma that is frequently experienced by patients with BPD, is childhood sexual abuse - with a prevalence rate of about 40-70%[128].

In a longitudinal study of child abuse in patients with personality disorders, Battle et al.[129] confirmed that sexual abuse frequently occurs in patients with BPD.

When compared to healthy controls or to patients with other psychiatric disorders, borderline patients show significantly higher prevalence rates of sexual abuse during childhood[44, 130-132] Silk et al. (1993) studied 55 borderline patients from which 75% reported having been sexually abused in some way. In a study of Zanarini et al.[133], 62.4% of patients reported of sexual abuse during childhood. Bandelow et al. [123], found 60.3% of the borderline sample being affected by childhood sexual abuse compared to only 2.3% in the control group. Ogata et al.[131] compared BPD patients with depressed patients and found that 71% of the borderline sample and 22% of the depressed sample reported childhood sexual abuse.

Drawn from these studies, it is evident that sexual abuse is very common among borderline patients and it seems to represent a significant risk factor in this disorder.

Studies that examined the severity of sexual abuse, show that borderline patients often experienced sexual abuse in the most severe form[131]. In the sample of borderline patients, assessed by Silk et al. [134], 75% were sexually abused of whom 54% reported longer-lasting abuse, 44% reported of sexual intercourse and 32% were abused by a parent. Zanarini et al. [133] reported that three-quarters of their assessed sample have been abused over a period of at least one year. From these patients, 23.8% were abused at least once in a month and 58% became victims of weekly/daily assaults. Studies that examined the degree of relationship of the offender concluded that a high percentage of offenders were first or second degree relatives or primary caregivers. Paris et al. [132] studied a sample of female borderline patients who were sexually abused and found that 42% of the patients were abused by a parent or another primary caregiver. In the study of Zanarini et al. [133], 43.6% of borderline patients reported abuse by a parent or primary caregiver, 54.7% of patients were abused by a friend or by siblings. Ogata[131] compared borderline patients with a sample of depressive patients, and showed that borderline patients frequently reported sexual abuse by close relatives, such as father (21% vs. 6%), mother (4% vs. 0%), siblings (29% vs. 0%) and other relatives (25% vs. 0%). In addition, 35.4% of the reported sexual abuse has been committed by one single perpetrator, 24.9% by two perpetrators and 39.8% by three or more perpetrators[133]. In 33-78% of cases [132-134], the type of abuse is sexual intercourse, in 19.9%

touching and in 1.7% of cases watching without physical contact[133]. 50.8% of borderline patients experienced sexual abuse combined with physical violence[133].

Silk et al. [134] examined in which way the borderline symptomatology is affected by the severity of sexual abuse. They found that the severity of abuse, most notably repeated abuse, was associated with parasuicidal behaviour and regression in psychotherapy. Sexual abuse by a parent was associated with chronic feelings of hopelessness and worthlessness as well as intolerance against being left alone. From these results, Silk et al. [134] drawn the conclusion that prolonged, repeated sexual abuse may lead to interpersonal problems which are commonly seen in borderline patients.

Taken together, the prevalence and the severity of sexual abuse appear more frequently and in more severe forms in patients with BPD when compared to healthy controls or to patients with other psychiatric disorders[129].

However, it is important to note that sexual abuse is neither a necessary nor a sufficient risk factor for a diagnosis of BPD[44]. There are borderline patients who were never sexually abused and, on the other hand, there are victims of sexual abuse who never develop a borderline diagnosis.

Physical Abuse

Previous studies reported of 46%[121] to 71%[130] physical abuse in borderline samples. In a study of Zanarini et al. [44], 58.9% of the assessed borderline patients were physically abused and mistreated by a primary caregiver. These findings differed significantly from patient groups with other personality disorders, among which only 33% were physically abused. Other studies reported a proportion of 10-73% of parents or other adult caregivers who physically abused their children[121, 130, 131]. Physical abuse in borderline patients often co-occurs with sexual abuse[44, 135]. Thus, in a sample of sexually abused patients, 70% were also physically abused, whereas borderline patients who were not sexually abused reported of physical abuse in only 41.3% of cases[44].

Physical and Emotional Neglect

In addition to sexual and physical abuse, physical and emotional neglect is also common in samples of borderline patients. Zanarini et al. [121] compared borderline patients with patients of antisocial personality disorder and found that physical neglect occurs frequently in BPD but does not significantly distinguishing from patients with antisocial personality disorder. In particular, emotional rejection by the primary caregiver seems to differentiate borderline patients from patients with antisocial personality disorder[121]. Zweig-Frank et al. [136] used the 'Parental Bonding Instrument'[137] to assess the perceived relationship of borderline patients to their parents and showed that borderline patients perceived their parents as emotionally neglecting. These findings are consistent with previous studies[138-140]. In a study of Zanarini et

al. [44], a high percentage of 69.8% borderline patients reported lack of a close relationship to their primary caregivers. Therefore, many borderline patients indicated that their primary caregivers denied their emotions (70.4%) and failed to provide protection (55.6%).

Emotional Abuse

Similar to the described forms of child maltreatment, emotional abuse may also affect parent-child relationship and is critical for the child's further development.
In the study of Zanarini et al.[44], 72.6% of borderline patients reported emotional abuse by a primary caregiver. The authors define emotional abuse as being humiliated or humbled, respectively, being brought to a difficult and hopeless situation. In particular, caregiver's emotional abuse and emotional withdrawal discriminates significantly between borderline patients and patients with other personality disorders. In a study of Bornovalova[141], emotional abuse turned out as the most reliable predictor for the diagnosis of BPD.

Experiences of Early Separation

Early separation from parents or primary caregivers may be a serious life event, especially for young children. The basis for a secure bonding and attachment is set during infancy and early childhood, so that a prolonged or permanent separation from an attachment figure may lead to interpersonal trauma. That may have significant effects on the emotional development of a child[142-144]. Separation from parents or from significant others may occur due to death, divorce, or extended absence. Zanarini et al.[121] reported that 46% of their borderline sample experienced at least one prolonged period of separation from their parents during early childhood (at least one month or longer). In the sample of Ludolph et al.[145], 50% of the assessed borderline patients reported of long periods of separation from mothers or fathers. However, it is important to note that similar distributions of early separation appeared in the psychiatric comparison group. Thus, experiences of early separation constitute no specific risk factor of BPD. However, Crawford et al.[146] showed in a long-term study that prolonged separation from mothers before the age of five is a predictor for borderline symptomatology. Divorce of parents is an event that occurs in about 50% of cases during borderline patients' childhood. However, this factor is not suitable to distinguish these patients from other psychiatric groups. Notably, many borderline patients are of very young age (29.6%: 0-4years) at the time of their parents' divorce, compared to the control group (8.7% [145]).

Other adverse Childhood Experiences

Apart from the previously mentioned traumatic childhood experiences, there are a number of further adversities, which may contribute to the accumulated environmental risk factors in BPD. Thus, many borderline patients reported being grown up in chaotic family situations. These intrafamilial problems may strain the relationship to important caregivers[147]. Familial

problems, such as alcohol abuse of fathers and violent behaviour towards other family members are common in families of BPD patients[123]. Furthermore, the financial situation is often difficult and parents of borderline patients are occasionally unemployed[123]. Another stressful situation may be the rate of mental disorders in first-degree relatives of borderline patients. However, the rates of mental disorders in relatives of BPD patients are comparable to those of patients with other psychiatric diagnoses[145]. Depressive disorders are more common in mothers of borderline patients, drug abuse and alcohol abuse seems to be more common among fathers of BPD patients. Furthermore, mothers of borderline patients were more often diagnosed having themselves a personality disorder[145]. Studies confirmed that borderline patients perceive the relationship to their parents as difficult[148]. They often describe their parents as less caring and too controlling. Zanarini et al.[44] showed some patterns of parent-child interaction that differentiate between BPD and other personality disorders, such as denial of the child's thoughts and emotions, inconsistent behaviour towards the child, providing not enough protection or bringing the child into the role of a parent.

These findings show that borderline patients were often exposed to multiple traumas during childhood. This distinguishes them from patients with other mental disorders. However, it has to be considered that most of the reported studies were conducted retrospectively.

One study assessed childhood trauma in a longitudinal design and aimed to investigate whether sexually and physically abused and neglected children are more likely to develop a borderline diagnosis later in life compared to children without those traumatic experiences[119]. The results from this study suggest that child abuse and neglect increases the risk of BPD later in life[119]. However, further investigations - especially prospective longitudinal studies - are necessary to generate valid results of the association between childhood trauma and the diagnosis of BPD.

Bonding and Attachment

As described above, a pattern of unstable but intense interpersonal relationships is one of the key symptoms in BPD. These difficulties seem to be associated with disturbed attachment patterns, which have often been described in borderline patients. West et al. [135] even defined BPD as a disorder of the bonding system. Secure bonding and attachment develops very early in life. Attachment behaviour in infants is characterized by crying, clinging and running after someone. These behaviours aim to ensure the availability and proximity of the infant's attachment figures and shall activate their protective and caregiving behaviour. To provide a basis for a secure attachment, it is important to respond appropriate and consistent to the infant's needs. This increases the likelihood for the development of a secure attachment and 'basic trust' in other people.

Numerous studies found evidence of insecure attachment patterns in patients with BPD [149]. In most cases, these attachment problems are associated with adverse childhood experiences, such as childhood trauma[150]. A history of childhood trauma may thus seriously impact the bonding system and may lead to insecure attachment later in life[150].

2.2 Early Life Programming

2.2.1 Introduction

There is compelling evidence that adverse events, experienced during early life, are associated with an increased risk for somatic and mental health problems in adulthood[1, 2, 4, 9]. A large body of literature demonstrates that prenatal adversity may lead to an impaired intrauterine development and to an increased risk for chronic diseases in adulthood, such as cardiovascular disorders, hypertension, dyslipidaemia, diabetes type 2, metabolic syndrome, obesity, as well as psychiatric disorders[1, 2]. Low birth weight – a crude marker of a suboptimal intrauterine environment - has repeatedly been shown to predict later disease risk[151, 152]. Thus, robust associations between reduced birth weight and increased risk of later disorders have been found in numerous populations worldwide[152, 153].

Prenatal adverse events, such as prenatal maternal stress, malnutrition, infection, inflammation, smoking, toxins, alcohol intake, and synthetic glucocorticoids have the potential to permanently alter the developing organism and may thus contribute to an increased susceptibility for later pathophysiology. The above mentioned agents may contribute to alterations in offspring's organ structure and function and may cause changes in the set point of neuroendocrine systems, such as the HPA axis [154]. These alterations provide an increased vulnerability for later somatic and mental diseases. If the challenge occurs during so called 'sensitive periods' or 'developmental windows', the organism is specifically sensitive for those early environmental signals[1]. The phenomenon of an increased disease risk following prenatal adversity has been termed 'early life programming'[151, 155-157].

From an evolutionary perspective, early life programming and associated lifelong physiological and behavioural changes may be of advantage if they contribute to the development of a phenotype which is best suited for the extrauterine environment - forecast by the clues available during fetal life. However, if the real environment does not match with the expected environment, the intrauterinely programmed changes may be maladaptive and lead to increased disease susceptibility[2, 10, 154]. For instance, adaptation to limited nutrients in utero has been reported to promote the development of a 'thrifty phenotype', which is characterized by reduced fetal growth and later metabolic efficiency [152, 158]. These metabolic changes increase the likelihood of developing later central obesity, insulin resistance, type-2 diabetes and hypertension, when followed by postnatal overnutrition[12, 152]

However, not only alterations in metabolism and hormone systems may be determined during early life. There is increasing evidence that also behavioural alterations, such as hyperactivity / inattention and the risk for psychiatric disorders - such as mood disorders and schizophrenia - may be programmed in utero[2].

In sum, according to the model of early life programming, harmful prenatal exposures can alter fetal growth and development, producing long-term pathophysiological alterations which may lead to adverse physical or mental health ourcome during childhood, adolescence and adulthood[9, 159-165].

2.2.2 Factors and Mechanisms of Early Life Programming

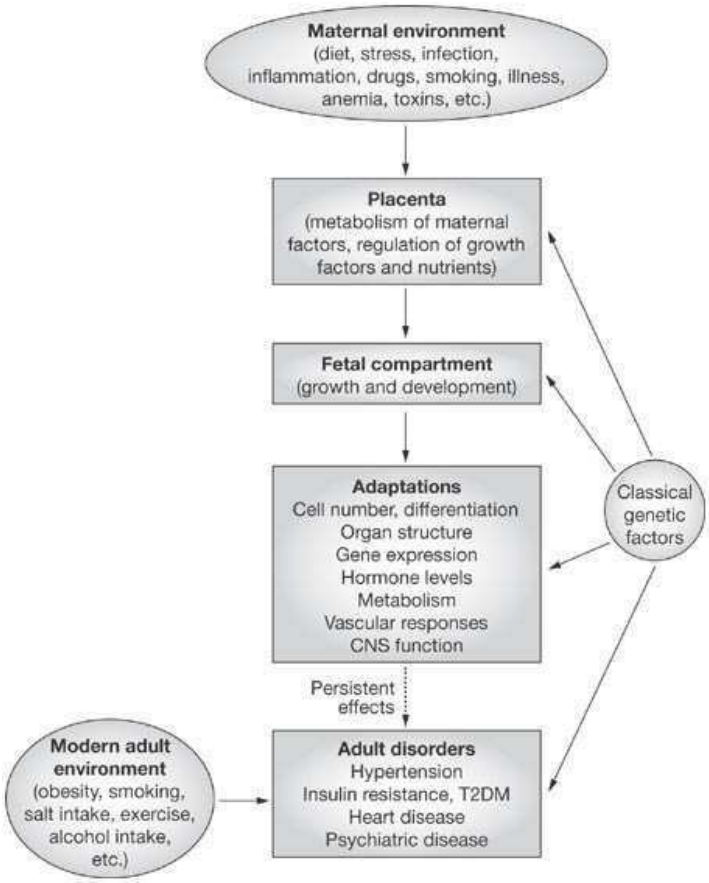
The mechanisms underlying the process of fetal programming are still not fully understood. Possible mechanisms involve changes in neurodevelopment, changes in the set point of neuroendocrine systems, as well as epigenetic changes[2].

Several factors have been described to affect fetal development, such as malnutrition, tobacco smoking, alcohol consumption, drug exposure, maternal infection, maternal diseases as well as prenatal maternal stress (see **Fig. 2**). These factors may affect the fetus either directly by transfer of glucocorticoids or other agents across the placenta or indirectly by altering the oxygen and nutrition supply to the fetus. Stress hormones or toxins, such as nicotine, may act vasoconstrictive to the placenta, and may thus contribute to an impaired transfer of nutrients and oxygen to the developing offspring[2, 166-169].

2.2.2.1 Maternal Stress and Cortisol

One potential mechanism that has repeatedly been assessed is fetal overexposure to maternal stress hormones. These stress hormones may - to a certain extent - cross the placenta and affect the offspring's developing HPA axis. It has been reported that excess glucocorticoids may lead to a downregulation of hippocampal glucocorticoid (GR) and mineralocorticoid receptors (MR) which play a crucial role in the termination of the stress response. Due to these mechanisms, the offspring's HPA axis may be permanently malprogrammed towards an elevated stress sensitivity and reactivity[154]. Numerous studies suggest effects of prenatal maternal stress on behavioural outcomes, such as altered temperament, behavioural problems and impaired cognitive function later in life[2]. Furthermore, an increased risk for schizophrenia[170-172], depression[173] and autism[174, 175] in the offspring has been reported.

Figure 2.2. The Concept of Developmental Programming (Seckl & Holmes, 2007).



Placental CRH

During pregnant state, the placenta itself produces corticotrophin-releasing hormone (CRH) – a hormone which is usually secreted in response to stressful life events by the hypothalamus. CRH stimulates the release of adrenocorticotropin hormone (ACTH) from the pituitary gland, which in turn stimulates the secretion of cortisol by the adrenal cortex [164, 176]. In primates, placental CRH (pCRH) production is stimulated by a positive feedback mechanism, triggered by the presence of cortisol[164, 176]. Thus, abnormally high pCRH concentrations may lead to fetal overexposure to maternal glucocorticoids[177].

11β-Hydroxysteroid Dehydrogenase Type-2

During pregnancy, the placenta constitutes a biochemical 'barrier' to maternal stress hormones which protects the fetus from excess glucocorticoids[177]. This protective mechanism is mediated by the enzyme 11β-hydroxysteroid dehydrogenase type-2 (11β-HSD2), a placental enzyme that rapidly converts active cortisol into inert cortisone[177]. However, the placental barrier is apparently incomplete, as a proportion of maternal

concentrations correlate with lower birth weight and with higher blood pressure later in life[1]. Similar effects were observed in animal models, where inhibition or knockout of placental 11β-HSD2 associates with lower birth weight[152].

2.2.2.2 Nutrition

Adequate fetal supply with nutrients is a crucial precondition during offspring's brain development[178]. It has been reported that lack of micronutrients during pregnancy, such as iron, fatty acids, folate as well as fish intake is associated with later behavioural problems and impaired cognitive function[2, 179-183].

2.2.2.3 Exposure to Tobacco

Another agent that may cause changes in neurodevelopment is nicotine, deriving from maternal cigarette smoke. It binds to fetal nicotinic acetylcholine receptors and may alter the function of the cholinergic as well as other neurotransmitter systems[184-186]. Furthermore, nicotine and other components in tobacco smoke may modulate morphological and functional systems as well as brain circuits involved in the control of emotions. Heath et al. [187] found the cortico-thalamic circuit to be vulnerable for nicotine exposure through the early development. It has been reported that these mechanisms may enhance the risk of hypersensitive passive avoidant behavior [187], irritability, poor self-control and impulsivity in the offspring[188, 189]. Furthermore, several studies have shown that maternal tobacco consumption during pregnancy is an important risk factor for ADHD[190, 191], difficult temperament[192, 193], conduct disorders and externalizing and internalizing problems in children[188, 189]. In a study of Huijbregts et al.[194], prenatal tobacco exposure has been associated with altered neurobiological and behavioral stress reactivity. Furthermore, Ekblad et al. [195] found an increased risk of mental disorders in children, adolescents and young adults who were exposed to prenatal maternal tobacco smoke.

2.2.2.4 Exposure to Drugs and Alcohol

Findings from the literature suggest that prenatal alcohol exposure increases the risk for behavioural problems, cognitive deficits and stress reactivity in the offspring later in life [196-199]. These effects are more pronounced, if the mother consumed high doses of alcohol [199, 200]. Similar effects have been reported after exposure to drugs, such as cocaine[201-203] or marijuana[204, 205]. Fetal exposure to drugs has been shown to increase the risk for behavioural problems as well as cognitive deficits later in life[201, 205].

2.2.2.5 Maternal Prenatal Infection

Maternal infection and diseases during pregnancy seem to be associated with adverse health outcome in the offspring. For instance, prenatal infection appears to increase the risk of schizophrenia later in life[206-211].

2.2.2.6 Epigenetic Effects

These prenatally programmed changes on fetal tissue are thought to be mediated in part by epigenetic changes[152]. For instance, tissue-specific expression of the intracellular glucocorticoid receptor may be affected by early life environmental signals[152]. Thus, excess glucocorticoid exposure during pregnancy may permanently alter tissue glucocorticoid signalling. Notably, these effects may have short-term adaptive benefits but may increase the risk of adverse health outcome later in life[152].

2.2.3 Programming of Physical Health Outcomes

2.2.3.1 Programming of the Heart

Several population-based studies identified a link between low birthweight and increased risk of cardiovascular disorders as well as mortality later in life[7, 212]. Processes of prenatal programming appear to underlie those associations. Thus, it has been reported that fetal exposure to maternal or synthetic glucocorticoids may alter cardiovascular functions in the offspring due to alterations in the development of the cardiac noradrenergic and sympathetic systems [213]. Prenatal glucocorticoid exposure may also increase the reactivity of the enzyme cardiac adenylate cyclase[214] as well as metabolic processes in the heart[215, 216]. Fetal exposure to glucocorticoids appears to increase the protein calreticulin whose overexpression has been associated with cardiac dysfunction and mortality from cardiovascular disorders[177]. These findings may reflect mechanisms of prenatal programming associated with cardiac dysfunctions and death from coronary heart disease in populations characterized by low birth weight[1].

2.2.3.2 Programming of Blood Pressure

The link between birth parameters and alterations in adult blood pressure is one of the best documented and established features of prenatal programming. It has been reported that prenatal glucocorticoid exposure is associated with elevated blood pressure in different species[217-220], including humans[221]. However, not only prenatal exposure to glucocorticoids but also inhibition of 11ß-HSD2 is associated with adult hypertension[222]. Apparently, the timing of exposure is also important: in rats, exposure to glucocorticoids during the final week of pregnancy has been shown to produce permanent hypertension in the adult animal[223]. There are diverse mechanisms involved in the fetal programming of adult hypertension:

Prenatal glucocorticoid exposure leads to irreversible reductions in nephron number[224, 225], it affects vascular responses to vasoconstrictors[226, 227] and it affects the receptor density of the renin-angiotensin system as well as tissue synthesis [228]. Thus, after prenatal administration of dexamethasone, angiotensin 1 and and angiotensin 2 receptors in the kidney are increased and glomerular filtration rate in response to angiotensin 2 is reduced. Finally, prenatal glucocorticoid exposure may alter key barocontrol centers in the brain stem – contributing to adult hypertension[1, 229].

2.2.3.3 Programming of the Kidney

Based on its role in regulating arterial blood pressure[230], the kidney has been studied in the etiology of cardiovascular disorders and hypertension. A reduced number of nephrons is believed to lead to the development of hypertension and renal disease[231]. Numerous studies in animal models and humans suggest that perturbations in the intrauterine environment and subsequent intrauterine growth restriction may result in decreased nephrogenesis[232]. Although decreased nephrogenesis may not be the only factor that is responsible for the generation of a hypertensive phenotype, anyhow, it may contribute to its development[232, 233]. Several factors, such as placental insufficiency, maternal protein restriction, glucocorticoid exposure and high-fat feeding in utero are known to impact the regulation of the renin–angiotensin system; however, also processes of prenatal programming have been discussed[234, 235] .

2.2.3.4 Programming of the Pancreas

Fetal undernutrition has been reported to impair pancreatic β-cell development[236, 237]. It may reduce β-cell mass and contribute to the development of glucose intolerance in the offspring. Maternal malnutrition leads to elevated glucocorticoid levels in the mother and the fetus. The amount of fetal pancreatic insulin correlates inversely with fetal glucocorticoid levels[238]. It has been reported that synthetic glucocorticoids (e.g. dexamethasone) may downregulate beta cell Pdx-1 and induce C/EBPβ key factors in the induction and repression of insulin expression[239]. However, the mechanisms by which pancreatic development is modulated by glucocorticoids are not fully understood[1].

2.2.3.5 Programming of Glucose-Insulin Homeostasis and Metabolism

Studies in animals revealed that fetal overexposure to glucocorticoids may lead to a prenatally ‘programmed’ hyperglycemia and hyperinsulinemia in the offspring later in life[240]. These ‘programming’ mechanisms occur in particular during the last trimester of gestation. Similar effects occur due to prenatal maternal stress or inhibition of 11ß-HSD2[241]. The timing of glucocorticoid exposure seems to be of importance, because exposure to dexamethasone earlier or later during pregnancy does not lead to those effects in the offspring[242, 243].

Glucocorticoids regulate the expression of important hepatic metabolic enzymes, such as phosphoenolpyruvate carboxykinase (PEPCK), which catalyzes a rate-limiting step in the process of gluconeogenesis. Exposure to excess glucocorticoids in rats may lead to offspring that are characterized by permanent elevations in PEPCK mRNA and enzyme activity [242]. Overexpression of PEPCK in hepatoma cells may lead to impairment of insulin suppression during gluconeogenesis[244]. Furthermore, an increased expression of glucocorticoid receptors occurs in the liver of dexamethasone-programmed rats[242, 245]. These animals also show greater plasma glucose responses to exogenous corticosterone, which suggests increased tissue sensitivity to glucocorticoids[1, 242].

2.2.3.6 Programming of Adipose Tissue

It has been reported that prenatal exposure with dexamethasone may program the metabolism of adipose tissue in rats[246]. This may cause a significant increase in the expression of glucocorticoid receptors in the adult animal – but only in visceral fat tissue[246, 247]. One underlying mechanism that may contribute to adiposity and insulin resistance in adulthood seems to be an elevated expression of glucocorticoid receptors in the adipose tissue due to prenatal programming[245].

It has been reported that leptin concentrations in human fetal cord blood correlate with body weight and adiposity at birth[248]. Furthermore, treatment of pregnant rats with dexamethasone is associated with a reduced level of fetal plasma leptin and placental leptin[240, 249] and with placental expression of the Ob-Rb receptor which mediates leptin action[249]. An intriguing finding is that leptin treatment of malnourished pregnant and lactating rats seems to be able to partially reverse the prenatally programmed metabolic changes in the adult animal[1, 250].

2.2.4 Early Life Programming of Behaviour and Mental Health

2.2.4.1 Prenatal Programming of Temperament and Behavioural Traits

Processes of prenatal programming may not only affect physical health, but may also increase the risk for mental disorders and behavioural problems later in life. An increased vulnerability to psychopathology may be mediated by prenatal programming of temperamental traits - which are known to act as potential precursors of later mental health problems[2]. There are several temperamental traits that have been associated with prenatal adversity, such as 'negative affectivity'[251], 'fear of uncertainty and shyness'[252], 'hostile behaviour'[253], as well as inattention and problems in self-regulation[254]. Furthermore, abnormal behavioural outcomes in infants, such as emotional and cognitive deficits have been associated with prenatal adversity. These alterations were reflected in a poor performance in the Bayley Scales of Infant Development in infants whose mothers

experienced high levels of stress and anxiety during pregnancy – associated with high levels of cortisol[168, 255-258].

Temperamental differences, behavioural traits and personality characteristics can be observed very early in life and have been reported to be associated with an increased risk for later psychopathology[2]. In particular, emotional disorders, such as anxiety and depression, as well as disruptive disorders, such as conduct disorders and ADHD[259] were often preceded by temperamental alterations.

2.2.4.1 Behavioral and Mental Health Problems in Childhood and Adolescence

Several studies showed increased risk for hyperactivity and inattention in children with low birth weight[260-264]. Similar effects were reported for peer problems, antisocial behaviour[265-268], general behavioural problems[261, 269-273] and total behavioural difficulties[254, 268]. Prenatal adversity seems to be associated with increased risk of both, internalising and externalising problems – which has been shown, for instance, in a longitudinal cohort study of Bohnert and Breslau[274]. A recent review reports increased emotional problems in children, exposed to prenatal adversity, which were born with low birth weight[275]. Similar problems were observed in animal models. Rats that were intrauterinely exposed to prenatal maternal stress showed more anxiety-like behaviour as well as increased locomotor reactivity[276-278]. These associations suggest that both externalizing and internalizing problems may be mediated by prenatal programming.

However, prenatal adversity is not only associated with behavioural problems during childhood and adolescence – it has also been reported to be related to mental health problems in adult life. Thus, an adverse intrauterine environment has been described in schizophrenia[279], depression[280, 281], anxiety disorders [282], psychotic symptoms[283], PTSD[284], and personality disorders[285, 286].

2.2.4.2 Mental Health Problems in Adulthood

Schizophrenia

There is evidence that prenatal adverse environmental events play a role in the pathogenesis of schizophrenia[287]. Evidence for histopathological alterations in different brain regions (cerebral cortex, cerebellar vermis, limbic system, brain stem) and findings of cerebral asymmetry may suggest a developmental component in that disorder[288]. A meta-analysis revealed that low birth weight and other obstetric complications act as significant risk factors in schizophrenia[289, 290]. Wahlbeck et al.[290] found in a large population-based cohort study that the diagnosis of schizophrenia was associated with low birth weight, small size at birth, low placental weight and low maternal body mass index. Studies of the Dutch wartime famine suggest a 2-fold increased risk of schizophrenia in individuals conceived during the hunger

winter[291, 292]. Prenatal famine exposure in schizophrenic patients has been reported to be related to decreased intracranial volume and a high number of brain abnormalities[293].
These studies suggest an increased relative risk for schizophrenia, associated with prenatal adversity and low birth weight. However, mixed results have been reported[2, 294].

Mood disorders

There is increasing evidence that early environmental events may also impact the risk for mood disorders. Quite similar to the findings in schizophrenic patients, exposure to Dutch famine seems to be associated with increased risk for depressive disorders - especially when exposed during the second or third trimester of pregnancy[295, 296]. A Swedish study found higher suicide rates in individuals of lower birth weight[297] which may suggest that mood disorders might be associated with prenatal adversity and altered fetal growth.
A British cohort study revealed that women who were small at birth (<3.5 kg) showed a 1.3-fold increased risk of depression in adult life - compared with those who had higher birth weights (>3.5 kg) [298]. Furthermore, prenatal adversity has been shown to be a significant risk factor for depression in adolescent girls even when adjusted for several confounding variables[281]. However, there are diverse studies who did not find an association between prenatal adversity / fetal growth and later risk of affective disorders[2, 299, 300]. Taken together, associations of fetal growth and mood disorders are relatively weak and show partly inconsistent results.

Personality disorders

There are several studies that found associations of prenatal adversity with later personality disorders. Male individuals, exposed to the Dutch wartime famine during the first or second trimester of pregnancy showed an increased risk for antisocial personality disorder[286]. These findings are consistent with studies of antisocial behaviour problems in children, following prenatal adversity[265-268]. In the same cohort of men and women which were intrauterinely affected by the famine, Hoek et al.[285] reported an increased risk for schizoid personality disorder. These findings are consistent with the reported risk for schizophrenic disorders in individuals exposed to famine during fetal life, as described above – which may suggest an association of prenatal adversity and increased risk for schizophrenic spectrum disorders[2].

As reviewed in this chapter, there is a large body of evidence, linking prenatal adversity with adverse physical and mental health outcome in the offspring. To the best of our knowledge, this association has not yet been studied in patients with BPD. In the following three chapters, the results from our own study of pre- and perinatal adversity in borderline patients and healthy controls are presented, interpreted and discussed.

Chapter 3

PRENATAL ADVERSITY –

A RISK FACTOR IN BORDERLINE PERSONALITY DISORDER?

3.1 Abstract

Background

Patients with borderline personality disorder (BPD) show a high prevalence of early adversity, such as childhood trauma. However, it has been reported that even prenatal adverse conditions, such as prenatal maternal stress, drugs, tobacco smoking or medical complications, may be associated with an increased risk of mental disorders in the offspring. We here investigated prenatal adversity as a potential risk factor in the pathogenesis of BPD and tested the predictive value of the supposed prenatal risk factors.

Methods

100 patients with a DSM-IV diagnosis of BPD and 100 matched healthy controls underwent semi-structured interviews about the course of pregnancy, maternal stressors, birth complications and childhood trauma. Further information was obtained from participants' mothers and from prenatal medical records.

Results

Borderline patients were significantly more often exposed to adverse intrauterine conditions, such as prenatal maternal stress, like traumatic stress (p=.015), familial conflicts (p=.004), low social support (p=.004), and relationship problems (p=.014), but also prenatal medical complications (p=.008) and prenatal tobacco exposure (p=.004).

Logistic regression analyses revealed that reported prenatal risk factors account for 25.7% of the variance in BPD. Prenatal tobacco exposure (OR 3.37; CI=1.49-7.65; p=.004) and prenatal medical complications (OR 2.87; CI=1.29-6.38; p=.010) seem to mark important risk factors. After controlling for childhood adversity and parental socioeconomic status, prenatal risk factors still account for 10.4% of the variance in BPD.

Conclusions

This study provides first evidence of an association between prenatal adversity and the diagnosis of BPD. Our findings suggest that prenatal adversity constitutes a potential risk factor in the pathogenesis of BPD.

3.2 Introduction

Borderline personality disorder (BPD) is a common psychiatric disorder and the most frequent personality disorder in clinical settings [13, 24]. It affects about 1–6% of the general population and 10%-25% of psychiatric inpatients [20, 23, 301, 302]. Although its etiology is only partly known, most studies recognized a range of possible determinants, including genetic, neurobiological, and psychosocial factors, which interact at various levels [13]. While twin studies estimated the heritability of BPD/BPD traits to be 30-40% [51, 303, 304], a high prevalence of childhood trauma is reported consistently by patients with BPD. The majority of borderline patients report various types of adverse childhood experiences, such as sexual abuse, physical maltreatment and emotional neglect [44, 113-116, 119, 121, 122, 305].

However, genetic liability and a history of childhood trauma may not be the only risk factors for BPD: During the past two decades, a large body of evidence emerged, suggesting that even *prenatal* adversity is an important risk factor for psychopathology [2, 306]. It has been reported that prenatal maternal stress [152], drugs [307, 308], tobacco smoking [309, 310], or medical complications [310] may lead to intrauterine growth restriction [311] and to an impaired fetal development. In the long-run, these factors may increase the risk for somatic and mental disorders in adulthood [4, 281, 312, 313] - a phenomenon called 'prenatal programming' [11, 314, 315]. Furthermore, the exposure to an adverse fetal environment is related to abnormal behavioural outcomes in infants, such as emotional and cognitive deficits in early life [168, 255-258, 316]. Prenatal adversity has been associated with mental disorders such as schizophrenia [279, 317], depression [280, 281], posttraumatic stress disorder [284], and attention deficit hyperactivity disorder (ADHD) [318].

Although it is now widely recognized that the exposure to an adverse fetal environment can have persisting effects on individual's physiology and mental health, this association has not yet been studied systematically in BPD.

We hypothesized that prenatal adversity serves as an additional risk factor in the pathogenesis of BPD. Thus, the purpose of the present study is to investigate whether patients with BPD were exposed more often to prenatal adverse conditions compared to healthy controls and to test the predictive value of the observed risk factors.

3.3 Methods and Materials

3.3.1 Sample

One hundred patients who met the DSM-IV [19] criteria for borderline personality disorder and 100 healthy control subjects participated in the study. Patients and controls were matched for sex, age and education (see **Table 3.1**).

Patients were recruited from university hospitals (University Medical Centre Mainz (N=39), University Hospital Freiburg (N=17), public psychiatric hospitals (Wiesbaden (N=7), Klingenmünster (N=3), Alzey (N=2)), psychiatric and psychotherapeutic practices (N=10), support groups (N=3) and via internet-announcements (N=19) in Germany. The patient sample consists of 22 (22%) inpatients, 52 (52%) outpatients and 26 (26%) patients without a current treatment. In the patient group, 86% (n=86) showed at least one or more comorbid DSM-IV axis-I disorders and 68% (n=68) of patients were diagnosed having one or more comorbid DSM-IV axis-II disorders (see **Table 3.2**).

Initially, 106 patients were recruited, from which six patients were excluded because they did not fulfil the diagnostic criteria of BPD (n=2) or could not provide sufficient information about the time of pregnancy (n=4). Furthermore, we excluded 11 control subjects who did not meet the required matching criteria (sex (n=3), age (n=5), education (n=2)) and one participant who showed a history of a severe mental disorder as well as another subject who refused participation.

The recruitment was completed when 100 subjects in each group fulfilled the inclusion criteria and confirmed participation. Demographic variables of patients and controls are presented in **Table 3.1**.

3.3.2 Procedure

After a full description of the research procedure, written informed consent was obtained from all subjects. The study protocol was approved by the local ethics committee. The investigation was conducted in accordance with the guidelines described in the declaration of Helsinki.

All patients and controls were diagnosed using the Structured Clinical Interview (SCID [319]) for DSM-IV. The diagnostic interviews were conducted by a trained psychologist with extensive clinical and research experience.

Prenatal adversity was assessed using a semi-structured interview about pre- peri- and postnatal life events, based on Neuropattern Diagnostics[320]. One part of the Neuropattern instrument is the Pre/Peri/Postnatal Stress Questionnaire (NPQ-PSQ, see below). The participants were instructed to review the interview questions together with their mothers

prior to the interview. Mothers of participants were asked to fill in the NPQ-PSQ and to provide objective information about maternal age at birth, maternal parity, length of gestation and subjects' weight, height and head circumference at birth. These data were obtained from prenatal medical records which are handed to the mother during her first prenatal visit by the obstetrician. All interviews were conducted personally by trained health professionals. The raters were regularly supervised.

Information about prenatal adversity could be obtained from 180 (90.5%) mothers of participants, from 73 (36.7%) fathers or other close relatives and from 75 (37.5%) prenatal medical records. Participants were excluded if they had no access to information about birth parameters, prenatal adversity, birth complications and childhood trauma. Further exclusion criteria were acute suicidality, acute intoxication (alcohol, drugs), a history or a current episode of schizophrenia, bipolar disorder I, organic mental disorders or intellectual disability.

Table 3.1. Demographic Variables

	N or Mean (SD)	
Characteristic	**Patients**	**Controls**
Age, y		
18-20	9	8
21-30	49	45
31-40	19	25
41-50	20	17
51-60	3	5
Mean age	31.63 (09.73)	32.02 (10.25)
Sex		
F/M	90/10	90/10
School Education		
High school graduation	43	45
Advanced technical college entrance graduation	7	6
Secondary school graduation	37	38
Secondary general school graduation	12	11
No school leaving certificate	1	0
Education		
University degree	13	14
Technical college degree	2	3
Student	17	23
University drop-out	2	0
Professional education	46	50
Apprentice	9	9
Without professional education	11	1

SD= Standard Deviation; N= Number; Y= Years; F= Female; M= Male.

Table 3.2. Axis I and II Comorbidities in Patients with BPD

	Frequency	
Diagnosis	**N**	**%**
DSM-IV Axis II Comorbidities		
Cluster A Personality Disorder	27	27
Cluster B Personality Disorder	21	21
Cluster C Personality Disorder	52	52
DSM-IV Axis I Comorbidities		
Panic Disorder	24	24
Social Phobia	21	21
Specific Phobia	32	32
Generalized Anxiety Disorder	21	21
Posttraumatic Stress Disorder	31	31
Obsessive Compulsive Disorder	12	12
Major Depression	37	37
Dysthymia	10	10
Somatoform Disorders	15	15
Eating Disorders	15	15
Substance Abuse / Dependency	41	41
Attention Deficit Hyperactivity Disorder	28	28.9

N= Number.

3.3.3 Instruments

To assess the overall adversity during pregnancy, the Pre/Peri/Postnatal Stress Questionnaire[320] contains an 'adversity score' that measures the individual number of prenatal adverse events. The NPQ-PSQ consists of items about prenatal maternal stressors (such as traumatic stress, chronic stress, low social support, family conflicts, partnership problems, sexual harassment, physical threat), medical complications, drug intake, malnutrition or smoking, socioeconomic variables (such as financial constraints, monthly income, parental education), birth complications (such as caesarean section, forceps delivery, hypoxia), birth risk factors, birth outcome (such as size, weight, and head circumference at birth), length of gestation, postnatal adversity, and childhood trauma.

The presence or absence of any event is assessed by binary questions. If any question has been affirmed by the mother, she was asked to specify the week of gestation for each particular event.

The NPQ-PSQ further contains a rating scale on perceived stress during pregnancy, on a 0- to 10-point Likert scale, where 0 means 'no perceived stress' and 10 means 'high perceived stress'. The NPQ-PSQ data on postnatal adversity were validated by the accordant subscales of the Childhood Trauma Questionnaire (CTQ [321], German adaptation [322]), a reliable and valid self-rating questionnaire that is used to investigate subjects' childhood

trauma history. It measures 3 types of abuse (physical, sexual, emotional), and 2 types of neglect (physical, emotional). The CTQ is the most validated and widely used retrospective trauma questionnaire.

To assess the impact of prenatal adversity on different sub-domains of borderline symptomatology, we applied measures on borderline-specific domains, such as impulsivity (UPPS Impulsive Behavior Scale, German adaptation [323]), affective instability (Affective Lability Scale (ALS) [324]), identity disturbance (Identity Disturbance Questionnaire (IDQ) [325]), dissociative behaviour (Dissociative Experience Scale (FDS), German adaptation [326]), sensation seeking (Sensation Seeking Scale, (SSS-V), German adaptation [327]), borderline symptoms in general (Borderline Symptom List (BSL) [328]) and borderline symptoms severity (Borderline Personality Disorder Severity Inventory (BPDSI) [329]).

3.3.4 Statistical Analyses

The data were expressed as percentages or mean values and standard deviation. The differences between the groups were tested for significance, using Student's *t* test, Fisher's exact test and Mann-Whitney-U-test, when appropriate. The point biserial correlation coefficient (r_{pb}) was used to assess correlations between metric and dichotomous variables.

To determine the predictive value of prenatal risk factors, a logistic regression analysis was performed that contains the diagnosis of BPD as dependent variable and 15 prenatal risk factors as independent variables.

In the next step, we applied a hierarchical logistic regression model to control for childhood trauma and for parental socioeconomic status. In the first block, we controlled for sexual abuse, physical maltreatment and emotional neglect and in the second block for maternal education and parental monthly income (1=low; 2=average; 3=high).

In the third step, multiple linear regression models (stepwise) were performed to identify the predictive value of prenatal risk factors in specific sub-domains of borderline symptomatology. Statistical significance was set at 0.05. All analyses were carried out using the SPSS for Windows 18.0 program.

3.4 Results

3.4.1 Prenatal Adversity

We found evidence of a high prevalence of prenatal adversity in BPD. The number of prenatal adverse events – measured by the PSQ adversity score - differed highly significant between the patient- and the control group. On average, borderline patients achieved a score of 4.94 (SD=2.95) prenatal adverse events, whereas the control group achieved a score of 3.52 (SD=2.31; t_{198}=3.79; p<.001) prenatal adverse events.

Furthermore, mothers of borderline patients perceived their pregnancy as significantly more stressful compared to mothers of healthy controls (BPD: 4.24 (SD=3.13); CG: 3.35 (SD=3.05); t_{196}=2.02; p=.044). The perceived stress scale was highly correlated with the 'PSQ adversity score' (r=.760; p<.001).

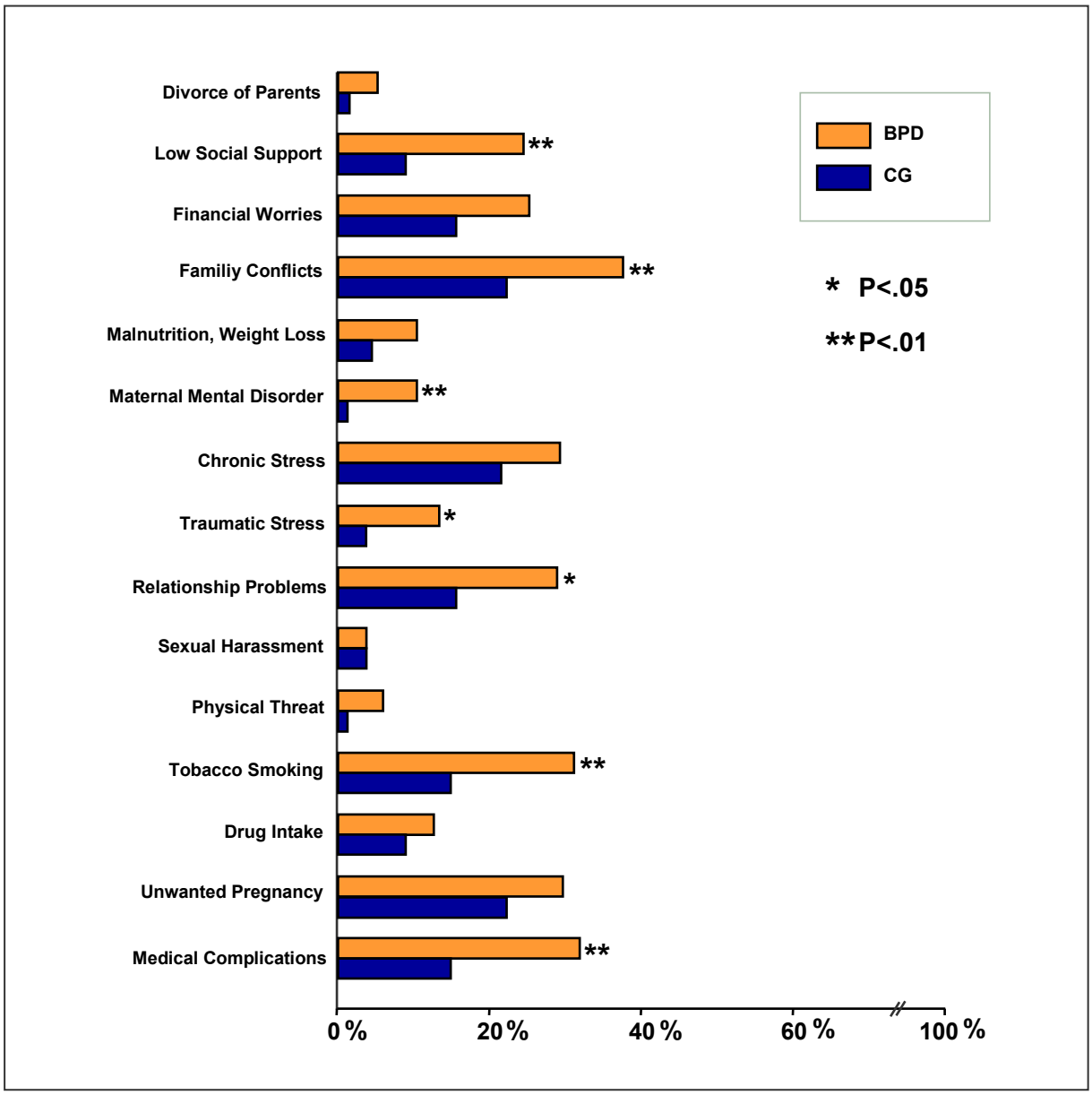
Post hoc analyses revealed that mothers of borderline patients were exposed significantly more often to severe traumatic stress during pregnancy (BPD: n=12 (12%), CG: n=3 (3%); p=.015) such as death or suicide of a close relative, death of a child, severe material loss or rape during pregnancy. They reported significantly more often of severe familial conflicts (BPD: n=38 (38%), CG: n=20 (20%); p=.004) and relationship problems during gestation (BPD: n=29 (29%), CG: n=15 (15.2%); p=.014) as well as of low social support by others (BPD: n=24 (24%), CG: n=9 (9.1%); p=.004).

Furthermore, mothers of borderline patients smoked tobacco significantly more often during pregnancy (BPD: n=31 (31%), CG: n=14 (14.1%); p=.004). Medical complications, such as preterm contractions, preterm opening of the cervix, bleeding, nausea and vomiting with weight loss or pelvic presentation emerged more often in pregnancies of borderline patients compared to healthy controls (BPD: n=30 (30.9%), CG: n=15 (15.2%); p=.008). Furthermore, mothers of borderline patients had themselves more often a psychiatric diagnosis during pregnancy (e.g. schizophrenia, depression, BPD, or alcohol abuse; BPD: n=10 (10%), CG: n=1 (1%); p=.005)). No significant differences were found with respect to malnutrition, weight loss, drug intake (e.g. cortisone), financial situation and diverse psychosocial stressors (e.g. sexual harassment, physical threat). The differences of prenatal adverse events in borderline patients and healthy controls are presented in **Figure 3.1**.

3.4.2 Postnatal Adversity

We also found a high prevalence of postnatal adversity and childhood trauma in patients with BPD. Borderline patients reported significantly more often of childhood sexual abuse (BPD: n=49 (49%); CG: n=5 (5%); p<.001), physical maltreatment (BPD: n=41 (41%); CG: n=4 (4%); p<.001) and emotional neglect (BPD: n=63 (63%); CG: n=14 (14%); p<.001) compared to healthy controls. These findings could be confirmed in the total scores of the corresponding CTQ subscales: sexual abuse (BPD: 9.37 (SD=5.92); CG: 5.53 (SD=2.10); t_{190}=5.98; p<.001), physical maltreatment (BPD: 8.66 (SD=5.45); CG: 5.66 (SD=1.59); t_{191}=5.16; p<.001), emotional neglect (BPD: 13.34 (SD=6.63); CG: 8.05 (SD=3.40); t_{190}=6.91; p<.001). PSQ and CTQ subscales were highly correlated (sexual abuse: r_{pb}=.720; p<.001, physical maltreatment: r_{pb}=.728; p<.001, emotional neglect: r_{pb}=.574 p<.001).

Figure 3.1. Prenatal Adversity in Borderline Patients and Healthy Controls



BPD = Borderline Patients; CG= Control Group; *P* = Probability Score.

3.4.3 Birth Outcome and Maternal Data

There were no significant differences in birth outcome between borderline patients and healthy controls (**Table 3.3**). Birthweight, size at birth, head circumference and gestational length differed not significantly; as well as duration of delivery and time when the mother came to know to be pregnant. The same applies to mothers' size and body weight which differed not significantly between both groups. However, mothers of borderline patients were slightly younger than mothers of healthy controls and had a lower level of education, whereas father's educational level differed not significantly between both groups (maternal education: Mann-Whitney *U*: p=.008; paternal education: Mann-Whitney *U*: p=.616). For detailed information on parental educational level, see **Table 3.4**.

Table 3.3. Birth Outcome and Maternal Data

	Mean (SD)		T	df	*P*
Birth Outcome	**Patients**	**Controls**			
Birthweight (gr.)	3231.11 (654.29)	3360.71 (550.91)	-1.47	185	.144
Size at birth (cm)	50.64 (4.30)	51.34 (2.72)	-1.31	171	.192
Length of gestation (week of gestation)	39.07 (2.99)	39.33 (2.59)	-6.54	189	.514
Head circumfence (cm)	34.49 (1.97)	33.95 (5.43)	1.13	87	.261
Duration of delivery (h)	6.91 (7.66)	7.07 (7.46)	-0.14	169	.887
Week of gestation when mother came to know to be pregnant	6.35 (4.18)	6.24 (2.92)	0.20	164	.843
Maternal Data	**Patients**	**Controls**			
Age of mother when she became pregnant (y)	26.27 (5.62)	27.86 (5.30)	-2.04	196	.042
Weight of mother when she became pregnant (kg)	61.98 (15.68)	61.75 (8.34)	0.12	171	.905
Size of mother (cm)	165.39 (7.14)	164.90 (6.61)	0.51	196	.613

T = *t*-value; df = degrees of freedom; *P* = Probability Score.

Table 3.4. Parental Education

	N (%)	
Maternal Education	**Patients**	**Controls**
University degree	5 (5%)	16 (16%)
Technical college degree	1 (1%)	7 (7%)
High school graduation	5 (5%)	7 (7%)
Secondary school graduation	34 (34%)	28 (28%)
Secondary general school graduation	52 (52%)	39 (39%)
No school leaving certificate	3 (3%)	3 (3%)
Paternal Education		
University degree	18 (18.8%)	21 (21%)
Technical college degree	4 (4.2%)	8 (8%)
High school graduation	7 (7.3%)	5 (5%)
Secondary school graduation	19 (19.8%)	20 (20%)
Secondary general school graduation	44 (45.8%)	40 (40%)
No school leaving certificate	4 (4.2%)	6 (6%)

N= Number.

3.4.4 Prenatal Adversity as a Predictor for the Diagnosis of Borderline Personality Disorder

The logistic regression analysis revealed that prenatal risk factors account for 25.7% of the variance in the diagnosis of BPD. Prenatal maternal tobacco smoking (OR 3.37; CI=1.49-7.65; p=.004) and medical complications (OR 2.87; CI=1.29-6.38; p=.010) turned out to be significant predictors for the diagnosis of BPD.

Trend findings were obtained for stress-related variables, such as 'low social support during pregnancy' (p=.058), 'traumatic maternal stress' (p=.066) and 'sexual harassment during pregnancy' (p=.080).

3.4.5 Delineating Prenatal from Postnatal Risk Factors

To delineate prenatal from postnatal risk factors, a hierarchical logistic regression analysis was performed. In the first block, we controlled for postnatal adversity (childhood sexual abuse, physical maltreatment, emotional neglect) and in the second block, we controlled for parental socioeconomic status (maternal education and parental income).

Childhood trauma alone accounted for 48.4% of the variance of the diagnosis of BPD whereas parental socioeconomic status accounted for 0.8% of the variance.

After controlling for childhood adversity and parental socioeconomic status, prenatal risk factors still account for 10.4% of the variance of the diagnosis of BPD (**Table 3.5**). In both regression models, we adjusted for maternal mental disorders.

3.4.6 Sub-Domains of Borderline Personality Disorder

After identifying prenatal risk factors as significant predictors for the diagnosis of BPD, we tested - in the next step - which specific risk factors predicted particular borderline sub-domains which constitute parts of the whole borderline symptomatology.

For that reason, we applied stepwise multiple linear regression models with impulsivity (UPPS), affective instability (ALS), dissociation (FDS), identity disturbance (IDQ), sensation seeking (SSS-V) and severity of borderline symptoms (BSL; BPDSI) as dependent variables and prenatal risk factors as independent variables. The same set of prenatal predictors was investigated as in the previous analysis (see Table 5 for complete list).

In each regression model, we adjusted for childhood trauma (sexual abuse, physical maltreatment, emotional neglect) and for maternal mental disorders. The predictors and findings of each borderline sub-domain are presented in **Table 3.6**.

The regression models revealed that the variables 'prenatal maternal smoking' and 'prenatal medical complications' constitute again important risk factors. Tobacco smoking during pregnancy turned out to be a significant predictor for the sub-domains 'impulsive behaviour' (p=.001), 'affective instability' (p=.022) and 'sensation seeking behaviour' (p=.013). Separate analyses revealed that these results were not an effect of a comorbid diagnosis of ADHD, since prenatal tobacco exposure remained a significant predictor in the group of borderline patients without a comorbid ADHD diagnosis: Impulsivity (BPD without ADHD (n=69): p=.034; BPD with ADHD (n=28): p=.284); affective instability (BPD without ADHD (n=69): p=.039; BPD with ADHD (n=28): p=.660). Since n=31 (31%) patients and n=14 (14%)

Table 3.5. Prenatal Adversity, Childhood Trauma, Socioeconomic Status (Hierachical Logistic Regression Analysis)

			Block 1			Block 2			Block 3	
	Predictors	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**	**OR**	**95%CI**	**P**
Childhood Adversity	Sexual abuse	7.52	2.55-22.13	<.001	7.47	2.53-22.09	<.001	15.24	3.89-59.67	<.001
	Physical maltreatment	5.07	1.51-17.03	.009	4.64	1.35-15.89	.015	7.27	1.37-38.67	.020
	Emotional neglect	5.52	2.514-12.14	<.001	4.87	2.18-10.92	<.001	7.47	2.61-21.42	<.001
Parental Socio-Economic Status	Maternal education				1.16	0.87-1.56	.308	1.15	0.81-1.62	.436
	Parental income				1.21	0.73-2.02	.462	1.44	0.79-2.61	.237
Prenatal Adversity	Divorce of parents							1.13	0.06-20.78	.935
	Low social support							3.79	0.70-20.39	.121
	Financial worries							0.12	0.02-0.51	.005
	Family conflicts							1.71	0.55-5.31	.356
	Malnutrition/weight loss							1.43	0.26-8.03	.682
	Maternal mental disorder							0.41	0.02-7.79	.555
	Chronic stress							0.29	0.08-1.03	.055
	Traumatic stress							7.88	0.76-81.45	.083
	Relationship problems							2.35	0.65-8.57	.194
	Secual harassment							0.12	0.01-2.91	.192
	Physical threat							0.06	0.02-1.49	.086
	Tobacco consumption							1.45	0.46-4.58	.522
	Drugs (Cortisone)							1.41	0.31-6.37	.658
	Unwanted pregnancy							1.59	0.53-4.74	.408
	Medical complications							2.43	0.91-6.51	.077

OR= Odds Ratio; CI= Confidence Interval; *P*= Probability Score.

controls were either only prenatally or pre- and postnatally exposed to tobacco smoke and n=30 (30%) patients and n=18 (18%) controls were only postnatally exposed to tobacco smoke, we adjusted for postnatal tobacco exposure in the stepwise linear regression models. The effects of prenatal maternal smoking remained stable in impulsivity (p=.001), affective instability (p=.022) and sensation seeking behaviour (p=.013) despite adjusting for postnatal tobacco exposure.

The variable 'prenatal medical complications' emerged as predictor for borderline symptomatology in general (p=.022), measured by the Borderline Symptom List (BSL) as well as for the general severity of borderline symptoms (p=.049), (measured by the Borderline Personality Disorder Severity Index (BPDSI)). Furthermore, medical complications act as predictor for identity disturbance (p=.029) and affective instability (p=.041).

Table 3.6. Sub-Domains of Borderline Personality Disorder (Stepwise Linear Regression Analysis)

Subdomains	Predictors			
Impulsivity (UPPS)		**ß**	**T**	**P**
	Tobacco consumption (prenatal)	0.22	3.25	.001
	Financial worries (prenatal)	-0.20	-2.64	.009
	Relationship problems (prenatal)	0.29	3.91	<.001
	Emotional neglect (postnatal)	0.28	3.97	<.001
Affective Instability (ALS)				
	Tobacco consumption (prenatal)	0.16	2.31	.022
	Medical complications (prenatal)	0.14	2.06	.041
	Sexual abuse (postnatal)	0.18	2.40	.017
	Emotional neglect (postnatal)	0.27	3.79	<.001
Sensation Seeking (SSS-V)				
	Tobacco consumption (prenatal)	0.18	2.51	.013
	Financial worries (prenatal)	-0.22	-2.87	.005
	Family conflicts (prenatal)	0.15	2.01	.046
Dissocation (FDS)				
	Medical complications (prenatal)	0.15	2.37	.019
	Sexual abuse (postnatal)	0.36	5.23	<.001
	Emotional neglect (postnatal)	0.26	4.14	<.001
Identity Disturbance (IDQ)				
	Medical complications (prenatal)	0.14	2.21	.029
	Sexual abuse (postnatal)	0.32	4.53	<.001
	Emotional neglect (postnatal)	0.25	3.79	<.001
Borderline Symptoms (BSL)				
	Medical complications (prenatal)	0.15	2.31	.022
	Low social support (prenatal)	0.15	2.40	.017
	Sexual abuse (postnatal)	0.30	4.40	<.001
	Emotional neglect (postnatal)	0.29	4.19	<.001
Borderline Severity (BPDSI)				
	Medical complications (prenatal)	.021	2.00	.049

ß = Beta; T= T-value; *P* = Probability Score.

3.5 Discussion

To the best of our knowledge, this is the first study that systematically and comprehensively assesses prenatal adversity as a potential risk factor in the etiology of BPD. This research may be of importance in terms of elucidating another potential component in the multifactorial genesis of BPD. Prenatal adversity has been extensively assessed in a large, carefully matched and reliably diagnosed sample of 200 participants. We obtained objective and subjective information from participants as well as from mothers or close relatives.

Our aims were to investigate whether borderline patients were exposed more often to prenatal adverse events compared to healthy controls and to test which risk factors might play a role in the etiology of BPD. Furthermore, we aimed to identify particular prenatal risk factors that might predict single sub-domains of borderline symptomatology.

We found that borderline patients reported significantly more often of adverse intrauterine conditions compared to healthy controls. Significant group differences emerged in several stress-related variables, such as 'traumatic stress', 'familial conflicts' or 'low social support' but also in the variables 'tobacco exposure during pregnancy' and 'prenatal medical complications'. Analogous to the high number of prenatal adverse events, mothers of borderline patients perceived their pregnancy as significantly more stressful compared to mothers of healthy controls.

Prenatal risk factors account for a substantial percentage of 25.7% of the variance in the diagnosis of BPD. Hereby, prenatal tobacco exposure and prenatal medical complications emerged as the most important predictors. These findings could be confirmed in relevant borderline sub-domains, such as impulsivity, affective instability, sensation seeking behaviour, identity disturbance and severity of borderline symptoms. After adjusting for childhood trauma and parental socioeconomic status, prenatal risk factors still account for 10.4% of the variance in the diagnosis of BPD. Our findings are consistent with previous research that report prenatal adversity in several other axis-I and axis-II disorders [2].

In the present study, prenatal tobacco exposure turned out to be a significant predictor for the diagnosis of BPD. In particular, the sub-domains 'impulsivity', 'affective instability' and 'sensation seeking behavior' are closely associated with prenatal maternal smoking. Several studies have shown that maternal tobacco consumption during pregnancy is also an important risk factor for the diagnosis of ADHD [190, 191, 330-332], a disorder whose symptomatology (especially impulsivity, affective instability and sensation seeking behavior) is partly overlapping with borderline psychopathology. These findings may suggest a common prenatal pathogenetic pathway which may be reflected in the high comorbidity rates between both disorders. However, the effects of prenatal tobacco exposure remained stable even after controlling for a comorbid ADHD diagnosis.

Human and animal studies suggest an association between prenatal tobacco exposure and structural and neurobiological changes in the offspring' brain. These alterations include smaller volume of specific brain structures [333], cortical thinning [334], disruptions of white matter microstructure [335] and alterations in receptor density in specific brain regions [336, 337]. It is unclear whether structural or functional brain abnormalities seen in BPD, such as volume reductions in frontolimbic and parietal areas [13, 17, 98, 338-340], impaired connectivity [18, 341-343] or impaired inferior frontal white matter microstructure [344], are at least in part mediated by pre- and/or postnatal tobacco exposure. Our results suggest that future brain imaging studies should control for pre- and postnatal tobacco exposure, since alterations in central nervous system might be mediated by nicotine and other components in cigarette smoke. Nicotine can bind to fetal nicotinic acetylcholine receptors and exhibit profound effects on neurodevelopment that may result in behavioral alterations [187], altered stress reactivity [194], or elevated risk for mental disorders later in life [195, 345].

In our sample, 30.9% of mothers of borderline patients reported medical complications during pregnancy. These complications could reflect a poor fetal environment which has been shown to be linked with adverse health outcomes in the offspring [345]. In the present study, 'prenatal medical complications' were not only associated with the borderline diagnosis itself, but predicted moreover a more severe phenotype according to BSL and BPDSI total scores. Furthermore, we found medical complications as predictor for the sub-domains 'identity disturbance' and 'affective instability'.

There is the possibility that postnatal adversity could be influenced by a 'prenatal priming' due to tobacco exposure, medical complications and prenatal maternal stressors. If so, postnatal adverse events could result from prenatally acquired disturbances, promoting their postnatal occurrence. That could mean that 25.7% of the explained variance of BPD may be more relevant than the obtained value after the adjustment of postnatal factors. However, the research design of an epidemiologic study is not predisposed to assess those associations, so that future studies should address this issue in a prospective approach.

Earlier studies [123, 140], investigated childhood trauma and developmental histories in borderline patients, but assessed only single prenatal adverse events or birth risk factors. Soloff & Millward [140] found pregnancy complications in eight (17.8%) of the n=45 examined borderline patients. However, no healthy control group has been assessed. Bandelow et al. [123] reported of an increased incidence of premature birth in n=14 (21.5%) patients in a sample of n=66 BPD patients. We confirmed the prevalence of premature birth in n=21 (22.1%) patients in our larger sample. But the difference in premature birth between patients and controls n=17 (17.7%) was not significant. In both of the above mentioned studies, other prenatal risk factors such as maternal psychosocial stress, tobacco exposure, alcohol consumption, drug intake, maternal illness or infection, malnutrition or parental

socioeconomic variables were not assessed. Furthermore, both studies consulted no [123] or only a few [140] family informants.

Our data correspond with numerous human and animal studies that identified behavioural problems after exposure to prenatal maternal stress [152, 306, 346], tobacco smoke [347-349], and medical complications [310]. The underlying mechanisms of adverse health outcomes after exposure to prenatal adversity base upon alterations in brain structure and function during specific sensitive periods of brain development. Affected are - amongst others - brain structures that underlie emotional functioning and endocrine responses to stress, such as the fetal hypothalamic-pituitary-adrenal (HPA) axis whose maladaptation makes the individual hypersensitive to stress and susceptible for stress-related disorders in adulthood [2].

An elevated vulnerability and reactivity to stress has also been described in patients with BPD [83, 84]. Research consistently demonstrates that fetal overexposure to maternal stress hormones (glucocorticoids) may alter the offspring's endocrine system and permanently program it's HPA axis [350]. One possible mechanism is the downregulation of hippocampal mineralocorticoid and glucocorticoid receptors which play a crucial role in the termination of the stress response [346, 351]. Thus, the long term consequence of a prenatally programmed HPA axis may often result in permanently elevated stress reactivity [352].

These mechanisms have been described as an underlying vulnerability for behavioral problems and adverse mental health outcomes later in life [313]. Remarkably, several studies report a maladapted HPA axis in borderline patients [83, 84], which might indicate a potential prenatal programming effect. According to these findings, mothers of borderline patients in the present study perceived their pregnancy as significantly more stressful compared to mothers of healthy controls. They reported significantly more often of severe stress during pregnancy, such as severe traumatic stress, familial conflicts, relationship problems and low social support.

Although we found a high prevalence of prenatal adversity in borderline patients, it seems not to be a specific risk factor for the diagnosis of BPD, since an adverse intrauterine environment may increase the vulnerability for diverse pathologies. It is speculated that - after exposure to prenatal adversity - postnatal environmental factors, neurobiological factors and/or genetic factors may then determine the developmental course of psychopathology.

It has been reported that the effects of 'prenatal programming' or 'developmental plasticity' base upon epigenetic mechanisms that have the potential to permanently alter individuals' gene expression and thus may constitute an increased vulnerability for adverse health outcome later in life[4]. Recent studies suggested that gene regulation due to DNA methylation may determine the risk for psychiatric disorders in adulthood [353-356]. We hypothesize that

prenatal programming, mediated by epigenetic effects, contributes to the developmental origins of BPD (Schwarze et al., in preparation).

With respect to limitations of the present study, it has to be considered that the findings are based on retrospective self report data which bear the risk of a possible memory bias or response shift bias. To minimize these effects, we strove to collect as objective information as possible. Therefore, we gathered objective information about medical complications, birth risk factors, birth outcome and maternal data from prenatal medical records. All participants were instructed to review the interview questions carefully together with their mothers prior to the interview. Moreover, we applied strict exclusion criteria: If participants were not able to provide information at first hand - from mothers or close relatives - they were excluded from participation.

With respect to one of our main findings - prenatal tobacco exposure - a high validity of maternal recall on smoking during pregnancy has been reported in an earlier study[357]. Jaspers et al. [357] found high concordance rates between maternal recall and documented smoking behavior after more than one decade after birth.

Another limitation of the present study is that the associations we found, may potentially be confounded by genetic factors. Genetic factors may account for maternal health related behavior during pregnancy as well as for psychopathologic outcome in the offspring.

Furthermore, assuming causation of prenatal risk factors on postnatal psychopathology has to be considered with caution. However, twin studies revealed independent effects of prenatal adversity on later psychopathology/behavioral problems that were not explained by shared genetic factors[358-360]. Separation of genetic and environmental effects may also be possible due to reproductive technologies, in which pregnant women were biologically unrelated to their offspring (e.g. due to a donated embryo or egg)[361]. Existing studies suggest that the effects of prenatal adversity on behavioral problems later in life cannot be accounted for by genetic factors alone[358-360]. However, future studies should disentangle these different effects by appropriate research designs. There is now increasing evidence suggesting that gene x prenatal environment interactions have an impact on postnatal behavior[362] whereas other studies reported prenatal adversity acting independently from genetic factors[2]. Data from our research group suggest gene x prenatal environment interactions as well as independent prenatal effects on psychopathology and associated BPD traits later in life (Schwarze et al., in preparation). Disentangling genetic and fetal environmental effects should be a major topic of future research. Prenatal adversity may even precede the occurrence of postnatal trauma. Thus, Pawlby et al[363] found prenatal maternal depression to be associated with both, increased risk of psychopathology and childhood maltreatment in the offspring.

Taken together, an adverse prenatal environment has the potential to alter brain structure and function as well as endocrine systems during specific sensitive periods of fetal development. These alterations may lead to increased stress vulnerability and to a greater susceptibility for diverse psychopathologies later in life. Stressful life events could thus be aggravated in individuals who show an enhanced vulnerability due to prenatal adversity. A combination of childhood adversity and prenatal risk factors may thus substantially contribute to the development of BPD.

Our findings suggest that prenatal tobacco exposure and prenatal medical complications might play a substantial role in the pathogenesis of BPD. Neurobiological studies should consider these prenatal risk factors as possible underlying agents for alterations in brain structure and function. Future prospective longitudinal studies are essential to verify the impact of the observed risk factors.

Chapter 4

PHYSICAL HEALTH CONDITIONS ASSOCIATED WITH PRENATAL ADVERSITY IN BORDERLINE PERSONALITY DISORDER

4.1 Abstract

Context

Borderline personality disorder (BPD) is associated with a high prevalence of somatic comorbidities, such as cardiovascular diseases, hypertension, gastrointestinal disorders, endocrinological disorders, arthritis and obesity. It is unclear whether – apart from common risk factors - prenatal adverse conditions, such as prenatal maternal stress, malnutrition, medical complications or prenatal tobacco exposure - constitute a risk factor for the development of somatic comorbidities in BPD.

Methods

The prevalence of somatic comorbidities was assessed in 100 patients with BPD and 100 matched healthy controls. Physical health conditions were assessed using a questionnaire for anamnestic interviews whose results were validated in a personal interview.
Multiple regression analyses were used to assess the predictive value of prenatal risk factors in the assessed physical health domains.

Results

Borderline patients reported significantly more often of lifetime cardiovascular disorders ($p=.001$), gastrointestinal disorders ($p<.001$), disorders of hormone system and metabolism ($p=.002$), sensory and neurological disorders ($p<.001$), skin disorders ($p<.001$), urogenital symptoms ($p<.001$), pain disorders and musculoskeletal disorders ($p<.001$) as compared to healthy controls. These group differences remained significant after applying Bonferroni correction for multiple testing.
Multiple linear regression analyses revealed that prenatal risk factors account for 6.2 to 21% of the variance in the observed physical health domains. Prenatal maternal stress, such as stress at work, traumatic stress or low social support emerged as important predictors for the assessed somatic comorbidities.

Conclusion

This study provides first evidence of an association between prenatal adversity and somatic comorbidities in BPD. According to the logistic regression models, prenatal risk factors - in particular prenatal maternal stress – may contribute to the development of poor physical health conditions in BPD.

4.2 Introduction

Borderline personality disorder (BPD) is a prevalent psychiatric disorder, estimated to affect 1.5% [23, 302] to up to 5.9% [20] of the general population. Furthermore, BPD is the most frequent personality disorder in clinical settings [13, 20, 24].

Prior studies show that the diagnosis of BPD is related to a high number of somatic comorbidities, such as cardiovascular, metabolic, neuroendocrine and musculoskeletal disorders. El Gabalawy et al.[39] found a high rate of arteriosclerosis and hypertension, cardiovascular diseases, stroke, diabetes, gastrointestinal diseases, arthritis, venereal diseases, and hepatic diseases in a recent, population-based study (The National Epidemiologic Survey on Alcohol and Related Conditions, NESARC, Wave 2, n=34.653) in 2231 patients with a diagnosis of BPD. Frankenburg & Zanarini[14] found that patients with a current borderline diagnosis reported more medical problems compared to those with remitted borderline diagnoses. Nonremitted borderline patients were found to be significantly more likely to show a history of hypertension, diabetes, osteoarthritis, chronic back pain, urinary incontinence and syndrome-like conditions, such as chronic fatigue syndrome, fibromyalgia and temporomandibular joint syndrome[14]. Furthermore, an elevated body mass index (BMI) or obesity has been repeatedly associated with BPD[14, 40, 41].

In sum, medical comorbidity seems to be highly prevalent and clinically important in borderline patients. However, the etiological determinants wait to be clarified. Apart from common risk factors, such as smoking, alcohol consumption, poor nutrition or lack of exercise, another important risk factor emerged in the literature during the past two decades - namely ‘prenatal adversity’. Prenatal adverse conditions have been shown to have a considerable impact on disease susceptibility in the offspring later in life[306, 314, 364]. Over the past 20 years, there has been an enormous increase in research on prenatal adversity and it is now established that early-life environmental factors influence prenatal development and may cause structural and functional changes in organ structure and brain development which persist for the lifespan[9]. Thus, epidemiologic evidence suggests that prenatal risk factors affect fetal development and are associated with an increased risk of coronary heart disease, hypertension, type-2 diabetes, insulin resistance, obesity, metabolic syndrome, and psychiatric disorders[177]. The phenomenon of an increased disease risk following prenatal adversity is known as ‘prenatal programming’ or ‘developmental plasticity’[11, 314, 315].

In particular, prenatal maternal stress and its effects on offspring health has been extensively studied in humans and animals[306]. It has been shown that prenatal maternal stress may lead to a fetal overexposure with maternal stress hormones (glucocorticoids) which may cause a lifelong malprogramming of the fetal hypothalamic pituitary adrenal (HPA) axis[9, 177, 306, 365]. Empirical studies in animals and humans have shown that these mechanisms are likely to be

a key factor in mediating associations with disorders that are frequently characterized by HPA overactivity[366]. The exposure to excess glucocorticoids affects tissue structure and function during specific sensitive periods of fetal development[177] which may persist throughout life and may increase the vulnerability for stress related disorders in adulthood[313]. Furthermore, an adverse intrauterine environment has been reported to be possibly manifested in low birthweight, indicating an impaired fetal development. Low birthweight – a crude marker of prenatal adversity – predisposes individuals to diverse pathologies in adulthood[314]. Remarkably, the association between prenatal adversity, low birthweight and adult disease is largely independent of adult lifestyle risk factors, such as smoking, alcohol consumption, low social class, lack of exercise and obesity[177].

In an earlier publication (Schwarze et al., under review), we assessed prenatal risk factors in BPD and found that borderline patients were exposed significantly more often to prenatal adversity compared to healthy controls. Mothers of borderline patients reported significantly more often of psychosocial stress during pregnancy, and perceived their pregnancy as significantly more stressful compared to mothers of healthy controls. Furthermore, they smoked significantly more tobacco during pregnancy and experienced more medical complications.

The purpose of the present study is to assess whether patients with BPD show a higher prevalence of somatic diseases and complaints compared to healthy controls and - more importantly - to test whether prenatal risk factors serve as potential predictors of adverse physical health conditions. We hypothesized that prenatal adversity constitutes a risk factor for somatic disorders and complaints in BPD.

To the best of our knowledge, this is the first study, addressing the role of prenatal risk factors as potential predictors of somatic disorders in BPD.

4.3 Methods

4.3.1 Sample

One hundred patients who met the DSM-IV[19] criteria for BPD and 100 healthy control subjects participated in the study. Patients and controls were matched for sex, age, and education (see **Table 4.1**). An in depth description of the study population is provided in an earlier publication on prenatal adversity in BPD (Schwarze et al., under review).

Table 4.1. Demographic Variables

	N or Mean (SD)	
Characteristic	**Patients**	**Controls**
Age, y		
18-20	9	8
21-30	49	45
31-40	19	25
41-50	20	17
51-60	3	5
Mean age	31.63 (09.73)	32.02 (10.25)
Sex		
F/M	90/10	90/10
School Education		
High school graduation	43	45
Advanced technical college entrance graduation	7	6
Secondary school graduation	37	38
Secondary general school graduation	12	11
No school leaving certificate	1	0
Education		
University degree	13	14
Technical college degree	2	3
Student	17	23
University drop-out	2	0
Professional education	46	50
Apprentice	9	9
Without professional education	11	1

SD= Standard Deviation; N= Number; Y= Years; F= Female; M= Male.

4.3.2 Procedure

After a full description of the research procedure, written informed consent was obtained from all subjects. The study protocol was approved by the local ethics committee. The investigation was conducted in accordance with the guidelines described in the declaration of Helsinki.

Lifetime physical health conditions and complaints were assessed using a questionnaire for anamnestic interview, containing 11 domains of somatic disorders, such as cardiovascular, gastrointestinal or metabolic disorders (Neuropattern Questionnaire, NPQ-A, Neuropattern Diagnostics[320]). After completion of the questionnaire, the data were validated in a personal interview. Furthermore, the body mass index (BMI) was determined for each participant.

All patients and controls were diagnosed using the Structured Clinical Interview for DSM-IV[367]. The diagnostic interviews were conducted by a trained psychologist with extensive clinical and research experience.

Prenatal adversity was assessed using a semi-structured interview about pre- peri- and postnatal life events, based on Neuropattern Diagnostics[320]. One part of the Neuropattern instrument is the Pre/Peri/Postnatal Stress Questionnaire (NPQ-PSQ, see below). The participants were instructed to review the interview questions together with their mothers prior to the interview (see also Schwarze et al., under review). Mothers of participants were asked to fill in the NPQ-PSQ and to provide objective information about birthweight, size at birth and length of gestation. These data were obtained from prenatal medical records which are handed to the mother during her first prenatal visit by the obstetrician. All interviews were conducted personally by trained health professionals. The raters were regularly supervised.
Information about prenatal adversity could be obtained from 90.5% (n=180) of participants' mothers, from 36.7% (n=73) of participants' fathers or other close relatives and from 37.5% (n=75) prenatal medical records.
Participants were excluded if they had no access to information about birth parameters, prenatal adversity, birth complications, and childhood trauma. Further exclusion criteria were acute suicidality, acute intoxication (alcohol, drugs), a history or a current episode of schizophrenia, bipolar disorder I, organic mental disorders or intellectual disability.

4.3.3 Instruments

The Neuropattern Questionnaire (NPQ-A[320]) contains questions of 11 domains of physical health conditions that represent different subdomains, such as cardiovascular disorders (e.g. hypertension, hypotension, cardiac arrhythmia, coronary heart disease, cardiac insuffiency), gastrointestinal disorders (e.g. irritable bowel disease, gastritis, reflux, dyspepsia, colitis ulcerosa, morbus Crohn) metabolic and hormonal disorders (e.g. diabetes, dyslipidaemia, hypothyroidism, hyperthyreosis, osteoporosis, morbus cushing), skin disorders (e.g. neurodermatitis, psoriasis, hyperpigmentation, acne), respiratory diseases (e.g. chronic obstructive pulmonary disease, sleep apnoea syndrome), musculoskeletal disorders and pain disorders (e.g. back pain, joint pain, migraine, headache, fibromyalgia, tremor), sensory or neurological disorders (e.g. tinnitus, hearing loss, algesia, increased sweating), immunological disorders (allergic asthma, Hashimoto, morbus Bechterew, lupus erythematodes), urogenital symptoms (e.g. irritable bladder, infertility, abnormal oestrous cycle, premenstrual syndrome, erectile dysfunction), dental disorders (e.g. periodontosis) and ophtalmic diseases (e.g. glaucoma). Furthermore, the NPQ-A assesses health related behaviour, such as smoking or alcohol abuse. The presence or absence of any symptom was assessed by binary questions (yes=1 / no=0). For each physical health domain, a score was generated, indicating the number of the corresponding lifetime diagnoses and complaints. Eighty seven patients and 96 controls completed the NPQ-A. Subsequently, the

questionnaire data were validated in a personal interview by health professionals. All items that have been answered by 'yes' were reassessed in the interview.

Prenatal adversity was investigated using the Pre/Peri/Postnatal Stress Questionnaire (NPQ-PSQ[320] (see also Schwarze et al., under review). The NPQ-PSQ consists of questions about maternal stressors during pregnancy (such as traumatic stress, chronic stress, low social support, stress at work, financial sorrows), medical complications, medication, malnutrition, smoking, socioeconomic variables (such as financial constraints, monthly income, parental education) and birth outcome (such as weight and head circumference at birth).

If any question has been affirmed by the mother, she was asked to specify the week of gestation for each particular event. The information about prenatal adversity was investigated in detail in a personal interview.

4.3.4 Statistical Analyses

The data were expressed as percentages or mean values and standard deviation. The differences between the groups were tested for significance, using Student's *t* test and Fisher's exact test.

To determine the predictive value of prenatal risk factors, multiple linear regression analyses were performed. Fifteen prenatal risk factors, such as maternal stressors, infections or toxins were used as independent variables (high workload, divorce, low social support, family conflicts, partnership problems, sexual insault, physical threat, traumatic stress, financial worries, severe illness or death of a close relative, medical complications, weight loss or malnutrition, maternal infection, tobacco smoking, medication, e.g. synthetic glucocorticoids). Somatic disorders and BMI were included as dependent variables.

In the next step, we applied a stepwise linear regression model to adjust for health related behaviour, such as alcohol abuse and smoking. Furthermore, we adjusted for socioeconomic variables, such as participants' educational level, parental education and parental monthly income (1=low; 2=average; 3=high). Moreover, we adjusted for the diagnosis of BPD. In a separate linear regression model, we assessed participants' birthweight as predictor for poor physical health conditions. Statistical significance was set at 0.05. All analyses were carried out using SPSS for Windows 18.0 program.

4.4 Results

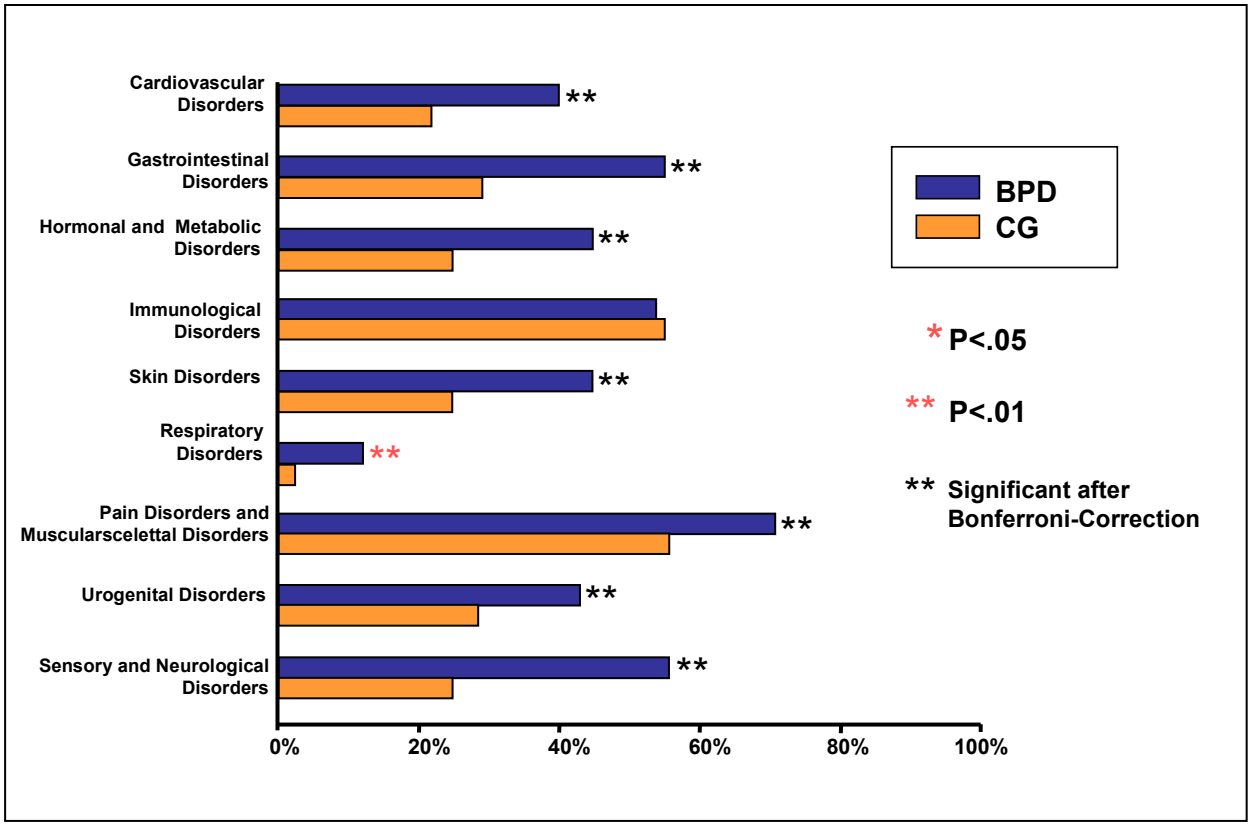
4.4.1 Somatic Comorbidities

Borderline patients showed a high lifetime prevalence of somatic comorbidities in most of the assessed physical health domains, compared to healthy controls (see **Figure 4.1**).

Patients with BPD reported significantly more often of cardiovascular diseases ((BPD: n=12 (12%), CG: n=3 (3%); p=.001)), gastrointestinal disorders ((BPD: n=55 (64.7%), CG: n=32 (34%); p<.001)), disorders of hormone system and metabolism ((BPD: n=44 (52.4%), CG: n=25 (26.6%); p=.002)), sensory and neurological disorders and complaints ((BPD: n=56 (65.9%), CG: n=24 (25.5%); p<.001)), skin disorders ((BPD: n=45 (52.9%), CG: n=24 (25.5%); p<.001), urogenital disorders ((BPD: n=43 (51.2%), CG: n=29 (30.9%); p<.001), respiratory diseases ((BPD: n=12 (14.3%), CG: n=3 (3.2%); p=.007), pain disorders and muscular skeletal disorders ((BPD: n=71 (83.5%), CG: n=56 (59.6%); p<.001).

Apart from respiratory diseases, these group differences remained significant after applying Bonferroni correction for multiple testing. There were no significant differences in immunological disorders ((BPD: n=53 (62.4%), CG: n=55 (57.3%); p=.294)) and dental disorders ((BPD: n=12 (14.5%), CG: n=7 (7.4%); p=.136)) between patients and controls. No participant confirmed a lifetime diagnosis of ophthalmic diseases ((BPD: n=0 (0%), CG: n=0 (0%)). Differences of somatic disorders in borderline patients and healthy controls are presented in **Figure 4.1**.

Figure 4.1. Prevalence of Lifetime Somatic Comorbidities in Borderline Patients and Controls



BPD = Borderline Patients; CG= Control Group; *P* = Probability Score.

4.4.2 Body Mass Index

Furthermore, we found an elevated body mass index of marginal significance in borderline patients compared to healthy controls (BPD: 26.17 (SD 7.22); CG Controls: 24.49 (SD 4.40), p=.056). After exclusion of n=5 patients with a current DSM-IV diagnosis of anorexia nervosa (BMI<17.5), the average BMI in the patient group was 26.70 (SD 7.06) and the difference between the groups became statistically significant (p=.012).

4.4.3 Predictors of Physical Health Conditions

Multiple linear regression analyses revealed that prenatal risk factors account for 6.2% to 21% of the variance in the assessed physical health domains (see **Table 4.2**). The predictive value of prenatal risk factors seems to be particularly pronounced in respiratory diseases (21% of variance), cardiovascular disorders (20.2% of variance), disorders of hormone system and metabolism (19.3% of variance), gastrointestinal disorders (15.8% of variance) as well as pain and musculoskeletal disorders (15.2% of variance).

Table 4.2. Predictive Value of Prenatal Adversity in Somatic Disorders (Linear Regression)

Physical Health Domains		
	R^2	**Predictive**
Cardiovascular Disorders	.202	20.2 %
Gastrointestinal Disorders	.158	15.8 %
Disorders of Hormone System and Metabolism	.193	19.3 %
Sensory and Neurological Disorders	.117	11.7%
Skin Disorders	.138	13.8 %
Urogenital Symptoms	.077	07.7 %
Respiratory Diseases	.210	21.0 %
Pain Disorders and Musculoskeletal Disorders	.152	15.2 %
Immunological Diseases	.062	06.2 %
Dental Disease	.077	07.7 %

R^2 = Determination Coefficient

In a stepwise linear regression model, we adjusted for health related variables, such as smoking, alcohol consumption, participant's age, participant's educational level, parental socioeconomic status (mother's and father's educational level and parental monthly income), and diagnosis of BPD. In particular 'prenatal maternal stress' emerged as a significant predictor in six of the assessed physical health domains (see **Table 4.3**). Prenatal maternal stress significantly predicts cardiovascular disorders, gastrointestinal disorders, disorders of hormone system and metabolism, respiratory diseases, pain and musculoskeletal disorders.

The effects of prenatal adversity remained stable even after adjusting for participant's health related behavior, participant's age, participant's educational level, parental education, parental monthly income and borderline diagnosis.

Furthermore, prenatal risk factors account for 7.9% of the variance in the assessed body mass index. Hereby, prenatal tobacco exposure (Beta: 148; p=.051) and prenatal maternal stress (divorce of parents, Beta: 137; p=.072) emerged as predictors of marginal significance.

In a separate linear regression analysis, we assessed low birthweight as a potential predictor for adverse physical health outcome. According to that regression model, low birthweight significantly predicts skin disorders (R^2=.044; p=.006) and gastrointestinal disorders (R^2=.040; p=.009). Sensory and neurological disorders (R^2=.020; p=.065), urogenital disorders (R^2=.018; p=.078), as well as respiratory diseases (R^2=.018; p=.081) were predicted by low birthweight with marginal significance.

Table 4.3. Physical Health Domains and Associated Risk Factors

Physical Health Domains	Predictors	β	T	*P*
Cardiovascular Disorders				
	Prenatal Stress: Stress at Work	.232	3.354	.001
	Age	.229	3.304	.001
	Smoking	.150	1.994	.048
	BPD Diagnosis	.319	4.278	.000
Gastrointestinal Disorders				
	Prenatal Stress: Stress at Work	.191	2.784	.006
	Maternal Education	-.171	-2.417	.017
	BPD Diagnosis	.311	4.402	.000
Disorders of Hormone System and				
	Prenatal Stress: Traumatic Stress	.263	3.701	.000
	Prenatal Stress: Low Social Support	.156	2.193	.030
	Maternal Education	-.199	-2.840	.005
Sensory and Neurological Disorders				
	Age	.175	2.570	.011
	BPD Diagnosis	.412	6.053	.000
Skin Disorders				
	Prenatal Stress: Stress at Work	.199	2.814	.005
	Maternal Education	-.172	-2.363	.019
	BPD Diagnosis	.225	3.088	.002
Urogenital Symptoms				
	Age	.181	2.527	.012
	BPD Diagnosis	.295	4.123	.000
Respiratory Diseases				
	Prenatal Stress: Traumatic Stress	.137	1.975	.050
	Prenatal Stress: Death / Illness of a	.191	2.688	.008
	Prenatal Drug Exposure (Cortisone)	-.161	-2.270	.024
	Prenatal Tobacco Exposure	.170	2.432	.016
	Prenatal Medical Complications	.289	4.105	.000
	Age	.180	2.578	.011
Pain Disorders and Muscular Skeletal				
	Prenatal Stress: Stress at Work	.201	3.104	.002
	Prenatal Maternal Malnutrition or	.144	2.202	.029
	Paternal Education	-.228	-3.550	.000
	Alcohol Abuse	-.166	-2.426	.016
	BPD Diagnosis	.319	4.718	.000
Immunological Disorders				
	Maternal Education	-.169	-2.256	.025
Dental Disease				
	Alcohol Abuse	-.175	-2.804	.006
	Age	.209	2.804	.006

β = Beta; T= T-value; *P* = Probability Score.

4.5 Discussion

As previously reported (see Schwarze et al., under review), borderline patients were exposed significantly more often to adverse conditions during pregnancy compared to healthy controls. Mothers of borderline patients reported significantly more often of psychosocial stress during pregnancy, such as traumatic stress, low social support, family conflicts and partnership problems and perceived their pregnancy as significantly more stressful compared to mothers of healthy controls. Furthermore, mothers of borderline patients smoked significantly more tobacco during pregnancy and experienced more medical complications than mothers of healthy controls.

To the best of our knowledge, the present study is the first investigation that assesses prenatal adversity as a potential predictor of somatic comorbidities in BPD.

Our aims were to assess the prevalence of somatic disorders in borderline patients compared to healthy controls and - more importantly - to test whether physical disorders were predicted by prenatal risk factors.

We found a high lifetime prevalence of somatic comorbidities in patients with BPD compared to healthy controls. Borderline patients show significantly more often lifetime somatic diagnoses, such as gastrointestinal disorders, cardiovascular disorders, skin disorders, neurological disorders, musculoskeletal disorders, disorders of hormone system and metabolism and respiratory diseases. Furthermore, we found a significantly elevated body mass index in borderline patients compared to healthy controls. Our findings are consistent with previous research that demonstrated a high prevalence of somatic disorders in borderline patients.

In the present study, most of the assessed physical health domains were predicted to some extent by prenatal risk factors. The most important risk factor seems to be prenatal maternal stress which predicts cardiovascular disorders, gastrointestinal disorders, disorders of hormone system and metabolism, respiratory diseases, as well as pain and musculoskeletal disorders.

Despite adjusting for smoking, alcohol abuse, participant's age and education, parental education and monthly income as well as the diagnosis of BPD, prenatal risk factors remained significant predictors for the assessed physical health domains.

Our data correspond with numerous human and animal studies that identified somatic and mental disorders in the offspring after exposure to prenatal maternal stress [9, 306, 365].

Neurobiological findings support our hypotheses of adverse physical health conditions associated with prenatal stress exposure. Thus, research consistently demonstrates that fetal overexposure to maternal stress hormones (glucocorticoids) is associated with alterations in the fetal endocrine system and with a permanently programmed HPA axis in

the offspring[350]. Prenatal glucocorticoid overexposure may downregulate hippocampal mineralocorticoid and glucocorticoid receptors which play a crucial role in the termination of the stress response[346, 351]. Thus, the long term consequence of a prenatally programmed HPA axis may often result in permanently elevated stress reactivity in the offspring[352]. These mechanisms have been described as underlying vulnerability of stress related disorders in adulthood[365]. Remarkably, several studies report a maladapted HPA axis in borderline patients[83, 84] which might indicate a potential prenatal programming effect.

However, a diagnosis of BPD itself is associated with an elevated risk of somatic disorders. Suffering from BPD may be per se related to an unhealthy lifestyle, since borderline patients often show an excessive use of alcohol, tobacco or medication[368, 369]. Furthermore, borderline patients often present disturbed eating behavior[370] (such as restraint eating, binge eating, purging) as well as poor quality of sleep[371, 372] and an irregular lifestyle[14]. Suffering from BPD may be associated with a higher level of psychosocial stress, which is known to be a risk factor for stress-related somatic disorders. A current diagnosis of BPD is associated with worse health conditions which could be demonstrated in the study of Frankenburg & Zanarini[14], who found more medical problems in non-remitted compared to remitted borderline patients. We were able to confirm the high prevalence of somatic disorders in our sample. The borderline diagnosis itself emerged as a significant predictor for several of the assessed physical health domains.

In the present study, another important risk factor emerged as predictor of poor physical health outcome, namely ‘low parental education’. These findings are consistent with previous research that describes low socioeconomic status as a risk factor of diverse pathologies[373, 374]. In the present study, participants whose mothers showed a lower level of education were more likely suffering from lifetime diagnoses such as gastrointestinal disorders, endocrinological and metabolic disorders, skin disorders, and immunological disorders. As expected, participant’s age emerged as another predictor for several physical health domains. Being of higher age was associated with higher risk of somatic disorders and complaints (e.g. cardiovascular disorders, urogenital symptoms, dental disorders).

Although the exact underlying mechanisms of developmental origins of health and disease are still not fully elucidated, recent findings suggest that epigenetic programming may determine the risk for somatic and mental health problems in adulthood. Early environmental risk factors have the potential to permanently alter individuals’ gene expression and thus may constitute an increased vulnerability for adverse health outcome later in life[365]. Recent studies suggest that gene regulation due to DNA methylation, may modulate the risk for psychiatric[353-356] and somatic[375, 376] disorders in adulthood.

Our findings suggest that somatic comorbidities in BPD are determined multifactorial and are predicted to some extent by prenatal risk factors, such as prenatal maternal stress.

With respect to limitations of the present study, it has to be considered that the findings are based on retrospective self-report data which bear the risk of a possible memory bias.

To minimize these effects, we strove to collect as objective information as possible. Therefore we gathered objective information about medical complications, birth risk factors, birth outcome and maternal data from prenatal medical records. Furthermore, information on pre- and perinatal life events base on mothers' statements which personally completed the NPQ-PSQ (90.5% of mothers). All participants were instructed to review the interview questions carefully together with their mothers prior to the interview.

Moreover, we applied strict exclusion criteria: If participants were not able to provide information at first hand - from mothers or close relatives - they were excluded from participation.

An adverse prenatal environment has the potential to alter organ structure and function as well as endocrine systems during specific sensitive periods of fetal development. These alterations may lead to increased stress responsiveness in adulthood and to a greater susceptibility for diverse pathologies later in life. In association with an unhealthy lifestyle, prenatal risk factors might substantially contribute to the high prevalence of somatic comorbidities in BPD.

Our findings suggest that prenatal adversity – in particular prenatal maternal stress - plays a substantial role in the pathogenesis of physical disorders in BPD.

Future prospective longitudinal studies are essential to verify the impact of the observed prenatal risk factors.

Chapter 5

LACK OF BREASTFEEDING AND BORDERLINE PERSONALITY DISORDER

5.1 Abstract

Introduction

Borderline personality disorder (BPD) is characterized by a pattern of intense but unstable interpersonal relationships. It has been reported that dysfunctional interpersonal relationships and insecure adult attachment are associated with a history of childhood adversity - which has frequently been described in BPD. However, maternal bonding, insecure attachment and attachment-related attitudes may have their origins even earlier in life, i.e. during the early postnatal period. Lack of breastfeeding has been shown to be related to maternal bonding, attachment and mental health problems in the offspring.

Methods

We here investigated whether lack of breastfeeding is associated with a diagnosis of BPD, perceived maternal bonding and adult attachment-related attitudes. Therefore, we assessed breastfeeding in 100 patients with a DSM-IV diagnosis of BPD and 100 healthy controls, matched for sex, age and education.

All participants underwent semi-structured interviews about pre-, peri- and postnatal life events, such as course of pregnancy, birth complications, lack of breastfeeding or childhood trauma. Further information was obtained from participants' mothers and from prenatal medical records. The 'Adult Attachment Scale' and the 'Parental Bonding Instrument' have been used to assess attachment-related attitudes and perceived maternal bonding.

Results

Patients with BPD were significantly less breastfed compared to healthy controls (no breastfeeding in BPD: n=42; no breastfeeding in CG: n=18; $p<.001$).

Logistic regression analyses revealed that breastfeeding accounts for 9.1% of the variance for the diagnosis of BPD. Hereby, the variable 'no breastfeeding' turned out to be a significant predictor for BPD (OR 3.32; CI 1.74-6.34; $p<.001$). Furthermore, lack of breastfeeding predicts perceived maternal bonding (maternal care; $p=.006$) and discomfort in interpersonal relationships ($p=.021$). After adjustment for childhood trauma and several confounding variables, the factor 'breastfeeding' remained a significant predictor for the diagnosis of BPD ($p=.001$).

Conclusion

This study provides first evidence of an association between lack of breastfeeding and the diagnosis of BPD. Breastfeeding may act as an indicator of early mother-child relationship

and seems to be relevant for maternal bonding, attachment patterns and mental health problems later in life. However, the exact mechanisms have to be clarified.

5.2 Introduction

Borderline personality disorder (BPD) is a common psychiatric disorder, characterized by a pervasive pattern of impulsivity, emotional instability, identity disturbance and dysfunctional interpersonal relationships[13, 24]. In particular, intense but unstable relationships - with frequent alterations between idealization and devaluation, repeated break ups and discomfort in close and intimate relationships - have consistently been described as characteristic features of BPD. These interpersonal dysfunctions may have their origins in impaired bonding and attachment-related attitudes that were – to some extent - determined during early life. In several studies, disturbed attachment, such as insecure attachment, has been identified in patients with BPD[135, 377-381]. However, the exact underlying mechanisms still remain unclear. One risk factor may be a history of severe childhood trauma, such as sexual abuse, physical maltreatment or emotional neglect[150]. However, it may be possible that the basis of impaired mother-infant bonding and dysfunctional attachment lays even earlier in life, i.e. during the early postnatal period. Lack of breastfeeding could be one possible underlying factor for impaired bonding, attachment-related problems and borderline symptomatology. Empirical studies found lack of breastfeeding as significantly related to an increased risk for mental health problems in the offspring[382-384]. For example, a shorter duration of breastfeeding has been shown to be associated with mental health morbidity during childhood and adolescence[382], and infants who were breastfed for at least six months were reported to have distinct developmental advantages over non-breastfed infants[385].

Several studies demonstrate that breastfeeding has positive effects on offspring's health, development and attachment patterns. A meta-analysis revealed that breastfeeding positively affects infant's cognitive development[386], reduces stress hormone release[387] and blood pressure[388] and increases neurobehavioral self-regulation[389]. Infants of bottle-feeding mothers displayed more dysregulation and emotional irritability than those of breastfeeding mothers[390]. Furthermore, breast-fed children, compared to formula-fed children, show fever emotional or behavioural problems[391-393] and fewer minor neurological problems later in life[394, 395].

Breastfeeding also influences the quality of mother-infant relationship[396, 397]. The physical closeness and the skin-to-skin contact during breastfeeding contribute to the establishment of a close bond between mother and child which increases proximity[398, 399] and promotes maternal sensitivity in interaction with her infant[400, 401]. It has been reported that the more

physical contact exists between mother and child, the more caregiving behaviour is shown by the mother - and the more likely the child develops a secure attachment[402, 403].

Poor or unstable early care often results in persisting difficulties in forming and maintaining social relationships and may result in increased vulnerability to depression, anxiety disorders, substance abuse, personality disorders, and adult physical health disorders[46, 404-406]. Neonatal breastfeeding may constitute one aspect of early care and closeness between mother and child. Thus, it might be possible that the absence of maternal breastfeeding results in a range of negative consequences, such as altered maternal bonding, impaired attachment patterns or an increased risk for mental disorders.

However, the relationship between breastfeeding, BPD, maternal bonding and attachment has not yet been studied.

It was the purpose of the present study to investigate the prevalence of breastfeeding in borderline patients compared to healthy controls and to assess the predictive value of breastfeeding for the diagnosis of BPD, perceived maternal bonding and adult attachment-related attitudes. We hypothesized that breastfeeding is less prevalent in patients with BPD compared to healthy controls. Furthermore, we hypothesized that lack of breastfeeding serves as an additional risk factor for the pathogenesis of BPD and constitutes a predictor for impaired perceived maternal bonding and altered attachment-related attitudes.

5.3 Methods

5.3.1 Sample

One hundred patients who met the DSM-IV[19] criteria for BPD and 100 healthy control subjects participated in the study. Patients and controls were matched for sex, age, and education (**Table 5.1**). An in depth description of the study population is provided in a related article on prenatal adversity in BPD (Schwarze et al., under review).

5.3.2 Procedure

After a full description of the research procedure, written informed consent was obtained from all subjects. The study protocol was approved by the local ethics committee. The investigation was conducted in accordance with the guidelines described in the declaration of Helsinki.

All patients and controls were diagnosed using the Structured Clinical Interview for DSM-IV (SCID[367]). The diagnostic interviews were conducted by a trained psychologist with extensive clinical and research experience.

Perinatal adversity, including information on breastfeeding, was assessed using a semi-

Table 5.1. Demographic Variables

	N or Mean (SD)	
Characteristics	**Patients**	**Controls**
Age, y		
18-20	9	8
21-30	49	45
31-40	19	25
41-50	20	17
51-60	3	5
Mean age	31.63 (09.73)	32.02 (10.25)
Sex		
F/M	90/10	90/10
School Education		
High school graduation	43	45
Advanced technical college entrance graduation	7	6
Secondary school graduation	37	38
Secondary general school graduation	12	11
No school leaving certificate	1	0
Education		
University degree	13	14
Technical college degree	2	3
Student	17	23
University drop-out	2	0
Professional education	46	50
Apprentice	9	9
Without professional education	11	1

SD= Standard Deviation; N= Number; Y= Years; F= Female; M= Male.

structured interview, based on Neuropattern Diagnostics[320]. One part of the Neuropattern instrument is the Pre/Peri/Postnatal Stress Questionnaire (NPQ-PSQ, see below). The participants were instructed to review the interview questions together with their mothers prior to the interview. Mothers of participants were asked to fill in the NPQ-PSQ and to provide information about the feeding mode (breastfeeding versus non-breastfeeding). Objective information about maternal age at birth, length of gestation, birth risk factors, birth complications and subject's bithweight and size at birth were obtained from prenatal medical records which are handed to the mother during her first prenatal visit by the obstetrician. Information about perinatal adversity could be obtained from 180 (90.5%) mothers of participants, from 73 (36.7%) fathers or other close relatives and from 75 (37.5%) prenatal medical records. All interviews were conducted personally by trained health professionals. The raters were regularly supervised.

5.3.3 Instruments

5.3.3.1 Pre/Peri/Postnatal Stress Questionnaire (NPQ-PSQ)

Lack of breastfeeding was assessed as part of perinatal adversity, using the Pre/Peri/Postnatal Stress Questionnaire (NPQ-PSQ)[320]. The NPQ-PSQ assesses pre- and perinatal adversity such as birth complications (caesarean section), birth risk factors, medical procedures after birth (oxygen tent, incubator), maternal stressors (unwanted pregnancy, low social support, family conflicts, partnership problems, high workload, financial worries), maternal smoking, lack of breastfeeding, socioeconomic variables (financial constraints, monthly income, parental education) and birth outcome (birthweight, size at birth, gestational length).

5.3.3.2 Parental Bonding Instrument (PBI)

The perceived parental bonding was assessed by the Parental Bonding Instrument (PBI[137], German adaptation[407]), a retrospective self-report questionnaire that assesses the perceived parent-child bonding during the first 16 years of life by the individual.

The respondents report how they perceived the two parental styles 'care' and 'overprotection'. The scale 'care' measures the dimension from parental affection, warmth and empathy (high scores) to parental coldness, indifference and rejection (low scores) on a 4-point Likert scale. The Scale 'overprotection' measures dimensions from control and intrusiveness (high scores) to independence and autonomy (low scores). Both scales were completed separately for mother and father. The PBI was developed as a standardized measure of parent-child bonding. It has been widely used and shows excellent psychometric properties[408].

5.3.3.3 Adult Attachment Scale (AAS)

In order to assess adult attachment-related attitudes, the Adult Attachment Scale (AAS, developed by Collins & Read[409]; revised version by Collins[410]; first German adaptation by Büsselberg[411, 412]) has been applied. The AAS is a self-rating questionnaire that measures general attachment-related attitudes in close relationships. It consists of 3 dimensional scales ('trust', 'closeness', 'anxiety') that are each represented by 6 items, scored on a 5-point Likert-scale, where 1 means 'not at all characteristic of me' and 5 means 'very characteristic of me'. The scale 'closeness' assesses, to what extent an individual feels comfortable in close and intimate relationships with others (e.g. 'I am uncomfortable when anyone gets too emotionally close to me'). The scale 'trust' measures, to what extent an individual trusts in others to be there, when he/she needs them (e.g. 'I know that people will

be there when I need them'). The third scale 'anxiety' assesses how frightened a person is to be unloved or abandoned by others ('I often worry that other people don't really love me').

5.3.3.4 Childhood Trauma Questionnaire (CTQ)

The individuals' history of childhood trauma and adversity was assessed by the 'Childhood Trauma Questionnaire' (CTQ[321]). The CTQ is a reliable and valid self-rating questionnaire that is used to investigate subjects' childhood trauma history. It measures 3 types of abuse (physical, sexual, and emotional), and 2 types of neglect (physical and emotional). The CTQ is the most validated and widely used retrospective trauma questionnaire.

93 patients and 95 controls completed the PBI, 98 patients and 96 controls completed the AAS and 98 patients and 95 controls completed the CTQ.

5.3.4 Statistical Analyses

The data were expressed as percentages or mean values and standard deviation. The differences between the groups were tested for significance, using Student's *t* test and Fisher's exact test. To determine the predictive value of 'breastfeeding' for the diagnosis of BPD, a logistic regression analysis was performed, using 'breastfeeding' as independent variable and the borderline diagnosis as dependent variable. We adjusted for childhood trauma (CTQ total score), parental monthly income, maternal education, maternal age at child's birth, maternal mental disorders, unwanted pregnancy, preterm birth, birthweight, birth complications and cesarian section.

To determine potential predictors for the feeding mode (breastfeeding versus non-breastfeeding) a separate logistic regression analysis was performed with breastfeeding as dependent variable and 18 predictors as independent variables (unwanted pregnancy, gestational length, birthweight, incubator, oxygen tent, sustained hospitalization, medical procedures, cesarian section, birth complications, maternal age at child's birth, maternal education, maternal prenatal smoking, low social support during pregnancy, financial worries, familial conflicts, high workload, maternal mental disorders during pregnancy, partnership problems).

To detect the potential influence of breastfeeding on maternal bonding, we performed a Multivariate Analysis of Covariance (MANCOVA) with two independent variables (breastfeeding and the diagnosis of BPD) and two dependent variables (maternal care and maternal overprotection). To control for childhood trauma, we included the CTQ total score as covariate. The outcome variables of the MANCOVA were tested by separate Univariate Analyses of Covariance (ANCOVAs).

A multiple linear regression model was used to test the predictive value of breastfeeding for adult attachment-related attitudes, with 'breastfeeding' as independent variable and the 3

subscales of the Adult Attachment Scale as dependent variables. Statistical significance was set at 0.05. All analyses were carried out using SPSS for Windows 18.0 program.

5.4 Results

5.4.1 Lack of Breastfeeding and Borderline Personality Disorder

Significantly more patients with BPD (n = 42, 42.4%) than controls (n=18, 18.2%) were not breastfed (p<.001). To determine the explained variance of breastfeeding for the diagnosis of BPD, we applied a logistic regression analysis. The analysis revealed that the factor 'breastfeeding' accounts for 9.1% of the variance for the diagnosis of BPD. Lack of breastfeeding turned out as a highly significant predictor for the borderline diagnosis (OR 3.32; CI 1.74-6.34; p<.001). After adjustment for childhood trauma (CTQ total score), parental monthly income, maternal education, maternal age at child's birth, maternal mental disorders, unwanted pregnancy, preterm birth, birthweight, birth complications and cesarian section, the variable breastfeeding still predicts significantly the diagnosis of BPD (OR 4.68; CI 1.88-11.66; p=.001; **Table 5.2**).

Table 5.2. Breastfeeding as Predictor for the Diagnosis of BPD – Logistic Regression Analysis

Predictors	OR	95%CI	P
Breastfeeding	4.681	1.880	.001
CTQ Total Score	1.093	1.059	<.001
Parental Monthly Income	1.090	.591	.783
Maternal Age at Child's Birth	.950	.871	.253
Maternal Education	.946	.683	.737
Maternal Mental Disorder during Pregnancy	.511	.044	.591
Preterm Birth	.800	.291	.665
Birthweight	.845	.193	.823
Birth Complications	.639	.231	.389
Cesarian Section	2.394	.445	.309
Unwanted Pregnancy	3.272	1.054	.040

OR = Odds Ratios; 95%CI = 95% Confidence Interval; *P* = Probability Score.

5.4.2 Breastfeeding and Perceived Maternal Bonding

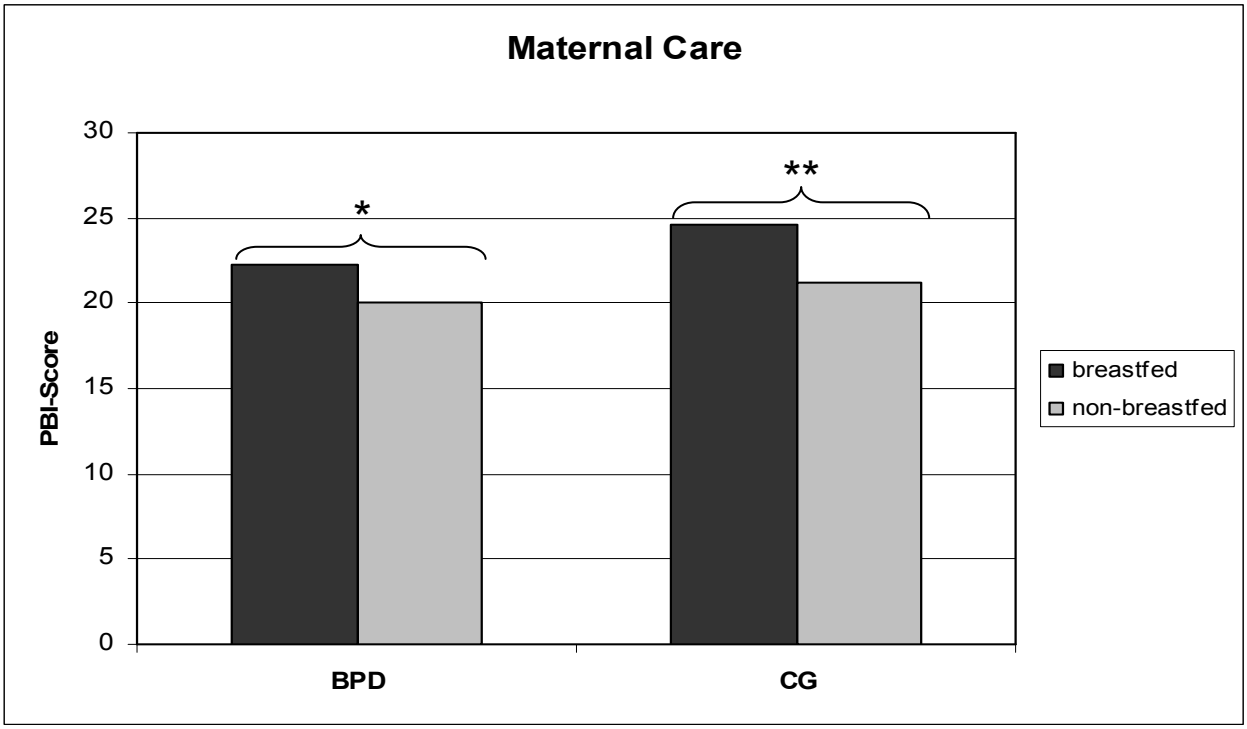
To assess whether breastfeeding has an effect on perceived maternal bonding, a MANCOVA was performed with breastfeeding and the diagnosis of BPD as independent variables, perceived maternal bonding as dependent variables and childhood trauma as covariate.

The analysis revealed two significant main effects: (1) Breastfeeding has a significant effect on maternal bonding. Using Pillai's trace, we found a significant effect of breastfeeding on

maternal care and maternal overprotection, *F* (2,180) = 4.01, p=.020. Separate univariate ANCOVAs on the outcome variables revealed significant effects on perceived maternal care *F* (1)=7.72, p=.006, but not on perceived maternal overprotection *F* (1)=0.45, p=.504. (2) Furthermore, the borderline diagnosis itself had a significant effect on maternal bonding (Pillai's trace), *F* (2,180) = 7.93, p<.001. Using separate univariate ANCOVAs, we found significant effects on perceived maternal overprotection *F* (1)=15.91, p<.001, but not on perceived maternal care *F* (1)=2.34, p=.125. See also **Figure 5.1.**

There was no significant interaction between breastfeeding and the diagnosis of BPD which implies two independent predictors. According to these analyses, the feeding mode (breastfeeding versus non-breastfeeding) affects more the perceived maternal care, whereas the diagnosis of BPD shows a more pronounced effect on perceived maternal overprotection. These findings emerged in consideration of controlling for childhood trauma, using CTQ total score as covariate (**Table 5.3**).

Figure 5.1. Breastfeeding and Perceived Maternal Bonding



PBI= Parental Bonding Instrument; BPD= Borderline Personality Disorder; CG= Control Group; **P-Value <.01; *P-Value <.05

5.4.3 Breastfeeding and Adult Attachment-Related Attitudes

There was a highly significant difference between borderline patients and healthy controls in attachment-related attitudes, measured by the Adult Attachment Scale. Patients with BPD achieved significantly higher scores on the AAS subscales 'trust' (p<.001), 'closeness' (p<.001) and 'anxiety' (p<.001). Thus, borderline patients show deviant patterns of

attachment-related attitudes in close relationships - characterised by fear of abandonment or fear of being unloved, mistrust in other people and discomfort in close and intimate relationships (see **Table 5.4**).

Table 5.3. Breastfeeding and Perceived Maternal Bonding (MANCOVA)

Independent Variable	**F**	**df**	***P***
Breastfeeding	4.01	2	.020
Borderline Diagnosis	7.93	2	<.001
Childhood Trauma	64.91	2	<.001
Interaction Breastfeeding * Borderline Diagnosis	.17	2	.843
Error		180	
ANCOVA			
Independent Variable	**F**	**df**	***P***
Maternal Care			
Breastfeeding	7.72	1	.006
Borderline Diagnosis	2.38	1	.125
Childhood Trauma	130.53	1	<.001
Interaction Breastfeeding * Borderline Diagnosis	.339	1	.561
Maternal Overprotection			
Breastfeeding	.45	1	.504
Borderline Diagnosis	15.91	1	<.001
Childhood Trauma	23.35	1	<.001
Interaction Breastfeeding * Borderline Diagnosis	.049	1	.759
Error		180	

df = Degrees of Freedom; T = *t*-value; *P* = Probability Score; F = F-Statistics.

In the next step, we assessed if breastfed individuals (n=134) differ significantly from non-breastfed individuals (n=59) regarding adult attachment-related attitudes. We found that non-breastfed individuals reported significantly more 'discomfort in close relationships' (p=.021) compared to breastfed individuals. The AAS subscales 'trust' and 'anxiety' differed not significantly between both groups. Thus, non-breastfed individuals show deviant adult attachment-related attitudes, characterized by feeling uncomfortable in emotionally close relationships (**Table 5.4**).

The applied regression analysis revealed that the scale 'closeness' was significantly predicted by the variable breastfeeding, however, after adjustment for childhood trauma, the variable just missed significance (p=.063). Individuals who were not breastfed are – as a trend finding - more likely to show attachment-related problems, characterized by feeling uncomfortable in close relationships.

Table 5.4. Adult Attachment-related Attitudes – Group Differences

	Mean (SD)		T	df	*P*
AAS-Subscales	**Patients**	**Controls**			
Closeness	16.63 (4.27)	8.99 (3.75)	13.24	192	<.001
Trust	16.59 (4.43)	9.60 (3.78)	11.90	192	<.001
Anxiety	15.83 (4.66)	8.74 (3.09)	12.51	169	<.001
AAS-Subscales	**Breastfed**	**Non-breastfed**			
Closeness	12.21 (5.59)	14.20 (5.21)	-2.33	191	.021
Trust	12.70 (5.38)	14.05 (5.31)	-1.61	191	.109
Anxiety	11.96 (5.96)	13.03 (5.31)	-1.30	191	.194

T = *t*-Value; df = Degrees of Freedom; *P* = Probability Score.

5.4.4 Predictors for Breastfeeding

To detect potential predictors for the feeding mode, eighteen independent variables were included in a separate logistic regression model. The analysis revealed that the factor 'unwanted pregnancy' significantly predicts breastfeeding (OR=.40; CI=.16-.98; p=.045). Mothers who reported an unplanned pregnancy were less likely to breastfeed their infants.
Trend findings (p<.1) emerged for the following items: low maternal education, partnership problems during pregnancy, familial conflicts and prenatal maternal smoking.

5.5 Discussion

To the best of our knowledge, this is the first study that investigates the prevalence of breastfeeding in BPD and its association with perceived maternal bonding and adult attachment.
Our aims were to assess whether borderline patients were less breastfed compared to controls and to test the predictive value of breastfeeding in the diagnosis of BPD. Furthermore, we aimed to assess the difference of breastfed versus non-breastfed individuals in maternal bonding and adult attachment-related attitudes and to test lack of breastfeeding as a potential predictor for deviant adult attachment and maternal bonding.
We found that borderline patients were significantly less breastfed compared to healthy controls. The variable 'breastfeeding' accounts for a substantial percentage of 9.1% variance for the diagnosis of BPD. Hereby, breastfeeding emerged as an important and significant predictor. Despite adjustment for childhood trauma, parental socioeconomic status and a range of further confounding variables, breastfeeding remained a strong and significant

predictor for the diagnosis of BPD. Lack of breastfeeding may therefore constitute an additional risk factor for the diagnosis of BPD.

Remarkably, breastfed individuals differ significantly from non-breastfed individuals in perceived maternal care. Furthermore, we found significant differences in adult attachment-related attitudes (discomfort in close relationships) between breastfed and non-breastfed individuals. Breastfeeding predicts perceived maternal care, independently from a history of childhood trauma and from the diagnosis of BPD.

It is evident that the breastfeeding rate in our borderline sample (57.6%) is far below the prevalence of breastfeeding in the general population, which has been reported to be 91%[413]. The breastfeeding rate in the control group however, equates to the reported breastfeeding rates in the general population (81.8%). Our findings are consistent with previous studies that found lower rates of breastfeeding in patients with mental disorders[383, 384]. A study in schizophrenic patients reported low breastfeeding rates of only 29% in those patients. During childhood, these non-breastfed patients showed more schizoid and schizotypal personality traits as well as a poorer social adjustment[384]. The authors concluded that lack of breast milk may be a risk factor in the neurodevelopmental form of schizophrenia. Moreover, a diagnosis of major depressive disorder has been reported to be associated with lack of breastfeeding[383]. Furthermore, a recent pregnancy cohort study, that included 2.900 pregnant women, revealed that children who have never been breastfed showed significantly more often externalizing and internalizing mental health problems compared to breastfed children[382]. However, not all studies found those associations[414].

Lack of breastfeeding may be a risk factor for impaired maternal bonding and disturbed attachment in the offspring. In the present study, borderline patients differed significantly from healthy controls in perceived maternal bonding and in all subscales of the adult attachment inventory that represents patterns of disturbed attachment-related attitudes. These findings are consistent with previous reports that consistently revealed insecure attachment in patients with BPD[135, 377-380, 415, 416]. Nearly all borderline patients have been described as being insecurely attached[149], mostly classified as showing a preoccupied or unresolved attachment style[417]. Thus, Patrick et al.[416] reported that 75% of their assessed borderline patients were classified as ‘unresolved attached’. Liotti[418] described BPD as an attachment disorder of the disorganized type. He stated that a disorganized attachment style leads to adult symptoms that are comparable to those of BPD. Furthermore, we confirmed findings from the literature that borderline patients perceived their mothers as more overprotective and less caring compared to controls[120]. Remarkably, it has been reported that the quality of mother-infant relationship is influenced by the feeding mode[396, 397]. The physical closeness and the skin-to-skin contact during breastfeeding may contribute to the establishment of a more intense mother-infant bonding. It has been reported that

breastfeeding increases maternal sensitivity, shown in the interaction with the child[400, 401]. Breastfeeding also increases maternal caregiving behaviour[402] as well as bonding behaviour which promotes the development of a secure attachment[403]. Breastfeeding mothers have been described as showing more social interaction and react more responsive and adequate to their children's needs, than non-breastfeeding mothers[419, 420]. This positive effect of breastfeeding on maternal bonding may in turn affect the attachment from a child to its mother. Consistent with these reports, we found that breastfed individuals describe the relationship to their mothers as being significantly more careful, warm and sensitive compared to mothers of non-breastfed individuals. These results match with findings from the literature in which breastfed children reported higher levels of parental attachment and perceived their mothers as being more caring and less overprotective compared with bottle-fed children[421].

These mechanisms may, amongst others, possibly be mediated by oxytocin - a neuropeptide that is also referred to as 'bonding hormone'. Mechanical stimulation of the nipples during breastfeeding promotes hypothalamic oxytocin release which promotes mother-infant bonding and maternal caregiving behaviour[422-424]. Furthermore, it influences maternal bonding-related behaviour, such as eye contact, vocalization, positive affect, attachment-related thoughts, and frequent looking after the child [425]. Since oxytocin has a stress reducing and -inhibiting effect in lactating women, they seem to be calmer and more social interactive[426, 427]. This enhanced sensitivity and social behaviour plays an important role in the mother-child interaction[428, 429] and may promote the development of a secure attachment and mental health in the offspring.

Further roots of attachment problems often lie in traumatic childhood experiences - which are common among borderline patients[430]. It has been reported that an insecure/disorganized attachment style often appears in children who experienced a history of trauma or difficult home environments[430]. In the present study, we found that impaired maternal bonding is associated with lack of breastfeeding - independently from childhood trauma. On the contrary, breastfeeding may even constitute a protective factor against child maltreatment. Thus, Strathearn et al.[431] demonstrated in a prospective study an association of decreasing prevalence of maternal child maltreatment with increasing duration of breastfeeding.

Furthermore, we assessed possible predictors for the feeding mode and found that mothers who reported an 'unwanted pregnancy' were more likely not to breastfeed. Marginal significant results were found for an elevated likelihood not to breastfeed in mothers with a lower level of education, who reported partnership problems and familial conflicts during pregnancy and who smoked during pregnancy. These results are consistent with the current literature: Oddy et al.[382] found that mothers with lower educational level, lower income, postnatal depression, who smoked during pregnancy or who experienced significant

stressors were more likely not to breastfeed - respectively to breastfeed for a shorter period of time. In other studies, the method of infant feeding was correlated with socioeconomic factors such as educational attainment, parental intelligence, smoking, and socioeconomic status[432].

Our results suggest that lack of breastfeeding may contribute to impaired bonding and attachment problems which are characteristic features of BPD. An impaired mother-child bonding may thus constitute an early environmental risk factor for later interpersonal problems and psychopathology. It is speculated that further risk factors, such as genetic vulnerability, childhood trauma and an adverse learning history may then determine the developmental course of BPD.

Although we found breastfeeding as a highly significant predictor for the diagnosis of BPD and maternal bonding, we can not exclude that the reported associations reflect effects of maternal characteristics or other social and contextual factors related to breastfeeding, rather than a direct effect of the feeding mode. To address this issue, we adjusted for a broad range of confounding variables, such as childhood trauma, parental monthly income, maternal education, maternal age at child's birth, unwanted pregnancy, preterm birth, birthweight, birth complications, cesarian section and maternal mental disorders. So, we covered a broad range of suggested potential confounders, named by Anderson et al.[386] who recommended in their meta-analysis to control for maternal age at child's birth, maternal education, parental socioeconomic status, maternal smoking history, infant's birth weight, gestational age and adverse childhood experiences[386]. Furthermore, we have no data about the duration of breastfeeding. Therefore, potential effects of breastfeeding duration could not be tested.

Our findings are based on retrospective self report data which bear the risk of a possible memory bias. However, it has been reported that mothers are able to correctly recall the feeding mode even after a period of up to almost two decades[433]. The author has shown that in 97% of cases, the information provided was in accordance with medical records. In another study, after a period of 18 years, 99% of mothers emphasized the accuracy of information about breastfeeding[394].

To further minimize the effects of a potential memory bias, we collected as objective information as possible. For that reason, we gathered objective information from medical records about medical complications, birth risk factors, birth outcome and maternal data. We could obtain information from 90.5% of mothers who personally completed the NPQ-PSQ.

Breastfeeding may act as an indicator of early mother-child relationship which may be neurobiologically characterized and which seems to be relevant for maternal bonding and attachment patterns later in life.

It has been broadly accepted that the diagnosis of BPD has a multifactorial genesis which includes genetic, neurobiological, psychosocial and environmental factors that interact at

various levels. Environmental risk factors affect the individual even during early postnatal life – which is known to be a highly vulnerable and sensitive period of brain development. Thus, lack of breastfeeding may constitute one more component in the susceptibility of BPD and its characteristic problems in interpersonal relationships. A combination of childhood adversity and perinatal risk factors - such as lack of breastfeeding - may thus substantially contribute to the development of BPD.

However, the exact underlying mechanisms wait to be clarified. Future prospective longitudinal studies are essential to verify the impact of the observed findings and neurobiological studies are recommended to elucidate their underlying neuroendocrine mechanisms.

Chapter 6

GENERAL DISCUSSION

6.1 Discussion

6.1.1 Aim of the Study

The purpose of the present study was to investigate the prevalence of pre- and perinatal risk factors in borderline patients and healthy controls. We aimed to assess whether these early environmental factors may possibly be involved in the etiology of BPD.

In addition to the well recognized effects of genetics, childhood adversity, and neurobiological abnormalities – we aimed to assess a risk factor that may potentially act very early in life, namely prenatal adversity. Another goal of the present study was to identify possible pre- and perinatal factors that may predict single sub-domains of borderline symptomatology, such as impulsivity, affective instability, disturbed bonding and adult attachment. Furthermore, we tested whether prenatal risk factors may predict the high prevalence of somatic comorbidities in BPD. To test these hypotheses, a detailed risk profile has been generated in a sample of 200 well matched patients and controls by means of semi-structured interviews, based on Neuropattern Diagnostics[320].

6.1.2 Summary of the Study Results

In the present study, we found that borderline patients - compared to healthy controls - were significantly more often exposed to adverse prenatal conditions. Mothers of borderline patients reported significantly more often of massive stressors during pregnancy, such as traumatic stress, partnership problems, familial conflicts and low social support. They suffered significantly more often from obstetric medical complications and had themselves more often a psychiatric diagnosis during pregnancy. The total number of prenatal adverse events differed highly significant between both groups. This high adversity load in patients' mothers was also reflected in high scores of perceived maternal stress during pregnancy.

A striking finding was that mothers of borderline patients smoked tobacco significantly more often during pregnancy. In our study, prenatal tobacco exposure turned out as one of the most important prenatal predictors for the diagnosis of BPD.

In addition to this high exposure of prenatal adversity, another core finding of the study has been obtained. We found that a high percentage of borderline patients have not been breastfed as infants. Evidence from our study emerged that lack of breastfeeding was one of the most important early predictors for the borderline diagnosis. Moreover, lack of breastfeeding may be one early underlying factor in the development of impaired bonding and disturbed attachment – which represent characteristic features of BPD.

In the present study, we also confirmed a significantly higher rate of physical health problems in borderline patients compared to controls, such as lifetime cardiovascular disorders, gastrointestinal disorders, disorders of hormone system and metabolism, sensory and

neurological disorders, skin disorders, urogenital symptoms, pain disorders and musculoskeletal disorders. All of these complaints are supposed to be 'stress-related disorders', whose susceptibility may be determined in utero. Prenatal maternal stress – such as stress at work – turned out to predict most of the assessed physical health domains.

With respect to postnatal adversity, we were able to confirm the high rate of childhood trauma in the history of patients with BPD. The prevalence of reported childhood trauma, such as sexual abuse, physical maltreatment and emotional neglect matched with the findings from the literature and differed highly significant between both groups.

Taken together, these results suggest a high exposure of early risk factors in the individual development of patients with BPD. Our findings imply that exposure to early adversity in BPD occurs prenatally, continues during perinatal period and infancy and results in a high exposure of postnatal stressors, such as severe childhood trauma.

6.1.3 Consequences of Early Adversity and corresponding Findings in BPD

As stated above, the exposure to prenatal adversity may have deleterious consequences for the offspring's mental and physical health. Here, we highlight the core findings of our study in consideration of findings from the literature, including pre- and perinatal adversity and their potential impact on BPD.

6.1.3.1 Prenatal Maternal Stress

Prenatal maternal stress or excess glucocorticoids were reported to have deleterious effects on offspring mental and physical health later in life. High levels of maternal or synthetic glucocorticoids affect brain structure during sensitive periods of fetal development. This alters synaptic plasticity and neurotransmitter activity and may result in subtle or pronounced changes in the offspring' brain function, behaviour, cognition[350], temperament [2] and mental health[365].

Programming of the HPA axis

In the present study, borderline patients were significantly more often exposed to prenatal maternal stress, such as maternal traumatic stress, familial conflicts, partnership problems, and low social support. These findings are consistent with previous reports that showed associations of prenatal stress or excess glucocorticoids with behavioural alterations and adverse physical and mental health outcome in the offspring later in life[306]. Rats, exposed to prenatal restraint stress, show a long-lasting hyperactivation of the HPA response as well as altered circadian rhythm of the corticosterone secretion[434]. Furthermore, prenatal exposure to excess glucocorticoids permanently increases basal plasma corticosterone levels in the adult animal[223, 435]. Although these associations have been amply demonstrated in animal

experiments, several studies suggest the same processes in human populations[154]. Accordingly, low birthweight babies have higher plasma cortisol levels throughout life, which indicates HPA axis programming[177]. Other studies report reduced HPA axis activity in the neonate after prenatal glucocorticoid exposure and no clear association with elevated cortisol levels in later life[436]. Remarkably, a dysfunctional HPA axis has repeatedly been reported in patients with BPD[83]. Dysfunctional HPA axis functioning, high perceived stress levels and pronounced emotional responding to stressful situations is characteristic for borderline patients and may suggest a potential prenatal programming effect. However, knowledge about the underlying neurobiological mechanisms is scarce. Processes of prenatal programming may be one missing link in the described associations. In support of this notion, Entringer et al.[352] found greater cortisol responses during a psychosocial stress test (Trier Social Stress Test; TSST[89]) in those individuals whose mothers experienced severe stress during pregnancy. Moreover, Wüst et al.[437] reported higher salivary cortisol responses to the TSST in individuals of lower birthweight. And the offspring of mothers who self-report anxiety and/or depression during pregnancy show higher basal HPA axis activity[438]. In this way, prenatal programming processes could shed some light on the underlying mechanisms of deviant HPA axis functioning and stress reactivity in patients with BPD. Prenatal maternal stress - similar to those obtained in our study - such as family conflicts, low social support, partnership problems or traumatic stress - may possibly act as underlying vulnerability factors for a malprogrammed HPA axis and later psychopathology in borderline patients. Future studies should take possible prenatal stressors - with respect to sex differences and timing of the exposure - into account when assessing HPA axis abnormalities in BPD.

Programming Behaviour, Temperament and Mental Health

In the present study, prenatal maternal stress is associated with the diagnosis of BPD. Mothers of borderline patients perceived their pregnancy as significantly more stressful compared to mothers of healthy controls – and the total number of prenatal adverse events differed highly significant between both groups. Prenatal maternal stress, altered HPA axis function and associated stress reactivity have been described as vulnerability factors for mental health problems and behavioural alterations in the offspring later in life[2].

These associations have been amply demonstrated in experimental animal studies in which offspring of rats, that were prenatally exposed to maternal restraint stress, showed behavioural alterations in adulthood, such as high anxiety levels and depression-like behaviour[434]. In humans, maternal stress has also been linked with depression, attention deficit, hyperactivity disorders as well as aggressive and antisocial behaviour in children and adults[350]. Bergman et al.[255] found that prenatal partnership strain accounted for a substantial percentage of the variance in fearfulness and cognitive ability in the offsping. Notably, in the

present study, partnership problems and familial conflicts during pregnancy appeared as important risk factors that were significantly more often reported by mothers of borderline patients, compared to mothers of healthy controls. Furthermore, mothers of borderline patients reported significantly more often of traumatic stress during pregnancy, such as death or suicide of a close relative, death of a child, severe material loss or rape during pregnancy. Strikingly, severe trauma (e.g. death of a close relative) during the first trimester of pregnancy has been reported to associate with an increased risk of developing schizophrenia in adulthood[170]. Eventually, those or similar prenatal traumatic stressors may also promote the risk of developing BPD later in life.

Possible underlying neurobiological mechanisms may be the prenatal programming of the amygdala. The amygdala is a key structure that mediates affective states, such as fear and anxiety and is characterized by increased activity[106-108] and smaller volumes in patients with BPD[96, 97]. In rats, prenatal programming of the amygdala due to prenatal maternal stress has been described to lead to 'hyper-emotional' states in the adult offspring[439]. Intriguingly, affective instability and 'hyper-emotional' states are also core symptoms of BPD[13]. A direct injection of CRH into the amygdalae increases anxiety-related behaviour in rats[440]. Furthermore, programming of GR and increased CRH levels in the central nucleus of the amygdala have been reported in those rat offspring that were prenatally stressed or overexposed by synthetic glucocorticoids[435, 439, 441]. In the present study, we found massive prenatal stressors in mothers of borderline patients as well as high levels of perceived maternal stress. Since borderline patients show a pronounced hyperactivity of the amygdalae, accompanied by hyper-affective states and recurrent fear and anxiety - it may be possible that prenatal programming process act as underlying factors for BPD and its associated symptoms.

Programming Physical Health

In the present study, prenatal maternal stress was also associated with a high rate of comorbid somatic disorders and complaints, such as cardiovascular disorders, gastrointestinal disorders, disorders of hormone system and metabolism, sensory and neurological disorders, skin disorders, urogenital symptoms, pain disorders and musculoskeletal disorders.

These findings are consistent with a broad range of human and animal studies, suggesting that prenatal maternal stress permanently 'programs' physiology and increases the risk of cardiovascular, metabolic and neuroendocrine disorders in adulthood[177]. In the present study, high stress at work during pregnancy was an important predictor of most of the assessed physical health domains. There is compelling epidemiological evidence that prenatal maternal stress or excess glucocorticoid exposure is associated with increased risk

of adult diseases[306]. Numerous experimental animal models have shown that prenatal excess glucocorticoids - either from endogenous overexposure to maternal stress or through exogenous administration - reduce birthweight and cause lifelong hypertension, hyperglycaemia and metabolic diseases in the offspring[177, 442]. These programming mechanisms are thought to act via changes in gene expression patterns which occur in response to a stressor and lead to alterations of specific tissue and organ structure during their most critical time of development[443].

It is known from the literature that increased disease risk, following prenatal maternal stress, appears largely independent of classical lifestyle risk factors, such as smoking, excess alcohol intake, and social class[1]. We controlled for all of these confounding variables and found independent effects of prenatal maternal stress on the assessed somatic disorders and complaints. However, despite the strong associations of prenatal adversity and physical disorders, several other risk factors appear to be of importance and may increase the risk for physical health disorders. Thus, we found participants' age, parental socioeconomic status and the borderline diagnosis itself as further predictors for somatic comorbidities. Those factors may act additive to the adverse effects of prenatal risk factors[151]. Altogether, our findings suggest that poor physical health outcome in BPD is determined multifactorial and strongly related to prenatal maternal stress.

6.1.3.2 Exposure to Tobacco Smoke

In the present study, prenatal tobacco exposure turned out to be a significant predictor for the diagnosis of BPD. Empirical evidence has shown that tobacco exposure in utero affects fetal brain development and may lead to temperamental and behavioral alterations later in life, such as increased impulsivity, inattention, externalizing and internalizing behavioral problems, conduct disorders[188, 189], and hypersensitive passive avoidant behavior[187]. Those temperamental differences can be observed very early in life and are known to be possible precursors for later psychopathology (such as ADHD, conduct disorders, depression and anxiety disorders[259]). Temperamental and behavioral alterations as described above have also been found in children and adolescents that develop BPD later in life[15, 16]. These temperamental traits may possibly be programmed in utero – eventually in part due to prenatal smoke exposure - and may act as early vulnerability factors for the development of BPD. Consistent to this assumption, we found prenatal smoke exposure as significantly related to adult BPD characteristics, such as impulsivity, affective instability and sensation seeking behavior. We have shown that these sub-domains were predicted by prenatal maternal smoking, independently from other pre- and postnatal adversities. Remarkably, behavioral traits, such as impulsivity, affective instability and sensation seeking behavior are also core features of ADHD, a neurodevelopmental disorder which has repeatedly been

associated with prenatal tobacco exposure[189, 190]. These findings and the high comorbidity rate of BPD and ADHD of about 50% may suggest a possible common pathogenetic pathway of both disorders. However, in the present study, the effects of prenatal tobacco exposure remained stable even after controlling for a comorbid ADHD diagnosis.

In the literature, prenatal tobacco exposure has been associated with structural and neurobiological changes in the offspring's brain. This could be demonstrated in several human and animal studies that found smaller volume of specific brain structures[333], cortical thinning[334], disruptions of white matter microstructure[335] and alterations in receptor density in specific brain regions[336, 337] in offspring that were prenatally exposed to tobacco. Heath et al.[187] described the cortico-thalamic circuit to be vulnerable for nicotine exposure through the early development.

Intriguingly, some of these brain alterations have also been described in patients with BPD. Hence, volume reductions in frontolimbic and parietal areas[17, 98, 338-340], an impaired frontolimbic connectivity[18, 341-343] and impaired inferior frontal white matter microstructure have been reported in brain imaging studies of borderline patients[344]. These findings show surprising parallels with those brain alterations, detected in offspring exposed to prenatal tobacco smoke. It might be possible that brain alterations that are thought to underlie the emotional dysregulation in BPD - such as impaired connectivity of different brain areas - may potentially be co-determined by prenatal tobacco exposure.

A potent agent that may cause those changes in neurodevelopment and central neurotransmitter systems is nicotine, deriving from maternal cigarette smoke. It binds to fetal nicotinic acetylcholine receptors and may alter the function of the cholinergic as well as other neurotransmitter systems[184, 186, 187, 337, 444]. Emotional lability in BPD, a hallmark of the disorder, is supposed to be associated with deficits in the cholinergic and noradrenergic neurotransmitter systems[42]. Eventually, those alterations may be in part determined due to prenatal tobacco smoke, because those biological systems are highly sensitive to early life environmental inputs[42]. Taken together, nicotine and other components in tobacco smoke may cause structural and functional brain alterations and exhibit profound effects on neurodevelopment. These early alterations have been reported to result in behavioral problems[187], altered stress reactivity[194], temperamental traits[188, 189] and elevated risk for mental disorders later in life[195, 345].

It might be possible that structural und functional brain alterations, as well as alterations in neurotransmitter systems in BPD may be mediated by pre- and/or postnatal tobacco exposure. However, future prospective studies are essential to disentangle those complex possible mechanisms. Future brain imaging studies in BPD should take account of pre- and postnatal tobacco exposure.

6.1.3.3 Medical Complications

In the present study, 30.9% of mothers of borderline patients reported medical complications during pregnancy. Medical complications, such as preterm contractions, preterm opening of the cervix, bleeding, nausea and vomiting with weight loss or pelvic presentation may represent a surrogate marker of general gestational adversity. Medical complications could thus reflect a poor fetal environment which has already been shown to be linked with adverse health outcomes in the offspring[345]. In the present study, prenatal medical complications were not only associated with the borderline diagnosis itself, but predicted moreover a more severe phenotype according to BSL and BPDSI total scores. Furthermore, we found medical complications as predictor for the sub-domains 'affective instability' and 'identity disturbance' in BPD.

In general, associations of prenatal adversity with behavioural and mental health outcome in the offspring are probably co-determined by several prenatal adverse events. Earlier studies have shown that different prenatal risk factors cause similar effects in the offspring, suggesting that prenatal adverse events act not very specific on behavioural outcomes. Thus, it is remarkable that very different factors, such as maternal stress or prenatal smoke exposure, show quite similar patterns of increased risk for behavioural problems later in life. These effects may be mediated by similar transplacental mechanisms and may result in similar neurodevelopmental alterations. However, despite the observed similarities of the resulting effects, it is likely that the precise alterations of brain development are different for different factors[2].

Altogether, we found a high prevalence of prenatal adversity in BPD that may act as a basic vulnerability factor for psychopahtology. However, prenatal adversity does not seem to be a specific risk factor for the diagnosis of BPD, since an adverse intrauterine environment appears to increase the vulnerability for diverse pathologies[2]. We suppose that – after exposure to prenatal adversity - postnatal environmental factors, neurobiological factors and/or genetic factors may then determine the developmental course of BPD.

6.1.3.4 Lack of Breastfeeding

BPD has been described as a disorder of disturbed attachment[135 418]. And thus, attachment problems represent one core symptom of BPD. In the present study, we confirmed the high prevalence of attachment problems and disturbed bonding in our borderline sample. Our findings suggest that bonding-related problems as well as the borderline diagnosis itself may be associated with lack of breastfeeding during the early postnatal period. Consistent with these findings, several studies report lower breastfeeding rates in individuals who later developed mental health problems and psychiatric diagnoses such as schizophrenia[384] and depression[383]. However, not all studies found those associations[414].

The process of breastfeeding represents a setting of proximity between mother and child, close skin-to-skin contact and feelings of security[398, 399]. It has been reported that breastfeeding promotes maternal sensitivity and social behaviour in interaction with the infant. These variables are thought to be essential for building a secure attachment and a tight bond between mother and child[400, 401]. In our sample of borderline patients, it was evident that the breastfeeding rate of only 57.6% is far below the prevalence of breastfeeding in the general population[413]. In the present study, lack of breastfeeding significantly predicts BPD, even after adjustment for a range of confounding variables. A recent pregnancy cohort study that included 2.900 pregnant women showed that children who have never been breastfed showed significantly more externalizing and internalizing mental health problems compared to breastfed children[382].

Furthermore, we found evidence of bonding-related problems in individuals who were not breastfed. Non-breastfed participants described the relationship to their mothers as being significantly less careful, warm and sensitive compared to breastfed individuals. These results match with findings from the literature in which bottle-fed children reported lower levels of parental attachment and perceived their mothers as being less caring and more overprotective compared to mothers of breast-fed children[421].

The underlying mechanisms may, amongst others, possibly be mediated by oxytocin - a neuropeptide that is also referred to as ‘bonding hormone'. Mechanical stimulation of the nipples during breastfeeding promotes hypothalamic oxytocin release which promotes mother-infant bonding and maternal caregiving behaviour[422-424]. Furthermore, it influences maternal bonding-related behaviour, such as eye contact, vocalization, positive affect, attachment-related thoughts, and frequent looking after the child[425]. Since oxytocin has a stress reducing and -inhibiting effect in lactating women, they seem to be calmer and more social interactive compared to bottle-feeding mothers[426, 427]. This enhanced sensitivity and social behaviour plays an important role in the mother-infant interaction[428, 429] and may promote the development of a secure attachment in the offspring.

One prospective study demonstrated that breastfeeding may even constitute a protective factor against child maltreatment[431]. The authors found a decreased prevalence of child maltreatment in association with increasing duration of breastfeeding.

However, despite these demonstrative findings, it is not clear if other components or maternal characteristics – independently from breastfeeding – may mediate the observed associations. Breastfeeding may thus constitute a marker of early mother-infant-relationship.

6.1.3.5 Postnatal Adversity

Although there is clear evidence for an association of prenatal adversity with later mental health problems, it is important to take other factors into account that also may affect the

outcome in the offspring. Postnatal adversity is known to be an important risk factor for later psychopathology and has been shown to be associated with a broad range of mental disorders[116, 124, 125]. Although the causal pathways are tremendously complex, a number of environmental characteristics are known to increase the risk for psychopathology in childhood, adolescence and adulthood: for example sexual abuse, parental violence, emotional neglect and abuse, physical maltreatment, parental psychopathology and low socioeconomic status[123, 445].

Especially BPD is a mental disorder which is characterized by a high prevalence of childhood adversity[44]. In the present study, we confirmed the high rates of adverse childhood experiences in patients with BPD, such as sexual abuse, physical maltreatment and emotional neglect. Early adverse life events – such as pre-, peri- and postnatal stressors - have the potential to affect the experience-dependent maturation of brain structures during specific sensitive periods of brain development and may thus lead to a greater susceptibility for mental disorders later in life.

However, in human studies, it is difficult to disentangle pre- from postnatal adverse effects, because experimental designs are not feasible. Both, pre- and postnatal adverse events represent unfavorable environmental influences which seem to 'program' brain structures that underlie emotional functioning and endocrine responses to stress. There are environmental factors that act on the fetus pre- *and* postnatally, such as low socioeconomic status, maternal stress or family conflicts. Thus, postnatal events may confound potential prenatal programming effects. Therefore, it is essential to take postnatal factors into account when assessing prenatal adversity. An approach to face this issue is to control for those variables, such as maternal socioeconomic status, because adverse environmental factors tend to cluster in families with low socioeconomic status[2]. In the present study, we strictly controlled for parental socioeconomic status and childhood trauma in all relevant analyses. We chose a very conservative statistical approach – a blockwise-hierarchical regression analysis – which enables to statistically disconnect confounding variables. We further adjusted for maternal mental health problems. However, controlling for variables, such as parental socioeconomic status may conceal fetal effects, because those influences may already affect the developing fetus. This may explain why in some studies significant associations attenuated or disappeared when adjusting for parental socioeconomic status or other indicators of continuing adversity. In our study, the findings remained significant, even though adjusting for childhood trauma, socioeconomic status and a range of further confounding variables. It may even be possible that the assessed prenatal risk factors 'prime' for postnatal adversity. In this way, postnatal adverse events could result from prenatally acquired disturbances which may promote their postnatal occurrence. With respect to the present study, it could be possible that the high percentage of explained variance of BPD

that revealed for prenatal adversity (25.7%) may be more relevant than the obtained value after the adjustment of postnatal factors.

In sum, evidence supports the assumption of long-lasting effects of prenatal adversity on mental health and behaviour but also illustrates the importance of controlling for postnatal environmental factors. Future studies should not only control for potential confounding factors of postnatal life, but should also investigate the role of these factors in the pathway from prenatal adversity to mental health problems later in life.

6.1.4 General Discussion of Early Risk Factors in BPD

Taken together, the results from the present study suggest an association of pre- and perinatal risk factors and the diagnosis of BPD. An increased risk for BPD and its' characteristic features may potentially be mediated by processes of early life programming.

Our findings suggest an accumulated risk profile in borderline patients. The adversity seems to start during fetal life, by exposure to prenatal maternal stress, tobacco smoke and medical complications. During early infancy, these patients may experience a lack of maternal closeness, maternal care and feelings of security – due to a lack of breastfeeding, which simultaneously seems to promote bonding-related problems. During childhood, patients with BPD were exposed to diverse traumatic experiences, from low parental socioeconomic status and maternal mental disorders to massive childhood trauma, such as sexual abuse, physical maltreatment and emotional neglect.

In general, there are several hints that may suggest a potential process of early life programming in patients with BPD. Supporting this assumption, numerous studies documented an elevated stress sensitivity, symptoms of distress and altered HPA axis function in BPD. These characteristics are also typically seen in individuals who were exposed to prenatal adversity, such as prenatal maternal stress.

Furthermore, temperamental alterations, such as elevated impulsivity and affective instability are typical features of BPD and may predispose an individual to develop mental health morbidity later in life. Such temperamental alterations have been described to be prenatally programmed and are assumed to act as precursors for later psychopathology. Intriguingly, impulsive temperament and affective instability have been reported to be mediated by prenatal tobacco exposure – which could be confirmed in the present study.

Furthermore, BPD is characterized by a broad range of somatic comorbidities and complaints. Most of them are stress-related disorders which are known to be determined - at least in part - in utero. Experimental studies in animals as well as large cohort studies in humans amply demonstrate clear associations between prenatal adversity, impaired intrauterine development and later disease risk. We found a high prevalence of those disorders in our borderline sample and revealed close associations with maternal stress

during pregnancy. Thus, somatic comorbidities in BPD may – to some extent – be programmed in utero.

A lack of maternal closeness and early maternal care may be another perinatal risk factor, experienced during early life, by lack of breastfeeding. Early maternal care has been demonstrated to produce neurobiological changes in animals' brain structure, such as epigenetic programming of hippocampal glucocorticoid receptor density due to maternal licking and grooming[353] or early handling of the rat pups[446]. Similar processes of early programming may underlie the association of lack of breastfeeding, bonding-related problems and the diagnosis of BPD.

Altogether, these findings may suggest possible pre- and perinatal programming effects in BPD.

6.1.5 Limitations

Retrospective Design

With respect to limitations of the present study, it has to be considered that the findings are based on retrospective self report data which bear the risk of a possible memory bias or response shift bias. To minimize these effects, we strove to collect as objective information as possible. Therefore, we gathered objective information about medical complications, birth risk factors, birth outcome and maternal data from prenatal medical records. Furthermore, information on pre- and perinatal life events base primarily on mothers' statements who personally completed the NPQ-PSQ (90.5% of mothers). All participants were instructed to review the interview questions carefully together with their mothers prior to the interview.

To further reduce possible memory effects, information was obtained from several diverse informants (mothers, fathers, the offspring themselves and/or further relatives). Each participant rated the validity of the provided information on a 0- to 10-point Likert scale. We generally obtained high evaluation scores of 8.08 points in the patients' group and 8.67 points in the control group. Moreover, we applied strict exclusion criteria: If participants were not able to provide information at first hand - from mothers or close relatives - they were excluded from participation.

The most important predictors in our study - namely prenatal tobacco exposure and medical complications - are variables that are better verifiable than more subjective variables such as perceived stress. Thus, medical complications could in part be verified by comparison with prenatal medical records. With respect to our main finding - prenatal tobacco exposure - a high validity of maternal recall on smoking during pregnancy has been reported in an earlier publication[357]. Jaspers et al.[357] found a high concordance rate between maternal recall and documented smoking behavior after more than one decade after birth. Thus, the authors found a kappa of .77 for maternal smoking during pregnancy that represents the highest

validity of all retrospectively obtained data in their study. Therefore, the prenatal variables that predicted BPD most significantly in the present study, appear to be more 'verifiable' compared to other recalled information.

Genetic Factors

Another issue that deserves consideration is a possible confounding effect of genetic factors. Hence, we cannot exclude that the obtained associations of prenatal risk factors and BPD may possibly be mediated in part by genetic variables. Psychopathology or temperamental alterations, such as impulsivity, may be heritable traits and may be genetically transmitted from mothers to the offspring. Furthermore, genetic factors may account for maternal health related behavior during pregnancy as well as for psychopathologic outcome in the offspring. However, existing studies strongly suggest that the effects of prenatal adversity on behavioral problems later in life cannot be accounted for by genetic factors alone. Thus, twin studies revealed independent effects of prenatal adversity/low birthweight on later behavioral problems that were not explained by shared genetic factors[358-360]. Studies, in which independent prenatal effects can be obtained, use reproductive technologies, in which a donated embryo (or egg) carries no 'maternal' genes – and thus the effects were independent from shared heritable components[361]. Furthermore, there is now increasing evidence, suggesting gene x prenatal environment interactions. Data from our own research group also suggest gene x prenatal environment interactions as well as independent prenatal effects on psychopathology and associated behavioral traits (Schwarze et al., in preparation). These findings might shed some light on the relationship between genetic variants and early environmental risk factors. Disentangling genetic and fetal environmental effects should be a major topic of future research.

Postnatal Adversity

Although literature clearly demonstrates associations of prenatal adversity and later mental and physical health, it is necessary to take postnatal factors into account that are known to impact behavioural outcome in the offspring. One of these factors is postnatal adversity, such as childhood trauma. It is known that postnatal adversity is a strong and important predictor for poor mental health outcome later in life[116, 124]. To minimize possible confounding effects of postnatal adversity, we strictly controlled for relevant postnatal risk factors such as childhood trauma and parental socioeconomic status. However, in human studies, it is difficult to completely disentangle pre- from postnatal influence, because pre- as well as postnatal adversity may be mediated by the same mechanisms (e.g. low maternal socioeconomic status). Experimental animal studies removed confounding maternal or postnatal effects due to specific research designs, such as cross-fostering[447]. However, experimental designs are not feasible in human studies and many variables interact in a tremendously complex way. In

the present study, our findings remained significant despite controlling for postnatal adversity. We even chose a very conservative method to statistically disconnect pre- from postnatal factors. To assess interactions as well as potential mediator- and moderator-effects of pre- and postnatal adverse events, investigation of the underlying pathways are recommended. Future studies should control for postnatal confounding factors but should also investigate the role of these factors in the pathway from prenatal adversity to later psychopathology.

Breastfeeding and Maternal Characteristics

With respect to perinatal adversity, we found breastfeeding as a highly significant predictor for the diagnosis of BPD and impaired maternal bonding. However, as stated above, we cannot exclude that the reported associations reflect in part effects of maternal characteristics or other social and contextual factors related to breastfeeding, rather than a direct effect of the feeding mode. To address that issue, we adjusted for a broad range of confounding variables, such as childhood trauma, maternal education, parental monthly income, maternal age at child's birth, unwanted pregnancy, preterm birth, birthweight, birth complications, cesarian section, and maternal mental disorders. So, we covered a broad range of suggested potential confounders.

Due to the dichotomous assessment of the feeding mode (breastfeeding versus non-breastfeeding), we do not have data about the duration of breastfeeding. Therefore, potential effects of breastfeeding duration could not be assessed.

Although maternal breastfeeding has been assessed retrospectively, the validity of recalled events, such as breastfeeding, seems to be quite reliable. Accordingly, Bogaard.[433] has shown that in 97% of cases, the information provided by the mothers was in accordance with medical records. The author concluded that mothers are able to recall the feeding mode quite correctly even after a period of almost two decades[433]. In another study, 99% of mothers emphasized the accuracy of memories on the feeding mode after a period of 18 years[394].

Physical Health

With respect to the assessed somatic comorbidities, we carefully validated the provided information on current or lifetime diagnoses in a personal interview with all participants. However, an element of risk remains that patients with BPD were eventually characterized by elevated complaining about symptoms which would be an alternative explanation of the high prevalence of somatic disorders in BPD. However, it is unlikely, that the obtained findings were completely attributable to elevated complaining, because a great deal of previous studies found prenatal programming effects of somatic disorders in individuals that were prenatally exposed to adversity and maternal stress[1, 9]. Furthermore, several studies, among

them a recent, representative population based study, confirms the high prevalence of somatic disorders in BPD[39].

6.1.6 Summary

Taken together, the findings of the present study suggest an accumulated early risk profile in patients with BPD – possibly starting during fetal life, and accumulating in infancy and childhood. This may be a novel approach in the assessment of the etiology of BPD. To the best of our knowledge, pre- and perinatal adversity in BPD has never been assessed before in such detail.

Our findings suggest that prenatal adversity – in particular prenatal tobacco exposure and prenatal medical complications – may play a substantial role in the pathogenesis of BPD.

In addition, variations in core features of BPD, such as impulsivity, affective instability and sensation seeking behavior, seem to be particularly affected by prenatal tobacco exposure. Moreover, further prenatal risk factors – notably prenatal maternal stress - appear to be involved in the high prevalence of somatic comorbidities in BPD. This lends support to the assumption of fetal origins of health and disease - which may also act in borderline patients.

Finally, lack of breastfeeding appears to be another important predictor for the borderline diagnosis and may also promote impaired bonding and disturbed attachment later in life.

Remarkably, we found that the observed pre- and perinatal risk factors appear largely independent from postnatal adversity, such as childhood trauma, lifestyle risk factors and parental socioeconomic status.

Taken together, an adverse early environment has the potential to alter brain structure and function as well as endocrine systems during specific sensitive periods of fetal development. These alterations may lead to increased stress vulnerability and to a greater susceptibility for diverse pathologies later in life. Stressful life events could thus be aggravated in individuals, made vulnerable due to pre- and perinatal adversity. In the pathogenesis of BPD, pre- and perinatal adverse events may thus constitute risk factors of basic vulnerability. Genetic factors as well as continuation of adversity (such as childhood trauma) may then determine the developmental course of BPD. Thus, a combination of pre- and perinatal adversity, in association with later adverse events may substantially contribute to the multifactorial genesis of BPD.

6.1.7 Future Perspectives

The long-term goal of examining the adverse effects of pre-, peri- and postnatal life events in BPD is to contribute to a better understanding of the underlying mechanisms of health and disease and - based on that knowledge - to provide improved opportunities to diagnose and treat affected individuals as well as to provide appropriate prevention programs.

Possible prevention and intervention programs that could be drawn from the findings of the present study may consist in future establishment of certain support- and information-centres for expectant parents, in which they were educated about possible risk factors for their developing child, such as glucocorticoids, toxins, medication, infection, diseases, certain foodstuffs, alcohol and tobacco consumption. That kind of education may base on latest knowledge, derived from basic research on prenatal adversity. By means of specific stress management programs, pregnant women may be trained in more functional handling and improved coping of life stress or daily hassles, in order to minimize the deleterious effects of excess glucocorticoids on their offspring.

Another possible transfer of the obtained findings to the general public could consist in information campaigns which may broadly spread information about possible consequences of maternal stress and health behaviour during pregnancy and indication of appropriate information- and support- centres, where expectant parents could get further advice. Those or similar programs could contribute to prevent behavioural problems in the offspring and may increase health and well-being of children later in life.

Psychobiological processes that underly stress-related mental and bodily disorders are characterized by a tremendous complexity – so, in future, it will be indispensable to diagnose and treat physical and mental health problems with individualized diagnostic and therapeutic tools[320]. Without much doubt, this will be the next and necessary step in medicine and psychotherapy to integrate findings from basic sciences into treatment and prevention of stress related disorders. The long-term goal examining early risk factors may thus consist in making this knowledge available for the patients' health and wellbeing. This process can also be described as a transfer of scientific knowledge "from bench to bedside"[320]. This approach is already just being realized with neuro-pattern^{TM} diagnostics, a new method, created by Dirk H. Hellhammer and developed at the University of Trier, Germany, by his research group[320]. Neuropattern is a diagnostic tool that aims to measure the activity of interfaces which are involved in the crosstalk between the brain and peripheral organs during stress. Relevant survey instruments and questionnaires that have been used in the present study were derived from neuropattern diagnostics.

The present study provides basic evidence of an association of prenatal risk factors and the diagnosis of BPD. From these findings, future research may be derived.

Most importantly, prospective longitudinal studies are essential to evaluate and potentially confirm the obtained findings. Such a large-scale prospective study is currently running in the USA and is named 'National Child Study'. In this study, 100.000 pregnant women are being included and getting assessed in detail for certain risk factors. The offspring of those mothers will be accompanied over a time span of about 21 years, in which effects of environmental factors and parameters of physical and mental health will continuously be assessed.

Future neuroimaging studies - such as MRI, fMRI, and PET studies – that assess functional and/or morphological brain anomalies - may detect a possible link between CNS abnormalities in BPD and exposure to prenatal adversity - especially maternal tobacco smoke. Hereby, also the timing of the exposure should be taken into account. Furthermore, there is some evidence that low birth weight, coupled with lower levels of maternal care, associate with reduced hippocampal volume in adult women[448]. Similar associations may also underlie reduced volume of specific brain structures in BPD and may be assessed in future studies.

Studies that focus on the assessment of the HPA axis in borderline patients should also take pre- and perinatal risk factors into account - with special regard to differential gender effects as well as certain timing of the exposure. Genetic studies may elucidate possible gene x environment interactions with respect to pre- and perinatal adversities.

Finally, an upcoming - and very promising - approach is the analysis of the 'epigenome'. In particular, genome-wide methylation studies are recommended (personal communication, Szyf, 2010, Leiden, The Netherlands). By means of this approach, correlations between epigenetic changes (e.g. changes in DNA methylation patterns) and early environmental risk factors (such as prenatal adversity or early trauma) may be detected. Due to epigenetic processes, experiences of early life seem to get 'biologically manifest' and become objectifiable matter. Since borderline patients show a high load of early life stress, studying the epigenome may thus be a promising approach to further characterize the neurobiological basis of BPD. Moreover, epigenetic mechanisms may even have implications for the treatment of BPD and other mental disorders, since the plasticity due to methylation or demethylation processes allows to reverse negative effects due to positive environmental experiences, such as interpersonal care, social support or psychotherapy. Considering that, new inside into a potential biological basis of psychotherapeutic interventions may result (see also Grawe[449], 'Neuropsychotherapy'). The efficacy of therapeutic interventions in BPD which could repeatedly been proven for dialectic behavioural therapy, DBT[450] and schema therapy[451] may base on the caring, appreciative, respectful and warm therapeutic attitude towards the patient. A protective factor and a mechanism of early prevention may thus constitute in a warm and careful early environment, provided for the developing child. This protective effect of positive inter-subjective experiences has also impressively been demonstrated in studies of neonatal handling[446] and maternal licking and grooming[353] in rat offspring. In these studies, neonatal handling as well as maternal care behaviour obviously led to CNS changes due to epigenetic programming, resulting in changed hippocampal mineralocorticoid and glucocorticoid receptor numbers and altered HPA parameters. The neonatal handling/licking and grooming paradigm thus emphasizes the importance of early maternal/parental care and nurturing behaviour - which may promote the development of a

more resilient phenotype. Remarkably, this kind of experience is often lacking in the development of patients with BPD.

Taken together, the results of the present study again demonstrate the importance of early life experiences. We suspect that processes of pre-, peri- and postnatal programming of BPD may also be mediated by epigenetic effects. Future investigations will possibly reveal an epigenetic basis of BPD. The present study may contribute to early prevention and intervention programs for affected individuals.

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