The Spectrum of Borderline Personality Disorder: A Neurophysiological View

Michael H. Stone

Abstract Borderline Personality Disorder (BPD) has been defined as a personality disorder in all editions of DSM since 1980; namely, DSM III through V. The criteria are a mixture of symptoms and traits; the etiology, a heterogeneous array of genetic, constitutional, and environmental factors. Until recently the diagnosis relied on clinical descriptions. In the last two decades, neurophysiological data, including MRI and fMRI, have established correlates in various brain regions, particularly those involving the frontal lobes and various limbic structures, that show promise of providing a more substantial basis for diagnosis—relying primarily on (internal) brain changes, rather than on (external) clinical observation. Some of the changes in BPD consist of decreased volume in the orbitofrontal and dorsolateral prefrontal cortices and smaller volume in both the amygdala and hippocampus, though with heightened reactivity in the amygdala. Similar abnormalities have been noted in bipolar disorders (BDs) and in ADHD, both of which often accompany BPD and share certain clinical features. Persons with strong genetic predisposition to BDs can develop BPD even in the absence of adverse environmental factors; those with extreme adverse environmental factors (chiefly, early sexual molestation) can develop BPD in the absence of bipolar vulnerability. In some BPD patients, both sets of factors are present. As ideal treatment depends on careful analysis of these factors, neurophysiological testing may permit both more rational, brain-based diagnostic decisions and more appropriate therapeutic strategies.

Keywords Borderline personality disorder · Bipolar disorder · Attention-deficit disorder · Neurophysiology · Frontolimbic circuitry · MRI

M. H. Stone (✉)
Professor of Clinical Psychiatry, Columbia College of Physicians and Surgeons,
225 Central Park West, New York, NY 10024, USA
e-mail: michaelhstonemd@gmail.com

Curr Topics Behav Neurosci (2014) 21: 23–46
DOI: 10.1007/7854_2014_308

Published Online: 22 May 2014

Contents

1 A Historical Note

Borderline Personality Disorder (BPD) as a clinical diagnosis has its origins a little over a century ago, though it was not originally called a "personality disorder"; rather, a condition intermediate between the then widely used concepts of neurosis and psychosis. The term evolved out of a kind of triage, where it was recognized that in between better-functioning patients who had a good grip on reality and the seriously disturbed (i.e., psychotic) patients whose hold on reality was critically weakened, there was a third group whose symptoms and everyday function fell somewhere in the middle of neurosis and psychosis. Kraepelin, for example, wrote of a *Zwischengebiet*—and in-between territory—where he situated the temperaments noted in some of the relatives in the families of manic-depressive persons (Kraepelin 1905, 1921). Persons exhibiting one of the temperaments: depressive, manic, irritable, and cyclothymic—often showed a clinical picture reminiscent of our contemporary BPD patients. *Irritable temperament* was associated, for example, with irascibility, lability of mood, impulsivity, and mild paranoid tendencies—which map onto four of the criteria for the current definition of BPD (Stone 1980, pp. 326–327). Some patients in this intermediate realm were understood as inhabiting the borderland touching clear-cut manic-depression (such as those with the Kraeplinian temperaments); others, whose symptoms were more cognitive than behavioral in nature, were seen as occupying the borderland of schizophrenia. There was a strong conviction within psychiatry that there was a hereditary component to both the obvious psychoses and to their less serious close-cousins—the "borderline" conditions. Whatever it was that was going on in the brain in these conditions remained, however, elusive. Freud, who started out as a neurologist, had speculated along such lines in his 1895 Project for a Scientific Psychology. Kraepelin was similarly convinced of a hereditary predisposition for both major psychoses [his *dementia praecox*, superseded terminologically by

Bleuler's *schizophrenia*; and *manic-depression*, now more often subsumed under the heading of *Bipolar Disorder* (*BD*)]. But their hunches remained at the speculative level: the neurology of their times could not as yet pinpoint areas of the brain peculiarities of which might underlie the illnesses on which they focused. Not for want of trying: Kraepelin hoped that his neurologist-associate, Alzheimer, might discover some neuroanatomical correlates of the major psychoses, but his success lay only in the area of the eponymous dementia.

Absent superior ways of finding brain correlates to the major psychiatric disorders during the first three-quarters of the last century, diagnostic distinctions tended to remain at the descriptive/phenomenological level. Definitions offered by various groups within psychiatry differed in many instances in accordance with the primary interest and primary treatment methods used by one or another group. The definitions of "borderline" formulated by psychoanalysts relied upon certain qualities that affected one's amenability to psychoanalytic treatment. Stern's definition (Stern 1938) relied on such criteria as *psychic bleeding* (paralysis in the face of crisis), *organic insecurity* (constitutional incapacity to tolerate much stress), and *difficulties in reality testing* (but short of gross psychosis). The term "borderline" also signified that the patient in question was not capable of tolerating conventional psychoanalysis, with its multiple weekly sessions on the couch. Until the 1950s psychiatrists, whether psychoanalytic in their orientation or otherwise, tended to assume that schizophrenia was the psychosis upon whose border their "borderline" patients were situated. Zilboorg (1941) spoke of a borderline variant of schizophrenia that he called "ambulatory schizophrenia"—where patients were able to preserve an adequate social façade and did not require hospitalization. To have any *trait* associated with schizophrenia was more important in Zilboorg's nosology, than was embodying the schizophrenic *state*. This approach dominated psychiatry in the US at mid-century, and led to what we would now see as a widespread overuse of the term "schizophrenia", and to the unrealistic assumption that the so-called borderline cases likewise belonged to the domain of schizophrenia.

The analyst Edith Jacobson realized that this conception was too narrow, and in the 1953 paper expressed the view that certain "borderline" patients were within the penumbra of manic-depression. Some milder cases, that is, of depression and hypomania could best be understood as within the (hereditarily predisposed) province of the manic-depressive disorders. Even so, she understood the psychoses as representative of various stages of psychosexual development, oriented linearly, such that schizophrenia harkened back to a more primitive stage of development, whereas the manic-depressive subtypes answered to a more advanced (and thus less primitive, less "ill") stage—for which reason they seemed more amenable to therapy.

The competing definitions of "borderline" that were ultimately to converge toward our current conception of BPD varied, during the 1960s and 1970s, in their emphasis on hereditary factors, primary observable traits, descriptions of typical signs and symptoms, or on treatment response. Kernberg (1967) deemphasized heredity, placing reliance more on a constellation of signs and symptoms: an

enfeebled sense of identity though with adequate preservation of reality testing, along with impulsivity and weakened ability to handle anxiety-laden situations. Gunderson also focused on signs and symptoms: impulsivity, manipulative suicidal threats, mild/brief psychotic episodes, and disturbances in close relationships (Gunderson and Singer 1975). The inclusion of suicidal threats could be understood as an acknowledgement of the importance of an affective factor (in line with Jacobson's view), since patients with depression or other mood disorders are more prone to suicidal gestures than are most other types of patients. Kohut (1971) used the term *borderline* as a label for patients who proved unable to withstand, or to improve via, conventional psychoanalytic treatment. Despite these competing and often parochial views as to what constituted the essence of "borderline" conditions, the red thread that ran through all the definitions was *impulsivity*.

The viewpoints emerging in the 70s culminated in the inclusion of "borderline"—now as BPD—in the next edition of our Diagnostic and Statistical Manual of Psychiatric Disorders [DSM-III] (1980). Those DSM definitions were to be considered *atheoretic*, since there was not enough information in the field to speak authoritatively about underlying causes. There was, nevertheless, a kind of unspoken acceptance that the new BPD was built more along the lines of the mood disorders; viz., manic-depression, than along the lines of schizophrenia. Indeed, aberrations of personality that were more reminiscent of schizophrenia were now divided off into the new definition of Schizotypal Personality Disorder.

As it is not in the nature of scientific enterprises to avoid the search for underlying causes, controversy about the etiology of BPD became animated during the last quarter of the last century, particularly in regard to a possible allegiance to the more severe mood disorders of manic-depressive psychosis—a group of disorders now more often referred to as the BDs. Some investigators espoused the idea that a fair percentage, though by no means all, patients with BPD could be viewed as *formes frustres* of BD (Akiskal 1981; Stone 1981). This led to the emergence of two camps: one group taking a more extreme view and seeing BPD as the other side of the same coin as BD; the other group downplaying the connection to an almost opposite extreme. A more sober note was sounded by (Gunderson 2001; Gunderson et al. 2006) who, though tending to deemphasize the connection, acknowledged that, given an initial diagnosis of BPD, about 10 % of the patients could also (or eventually) be diagnosed with Bipolar-II disorder and another 5 % with Bipolar-I. Conversely, given an initial diagnosis of a BD, 20 % of the Bipolar-II patients were "co-morbid" for BPD and another 15 % of Bipolar-I patients could likewise be diagnosed with BPD (2001, p. 39). As for patients with Major Depression, about 15 % also met criteria for BPD, whereas half the patients in whom BPD was diagnosed first, half could also be considered to suffer from Major Depression. My own impressions (Stone 1990a, p. 74) regarding the overlap between BPD and BDs is similar to the observations of Gunderson just cited, though I have always emphasized the connection more vigorously. That Gunderson cites the percentages that he does reflects the tighter definition he has formulated for BPD—quite similar to that of DSM, both these definitions mapping out a smaller territory on the psychpathological map than is occupied by

Kernberg's "Borderline Personality Organization" (BPO). BPO, with its broad criteria of weakened identity sense, adequate reality-testing, impulsivity and poor ability to handle stress—reaches out to some 10 or 11% of the general population. BPO will include antisocial persons (including psychopaths), narcissistic persons who tend not to indulge in self-harm or suicidal behaviors, and other persons with marked aberrations of personality. The percentage of patients meeting these broad criteria—who in addition show the signs of BD—is of course lower than will be found among the more narrowly defined group with (DSM's or Gunderson's) BPD. These distinctions are important, for if we are to pan for the "gold" of bipolarity in the waters of the "borderline", our yield will be considerably higher (perhaps by a factor of four) if we begin with a sample of BPD patients, rather than of one with BPO. This has relevance when, in the next section, we review the findings of studies on the neurophysiology of borderline conditions (which indeed do rely on samples of BPD patients). There is an added factor pertaining to variations in sample. The overlap percentages for BPD and BD mentioned by Gunderson were derived from carefully analyzed samples: he referred to those, among others, of Fyer et al. (1988), Gunderson et al. (1999), and Zanarini et al. (1988). But there are other samples composed of borderline patients from generally higher socioeconomic class and from cultural backgrounds where parental neglect, brutality, and incest are quite rare: patients (females in particular) from these more protected settings may show a heightened overlap-ratio with BD—there being little else to account for their (dual) pathology apart from risk genes for bipolarity. Patients with BPD from settings of an opposite sort, where adverse environmental factors (sexual molestation, especially) are present to a marked degree, appear to develop their borderline clinical picture primarily from the early traumata; a family history of BDs may be quite uncommon in such samples—where even Gunderson's somewhat conservative percentages would seem much too high. Perhaps most common are BPD patients who occupy a middle ground in the nature/nurture debate—in whom the brain systems regulating impulsivity and emotion may partly have their origin in the "nature" side, but in whom the full-blown picture of BPD is pushed into clinical recognizability by adverse environmental factors (Pally 2002). I have, for example, served as consultant to a hospital unit devoted to BPD patients in Brisbane, Australia—where the family history of BDs was negligible, but where a history of incest and parental brutality was near universal (Stone et al. 1988). Clinicians attached to centers with sample differences of this kind are prone to develop hypotheses about the origins of BPD that were indeed "correct" for their clinic or hospital—but widely divergent from the hypotheses generated by clinicians from other centers. It was sample differences of this sort that, I believe, helped to account for the often acrimonious disputes about the degree to which BD, PTSD, incest, or dissociative identity disorder should be awarded "pride of place" in the etiological hierarchy of BPD. This disputation was common, if not inevitable, in the era antedating the neurophysiological studies of the past two decades: studies which have begun to shed at least a little light into the inner workings of the brain in BPD and in a number of other conditions that either overlap with, or could be confused with, BPD.

Before we address the data from these neurophysiological studies, we should pay attention to another stream of data, stemming from recent studies in evolutionary psychiatry—for it is these that help us to understand the erstwhile puzzling but long-known lopsided sex distribution among BPD patients. They are mostly female (Oglodek 2011). Women with BPD are more prone to experience premenstrual dysphoric disorder (with its temporarily heightened depressed mood, irritability, anxiety, and lability of affect—as outlined in DSM-V 2013). In some women, not previously regarded as "borderline", the symptoms may be particularly intense and may be accompanied by suicidal feelings or self-injurious behaviors, along with the "inordinate anger" that suggest to the clinician the presence of BPD. The syndrome tends to be a more regular feature, and more pronounced in its intensity, in women with BDs (such as Bipolar-II)—each condition alerting the clinician to the possible presence of the other. One will, to be sure, encounter other women with certain gynecological conditions (e.g., polycystic ovary) who experience severe premenstrual dysphoria (sometimes with endometriosis as well), who do not show the additional features of either BPD or BD. But mood disorders characterized primarily by depression are more common in women—in a way that appears to have implications for our evolution as a species. Annette Schirmer in her comprehensive chapter on sex and emotion (2013) summarizes the sex differences in this way: "For some emotions, men show stronger subjective feelings, cognitive, and/or behavioral effects than women (e.g., anger and contempt), whereas for other (emotions) we find the opposite (e.g., sadness, fear, disgust)," (p. 605) (the latter emotions being more often stronger in women). She adds: "…territorial behavior, in humans and other primates, is more strongly developed in males. Thus, emotional responses that facilitate aggression (anger, contempt) may have been of greater value to men…Conversely, early female typical tasks such as food gathering and child care were less confrontation and dangerous…Women present more often than men with disorders of prosocial emotions. That is, they are more likely than men to suffer from intense and prolonged feelings of fear and sadness" (ibid, p. 605). This sex-difference factor, coupled with the far greater vulnerability of daughters, compares with sons, to childhood sexual molestation by older-generation relatives (which can promote the later development of BPD symptomatology) helps one understand why many of the neurophysiological studies of BPD are based preponderantly on female subjects (Stone 1990b).

2 Neurophysiological Studies in the Borderline Domain

Since the last quarter of the last century, the biological aspects of psychiatry have become increasingly important. Electroencephalography (EEG) had already been in use for a long time. As for BPD, electrophysiological studies, until recently, offered only modest help in our understanding of the relevant brain changes (Boutros et al. 2003).

But newer techniques have now been brought more and more into use, such as Single Photon Emission Computed Tomography (SPECT) and Magnetic Resonance Imaging (MRI). These and related techniques have helped to establish a deeper understanding of brain correlates in many of the major psychiatric disorders. They have also shown promise in enabling us to base diagnostic distinctions along more objectifiable lines, rather than having to depend solely on the external criteria discernible to the clinician. In traditional psychiatry, that is, only the patterns of *thought-emotion-behavior* were available for making diagnostic decisions—patterns that often show confusing degrees of overlap between one supposedly "distinct" entity and another.

The use of MRI for medical purposes began in the 1970s (Goldstein and Price 2004) but has blossomed in the last 15 years. The spotlight in this article is on BPD, though MRI and other imaging studies relative to conditions that often overlap of co-occur are also included.

3 MRI and Related Findings in BPD

One of the earliest MRI studies of BPD reported smaller frontal lobe volumes in the patients, though the authors (Lyoo et al. 1998) mentioned that findings were inconsistent in other reports. Electroencephalographic studies of event-related potentials (ERPs) have demonstrated abnormalities in fluctuations 300 milliseconds after the presentation of certain (auditory or visual) "events"—the P300 response—in various psychiatric disorders, including BPD. But the P300 changes are not very specific, since they are noted in such other conditions as panic-disorder, substance abuse, schizophrenia, and PTSD (Kuperberg 2004). Viewed from one perspective, it is not surprising that unanimity was not found in the neuroimaging and EEG studies. BPD has long been recognized as heterogeneous from an etiological standpoint, better viewed as an array of dimensions (i.e., as a syndrome) rather than as a specific disorder (Stone 1980; Schmahl et al. 2002). We have alluded earlier to a number of routes that may converge into the BPD syndrome: genetic factors, parental neglect or brutality, early sexual abuse, and serious traumata of other sorts. There are also cases where maternal abuse of illicit drugs in the first trimester of pregnancy, very low birth weight or fetal hypoxia at delivery can also predispose to a clinical picture of BPD later on. Yet despite all this heterogeneity, there is widespread consensus that the essential clinical features of BPD are *impulsivity* and *emotional dysregulation*. These abnormalities occur in BPD, as Hughes et al. (2012) mention, almost invariably within an interpersonal context. But this consensus about the key features has spawned an outpouring of studies dedicated to discovering what brain peculiarities may underlie impulsivity and emotional dysregulation.

Many investigators of brain changes in BPD have drawn attention to the kind of *frontolimbic dysfunction* Hughes regarded as the predominant neural substrate underlying the personality disorder. The "fronto" aspect has been characterized in

general as a diminished "top-down" control of affective responses; specifically, because of decreased responsiveness of certain midline areas of the prefrontal cortex (New et al. 2008). As these authors mention, besides neuroanatomical abnormalities there may also be a neuroendocrine factor, such as reduced serotonin availability—with a resultant dysregulation in the form of emotional *disinhibition*. In agreement with these impressions are the observations of Dell'Osso et al. (2010), how noted alterations in the serotonin system, but also in dopaminergic and glutaminergic systems, appear to play a role in the impulse dyscontrol and aggressivity in borderline patients. In a more recent study, Kamphausen et al. (2013) pinpoints *ventromedial prefrontal cortex* (vmPFC) dysfunction as the "top-down" element and, in their fMRI analysis of female BPD patients exposed to visual "threat" stimuli, a prolonged *amygdala* response, as the "bottom-up" component (Herpertz et al. 2001). The patients also showed an increased connectivity between the amygdala and the vmPFC. In a similar study higher connectivity was noted, during an fMRI "fear-scan", between the amygdala and the rostral portion of the *anterior cingulate cortex* (ACC) (Cullen et al. 2011). Borderline patients were shown to make more mistakes on fMRI than did the controls in a task involving distinguishing emotional from neutral faces in other areas as well, such as the insula, amygdala, and fusiform gyrus (Guitart-Masip et al. 2009; Koenigsberg et al. 2009). Abnormalities of this sort were seen as contributing to the heightened sensitivity in BPD to negative emotion, with consequent social disturbances: particularly, the tendency in borderline patients to become too angry too quickly in interpersonal situations others handle more calmly (Domes et al. 2009). Similar difficulties in suppressing their reaction to negative emotion was noted also in an ERP study of borderline patients (Marissen et al. 2010). In another study, reduced gray matter in female BPD patients was noted in the dorsolateral prefrontal cortex (dl-PFC) (bilaterally) and in the left orbitofrontal cortex (OFC); the prefrontal cortical changes did not, however, appear specific to BPD, insofar as similar changes were observed in a control group of other psychiatric disorders (Brunner et al. 2010), and also in a still wider array of psychiatric disorders including panic disorders and other Cluster-B personality disorders (Jackowski et al. 2012). White-matter abnormalities have also been implicated: BPD patients were shown to have abnormalities in the long association bundles connecting the association cortex with the hippocampus and thalamus—of a sort that appeared to play a role in the disruption of emotional regulation in BPD (Maier-Hein et al. 2014). In general, it is the OFC that plays a major role in top-down inhibitory control via "reverse-learning"—where maladaptive impulses and choices are suppressed in favor of more adaptive/socially appropriate choices (Jentsch 2012; Jentsch et al. 2002). This has relevance to BPD, but also to abuse of certain drugs such as cocaine and methamphetamine—which cause blockade of the dopamine-related D-2 receptors and impairment of the inhibitory control otherwise exercised by the OFC. Abuse of such drugs is common in BPD, aggravating a problem in top-down control typical of BPD psychopathology even in the absence of drug-abuse.

Neuroanatomically, size appears to matter, as in the study of Ruocco et al. (2012), in whose meta-analysis of MRI research in BPD–volume reductions of about 11 %

were noted in the amygdala, with comparable reductions also in the hippocampus. Similar reduction in amygdalar volume (from 11 to 17 %) was noted by Tebartz van Elst et al. (2007), who also found an *increased creatine concentration* in the left amygdala.The latter correlated with the patient's anxiety level, and might provide another clue to the emotional dysregulation in BPD—this time in the form of a neurochemical abnormality. Volume reduction in amygdala and hippocampus has been seen as correlates of other "bottom-up" (i.., limbic) abnormalities in BPD that lead to impulsivity and heightened aggression associated with this disorder (Nunes et al. 2009). Berdahl (2010) has advocated that we include even deeper—in effect, sublimbic—regions in the circuitry relevant to BPD: a network involving not only the Anterior Cingulate and ventromedial prefrontal cortex (ACC/vmPFC) and the amygdala, but also the brain-stem center—the periaqueductal gray. Panksepp and Biven (2012) have underlined the importance of the periaqueductal gray as constituting the first portal of entry for incoming stimuli affecting the emotions in humans and in other animals, including the negative emotions of fear, rage, and panic/grief. Unregulated feelings of the PANIC/GRIEF system may, in their view, underlie the stormy social relationships, depression, and avoidance of abandonment that plague the patients we label as BPD (Panksepp and Biven 2012, p. 75).

A number of authors have drawn attention to the ironical situation of reduced amygdala volume in BPD patients, yet *hyperactivity* in the amygdala's responses when confronted with emotion-related stimuli (Stein 2009; Siever and Weinstein 2009; O'Neill and Frodl 2012). Allele differences in the 5-hydroxytryptamine-1a receptor (5-HTR-1a) gene may account for some of the disagreement in the literature about amygdala-size: BPD patients with the G allele had smaller amygdala sizes than did those with the C/C genotype, and may be more prone to the impulsive and aggressive behavior that characterizes BPD (Zetzsche et al. 2007). Presumably, however, it is ultimately dysfunction in the top-down centers that should be held responsible for the dysregulation of impulse and affect in BPD (Soloff et al. 2008), since the amygdala (and perhaps before that—the periaqueductal gray) are the earlier recipients of stimuli carrying negative emotional valence, thence broadcast to the higher centers for evaluation and reaction.

Another peculiarity noted in many BPD patients, besides their emotional overreactivity etc., is a comparative insensitivity to pain. This, too, may answer to abnormalities in cortico-limbic centers: Kluetsch et al. (2012) noted that painful stimulation is handled differently in normals than in borderline patients. In their study of 25 women with BPD, almost all of whom (23) had a history of self-harm, showed altered pain-processing in regions (such as the cingulate- and left dorsolateral prefrontal cortices) involved in cognitive and affective evaluation of pain. This paradoxical reaction may underlie the tendency in many BPD patients to self-cut: they are less sensitive than other people to the sheer *physical* pain but able to use the (for them, milder) physical pain to distract them from the often overwhelming *psychological* pain of their everyday life.

Although contemporary research on brain changes associated with BPD has relied on MRI, Several groups using EEG have also made notable contributions. Brain activation as assessed by EEG-vigilance, for example, was noted to be lower in a

sample of BPD patients (compared with OCD patients); the lowered vigilance has, in turn, been associated with the impulsivity and sensation-seeking manifested by many borderline patients (Hegerl et al. 2008). In another study EEG was used along with thyrotropin-releasing hormone (TSH), neurological soft-signs, and dexamethasone suppression in a search for associations between otherwise seemingly unrelated variables (De la Fuente et al. 2011). EEG and TSH emerged as the variables that influenced most of the others, in their Bayesian network model, raising the hope that such measures might strengthen subsequent diagnostic criterion-sets for BPD.

4 Borderline Personality Disorder and Aggression

Although violence *per se* is not among the DSM criteria for BPD, many BPD patients manifest the "items": inappropriate intense anger, impulsivity, and transient paranoid ideation under stress. These attributes may culminate in outbursts of violence. In less dramatic instances the violence may be limited to punching a lover or mate, or to smashing glassware. But in the forensic hospital where I work, most of the female patients carry the BPD diagnosis (often with "antisocial" comorbidity), and were remanded to the hospital following acts of greater violence: assault, arson, or murder. The same "top-down" and "bottom-up" abnormalities mentioned earlier are usually operative in such case: hyper-responsivity in the amygdala, and concomitant failure of the "braking system" in the prefrontal cortex (Siever 2008). The predisposition to violence may be aggravated by insufficient availability of serotonin, upon which the cortical braking system is partly dependent (Brendel et al. 2005; Siever 2008). These findings are mirrored in the important work by Coccaro and his colleagues on impulsive aggression and on the syndrome of Intermittent Explosive Disorder (IED): disorders noted frequently in persons comorbid for both BPD and antisocial personality disorder (ASPD), such as the female forensic patients just mentioned (Coccaro et al. 2007, 2011).

5 Borderline Personality Disorder and Childhood Abuse

A group of Québec researchers interested in BPD, aware of the importance of building a bridge between neurophysiological data and psychological material, brain and mind being two sides of the same coin, have drawn attention to the way in which childhood abuse can aggravate, or perhaps bring about de novo, the executive and frontal dysregulation that underlay the BPD syndrome (Bouchard et al. 2010). Severe and prolonged childhood abuse (especially physical and sexual) has been implicated in epigenetic changes—where otherwise silent genes become activated (here: in response to the abuse) but without any actual change in the sequence of DNA (Lewin 2008, p. 819). Such changes, as part of the body's mechanism in coping with the abuse, may take on the kind of permanence as though the child had

inherited the genome transformations that developed as a consequence. Minzenberg et al. (2008) found a linkage between BPD patients with an abuse history and executive dysfunction; specifically, attachment-avoidance that correlated with temporo-limbic dysfunction (whether brought about, or made worse by the abuse). The avoidance apparently served in such patients as a compensatory mechanism whereby they could sidestep the kinds of interpersonal stresses that would otherwise reawaken the abnormal frontal lobe processing to which the earlier abuse had predisposed them. The various brain regions involved were outlined in an earlier fMRI study that dealt with facial emotion processing in BPD (Minzenberg et al. 2007).

6 Borderline Personality Disorder and Dissociative States

From a neurophysiological perspective, dissociative disorders, which often accompany BPD, have been connected with abnormalities in the parietal lobe. In a study out of Göttingen in Germany, young women with BPD who had been the victims of childhood sexual and physical abuse were shown, via structural MRI, to have a 9 % smaller volume in the right-precuneus area of the parietal lobe, and a 13 % increased volume in the left post-central gyrus of the superior lobe. The latter finding was correlated with the clinical conditions of dissociative amnesia and dissociative identity disorder (akin to the former "multiple personality") (Irle et al. 2007). A different brain area was implicated in another study: abnormalities in the function of the OFC appeared linked to the impulsivity, over-reaction to negative emotion, and to difficulty in retrieving autobiographical memories in BPD patients. The latter type of impairment was correlated with the *dissociative* symptoms that frequently occur in BPD (Poletti 2009). These brain areas are involved in memory, such that abnormalities in size or function might predispose to the varieties of dissociative and related memory disturbances seen in BPD, especially in patients who had been subjected to early abuse. Issues concerning causation versus correlation remain to be further elucidated. Irle et al. speculated that some BPD patients might have a neurodevelopmental defect of the right cerebral hemisphere that could render them more susceptible to the effects of early abuse. If so, this would suggest that being born with such a defect might heighten the vulnerability to abuse during childhood, as opposed to a situation where the early abuse somehow caused volume changes in key brain areas.

7 Borderline Personality Disorder and Post-Traumatic Stress Disorder

Women (and to a much smaller extent, men) who had been exposed to severe sexual abuse, especially by an older male relative, may develop the clinical picture of post-traumatic stress disorder (PTSD), with its chronic anxiety, flashback

memories, nightmares, and startle-responses. Some of course will show dissociative symptoms or depersonalization as well. Irle et al. (2005) noted in women with both BPD and PTSD a 17 % smaller hippocampal size. They also noted a leftward asymmetry in the parietal cortex, which correlated with a greater vulnerability to schizoid traits and to psychotic symptoms. In a similar study hippocampal volumes were reduced in BPD patients in general, but particularly so in those with concomitant PTSD (Rodrigues et al. 2011). Also in the combined BPD with PTSD women, marked reduction (34 %) was found in the amygdala size: a greater reduction than was noted in the BPD patients who had experienced trauma, but did not show the PTSD picture—where the reduction is size was about 22 % (Weninger et al. 2011). The question about amygdalar size remains controversial, inasmuch as a Brazilian group, in their meta-analysis, noted smaller amygdala size in BPD where PTSD was not an accompaniment; they suggested that the reduced amygdalar volume in BPD might not be explainable as a consequence of concomitant PTSD (de-Ameida et al. 2012). In their observation about stress, in general, and its effect on limbic structures, Wingenfild et al. (2010) viewed that stress exerted damaging effects on the hippocampus, which had special relevance to BPD. These authors underlined the importance of studying further the hypothalamus-pituitary-adrenal (HPA) axis and its vicissitudes vis-à-vis BPD patients who have endured marked stresses, whether from abuse or neglect, in their formative years. The role of the HPA axis in BPD has been studied extensively by (Teicher et al. 2003), who point out that the major brain-structural consequences of stress related to childhood traumata concern not only the neocortex, amygdala, and hippocampus, but also the corpus callosum (CC) (where reduced size has been noted in its mid-portion—in children with a history of PTSD). Regarding hippocampal changes, severe early stress may be more associated with dissociative symptoms than simply withy declarative memory (Stein 1997), and thus have particular relevance to BPD.

On the neuropeptide side, Prossin et al. (2010) have shown greater regional mu-opioid non-displaceable binding potential (BP-ND) via PET scan in female patients with BPD, when compared with normal subjects. Brain regions involved included the amygdala, caudate, N accumbens, and OFC. Negative emotion challenges (sadness induction) led to greater reductions in BP-ND in the BPD patients, especially in left-sided regions. The authors did not focus on BPD with comorbid PTSD. The differences in response to negative emotion and the accompanying stress did, however, appear related to some of the typical stress-related phenomena in BPD patients. In their commentary on such stresses as rejection and abandonment, Stanley and Siever (2010) drew attention to how the reactions elicited by these stresses in BPD patients (viz., impulsive and self-destructive/suicidal behaviors) suggest a malfunction of psychological systems oriented to attachment and affiliation. This in turn lends an importance, for enhancing our understanding BPD, to certain neuropeptides that play a role in these interpersonal actions; specifically, opioids (in pain-related phenomena), oxytocin (in affiliative responses), and vasopressin (in homeostasis and memory formation).

8 Bipolar Disorder: Neurophysiological Aspects and Relation to BPD

Compared with the etiologically heterogeneous BPD, BDs represent a more unified nosologic construct, since genetic factors appear to play the primary role in their origin. Confusion and controversy in the domain of bipolar and borderline conditions stem from the observation of similarities in symptom presentation, similarities in neurophysiological underpinnings, and the fact, as mentioned in Gunderson's work cited earlier, that an impressive proportion of persons diagnosed in adolescence or early adult life with BPD are seen later to show the characteristics of a BD, and *mutatis mutandis*, persons diagnosed as "bipolar" in their teens frequently meet, later on, criteria for BPD.

Some of the similarities are outlined by Antoniadis et al. (2012), who point to the main clinical features of BD; namely, impulsivity and affective instability—the same as found in BPD. Alterations in the limbic system have been found on MRI in both, though amygdala size has been reported as smaller in BPD; larger, in BD. Heritability, clearer significant in BD, has been found in some studies of BPD, but there do not appear to be genes specific in any way for the disorder. Environmental factors, meanwhile, appear to be more important in BPD than in BD. At the clinical level, Benazzi (2006a, b) takes the position, in the dispute whether BPD is a bipolar "spectrum" condition or is a separate entity, that the DSM-IV (1994) definition of BPD may be conflating two sets of unrelated features: an emotional instability related more to BD (especially to the milder form of Bipolar-II disorder), and an impulsivity dimension more applicable to BPD. In Bipolar-II patients cyclothymic temperament (an inherited quality) and borderline traits (short of meeting full criteria for BPD) clustered more with Bipolar-II Disorder than with Major Depressive Disorder. Among the BPD traits, lability of affect (*unstable mood*), unstable interpersonal relationships, identity weakness (*unstable self-image*), and chronic anger sorted in factor analysis—more with Bipolar-II, but impulsivity did not (Benazzi 2006a). Coulston (2012) was also struck by the clinical similarity between BD and BPD, the presence of one predicting the (sooner or later) presence of the other. In his view, childhood trauma predisposed to both conditions, and also to rapid cycling (in BD) or to the analogous quickly fluctuating "mood lability" in traumatized BPD patients. But in BPD the mood changes tend to be briefer and vary between anxiety, on the one side, versus anger and depression, on the other. This in contrast with the rapid cycling in BD, where the shifts tend to vary between elation and sadness (Fiedorowicz and Black 2010). Mackinnon and Pies (2006) also comment on the similarity between the rapid cycling in BD and the affective instability/mood lability in BPD, adding that anticonvulsant medications are regularly helpful in BD and often so in BPD as well. They regard this as pointing to a biological overlap, though do not buttress their argument with data from neurophysiological research.

What neurophysiological data do exist are also equivocal regarding the question: are BD and BPD separate conditions—or two sides of the same coin. Rossi et al. (2012), using an MRI technique, studied 26 mostly female BPD patients and

15 mostly male BD patients. The BPD group showed smaller hippocampal volumes bilaterally; in the Bipolar patients, there was smaller right-hippocampal volume (of the right dentate gyrus that lies between the fimbria of the hippocampus and the hippocampal gyrus). The authors speculated that these volumetric differences might be related to the clinical phenomenology of each disorder. In a subsequent paper (Rossi et al. 2013) where gray and white matters were compared in the two conditions, it was noted that gray-matter density changes were more diffuse and severe in BD than in BPD. Each disorder had specific regions of abnormality involving both cortical and subcortical structures in BD; in BPD—mainly fronto-limbic regions. Despite areas of overlap in gray matter changes, the topography in those changes appeared more consistent with a "separate-conditions" hypothesis. The separate-conditions hypothesis finds support in a psychological study of set-shifting and reversal learning in BPD (Barker et al. 2014). BPD patients in this study did not show significant deficits in extra-dimensional shift (EDS) or in reversal learning; this appeared to distinguish them from bipolar subjects—who did demonstrate deficits in tests of EDS. MRI suggests that performances on reversal learning reflects OFC functioning, whereas EDS relies on prefrontal cortex function. Since deficits in these tasks were not found in the BPD patients, the authors suggested that, in contrast to the bipolar patients, the limbic system was the primary locus of pathology in BPD (Barker et al. 2014, p. 9).

In some patients there is a convergence clinically between the symptoms and traits of BPD and *Bipolar Depression*. Patients with (depressive) mood disorder are known to have a higher prevalence of BPD—the combined condition showing marked instability of mood and poorer response to medication (Radaelli et al. 2012). When MRI data were obtained from patients with Bipolar Depression alone and with those diagnosed with both conditions, the Depression + BPD group showed a lower activation of the dlPFC than in the Depression-only patients. Emotional dysregualtion appeared greater in the combined group. In contrast, MRI data from another research group found an important abnormality in the ACC (Brodmann Area #24), whose function is ordinarily to assess the salience of emotional information and to help regulate emotional responses. This gray matter (but not white) in this area was shown to be smaller in patients with BPD adolescents with Major Depression (Goodman et al. 2011). Still, there are many areas of overlap on the biologic side between BPD and Major Depression: amygdala hyper-reactivity, smaller ACC volume, and diminished serotonergic function, such that the data that might help firm up the similarities and also make more meaningful distinctions between the two are not as yet available (Goodman et al. 2010).

9 The Spotlight on Bipolar-I Disorder

The mood dysregulation characteristic of BD has been ascribed to dysfunction in the prefrontal cortex, leading to inhibitory dyscontrol (Anticevic et al. 2012). In their study, based on BD patients with psychosis, there was reduced medial

prefrontal cortex (mPFC) connectivity within the prefrontal cortex as a whole, and also reduced connectivity between the amygdala and the dl-PFC. The mPFC is considered the key region for emotional regulation. Dysconnectivity was also noted even in remitted bipolar patients, suggesting that this abnormality might constitute a risk factor for the phasic (mood-fluctuating) features of BD. The memory deficits sometimes associated with BD were linked, in another study, to the lowered hippocampal volume, as documented above by a number of other investigators (Chepenik et al. 2012). Improvement in memory was noted in some BD patients following treatment with antidepressant medications, though whether the memory improvement was associated with morphological changes in the hippocampus (such as regaining its volume) was not assessed. The hyper-reactivity of the amygdala to emotional stimuli (looking at sad faces, for example, in fMRI experiments) was noted in BD and linked to deficient activation in the dl-PFC (Garrett et al. 2012)—as a factor in the emotional dysregulation in BD—comparable, however, to what has been noted in BPD as well. Amygdalar hyperactivity to emotional facial expressions has been found to be particularly marked in children and adolescents (aged 7–18) with BD (Kim 2012). Yet in a study of Bipolar-II patients with depression, Vizueta and colleagues (2012) found amygdalar *hypo*-activity (which they felt might be state-dependent), though *OFC hypoactivation* was similar to what has been observed in Bipolar-I—which might therefore warrant consideration as a trait-marker of BDs in general.

Hajek et al. (2012, 2013a) have shown in an fMRI study that BD patients underactivated the right inferior frontal gyrus (R-IFG) relative to a control group, irrespective of current mood state. This suggested that the impaired response inhibition to emotional stimuli (in effect: poorer top-down control) in BD may be a biological marker for the condition. Oddly, the authors noted that the IFG was significantly larger not only in the BD patients, but also in their family members (with or without the disorder). Usually, abnormal function has been associated with smaller-, rather than with larger volumes in the affected regions. Further along in the course of bipolar illness, however, they noted that the IFG became smaller than normal—possibly because of the neurotoxic effects of the illness on gray matter (cf. also: Hajek et al. 2013a). But lithium-treated BD patients eventually were shown to have normal R-IFG volume, despite having had the condition for a long time (Hajek et al. 2013b). Hippocampal volumes in BD, smaller in volume at the outset, were also noted to appear normal in volume following two years or more of lithium treatment (Hayek et al. 2013c). As for other higher centers, a London-based group found evidence in their meta-analysis–of *reduced* gray matter in BD in the right ventral prefrontal cortex (r VPRC), as well as in the temporal cortex and insula (Selvaraj et al. 2012). Malhi et al. (2013), in a review concerning the effects of lithium, mentioned that lithium may exert its beneficial effects in BD via helping to preserve or even increase the volume of brain structures involved in emotional regulation.

In an effort to develop a consensus concerning the evolution of BD and key brain areas involved, a workgroup organized by the University of Cincinnati Department of Psychiatry met to discuss their research. Their impression was that

in the early development of BD there was disruption of brain networks that modulate emotional responses. Because of what may be excessive prefrontal pruning during adolescence, one finds decreased connectivity among ventral prefrontal networks and the relevant limbic centers, especially the amygdala. These changes appear to prepare the path for manic symptomatology (Strakowski et al. (2012). In a study devoted to finding neurophysiological signs that might be helpful in distinguishing BD from schizophrenia in a reliable way, Whalley et al. (2012) examined the fMRI literature, from which they found evidence that over-activation in the medial temporal lobe in emotion and memory tasks—occurred in BD more so than in schizophrenia. As to the distinction between, versus the similarity of, BD and schizophrenia, at least from the standpoint of pharmacological response, it is of interest that in a recent Danish study, clozapine proved useful not just in schizophrenia, but also in refractory BD (Nielsen et al. 2012). Vacheron-Trystram et al. (2004) found clozapine more useful in BD even than in schizophrenia.

10 Attention-Deficit Disorder, BPD, and BD: Similarities and Differences

The conceptual and, to an increasing extent, neurophysiological overlap between BPD and the spectrum of BDs—in a significant percentage of cases—is also pertinent to Attention-Deficit Hyperactivity Disorder (ADHD). This is because, in the same way that BPD is over-represented in samples of BD and vice versa, ADHD is over-represented in a similar way. Granted that ADHD tends to be over-diagnosed in the US, nevertheless young persons with the genuine disorder are more likely, as they enter adulthood, to be diagnosed also with either BPD or BD or both (Makris et al. 2012). Similarly, in the background of adults with BPD or BD, there is a higher proportion of ADHD histories than would be expected in the general population (Faraone et al. 2012). (Philipsen 2006), besides mentioning the clinical interconnection between ADHD and BPD, expressed the view, in the light of recent neuroimaging studies, that ADHD and BPD may be not so much two distinct disorders, but rather a manifestation of two aspects or dimensions of one (underlying) disorder. In a like manner, Rüsch et al. (2007) examined a group of women with BPD who were comorbid also for ADHD. In their imaging study the women with BPD had a narrower *isthmus* of the CC (i.e., the portion where the anterior parts of the CC: rostrum, genu, and body and the posterior part: the splenium—are fused during embryogenesis). A history of childhood sexual abuse was associated with a thinner posterior body of the CC, indicating a possible loss of some of the 190,000,000 axons that make up the CC and subserve interhemispheric connectivity. This may account for some of the deficits in the combined BPD/ADHD disorder. In the study of Posner et al. (2011) the focus was on the amygdala and the lateral prefrontal cortex (LPFC) in their fMRI assessment (using

subliminal presentation of fearful faces) of adolescents with ADHD. Their strategy was based on the connection of the amygdala and the LPFC in monitoring emotional reactivity. They found that activity in the right amygdala was greater in adolescents with ADHD than in the control group, along with greater connectivity between the amygdala and the LPFC. Parenthetically, they noted that stimulants (a common treatment for ADHD) had a normalizing effect on the activity of the right amygdala and on its connections with the LPFC. ADHD is associated with deficits in cortical inhibition, as has been noted in BPD, but also in Gilles de la Tourette syndrome. Barnow et al. (2009) used transcranial magnetic stimulation (TMS) to assess whether BPD patients showed decreased cortical inhibition, or else—increased cortical excitation. They controlled their result for ADHD symptomatology and still noted an association between BPD and deficits in cortical inhibition.

11 Discussion

There is fairly good agreement among investigators concerning the neurophysiological alterations in BPD. The brain-regions chiefly implicated in BPD, along with neurophysiological correlates noted in other disorders: Bipolar, Major Depressive, and ADHD—are summarized in Table 1.

The various studies, relying primarily on MRI, invoke fronto-limbic malfunction as the most general way of addressing the impulsivity and emotional dysregulation that characterize BPD. Because of the widespread recognition that BPD, BDs (whether fluctuating between manic and depressive episodes, or predominantly depressive), and Attention-Deficit/Hyperactivity Disorder often co-occur in various combinations and sequences, imaging researchers who focus on one disorder often include patients with the related conditions as well. The very fact that patients with all three disorders are well-known to clinicians has spurred interest in finding possible commonalities at the deeper level of brain physiology. Eagerness to explore this area has been heightened further following the recent discovery by the Cross-Disorder Group of the Psychiatric Genomics Consortium (2013), that five psychiatric disorders viewed as distinct from a *clinical* perspective nevertheless share certain *genetic* features in common; namely, single nucleotide polymorphisms (SNPs) in two genes involved in calcium-channel activity.

Alessandro Serretti and Chiara Fabbri (2013) and colleagues from the Human Genome Project contributed importantly to this work, which has been reviewed recently by Smoller (2013). The five disorder: Autism, Attention Deficit-Hyperactivity Disorder, BD, Major Depressive Disorder, and Schizophrenia include three of relevance to the topic of BPD. Serretti and Fabbri have argued that there is abundant pleiotropy in human complex disorders, such that the same genetic variant may play a role in several diseases that—to the clinical eye—have appeared separate and unrelated.

Table 1 Neurophysiological abnormalities noted in brain regions in BPD and related conditions

Disorder	Cortical/subcortical regions	Limbic regions
BPD	Prefrontal cortex, orbitofrontal cortex, dorsolateral PFC (including decreased gray matter), ventromedical PFC, parietal lobe, right hemisphere, corpus callosum, insula, N accumbens	Amygdala size (decreased), amygdala reactivity (increased) hippocampus size (decreased)
Bipolar I, II	Prefrontal cortex, dorsolateral PFC, middle prefrontal cortex, right inferior frontal gyrus, medial temporal lobe, right ventral prefrontal cortex	Amygdala size (decreased), amygdala reactivity (decreased; though increased in bipolar-II), hippocampal size (decreased)
Major depression	Dorsolateral prefrontal cortex, anterior cingulate cortex	Amygdala reactivity (increased)
ADHD	Lateral prefrontal cortex, corpus callosum	Amygdala reactivity (increased)

Note The abnormalities observed in the cortical regions usually involved smaller than normal volumes, though in Bipolar-I the R Inferior Frontal Gyrus was larger than normal initially, but smaller—as the illness progressed (Hajek et al. 2013a)

The new research will enable us to move beyond a nosology based on description of signs and symptoms, toward a classification based progressively more on fundamental causes. An effort was recently made in regard to BPD by Calati et al. (2013): she and her colleagues looked for serotonergic polymorphisms, but did not find a direct role in BPD for the three genetic polymorphisms of interest. Perhaps this is less surprising—to the extent that BPD, as noted above, is a markedly heterogeneous clinical syndrome based more on adverse environmental factors than on putative genetic factors. There is in all likelihood a *subset* of BPD cases where genetic factors play a major, not to say, a determinative, role in predisposing to the development (usually discernible at puberty) of the borderline syndrome (à la DSM). Persons with clear-cut and severe BD, who in addition have a family history of bipolar disorders—but who have *no history* of neglect, abuse (whether sexual, physical, or verbal), perinatal complications, drug abuse, or head injury—would constitute the most concentrated pool of patients for the assessment of a genetic linkage to BD, and also for whatever gene polymorphisms may be a part of the picture. There are also social-class and cultural factors to take into account. Persons from economically poorer backgrounds are much more likely to have experienced childhood physical abuse than their better-off counterparts (Straus and Gelles 1992). Incest histories are common in certain cultural settings; rare, in others. In many samples of BPD patients, including those devoted to MRI and fMRI studies, these factors are not separated out, thus complicating any search for specific gene peculiarities. Given the difficulties inherent in carrying out MRI analyses in infants or very young children, it is not easy to determine whether the brain-changes associated with bipolar disorder were already detectable at birth (and later paved the way for development of BPD), or whether

they were epiphenomena of adverse environmental factors. We still tend to be divided into two camps: the "lumpers" and the "splitters": diagnostic lumpers who might argue that BPD, BD, and ADHD are three continents of the same nosologic planet, and the splitters, who claim that they are diagnostically, and perhaps even genetically, separable. As for the BPD question, the time is ripe for further genetic analysis, based on patient-samples that have been more scrupulously homogenized: borderline patients with no family history and no diagnostic indications of bipolarity, versus bipolar patients with a strong family history of BD and no signs at all of environmental adversity. Further neurophysiological and genetic analysis of such groups will help resolve many of the as yet unanswered questions in this domain.

References

Akiskal HS (1981) Subaffective disorders: dysthymic, cyclothymic, and bipolar-II disorders in the 'borderline' states. Psychiatr Clin North Am 4(1):25–46

Anticevic A, Brumbaugh MS, Winkler AM, Lombardo LE, Barrett J, Corlett PR, Kober H, Gruber J, Repovs G, Cole MW, Krystal JH, Pearlson GD, Glahn DC (2012) Global prefrontal and fronto-amygdala dysconnectivity in bipolar-I disorder with psychosis history. Biol Psychiatry. doi:10.1016/j.biopsych.2012.07.031

Antoniadis D, Samakouri M, Livaditis M (2012) The association of bipolar spectrum disorders and borderline personality disorder. Psychiatr Q 83:449–465

Barker V, Pope M, Smith S, Brown V, Hall J (2014) Set shifting and reversal learning in borderline personality disorder. Pers Ment Health 8:1–13

Barnow S, Völker KA, Möller B, Freyberger HJ, Spitzer C, Grabe HJ, Daskalakis ZJ (2009) Neurophysiological correlates of borderline personality disorder: a transcranial magnetic stimulation study. Biol Psychiatry 65:313–318

Benazzi F (2006a) Does temperamental instability support a continuity between bipolar-II disorder and major depressive disorder? Eur Psychiatry 21:274–279

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

Berdahl CH (2010) A neural network of borderline personality disorder. Neural Netw 23:177–188

Bouchard S, Lemelin S, Dubé C, Giguère JF (2010) Dysregulation of the executive system and theory of mind: clinical interest of a neuroscientific conception of BPD. Santé Ment Québec 35:227–251

Boutros NN, Torello M, McGlashan TH (2003) Electrophysiological aberrations in borderline personality disorder: state of the evidence. J Neuropsychiatry Clin Neurosci 15:145–154

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

Brunner R, Henze R, Parzer P, Kramer J, Feigl N, Lutz K, Essig M, Resch F, Stieltjes B (2010) Reduced prefrontal and orbitofrontal gray matter in female adolescents with borderline personality disorder: is it disorder specific? Neuroimage 49:114–120

Calati R, Gresier F, Balestri M, Serretti A (2013) Genetic modulation of borderline personality disorder: systematic review and meta-analysis. J Psychiatr Res 47:1275–1287

Chepenik LG, Wang F, Sencer L, Spann M, Kalmar JH, Womer F, Kale-Edmiston E, Pittman B, Blumberg HP (2012) Structure-function associations in hippocampus in bipolar disorder. Biol Psychol 90:18–22

Coccaro EF, McCloskey MS, Fitzgerald DA, Phan KL (2007) Amygdala and orbitofrontal reactivity to social threat in individuals with impulsive aggression. Biol Psychiatry 62:168–178
Coccaro EF, Sripada CS, Yanowitch RN, Phan KL (2011) Corticolimbic function in impulsive aggressive behavior. Biol Psychiatry 69:1153–1159
Coulston CM, Tanious M, Mulder RT, Porter RJ, Mahli GS (2012) Borderling onbipolar: the overlap between borderline personality disorder and bipolarity. Aust NZ J Psychiatry 46:506–521
Cross-Disorder Group of the Psychiatric Genomics Consortium (2013) Nat Genet 45:984–994
Cullen KR, Vizueta N, Thomas KM, Han GJ, Kim LO, Camchong J, Mueller BA, Bell CH, Heller MD, Schultz SC (2011) Amygdala functional connectivity in young women with borderline personality disorder. Brain Connect 1:61–71
de Almeida CP, Wenzel A, de Carvalho CS, Powell VB, Araújo-Neto C, Quarantini LC, Oliveira IR (2012) Amygdalar volume in borderline personality disorder with and without comorbid post-traumatic stress disorder: a meta-analysis. CNS Spectr 17:70–75
De la Fuente JM, Bengoetxea E, Navarro F, Bobes J, Alarcon RD (2011) Interconnection between biological abnormalities in borderline personality disorder: use of the Bayesian networks model. Psychiatry Res 186:315–319
Dell'Osso B, Berlin HA, Serati M, Altamura AC (2010) Neuropsychobiological aspects, comorbidity patterns and dimensional models in borderline personality disorder. Neuropsychobiology 61:169–179
Diagnostic and statistical manual of psychiatric disorders [DSM-III] (1980), 3rd edn. American Psychiatric, Washington DC
Diagnostic and statistical manual of psychiatric disorders [DSM-IV] (1994), 4th edn. American Psychiatric, Washington DC
Diagnostic and statistical manual of psychiatric disorders [DSM-V] (2013), 5th edn. American Psychiatric, Washington DC
Domes G, Schulze L, Herpertz SC (2009) Emotion recognition in borderline personality disorder: a review of the literature. J Pers Disord 23:6–19
Faraone SV, Biederman J, Wozniak J (2012) Examining the comorbidity between attention deficit hyperactivity disorder and bipolar I disorder: a meta-analysis. Am J Psychiatry 169:1256–1266
Fiedorowicz JG, Black DW (2010) Borderline, bipolar or both? Curr Psychiatry 9:21–31
Fyer MR, Frances AJ, Sullivan T et al (1988) Comorbidity of borderline personality disorder. Arch Gen Psychiatry 45:348–352
Garrett AS, Reiss AL, Howe ME, Kelley RG, Singh MK, Adleman NE, Karchsmsky A, Chang KD (2012) Abnormal amygdala and prefrontal cortex activation to facial expressions in pediatric bipolar disorder. J Am Acad Child Adolesc Psychiatry 51:821–831
Goldstein MA, Price BH (2004) Magnetic resonance imaging. In: Dougherty DD, Rauch SL, Rosenblum JF (eds) Essentials of neuroimaging for clinical practice. American Psychiatric, Washington, DC, pp 21–73
Goodman M, EA Hazlett, Avedon JB, Siever DR, Chu KW, New AS (2011) Anterior cingulated volume reduction in adolescents with borderline personality disorder and co-morbid major depression. J Psychiatr Res 45:803–807
Goodman M, New AS, Triebwasser J, Collins KA, Siever LJ (2010) Phenotype, endophenotype, and genotype comparisons between borderline personality disorder and major depressive disorder. J Pers Disord 24:38–59
Guitart-Masip M, Pascual JC, Carmona S, Hoekzema E, Bergé D, Pérez V, Soler J, Soliva JC, Rovira M, Bulbena A, Villaroya O (2009) Neurla correlates of impaired emotional discrimination in borderline personality disorder: an fMRI study. Prog Neuropsychopharm Biol Psychiatry 33:1537–1545
Gunderson JG (2001) Borderline personality disorder: a clinical guide. American Psychiatric, Washington, DC
Gunderson JG, Singer MT (1975) Defining borderline patients: an overview. Am J Psychiatry 132:1–10

Gunderson JG, Triebwasser J, Phillips KA (1999) Personality and vulnerability to affective disorders. In: Cloninger CR (ed) Personality and psychopathology. American Psychiatric, Washington, DC, pp 3–32

Gunderson JG, Weinberg I, Daversa MT, Kueppenbender KD, Zanarini MC, Shea MT, Skodol AE, Sanislow CA, Yen S, Morey LC, Grilo CM, McGlashan TH, Stout RL, Dick I (2006) Descriptive and longitudinal observations on the relationship of borderline personality disorder and bipolar disorder. Am J Psychiatry 163:1173–1178

Hajek T (2012) Brain-region size may be long-sought biomarker. Psychiatric News, (reported by J Arehart-Treichel). Accessed 17–19 Sept 2012

Hajek T, Alda M, Hajek E, Ivanoff J (2013a) Functional neuroanatomy of response inhibition in bipolar disorders: combined voxel-based and cognitive performance meta-analysis. J Psychiatr Res 47:1955–1966

Hajek T, Cullis J, Novak T, Kopecek M, Blagdon R, Propper L, Stopkova P, Duffy A, Hoschl C, Uher R, Paus T, Young LT, Alda M (2013b) Brain structural signature of familial predisposition for bipolar disorder: replicable evidence for involvement of the right inferior frontal gyrus. Biol Psychiatry 73:144–152

Hajek T, Cullis J, Novak T, Kopecek M, Höschl C, Blagdon R, O'Donovan C, Bauer M, Young LT, Macqueen G, Alda M (2013c) Hippocampal volumes in bipolar disorders: opposing effects of illness burden and lithium treatment. Bipolar Disord 14:261–270

Hegerl U, Stein M, Mulert C, Mergl R, Olbrich S, Dichgans E, Rujescu D, Pogarell O (2008) EEG-vigilance differences between patients with borderline personality disorder, patients with obsessive-compulsive disorder and healthy controls. Eur Arch Psychiatry Clin Neurosci 258:137–143

Herpertz SC, Dietrich TM, Wenning B, Krings T, Erberich SG, Willmes K, Thron A, Sass H (2001) Evidence of abnormal amygdala functioning in borderline personality disorder: a functional MRI study. Biol Psychiatry 50:292–298

Hughes AE, Crowell SE, Uyeji L, Coan JA (2012) A developmental neuroscience of borderline pathology: emotional dysregulation and social baseline theory. J Abnorm Child Psychol 20:21–33

Irle E, Lange C, Sachsse U (2005) Reduced size and abnormal symmetry of parietal cortex in women with borderline personality disorder. Biol Psychiatry 57:173–182

Irle E, Lange C, Weninger G, Sachsse U (2007) Size abnormalities in the superior parietal cortices are related to dissociation in borderline personality disorder. Psychiatry Res 156:139–149

Jankowski AP, Araújo Filho GM, Almeida AG, Araújo CM, Reis M, Nery F, Batista IR, Silva I, Lacerda AL (2012) The involvement of the orbitofrontal cortex in psychiatric disorders: an update of neuroimaging findings. Rev Bras Psiquiatr 24:207–212

Jentsch JD (2012) Lecture on inhibitory control. New York State Psychiatric Institute, New York

Jentsch JD, Olausson P, De La Garza R, Taylor JR (2002) Impairments in reversal learning and response perseveration after repeated, intermittent cocaine administration to monkeys. Neuropsychopharmacology 26:183–190

Kamphausen S, Schröder P, Maier S, Bader K, Feige B, Kaller CP, Glauche V, Ohlendorf S, Tebartz van Elst L, Klöppel S, Jacob GA, Silbersweig D, Lieb K, Tüshcer O (2013) Medical prefrontal dysfunction and prolonged amygdala response during instructed fear processing in borderline personality disorder. World J Biol Psychiatry 14:307–318

Kernberg OF (1967) Borderline personality organization. J Am Psychoanal Assoc 15:641–685

Kim P, Thomas LA, Rosen BH, Moscicki AM, Brotman MA, Zarate CA Jr, Blair RJ, Pine DS, Leibenluft E (2012) Differing amygdala responses to facial expressions in children and adults with bipolar disorder. Am J Psychiatry 169:642–649

Kluetsch RC, Schmahl C, Niedfeld I, Densmore M, Calhoun VD, Daniels J, Kraus A, Ludaescher P, Bohus M, Lanius RA (2012) Alterations in default mode network connectivity during pain processing in borderline personality disorder. Arch Gen Psychiatr 69:993–1002

Koenigsberg HW, Siever LJ, Lee H, Pizzarello S, New AS, Goodman M, Cheng H, Flory J, Prohovnik I (2009) Neural correlates of emotion processing in borderline personality disorder. Psychiatry Res 172:192–199
Kohut H (1971) Analysis of the self. International Universities Press, New York
Kraepelin E (1905) Einfürung in die psychiatrische Klinik, 2nd edn. Leipzig, Barth
Kraepelin E (1921) Manic-depressive insanity and paranoia. E. & S. Livingstone, Edinburgh
Kuperberg GR (2004) Electroencephalography, event-related potentials and magnetoencephalography. In: Dougherty DD, Rauch SL, Rosenblum JF (eds) Essentials of neuroimaging for clinical practice. American Psychiatric, Washington DC, p 117–127
Lewin B (2008) Genes IX. Jones & Bartlett, Boston
Lyoo IK, Han MH, Cho DY (1998) A brain MRI study in subjects with borderline personality disorder. J Affect Disord 50:235–243
Mackinnon DF, Pies R (2006) Affective instability as rapid cycling: theoretical and clinical implications for borderline personality and bipolar spectrum disorders. Bipolar Disord 8:1–14
Mahli GS, Tanious M, Das P et al (2013) Potential mechanisms of action of lithium in bipolar disorder: current understanding. CNS Drugs 27:135–153
Maier-Hein KH, Brunner R, Lutz K, Henze R, Parzer P, Feigl N, Kramer J, Meinzer HP, Resch F, Stieltzes B (2014) Disorder-specific white matter alterations in adolescent borderline personality disorder. Biol Psychiatry 75:81–88
Makris N, Seidman LJ, Brown A et al (2012) Further understanding of the comorbidity between attention-deficit/hyperactivity disorder and bipolar disorder in adults: an MRI study of cortical thickness. Psychiatry Res 202:1–11
Marissen MA, Meuleman L, Franken IH (2010) Altered emotional information processing in borderline personality disorder: an electrophysiological study. Psychiatry Res 181:226–232
Minzenberg MJ, Fan J, New AS, Tang CY, Siever LJ (2007) Fronto-limbic dysfunction in response to facial emotion in borderline personality disorder: an event-related fMRI study. Psychiatry Res 155:231–243
Minzenberg MJ, Poole JH, Vinogradov S (2008) A neurocognitive model of borderline personality disorder: effects of childhood sexual abuse and relationship to adult social attachment disturbance. Dev Psychopathol 20:341–368
New AS, Goodman M, Triebwasser J, Siever L (2008) Recent advances in the biological study of personality disorders. Psychiatr Clin North Am 31:441–461
Nielsen J, Kane JM, Correll CU (2012) Real-world effectiveness of clozapine in patients with bipolar disorder: results from a two-year mirror-image study. Bipolar Disord 14:863–869
Nunes PM, Wenzel A, Borges KT, Porto CR, Caminha RM, de Oliveira IR (2009) Volumes of the hippocampus and amygdala in patients with borderline personality disorder: a meta-analysis. J Pers Disord 23:333–345
Oglodek E (2011) Emotional dysregulation in borderline personality disorder. Pol Merkur Lekarski 30:160–163
O'Neill A, Frodl T (2012) Brain structure and function in borderline personality disorder. Brain Struct Funct 217:767–782
Pally R (2002) The neurobiology of borderline personality disorder: the synergy of "nature and nurture". J Psychiatric Pract 8:133–142
Panksepp J, Biven L (2012) The archaeology of mind. WW Norton, New York
Philipsen A (2006) Differential diagnosis and comorbidity of attention-deficit/hyperactivity disorder (ADHD) and borderline personality disorder (BPD) in adults. Eur Arch Psychiatry Clin Neurosci 256(1):i42–i46
Poletti M (2009) Neurocognitive functioning in borderline personality disorder. Riv Psichiatr 44:374–383
Posner J, Nagel BJ, Maia TV, Mechling A, Oh M, Wang Z, Peterson BS (2011) Abnormal amygdalar activiation and connectivity in adolescents with attention-deficit/hyperactivity disorder. J Am Acad Child Adolesc Psychiatry 50:828–837
Prossin AR, Love TM, Koeppe RA, Zubieta JK, Silk KR (2010) Dysregulation of regional endogenous opioid function in borderline personality disorder. Am J Psychiatry 167:925–933

Radaelli D, Poletti S, Dallaspezia S, Colombo C, Smeraldi E, Benedetti F (2012) Neural responses to emotional stimuli in comorbid borderline personality disorder and bipolar depression. Psychiatry Res 203:61–66
Rodrigues E, Wenzel A, Ribeiro MP et al (2011) Hippocampal volume in borderline personality disorder with and without comorbid posttraumatic stress disorder: a meta-analysis. Eur Psychiatry 26:452–456
Rossi R, Lanfredi M, Pievani M, Beneduce R, Rillosi L, Giannakopoulos P, Thompson PM, Rossi G, Frisoni GB (2012) Volumetric and topographic differences in hippocampal subdivisions in borderline personality disorder and bipolar disorders. Psychiatry Res 203:132–138
Rossi R, Pievani M, Lorenzi M et al (2013) Structural brain features of borderline personality and bipolar disorders. Psychiatry Res 213:83–91
Ruocco AC, Amirthavasagam S, Zakzanis KK (2012) Amygdala and hippocampal volume reductions as candidate endophenotypes for borderline personality disorder: a meta-analysis of magnetic resonance imaging studies. Psychiatry Res 201:245–252
RüschN Luders E, Lieb K, Zahn R, Ebert D, Thompson PM, Toga AW, van Elst LT (2007) Corpus callosum abnormalities in women with borderline personality disorder and comorbid attention deficit hyperactivity disorder. J Psychiatry Neurosci 32:417–422
Schirmer A (2013) Sex and emotion. In: Armony J, Vuilleumier P (eds) The Cambridge handbook of human affective neuroscience. Cambridge University Press, New York, pp 591–610
Schmahl CG, McGlashan TH, Bremner JD (2002) Neurobiological correlates of borderline personality disorder. Psychopharmacol Bull 36:69–87
Selvaraj S, Arnone D, Job D, Stanfield A, Farrow TF, Nugent AC, Scherk H, Gruber O, Chen X, Sachdev PS, Dickstein DP, Malhi GS, Ha TH, Ha K, Phillips ML, McIntosh AM (2012) Grey matter differences in bipolar disorder: a meta-analysis of voxel-based morphometry studies. Bipolar Disord 14:135–145
Serretti A, Fabbri C (2013) Shared genetics among major psychiatric disorders. Lancet 381:1339–1341
Siever LJ (2008) Neurobiology of aggression and violence. Am J Psychiatry 165:429–442
Siever LJ, Weinstein LN (2009) The neurobiology of personality disorders: implications for psychoanalysis. J Am Psychoanal Assoc 57:361–398
Smoller JW (2013) Disorders and borders: psychiatric genetics and nosology. Am J Med Genet B Neuropsychiatry Genet. doi:10.1002/ajmg.b.32174
Soloff P, Nutche J, Goradia D, Diwadkar V (2008) Structural brain abnormalities in borderline personality disorder: a voxel-based morphometry study. Psychiatry Res 164:223–236
Stanley B, Siever LJ (2010) The interpersonal dimension of borderline personality disorder: toward a neuropeptide model. Am J Psychiatry 167:24–39
Stein D (2009) Borderline personality disorder: toward integration. CNS Spectr 14:352–356
Stein M (1997) Hippocampal volume in women victimized by childhood sexual abuse. Psychol Med 27:951–959
Stern A (1938) Psychoanalytic investigation and therapy in the borderline group of neuroses. Psychoanal Q 7:467–489
Stone MH (1980) The borderline syndromes. McGraw Hill, New York
Stone MH (1981) Borderline syndromes: a consideration of subtypes and an overview. Psychiatric Clin N Am 4(1):3–24
Stone MH (1990a) The fate of borderline patients: successful outcome and psychiatric practice. Guilford, New York
Stone MH (1990b) Incest in borderlines. In: Kluft R (ed) Incest-related syndromes of adult psychopathology. American Psychiatric, Washington DC, pp 183–204
Stone MH, Unwin A, Beacham B, Swenson C (1988) Incest in borderlines: its frequency and impact. Int J Fam Psychiatry 9:277–293
Strakowski SM, Adler CM, Almeida J, Altschuler LL, Blumberg HP, Chang KD, DelBello MP, Frangou S, McIntosh A, Phillips ML, Sussman JE, Townsend JD (2012) The functional neuroanatomy of bipolar disorder: a consensus model. Bipolar Disord 14:313–325

Straus MA, Gelles RJ (1992) Physical violence in American families, 2nd edn. Transaction, New Brunswick

Tebartz van Elst L, Ludaescher P, Thiel T, Büchert M, Hesslinger B, Bohus M, Rüsch N, Hennig J, Ebert D, Lieb K (2007) Evidence of disturbed amygdalar energy metabolism in patients with borderline personality disorder. Neurosci Lett 417:36–41

Teicher MH, Anderson SL, Polcari A, Anderson CM, Nvalta CP, Kim DM (2003) The neurobiological consequences of early stress and childhood maltreatment. Neurosci Biobehav Rev 27:33–44

Vacheron-Trystram MN, Braitman A, Cheref S, Auffray L (2004) Antipsychotics in bipolar disorders. Encéphale 30:417–424

Vizueta N, Rudie JD, Townsend JD, Torrisi S, Moody TD, Bookheimer SY, Altschuler LL (2012) Regional fMRI hypoactivation and altered functional connectivity during emotion processing in nonmedicated depressed patients with bipolar-II disorder. Am J Psychiatry 169:831–840

Weninger G, Lange C, Sachsse U, Irle E (2011) Reduced amygdala and hippocampal size in trauma-exposed women with borderline personality disorder and without posttraumatic stress disorder. J Psychiatry Neurosci 34:383–388

Whalley HC, Papmeyer M, Sprooten E, Lawrie SM, Sussman JE, McIntosh AM (2012) Review of functional magnetic resonance imaging studies comparing bipolar disorder with schizophrenia. Bipolar Disord 14:411–431

Wingenfeld K, Spitzer C, Rullkötter N, Löwe B (2010) Borderline personality disorder: hypothalamus-pituitary-adrenal axis and findings from neuroimaging studies. Psychoneuroendocrinology 35:154–170

Zanarini MC, Frankenburg FR, Dubo ED et al (1988) Axis I comorbidity of borderline personality disorder. Am J Psychiatry 155:1733–1739

Zetzsche T, Preuss UW, Bondy B, Frodl T, Zill P, Schmitt G, Koutsouleris N, Rujescu D, Born C, Reiser M, Möller H-J, Meisenzahl EM (2007) 5-HT-1areceprot gene C-1019G polymorphism and amygdala volume in borderline personality disorder. Genes Brain Behav 7:306–313

Zilboorg Z (1941) Ambulatoiry schizophrenia. Psychiatry 4:149–155