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NEUROPSYCHOLOGICAL FUNCTIONS IN WOMEN WITH BORDERLINE PERSONALITY DISORDER AND A HISTORY OF SUICIDE ATTEMPTS

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To the coolest people I have ever met:
my daughters Linnea, Moa and Annie

"All mental processes derive from operations of the brain. These processes include not only simple motor behaviors, but also complex cognitive actions such as thinking, speaking and creating works of literature, music, and art. Thus, behavioral disturbances that characterize psychiatric disorders are disturbances of brain function – even those, that are clearly environmental in origin."

Eric Kandel (Am J Psychiatry, 1998, 155(4): p. 460)

ABSTRACT

Borderline personality disorder (BPD) is a complex psychiatric disorder that leads to intense suffering for afflicted individuals, and extensive use of health care resources. Self-injurious and suicidal behaviors are common among individuals diagnosed with BPD, and as many as 10% of these will eventually die from suicide. BPD presents a clinical challenge as the condition is not well-understood, and has been notoriously difficult to treat. Recent research has confirmed the complex etiology and symptomatology of BPD, and a number of neurobiological and cognitive abnormalities have been indicated. Elucidating such underpinnings of BPD is called for in order to render effective treatment possible. Of great importance is to identify factors that contribute to the extraordinarily high rate of suicidal and self-injurious behavior, and the investigation of gene-environment interactions that occur when the effect of environmental stress is conditional on the genotype of the individual.

In this thesis we examined executive functions such as social problem solving and decision-making, and we examined memory functions, and affective symptoms, in 51 (77 in Study IV) women with BPD who had made several suicide attempts. These factors were studied in relation to co-occurring diagnoses of depression and post-traumatic stress disorder (PTSD), traumatic experiences, suicidal and self-harming behavior, and variants of genes within the serotonergic system in order to examine possible associations between them. These results were compared with those of 30 non-clinical control participants who were matched to the BPD group for age and education.

In Study I, we examined autobiographical memory in order to study whether the clinical impression that persons with BPD have problems in remembering specific details of their own experiences, holds good. We also studied the role of autobiographical memory in social problem solving, since specific personal memories provide a database of possible solutions to social dilemmas. We further examined the relationship of autobiographical memory to depression and PTSD, traumatic experiences, and level of suicidal and self-harming behavior. It was shown that the individuals in the BPD group produced significantly less specific autobiographical memories than controls. This was associated with difficulties in solving social problems, but not with concurrent diagnoses of depression or PTSD, traumatic experiences, or level of suicidal and self-harming behavior.

In Study II, we investigated executive functions of concept formation, goal maintenance, planning ability and working memory in relation to suicidal and self-injurious behaviors. Executive dysfunctioning may be one risk factor for self-harming behavior because such functions are important determinants for adequate cognitive and emotional self-regulation. The BPD group showed greater problems with goal maintenance and planning ability than controls. In addition, deficits in planning ability were associated with life-time number of non-suicidal self-injurious events, and poor concept formation was associated with life-time number of suicide attempts.

In Study III, we examined emotionally controlled decision-making, indicated to be impaired in individuals with BPD. Serotonin dysfunction has been associated with both decision-making and BPD, and for this reason we also studied the relationship between impaired decision-making and a variant of the gene coding for tryptophan hydroxylase (TPH), the rate-limiting enzyme in serotonin synthesis. The results indicated decision-making problems in persons with BPD, and that these difficulties were associated with a specific haplotype of the TPH-1 gene.

In Study IV, we tested for an association between variants of the serotonin transporter gene polymorphisms 5-HTTLPR and rs25531 and relevant clinical features of BPD. The presence of one or two copies of the short (s) allele of the 5-HTTLPR polymorphism, and the rs25531 G allele, have been associated with reduced serotonin transporter expression and function, and

vulnerability to affective disorders. The study demonstrated that individuals with BPD who carried two *s* alleles of the 5-HTTLPR (including rs25531 *G* variants) reported more core borderline symptoms, depression, and anxiety, and obsessive-compulsive behavior, but not suicidal or self-injurious behavior.

In conclusion: the present thesis, based on a combination of neuropsychological testing, clinical assessment and genotyping, describes specific impaired functions in individuals with BPD and a history of suicide attempts. These findings concern specific problems with autobiographical memory associated with the core difficulties of BPD in solving social problems. Further, we show that executive dysfunctions are coupled to some of the most distressing and clinically relevant symptoms of BPD, namely suicidal and self-harming behaviors. These impairments are likely to be related to prefrontal brain regions. Some of the indicated impairments, together with several psychiatric symptoms, seem to be related to serotonin system gene variants, indicating serotonergic dysfunction. Based on these findings, we propose that the core problems of BPD, such as impaired emotionally relevant decision-making, are related to serotonergic function in prefrontal areas.

LIST OF PUBLICATIONS

This thesis is based on the following papers, referred to by Roman numbers:

I. *Maurex L*, Lekander M, Nilsonne Å, Andersson E E, Åsberg M, Öhman A. Social problem solving, autobiographical memory, trauma and depression in women with borderline personality disorder and a history of suicide attempts. *British Journal of Clinical Psychology*, 2009, in press, doi:10.1348/014466509X454831.

II. *Maurex L*, Lekander M, Nilsonne Å, Åsberg M, Öhman A. Executive dysfunctioning in borderline personality disorder is associated with suicidal and self-injurious behavior. *Submitted.*

III. *Maurex L*, Zaboli G, Wiens S, Åsberg M, Leopardi R, Öhman A. Emotionally controlled decision-making and a gene variant related to serotonin synthesis in women with borderline personality disorder. *Scandinavian Journal of Psychology*, 2009, 50(1), 5-10.

IV. *Maurex L*, Zaboli G, Leopardi R, Åsberg M, Öhman A. The serotonin transporter gene polymorphism (5-HTTLPR) and affective symptoms among women diagnosed with borderline personality disorder. *European Psychiatry*, 2009, in press, doi:10.1016/j.europsy.2009.05.001.

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LIST OF ABBREVIATIONS

5-HTT	serotonin transporter
5-HTTLPR	serotonin transporter linked polymorphic region
5-HTR1A	serotonin receptor (1A)
ACC	anterior cingulate cortex
ADHD	attention deficit hyperactivity disorder
AMT	the autobiographical memory test
APA	American psychiatric association
BADS	behavioral assessment of the dysexecutive syndrome
bp	base pair
BPD	borderline personality disorder
CPRS	comprehensive psychopathological rating scale
CPRS-S-A	comprehensive psychopathological rating scale as a self-rating scale
DA	dopamine
DBT	dialectical behavior therapy
DNA	deoxyribonucleic acid
DSM	diagnostic and statistical manual of mental disorders
EEG	electroencephalography
fMRI	functional magnetic resonance imaging
HPA	hypothalamic-pituitary-adrenal
ICD	international statistical classification of diseases and related health problems
IGT	the Iowa gambling task
KABOSS-S	The Karolinska affective and borderline symptoms scale as a self-rating instrument
KIV	The Karolinska interpersonal violence rating scale
l allele	long allele of 5-HTTLPR
MEPS	the means-end problem solving procedure
mRNA	messenger ribonucleic acid
PCR	polymerase chain reaction
PFC	prefrontal cortex
PTSD	post-traumatic stress disorder
RCFT	Rey complex figure test
s allele	short allele of 5-HTTLPR
SASII	the suicide attempt self-injury interview
SCID	structured clinical interview for DSM-IV
SD	standard deviation
SERT	serotonin transporter
SKIP	Stockholm county council and Karolinska Institutet psychotherapy project for suicide-prone women
SNP	single nucleotide polymorphism
SSRI	selective serotonin reuptake inhibitors
TPH	tryptophan hydroxylase
VMPFC	ventromedial prefrontal cortex
WAIS-R	the Wechsler adult intelligence scale-revised
WAIS-R-NI	the Wechsler adult intelligence scale-revised as a neuropsychological instrument
WCST	Wisconsin card sorting test
WHO	world health organization

INTRODUCTION AND BACKGROUND

Psychiatric disorders involve complex symptoms and etiologies, and borderline personality disorder (BPD) may be one of the most complex psychiatric diagnoses. It is associated with intense suffering for those afflicted, and it puts heavy demands on psychiatric and medical resources. Even though BPD is said to be the least valid of the personality disorders, and despite the heterogeneity within the disorder, it has been established as a clinically useful diagnosis, although awaiting more conclusive evidence of measurable pathology (Gunderson & Links, 2008). It is important to study and understand the BPD diagnosis in greater depth since one-tenth to one-fifth of patients in psychiatric settings are diagnosed with this disorder (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004).

One approach for a better understanding and management of this disabling condition is to study specific and relevant cognitive and emotional functions and how these relate to genetic and environmental factors and their interactions as well as to other clinical characteristics in BPD. The methods used in what has traditionally been called "clinical neuropsychology" are well-suited within the field of clinical psychology and psychiatry. The understanding of the specific neural base of psychological functions, i.e. cognition, emotion and behavior, is becoming so articulated that it contributes to a better understanding at the psychological level.

The most frequently reported cognitive dysfunctions for people diagnosed with BPD are related to executive cognition and memory functions (Fertuck, Lenzenweger, Clarkin, Hoermann, & Stanley, 2006; LeGris & van Reekum, 2006). Emotional dysfunction displayed as high sensitivity to emotional stimuli, unusually strong reactions, and problems in identifying emotions, are at core of the BPD diagnosis (Ebner-Priemer, et al., 2007).

The biological mechanisms of cognition and emotion depend on a wide range of neuroanatomical structures and neurotransmitters. A dysfunctional frontolimbic network seems to mediate much of the BPD symptomatology. A neurotransmitter of central importance for cognition, emotion and behavior is serotonin. Serotonin plays an important role in emotional reactivity and impulsive aggression (Johnson, Hurley, Benkelfat, Herpertz, & Taber, 2003). Neuroimaging studies show abnormalities of serotonergic activity in BPD (e.g. Siever, et al., 1999; Soloff, Meltzer, Greer, Constantine, & Kelly, 2000) and the frontolimbic brain areas mentioned above also seem to be involved in dysfunctional serotonergic neurotransmission (Schmahl & Bremner, 2006).

Although the mechanisms of BPD are not fully understood, both genetic factors manifested as predispositions to impulsivity and emotional dysregulation, and adverse childhood experiences, such as sexual and physical abuse, are associated with the development of the disorder (Lieb, et al., 2004). This stresses the importance of bridging genetics, environmental exposure, brain and behavior in order to understand this complex psychiatric disorder.

Due to earlier psychotherapeutic failures to efficiently treat BPD, individuals with this diagnosis were said to be "difficult". They had a rumor of being angry and thorny and, unfortunately, the diagnosis of BPD remains unfairly stigmatized. Because of this, many of these persons have had a messy relationship with psychiatric institutions. An increased public awareness of BPD is needed to decrease this stigma. Also, learning more about the specific strengths and weaknesses of individuals with this diagnosis may lead to more potent therapies that can be effectively tailored to each individual.

In order to increase our understanding of specific problems in individuals with BPD, the aim of this thesis was to study executive functions such as social problem solving, decision-making, and planning abilities, as well as memory functions, and affective symptoms, in suicide-prone women with BPD in relation to variants of genes within the serotonergic system, traumatic experiences, suicidal and self-harming behavior, and co-occurring diagnoses of depression and PTSD in order to examine possible associations between them.

Knowledge about specific functions, impairments and strengths in individuals with BPD is essential for the development of much-needed individualized interventions that are susceptible to evaluation.

BORDERLINE PERSONALITY DISORDER

Individuals with a diagnosis of BPD experience a characteristic and long-term pattern of instability in the regulation of emotion, impulse control (particularly in the context of stress or negative emotionality), interpersonal relationships, and self-image (APA, 1994). Clinically, intense and dysregulated emotions related to affective lability, impulsive aggression, and self-destructiveness - including suicide attempts - seem to be at core of BPD. This leads to emotional and behavioral instability, which has a negative impact on most aspects of daily life. The difficulty of self-management, of interacting with others and of achieving goals can become overwhelming, leading to intense negative emotion. When life becomes too demanding, hopelessness, anger, anxiety and/or depression can set in. Many individuals with BPD then try to cope by self-destructive and suicidal behavior.

Epidemiological studies indicate that BPD affects about 1-2 % of the population, 10 % of psychiatric outpatients, and 20 % of psychiatric inpatients (Lieb, et al., 2004). About 75 % of those diagnosed with BPD are women (Gunderson & Hoffman, 2005), although some recent studies indicate that there are equally many men as women who qualify for a BPD diagnosis in the general population (Grant, et al., 2008; Lenzenweger, Lane, Loranger, & Kessler, 2007). Besides a high consumption of psychiatric treatment, individuals with BPD also show high somatic health care utilization (Frankenburg & Zanarini, 2004; Sansone, Wiederman, & Sansone, 1998). Understanding this patient group thus becomes a critical dimension of psychiatric and somatic health care.

History of BPD

Borderline patients were first described by the psychoanalyst Adolph Stern in 1938 as individuals not fitting into the classification system of that time of either psychotic or neurotic patients (Gunderson & Links, 2008). This classification was done in order to decide whether a person was analyzable, that is treatable, or not. Individuals with neuroses were considered to be treatable, while those with psychoses were not (Gunderson, 2009).

In the late sixties, Otto Kernberg (Kernberg, et al., 1981) defined a borderline personality organization characterized by diffuse identity, "primitive defences" and temporary stress-related difficulties to test reality. At the same time, Roy Grinker and colleagues initiated the first empirical study of borderline patients, which established diagnostic criteria of weak self-identity, dependent relationships, depression and expressive anger (Gunderson & Links, 2008). Some years later, John Gunderson began a study to define borderline patients, narrowing the symptoms described by Kernberg and Grinker, leading to the development of a structured interview for diagnostics (Gunderson, Kolb, & Austin, 1981).

The BPD diagnosis was included in the Diagnostic and Statistical Manual of Mental Disorders-III (DSM-III) in 1980 (APA, 1980) and in the International Classification of Diseases-10 (ICD-10) in 1992, where it is called more appropriately "emotionally unstable personality disorder" (WHO, 1992). Because the DSM-III definition of BPD included specific and measurable criteria, the validity of the diagnosis was systematically tested and a large number of clinical research projects on BPD were carried out (Gunderson, 2009). This research showed BPD to be an internally consistent, coherent and familial diagnosis, and that 70% of individuals diagnosed with BPD reported histories of abuse (Gunderson, 2009).

By the time DSM-IV was published (APA, 1994), psychiatry was influenced by biological explanations of psychiatric syndromes. Affective dysregulation (suggested to be effected by the noradrenergic system) and behavioral dyscontrol (influenced by the serotonergic system) were proposed to be important features of BPD (Siever & Davis, 1991).

Much recent research has been associated with the etiology underlying the development of BPD, reflecting both an appreciation of the newly available neurobiological and genetic technologies, and a growing impatience with the extensive comorbidities that arise from the current classification system (Gunderson, 2009).

The diagnosis of BPD

To be diagnosed with any personality disorder, DSM-IV (APA, 1994) stipulates general criteria that must be fulfilled. These criteria constitute an extended pattern of inner experiences and behaviors that markedly deviates from what is expected within the individual's culture. This pattern is to be manifested in two (or more) of the individual's thoughts, feelings, relations and/or self-regulation, and it must result in significant problems to function socially and professionally.

A DSM-IV diagnosis of BPD (APA, 1994) is characterized by a pervasive pattern of instability of interpersonal relationships, self-image, and affects, as well as of a marked impulsivity beginning by early adulthood. This pattern must be present in a variety of contexts as indicated by five (or more) of the symptoms presented in Table 1.

Table 1. Borderline Personality Disorder - DSM IV Criteria

1 Frantic efforts to avoid real or imagined abandonment

2 A pattern of unstable and intense interpersonal relationships characterized by alternating between extremes of idealization and devaluation

3 Identity disturbance, 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, 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 hours and only rarely 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.

The BPD diagnosis is established by a Structured Clinical Interview for DSM-IV (SCID-II), based on the DSM-IV diagnostic criteria. The use of structured diagnostic interviews is time-consuming and requires a considerable level of clinical expertise. However, the reliability of the diagnosis of BPD is good when trained clinicians use standardized interviews (Gunderson & Hoffman, 2005).

Nonetheless, there are limitations to the DSM categorical conceptualizations of personality disorders (Skodol & Bender, 2009). Disorders co-occur and there is extreme heterogeneity among individuals who receive the same diagnosis, and also arbitrary diagnostic thresholds for the boundaries between pathological and "normal" personality functioning (Skodol & Bender, 2009). It has been argued that a new approach to the categorical personality

psychopathology of the DSM is needed in the planned revision for DSM-V. Inclusion of sets of dimensions of psychopathology, rather than multiple categories representing mental disorders, is suggested to be more useful in a clinical setting and thereby improve patient care (Skodol & Bender, 2009). A recent study (Rottman, Ahn, Sanislow, & Kim, 2009) examining the use of a dimensional five-factor personality model (Bagby & Ryder, 2000) to make diagnoses of prototypic cases of personal disorders found, however, that clinicians were largely unable to do this. When psychiatrists instead read prototype descriptions based on DSM-IV criteria, this led to more correct diagnoses (Rottman, et al., 2009). The clinical inutility of the dimensional personality model used in the Rottman et al. study (2009), may be due to all too unspecific items that were not framed in the context of a diagnosis. An inclusion and integration of both dimensional and categorical representations, is probably the best suggestion for the revision of diagnostic systems (Dahl, 2008).

Since an individual diagnosed with BPD only has to fulfill five of the nine DSM-IV criteria, it is possible for two persons with this diagnosis to only have one symptom in common. These nine criteria can make up 126 possible combinations, contributing to the heterogeneity within the BPD diagnosis. This heterogeneity has led to a search of the core problems of BPD, now thought to be emotional and behavior dysregulation, and interpersonal problems (New, Triebwasser, & Charney, 2008). These three factors have, however, proven to be too highly intercorrelated to be considered separate factors (New, et al., 2008). Current research and clinical work are focused on understanding the genetic, neurobiological and environmental bases of BPD core symptoms.

Most clinical studies have shown that three out of four individuals diagnosed with BPD are women (Lieb, et al., 2004). A couple of recent epidemiological studies, however, have suggested that BPD is as common in men as it is in women (Grant, et al., 2008; Lenzenweger, et al., 2007), even though the mental and physical health burdens of BPD proved to be considerably higher among women in the study by Grant et al. (2008). This may be due to a sampling bias, that women are more prone to seek help than men, or to a diagnostic bias, that impulsive and aggressive behaviors are seen as more pathological in women. A true gender difference in the prevalence of BPD is also possible. Sexual abuse, thought to be an important risk factors, is about 4-10 times more common for girls than boys (Choudhary, Coben, & Bossarte, 2008; Gunderson & Hoffman, 2005).

Although BPD is associated with significant functional impairment, an extensive use of health care resources, and an increased risk of suicide its prognosis may be better than formerly believed (Grant, et al., 2008; Gunderson & Hoffman, 2005). Symptoms remit with age and by the age of 40, as many as 75% of formerly diagnosed individuals no longer meet the diagnostic criteria for BPD (Paris, 2009; Zanarini, Frankenburg, Hennen, & Silk, 2003; Zanarini, et al., 2008). This may be due to socialization influences, brain maturation and/or intervention effects.

Suicidal and self-injurious behavior in BPD

As many as 75% of individuals with a diagnosis of BPD engage in self-harming behavior (LeGris & van Reekum, 2006), and 60-70% attempt suicide (Oldham, 2006). About 10% of persons with BPD complete suicide (Paris & Zweig-Frank, 2001). This is almost 50 times as common as in the general population (APA, 2001) and a Swedish study of young persons who had completed suicide showed that 33% of these suicides were committed by individuals with BPD (Runeson & Beskow, 1991). A history of suicidal behavior is the most reliably replicated risk factor for future suicide attempt or completion (Oquendo, Baca-Garcia, Mann, & Giner, 2008), and the importance of actively addressing and prioritizing suicidality in

individuals with BPD is emphasized in the APA Practice Guideline for the Treatment of Patients with Borderline Personality Disorder (APA, 2001).

According to interviews with individuals who self-harm without suicidal intent, the functions of self-injurious behavior are variable: it provides relief from negative mood states, reduces distress, punishes oneself for being bad, overcomes numbness and dissociation in order to feel again, and expresses inner pain in a symbolic fashion (Gunderson & Links, 2008).

Co-occurrence of other psychiatric diagnoses in BPD

Individuals with BPD often have several comorbid psychiatric diagnoses, mainly other personality disorders and mood and anxiety disorders (Lieb, et al., 2004). Co-occuring diagnoses described in the literature are e.g. bipolar disorder (Paris, Gunderson, & Weinberg, 2007), attention-deficit hyperactivity disorder (ADHD) (Philipsen, 2006), substance dependence (Bornovalova, Lejuez, Daughters, Zachary Rosenthal, & Lynch, 2005), and PTSD (Golier, et al., 2003). These additional disorders add to the heterogeneity of BPD. The reason for these co-existing diagnoses is not clear. Shared environmental, as well as shared biological risk factors, may be associated with various psychiatric disorders. Some symptoms, such as substance abuse and eating disorders, may also be attempts (efficient in the short run, but devastating in the long run) to solve problems and to reduce emotional distress. It may also be that our current diagnostic systems, DSM-IV (APA, 1994) and ICD-10 (WHO, 1992), have too much of a categorical model of psychiatric diagnoses. An integration of categorical and dimensional approaches to personality disorders is proposed for inclusion in the next revision of the psychiatric classifications (Dahl, 2008).

The diagnostic comorbidity of psychiatric disorders refers to an overlap of symptoms at the descriptive level and says nothing of possible etiologies (Lilienfeld, Waldman, & Israel, 1994). The criteria for personality disorders are a mixture of stable traits, which may be associated with chronic impairment, and acute symptoms, which may contribute to a lower diagnostic stability (Beauchaine, Klein, Crowell, Derbidge, & Gatzke-Kopp, 2009).

MECHANISMS OF BPD

The biological mechanisms of BPD concern several neuroanatomical structures and chemicals in the brain. The frontal and limbic parts of the brain seem to be particularly involved in BPD symptomatology (Schmahl & Bremner, 2006). The stress hormone cortisol and the neurotransmitters dopamin and serotonin are proposed to be important modulators in BPD. In this thesis I have focused on serotonin, by studying several genetic variants at critical bottlenecks of the serotonin system. Serotonin plays an important role in emotional reactivity and impulsive aggression (Johnson, et al., 2003). Neuroimaging studies show abnormalities of serotonergic activity in BPD (e.g. Siever, et al., 1999; Soloff, et al., 2000), while frontolimbic brain areas also seem to be involved in dysfunctional serotonergic neurotransmission (Schmahl & Bremner, 2006). In the following, neuroanatomical findings in BPD will be reviewed. Thereafter, mechanisms of BPD will be discussed from a neurochemical perspective, and from a behavioral genetic perspective.

Neuroanatomical correlates of BPD

A large number of brain imaging studies indicate that individuals with BPD suffer from impairments in brain systems that regulate impulsivity, aggression, and emotion, and that are

important in the pathophysiology of affective illness. A dysfunctional frontolimbic network is proposed to mediate much of the BPD symptomatology. This circuitry is composed of the anterior cingulate cortex (ACC), the orbitofrontal and dorsolateral prefrontal cortex (PFC), the hippocampus, and the amygdala (Schmahl & Bremner, 2006), and has been said to be "skewed" in mood disorders resulting in too much emphasis on somatic-emotional processing at the expense of cognitive-attentional functioning (Mayberg, 1997). A diminished top-down control of emotional responses, where the prefrontal circuit involved in inhibiting behavioral reactivity is not sufficient in controlling the forceful limbic activity involved in BPD, may underlie the affective hyper-responsiveness seen in this disorder. Silbersweig et al. (2007) performed a functional magnetic resonance imaging (fMRI)-study of conditions associated with the interaction of behavioral inhibition and negative emotion, where individuals diagnosed with BPD showed less ventromedial prefrontal (VMPFC) activity and increased limbic activity than healthy subjects showed. Thus, the BPD persons showed brain activity associated with automatic emotional reactions indicating that they may not have access to flexibly used brain mechanisms that would regulate these emotions appropriately (Silbersweig, et al., 2007). Scientific evidence indicates also that the amygdala and hippocampus are hyperactive and abnormally small in BPD, which may result in a weaker control of negative emotions (Meyer-Lindenberg, 2009). According to LeDoux (1998), the very goal of psychotherapy is to teach the cortex to control the amygdala, which may be especially true for interventions with BPD patients.

The frontolimbic network further seems to be involved in the serotonergic dysfunction that appears to be related to the impulsive and self-destructive behaviors seen in many individuals with BPD (Tajima, et al., 2009).

Another brain area that may be relevant for BPD is the anterior insula which has appeared as a key area associated with the processing of fairness in social interactions, subjective emotional awareness (Craig, 2009), facial emotion (Adolphs & Spezio, 2006) and the appreciation of the intentions and emotional states of others (Adolphs, Damasio, Tranel, Cooper, & Damasio, 2000), such as empathy (Singer, et al., 2004; Singer, et al., 2006). King-Casas et al. (King-Casas, et al., 2008) found that individuals with BPD had reduced activity of the bilateral anterior insula during a trust game as compared to controls. These individuals also had problems in maintaining cooperation with their game partner, and were further impaired in their ability to repair broken cooperation. The authors interpreted this as a consequence of the norms used in perception of social gestures being dysfunctional or missing in individuals diagnosed with BPD. This study suggests that activation of the anterior insula in a social context represents an evaluation of perceived or planned action. When such an evaluation is perceived as negative, it may be associated with a feeling of discomfort. If true, this implies that individuals with BPD may have problems in cooperation because they lack the "gut feeling" (corresponding to the anterior insula signal) that the relationship is in jeopardy and/or expect such behavior from the outset (Meyer-Lindenberg, 2008). The fact that individuals with BPD were less likely to establish or maintain a cooperative relationship may then be the result of difficulties in trusting others.

Whether or not the development of BPD is mainly driven by environmental stress or by genetic vulnerability, the above studies show clearly that BPD is a disorder of the brain.

The prefrontal cortex

The prefrontal cortex (PFC) is a brain area crucial for emotional and cognitive control (Gazzaniga, Ivry & Mangun, 2009).

Volumetric abnormalities in the orbitofrontal cortex have been shown early in the course of BPD. In a group of teenagers with first-presentation of BPD, a reversal of the normal

(right>left) asymmetry of orbitofrontal grey matter was found. A right-sided orbitofrontal grey matter loss that was not related to gender or the clinical features of BPD was found in the BPD group (Chanen, et al., 2008). A reduced PFC volume in BPD participants is consistent with previous structural imaging studies of the frontal lobes in adults with BPD (e.g. Lyoo, Han, & Cho, 1998; Tebartz van Elst, et al., 2003). Nevertheless, Soloff et al. (2008) did not find structural abnormalities in the orbitofrontal or ventromedial PFC (VMPFC) among BPD subjects (Soloff, Nutche, Goradia, & Diwadkar, 2008). The differences between studies may be due to differences in samples with respect to size, gender and/or co-morbidity.

Functionally, the orbitofrontal cortex has been shown to be less active in persons with BPD than in controls (Silbersweig, et al., 2007), indicating an inefficient top-down inhibitory control function of the PFC. Further, impulsivity and negative affect has been related to orbitofrontal dysfunction in BPD (Berlin, Rolls, & Iversen, 2005).

Studies of PFC function are largely in line with the symptoms of dysfunctional emotional control in BPD.

The amygdala

The amygdala is important in attributing emotional significance to our experiences and memories, and it is a central brain structure in the generation of both normal and pathological emotional behavior, such as mood disorders (LeDoux, 1998). The amygdala, together with the hippocampus, also modulates and regulates expression of fear responses. A loss of inhibitory regulation in these limbic circuits results in disinhibited fear response, and in anger and impulsive-aggressive behaviors (LeDoux, 1998), which are symptoms that are common in BPD. This might reflect impaired saliency detection guiding behavior in BPD, leading to a dysfunction of emotional processing, suggesting a contributing, bottom-up substrate for disordered emotional behavior in BPD (Silbersweig, et al., 2007).

A number of studies on women with BPD have shown amygdala volume reductions (Driessen, et al., 2000; Schmahl, et al., 2009; Soloff, et al., 2008; Tebartz van Elst, et al., 2003), especially associated with histories of childhood abuse (Driessen, et al., 2000; Schmahl, Vermetten, Elzinga, & Douglas Bremner, 2003). However, one study found no evidence for smaller amygdala volume in a mixed-gender sample of individuals with BPD (Brambilla, et al., 2004), while another study found an enlargement of the amygdala in female individuals with BPD and comorbid depression (Zetzsche, et al., 2006). This has previously been found in depressed patients (Zetzsche, et al., 2006). Further, Zetzsche et al. (2008) reported that women with BPD carrying the G allele of the 5-HTR1A receptor gene showed a smaller volume of the amygdala than healthy controls, even though there were no differences of allelic distribution or amygdala volume between individuals with BPD and controls. This association between 5-HTR1A genotype and amygdala volume was thus present only in the BPD group and not in controls, suggesting a specific interaction between genetic variants, brain, and the development of BPD symptoms (Zetzsche, et al., 2008).

An inherent hyperactivity of the amygdala has been suggested, possibly correlated with interpersonal hypersensitivity (Donegan, et al., 2003), which may be displayed as the overreaction to negative or even neutral facial expressions that has been shown in BPD (Donegan, et al., 2003; Herpertz, et al., 2001).

The hippocampus

The hippocampus is important in spatial ability and in memory functions (Hassabis, et al., 2009), and plays an inhibitory role in the regulation of the hypothalamic-pituitary-adrenal (HPA) axis of the stress system (McEwen & Chattarji, 2004).

Hippocampus volumes of patients with BPD have been shown to be smaller than those of healthy controls (Brambilla, et al., 2004; Driessen, et al., 2000; Schmahl, et al., 2003; Soloff, et al., 2008; Tebartz van Elst, et al., 2003). It is interesting to note that reported childhood trauma or abuse has been related to smaller hippocampi in some studies (Brambilla, et al., 2004; Schmahl, et al., 2003; Tebartz van Elst, et al., 2003), though not all (Zetzsche, et al., 2006). The duration and severity of childhood trauma have been related to the degree of hippocampal volume loss (Driessen, et al., 2000). A recent study showed smaller hippocampi only in individuals with BPD who also had a co-occurring diagnosis of PTSD (Schmahl, et al., 2009). Abnormally high glucocorticoid levels are known to have neurodegenerative effects (e.g. dendritic shrinkage) in animals and humans, particularly in the hippocampus (McEwen & Chattarji, 2004; Zimmerman & Choi-Kain, 2009), suggesting that the volume reductions reported for the hippocampus in BPD could be stress-related.

The anterior cingulate cortex

The anterior cingulate cortex (ACC) is involved in cognitive and emotional functions that are likely to underpin relevant symptoms of BPD, including emotional instability, impulsivity, and cognitive impairments concomitant with emotional distress (Whittle, et al., 2009). The left lateralized ACC structure is particularly important for executive functioning and behavioral/emotional regulation (Whittle, et al., 2009).

Studies of both women and men with BPD have shown decreased volume in the ACC, especially of gray matter, as compared to healthy control persons (Hazlett, et al., 2005; Minzenberg, Fan, New, Tang, & Siever, 2008; Tebartz van Elst, et al., 2003). In a recent study, bilateral reductions in gray matter concentrations in the ACC was found in men, but not women, with a diagnosis of BPD (Soloff, et al., 2008).

It is unknown whether a smaller ACC reflects a vulnerability to develop BPD. One study found an atypical anterior P300 signal, which is a neural event related potential and which can be recorded with electroencephalography (EEG), in a community sample of girls with mild BPD symptoms, indicating abnormal maturation of function in the ACC as a possible predisposing factor (Houston, Ceballos, Hesselbrock, & Bauer, 2005). Another study showed ACC volumetric decrease early in the course of BPD, which was correlated with self-injurious behavior and impulsivity (Whittle, et al., 2009).

Neurochemical correlations of BPD

The cortisol system

The stress-response varies between individuals and is guided by genetic set-up and previous experiences/learning. Altered hypothalamic-pituitary-adrenal (HPA)-axis stress reactivity is thus a trait influenced by both genes and adversity in early life (Mann, et al., 2009). Evidence suggests that chronic stress leads to elevated HPA axis reactivity, which can have potentially long-lasting effects on the functioning of the brain regions that regulate the release of cortisol (Lupien, McEwen, Gunnar, & Heim, 2009). The HPA-axis can become abnormal after childhood adversity so that it becomes super-sensitive to environmental stress. The cortisol response can then be reset, and the reset response may be present into adulthood (Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). Animal studies have demonstrated that early-life stress results in both acute and chronic changes to the reactivity of the HPA axis to stress, as well as in behavioral and cognitive dysfunction related to changes in the functioning of the cortisol system (Zimmerman & Choi-Kain, 2009). Dysfunctions in the HPA system are associated with depression and suicidality (Pfennig, et al., 2005). Thus, perinatal and childhood exposure to stress and trauma may influence individual sensitivity to strong

emotions, something of obvious relevance for the symptomatology and behavioral problems in BPD. Some few findings (Heim, et al., 2008; Lupien, et al., 2009) indicate that stress-related changes of the HPA-axis can have far-reaching consequences.

A dysfunctional HPA responsivity in BPD has been suggested. A dysregulated feedback inhibition has been shown, especially associated with comorbid depression or PTSD, and self-destructive behaviors (Zimmerman & Choi-Kain, 2009). Comorbid depression and PTSD, as well as childhood abuse, are significant factors that determine the level of dysfunction detected in the HPA axis. One potential mechanism for dysregulated cortisol levels in BPD is "glucocorticoid programming," either prenatally or as the effect of early trauma or neglect, which are known to be common in individuals with BPD (Zimmerman & Choi-Kain, 2009).

There is also increasing evidence that the HPA axis is involved in suicidal behavior (Crowell, Beauchaine, & Linehan, 2009), especially completed suicide (Jovev, et al., 2008).

The dopaminergic system

Human and animal studies indicate that dopamine activity plays an important role in emotion information processing, impulse control, and cognition. Therefore, the role of dopamine functioning in BPD is motivated to explore (Friedel, 2004). There is evidence of dopamine dysfunction in BPD that has been obtained from provocative challenges with amphetamine and methylphenidate. Further, antipsychotic agents have shown effects on emotional dyscontrol, impulsivity, and cognitive impairment in controlled clinical trials in BPD (Friedel, 2004).

Moreover, dopamine activity appears to play a major role in the positive reinforcement of goal-directed behaviors and the experience of pleasure (Öhman, 2006). It is possible that dopamine dysfunction that affects the reward neural circuits may be related to impaired motivation and positive behavioral reinforcement in BPD. Many individuals with BPD cannot find anything that usually makes them feel happy or excited. Dysphoric symptoms common in BPD may be related in part to dopamine dysfunction (Fridel, 2004).

Further, one study showed an association between the presence of a dopamine transporter polymorphism and BPD in two independently recruited depressed out-patient samples, supporting a dopamine dysfunction hypothesis of BPD (Joyce, et al., 2006).

The serotonergic system

Serotonin is the most widely distributed neurotransmitter in the human brain, phylogenetically ancient and implicated in emotions and their regulation (Lesch, 2007). It is suggested that moderate serotonin levels inhibit anger and depression, but that low levels in the hypothalamus and amygdala make this inhibition difficult (Eysenck, 2004). Serotonin is also an important regulator of early brain development and adult neuroplasticity (Lesch, 2007).

Since the blood-brain barrier prevents serotonin from being imported from outside the brain, all serotonin used by brain cells must be produced within the neurons. Serotonin is synthesized from the amino acid tryptophan, which is obtained in the diet. The rate-limiting step of synthesis is the hydroxylation of tryptophan by tryptophan hydroxylase (Cooper & Melcer, 1961). The serotonin synthesis can be summarized in a few steps as can be seen in Figure 1.
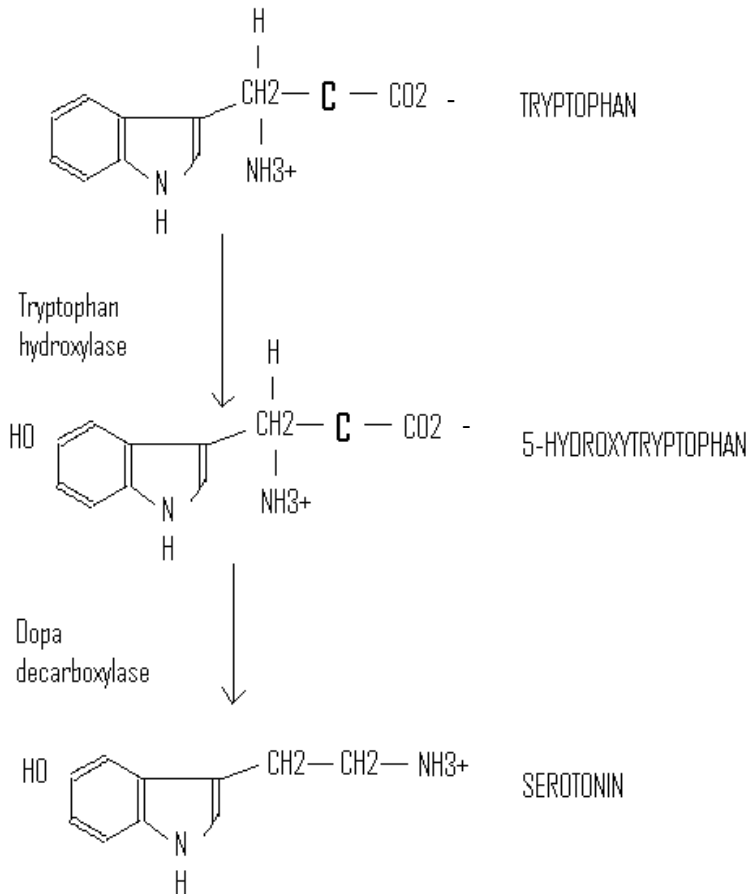
Figure 1. Schematic presentation of serotonin synthesis. Adapted from Zaboli (2006) with permission.

The serotonin transporter (5-HTT or SERT) is one of the prime modulators of brain serotonin. It removes serotonin from the synaptic cleft by reuptake into the presynaptic neuron, where serotonin is stored in vesicles or degraded. Thus, the 5-HTT plays an essential role in the duration and intensity of the serotonergic communication with its receptors on postsynaptic targets (Hariri & Holmes, 2006). The medial PFC is rich in 5-HTT sites (Mantere, et al., 2002).

Serotonergic neurons are grouped in midline raphe nuclei of the midbrain, pons and medulla. Raphe nuclei have heavy ascending serotonin projections to the cortex, thalamus, hypothalamus and limbic system (Serretti, Calati, Mandelli, & De Ronchi, 2006).

The serotonin system in BPD

Emotional lability, suicidal behaviors, and impulsive aggression are core symptoms of BPD associated with serotonergic dysfunction (Hansenne, et al., 2002). Prefrontal serotonergic neurotransmission may play a role in modulating amygdala-driven emotional

behavior. A dysfunctional serotonergic regulation could predispose individuals to the emotional disinhibition and impulsive aggression responsible for many of the volatile behaviors seen in BPD (Johnson, et al., 2003).

Neuroimaging studies have shown abnormalities of serotonergic activity in BPD in the PFC, especially the orbital and medial areas (Soloff, et al., 2000), as well as in adjacent ventromedial and cingulated cortex (Siever, et al., 1999), precisely the brain areas that seemingly account for much of the BPD symptomatology, such as impulsivity and emotional dysregulation.

Basic genetics

Simply put, a gene is a unit of inheritance containing instructions to produce a protein, even though the "one gene, one protein" paradigm has recently been shown to be too simplistic (Pearson, 2006). The physical site of a gene on a chromosome is called a "locus", where several variants of the gene, which are known as "alleles", can be present. Two or more alleles are possible at each locus in different individuals, but no more than two per individual, i.e. one on each chromosome. We inherit half of our DNA from each parent. This double heritage can be identical (producing a homozygous genotype) or different (producing a heterozygous genotype). The relative frequencies of alleles can vary substantially across populations (e.g. Gelernter, Cubells, Kidd, Pakstis, & Kidd, 1999). A specific allelic combination at a specific locus for a certain gene is called a "genotype", and the physical appearance of an organism is called a "phenotype" (Plomin, DeFries, McClearn & McGuffin, 2008). The phenotype depends upon genotype, activation and deactivation of genes, and environment. An "endophenotype" is described as an internal phenotype, e.g. something defining the individual that is not a readily visible trait, e.g. working memory capacity (Gottesman & Gould, 2003).

Genetic markers to be studied in relation to disease or endophenotypes are for example, insertion/deletion variants, variable numbers of tandem repeats consisting of nucleotide sequences organized as tandem repeat units (Jeffreys, Wilson, & Thein, 1985), and single nucleotide polymorphisms (SNPs), which are small genetic variations occurring when a single nucleotide base (adenine, thymine, cytosine or guanine) differs between individuals in a population (Braff, Freedman, Schork, & Gottesman, 2007). A combination of genetic markers within a chromosome is called a "haplotype". Specific allelic combinations at closely linked sites of a chromosome form "haplotype blocks" (Gabriel, et al., 2002).

Genetic variants within a population can be studied in a number of ways. Genome-wide association studies are examinations of genetic variation across the complete set of DNA, or genome, of large samples to find genetic variations associated with observable traits or a particular disease (Frazer, Murray, Schork, & Topol, 2009). Linkage studies are statistical measures of the association of sequence variants at different positions along the chromosome, obtained within a population of related individuals (Bearden, Jasinska, & Freimer, 2009). Genetic association studies are designed to investigate a possible association between a genetic marker and a complex disorder (Romero, Kuivaniemi, Tromp, & Olson, 2002). One approach to study genes in association with complex disorders is candidate gene analysis, where genetic variants thought to influence a disorder are studied in association with that disorder (Munafo, 2006).

Genetics, behavior and psychiatric disorders

The present decade has been called "the decade of the gene" and is considered by many to be the dawn of cognitive genetics (Pinker, 2001). Recently, substantial resources have been

dedicated to the study of the multigenetic influence on development of both well-functioning and dysfunctional cognition, and emotion, in individuals who are healthy, and in those diagnosed with different disorders such as depression. That genes strongly influence how we act is beyond question, but to define the genes that underlie specific behaviors has proven highly difficult (Holden, 2008). Also, genes interact with each other and the environment. One aspect of gene-gene interactions is epistasis, which is the modification of the effect of one gene by one or several other genes (Frazer, et al., 2009). Complicating matters further, any single biological function may be affected by multiple genes, and any single gene may play a role in several seemingly disparate functions (Holden, 2008).

Contrary to Mendelian diseases, where a single gene or a small number of genes carry a mutation that is necessary, as well as sufficient to cause a disorder such as Huntington's disease, psychiatric disorders have a more complex model of inheritance with interacting genes (Prathikanti & Weinberger, 2005), and with influence from environmental factors. To add the measurement of environmental events improves the reliability of genetic research within psychiatry (Uher & McGuffin, 2008), since social and other environmental factors alter the expression of genes in the brain, as well as behavior (Robinson, Fernald, & Clayton, 2008). Environmental influences may bring out, neutralize, or even negate a gene's impact (Holden, 2008). The effect of any genetic variant may thus be enhanced or suppressed, depending upon the context provided by other genes and the interaction of genes and the environment (Brown & Hariri, 2006). This stresses the important impact of the environment, particularly early experience, and development on the functional consequences of genetic polymorphisms, probably because gene variations affect the brain's response to such experiences (Hariri & Weinberger, 2003).

As psychiatric disorders are complex, they are not well-suited for genetic association studies. Instead, a better approach may be the definition and study of quantifiable variables, such as the specific symptoms of a disorder. Such measurable variables can be defined as endophenotypes when they have a clear genetic connection and thus better reflect biological underpinnings. Cognitive functions, as well as specific psychiatric symptoms, are excellent endophenotype candidates (Bearden, et al., 2009), and as such they may help reveal or characterize subgroups within psychiatric disorders.

Serotonergic gene variants

Serotonergic gene variants have been studied in psychiatry, as abnormalities in serotonin function have been associated with several disorders, primarily mood and anxiety disorders (Lesch & Mossner, 1998). Among many candidates, the most promising have shown to be those coding for critical proteins in the serotonin system.

The genes coding for the rate-limiting enzyme tryptophan hydroxylase (TPH) in serotonin synthesis (TPH-1, and TPH-2) have shown critical associations with psychiatric disorders (Sugden, Tichopad, Khan, Craig, & D'Souza, 2009).

Similarly, the serotonin transporter (5-HTT) gene (SLC6A4) has generated an abundant literature associating its role to a number of psychiatric disorders. The 5-HTT is also a target for drugs that are efficacious in treating these disorders (Serretti, et al., 2009), such as selective serotonin reuptake inhibitors (SSRIs).

In this thesis, variants of the TPH-1 gene and the *5-HTT* gene have been studied, since they represent crucial bottlenecks in serotonin synthesis and reuptake, which may lead to the most dramatic alterations in serotonergic neurotransmission and, thereby, also in brain functioning (Brown & Hariri, 2006).

A genetic contribution to BPD is supported by the fact that BPD tends to run in families, has a higher concordance in identical (~35%) than in fraternal (~7%) twins, and has a higher frequency in biological than in adoptive relatives (Skodol, et al., 2002; Torgersen, et al., 2000). There are even more data indicating a hereditary factor for symptom components of BPD, especially impulsivity and emotional instability (Beauchaine, et al., 2009; Skodol, et al., 2002), indicating that it may be the traits associated with the disorder, rather than the disorder itself, that are heritable. Early impulsivity is most possibly a predisposing vulnerability for both current and future difficulties with emotion regulation, and impulsivity is among the earliest emerging traits among those who later receive a BPD diagnosis (Crowell, et al., 2009).

A large quantitative twin study on personality disorders showed one genetic factor of neuroticism/negative emotionality that was associated with many different personality disorders (Kendler, et al., 2008). The authors suggest that dimensions of normal and disordered personality may, in part, result from the same genetic architecture reflecting what is known as the "five-factor model" (openness, conscientiousness, extraversion, agreeableness and neuroticism) (Bagby & Ryder, 2000), influenced by five underlying genetic factors. A second genetic factor, thought to reflect disinhibition or impulsive aggression, was quite specific with high loadings on BPD and antisocial personality disorder (Kendler, et al., 2008).

Overwhelming evidence suggests that deficits in serotonin functioning are associated with BPD-related conditions and behaviors, such as mood disorders, suicidal and nonsuicidal self-injury, and aggression (e.g. Kamali, Oquendo, & Mann, 2001). Thus, serotonergic genes have been studied for their relation with BPD, impulsive, and self-injurious behaviors (e.g. Anguelova, Benkelfat, & Turecki, 2003; Currier & Mann, 2008; Ni, Chan, Chan, McMain, & Kennedy, 2009).

One of the genes in the serotonin system that is considered to be a candidate gene for a hereditary disposition to BPD, particularly in individuals with suicidal behavior, is the gene coding for the enzyme tryptophan hydroxylase (TPH) (Roy, Rylander, & Sarchiapone, 1997). Since TPH is the rate-limiting enzyme in the biosynthesis of serotonin (Cooper & Melcer, 1961) and thus has a major function in regulating the serotonergic system, TPH variants might be related to pathogenic events resulting in dysfunction of the serotonin system. TPH variants have been related to aggression, anger, impulsivity, depression and suicidal behavior (Abbar, et al., 1992; Kunugi, et al., 1999; Mann, et al., 1997; Nielsen, et al., 1998; van den Bogaert, et al., 2006). There are two TPH isoforms, TPH-1 and TPH-2. The gene coding for TPH-1 is situated on chromosome 11p15 and the gene coding for TPH-2 is located on chromosome 12q21. TPH-2 is the predominant isoform in the adult brain, while TPH-1 is primarily active in the periphery (Sakowski, et al., 2006). Recent research (Zill, et al., 2007) suggest that TPH-1 is expressed in several human brain regions such as the frontal cortex, thalamus, hippocampus, hypothalamus and amygdala. TPH-2 is mainly expressed in the raphe nuclei and to a lesser extent in the cortex, thalamus, hippocampus, hypothalamus and amygdala in the human brain. A significantly higher expression of TPH-1 as compared to TPH-2 mRNA levels has been shown in the amygdala and hypothalamus (Zill, et al., 2007), which are relevant brain areas in BPD. A recent post-mortem study showed that TPH-1 and TPH-2 were expressed in all brain regions similarly, except for within the striatum and cerebellum, where TPH-1 was expressed at a significantly higher level than TPH-2 (Sugden, et al., 2009). The mechanisms by which TPH-1 influences serotonin levels in the brain are not yet known. However, animal studies have shown that TPH-1 seems to be important for the effect of serotonin on neuron development, because it is expressed to a significantly higher degree in the brain during the late prenatal period (Nakamura & Hasegawa, 2007). These early

developmental effects may have long-lasting effects on central serotonergic function, thereby affecting behavior and psychopathology in adulthood (Wilson, et al., 2009). A risk haplotype analysis has been used to explore variants of the TPH-1 isoform in a sample of suicidal women with BPD (Zaboli, et al., 2006). This study showed that a specific TPH-1 haplotype of six SNPs (ACGCCG) located in a region between the gene promoter and intron 7, was uniquely associated with BPD (Zaboli, et al., 2006). Another study showed that variants of TPH-1 were related to the diagnosis of BPD, independent of suicide attempter status (Wilson, et al., 2009). However, yet another study found no association between BPD and TPH-1 variants (Ni, et al., 2009).

Another candidate gene for BPD is the serotonin transporter (5-HTT or SERT) gene (SLC6A4) which maps to chromosome 17q11 (Ramamoorthy, et al., 1993), and contains a functional 43 base pair (bp) insertion/deletion polymorphism within the promoter region (5-HTTLPR) giving rise to two allelic forms, a short (*s*) and a long (*l*) variant (Heils, et al., 1996). The insertion/deletion appears to affect transcriptional rates of the *5-HTT* gene and availability of the serotonin transporter (Lesch, et al., 1996). The presence of one or two copies of the *s* allele of the 5-HTTLPR is correlated with a nearly 50 % reduction of serotonin transporter expression and function, and it appears to result in a faster reuptake of serotonin from the synaptic cleft (Serretti, et al., 2006). The *s* allele is associated with increased fear and anxiety-related behaviors (Hariri, et al., 2002; Lesch, 2007), neuroticism and impulsivity (e.g. Goodman, New, & Siever, 2004; Lesch, et al., 1996), and a greater risk for developing depression, especially following stressful life events (Caspi, et al., 2003). The vulnerability of *s* carriers to develop depression following adversity appears to be much stronger in women than in men (e.g. Brummett, et al., 2008). However, a recent meta-analysis of studies on the interaction between the serotonin transporter gene variants and stressful life events on depression found no association between the 5-HTTLPR genotype and depression (Risch, et al., 2009).

To explore the neural basis of the apparent relationship between serotonin and emotional behavior, Hariri and colleagues (for an overview, see Hariri & Holmes, 2006) have used an imaging genetics strategy with fMRI focusing on the 5-HTTLPR polymorphism. This research aimed at understanding the impact of genetically driven variation in serotonin function on the development and function of neural systems important for emotional behaviors. Most important is the amygdala, which is densely innervated by serotonergic neurons, and rich in serotonin receptors (Azmitia & Gannon, 1986; Hariri & Holmes, 2006). The studies from Hariri and colleagues (e.g. Hariri & Holmes, 2006) suggest that the presence of one or two copies of the *s* allele of the 5-HTTLPR leads to less serotonin availability and is associated with amygdala hyper-responsivity to environmental threat.

Most studies have not found an over-representation of the *s* allele in individuals with BPD as compared to healthy controls, (e.g. Pascual, et al., 2008; Tadic, et al., 2009). Nonetheless, some studies have found associations between specific features of BPD and 5-HTTLPR, such as sociability (Pascual, et al., 2007) and impulsivity (Wagner, Baskaya, Lieb, Dahmen, & Tadic, 2009).

Another functional variant of the *5-HTT* gene, rs25531, is a SNP located in close proximity to 5-HTTLPR that represents a G→A substitution (Kraft, Slager, McGrath, & Hamilton, 2005). The less common *G* variant is almost always in phase with the 5-HTTLPR *l* allele, hence appearing as a bi-allellic polymorphism of the *l* allele (*lA/lG*) (Parsey, et al., 2006; Zalsman, et al., 2006). The *G* variant leads to a reduced 5-HTT expression similar to that seen for the 5-HTTLPR *s* allele in serotonin (Zalsman, et al., 2006). Some of the inconsistent findings regarding 5-HTTLPR may in part be due to the fact that few studies have examined the joint effects of 5-HTTLPR and rs25531.

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Environmental factors in the development of BPD

Clinical data indicate adverse experiences in the development of BPD. For example, childhood trauma of sexual and/or physical abuse is common in individuals with BPD (Gunderson, 2008). Abuse may reset "stress systems," such as the hypothalamic-pituitary-adrenal (HPA) axis, and their relationships to serotonin (Skodol, et al., 2002).

A recently published longitudinal study showed that extended separations from mother before the age of five were associated with BPD symptoms in adolescence and adulthood, up to 30 years later (Crawford, Cohen, Chen, Anglin, & Ehrensaft, 2009). Early separations may lead to an insecure attachment relationship between parent and child (Rusby & Tasker, 2008). The sensitivity of parents to be responsive and available to their child is important insofar as young children have a limited capacity to regulate their physiological and emotional reactivity on their own, since these neurobiological systems are immature and need to be shaped in close relation with caregivers (Gunnar, 1998). Because early experiences occur in the context of a developing brain, neural development and social interaction are inseparably linked (van der Kolk, 2005).

Invalidation has been proposed as a risk factor to develop BPD (Kåver & Nilsonne, 2002; Linehan, 1993). An invalidating environment is intolerant toward the expression of emotional experiences, and these expressions will be met by arbitrary, inappropriate or extreme reactions. Furthermore, although invalidating environments intermittently reinforce extreme displays of emotion (since this may be the only way to invoke the environment), they simultaneously communicate to the child that such emotional expressions are unjustified and that emotions should be coped with in private and without parental support. Such an environment is not a good breeding ground to learn to identify and express emotions, and one consequence may be that a child who grows up invalidated does not learn how to understand, label, regulate, or tolerate emotional reactions; and instead learns to fluctuate between the inhibition and the extreme expression of emotions and behaviors. Other consequences may be a lack of tools to solve the problems contributing to these emotional reactions, and an impaired ability to trust own emotions and interpretations of what is going on (Crowell, et al., 2009; Kåver & Nilsonne, 2002). Marsha Linehan (1993) describes sexual abuse as the ultimate invalidation, the ultimate lack of empathy and respect.

Contribution of genes and environment in the development of BPD

There is no longer an issue whether genes play a role in psychiatric disorders, the question concerns instead what the specific gene-gene and gene-environment interactions are. Genes and environment mutually influence one another in the development and course of BPD, in that a combination of genetic factors and negative childhood experiences mold the brain and the behaviors that determine the risk for BPD. The neurobiology associated with BPD probably serves as predisposing vulnerabilities that interact with personal stressful experiences to shape and maintain the dysregulated emotional, behavioral, interpersonal, and cognitive aspects of BPD (Crowell, et al., 2009). The developing brain starts out highly interconnected across regions and is neither localized nor specialized at birth, allowing interaction with the environment to play an important role in gene expression and the ultimate cognitive phenotype (Karmiloff-Smith, 2006). It is suggested that aversive environments are more likely to worsen underlying biological vulnerabilities, whereas benevolent environments are more likely to mitigate the negative impact of these vulnerabilities (Pally, 2002).

A biosocial developmental model of BPD that takes biological disposition, learning history and their interaction into account is presented in Figure 2.
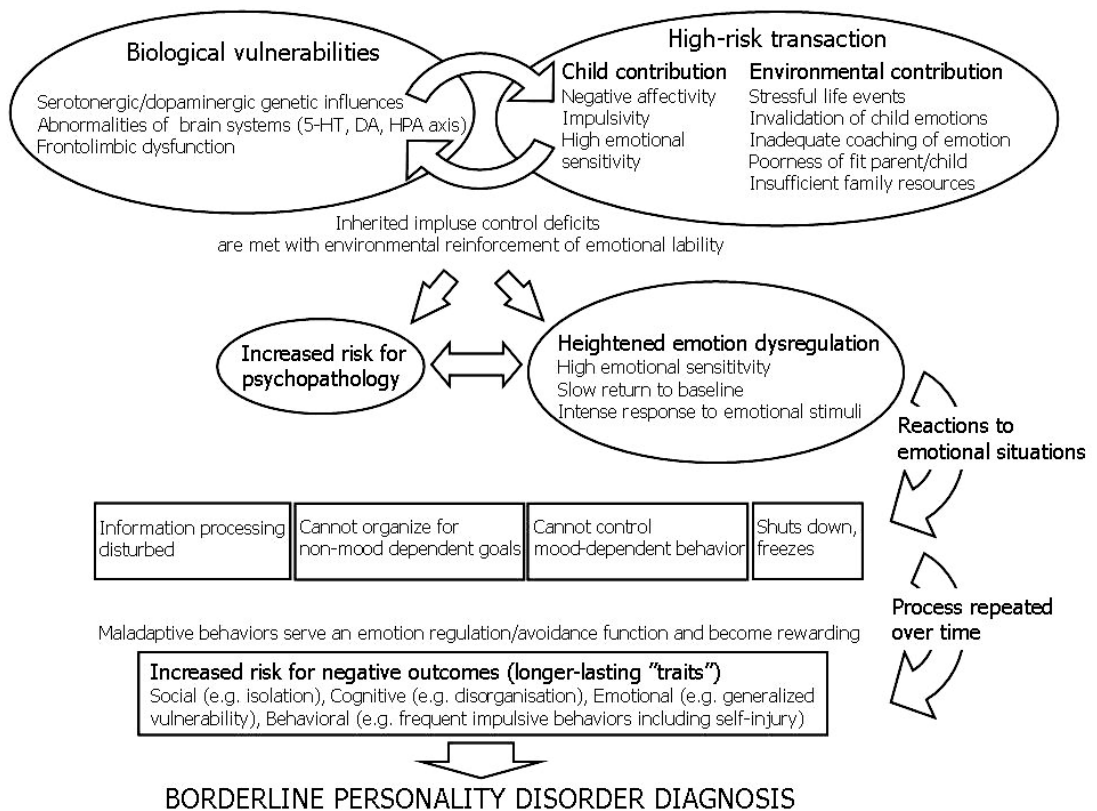
Figure 2. A biosocial developmental model of borderline personality.
5-HT = serotonin; DA = dopamine; HPA = hypothalamic–pituitary–adrenal.
Adapted from Figure 1 in Sheila E. Crowell, Theodore P. Beauchaine, and Marsha M. Linehan. A Biosocial Developmental Model of Borderline Personality: Elaborating and Extending Linehan's Theory, *Psychol Bull*. 2009 May ; 135(3): p.503.
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NEUROPSYCHOLOGY

Neuropsychology is an applied science aiming to understand how the structure and function of the brain relate to specific psychological processes, such as cognition and emotion, and behaviors. This includes attentional processes, memory functions, abstract reasoning, mental flexibility, processing speed, motor functions, and sensory-perceptual functions.

Neuropsychological functions are frequently studied via the use of neuropsychological tests. These tasks have been designed to link the performance on the task to specific cognitive processes. These tests are mostly standardized, meaning that they have been administered to a large number of individuals before being used with specific individuals, thus producing normative data. These standard scores allow for comparison and for understanding where an individual is on a normal distribution for particular functions.

The development of modern neuropsychology

The human brain in its present form is about 100 000 years old. There have been early theories on its functions, ranging from that of being a cooler of the blood (Aristotle, 384-322 BCE) to being the source of the intellect (Herophilus, 335-280 BCE) (von Staden, 1989).

The brain and how it works began to be studied in the 17th century, by men like the philosopher and scientist Rene Descartes, who suggested that mental and bodily functions are separated, and the physician Thomas Willis, who linked behavior to brain and who also published the first detailed anatomy of the brain (Gazzaniga, et al., 2009).

In the early 19th century, the Austrian physician Franz Joseph Gall introduced "phrenology", presenting some 35 functions thought to be supported by specific brain regions (Gazzaniga, et al., 2009). Phrenologists believed that the parts of the brain that represented the functions that were mostly used, would also increase in size, and form corresponding bumps that could be measured on the skull. Gall's contribution to the field of neuropsychology was the theory of localization, that different human functions are localized to specific brain regions (Marshall & Gurd, 2003).

Later that century, several neurologists published observations on individuals with different kinds of brain damage. Paul Broca, for example, described a patient who had had a stroke in his left inferior frontal lobe, and who could no longer speak, even though he understood language and could control the muscles of his mouth. Some years later, Carl Wernicke noticed a patient with a stroke in the posterior part of the left hemisphere, who spoke quite freely, but who did not understand language (Gazzaniga, et al., 2009). These findings lay the foundations of the localization theory of cerebral functioning.

At about the same time, John Hughlings Jackson reported that some of his epileptic patients at the onset of a seizure moved in a way that implied that the seizure stimulated a set map of the body in the brain, which led Jackson to suggest a topographic organization in the cerebral cortex (Gazzaniga, et al., 2009). Hughlings Jackson also proposed a hierarchical organization of the brain, and that behaviors are organized in systems distributed over wide areas of the brain (Kolb & Wishaw, 2003).

Through the discovery of methods for fixing and staining nerve tissue, cortical map makers, such as Korbinian Brodmann, studied the cytoarchitecture of the brain during the early 20th century, and supported a localized, yet interconnected view of the brain (Gazzaniga, et al., 2009).

During the first half of the 20th century, two world wars resulted in focal brain injuries in young and previously healthy individuals (Marshall & Gurd, 2003), which led to a demand for examination and rehabilitation procedures (Lezak, Howieson & Loring, 2004). Formal test methods, i.e. standardized tests and test-batteries, were developed to assess cognitive functions and dysfunctions. The French psychologists Alfred Binet and Theodore Simon had early in the century published an intelligence scale for children in order to identify pupils who needed special help in coping with school work. In 1916, the Stanford psychologist Lewis Terman released a revision of Binet's scale, called the "Stanford-Binet" for short, in which the intelligence quotient (IQ) was first used (Kolb & Wishaw, 2003). Following this pioneering work to measure cognitive abilities, a vast amount of examination techniques were developed to classify recruits for the military and to estimate educational ability (Lezak, et al., 2004). Educational testing has been well-accepted by society and led to validation studies, more reliable test methods, statistical tools for standardization and the development of normative data. Experimental studies of cognition in both healthy and brain-injured humans and animals have contributed more knowledge (Lezak, et al., 2004).

By the end of the 1950s, psychologists were a part of the assessment and rehabilitation of individuals with cognitive dysfunctions (Marshall & Gurd, 2003). Early on, much of

neuropsychological work was directed at diagnostic issues. However, the use of neuropsychological assessment as a tool for localizing brain lesions has decreased due to the development of neuroimaging techniques (Lezak, et al., 2004). Nonetheless, neuropsychological tests are still useful in the diagnostics of neuropsychiatric disorders such as ADHD and as the earliest evidence of dementia.

A common purpose of the neuropsychological assessment of today is to identify and describe an individual's cognitive and behavioral strengths and deficits and possible compensation strategies. A comprehensive neuropsychological examination includes the tested individual's background, history and present situation considered together with quantitative test scores and qualitative observations. The descriptive evaluations of the neuropsychological report are important in planning care and rehabilitation, and can serve as a pedagogic tool to educate the assessed individual and the family concerning the condition, and to set realistic goals. Neuropsychologists are also involved in rehabilitation programs for cognitive and behavioral impairments, as well as in evaluating the efficacy and possible side-effects of cognition-enhancing drugs, and the effects of neurosurgery and rehabilitation (Lezak, et al., 2004; Meyer, et al., 2001). Newer areas studied by neuropsychologists are emotions, social cognition, and decision-making, and the interaction of genetics, development and environment on psychiatric disorders (Marshall & Gurd, 2003).

The use of neuropsychological tests in research differs from a clinical neuropsychological assessment. In research, these tests are used to answer a specific question, for example "Do individuals with a diagnosis of BPD show working memory problems?". In order to draw a conclusion about working memory functions in BPD, results of performance (i.e. scores on a test) on working memory tasks are compared between a group individuals with BPD and a group without BPD. Qualitative observations are usually not of interest and these test results cannot be used for selection, counseling, or operational purposes.

Neuropsychological testing

A perfect neuropsychological test would correspond to everyday life function, prove a strong link to the operation of one particular brain region or system, show well-understood psychometric properties and have a comprehensive theory as to what it measures (Burgess, 2003). Unfortunately, like most forms of measurement, neuropsychological tests are not perfectly precise. Obtained test scores are estimates of functions, associated with some degree of measurement error (Strauss, Sherman & Spreen, 2006). In order to reduce some of the error variance, it is important to create an optimal and standardized test situation. This includes freedom from distractions, a relaxed and positive atmosphere, and that tasks are administered in a standard fashion. Many neuropsychological tests are also complex and capture several functions, which can make interpretation difficult.

To know whether or not an obtained score of a test instrument is accurate, we need to know how reliable and valid the instrument is.

Reliability is a measure of a test's stability and consistency across time and situations, i.e. that a person's test score will be similar independent of when and where the test is taken. Reliability of test scores can be studied via repeated measurements with the same instrument or by using parallel forms of a test. Interrater reliability is evaluated by comparing agreement or disagreement between independent raters administering or scoring the same test results. Internal consistency can be calculated by splitting an instrument into two halves, and then correlating these two halves. Reliability is a necessary, but not a sufficient, condition for validity.

Validity is a measure of the degree to which a test instrument indeed measures what it is intended to measure, and thus, whether interpretations based on test scores are justified.

Hence, a valid test can disclose the effect of variation in the phenomenon one intends to measure. Validity defines the meaning of the test scores, and is calculated as a correlation between the scores of the test and some other criterion representing the construct that is to be measured, e.g. other standard test methods, some practical task, or future behavior or achievement. However, even though validation is about correlation, the concept of validity is not solved by psychometric techniques or models alone (Borsboom, Mellenbergh, & van Heerden, 2004). The validity concept expresses nothing less, but also nothing more, than that a theoretically explained phenomenon exists, and that measurement of this phenomenon can be accomplished with a given test because the test scores are causally affected by variation in the phenomenon (Borsboom, et al., 2004).

Neuropsychological testing and psychotropic medication

Psychotropic drugs affect several neurotransmitter systems, and can possibly have both positive and negative effects on cognitive functioning. However, a recent study on neuropsychological functioning in individuals with BPD found no significant differences between medicated and unmedicated participants with respect to attention, working memory, learning and memory, or executive functioning (Haaland, Esperaas & Landro, 2009).

Neuropsychological functions in BPD

In the last three decades, there has been a growing interest in neurobiological factors in the development of BPD. The first studies aimed at neuropsychological functions were published in the 1980s, some of these suggesting brain dysfunction in BPD (Andrulonis, et al., 1981; Berg, 1983; Gardner, Lucas, & Cowdry, 1987). During the 1990s, some ten or so studies on neuropsychological functions in BPD were accomplished, mostly on small samples (e.g. Burgess, 1992; O'Leary, Brouwers, Gardner, & Cowdry, 1991; Swirsky-Sacchetti, et al., 1993; van Reekum, Conway, Gansler, White, & Bachman, 1993). These studies tentatively showed impairments in memory, visual, and executive functions in individuals with BPD. The body of research on cognition in BPD has increased rapidly during the 2000s (e.g. Bazanis, et al., 2002; Dinn, et al., 2004; Haaland & Landro, 2007; Lenzenweger, Clarkin, Fertuck, & Kernberg, 2004; Sprock, Rader, Kendall, & Yoder, 2000), but studies have not produced a consistent pattern of findings, and deficits have been reported for a wide range of cognitive functions, while some studies have not found any evidence for cognitive problems in BPD. Several meta-analyses and reviews have concluded that the most frequently reported cognitive impairments in BPD involve executive functions and attention and memory functions (Fertuck, et al., 2006; LeGris & van Reekum, 2006; Ruocco, 2005), proposed to reflect prefrontal dysfunctioning, particularly in the right hemisphere (LeGris & van Reekum, 2006; Ruocco, 2005). Clinical observations, on the other hand, have suggested impairments in the abilities to organize experiences, to use problem solving and decision-making tools, to predict future events, and for effective engagement in social interactions, as well as in working memory capacity and autobiographical memory specificity. In this thesis I have focused on memory and executive functions, since impairments in these cognitive aspects seem to be of particular relevance in BPD.

Cognitive functions

Cognition refers to the process of knowing, that is how information is acquired, stored, and processed, and it encompasses those mental processes that allow us to perform everyday

functions, such as the ability to remember what to buy for dinner and to help your child solve her math problems for home work.

Memory functions

Memory is not a single concept, but can be divided into several processes, temporal storage and system components (Squire & Knowlton, 1996).

Memory processes consists of the acquisition, consolidation, storage, and retrieval of information. Memory can also be separated by how long we remember learned information, as for milliseconds to seconds (sensory memory), for seconds to minutes (short-term memory) or for days or years (long-term memory) (Gazzaniga, et al., 2009).

Working memory is an active form of short-term memory representing a limited-capacity store of information that is to be manipulated (Purves, et al., 2008).

Long-term memory can be classified into implicit nondeclarative and explicit declarative memory. Nondeclarative memory encompasses skill learning (procedural memory), priming of previously exposed perceptions (perceptual priming), associations of stimuli (conditioning), and between responses and stimuli (operant conditioning), and habituation/sensitization (non-associative learning) (Gazzaniga, et al., 2009). Declarative memory can be further parted into memories of facts (semantic memory) and memories of events (episodic memory) (Tulving, 2002).

Autobiographical memory

One kind of episodic memory is autobiographical memory, which concerns recollections of personally meaningful events, providing building-blocks for constructing the history of one's life. Autobiographical memories serve as models of oneself, other people and the surrounding world, and are thus important for everyday functioning. According to Conway and Holmes (2004), the ultimate function of autobiographical memory may be goal processing, to allow human beings to imagine the future and to make plans. Specific personal memories have been shown to be of importance for social problem-solving skills, because they provide a database that is helpful in suggesting solutions to social dilemmas (Williams & Broadbent, 1986). Also, if emotional experiences are processed with greater specificity, it has advantages for improved emotion regulation as compared to emotional processing that is overgeneral or non-specific (Linehan, Bohus & Lynch, 2007).

A lack of specificity in personal memories in BPD was found in two studies (Jones, et al., 1999; Startup, et al., 2001), but two other studies found no evidence for overgeneral memories among individuals diagnosed with BPD (Arntz, Meeren, & Wessel, 2002; Renneberg, Theobald, Nobs, & Weisbrod, 2005). Yet another study reported that only those individuals with BPD who also had a diagnosis of depression retrieved less specific memories than controls (Kremers, Spinhoven, & Van der Does, 2004). Thus, it remains unclear whether a diagnosis of BPD, depression, or PTSD is the primary correlate of reduced specificity in autobiographical memory.

Executive functions

Executive functioning is a broad concept for the control of behaviors (self-regulation) adaptive to non-routine situations. Executive functions enable the evaluation of alternative actions, flexibility in strategies, and the inhibition of irrelevant behavior. Although different executive functions are separable, they are also correlated, showing both diversity and unity

(Miyake, et al., 2000). Executive functions also operate on other cognitive functions (Miyake, et al., 2000).

Even mild deficits of executive functions may have a disastrous impact upon effectiveness in everyday life, and upon relationships with others (Burgess, 2003). Impaired executive behavior typically involves problems in many aspects of executive function (Lezak, et al., 2004).

Executive problems that have been documented in individuals with BPD are difficulties with executive control (Fertuck, Lenzenweger, & Clarkin, 2005), executive inhibitory mechanisms (Nigg, Silk, Stavro, & Miller, 2005), decision-making (Bazanis, et al., 2002; Haaland & Landro, 2007), and social problem-solving (Bray, Barrowclough, & Lobban, 2007).

Executive functions are primarily associated with different regions of the frontal lobes, but also with a wide cerebral network including subcortical structures and thalamic pathways (Jurado & Rosselli, 2007).

Working memory

Working memory refers to a limited-capacity store of information that is to be updated and manipulated (e.g. Purves, et al., 2008). This information can be acquired from sensory inputs or from long-term memory. Working memory is about attending to actively held relevant information, and being able to keep on doing this in the face of distraction (Gazzaniga, et al., 2009), that is active maintenance and executive control. Working memory is thus a concept close to both attention and executive functions. The function of working memory is to guide goal-directed thoughts and behavior (Westerberg, 2004). Alan Baddeley (e.g. 1996) has suggested a three-part working memory system encompassing a central executive mechanism that controls two subordinate slave systems involved in rehearsal of either phonological or visuospatial information. Baddeley has later added a forth component to working memory, a multimodal store capable of integrating information from a range of systems including long-term memory, termed episodic buffer (Baddeley, 2000). Temporary storage of information is necessary for performing a wide range of other cognitive operations, including comprehension, learning, reasoning, and planning (Baddeley, 1996).

Goal-oriented behavior

Goal-oriented behavior is about making clear one's personal wants or needs and how one is to go about in order to fulfil these needs. This includes motivation, goal clarification, formulating and carrying through intentions, application of strategies, prospective memory, and regard for long-term consequences (Worthington, 2003).

Planning abilities

To be able to achieve a goal, one has to be able to identify and organize the necessary steps to do this. This includes the ability to create alternatives and the ability to compare and choose between them. It also involves the ability to anticipate temporal sequencing (Lezak, et al., 2004). Planning is closely related to problem solving and decision-making.

Problem-solving skills

To solve a problem, one has to orient to and define the problem situation, to analyze causes, to generate solutions, assess and choose between multiple options, to reason, and to decide on a solution, to implement it, and to evaluate whether the problem was solved or not.

Decision-making

Human beings make decisions of varying importance every day. In making a decision, several choices are compared, and hypothetic expectations can be formed and evaluated about possible outcomes of these choices (Purves, et al., 2008). When making a decision, we aim to choose the outcome that has the highest probability of success and that best fits with our goals and values in life. However, complete knowledge about all possible outcomes is seldom possible, and thus every decision involves a certain amount of uncertainty and risk. To gather information before making a decision is an attempt at reducing this uncertainty and risk. Many decisions must be made in complex situations involving other people. Social decision-making has been much studied within game-theory (Purves, et al., 2008).

Inhibition

Inhibition is a control process concerning the deliberately intended suppression of dominant, automatic, or prepotent responses when necessary (Miyake, et al., 2000). Insufficient inhibition may be devastating for an individual's social life. Inhibition is also about preventing irrelevant information from interfering with other processes, such as working memory (Purves, et al., 2008).

Concept formation

Concept formation is a process by which a person organizes specific experiences into useful generalizations, which contributes to a better understanding of the world we live in, as well as of ourselves (Fine, et al., 2008; Hartman & Stratton-Salib, 2007). This ability to assume an abstract attitude, to formulate relevant concepts and generalizations, attaches meaning to the world and guides behavior, especially in non-routine and demanding situations.

Shifting

Shifting is about flexibility, to be able to shift between tasks or mental sets when necessary (Miyake, et al., 2000). Shifting is supposed to be an important aspect of executive control. Shifting may reflect the ability to engage and disengage in appropriate task sets per se, but may also (or even instead) involve the ability to perform a new operation in the face of proactive interference from previously having performed a different operation in response to the same kind of stimuli (Miyake, et al., 2000).

Monitoring

To monitor is to be aware of one's own performance by continuously observing one's possible efficacy and any changes to the situation. Monitoring is an evaluation that allows for predicting results and thereby regulating one's behavior in order to maximize one's potential to succeed.

Emotional functions

Emotions are central to human survival and adaptation, and involve neurophysiological processes, behavioral expressions, and subjective experiences. Human feelings reflect the subjective experience of bodily states (Panksepp, 1998; Damasio, 1999). Basic emotions, universal across cultures (and in many other species, too), are anger, fear, sadness, joy, surprise, and disgust (Ekman, 1992). Emotions focus attention onto what is relevant at the present moment, and serve as guides to action in that they tend to trigger certain perceptual, cognitive, and behavioral processes. Further, emotions give value to what we experience in the way that we approach what we like and avoid what we dislike (Öhman, 2006).

Moods are emotional states that last for hours, days or longer (Ketai, 1975). For example you may wake up feeling a bit down and stay that way for most of the day.

A dual-process model of social/emotional cognition has been suggested, with a separation between a "reflexive" and a "reflective" neural system (Öhman, 2006). The former, including the amygdala, superior temporal sulcus, orbitofrontal cortex, dorsal anterior cingulate and basal ganglia, supplies an automatic, rapidly operating emotional response; while the latter, incorporating the lateral and medial prefrontal areas, the medial temporal lobe and the rostral anterior cingulate, renders a more graded, experience-based, but slower-responding emotional evaluation (Koenigsberg, et al., 2009).

Emotional dysfunction in BPD

Even though emotions make life worth living and are essential to help us decide which actions should be prioritized, they may also make life difficult to cope with, if you lack the proper tools to regulate them. The regulation of emotions, especially potentially destructive ones such as anger, is important for well-being, social functioning, and health. In BPD, emotion regulation is frequently a difficult task and emotions may be both under- and overregulated (Kåver & Nilsonne, 2002). Emotions must be relatively short-lived to be adaptive in continually changing circumstances (Purves, et al., 2008). However, many individuals with BPD show a slow and delayed return to emotional baseline (Linehan, Bohus & Lynch, 2007).

Individuals with BPD may be primed to overanticipate and overreact to criticism or rejection, but they may also misinterpret disinterest or inattention from others as directed at them personally. Moreover, resulting states of intense negative emotions are difficult to overcome due to impairment in the usual cortical capacity to downregulate or inhibit this limbic-driven emotionality or impulsivity (Oldham, 2009b).

Persistence of sadness and anxiety, as well as emotional shifting between anxiety, sadness and anger, are parts of the emotional dysregulation seen in persons with BPD (Reisch, Ebner-Priemer, Tschacher, Bohus, & Linehan, 2008). Because of frequent mood swings, BPD has been labeled an "emotion-regulation disorder" (Linehan, 1993).

Individuals with BPD have shown an impaired ability to understand emotional information, in addition to problems with regulating emotions (Hertel, Schutz, & Lammers, 2009). The emotional instability in BPD may be related to a heightened attention or sensitivity to social-emotional cues in interpersonal relations, a tendency to self-referential emotional processing or to dysregulated emotional processing mechanisms (Koenigsberg, et al., 2009).

In an fMRI study by Koenigsberg and colleagues (2009), individuals with BPD showed different patterns of neural activation during the processing of emotional pictures than those of healthy controls. BPD persons responded to negative and positive social-emotional scenes with a hyperarroused visual processing system, and with a more activated premotor cortex. In

response to negative stimuli, persons with BPD appeared to show greater activity in the amygdala, fusiform, precuneus and parahippocampal regions, while healthy controls mobilized dorsolateral and insular regions instead. The authors interpret this as a use of a more reflexive, hypervigilant and action-prone system to process social emotional stimuli in BPD individuals, which may help explain the greater emotional sensitivity and reactivity seen in these individuals, whereas controls employ a more reflective and less reactive network (Koenigsberg, et al., 2009).

TREATMENT OF BPD

The fact that patients with BPD have been considered "difficult" and have in the past had a reputation for being manipulative and exploitative may be due to early psychoanalytically oriented interventions that made these patients worse with a blame-the-victim idea (because the therapist felt inadequate and deskilled), leading to increased anger and behavior problems that were hard to manage (Gunderson & Hoffman, 2005; 2008; Linehan, 1993).

Individuals with BPD often receive a mixture of different treatments, which generally includes extensive use of medications for which there is not a good evidence-base. This undiscriminated treatment is often not effective, and BPD patients become understandably discouraged and skeptical (Oldham, 2009a).

A complex disorder such as BPD calls for active and focused interventions including several components such as skills training, psychoeducation, and well thought-out, carefully monitored pharmacology. A new climate of understanding and treatment, containing newer forms of psychotherapeutic interventions directed at BPD, seems to be especially promising. Research and innovative treatment strategies during the last decade have proven that BPD is a highly treatable disorder and that individuals with this diagnosis can learn to live rewarding lives (Gunderson & Hoffman, 2005). A Cochrane review showed that dialectical behavior therapy (DBT) (Linehan, 1993), which contains clear treatment goals and a range of treatment strategies such as validation, around-the-clock telephone coaching, skills training, cognitive modification, exposure to emotional cues, reflection, and acceptance, seems to function on a wide array of outcomes, e.g. hospital admission (Binks, et al., 2006b). DBT teaches these skills in a skills training group, and these skills are later applied in individual sessions and homework (Goodman, Hazlett, New, Koenigsberg, & Siever, 2009). Psychoanalytically oriented outpatient therapy also seems to decrease admission and the use of prescribed medication and to increase social adjustment (Binks, et al., 2006b). However, the small size of the included studies limit confidence in these findings, making additional well-designed studies needed (Binks, et al., 2006b). Schema-focused therapy is another intervention that seems to be both efficient and cost-effective for BPD. It is founded on the principles of cognitive-behavioral therapy. The goal is to change destructive life patterns, or schemas, using cognitive, behavioral, and emotion-focused techniques (Farrell, Shaw, & Webber, 2009; van Asselt, et al., 2008).

Evidence of the effects of commonly prescribed drugs is poor (Binks, et al., 2006a). Antidepressants are often employed in routine care, and trial evidence suggests that there may be some positive effects (Binks, et al., 2006a). Specific serotonin reuptake inhibitors (SSRIs) used to target depressive symptoms seem to be more effective in reducing anger and impulsivity, and possibly also mood swings, in BPD (Paris, 2009).

AIMS OF THE THESIS

The general intent of this thesis was to study neuropsychological functions that might be of relevance for the understanding and treatment of women with BPD who have made several suicide attempts. This was accomplished by comparing female BPD individuals who had a history of suicide attempts with healthy control participants on relevant functions and their relations to co-occuring psychiatric disorders and symptoms, traumatic experiences, suicidal/self-injurious behavior, and serotonergic-related gene variants. To achieve this object, more specific purposes were formulated.

The specific objects were to:

- Study the retrieval of autobiographical memory and social problem-solving performance in the BPD group, including the role of concurrent diagnoses of depression and/or PTSD. Additionally, the relationships between autobiographical memory, social problem-solving skills, and co-occuring psychiatric disorders, traumatic experiences, and suicidal/self-injurious behavior were examined in the BPD group (Study I).

- Investigate specific executive dysfunctions of concept formation, goal maintenance, planning ability and working memory in the BPD group, and to study possible associations between these executive dysfunctions and suicidal/self-injurious behavior (Study II).

- Examine emotionally controlled decision-making in the BPD group, and to study the relationship between decision-making and a haplotype of the TPH-1 gene, of relevance for serotonin synthesis (Study III).

- Analyze the relationship between core borderline symptoms, depression, anxiety and obsessive-compulsive behavior, as well as the lifetime incidence of suicide attempts and self-harming acts, and 5-HTTLPR polymorphisms of relevance for serotonin reuptake (Study IV).

MATERIALS AND METHODS

Participants

All participants provided informed consent that was approved by the ethical committee at the Karolinska Institutet, in agreement with the Declaration of Helsinki.

Research participants with borderline personality disorder

Fifty-one women with a diagnosis of BPD were recruited between June 1999 and December 2002, for neuropsychological testing from the treatment outcome study "Stockholm county council and Karolinska Institute Psychotherapy project for suicide-prone women" (SKIP) prior to treatment start. The diagnostics were performed by trained psychiatrists, using the SCID-I and -II interviews. All 51 women (mean age = 30.2 years, SD 8.1, mean education level = 12.0 years, SD 2.1) were diagnosed as having BPD, based on DSM-IV criteria. For Study IV, data from 77 SKIP participants were analyzed.

The SKIP project is a randomized controlled trial, comparing the efficacies of two forms of psychotherapy, and general psychiatric care (treatment as usual). The psychotherapeutic methods are DBT (Linehan, 1987; Lynch, Trost, Salsman, & Linehan, 2007) and a modification of the transference focused therapy (Kernberg, Yeomans, Clarkin, & Levy, 2008), called "object relations therapy". Participant inclusion in the SKIP project started in June 1999 and continued until December 2004. Follow-up analyses are in progress and a five-year follow-up will be completed during 2009.

Inclusion criteria to enter the SKIP study were to speak and understand Swedish, to be between 18 and 50 years old, and to plan to stay in the Stockholm county during the upcoming years. Exclusion criteria were current diagnoses of substance dependence, a psychotic disorder or a major depressive illness with melancholic features, evidence of dementia or other irreversible organic brain syndrome, or a life-threatening eating disorder.

The participants were also selected to have engaged in two or more lifetime suicide attempts with at least one attempt having occurred within the six-month period prior to referral to the study. The reason for this was to find efficient treatment strategies for the patients who are most difficult to treat, and a higher rate of suicide attempts is associated with more impaired individuals who require more psychiatric care (Brodsky, Groves, Oquendo, Mann, & Stanley, 2006).

A total of 162 women with BPD were invited to take part in the SKIP project. Of these individuals, 14 declined to join the study, 41 were excluded due to not fulfilling inclusion criteria or to fulfilling exclusion criteria and one completed suicide before joining the study. Thus, out of 162 persons, 65% (106) took part in the SKIP study.

The recruitment period for neuropsychological testing was interrupted between July 2000 and September 2002 due to the investigator's maternity leave. During the remaining time, all SKIP participants were consecutively invited to join in the neuropsychological testing. Two participants declined, and two others did not show up at appointments, while a further two only went through with the first neuropsychological testing session. Thus, out of 57 women, 89 % (51) participated in the study.

Many of the BPD participants also qualified for other DSM-IV psychiatric diagnoses. Information on comorbidity for the 51 participants who took part in the neuropsychological testing is presented in Table 2 and Table 3. It might seem difficult to draw conclusions on BPD when the sample contains individuals with so many co-occuring diagnoses. This is, however, representative of the general clinical BPD population (Lieb, et al., 2004). There are hardly any "pure" BPD patients.

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The majority of participants reported use of psychotropic medication, mostly SSRI-drugs (N=27), benzodiazepines (N=16), and/or neuroleptics (N=15). Because medication with psychotropic drugs may constitute a potentially confounding variable on neuropsychological test results, BPD participants on SSRI-medication, benzodiazepines, and neuroleptics, respectively, were compared with those participants who did not medicate with these drugs. There were no significant differences found between these groups on any of the neuropsychological tasks.

Table 2. DSM IV Axis I diagnoses (Clinical mental disorders except personality disorders and mental retardation)

Diagnosis	N
Depression	34
Post-traumatic stress disorder	23
Generalized anxiety disorder	12
Panic disorder with agoraphobia	12
Bulimia nervosa	10
Panic disorder	10
Social phobia	8
Dysthymia	7
Specific phobia	7
Anxiety disorder UNS	5
Anorexia nervosa	4
Obsessive-compulsive disorder	4
Bipolar disorder	3
Agoraphobia	2
Body dysmorphic disorder	1
Schizoaffective syndrome	1

Table 3. DSM-IV Axis II diagnoses (Personality disorders and mental retardation)

Diagnosis	N
Phobic PD	13
Paranoid PD	8
Histrionic PD	4
Obsessive-compulsive PD	4
Antisocial PD	3
Dependent PD	3
Narcissistic PD	2
Schizotypal PD	1

Comparison participants

The comparison group consisted of 30 women who were slightly younger (mean age = 25.5 years, SD 10.0, as compared to mean age = 30.2 years, SD 8.1 for the BBD group), but well-matched for educational level to the BPD group (mean education level = 12.8 years, SD 1.7, as compared to mean education level = 12.0 years, SD 2.1 for the BPD group). Since many of the women with BPD had terminated their education early, it was hard to find controls with matching education levels. Hence, because education is more closely associated

with cognitive functions than age, it was considered the more important matching variable, which resulted in a slightly younger control group.

Advertisements concerning the study and the need for controls were put up in grocery stores, bus stops, libraries and similar places. The responding women filled out the SCID II-screening questionnaire (a comprehensive self-report version of the Structured Clinical Interview for DSM-IV that has shown good agreement (kappa 0.78) with the interview (Ekselius, Lindstrom, von Knorring, Bodlund, & Kullgren, 1994). Five points or more on the borderline personality scale, as well as traumatic experiences, led to exclusion from the study. These actions were taken in order to make the diagnosis of BPD and trauma to be specific to the BPD group. The comparison participants were paid for their participation.

Neuropsychological tests

Memory functions

One memory test was included to evaluate the specificity of autobiographical memory.

The Autobiographical Memory Test (AMT)

To investigate the participants' ability to recollect specific events from their own lives, the Autobiographical Memory Test (AMT), as adapted by Williams and Broadbent (1986), was used in a version with 36 cue words, obtained from Professor JMG Williams in 1998. The AMT is the most widely used method to study autobiographical memory (Williams, et al., 2007), and it consists of an equal number of positive, negative and neutral cue words, such as proud, hopeless, or grass, read aloud to the respondents. Respondents were instructed to retrieve a personal memory located in a specific place at a specific time, which was cued by the word. A time limit of 30 seconds was set for the beginning of a memory report. A specific memory was considered to be a recollection of an event that took place on a particular day. Memories of events that happened over extended time periods were scored as extended memories. Recollections of repeated events were considered to be categoric memories. Mere semantic associations to the words, that held no component of personal memory, were scored as associations. The absence of responses, as well as memories that began to be reported after the time limit of 30 seconds, were scored as omissions.

An interrater reliability calculation showed an intra-class correlation coefficient of .99 for specific responses.

Executive functions

Eight tests of executive functions were included in this thesis, meant to cover different aspects of the concept.

The Means-End Problem Solving (MEPS) Procedure

The MEPS Procedure (Platt & Spivack, 1989) is a frequently used method to study interpersonal problem solving. It involves stories of social dilemmas to be solved by the participant. The MEPS-stories present both a problem to be solved, and an end describing the goal that is to be reached. The task of the respondent is to conceptualise the ideal solution and to describe the means for reaching the stipulated goal.

A version of five problem situations (Hawton, Kingsbury, Steinhardt, James, & Fagg, 1999) was used in Study I. Each of the five stories was read aloud to the respondent and she

was told to say what she would do if she was put in this situation to arrive at the defined goal. The mean of the total number of steps to reach the goal of each story, and experimenter ratings of effectiveness, were scored according to the scoring guidelines of Hawton et al. (1999). An interrater reliability calculation showed intra-class correlations of .98 for total number of relevant means and .77 for effectiveness.

Difficulties uncovered by this procedure have been related to real-life social problem-solving behavior (e.g. Williams, Barnhofer, Crane, & Beck, 2005)

The Wisconsin Card Sorting Test (WCST)

In the WCST, participants are presented with two decks of 64 cards each with the instruction to match these to four stimulus cards. The participants are not told how to match the cards, but receive feedback whether a particular match is right or wrong. The principles of matching change, and the participants are expected to adjust their strategy based on the feedback provided by the examiner.

The WCST is a complex task measuring the ability to form abstract concepts, to shift and maintain set, and to use feedback (Strauss, et al., 2006). The successful completion of the test relies upon a number of intact cognitive functions, including attention, working memory, general reasoning and visual processing. Poor performance on such a complex task can thus arise for many different reasons.

However, the WCST is considered a test of executive function in that it requires strategic planning, organized searching, goal-oriented behavior, shifting, and inhibition of impulsive responding (Strauss, et al., 2006). It provides a number of sub-scores rendering information on several problem-solving related behaviors, including perseverations and number of categories achieved (Strauss, et al., 2006).

Performance declines with age, is slightly influenced by education, but not gender (Strauss, et al., 2006).

Test-retest reliability is hard to calculate for the WCST, since after a person has figured out the category sorts and shift principle, a subsequent administration of the WCST will no longer measure problem solving (Lezak, et al., 2004). The WCST has an excellent interrater reliability (intraclass correlations above .83) (Greve, 1993; Heaton, Chelune, Talley, Kay, & Curtiss, 1993), and a large number of factor analytic studies have confirmed a three-factor solution including the ability to shift-set, problem solving/hypothesis-testing, and response maintenance (Greve, Stickle, Love, Bianchini, & Stanford, 2005). Other studies have shown performance on the WCST to be significantly predicted by shifting ability, without explaining the contribution from other types of executive functions (e.g. Miyake, et al., 2000). Although this seems reasonable, the specific cognitive processes underlying WCST performance need to be established (Strauss, et al., 2006).

Results on the WCST are associated with everyday life functioning, thus providing ecological validity (Burgess, Alderman, Evans, Emslie, & Wilson, 1998).

The WCST performance is primarily associated with activation of the dorsolateral prefrontal cortex, as well as the ventromedial and orbitofrontal cortices (Alvarez & Emory, 2006).

The Tower of Hanoi

The Tower of Hanoi consists of three upright pegs, and five discs of different sizes which can be put onto any peg. The test starts with the discs stacked in order of size on one peg, smallest at the top, thus making a conical shape. The participants are required to move a stack

of five discs, one at a time, to one of the other pegs, while not placing any disc on top of a smaller one. The task shall be accomplished with the fewest possible moves.

It is designed to measure sequential planning ability and problem solving (Lezak et al., 2004). It also taps into response inhibition and working memory (Miyake, et al., 2000; Zook, Davalos, Delosh, & Davis, 2004).

The retest reliability of the Tower test is low, probably due to learning and practice effects. The internal consistency is marginal (Strauss, et al., 2006).

This test has been shown to engage the right dorsolateral prefrontal cortex, as well as bilateral parietal and premotor areas (Fincham, Carter, van Veen, Stenger, & Anderson, 2002).

The Zoo Map Test

The Zoo Map Test, from the Behavioural Assessment of the Dysexecutive Syndrome test battery (BADS) (Alderman, Burgess, Emslie, Evans & Wilson, 1996), is a measure of the ability to form and carry out plans, in which the participants are given a map of a zoo and are instructed to plan a route that will take them to designated places, while respecting a set of rules. In the first high-demand version, the participants are not aided by external structure. In the second low-demand version the participants simply follow a concrete, externally imposed strategy to plan the route.

This test has been shown to have a good ecological validity considering daily-life executive function and it has an interrater reliability of 0.97 for both the first and the second version (Alderman et al., 1996).

The Modified Six Element Test

The Modified Six Element Test from BADS (Alderman et al., 1996) is a multitasking test in which six different tasks are to be carried out during a time period of ten minutes without breaking a given rule, and where the degree of adequate performance has to be decided by the participant herself. It measures how well the participant organizes herself and depends upon the ability to flexibly apply strategies (Burgess, 2000). It also taps into prospective memory (Burgess, et al., 1998). A key characteristic of successful performance on the test is the ability to create and subsequently activate delayed intentions (Burgess, Veitch, de Lacy Costello, & Shallice, 2000).

The test has an interrater reliability of 1.00 (Alderman, et al., 1996) and test results have been consistently related to performance in everyday planning and organization, providing clear support for its ecological validity (Burgess, et al., 1998; Burgess, et al., 2000).

The Rey Complex Figure Test (RCFT) Copy trial

The RCFT Copy trial is a measure of visual-constructional ability, which permits the assessment of planning and organizational skills as well as problem-solving strategies (Waber & Holmes, 1986). These variables have been found to be significantly correlated with traditional executive measures (Shin, Park, Park, Seol, & Kwon, 2006).

The participants are presented with a printed stimulus card of a complex geometric figure that consists of rectangles, triangles, crosses and various other details, and are asked to copy the figure as precisely as possible.

Performance on the RCFT declines slightly with age, but does not seem to be correlated with education or gender (Strauss, et al., 2006). One study showed that impulsive individuals followed a less well-organized plan on the RCFT (Cornell, Roberts, & Oram, 1997).

A median interrater reliability coefficient of 0.94 has been reported (Meyers & Meyers, 1995), as has good construct validity (Meyers & Meyers, 1995; Poulton & Moffitt, 1995).

Block Design

Block Design from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981) is a test of visual-spatial ability in which the participants replicate patterns printed in smaller scale on cards by putting sets of red and white blocks together.

The Block Design is sensitive to prefrontal brain damage (Lezak et al., 2004) and requires executive functions such as planning and organization as well as the ability to apply these skills in a quick, efficient manner.

It has a split-half reliability coefficient of 0.86 and a test-retest reliability coefficient of 0.82 (Kaufman & Lichtenberger, 1999).

Digit Span Backwards and Block Span Backwards

Digit Span Backwards from the Wechsler Adult Intelligence Scale-Revised (WAIS-R) (Wechsler, 1981) and Block Span Backwards from WAIS-R as a neuropsychological instrument (WAIS-R NI) (Kaplan, Fein, Morris & Delis, 1991) are measures of verbal and visual working memory, respectively. In Digit Span Backwards, consecutively longer series of digits are read aloud at the rate of one digit per second. The respondents' task is to repeat the digits in an exactly reversed order. In Block Span Backwards, the examiner points to consecutively longer series of an unstructured array of ten identical, blue blocks affixed to a white board. The respondents' task is to point to the blocks in an exactly reversed order. The tasks go on until the participants fail to repeat two trials of equal length.

The Digit Span has a split-half reliability coefficient of 0.90 and a test-retest reliability coefficient of 0.83 (Kaufman & Lichtenberger, 1999).

The Iowa Gambling Task (IGT)

The IGT is constructed to simulate real-life social or emotional decision-making (Bechara, Damasio, Damasio, & Anderson, 1994) and was initially designed for evaluating the effects of damage to the ventromedial prefrontal cortex (VMPFC) (Bechara, Damasio, Tranel, & Damasio, 1997). The performance on the IGT is supposed to be influenced by somatic markers. Somatic markers are biasing signals from the body suggested to aid in emotional decision-making. Somatic states include sensations from the viscera, internal milieu, and the skeletal and smooth muscles (Damasio, 1994). Through experience, we learn to associate physiological states with rewarding or punishing events, and these bodily states give positive or negative values to events. These types of associations are stored as somatic markers, particularly in the VMPFC. During future decision-making, somatic-marker associations are reinstated physiologically and help to reduce the problem-space by guiding behavior to the selection of the appropriate action. Perception of somatic state information thus makes us more likely to approach or withdraw from a situation (Damasio, 1994).

According to Guillaume and colleagues (2009), the IGT requires both emotional processing and cognitive processing.

Participants are presented with four decks of cards. They are instructed to continuously pick cards from any desk, and they are told that each time they choose a card they will win some game money, and sometimes they will also lose some money. Thus, some decks are "bad decks", and other decks are "good decks", because some will lead to losses over the long run, and others will lead to gains. The two "bad decks" are risky (large rewards and even

larger punishments) while the "good decks" are safer (small rewards and even smaller punishments). The task is completed after 100 picked cards. In order to reach the goal of earning as much money as possible, participants have to learn to avoid the bad decks and consistently pick cards from the good decks. The dependent variable on this task is the net score, that is, the total number of cards selected from good minus the total number of cards selected from bad decks.

There have been no studies on the reliability of the IGT, but several studies have shown learning effects between trials (Buelow & Suhr, 2009). Some studies have found difficulties on the IGT to be specifically associated with damage to the VMPFC, while others have not. Overall, the results of lesion and imaging studies show a link between IGT impairment and damage to the frontal cortex and amygdala, while damage to other areas of the brain is not associated with IGT impairment (Buelow & Suhr, 2009). More selections are made from advantageous decks with increasing developmental age, supporting the IGT's validity as a measure of executive functioning, even though mixed results have been found when performance on the IGT is compared with performance on other measures of executive functioning (Buelow & Suhr, 2009). Tentative results from clinical studies suggest a link between IGT and real-world risky behaviors, including substance abuse, gambling, and psychopathic behavior, indicating ecological validity of the IGT (Buelow & Suhr, 2009).

The procedure of neuropsychological testing

The neuropsychological tests were administered individually at two sessions of two hours each with a total testing time of four hours. The WAIS-tests, the Tower of Hanoi, the RCFT, the MEPS, and the Zoo Map Test were administered at the first session, while the WCST, the AMT, the IGT, and the Modified Six Element Test were administered at the second session. The tests were administered in the same order for all the participants. The second session usually took place within two weeks of the first.

Clinical methods

The SCID-I-interview

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) (APA, 1994) is a semistuctured interview for making the major DSM-IV Axis I diagnoses, which was administered by trained psychiatrists to formally assess the presence of current diagnoses of PTSD and depression among the individuals with BPD. The questions related to PTSD were also used as a measure of trauma exposure. Trauma was defined as sexual or physical abuse before the age of 18 and/or early separation from significant others.

The Karolinska Affective and Borderline Symptoms Scale as a Self-rating instrument (KABOSS-S)

The KABOSS is a 27-items symptoms scale designed to assess psychiatric symptoms concerning depression, anxiety, obsessive-compulsive behaviors, and borderline personality disorder (Andersson, et al., unpublished manuscript). KABOSS is an extension of the CPRS Self-rating Scale for Affective Syndromes (CPRS-S-A) (Svanborg & Åsberg, 1994) taken from the Comprehensive Psychopathological Rating Scale (CPRS) (Åsberg, Montgomery, Perris, Schalling, & Sedvall, 1978). The CPRS-S-A is used to rate the symptom degree of depression, anxiety and obsessive-compulsive behaviors, and the KABOSS contains eight additional statements relevant for BPD concerning mood swings, ability to understand one's own feelings, self-control, ability to comfort oneself, feelings of abandonment and emptiness, self-image, and reality presence (Andersson, et al., unpublished manuscript).

Each item is scored on a Likert scale from 0 (no presence of the symptom) to 6 (a severe grade of the symptom). The CPRS-S-A has been well-accepted by patients (Svanborg & Åsberg, 1994) and has shown high correlations between self-ratings and ratings by psychiatrists on the original, interview-based subscales of depression (r = 0.83) and anxiety (r = 0.76) from the CPRS (Mattila-Evenden, Svanborg, Gustavsson, & Åsberg, 1996).

The aim of the KABOSS scale is to assess symptom severity over time, since the symptoms of BPD may fluctuate and vary in intensity. KABOSS yields four factor analytically defined scores reflecting depression, anxiety, obsession-compulsion and borderline symptoms, respectively.

The Suicide Attempt Self-Injury Interview (SASII)

The SASII is an extensive structured interview about numbers of suicidal and self-injurious acts during the life-time and during the previous year, and also regarding details of such situations described by the respondent (Linehan, Comtois, Brown, Heard, & Wagner, 2006). The SASII was formerly known as The Parasuicide History Interview (Brown, Comtois, & Linehan, 2002). It was used here only to record the frequency of suicidal acts, and self-harming acts with no suicidal intent, of the respondents. These acts were scored as 0 if the respondent responded "never", 1 if less than 5 times, 2 if 5 to 9 times, 3 if 10 to 20 times and 4 if more than 20 times.

The Karolinska Interpersonal Violence Rating Scale (KIV)

The KIV (Forslund & Ahnemark, unpublished manuscript) was administered to record whether and to what extent the participants with BPD had been a victim of violence as children (6-14 years of age) and/or as adults (15 years and older). The extent of violence is scored on a Likert scale from 0 (no violence) to 6 (serious violence).

The procedure of clinical testing

The clinical tests were administered by psychiatrists and psychologists within the SKIP-project on different occasions during a period of about a month concurrently with the neuropsychological tests.

Genotyping

BPD participants, but not controls, were subjected to genetic analyses.

Sample handling

Venous blood was drawn and immediately frozen in aliquots at –70° C or below until analyzed. Genomic DNA was prepared from whole blood by the use of the QIAamp® DNA Blood Mini kit (Qiagen, CA, USA). The extracted DNA was stored at 4°C until analyzed.

Tryptophan hydroxylase-1 (TPH-1) polymorphisms

DNA (50 ng/reaction) was amplified by polymerase chain reactions (PCR), carried out in a T3 Thermocycler (Biometra® GmbH) in a total volume of 25 µl. The PCR products were then digested overnight with appropriate restriction enzymes, subjected to electrophoresis on 2% agarose gels (Roche Diagnostic GmbH), and visualized after an ethidium bromide staining.

Primer sequences, detailed PCR conditions and the restriction enzymes used for each SNP are reported in (Gizatullin, Zaboli, Jonsson, Åsberg, & Leopardi, 2006).

In one case (SNP rs1799913) pyrosequencing was employed, using a Pyrosequencer PSQ 96 and a PSQ 96 SNP Reagent Kit (Pyrosequencing AB Uppsala, Sweden) according to the manufacturer's instructions.

Statistical analysis of TPH-1 haplotype. The frequency of a TPH-1 six SNPs (ACGCCG) haplotype previously uniquely associated with BPD (Zaboli, et al., 2006) was calculated.

Haplotype frequencies were estimated using a haplotype reconstruction algorithm (Arlequin program, version 2.0; http://lgb.unige.ch/arlequin/software/2.000/manual/Arlequin.pdf). This approach, currently standard in population genetics, allows the precise estimate of haplotype frequencies within a group of individuals (population) but does not allow haplotype characterization in individuals. All genotyped SNPs were in Hardy-Weinberg equilibrium.

The serotonin transporter polymorphisms (5-HTTLPR/rs25531)

DNA (50 ng/reaction) was amplified by polymerase chain reaction (PCR), carried out in a T3 Thermocycler (Biometra$^®$ GmbH, Göttingen, Germany). The 5-HTTLPR polymorphism was genotyped by PCR amplification. PCR products were separated by electrophoresis on a 2 % agarose gel (Roche Diagnostic GmbH) and visualized by ethidium bromide staining. Primer sequences, detailed PCR conditions, and the restriction enzymes used can be seen in (Zaboli, et al., 2006).

To distinguish the A/G alleles of rs25531, the PCR products were incubated at 37 °C for 12 hours with restriction endonuclase *MspI* (10 U/ul). The digested products were subjected to electrophoresis on 4% agarose gels (Roche Diagnostic GmbH), and visualized after an ethidium bromide staining. The digested fragments were as follows: l_A = 340 + 127 + 62 bp , l_G= 173 + 166 + 127 + 62 bp, and s = 298 + 127 + 62 bp.

Statistical analysis for 5-HTTLPR. Genotype distributions of the serotonin transporter gene polymorphism 5-HTTLPR were in Hardy-Weinberg equilibrium (p=0.295), and closely resembled what has previously been found for both BPD and healthy individuals (Pascual, et al., 2008; Tadic, et al., 2009).

Statistical analyses

In study I, the statistical methods applied were one-way between-subjects analyses of covariance (ANCOVAs) to test differences between groups adjusting for group differences in age and education, two-tailed tests of correlation to test relationships between variables, and tests of single measure intraclass correlation as measures of interrater reliability. Follow-up tests of ANCOVAs were done applying posthoc pairwise comparisons. A Bonferroni correction was calculated to adjust for multiple correlation analyses

In Study II, the statistical methods applied were an exploratory factor analysis to establish separable executive functions, independent two-tailed t-tests and a logistic regression analysis to test differences between groups, and multiple regression analyses to test relationships between executive functions and suicidal and self-injurious behaviors.

In study III, analyses of variance (ANOVAS) and t-tests were used as appropriate to compare differences between groups.

In study IV, we used independent two-tailed t-tests for each dependent variable to compare results between the genotype groups.

Differences were considered to be significant when p ≤ 0.05. All statistics are two-tailed.

Ethical considerations

All participants read a short description of the study and were informed of the nature and purpose of the project before verbally consenting to participate. The protocol was approved by the institutional human ethics committee of Karolinska Institutet: registration numbers 03-514 and 95-283.

RESULTS AND DISCUSSION

When the work on this thesis began, there were still few studies published on neuropsychological functions in BPD. Since then the field has expanded rapidly and by now there are some 100 articles published on the subject. However, findings have not been conclusive, and it is still unclear to what extent cognitive deficits contribute to impairments in BPD. Further, there is still some controversy regarding subgroups within the diagnosis, and if special features such as suicidal behavior are associated with specific cognitive problems.

Study I

In clinical work it has been obvious that many individuals with a BPD diagnosis have problems in retrieving specific personal memories, sometimes to the extent that a tape recorder has to be used in the early phase of psychotherapy as a reminder of what has been said during therapy sessions (Anna Kåver, personal communication). Cognitive deficits may explain the difficulties of individuals with BPD in the accurate recall of past experiences, and their difficulty in maintaining a continuous sense of self. A weak self-identity is painful in itself, and because self-identity is closely intertwined with life goals and plans for the future, a weak self-identity leads to impaired goal formulation and maintenance.

Unspecific or over-general autobiographical memory has been viewed as an attempt to control emotion, as a result of lacking executive resources, and/or diminished availability of cognitive resources due to self-focused rumination (Williams, et al., 2007).

Specific autobiographical memories are important for social problem-solving skills, because they provide a database that is helpful in suggesting solutions to social dilemmas (Williams & Broadbent, 1986). Problem solving, especially in the social domain, is a common problem for individuals with BPD (e.g. Bray, et al., 2007), and such individuals may also have difficulties in imagining the future, which is a key capacity for solving interpersonal problems (e.g. Pollock & Williams, 2001).

Suicidal behavior, as well as diagnoses of depression, PTSD and more inconclusively BPD, has been associated with autobiographical memory problems in different studies. It remains unclear, however, which of these factors is the primary correlate of reduced specificity in autobiographical memory.

The purpose of Study I was to clarify these inconsistencies by examining autobiographical memory in individuals diagnosed with BPD, the relationship of overgeneral memory to depression and PTSD, and its role in social problem solving, traumatic experiences, and suicidal/self-injurious behaviors.

Our results confirmed that reduced specificity of autobiographical memory is an important characteristic of BPD individuals with a history of suicide attempts, independent of depression, or PTSD ($F(1; 73) = 21:76$, $p < .001$, partial $\eta^2 = .23$). Our finding of over-general autobiographical memory in BPD is consonant with some studies (Jones, et al., 1999; Startup, et al., 2001), but not in others (Arntz, et al., 2002; Renneberg, et al., 2005), while one study (Kremers, et al., 2004) found evidence for over-general memory only in depressed individuals with BPD. These contrasting results may reflect both methodological and sample differences between the studies.

However, the fact that all our BPD participants had a history of suicide attempts precludes disentangling the influence of suicidal behavior and the diagnosis of BPD on our results. Nevertheless, there is one study showing equally impaired autobiographical memory specificity in suicidal patients with or without a diagnosis of depression (Leibetseder, Rohrer, Mackinger, & Fartacek, 2006), thus suggesting that suicidality - and not depression - is critical for reduced memory specificity. We have shown another association between

cognition, namely executive dysfunction, and self-destructive behavior (Study II), indicating that cognitive processes are relevant for self-injury and suicidality. We did not confirm the previously reported associations between autobiographical memory and level of suicidal/self-injurious behavior (Startup, et al., 2001) in our group of individuals diagnosed with BPD, which could imply that it is the practice of self-destructive behaviors, rather than its extensiveness, that is associated with autobiographical memory processes.

Reduced specificity of autobiographical memory was further related to poor social problem-solving capacity in the BPD group ($r = .44$; $p < .05$). This contrasts with another study on BPD participants (Kremers, Spinhoven, Van der Does, & Van Dyck, 2006), which did not find this association. Possibly this inconsistency is related to differences between the study samples. In Kremers and colleagues' study, just over half of the participants with BPD had attempted suicide, while all our participants had been suicidal. Another difference between the studies is the use of one different test version and scoring system. However, the results of our study support prior work on other emotional disorders, suggesting a relationship between poor autobiographical memory and difficulties in social problem solving. There was a tendency of only depressed individuals to differ from controls on problem-solving ability. This may be explained by more rumination and reduced concrete thinking, as well as a lack of motivation (Donaldson & Lam, 2004; Watkins & Moulds, 2005) compromising the social problem-solving ability in the depressed group.

Personal memories are summary records of experience. This means that they are experience-near and correspond to experience but they are more representative of an experience than they are a literal record (Conway, 2009). Many memories are rapidly forgotten, suggesting that what is remembered is, to at least some extent, of adaptive value for the individual. Being able to remember one's experiences in a relevant way, rather than literally, is critical to focused and fluent everyday cognition and action, and in order to keep a specific record of aspects of experiences appropriate to goal processing and future plans (Conway, 2009).

The content of relevant representations of experiences that is stored in autobiographical memory helps humans to reflect upon the past, the future, and the minds of others. This reflective capacity to make sense of ourselves and others may be compromised in individuals with BPD, contributing to difficulties in effectively navigating the social world and in developing an enriched, stable sense of self (Eizirik & Fonagy, 2009). The ability to understand one's own and others' needs, feelings, beliefs, wishes, and reasons contributes to meaningful interpretations of the world that can be communicated and acted upon (Choi-Kain & Gunderson, 2008). Problems with these meta-cognitive functions may partly explain the difficulties in solving social problems that are present for many individuals with BPD. If you do not remember events and thus cannot learn from your mistakes, you are bound to repeat them. To repeatedly end up in the same problem situations and time and again fail to solve them can lead to self-contempt and hopelessness.

Thus, knowledge about existing difficulties with personal remembering and problem solving is helpful for afflicted individuals as this enables them to not be too judgmental about their failures. It is also essential knowledge for the psychotherapists treating these individuals. The promising results from studies training memory specificity in clinical populations (e.g. Williams, Teasdale, Segal, & Soulsby, 2000) warrant further studies of individuals with BPD in order to improve components of their social interaction skills and to decrease isolation from society and working life in this patient group.

Study II

Why are self-injurious and suicidal behaviors so common among persons diagnosed with BPD? One possible explanation is that these behaviors are epiphenomena of the marked instability seen in this patient group. However, this does not take into consideration the deep personal pain, and the inadequate psychological tools that many BPD individuals have with which to handle their overwhelming negative emotions. Inadequate constructive coping strategies for dealing with life stress that are not based on executive functions may lead to coping by self-harming. Since suicide is a major cause of death in individuals with BPD, an improved understanding of contributing factors to suicidal behavior in this group is urgent.

In Study II, we investigated executive functions in relation to suicidal and self-injurious behaviors in individuals with BPD who had attempted suicide, considering that executive dysfunctioning may be one risk factor for self-harming behavior given that such functions are important determinants for adequate cognitive and emotional self-regulation. The biological background of impaired executive deficits and suicidality may be a diminished prefrontal top-down control of behavior mediated by a serotonergic and/or dopaminergic brain dysfunction (Robbins & Arnsten, 2009).

As executive tests are complex and multi-dimensional, we used an exploratory factor analysis to establish separable factors representing more specific aspects of executive functioning. This is not a highly theory-driven technique, but because of the complexity of executive tasks it is arduous to describe executive functions from these tests from a strictly theoretical standpoint. The results were four separate executive components thought of as representing concept formation, goal maintenance, planning ability and working memory.

Individuals with a diagnosis of BPD showed problems with goal maintenance and planning ability as compared to controls. A logistic regression analysis was performed with group as the dependent variable and concept formation, goal maintenance, planning ability and working memory as the predictor variables. A total of 81 participants were analysed and the full model significantly predicted group status (omnibus chi-square = 27.43, df = 4, $p < .001$). The model accounted for between 28.7% and 39.2% of the variance in group status, with 86.3% of the BPD participants successfully predicted. In the control group, 66.7% were accurately predicted.

We further found an association between deficiency in planning ability and life-time number of non-suicidal self-injurious events ($F(1,49) = 5,158$, $p = .028$), and between poor concept formation and life-time number of suicide attempts ($F(1,49) = 4,061$, $p = .049$). These findings support the hypothesis that dysexecutive functioning is coupled to more of self-harming and suicidal behavior. The results indicate differences in executive functioning between individuals who do not self-harm, or seldom self-harm, and those who frequently self-harm, as well as between individuals who make few suicide attempts and those who make many suicide attempts. In our data, more of planning problems is associated with more of self-injurious behavior. This may be a reflection of the emotional instability and impulsivity seen in many individuals with BPD, affecting the ability to use preplanned actions rather than momentary reactions to cope with the demands of living. Our results also suggest an association between poorer concept formation and a greater number of suicide attempts. A fuzzy view of the world, and of what can be expected in life, is a bad starting point for consciously thought-out action-based coping skills. The result may be emotion-based coping strategies such as self-injurious and suicidal acts that often reduce distress, without addressing the source of the adversities. Such immediate relief from distress may be reinforcing, but is temporary and outright dangerous.

Executive dysfunctioning explained less than 10% of self-injurious/suicidal behavior in our study, showing that the background to self-destructive behaviors is multi-factorial. However,

problems in controlling cognition and emotion, such as difficulties in formulating and pursuing goals, and in planning and finding solutions to problems at hand, lead to an impaired ability to deal with demanding situations. Difficulties in formulating concepts and making generalizations will make it hard to attach meaning to the world and to properly guide behavior, especially in non-routine and demanding situations. Repeated experiences of failure to deal with life stress lead to feelings of discouragement and hopelessness. This may result in catastrophic thoughts about the future and one's inadequate potentials to deal with what lies ahead. Such despair may contribute to drastic problem solutions such as suicidal behavior. Effective executive functions are a necessary base for the important coping skills we all need to confront life's adversities and problems, skills that many individuals with BPD have not had the opportunity to learn. This suggests that executive functions are possible targets for therapeutic interventions with suicide-prone individuals with borderline personality disorder.

Study III

We continually make decisions about suitable courses of action in our daily life. In some situations, the consequences of the decision are not completely foreseeable and we do not have any information about how likely positive or negative consequences are (Brand, Heinze, Labudda, & Markowitsch, 2008). To guide decisions in the most favorable direction we are helped by "somatic markers", physiological states related to earlier experiences of rewarding or punishing situations that are reinstated during the decision process (Damasio, 1994). These somatic markers unconsciously bias behavior to the selection of the appropriate decision. For most of us decision-making is a rather uncomplicated process, but for individuals with BPD it may be an unconquerable task to make the right decisions and to reach relevant goals.

The Iowa Gambling Task (IGT) was originally created to be used with patients with damage to the ventromedial PFC (VMPFC). These are patients who show similar deficits in social decision-making as many persons with BPD do. The IGT was designed to simulate the uncertainties of real-life social or emotional decision-making as guided by unconscious biasing somatic signaling (e.g. Bechara, et al., 1997). A recent study showed, however, that performance on the IGT is affected not only by the autonomic responding of somatic markers, but also by conscious knowledge about the underlying contingencies of the IGT, and that conscious knowledge and somatic responding seem to be unrelated (Guillaume, et al., 2009). It has been proposed that the optimal way of decision-making in risky situations is to use both cognitive strategies as well as biasing emotional signals (Brand, et al., 2008).

Since impaired social/emotional decision-making is common in individuals with BPD, we used the IGT to examine this in our participants with BPD. Studies have shown that serotonin dysfunction is associated with both decision-making (Bechara & Damasio, 2002) and BPD (Hansenne, et al., 2002), and this is the reason that we also wanted to study aspects of serotonin in relation to decision-making in this group. Because more than half of our BPD participants used SSRI drugs, it was not reasonable to analyze serotonin in platelets. Instead, we studied the relationship between impaired decision-making and a gene coding for the rate-limiting enzyme tryptophan hydroxylase (TPH) in serotonin synthesis, the TPH-1 gene. The TPH-1 gene was chosen because a specific TPH-1 haplotype has previously been shown to be uniquely associated with BPD (Zaboli, et al., 2006). The frequency of this specific TPH-1 haplotype was calculated in the BPD group.

On the IGT, the BPD group chose significantly more cards from the bad decks than the control group across the last three blocks, ($t(76) = 2.05$, $p < 0.04$), whereas the groups did not differ during the first two blocks, ($t(76)$, $p < 1$).

Furthermore, we found that, on a group level, the frequency of the specific haplotype was 35% in the group of BPD participants with low IGT performance, but only 12% in the BPD

group with normal net scores. This three-fold difference was statistically significant ($\chi^2[1, N = 42] = 5.4$, $p < 0.02$), with a large effect size ($d = 0.76$).

These findings suggest that emotional decision-making (as measured by the IGT) is a problem for many individuals with BPD that may be associated with serotonin dysfunction. Nevertheless, as TPH-1 allele frequencies vary even between northern and southern Europe (Nielsen, Jenkins, Stefanisko, Jefferson, & Goldman, 1997), the contribution of TPH-1 variants to variance in emotional decision-making must be put in a larger context in future research.

Interestingly, the BPD participants differed from the control group only on the last three blocks of the IGT, i.e. the knowledge-using phase (when accumulated experience should be used to guide performance in the most profitable direction, even though decisions are still made under some uncertainty). An association with TPH-1 and the 5-HTTLPR *ss* genotype, but not TPH-2, has previously been shown in suicidal individuals for the later trials of IGT (Jollant, et al., 2007). Of relevance, it has been shown that the serotonergic system is implicated in the later stages of the IGT, perhaps reflecting a cognitive control system with importance for the learning process during IGT that involves the maintenance of options that promise future reward (van den Bos, Houx, & Spruijt, 2006). Taken together, it is suggested that decision-making is modulated by serotonergic genetic polymorphisms.

Decision-making deficits are also seen in patients with localized damage to the VMPFC (Bechara et al., 1997), an area with documented alterations in different aspects of serotonin transmission in suicidal patients (Mann, 2003). The VMPFC has also shown to be active during exploitative decision-making (Daw, O'Doherty, Dayan, Seymour, & Dolan, 2006), i.e. when accumulated knowledge is to be applied. Thus, the reported difficulties with decision-making and its association with a TPH-1 variant might be related to serotonergic gene expression and regulation in this particular brain area in BPD.

Study IV

Several of the core symptoms of BPD, such as affective lability, suicidal behavior and impulsive aggression have been related to serotonergic dysfunction (Hansenne, et al., 2002). Genes involved in the serotonin system are thus promising candidates for elucidating the genetic underpinnings of BPD symptoms (Lis, Greenfield, Henry, Guile, & Dougherty, 2007).

Variants of the serotonin transporter (5-HTT or SERT) gene have been associated with a vulnerability to affective disorders, and thus variants of this gene are especially suitable for the study of symptoms related to psychiatric syndromes co-occurring with BPD. In particular, the presence of one or two copies of the short (*s*) allele of the 5-HTTLPR polymorphism has been associated with reduced serotonin transporter expression and function, and vulnerability to affective disorders.

Studies of associations between 5-HTTLPR and suicidal behavior have, however, not been conclusive. Some studies failed to find an association (Geijer, et al., 2000; Helbecque, Sparks, Hunsaker, & Amouyel, 2006), others suggest a relationship between the *s* allele and suicidality (Bondy, Erfurth, de Jonge, Kruger, & Meyer, 2000; Neves, et al., 2008), while yet others indicate that the long (*l*) allele is associated with suicidal behavior (e.g. Gaysina, Zainullina, Gabdulhakov, & Khusnutdinova, 2006).

It should be noted that there seems to be no overrepresentation of the *s* allele in individuals with BPD, which indicates that this genotype does not contribute to the diagnosis itself (Pascual, et al., 2008; Tadic, et al., 2009). However, there may be associations between the *s* allele and specific characteristics of BPD.

To test for an association between variants of the 5-HTTLPR and relevant clinical features of BPD, 77 women with BPD were genotyped in the 5-HTTLPR polymorphism.

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Additionally, we analyzed another functional variant of the 5-HTT gene (rs25531), which is located in close proximity to 5-HTTLPR and represents a G→A substitution (Kraft, et al., 2005). The less common *G* variant is almost always in phase with the 5-HTTLPR *l* allele (Parsey, et al., 2006; Zalsman, et al., 2006), and leads to a reduced 5-HTT expression similar to that seen for the 5-HTTLPR *s* allele (Zalsman, et al., 2006). Since the *lG* and the s allele show comparable serotonin expression profiles, the groups were formed accordingly. The *ss* group consisted of the *ss*, *lG/s*, and the *lG/lG* genotypes (N = 22), the *l/s* group consisted of the *lA/s* and the *lA/lG* genotypes (N = 39), and the *ll* group consisted of the *lA/lA* genotype (N = 16).

The participants rated their subjective experience of core borderline, depressive, anxious and obsessive-compulsive symptoms, and were interviewed about lifetime incidence of suicide attempts and self-harming acts. Carriers of two *s* alleles of the 5-HTTLPR reported more symptoms of borderline, depression, and anxiety, and of obsessive-compulsive behaviors, suggesting that the *ss* variant might influence serotonin function, thus affecting susceptibility to these symptoms in BPD, and contributing to subtypes within the diagnostic category of BPD. The clinical heterogeneity within BPD may be due to genetic heterogeneity, since symptomatic features of BPD show familial aggregation. After six years, as many as 75 % of individuals diagnosed with BPD will no longer meet the criteria for BPD, even though affective symptoms, such as depression, are likely to be still present (Zanarini, et al., 2003). Thus, these affective symptoms may be genetically based temperamental features and, as such, relatively resistant to change.

We found no association between 5-HTTLPR and suicidal and self-injurious behaviors. This suggests that *5-HTT* gene variants may not be as influential on suicidal and self-harming behavior in BPD. Possibly, suicide attempts, self-injury and other impulsive behaviors may be more associated with other genetic variants within the serotonin system, such as TPH polymorphisms, rather than *5-HTT* variants.

The results we describe here and in Study III provide examples of the influence of genetic variants on human behavior, which may be of relevance for the symptomatology involved in psychiatric diagnoses. Determining subgroups, as well as an appreciation of individual characteristics, within BPD is clinically relevant for a further understanding of this complex diagnosis, and will hopefully improve the tailoring of treatments to individual patients, leading to more effective therapeutic interventions.

General discussion

It might seem to be a difficult task to encourage 51 women with BPD to take part in four hours of cognitive testing. However, all the participants after information about the study agreed on the potential importance of furthering our understanding of the diagnosis by collecting neuropsychological data. Occasionally, participants did not show up for a planned testing session, and had to be re-scheduled for another appointment. One consequence of the instability associated with BPD is that individuals with this diagnosis might feel awful one day, and then the next day be in a far better mood. When participants found the strength to come to testing, it was probably on one of these better days. The participants seemed motivated and to do their very best during the two testing sessions. Nevertheless, some BPD participants interrupted some tests more often than controls did, perhaps discouraged by what was perceived as non-optimal performance or because of mental fatigue.

Applied research questions and hypotheses are frequently based on clinical problems that are difficult to investigate within the clinical framework. One example may be "Why do patients with BPD have such problems to remember therapy sessions?". However, clinical and experimental knowledge stem from different traditions and tend to develop under

different conditions. Sometimes clinicians do not see the immediate clinical relevance of research results, and researchers are suspicious of the empirical evidence of clinical work. Such a situation is far from a "scientist-practitioner" model, where basic and applied psychology inform and cross-fertilize each other (Shapiro, 1985), which has been advocated for many years. The work of this thesis has been done with the aim and hope that it will be useful for clinicians and benefit their patients. The findings of this thesis will lead to a greater clinical recognition of neuropsychological impairments in BPD, and can further advise improvement in psychotherapeutic and pharmacological interventions for this patient group. The more we know, the less range there will remain for ideological controversies on the genesis and treatment of disorders.

The collected evidence of this thesis suggests that problems with autobiographical memory and executive functions influence the lives of many individuals with BPD and a history of suicide attempts. Some of these deficits, together with several psychiatric symptoms, seem to be associated with serotonergic dysfunction, and they have the potential to interfere with all domains of life, including professional and interpersonal areas.

The results of the thesis point to the multi-factorial genesis of BPD. The thesis further picks out specific areas of relevance for understanding individuals with this diagnosis and for planning therapeutic interventions. Psychotherapeutic treatments are all about teaching clients better ways to cope with life. To have a diagnosis of BPD does not mean that a person has no potential to learn new strategies for better daily functioning. The ability to learn to cope more adaptively with BPD symptoms and life demands, will lead to developmental change and an improved quality of life. Applied behavior analysis breaks down behavior into specific components, allowing for the identification of specific skills to be learned.

Why are the functions and processes studied for this thesis called "neuropsychological" instead of just "psychological"? Is it not a truism to state that behaviors and symptoms are products of the brain? For anyone working in the field of clinical neuroscience, it is. In the general population, however, and indeed among some psychologists and psychiatrists, biological processes are often viewed as something separate from psychological processes. Some 450 years ago, psychology emerged as a discipline within philosophy. Psychology has then, at least in Sweden, become incorporated into the social sciences and during my five-year-long education to become a psychologist we only had a few weeks of courses that were related to biology. I therefore think it is relevant to state that BPD, just as any other psychiatric disorder, is a disorder of the brain. Individuals with BPD are not manipulative or unreasonable, but have real difficulties that reflect neurobiological processes.

I have not studied brain processes in this thesis. However, the results of executive dysfunctioning, including social decision-making and problem-solving abilities, indicate a non-optimal functioning of the PFC in BPD. Further, autobiographical memory problems can involve not only prefrontal (for retrieval) dysfunction, but also hippocampal (for storage and consolidation) dysfunction. The reported associations between serotonergic polymorphisms and symptoms and behavior in BPD suggest that this neurotransmitter is of importance for BPD. It is possible that serotonergic function or the serotonergic gene expression and regulation in prefrontal areas is responsible for much of the findings in this thesis.

Limitations of the studies

The inclusion criteria of two or more life-time suicide attempts may have biased the participant group such that it was not representative of a general clinical sample of individuals with BPD. The results may, therefore, not be completely generalizable to BPD persons in general. However, individuals with BPD are likely to self-harm and to have attempted suicide (Zanarini, et al., 2008). Only 4% with this diagnosis in a longitudinal study had neither self-

harmed nor attempted suicide (Zanarini, et al., 2008). Several suicide attempts are associated with more deeply impaired individuals requiring more psychiatric care (Brodsky, et al., 2006), and one aim of the SKIP project was to find efficient interventions for the patients most difficult to treat.

The generalizability of our study is also restricted because our sample included only women. Nevertheless, according to most clinical studies, BPD is more common in women than men, with a 3:1 female to male gender ratio e.g. (Skodol & Bender, 2003). There is also evidence for gender differences in the neural underpinnings of BPD (Soloff, Meltzer, Becker, Greer, & Constantine, 2005). For example, there is evidence of gender effects in serotonergic brain function. The mean rate of serotonin synthesis is 52% higher in the brains of males than in those of females (Young, Leyton, & Benkelfat, 1999).

Further, the sample size is small for associating genes to behavior, which leads to a low statistical power in Studies III and IV. The results of these studies must, therefore, be interpreted with caution until replicated. The complexity of psychiatric disorders will hardly be related to single genes, and genotype-phenotype mappings are somewhat futile. Still, preliminary studies addressing tentative questions are a starting point for developing hypotheses to be tested. Studies, such as the present ones, that explore behavioral, genetic and neuropsychological findings may be early moves in the very complex task of mapping interactions between genes and psychiatric disorders in particular.

As mentioned, many commonly used neuropsychological tests are complex, which is especially true for instruments designed to measure executive functions. These tests place heavy demands not only on executive processes of interest, but also on non-executive processes (Miyake et al, 2000). Further, the solution of a task may require a cognitive process where only the end production of the solution is measured, thus missing important steps on the way to the solution. This is a problem concerning the validity of executive tests as to what they really measure. In clinical neuropsychology where an experienced examiner administeres a number of tests that can be compared with each other and that can be considered also in relation to qualitative data, this is less of a problem than in research. In order to help resolve the construct validity problem of the executive tests used, a less theory-driven, but common solution of factor analysis was applied in the present thesis. By doing this, it is possible that we have missed some essential features of these tasks, or worse, interpreted functions that were actually not captured by the tests. However, the neuropsychological tests used in this thesis have been selected to cover cognitive functions of interest, to be commonly used and well-known, and to be adequately standardized, and they have been used according to scientific evidence and proven experience to the best of my professional knowledge.

CONCLUSIONS AND COMMENTS

This thesis has contributed to our knowledge of neuropsychological functions in individuals with BPD who have made several suicide attempts. This is a group of individuals thought to be the most disturbed of the BPD population, with severe problems and intense misery that present a great treatment challenge (Linehan, 1993). The findings presented in this thesis suggest that:

- Many of these individuals have problems in remembering specific personal memories, which is indicated to contribute to poor social problem-solving abilities.
- Many also display executive problems, difficulties that will make daily life and its challenges hard to deal with. Moreover, the executive problems are indicated to contribute to suicidal and self-injurious behavior.
- Decision-making, as well as core borderline, depressive, anxious and obsessive-compulsive symptoms, are affected by serotonergic genetic polymorphisms.

Taken together, the collected evidence of this thesis suggests that problems with autobiographical memory and executive functions influence the lives of many individuals with BPD and a history of suicide attempts, and that some of these deficits, together with several psychiatric symptoms, are associated with serotonergic dysfunction. These impairments are likely to be related to prefrontal brain regions. It is possible that serotonergic function or serotonergic gene expression and regulation in prefrontal areas is responsible for many of these results. Deficits such as those described here have the potential to interfere with all domains of life, including professional and interpersonal areas. Hopefully, the findings of this thesis will lead to a greater clinical recognition of neuropsychological impairments in BPD, and further suggest improvements in psychotherapeutic and possibly also pharmacological interventions for this patient group.

Future prospects

If I were to do the research of this thesis again, and if time and money were of no concern, there are some things I would do differently. These limitations of this thesis may in fact be interesting starting points for future research.

To make the interpretation of results on executive tests a bit less challenging, I would use test methods with greater specific value. The executive tests we have administered in this study are multi-dimensional and involve e.g. components of attention and sometimes visual-spatial abilities, in addition to several aspects of executive function. These components could be controlled for by using a more extensive and specific test battery.

I would also include psychiatric control groups of individuals with depression and PTSD, respectively, since these diagnoses commonly co-occur with BPD. This could be a means of disentangling influences from the different diagnoses.

Since epidemiological studies suggest that BPD is as common in men as in women in the general (though not the clinical) population, comparing male and female individuals with BPD would have been interesting and may have clarified the role of gender in BPD. Only focusing on women with BPD might have meant leaving out interesting findings.

Further, I would be very interested in studying social cognition and interpersonal relations in BPD, since interpersonal impairment is central for many persons with BPD (Gunderson & Links, 2008). Interpersonal relations are of great importance to human beings, and social skills are essential for our potential to create and maintain such secure and rewarding relations.

Many individuals with BPD find it difficult to form and maintain supportive relationships. Failure to achieve closeness is associated with an increased risk for mental and physical

illness, and suicide (Bartz & McInnes, 2007). Understanding the social hurdles faced by individuals with BPD, and enhancing their ability to function in a social setting are thus crucial steps towards improving their quality of life.

POPULÄRVETENSKAPLIG SAMMANFATTNING PÅ SVENSKA

Borderline personlighetsstörning (BPD) är ett livshotande och mytomspunnet tillstånd. Namnet kommer från 1930-talets psykoanalytiska syn på psykiatrisk sjuklighet som delades in i lättare och behandlingsbara tillstånd som kallades neuroser, och svårare och obehandlingsbara tillstånd som kallades psykoser. Patienter som inte var psykotiska men ändå visade sig vara svåra att behandla med den tidens metoder uppfattades som en mellangrupp, och de kallades därför "borderline". Många inom psykiatrin använder numera den mer beskrivande beteckningen Emotionellt instabil personlighetsstörning.

BPD är ett tillstånd som drabbar 1-2% av befolkningen. Inom den psykiatriska öppenvården har var tionde patient denna diagnos, och inom slutenvården var femte. Befolkningsstudier talar för att BPD är lika vanligt bland män som hos kvinnor, men inom den psykiatriska vården är tre fjärdedelar av dem som diagnosticerats med BPD kvinnor. Var tionde patient som diagnostiserats med BPD dör till följd av självmord. Det är även vanligt med samtidiga andra personlighetsstörningar eller annan psykiatrisk sjuklighet, t ex depression, ätstörning, drogmissbruk och ångest.

BPD kännetecknas av instabila känslor, bristande impulskontroll, svårigheter i relationer till andra människor och låg självkänsla. Det är påfrestande att leva med starka, lättutlösta smärtsamma känslor. De orsakar lidande i sig och dessutom kan tvära kast i humöret vara svåra att begripa och leva med både för människor i omgivningen och för den drabbade själv. Personliga relationer tenderar därmed att bli stormiga, intensiva och kaotiska. Människor med BPD har ofta en upplevelse av att vara dåliga eller rent av värdelösa, vilket förstärks av deras misslyckade försök att få till goda relationer till andra och att klara livets utmaningar. Livet kan bli så svårt att hantera att personer med BPD tar till drastiska lösningar som självskada eller självmord.

Få psykiatriska tillstånd är så utmanande för vår förståelse. Kombinationen av föga framgångsrika försök att behandla människor med BPD, och deras starka, lättutlösta känslor, har gjort att de fått dåligt rykte inom psykiatrin. De sägs vara arga, manipulativa, knepiga och omotiverade för behandling. Detta är fördomar, och dessa bemöts bäst med kunskap. En ansats till en bättre förståelse för BPD är att studera hur personer med BPD tänker, känner, minns och löser problem. Sedan kan förhållandet mellan eventuella svårigheter och bakgrundsfaktorer som gener, miljö, samt andra kliniska karaktäristika undersökas för att få en bättre förståelse för vilka faktiska psykologiska funktionshinder personen har, och hur de kan ha uppkommit.

Beteende styrs från hjärnan, och individer med BPD verkar bland annat ha en sämre förbindelse mellan de djupa delar av hjärnan som ger upphov till exempelvis rädsla, och de ytligare delar som ska styra känslans riktning och styrka. Serotoninet, en av hjärnans viktiga kemiska budbärare som är inblandad i känslomässig reaktivitet och impulsivitet, verkar också vara påverkat vid BPD. Vi vet därmed att BPD patienten inte bara "beter sig illa", utan att det finns underliggande förändringar i hans eller hennes hjärna som leder till deras problem.

Syftet med denna avhandling var att bidra till kunskapen om vilka specifika svårigheter individer med BPD lever med. Vi har studerat minne, problemlösningsförmåga, förmåga att formulera mål, planera och att ha överblick i en grupp kvinnor med BPD som gjort minst två självmordsförsök. BPD gruppen jämfördes med ickekliniska kontrollpersoner, och i BPD-gruppen undersöktes även genvarianter inom serotoninsystemet.

Avhandlingen bygger på fyra studier som har visat att:
- Många inom BPD-gruppen hade svårt att plocka fram specifika personliga minnen. Denna bristande tillgång till tidigare erfarenheter var kopplad till en nedsatt förmåga att lösa sociala problem. (Studie 1)

- Många uppvisade i test också svårigheter att styra sina handlingar på ett flexibelt och klokt sätt vilket vi behöver göra för att lösa alla våra vardagliga utmaningar. Denna oförmåga var kopplad till både självskade- och självmordsbeteende. (Studie 2)
- Beslutsfattande och kärnsymptom inom BPD samt symptom på depression, ångest och tvång var kopplade till genetiska varianter inom serotoninsystemet. (Studie 3 och 4)

Sammanfattningsvis kan sägas att avhandlingens studier visar att individer med BPD är handikappade i sina liv genom en nedsatt förmåga att använda sig av en del viktiga psykologiska funktioner. Den som inte kan minnas exakt vad som hänt vid tidigare tillfällen kan inte lära sig, utan kommer att göra om samma misstag. Den som inte kan styra sina känslor kommer att drabbas av starka, skrämmande känsloutbrott.

Vidare visar studien ett samband mellan genetiska varianter som påverkar serotininfunktionen, och dels svårigheter att fatta kloka beslut baserade på känslor, dels negativa känslor som rädsla och nedstämdhet.

De beskrivna problemen hänger sannolikt ihop med pannlobsfunktionen, och det är tänkbart att förändrad serotoninfunktion i detta hjärnområde kan förklara många av de resultat som visas i studierna.

De svårigheter som kartlagts i studierna försvårar en människas förmåga att fungera i så gott som alla viktiga situationer - på arbetet, i sina relationer, inför stora och små beslut. I bästa fall kan resultaten i denna avhandling leda till en större klinisk uppmärksamhet på neuropsykologiska problem hos individer med BPD och även bidra med information för att åstadkomma förbättrade och även mer specifika psykoterapeutiska och kanske även farmakologiska behandlingar.

Arbete kring personer med BPD är viktigt därför att okunskap har gjort att en stor patientgrupp har stigmatiserats och inte fått den behandling de behöver och har rätt till. Deras symtom har inte uppfattas som tecken på dysfunktion i nervsystemet, utan som elakhet eller oresonlighet. Deras bristande självkontroll har setts som en moralisk defekt, eller bristande vilja att uppföra sig på ett korrekt sätt, snarare än en oförmåga att göra detta. Deras oförmåga att fatta kloka beslut har setts som en provokation mot omgivningen, inte ett uttryck för en bristande förmåga att välja det bästa alternativet. Kunskap om de specifika styrkor och svagheter som finns hos människor med denna diagnos behövs för att vi ska kunna utveckla välbehövliga, riktade, individualiserade och utvärderingsbara behandlingsinsatser i framtiden.

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