RESEARCH ARTICLE

The Neurobiological Basis of Adolescent-onset Borderline Personality Disorder

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Abstract

Objective: Over the past two decades, neurobiological studies in adult onset borderline personality disorder have made important strides, but inquiry into adolescent-onset BPD is still in its infancy and our understanding of the neurobiology of adolescent BPD remains highly tentative. **Methods:** This paper highlights recent findings in genetics, neuroendocrinology and neuroimaging for adult and adolescent-onset BPD. **Results**: Neurobiological studies of adolescent-onset BPD to date have focused mainly on volumetric studies of various brain regions and measurements of HPA axis components, with comparatively few publications on brain functioning. **Conclusion:** Such information is essential to developing more effective screening, treatment and preventive strategies.

Key Words: *Borderline Personality Disorder, adolescent, neurobiology, neuroimaging*

Résumé

Objectif: Au cours des vingt dernières années, les études neurobiologiques du trouble de la personnalité limite (TPL) apparu à l'âge adulte ont fait de grands progrès, mais l'étude de l'apparition de la TPL à l'adolescence en est encore à ses premiers pas, et notre compréhension de la neurobiologie du TPL adolescent demeure très provisoire.
Méthodes: Cet article présente les résultats récents de la génétique, de la neuroendocrinologie et de la neuroimagerie pour le TPL apparu à l'âge adulte et à l'adolescence. **Résultats:** Les études neurobiologiques du TPL apparu à l'adolescence ont porté jusqu'ici surtout sur les études volumétriques des diverses régions cérébrales et sur des mesures des composantes de l'axe hypothalamo-hypophyso-surrénalien, et n'ont donné lieu comparativement qu'à peu de publications sur le fonctionnement du cerveau. Conclusion: Cette information est essentielle au développement de stratégies efficaces de dépistage, de traitement et de prévention.

Mots clés: *trouble de la personnalité limite, adolescent, neurobiologie, neuroimagerie*

Borderline personality disorder (BPD) is a disabling disorder characterized by poor affect regulation and impulse control. This often results in impaired interpersonal relationships and maladaptive behavior patterns, including aggression towards others and deliberate self-harm. The disorder remains notoriously difficult to treat effectively, with many patients responding poorly or partially even to the most widely accepted treatment strategies (Paris, 2005). Evidence suggests that early detection of BPD can attenuate the severity of symptoms (Chanen et al., 2008a); however, little is known about early predictors of this disorder. By assessing adolescents using diagnostic instruments similar to those used in adults, researchers are exploring the adolescent presentation of BPD in an effort to describe its incidence, phenomenology and prognostic import for the development of Axis I/II disorders in adulthood (Chanen et al., 2008b; Crawford et al., 2008). Prevalence estimates of adolescent-onset BPD in the community range from 0.9 to 3.0% (Lewinsohn, Rohde, Seeley, & Klein, 1997; Bernstein et al., 1993), while the prevalence in clinical populations is considerably higher – 11% in outpatient populations (Chanen et al, 2004) and 32-49% in adolescent inpatient units (Burket & Myers, 1995; Grilo et al., 1996).

Clarifying the underlying biology of BPD, including etiological mechanisms, genetic factors and pathological processes, is essential for a full understanding of the disorder

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and for the development of more effective treatment and preventive strategies (Beauchaine, Hong, & Marsh, 2008). Over the past two decades, neurobiological studies in adult BPD have made important strides, but inquiry into adolescent-onset BPD is still in its infancy.

Genotypes and Endophenotypes in BPD

Because of the complex genetics of psychiatric disorders (Plomin, Owen, & McGuffin, 1994), any hopes of uncovering Mendelian inheritance patterns for the most part have been abandoned in favor of models incorporating genetics, epigenetics (Wong, Gottesman, & Petronis, 2005), environmental factors (Kendler, 1995) and gene-environment interactions (Caspi et al., 2003). It has further become apparent that, rather than conforming to a "one gene-one illness" model, the risk of developing psychopathology is conveyed by multiple genes of small effect (Collins, Brooks, & Chakravarti, 1998). In order to derive meaningful information about the genotypes underlying mental illnesses, researchers have increasingly focused their attention on "endophenotypes," defined in one review as "measurable components unseen by the unaided eye along the pathway between disease and distal genotype" (Gottesman & Gould, 2003). To be considered an endophenotype, a feature should be reproducible and state-independent, and it should occur at a greater rate in affected probands than in unaffected family members and at a greater rate in unaffected family members than in the general population (Balanza-Martinez et al., 2008).

The quest for biological endophenotypes of BPD, though gaining momentum, is still young. Recent advances include a meta-analysis highlighting reduced amygdala and hippocampal volumes (Ruocco, Amirthavasagam, Choi-Kain, & McMain, 2012), but few proposed candidates currently exist. This paper will review neurobiological findings including genetic, neuroendocrine and neuroimaging studies relevant to BPD and focus on data pertaining to adolescents.

Genetic studies

Adult BPD

Genetic Vulnerability:

As with many other illnesses, the etiology of BPD is likely to be an interaction of heritable vulnerability with environmental factors that combine to bring about the full presentation of disease (Distel et al., 2011).

Family/Twin Studies:

Family studies can reflect heritability indirectly; however, only twin studies provide definitive evidence for genetic heritability. Unfortunately, only limited data from twin studies are available for BPD. Recent data examining genetic and environmental risk of endorsed DSM personality disorder criteria in 2894 members of the Norwegian Institute of Public Health Twin Panel suggest a broad heritability to personality pathology suggestive of negative emotionality and a specific heritability of the BPD intermediate phenotype impulsive aggression (Kendler et al., 2008). Another twin study of BPD examining 92 monozygotic twins and 129 dizygotic twins showed that BPD was substantially heritable, with a heritability score of 0.69, i.e., 69% of the variance in BPD was accounted for by genetic factors (Torgersen, 2000). A more recent web-based cohort (n=44,112) including 542 twin pairs (Kendler, Myers, & Reichborn-Kjennerud, 2011) found that four BPD scales loaded as one highly heritable factor (heritability = 60%).

Genetic Studies:

Research into the specific genes involved in BPD is at a very early stage, but an important role for the serotonin system seems to be emerging. A case-control study showed a significant association between the serotonin transporter (5-HTT) gene and BPD, with higher frequencies of the 10 repeat of the VNTR marker and the S-10 haplotype, and fewer 12 repeat and LA-12 haplotype, in BPD patients compared with healthy controls (HCs) (Ni et al., 2006). This result is consistent with findings of a genetic association between the low-expressing S allele and aggressive behavior (Cadoret et al., 2003) as well as with elevated NEO ratings of neuroticism, which is characterized by negative emotionality including anxiety, depression, vulnerability and hostility (Sen et al., 2004). A simultaneous case-control study of the same gene in BPD, however, was unable to replicate the association found by Ni and colleagues (Pascual et al., 2007).

Another gene that has been implicated in impulsive aggression and suicidal behavior, common features of BPD, is that for tryptophan hydroxylase (TPH), the rate-limiting enzyme in serotonin biosynthesis. Two isoforms, TPH-1 and TPH-2, are known. TPH-1 has been correlated with various psychiatric and behavioral disorders by gene polymorphism association studies. A recent case-control study of 95 women with BPD and 98 HCs showed that one six-SNP haplotype was absent from the control group, while representing about one-quarter of all haplotypes in the BPD group. A "sliding window" analysis attributed the strongest disease association to haplotype configurations located between the gene promoter and intron 3 (Zaboli et al., 2006). More recent studies (Perez-Rodriquez et al., 2010) found an association between the previously identified "risk" haplotype at the TPH-2 locus and BPD diagnosis, impulsive aggression, affective lability, and suicidal/parasuicidal behaviors. Wilson and colleagues (2009) reported an association between the TPH-1 A218C polymorphism and BPD diagnosis, but not suicidal behavior.

Single reports were published for 5-HT2a (Ni et al., 2006) 5HT2c (Ni et al., 2009) and monoamine oxidase A (Ni et al., 2007). While these preliminary studies of specific genes implicated in BPD are suggestive and support the presence

of a serotonergic abnormality in this disorder, they will require replication for any clear conclusions to be drawn.

Adolescent BPD

There exists only one candidate gene association study of BPD traits in youth. Hankin and colleagues (2011) report on an association between the short allele of 5-HTTLPR and BPD traits in two independent studies of community youth that persisted after controlling for depression. While preliminary, these promising data suggest links between the 5-HTT and developmental aspects of BPD.

Neuroendocrine: HPA axis

Adult BPD

Several investigators (Rinne et al., 2002; W. Lange et al., 2005; Grossman et al., 2003) have found enhanced cortisol suppression in individuals with BPD and co-morbid post-traumatic stress disorder (PTSD), though they have concluded that the response was due to the co-morbid PTSD and not BPD itself. However, a brief report (Carrasco et al., 2007), using a 0.25mg dexamethasone suppression test dose, found enhanced cortisol suppression in individuals with BPD without PTSD, suggesting that increased feedback inhibition of the hypothalamic-pituitary-adrenal (HPA) axis may exist in BPD that is not accounted for by PTSD. Walter and colleagues (2008), in a small pilot study, noted a delayed cortisol response after psychosocial stress in BPD compared to HC subjects.

Adolescent BPD

Pituitary volume in adolescent BPD has been found not to differ from HCs' (Garner et al., 2007), but pituitary volume has been correlated with number of parasuicidal events (Jovev et al., 2008). In a small sample of adolescents with non-suicidal self injury, a potential precursor to BPD, reductions in cortisol secretion in response to acute stress was found, suggesting that HPA axis is hyporesponsive in these adolescents (Keass et al., 2012). The authors speculate on the role of hyposecretion of cortisol and vulnerability to maladaptive stress responses in the development of BPD.

Evoked Potentials

Adult BPD

Psychiatric research on P300, also known as P3b, a component of event related potentials, has revealed abnormal P3b amplitudes in adult subjects with BPD, suggesting deficits in novelty detection and orienting as well as the inhibitory aspect of the attentional process (Meares, Schore & Melkonian, 2011). Schuermann and colleagues (Schuermann, Kathmann, Stiglmayr, Renneberg, & Endrass, 2011) found that BPD patients' P3b amplitudes were increased following negative feedback, relative to control subjects', while engaging in the Iowa Gambling Task.

Adolescent BPD

There exist several studies using P300 in adolescent BPD. Using a visual oddball task, Houston and colleagues (2005) found that adolescent female BPD subjects did not exhibit the expected age-related reduction in P3b amplitudes, suggesting abnormal brain maturation in adolescents with BPD features (Houston, Ceballos, Hesselbrock, & Bauer, 2005). This conflicts with another study using the same paradigm, but separating out subjects with conduct disorder (CD) from those with BPD features; only the adolescents with CD demonstrated the P300 abnormalities (Ceballos, Houston, Hesselbrock, & Bauer, 2006). However, other research in adolescents with BPD, using a Stroop color-word task, demonstrated neurophysiological abnormalities even after controlling for depression and CD (Houston et al., 2004). These results highlight the complexity of unraveling the contribution of Axis I disorders from that of BPD itself, an especially important consideration in view of the high frequency of psychiatric co-morbidities in this patient group.

Neuroimaging

Over the past decade, much of the research into the biological basis of BPD in both adults and adolescents has shifted from endocrine parameters to direct visualization of brain structure and function through neuroimaging.

Anterior Cingulate Cortex (ACC) and ACC/Orbital Frontal Cortex (OFC) coupling

Adult BPD

Evidence suggests decreased gray matter volume and increased white matter volume in rostral (Hazlett et al., 2007) and subgenual (Minzenberg, Fan, New, Tang, & Siever, 2008) cingulate in individuals with BPD compared to HCs.

Functional imaging studies in BPD have tended to show decreased activation of ACC in response to provocation. Schmahl and colleagues (2006) noted in 12 BPD subjects (one with current major depressive disorder (MDD) and eleven with history of MDD) diminished activation of perigenual ACC with induction of pain. Several other functional resonance imaging studies (fMRI) in BPD also show decreased activation of ACC in response to provocation (e.g., Hazlett et al., 2005; Minzenberg, Fan, New, Tang, & Siever, 2007; Schnell, Dietrich, Schnitker, Daumann, & Herpertz, 2007). Silbersweig and colleagues (2007), using a behavioral inhibition task during the induction of negative emotion with fMRI, demonstrated decreased activation in subgenual ACC and OFC, with increases in amygdala activity, prompting his group and another (Siegle, 2007) to propose that BPD sits at the "intersection of cognition and emotion" and wonder whether this constellation of impaired regions is specific to BPD.

Pharmacologic probes have also shown decreased metabolic activity in ACC and OFC in response to serotonergic challenge in impulsive aggressive patients with BPD (Siever et al., 1999; New et al., 2002) and BPD patients with affective instability (Soloff et al., 2003) compared to HCs, and decreased coupling of resting metabolism between OFC and ventral ACC has been reported by our group (New et al., 2007). A recent case study of a patient with schizencephaly (da Rocha et al., 2008) resulting in a primary ACC and secondary OFC lesion, who manifested prominent symptoms of BPD, supports the notion of important interconnections between these two brain regions in BPD's development.

Adolescent BPD

Only three morphometric studies have been published that examine ACC volume in adolescents with BPD (Goodman et al., 2011; Brunner et al., 2010; Whittle et al., 2009) and the results are conflicting. Using region-of–interest methodology, Whittle and colleagues (2009) reported decreased left ACC volume in 15 female BPD adolescents with a wide range of Axis I co-morbidities. More recently, Brunner and colleagues (2010) compared 20 female adolescents with BPD, 20 psychiatric ill adolescents without BPD and 20 HC subjects, using voxel-based morphology (VBM), and reported no ACC abnormalities. The primary finding of Goodman and colleagues (2011) is that adolescents with BPD and co-morbid MDD have reduced Brodmann Area (BA) 24 gray matter volume compared to HCs but no differences in PFC. This finding raises the possibility of a neurodevelopmental abnormality in BPD, as our group has previously reported similar gray matter volume reduction in BA 24 in adults with BPD (Hazlett et al., 2005) using the identical methodology to the present study.

The conflicting results in these three adolescent BPD studies may stem from small sample sizes and/or from differences in subject selection, psychiatric co-morbidities and imaging methodology. The Goodman and colleagues (2011) adolescents were all inpatients with co-morbid MDD and may represent a more severely ill group with greater treatment duration and co-morbid psychopathology. Alternatively, Brunner and colleagues (2010) employed a whole brain VBM approach that may be less sensitive to group differences than the cytoarchitecturally-derived approach used by Goodman and colleagues.

To date there are no fMRI studies of any brain region in adolescent BPD.

Research examining adolescent BPD OFC volumes has included Chanen and colleagues' (2008) study that compared 20 BPD adolescent outpatients referred to an at-risk clinic with 20 HCs, and the Brunner and colleagues (2010) and Goodman and colleagues (2011) studies described above. Chanen and colleagues (2008b) and Brunner and colleagues (2010) both found that BPD patients exhibited volume reductions in OFC gray matter compared with HCs, which was not found by Goodman and colleagues (2011).

Amygdala

Adult BPD

Structural imaging of amygdala volume in adult BPD has yielded discrepant results, with reports of volume reduction (Driessen et al., 2000), perhaps reflecting excitotoxicity with volume loss, alongside studies finding no volume differences (Brambilla et al., 2004; Zetzsche et al., 2006; New et al., 2007).

The amygdala has been viewed as the subcortical structure from which fear and perhaps anger may emerge. Amygdala activity is typically studied *after* exposure to a fear-inducing stimulus. fMRI studies in BPD show increased amygdala activity to specific types of stimulus (e.g., "unresolved" life events) (Schmahl et al., 2006), emotional faces (Donegan et al., 2003) positive and negative emotional pictures (Hazlett et al., 2012), but not at rest as in MDD. Similar amygdala hyperactivity is seen in impulsive aggressive personality disordered subjects in response to emotional faces (Coccaro, McCloskey, Fitzgerald, & Phan, 2007). In addition, BPD patients seem to show particularly robust responses to other emotions, including anger (Minzenberg et al. , 2007).

Adolescent BPD

In the only study to date that has investigated amygdalar volumes in adolescent BPD, Chanen and colleagues (2008) did not find any differences in amygdalar volume between BPD and HCs; no fMRI data exist for amygdalar activity in BPD adolescents.

Hippocampus

Adult BPD

In adult BPD, hippocampal volume loss has been reported in some studies, Schmahl et al, 2003 (C. G. Schmahl, Vermetten, Elzinga, & Douglas Bremner, 2003), (Chanen et al., 2008), but it appears to be associated with extent of trauma (Irle, Lange, & Sachsse, 2005) and abuse history (Brambilla et al., 2004), reflecting co-morbidities with PTSD rather than specificity to BPD itself. An exception to the generalized finding of decreased hippocampal volumes in BPD is a recent study (Zetzsche et al., 2007) that found hippocampal volume reductions in BPD to be inversely correlated with aggressive but not impulsive symptomatology.

Adolescent BPD

Chanen and colleagues (2008b) found no differences in hippocampal volume between their cohort of 20 adolescent BPD subjects and HCs.

Table 1. Neuroimaging Studies in adolescent BPD

Study name	Region of interest	Number of subjects	Methodological considerations	Findings
Brunner et al., 2010	Frontolimbic structures	20 BPD, 20 HC, 20 clinical comparison (CC); all right handed females only	VBM	↓DLPFC gray bilaterally & ↓ left OFC in BPD compared to controls, no difference between BPD and CC, no difference in limbic structures
Chanen et al., 2008	Frontolimbic structures	20 BPD, 20 HC mixed gender	ROI	↓OFC gray matter BPD, no difference hippocampus or amygdala
Goodman et al., 2011	Anterior cingulate, OFC, DLPFC	13 BPD-MDD mixed gender, 13 HC	ROI	↓BA 24 gray but not white matter. Smaller BA 24 volume associated with BPD but not MDD indices. No differences in OFC, DLPFC
Garner et al., 2007	Pituitary volume	Same subjects as Chanen et al., 2008b	ROI	No difference in pituitary volume in BPD and HC. + childhood trauma was associated with ↓size
Jovev et al., 2008	Pituitary volume	Same subjects as Chanen et al., 2008b	ROI	↑Pituitary volume was associated with ↑ # lifetime parasuicidal events
Takahashi et al., 2009b	Insular cortex	Same subjects as Chanen et al., 2008b	ROI	No differences in the gray matter volume of the insula in BPD vs HC. Violent BPD had smaller insula bilaterally compared to non-violent BPD
Takahashi et al., 2009a	Adhesio interthalamica (AI), cavum septum pellucidum (CSP), third ventricle	Same subjects as Chanen et al., 2008b	ROI	Shorter AI in BPD, no differences in CSP between BPD and HC, larger third ventricle size in BPD; but no clinical correlations with findings
Walterfang et al., 2010	Corpus callosum, ventricular volume	Same subjects as Chanen et al., 2008b	ROI	No difference in total callosal area, length, curvature, shape or ventricular volume in BPD and HC
Whittle et al., 2009	Anterior cingulate	Subset of Chanen et al., 2008b; 15 females	ROI	↓ left ACC volume in BPD; correlate with measures of impulsivity and parasuicidal behavior

Other brain regions

Adult BPD

In BPD, findings of posterior cingulate activation were noted by New and colleagues (2002) in their 5-HT challenge study; however, other findings include volume loss (Hazlett et al., 2005) in the region and diminished uptake with positron emission tomography (PET) scanning in BPD females with dissociation and history of childhood sexual trauma, phenomena which complicate the clinical picture and obscure the direct contribution of BPD symptomatology to the posterior cingulate findings (Lange, Kracht, Herholz, Sachsse, & Irle, 2005). A recent meta-analysis of fMRI studies of negative emotionality in BPD (Ruocco et al., 2012) identifies abnormal processing of negative emotion with heightened activity in the posterior cingulate cortex and insula and less activation in the subgenual ACC and dorsolateral prefrontal cortex (DLPFC). Corpus callosum abnormalities have been reported in adult BPD with co-morbid attention deficit disorder (Rüsch et al., 2007), but no differences were found in another pilot study (Zanetti et al., 2007).

Adolescent BPD

Using the same BPD adolescents studied by Chanen and colleagues (2008b), Takahashi and colleagues (2009a) assessed the volume of midline brain structures and found a shorter adhseio interthalamica, with no clinical correlations and no differences in the cavum septum pellucidum. In addition, in two separate analyses of Chanen and colleagues' 20 teenage BPD subjects (2008b), corpus callosum volume, shape, curvature and third ventricle volume (Walterfang et al., 2010) and insular cortex volume (Takahashi et al., 2009b) was assessed and compared to HC. Both studies had largely negative findings, though insular volume reductions were found in impulsive adolescent BPD compared to non-impulsive adolescent BPD.

Conclusion

This paper highlights recent findings in genetics, neuroendocrinology and neuroimaging in adolescent-onset BPD. Our understanding of the neurobiology of adolescent BPD remains highly tentative. Studies to date have focused mainly on volumetric studies of various brain regions and measurements of HPA axis components, with comparatively few publications on brain functioning.

Findings so far await replication. The discrepant results in the extant literature are not surprising given the small sample sizes, methodological differences and study subjects' wide range of psychopathology, including both co-morbid Axis I disorders and severity of symptoms. Future work examining larger samples, making increased use of newer methodologies such as fMRI, paying careful attention to co-morbidity and following patients longitudinally, will enhance our understanding of adolescent-onset BPD.

Important, as yet unanswered, questions include: 1) Is adolescent-onset BPD, similar to early-onset schizophrenia, a more severe biological disturbance than adult-onset BPD?; 2) What can the study of adolescent-onset BPD inform us about the early biological manifestations of BPD?; 3) Are there potential targets for treatment interventions in adolescent BPD?; 4) Can we identify biomarkers to identify those at greatest risk for more severe illness, adverse outcome, and positive or negative treatment effect?; 5) What are the ways in which environmental influences interact with biological vulnerabilities in bringing about the BPD phenotype?; and, 6) How does Axis II psychopathology interact with Axis I co-morbidities?

Biological studies in both adult and adolescent-onset BPD will continue to shed light on the etiological mechanisms, genetic factors and pathological processes of this widespread and often crippling disorder, information essential to developing more effective screening, treatment and preventive strategies.

Acknowledgements/Conflicts of Interest

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