Verbal Memory Functioning in Borderline Personality Disorder:

Neuropsychological and Neuroimaging Perspectives

Dissertation to Achieve
a Doctorate in Natural Science (Dr. rer. nat.)
of the University of Bielefeld

Presented by
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Bielefeld, June 2006

First referee: PD Dr. Michael Bulla-Hellwig

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For Mum, Dad, and Grandma

Acknowledgements

This work was only possible with the cooperation of many people. First of all, I would like to thank our patients and control subjects for their participation in both studies. Moreover, I thank the teams of the inpatient units A7 and A8 of the Ev. Hospital Bielefeld for their kind cooperation in the recruitment of patients, especially Dr. Matthias Lindner and Dr. Hedda Ribbert as well as Hella Wulff, who further supported the studies with clinical supervision.

Prof. Dr. Martin. Driessen supported this work with enthusiasm and supplied experienced supervision. Parts of the studies presented here were supported by grants supplied to Prof. Driessen by the Deutsche Forschungsgemeinschaft (DFG; grant Dr 358 / 5-2) and by the von Bodelschwinghschen Anstalten Bethel.

Further, I wish to express my sincere gratitude to PD Dr. Thomas Beblo who supported this work by supervising the development of the methods used, and who provided helpful discussions, and useful feedback.

Moreover, I am also grateful to Dr. Friedrich G. Wörmann of the Society for Epilepsy Research Bethel / Mara Hospital for his contributions to the discussion of the fMRI findings.

I am also grateful to my research colleagues Dr. Katja Wingenfeld, Nina Rullkötter, Anamaria Silva Saavedra, and Susanne Ratzka who contributed to the conception, execution, and analysis of this work and who all supported me during this study. Further, I wish to thank our student assistants Christian Steil, Nicole Schlosser, and Camille Schaffrath for their contribution in the execution of the second study.

Further, I say thank you to Thony Christie for his valuable help with the manuscript.

In particular, I am very grateful to PD Dr. Michael Bulla-Hellwig who provided me with experienced and valuable supervision in the conception and writing of this thesis.

I am also very grateful to Prof. Dr. Wolfgang Hartje for his kind cooperation and his willingness to supervise this work.

Bielefeld, 2006

Contents

Abbreviations

5-HT	5-hydroxytryptamine
ACC	Anterior cingulate cortex
ADHD	Attention deficit/hyperactivity disorder
Alpha $_{BC}$	Alpha, Bonferroni corrected
Alpha-MTrp	Alpha[11C]methyl-L-tryptophan
Alpha $_{STD}$	Alpha, standard ($p < .05$)
ANOVA	Analysis of variance
APA	American Psychiatric Association
AVLT	Auditory Verbal Learning Test
BA	Brodmann area
BC	Baseline condition
BDI	Beck Depression Inventory
BOLD	Blood oxygenation level dependent
BPD	Borderline personality disorder
BPD-C	Community sample of BPD subjects
BPD-H	Hospitalized BPD patients
CD	Compact disc
DLPFC	Dorsolateral prefrontal cortex
DSM-III	Diagnostic and Statistical Manual for Mental Disorders, 3rd edition
DSM-III-R	Diagnostic and Statistical Manual for Mental Disorders, 3rd edition, revised form
DSM-IV	Diagnostic and Statistical Manual for Mental Disorders, 4th edition
DSS	Dissoziations-Spannungs Skala (Dissociation Tension Scale)
DST	Digit Suppression Test
e.g.	For example
EMR	Episodic memory retrieval
FAS	Lexical retrieval task concerning letters F, A, and S
FCP	Patients with frontal lesions outside the orbitofrontal cortex
FDG-PET	[18F]Deoxyfluorglucose Positron Emission Tomography
FLAIR	Fluid attenuated inversion recovery
FMRI	Functional magnetic resonance imaging

FOV	Field of view
HCG	Healthy control group
HDRS	Hamilton Depression Rating Scale
HPA axis	Hypothalamic-pituitary-adrenal axis
IAG	Patients with impulsive aggression
ICD-10	International Classification of Diseases
i.e.	That is
IES-R	Impact of Event Scale, revised form
L	Left
LPS	Leistungsprüfsystem
M	Mean
MD	Patients with major depression disorder
MNI	Montreal Neurological Institute
MPRAGE	Magnetization prepared gradient echo
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
ms	Milliseconds
N	Number
N.R.	Not reported
NART	National Adult Reading Test
OFC	Orbitofrontal cortex
OFP	Patients with lesions in the orbitofrontal cortex
PCC	Posterior cingulate cortex
PCG	Psychiatric control group
PD-C	Patients with personality disorder of cluster C
PET	Positron Emission Tomography
PDS	Posttraumatic Stress Diagnostic Scale
PTSD	Posttraumatic stress disorder
R	Right
RFX	Random Effects Analysis
s	Seconds
SCID	Structured Clinical Interview for DSM-IV
SD	Standard deviation
SMR	Semantic memory retrieval

SPM	Statistical Parametric Mapping
SPSS	Statistical Package for the Social Sciences
STAI	State-Trait Anxiety Scale
TCG	Temperamentally matched control group
TE	Time to echo
TI	Time to inversion
TR	Time to repetition
UK	United Kingdom
WAIS	Wechsler Intelligence Scale
WMS-R	Wechsler Memory Scale, revised form

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1 Theoretical background

1.1 Borderline personality disorder

The nosological term “Borderline” was introduced by the psychoanalyst Stern (1938). Noting ongoing resistance of some patients to psychoanalytic treatment, Stern suggested this form of pathology falls on the border between “neurosis” and “psychosis”. Mainstream psychiatry never accepted this point of view and it fell out of use entirely, when neo-Kraepelin ideas become prominent (Klerman, 1986).

Following more accurate clinical descriptions (Kernberg, 1967; Grinker, Werble & Drye, 1968) it was shown, that “Borderline” could be operationalized with observable criteria, using semi-structured interviews with psychometric properties (Gunderson & Singer, 1975). Largeley based on the work of Gunderson, Borderline Personality Disorder was accepted into DSM-III (APA, 1980).

Table 1.1: DSM-IV criteria for the diagnosis of borderline personality disorder

1. Frantic efforts to avoid real or imagined abandonment (does not include suicidal or self-mutilating behavior as covered in criterion 5).
2. A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation.
3. Identity disturbances: Markedly and persistently unstable self-image or sense of self.
4. Impulsivity in at least two areas that are potentially self-damaging (e.g. spending, sex, substance abuse, reckless driving, binge eating).
5. Recurrent suicidal behavior, gestures, or threats, or self-mutilating behavior.
6. Affective instability due to a marked reactivity of mood (e.g. intense episodic dysphoria, irritability, or anxiety usually lasting a few hour and only rare more than a few days.
7. Chronic feelings of emptiness.
8. Inappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights.
9. Transient, stress-related paranoid ideation or severe dissociative symptoms.

Borderline personality disorder (BPD) as currently defined by DSM-IV (APA, 1994, 2000) is a complex, multidimensional syndrome. The ICD-10 (WHO, 1992) definition of

“emotionally instable personality, borderline type” is not notable different (Paris, 2005). The symptoms of patients diagnosed for BPD include affective, impulsive, and cognitive phenomena (Gunderson & Ridolfi, 2001; Paris, 2003). Generally, BPD is characterized by a pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning in early adulthood. Five (or more) criteria have to be present in a variety of contexts, to diagnose for BPD. The criteria are indicated by table 1.1 (page 1).

1.1.1 Epidemiology

Based on population estimates, one to two percent of adults meet the criteria for BPD (e.g. Lenzenweger, Loranger, Korfine & Neff, 1997; Samuals et al., 2002; Torgersen, Kringlen & Cramer, 2001). Furthermore, about ten percent of psychiatric outpatients and approximately twenty percent of inpatients met criteria for BPD (Torgersen et al., 2001). BPD is diagnosed more frequently in females than in males with a female to male gender ratio of 3:1 (APA, 2000; Skodol & Bender, 2003). Further, BPD is more common in younger adults than in older and BPD symptoms seem to remit with increasing age (Zanarini, Frankenburg, Hennen & Silk, 2003). Suicide rates of patients diagnosed for BPD are estimated at approximately ten percent, and thus are comparable to other psychiatric disorders like major depression and schizophrenia (Paris, 2002). In addition, 69 to 75 percent of individuals with BPD are engaged in self-injurious behavior, and the frequency of self-injurious behavior is higher than in any other psychiatric diagnosis (Clarkin, Widiger, Frances, Hurt & Gilmore, 1983; Cowdry, Pickar & Davies, 1985).

1.1.2 Comordidity

A part of the complexity arises from the DSM-IV definition of BPD, which includes substance abuse, disordered eating behavior, abnormalities in mood state, and psychotic-like phenomena. All of these features predispose BPD toward the comorbidity of further axis-I disorders. Several large studies revealed a large number of comorbid axis-I and axis-II disorders in patients diagnosed for BPD (Widiger & Weissman, 1991; Zanarini et al., 1998; Zanarini, Gunderson, Marino, Schwartz & Frankenburg, 1989; Zimmermann & Mattia, 1999). Generally, frequently reported high rates of co-occuring axis-I disorders include depression, substance abuse, anxiety, and eating disorders. For instance, a study by Zanarini et al. (1998) revealed for BPD high lifetime prevalence rates of major depression (83%), alcohol abuse and

dependence (52%), panic disorder (48%), posttraumatic stress disorder (56%), bulimia (26%), and anorexia (21%). Frequently reported axis-II disorders are avoidant, histrionic, schizotypal, and antisocial personality (Widiger & Weissman, 1991). These high rates of comorbid psychiatric disorders in BPD led Skodol, Gunderson et al. (2002) to the conclusion that any patient samples which are limited to patients with a sole BPD diagnosis cannot be considered as representative for BPD as it is diagnosed in in- and outpatient settings.

1.1.3 Etiology

Multifactorial diathesis-stress etiological models of the cause of BPD are most common (Clarkin & Posner, 2005; Driessen et al., 2002; Kernberg, 1975; Zanarini & Frankenburg, 1997). Prominent researchers suggest that BPD psychopathology might be the final product of innate temperament, adverse childhood experiences, and relative subtle forms of neurological and biochemical dysfunction (Paris, 1994; Zanarini & Frankenburg, 1997).

The multifactorial point of view of the cause of BPD is supported by several findings. Patients with BPD show a temperament / personality characterized by a high degree of neuroticism and low agreeableness (Clarkin, Hull & Hurt, 1993; Soldz, Budman, Demby & Merry, 1993; Trull, 1992). Further, BPD patients show both, harm-avoidance as well as high novelty seeking (Svrakic, Whitehead, Przybeck & Cloninger, 1993). Multivariate genetic analyses of personality disorder showed a large genetic basis of emotional dysregulation, a factor that is closely related to BPD, and its inheritability is estimated at 47% (Livesley, Jang & Vernon, 1998; Skodol, Gunderson et al., 2002; Skodol, Siever et al., 2002).

Further, it has been shown that fundamental BPD features as unstable, intense relationships, feelings of emptiness, bursts of rage, abandonment fears and intolerance of aloneness may stem from impaired attachment organization (Fonagy et al., 1996; Gunderson, 1996). Samples of BPD patients show high rates of childhood sexual abuse, separation from caregivers, and neglect (Ogata et al., 1990; Zanarini et al., 1989). The high rate of traumatic experiences led some authors to conceptualize BPD as a complex form of PTSD (e.g. Driessen et al., 2002; Reddemann & Sachsse, 2000).

Several studies underline that patients diagnosed for BPD show difficult to detect, subtle forms of developmental neurological dysfunction like a history of learning disability or attention-deficit hyperactivity disorder and acquired neurological dysfunction secondary to trauma (Andrulonis, Glueck, Stroebel & Vogel, 1982; Gardner, Lucas & Cowdry, 1987). Further, biochemical alterations according to the serotonergic system (Leyton et al., 2001)

and the hypothalamic-pituitary-adrenal axis (Grossman et al., 2003; W. Lange et al., 2005; Rinne et al., 2002) have been documented in patients with BPD.

1.1.4 Course

Patients with BPD utilize health care services more frequently than any other group (Bender et al., 2001). Treatment efforts in these patients are characterized by high drop-out rates and variable improvement in psychotherapy (Clarkin, 1996) as well as a few responders to psychotropic treatment (Soloff, 2000).

Two recent prospective studies of the course of BPD showed higher rates of symptom remission than once thought. A one-year follow-up indicated that the course of BPD symptoms did not consistently meet diagnostic thresholds, and the mean number of BPD criteria declined within a year (Shea et al., 2002). Further, a six-year follow-up study using a sample of BPD patients that were hospitalized at the start of the study showed that about 75% of patients no longer met the DSM-IV criteria (Zanarini et al. 2003). This study also examined the phenomenology of four general categories of BPD symptoms with regard to affective, cognitive, impulsive, and interpersonal features. Affective symptoms were the least likely to remit and were present in about 70% of patients after six years. Impulsivity showed mixed results: after six years, self-mutilating behavior and suicidality declined whereas other forms of impulsivity as binge-eating and verbal outbursts remained more stable. Cognitive and interpersonal features also declined with the exception of the intolerance of aloneness and abandonment fears.

In sum, these findings suggest that BPD phenomenology may consist of stable, trait-like features (i.e. affective instability) with more state-like crisis behavior (i.e. self-mutilation, suicidality, psychotic-like symptoms) that declines quickly over time. (Bohus, Schmahl & Lieb, 2004).

1.1.5 The question of neuropsychological impairment

BPD is characterized by unstable patterns of affect regulation and impulsivity. Patients with BPD have an unstable self-image and unstable feelings of self-esteem and experience a repetitive pattern of disorganization and instability in personal relationships. Additionally, they show recurrent suicidal and self-mutilating behavior, and further psychopathologic symptoms or psychiatric disorders (comorbidity). Furthermore, clinical reports characterized

BPD patients as temporary suffering from psychotic and dissociative symptoms. These symptoms often co-occur with disturbances of perception and of cognition including abnormalities of language, memory, attention, and executive functions (Kernberg, Dulz & Sachsse, 2000; Sternbach, Judd, Sabo, McGlashan & Gunderson, 1992; Zanarini, Gunderson & Frankenburg, 1990). According to these clinical observations, it seems likely that patients with BPD also show impaired neuropsychological functions.

Further, there is another reason to suspect that there are disruptions of basic neuropsychological functions in BPD, e.g. impairment of memory functions, interference control and inhibition (Fertuck, Lenzenweger, Clarkin, Hoermann & Stanley, 2006). A central feature of BPD is an unstable and dysregulated inhibitory control over behavior, emotion, and cognition. The acquisition of inhibition is closely linked to the development of emotion and personality (Derryberry & Reed, 1994). Furthermore, inhibitory capacity has been shown to influence the acquisition of pro-social behaviors, affect regulation, and problem solving abilities (Posner & Rothbart, 2000) and these capacities are commonly impaired in BPD.

1.2 Neuropsychology of borderline personality disorder

Early phenomenological investigations of BPD used neuropsychological and projective tests to characterize “Borderline personality organization”, a forerunner of the current BPD nomenclature (Fertuck et al., 2006). Psychological testing of cognition and perception were most often utilized by the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955) and the Rorschach Inkbot Test. According to these tests, borderline subjects revealed a relatively unimpaired intellectual performance, but disturbed Rorschach responses (Rapaport, Gill & Schafer, 1968). Reviews of early cognitive research in borderline subjects have later questioned, whether these early studies would have been considered BPD by DSM standards, as well as questioning methodological issues and data analysis (Widiger, 1982).

Followed by the advent of DSM-III (APA, 1980) with its atheoretical definition of axis-II disorders, a shift in psychiatry to empirical research emphasizing reliability, validity, and psychometric properties of assessment became evident. Consequently, neuropsychological batteries which were evolved to assess a wide range of cognitive functions were applied to psychiatric populations. In accordance with this development, systematic investigations of neuropsychological functions in patients diagnosed for BPD using standardized tests and comparisons with control groups started in the late 1980s.

Over the last few years, a growing body of research addressed the question of neuropsychological impairment in BPD. By the use of PsychInfo and PubMed databases and references to prior reviews (Beblo, Silva Saavedra, Mensebach & Driessen, 2004; Fertuck et al., 2006; O'Leary, 2000; Ruocco, 2005) twenty-two studies could be identified. Inclusion criteria were: Studies reporting neuropsychological performances of patients with BPD, providing comparisons with a healthy control group or norm data, and study results have been published in a peer-reviewed journal.

Table 1.2 reports all included studies, the kind of control groups, demographical features and the outcomes of the assessed neuropsychological functions. All tests that were used in these studies were categorized with respect to well-established neuropsychological constructs (see Lezak, 1995; Spreen & Strauss, 1998) as the following: memory, attention, visuo-spatial abilities, and executive functions. Memory which was assessed most frequently was further subdivided following the verbal/visual distinction (Paivio, 1971) and the working memory/delayed memory distinction (Atkinson & Shiffrin, 1968; Baddeley, 1986; Tulving, 1983). Consequently, the findings of the neuropsychological studies were categorized with respect to the following categories:

(i) Verbal Working Memory: All tests that include immediate recalls and / or immediate recognition of verbal information and verbal span measures.

(ii) Visual Working Memory: All tests that include immediate recalls and / or immediate recognition of visual information and visual span measures.

(iii) Verbal Delayed Memory: All tests that require delayed recall and / or delayed recognition of verbal information over an interval of more than fifteen minutes.

(iv) Visual Delayed Memory: All tests that require delayed recall and / or delayed recognition of verbal information over a interval of more than fifteen minutes

(v) Attention: All tests assessing alertness, selected attention, sustained attention, divided attention, shifting, vigilance, and visuo-motor processing speed.

(vi) Visuo-spatial abilities: All tasks assessing construction abilities, embedded figures, and mental rotation.

Table 1.2: Overview on selected studies reporting neuropsychological data for BPD

	Study	Sample	Diagnostic System	Ratio of female/male BPD patients	Medication reported?	Axis I co-morbidity included?	Age differences ?	IQ differences ?	Education differences ?	Sex Matched HCG?
1	Cornelius et al. (1989) [a]	24 BPD	DSM-III-R	16/8	NO	IN PART	---	---	---	---
2	Burgess (1990)	18 BPD; 14 HCG	DSM-III-R	6/12	NO	NO	NO	N.R.	N.R.	YES
3	O'Leary et al. (1991)	16 BPD; 16 HCG	DSM-III-R	13/3	NO	IN PART	NO	YES	NO	YES
4	Judd & Ruff (1993)	25 BPD; 25 HCG	DSM-III	20/5	NO	IN PART	NO	NO	N.R.	YES
5	Swirsky-Sacchetti et al.(1993)	10 BPD; 10 HCG	DSM-III-R	10/0	YES	NO	NO	YES	NO	YES
6	Arntz et al. (2000)	16 BPD; 12 PD-C; 15 HCG	DSM-III-R	N.R.	NO	YES	NO	N.R.	N.R.	N.R.
7	Driessen et al. (2000) [b]	21 BPD; 21 HCG	DSM-IV	21/0	IN PART	YES	NO	IN PART	NO	YES
8	Korfine & Hooley (2000)	22 BPD-H; 23 BPD-C; 20 HCG	DSM-IV	20/2; 18/5	NO	N.R.	NO	IN PART	NO	YES
9	Sprock et al. (2000) [c]	18 BPD; 18 MD; 18 HCG	DSM-III-R	18/0	NO	N.R.	BPD>HCG	NO	NO	YES
10	Sprock et al. (2000) [c]	18 BPD; 18 MD; 18 HCG	DSM-III-R	18/0	NO	IN PART	MD>BPD	NO	NO	YES
11	Bazanis et al. (2002)	42 BPD; 42 HCG	DSM-III-R	25/17	IN PART	IN PART	NO	N.R.	NO	YES
12	Harris et al. (2002)	15 BPD; 15 HCG	DSM-IV	10/5	NO	N.R.	NO	N.R.	N.R.	YES
13	Posner et al. (2002)	39 BPD; 22 TCG; 30 HCG	DSM-IV	38/1	NO	N.R.	HCG<BPD	N.R.	N.R.	IN PART
14	Kunert et al. (2003)	23 BPD; 23 HCG	DSM-IV	20/3	YES	NO	NO	NO	NO	YES
15	Dinn et al. (2004)	9 BPD; 9 HCG	DSM-IV	9/0	YES	YES	NO	N.R.	YES	YES
16	Dowson et al. (2004)	19 BPD; 19 ADHD; 19 HCG	DSM-IV	15/4	IN PART	IN PART	NO	NO	NO	YES
17	Lenzenweger et al. (2004)	24 BPD; 68 HCG	DSM-IV	24/0	NO	IN PART	NO	N.R.	NO	YES
18	Monarch et al. (2004) [a]	12 BPD	DSM-IV	12/0	IN PART	IN PART	---	---	---	---
19	Stevens et al. (2004)	22 BPD; 25 HCG	DSM-IV	22/0	IN PART	NO	NO	NO	NO	YES
20	Berlin et al. (2005)	19 BPD; 23 OFP; 20 FCP; 39 HCG	DSM-IV	18/1	NO	N.R.	N.R.	N.R.	N.R.	NO
21	Irle et al. (2005)	30 BPD; 25 HCG	DSM-IV	30/0	YES	YES	NO	YES	NO	YES
22	Beblo, Silva Saavedra et al. (2006)	22 BPD; 21 HCG	DSM-IV	21/0	YES	YES	NO	YES	NO	YES

ADHD: attention-deficit hyperactivity disorder; BPD: borderline personality disorder; BPD-C: community Sample of BPD subjects; BPD-H: hospitalized BPD patients; FCP: patients with frontal lesions outside the orbitofrontal cortex; HCG: healthy control group; MD: patients with major depression; N.R.: not reported; OFP: patients with lesions in the orbitofrontal cortex; PD-C: patients with personality disorder of cluster C; TCG: temperamentally matched control group.

[a] Comparison with norm data; [b] analysis included statistical control of self-rated depression which had an impact on most neuropsychological measures; [c] the Sprock et al. (2000) study did include two separate samples.

Table 1.2 (continued): Overview on selected studies reporting neuropsychological data for BPD

	Study	Verbal Working Memory	Visual Working Memory	Verbal Delayed Memory	Visual Delayed Memory	Visuo-spatial abilities	Attention	Executive Functioning
1	Cornelius et al. (1989) [1]	O	O	O	O	O	•	•
2	Burgess (1990)	O	•	▼	•	•	•	▼
3	O'Leary et al. (1991)	▼	▼	▼	▼	▼	O	O
4	Judd and Ruff (1993)	▼	▼	▼	O	▼	O	▼
5	Swirsky-Sacchetti et al. (1993)	O	▼	O	▼	▼	▼	O
6	Arntz et al. (2000)	•	•	•	•	•	▼	•
7	Driessen et al. (2000) [2]	O	O	O	O	O	O	O
8	Korfine and Hooley (2000)	O	•	•	•	•	•	•
9	Sprock et al. (2000) [3]	•	O	•	O	O	O	O
10	Sprock et al. (2000) [3]	O	O	O	O	O	O	O
11	Bazanis et al. (2002)	•	•	•	O	•	•	▼
12	Harris et al. (2002)	•	▼	•	▼	▼	•	•
13	Posner et al. (2002)	•	•	•	•	•	▼	•
14	Kunert et al. (2003)	O	O	O	O	O	O	O
15	Dinn et al. (2004)	▼	▼	•	•	▼	▼	▼
16	Dowson et al. (2004)	•	O	•	O	•	•	O
17	Lenzenweger et al. (2004)	•	O	•	•	•	O	▼
18	Monarch et al. (2004) [1]	▼	▼[4]	▼	▼[4]	▼	▼	▼
19	Stevens et al. (2004)	•	▼	•	•	▼	•	•
20	Berlin et al. (2005)	•	▼	•	•	•	•	▼
21	Irle et al. (2005)	O	▼	▼[5]	▼[5]	•	•	▼
22	Beblo, Silva Saavedra et al. (2006)	O	▼	O	▼	▼	O	▼

• Not assessed; ▼ impaired performance of BPD patients compared with healthy control group reported; O no group differences between BPD patients and healthy control subjects reported.

[1] Comparison with norm data; [2] analysis included statistical control of self-rated depression which had an impact on most neuropsychological measures; [3] the Sprock et al. (2000) study did include two separate samples; [4] one general score for immediate and delayed recall; [5] one general score for delayed recall.

(vii) Executive Functions: All tests assessing planning, decision making, flexibility, and fluency[1] measures.

Further, the selected studies were classified as to whether they used intelligence-matched control groups. Intelligence was defined by the use of standard intelligence tests, e.g. the Wechsler Adult Intelligence Scale (WAIS; Wechsler, 1955; 1995) or the National Adult Reading Test (NART; Nelson, 1982)

1.2.1 Memory

Although memory was among the first neuropsychological functions that was investigated as being possibly impaired in BPD (Burgess, 1990; O'Leary, Brouwers, Gardner & Cowdry, 1991) study outcomes have been quite heterogeneous. Based on early neuropsychological findings, it has been suggested that memory impairment in BPD would be evident if "complex" rather than "simple" stimulus material is used (O'Leary, 2000). This view is not supported by recent studies, which were not able to detect deficits in complex verbal memory tests like the "Logical Memory" subtest of the revised Wechsler Memory Scale (i.e. Beblo, Silva Saavedra et al., 2006; Sprock, Rader, Kendall & Yoder, 2000). Further evidence against a relation between memory impairment and the complexity of the used test comes from a recent study which reported for BPD a general deficit in visual memory that was independent of task load (Stevens, Burkhardt, Hautzinger, Schwarz & Unckel, 2004).

Sub-analyzing memory findings with respect to the verbal/visual and the working memory/delayed memory distinctions also does not demonstrate a consistent constellation of findings. One study reported deficits in all four memory categories (O'Leary et al., 1991), others were not able to detect deficits in any category (Kunert, Druecke, Sass & Herpertz, 2003; Sprock et al., 2000). A recent meta-analysis suggested that among memory functions, visual memory is stronger affected than verbal memory (Ruocco, 2005). Since the meta-analysis was only based on ten studies, these conclusions have to be considered as preliminary.

Some studies investigated the impact of emotional valence on working memory performance in BPD. An initial study revealed for BPD a tendency for a deficient inhibition of emotional negative interference (Swirsky-Sacchetti et al., 1993). Using a task which first

[1] Verbal fluency measures have also been conceptualized as an indicator of semantic memory (e.g. Herrmann et al., 2001). Since the majority of studies reported here used fluency tasks as indicators for executive functioning, this chapter follows this distinction.

requires the encoding of target words followed by a distraction task with emotional negative valence followed by a free recall of targets, BPD patients as compared to control subjects showed a decreased memory performance. More recently, a study using a comparable task revealed no significant impact of emotional negative distraction on memory performance of BPD patients (Sprock et al., 2000). However, first clear evidence for a memory bias according to negative salient stimuli comes from a study using a directed forgetting task (Korfine & Hooley, 2000). Directed forgetting as used in that study demands subjects to encode target words they are instructed to encode and to inhibit distractor words they are instructed to forget. Korfine and Hooley found that their BPD patients revealed a normal performance according to the "remember"-condition, however, BPD patients relative to control subjects remembered more words of negative valence that they had been instructed to forget. Korfine and Hooley interpreted their findings as reflecting an enhanced encoding and / or a reduced inhibition of emotional negative interference.

Generally, neuropsychological studies provide some evidence for impaired memory functioning in BPD. To date, impairment seems non-specific with regard to the working memory/delayed memory distinction. Furthermore, there may be a tendency towards stronger affected visual rather than verbal memory in BPD. Further investigation is needed to clarify a deficient processing of emotional salient stimuli during memory tasks, specifically interference control and inhibition.

1.2.2 Attention

Several studies aimed at the investigation of interference in BPD. Using the Attention Network Test, Posner et al. (2002) showed BPD patients to perform well on alertness and orienting tasks, but showed affected performance in a conflict task. The used conflict task requires, comparable to the stroop task, the control and inhibition of irrelevant interference. In line with impaired abilities of BPD patients to resolve cognitive conflict are several studies on stroop interference. Two studies reported an impaired functioning of BPD patients on the color-word interference (Dinn et al., 2004; Swirsky-Sacchetti et al., 1993). A further study showed BPD subjects to perform well on standard word-color interference, but reported a deficient performance concerning emotional negative words (Arntz, Appels & Sieswerda, 2000). By contrast, other studies were not able to detect an increased liability to stroop interference, neither by the use of color-words, nor by the use of emotional negative words (Judd & Ruff, 1993; Sprock et al., 2000).

Further, several studies reported unaffected visuo-motor processing speed (Beblo, Silva Saavedra et al., 2006; Monarch, Saykin & Flashman, 2004; O'Leary et al., 1991; Sprock et al., 2000), sustained attention (Lenzenweger, Clarkin, Fertuck & Kernberg, 2004), vigilance (Monarch et al., 2004), alertness and divided attention (Beblo, Silva Saavedra et al., 2006).

In sum, there is no evidence for a general impairment of attention in BPD. However, several studies suggested that BPD patients show a specific impairment in dealing with attention tasks that include interference and conflict.

1.2.3 Visuo-spatial abilities

Malfunctioning of visual-spatial abilities in BPD has often been reported. Several studies found impaired visuo-construction (Beblo, Silva Saavedra et al., 2006; Harris, Dinn & Marcinkiewicz, 2002; Judd & Ruff, 1993; Swirsky-Sacchetti et al., 1993), however, some argued against this (Sprock et al., 2000). Further impairment has been reported for spatial orientation and visual discrimination concerning embedded figures (Beblo, Silva Saavedra et al., 2006; O'Leary et al., 1991) as well as spatial imagination and mental rotation (Beblo, Silva Saavedra et al., 2006; Stevens et al., 2004). However, some studies were not able to detect any deficits concerning visual-spatial abilities (Kunert et al., 2003; Sprock et al., 2000). The meta-analysis of Ruocco (2005) characterized visuo-spatial abilities to be moderately affected.

Generally, deficient visuo-spatial abilities of patients with BPD are supported by most, but not all studies. More specifically, visuo-construction has found to be most consistently impaired.

1.2.4 Executive functioning

Several studies investigated cognitive flexibility in patients diagnosed for BPD. The outcome of most studies argued for a reduced flexibility (Bazanis et al., 2002; Beblo, Silva Saavedra et al., 2006; Dinn et al., 2004; Lenzenweger et al., 2004; Monarch et al., 2004), however, this was not supported by other studies (Kunert et al., 2003; O'Leary et al., 1991; Swirsky-Sacchetti et al., 1993). Further, planning and problem-solving abilities have been investigated in BPD. Some studies reported unaffected planning and problem-solving abilities in BPD (Kunert et al., 2003; Sprock et al., 2000), whereas others found these functions impaired in BPD (Beblo, Silva Saavedra et al., 2006; Dinn et al., 2004).

Several studies aimed at the investigation of fluency performances in BPD. Verbal fluency revealed mixed results with one study reported an impaired performance (Dinn et al., 2004) whereas another did not (Beblo, Silva Saavedra et al., 2006). Visual (figural) fluency was consistently found to be impaired (Beblo, Silva Saavedra et al., 2006; Dinn et al., 2004; Judd & Ruff; 1993).

In sum, impaired flexibility abilities of patients diagnosed for BPD were found most consistently, whereas planning and problem-solving revealed mixed results. Investigations of fluency support impaired visual fluency, whereas verbal fluency impairment seems ambiguous.

1.2.5 Conclusion

Although neuropsychological investigations in BPD did not provide a consistent constellation of findings some evidence is available for a non-specific impairment in multiple domains of memory, attention, visuo-spatial abilities and executive functioning. The heterogeneity of findings may be in part due to the fact that many studies lack power since they used small samples (e.g. samples including ten or less BPD patients: Dinn et al., 2004; Swirsky-Sacchetti et al., 1993) and some studies only provided comparisons with norm data (Cornelius et al., 1989; Monarch et al, 2004). Furthermore, studies differed extensively in their inclusion criteria. Some studies used a very strict cut-off excluding all BPD patients with axis-I comorbidity (Kunert et al., 2003), which has been criticized as leading to an unrepresentative sample (Skodol, Gunderson et al., 2002). On the other hand, some studies included a large number of patients who met the criteria for antisocial personality disorder (Bazanis et al., 2002) or schizoaffective disorders (Dinn et al., 2004). These psychiatric disorders themselves have been demonstrated to produce striking neuropsychological deficits (Dolan & Park, 2002; Schatzberg et al., 2000). Some studies tried to control for possible interfering variables (i.e. Driessen et al., 2000; Sprock et al., 2000). The statistical control for interfering variables effects requires a substantial theoretical basis. The Driessen et al. study controlled differences with regard to symptoms of depression in BPD patients and control subjects and found no different neuropsychological outcomes. However, this may be attributed to a statistical control for symptoms of depression. A control for symptoms of depression in BPD samples is not unambiguous since affective symptoms are an important feature of BPD symptoms and thus, this approach may lead to over-correction.

With respect to these differences in methodology, sample selection and sample size it is no wonder that studies investigating neuropsychological functioning in BPD are characterized by a heterogeneous constellation of findings. To date, there is some evidence for non-specific deficits in memory functioning with a tendency towards more strongly affected visual rather than verbal memory. Further, investigations of visuo-spatial abilities have repeatedly revealed malfunctioning in patients diagnosed for BPD. Attention and executive functions have also repeatedly been reported to be affected. A recent review hypothesized that deficient attention and executive functioning might be due to tasks that require the control of interference and the ability of cognitive, affective, and behavioral inhibition (Fertuck et al., 2006).

1.3 Neurophysiological correlates of borderline personality disorder

Neuroimaging investigations of BPD started in the 1980s. Since earlier conceptualizations of BPD implied a relation to schizophrenia, first studies aimed in the investigation of brain volumes and ventricle sizes, which have been found altered in schizophrenia. However, computer-tomography findings did not reveal enlarged ventricles or an increased ventricle to brain ratio in BPD (Lucas, Gardner, Cowdry & Pickar, 1989; Schulz et al., 1983). Since core symptoms of BPD such as affective instability and impulsivity suggested prefrontal and limbic brain dysfunctions, the focus of further research mainly aimed at the investigation of these brain areas (e.g. De La Fuente et al., 1997; Lyoo, Han & Cho, 1998).

The present overview includes studies that were identified by the use of PsychInfo and PubMed databases and by references to recent reviews (Clarkin & Posner, 2005; McCloskey, Phan & Cocarro, 2005; Schmahl & Bremner, 2006). Inclusion criteria were: Studies reporting neurophysiological data of patients with BPD, provide comparisons with healthy or psychiatric control groups, and study results have been published in a peer-reviewed journal. All included studies are shown in table 1.3. Following a proposal by Schmahl and Bremner (2006) studies were categorized with regard to four features: The first category includes studies which addressed volumetric and spectroscopic alterations in BPD. Neuroimaging studies investigating brain metabolism with regard to restating stage conditions constitute the second category. The third category included studies which aimed at the investigation of

Table 1.3: Overview of neuroimaging studies investigating BPD

Study	Sample	Diagnostic System	Ratio of female/male BPD patients	Medication reported?	Axis I comorbidity included?	Age Differences?	IQ differences?	Education differences?	Sex-matched control group?
(A) Structual Imaging / Spectroscopy									
1 Lyoo et al. (1998)	25 BPD; 25 HCG	DSM-III-R	23 / 2	NO	NO	NO	NO	NO	YES
2 Driessen et al. (2000)	21 BPD; 21 HCG	DSM-IV	21/ 0	FREE	IN PART	NO	NO	NO	YES
3 van Elst et al. (2001)	12 BPD; 14 HCG	DSM-IV	12 / 0	FREE	IN PART	NO	N.R.	NO	YES
4 Rüsch et al. (2003)	20 BPD; 21 HCG	DSM-IV	20 / 0	NO	IN PART	NO	N.R.	N.R.	YES
5 Schmahl, Vermetten et al. (2003)	10 BPD; 23 HCG	DSM-IV	10 / 0	NO	YES	NO	N.R.	HCG > BPD	YES
6 van Elst et al. (2003)	8 BPD; 8 HCG	DSM-IV	8 / 0	FREE	IN PART	NO	N.R.	NO	YES
7 Brabilla et al. (2004)	10 BPD; 20 HCG	DSM-IV	4 / 6	YES	IN PART	NO	N.R.	NO	YES
8 Hazlatt et al. (2005)	50 BPD; 50 HCG	DSM-III-R	23 / 27	NO	IN PART	NO	N.R.	N.R.	YES
9 Irle et al. (2005)	30 BPD; 25 HCG	DSM-IV	30 / 0	YES	IN PART	NO	YES	N0	YES
10 Zetzsche et al. (2006)	25 BPD; 25 HCG	DSM-IV	25 / 0	YES	IN PART	NO	NO	NO	YES
(B) Brain Metabolism with regard to Resting Conditions									
11 De La Fuente et al. (1997)	10 BPD ; 15 HCG	DSM-III-R	8 / 2	FREE	NO	NO	N.R.	N.R.	NO
12 Juengling et al. (2003)	12 BPD; 12 HCG	DSM-IV	12 / 0	FREE	IN PART	NO	N.R.	NO	YES
13 Soloff et al. (2003)	13 BPD; 9 HCG	DSM-III-R	13 / 0	FREE	IN PART	NO	N.R.	N.R.	YES
14 C. Lange et al. (2005)	17 BPD; 9 HCG	DSM-IV	17 / 0	YES	YES	NO	YES	NO	YES
(C) Emotional Processing / Autobigraphical Memory									
15 Herpertz et al. (2001)	6 BPD; 6 HCG	DSM-IV	6 / 0	NO	NO	NO	N.R.	NO	YES
16 Donegan et al. (2003)	15 BPD; 15 HCG	DSM-IV	13 / 2	YES	YES	NO	N.R.	N.R.	YES
17 Schmahl, Elzinga et al. (2003)	10 BPD; 10 PCG	DSM-IV	10 / 0	YES	YES	NO	N.R.	N.R.	YES
18 Driessen et al. (2004)[a]	12 BPD	DSM-IV	12 / 0	YES	IN PART	YES	N.R.	NO	YES
19 Schmahl et al. (2004)	10 BPD; 10 PCG	DSM-IV	10 / 0	YES	YES	NO	N.R.	N.R.	YES
20 Beblo, Driessen et al. (2006)	20 BPD; 21 HCG	DSM-IV	20 / 0	YES	IN PART	NO	YES	NO	YES
(D) Imaging of the Serotogergic System									
21 Soloff et al. (2000)	5 BPD; 8 HCG	DSM-IV	5 / 0	FREE	IN PART	NO	N.R.	N.R.	YES
22 Leyton et al. (2001)	13 BPD; 11 HCG	DSM-IV	5 / 8	FREE	IN PART	NO	N.R.	N.R.	YES
23 Soloff et al. (2005)	22 BPD; 24 HCG	DSM-III-R	15 / 7	FREE	IN PART	NO	N.R.	N.R.	YES

BPD: borderline personality disorder; HCG: healthy control group; PCG: psychiatric control group; IAG: patients with impulsive aggression; PTSD: posttraumatic stress disorder; N.R.: not reported, [a] subgroup analysis of BPD patients with and without comorbid PTSD.

Table 1.3 (continued): Overview of Neuroimaging Studies investigating BPD

	Study	Main findings in BPD patients as compared to control subjects
(A) Structual Imaging / Spectroscopy		
1	Lyoo et al. (1998)	Volume reduction: frontal lobe
2	Driessen et al. (2000)	Volume reduction: hippocampus, amygdala
3	van Elst et al. (2001)	Reduction of N-acetylaspartate: DLPFC
4	Rüsch et al. (2003)	Volume reduction: amygdala (gray matter)
5	Schmahl, Vermetten et al. (2003)	Volume reduction: hippocampus, amygdala
6	van Elst et al. (2003)	Volume reduction: hippocampus, amygdala, right ACC, left OFC
7	Brambilla et al. (2004)	Volume reduction: hippocampus
8	Hazlatt et al. (2005)	Volume reduction: ACC, PCC
9	Irle et al. (2005)	Volume reduction: hippocampus, right parietal lobe; stronger leftward asymmetry of the parietal cortex
10	Zetzsche et al. (2006)	Volume reduction: ---
(B) Brain Metabolism under resting conditions		
11	De La Fuente et al. (1997)	Decreased metabolism: DLPFC, ACC, thalamus, caudate, lenticular nuclei
12	Juengling et al. (2003)	Decreased metabolism: left hippocampus, left cuneus; increased metabolism: DLPFC, ACC
13	Soloff et al. (2003)	Decreased metabolism: medial OFC
14	C. Lange et al. (2005)	Decreased metabolism: right temporo-parietal, left PCC, left precuneus
(C) Emotional Procesing / Autobigraphical Memory		
15	Herpertz et al. (2001)	Increased neural response to emotionally aversive pictures: amygdala
16	Donegan et al. (2003)	Increased neural response to emotional faces: amygdala
17	Schmahl, Elzinga et al. (2003)	Increased metabolism in response to abandonment scrits: bilateral DLPFC; right cuneus; decreased metabolism: right ACC
18	Driessen et al. (2004)	Increased activation in response to trauma recall of the OFC and left DLPFC in BPD patients without PTSD
19	Schmahl et al. (2004)	No increased activation in response to trauma scripts; decreased activation: ACC, OFC, DLPFC
20	Beblo, Driessen et al. (2006)	Increased activation in response to trauma recall of frontal cortex, including insula, OFC, temporal activation including the amygdala
(D) Imaging of the Serotogergic System		
21	Soloff et al. (2000)	Decreased glucose uptake in response to fenfluramine in right medial/ OFC, left temporal lobe, left parietal lobe and left caudate
22	Leyton et al. (2001)	Decreased Alpha[^{11}C]Methyl-L-Tryptophan in medial OFC, ACC, temporal lobe, and corpus striatum
23	Soloff et al. (2005)	Decreased glucose uptake in response to fenfluramine in male BPD patients in the left temporal lobe

ACC: anterior cingulate cortex; BPD: borderline personality disorder; DLPFC: dorsolateral prefrontal cortex; OFC: orbitofrontal cortex; PCC: posterior cingulate cortex; PTSD: posttraumatic stress disorder.

brain responses to stressful challenges. Finally, brain-imaging studies of the serotonergic system are reviewed.

1.3.1 MRI-volumetry and spectroscopy

An initial study reporting structural alterations in BPD was carried out by Lyoo et al. (1998). With the advent of fMRI, Lyoo and colleagues found a marginally significant decrease of the frontal lobe in BPD. However, this study has been criticized for technical reasons as well as for the lack of head tilt correction (Schmahl & Bremner, 2006). Further studies showed reduced volumes of the orbitofrontal cortex (van Elst et al., 2003) and a reduction of N-acetylaspartate in the dorsolateral prefrontal cortex (van Elst et al., 2001). Further some evidence showed reduced volumes for the anterior cingulate cortex (van Elst et al., 2003; Hazlett et al., 2005).

The first study that investigated hippocampus and amygdala volumes was carried out by Driessen et al. (2000). The findings of this study reporting significant volume reductions of the hippocampus and the amygdala have been replicated by other workgroups (Schmahl, Vermetten, Elzinga & Bremner, 2003; van Elst et al., 2003). Further studies did show reduced volumes of the hippocampus (Irle, Lange & Sachsse, 2005) and of both, the amygdala and the hippocampus, but the reduction of the amygdala volume was not of a significant level (Brambilla et al., 2004). In contrast, a recent study did not find volume losses of the amygdala in BPD (Zetzsche et al., 2006) but suggested enlarged amygdala volumes in BPD patients with additional major depression.

Only a few studies investigated structural alterations of the posterior cortex. Unreplicated findings indicated a reduced volume size of the right parietal cortex (Irle et al., 2005) and of the posterior cingulate cortex (Hazlett et al., 2005).

1.3.2 Brain metabolism with regard to resting conditions

Several studies used [^{18}F] fluorodeoxyglucose Positron-Emission-Tomography (FDG-PET) to investigate the brain metabolism with regard to resting conditions. One pioneering study revealed a decreased metabolism in premotor areas, in the dorsolateral prefrontal cortex, parts of the anterior cingulate cortex as well as of thalamic, caudate, and lenticular nuclei (De la Fuente et al., 1997). A further study on impulsive BPD patients found a decreased metabolism only in the medial orbitofrontal cortex (Soloff et al., 2003). However, a recent PET investigation of severely traumatized BPD patients did not find a decrease in glucose

metabolism in prefrontal areas but in the posterior cortex (C. Lange, Kracht, Herholz, Sachsse & Irle, 2005). The reduced glucose metabolism in this study extended from the right temporal pole into the right fusiform gyrus also covering the left posterior cingulate cortex and the left precuneus. Further, C. Lange and colleagues found for BPD an association between a decreased resting stage brain metabolism with decreased memory performance a few day prior to their PET investigation.

Although most studies showed regional brain hypometabolism, one study also reported a hypermetabolism. Studying brain metabolism in BPD patients without concurrent major depression, Juengling et al. (2003) reported both, an increase of the regional brain metabolism in dorsolateral prefrontal areas and the anterior cingulate cortex as well as a decrease in the hippocampus and the cuneus.

1.3.3 Neuroimaging of the serotonergic system

Impulsive aggression is an important feature of the BPD phenotype and little is known about its neurobiology (Schmahl & Bremner, 2006). Impulsive aggression has been found to be associated with reduced serotonergic metabolite and pharmacologic challenge studies (Cocarro et al., 1989). Pre-clinical and human studies suggest that the orbitofrontal and the anterior cingulate cortex play an important inhibitory role in the regulation of aggression (Schmahl & Bremner, 2006). To date, few studies aimed at the investigation of the serotonergic system in BPD and localization of serotonergic dysfunction. These studies use FDG-PET in conjunction with serotonergic agents such as fenfluramine. Fenfluramine enhances the serotonergic activity by direct release of serotonin, antagonism of serotonergic reuptake and possible direct receptor effects (Cocarro, Kavoussi, Cooper & Hauger, 1996).

There are several studies investigating fenfluramine challenge in patients with impulsive aggression, but only a few limited their inclusion criteria to BPD. A first study investigating fenfluramine challenge in BPD using PET was carried out by Soloff, Meltzer, Greer, Constantine & Kelly (2000). The authors reported a reduced glucose metabolism of the right medial and orbital frontal cortex, left temporal and parietal areas and the left caudate body in response to fenfluramine. A further study of this workgroup highlighted gender differences of BPD patients (Soloff, Meltzer, Becker, Greer & Constantine, 2005). In response to fenfluramine, male but not female patients with BPD showed a reduced glucose metabolism in the left temporal lobe.

Another method to assess the functioning of the serotonergic system is to use PET with the 5-hydroxytryptamine (5-HT) precursor analogue Alpha[^{11}C]methyl-L-tryptophan (Alpha-MTrp). Alpha-MTrp is taken up by 5-HT neurons, where it is trapped in the 5-HT precursor pool. The trapping rate provides an index for 5-HT synthesis capacity (Chugani & Muzik, 2000). A study investigated regional brain Alpha-MTrp trapping in BPD using PET (Leyton et al., 2001). Men with BPD as compared with healthy men, showed a lower Alpha-MTrp trapping in the medial frontal, the anterior cingulate, and superior temporal gyri as well as in the corpus striatum. In females with BPD, fewer regions with slower trapping were reported. However, for men and women with BPD, a negative correlation were found for Alpha-MTrp trapping in the medial frontal, anterior cingulate and temporal gyri as well as striatum and impulsivity scores.

These studies gave support for an association of serotonergic system dysfunction and impulsivity in BPD. However, it should be mentioned that dysfunctions in other neurochemical systems might also underlie parts of BPD symptoms, i.e. the HPA-axis and the opiod system (Schmahl & Bremner, 2006).

1.3.4 Functional neuroimaging of emotional processing and autobiographical memory

BPD was suggested by several authors to be part of a spectrum of stress-related disorders, together with PTSD, depression and dissociative disorders (e.g. Bremner, Vermetten, Southwick, Krystal & Charney, 1998; Heim, Bremner & Nemeroff, 2005). Reactivity to stress appears to underlie affective dysregulation in BPD. Several brain imaging studies investigated the reactivity to emotional stimuli and stressful memories.

Two studies using fMRI analyzed neural response to aversive stimuli. Using emotional negative photographs, Herpertz et al. (2001) found increased activity of the amygdala in BPD patients compared with control subjects. Similar results were revealed by a study investigating neural responses to faces which expressed a specific emotion such as anger, fear, or sadness (Donegan et al., 2003). However, this study showed differences in activation patterns of patients with and without additional PTSD. BPD patients without PTSD showed a bilateral activation of the amygdala, whereas patients with comorbid PTSD revealed only left-lateralized amygdala hyper-responsiveness.

Four studies investigated neural responses to memories of major negative life events in BPD. Using personalized scripts of childhood trauma or of events of abandonment in

conjunction with PET, Schmahl and his workgroup found different blood flow rates in patients with BPD compared with psychiatric control subjects (Schmahl, Elzinga et al., 2003; Schmahl, Vermetten, Elzinga & Bremner, 2004). Among females without BPD, memories of childhood abuse were associated with an increase of blood flow in the right dorsolateral prefrontal cortex and a decrease in the left dorsolateral prefrontal cortex (Schmahl et al., 2004). Further females without BPD showed blood flow increases in the anterior cingulate cortex and in the left orbitofrontal cortex. Women with BPD failed to activate the anterior cingulate and the orbitofrontal cortex. Additionally, no changes in the dorsolateral prefrontal cortex were found.

In a second study of this workgroup, differing blood flow was found in females with and without BPD in response to scripts of abandonment (Schmahl, Elzinga et al., 2003). Fears of abandonment are also a central symptom of BPD patients. Memories of abandonment were associated with blood flow increases in the BPD group according to the dorsolateral prefrontal cortex as well as in the right cuneus. Further, greater blood flow decreases for women with BPD were found in the anterior cingulate cortex, in the left temporal and the left visual association cortex.

Two fMRI studies analyzed memories of major negative life events and traumatic events in BPD using fMRI (Beblo, Driessen et al., 2006; Driessen et al., 2004). In one study, brain activation in response to major negative life events versus minor negative life events was analyzed in BPD patients minus control subjects (Beblo, Driessen et al., 2006). BPD patients showed a pattern of increased activation of the frontal cortex including parts of the insula and the orbitofrontal cortex, temporal activation including the amygdala and am activation of the right occipital cortex.

In a second study, memories of traumatic and aversive but non-traumatic events were analyzed in BPD patients with and without additional PTSD (Driessen et al., 2004). In the subgroup without PTSD, activation of the orbitofrontal cortex on both sides and of the Broca area predominated, while in the subgroup with additional PTSD activation was primarily observed in limbic areas, including the amygdala.

In sum, a dysfunction of the dorsolateral and medial prefrontal cortex may be associated with the recall of traumatic memories in BPD. Generally, patients with BPD revealed different activation patterns in response to aversive stimulation with a hyper-responsiveness of the amygdala. However, there is some support for subgroup differences within BPD patients. BPD subjects with additional PTSD showed a different engagement of the amygdala in response to aversive pictures and traumatic memories.

1.3.5 Conclusion

A growing body of neuroimaging studies supports brain alterations in BPD with regard to structure and function. Neuroimaging research has been stimulated by methods used in the investigation of PTSD, e.g. structural imaging of hippocampus and amygdala as well as by the use of challenge studies using stressful autobiographical material. Structural imaging consistently reported reduced hippocampus volumes in BPD, which were also known in PTSD (i.e. Bremner et al., 1995). However, volume reductions of the amygdala may set BPD apart from PTSD where no structural losses were found. Recently reported enlarged amygdala volumes in depressive BPD patients (Zetzsche et al., 2006) highlights the importance of running subgroup analysis with respect to the most common axis-I comorbidity such as major depression and posttraumatic stress disorder. Further resting-stage brain metabolism studies as well as challenge studies investigating the serotonergic system frequently showed prefrontal abnormalities in BPD also raising the question of gender differences in BPD. Studies investigating brain responses to aversive stimuli and major negative life events in BPD also showed dysfunctions in prefrontal and limbic areas. In general, structural and functional neuroimaging revealed brain alterations mainly in frontolimbic areas involving the anterior cingulate cortex, dorsolateral and orbitofrontal prefrontal cortex, the hippocampus and the amygdala. These brain areas participate in a broad variety of neuropsychological functions, e.g. episodic and semantic memory, working memory, control for interference, and executive functioning (see Cabeza & Nyberg, 2000). With the exception of autobiographical memory, research is lacking from studies that aim at the investigation of basic neuropsychological functions in BPD.

1.4 Neurobehavioral alterations in borderline personality disorder

Clinical features of BPD as an unstable and dysregulated control over behavior, emotion, and cognition, as well as clinical descriptions of temporary disturbances of perception and cognition led to the question of neuropsychological deficits and brain dysfunctions. Neuropsychological and neurophysiological research demonstrated several dysfunctions and alterations in BPD. Generally, neuropsychological functioning in BPD may characterized by a non-specific impairment in a broad variety of cognitive domains as memory, visuo-spatial abilities, control for interference, inhibition, as well as of executive

functions in general. The outcomes of these neuropsychological studies as well as the aforementioned clinical features have been repeatedly interpreted as reflecting prefrontal and temporo-limbic brain dysfunctions (Dinn et al., 2004). Furthermore, brain imaging provided evidence for structural reductions and functional alterations for these brain areas (Schmahl & Bremner, 2006).

Different models described the prefrontal cortex as not being a unitary structure and suggest a functional fractionalization of this brain area (e.g. Alexander, DeLong & Strick, 1986; Cummings, 1993; Middleton & Strick, 2001). Chow and Cummings (1999) in their model suggested three prefrontal-subcortical circuits that may associated with neurobehavioral consequences from brain damage and dysfunctions: the dorsolateral, the orbitofrontal, and the anterior cingulate cortex. The dorsolateral prefrontal cortex is generally associated with classic executive functions such as problem-solving, decision-making, verbal fluency, and working memory (Cabeza & Nyberg, 2000), whereas the orbitofrontal region is more closely connected with the limbic system and it has been suggested that it is involved in the processing of emotions, the regulation of social behavior and social interactions (Rolls, 2004). The anterior cingulate cortex it thought to mediate motivational systems, action selection, and supervisory attention (Bush, Luu & Posner, 2000). Neuropsychological findings revealed deficits for BPD in functions that might differentially attributed to dysfunctions within these circuits. Impairment in working memory and executive functions might be attributed to malfunctioning of the dorsolateral prefrontal cortex, whereas deficient control for interference and reduced inhibition capacity might reflect anterior cingulate dysfunctions and dysregulated control for affect-laden information may be due to dysfunctions of the orbitofrontal cortex.

Aside from prefrontal brain regions, neuropsychological impairment as well as core psychopathological symptoms of BPD patients have also been considered to reflect temporo-limbic brain dysfunctions. Epileptic patients with partial seizures originating from temporo-limbic areas may present diverse characteristics that seem similar to BPD patients, as affective instability, impulsivity, and psychotic episodes (Harris et al., 2002). Furthermore, patients with right-lateralized partial seizures revealed poor performance in visual and spatial learning and memory. These neuropsychological findings have also been described for BPD, e.g. impaired visual memory (Ruocco, 2005). These findings led to the hypothesis that a subgroup of BPD patients may suffer from an undiagnosed partial seizure disorder originating from temporo-limbic areas (Dinn et al., 2004; Harris et al., 2002). However, no direct evidence for the “undiagnosed-seizure”- hypothesis is available.

Although often reported deficient neuropsychological outcomes in BPD patients might be attributed to prefrontal and temporo-limbic brain dysfunctions, these interpretations remain preliminary and in part speculative. To date, brain imaging research has provided evidence for structural and functional changes in these brain structures. However, neuroimaging studies only focused on the investigation of volumetry, resting-stage brain metabolism, neural responses to stressful challenges, and on serotonergic system functioning. With the exception of autobiographical memory little is known about neural correlates of basic neuropsychological functions in BPD. Thus, further brain imaging studies should address neural correlates of basic neuropsychological functions to clarify possible brain mechanisms of impairment, e.g. working memory and executive functioning.

Aside from the question of brain origins of neuropsychological impairment in BPD the question of clinical relevance of neuropsychological impairment has to be specified. According to Keefe (1995), one major aim of clinical neuropsychology should be the prediction of everyday functioning. This consideration led to the relevant question, whether the use of comprehensive test batteries mostly using non-valent stimulus material provides enough information to answer the question of everyday functioning for BPD. Although patients with acquired prefrontal brain damage are often characterized by highly disorganized everyday functioning this has not been taken into consideration in standard laboratory neuropsychological tests. Some clearly prefrontal lobe damaged patients show dissociations between laboratory assessment and everyday functioning (Sarazin et al., 1998). Sarazin and colleagues suggested that the kind of executive functions required in everyday life may require affect-laden decisions that are not being assessed by traditional laboratory tests, e.g. of executive functioning. Several executive laboratory tasks only require networks within the dorsolateral prefrontal cortex, e.g. the Wisconsin Card Sorting Test (see Demakis, 2003). In contrast, everyday executive functions demands often require affect-laden decisions, which further involve the orbitofrontal cortex.

These examples of difficulties in determining neuropsychological impairment in some frontal brain damaged patients by the use traditional neuropsychological tasks underline the importance of including affect-laden stimuli and processing. Aside from a few studies, neuropsychological investigations of BPD are restricted by the use of traditional comprehensive test batteries that lack emotional relevant stimuli and also do not include affect-laden processing. The importance of emotion for neuropsychology is further suggested by a consideration of Damasio, Tranel and Damasio (1991). The authors developed a “somatic marker” hypothesis to explain the interrelationship of the orbitofrontal cortex and

the anterior cingulate cortex and their contributions to decision-making. In their model, they suppose that complex reasoning and emotion are intertwined such that quick rational decisions demand an emotional valence attached to the various elements of the decision process.

In sum, the understanding of BPD has profited from neuropsychological and neuroimaging findings. Brain imaging supports brain alterations mainly to the prefrontal and limbic brain. Neuropsychological findings provide for an impairment of memory, visuo-spatial abilities, and the control for interference and inhibition as well as executive functioning in general. However, the current knowledge of neuropsychological functioning in BPD is restricted to behavioral data which often lacks emotional relevant stimuli and emotional processing. Furthermore, brain imaging studies that address basic neuropsychological functions are missing. Therefore, further research would benefit by considering three major principles: (i) Research should use brain imaging methods to examine basic neuropsychological functions as memory, attention, and executive function. (ii) Neuropsychological studies should include tasks that allow the assessment of neuropsychological performance with regard to neutral and emotional relevant stimuli demanding neutral and affect-laden processing. (iii) Furthermore, investigation of neuropsychological functions should use test batteries that are closely related to everyday requirements.

2 Study I: Neural correlates of episodic and semantic memory retrieval in borderline personality disorder

2.1 Background

Neuropsychological findings concerning verbal memory functioning in BPD do not show a consistent constellation of findings (Beblo et al., 2004; Fertuck et al. 2006). A recent meta-analysis based only on few studies characterized impairment in BPD patients in this domain as mild to moderate (Ruocco, 2005). Some neuroimaging studies investigated neurophysiological correlates of autobiographical memory retrieval in BPD. These studies focused on the investigation of memories concerning major negative life events such as traumatic events (Beblo, Driessen et al., 2006; Schmahl et al, 2004), or memories that are closely related to BPD symptoms, like fears of abandonment (Schmahl, Elzinga et al., 2003). According to the results of these studies, BPD patients compared with healthy subjects or psychiatric controls showed increased activation patterns mainly in prefrontal and limbic areas during retrieval processing (Beblo, Driessen et al., 2006; Schmahl, Elzinga et al., 2003; Schmahl et al., 2004). Since some authors argue for a higher responsiveness of BPD patients to emotionally relevant stimuli (Donegan et al., 2003; Herpertz et al., 2001) it remained unclear whether differing brain functioning during memory retrieval is specific for emotionally highly relevant autobiographic memories, or represents a more general dysfunction of the neural circuits underlying memory retrieval processes.

Structural brain imaging studies of BPD found alterations of areas that are involved in memory functioning, e.g. volume losses in limbic and perhaps in prefrontal areas. Reduced volume of the hippocampus and the amygdala were reported most often (Brambilla et al., 2004; Driessen et al., 2000; Irle et al., 2005; Rüsch et al., 2003; Schmahl, Vermetten et al., 2003; van Elst et al., 2003). In addition, a recent study showed volume sizes of the right hippocampus to be a predictor of episodic memory performance in BPD (Irle et al., 2005). Recent studies also yielded volume reductions of the anterior (van Elst et al., 2003) and of the posterior cingulate cortex (Hazlett et al., 2005) in BPD as compared to controls.

In sum, brain imaging revealed for BPD alterations mainly in prefrontal and limbic brain areas. These brain areas seem to be crucial for both, episodic memory (memory for events and the context) and semantic memory (memory of facts/knowledge) (Cabeza &

Nyberg, 2000; Markowitsch, 2000; Markowitsch, 2005). In detail, episodic memory retrieval tasks predominantly involve right-hemispheric temporo-frontal and limbic structures, whereas semantic memory retrieval tasks predominantly involve left-hemispheric temporo-frontal areas (Cabeza et al., 2003; Reinhold, Kuehnel, Brand & Markowitsch, 2006).

Since BPD patients show structural and functional brain alterations in memory-related structures and some neuropsychological examinations emphasized verbal memory impairment for BPD patients, these findings suggest general distortions in memory-related neural circuits. However, since no neuroimaging study directly investigated verbal memory functions these conclusions remain preliminary.

2.2 Aims and hypotheses

Following the findings reported above, study I aimed at the analysis of neurophysiological correlates of memory retrieval processes in BPD. In an fMRI experiment, regional blood oxygenation level dependent (BOLD) signals as indicator for brain activity were measured during two experimental conditions of interest (episodic memory retrieval, semantic memory retrieval) and a low-level baseline in BPD patients and healthy controls. It was hypothesized that BPD patients compared with healthy control subjects would show increased regional BOLD responses in prefrontal and limbic brain areas during the retrieval of episodic and semantic information of neutral valence.

Three contrasts were calculated to analyze whether task-specific brain activation differs between BPD patients and healthy control subjects. The first contrast calculated the task-specific brain activation for episodic and semantic memory retrieval as indicated by regional BOLD signal changes. According to this contrast, it was analyzed which brain areas were “activated” during the retrieval of episodic and semantic information. Using BOLD response data, the difference „retrieval condition minus baseline condition” was computed (Contrast 1). This contrast was run separately for both groups (patients and controls) and separately for both retrieval conditions (episodic and semantic memory retrieval condition).

After calculating the task-specific activation (contrast 1), it was analyzed, whether brain activation during the retrieval of episodic and semantic information differs between BPD patients and controls. Contrast 2 was calculated according to the hypothesis that patients would show increased regional brain activation patterns during the retrieval of episodic and

semantic information. Using BOLD response data, the difference „retrieval condition minus baseline condition" in control subjects was subtracted from the difference „retrieval condition minus baseline condition" in BPD patients (Contrast 2). This contrast was run separately for both retrieval conditions (episodic and semantic memory retrieval condition).

To analyze whether against the hypotheses control subjects would show increased regional brain activation patterns compared with BPD patients during the retrieval of episodic and semantic information a third contrast was calculated. Using BOLD response data, the difference „retrieval condition minus baseline condition" in BPD patients was subtracted from the difference „retrieval condition minus baseline condition" in control subjects (Contrast 3). This contrast was run separately for both retrieval conditions (episodic and semantic memory retrieval condition).

According to the hypotheses and based on prior neuroimaging results, it was expected that BPD patients compared with healthy control subjects would show increased regional brain activation ("hyperactivity") in prefrontal and limbic areas during the retrieval of episodic as well as in the retrieval of semantic information. This hypothesized task-specific hyperactivity is indicated by increased regional BOLD responses of BPD subjects as compared with healthy subjects according to contrast 2.

2.3 Method

2.3.1 Participants

18 female patients with BPD and 18 age- and education-matched healthy female subjects with no history of psychiatric disorders took part. The subjects were Caucasian, native German speakers and strictly right-handed. Patients met the DSM-IV criteria of BPD as assessed by the treating psychotherapists within the first week after admission. All patients were treated for BPD as inpatients in the Ev. Hospital Bielefeld, Germany. The healthy control group was recruited by regional advertisement. None of the subjects was pregnant or had one of the following concurrent or previous medical conditions, which were assessed by their medical history, by careful clinical examination, and by laboratory means: endocrine system disorders, malignant diseases, liver cirrhosis, neurological diseases, loss of consciousness (lifetime), or mental retardation. Further exclusion criteria were current infectious diseases, anorexia, schizophrenia, schizoaffective disorders, and major depressive

disorder with psychotic symptoms. Clinical diagnoses of alcohol and/or drug dependence during the six months prior to the study also led to exclusion. In all subjects urinary drug screenings (Triage© -Test, Merck, Germany), and a venous blood sample was obtained for clinical routine. No pathological measures were found in any participant. Informed written consent to participate in the study was obtained from all subjects. Subjects received financial remuneration for their efforts (€50). The study was approved by the University of Muenster Ethics Committee.

2.3.2 Clinical assessment

Participants completed the Structured Clinical Interview for DSM IV (SCID) (Wittchen, Zaudig & Fydrich, 1997). The SCID is a valid semistructured clinical interview, which allows the assessment of axis-I and II diagnoses with respect to the DSM-IV criteria. It consists of two parts: The first interview assesses current and lifetime axis-I disorders, the second interview assesses personality disorders. The SCID interview was applied by one of four clinicians (two clinical psychologists and two clinical psychiatrists), who received a SCID-training at the beginning of the study.

The psychopathologic assessment further included self- and observer ratings for depressive mood and self-rated post-traumatic stress. The Beck Depression Inventory (BDI; Beck & Steer, 1994) was used to assess self-rated depressive mood. This questionnaire includes twenty-one items with regard to behavioral, cognitive and emotional features of depression. The subjects rate their symptoms by four alternative statements with regard to the last seven days.

Observer-rated depressive mood was assessed with the Hamilton Depression Scale (HDRS; Hamilton, 1996). The HDRS provides twenty items which represent behavioral, cognitive, and emotional features of depressive mood. The observer has to rate depressive symptoms with regard to the last seven days. The HDRS-rated depressive mood was estimated by the clinician who held the SCID interview. A general score is calculated which gives information about current observer-rated depressive symptoms.

The Impact of Event Scale (IES-R; Maercker & Schützwohl, 1998) was applied to assess self-rated posttraumatic stress with regard to the last week. At first, the questionnaire assessed whether the subject has been exposed to specific traumatic events according to the DSM-IV PTSD A-criterion which includes the “exposure to an extreme traumatic stressor involving direct or indirect personal experience” with the “person's response to the event must

involve intense fear, helplessness, or horror reaction" (APA, 1994). The second part of the IES-R was conducted only if the subject had been exposed to a traumatic event. There, the subject has to rate posttraumatic stress symptoms according to the three symptom clusters of the DSM-IV PTSD section: intrusions, avoidance, and arousal.

2.3.3 Neuropsychological assessment

The day before fMRI acquisition, the participants completed a comprehensive neuropsychological examination with two tasks of interest for the present study. The Auditory Verbal Learning Test (AVLT, Helmstaedter, Lendt & Lux, 2003) was carried out as a measure for episodic memory. Subjects have to learn a fifteen item wordlist in five trials which are followed by immediate free recalls. After the fifth free recall, a fifteen-item interference wordlist is presented which has also to be recalled by the subjects. The interference list is followed by a sixth free recall of the first wordlist. After 30 minutes, the subjects again have to recall the first word list. This last free recall is followed by a recognition task. To assess recognition performance, a sixty item word list is presented to the subjects including words of the first and second list as well as words with a semantic or phonological similarity to the words of the first list.

Several scores are calculated to characterize verbal memory performance. The number of correctly recalled words of the first recall leads to an estimation of immediate free recall. The sum of correctly recalled target words of trial 1 to 5 gives information on learning memory performance. The mean number of correctly recalled words of the interference list leads to an estimation of proactive interference, and the first free recall of the first list deals as indicator of retroactive interference. The delayed free recall after thirty minutes as well as the number of correct recognized words are indicators of verbal delayed memory performance. The number of incorrectly recalled target words of trials 1 to 5 are a measure of intrusions.

Further, a semantic memory task was carried through consisting of lexical word fluency (F, A and S; see Lezak, 1995). Subjects have to name words starting with the letters F, A, and S. Subjects are instructed to name as many words as possible within one minute per letter. Further instructions were given on the kind of words that are not allowed to name: "it is not allowed to name proper nouns, e.g. persons, cities, states, each word should only named once, and it is not allowed to use several words including the same word stem". Three scores are indicating subjects' performance: The number of correctly named words indicates a general performance score. Further score assess rule violations and word repetition. Rule violations are calculated by the number of words that include the false first letter, being a

proper noun or words using the same word stem for more than one word. The word repetition score assesses the number of words that have been named more than one time.

2.3.4 fMRI stimulus presentation and design

Anatomical MR scans were acquired a few days prior to fMRI measurement to exclude brain damage. All technical and study details were explained and informed consent was obtained. A box car design was applied with two activation conditions and a low level baseline condition (BC). The activation conditions consisted of an episodic memory 24-hour delayed recall (EMR) of a fifteen item word list (AVLT) and a semantic memory retrieval task (SMR) using a verbal lexical fluency task (letters W, D, R, L, P and T)[2]. The design consisted of 3 x 6 blocks with each block including EMR, SMR, and the baseline condition (figure 2.1). Each condition was introduced by key-words (cues) using the scanner's intercom. In response to the key-words, subjects covertly recalled the learned word list (EMR), completed lexical retrieval (SMR) or concentrated on the scanners' sound (BC). The beginning of the BC was indicated by the word "noise" used as a cue to stop recall and concentrate on the sound of the MRI machine. Each activation condition and each BC lasted 30 s. During each condition, 10 sets of 16 axial T2*- weighted MR-slices were obtained.

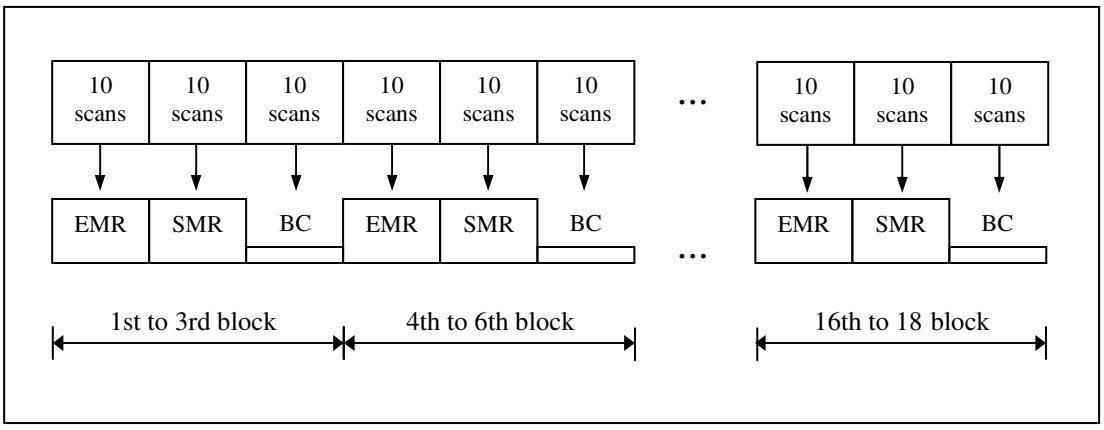


Figure 2.1: fMRI box car design with episodic (EMR) and semantic memory retrieval (SMR) activation conditions and low-level baseline conditions (BC)

2.3.5 MRI acquisition

MRI scanning was performed on a 1.5 Tesla scanner (Siemens Magnetom Symphony, Erlangen, Germany) equipped with a standard head coil. Sagittal T1-weighted images were

[2] Instructions were the same as for the FAS task, see chapter 2.3.3

obtained for each subject to position the axial T2*-weighted images along the anterior commissure - posterior commissure (AC-PC) line. For fMRI, 16 contiguous axial T2*-weighted images, slice thickness 7 mm, covering the whole brain were obtained using a standard EPI sequence (TR = 3000 ms, TE = 50 ms, field of view [FOV] 192 mm, matrix 64 x 64). 180 scans were acquired over a 9-min period. For anatomical reference and to exclude gross brain pathology, a T1-weighted 3D-sequence (magnetization prepared gradient echo [MPRAGE], TR = 11.1 ms, TE = 4.3 ms, slice thickness 1.5 mm, FOV 201 x 230 mm, matrix 224 x 256) and an axial FLAIR data set (TR = 9000 ms, TE = 110 ms, TI = 2500 ms, slice thickness 5 mm, FOV 201 x 230, matrix 220 x 256) were obtained for each subject.

2.3.6 Image and statistical analyses

fMRI data were analyzed using SPM99 (http://www.fil.ion.ucl.ac.uk/spm/software/spm99, The Wellcome Department of Cognitive Neurology, University College London, UK) for all image preprocessing and voxel-based statistical analyses within the context of the general linear model. Image realignment corrected for head movement using the SPM99 default algorithm. Spatial normalization reduced anatomical differences prior to group comparisons using default settings and the standard stereotactic space of SPM99, the MNI brain (Montreal Neurological Institute). Spatial smoothing followed with a Gaussian kernel of 10 mm FWHM to increase both signal and anatomical conformity. Effects were computed at the random effects (RFX) level (Friston, Holmes & Worsley, 1999) to take into account within and between individual variability of changes of the Blood Oxygenation Level Dependent contrast (BOLD). On the second analysis level two-sample t-tests against the null hypothesis of zero mean differences have been estimated for each contrast using the appropriate option in SPM99.

Using random effect statistical analysis on a voxel-by-voxel basis, differences between conditions were analyzed for the patients and healthy subjects, separately. For random-effects analyses, MNI coordinates of major activations were transformed to the Talairach space (Talairach & Tournoux, 1988). The procedure to obtain anatomical projections of maximum activation was automatically performed, i.e. without any observer interaction (http://wwwneuro03.uni-muenster.de/ger/t2tconv/conv3d.html; University Hospital Muenster, Department of Neurology, University of Muenster, Germany). Areas of activation were only identified as significant, if they past the threshold of alpha = .001, uncorrected for multiple comparisons on the voxel-level).

Statistical analyses of data other than fMRI were performed using SPSS version 12.0. Two-tailed t-tests were applied for the basic analyses of group differences, with level of statistical significance was set to alpha = .05.

2.3.7 Study design

The current study was part of a large project addressing several issues of BPD with regard to psychopathology, adversive childhood history such as abuse and neglect, neuroendocrinology, neuropsychology, structural neuroimaging and functional neuroimaging of memory. The neuropsychological data from this study has recently been published (Beblo, Silva Saavedra et al., 2006). The present study uses a sub-sample of the Beblo et al. study: Only strictly right-handed BPD patients were selected to control for the possibility of probably right-lateralized language.

The two neuropsychological tasks used in the present study were part of a comprehensive neuropsychological examination which further covered attention, visual memory, and executive functioning. The neuropsychological investigation lasted 2.5 hours in total (see Beblo, Silva Saavedra et al., 2006 for further details).

The data presented here were assessed in the following order. After giving their written consent to take part in the study, participants completed the psychopathologic assessment and the assessment of adversive childhood experiences. This assessment was followed by a neuroimaging scanning session. This first neuroimaging part included structural MRI of the whole brain and was also applied to get the subjects used to the scanner. Within one week, the neuropsychological examination was carried out. The day after the neuropsychological assessment the second neuroimaging session was obtained, which included functional MRI with regard to memory retrieval. After this session, participants were debriefed and received their financial remuneration.

2.4 Results

2.4.1 Demographic, clinical, and neuropsychological data

BPD patients and control subjects were comparable in terms of age (M = 31.94, SD = 8.13 years versus M = 32.94, SD = 8.33; t_{34} = -0.36; $p < .718$) and years of basic education (M = 10.94, SD = 1.51 versus M = 11.44, SD = 1.62; t_{34} = -0.96; $p < .345$). None of the control

subjects had any current or lifetime psychiatric disorder. The BPD group showed high levels of psychopathology (table 2.1) with respect to depressive mood (BDI, HAMD) and posttraumatic stress (IES-R).

A high rate of comorbid disorders was found, mainly posttraumatic stress disorder (PTSD; $N = 9$), depressive disorders (major depression, $N = 5$; dysthymia, $N = 1$), and panic disorder ($N = 4$). Some patients met criteria of further anxiety disorders, namely agoraphobia ($N = 1$), obsessive compulsive disorder ($N = 2$), agoraphobia with panic disorder ($N = 1$), and of other phobias ($N = 2$). Two patients suffered from bulimia nervosa, one patient from somatization disorder. All patients were treated by dialectic behavioral therapy, and ten of them also received psychotropic medication (selective serotonin reuptake inhibitors: $N = 5$, tricyclics: $N = 1$, neuroleptics: $N = 3$, benzodiazepines: $N = 2$, acamprosate: $N = 1$,

Table 2.1: Psychopathology and neuropsychological performance in BPD and control subjects one day prior to fMRI

	BPD patients		**Control subjects**		**Group comparisons**		
	M	***SD***	***M***	***SD***	***T***	***df***	***p****
Psychopathology							
HDRS	15.72	8.60	1.56	2.12	6.78	34	**< .001**
BDI	22.76	9.91	2.72	5.04	7.61	33	**< .001**
IES-R Intrusions	19.33	11.59	1.94	4.89	5.87	34	**< .001**
IES-R Avoidance	21.94	10.95	3.06	7.49	6.04	34	**< .001**
IES-R Hyperarousal	21.94	10.45	0.44	0.92	8.69	34	**< .001**
Episodic Memory (Wordlist learning)							
AVLT, 1st trial	7.44	3.09	8.00	2.03	-0.64	34	< .528
AVLT, sum (1st to 5th trial)	56.50	11.67	60.83	6.19	-1.39	34	< .173
AVLT, interference trial	7.11	2.78	6.89	1.68	0.29	34	< .774
AVLT, free recall	13.17	2.60	13.61	1.75	-0.60	34	< .551
AVLT, delayed recall (30 min.)	13.06	2.39	13.89	1.18	-1.33	34	< .193
AVLT, intrusions	0.50	1.20	1.28	1.45	-1.75	34	< .088
AVLT, recognition	14.56	0.70	14.33	0.97	0.79	34	< .437
Semantic Memory (Verbal Fluency)							
FAS, distinct words	31.11	8.84	36.17	10.37	-1.57	34	< .125
FAS, word repetition	1.22	1.22	0.72	1.13	1.28	34	< .209
FAS, rule violations	0.39	0.61	0.44	1.04	-0.20	34	< .846

AVLT: Auditory Verbal Learning Test; BDI: Beck Depression Inventory; FAS: Lexical word fluency; HDRS: Hamilton Depression Rating Scale; * level of significance: $p < .05$; significant group differences are printed in bold.

betablocker: $N = 2$). The neuropsychological examination on the day prior to fMRI showed similar performances of patients and controls regarding verbal episodic memory retrieval (AVLT) and verbal semantic memory retrieval (FAS; see table 2.1).

2.4.2 Activation patterns of episodic memory retrieval (EMR)

During EMR (contrast 1: EMR - BC), control subjects showed an extended bilateral activation ($p < .001$, RFX, uncorrected) of frontal and parietal areas (see table 2.2). The activation pattern included anterior prefrontal, fronto-lateral and fronto-medial areas (Brodmann areas [BA] 4, 6, 8-10, 32, 38, 44-46, Insula). The parietal clusters comprised bilateral activation of the superior parietal area (BA 7, 40).

FMRI activation patterns in BPD patients during EMR (contrast 1: EMR - BC) were similar to controls, but had larger cluster sizes and extended to the right orbitofrontal area (BA 11) and the cingulate gyrus (BA 24, 32) of both hemispheres. Furthermore, additional left temporal (BA 22), bilateral thalamic, midbrain and cerebellar activation was found in patients with BPD.

When directly contrasting EMR minus BC in patients versus EMR minus BC in control subjects (contrast 2: patients [EMR – BC] – controls [EMR – BC]) (see table 2.3 and figure 2.2), increased BOLD responses were found ($p < .001$, RFX, uncorrected) in the posterior cingulate cortex (BA 31) bilaterally, in the left middle (BA 21), in the superior temporal gyrus (BA 22), in the right frontal (BA 45) and the right angular gyrus (BA 39). The reverse contrast (contrast 3: controls [EMR – BC] – patients [EMR – BC]) did not reveal any differences in brain activation (threshold: $p < .001$, RFX, uncorrected).

Further, a subgroup analysis within the BPD group was run to control for possible effects of PTSD as the comorbid disorder most prominent on episodic memory retrieval. No differences in activation patterns of patients with PTSD compared with patients without were found to meet the threshold (threshold: $p < .001$, RFX, uncorrected) according to the following contrasts: “BPD patients with PTSD [EMR – BC] – BPD patients without PTSD [EMR – BC]” or: “BPD patients without PTSD [EMR – BC] – BPD patients with PTSD [EMR – BC])”.

Table 2.2: Areas showing greater BOLD response during episodic memory retrieval (EMR) minus baseline condition in control subjects and BPD patients (random effects analysis, $p <$ .001, uncorrected for multiple comparisons)

Localization of Activation Maximum	Peak Coordinates Max. Difference Projections (x,y,z)*			Z	Cluster size	Cluster Localization (BA)
Control subjects						
L superior frontal gyrus (BA 8)	-3	14	49	5.85	1646	bilateral: medial frontal (BA 6), anterior cingulate cortex (BA 32), left lateral frontal (BA 4, 8, 9, 44-46, insula)
L inferior frontal gyrus (BA 4)	-39	-2	22	5.59		
L middle frontal gyrus (BA 8)	-53	8	38	5.27		
R middle frontal gyrus (BA 46)	36	42	17	4.54	83	right: anterior lateral prefrontal (BA 9, 10, 46)
L superior parietal (BA 7)	-27	-51	33	4.30	236	left: superior parietal (BA 7, 40)
L superior parietal (BA 7)	-15	-65	50	4.10		
L superior parietal (BA 7)	-27	-59	39	4.07		
R superior parietal (BA 7)	9	-70	51	4.14	56	right: superior parietal (BA 7)
R inferior frontal gyrus (BA 47)	42	14	-6	3.91	41	right: inferior frontal gyrus (BA 47), insula
R supramarginal gyrus (BA 40)	42	-36	35	3.87	105	right: supramarginal gyrus (BA 40)
R pons	3	-33	-21	3.48	13	right: pons
L middle frontal gyrus (BA 10)	-33	47	11	3.38	15	left: middle frontal gyrus (BA 10)
BPD patients						
R Insula	39	20	2	5.10	215	right: dorsolateral prefrontal (BA 45, 47), insula, temporal pole (BA 38)
L superior frontal gyrus (BA 8)	-3	23	46	4.88	2096	bilateral: medial frontal (BA 4, 6, 8), anterior cingulate cortex (BA 24, 32), left: lateral prefrontal (9, 10, 44-47), insula, lateral temporal (BA 22)
L middle frontal gyrus (BA 46)	-36	44	14	4.80		
L inferior frontal gyrus (BA 47)	-56	15	-1	4.73		
L superior parietal (BA 7)	-30	-48	38	4.64	644	left: superior parietal (BA 7, 19, 40)
L superior parietal (BA 7)	-27	-59	42	4.63		
L superior parietal (BA 7)	-36	-42	35	4.59		
R middle frontal gyrus (BA 9)	45	42	26	4.30	315	right: anterior prefrontal (BA 9-11), lateral prefrontal (BA 46)
R superior frontal gyrus (BA 11)	33	49	-13	4.05		
R superior frontal gyrus (BA 11)	30	52	-5	3.87		
R superior parietal (BA 7)	30	-56	39	4.29	309	right: superior parietal (7, 19, 39, 40)
R superior parietal (BA 7)	18	-65	42	3.56		
L midbrain	-6	-21	-17	4.23	50	left: midbrain
R posterior cingulate cortex (BA 23)	3	-25	23	3.84	57	bilateral: posterior cingulate cortex (BA 23)
L posterior cingulate cortex (BA 23)	-6	-13	28	3.73		
L superior temporal gyrus (BA 22)	-59	-37	10	3.59	25	left: superior temporal gyrus (BA 22)
L thalamus	-9	-20	12	3.56	27	left: thalamus
R thalamus	21	-2	19	3.55	66	right: thalamus, subcortical
R subcortical	15	0	15	3.43		
R middle frontal gyrus (BA 9)	50	19	27	3.45	14	right: middle frontal gyrus (BA 9)
R cerebellum	3	-51	-18	3.34	20	bilateral: cerebellum

BA: Brodmann areas; L: Left hemisphere; R: Right hemisphere; * Talairach & Tournaux space.

Table 2.3: Areas showing greater BOLD response during episodic memory retrieval (EMR) minus baseline condition (BC) in BPD patients minus control subjects (random effects analysis, $p < .001$, uncorrected for multiple comparisons)

Localization of Activation Maximum	Peak Coordinates Max. Difference Projections (x, y, z)*			Z	Cluster size	Cluster Localization (BA)
R posterior cingulate cortex (BA 31)	9	-27	35	4.07	99	bilateral: posterior cingulate cortex (BA 23, 31)
R posterior cingulate cortex (BA 23)	9	-43	21	3.54		
L posterior cingulate cortex (BA 23)	0	-16	31	3.17		
L middle temporal gyrus (BA 21)	-56	2	-15	3.84	20	left: middle temporal gyrus (BA 21)
L superior temporal gyrus (BA 22)	-59	-37	13	3.52	18	left: superior temporal gyrus (BA 22)
R inferior frontal gyrus (BA 45)	48	21	4	3.37	8	right: inferior frontal gyrus (BA 45)
R angular gyrus (BA 39)	42	-60	31	3.22	6	right: angular gyrus (BA 39)

BA: Brodmann areas; L: Left hemisphere; R: Right hemisphere; * Talairach & Tournaux space.

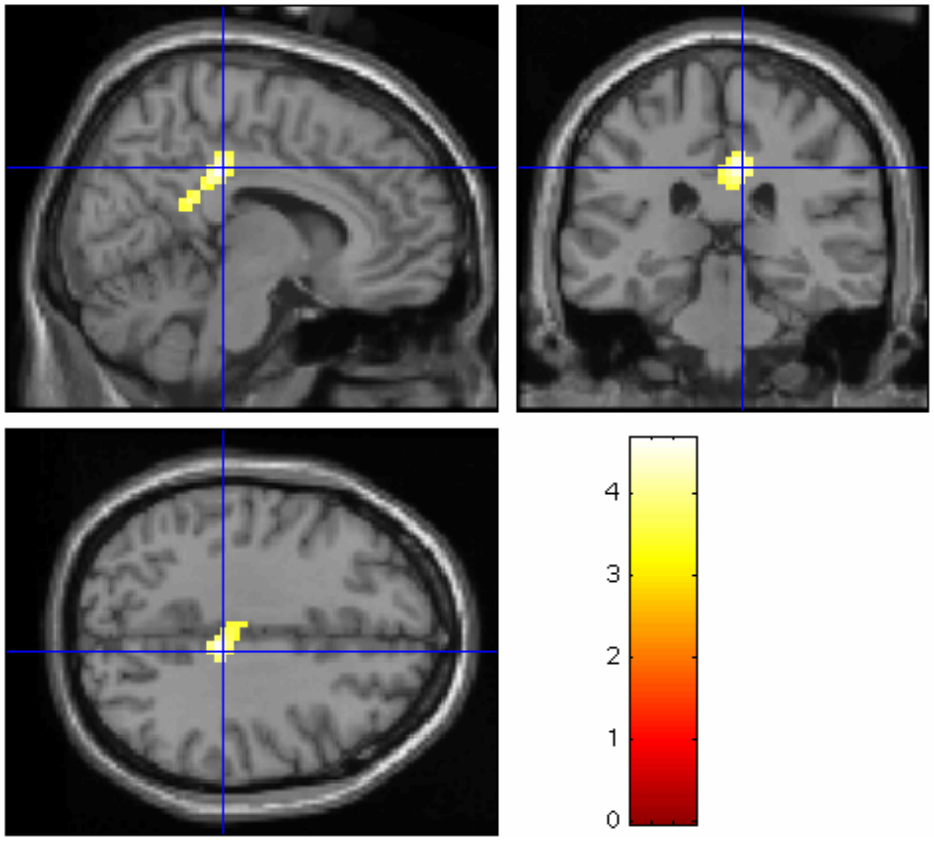


Figure 2.2: Posterior cingulate cortex (BA 31; x = 9, y = -27, z = 35) shows greater BOLD response during episodic memory retrieval (EMR) minus baseline condition (BC) in BPD patients minus control subjects (random effects analysis, $p < .001$, uncorrected for multiple comparisons).

2.4.3 Activation patterns of semantic memory retrieval (SMR)

When retrieving lexical information (contrast 1: SMR – BC, $p < .001$, RFX, uncorrected) control subjects showed a large left anterior and lateral prefrontal activation (see table 2.4), which extended to temporo-lateral areas (BA 9, 10, 38, 44-47, insula). This cluster also included bilateral medial frontal regions (BA 6, 8), as well as the anterior cingulate cortex (BA 32) and diencephalic structures (thalamus). A left-hemispheric cluster of activation of the fusiform gyrus (BA 37) and of the superior parietal area (BA 7) was also observed. Furthermore, control subjects showed bilateral midbrain and cerebellar activation.

The activation patterns in BPD subjects during SMR were again similar with larger cluster sizes (contrast 1: SMR – BC, $p < .001$, RFX, uncorrected). In BPD, frontal activation included right-hemispheric activation of prefrontal regions (BA 9, 45). Furthermore, BPD patients showed lateral temporal activation on both hemispheres (BA 21, 22 and 38). Additional activation was also found in diencephalic, midbrain and cerebellar regions.

When directly contrasting neural activity of patients versus controls (contrast 2: patients [SMR – BC] – controls [SMR – BC]), an increased BOLD response was found ($p < .001$, RFX, uncorrected) in the right posterior cingulate cortex (BA 31), in the right fusiform gyrus (BA 37), in the left anterior cingulate cortex (BA 24), and in the left postcentral gyrus (BA 1, 2, 3) (table 2.5, figure 2.3). Again, the reverse contrast (contrast 3: controls [SMR – BC] – patients [SMR – BC]) did not reveal any differences (threshold: $p < .001$, RFX, uncorrected).

Further, a subgroup analysis within the BPD group was run to control for possible effects of PTSD as the comorbid disorder most prominent on semantic memory retrieval. No differences in activation patterns of patients with PTSD compared with patients without were found to meet the threshold (threshold: $p < .001$, RFX, uncorrected) according to the following contrasts: “BPD patients with PTSD [SMR – BC] – BPD patients without PTSD [SMR – BC]” or: “BPD patients without PTSD [SMR – BC] – BPD patients with PTSD [SMR – BC])”.

Table 2.4: Areas showing greater BOLD response during semantic memory retrieval (SMR) minus baseline condition (BC) in control subjects and BPD patients (random effects analysis, $p < .001$, uncorrected)

Localization of Activation Maximum	Peak Coordinates Max. Difference Projections (x,y,z)*			Z	Cluster size	Cluster Localization (BA)
Control subjects						
L superior frontal gyrus (BA 6)	-3	14	49	6.21	3045	bilateral: medial frontal (BA 6, 8), anterior cingulate cortex (BA 32), left: lateral frontal (4, 9, 10,44-47), insula, thalamus, temporal pole (BA 38)
L Insula	-36	15	10	6.13		
L middle frontal gyrus (BA 46)	-42	30	12	5.77		
R cerebellum	3	-76	-11	4.50	45	right: cerebellum
R cerebellum	6	-42	-16	4.35	422	bilateral: cerebellum, midbrain
L midbrain	-6	-18	-9	4.17		
L cerebellum	-6	-39	-21	3.83		
R thalamus	21	-14	17	4.19	25	right: thalamus
L superior parietal (BA 7)	-27	-51	36	4.04	107	left: superior parietal (BA 7, 40)
L fusiform gyrus (BA 37)	-50	-56	-17	3.43	13	left: fusiform gyrus (BA 37)
BPD subjects						
L middle frontal gyrus (BA 6)	-9	17	46	6.24	2926	bilateral: medial frontal (BA 6, 8), anterior cingulate cortex (BA 24, 32), left: lateral frontal (4, 9, 12, 44-47), insula, lateral temporal (BA 22, 38)
L anterior cingulate cortex (BA 32)	0	23	38	5.72		
L Inferior frontal gyrus (BA 44)	-47	13	24	5.62		
R Insula	39	20	2	5.52	243	right: insula, temporal pole (BA 38), dorsolateral prefrontal (BA 45, 47)
R superior temporal gyrus (BA 38)	45	14	-8	4.60		
L superior parietal (BA 7)	-27	-56	42	5.12	461	left: superior parietal (BA 7), supramarginal gyrus (BA 40)
L supramarginal gyrus (BA 40)	-42	-39	38	4.99		
L supramarginal gyrus (BA 40)	-36	-45	38	4.84		
L thalamus	-6	-14	15	4.53	438	bilateral: midbrain, left: thalamus, putamen
L thalamus	-18	-11	9	4.13		
L midbrain	-12	-21	-14	3.99		
L fusiform gyrus (BA 37)	-48	-50	-18	4.14	112	left: fusiform gyrus (BA 37)
L fusiform gyrus (BA 37)	-42	-50	0	3.76		
R subcortical	18	-11	20	4.13	78	right: subcortical
R subcortical	15	-9	0	3.18		
R cerebellum	3	-44	-5	3.98	129	bilateral: cerebellum
L cerebellum	0	-44	-13	3.80		
R cerebellum	6	-67	-9	3.84	47	bilateral: cerebellum
R middle frontal gyrus (BA 9)	45	42	26	3.64	15	right: middle frontal gyrus (BA 9)
R middle frontal gyrus (BA 9)	45	41	12	3.16		
R fusiform gyrus (BA 37)	39	-47	2	3.6	22	right: fusiform gyrus (BA 37)
R fusiform gyrus (BA 37)	33	-55	3	3.41		
L superior temporal gyrus (BA 22)	-53	-32	-3	3.49	41	left: lateral temporal (BA 21, 22)
L middle temporal gyrus (BA 21)	-56	-41	2	3.41		
L cerebellum	-15	-56	-15	3.32	15	left: cerebellum

BA: Brodmann areas; L: Left hemisphere; R: Right hemisphere; * Talairach & Tournaux space.

Table 2.5: Areas showing greater BOLD response during semantic memory retrieval (SMR) minus baseline condition (BC) in BPD patients minus control subjects (random effects analysis, $p < .001$, uncorrected for multiple comparisons)

Localization of Activation Maximum	Peak Coordinates Max. Difference Projections (x, y, z)*			Z	Cluster size	Cluster Localization (BA)
R posterior cingulate cortex (BA 31)	3	-27	40	3.84	45	right: posterior cingulate cortex (BA 31)
R fusiform gyrus (BA 37)	39	-49	2	3.76	19	right: fusiform gyrus (BA 37)
L postcentral gyrus (BA 1,2,3)	-33	-32	62	3.68	20	left: postcentral gyrus (BA 1-3)
L Anterior cingulate cortex (BA 24)	-1	16	27	3.29	8	left: anterior cingulate cortex (BA 24)

BA: Brodmann areas; L: Left hemisphere; R: Right hemisphere; * Talairach & Tournaux space.

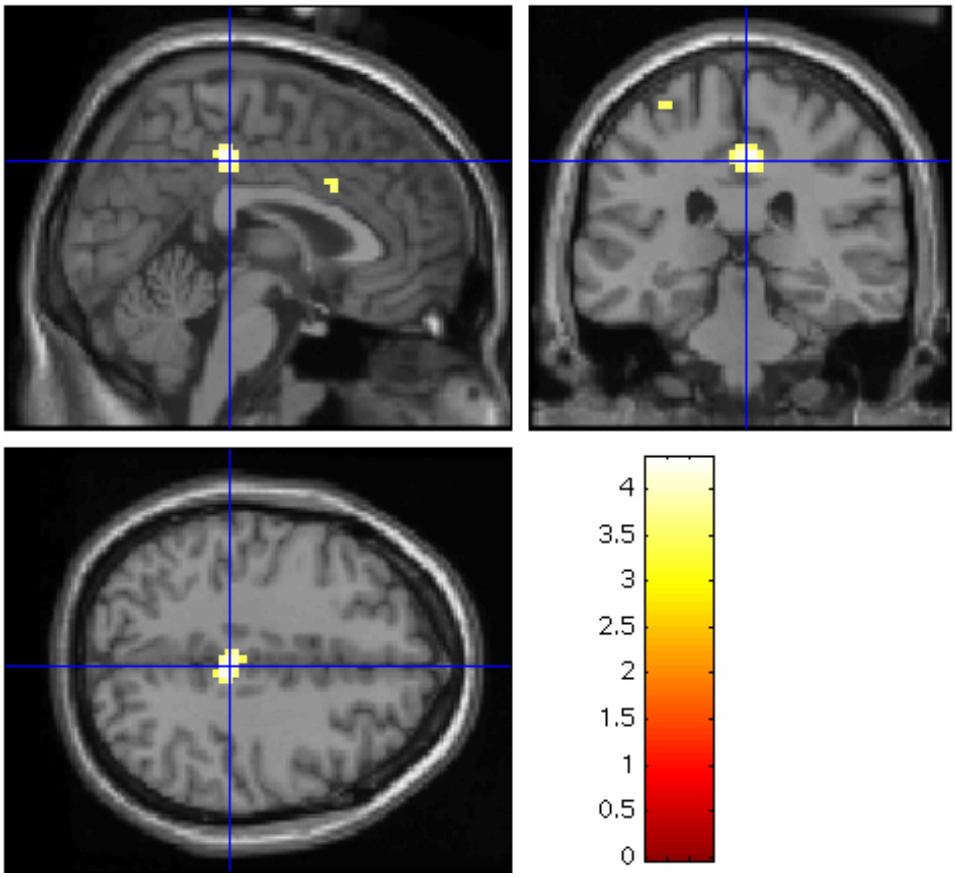


Figure 2.3: Posterior cingulate cortex (BA 31; x = 3, y = -27, z = 40) shows greater BOLD response during semantic memory retrieval (SMR) minus baseline condition (BC) in BPD patients minus control subjects (random effects analysis, $p < .001$, uncorrected for multiple comparisons)

2.5 Discussion

This study investigated neurophysiological correlates of verbal episodic (EMR) and semantic memory retrieval (SMR, "verbal fluency") in patients with BPD compared to healthy control subjects. Memory retrieval performance assessed on the day prior to scanning indicated similar performance in both groups. These results, unaffected verbal episodic and semantic memory retrieval performance in BPD, are in line with some recent studies (Kunert et al., 2003; Sprock et al., 2000), but not all studies (Dinn et al. 2004; O'Leary et al., 1991). According to the present findings of unimpaired episodic and semantic memory retrieval performances of BPD patients it is important to notify that the used sample consisted of patients showing severe BPD symptoms. Implications of the present study sampling are discussed with regard to other limitations (see page 41).

In both groups imaging data of EMR revealed task-related activity mainly in bilateral frontal, temporal and parietal neocortical areas. These neocortical brain regions are typically involved in episodic memory retrieval processes (Cabeza & Nyberg, 2000; Naghavi & Nyberg, 2005). Although patients and controls exhibited a similar pattern of cerebral activity, group differences in activation patterns became evident. Compared with the control subjects BPD patients showed a task-specific hyper-activation of the bilateral posterior cingulate cortices (BA 31), of the left middle (BA 21) and superior temporal gyri (BA 22), as well as of the right inferior frontal (BA 45) and the right angular gyrus (BA 19).

SMR-related activation comprised left lateral frontal and temporal, bilateral medial frontal and left parietal neocortical regions. These areas have been reported to participate in semantic memory retrieval (Cabeza & Nyberg, 2000; Naghavi & Nyberg, 2005; Thompson-Schill, 2003). Compared to the control subjects, BPD patients were found to show increased cerebral activity in the right posterior cingulate cortex (BA 31), in the right fusiform gyrus (BA 37), in the left postcentral gyrus (BA 1,2,3) and in the left anterior cingulate cortex (BA 24).

Hyper-activation of the posterior cingulate cortex during memory retrieval was also observed in recent studies of autobiographical memory retrieval in BPD (Beblo, Driessen et al., 2006; Driessen et al., 2004). In general, the posterior cingulate cortex has been found to be engaged in episodic (Fletcher et al., 1995) and semantic (Mummery, Patterson, Hodges & Price, 1998) memory retrieval as well as in emotional processing in healthy subjects (Vogt, Finch & Olson, 1992). The posterior cingulate cortex is directly and indirectly connected with the medial temporal lobe and with the prefrontal cortex (Nieuwenhuys, Voogt & van Huizen,

1988). Thus, it could be speculated that hyperactivity of this region might serve as a compensation of medial temporal malfunctioning, e.g. of hippocampus shrinkage (Driessen et al., 2000; Irle et al., 2005) or of frontal lobe dysfunction (Schmahl & Bremner, 2006). Since bilateral volume reductions of the posterior cingulate cortex have also been reported (Hazlett et al., 2005), EMR as well as SMR task-related heightened activity in this area might also be attributed to compensation processes.

BPD patients showed further patterns of additional activation during EMR. The present data indicates a more pronounced activation of the right inferior frontal gyrus (BA 45) in EMR. In general, the right prefrontal cortex has been emphasized for retrieval attempt, but not success (Wagner, Desmond, Glover & Gabrieli, 1998). According to the results of a study by Shivde and Thompson-Schill (2004), activation of the right inferior frontal gyrus is also related to working memory maintenance.

Furthermore, right-hemispheric over activation during EMR in the BPD patients did also comprise the angular gyrus (BA 39). Activation of the angular gyrus was shown in a variety of semantic processing and production tasks (Price, 2000); however activity in the ventral inferior parietal lobe in general may reflect involvement in phonological working memory (Ravizza, Delgado, Chein, Becker & Fiez, 2004) or in the dedication of attentional resources to verbal language and memory (Chein, Ravizza & Fiez, 2003). During verbal tasks, angular gyrus activation is often reported to be left-lateralized, or, with increasing task-load, bilateral (Schmithorst, Holland & Plante, 2006).

The present results indicate increased BOLD responses of BPD patients during EMR in left temporal regions. Whereas the left middle temporal gyrus has shown to be activated in semantic working memory maintenance (Shivde & Thompson-Schill, 2004), this area might be recruited for non-domain-specific integrative processes (Friederici, Ruschemeyer, Hahne & Fiebach, 2003). The posterior superior temporal gyrus is part of the network of language comprehension (Gazzaniga, Ivry & Mangun, 1998). Lesions in this area were found to cause short-term memory impairment (Takayama, Kinomoto & Nakamura, 2004).

In the present study, BPD patients as compared to control subjects showed additional activation during SMR. Besides increased posterior cingulate cortex activation discussed above, patients exhibited an extended activation of the anterior cingulate cortex (BA 24). Generally, the anterior cingulate cortex is regarded as a central part of a supervisory attentional system which is activated in novel and difficult situations, error correction, overcoming habitual responses and decision making (Gazzaniga et al., 1998). One major function of the anterior cingulate cortex is to control emotion via the amygdala (Bush et al,

2000). An increased activation of the anterior cingulate cortex had been previously reported in a fMRI study addressing response inhibition in a sample of impulsive patients with most of them suffering from BPD (Völlm et al., 2004).

Further SMR-related hyperactivity in patients was observed in the right fusiform gyrus (BA 37). Using FDG-PET, right posterior temporal resting state glucose metabolism in BPD was shown to be correlated with attention and verbal memory performance (C. Lange et al., 2005). In addition, a hyper-activation of the middle temporal gyrus was also reported by a study investigating response inhibition of impulsive patients with most of them met the BPD diagnosis (Völlm et al., 2004). The authors suggested that this hyper-activation may reflect increased participation of working-memory during task-processing.

Thus, despite similar neuropsychological performance of BPD and control subjects in EMR and SMR tasks the day prior to scanning, BPD patients revealed additional activation of prefrontal, temporal and parietal cerebral areas. This functional over-activation suggests that BPD patients need to recruit additional cortical resources in order to successfully retrieve information. Increased recruitment was repeatedly discussed as a compensatory function of brain disturbances, e.g. in the frame of ageing processes (Buckner, 2004; Cabeza, Anderson, Locantore & McIntosh, 2002). Following this assumption, increased recruitment of brain areas by the BPD patients in the present study may operate as compensation ("cognitive reserve capacity") in order to perform on a high level. In agreement with these assumptions, the brain areas that were recruited additionally by the BPD group in the present study are part of the network related to increased effort, attention, working memory and emotional control. The retrieval of episodic and semantic information in the present investigation is primarily determined by internal processes. Additional activation in the patients could also reflect differing strategies in retrieval of patients and controls.

The present study suffers from some methodological limitations. First, the majority of patients also fulfilled diagnostic criteria from a variety of other axis I disorders, with posttraumatic stress disorder and major depression most prominent, but BPD was regarded as the main diagnosis in each. Symptoms of comorbid disorders are typical for BPD (Paris, 2005) and exclusion would have lead to the sampling of a non-representative patient group (Skodol, Gunderson et al., 2002). It cannot be ruled out that the results reported here may also be related to these comorbid disorders rather than to BPD per se. However, an explorative subgroup analysis controlling for PTSD as most common psychiatric comorbid disorder did not show any significant differences in activation patterns. Second, medication may have influenced BOLD responses of the patients in the present study. However, medication intake

is typical for a sample of patients exhibiting severe borderline symptoms (e.g. Schmahl et al., 2004). Third, due to covert memory retrieval it was not possible to control exactly what the subjects did in the scanner. Future studies should aim at integrating neuroimaging, behavioral and objective measures by using memory tasks which allow to directly control task-processing in the scanner. Forth, the present results are limited to female patients with BPD since male were not included.

In summary, the present study showed both, unaffected retrieval performance of BPD patients in episodic and semantic memory retrieval tasks as well as increased BOLD responses during retrieval processing in BPD patients compared to control subjects. This suggests that BPD patients need to engage larger brain areas to maintain a high level of performance. Increased activation might indicate additional networks for adequate retrieval needed by BPD patients, i.e. increased effort, attention, working memory or emotional control.

3 Study II: The impact of learning with irrelevant interference on verbal memory performance in BPD

3.1 Background

Although memory functions were among the first to have been discussed for impairment in BPD (Burgess, 1990; O'Leary et al. 1991) the outcomes of the neuropsychological studies did not reveal a consistent pattern of findings (Fertuck et al., 2006). Recently, a meta-analysis considered verbal working and delayed memory functioning of BPD patients as being impaired within mild to moderate ranges (Ruocco, 2005). However, the implications of these findings for everyday memory functioning seems limited to date. The requirements of standardized memory tests must be characterized as only having a weak association with everyday demands (Chaytor & Schmitter-Edgecombe, 2003). Standard memory tests aim at the controlled analysis of memory functions with the strict exclusion of interfering stimuli. However, memory functions, as with other cognitive functions in general, are usually not required in isolation in every day life. For example, telephone numbers, names, or duties have to be memorized while distracting voices are present in the background. Therefore, everyday memory requirements additionally demand the control for interference and the inhibition of emotionally more or less irrelevant interfering stimuli. The control for interfering stimuli has been conceptualized in theories on working memory. With regard to the model of Baddeley (2001; Baddeley & Hitch, 1974), working memory is divided in several subsystems with a supervisory system, the central executive, responsible for attentional control. One major function of the central executive is the inhibition of irrelevant interference (Baddeley, 2001; Nigg, 2000). Neuroimaging research indicated that the recruitment of brain areas during verbal working memory tasks depends on the requirement of interference control and inhibition (Gisselgard, Petersson, Baddeley & Ingvar, 2003; Gisselgard, Petersson & Ingvar, 2004).

Although a significant number of neuropsychological investigations of BPD addressed verbal working memory only a few studies used tasks that require the inhibition of irrelevant information during encoding or rehearsal. An initial study investigated the impact of interference on the recall of two lists of eight neutral words (Swirsky-Sacchetti et al., 1993). Two interference conditions were investigated: For emotional interference, a stimulus card of

the Thematic Apperception Test (Murray, 1943) was used which usually described a rape or murder scene. The neutral interference condition consisted of a cognitive counting backwards task. As expected, BPD patients showed a memory performance that was comparable to the control group in the condition with neutral interference. Regarding the condition with emotional negative interference, BPD patients showed a tendency for a reduced ability when compared with the performance of the control subjects; however, this comparison did not achieve statistical significance.

More recently, the procedure used in the study of Swirsky-Sacchetti et al. (1993) was transferred to a sample including BPD patients and patients with major depression (Sprock et al., 2000). The outcome of the Sprock et al. study did not demonstrate differences between patients with BPD, patients with major depression and healthy control subjects, either in the condition with neutral, or in the condition of emotional negative interference.

Another experimental approach to investigate the ability of BPD patients to inhibit irrelevant information while performing a verbal memory task was used in a study carried out by Korfine and Hooley (2000). In their study, a directed forgetting paradigm was used to address memory functioning in BPD. This working memory paradigm needs subjects to sustain attention on words they were instructed to remember and to discharge attention from words they are instructed to forget. Korfine and Hooley used 42 words, 14 each with positive, neutral, and (borderline-related) negative valence. The 42 words were presented in one trial. The presentation of each word was followed by the instruction to remember or to forget this word. After the presentation of the words, subjects were asked to recall any word they would remember, regardless of the prior instruction. BPD patients' memory performances for words they were asked to remember were comparable with the performances of control subjects, regardless of valence. However, BPD patients showed an increased recall of emotional negative words they were instructed to forget, whereas no differences were found for both other valence types.

These first studies investigating interference control and the inhibition of irrelevant interference gave some evidence for an impaired inhibition of emotional negative verbal information. The study of Swirsky-Sacchetti et al. (1993) revealed for BPD a tendency for an impaired recall of previously learned words after emotional negative interference. Korfine and Hooley (2000) in their study found BPD patients to show an increased recall of emotional negative words that they had been instructed to forget. Both study outcomes could be interpreted as reflecting a reduced inhibition of emotional negative stimuli. Considering these limited findings, first evidence suggests reduced inhibition capacities of BPD patients during

working memory tasks. However, BPD patients' reduced inhibition capacities might be restricted only to the inhibition of negatively valenced interference. Since study outcomes are heterogeneous, further research is needed to confirm this hypothesis. Therefore, it seems promising to use experimental tasks, which provide conditions that need participants to differentially engage interference control, and/or inhibition processes during encoding with regard to neutral and emotional relevant stimuli.

3.2 Aims and hypotheses

With regard to the considerations mentioned above, the present study aimed at the comprehensive investigation of verbal memory functioning in BPD with higher attention paid to everyday requirements. Therefore, the major focus of the study is the investigation of BPD patients' abilities to inhibit interference during a verbal learning task. Based on first evidence, it was hypothesized that BPD is characterized by a reduced ability to inhibit negatively valenced interference, but an unaffected ability to inhibit neutral valenced interference.

To fit the purpose of the present study, an experimental verbal learning/interference task was developed (Beblo, Mensebach, Wingenfeld, Rullkötter & Driessen, 2006). This task allows comparisons of memory performance concerning three learning conditions: (i) Learning without interference, (ii) learning with interference of neutral valence, and (iii) learning with interference of negative valence. The learning conditions ii and iii require the control for interference and the inhibition of this irrelevant interference. Whereas condition ii requires the cognitive inhibition of neutral interference, condition iii requires the cognitive inhibition of emotional negative interference. As shown in a prior study, healthy subjects exhibited a decreased memory performance if learning includes interfering stimuli (Beblo, Mensebach et al., 2006). The decreased memory performance of healthy subjects after learning with interference, in this study, was independently of the emotional valence of interference.

With regard to the memory performance of BPD patients and healthy control subjects in the learning/interference task, an interaction effect of learning condition (without interference, neutral interference, negative interference) and group (BPD patients, healthy control subjects) on memory performance was expected as assessed by the number of correctly recalled target words. It was expected that BPD patients would exhibit comparable memory performance with healthy subjects if learning only includes the encoding of learning

stimuli. Furthermore, it was also expected that BPD patients would show unimpaired memory performances if learning additionally requires the control and inhibition for interfering stimuli of neutral valence. In contrast to both other conditions, it was expected that BPD patients would show a decreased memory performance compared with control subjects if learning additionally requires the control and inhibition for emotional negative interference.

To control for other deficient verbal functions, a battery of standard tests covering verbal functioning was additionally applied. Additional applied neuropsychological tests addressed verbal working memory, delayed memory and semantic memory. Since no consistent findings support deficient performances for BPD in these tasks, no differences in these tasks between BPD patients and control subjects were expected, but these tasks were applied to control for possible impairment.

3.3 Method

3.3.1 Participants

32 patients with BPD and 35 healthy subjects matched with respect to sex, age, and intelligence took part. All subjects were native German speakers. None of the control subjects showed a history of psychiatric disorders. Patients met the DSM-IV criteria for BPD as assessed by the treating psychotherapists within the first week after admission. All patients were treated for BPD in the Ev. Hospital Bielefeld, Bethel, Germany. Four were treated as outpatients, 29 as inpatients. None of the subjects was pregnant or had one of the following concurrent or previous medical conditions, which were assessed by their medical history and by careful clinical examination: endocrine system disorders, malignant diseases, liver cirrhosis, neurological diseases, loss of consciousness (lifetime), or mental retardation. Further exclusion criteria were concurrent infectious diseases, anorexia, schizophrenia, schizoaffective disorders, bipolar disorder, and major depressive disorder with psychotic symptoms. Clinical diagnoses of alcohol and/or drug dependence during the six months prior to the study also led to exclusion. Control subjects were recruited by local adverting. Informed written consent to participate in the study was obtained from all subjects. Subjects received financial remuneration for their efforts (€50). The study was approved by the University of Muenster Ethics Committee.

3.3.2 Clinical assessment

Participants completed the Structured Clinical Interview for DSM-IV (SCID) (Wittchen et al., 1997). The SCID is a valid semi structured clinical interview, which allows assessment for axis-I and II diagnoses with respect to the DSM-IV criteria. It consists of two parts: The first interview assesses current and lifetime axis-I disorders; the second interview assesses axis-II personality disorders. The SCID interview was applied by one of three clinical psychologists, who received a SCID-training at the beginning of the study.

The psychopathologic assessment further included self-rated depressive mood, post-traumatic stress, anxiety, and dissociation. To assess self-rated depressive mood, the Beck Depression Inventory (BDI; Beck & Steer, 1994) was used. This questionnaire includes twenty-one items with regard to behavioral, cognitive and emotional features of depression. The subjects have to rate their symptoms with regard to twenty-one items covering the last seven days. A general score is calculated that gives information about the severity of current depressive symptoms.

The Posttraumatic Stress Diagnostic Scale (PDS; Foa, 1995) was applied to assess self-rated posttraumatic stress with regard to the last week. At first, the questionnaire assessed whether the subject has been exposed to specific traumatic events according to the DSM-IV PTSD A-criterion which includes the “exposure to an extreme traumatic stressor involving direct or indirect personal experience” with the “person's response to the event must involve intense fear, helplessness, or horror reaction” (APA, 1994). Only if the subject has been exposed to such a traumatic event, was the second part of the PDS, consisting of seventeen items, applied. With regard to these items, the subject has to rate posttraumatic stress symptoms according to the three symptom clusters of the DSM-IV PTSD section: intrusions, avoidance, and arousal. A general score gives information about the current amount of posttraumatic stress with regard to the last week.

The Dissociation-Tension Scale (DSS; Stiglmayr, Braakmann, Haaf, Stieglitz & Bohus, 2003) provides a measure of current tension and perceived dissociative phenomena. The subject has to rate perceived state tension and dissociation with respect to twenty-one items. A general score represents an indicator of the current state of tension and dissociative experiences.

The State-Trait Anxiety Inventory - state version (STAI; Spielberger, 1983) provides a measure for perceived state anxiety. The STAI – state version consists of twenty items addressing subjective, consciously perceived feelings of tension and apprehension as well as

heightened autonomic nervous system activity. A general score is calculated giving information about the current amount of state anxiety.

3.3.3 Experimental verbal learning/interference task

Procedure: Subjects learned three lists of 15 simple words in three trials each. Each learning trial was followed by an immediate free recall. All subjects were subjected to three conditions: To assess baseline memory performance subjects learned a list of words without interfering stimuli. Further, two interference conditions with additional presented words of neutral valence and negative valence, respectively, were administered. The three experimental learning conditions were presented in randomized order. The subjects were instructed to remember each word of the learning list. In the interference conditions, subjects' were additionally instructed to try to ignore the distracting words. The experimental design is shown by figure 3.1.

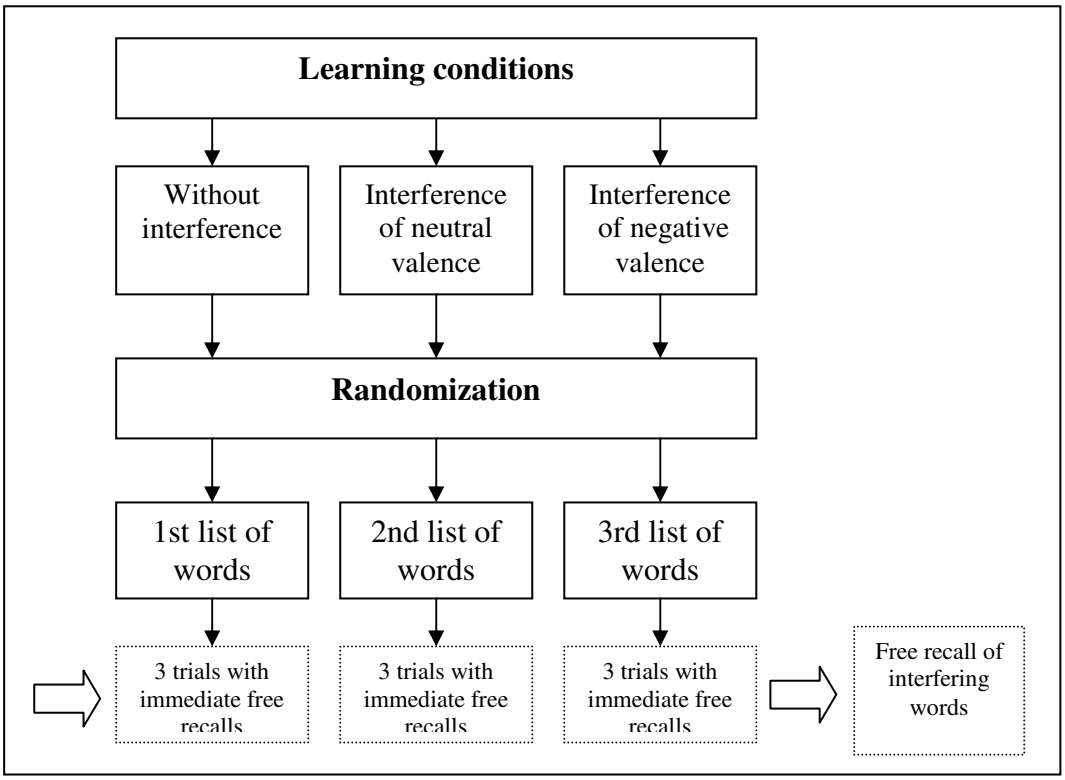


Figure 3.1: Experimental conditions of verbal learning/interference task

Stimulus presentation: Learning and distracting stimuli were presented via ear coils of a standard portable CD-Player. Duration of one trial was 33 seconds. In the baseline condition, the words of one 15-item word list were presented by a female voice. In both

distraction conditions, words of the learning list and additional interfering words were presented in alternate order starting with a distractor. The words of the learning list were presented by a female voice, the distracting words by a male voice. In each learning trial different distractor words were presented. After completing all learning conditions and subsequent recalls, subjects were asked to recall all distractor words they remembered.

Dependent Variables: Dependent variables were the mean number of correctly recalled target words per learning condition, the number of incorrectly recalled targets (intrusions) per condition, and the mean number of recalled distractors of neutral and negative valence after completing all learning conditions.

Task Development: The three word lists were drawn from the Auditory Verbal Learning Test (AVLT; Rey, 1964). Pre-tests of the word lists used showed comparable results. The distractor words were drawn from a study of Borsutzky, Fujiwara & Markowitsch (2002) providing statistical norms of 551 German nouns considering the word features familiarity, emotionality, imagery, and frequency. Based on norm data, emotionality (subjective emotional valence, rating from "very negative = 1" to "very positive = 5") of the selected 45 negative and 45 neutral words was tested. As expected, the ratings of emotionality showed significant mean differences (negative words: $M = 1.43$, $SD = 0.12$; neutral words: $M = 2.97$, $SD = 0.03$; $t_{88} = -78.335$; $p < .0001$).

3.3.4 Comprehensive neuropsychological test battery

Estimation of Intelligence:

The test "Logical Thinking" of the Leistungsprüfsystem (LPS; Horn, 1983) was administered. The Logical Thinking tests consisted of 40 items. Each item consisted of a series of digits and letters arranged, with one exception, according to a basic rule. The test requires the subject to identify the wrong element and includes a time limit of eight minutes. The number of correctly performed items is assessed.

Verbal Working and Delayed Memory:

The test "Logical Memory" of the Wechsler Memory Scale - revised (Wechsler, 1987) provides measures for both memory types. The subjects have to recall two short stories as accurately as possible. Recall performance is assessed immediately after each story (immediate recall) and after twenty minutes (delayed recall). The number of correctly recalled memory units is calculated for immediate (working memory) and delayed recall.

Immediate memory spans were assessed by the digit span subtest of the Wechsler Memory Scale - revised (Wechsler, 1987). Subjects had to repeat a series of digits in the given order (Digit Span Forward). The number of correctly recalled digit spans is assessed.

Further, the Digit Suppression Test (DST; Beblo, Macek, Brinkers, Hartje & Klaver, 2004) was obtained. This test provides a sophisticated memory span measure with a higher cognitive load. The subjects are instructed to repeat only every second digit in a given sequence. The number of correctly recalled digit spans is assessed.

Verbal Semantic Memory:

The "FAS"-task assessing lexical word fluency was applied (see Lezak, 1995). Subjects have to name words commencing with the letters F, A, and S. Subjects are instructed to name as many words as possible within one minute per letter. Further instructions were given on the kind of words that are not allowed to name: "it is not allowed to name proper nouns, e.g. persons, cities, states, each word should only be named once, and it is not allowed to use several words including the same word stem. Three scores indicate the subjects' performance: The number of correctly named words indicates a general performance score. Further score assess rule violations and word repetition. Rule violations are calculated by the number of words that include the false first letter, being a proper noun or words using the same word stem for more than one word. The word repetition score assesses the number of words that have been named more than one time.

Further, the "animals" task assessing verbal semantic fluency was applied (see Lezak, 1995). Subjects have to name as many distinct animals as possible within one minute. Further instructions were given on the kind of animals that are not allowed to name: "it is allowed to name animal species (e.g. shark) and genus (e.g. fish), but it is not allowed to name an animal with synonyms (e.g. cob for horse etc.)". Three scores indicated the subjects' performance: The number of correctly named animals indicates a general performance score. Further scores assess rule violations and word repetition. Rule violations are calculated by naming other categories than animals, as well as using synonyms for animals that have already be named. The word repetition score assesses the number of animals that have been named more than one time.

3.3.5 Statistical analyses

All statistical analyses were performed using the "Statistical Package for the Social Sciences 12.0 (SPSS 12.0)". Level of significance was set to standard $alpha_{STD}$ = .05 for all analyses if not further specified. All applied t-tests and Pearson correlation coefficients were two-tailed. If further specified, t-tests and correlation coefficients underwent a Bonferroni correction to control for multiple comparisons according to the following formula: $alpha_{BC}$ = $alpha_{STD}$ / number of applied t-tests.

To analyze the effect of learning condition, trial and group on memory performance in the learning interference task, a repeated measures 3R (learning condition) x 3R (trial) x 2 (group) ANOVA was obtained. Post-hoc t-tests (two-tailed) were calculated to examine the hypothesized group differences within learning conditions. According to the use of three post-hoc tests, the Bonferroni corrected level of significance was set to $alpha_{BC}$ = .017. Further, possible differences according to the number of correctly recalled interfering words of neutral and negative valence were tested with t-tests (two-tailed). With regard to the two tests used, Bonferroni corrected level of significance was set to $alpha_{BC}$ = .025.

To compare the performances of BPD patients and control subjects regarding the neuropsychological test battery, t-tests (two-tailed) were conducted. According to the ten comparisons that were calculated, the Bonferroni corrected level of significance was set to $alpha_{BC}$ = .005.

To investigate possible relationships between the memory performance in the learning interference task and psychopathology self-ratings within the BPD group, bivariate Pearson correlation coefficients were calculated. Twelve correlation coefficients were calculated, therefore, the Bonferroni corrected level of significance was set to $alpha_{BC}$ = .004.

3.3.6 Study design

The present study was part of a large project addressing several issues of BPD and major depression with regard to psychopathology, adversive childhood history as abuse and neglect, neuropsychology, structural neuroimaging and functional neuroimaging of traumatic memory.

The data of the present study were assessed in the following order. After giving their written consent to take part in the study, participants completed the psychopathologic assessment and the assessment of adversive childhood experiences. Within one week, the neuropsychological examination was conducted. The neuropsychological examination

consisted of a comprehensive test battery with regard to attention, memory, visuo-spatial abilities, and executive functions. For the present study, only tests were selected that covered the verbal domain of functioning. The neuropsychological examination lasted about 2.5 hours in total and included a break of about 15 minutes.

3.4 Results

3.4.1 Sample characteristics and clinical data

BPD patients and control subjects were comparable in terms of age, sex, and estimated intelligence (table 3.1). The BPD group showed high levels of psychopathology (table 3.1) with respect to depressive mood (BDI), and posttraumatic stress (PDS). Furthermore, BPD patients showed higher state-anxiety (STAI-state) before the neuropsychological examination and further experienced more dissociative features (DSS-state).

Table 3.1: Demographic and clinical characteristics of BPD patients and control subjects

	BPD patients (N = 32)		**Control subjects** (N = 35)		**Group Comparisons**		
	M	***SD***	***M***	***SD***	***t***	***df***	***p***
Age (years)	28.31	11.35	25.29	8.98	1.216	65	.228
Sex (female/male)	21 / 12		22 / 12				
Education (years)	10.97	1.58	11.85	1.25	-2.350	65	.022
Handedness (right/left/ambidextrous)	26 / 5 / 1		32 / 2 / 0				
Estimated IQ (LPS Logical Thinking)	111.13	11.83	112.11	9.67	-0.370	65	.712
BDI [1]	26.04	12.41	3.09	3.53	9.949	64	.001
PDS [2]	21.63	17.88	1.49	4.16	6.034	63	.001
STAI-state [2]	50.17	11.32	34.54	6.92	6.580	63	.001
DSS-state [1]	26.95	5.15	3.96	5.15	5.012	64	.001

BDI: Beck Depression Inventory; DSS state: Dissociation Tension Scale; LPS: Leistungsprüfsystem; PDS: Posttraumatic Stress Disorder Symptom Scale; STAI: State-Trait Anxiety Inventory, state; [1] Two patients felt unable to complete the questionnaires; [2] one patient felt unable to complete the questionnaires; level of significance: $p < .05$; significant group differences are printed in bold.

A high rate of comorbid disorders was found, mainly posttraumatic stress disorder (PTSD; N = 14), depressive disorders (major depression, N = 10; dysthymia, N = 6), and

bulimia nervosa (N = 5). Some patients met criteria of further anxiety disorders, namely agoraphobia (N =1), agoraphobia with panic disorder (N = 2), panic disorder (N = 3), obsessive-compulsive disorder (N = 1), social phobia (N = 1), generalized anxiety disorder (N = 1), anxiety disorder not otherwise specified (NOS) (N = 1), and of other phobias (N = 1). One patient each met the criteria for somatization disorder, alcohol abuse and sedative abuse.

Some patients met criteria of further axis-II disorders, namely avoidant (N = 3), schizoide (N = 1), schizotypal (N = 1), dependent (N = 3), and depressive personality disorders (N = 3). All patients were treated by dialectic behavioral therapy, and 18 of them also received psychotropic medication (selective serotonin reuptake inhibitors: N = 10, tricyclics: N = 3, further antidepressants: N = 4, high-potential neuroleptics: N = 4, low-potential neuroleptics: N = 7, mood stabilizer: N = 1, benzodiazepines: N = 3, betablocker: N = 1).

3.4.2 Memory performances in the verbal learning/interference task

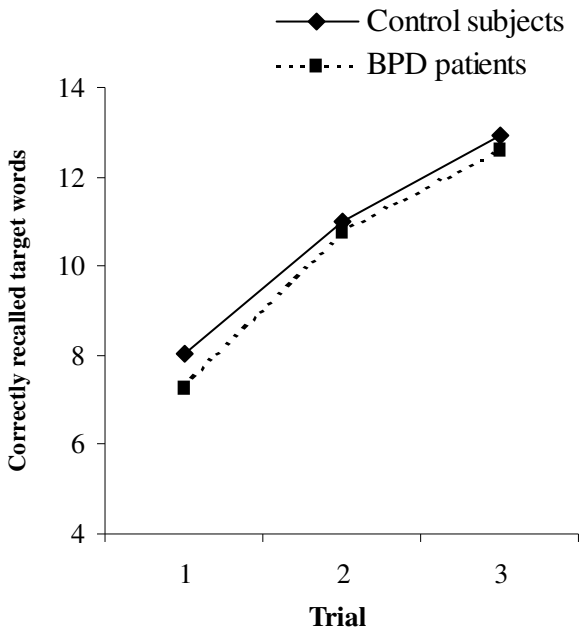
The mean number of correctly recalled target words within each of the three learning conditions as well as group differences between BPD patients and control subjects are given in figure 3.2. Repeated measures learning condition (baseline without distractors, neutral valence distraction, negative valence distraction) by trial (1, 2, 3) by group (BPD patients, control subjects) analysis of variance (ANOVA) revealed a main effect of learning condition

Table 3.2: The impact of learning condition, trial, and group on memory performance in the verbal learning/interference task (ANOVA)

	F	***df***	***p****
Main effects:			
Learning condition	30.081	2; 64	**.001**
Trial	664.589	2; 64	**.001**
Group	3.352	1; 65	.072
Interaction effects:			
Learning condition x Trial	1.743	4; 62	.141
Learning condition x Group	17.116	2; 64	**.044**
Trial x Group	0.030	2; 64	.986
Learning condition x Trial x Group	1.730	4; 62	.144

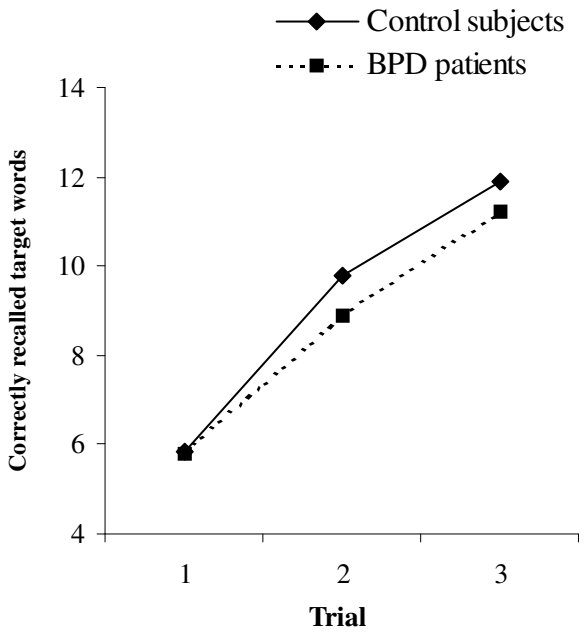
* Level of significance: $p < .05$ (all p-values are Huynh-Feldt corrected due to the violation of the assumption of sphericity); significant effects are printed in bold.

Condition 1: Learning without distractors (baseline)



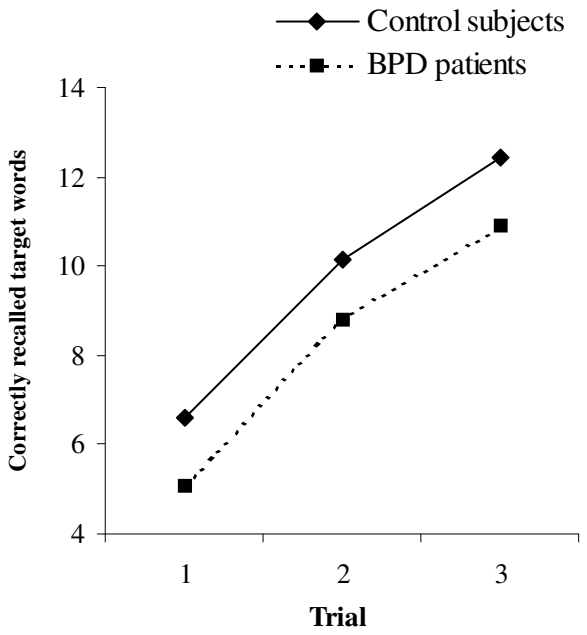
BPD patients		Control subjects	
M	*SD*	*M*	*SD*
7.28	2.26	8.03	2.13
10.78	2.32	11.00	2.06
12.63	1.62	12.91	1.84

Condition 2: Learning with distractors of neutral valence



BPD patients		Control subjects	
M	*SD*	*M*	*SD*
5.81	2.22	5.83	2.90
8.88	2.88	9.77	2.82
11.22	2.67	11.89	2.19

Condition 3: learning with distractors of negative valence



BPD patients		Control subjects	
M	*SD*	*M*	*SD*
5.09	2.07	6.60	2.20
8.81	2.42	10.14	2.30
10.91	2.70	12.43	1.99

Figure 3.2: Memory performances of BPD patients and control subjects in the learning/interference task with regard to the three learning conditions

($F_{2;\,64}$ = 30.081; p < .001) and trial ($F_{2;\,64}$ = 664.589; p < .001) but not of group ($F_{1;\,65}$ = 3.352; p = .072). Of the interactions, only learning condition by group became significant ($F_{2;\,64}$ = 3.274; p < .044). Table 3.2 gives the test statistics for the ANOVA. To apply post-hoc comparisons, the number of correctly recalled target words was calculated for each learning condition separately for BPD patients and the control subjects Figure 3.3, Table 3.3). The post-hoc comparisons indicated no memory differences between BPD patients and control

Table 3.3: Memory performance of BPD patients and control subjects (sum of trials 1-3) and group differences in the verbal learning/interference task

Learning condition	BPD patients		Control subjects		Group Comparisons		
	M	*SD*	*M*	*SD*	*t*	*df*	*p**
Without interference	30.69	5.53	31.94	5.22	.955	*65*	< .343
With neutral interference	25.91	7.20	27.49	6.90	.916	65	< .363
With emotional negative interference	24.81	6.33	29.17	5.88	2.922	65	**< .005**

* Bonferroni-corrected level of significance: p < .017; significant group differences are printed in bold.

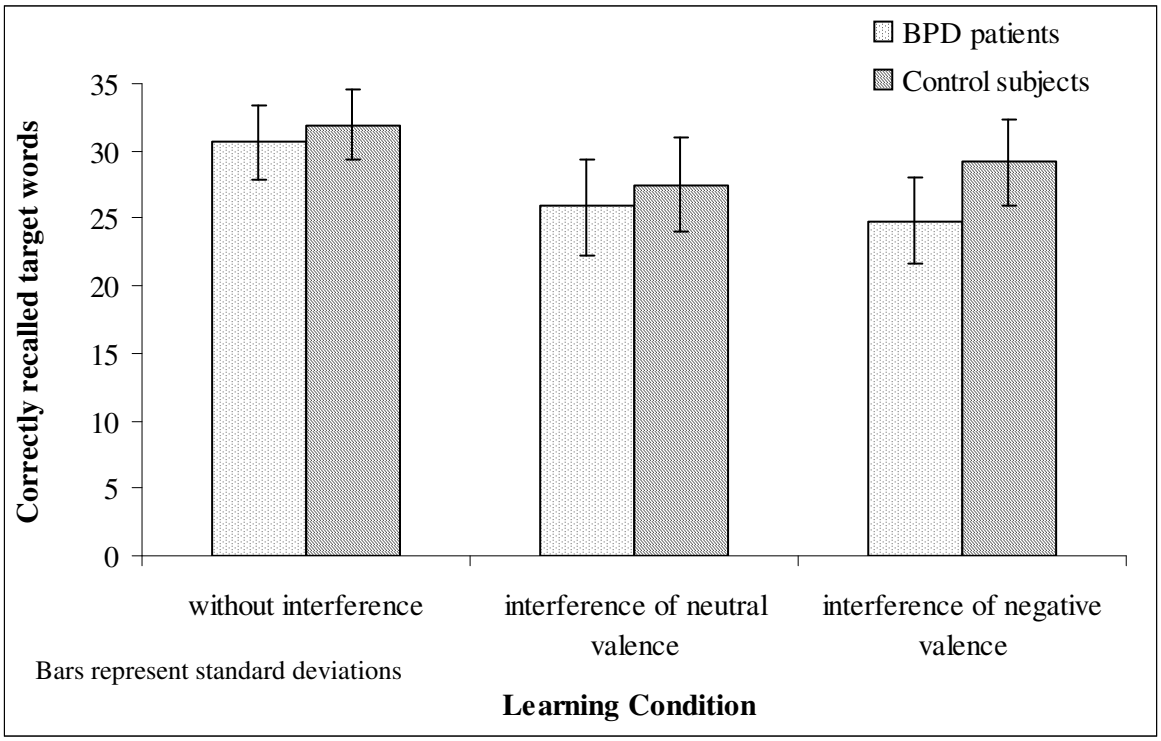


Figure 3.3: Memory performance of BPD patients and control subjects (sum of trials 1-3) in the learning/interference task

subjects in the conditions without interference ($p < .343$) and with neutral interference ($p < .363$), but revealed a significance difference in memory performances according to the condition with interference of negative valence ($p < .005$). After completing the learning/interference task, participants were asked for interfering words they would remember. Concerning distractors of negative valence, patients recalled $M = 2.69$ ($SD = 2.12$) words and control subjects $M = 2.46$ ($SD = 1.88$). Further, patients recalled $M = 0.22$ ($SD = 0.55$) distractors words of neutral valence, control subjects $M = 0.11$ ($SD = 0.32$). T-tests showed no group differences in the number of recalled distractors words, neither of negative ($t_{65} = -0.471$, $p < .639$), nor of neutral valence ($t_{65} = -0.934$, $p < .355$).

3.4.3 Correlations between memory performance in the verbal learning/ interference task and psychopathology within the patient group

The calculated correlation coefficients between the memory performances in the learning/interference task and self-rated psychopathologic symptoms within the BPD are presented in table 3.4. No significant correlations between memory performances and self-rated psychopathology were found.

Table 3.4: Bivariate Pearson correlations between memory performance in the verbal learning/interference task and self-rated symptoms of posttraumatic stress, depression, state dissociation, and state anxiety in the BPD group

	Learning Condition		
	Without interference	**Interference of neutral valence**	**Interference of negative valence**
	***r* (*p*)**	***r* (*p*)**	***r* (*p*)**
PDS [1]	-.32 ($p < .080$)	-.25 ($p < .185$)	-.33 ($p < .076$)
BDI [2]	.06 ($p < .764$)	-.20 ($p < .291$)	-.22 ($p < .227$)
DSS-state [2]	-.15 ($p < .436$)	-.37 ($p < .039$)	-.27 ($p < .135$)
STAI-state [1]	-.22 ($p < .241$)	-.33 ($p < .072$)	-.30 ($p < .104$)

BDI: Beck Depression Inventory; DSS-state: Dissociation Tension scale; PDS: Posttraumatic Stress Disorder Symptom Scale; STAI-state: State-Trait Anxiety Inventory, state version. [1] Two patients felt unable to complete the questionnaires; [2] One patient felt unable to complete the questionnaires. Bonferroni-corrected level of significance: $p < .0025$).

3.4.4 Further neuropsychological results

The performances of BPD patients and control subjects in further neuropsychological tests are given in table 3.5. T-Tests did not indicate any differences between BPD patients and control subjects with regard to working memory, delayed memory or semantic memory performance.

Table 3.5: Neuropsychological performance in BPD patients and control subjects

	BPD patients (N=32)		**Control subjects (N=35)**		**Group comparisons**		
	M	***SD***	***M***	***SD***	***t***	***df***	***p***
Logical Memory	29.72	7.64	33.03	5.26	-2.047	65	< .045
Logical Memory, 30 min.	25.53	8.39	27.69	5.40	-1.237	65	< .222
Digits, forward	7.88	1.96	8.09	1.72	-0.468	65	< .641
Digit Suppression Test	11.31	3.76	11.40	3.34	-0.101	65	< .920
FAS, distinct words	40.35	11.29	41.74	7.93	-0.583	65	< .562
FAS, repetition	0.55	0.72	1.06	1.06	-2.255	65	< .028
FAS, rule violation	0.94	1.18	1.46	2.01	-1.266	65	< .210
Animals, distinct words	25.68	5.76	26.60	4.74	-0.713	65	< .478
Animals, repetition	0.48	0.63	0.63	0.84	-0.783	65	< .436
Animals, rule violations	0.10	0.4	0.09	0.28	-0.131	65	< .896

WMS-R: Wechsler Memory Scale – revised; DST: Digit Suppression Test; FAS: lexical fluency; Animals: semantic fluency; * Bonferroni-corrected level of significance $p < .005$.

3.5 Discussion

The present study aimed in the investigation of interference control and inhibition capacities of BPD patients during a verbal learning task. Further, this study addressed verbal domain functioning of BPD patients with respect to verbal working and delayed memory as well as fluency. Although the present study were not able to detect deficient performances of the BPD patients in any of the applied standard test, this study showed, as hypothesized, a decreased memory performance of BPD patients if learning included interference by emotional negative stimuli.

According to results in the learning/interference task, a significant effect of the interaction learning condition by group on memory performance was found, but no main effect of group. Post-hoc analysis showed that the interaction reflects reduced memory performances of the BPD patients compared to control subjects in the condition with emotional negative interference, but comparable performances of both groups in the other conditions. These results suggest a specific impairment in the control and inhibition of emotional valence interference of BPD patients during learning.

An unaffected ability to inhibit irrelevant interference of neutral valence shown for BPD in the experimental task is further supported by results pattern of the Digit Suppression Test. In this test, subjects were instructed to repeat only every second digit in a given order. Thus, completing this test also requires an effort from the individual to inhibit irrelevant information. Comparable performances for both groups in this task as well as in the experimental learning/interference task also suggest no general deficient inhibition of neutral information concerning the verbal domain for BPD.

Aside from deficient inhibition of emotional salient stimuli, BPD patients have been found to perform well in verbal tests using non-affective neutral stimulus material. Unimpaired immediate memory spans and semantic memory performances with regard to the fluency measures are in line with prior reports (Beblo, Silva Saadedra et al., 2006; Dinn et al., 2004; Judd and Ruff, 1993). The further unimpaired verbal working and delayed memory performances of BPD patients that was found in the present investigation are supported by some (e.g. Dinn et al., 2004; Kunert et al., 2003; Sprock et al., 2000) but not all studies (e.g. Burgess, 1990; O'Leary et al., 1991).

The reduced inhibition concerning emotional negative words, which was found in the present study has been previously noted by a report concerning directed forgetting in BPD (Korfine & Hooley, 2000). As the learning/interference task, directed the forgetting paradigm needs the subject to focus attention on targets, to encode them, and to inhibit non-targets (distractors). Therefore, both tasks require the inhibition of neutral and emotional relevant stimuli. According to the results of Korfine and Hooley (2000), BPD patients were found to exhibit an unimpaired memory performance for words they were instructed to learn, but they showed a higher recall of emotional negative words that they were instructed to forget. Korfine and Hooley interpreted the increased recall of emotional salient words as reflecting an enhanced encoding and a reduced inhibition of emotional negative words. In contrast to these results, the present findings gave no support for an enhanced encoding of emotional salient information but only for a reduced inhibition. Patients and controls did not differ in their

recall performance of distractors, neither of neutral, nor of emotional negative distractors. This finding is not in accordance with the report of Korfine and Hooley (2000), but could be attributed to the differences in methodology. The major focus of the study of Korfine and Hooley was the investigation of inhibition processes on working memory performance. Thus, they used an approach with single presentation of target and distractor words. In contrast, the major focus of the present study was the ability of BPD patients to inhibit interference during a learning task. Therefore, an experimental learning task with different learning conditions was used. Whereas target words were repeatedly presented according to three learning trials, different distractors were used in the three trials. Depending on the randomization, some participants were suffered interference by emotional negative valenced words during learning of the first list of words, whereas other subject received this emotional negative interference during the second or the third list of words. Thus, the interval between the presentation of conditions with interfering words and the recall of these distractors differed according to the experimental randomization. Furthermore, the subjects in the present task already knew which stimuli had to be encoded (female voice) and which had to be ignored (male voice). The directed forgetting paradigm used by Korfine and Hooley (2000) first presents a word and afterwards subjects are instructed if the presented word was a target or a distractor. With regard to these considerations, striking differences in the methodology between Korfine and Hooley's directed forgetting study and the present learning/interference task are evident. Whereas the directed forgetting paradigm can be characterized as a working memory task, in the learning/interference task, only the first trial can considered to assess working memory, whereas both other trials are more closely related to learning. It has to be noted that the differing findings of both studies may, in part, represent the same underlying process, which can be considered as reflecting a reduced inhibition of emotional negative interference.

What are possible mechanisms behind the reduced ability of BPD patients to inhibit emotional salient stimuli during learning? From a cognitive and personality psychology point of view, the reduced inhibition for emotional negative words of the BPD patients in the present investigation might be explained by an altered cognitive resource allocation (Ellis & Ashbrock, 1988). The emotional negative words used in the present study might trigger task-irrelevant thoughts, that is, limited resources are required by both, task-processing and irrelevant thoughts. The experimental induction of task-irrelevant thoughts ("rumination") has been shown to decrease cognitive performance in both, healthy and clinical depressive subjects (e.g. Watkins & Brown, 2002). Furthermore, since BPD patients were found to show a more self-deprecatory attributional style (Pinto, Grapentine, Francis & Picariello, 1996) than

healthy subjects, distracting task-irrelevant thoughts in the condition with emotional negative interference should be more likely.

Cognitive neuroscience may also contribute to the understanding of BPD patients' reduced inhibition of emotional negative interference. Neuroimaging studies revealed for BPD patients increased neural responses of the amygdala to emotional aversive pictures and faces (Donegan et al., 2003; Herpertz et al., 2001). The amygdala is assumed to act as a key structure during the processing of anxiety, and more general, emotional arousal (LeDoux, 2000). Whereas a moderate activation of the amygdala has been shown to improve cognitive processing, e.g. by modulating the hippocampus, (McGough, Roozendaal & Cahill, 2000), high levels of activation inhibiting the hippocampus led to a decrease of cognitive performance (Squire & Zola-Morgan, 1991). Increased emotional arousal has been sufficiently documented to interfere with cognitive processing, e.g. working memory functioning (Gazzaniga et al., 1998). Therefore, increased emotional arousal of BPD patients may serve as explanation for the reduced memory performance concerning the learning condition with emotional negative interference. Possibly, this is due to reduced top-down control of emotion by the anterior cingulate or the orbitofrontal cortex, which has also been altered in BPD (Hazlett et al., 2005; van Elst et al., 2003).

A major critical aspect of the present study has to be considered. Due to the high number of BPD patients showing comorbid disorders, it may argued that the deficient inhibition for emotional negative interference may be strongly affected by comorbid disorders, specifically major depression and posttraumatic stress disorder. Generally, patients with these disorders were also found to show a deficient inhibition of emotional negative stimuli according to memory functioning, either generally as in major depression (e.g. Power, Dalgleish, Claudio, Tata & Kentish, 2000) or, more specific, in response to trauma stimuli as in posttraumatic stress disorder (e.g. McNally, 1998). Some evidence against these hypotheses can be derived from the correlations between self-rated psychopathology and memory performances in the different experimental conditions. If specific psychopathological symptoms would be associated with memory performance after learning negatively valenced interference, this should be evident by significant correlation coefficients. However, none of the correlation coefficients met the corrected level of significance. Furthermore, investigation correlation coefficients at the less conservative level (alpha = .05), only the correlation coefficient between self-rated dissociation and memory performance regarding the neutral interference condition became significant. The missing association between memory performances of the condition with interference of negative valence made the possibility of a

strong impact of comorbid disorders on the inhibition of negative valence interference unlikely.

As considered above, aside from a reduced inhibition for emotional negative interference during verbal learning, no differences in the performances of BPD patients and control subjects were found. It is interesting to ask, why verbal working and delayed memory performances have often been described as impaired, but more recent studies including the present study, were not able to detect these deficits. A general explanation for heterogeneous results of studies investigating verbal neuropsychological performances in BPD is the lack of adequately matched control groups. Many pioneering studies did not include an intelligence-matched control group (Fertuck et al., 2006). This seems important as some neuropsychological functions show a strict association with intelligence, e.g. working memory measures (Engle, Tuholski, Laughlin & Conway, 1999). Furthermore, a large number of neuropsychological findings in BPD are based on small sample sizes, and did not control for severe comorbid axis-I and II disorders such as schizoaffective disorders and antisocial personality disorder. Thus, previously reported deficits of BPD patients within verbal memory and fluency might be in part attributed to small sample sizes, to a lack of adequate intelligence-matched control groups, and to a lack of controlling for severe comorbid disorders.

Some limitations of this study have to be discussed. The present study sample consisted of seriously affected patients showing a large number of comorbid psychiatric disorders, which led to the majority of patients receiving in-patient treatment. Furthermore, the majority of patients received psychotropic medication. The high rate of comorbid disorders as well as a high rate of patients receiving psychotropic medication is not a specific shortcoming of this study but is strongly related to BPD with its current descriptive diagnostic criteria (Paris, 2002; Skodol, Gunderson et al., 2002). With respect to the background of high rates of comorbidity and high rates in the use of psychotropic medication, it is notable that BPD patients did perform well on all standard neuropsychological tests using non-affective stimulus material that were applied to them. Considering this aspect, it seems unlikely, that the sample used in this study may have led to an overestimation of neuropsychological deficits.

One major difficulty of the main result, a selective deficient control and inhibition of BPD patients according to emotional negative interference during learning is the specific allocation of this finding. It seems likely, that patients with major depression or posttraumatic stress disorder exhibit similar patterns of results. Since a psychiatric control group is missing,

the specification of the present findings has to remain unclear. A conservative comparison should include a mixed psychiatric control group also exhibiting high rates of comorbid disorders, but without BPD. Aside from the use of direct comparisons with psychiatric control groups, further research should address the question whether the deficient inhibition of emotional negative stimuli is associated with specific traits of BPD, e.g. a low effortful control and a high negative affect.

Some implications of the present results for everyday memory functioning of BPD patients have to be considered. Although no deficient performances of BPD patients in standard verbal memory tasks through the use of neutral stimuli were found, a deficient memory performance became evident if learning included the additional presentation of emotional negative interference. Interfering stimuli are still present in everyday requirements and a successful performing of everyday cognitive demands includes a well functioning interference control and inhibition. The deficient interference control and inhibition that was found in the present study may indicate, that BPD patients' cognitive capacity is seriously compromised at relatively low levels of emotional arousal in response to threateningly perceived stimuli.

In sum, the present study was not able to detect for BPD a general deficient verbal memory functioning. BPD subjects performed well in verbal tests using non-affective stimulus material with respect to working and delayed memory as well as to semantic memory tasks. Furthermore, no general deficient control and inhibition of interfering stimuli during learning was detected. However, BPD may be characterized by an impaired ability to control for and inhibit emotional negative interference.

4 General discussion

This thesis set out from the consideration that neuropsychological research in BPD supports non-domain-specific impairment with respect to memory, attention, visuo-spatial abilities and executive functioning (e.g. Fertuck et al., 2006). Most neuropsychological investigations of BPD are based on standard neuropsychological test batteries using mainly neutral valenced stimuli, whereas everyday requirements include a variety of emotional stimuli and further may demand affect-laden processing. Neuroimaging of basic neuropsychological functions in BPD is restricted to the investigation of major negative autobiographical memories resulting in a lack of knowledge concerning neural correlates of memory functioning in general. According to the current state of research, it was argued (chapter 1.4) that further investigations of possible neuropsychological deficits in BPD could benefit by the incorporation of three major methodological principles: (i) The investigation of basic neuropsychological functions with brain imaging methods, (ii) the inclusion of emotional stimuli and affect-laden processing, and (iii) by the inclusion of tests with higher regard to everyday functioning. With regard to these considerations, both studies presented for this thesis aimed at the comprehensive investigation of verbal memory functioning in BPD. This general discussion section summarizes the main findings of both studies, critically evaluates the used sampling, methods and designs aiming at a characterization of the validity of these findings. This evaluation is followed by considerations of the utilization of the basic methodological principles on which the present studies were based also including the impact of the present findings for further research and clinical practice. Finally, a general conclusion is drawn.

4.1 Summary of the present results taking prior findings into account

Study I addressed neural correlates of verbal episodic and semantic memory. On the basis of prior neuropsychological results and neuroimaging findings, it was hypothesized that BPD patients would show an enhanced engagement of prefrontal and limbic areas during the retrieval of episodic and semantic memory contents. In line with the hypotheses, BPD patients

compared to control subjects did show an increased activation of these brain areas. However, the patterns of increased brain engagement which were found for BPD during retrieval were not only restricted to prefrontal and limbic areas, but also included temporal and parietal areas. Patterns of increased brain activation of BPD patients during the retrieval of episodic and semantic information might indicate additional networks for adequate retrieval needed by BPD patients, i.e. increased effort, attention, working memory or emotional control. However, it has to be noted that the results of the brain imaging study are limited to female patients with BPD, since no male were included.

Study II investigated verbal memory functioning with higher regard to everyday requirements. Therefore, a verbal memory task was conducted including learning conditions, which additional require the control and inhibition of irrelevant interference. With respect to pioneering studies (e.g. Korfine & Hooley, 2000), it was hypothesized that BPD patients would show a decreased control and inhibition of emotional negative interference. Thus, BPD patients should exhibit a decreased memory performance if learning additionally requires the control and inhibition for emotional relevant stimuli. By contrast, it was expected that learning without interference as well as learning with additionally presented interference of neutral valence would lead to unimpaired performances of BPD patients compared with control subjects. No directional hypotheses were set for further neuropsychological tests that were applied for control purposes covering verbal working memory, delayed memory and semantic memory. In accordance with the major hypotheses a decreased memory performance was found if learning required interference control and inhibition with respect to emotional negative stimuli. Further, BPD patients showed unimpaired memory performances according learning without interference and learning with neutral valenced interference, respectively. The outcome of further applied neuropsychological tests did not show any deficient performances of BPD patients as compared with control subjects. These patterns of results were interpreted as reflecting widely unimpaired performances of BPD patients relating to verbal memory functions. However, memory functions in BPD may be characterized by a specific impairment of the abilities to control and inhibit emotional negative interference.

In sum, both studies were not able to detect general deficits in verbal memory functioning in BPD. Prior research regarding verbal memory functioning has revealed mixed results: Although some studies reported deficits with respect to verbal working and delayed memory (Judd & Ruff, 1993; O'Leary et al., 1991) as well as semantic memory (Dinn et al., 2004), some others were not able to provide evidence for deficient performances within these neuropsychological functions (Kunert et al., 2003; Sprock et al., 2000). Considering findings

of more recent studies a general tendency in study outcomes towards unimpaired verbal memory functioning is suggested. Although the present findings support unimpaired verbal memory functioning in BPD, some specific dysfunctions became evident. The first study suggested that BPD patients utilize additional brain resources to perform on a level that is comparable to non-psychiatric control subjects. As considered before, this may be attributed to a compensation of prefrontal and limbic brain volume losses, e.g. of the hippocampus (Driessen et al., 2000; Irle et al, 2005). Further, the outcome of study II suggests that BPD patients have difficulties in performing a verbal learning task, which demands the control and inhibition of emotional aversive stimuli. This result is in good accordance with prior findings regarding the processing of emotional relevant stimuli in verbal working memory task (Korfine & Hooley, 2000).

As outlined in chapter 1.2, neuropsychological research in BPD extensively differed in study sampling with regard to the control of neurological and additional psychiatric disorders. Due to these possible influences on the outcomes of the present studies, implications of the sampling and of further variables that might have influenced the present findings as study methods and designs are discussed in the following sections.

4.2 Critical evaluation of the present studies

4.2.1 Characterization of the used samples

Any study in the field of BPD has to deal with the difficulty of diagnostic thresholds. As outlined in chapter 1.4, BPD patients typically show a large amount of comorbid disorders, which can be, in part, attributed to the diagnostic criteria of BPD (Skodol, Gunderson et al., 2002). A recent review of neuropsychological functioning in BPD highlighted the importance of inclusion criteria and the control for intervening variables (e.g. history of neurological disorder) on study outcomes (Fertuck et al., 2006).

The present studies did not include patients with additional diagnoses of concurrent psychotic disorders (except psychotic disorder not otherwise specified), anorexia nervosa, and substance use disorders. Can therefore the present samples of BPD patients considered as representative? According to epidemiological studies, most frequently reported comorbid disorders are affective and anxiety disorders (e.g. Torgerson et al., 2001). The studies presented here consisted of patients with most them having received additional diagnoses,

especially affective (e.g. major depression and dysthymia) and anxiety disorders (e.g. posttraumatic stress disorder). The exclusion of most psychotic disorders, anorexia nervosa, and substance abuse was only limited to concurrent diagnoses whereas patients with prior diagnoses in their lifetime were included. Since all of the excluded psychiatric comorbid disorders have been demonstrated striking neuropsychological impairment, e.g. psychotic disorders within working memory functions (Lee & Park, 2005), the inclusion of patients with these disorders would have led to the question whether the present findings can be attributed to BPD or not.

Otherwise, some patients of the present samples did not receive any additional axis-I diagnosis. Would a restriction of the inclusion criteria to patients without any comorbid disorder have increased the validity of the present findings? As noted by Skodol, Gunderson et al. (2002), any findings that are based on samples of patients with a sole diagnosis of BPD cannot be considered as representative for BPD. Therefore, the exclusion of patients, who also have additional diagnoses, is difficult. The present investigations considered this aspect and excluded only patients with psychiatric disorders that are known to cause moderate to severe neuropsychological deficits. Therefore, the loss of representativeness due to the exclusion of some patients with severe comorbid disorder seems tolerable.

Further, the present study samples did not include patients with a history of neurological damage or disorders. Early neuropsychological studies were not strictly controlled for this aspect and therefore their results have been questioned (see Fertuck et al., 2006). A recent study supported the argument that BPD patients with a history of neurological damage and disorders are characterized by worse neuropsychological performances than patients without (Travers & King, 2005). Therefore, the limitation of the present BPD samples to patients without neurological disorders seems important to ascertain that the present findings can be attributed to BPD and not to brain alterations due to neurological disorders.

Prior neuropsychological investigations have often been criticized due to the selection of inadequately matched control groups (Fertuck et al., 2006). The present studies considered this aspect. The control group of study I was matched with respect to age, gender and education, study II included a matching in terms of age, gender and estimated intelligence. Therefore, it can be concluded that the present study sampling did provide comparisons with adequately matched control groups.

A further important aspect that possibly influences the validity of the present findings is the gender distribution. Since epidemiological studies typically revealed gender ratios

(females/males) of 3:1 (APA, 2000; Skodol & Bender, 2003), the second study can be considered as representative with respect to gender, whereas the findings of the first study are limited to female patients.

One might argue that the present selection criteria led to the fact that only "well-functioning" patients were selected, whereas patients suffering from severe current psychiatric disorders were not included. An argument against this hypothesis is given by the findings of a study of Beblo, Silva Saavedra et al. (2006). The present brain imaging study used a sub-sample of Beblo et al. study, with only three left-handed / ambidextrous patients and four control subjects were excluded for brain imaging purposes due to control for the possibility of left-laterized language. Beblo et al. in their study found decreased performances of BPD patients within the visual domain of memory functioning and an impaired executive functioning. That supports the hypothesis of a recent meta-analysis that visual memory and executive functioning shows higher impairment than other neuropsychological functions as verbal memory.

What kind of conclusion can be drawn from the evidence of sample characteristics? On the basis of most aspects discussed above, it can be considered that the present study sampling can be regarded as being representative for BPD as it is diagnosed in inpatient and outpatient settings. Further, the use of adequately matched control groups helps to underline the validity of the present studies.

4.2.2 Considerations according methods and designs

As compared with prior studies, the tests used in the present study were predominantly standardized, e.g. the AVLT, FAS-test, the subtests of the WMS-R, and the Digit Suppression Tests. Most of them have been carefully investigated with regard to reliability and validity and have been shown to be sensitive to possible neuropsychological impairment (see Lezak, 1995; Spreen and Strauss, 1998). Furthermore, most of the used tests have been used in prior neuropsychological investigations addressing BPD or other psychiatric samples, e.g. the "Logical Memory" and "Digit span" subtest of the WMS-R (O'Leary et al. 1991; Sprock et al., 2000). Although the applied standard tests can generally considered as reliable and valid, it may be that neuropsychological impairment of BPD patients becomes only evident by the inclusion of emotionally relevant stimuli. As noted in chapter 1.4, disturbances in emotional regulation can be considered as a core psychopathologic symptom of patients diagnosed for BPD. Therefore, the utilization of neuropsychological tests, which include emotional relevant

stimuli also demanding affect-laden processing, might be more appropriate to characterize neuropsychological functioning in BPD. The outcomes of study II, which examined the impact of emotional relevant and neutral interference during learning on memory performances, underline the relevance of this consideration. Although the use of standard verbal memory tests using neutral stimuli for neuropsychological investigations addressing BPD might be questionable, it may be more appropriate in the combination with brain imaging. Study I revealed no differences in neuropsychological performances regarding episodic and semantic memory retrieval the day before fMRI, whereas the fMRI outcomes suggest that BPD patients might engage additional brain circuits to perform on a level comparable with control subjects. Therefore, it can be concluded that further studies of verbal memory functioning or, more general, neuropsychological functioning in BPD should include both, neutral, as well emotional relevant stimuli.

A further important consideration addresses the adequacy of the present sample sizes to detect neuropsychological deficits. Comparing the sample size of the fMRI study with prior neuroimaging studies, it can be considered as relatively large. According to neuroimaging studies, which addressed the question of the appropriate samples, the present study sample used for the fMRI study is appropriate to use the random effects analysis approach, which allows the generalization of findings to the population (Friston et al., 1999). The sample size of study II can be considered as appropriate to detect large to moderate effects (Bortz & Döring, 1995), but not small effects. Since the purpose of the present studies was not the specification of subtle impairment of BPD patients regarding verbal memory the used samples can be considered as appropriate.

Since both studies aimed at different aspects of verbal memory functioning of BPD patients, the study designs have to be discussed separately. The chosen fMRI design can be described as appropriate for a first examination of neural correlates of verbal episodic and semantic memory, but met some specific limitations. As mentioned before, due to the covert recall, no data regarding the participants' behavior during scanning is available. That may be specifically relevant with regard to the baseline condition, which needs the participants to listen to the scanners' noise. Listening to a monotone noise can be characterized as a task with only small "task-load" and therefore provides a high degree of freedom for the participants during task-processing. The small task-load of the baseline condition further increases the likelihood that patients and controls differed with respect to the occurrence of task-irrelevant thoughts, e.g. the BPD patients could have exhibited more dysfunctional thoughts. However, if the control subjects had had fewer dysfunctional thoughts during the baseline condition

than the BPD patients, than the differences between the baseline condition and the experimental retrieval conditions would be smaller for patients than for controls. Therefore, the fMRI design used might have led to an underestimate of possible differences in brain activations between BPD patients and control subjects. Further research should use experimental conditions, which allow more control over task-processing by utilizing designs which provide behavioral data, e.g. by assessing the number of recalled items. Further, a more sophisticated baseline condition with a higher task load should be used that makes task-irrelevant thoughts less likely, e.g. by using an "easy" working memory as the "one-back task" or an "easy" attention task as an alertness task.

The design of study II included both standardized neuropsychological tests and an experimental verbal learning/interference task. The task used allowed the comparison of the verbal memory performances of an individual with respect to three learning conditions. A major advantage of the used learning/interference task is the possibility to calculate within-subjects comparisons that ascertain that the performance within one condition is compared with its performance within the other conditions. One major aim regarding the development of the learning/interference task was a memory measure paying more regard to everyday functioning (Beblo, Mensebach et al., 2006). Further studies should provide evidence that the interference conditions provide a valid measure of everyday memory functioning.

Some general considerations of neuropsychological research covering BPD - that are also relevant to the present investigations - have to be discussed. Generally, the use of cross-section designs for characterizing neuropsychological impairment of BPD is only the first step. Since BPD symptoms show differing stability with some features likely to decrease quickly over time (e.g. dissociative and psychotic symptoms), while others have been found relatively stable (e.g. affective instability; see Zanarini et al. 2003). It would be very interesting to investigate whether state-like features impairment is related to a specific impairment. The present studies tried to control some aspects of state-like symptoms. Study I included a subgroup analysis according to the impact of posttraumatic stress disorder on activation patterns of BPD patients during retrieval processing. No evidence was found that BPD patients with and without posttraumatic stress symptoms differed in their activation patterns during retrieval processing. Study II included an analysis of associations between memory performances and possible associations of state-like symptoms such as anxiety, dissociation, posttraumatic stress and depression. The correlational analysis revealed no significant associations between these symptom variables and memory performances. Although the outcomes of both studies did not provide evidence for an impact of state-like

features on neuropsychological performances of BPD patients, further studies should utilize longitudinal study designs to address the question of the stability of neuropsychological and neurophysiological alterations.

4.3 The scientific contribution of the present methods and findings

The present studies were conducted considering three major methodological principles which postulated that neuropsychological research addressing BPD could benefit by the incorporation of brain imaging methods, the inclusion of emotional relevant stimuli and by the utilization of tasks with higher regard to everyday demands. Both, the investigation of memory functioning with brain imaging method as well the inclusion of conditions, which require interference control and inhibition, can be characterized as helpful in the understanding of neuropsychological functions in BPD. The present findings may lead to the conclusion that verbal memory dysfunction is less severe than once thought. Furthermore, the efforts of the present studies led to an important contribution to a more concrete determination of possible mechanisms that are impaired during the processing of memory tasks in BPD.

An interesting question is the specificity of the present findings for verbal memory functioning. Are the present findings limited to verbal memory functioning or do the present findings give some information that might be generalized with respect to further neuropsychological functions of BPD? As mentioned earlier, the task-specific patterns of increased brain engagement that were found for BPD during the retrieval of episodic and semantic information cannot clearly be interpreted as related to memory retrieval itself. As lined out in the prior discussion section of study I (chapter 2.4), the patterns of increased regional brain activation of BPD patients during memory retrieval are supported for their engagement in a variety of cognitive functions and thus may reflect increased effort, attention, working memory or emotional control. It may be argued that the present findings reflect a general compensation process (“cognitive reserve capacity”) which could indicate diffuse brain alterations or, otherwise, simply reflects the consequence of present psychopathology, i.e. dysfunctional strategies or thoughts. Thus, an increased brain activation of BPD patients may also become evident during the processing of further neuropsychological functions, e.g. attention or executive functioning. Based on the present findings it seems important to determine the specificity of the present brain imaging findings (study I) by comparisons of neurophysiologic correlates of further neuropsychological functions. In line with the

aforementioned consideration regarding the specificity of neuroimaging findings, the reduced interference control and inhibition for emotional relevant stimuli might not be restricted to memory functions themselves. For example, neuropsychological research further supports a reduced interference control during attention tasks. Interestingly, the findings of reduced interference control regarding attention tasks are not restricted to emotional relevant interference. As shown in a recent study, BPD patients showed an impaired ability to perform a cognitive conflict task that requires the focusing on target stimuli and the inhibition of distractors (Posner et al., 2002). More generally, some authors have concluded that reduced interference control and inhibition may be a promising target in the search of an endophenotype of BPD (Clarkin & Posner, 2005; Fertuck et al., 2006). However, genetic analyses to date were not able to confirm this hypothesis (Clarkin & Posner, 2005). Therefore, further investigation of interference control and inhibition including neutral and negative valenced stimuli seems to be a promising route to follow.

Aside from implications for further investigations addressing neuropsychological functioning in BPD, the study outcomes have some implications for clinical practice. Although the findings of the present study suggested widely unimpaired verbal memory functioning with respect to tasks which include neutral stimuli, further neuropsychological and neuroimaging results may be interpreted as reflecting an increased “vulnerability” of memory functions. Clinicians should be aware, that BPD patients’ verbal memory functions might be severely affected at a relatively low level of stress. Further research should aim at a more precise determination of circumstances that may be associated with possible impairment of verbal memory as well as other neuropsychological functioning. Therefore the utilization of experimental approaches which allow the investigation of neuropsychological functions in response to affective and stressful challenges - e.g. after mood induction or after the obtainment of social stress - seems promising.

In sum, the present studies yielded three major findings: Verbal memory dysfunctions of BPD patients may be less severe impaired than once thought. The use of standard neuropsychological tests suggested no general impaired verbal memory functioning in BPD. However, BPD patients may use additional brain resources during the retrieval of verbal memory contents to perform on a high level comparable to control subjects. Further, BPD patients show a reduced control for interference and inhibition during learning. More specifically, the reduced interference control and inhibition during verbal learning was restricted to emotional relevant stimuli.

5 Summary

Clinical features of Borderline Personality Disorder (BPD) as an unstable and dysregulated control over behavior, emotion, and cognition as well as clinical descriptions of temporary disturbances of perception and cognition led to the question of neuropsychological deficits. Although neuropsychological investigations of BPD did not provide a consistent constellation of findings, some evidence is available for a non-domain-specific impairment in multiple domains of memory, attention, visuo-spatial abilities and executive functioning (Fertuck et al., 2006). The clinical features of BPD and neuropsychological findings have been repeatedly discussed as reflecting prefrontal and temporo-limbic dysfunctions. Neuroimaging research provides support for alterations within these brain areas with respect to structure and function (Schmahl & Bremner, 2006). Although often reported neuropsychological outcomes have been repeatedly interpreted as reflecting prefrontal and temporo-limbic brain dysfunctions, these interpretations have to be preliminary since little is known about neurophysiological correlates of basic neuropsychological functions in BPD. With regard to the current state of research, it was considered that further neuropsychological research could benefit by considering three major principles: (i) The investigation of basic neuropsychological functions by the use of brain imaging methods, (ii) the inclusion of neuropsychological tasks with regard to emotional relevant stimuli and affect-laden processing, and (iii) the use of neuropsychological test that consider everyday demands. With regard to these considerations, the studies presented in this thesis aimed at the comprehensive investigation of verbal memory functioning in BPD.

The first study examined the neural correlates of verbal memory retrieval in BPD compared with non-psychiatric control subjects. Some prior neuropsychological findings argued for verbal memory malfunctioning in BPD. Furthermore, brain-imaging findings support alterations in prefrontal and limbic brain areas of BPD patients. Since these brain areas have been suggested to be crucial in both, episodic (memory for events and the surrounding context) and semantic memory (memory for facts / knowledge) retrieval (Cabeza & Nyberg, 2000; Markowitsch, 2005), these brain alterations may indicate general deteriorations in memory-related brain circuits. In an fMRI experiment, regional blood oxygenation level dependent (BOLD) signals were assessed during two experimental

conditions of interest (episodic retrieval: 24-hour delayed recall of a wordlist; semantic retrieval: completing a lexical fluency task) and a low level baseline (listening to MRI noise) in 18 female right-handed BPD patients and 18 non-psychiatric control subjects matched with respect to sex, age, and education. It was hypothesized that BPD patients would show increased regional BOLD responses in prefrontal and limbic brain areas during both memory retrieval conditions. Although BPD patients and control subjects showed comparable performances in verbal episodic and semantic retrieval, important group differences in regional brain activation became evident. During the retrieval of episodic information, BPD patients showed patterns of increased task-specific regional BOLD responses as compared to controls in the posterior cingulate cortex (BA 23, 31) bilaterally, in the left middle (BA 21) and superior temporal (BA 22) gyri, in the right inferior frontal gyrus (BA 45) and in the right angular gyrus (BA 39). Further, control subjects compared with BPD patients did not show areas with increased BOLD responses. During the retrieval of semantic information, BPD patients as compared with control subjects showed areas of task-specific BOLD responses with respect to the right posterior cingulate cortex (BA 31), right fusiform gyrus (BA 37), left postcentral gyrus (BA 1,2,3) and the left anterior cingulate cortex (BA 24). Again, no areas of increased task-specific BOLD responses of control subjects compared with BPD patients could be found. Despite similar neuropsychological performances of BPD patients and control subjects in episodic and semantic memory tasks the day prior to scanning, the BPD patients showed, as hypothesized, patterns of increased brain activation. However, against the hypotheses, increased regional brain activation was not only evident in prefrontal and limbic brain areas but included further parietal areas. The increased regional brain suggests that BPD patients need to recruit additional cortical resources in order to successfully retrieve information. Thus, increased activation of BPD patients during retrieval might serve as compensation (“cognitive reserve capacity”) to perform on a high level comparable to controls. Therefore, increased activation might indicate additional networks for adequate retrieval needed by BPD patients, i.e. increased effort, attention, working memory, or emotional control. However, it has to be noted that the results of the brain imaging study are limited to female patients with BPD since no male were included.

Study II examined the neuropsychology of verbal memory functioning in BPD. Most neuropsychological tests used neutral stimulus material to analyze verbal memory functioning whereas everyday requirements often include a variety of emotional relevant stimuli. Further, only few studies used verbal working memory tasks, which demand the control, and inhibition of interference as required in everyday demands. Limited evidence is available

suggesting that BPD patients might show a reduced inhibition of emotionally relevant interference during memory tasks (Korfine & Hooley, 2000). For a closer investigation of the impact of interference on memory performance of BPD patients, a verbal learning/interference task was developed (Beblo, Mensebach et al., 2006). This task includes besides a learning condition without interference, conditions which utilize the presentation of additional stimuli of neutral and negative valence for interference purposes. With respect to the verbal/learning interference task, an interaction effect of learning condition (without interference, neutral valenced interference, negative valenced interference) and group (BPD patients, control subjects) on memory performance was expected. BPD patients were expected to show a decreased memory performance compared with control subjects if learning includes the control and inhibition of emotional negative interference, whereas their memory performance was expected to be comparable with control subjects regarding the learning conditions with neutral valenced interference and without interference. Besides the experimental verbal learning/interference task additional standard verbal memory tests covering verbal working memory, delayed memory and semantic memory were applied to control for possible impairment of the BPD patients with regard to standard conditions. 32 (21 females, 11 male) patients with BPD and 35 (23 females, 12 males) non-psychiatric control subjects matched with respect to sex, age, and intelligence took part. The results showed the hypothesized constellation of findings. Whereas memory performance of BPD patients were comparable with the controls subjects regarding the learning conditions without interference and with neutral interference, BPD patients showed a significant decrease of memory performance as compared to control subjects in the condition with interference of negative valence. No group differences were found in the further neuropsychological tests, which were applied covering verbal working, delayed and semantic memory performance. These results suggest no general impairment of verbal memory functions in BPD. However, BPD may be characterized by a selective impairment of interference control and inhibition in BPD regarding emotional negative stimuli during learning.

The investigation of memory functioning with brain imaging method as well the inclusion of conditions, which require interference control and inhibition, can be characterized as helpful in the understanding of neuropsychological functions in BPD. The present findings may lead to the conclusion that verbal memory functioning is less severe than once thought. Furthermore, the efforts of the present studies made an important contribution to a more concrete determination of possible mechanisms that are impaired during the processing of memory tasks in BPD.

In sum, the present studies yielded three major findings: Verbal memory dysfunctions of BPD patients may be less severe impaired than once thought. The use of standard neuropsychological tests suggested no general impaired verbal memory functioning in BPD. However, BPD patients may use additional brain resources during the retrieval of verbal memory contents to perform on a level comparable to control subjects. Further, BPD patients show a reduced control for interference and inhibition during learning. More specifically, the reduced interference control and inhibition during verbal learning was restricted to emotionally relevant stimuli.

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Declaration

I declare that the work presented in this thesis entitled

"**Verbal Memory Functioning in Borderline Personality Disorder: Neuropsychological and Neuroimaging Perspectives**"

is my own work. None but the cited methods and materials were used. This work has not been submitted in this or another form at any other university or faculty.

Date Signature