In: Borderline Personality Disorder: New Research ISBN: 978-1-60692-460-0
Editors: Marian H. Jackson and Linda F. Westbrook

Chapter 3

NEUROPSYCHOBIOLOGY, COMORBIDITY AND DIMENSIONAL MODELS IN BORDERLINE PERSONALITY DISORDER: CRITICAL ISSUES FOR TREATMENT

Bernardo Dell'Osso*[1], Heather Berlin[2], Marta Serati[1] and Alfredo Carlo Altamura[1]

[1]Department of Psychiatry, University of Milan, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena; Via F. Sforza 35, 20122, Milano, Italy.
[2] Department of Psychiatry, Mount Sinai School of Medicine, One Gustave L. Levy Place, Box 1230, New York, NY 10029.-USA

ABSTRACT

Borderline Personality Disorder (BPD) affects approximately the 1-2% of the general population in the US, with an incidence up to 20% in psychiatric settings. The pathogenesis of BPD involves complex interactions between genetic, neurobiological and environmental factors, resulting in core dimensional symptoms such as emotional dysregulation, impulse dyscontrol, aggression, cognitive dysfunctions and dissociative states. BPD is often comorbid with other mental disorders such as mood disorders, anxiety disorders, psychotic spectrum disorders, other personality disorders and substance abuse/dependence. Moreover, the comorbidity between bipolar disorder, particularly type II, and BPD has been investigated in several studies, showing interesting results in terms of clinical presentation and outcome. In addition, suicidal ideation is frequently experienced by BPD subjects and almost 10% of affected patients commit suicide by adulthood. As a consequence, BPD patients are high utilizers of health care resources and the correct clinical management of this disorder represents a challenge for psychiatrists.

Recently, neurobiological studies showed that symptoms and behaviors of BPD are partly associated with alterations in basic neurocognitive processes, involving

* Corresponding author: Dr. Bernardo Dell'Osso Department of Psychiatry, University of Milan, Fondazione IRCCS Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena. Via Francesco Sforza 35, 20122, Milan.Tel.: +39 02 55035994; Fax: +39 02 50320310 Email: bernardo.dellosso@policlinico.mi.it

glutamatergic, dopaminergic and serotoninergic systems. In addition, neuroimaging studies in BPD patients indicated differences in the volume and activity of specific brain regions related to emotion and impulsivity, such as the prefrontal cortex, cingulate cortex, amygdala and hippocampus.

The treatment of BPD, as reported in currently available guidelines, includes both pharmacotherapy and psychotherapy. Pharmacological treatment is generally recommended in the acute treatment of the core symptoms of BPD and in cases with Axis I comorbidity and severe impulse dyscontrol. Over the past decade, antidepressants - SSRIs in particular - have been considered the first pharmacological choice in the treatment of BPD, whereas, more recently, converging evidence indicates the efficacy of other compounds such as mood-stabilizers and atypical antipsychotics. With regard to psychotherapic interventions, long-term approaches including transference-focused psycotherapy, dialectical-behavioural psychoterapy and mentalization-based therapy seem to be particularly useful.

In light of the continuing evolution of the BPD diagnosis, of its principal clinical features and of the high incidence of comorbidity, it is very tough to draw a well defined and complete picture of the disorder and future contributions from genetic, neurobiological and neuroimaging studies are warranted.

Key words: BPD, comorbidity, neuropsychological features, psychopharmacology.

INTRODUCTION

Borderline Personality Disorder (BPD) is a prevalent and impairing condition, included among the Axis II Personality Disorders, cluster B (Dramatic), by the DSM-IV-TR [APA, 2000].

BPD is a multidimensional syndrome characterized by heterogeneous symptom domains including affective instability, impulsivity, unstable relationships and cognitive defects, each of which may reflect different diatheses [Paris, 2007].

Affective instability in BPD is characterized by rapid, exaggerated shifts in emotion in response to environmental stimuli such as criticism, separation from a significant person, or frustration that may impair a stable sense of self and thus disrupt inter-personal relationships.

A recent epidemiologic survey conducted in the U.S. reported a lifetime prevalence for BPD of approximately 5.9% with no differences in the rates among men and women. In addition, BPD was found to be more prevalent in younger and separated/divorced/widowed adults and those with lower incomes and education [Grant et al., 2008].

Even though BPD is considered a chronic condition, most patients tend to improve with time, and the majority of BPD patients regain close to normal functioning by the age of 40 years [Paris, 2002]. In fact, results from the NIMH Collaborative Longitudinal Personality Disorders Study indicate that at 2 years after BPD diagnosis, only 44% of the patients retain the original diagnosis [Grilo et al., 2004].

Like the majority of mental disorders, no single factor can explain BPD's etiology and multiple factors (biological, psychological and social) are thought to play a role in the development of the disorder. In addition, given the clinical heterogeneity of BPD as well as the frequent comorbidity with other psychiatric conditions, BPD has been incorporated within different dimensional models based on specific neurobiological data, neuropsychological findings, and common patterns of treatment response.

The aim of the present review is to provide a comprehensive and updated overview of the more recent neurobiological, neuropsychological and clinical findings of BPD with a specific emphasis on comorbidity patterns and dimensional models. Implications for treatment are also discussed.

2. NEUROBIOLOGICAL DATA

A better understanding of the neurobiological mechanisms of BPD has the potential to open new avenues for treatments as well as to reduce the stigma that worsens the clinical course and outcome of this already disabling and hard-to-treat condition [New et al., 2008].

The neurobiological basis of BPD is supported by the existence of serotoninergic dysfunction, genetic susceptibility, functional brain abnormalities and cognitive dysfunction [Berlin et al., 2005].

Given the clinical heterogeneity of BPD [Lieb et al., 2004], potentially reflecting different underlying neurobiological pathways, it is of clinical interest to assess the possible existence of different subgroups of patients with BPD in order to identify individuals at greater risk for specific impairments, comorbid illnesses or self-harm behaviors, and preferential response to specific treatments.

A study by Paris and colleagues [2004] tested the hypotheses originally presented by Siever and Davis [1991], that the neurobiological correlates of BPD reflect two underlying trait dimensions: impulsivity associated with lower central serotoninergic activity and affective instability associated with lower noradrenergic and cholinergic activity. The results of the study only supported a relationship between impulsive symptoms in borderline patients and abnormalities in central serotonergic transmission.

Genetic studies on BPD are still in the initial stages. The heritability of BPD has been suggested to be moderate to high, based on findings of concordance between monozygotic twins of approximately 35%, and 7% for dizygotic twins [Torgersen, 1984]. Furthermore, anecdotal evidence suggests that many of the core symptoms/dimensions of BPD are highly heritable, including impulsiveness and aggression [Coccaro et al., 1993,1997]. The genes that so far appear to be most linked to BPD are those involved in the serotonin system. The gene-linked polymorphic region of the 5-HT transporter gene polymorphism (5-HTTLPR) has been found to have short and long alleles, and Retz and colleagues [2004] found that the short allele is associated with violent behavior in humans.

Lyons-Ruth and co-workers [2007] hypothesized an association between the short allele of the 5HTTLPR and borderline or antisocial traits in young adulthood, indicating that young adults with lower socioeconomic status who carry the short 5HTTLPR allele may be particularly vulnerable to develop antisocial or borderline traits.

A recent study evaluated whether a functional polymorphism of the 5-hydroxytryptamine(1A) receptor (5-HTR(1A)) gene C -1019 G is associated with structural changes of the amygdala in patients with BPD and its conclusions support an involvement of the amygdala in the biopathogenesis of BPD [Zetzsche et al., 2008].

With regard to structural and functional abnormalities in BPD, neuroimaging data revealed a dysfunctional network of specific brain regions, such as the fronto-limbic areas, that seem to mediate much, if not all of the BPD symptoms. This fronto-limbic network

consists of anterior cingulate cortex, orbitofrontal and dorsolateral prefrontal cortex, hippocampus and amygdala. In particular, some core symptoms of BPD have been linked to the amygdala and limbic systems that control emotion, rage, fear and impulsive automatic reactions. It has been shown that the hippocampus and amygdala may be as much as 16% smaller in people with BPD, suggesting that experiences of trauma may lead to these neuroanatomical changes [Driessen et al., 2000]. Taken as a whole, these findings suggest that, in contrast to PTSD, not only hippocampus but also amygdala volumes seem to be reduced in patients with BPD.

Tebartz van Elst and colleagues [2007] analysing the relationship between amygdalar volume loss and altered amygdalar neurochemistry by morphometric and spectroscopic MRI, found a significant reduction of amygdalar volumes in patients with BPD. In addition, they found a significant increase of left amygdalar creatine concentrations in BPD patients suggesting a possible link between amygdalar volume loss, psychopathology and neurochemical abnormalities in terms of creatine signals.

Another interesting neurobiological finding in BPD is the reduction of hippocampal volume as assessed by MR-based volumetry [Bremner et al., 2003]. Nevertheless, there is an ongoing debate whether this volume reduction is due to an elevated activity of stress-associated neurobiological systems, such as the HPA axis, or it is genetically determined [Gilbertson et al., 2002]. In fact, it is well established that hippocampal volume loss is not specific to BPD but has been reported in subjects with chronic PTSD, as well as in patients with MDD, especially with histories of childhood abuse [Bremner et al., 2003]. This volume loss may be the result of chronic stress, HPA dysfunction, hypercortisolemia and the neurotoxic effects of cortisol on hippocampal neurons, including diminished brain derived neurotrophic factor [Sapolsky, 2000].

A dysfunction of the dopaminergic system has been suggested to be related to some BPD symptoms as well. Dopamine, in fact, is thought to play an important role in three symptoms of BPD: emotional dysregulation, impulsivity, and cognitive-perceptual impairment. These hypotheses are supported by the potential efficacy of some conventional and atypical antipsychotics in BPD. In addition, hyperactive dopamine function has been proposed as a potential cause of hyperactive amygdala function, leading to emotional dysregulation and negative reactions to social situations [Friedel, 2004].

Multiple cognitive dysfunctions and symptoms reported by BPD patients, like dissociation, psychosis and impaired nociception, may also result from the dysregulation of glutamate neurotrasmission. Abnormalities in glutamatergic system in some BPD patients might benefit from the use of treatment such as NMDA partial/full agonist, in order to improve memory, learning and cognition processes [Grosjean et al., 2007].

Positron emission tomography (PET) studies have shown that patients with BPD present hypometabolism of glucose in various brain structures, including frontal cortex (dorsolateral frontal cortex) and limbic system (anterior cingulate cortex) compared to normal controls, suggesting that the disorder may result from a failure of the prefrontal cortex to regulate the limbic system [De la Fuente et al., 1997]. Furthermore, decreased glucose uptake in medial OFC has been found in BPD patients and it may be associated with diminished regulation of impulsive behavior [Soloff et al., 2003].

3. NEUROPSYCHOLOGICAL FINDINGS IN BPD

BPD patients have been characterized clinically as having disturbances of cognition and perception, including abnormalities of memory, attention, language, and executive functions [Kernberg et al., 2000; Sternbach et al., 1992; Zanarini et al., 1990]. Neuropsychiatric abnormalities, such as neurological soft signs (subtle abnormalities on neurological examination), and associated impairment on select neuropsychological (NP) tests have been found in BPD patients [Gardner et al., 1987; Quitkin et al., 1976; Stein et al., 1993; Van Reekum et al., 1993a]. Soft signs have been shown to be more prevalent on the left side (suggestive of right hemisphere impairment), and associated with frontal lobe executive function impairment [Stein et al., 1993]. Initial neurobehavioral studies also suggest an association between BPD and acquired or developmental brain dysfunction (prefrontal and temporolimbic dysfunction in particular), implying that the impaired cognitive performance of some BPD patients may be partly due to organic factors [Van Reekum et al., 1993a; Andrulonis et al., 1981,1982,1984; Stone et al., 1998; Streeter et al., 1995; Travers et al., 2005; Van Reekum, 1993b; Van Reekum et al., 1996a-b].

A review of 14 NP studies of BPD [Monarch et al., 2004], revealed that most studies (71%) report significant impairment across a wide range of cognitive domains. BPD patients have shown deficits in verbal and nonverbal (visual) memory, visual perception, visuomotor speed, rhythm reproduction, complex cognitive tasks involving multi-step, multi-element, associative operations (e.g. delayed memory, similarity comparisons, and proverb interpretations) [Burgess, 1990-1992; Kirkpatrick et al., 2007a; O'Leary et al., 1991; Stevens et al., 2004], visuospatial function, attention [Burgess, 1992; Dinn et al., 2004; Judd et al., 1993; Posner et al. 2002; Swirsky-Sacchetti et al., 1993], emotion recognition [Wagner et al., 1999], and executive dysfunctions like planning, cognitive flexibility and decision-making under uncertainty [Bazanis et al., 2002]. BPD patients' attentional deficits appear to primarily affect conflict resolution, indicating impaired frontal functioning, rather than other attentional functions like alertness [Posner et al. 2002].

Many of the more recent NP studies of BPD used more comprehensive batteries than in earlier studies and seem to identify more specific neurocognitive impairments. Several studies suggest that BPD patients exhibit executive or, more precisely, inhibitory dysfunction (e.g. tested with a Go-NoGo response inhibition task), which is thought to be related to a prefrontal disturbance [Swirsky-Sacchetti et al., 1993; Bazanis et al., 2002; Berlin et al., 2004a; Nigg et al., 2005; Rentrop et al., 2008]. BPD patients have shown particular difficulty in actively suppressing irrelevant information when it is of an aversive nature, which correlates with their unstable affect [Domes et al., 2006]. They also made more inhibition errors than healthy controls on an anti-saccade task (especially patients with psychotic-like symptoms), distinct from their general predisposition to respond impulsively as measured by anticipatory errors [Grootens et al., 2008]. Berlin and Rolls [2004b] found that impulsivity was related to a faster subjective sense of time in BPD patients and that some symptoms of BPD may be related to problems associated with the orbitofrontal cortex (OFC). This study suggests that different symptoms of the borderline syndrome may be separable, and therefore, related to different cognitive deficits, and potentially to different brain systems.

Although results have been variable, studies generally suggest that BPD patients exhibit cognitive deficits suggestive of prefrontal and temporolimbic dysfunction [Sprock et al.,

2000], which is thought to underlie the behavioral dyscontrol, affective dysregulation, and social cognition deficits that characterize BPD [Streeter et al., 1995; Van Reekum, 1993b]. For example, several authors found that compared to healthy controls, BPD patients had deficits in visual/nonverbal memory [Beblo et al., 2006; Dinn et al., 2004], executive functions (planning, flexibility, fluency), especially on nonverbal tasks [Bazais et al., 2002; Beblo et al., 2006; Dinn et al., 2004], and visuo-spatial functions [Beblo et al., 2006; Judd et al., 1993; O'Leary et al., 1991; Swirsky-Sacchetti et al., 1993]. Monarch et al. [2004] found that relative to healthy controls, BPD inpatients were impaired in attention-vigilance and verbal learning and memory domains which implicate the frontal-subcortical and temporal limbic brain regions. In a recent review of 29 NP studies of BPD [LeGris et al., 2006], 83% of studies found impairment in one or more cognitive domains, irrespective of depression, involving generalized or specific deficits linked to the OFC and dorsolateral prefrontal cortex. A meta-analysis of 10 NP studies [Ruocco, 2005] revealed that BPD patients perform more poorly than healthy controls in all NP domains tested (attention, cognitive flexibility, learning, memory, planning, speeded processing, and visuospatial abilities), and nonverbal functions were predominantly affected suggesting these deficits were more strongly lateralized to the right hemisphere.

In sum, the data suggests that the pattern of NP deficits found in BPD patients reflects a fronto-temporal dysnfunction, primarily of the right hemisphere (e.g. nonverbal executive function and visual memory deficits) [Beblo et al., 2006; Dinn et al., 2004; Ruocco, 2005; Niederhofer, 2004]. This is consistent with neuroimaging studies of BPD, which document structural and functional abnormalities in the frontolimbic network, involving both OFC and amygdala regions, thought to mediate BPD symptomology [Schmahl et al., 2006; Brendel et al., 2005].

3.1 Prefrontal Dysfunction

Many NP studies suggest that primary deficits displayed by BPD patients, like those in executive function such as poor/risky decision making and planning [Bazanis et al., 2002; Haaland et al., 2007; Kirkpatrick et al., 2007b; Lenzenweger et al., 2004], reflect a frontal and possibly primarily orbitofrontal system dysfunction [Bazanis et al., 2002; Burgess, 1990; Stein et al., 1993; Swirsky-Sacchetti et al., 1993; Van Reekum, 1993b-1996a]. BPD patients' decision making deficits may be related to both their behavioral characteristics of affective dysregulation and/or impulsivity, and to proposed dysfunctions and reduced volume of the OFC and/or the amygdala [Berlin et al., 2005; Soloff et al., 2003; Bechara et al., 1999; Damasio, 1996; Donegan et al., 2003; Tebartz van Elst et al., 2003]. The "frontal" pattern of cognitive deficits found in BPD patients is consistent with the cognitive and physiological effects observed in OFC lesion patients [Cummings, 1985], and with the behavioral disturbances that define BPD like impulsivity, which is thought to have a neurobiological basis [Stein et al., 1993].

Berlin et al [2005] found that BPD patients had NP deficits similar to those of OFC and dissimilar to non-OFC lesion patients. The results imply that some of the core characteristics of BPD, in particular impulsivity, are similar to the effects of OFC damage, suggesting that OFC dysfunction (e.g. decreased volume or activity of the OFC) may contribute to some of the deficits in BPD, and that other characteristics of BPD, such as their high emotionality, and

personality disturbances (neurotic, introverted, low conscientiousness) are related to other brain systems. BPD patients may have a neurochemical imbalance or a hyperactive/responsive amygdala [Herpertz et al., 2001], which OFC patients may not have, which exacerbates their emotional and personality disturbances. The OFC, with its extensive reciprocal connections with the amygdala, may play a role in correcting/regulating emotional and behavioral responses [Drevets, 1998; Hornak et al. 1996-2003-2004; Rolls et al., 1994] and in guiding decision-making and adaptive response selection based on stimulus-reinforcement associations [Berlin et al., 2005]. Increased limbic discharge, decreased OFC function, and/or hypoactive frontolimbic circuitry may be involved in BPD, at least in a subgroup of patients [Van Reekum, 1993b]. Impulse control and social cognition deficits in BPD patients may result, at least in part, from OFC hypofunction, while their explosive emotionality may be associated with temporolimbic dysfunction [Berlin et al., 2005; Van Reekum, 1993b].

3.2 Temporolimbic Dysfunction

NP testing has also revealed a pattern of neurocognitive impairment among BPD patients that implicates the temporal lobes [Judd et al., 1993; O'Leary et al., 1991; Swirsky-Sacchetti et al., 1993], like deficits in complex auditory and visual memory, visual discrimination and filtering [O'Leary et al., 1991]. Patients with temporal lobe epilepsy (TLE) show a similar pattern of impairment on tests assessing verbal and nonverbal memory [Abrahams et al., 1999; Baxendale et al., 1998; Falk et al., 2002; Helmstaedter et al., 1991; Wegesin et al., 2000]. Interstingly, the diagnostic criteria for BPD resemble classical descriptions of the interictal behavioral syndrome (i.e., the temporal lobe personality) [Bear et al., 1984]. Performance deficits on tests sensitive to temporal lobe dysfunction (e.g., tests of verbal and nonverbal memory) among patients with BPD lends support to the hypothesis that a subset of BPD patients have an undiagnosed seizure disorder (e.g., temporolimbic epilepsy) [Harris et al., 2002], but more investigation is needed.

A temporal limbic dysfunction is also implicated from studies which report deficits in facial emotion recognition and emotional awareness in BPD patients compared to controls [Levine et al., 1997; Minzenberg et al., 2006]. BPD patients have also been shown to have more intense responses to negative emotions than healthy controls [Levine et al., 1997], and to be more accurate in recognizing fearful facial expressions, which relates to a response bias toward fear [Wagner et al., 1999]. A functional brain imaging study suggests that the negative attributional bias of BPD patients may be related to heightened amygdala responsivity to facial emotion [Donegan et al., 2003].

Finally, NP testing of BPD also reveals deficits of visuospatial capacity (a function localized to the inferior parietal lobe [Swinton, 2003], and the medium-to-large effect size for the visuospatial domain found in the review by Ruocco [2005] suggest possible parietal lobe pathology [Aleman et al., 2002; Fincham et al., 2002; Jacobs et al., 2002; Newman et al., 2003; Zago et al., 2002]. This brain area may be dysfunctional in those patients with BPD who have multi-modal hallucinations [Swinton, 2003].

4. COMORBIDITY AND DIMENSIONAL MODELS FOR BPD

The complexity of the neurobiological and neuropsychological data reported in BPD certainly reflects the clinical heterogeneity of the disorder as well as its frequent comorbidity with other psychiatric conditions.

Approaching comorbidity issues in BPD requires a preliminary epidemiologic assessment of some specific comorbidity patterns and a subsequent classification of the main dimensional models in which BPD may be incorporated.

With respect to the relationship between gender and comorbidity in BPD, Johnson and colleagues [2003] within the Collaborative Longitudinal Personality Disorders Study found that women were more likely to present comorbid PTSD, eating disorders, and the identity disturbance criterion of BPD, while men had a greater frequency of comorbid substance use disorders and schizotypal, narcissistic, or antisocial personality disorders.

A recent study compared symptom severity, frequency, and pattern of psychiatric comorbidity, quality of life, and health care utilization in men and women with BPD showing important differences. Women were more likely than men to have an anxiety disorder (particularly, generalized anxiety disorder), somatoform disorders, and histrionic personality disorder. Antisocial personality disorder was more common in men. Women had higher dimensional ratings of depression, anxiety, obsessive-compulsive behavior, work dysfunction, and negative affectivity; they were also more likely to endorse the "paranoia/dissociation" BPD criterion. In addition, women reported worse emotional symptoms, social role, and mental health functioning than men [McCormick et al., 2007].

Asnaani and colleagues [2007] using the number of BPD criteria in order to assess the severity of the disorder, found that patients with an increasing number of criteria for BPD had a greater lifetime history of comorbid drug use disorders, more frequent suicidal behaviors and greater comorbidity with other Axis II disorders.

With respect to the relationship between BPD and suicide, it has been reported that approximately 10% of the BPD population eventually succeeds in committing suicide, with suicidality peaking around the early 20s, and completed suicide more common after 30, particularly in treatment resistant patients [Paris, 2002]. Clinical predictors of suicidality in BPD seem to change over time: on one hand, comorbidity with Major Depressive Disorder (MDD) appears to influence the suicide risk in the short-term (e.g. in the first year), while poor social adjustment might increase the risk over the long-term [Soloff et al., 2008].

Zanarini and co-workers [2007] tried to characterize the course of 24 symptoms of BPD in terms of time to remission. The prevalence of five core symptoms was found to decline with particular rapidity: psychotic thought, self-mutilation, help-seeking suicide efforts, treatment regressions and counter-transference problems. In contrast, feelings of depression, anger, and loneliness/emptiness were more stable.

A previous follow-up study addressed whether impulsivity versus other clinical symptoms of BPD were stable over a 7-year follow-up period, finding that impulsivity was stable over time and suggesting that the treatment of impulsivity may impact the course of BPD [Links et al., 1999].

BPD has been reported to show high rates of comorbidity not only with other Axis I and II disorders but also with nonpsychiatric conditions. For example, Frankenburg and co-workers [2004] found that BPD non-remitters were significantly more likely than remitters to

have a history of a "syndrome-like" condition (i.e., chronic fatigue, fibromyalgia, or temporomandibular joint syndrome) or to have a history of obesity, osteoarthritis, diabetes, hypertension, back pain or urinary incontinence. In addition, non-remitters were significantly more likely to have had at least 1 medically related emergency room visit, 1 medical hospitalization, or 1 of each. Therefore, it could be argued that the failure to remit from BPD may be associated with a higher risk of suffering from chronic physical conditions, making poor health-related lifestyle choices, and using costly forms of medical services. The authors also found four significant risk factors: chronic PTSD, lack of exercise, a family history of obesity, and a recent history of psychotropic polypharmacy, highlighting that obesity is common among BPD patients and is associated with several chronic medical disorders.

The frequent comorbidity of BPD is not surprising if we focus on the psychopathological core features of BPD. These core symptom dimensions of BPD along with some aspects of its' comorbidity have allowed many authors to conceptualize BPD as belonging to different dimensional models. The results of a study by Skodol [2005] support the clinical use of dimensional representations in DSM-IV personality disorders. Kass and associates [1985], moreover, underscored that the use of dimensions in personality disorders convey more clinically relevant informationn about the maladaptive personality traits of patients compared to the use of categorical models. In fact, it is well established that a substantial proportion of patients with personality disorders have clinically significant traits that are below the threshold for diagnosis. Dimensional models also provide a more useful clinical tool to measure functional impairment compared to categories, and thus have greater validity to capture key aspects of disordered personality. Furthermore, from a dimensional perspective, individuals possessing the same genotype could express milder forms of the clinical disorder within a spectrum of related traits.

Several authors have associated some core features of BPD to neurobiological and neuropsychological data and clinical aspects of treatment response, and have conceptualized BPD as belonging to distinct dimensional models, in which the main psychiatric disorders of reference are substance abuse/dependence, impulse control disorders and affective disorders. In addition, BPD has been suggested to be part of a trauma related spectrum of disorders, with PTSD as the core disorder, but also including mood and dissociative disorders [Bremner, 2002].

With respect to the potential inclusion of BPD within an addictive spectrum disorders, McGlashan [2000] reported in the Collaborative Longitudinal Personality Disorders Study a high co-occurrence between substance and alcohol use disorders and BPD. The co-occurrence of substance use disorders and BPD is one of the most replicated finding in the Axis I/II comorbidity literature [Siever, 1991]. In particular, the presence of substance use disorders has been associated with the failure to achieve remission in BPD [Zanarini et al., 2004a].

The consequences of the comorbidity between BPD and substance abuse were analyzed by Links [1995] in order to assess the prognostic significance of such comorbidity. BPD patients with comorbid substance abuse were significantly different from subjects with BPD only, substance abuse only and healthy controls, having more self-destructive and suicidal thoughts and behaviors. Probands with the initial diagnoses of BPD and comorbid substance abuse were twice as likely to receive a diagnosis of BPD in the long-term than probands with the initial diagnosis of BPD only.

With regard to the relationship between BPD and impulse control disorders (ICDs), it has been proposed that BPD and ICDs may be included within a wider obsessive-compulsive

spectrum of disorders (OCSDs). Within the OCSDs, each disorder may be located on a *continuum* of different conditions on the basis of specific symptom dimensions. For example, on the harm-avoidance/risk-seeking dimension characterized by the overestimation of potential harm, OCD would represent the condition that overestimates potential harm on one end of the spectrum, while BPD would fit in on the opposite end of the spectrum as they appear to underestimate potential harm and act impulsively taking unnecessary risks [Hollander et al., 1999].

The affective spectrum model seems to be one of the more consistent for the inclusion of BPD. A recent study by Berrocal and colleagues [2008] showed that patients with BPD, even if they do not meet DSM-IV criteria for any mood disorder, tend to present subthreshold fluctuations of mood, energy levels, and cognition, both on the depressive and the manic/hypomanic side of the mood spectrum. Specific cognitive aspects may distinguish BPD patients from unipolar depressives, whereas the peculiar mood phenomenology of BPD patients might be more similar to that of the bipolar subjects. The relationship between BPD and bipolar spectrum disorders has been studied by several authors, showing mixed results. Benazzi [2006] suggested that BPD may be a mix of two sets of unrelated items: an affective instability dimension related to BP-II and an impulsivity dimension not related to BP-II. Taken as a whole, however, these findings along with other studies investigating the relationship between BPD and bipolar spectrum disorders [Deltito et al., 2001; Perugi et al., 2002] indicate that the exact nature of this link remains to be elucidated.

More recently, New and colleagues [2008] proposed the inclusion of BPD within the mood spectrum disorders because of the centrality of affective dysregulation symptoms in BPD as well as the comorbidity and co-familiality with MDD. In fact, when BPD and MDD co-occur, they can have independent courses but, more often, improvements in MDD are predicted by prior improvements in BPD. Therefore, clinicians should take into account that treatment of MDD may be followed by improvement of BPD [Gunderson et al., 2004].

Interestingly, Zanarini and colleagues [1998] found that a cognitive or micropsychotic dimension (paranoid thinking, hallucinatory phenomena, and depersonalization) is the most useful feature for discriminating BPD from other Axis II disorders.

After examining the complex relationship between BPD and other comorbid disorders in light of a dimensional prospective, it is noteworthy to highlight that being able to explain BPD using different models does not necessarily imply that these models are incompatible. Rather it may suggest the possible presence of distinct subgroups of BPD patients. Furthermore, the different models of categorization could provide the basis and rationale for the use of specific treatments in BPD patients, indicating the presence of specific subgroups of patients with similar core features, comorbid profiles and treatment-responses within the wider population of BPD patients. Therefore, being able to identify different subtypes of BPD patients that share similar phenomenological and clinical characteristics might not only lead to a better understanding of this disorder, but also to a better use of pharmacological options. In fact, if it is possible to distinguish different clinical subtypes, it would seem logical that pharmacological treatments could be optimized to fit specific subgroups.

5. TREATMENT OPTIONS IN BPD

5.1 Pharmacological Treatments

The ability of specific pharmacological treatments to improve some symptoms in some BPD patients and the lack of efficacy in other patients, supports the presence of different subgroups of patients and encourages the choice of a pharmacotherapy based on patient's unique symptom profile and comorbidity.

Several core symptoms of BPD could conceivably be targeted for treatment: impulsive symptoms, compulsive behaviors, and affective and addictive symptoms.

A rational pharmacological choice would take into account which of these symptom domains seem to dominate, as well as comorbid disorders, because treatment should ultimately target all clinically significant symptoms in the individual patient.

In particular, for the management of the affective dysregulation symptoms (liability, inappropriate anger, bursts of temperament, depressive episodes), the American Psychiatry Association guidelines suggest the use of SSRIs as first-line treatment, given that these agents can reduce the severity of global symptomatology, impulsive aggression and affective instability in patients with BPD [APA, 2001].

The impulsive dimension, responsible for the self injurious behaviours (drug intoxications, physical injuries, self and hetero aggressivity), substance abuse and bulimic behaviours, appears to be related to a serotoninergic dysfunction: in fact, low levels of serotonin have been associated to greater impulsivity [Paris, 2004]. In order to improve impulse dyscontrol (e.g., aggressive impulse, self-mutilation, self-destructive behaviours), the APA guidelines still recommend the SSRIs as the first pharmacologic option, considering the use of low doses of antipsychotics as second-line treatment. If both strategies fail, the use of mood stabilizers or MAOIs should be considered.

Recently, Abraham and Calabrese [2008] suggested the need for a shift from antidepressants to mood stabilizers/anticonvulsants and atypical antipsychotics. In particular, anticonvulsant drugs have been indicated as effective for the affective instability. Among these compounds, Valproate has been shown to improve mood symptoms of BPD patients in different trials [Hollander et al., 2005; Simeon et al., 2007].

Another anticonvulsant, Lamotrigine, was found to be effective and safe in both the acute and long term treatment of BPD patients displaying pathological aggression [Leiberich et al., 2008]. Carbamazepine also may be effective in reducing impulsive behaviors and angry outbursts in BPD patients [Cowdry et al., 1988] with a potential efficacy over affective instability. Topiramate, which has a well-established efficacy in alcohol dependence, cocaine dependence, pathological gambling, and some eating disorders, may also represent a valid alternative for the treatment of personality disorders dominated by impulsivity like BPD [Nickel et al., 2008].

Taken as a whole, the studies conducted with mood stabilizers in BPD indicate that these drugs are particularly suitable for patients with BPD given their efficacy in treating both impulsive behaviors and affective swings. Given that these two dimensions may be related, clinicians may also expect that a decrease in any of the two domains would improve the other one, improving the overall clinical condition.

Recently, low doses of atypical antipsychotic have been used with positive results in BPD patients [Mobascher et al., 2007]. According to the APA guidelines, antipsychotic agents are recommended in patients with BPD who present with cognitive-perceptual symptoms, acute anger, hostility, assaultiveness and self-injury.

Among atypical antipsychotics, Ziprasidone has been studied in a double-blind, placebo-controlled trial in BPD patients without showing significant effect [Pascual et al., 2008].

Few data are available on the use of Quetiapine in BPD. Van den Eynde and colleagues [2008] have recently investigated, in a 12-week open-label study, the effect of Quetiapine for impulsivity and a broad range of affective symptoms in BPD. The results suggest that Quetiapine may be effective in the treatment of BPD.

The results of Zanarini et al.'s [2004b] direct comparison of Olanzapine–Fluoxetine combined (O-FC) versus Fluoxetine and Olanzapine monotherapies are of particular interest. Even though a placebo group was lacking, and patients in all arms seemed to improve, both Olanzapine and O-FC were superior to Fluoxetine alone. Olanzapine, however, was superior to O-FC in the treatment of depressive symptoms.

A recent pilot study tested the efficacy and tolerability of Risperidone in patients with BPD, evaluating the utility of a new self-report treatment outcome measure for BPD, the Borderline Disorder Rating Scale (BDRS). Risperidone, at a mean final dose of 1.8 mg/day after 8 weeks of treatment, resulted in a statistically significant overall improvement and in each symptom dimension of BPD [Friedel et al., 2008].

Nevertheless, a major problem in the treatment of BPD may be the lack of compliance derived from the pathological impulsivity which is characteristic of many patients. Along these lines, a recent study has evaluated the use of intramuscular long-acting Risperidone for a six-month period in a sample of BPD patients refractory to previous treatments, showing a significant clinical and functional improvement combined with an excellent tolerability [Diaz-Marsà et al., 2008].

An innovative therapy with Omega-3 Fatty Acids has shown promising results in BPD. The rational for this therapy is based on the fact that the administration of eicosapentaenoic acid (EPA), a structural component of the neuronal membranes, and of docosahexaenoic acid (DHA) that participates in neuronal activity, would improve brain functioning [Peet et al., 2005]. A previous double blind study has also suggested that Omega-3 Fatty Acid Treatment improves aggression in female patients with BPD [Zanarini et al., 2003].

Previous investigation has suggested that alterations of the endogenous opiate system may contribute to dissociative symptoms in patients with BPD and PTSD and that these symptoms may respond to treatment with opiate antagonists. In accordance, several case reports and open trials found Naloxone and Naltrexone to be helpful for self-injurious behaviors and dissociative symptoms in developmental and personality disorders including BPD [Bohus et al., 1999; Schmahl et al., 1999].

5.2 Psychotherapic Interventions

Several guidelines and authors indicate psychotherapy as the primary, or core-treatment for BPD and report that adjunctive, symptom-targeted pharmacotherapy can be helpful in the treatment of several symptom domains. Binks and colleagues [2008] have recently suggested

that some of the problems frequently encountered by people with BPD may be amenable to talking/behavioral treatments.

Clinical experience suggests that there are a number of common features that lead the psychotherapist, regardless of the specific type of therapy used. These features include building a strong therapeutic alliance and monitoring self-destructive and suicidal behaviors. Some therapists create a hierarchy of priorities to consider within the treatment (e.g., first focusing on suicidal behavior). Furthermore, it has been suggested that assessing and supporting family, work and social relationships may decrease suicidal behavior in BPD and should be considered a principal focus of long-term treatment [Soloff et al., 2008].

Other valuable interventions include validating the patient's suffering and experience as well as helping the patients to take responsibility for their actions. Because patients with BPD may exhibit a broad array of strengths and weaknesses, flexibility is a crucial aspect of effective therapy. Other components of effective therapy for patients with BPD include managing feelings (in both patient and therapist), promoting reflection rather than impulsive action, reducing patient's tendency to engage in splitting, and setting limits on any self-destructive behavior.

Randomized controlled trials of BPD psychotherapies suggest that more than one type of psychotherapy is effective. In particular, two psychotherapeutic approaches have been shown to be useful in BPD: psychoanalytic/psychodynamic therapy and dialectical behavior therapy.

Psychodynamic psychotherapy has been defined as a therapy that involves careful attention to the therapist-patient interaction with, when indicated, thoughtfully timed interpretation of transference and resistance embedded in a sophisticated appreciation of the therapist's contribution to the two-person field. Psychodynamic psychotherapy is usually conceptualized as operating on an exploratory-supportive (also called expressive-supportive) continuum of interventions. At the more exploratory end of the continuum, for example, the goals of psychodynamic psychotherapy with patients with BPD are to make unconscious patterns more consciously available, to increase affect tolerance, to build a capacity to delay impulsive actions, to provide insight into relationship problems, and to develop reflective functioning so that there is greater appreciation of internal motivation in self and others [APA, 2001].

Dialectical behaviour therapy (DBT) has been shown in a randomized controlled trial to be effective for borderline symptoms in patients with comorbid substance abuse, though no improvement was shown for the substance abuse itself [Van der Bosch et al., 2002]. These findings suggest that patients with both BPD and substance abuse should be encouraged to focus on their abuse problems as a priority.

6. CONCLUSION

The continuing evolution of the diagnostic criteria and essential features of BPD along with several neurobiological and neuropsychological recent findings may in part justify the complex clinical approach to this frequent and disabling personality disorder.

Neurobiological and neuropsychological studies in BPD have provided important contributions in the attempt to elucidate the complex pathway from specific alterations of certain brain circuits to core symptoms of BPD. On the other hand, it is extremely difficult to

link neurobiological and clinical issues within a comprehensive and homogeneous model that might help clinicians understand the etiology of BPD and target the most effective treatment. This situation may be partially explained by the fact that diagnostic criteria for BPD, like other mental conditions, are clinically derived. Therefore, it may be expected that continuous acquisitions in the neurobiological field of BPD will confirm the heterogeneity of the disorder and support a further differentiation of distinct phenotypes of BPD with more homogeneous features and patterns of treatment response.

Strongly related to the clinical heterogeneity of BPD is its' frequent comorbidity. Thus, a dimensional approach to BPD may help to integrate neurobiological data to clinical practice. A clinical dissection and a precise characterization of the main symptom domains and comorbidity profiles of BPD patients represents a rational and valid approach to define patients clinical picture and select the best treatment options.

REFERENCES

Abraham, PF; Calabrese, J. Evidenced-based pharmacologic treatment of borderline personality disorder: A shift from SSRIs to anticonvulsants and atypical antipsychotics? *J Affect Disord*, 2008, 111(1):21-30.

Abrahams, S; Morris, RG; Polkey, CE; Jarosz, JM; Cox, TC; Graves, M et al. Hippocampal involvement in spatial and working memory: a structural MRI analysis of patients with unilateral mesial temporal lobe sclerosis. *Brain Cogn*, 1999, 41:39-65.

Aleman, A; Schutter, DJ; Ramsey, NF; van Honk, J; Kessels, RP; Hoogduin, JM et al. Functional anatomy of top-down visuospatial processing in the human brain: evidence from rTMS. *Brain Res Cogn Brain Res*, 2002, 14:300-302.

American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed, text revision (DSM-IV-TR). Washington, DC: American Psychiatric Association, 2000.

American Psychiatric Association: Practice guideline for the treatment of patients with borderline personality disorder. *Am J Psychiatry*, 2001,158:1–52.

Andrulonis, PA; Glueck, BC; Stroebel, CF; Vogel, NG; Shapiro, AL; Aldridge, DM. Organic brain dysfunction and the borderline syndrome. *Psychiatr Clin North Am*, 1981, 4:47-66.

Andrulonis, PA; Glueck, BC; Stroebel, CF; Vogel, NG. Borderline personality subcategories. *J Nerv Ment Dis*, 1982, 170:670-679.

Andrulonis, PA; Vogel, NG. Comparison of borderline personality subcategories to schizophrenic and affective disorders. *Br J Psychiatry*, 1984, 144:358-363.

Asnaani, A; Chelminski, I; Young, D; Zimmerman, M. Heterogeneity of borderline personality disorder: do the number of criteria met make a difference? *J Personal Disord*, 2007, 21(6):615-25.

Baxendale, SA; Thompson, PJ; Van Paesschen, W. A test of spatial memory and its clinical utility in the pre-surgical investigation of temporal lobe epilepsy patients. *Neuropsychologia*, 1998, 36:591-602.

Bazanis, E; Rogers, RD; Dowson, JH; Taylor, P; Meux, C; Staley, C et al. Neurocognitive deficits in decision-making and planning of patients with DSM-III-R borderline personality disorder. *Psychol Med*, 2002, 32:1395-1405.

Bear, DM; Freeman, R; Greenberg, M. Behavioral alterations in temporal lobe epilepsy. In: Blumer D editor. Psychiatric Aspects of Epilepsy. Washington, DC: American Psychiatric Press, 1984, 197–227.

Beblo, T; Saavedra, AS; Mensebach, C; Lange, W; Markowitsch, HJ; Rau, H et al. Deficits in visual functions and neuropsychological inconsistency in Borderline Personality Disorder. *Psychiatry Res*, 2006, 145:127-135.

Bechara, A; Damasio, H; Damasio, AR; Lee, GP. Different contributions of the human amygdala and ventromedial prefrontal cortex to decision-making. *J Neurosci*, 1999, 19:5473-5481.

Benazzi, F. Borderline personality-bipolar spectrum relationship. Prog Neuropsychopharmacol Biol Psychiatry, 2006, 30(1):68-74.

Berlin, HA; Rolls, ET; Iversen, SD. BPD, impulsivity, and the OFC. *Am J Psychiatry*, 2005, 162:2360–73.

Berlin, HA; Rolls, ET. Time perception, impulsivity, emotionality, and personality in self-harming borderline personality disorder patients. *J Personal Disord*, 2004a, 18:358-378

Berlin, HA; Rolls, ET; Kischka, U. Impulsivity, time perception, emotion and reinforcement sensitivity in patients with OFC lesions. *Brain*, 2004b, 127:1108-1126.

Berrocal, C; Ruiz Moreno, MA; Rando, MA; Benvenuti, A; Cassano, GB. Borderline personality disorder and mood spectrum. *Psychiatry Res*, 2008, 159(3):300-7.

Binks, CA; Fenton, M; McCarthy, L; Lee, T; Adams, CE; Duggan, C. Psychological therapies for people with borderline personality disorder (Review). The Cochrane Collaboration and published in The Cochrane Library 2008, Issue 2.

Bohus, MJ; Landwehrmeyer, GB; Stiglmayr, CE; Limberger, MF; Böhme, R; Schmahl, CG. Naltrexone in the treatment of dissociative symptoms in patients with borderline personality disorder: an open-label trial. *J Clin Psychiatry*, 1999, 60(9):598-603.

Bremner, JD; Vythilingam, M; Vermetten, E; Southwick, SM; McGlashan, T; Nazeer, A et al. MRI and PET study of deficits in hippocampal structure and function in women with childhood sexual abuse and posttraumatic stress disorder. *Am J Psychiatry*, 2003, 160:924–32.

Bremner, JD. Does Stress damage the brain? New York: Norton, 2002.

Brendel, GR; Stern, E; Silbersweig, DA. Defining the neurocircuitry of borderline personality disorder: functional neuroimaging approaches. Dev Psychopathol,2005,17:1197-1206.

Burgess, JW. Cognitive information processing in borderline personality disorder. *Jefferson Journal of Psychiatry*, 1990, 3:34-49.

Burgess, JW. Neurocognitive impairment in dramatic personalities: histrionic, narcissistic, borderline, and antisocial disorders. *Psychiatry Res*, 1992, 42:283-290.

Coccaro, EF; Bergeman, CS; Kavoussi, RJ. Heritability of aggression and irritability: a twin study of the Buss-Durkee aggression scales in adult male subjects. *Biol Psychiatry*, 1997, 41:273-84.

Coccaro, EF; Bergeman, CS; McClearn, GE. Heritability of irritable impulsiveness: a study of twins reared together and apart. *Psychiatry Res*, 1993, 48:229-42.

Cowdry, RW; Gardner, DL. Pharmacotherapy of borderline personality disorder. Alprazolam, carbamazepine, trifluoperazine, and tranylcypromine. *Arch Gen Psychiatry*, 1988 ,45(2):111-9.

Cummings, JL. Clinical neuropsychiatry,1985. Orlando, FL: Grune & Stratton.

Damasio, AR. The somatic marker hypothesis and the possible functions of the prefrontal cortex. *Philos Trans R Soc Lond B Biol Sci*, 1996, 351:1413-1420.

De la Fuente, JM; Goldman, S; Stanus, E; Vizuete, C; Morlán, I; Bobes, J et al. Brain glucose metabolism in BPD. *J Psychiatr Res*, 1997, 31:531-41.

Deltito, J; Martin, L; Riefkohl, J; Austria, B; Kissilenko, A; Corless, C et al. Do patients with borderline personality disorder belong to the bipolar spectrum? *J Affect Disord*, 2001, 67(1-3):221-8.

Díaz-Marsá, M; Galian, A; Montes, R; Fernández, R; Arza, JJ; López-Ibor, J et al.. Long-acting injectable risperidone in treatment resistant borderline personality disorder. A small series report. *Actas Esp Psiquiatr*, 2008, 36(2):70-74.

Dinn, WM; Harris, CL; Aycicegi, A; Greene, PB; Kirkley, SM; Reilly, C. Neurocognitive function in borderline personality disorder. *Prog Neuropsychopharmacol Biol Psychiatr*y, 2004, 28:329-341.

Domes, G; Winter, B; Schnell, K; Vohs, K; Fast, K; Herpertz, SC. The influence of emotions on inhibitory functioning in borderline personality disorder. *Psychol Med*, 2006, 36:1163-1172.

Donegan, NH; Sanislow, CA; Blumberg, HP; Fulbright, RK; Lacadie, C; Skudlarski, P et al. Amygdala hyperreactivity in borderline personality disorder: implications for emotional dysregulation. *Biol Psychiatry*, 2003, 54:1284-1293.

Drevets, WC. Functional neuroimaging studies of depression: the anatomy of melancholia. *Annu Rev Med*, 1998, 49:341-361.

Driessen, M; Herrmann, J; Stahl, K; Zwaan, M; Meier, S; Hill, A et al. Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Arch Gen Psychiatry*, 2000, 57(12):1115-22.

Falk, MC; Cole, LC; Glosser, G. Pseudoword and real word memory in unilateral temporal lobe epilepsy. *J Clin Exp Neuropsycho*l, 2002, 24:327-334.

Fincham, JM; Carter, CS; van Veen, V; Stenger, VA; Anderson, JR. Neural mechanisms of planning: a computational analysis using event-related fMRI. *Proc Natl Acad Sci U S A*, 2002, 99:3346-3351.

Frankenburg, FR; Zanarini, MC. The association between borderline personality disorder and chronic medical illnesses, poor health-related lifestyle choices, and costly forms of health care utilization. *J Clin Psychiatry*, 2004, 65(12):1660-5.

Friedel, RO; Jackson, WT; Huston, CS; May, RS; Kirby, NL; Stoves, A. Risperidone treatment of borderline personality disorder assessed by a borderline personality disorder-specific outcome measure: a pilot study. *J Clin Psychopharmacol*, 2008, 28(3):345-7.

Friedel, RO. Dopamine dysfunction in BPD: a hypothesis. *Neuropsychopharmacology*, 2004, 29:1029-39.

Gardner, D; Lucas, PB; Cowdry, RW. Soft sign neurological abnormalities in borderline personality disorder and normal control subjects. *J Nerv Ment Dis*, 1987, 175:177-180.

Gilbertson, MW; Shenton, ME; Ciszewski, A; Kasai, K; Lasko, NB; Orr, SP et al. Smaller hippocampal volume predicts pathological vulnerability to psychological trauma. *Nat Neurosci*, 2002, 5:1242–7.

Grant, BF; Chou, SP; Goldstein, RB; Huang, B; Stinson, FS; Saha, TD et al. Prevalence, Correlates, Disability, and Comorbidity of DSM-IV BPD: Results From the Wave 2

National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*, 08, 69(4):533-45.

Grilo, CM; Shea, MT; Sanislow, CA; Skodol, AE; Gunderson, JG; Stout, RL et al. Two-year stability and change of schizotypal, borderline, avoidant, and obsessive-compulsive personality disorders. *J Consult Clin Psychol*, 2004, 72(5):767-75.

Grootens, KP; van Luijtelaar, G; Buitelaar, JK; van der Laan, A; Hummelen, JW; Verkes, RJ. Inhibition errors in borderline personality disorder with psychotic-like symptoms. Prog *Neuropsychopharmacol Biol Psychiatry*, 2008, 32:267-273.

Grosjean, B; Tsai, G. NMDA neurotransmission as a critical mediator of BPD. *J Psychiatry Neurosci*, 2007, 32(2):103-15.

Gunderson, JG; Morey, LC; Stout, RL; Skodol, AE; Shea, MT; McGlashan, TH et al. Major depressive disorder and borderline personality disorder revisited: longitudinal interactions. *J Clin Psychiatry*, 2004, 65(8):1049-56.

Haaland, VO; Landro, NI. Decision making as measured with the Iowa Gambling Task in patients with borderline personality disorder. J Int Neuropsychol Soc,2007,13:699-703.

Harris, CL; Dinn, WM; Marcinkiewicz, JA. Partial seizure-like symptoms in borderline personality disorder. *Epilepsy Behav*, 2002, 3:433-438.

Helmstaedter, C; Pohl, C; Hufnagel, A; Elger, CE. Visual learning deficits in nonresected patients with right temporal lobe epilepsy. *Cortex*, 1991, 27:547-555.

Herpertz, SC; Dietrich, TM; Wenning, B; Krings, T; Erberich, SG; Willmes, K et al. Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. *Biol Psychiatry*, 2001, 50:292-298.

Hollander, E; Swann, AC; Coccaro, EF; Jiang, P; Smith, TB. Impact of trait impulsivity and state aggression on divalproex versus placebo response in borderline personality disorder. *Am J Psychiatry*, 2005, 162(3):621-4.

Hollander, E. Managing aggressive behavior in patients with obsessive-compulsive disorder and borderline personality disorder. *J Clin Psychiatry*, 1999, 60(15):38-44.

Hornak, J; Bramham, J; Rolls, ET; Morris, RG; O'Doherty, J; Bullock, PR et al. Changes in emotion after circumscribed surgical lesions of the orbitofrontal and cingulate cortices. *Brain*, 2003, 126:1691-1712.

Hornak, J; O'Doherty, J; Bramham, J; Rolls, ET; Morris, RG; Bullock, PR et al. Reward-related reversal learning after surgical excisions in orbito-frontal or dorsolateral prefrontal cortex in humans. *J Cogn Neurosci*, 2004, 16:463-478.

Hornak, J; Rolls, ET; Wade, D. Face and voice expression identification in patients with emotional and behavioural changes following ventral frontal lobe damage. *Neuropsychologia*, 1996, 34:247-261.

Jacobs, R; Anderson, V. Planning and problem solving skills following focal frontal brain lesions in childhood: analysis using the Tower of London. *Child Neuropsychol*, 2002, 8:93-106.

Johnson, DM; Shea, MT; Yen, S; Battle, CL; Zlotnick, C; Sanislow, CA et al. Gender differences in borderline personality disorder: findings from the Collaborative Longitudinal Personality Disorders Study. *Compr Psychiatry*, 2003, 44(4):284-92.

Judd, PH; Ruff, RM. Neuropsychological dysfunction in borderline personality disorder. *J Personal Disord*, 1993, 7:275–284.

Kass, F; Skodol, AE; Charles, E; Spitzer, RL; Williams, JB. Scaled ratings of DSM-III personality disorders. *Am J Psychiatry*, 1985, 142:627–630.

Kernberg, OF; Dulz, B; Sachsse, U. Handbuch der Borderline-Störungen,2000,Stuttgart: Schattauer.

Kirkpatrick, T; Joyce, E; Milton, J; Duggan, C; Tyrer, P; Rogers, RD. Altered memory and affective instability in prisoners assessed for dangerous and severe personality disorder. *Br J Psychiatry*, 2007a,(49):s20-26.

Kirkpatrick, T; Joyce, E; Milton, J; Duggan, C; Tyrer, P; Rogers, RD. Altered emotional decision-making in prisoners with borderline personality disorder. *J Personal Disord*, 2007b, 21:243-26.

LeGris, J; van Reekum, R. The neuropsychological correlates of borderline personality disorder and suicidal behaviour. *Can J Psychiatry*, 2006, 51:131-142.

Leiberich, P; Nickel, MK; Tritt, K; Pedrosa Gil, F. Lamotrigine treatment of aggression in female borderline patients, Part II: an 18-month follow-up. *J Psychopharmacol*, 2008, 22(7):805-8.

Lenzenweger, MF; Clarkin, JF; Fertuck, EA; Kernberg, OF. Executive neurocognitive functioning and neurobehavioral systems indicators in borderline personality disorder: a preliminary study. *J Personal Disord*, 2004, 18:421-438.

Levine, D; Marziali, E; Hood, J. Emotion processing in borderline personality disorders. *J Nerv Ment Di*s, 1997, 185:240-246.

Lieb, K; Zanarini, MC; Schmahl, C; Linehan, MM; Bohus, M. Borderline Personality Disorder. *Lancet*, 2004, 364(9432):453-61.

Links, PS; Heslegrave, R; van Reekum, R. Impulsivity: core aspect of borderline personality disorder. *J Personal Disord*, 1999, 13(1):1-9.

Links, PS; Heslegrave, RJ; Mitton, JE; van Reekum, R; Patrick, J. Borderline personality disorder and substance abuse: consequences of comorbidity. *Can J Psychiatry*, 1995, 40(1):9-14.

Lyons-Ruth, K; Holmes, BM; Sasvari-Szekely, M; Ronai, Z; Nemoda, Z; Pauls, D. Serotonin transporter polymorphism and borderline or antisocial traits among low-income young adults. *Psychiatr Genet*, 2007, 17(6):339-43.

McCormick, B; Blum, N; Hansel, R; Franklin, JA; St. John, D; Pfohl, B et al. Relationship of sex to symptom severity, psychiatric comorbidity, and health care utilization in 163 subjects with borderline personality disorder. *Compr Psychiatry*, 2007, 48(5):406-12.

McGlashan, TH; Grilo, CM; Skodol, AE; Gunderson, JG; Shea, MT; Morey, LC et al. The Collaborative Longitudinal Personality Disorders Study: baseline Axis I/II and II/II diagnostic co-occurrence. *Acta Psychiatr Scand*, 2000, 102(4):256-64.

Minzenberg, MJ; Poole, JH; Vinogradov, S. Social-emotion recognition in borderline personality disorder. *Compr Psychiatry*, 2006, 47:468-474.

Mobascher, A; Mobascher, J; Schmahl, C; Malevani, J. Treatment of borderline personality disorder with atypical antipsychotic drugs. *Nervenarzt*, 2007, 78(9):1003-13.

Monarch, ES; Saykin, AJ; Flashman, LA. Neuropsychological impairment in borderline personality disorder. *Psychiatr Clin North Am*, 2004, 27:67-82.

New, AS; Triebwasser, J; Charney, DS. The Case for Shifting Borderline Personality Disorder to Axis I. *Biol Psychiatry*, 2008, 64(8):653-9.

Newman, SD; Carpenter, PA; Varma, S; Just, MA. Frontal and parietal participation in problem solving in the Tower of London: fMRI and computational modeling of planning and high-level perception. *Neuropsychologia*, 2003, 41:1668-1682.

Nickel, MK; Loew, TH. Treatment of aggression with topiramate in male borderline patients, part II: 18-month follow-up. *Eur Psychiatry*, 2008, 23(2):115-7.

Niederhofer, H. Left-handedness in a sample of nine patients with borderline personality disorder. *Percept Mot Skills*, 2004, 99:849-852.

Nigg, JT; Silk, KR; Stavro, G; Miller, T. Disinhibition and borderline personality disorder. *Dev Psychopathol*, 2005, 17:1129-1149.

O'Leary, KM; Brouwers, P; Gardner, DL; Cowdry, RW. Neuropsychological testing of patients with borderline personality disorder. *Am J Psychiatry*, 1991, 148:106-111.

Paris, J; Zweig-Frank, H; Kin, NM; Schwartz, G; Steiger, H; Nair, NP. Neurobiological correlates of diagnosis and underlying traits in patients with BPD compared with normal controls. *Psychiatry Res*, 2004, 121(3):239-52.

Paris, J. Chronic suicidality among patients with BPD. Psychiatr Serv,2002,53(6):738-42.

Paris, J. The nature of BPD: multiple dimensions, multiple symptoms, but one category. *J Personal Disord*, 2007, 21(5):457-73.

Pascual, C; Soler, J; Puigdemont, D; Pérez-Egea, R; Tiana, T; Alvarez, E et al. Ziprasidone in the Treatment of Borderline Personality Disorder: A Double-Blind, Placebo-Controlled, Randomized Study. *J Clin Psychiatry*, 2008, 69(4):603-8.

Peet, M; Stokes, C. Omega-3 fatty acids in the treatment of psychiatric disorders. *Drugs*, 2005, 65(8):1051-9.

Perugi, G; Akiskal, HS. The soft bipolar spectrum redefined: focus on the cyclothymic, anxious-sensitive, impulse-dyscontrol, and binge-eating connection in bipolar II and related conditions. *Psychiatr Clin North Am*, 2002, 25(4):713-37.

Posner, MI; Rothbart, MK; Vizueta, N; Levy, KN; Evans, DE; Thomas, KM et al. Attentional mechanisms of borderline personality disorder. *Proc Natl Acad Sci U S A*, 2002, 99(25):16366-16370.

Quitkin, F; Rifkin, A; Klein, DF. Neurologic soft signs in schizophrenia and character disorders. Organicity in schizophrenia with premorbid asociality and emotionally unstable character disorders. *Arch Gen Psychiatry*, 1976, 33:845-853.

Rentrop, M; Backenstrass, M; Jaentsch, B; Kaiser, S; Roth, A; Unger, J et al. Response inhibition in borderline personality disorder: performance in a Go/Nogo task. *Psychopathology*, 2008, 41:50-57.

Retz, W; Retz-Junginger, P; Supprian, T. Association of serotonin transporter promoter gene polymorphism with violence: relation with personality disorders, impulsivity, and childhood ADHD psychopathology. *Behav Sci Law*, 2004, 22:415-25.

Rolls, ET; Hornak, J; Wade, D; McGrath, J. Emotion-related learning in patients with social and emotional changes associated with frontal lobe damage. *J Neurol Neurosurg Psychiatry*, 1994, 57:1518-1524.

Ruocco, AC. The neuropsychology of borderline personality disorder: a meta-analysis and review. *Psychiatry Res*, 2005, 137:191-202.

Sapolsky, RM. The possibility of neurotoxicity in the hippocampus in major depression: a primer on neuron death. *Biol Psychiatry*, 2000, 48(8):755-65.

Schmahl, C; Bremner, JD. Neuroimaging in borderline personality disorder. *J Psychiatr Res*, 2006, 40:419-427.

Schmahl, C; Stiglmayr, C; Böhme, R; Bohus, M. Treatment of dissociative symptoms in borderline patients with naltrexone. *Nervenarzt*, 1999, 70(3):262-4.

Siever, LJ; Davis, KL. A psychobiological perspective on the personality disorders. *Am J Psychiatry*, 1991, 148:1647-1658.

Simeon, D; Baker, B; Chaplin, W; Braun, A; Hollander, E. An open-label trial of divalproex extended-release in the treatment of borderline personality disorder. *CNS Spectr*, 2007, 12(6):439-43.

Skodol, Oldham, Bender, Dyck**,** Dimensional Representations of DSM-IV Personality Disorders: Relationships to Functional Impairment. *Am J Psychiatry*, 2005, 162:1919–1925.

Soloff, PH; Fabio, A. Prospective Predictors of Suicide Attempts in BPD at One, Two, and Two-to-Five Year Follow-up. *J Personal Disord*, 2008, 22(2):123-34.

Soloff, PH; Meltzer, CC; Becker, C; Greer, PJ; Kelly, TM; Constantine, D. Impulsivity and prefrontal hypometabolism in BPD. *Psychiatry Res*, 2003, 123(3):153-63.

Sprock, J; Rader, TJ; Kendall, JP; Yoder, CY. Neuropsychological functioning in patients with borderline personality disorder. *J Clin Psycho*l, 2000, 56:1587-1600.

Stein, DJ; Hollander, E; Cohen, L; Frenkel, M; Saoud, JB; DeCaria, C et al. Neuropsychiatric impairment in impulsive personality disorders. *Psychiatry Res*, 1993, 48:257-266.

Sternbach, SE; Judd, PH; Sabo, AN; McGlashan, T; Gunderson, JG. Cognitive and perceptual distortions in borderline personality disorder and schizotypal personality disorder in a vignette sample. *Compr Psychiatry*, 1992, 33:186-189.

Stevens, A; Burkhardt, M; Hautzinger, M; Schwarz, J; Unckel, C. Borderline personality disorder: impaired visual perception and working memory. *Psychiatry Res*, 2004, 125:257-267.

Stone, VE; Baron-Cohen, S; Knight, RT. Frontal lobe contributions to theory of mind. *J Cogn Neurosci*, 1998, 10:640-656.

Streeter, CC; Van Reekum, RM; Shorr, RI; Bachman, DL. Prior head injury in male veterans with borderline personality disorder. *J Nerv Ment Dis*, 1995, 183:577-581.

Swinton, M. The role of the parietal lobe in borderline personality disorder. *Med Hypotheses*, 2003, 60:263-267.

Swirsky-Sacchetti, T; Gorton, G; Samuel, S; Sobel, R; Genetta-Wadley, A; Burleigh, B. Neuropsychological function in borderline personality disorder. *J Clin Psychol*, 1993, 49:385-396.

Tebartz van Elst, L; Hesslinger, B; Thiel, T; Geiger, E; Haegele, K; Lemieux, L et al. Frontolimbic brain abnormalities in patients with borderline personality disorder: a volumetric magnetic resonance imaging study. *Biol Psychiatry*, 2003, 54:163-171.

Tebartz van Elst, L; Ludaescher, P; Thiel, T; Büchert, M; Hesslinger, B; Bohus, M et al. Evidence of disturbed amygdalar energy metabolism in patients with borderline personality disorder. *Neurosci Lett*, 2007, 417(1):36-41.

Torgersen, S. Genetic and nosological aspects of schizotypal and BPDs: a twin study. *Arch Gen Psychiatry*, 1984, 41:546-54.

Travers, C; King, R. An investigation of organic factors in the neuropsychological functioning of patients with borderline personality disorder. *J Personal Disord*, 2005, 19:1-18.

Van den Bosch, LM; Verheul, R; Schippers, GM; van den Brink, W. Dialectical Behavior Therapy of borderline patients with and without substance use problems. Implementation and long-term effects. *Addict Behav*, 2002, 27(6):911-23.

Van den Eynde, F; Senturk, V; Naudts, K; Vogels, C; Bernagie, K; Thas, O et al. Efficacy of quetiapine for impulsivity and affective symptoms in borderline personality disorder. *J Clin Psychopharmacol*, 2008, 28(2):147-55.

Van Reekum, R; Conway, CA; Gansler, D; White, R; Bachman, DL. Neurobehavioral study of borderline personality disorder. *J Psychiatry Neurosci*,1993a,18:121-129.

Van Reekum, R. Acquired and developmental brain dysfunction in borderline personality disorder. *Can J Psychiatry*, 1993b, 38(1):S4-10.

Van Reekum, R; Links, PS; Finlayson, MA; Boyle, M; Boiago, I; Ostrander, LA et al. Repeat neurobehavioral study of borderline personality disorder. *J Psychiatry Neurosci*, 1996a, 21:13-20.

Van Reekum, R; Links, PS; Mitton, MJ; Fedorov, C; Patrick, J. Impulsivity, defensive functioning, and borderline personality disorder. *Can J Psychiatry*, 1996b, 41:81-84.

Wagner, AW; Linehan, MM. Facial expression recognition ability among women with borderline personality disorder: implications for emotion regulation? *J Personal Disord*, 1999, 13:329-344.

Wegesin, DJ; Nelson, CA. Effects of inter-item lag on recognition memory in seizure patients preceding temporal lobe resection: evidence from event-related potentials. *Int J Psychophysiol*, 2000, 37:243-255.

Zago, L; Tzourio-Mazoyer, N. Distinguishing visuospatial working memory and complex mental calculation areas within the parietal lobes. *Neurosci Lett*, 2002, 331:45-49.

Zanarini, MC; Frankenburg, FR; Hennen, J; Reich, DB; Silk, KR. Axis I comorbidity in patients with borderline personality disorder: 6-year follow-up and prediction of time to remission. *Am J Psychiatry*, 2004a, 161(11):2108-14.

Zanarini, MC; Frankenburg, FR; Parachini, EA. A preliminary, randomized trial of fluoxetine, olanzapine, and the olanzapine-fluoxetine combination in women with borderline personality disorder. *J Clin Psychiatry*, 2004b, 65(7):903-7.

Zanarini, MC; Frankenburg, FR; Reich, DB; Silk, KR; Hudson, JI; McSweeney, LB. The subsyndromal phenomenology of borderline personality disorder: a 10-year follow-up study. *Am J Psychiatry*, 2007, 164(6):929-35.

Zanarini, MC; Frankenburg, FR. Omega-3 Fatty acid treatment of women with borderline personality disorder: a double-blind, placebo-controlled pilot study. *Am J Psychiatry*, 2003,160(1):167-9.

Zanarini, MC; Gunderson, JG; Frankenburg, FR; Chauncey, DL. The Revised Diagnostic Interview for Borderlines: discriminating BPD from other axis II disorders. *J Personal Disord*, 1998,3:10-18.

Zanarini, MC; Gunderson, JG; Frankenburg, FR. Cognitive features of borderline personality disorder. *Am J Psychiatry*, 1990,147:57-63.

Zetzsche, T; Preuss, UW; Bondy, B; Frodl, T; Zill, P; Schmitt, G et al. 5-HT1A receptor gene C -1019 G polymorphism and amygdala volume in BPD. *Genes Brain Behav*, 2008, 7(3):306-13.