

Neuroimaging and genetics of borderline personality disorder: a review

Eric Lis, BSc; Brian Greenfield, MD; Melissa Henry, PhD; Jean Marc Guilé, MD;
Geoffrey Dougherty, MD

Lis, Greenfield, Henry — Faculty of Medicine, McGill University; Greenfield, Dougherty — Montréal Children's Hospital; Guilé — Douglas Hospital, Montréal, Que.

Borderline personality disorder (BPD) is a highly prevalent psychiatric disorder that carries a severe risk factor for adolescent and young adult suicide. Relatively little research has examined its biological etiology. Differences in the volume and activity in brain structures related to emotion and impulsivity have been observed between individuals who have BPD and those who do not. The present study seeks to assess current research on the neuroanatomical differences observed between individuals with and without BPD and the genes that may play a role in the development of this disorder.

Le trouble de la personnalité limite (TPL) est une affection psychiatrique très répandue qui comporte un facteur de risque grave de suicide chez les adolescents et les jeunes adultes. Il s'est fait relativement peu de recherche sur son étiologie biologique. On a observé des différences entre les sujets aux prises avec le TPL et ceux qui n'en sont pas atteints au niveau du volume et de l'activité de structures du cerveau reliées à l'émotion et à l'impulsivité. La présente étude vise à évaluer la recherche courante sur les différences neuro-anatomiques observées entre des sujets avec et sans TPL, ainsi que sur les gènes qui peuvent intervenir dans le développement de ce trouble.

Introduction

Borderline personality disorder (BPD) is prevalent, affecting as many as 1% to 2% of the general population,¹ and this incidence rises as high as 15% to 20% in psychiatric settings.² BPD is associated with high rates of suicide — nearly all BPD patients have experienced suicidal ideation and almost 10% commit suicide by adulthood.³ Although psychosocial causes of BPD have been explored in many studies, relatively little data exist regarding biological causes. The neurological and genetic factors of BPD have not yet been fully explored, perhaps because it is difficult to find BPD subjects to participate or because the technologies used are relatively young. The study of such factors may be a key to drawing new insights into the causes, comorbidities and treatments of BPD.

Methods

We reviewed research on BPD, using the PubMed and

PsycINFO databases. Relevant articles were found between 1980 and 2006, although we did not restrict our search to a particular time period. We selected about 49 relevant articles, using the following 3 processes: 1) we cited selected articles using a combination of the search terms "borderline personality disorder," "BPD," "MRI," "fMRI," "imaging," "PET," "genetics," "neuroanatomy," "5-HTT," "serotonin," "dopamine," "MAOA," "amygdala" and "prefrontal"; 2) we searched through articles and books cited as significant by recent authors; 3) from the articles we accumulated, we selected the first authors who were the earliest to demonstrate a given finding with a sufficient sample size. We did not cite replicated articles that did not demonstrate new findings. The articles we reviewed are summarized in Table 1 and Table 2.

Overall, use of neuroimaging in the study of BPD dates back only a few years. BPD has been linked to the amygdala and limbic systems of the brain, the centres that control emotion and, particularly, rage, fear and impulsive automatic

Correspondence to: Eric Lis, Faculty of Medicine, McGill University, 144 Fairview, Montréal QC H9A 1V6; fax 514 412-4250; ericlis@hotmail.com

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reactions.²¹ Studies have shown that the hippocampus and amygdala may be as much as 16% smaller in people with BPD and have suggested that experiences of trauma may lead to these neuroanatomical changes.⁵ Positron emission tomography (PET) scans have generally shown that people with BPD show hypometabolism of glucose in their prefrontal cortex and limbic system relative to people who don't have BPD,¹² suggesting that the disorder may result from a failure of the "rational" prefrontal cortex to regulate the "impulsive" limbic system.

One difficulty inherent in analyzing the data about neurological changes associated with BPD is that much of the research is contradictory. For example, the anterior cingulate cortex has been shown to have hypometabolism or hypermetabolism in different studies that used the same imaging technologies. Undoubtedly, this is partly owing to the complexity of imaging studies and the variety of possible confounding factors, including the drugs a participant might have had in their system, the potential effect of any comorbid psychiatric disorders on neurophysiology, and differences in images introduced by different resolutions, head tilts or laboratory conditions. The contradiction might also be due to the heterogeneity of people with BPD. Vast differences can be observed in manifestations of the disorder between 2 individuals,³ and it is reasonable to assume that there may be different neurological changes in a person who is highly impulsive versus someone with primarily dissociative symptoms.

A related difficulty in this area is the question of whether participants with comorbid psychiatric disorders should be excluded. Because most people with BPD have an additional mental disorder, frequently depression,³ excluding participants with these disorders reduces the generalizability of a study. Excluding people with multiple diagnoses ensures that abnormal brain volumes or metabolisms observed are associated with BPD, rather than some other illness, but the results may not apply precisely to the larger population of BPD patients with comorbid disorders.

Historically, work linking BPD to brain dysfunction dates as far back as 1980,²² when it was postulated that there may be a subgroup of patients whose illnesses had organic causes, such as brain injury. This prompted examinations of neuropsychological functioning in BPD patients. van Reekum and colleagues²³ examined data from medical charts and interviews with 48 war veterans, mostly men, with a mean age of 32 years. They found that BPD patients had a higher prevalence of brain injuries, developmental or acquired, than healthy control subjects and that greater brain dysfunction is linked to greater behavioural disturbances. This finding was replicated with a more representative group of participants²⁴ but was limited because it was retrospective; the authors could not demonstrate cause and effect (that brain injuries were a cause of BPD rather than that impulsive people were more likely to be in injurious situations). To address such uncertainties, imaging techniques were used to examine neurological function. The earliest studies typically found no neuroanatomical differences between control subjects and BPD patients, or they found differences that failed to achieve statistical significance.²⁵⁻²⁷

Electroencephalographic (EEG) technology was applied to BPD by Zanarini and others,²⁸ who found subtle abnormalities in the EEGs of patients with BPD. They suggested that, because childhood abuse is a known risk factor for the development of BPD, cranial trauma sustained during childhood may result in permanent functional abnormalities that would result in BPD symptoms. With the improvement of EEG technology, newer studies have been conducted. Working from the hypothesis that people with BPD have impeded maturation of higher-order consciousness, Meares and colleagues²⁹ tested prefrontal cortical systems of coordination and integration. They administered an auditory stimulus target detection task to subjects with BPD and used EEG to measure the P3 event-related brain potential, which can be measured as 2 components (P3a and P3b). They demonstrated that P3 is slightly delayed in BPD subjects and that, compared with age-matched healthy control subjects, the P3a of BPD subjects showed enhanced amplitude, failure of habituation and lack of temporal synchronicity with P3b. The authors suggested that these abnormalities indicated a general failure of coordination among diverse cortical networks. Further, on measuring and qualifying the characteristic P3 of people from various age groups, BPD patients were found to exhibit a P3 profile of people younger than themselves (i.e., failure of maturation and thus possibly failure of development of a sense of self). This study diagnosed patients using the *Diagnostic and Statistical Manual of Mental Disorders (DSM)*, third edition, revised (DSM-III-R³⁰) rather than the DSM, fourth edition (DSM-IV).³¹

Early attempts to use neuroimaging technology to study BPD, in conjunction with early EEG studies that demonstrated neurological abnormalities in BPD patients, laid the groundwork for more studies as imaging technologies improved. Higher-resolution, more easily accessible technology began to show structures in the brain that were abnormal in BPD patients. PET studies suggested that BPD patients had abnormalities in the frontal and temporal lobes. Two major works^{12,32} found that patients with BPD showed relatively low glucose metabolism in various brain structures, including the frontal cortex (dorsolateral frontal cortex) and limbic system (anterior cingulate cortex), as well as structures strongly associated with the limbic system (the basal ganglia and the thalamus) during the resting state. In contrast, Juengling and colleagues¹⁷ found hypermetabolism in the anterior cingulate and in several frontal cortex structures (superior frontal gyrus, right inferior frontal gyrus and opercular part of the right precentral gyrus). Hypometabolism was demonstrated in the limbic structure of the left hippocampus and in the left cuneus, an occipital structure involved in visual processing.

The ability of PET scans to observe brain activity in response to particular stimuli has allowed them to be used to examine neural correlates of particular BPD symptoms, as well as the illness itself (for example, Schmahl and colleagues¹⁰). Fear of abandonment is a major symptom of BPD, so the researchers presented scripts of abandonment situations to 20 women with a history of abuse, 10 of whom had BPD and 10 control women without BPD. In women with BPD, they observed increased activation (increased blood flow) of the bilateral dorsolateral prefrontal cortex and right

cuneus and decreased activation in the medial prefrontal cortex and various structures involved primarily in visual processing, including the left fusiform gyrus, left visual association cortex and left middle temporal gyrus. Women with and without BPD showed deactivation in the right precuneus (whose function has not yet been proven but which is believed to be a limbic structure) and the right caudate (involved primarily in voluntary movement), suggesting that these areas play a role in a generalized response to memories of abandonment nonspecific to BPD.

In one of the most recent PET studies of BPD, Lange and colleagues¹⁸ examined 17 female inpatients (mean age 32 yr) with dissociative symptoms and various other comorbid disorders, excluding only participants with neurological or psychotic diseases. Compared with healthy control subjects, the

patients with BPD demonstrated reduced glucose metabolism in right-sided ventromedial temporal and left-sided medial parietal or posterior cingulate cortices, areas associated with limbic function and memory. Further, memory performance was positively correlated with metabolism, suggesting a functional implication of the metabolic abnormalities.

The development of magnetic resonance imaging (MRI) as an alternative to CT, PET and EEG allowed researchers to measure the volumes of structures in the brain more effectively, with a clearer distinction between grey matter, white matter and cerebrospinal fluid and with generally superior resolution.³³ Perhaps the first published MRI-based investigation of brain abnormalities in people with BPD was Lyoo and colleagues.⁸ They recruited 25 people with BPD (diagnosed according to the DSM-III³⁴) and 25 control subjects without

Table 1: Summary of papers relating to anatomic brain changes

Study	Design	Subjects	Objective/hypothesis	Results	Limitations
Brambilla et al ⁴	MRI: hippocampus, amygdala, dorsolateral prefrontal cortex, temporal lobes, basal ganglia	10 participants (6 F) with various comorbidities, drug-free 2 mo	Examine hippocampal and amygdala volume reduction in BPD associated with childhood abuse; investigate areas important in the regulation of emotion and impulsivity	Decreased hippocampus volumes in BPD patients, especially those with childhood abuse; enlarged putamen volumes in BPD especially with comorbid substance use disorders	Small sample size
Driessen et al ⁵	MRI: hippocampus, amygdala, temporal lobes, prosencephalon	21 F with BPD, 21-40 yr, previously without comorbid psychiatric disorders	Volumes of studied brain structures will be smaller than in control subjects	Significantly reduced volumes of both brain structures (left hemisphere hippocampus reduced 15.7%, right hemisphere hippocampus reduced 15.8%, left hemisphere amygdala reduced 7.9%, right hemisphere amygdala reduced 7.5%); mean hippocampal volume negatively correlated with duration of abuse in history	Did not assess for past depression; did not control for history of psychotropic drug use
Hazlett et al ⁶	MRI: measure grey and white matter in BAs within the cingulate	50 patients (18-52 yr, mean 33) with various comorbidities, assessed with DSM-III criteria; 13 had SPD, 37 did not	Examine grey and white matter volume within BAs of the cingulate gyrus and frontal lobe, examine comorbidity by subgrouping into BPD patients with SPD and those without	Reduced cingulate grey and increased white matter volume in BA 24 and 31; BPD without SPD group showed this abnormality in BA 24 but 31 was spared; BPD with SPD group had reduced grey matter volume in both; grey matter loss in BA 31 was greater in the BPD with SPD subjects than BPD only subjects	DSM-III diagnoses
Irle et al ⁷	MRI: parietal cortex, hippocampus	30 F inpatients; excluded for history of neurological disease, electroencephalograph abnormalities indicative of temporal lobe epilepsy, hyperintense MRI signals, psychotic disorders; patients tested were also diagnosed with PTSD, panic disorder, generalized anxiety disorder, OCD, major depression, somatization disorder, anorexia, depersonalization disorder, dissociative amnesia, dissociative identity disorder	Examine anatomical changes in BPD via MRI	Reduced size of the right parietal cortex, stronger parietal leftward asymmetry; reduced leftward asymmetry associated with stronger psychotic symptoms and more schizoid personality traits; smaller hippocampal volumes associated with stronger clinical symptoms	High prevalence of axis 1 disorders in the participants might have added confounds but made the sample more representative of BPD; only F tested

any signs of BPD or neurological dysfunction. They compared images of the frontal and temporal lobes, lateral ventricles and overall cerebral hemispheres, demonstrating that BPD patients showed significantly reduced frontal lobe volume (6.2%) without other significant differences. Although innovative in its use of MRI, this study was limited in its generalizability because participants who demonstrated a history of axis I or axis II mental disorders other than BPD were excluded. The second limitation of this study was that head tilt during scanning was not corrected for, and subject movement or head rotation might have added measurement error. The authors also noted that, while differences in grey and white matter were not analyzed as part of the study, the relative amounts may make a difference in the results. The authors proposed that reduced frontal lobe volume may be associated with impulse control failures of people with BPD, given that people with frontal lobe damage due to trauma often display lack of impulse control.³⁵

Building on the work of Lyoo and colleagues,⁸ Driessen and others⁵ used MRI to specifically study the limbic structures of the hippocampus and amygdala. They recruited 21 female patients (aged 21–40, mean 29.9 yr) with BPD without comorbid psychotic disorders (i.e., schizophrenia or major depressive disorder with psychotic symptoms as assessed with the DSM-IV) and compared them with control subjects without BPD or other mental illness. Patients with BPD showed significantly reduced volumes of both brain structures (left hemisphere hippocampus reduced 15.7%, right hemisphere hippocampus reduced 15.8%, left hemisphere amygdala reduced 7.9% and right hemisphere amygdala reduced 7.5%). No significant difference in volumes were observed within the groups. BPD patients with comorbid post-traumatic stress disorder (PTSD) showed no significant differences from those without PTSD. Mean hippocampal volume was negatively correlated with duration of abuse in the patient's history, and correlations between amygdala

Table 1 continued

Study	Design	Subjects	Objective/hypothesis	Results	Limitations
Lyoo et al ⁸	MRI: frontal lobes, temporal lobes, lateral ventricles, cerebral hemispheres	25 subjects from inpatient and outpatient wards, with no other current axis 1 or 2 illnesses	Volumes of the frontal and temporal lobes of the brain may change in BPD subjects	Reduced frontal lobe volume (6.2%); no other significant differences	Participants were excluded if they demonstrated a history of axis I or axis II mental disorders other than BPD; head tilt during scanning not corrected for; differences in grey and white matter not analyzed
Rusch et al ⁹	Voxel-based morphometric study	20 BPD patients (F, mean age 29.3 yr) with various comorbidities; excluded for history of loss of consciousness and coma, schizophrenia, bipolar disorder, alcohol/drug abuse, current major depression, current anorexia; participants psychotropic-free for 2 wk and had completed schooling	Volume reduction and possibly loss of cortical grey matter density in hippocampus, amygdala, left orbitofrontal and right anterior cingulate cortex	Volume reduction in basolateral amygdala; no differences in regional cortical grey or white matter density or volume	Excluded current depression and anorexia; VBM limits: eliminates rater bias and error but its ability to detect subtle differences not yet been proven sufficiently
Schmahl et al ¹⁰	MRI: amygdala and hippocampus	10 F with BPD and history of sexual or childhood abuse; exclusion for organic mental disorder, history of head trauma, current alcohol abuse, history of psychotic disorder	Smaller hippocampal and amygdala volumes in BPD patients	Supported hypothesis	Small sample, history of psychotropic medication and/or drug use in most patients
Tebartz van Elst et al ¹¹	MRI: hippocampus, amygdala, and orbitofrontal, dorsolateral prefrontal, and anterior cingulate cortex	Eight F patients with BPD, aged 20–40 yr, finished regular schooling, no psychotropic drugs for 2 wk; exclusion criteria: lifetime diagnosis of schizophrenia, bipolar I disorder, alcohol/drug abuse in past 6 mo, current anorexia, major depression	Smaller amygdala and hippocampus in BPD patients, differences in prefrontal lobe	No significant difference in total brain volume; 20%–21% reduction of hippocampal and 23%–25% reduction amygdala volumes; 24% reduction of the left OFC, 26% reduction of the right ACC; amygdala volumes of both sides correlated with left orbitofrontal volume; positive correlation between no. of self-injurious incidents and bilateral anterior cingulate volume	Did not separate grey from white matter. Cannot specify which of the different gyri contributed most to the reported volume loss; exclusion reduced generalizability

F = female; BPD = borderline personality disorder; BA = Brodmann's area; DSM-III = *Diagnostic and Statistical Manual of Mental Disorders*, third edition; SPD = schizotypal personality disorder; PTSD = posttraumatic stress disorder; OCD = obsessive-compulsive disorder; VBM = voxel-based morphometry; OFC = orbitofrontal cortex; ACC = anterior cingulate cortex.

Table 2: Summary of papers relating to functional brain changes

Study	Design	Subjects	Objective/hypothesis	Results	Limitations
De la Fuente et al ¹²	PET: metabolism during resting state, closed eyes, unplugged ears, dimmed lights, low ambient noise, after 2 h fast	10 patients (8 F) 24-45 yr excluded for current axis I disorders and major depression, abnormal neurology or history of head trauma, abnormalities on standard blood test or ECG; 10 d washout for psychotropic medication	Study regional cerebral metabolism in BPD with PET	Hypometabolism in the dorsolateral part of the frontal cortex, anterior cingulate cortex, basal ganglia and thalamus	Frontal cortex hypometabolism is probably a nonspecific finding, common to many mental illnesses; DSM-III used for diagnoses
Donegan et al ¹³	fMRI: response to a fixation point or to happy, sad, fearful facial expressions	15 right-handed subjects (13 F), mean age approx. 35 yr, treated in the last 6 mo; excluded for organic mental impairment, schizophrenia, and substance intoxication. Also excluded if unable to refrain from abusing substances for a 2-wk period before the experiment or unable to undergo scanning	Amygdala hyperreactivity in BPD patients contributes to hypervigilance, emotional dysregulation, disturbed interpersonal relations	Greater left amygdala activation to facial emotion v. fixation point; debriefing revealed that some BPD patients had difficulty disambiguating neutral faces or found them threatening	Did not exclude based on most mental disorders (nearly every participant was comorbid for at least 1 personality disorder). Some participants were taking medications that might have altered results
Driessen et al ¹⁴	fMRI: metabolism while patients recalled traumatic episodes	12 BPD patients (F) with trauma and previously treated; excluded for endocrine system disorders, malignant diseases, liver cirrhosis, neurological diseases, loss of consciousness, mental retardation, current infectious diseases, anorexia, schizophrenia, schizoaffective disorders, MDD with psychotic symptoms	Traumatic memory in BPD patients is associated with activation patterns different from those associated with negative but nontraumatic memory and that PTSD modifies these patterns	Activation of the orbitofrontal cortex in both hemispheres, activation of Broca's area in patients with BPD without PTSD, minor activation of the OFC, no activation of Broca's area in patients with BPD and PTSD	Small sample size
Goethals et al ¹⁵	Brain perfusion SPECT: investigated whether BPD and antisocial personality disorder show unusual patterns of perfusion	37 patients APD (25 M, mean age 32.3 yr) admitted for impulsive behaviour and found to show as BPD; excluded for axis I diagnosis, inability to go medication-free, brain lesions found (CT); 27 patients were BPD, 10 were APD	Confirm the existence of a particular pattern of cerebral perfusion in BPD and APD without comorbid axis I disorders, substance abuse, or traumatic brain injury	Reduced regional cerebral blood flow in the right lateral temporal cortex and the polar and ventrolateral parts of the right prefrontal cortex	Exclusion of comorbidities; lack of sex- and age-matched healthy controls; absence of a psychiatric control population (would have shown whether reduced CBF was a nonspecific psychiatric finding)
Herpertz et al ¹⁶	fMRI: amygdala while emotionally aversive images are displayed to participants	6 BPD patients (F) who displayed no comorbid mental illness	BPD subjects will show a higher degree of activation in limbic/paralimbic structures in response to aversive images	Elevated blood oxygenation level dependent fMRI signal in the amygdala in both hemispheres, unusual activation in the prefrontal cortex (medial and inferolateral portions)	Small sample size, no patients with comorbidities, no analysis of the effect of participants' phase of their menstrual cycles
Juengling et al ¹⁷	PET: frontal and prefrontal metabolism during resting conditions	12 F, mean age 25 yr, free of psychotropic-free for 4 wk; excluded for lifetime schizophrenia, bipolar disorder, alcohol/drug abuse in the last 6 mo, current anorexia, major depression	Replicate results of De la Fuente et al, ¹² demonstrate alterations in function in prefrontal cortex, anterior cingulate, hippocampus	Glucose metabolism increased in the anterior cingulate, the superior frontal gyrus bilaterally, the right inferior frontal gyrus and the opercular part of the right precentral gyrus, and decreased in left cuneus and left hippocampus	Small sample size; exclusion of comorbidities
Lange et al ¹⁸	PET: metabolism in the right temporal pole/anterior fusiform gyrus and left precuneus and posterior cingulate cortex and correlate with failures of memory	17 F inpatients (mean age 32 yr) with strong dissociative symptoms and memory deficits who had participated in Irlé et al ⁷ ; excluded for neurological disease, psychotic disorder; various comorbid mental illnesses represented	Investigate whether brain glucose metabolism is reduced in temporo-parietal cortices of BPD subjects with dissociative symptoms; investigate whether temporo-parietal metabolic changes are related to clinical symptoms and to memory deficits of BPD subjects	Reduced glucose metabolism in right-sided ventromedial temporal and left-sided medial parietal/posterior cingulate cortices; memory performance correlated with metabolic activity in ventromedial and lateral temporal cortices (poorer memory performance is correlated to lower metabolism)	High comorbidity rate

Table 2 continued

Study	Design	Subjects	Objective/hypothesis	Results	Limitations
Schmahl et al ¹⁰	PET: blood flow while listening to stories of neutral or personal abandonment	10 F with BPD and 10 without BPD but with history of abuse, recruited through newspapers and flyers; excluded for serious medical or neurological illness, organic mental disorder or comorbid psychotic disorders, retained metal, history of head trauma, loss of consciousness, cerebral infectious disease, dyslexia; most participants had comorbidities, such as lifetime or current MDD and PTSD	Exposure to scripts of abandonment situations will result in decreased blood flow in medial prefrontal cortex, fusiform gyrus, and visual association cortex and in increased activation in dorsolateral prefrontal cortex in F with BPD	Exposure to scripts of abandonment resulted in increased activation of the bilateral dorsolateral prefrontal cortex and decreased activation in the left fusiform gyrus, left visual association cortex, medial prefrontal cortex and alterations in blood flow in other areas that were not hypothesized, including deactivation in left middle temporal gyrus and activation in right cuneus; both groups showed deactivation in right precuneus and right caudate, suggesting a generalized response to memories of abandonment nonspecific to BPD	Pilot study; small sample size; nearly all BPD subjects were taking psychotropic medication during the investigation control and experimental groups not matched for comorbid disorders
van Elst et al ¹⁹	Hydrogen-1 magnetic resonance spectroscopy with varied echo time: measurement of NAA concentrations in prefrontal cortex of BPD patients	12 unmedicated F BPD patients previously treated via dialectical behaviour therapy; excluded for lifetime schizophrenia, bipolar disorder, learning disorders, alcohol/drug abuse in past 6 mo, current severe anorexia, major depression	Short and long echo time MRS to investigate frontal and striatal brain pathology as a possible cause of the glucose hypometabolism, looking especially at NAA as a metabolite	Reduction of the absolute NAA concentrations in the dorsolateral prefrontal cortex which suggests hypometabolism, low neuronal density, and possibly neurodegeneration. No differences in NAA/creatine or choline/creatine ratios (which suggests that looking at these ratios is of no use for BPD)	Looked only at prefrontal cortex due to time constraints, so cannot comment on other brain areas of interest (such as orbitofrontal cortex and amygdala); excluded depression patients
Völlm et al ²⁰	fMRI: BPD or APD patients scanned during a Go/No Go task to observe activation associated with impulsivity	8 personality disorder patients (7 BPD) with various comorbid axis II disorders; excluded for history of significant head injury, history of neurological illness/pathological MRI scan, use of illicit substance in the past 2 mo, alcohol intake > 20 units/wk, current moderate or severe depression, manic or psychotic illness, current antidepressant medication and any contraindication for MRI scanning	Attenuated orbitofrontal cortex responses during performance of a Go/NoGo task compared with healthy control subjects	More widespread activation of prefrontal and temporal areas than healthy control; in control subjects, main focus of activation during inhibition was right dorsolateral and the left orbitofrontal cortex; in patients, observed more bilateral and extended activation across the medial, superior and inferior frontal gyri extending to the anterior cingulate	Small sample, with 2 disorders as the main focus; patients with severe depression excluded; no difference in impulsivity between patients and healthy control subjects (probably due to low power and patients underreporting impulsivity); impulsivity manifests differently in different disorders and may not be the same symptom in APD and BPD

PET = positron emission tomography; F = female; ECG = electrocardiogram; BPD = borderline personality disorder; DSM-III = *Diagnostic and Statistical Manual of Mental Disorders*, third edition; fMRI = functional MRI; M = male; MDD = major depressive disorder; PTSD = posttraumatic stress disorder; OFC = orbitofrontal cortex; SPECT = single photon emission computed tomography; APD = antisocial personality disorder; CBF = cerebral bloodflow; MRS = magnetic resonance spectroscopy; NAA = N-acetylaspartate.

volume and duration of abuse were insignificant. This study addresses several of the limitations of earlier studies. In addition to using the DSM-IV to define BPD, rather than the DSM-III, it corrected for head tilt and used less stringent exclusion criteria. The study is limited because the functioning of the brain regions studied was not assessed, thus the authors could not state whether the reduced volume had a functional impact or whether volume reductions were a cause or an effect of BPD.

Since Driessen and colleagues, other researchers have conducted similar MRI studies, including Tebartz van Elst and colleagues¹¹ who studied 8 female patients aged between 20

and 40 years, excluding those with a lifetime diagnosis of schizophrenia, bipolar I disorder, alcohol or drug abuse in the past 6 months, current anorexia or current major depression. The researchers demonstrated 20%–21% reductions of hippocampal volume and 23%–25% reductions of amygdala volume in people with BPD. They also demonstrated 24% reductions of the left orbitofrontal cortex (OFC, a frontal cortex structure implicated in decision-making and believed to be part of the limbic system) and 26% reductions of the right anterior cingulate cortex. This study was limited because grey and white matter were not separated; thus it could not be specified which gyri contributed to volume loss. The study

was additionally limited because it used a small sample size ($n = 8$). The generalizability was stronger than some previous studies because patients with a lifetime history of depression were included (4 of 8 participants had experienced major depression in their lifetime). Brambilla and colleagues⁴ later studied volume abnormalities in the putamen, a structure associated with the caudate and part of the basal ganglia that is believed to play a role in reinforcement learning and which is particularly vulnerable to abnormal enlargement in alcohol and drug abusers. Examining 10 subjects with BPD (6 women, aged 18–45 yr) with various comorbid disorders without taking medication for 2 months, they demonstrated that BPD patients had decreased hippocampal volume (especially those who were abused as children) and increased putamen volume (especially in substance users). They did not find volume differences in the amygdala or other structures that were noted by other investigators. The authors suggested that ongoing studies with larger sample sizes are needed to address conflicting results obtained by these different studies.

Even more recently, Irlé and colleagues⁷ tested 30 women with BPD and demonstrated that, relative to control subjects, they showed reduced volume of the right parietal cortex. They further demonstrated a stronger parietal leftward asymmetry in BPD patients, with reduced leftward asymmetry appearing related to stronger psychotic symptoms and more schizoid personality traits. The study replicated the finding that hippocampus size was reduced in people with BPD, with reduced volume being related to stronger trauma-related clinical symptoms. The authors speculated that a reduced leftward asymmetry of temporoparietal cortices may be a risk factor for developing psychotic symptoms after trauma and abuse, whereas increased leftward parietal cortex asymmetry may be protective. In line with Tebartz van Elst and others,¹¹ this study excluded people with neurological disease and psychotic disorders but included many DSM diseases, such as major depression (lifetime and current), PTSD, generalized anxiety disorder, somatization disorder, anorexia, depersonalization disorder and even dissociative identity disorder. These authors noted that, as with most studies on the neuroimaging of BPD patients, they tested only women but that temporoparietal cortex asymmetry has been shown to vary considerably with sex.

Current research has moved increasingly toward examining volume reductions in different subgroups of BPD, as in the work of Hazlett and colleagues.⁶ These researchers examined differences between people with BPD and without comorbid schizotypal personality disorder (SPD). The investigators used MRI to examine the overall cingulate gyrus grey and white matter volume and volume of Brodmann's areas 24 and 31 in the cingulate gyrus, comparing BPD subjects with healthy control subjects and subjects with BPD both with and without SPD. They found that BPD subjects had overall reduced grey and increased white matter volume in areas 24 and 31. Patients with BPD without SPD, however, had these reductions in area 24 while area 31 was spared; patients with BPD and SPD had reduced grey matter volume in both areas. Grey matter volume reduction in area 31 was

greater in the BPD and SPD group than in the BPD without SPD group, while the whole BPD group did not differ from control subjects in overall prefrontal brain or cingulate volume. These findings suggest that BPD patients do not differ from control subjects in the total volume of their cingulate gyri but that relative grey and white matter volumes in certain parts of that gyrus may be abnormal. The authors argued that it makes sense that area 24 (in the anterior cingulate, associated with recognition of affect) would show such abnormalities in all BPD patients, whereas abnormalities in area 31 (in the posterior cingulate, associated with affective processing) would be less abnormal in people with BPD without SPD. This study used the DSM-III-R to assess patients and provides insight into possible subgroupings of BPD.

Numerous other imaging methods exist and, while technologies such as MRI and functional MRI (fMRI) are most common, other technologies have recently been used to add to the body of research on BPD. Rusch and colleagues⁹ used voxel-based morphometry (VBM) to examine brain structures that MRI had shown lose volume in BPD patients. They selected VBM as their tool because it offers objective and automated measurement of changes in grey and white matter density and volume. Using this highly sensitive technology to compare the volume and density of the grey and white matter of BPD patients with control subjects, the researchers found significant volume reductions in the area of the basolateral amygdala and no differences in regional cortical grey or white matter density or volume. They did not confirm right amygdala volume loss or abnormalities in the prefrontal areas and suggested that this may be due to different methodologies used in different studies.

The increasing availability of data regarding anatomic changes in the brain led to an investigation of physiological changes, particularly with fMRI. Whereas MRI scans had begun to demonstrate anatomical abnormalities in the brains of people with BPD, fMRI allowed researchers to observe neural activation within the structures of interest. The function of the amygdala as a centre of emotion regulation and the evidence of structural abnormalities in the amygdala in cases of BPD made it a natural structure for fMRI investigation. Herpertz and colleagues¹⁶ first recruited 6 women with BPD who displayed no comorbid mental illness and 6 age-matched healthy control subjects. They then presented emotionally aversive and neutral slides and compared the amygdala functioning of both groups. It was demonstrated that participants with BPD showed an elevated blood oxygen-level dependent fMRI signal in the amygdala in both hemispheres and activation in the prefrontal cortex (medial and inferolateral portions) in response to aversive slides. Experimental and control groups both demonstrated increased activation in the temporo-occipital cortex, but the experimental group showed increased activation in the fusiform gyrus as well. The authors suggested that the increased activity in the amygdala demonstrates that BPD patients experience an exaggerated emotional response even to mild stimuli and that "abnormal" prefrontal cortical modulation of the individual's perceptions may result in that individual focusing excessively on emotionally relevant stimuli in the environ-

ment. The major limitation of this study was its sample size of only 6 participants, none of whom had comorbid mental illness. Additionally, this study did not analyze the effect of the participants' phase of their menstrual cycles, which the authors indicated may be a source of error. Estrogen levels can influence cerebral perfusion, and while this effect should be miniscule in a small brain structure such as the amygdala, it should be investigated.

Inspired by the earlier studies, Donegan and colleagues¹³ used fMRI scanning to observe the brains of people with BPD when presented with emotional facial expressions. Fifteen right-handed participants (13 female, mean age 35 yr) were recruited, excluding those with organic mental impairment, schizophrenia, substance intoxication, inability to refrain from abusing substances for a 2-week period before the experiment or inability to undergo fMRI scanning. Participants were shown a neutral stimulus (a fixation point) or a happy, sad or fearful facial expression; relative brain activation was measured. All participants predictably showed greater activity in the left amygdala in response to faces than to fixation points. Whereas control participants' activation did not exceed threshold criteria set by the researchers, subjects with BPD demonstrated activity in excess of the researchers' criteria. In addition to the amygdala, high activity was observed in the limbic structures of the regions containing the dorsal border of the amygdala, the bed nucleus of the stria terminalis, the lateral hypothalamic nuclei, the nucleus basalis (a proposed integrator of limbic information) and in the frontal lobes. Further, during the debriefing, BPD participants revealed that they had difficulty disambiguating neutral faces, interpreting them as unnecessarily negative or finding them threatening, which might have implications for the anxiety and social difficulties often observed in BPD. This study included participants with numerous comorbidities, for which the authors compensated with post hoc analyses, suggesting that none of the other disorders were responsible for a significant alteration in their results, except possibly PTSD. The effect of PTSD did not reach significance but did suggest that amygdala reactivity may be bilateral for patients with BPD but not PTSD and lateralized to the left hemisphere for subjects with BPD and PTSD. The sample size tested makes it difficult to conduct such analyses, and investigating the effect of PTSD on a larger group would be useful.

Evidence of the significance of the presence or absence of PTSD grew with the efforts of Driessen and colleagues.¹⁴ They recruited 12 women with BPD who had experienced trauma (aged 21–40 yr, mean 33 yr) and who had various comorbidities. The authors interviewed the participants to obtain cues about traumatic memories and aversive but non-traumatic memories and observed them via fMRI during recall of those memories. The researchers observed activation of the orbitofrontal cortex in both hemispheres and activation of Broca's area in patients with BPD without PTSD and observed only a minor activation of the orbitofrontal cortex and no activation of Broca's area in patients with BPD and PTSD. Because all BPD patients tested had experienced trauma but not all had PTSD, the authors argued that presence or absence of comorbid PTSD may be an important subgroup

classification for the diagnosis and treatment of BPD. Like most studies of the MRI and fMRI of BPD, this study was limited by a small sample size.

It has become increasingly common for BPD to be examined in terms of its symptoms, rather than as a disorder in and of itself. This has proven to be true in the study of impulsivity, which is a feature of several personality disorders. Völlm and colleagues²⁰ examined 8 patients with BPD or anti-social personality disorder (APD) or both (7 with BPD and 3 with APD, with some overlap between disorders) and scanned them during a Go/No Go task in which participants had to restrain their behaviour. They found that, while healthy control participants demonstrated activity in their right dorsolateral and left orbitofrontal cortex, patients with impulsive personality disorders exhibited more widespread activity, with more bilateral activation from their medial, superior and inferior frontal gyri to their anterior cingulate gyri. The implication of this study is that BPD patients may not only demonstrate abnormal metabolism in normal cortical areas but may also activate improper cortical areas entirely or, due to inefficient cortical processing, activate a wider cortical area to achieve the same regulation.

As with neuroanatomy, metabolism in the brain has been studied with technologies other than fMRI and PET. One such study was conducted by van Elst and others¹⁹ and used magnetic resonance spectroscopy to examine metabolites in the brain as a measure of metabolism. Using short echo time single voxel spectroscopy, 12 female BPD patients with no depression were found to have 19% reductions in N-acetyl-aspartate concentrations in the dorsolateral prefrontal cortex. Deficiency of this metabolite suggests a lower density of neurons and disturbed neuronal metabolism, consistent with results obtained by other imaging techniques. These researchers examined only one frontal subregion and thus could not comment on whether similar deficiencies might be observed in other areas where abnormalities have been linked to BPD. Another technology that has been used to study BPD is brain perfusion single photon emission computed tomography (SPECT), which is particularly well suited to observing local metabolism and is useful in differentiating Alzheimer's disease from strokes and other dementias.³⁶ Using SPECT, Goethals and colleagues¹⁵ demonstrated that patients with BPD or ADP both show reduced regional cerebral blood flow in the right lateral temporal cortex and the polar and ventrolateral right prefrontal cortex. This study included 2 disorders because its focus was to explain the impulsive behaviours common to both, and it broadens the field of research by considering BPD in terms of symptoms that it shares with other very different disorders. Because this study excludes participants with comorbid axis I disorders, its generalizability is limited.

If the study of neurological abnormalities of BPD can be said to be in its early stages, the study of genes associated with BPD is even less advanced. The heritability of BPD has been suggested to be moderate to high, based on findings of concordance between monozygotic twins in the area of 35% (examining 92 twin pairs) and dizygotic twins in the area of 7% (examining 129 twin pairs),³⁷ although previous studies

by the same researcher and with much smaller samples found no concordance between monozygotic twins.³⁸ Current research has suggested several promising directions for investigating genetic causes of BPD, although presently no specific genes have been clearly suspected as being causative. Because it is a disorder of great complexity commonly associated with multiple comorbid conditions and is linked to environmental stressors, research on genetic factors has tended to investigate the genetic etiology of individual symptoms rather than the disease as a whole. Evidence suggests that many of the major symptoms or dimensions of BPD are highly heritable, including impulsiveness³⁹ and aggression.⁴⁰

The genes that so far appear to be most persuasively linked to BPD are involved in the serotonin system. In monkeys, low levels of serotonin metabolites in the cerebral spinal fluid (CSF) have been associated with unusually high impulsive aggression and self-destructive behaviour, moderated strongly by the presence or absence of a nurturing atmosphere and secure attachments.⁴¹ Monkeys with short alleles for the serotonin 5-hydroxytryptamine (5-HT) transporter gene 5-HTT appear to be at elevated risk of developing symptoms analogous to BPD when taken from their natural mothers and raised in nonnurturing environments (peer groups or an inanimate mother), an effect that is largely negated when matched control monkeys are raised by their own nurturing mothers.⁴²

In humans, the gene-linked polymorphic region of the 5-HT transporter gene serotonin transporter gene promoter polymorphism (5-HTTLPR) has been found to have short and long alleles as well. The short allele has been associated with violent behaviour in humans by Retz and colleagues,⁴³ who demonstrated that, among criminal offenders, violent offenders were more likely to possess the short allele, although this accounted for only 5% of the variance of violent behaviour. In people with eating disorders, the less efficient short polymorphism has been found to be associated with higher rates of comorbidity with BPD and aggressive impulsivity in general.⁴⁴ Steiger and colleagues reported that every participant in their study with BPD had the short allele (although not all who had the short allele had BPD), and no participants with the long allele were found to have BPD comorbid with their eating disorder. The 5-HTTLPR region is expressed differently in different populations, and its association with BPD may be limited to certain diagnostic populations (such as groups of patients with eating disorders) but still has clear implications for the presence of BPD in a sizable clinical population. The effectiveness of selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine in the treatment of mood shifts and depression in patients with BPD lends credence to researchers who argue that serotonin dysfunction plays a role in BPD.⁴⁵

Related to the serotonergic system, dopamine dysfunction has been suggested as a factor in BPD symptoms as well. Dopamine is thought to play a role in emotional information processing and impulsivity, as well as in general cognition. Although evidence for dopamine dysfunction as a factor in BPD is mostly circumstantial, hyperactive dopamine function has been proposed as a potential cause of, for example,

hyperactive amygdala function, leading to emotional dysregulation and negative reactions to social situations.⁴⁶ There may be cause for future research to investigate dopamine's effect on the development of BPD.

Genes involved in the production of monoamine oxidase-A (MAOA) may also be involved in the development of BPD. The MAOA gene encodes MAOA enzyme, a potent metabolizer of norepinephrine, serotonin and dopamine, among other neurotransmitters. Caspi and colleagues⁴⁷ demonstrated that people with genetic polymorphisms resulting in MAOA deficiency who are abused as children are significantly more likely to show criminal behaviour than are those who were also abused but had normal or elevated MAOA levels; this indicates that MAOA may protect against negative outcomes of childhood abuse. When BPD patients were tested for the MAOA gene, they were found to not differ significantly from healthy control subjects.⁴⁸ The MAOA gene continues to be of interest to researchers studying the development of aggression, impulsivity and criminality in abused children.

Summary

In summary, research from a biological perspective has provided several findings about BPD. PET studies have demonstrated that BPD patients show relatively low metabolism in the dorsolateral frontal cortex, anterior cingulate cortex, basal ganglia, thalamus, right-sided ventromedial temporal cortex, left-sided medial parietal/posterior cingulate cortex, hippocampus and left cuneus. Other studies have shown hypermetabolism in the anterior cingulate gyrus, superior frontal gyrus, right inferior frontal gyrus and opercular part of the right precentral gyrus. PET studies have further shown hyperactivation of the bilateral dorsolateral prefrontal cortex and right cuneus and decreased activation in the medial prefrontal cortex in BPD patients who were presented with scripts of abandonment. These data suggest that, in BPD patients, areas of the brain that are used to regulate and control emotion are hypometabolic and that activation of limbic areas, when it occurs, is excessive. This might reflect a failure of rational thought to control emotional thought, leading to the emotional instability that is characteristic of BPD.

MRI studies have demonstrated that people with BPD have reduced volume in the frontal lobe, bilateral hippocampus, bilateral amygdala (a reduced volume that has not always been replicated in MRI studies), left orbitofrontal cortex, right anterior cingulate cortex, and right parietal cortex and increased putamen volume. In the cingulate gyrus of people with BPD, the volume of which is generally shown to be abnormal, Brodmann's areas 24 and 31 showed reduced grey and increased white matter volume; patients with BPD without comorbid SPD showed reduced grey matter in area 24 but not 31; those with both BPD and SPD had reduced grey matter volume in both areas. These data show abnormalities in limbic structures, particularly areas involved in negative affect. Although causality cannot be inferred, the data suggest that the anatomical changes are associated with the physiological changes.

fMRI studies have demonstrated that people with BPD show hypermetabolism in the amygdala bilaterally and abnormal activation in the medial and inferolateral prefrontal cortex and fusiform gyrus in response to emotionally aversive slides. In response to faces, people with BPD show excessive activity in the amygdala, the bed nucleus of the stria terminalis, the lateral hypothalamic nuclei, the nucleus and the frontal lobes. During recall of traumatic memories, patients with BPD without PTSD have shown greater activation of the orbitofrontal cortex in both hemispheres and Broca's area, relative to patients with BPD and PTSD. These physiological data confirm and supplement PET data and again illustrate hyperactivation of limbic structures.

Other imaging technologies have demonstrated several abnormalities. Patients with BPD show deficiencies in N-acetyl-aspartate concentrations in the dorsolateral prefrontal cortex, suggesting a lower density of neurons and disturbed neuronal metabolism (magnetic resonance spectroscopy). In addition, they show volume reductions in the basolateral amygdala (voxel-based morphometry). Finally, patients with BPD or APD show reduced regional cerebral blood flow in the right lateral temporal cortex and the polar and ventrolateral right prefrontal cortex (SPECT), suggesting that these areas are linked to impulsivity but that abnormalities therein are not specific to BPD. These data supplement other anatomical and physiological findings.

Research has most strongly implicated the serotonin transporter gene 5-HTT in the development of BPD, shorter alleles of which have been associated with lower levels of serotonin and greater impulsive aggression; genes for dopamine and MAOA may yet prove to have an etiological role. Genetic findings further consolidate the evidence that there are biological (not only psychological) differences between people with and without BPD.

Discussion

Several possible issues are raised by this body of research. First, it is apparent that there is disagreement and sometimes outright contradiction between different neuroimaging studies, even between those using the same technology and theoretically similar procedures. Studies select people with BPD on the assumption that such people represent the whole of the population. However, minute differences in sampling bias might considerably impact data obtained. For example, it remains a contentious issue in imaging whether patients with common comorbidities should be included in studies. Understandably, someone with BPD and major depression might have different neuroanatomical abnormalities from someone who has BPD and PTSD. Including people with comorbid disorders makes it more difficult to attribute observed differences to a single disease; however, we wonder whether it is possible for someone to have BPD without comorbid depression, given the disrupted lifestyle and interpersonal stresses that these people have. It seems reasonable to suggest that a full understanding of BPD requires that patients with comorbid disorders be included, and there appears to be a general trend in research to include such

patients. Other possible sources of conflicting data might include such confounds as, for example, how to persuade a clinically impulsive patient to lie still while an image is taken, and if they move, might this result in minute (or large) differences? Given the variety of factors that might influence the results of a neuroimaging study, it may not be a surprise to see even completely opposing results. Such confusion underscores the importance of replication in this area. Future meta-analyses should attempt to remove interstudy variability by applying statistical techniques that take sample size (and the question of inadequate sampling) into account, particularly given the small sample sizes common to costly and time-consuming neuroimaging studies.

Imaging technology has shown that structures that have reduced volume in BPD patients may show hypermetabolism. Perhaps some of the lost volume in these structures (notably, the amygdala) may be lost inhibitory neurons, and this lost inhibition could result in impulsive behaviour and overly negative attributions. An apt analogy may be that of a horse and rider: in BPD patients, affective brain structures (the horse) run wild, while the cognitive areas (the rider) are asleep, paralyzed or otherwise unable to reign in this excess activity.

We also wonder whether different developmental abnormalities may lead to different clinical manifestations of BPD and, specifically, if chronic versus acute abuse in childhood may be associated with different imaging abnormalities in adulthood.

What do the neuroimaging findings mean? How can we relate the structural and functioning abnormalities of the amygdala with the functional abnormalities of the frontal cortex? Is it possible that the limbic overreactivity overwhelms the frontal cortex, shutting it off? Alternatively, could the absence of frontal cortex restraints create a void compensated for by an overactive amygdala? Answering these questions requires the integration of findings from genetic and endophenotypic analyses. For example, impulsivity, aggression and nonwelfare affect are cardinal components of the BPD endophenotype. Although it has been hypothesized that we can link those components to a common genetic coding for serotonin, a definitive model of this link has not yet been devised; we are only in the beginning stages of neuroimaging.

To determine what research design would help advance our understanding of this disorder across the lifespan, we must reconcile the tension between examining the broader syndrome under investigation and the symptoms associated with that disorder. If the chosen strategy were to first focus on the syndrome, we risk losing sight of the symptoms. It might be wiser to study the syndrome's specific components with the intent of examining all possible evidence before deciding how to proceed. That approach would argue in favour of a continued thrust to further study such BPD symptoms as impulsivity. Such an approach gains support from a genetic perspective, because genes appear to be more proximally related to symptoms than to the broader endophenotypes.

Accordingly, an ideal research design would include consideration of molecular genetics, fMRI findings and a charac-

terization of symptoms. Choosing a comparison group would require consideration of potential confounds and whether it would be more productive to compare BPD with another syndrome (e.g., depression) with the risk of substantial endophenotypic overlap, or to another symptom, with the risk of genetic overlap. Whichever approach is taken, efforts should be made to represent as many endophenotypic variants as possible, with a preparedness to measure each genetically and via neuroimaging.

There are advantages and disadvantages to approaching the study of BPD in terms of its individual symptoms or as a syndrome. Because BPD is a complex disorder with a range of common manifestations, it can be tempting to attempt to break the disorder down and, for example, study it in terms of impulsivity alone. This is an approach that lends itself well to research, since it is often easier to quantify a participant's impulsivity than it is to establish a confident diagnosis of a personality disorder. Further, a study that examines one symptom of a larger disorder has the opportunity to establish findings or suggest implications regarding other disorders that may share that symptom (as demonstrated by authors whose studies of BPD have given insight into APD as well). There are, however, drawbacks to this approach. BPD is a collection of symptoms, and focusing exclusively on any one symptom at the expense of others has the risk of collecting data that may miss some insight. Studying impulsivity in a person with BPD may fail to uncover results related to the interaction of impulsivity with depression. An impulsive person with BPD might indulge in self-harm, whereas someone with APD does not, which suggests that the same basic symptom (and presumably similar neuroanatomical dysfunction) manifests differently because it interacts with other symptoms, such as depression or self-loathing. To create a full picture of this disorder, it is necessary to study BPD as both a syndrome and through individuals' symptoms.

Another important question raised by this research is whether there are neuroanatomical differences between patients who remit at different times? Few neuroimaging or genetic studies include a longitudinal component, often because not enough time has passed for a longitudinal component to be meaningful. Links and Heslegrave⁴⁹ found that, after 10 years, roughly one-half of BPD patients remit. Paris⁵⁰ found that this rate increased with age: by age 40 years, most BPD patients no longer met the criteria for the disorder. Most participants in the research we examined were aged between 20 and 30 years, so it is easy to imagine that some of them might have been nearer to remission than others. This caused us to wonder whether it could have influenced the results, or whether the severity of neuroanatomical abnormalities change over time as people overcome their symptoms. It would be interesting for future studies to return to their participants after 2 years and examine who, if anyone, no longer meets diagnostic criteria.

Most BPD research to date has focused on adults and, by definition, BPD emerges in late adolescence or early adulthood.³¹ BPD-like symptoms in children are often classified as borderline syndrome of childhood rather than BPD, and in certain cases, the child might more appropriately be labelled

by another name.⁵¹ Future research exploring BPD-like symptoms in younger patients will contribute to an understanding of this disorder and its development. Further, it may be useful to researchers who study the neurological and genetic etiology of BPD to explore whether the known abnormalities are exclusive to adults with BPD or are found in children as well.

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