

Neuropsychobiological Aspects, Comorbidity Patterns and Dimensional Models in Borderline Personality Disorder

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Key Words

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Abstract

Borderline personality disorder (BPD) is a comorbid and disabling condition with high prevalence in psychiatric settings. The pathogenesis of BPD involves complex interactions among genetic, neurobiological and environmental factors, resulting in multiple core symptom domains such as emotional dysregulation, impulse dyscontrol, aggression, cognitive dysfunctions and dissociative states. Neurobiological studies show that symptoms and behaviors of BPD are partly associated with alterations in glutamatergic, dopaminergic and serotonergic systems. In addition, neuroimaging studies in BPD patients indicate differences in the volume and activity of specific brain regions related to emotion and impulse control, such as the prefrontal and cingulate cortex, amygdala and hippocampus. Neurobiological alterations are related to cognitive disturbances in patients with BPD and neuropsychological tests have shown abnormalities of memory, attention, language, and executive functions. The aim of the present review is to provide an updated overview of the main neuropsychobiological aspects of BPD and their relation to clinical symptoms, comorbidity patterns and dimensional models.

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Introduction

Borderline personality disorder (BPD) is a prevalent and impairing condition, included among the axis II personality disorders, cluster B (dramatic), in DSM-IV-TR [1].

A recent epidemiologic survey conducted in the USA reported a lifetime prevalence for BPD of approximately 5.9% with no differences in the rates among men and women. In addition, BPD has been reported to be more prevalent in younger and separated/divorced/widowed adults and those with lower incomes and levels of education [2].

In clinical practice, BPD is a heterogeneous, multifaceted condition characterized by different symptom domains including affective instability, impulsivity, unstable interpersonal relationships and cognitive defects, each of which may reflect different diatheses from a psychobiological perspective [3].

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 [4]. 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 [5].

Like the majority of mental disorders, the etiology of BPD is associated with multiple factors (biological, psy-

chological and social). These factors reflect the clinical heterogeneity of BPD as well as its frequent comorbidity with other psychiatric conditions. Accordingly, BPD has frequently been included among different dimensional models on the basis of neurobiological and neuropsychological (NP) findings as well as clinical aspects of comorbidity and treatment response.

The aim of the present review is to provide a comprehensive and updated overview of the more recent neurobiological and NP findings of BPD with a specific emphasis on how these aspects are related to comorbidity patterns and dimensional models.

Neurobiological Data

Neurobiological bases of BPD are supported by the existence of dysfunction in serotonin and other neurotransmitter systems, genetic susceptibility, functional brain abnormalities and cognitive dysfunctions in affected patients [6].

Genetic Data

Genetic studies on BPD are still in the early stages. The heritability of BPD has been reported to be moderate to high, based on findings of concordance between monozygotic twins of approximately 35%, and 7% for dizygotic twins [7]. To date, genes that appear to be mostly linked to BPD are those involved in the serotonin system. The gene-linked polymorphic region of the serotonin transporter (5-HTTLPR) has been found to have short and long alleles, and Retz et al. [8] reported that the short allele is associated with violent behavior in humans.

An association between the short allele of the 5-HTTLPR and borderline and antisocial traits in young adulthood was hypothesized by Lyons-Ruth et al. [9], indicating that young adults with lower socioeconomic status who carry the short 5-HTTLPR 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 gene C-1019G is associated with structural changes of the amygdala in patients with BPD. Results indicated an involvement of the amygdala in the biopathogenesis of BPD [10].

The dopamine transporter (DAT) has also been investigated in BPD, and a recent study found a significant association between a polymorphism of the DAT (the 9-repeat allele of the DAT) and the presence of comorbid BPD

in a sample of outpatients with major depressive disorder (MDD) [11].

Neurochemical Data

Paris et al. [12] tested the hypothesis – originally presented by Siever and Davis [13] – that the neurobiological correlates of BPD reflect two underlying trait dimensions: impulsivity associated with lower central serotonergic activity and affective instability associated with lower noradrenergic and cholinergic activity. The results of the study only supported a relationship between impulsive symptoms and abnormalities in central serotonergic transmission. It has also been hypothesized that a dysfunction of the dopaminergic system may be related to some BPD symptoms. More specifically, dopamine may be associated with three symptoms of BPD: emotional dysregulation, impulsivity, and cognitive-perceptual impairment. These hypotheses are indirectly supported by the potential efficacy of some traditional 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 [14].

A possible dysregulation in glutamate neurotransmission has been put forward in the context of cognitive dysfunctions and symptoms reported by BPD patients, like dissociation, psychosis and impaired nociception. Abnormalities in the glutamatergic system might benefit from pharmacological treatment such as NMDA partial/full agonist, particularly in relation to memory, learning and cognition processes [15, 16]. In particular, a recent study found significantly higher total N-acetylaspartate and glutamate concentrations and a trend towards lower glutamine levels in women with BPD and comorbid attention deficit hyperactivity disorder (ADHD) as compared to healthy women suggesting that glutamatergic changes in the anterior cingulate may be associated with BPD and comorbid ADHD [17]. As a matter of fact, glutamate dysfunctions have been investigated and reported in BPD, ADHD as well as in other conditions included in the obsessive-compulsive spectrum disorders [18].

Neuroimaging Data

With respect to structural and functional abnormalities in BPD, neuroimaging data reveal a dysfunctional network of specific brain areas, such as the frontolimbic regions, that seem to mediate much, if not all of the BPD symptoms. This frontolimbic network consists of the anterior cingulate cortex, orbitofrontal and dorsolateral prefrontal cortex, hippocampus and amygdala. In particular,

some core symptoms of BPD have been linked to dysfunctions in the amygdala and limbic systems that control emotion, rage, fear and impulsive automatic reactions. It has been shown that the hippocampus and the amygdala may be as much as 16% smaller in women with BPD and early traumatization, suggesting that experiences of trauma may lead to these neuroanatomical changes [19]. Taken as a whole, these findings suggest that, in contrast to post-traumatic stress disorder (PTSD), not only hippocampus but also amygdala volumes seem to be reduced in patients with BPD. Nevertheless, another study did not find any significant difference in the caudate, amygdala, temporal lobe, dorsolateral prefrontal cortex and total brain volumes in BPD patients, whereas diminished hippocampal volumes were confirmed. Of note, increased putamen volumes were found in BPD patients, a finding that had not been previously reported [20].

The relationship between amygdalar volume loss and altered amygdalar neurochemistry has been analyzed by Tebartz van Elst et al. [21] by morphometric and spectroscopic magnetic resonance imaging. They found a significant reduction of amygdalar volumes in patients and a significant increase in left amygdalar creatine concentrations, suggesting a possible link between amygdalar volume loss, psychopathology and neurochemical abnormalities.

The reduction of hippocampal volume as assessed by MR-based volumetry is another interesting and controversial finding in BPD [22]. In fact, there is an ongoing debate whether this volume reduction is due to an elevated activity of stress-associated neurobiological systems, such as the hypothalamic-pituitary-adrenal axis, or it is genetically determined [23]. It is well established that hippocampal volume loss is not specific to BPD, being also reported in subjects with chronic PTSD, as well as in patients with MDD, especially with histories of childhood abuse [22]. Therefore, the volume loss may be the result of chronic stress, hypothalamic-pituitary-adrenal axis dysfunction, hypercortisolemia and related neurotoxic effects on hippocampal neurons, including diminished brain-derived neurotrophic factor [24].

Functional imaging studies (PET) have shown that patients with BPD present hypometabolism of glucose in various brain structures, including the frontal cortex (dorsolateral frontal cortex) and the 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 [25]. Furthermore, decreased glucose uptake in the medial orbitofrontal cortex (OFC) has been found in BPD patients and

it may be associated with diminished regulation of impulsive behavior [26].

Functional magnetic resonance imaging (fMRI) studies have recently been used in order to observe neural activation within different brain structures in BPD patients [27]. Herpertz et al. [28] found a higher degree of activation in limbic/paralimbic structures in response to aversive images and an abnormal prefrontal cortical modulation in patients with respect to controls, showing that BPD patients experience exaggerated emotional response even to mild stimuli. Another fMRI study by Donegan et al. [29] analyzed the effects of emotional facial expressions on BPD patients, showing amygdala hyperreactivity probably responsible for hypervigilance, emotional dysregulation, and disturbed interpersonal relations. Furthermore, BPD patients revealed difficulties in disambiguating neutral faces, interpreting them as unnecessarily negative or finding them threatening, probably explaining anxiety symptoms and social difficulties. A recent study investigating frontolimbic dysfunction in response to facial emotion in BPD concluded that adults with BPD exhibit changes in frontolimbic activity in the processing of fear stimuli, with exaggerated amygdala response and impaired emotion modulation of anterior cingulate cortex activity [30].

Silbersweig et al. [31], in a recent specifically designed fMRI study involving BPD patients and healthy controls, showed that healthy controls, when performing an emotional linguistic go/no-go task, displayed increased activity in the orbitofrontal and subgenual cingulate cortices that are brain regions related to emotion regulation and inhibition of limbic regions including the amygdala. On the other hand, BPD patients showed increased limbic activity. In addition, in response to negative words, BPD patients showed increased activity in the dorsal anterior cingulate cortex, a region associated with the detection of conflict in deciding what response to make. Interestingly, fMRI results implicate brain regions associated with affective disorders, which are frequently comorbid with BPD, and the stimulation of the subgenual cingulate region, in particular, seems to be effective for the treatment of resistant depression [31, 32].

A summary of the main BPD neurobiological data is reported in table 1.

Neuropsychological Findings in BPD

BPD patients have shown clinical disturbances of cognition and perception, including abnormalities of memory, attention, language, and executive functions [33–35].

Table 1. Main neurobiological data reported in patients with BPD

Type of study	Alterations	Clinical correlates
Neurochemical	<ul style="list-style-type: none"> - Deficit 5-HT [12] - Deficit NA [12] - Hyperactivity DA [14] - Glutamatergic dysregulation [16] 	<ul style="list-style-type: none"> - Impulsivity - Affective instability - Emotional dysregulation, impulsivity, cognitive-perceptual deficit - Dissociation, psychotic symptoms, nociceptive alterations
Structural (MRI) and functional neuroimaging (PET, SPECT, fMRI)	<ul style="list-style-type: none"> - MRI: reduction of hippocampal and amygdala volume [19] - Increase in amygdalar creatine concentrations [21] - PET: hypometabolism of glucose in dorsolateral prefrontal cortex and anterior cingulate cortex; failure of the prefrontal cortex to regulate the limbic system [25] - fMRI: exaggerated amygdala response and impaired emotion-modulation of anterior cingulate cortex activity [30] 	<ul style="list-style-type: none"> - Impulsivity

Neuropsychiatric abnormalities, such as neurological soft signs (subtle abnormalities on neurological examination), and associated impairment on select NP tests have been found in BPD patients [36–39]. 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 [38]. 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 [39–47].

A systematic review of 14 NP studies of BPD [45] 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 multistep, multielement, associative operations (e.g. delayed memory, similarity comparisons, and proverb interpretations) [40–54], visuospatial function, attention [51, 55–58], emotion recognition [59], and executive dysfunctions like planning, cognitive flexibility and decision making under uncertainty [60]. BPD patients' attentional deficits appear to primarily affect conflict resolution, indicating impaired frontal functioning, rather than other attentional functions like alertness [57].

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 execu-

tive or, more precisely, inhibitory dysfunction (e.g. tested with a go/no-go response inhibition task), which is thought to be related to a prefrontal disturbance [57, 60–63].

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 [60, 64–66], reflect a frontal and possibly primarily orbitofrontal system dysfunction [38, 46, 48, 50, 58, 60]. 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 [6, 26, 29, 67–69]. The 'frontal' pattern of cognitive deficits found in BPD patients is consistent with the cognitive and physiological effects observed in OFC lesion patients [70], and with the behavioral disturbances that define BPD like impulsivity, which is thought to have a neurobiological basis [38].

Berlin et al. [6] 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 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 [28], that

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 [71–75] and in guiding decision making and adaptive response selection based on stimulus-reinforcement associations [6]. Increased limbic discharge, decreased OFC function, and/or hypoactive frontolimbic circuitry may be involved in BPD, at least in a subgroup of patients [48]. 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 [6, 48].

BPD patients have shown particular difficulty in actively suppressing irrelevant information when it is of an aversive nature, which correlates with their unstable affect [76]. They also made more inhibition errors than healthy controls on an antisaccade task (especially patients with psychotic-like symptoms), distinct from their general predisposition to respond impulsively as measured by anticipatory errors [77]. Berlin and Rolls [61] 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 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 [78], which is thought to underlie the behavioral dyscontrol, affective dysregulation, and social cognition deficits that characterize BPD [44, 48]. For example, several authors found that compared to healthy controls, BPD patients had deficits in visual/nonverbal memory [55, 79], executive functions (planning, flexibility, fluency), especially on nonverbal tasks [55, 60, 79], and visuospatial functions [53, 58, 79, 80]. Monarch et al. [49] found that relative to healthy controls, BPD inpatients were impaired in attention/vigilance and verbal learning and memory domains which implicate the frontosubcortical and temporolimbic brain regions. In a recent review of 29 NP studies of BPD [81], 83% of studies found impairment in one or more cognitive domains, irrespective of depression, involving generalized or specific deficits linked to the OFC and the dorsolateral prefrontal cortex. A meta-analysis of 10 NP studies [82] revealed that BPD patients perform more poorly than healthy controls in all NP domains test-

ed (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 suggest that the pattern of NP deficits found in BPD patients reflects a frontotemporal dysfunction, primarily of the right hemisphere (e.g. nonverbal executive function and visual memory deficits) [55, 79, 82, 83]. This is consistent with neuroimaging studies of BPD, which document structural and functional abnormalities in the frontolimbic network, involving both the OFC and amygdala, regions thought to mediate BPD symptomatology [84, 85].

Temporolimbic Dysfunction

NP testing has also revealed a pattern of neurocognitive impairment among BPD patients that implicates the temporal lobes [53, 56, 58], like deficits in complex auditory and visual memory, visual discrimination and filtering [53]. Patients with temporal lobe epilepsy show a similar pattern of impairment on tests assessing verbal and nonverbal memory [86–90]. Interestingly, the diagnostic criteria for BPD resemble classical descriptions of the interictal behavioral syndrome (i.e., the temporal lobe personality) [91]. Performance deficits on tests sensitive to temporal lobe dysfunction (e.g. tests of verbal and nonverbal memory) among patients with BPD lend support to the hypothesis that a subset of BPD patients have an undiagnosed seizure disorder (e.g. temporolimbic epilepsy) [92], but more investigation is needed.

A temporolimbic dysfunction is also implicated from studies which report deficits in facial emotion recognition and emotional awareness in BPD patients compared to controls [93, 94]. BPD patients have also been shown to have more intense responses to negative emotions than healthy controls [93], and to be more accurate in recognizing fearful facial expressions, which relates to a response bias toward fear [59]. A functional brain imaging study suggests that the negative attributional bias of BPD patients may be related to heightened amygdala responsiveness to facial emotion [29].

Finally, NP testing of BPD also reveals deficits in visuospatial capacity (a function localized to the inferior parietal lobe) [95], and the medium-to-large effect size for the visuospatial domain found in the review by Ruocco [83] suggests possible parietal lobe pathology [96–100]. This brain area may be dysfunctional in those patients with BPD who have multimodal hallucinations [95].

Table 2. Main neuropsychological findings in patients with BPD

Clinical disturbances of cognition and perception, including abnormalities of memory, attention, language, and executive functions [33–35]
Deficits in verbal and nonverbal (visual) memory, visual perception, visuomotor speed, rhythm reproduction, complex cognitive tasks involving multistep, multielement, associative operations [40–54]
Inhibitory dysfunction (e.g. tested with go/no-go response inhibition task) [52, 57]
Difficulty in actively suppressing irrelevant information when it is of an aversive nature [76]
A faster subjective sense of time [61]
Deficits in complex auditory and visual memory, visual discrimination and filtering, facial emotion recognition and emotional awareness [53, 93, 94]
Deficit in executive function such as poor/risky decision making and planning [60]

Main NP data reported in patients with BPD are summarized in table 2.

Comorbidity and Dimensional Models for BPD

Comorbidity Issues in BPD

The complexity of the neurobiological and NP 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.

The relationship between gender and comorbidity in BPD has been studied by Johnson et al. [101] within the Collaborative Longitudinal Personality Disorders Study. They 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 comparing symptom severity, frequency, and pattern of psychiatric comorbidity, quality of life, and health care utilization in men and women with BPD

showed that 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 [102].

Asnaani et al. [103] used the number of BPD criteria to assess the severity of the disorder and found that patients meeting more criteria for BPD had a greater lifetime history of comorbid substance use disorders, more frequent suicidal behaviors and comorbidity with other axis II disorders.

Zanarini et al. [104] tried to characterize the course of 24 symptoms of BPD in terms of time to remission. Twelve of the 24 symptoms studied showed patterns of sharp decline over time (less than 15% of the patients reported them at 10-year follow-up). The other 12 symptoms showed patterns of substantial but less significant decline over the follow-up period. In particular, symptoms reflecting core areas of impulsivity (e.g. self-mutilation and suicide efforts) and active attempts to manage interpersonal difficulties (e.g. problems with demandingness/entitlement and serious treatment regressions) seemed to resolve the most quickly. In contrast, affective symptoms reflecting areas of chronic dysphoria (e.g. anger and loneliness/emptiness) and interpersonal symptoms reflecting abandonment and dependency issues (e.g. intolerance of aloneness and counterdependency problems) seemed to be the most stable. This follow-up study seems to suggest that BPD may consist of symptoms that are manifestations of acute illness and symptoms that represent more enduring aspects of the disorder. A previous follow-up study exploring whether impulsivity versus other clinical symptoms of BPD were stable over a 7-year follow-up period found that impulsivity was stable over time and suggests that the treatment of impulsivity may impact the course of BPD [105].

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 Zanarini [106] found that BPD nonremitters 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, dia-

betes, hypertension, back pain or urinary incontinence. In addition, nonremitters 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.

Dimensional Models

The frequent comorbidity of BPD is not surprising if we focus on the psychopathological core features of BPD which, along with some aspects of comorbidity, have allowed many researchers to conceptualize BPD as belonging to different dimensional models. The use of dimensions in personality disorders is thought to convey more clinically relevant information about the maladaptive personality traits of patients compared to the use of categorical models [107]. 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.

Several authors have associated some core features of BPD with neuropsychobiological 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 use disorders, 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 [108].

With respect to the potential inclusion of BPD within addictive spectrum disorders, McGlashan et al. [109] reported a high co-occurrence between substance and alcohol abuse and BPD in the Collaborative Longitudinal Personality Disorders Study. The co-occurrence of substance use disorders and BPD is one of the most replicated findings in the axis I/II comorbidity literature [13]. In particular, the presence of substance use disorders has

been associated with the failure to achieve remission in BPD [110]. The consequences of the comorbidity between BPD and substance abuse were analyzed in a 7-year follow-up study [111] 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. In fact, probands with initial diagnoses of BPD and substance abuse were twice as likely to be diagnosed with BPD on follow-up as probands with initial diagnosis of BPD only.

With regard to the relationship between BPD and impulse control disorders, it has been proposed that BPD and impulse control disorders may be included within a wider obsessive-compulsive spectrum of disorders. Within the obsessive-compulsive spectrum of disorders, 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, obsessive-compulsive disorder would represent the condition that overestimates potential harm on one end of the spectrum, while BPD would fit in on the opposite end, as people diagnosed with BPD appear to underestimate potential harm and act impulsively taking unnecessary risks [112].

The affective spectrum model seems to be one of the more consistent for the inclusion of BPD. A recent study by Berrocal et al. [113] 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 (hypercriticism, deteriorated daily activities, guilt, thoughts about surrounding hostility, hopelessness and suicidal ideation and attempts), 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 [114]. Benazzi [115] suggested that BPD may be a mix of two sets of unrelated items: an affective instability dimension related to the bipolar II subtype and an independent impulsivity dimension. More recently, New et al. [116] 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-

Table 3. Main dimensional models in BPD

Dimensional model	DSM-IV-related disorders
Addictive spectrum disorders [109]	– Substance use disorders
Affective spectrum disorder [116]	– MDD – Bipolar disorders
Obsessive-compulsive spectrum disorder [112]	– Obsessive-compulsive disorder – Impulse control disorders – Autism – Body dysmorphic disorder
Trauma spectrum disorders [108]	– PTSD – Dissociative disorders

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 [117].

Another important link between BPD and affective spectrum disorder is the relationship with suicide. In fact, 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 being more common after 30, particularly in treatment-resistant patients [4]. Clinical predictors of suicidality in BPD seem to change over time: on the one hand, comorbidity with MDD appears to influence the suicide risk in the short term, while poor social adjustment might increase the risk over the long term [118].

Of great clinical interest, a recent study by Neves et al. [119] underlined the strong relationship of suicide, bipolar disorder and comorbidity with BPD. In a sample of 239 bipolar patients, 100 of whom with a history of previous suicide attempts, authors found that psychiatric comorbidities associated with suicidal behavior were BPD, panic disorder, alcoholism, other drug addictions, generalized anxiety disorder, and smoking. However, when logistic regression analyses were used, only the diagnosis of BPD remained significant, indicating that a diagnosis of BPD was the only comorbidity independently associated with suicide in patients with bipolar disorder.

After examining the complex relationship between BPD and other comorbid disorders in light of a dimensional prospective, it is noteworthy to highlight that be-

ing able to explain BPD using different models does not necessarily imply that these models are incompatible. Different comorbidity patterns and dimensional models may in turn reflect different neurobiological and NP abnormalities and, ultimately, suggest the possible presence of distinct subgroups of BPD patients [3, 120]. Furthermore, the different models of categorization provide the rationale for the use of specific treatments in BPD patients, which suggests 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 treatment interventions.

Main dimensional models including BPD are reported in table 3.

Conclusion

The continuing evolution of the diagnostic criteria and essential features of BPD along with a consistent series of neurobiological and NP acquisitions justifies the complex clinical approach to this prevalent and disabling personality disorder.

Neurobiological and NP studies in BPD have provided important contributions in the attempt to elucidate the complex pathway from specific brain alterations 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. 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 emerging contributions in the neuropsychobiological field of BPD, confirming the heterogeneity of the disorder, would 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 into clinical practice. Currently, a clinical dissection and precise characterization of the main symptom domains and comorbidity profiles of BPD patients represents a rational and valid approach to better define the patients' clinical picture, choose more adequate therapy, and open new avenues for treatments.

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