Development and Psychopathology **17** (2005), 1151–1171
Copyright © 2005 Cambridge University Press
Printed in the United States of America
DOI: 10.1017/S0954579405050546

Developmental psychopathology and neurobiology of aggression

JACKIE K. GOLLAN, ROYCE LEE, AND EMIL F. COCCARO
University of Chicago

Abstract

The aim of this paper is to clarify how neural mechanisms at the molecular level, specifically the serotonergic (5-HT) system and the hypothalamic–pituitary–adrenal axis system (HPA) in conjunction with early life stress may contribute to the emergence of aggression, self-directed and otherwise, in borderline personality disorder (BPD). Chronic dysregulation of these biological systems, which function to regulate stress and emotion, may potentiate the development of impulsive aggression in borderline personality conditions. Our central premise in this paper is that brain development, stress regulation, and early pathonomic experience are interactive and cumulative in their mutual influence on the development of impulsive aggression in BPD. We review the parameters of impulsive aggression in BPD, followed by a discussion of the neurobiological and neuroendocrine correlates of impulsive aggression with and without BPD. We then focus on the developmental continuities in BPD with attention to brain maturation of 5-HT and HPA axis function during the life span and the influence of early adverse experiences on these systems. Finally, we comment on the data of the relative stability of aggression in BPD, adolescence as a developmental stage of potential vulnerability, and the course of aggressive behavior during the life span.

Borderline personality disorder (BPD) is a psychiatric disorder characterized by a pattern of dysregulated affective experience, impulse control, social behavior, and self-concept (American Psychiatric Association [APA], 1994, 2001). Estimates of the prevalence of BPD in the United States are between 0.3 and 0.7% of the general population (Lenzenweger, Loranger, Korfine, & Neff, 1997; Torgersen, Kringlen, & Cramer, 2001) and approximately 10% of psychiatric outpatients and 20% of inpatients (Grube, 2004; Swartz, Blazer, George, & Winfield, 1990). Incidence rates show that approximately 70% of patients diagnosed with BPD are female (Anderson, Sankis, & Wigider, 2001; Grilo et al., 1996). Although the gender breakdown of adolescent onset of BPD is not well documented, reports of both genders show that 11% of individuals between ages 9 and 19 years meet *DSM* criteria for BPD (Bernstein et al., 1993). BPD is associated with pervasive functional impairment, psychiatric comorbidity, history of self-injury, and mortality by suicide (Skodol et al., 2002). Individual histories of self-aggression, as often observed with individuals with BPD, are also linked with increased levels of lifetime aggression and anger directed toward others (Simeon & Favazza, 2001). Approximately 30% of individuals with BPD report significant impulsive aggression toward others (New et al., 2004). As many as 66% of individuals diagnosed with BPD report nonlethal self-directed aggression (Shearer, 1994). Between 40 and 60% of individuals with BPD report suicide attempts (Mann, Waternaux, Haas, & Malone, 1999; Suominen, Isometsa, Henriksson, Ostamo, & Lonnqvist, 2000).

The authors thank Caroline Cozza, Michael McCloskey, and Kurt Knoblett for their comments during the preparation of this manuscript. This research was supported by research funding from the American Foundation of Suicide Prevention (J.K.G.), Grant MH066888-01 (R.L.), and the Borderline Personality Disorder Research Foundation (E.F.C.).

Address correspondence and reprint requests to: Jackie Gollan, Clinical Neuroscience and Psychopharmacology Research Unit, Department of Psychiatry, 5841 South Maryland Avenue, MC 3077, Chicago, IL 60637; E-mail: jgollan@uchicago.edu.

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

The aim of this paper is to clarify how irregularities in the serotonin (5-hydroxytryptophan [5-HT]) and the hypothalamic–pituitary–adrenal (HPA) axis systems, in conjunction with early adverse experiences, provide one plausible explanation of the development of aggression. Our central premise is that the effect of early life stress influences the normative development and function of the 5-HT and the HPA axis systems, and that these irregularities contribute to the emergence of impulsive aggressive behaviors in BPD, directed toward other individuals and the self. In support of our proposal, we review the parameters of impulsive aggression in BPD. After this, we discuss the research investigating neurobiological and neuroendocrine correlates of impulsive aggression with and without BPD. We then focus on the developmental continuities in BPD with attention to brain maturation of 5-HT and HPA axis function during the life span and the influence of early adversity on these systems. We contextualize this work with a brief commentary of the principles of developmental psychopathology, along with data on relative stability of aggression in BPD, adolescence as a period of potential vulnerability, and the course of aggressive behavior during the life span. In addition, because we consider impulsive aggression is a phenotypic blend of interactive underlying systems of affective and behavioral instability, incentive motivation (exploration of novel stimulus conditions), and reduced behavioral control (Depue & Lenzenweger, 2001), and because it is likely that impulsive aggression in BPD has both neurobiological and psychosocial origins, we focus on the development of the 5-HT system in the brain and the effects of early life stress on HPA axis regulation to show how they are tied to the development of aggression and self-injury in BPD. A discussion of future directions of research will conclude our paper.

Categories of Aggression

Classification of direct and indirect dimensions of aggression, self-directed or otherwise, has been traditionally conceptualized using a systems-based approach focused on interactive constitutional and environmental factors (Barratt, 1991; Barratt & Slaughter, 1998). Aggressive behavior toward others is a normal dimension of the mammalian repertoire with adaptive advantages in protecting resources (Berkowitz, 1993). When aggression is excessive, out of context, or directed toward self, however, it is considered to be pathological. Aggression may be classified into one of three categories (Barratt, 1991; Barratt & Felthous, 2003), including medically related aggression, premeditated, and impulsive aggression. Medically related or secondary aggression is symptomatic of and due to a medical condition, including head injury and neurological conditions. This form of aggression presents as compulsive self-directed aggression and usually occurs in the context of a dyscontrol condition and in the form of repetitive behaviors (e.g., hair pulling, nail biting). Stereotypic aggressive behaviors directed toward oneself are also included in this category, and are often associated with pervasive developmental disorders (e.g., autism, mental retardation, Lesch–Nyhan syndrome). Aggressive behaviors do not have affective meaning, and they have a repetitious and rhythmic quality.

In contrast, premeditated aggression is situationally related and self-promoting and generally serves to aid the aggressor. This form of aggression, also referred to as instrumental aggression, is designed to help the individual maintain power or possession of situations or individuals for their own gain. Finally, impulsive aggression is related to affective instability and poor impulse control. Often triggered by hypersensitivity to specific stimuli, the individual experiences escalating agitation followed by an abrupt outburst of aggressive and threatening behavior. Self-directed impulsive aggression includes self-destructive behavior without suicidal intent, represented by acts of mutilation (e.g., cutting, burning, bruising) producing minimal to severe and permanent injury, with the goal of releasing tension, secondary gain, and emotion regulation. This form of impulsive aggression generally occurs rapidly, in the context of trivial and stressful circumstances, and typically in isolation.

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

Impulsive aggression differs from medically related and premeditated aggression on neurophysiological, cognitive, psychophysiological, and personality trait measures (Barratt, Stanford, Felthous, & Kent, 1997). Impulsive aggression is influenced more by elements of negative affect and impulsivity than by incentive motivation and logical thinking, as often found in premeditated aggression. Specifically, measurement studies highlight the distinctive nature of impulsive aggression. Coccaro, Schmidt, Samuels, and Nestadt (2004) have defined impulsive aggression using the Buss–Durkee Hostility Inventory (Buss & Durkee, 1957) and the Barratt Impulsivity Scale (Patton, Stanford, & Barratt, 1995) to distinguish between irritable–impulsive and aggression–assault dimensions of aggressive behaviors. Barratt's studies of psychiatric patients, incarcerated individuals, and undergraduate college students (Barratt et al., 1997) indicate that impulsive aggression was associated with higher gregariousness and lower emotional warmth on personality scales, and to the personality traits of impulsiveness and anger/hostility (Barratt, 1991). Neurophysiologically, electrophysiological studies showed that impulsive aggression was associated with prolonged latencies and diminished P300 amplitudes in event-related potentials (ERPs) recorded during the sessions of selected sensory discrimination tests (Barratt et al., 1997) compared to other forms of aggression. Finally, in contrast to medically related and premeditated aggression, impulsive aggression may occur with Axis I disorders, including substance abuse, intermittent explosive disorder (IED; Coccaro, 2004), posttraumatic stress disorder (PTSD; Pavic et al., 2003), mood disorders (Soloff, Lynch, Kelly, Malone, & Mann, 2000), substance use (Soloff, Lynch, & Moss, 2000), and BPD (Dubo, Zanarini, & Lewis, 1997; Dulit, Fyer, Leon, Brodsky, & Frances, 1994; Gardner & Cowdry, 1985). Notably, many of these disorders are associated with associated irregularities in 5-HT activity. To examine this further, we turn our discussion to neurobiological studies of aggression in BPD with attention to the 5-HT system.

Neurobiology Studies on Self- and Other-Directed Aggression

Dysfunction of 5-HT in frontal and limbic neural circuits is a risk factor for impulsive aggression. 5-HT is a monoamine transmitter in the mammalian brain that functions as an inhibitory neurotransmitter, inhibiting the production of postsynaptic action potentials. Research indicates that 5-HT is involved in the regulation of several functions, including mood, cognition, motor behaviors, social affiliation, circadian rhythms, and neuroendocrine activity. Cross-sectional data suggests a strong correlation between impulsive aggression and decreased 5-HT activity. Early studies linked low cerebrospinal fluid (CSF) levels of the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA), to aggression (Brown, Goodwin, Ballenger, Goyer, & Major, 1979; Linnoila & Virkkunen, 1992), and suicidal behavior (Åsberg, Traskman, & Thoren, 1976). Similar findings have been reported in animal studies (Higley et al., 1992). Not all studies; however, have found an inverse relationship between CSF 5-HIAA and aggression (Balaban, Alper, & Kasamon, 1996). This could be because of inherent noise of using CSF measures of a metabolite, rather than a more direct measure of 5-HT function. Psychopharmacological challenge studies with agents such as fenfluramine have been used to assess the peripheral response to stimulation of central neurotransmitter receptors, thereby providing a measure of 5-HT function. Fenfluramine administration leads to a release of synaptic 5-HT, resulting in a reliable limbic–hypothalamic mediated release of peripheral prolactin. In a sample of personality disordered patients, prolactin response to 60 mg of *d*,*l*-fenfluramine was inversely related to measures of recent impulsive aggressive behavior. This finding has been replicated in personality-disordered subjects (Coccaro & Kavoussi, 1997; Stein, Trestman, & Mitropoulou, 1996), in antisocial violent offenders (O'Keane et al., 1992), and in primates (Botchin, Kaplan, Manuck, & Mann, 1993). Other studies using serotonergic probes have also revealed a relationship between decreased 5-HT receptor function and impulsive aggression in a variety of psychiatric popula-

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

tions, including three studies finding aggression inversely correlated with diminished prolactin response by the 5-HT1A and $5HT_2$ agonist *meta*-chlorophenylpiperazine (*m*-CPP; Coccaro, Kavoussi, & Hauger, 1995; Handlesman et al., 1996; Moss, Yao, & Panzak, 1990), and the $5\text{-}HT_{1A}$ agonist ipsapirone (Coccaro et al., 1995).

Aggression directed at self and others may share common causal pathways. Individual histories of self-injury have increased levels of lifetime aggression, sociopathy, and anger (Simeon & Favazza, 2001). As with impulsive aggression toward others, suicidal and self-injurious behavior is associated with blunted hormonal response to fenfluramine (New et al., 1997) and *m*-CPP (Herpertz et al., 2001). These findings of decreased 5-HT receptor sensitivity are consistent with the finding of decreased CSF 5-HIAA levels in depressed patients with self-injurious behavior compared to depressed patients without self-injurious behavior. This suggests decreased global brain 5-HT production or metabolism (Lopez–Ibor, Saiz–Ruiz, & Perez de los Cobos, 1985), although negative studies have failed to find a link between self-aggression and CSF 5-HIAA levels (Gardner, Lucas, & Cowdry, 1990; Simeon et al., 1992).

Reduced 5-HT function in the brain would be expected to impair the processing ability of brain frontal and limbic circuits, which receive extensive serotonergic input from the dorsal raphe nuclei and express 5-HT receptors in both serotonergic and nonserotonergic neurons. Some preliminary evidence has been found implicating reduced 5-HT synthesis in corticostriatal pathways related to impulsivity in BPD (Leyton et al., 2001) using a positron emission tomography (PET) radioligand for the 5-HT precursor tryptophan. Consistent with this, following challenge with fenfluramine, impulsive aggressive compared to control subjects show blunted metabolic response as measured by PET in orbital frontal, adjacent medial frontal, and cingulate cortex (Siever et al., 1999). Similar findings were reported in studies published by Soloff, Lynch, et al. (2000) and New, Buchsbaum, et al. (2004). Thus, the relationship between 5-HT receptor dysfunction and impulsive aggression may be due to a processing deficit mediated by serotonergic receptor dysfunction in frontal limbic circuits implicated in anger and aggression (Dougherty et al., 2004). This could cause, or at the very least interact with, the structural brain structural abnormalities purported to be associated with BPD, such as decreased amygdalar volume (Driessen et al., 2000; Rusch et al., 2003), decreased frontal lobe volume (Lyoo, Han, & Cho, 1998), and decreased hippocampal size (Brambilla et al., 2004; Driessen et al., 2000; Tebartz van Elst et al., 2003). Decreased prefrontal cortex function, due to 5-HT dysregulation, in the face of compromised limbic cortex structure, could account for amygdala hyperreponsiveness to emotional stimuli found in functional magnetic resonance imaging (fMRI) studies of BPD (Donegan et al., 2003; Herpertz et al., 2001). We believe that this work, along with evidence of the association between diminished constraint with impaired neuropsychological function on a prefrontal/executive function (Lenzenweger, Clarkin, Fertuck, & Kernberg, 2004), reflects an important area of research, which in the future may be enhanced with the use of neurobiological, neuroimaging, and psychopsychological probes.

Treatment studies on impulsive behavior symptoms provide complementary evidence of the association between serotonergic function and impulsive aggression (Coccaro, Kavoussi, & Hauger, 1997; Cornelius, Soloff, Perel, & Ulrich, 1990). Treatment with selective serotonin reuptake inhibitors improved the outcome of individuals with impulsive aggression via increased serotonergic function, although treatment may need to extend the length of treatment and use higher dose regimes.

The relationship between impulsive aggression and 5-HT function may also have relevance to suicidality, which represents an important risk of BPD, and has also been linked to brain 5-HT function (Molcho, Stanley, & Stanley, 1991; Nordstrom & Åsberg, 1992). Evaluation of 5-HT in the brains of suicide victims indicates an increased number of postsynaptic 5-HT-2 receptors in brains of suicide victims. This finding has been reported in many, although not all, studies (Mann, Brent, & Arango, 2001). Finally, studies also show

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

that higher number of platelet 5-HT_{2A} binding sites among suicidal patients independent of diagnosis (Biegon et al., 1990; Pandey et al., 1995). These results could be interpreted as evidence of receptor upregulation in response to a hyposerotonergic state, but further work is necessary to understand the mechanistic implication of increased 5-HT receptor function in association with suicide.

Thus far, empirical studies inform a brain model of impulsive aggression in which decreased 5-HT receptor function in the prefrontal cortex results in increased risk for impulsive aggression. Future studies will need to examine (a) the role of 5-HT related genetic polymorphisms in prefrontal 5-HT function in aggressive and nonaggressive individuals; (b) the effect of 5-HT enhancing treatments on prefrontal 5-HT function in impulsive aggression; and (c) the interaction of 5-HT with other neurotransmitters, neuropeptides, and neurohormones in impulsive aggression.

HPA Axis Irregularities

Biological responses to stress, demonstrated by irregularities in limbic–HPA axis, have been compellingly associated with behaviors of self-injury and aggression. Specifically, aggression may be stimulated by the electrical activation of the hypothalamic area in animals (Halasz, Liposits, Meelis, Kruk, & Haller, 2002). In addition, cortisol irregularities have been observed with conditions of self-injury in rhesus monkeys (Novak, 2003) and aggressive behaviors in rats (Kruk, Halasz, Meelis, & Haller, 2004; Veenema, Meijer, de Kloet, & Koolhaas, 2003). Very interesting work shows that aggressive behavior is facilitated by corticosteroids (stress hormones) in anticipation of the confrontation with an adversary, implicating a mutual interaction between mechanisms that control brain areas involved in regulation of aggression and stress. For example, observable surges in corticosteroids are seen in rats in social challenge situations before aggressive behavior occurs (Kruk et al., 2004). It has yet to be definitively determined if the process occurs in humans, but the literature on children and adults suggest that the features most linked to aggression include irregularities in cortisol concentrations. Specifically, low salivary cortisol has been linked with early onset of aggressive symptoms (by age 10 years) in clinic-referred school-aged boys (McBurnett, Lahey, Rathouz, & Loeber, 2000), suggesting developmental psychopathology of persistent aggression. In addition, cortisol irregularities have been linked with sensation-seeking temperament in aggression in adults (Gerra et al., 1997), as well as aggression in personality disorder (Coccaro, Kavoussi, Hauger, Cooper, & Ferris, 1998). Collectively, these results have sparked important integrative research approaches to understanding the key role of the HPA axis system in modulating stress responses in aggression conditions (Lopez, Vazquez, & Olson, 2004).

Data regarding the function of the HPA axis studies of individuals with BPD also supports the possibility of increased adrenal activity and lowered feedback sensitivity to HPA axis. Adults with BPD show higher total cortisol response in the morning after awakening and higher daily total cortisol levels (Lieb, Zanarini, Schmahl, Linehan, & Bohus, 2004) as well as higher nonsuppression to administration of low-dose dexamethasone (DEX) compared to the control group. Carrasco et al. (2003) indicated in a small pilot study that 64% of their BPD patients, compared to 20% of patients exhibiting other personality disorders, showed a hypersensitive response to the DA test using plasma cortisol. Finally, Rinnes et al. (2002) indicate that hyperresponsiveness of HPA axis to combined DEX/corticotropin-releasing hormone (DEX/CRH) challenge in female BPD subjects with a history of sustained childhood abuse. Specifically, the study investigated the association between childhood abuse and HPA axis function using the combined DEX/CRH test in 39 BPD patients with and without sustained childhood abuse ($n = 24$, $n = 15$, respectively) and comorbid PTSD ($n = 12$), or major depressive disorder (MDD; $n = 11$), compared with healthy control subjects ($n = 11$). Results indicate that the subjects with chronic abuse exhibited significantly enhanced corticotropin (ACTH) and cortisol response to the DEX/CRH challenge compared with nonabused subjects. In addition, subjects with comorbid

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

PTSD showed a significantly attenuated ACTH response. Interpretations of these results suggest that hyperresponsiveness of the HPA axis in individuals with BPD and histories of chronic abuse may be due to the increased pituitary ACTH function. These results also suggest that early maltreatment, rather than the conditions of BPD, MDD, or PTSD, enhanced HPA axis suppression by DEX. We propose that additional research that aims to clarify the specific effects of early life stress with and without BPD on neuroendocrine function at different developmental stages may provide clarity regarding neuroendocrine profiles related to aggression in BPD.

Early Life Stress and Aggression

Exposure to early life maltreatment, in the form of childhood abuse and neglect, is a risk factor for affective instability, self-injury, and personality disorders (Green, 1978; Low, Jones, MacLeod, Power, & Duggan, 2000; Schaffer, Carroll, & Ambramowitz, 1982; Soloff, Lynch, Kelly, et al., 2000; Wiederman, Sansone, & Sansone, 1999). The longitudinal data provides evidence of a significant association between childhood maltreatment and self-injury during adolescence, particularly sexual abuse (Yates, 2004). Between 17 and 58% of individuals who self-injure report the occurrence of parent to child incest during their childhood (Babiker & Herbert, 1998). Likewise, 41% of physically abused children report engaging in self-injurious behaviors, compared to 17% of neglected children, and 7% of normal controls (Green, 1978). By extension, emotional neglect has been strongly associated with self-injurious behaviors compared to physical abuse and sexual abuse (Lipschitz et al., 1999).

We consider early life stress to be important in the developmental psychopathology of suicide and aggression, as such stress appears to have deleterious effects on normative developmental processes of brain development. However, research has yet to delineate differential effects of maltreatment on the development of impulsive aggression in BPD, with attention to the nature, severity, timing of onset, and chronicity of the maltreatment. New avenues of research might examine factors that buffer early life stress (e.g., supportive family environment, positive attention from a parental figure during abuse) on aggressive behaviors in BPD, in addition to research attending to the specific effects of life stress on BPD symptom severity and course (Bulik, Prescott, & Kendler, 2001). Given our interest in using the developmental psychopathology approach to guide this work, we will now discuss the developmental continuities of serotonergic function, HPA axis irregularities, early life stress, and aggressive behavior, and the chronobiology of these factors in the context of BPD.

Developmental Psychopathology of Aggression in BPD

Most of our discussion of the science of impulsive aggression in BPD thus far maps onto the defining features of the developmental psychopathology approach (Cicchetti & Cohen, 1995; Rutter & Sroufe, 2000), a model that offers an excellent set of principles for understanding the development of aggression in BPD. The developmental psychopathology approach examines the behavior in developmental context to define pathways of normative and pathologic development. For example, suicidality and aggression increase markedly during adolescence (Gould et al., 2004). In early adolescence, they may represent normative short-lived experimentation with increased risk taking, rule breaking, testing of parental limits, and fluctuating emotional states. However, for a subset of adolescents, impulsive aggression and suicidal behavior represents the early onset of personality pathology. Likewise, across the life span, aggressive and self-injurious behaviors occur within a continuum ranging from normal behavior (e.g., asserting self) to psychopathology (e.g., violent rage). At the normative middle of the continuum, anger expression is adaptive for individual and relationship health. At the pathologic opposite ends, patterns of under- or overexpression of anger may represent maladaptive behavior. Psychopathology is conceptualized as a deviation from normal developmental processes and pathways (Sroufe, 1990), and thus, understanding situational and developmental con-

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

text provides key data regarding normal development and pathologic processes.

The developmental psychopathology approach also promotes an appreciation for the diversity in causal processes and outcome with attention to the principles of equifinality (e.g., same outcome via different processes) and multifinality (e.g., different outcomes via common pathways; Cicchetti & Rogosch, 1996). Development is a varied process, and numerous individual differences affect the developmental pathways from precursor to pathology. The research, thus far, suggests individual differences in the psychosocial and biological processes that contribute to the emergence of aggressive behaviors. It is critical, therefore, to focus new research on *how and when* risk and resiliency factors influence the development of aggression and, as we discuss more below, how development influences the course of symptom trajectories.

Use of a life-span perspective is supported by the finding that early substrates of personality, for instance, temperament, manifests from birth onward, and that normative and pathologic features of personality emerge early during childhood and adolescence. For example, prospective research studies suggest that early child behaviors, such as disruptive behaviors, are strongly associated with later onset of adult personality disorders (Zweig–Frank & Paris, 2002). The key issue from a developmental perspective is whether aggressive behavior arising early in life is the same as those occurring in adulthood. Childhood, adolescence, and adulthood are continuous, transitional periods during which risk and resiliency factors influence an individual's capacity to respond to developmental challenges. Previous developmental experiences and biological processes set the stage for how the individual manages future challenges. Most individuals during childhood through adulthood negotiate these experiences successfully, whereas other individuals may face greater risk of initiating impulsive aggression as one method of managing the challenge. How individuals negotiate these challenges are critical for promoting health and normative functioning.

Finally, use of the integrative approach of developmental psychopathology allows for simultaneous attention to related processes, using multilevel analyses to the biological, social, and emotional processes and their integration over the life span (Sroufe, Egeland, & Carlson, 1999). Such an approach affords researchers and clinicians the option of evaluating biological and behavioral systems with attention to varying expressions of these systems over time. The developmental psychopathology approach allows us to conceptualize and compare aggressive and self-injurious conditions in terms of developmental timing and course trajectories. For example, there is a distinction between early-onset injurers (self-injuring before age 30) and the late-onset injurer in terms of course and outcome of BPD (Pattison & Kahan, 1983). Finding a clear distinction between adolescence-limited borderline behavior and persistent borderline behavior, for example, creates an opportunity for understanding and treating these clinical phenomena. In summary, concepts from the field of developmental psychopathology (Rutter & Sroufe, 2000) may facilitate a greater understanding of the precursors and the pathways toward the pathogenesis of aggression in BPD.

Guided by the developmental psychopathology model of aggression and self-injury, we focus on the interaction between early maltreatment and biological systems and show how 5-HT and HPA axis function are related with aggressive and injurious behaviors in BPD. We propose that early trauma interacts with diminished 5-HT, which may differentially lead to suicide-related and aggressive behaviors. This is based on research showing a strong association between childhood trauma, HPA axis irregularities, 5-HT functioning, and self-aggression in BPD. This model proposes that both early life stress and biological systems contribute to the development and function of neural substrates for impulsive aggression toward self and others. Neurotransmitter irregularities alone function as a significant liability for aggressive conditions. However, they also affect the environmental and social responses produced by the individual, thereby inflating the chance of adverse outcome and maladaptive experience. Research shows that environmental conditions, particularly early life stress

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

within the family domain, further compromise normal function of 5-HT and HPA axis regulation. In this model, biological and environmental processes are interactive and cumulative in their mutual influence on the developmental trajectory and biological and behavioral outcomes. Although certain individuals possess a genetic liability related to temperamental characteristics, which exist prior to the development of impulsive aggression, we point to the brain and behavior connection and the influence of development. In this model, neurotransmitter function may influence the environment, which may in turn, modify the liability for developing aggressive and self-injurious behavior.

Developmental Continuities

Using a developmental framework, we are faced with the initial question of which condition comes first, aggression/BPD or 5-HT or HPA axis abnormalities? Work that promotes an understanding that the prefrontal cortex and 5-HT development encounter a discontinuity in adolescence may help us to track the developmental course of aggression and BPD. It could be proposed that findings of dysregulated 5-HT and HPA axis function associated cross-sectionally with impulsive aggression may represent the biological consequences, rather than the causes of the behavior. In favor of this argument, we note that increased locomotor activity is associated with increased 5-HT activity. Likewise, frequent activation of the fight or flight response could potentiate findings if increased salivary cortisol levels were found in BPD subjects. This interpretation is rendered less persuasive by the fact that cross-sectional studies of impulsive aggression to date have measured subjects in an unprovoked state. Findings of increased reactivity of the HPA axis in some BPD subjects would not be consistent with a chronically stressed state, which would be expected to result in a counterregulatory hyposensitivity of the pituitary and adrenal glands. Most importantly, two strands of research, one regarding the development of 5-HT systems in the brain, the other regarding the effects of early life stress and maternal care on stress reactivity, are consistent with the development of these two systems playing a major role in brain development, and hence psychopathology. Using a translational approach to bridge findings from preclinical and clinical basic behavioral science studies, we hypothesize that the development of self- and other-directed aggression in BPD is tied to the development of problems with 5-HT and stress reactivity during adolescence, which is a period of vulnerability. This discontinuity in development marks the point at which behavioral traits are simultaneously in flux, and when they begin to diverge into separate, but related psychopathologies.

Brain Development Over the Life Span

Brain development over infancy, childhood, and adolescence must necessarily inform a developmental understanding of aggression in BPD. The defining character of human brain development is the slow rate of frontal cortex maturation, providing a relatively wide window of time during which social influences may impact the brain and behavior. This is even more remarkable, given that most neurons have migrated to appropriate locations within the cortex, hippocampus, cerebellum, and other brain structures at birth, and that by 3 years of age, most landmarks and major fiber tracts can be observed (Matsuzawa et al., 2001). What remains of neural development is myelination, synaptic pruning, and experience-dependent shaping of neuronal networks. These processes increase the efficiency and scope of interregional and intraregional connectivity. This unfolding process ensures that even relatively simple biological determinants such as genetic polymorphisms may result in complex, rather than focal, neurological lesions with well-defined symptoms (Johnson et al., 1999). In a complex model of brain development, subtle focal abnormalities may be present early in development, but these would be compounded through the infant's environmental interactions and increasingly complex neural circuitry. Discontinuities in neurobiological and behavioral development would be expected according to this model. Examples of this include the findings of greater neuroplasticity in language and motor processing in young chil-

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

dren compared to adults (Chugani, 1999; Mueller et al., 1997). Such complex processes are likely to be relevant to BPD, with its multidimensional symptom profile and noncontinuous course.

Brain development and adolescence: A period of vulnerability

Adolescence in humans is typically defined to span ages 12–18 years. There are several reasons that adolescence should be a period of heightened interest in the study of the development of BPD. First, the behavioral changes associated with adolescence share face validity with the deficits seen in BPD (i.e., identity disturbance, emotional dysregulation, and impulsivity). Second, adolescence marks the first period of time for which continuity between a borderline-like phenotype and BPD exists. The transition from childhood to adolescence marks a neurobiological and behavioral discontinuity. The behavioral discontinuity is marked by new demands, including (a) increased self-regulatory capacity in peer interaction, (b) increased novelty seeking and exploratory behavior, (c) increased stress reactivity, and (d) emergence of sexuality. The neurobiological changes underlying these environmental demands will be briefly described in this section.

Development of self-regulation, a core deficit of BPD, is one of the most important developmental processes of adolescence. Peer interactions and consequent peer conflict demand the ability to self-regulate emotions, impulses, cognitions, and other socially relevant behaviors (Pereira & Fairbanks 1993). Failure to meet such demands may partly potentiate the emergence during adolescence of self-injury, depression, substance abuse, eating disorders, and bipolar disorder (Rutter et al., 1993, Steinberg, Dahl, Keating, & Masten, 2004). Underlying self-regulatory processes are refinements in cortical neurobiology. Although total brain size does not increase after 5 years, frontal cortical gray matter peaks at 12.1 years for males and at 11 years for girls. After this peak, synaptic pruning begins, decreasing gray matter (Giedd et al., 1999) at an estimated rate of 30,000 synapses/s (Rakic, Bourgeois, & Goldman–Rakic, 1994), until 40% of all synapses are eliminated (Huttenlocher, 1984) by the early 20s (Chugani, Phelps, & Mazziotta, 1987). Although gray matter decreases, white matter myelination and growth continues (Giedd et al., 1999). Working memory improves, parallel with maturation of dorsolateral prefrontal cortex chandelier neurons and decrease in GABA alpha-2 receptors (Lewis, Cruz, Eggan, & Erickson, 2004). Inhibition of overlearned responses becomes more proficient in adolescence. This proficiency may be related to synaptic pruning as well as increasing myelination, as evidenced by functional neuroimaging studies finding that adolescents must utilize a greater extent of the dorsolateral prefrontal cortex, and show less evidence of widely distributed neural network activation during a task of visual response inhibition compared to adults and children (Luna & Sweeney, 2004). It is possible that BPD patients have failed to develop self-regulation during adolescence and early adulthood because of delayed or derailed cortical development. This has not yet been investigated.

One developmental change of adolescence is improved efficiency of self-regulation; another is an increase in impulsive novelty seeking. Although this may seem paradoxical, development of regulatory processes may in part depend on activation of networks that need regulation. In human adolescence, risk taking increases to the point that participation in delinquency appears to be a norm (Moffitt, 1993). As reviewed in Spear (2000), a shift occurs in relative balance between subcortical and cortical dopaminergic systems toward increased cortical and decreased subcortical dopamine (DA) activity. DA activity in the nucleus accumbens is lower, whereas DA inhibitory input to the prefrontal cortex is at its highest level. The sum of these changes contributes to the increase in sensation seeking and impulsivity found in normal adolescence. It is possible that a preprogrammed adolescent increase in impulsive novelty seeking is problematic in individuals who have failed to adequately develop a neural mechanism permitting self-regulation.

Another important change in adolescence is the increase in stress reactivity compared to

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

childhood. As reviewed in Spear (2000), adolescence is characterized by an increase in frequency of stressful events simultaneous with elevated biological stress sensitivity (e.g., less sleep, greater cardiovascular and pituitary response to laboratory stressors, increased basal cortisol, and increased amygdala reactivity to emotionally relevant stimuli). Stress-induced increases in DA would be expected to impair prefrontal cortex function, as mesocortical DA projections are more sensitive to activation by stressors (Dunn, 1988), and higher levels of DA are found in the prefrontal cortex of adolescent monkeys (Arnsten & Shansky, 2004). Although only a minority of adolescents will meet criteria for depression, the incidence of depressed mood increases as individuals emerge from childhood to adolescence (Rutter, Graham, Chadwick, & Yule, 1976). It is possible that increases in adolescent stress reactivity would be problematic if an individual has not developed the ability to regulate stress reactivity via prefrontal cortex inhibitory input on the limbic cortex and HPA axis.

Finally, one of the most dramatic developmental changes of adolescence is the emergence of sexuality, mediated in part by a reactivation of the production and secretion of adrenal androgens, ACTH, dehydroepiandrosterone, and dehydroepiandrosterone sulfate, gonadotropin-releasing hormone, follicle stimulating hormone, lutenizing hormone, and the gonadal hormones testosterone and estrogen. Gonadal hormones act on receptors in hippocampus, striatum, cerebellum, amygdala, and cerebral cortex, modulating cholinergic, serotonergic, noradrenergic, and dopaminergic projecting neurons (Cameron, 2004). Estrogen increases expression of alpha-1 adrenoceptors and decreases expression of alpha-2A adrenoreceptors (Karkanias, Li, & Etgen, 1997). Both of these changes serve to enhance the detrimental effects of high levels of stress on prefrontal cortex function, and could further undermine prefrontal cortex function in vulnerable individuals.

The emergence of increased capacity for self-regulation during a time of increased impulsivity and sexuality would suggest that adolescence marks a period during which factors promoting resilience are of key importance in shaping the development of BPD. It is unknown if such protective factors could prevent the development of BPD. It is also unknown during which phases of development these factors become most important: in utero, infancy, childhood, or adolescence? Understanding how protective and risk factors alter even just the severity of BPD in adulthood would be of clinical value, as incremental changes in impulsivity or self-destructive behavior could have important health and social consequences. Risk factors that interact with developmental processes occurring in adolescence may also be of importance. An example of this is the occurrence of MDD in childhood or adolescence, which may alter personality development because of its presence during an important developmental window. Adolescent depression is a risk factor for later personality disorder (Kasen et al., 2001). Young adult BPD is associated with chronic depression with an insidious onset (Skodol et al., 1999). Further work needs to be done to understand how early life depression might play a causal role in the development of personality disorder. It also is unknown if early, effective treatment of mood disorder in adolescence prevents the development of personality disorder. If mood disorders specifically alter neurobiological processes unique to adolescence, such as prefrontal cortex development, and if this alters personality development, would treatment of depression in adolescence benefit from being supplemented with specific, novel interventions bolstering self-esteem, secure identity, and other reliance factors? This area needs to be investigated.

5-HT and Development

The nonlinear development of serotonergic neurons over the life span is exemplified by four findings from preclinical and clinical research. First, 5-HT neurons have mostly migrated to their destinations in the brain by the end of gestation, during which experimentally induced excesses of 5-HT result in abnormal, unfocused development of target cortical fields (Rhoades et al., 1990; Siklich, Hickock, & Todd, 1990; Verney, Berger, Adrien, Vigny, & Gay, 1982). Second, postnatally some axon

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

terminal arborizations are still maturing in a preprogrammed but transient hyperserotonergic environment (Connell, Karikari, & Hohman, 2004). Third, 5-HT neurons still have an important formative role during key stages of postnatal development. Disruption of 5-HT function during certain development stages, using experimental conditional knockout 5-HT_{1A} receptor genes in mice, results in abnormal development of GABAergic and limbic cortical development that can be detected in adulthood (Gross et al., 2002; Sibille, Pavlides, Benke, & Toth, 2000). Fourth, the ontogeny of some 5-HT-related functions such as stress reactivity appear to be determined by interactive genetic and environmental factors, such as reported interactions of polymorphisms of the 5-HT transporter and rearing in macaque monkeys (Barr et al., 2004).

Consistent with nonlinear processes of 5-HT neurodevelopment, increased aggression in adolescence has been associated with increased prolactin response to fenfluramine, a finding that is reverse to that found in adults (Halperin et al., 1994; Pine et al., 1996). The divergent results may be due to measurement of different phenotypic expressions of aggression in adolescence and adulthood or that during the development of serotonergic function during adolescence, the relationship between aggression and 5-HT function reverses. Evidence for this latter possibility includes findings of increased, rather than decreased, 5-HT receptor sensitivity in aggressive adolescents (Darmani, Shaddy, & Gerdes, 1996; McBride, Tierney, DeMeo, Chen, & Mann, 1990). Further work is necessary to understand why findings in adolescents are reverse from those in adults. It is unknown if this has implications on the efficacy or side effect profile of 5-HT drugs such as 5-HT reuptake inhibitors.

In summary, the development of 5-HT function of the brain is characterized by both a role for 5-HT in guiding development of other brain systems as well as an evolving relationship with behaviors such as aggression. The development of 5-HT neurons significantly impacts the development of other brain functions, such as GABAergic function and anxiety during key stages in development. This would suggest that environmental effects on development, such as stress or drugs affecting serotonergic function, would have timing dependent effects. Risk factors could impact 5-HT function prenatally, in infancy, childhood, and adolescence, with each time point having unique implications for the development of 5-HT and 5-HT-mediated aggression. Change of other neurohormonal systems, like HPA axis function, may also play a role and extend our understanding here. Understanding the changing function of 5-HT over the life span is of critical clinical importance, given the availability of 5-HT enhancing and 5-HT blocking drugs.

Early Life Stress, HPA Axis, and Aggression

Understanding the development of HPA axis function through infancy, childhood, adolescence, and adulthood may inform a developmental understanding of aggression in BPD. Animal and human research shows that exposing infant offspring to uncontrollable stress and maternal separation permanently alters HPA axis regulation, along with long-term biological and behavioral changes (Heim, Newport, Bonsall, Miller, & Nemeroff, 2001; Ladd et al., 2000; Ogawa, Sroufe, Weinfeld, Carlson, & Egeland, 1997). Deprivation of parental care for nonhuman primates produced dramatic examples of self-destructive and self-stimulating behaviors, including huddling, self-clasping, self-sucking, and self-biting (Harlow & Harlow, 1971; Kraemer, Schmidt, & Ebert, 1997). Complementing this, Cross and Harlow (1965) noted that macaque monkeys reared in isolation displayed sucking and chewing behaviors long after the appropriate developmental phase and were equally predisposed to respond to external threat with self-directed aggression and other-focused attacks. It is notable, that with animal-based experimentally controlled studies investigating the impact of being deprived of maternal care (e.g., licking, grooming, and attentiveness), rat pups displayed marked increases of corticosteroid responses to injected ACTH, and higher pituitary adrenal responses and behavioral fear responses to acute stress (Liu, Caldji, Sharma, Plotsky, & Meaney, 2000;

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

Plotsky & Meaney, 1993). Animal deprivation studies have also linked maternal separation with decreased glucocorticoid receptor binding in the hippocampus, hypothalamus, and frontal cortex, and blunted negative feedback sensitivity among offspring (Ladd et al., 2000).

Neurobiological effects on infant monkeys are strongly illustrated in research, demonstrating the effects of stress derived from the variable foraging demand (VFD) paradigm (e.g., creating maternal–pup separation). Infant monkeys under the care of VFD mothers showed long-term biological and behavioral changes. Coplan et al.'s study (2001) showed increased CSF CRF concentrations among juveniles compared with normal controls. These changes remained through adulthood. In contrast, postnatal human handling of rodents, as well as positive maternal behavior (licking and grooming of pups), have been associated with reduced stress responses among infant offspring (Heim et al., 2001; Meaney et al., 1996) where blunted responses to stress continues from infancy to adulthood (Liu et al., 2000). Research advanced by Francis, Diorio, Plotsky, and Meaney (2002) demonstrates that this type of environmental enrichment of young rats, who were originally stress reactive, produced a functional reversal of the effects of maternal separation. It should be noted, however, that the reversal was achieved via compensatory mechanisms, rather than the reversal of the neuroendocrine changes due to the early life stress (Francis et al., 2002). Although a nurturing environment may modify the effects of stress, the data do not exclude the possibility that elevated levels of glucocorticoids during stress and impaired feedback regulation contribute to stress-related pathology like impulsive aggression and suicidal behavior.

With humans, HPA axis abnormalities are prominent among children and adolescents who have experienced significant abuse (Cicchetti & Rogosch, 2001). Children and adolescents exposed to abusive or neglectful care demonstrated elevated baseline cortisol and loss of the normal diurnal cortisol secretory patterns (Caldji, Diorio, & Meaney, 2000; Gunnar, 2003). Likewise, sexually abused children exhibited blunted ACTH secretion post-CRH infusion and a trend toward elevated cortisol (Kaufman et al., 1997). Similar findings have been observed among sexually abused school-age girls (DeBellis et al., 1999), with elevated levels of cortisol and catecholamines based on a 24-hr urinary sampling procedure, and a blunted ACTH response to CRH challenge compared to controls (DeBellis et al., 1999). To complicate matters, however, studies indicate that although depressed abused children may show significantly higher peak, total, and net ACTH secretion post-CRH, the HPA axis changes were evident during ongoing stress and disappeared when the abuse stopped (Kaufman & Charney, 1999; Kaufman et al., 1997).

Recent work from our laboratory, reviewing a large dataset of personality disordered individuals, showed that CSF CRH concentration was significantly and positively correlated with the individual's report of child maltreatment as measured by the Childhood Trauma Questionnaire (Lee, Geracioti, Kasckow, & Coccaro, 2005). Finally, new research has found that severe life stress during childhood has been associated with smaller hippocampal volume because elevated cortisol downsizes neuronal structures involved in stress regulation (Vythilingam et al., 2002). Although these studies highlight enduring effects of early life stress on the HPA axis, it is unclear if and how developmental timing of stress influences the direction of HPA axis function in impulsive aggression and in BPD (Carpenter et al., 2004). Research indicates that perceived early life stress was linked with increased or decreased CSF CRF concentrations depending on the developmental timing of the stress exposure, with stress between ages 0 and 6 years linked with elevated CSF CRF concentrations. In contrast, stress before birth, and later during the preteen years, was associated with low CRF concentrations (Carpenter et al., 2004). This work is consistent with the findings from Yehuda, Halligan, and Grossman (2001), who observed that early life stress increases the risk of HPA axis upregulation whereas stress occurring later in life leads to supersuppression and PTSD. Petitto, Quade, and Evans (1992) also report a strong negative correlation between the age of exposure to first loss (adversity) and post-DEX

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

levels. Collectively, this work suggests that the timing and intensity of the stress may influence the type of neuroendocrine responsivity. New avenues of research relating to the developmental timing of early life stress may add specificity of effects with maltreatment, HPA axis function, and aggression.

The relationship between the HPA axis and aggression has not been extensively studied. Coccaro et al. (1998) found that in a sample of male personality disordered subjects, life history of aggression was directly correlated with CSF vasopressin levels. Given that vasopressin is thought to potentiate the activity of CRH on the pituitary release of adrenocorticotropin hormone, the finding is consistent with a role of increased HPA axis activity in aggression. Further studies are needed to know if increased HPA reactivity in response to early life stress alters behavioral aggression.

Longitudinal Development of Aggression as a Behavioral Trait

Understanding the development of aggression in normal populations helps to put in context the abnormal pattern of development in BPD. A retrospective study of aggressive behavior, even in an at-risk population of Vietnam War veterans, found that most direct physical aggression stops in childhood (Windle & Windle, 1995). Only a minority of individuals showed continuity of aggressive behavior from childhood to adulthood (6.5%), and an equivalent portion showed aggression onset in adulthood (6.2%). This suggests that the normative development of aggression is to decrease over the life span, consistent with findings from two prospective studies (Kingston & Prior, 1995). Increasing capacity for effortful inhibition mediated by prefrontal cortex development from 12 months to adulthood (Nigg, 2003) may account for decreasing aggressive behavior. Risk factors from different phases of development may interact, as evidenced from findings that risk for aggressive outcomes of insecure attachment in infancy occurs only in the presence of continuing poor parenting (Greenberg, Speltz, & DeKlyen, 1993). An important question for future studies is whether aggression in BPD represents a persistence of childhood aggression, or the onset of aggression in adolescence or adulthood.

If aggressive behavior persists into adolescence, it tends to become a stable trait (Loeber & Hay 1997). Within IED subjects, many of whom meet criteria for BPD, the mean age of onset of serious aggressive behavior is 18.3 years. Seventy-five percent report life-long histories, with no significant gender differences in developmental course. Aggressive behavior begins in the first decade, peaks in the third decade, diminishes steadily after the fifth decade, and rarely occurs in the eighth decade (e.g., first decade = 18.8%, second decade = 56.3%, third = 87.5%, fourth = 75%, fifth = 43.8%, sixth = 18.8%; Coccaro, 2004). It is not clear if these cross-sectional findings in IED subject samples can be generalized to apply longitudinally to BPD.

Although conventional wisdom would hold that aggression is a mostly male behavior, evidence would suggest that gender differences in aggression are differences in typology, rather than prevalence. Boys between fourth and seventh grade increase the amount of physical aggression to other boys, whereas girls decrease aggression. However girls experience more social alienation, reflecting increased usage of indirect forms of aggression and a developmental divergence of pathways from early direct confrontation to indirect social aggression (Cairns & Cairns, 2000; Cairns, Cairns, Neckerman, Ferguson, & Gariepy, 1989; Crick & Bigbee, 1998). It is possible that the development of aggression in BPD actually represents a failure to learn more nuanced, socially sanctioned forms of aggressive behavior such as competition and social dominance. However, even nonphysical aggression against social relationships appears to be counterproductive. Aggression against relationships in 9- to 12-year-old children exhibited traitlike stability, and predicted worse, not enhanced, social adjustment longitudinally over a year (Crick, 1996). Aggression against relationships in adults is not a well-studied phenomenon, and is not operationalized in the current *DSM* description of BPD, except as it may be reflected in "intense and stormy relationships." Given the increased

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

prevalence of BPD in females, further work needs to be done to better define the importance of indirect aggression in BPD and its development.

In summary, the normative development of aggression is characterized by decreasing levels of direct aggression during a time in which prefrontal cortex function improves. Socialization may account for some of the preadolescent and adolescent decrease in aggression: possibly some aggressive tendencies persist in as-yet unmeasured variations on aggression such as competition or social dominance. Abnormal aggression, on the other hand, may appear in adolescence and continue into adulthood. Even indirect forms of aggression, as seen predominantly in females, are counterproductive and do not appear to have individual or social benefit. It is unknown to what extent the appearance and continuity of abnormal aggression in adolescence represents a failure of resilience factors, the result of traumatic factors such as abuse or depression, the continuation of an already abnormal neurodevelopmental course, or the appearance of latent genetic factors.

Longitudinal Course of BPD

Children with borderline-like features have presented as early as age 4 years with cognitive deficits in reality testing, social relationship problems, anxiety regulation, soft neurological signs, and attentional deficits (Cohen, Paul, & Volkmar, 1987). Similar findings are noted (Paris, Zelkowitz, Gudzer, Joseph, & Feldman, 1999) where borderline-like children compared to psychiatric controls had deficits in working memory and attention. The presence in childhood of a borderline-like syndrome has resulted in descriptive theoretical constructs (Kernberg, 1982; Lincoln, Bloom, Katz, & Boksenbaum, 1998; Pine, 1986; Towbin, Dykens, Pearson, & Cohen, 1993). In addition, Lofgren, Bemporad, King, Lindem, and O'Driscoll's (1991) follow-up of 19 children with borderline-like symptoms from age 6 to 10 years, for 10 to 20 years, then reassessed with the Structured Clinical Interview for *DSM-III-R*. No subjects received a diagnosis of affective disorder or schizophrenia. Sixteen subjects met criteria for a personality disorder, including three with borderline and five with antisocial personality disorder. Six individuals were diagnosed with substance abuse. The results of this study do not confirm a specific link between preadolescent borderline-like symptoms and BPD, but do indicate that the early presence of BPD-like symptoms predicts later personality disorder. Similar findings were reported by Johnson, Halit, Grice, and Karmiloff–Smith (2002). Likewise, the predictors of adolescent BPD-like symptoms is not specifically linked to BPD-like symptoms in childhood, but to a range of abnormal behaviors such as depression, behavioral problems, and delayed psychosocial adjustment (Bernstein et al., 1993). More severe cases of BPD in adolescence seem to be more diagnostically stable and present in adulthood, suggesting some degree of continuity between adolescence and adulthood for well-defined BPD cases (Garnet, Levy, Mattanah, Edell, & McGlashan, 1994).

Work also indicates variability in the longitudinal course of personality disorders. For example, Lenzenweger, Johnson, and Willett (2004) found in a sample of 250 college students that personality disorder symptoms decrease over time. It was noted that for Cluster B disorders, rate of change is −0.65 cluster B features per year. These changes were not related to the presence of Axis I disorder or treatment. Specifically, receipt of treatment was related to elevations for 7 of the 10 disorder dimension models that showed an improvement in fit with the addition of the treatment variables at Level II. This suggests that for seven of the disorder dimensions, on average, those persons who sought treatment showed greater symptoms. It is possible that those individuals whose personality disorders have become "clinical" may actually have a different course, suggesting worse or categorically different pathology. For example, over a 6-year follow-up, 73% of personality disorders met criteria for remission (Zanarini et al., 2004). However, persistence of individual symptoms was heterogenous: 90% of individuals had persistence of intense anger, affective instability, and unstable relationships whereas only 46% manifest persistence of self-injury or suicide

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

attempts (Yen et al., 2004). Similarly, impulsivity appears to decrease with age, whereas affective symptoms of cognitive disturbance and relationship problems do not (Stevenson, Meares, & Comerford, 2003), with anger as the most stable symptom dimension in BPD. This suggests that anger is an important, core feature of a BPD and may point the way to a candidate marker. Consistent with this, aggression in BPD is associated with greater stability and worse prognosis (Schmahl, McGlashan, & Bremner, 2002), as well as the presence of paranoid features, which is itself associated with poor response to treatment (Links, Heslegrave, & Vanreekum, 1998).

In summary, the developmental course of BPD-like symptoms, although not completely understood, suggests stabilization of BPD in adolescence through adulthood, with anger predicting severity and outcome. BPD-like symptoms in childhood may lead to BPD, but may also lead to other personality disorders, mood disorders, or anxiety disorders. BPD may be preceded in childhood by problems with mood and behavior, without all of the symptoms that would lead to an adult diagnosis of BPD. It is unknown, however, what factors lead to the crystallization of the BPD phenotype in adolescence. Candidate factors discussed in this review would include variables that influence serotonergic function such as early life parental care, childhood or adolescent depression, and interaction of genetic and environmental factors. Factors that influence the HPA axis could also account for this, given increased importance of stress reactivity in adolescence. These factors would include early life trauma or decreased parental care, 5-HT function, as well as current stress. Taken in the broader context of brain development, we hypothesize the 5-HT dysfunction leads to decreased capacity for the prefrontal cortex to process emotional information, resulting in increased impulsivity and emotional dysregulation. Altered HPA axis function results in, reflects, or feeds back on greater reactivity of limbic cortex to emotional stimuli. This would result in increased emotionality and altered social behaviors. Resilience would be increased by processes that restore prefrontal cortex and limbic cortex function. One such resilience factor appears to be age, which is associated with a decrease in some, but not all borderline symptoms. Environmental factors that increase 5-HT function and decrease HPA axis function should be helpful to decrease aggression and self-aggression in BPD. These could include stable, supportive relationships; success in social arenas of life such as in academics, career, or relationships; and opportunities for positive emotion.

Conclusions and Suggestions for Future Research

We propose that future research on impulsive aggression in BPD may be advanced using a developmental psychopathology perspective, with attention to the mutual interplay between early maltreatment, HPA axis function irregularities, and serotonergic function and the developmental periods in which plasticity in neurobiological and affective processing systems occur. On the basis of the literature, direct investigation of neurobiological functioning of impulsive aggression is a scientific advance that may broaden our understanding of how biological variables contribute to the emergence of these behaviors. Newer technologies in studying the human brain function such as fMRI offer opportunities to systematically examine the neural circuits and mechanisms involved in social cognitive and affective processing, thereby facilitating the development of new developmental theories about the pathways of onset. Ultimately, this knowledge will contribute to the understanding of the biobehavioral processes and pathways involved in the development of aggressive and self-destructive behaviors observed in BPD.

References

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders* (4th ed.). Washington, DC: Author.

American Psychiatric Association. (2001). Practice guidelines for the treatment of patients with borderline personality disorder. *The American Journal of Psychiatry*, *158*, 2–52.

Anderson, K. G., Sankis, L. M., & Wigider, T. M. (2001).

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

Pathology versus statistical infrequency: Potential sources of gender bias in personality disorder criteria. *Journal of Nervous and Mental Disease*, *189*, 661–668.

Arnsten, A. F. T., & Shansky, R. M. (2004). Adolescence: Vulnerable period for stress-induced prefrontal cortical function: Introduction to Part IV. *Annals of New York Academy of Sciences*, *2021*, 143–147.

Åsberg, M., Traskman, L., & Thoren, P. (1976). 5-HIAA in the cerebrospinal fluid. A biochemical suicide predictor? *Archives of General Psychiatry*, *33*, 1193–1197.

Babiker, G., & Herbert, M. (1998). Critical issues in the assessment of child sexual abuse. *Clinical Child and Family Psychology Review*, *1*, 231–252.

Balaban, E., Alper, J. S, & Kasamon, Y. L. (1996). Mean genes and the biology of aggression: A critical review of recent animal and human research. *Journal of Neurogenetics*, *11*, 1–43.

Barr, C. S., Newman, T. K., Schwandt, M., Shannon, C., Dvoskin, R. L., Lindell, S. G., et al. (2004). Sexual dichotomy of an interaction between early adversity and the serotonin transporter gene promotor variant in rhesus monkeys. *Proceedings of the National Academy of Science of the United States of America*, *101*, 12358–12363.

Barratt, E. S. (1991). Measuring and predicting aggression within the context of a personality theory. *Journal of Neuropsychology*, *3*, 535–539.

Barratt, E. S., & Felthous, A. R. (2003). Impulsive versus premeditated aggression: Implications for mens REA decisions. *Behavioral Sciences and the Law*, *21*, 619–630.

Barratt, E. S., & Slaughter, L. (1998). Defining, measuring, and predicting impulsive aggression: A heuristic model. *Behavioral Science and Law*, *16*, 285–302.

Barratt, E. S., Stanford, M. S., Felthous, A. R., & Kent, T. A. (1997). The effects of phenytoin on impulsive and premeditated aggression: A controlled study. *Journal of Clinical Psychopharmacology*, *17*, 341–349.

Berkowitz, L. (1993). *Aggression: Its causes, consequences, and control*. New York: McGraw–Hill.

Bernstein, D. P., Cohen, P., Velez, C. N., Schwab–Stone, M., Siever, L. J., & Shinsato, L. (1993). Prevalence and stability of the *DSM-III-R* personality disorders in a community-based survey of adolescents. *The American Journal of Psychiatry*, *150*, 1237–1243.

Biegon, A., Grinspoon, A., Blumenfeld, B., Bleich, A., Apter, A., & Mester, R. (1990). Increased serotonin 5-HT_2 receptor binding on blood platelets of suicidal men. *Psychopharmacology (Berlin)*, *100*, 165–167.

Botchin, M. B., Kaplan, J. R., Manuck, S. B., & Mann, J. J. (1993). Low versus high prolactin responders to fenfluramine challenge: Marker of behavioral differences in adult male cynomolgus macaques. *Neuropsychopharmacology*, *9*, 93–99.

Brambilla, P., Soloff, P. H., Sala, M., Nicoletti, M. A., Keshavan, M. S., & Soares, J. C. (2004). Anatomical MRI study of borderline personality disorder patients. *Psychiatry Research*, *131*, 125–133.

Brown, G. L., Goodwin, F .K., Ballenger, J. C., Goyer, P. F., & Major, L. F. (1979). Aggression in human correlates with cerebrospinal fluid amine metabolites. *Psychiatry Research*, *1*, 131–139.

Bulik, C. M., Prescott, C. A., & Kendler, K. S. (2001). Features of childhood sexual abuse and the development of psychiatric and substance use disorders. *British Journal of Psychiatry*, *179*, 444–449.

Buss, A., & Durkee, A. (1957). An inventory for assessing different kinds of hostility. *Journal of Consulting and Clinical Psychology*, *21*, 343–349.

Cairns, R. B., & Cairns, B. D. (2000). The natural history and developmental functions of aggression. In A. J. Sameroff, M. Lewis, & S. M. Miller (Eds.), *Handbook of developmental psychopathology* (2nd ed.). New York: Kluwer Academic/Plenum Press.

Cairns, R. B., Cairns, B. D., Neckerman, H. J., Ferguson, L. L., & Gariepy, J. L. (1989). Growth and aggression: 1. Childhood to early adolescence. *Developmental Psychology*, *25*, 320–330.

Caldji, C., Diorio, J., & Meaney, M. (2000). Variations in maternal care in infancy regulate the development of stress reactivity. *Biological Psychiatry*, *48*, 1164–1174.

Cameron, J. L. (2004). Interrelationships between hormones, behavior and affect during adolescence. *Annals of the New York Academy of Sciences*, *1021*, 110–123.

Carpenter, L. L., Tyrka, A. R., McDougle, C. J., Malison, R. T., Owens, M. J., & Nemeroff, C. B. (2004). Cerebrospinal fluid corticotropin-releasing factor and perceived early-life stress in depressed patients and healthy control subjects. *Neuropsychopharmacology*, *29*, 777–784.

Carrasco, J. L., Diaz–Marsa, M., Ignacio Pastrana, J., Molina, R., Brotons, L., & Horcajadas, C. (2003). Enhanced suppression of cortisol after dexamethasone in borderline personality disorder. A pilot study. *Actas Españolas de Psiquiatría*, *31*, 138–141.

Chugani, H. T. (1999). PET scanning studies of human brain development and plasticity. *Developmental Neuropsychology*, *16*, 379–381.

Chugani, H. T., Phelps, M. E., & Mazziotta, J. C. (1987). Positron emission tomography study of human brain functional development. *Annals of Neurology*, *22*, 487–497.

Cicchetti, D., & Cohen, D. (1995). *Developmental psychopathology: Vol. 1. Theory and methods*. New York: Wiley.

Cicchetti, D., & Rogosch, F. A. (1996). Equifinality and multifinality in developmental psychopathology. *Development and Psychopathology*, *8*, 597–600.

Cicchetti, D., & Rogosch, F. A. (2001). The impact of child maltreatment and psychopathology on neuroendocrine functioning. *Development and Psychopathology*, *13*, 783–804.

Coccaro, E. F. (2004). Intermittent explosive disorder and impulsive aggression: The time for serious study is now. *Current Psychiatry Reports*, *6*, 1–2.

Coccaro, E. F., & Kavoussi, R. J. (1997). Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. *Archives of General Psychiatry*, *54*, 1081–1088.

Coccaro, E. F., Kavoussi, R. J., & Hauger, R. L. (1995). Physiological responses to d-fenfluramine and ipsapirone challenge correlate with indices of aggression in males with personality disorder. *International Clinical Psychopharmacology*, *10*, 177–179.

Coccaro, E. F., Kavoussi, R. J., & Hauger, R. D. (1997). Serotonin function and anti-aggressive response to fluoxetine: A pilot study. *Journal of Biological Psychiatry*, *42*, 546–552.

Coccaro, E. F., Kavoussi, R. J., Hauger, R. L., Cooper, T. B., & Ferris, C. F. (1998). Cerebrospinal fluid vasopressin levels: Correlates with aggression and serotoninin function in personality-disordered subjects. *Archives of General Psychiatry*, *8*, 708–714.

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

Coccaro, E. F., Schmidt, C. A., Samuels, J. F., & Nestadt, G. (2004). Lifetime and 1-month prevalence rates of intermittent explosive disorder in a community sample. *Journal of Clinical Psychiatry*, *65*, 820–824.

Cohen, D. J., Paul, R., & Volkmar, F. (1987). Issues in the classification of pervasive developmental disorders and associated conditions. In D. J. Cohen & A. M. Donnelean (Eds.), *Handbook of autism and pervasive developmental disorders* (pp. 20–39). New York: Wiley.

Connell, S., Karikari, C., & Hohman, C. F. (2004). Sex-specific development of cortical monoamine levels in mouse. *Developmental Brain Research*, *151*, 187–191.

Coplan, J. D., Smith, E. L., Altemus, M., Scharf, B. A., Owens, M. J., & Nemeroff, C. B. (2001). Variable foraging demand rearing: Sustained elevations in cisternal cerebrospinal fluid corticotropin-releasing factor concentrations in adult primates. *Biological Psychiatry*, *50*, 200–204.

Cornelius, J. R., Soloff, P. H., Perel, J. M., & Ulrich, R. F. (1990). Fluoxetine trial in borderline personality disorder. *Psychopharmacology Bulletin*, *26*, 151–154.

Crick, N. R. (1996). The role of overt aggression, relational aggression, and prosocial behavior in the prediction of children's future social adjustment. *Child Development*, *67*, 2317–2327.

Crick, N. R., & Bigbee, M. A. (1998). Relational and overt forms of peer victimization: A multi-informant approach. *Journal of Consulting and Clinical Psychology*, *66*, 337–347.

Cross, H. A., & Harlow, H. P. (1965). Prolonged and progressive effects of partial isolation on the behavior of macaque monkeys. *Journal of Experimental Research in Personality*, *1*, 39–49.

Darmani, N. A., Shaddy, J., & Gerdes, C. F. (1996). Differential ontogenesis of three DOI-induced behaviors in mice. *Physiology and Behavior*, *60*, 1495–1500.

DeBellis, M. D., Keshavan, M. S., Clark, D. B., Casey, B. J., Giedd, J. N., & Boring, A. M. (1999). A. E. Bennett Research Award. Developmental traumatology. Part II: Brain development. *Biological Psychiatry*, *45*, 1271–1284.

Depue, R. A., & Lenzenweger, M. F. (2001). A neurobiological dimensional model. In W. J. Livesley (Ed.), *Handbook of personality disorders: Theory*, *research*, *and treatment* (pp. 136–176). New York: Guilford Press.

Donegan, N. H., Sanislow, C. A., Blumberg, H. P., Fullbright, R. K., Lacadie, C., Skudlarski, P., et al. (2003). Amygdala hyperreactivity in borderline personality disorder: Implications for emotional dysregulation. *Biological Psychiatry*, *11*, 1284–1293.

Dougherty, D. D., Rauch, S. L., Deckersbach, T., Marci, C., Loh, R., Shin, L. M., et al. (2004). Ventromedial prefrontal cortex and amygdala dysfunction during an anger induction positron emission tomography study in patients with major depressive disorder with anger attacks. *Archives of General Psychiatry*, *61*, 795–804.

Driessen, M., Herrmann, J., Stahl, K., Zwaan, M., Meier, S., & Hill, A. (2000). Magnetic resonance imaging volumes of the hippocampus and the amygdala in women with borderline personality disorder and early traumatization. *Archives of General Psychiatry*, *57*, 1115–1122.

Dubo, E. D., Zanarini, M. C., & Lewis, R. E. (1997). Childhood antecedents of self-destructiveness in borderline personality disorder. *Canadian Journal of Psychiatry*, *42*, 63–69.

Dulit, R. A., Fyer, M. R., Leon, A. C., Brodsky, B. S., & Frances, A. J. (1994). Clinical correlates of self-mutilation in borderline personality disorder. *American Journal of Psychiatry*, *151*, 1305–1311.

Dunn, A. J. (1988). Stress-related activation of cerebral dopaminergic systems. *Annals of the New York Academy of Sciences*, *537*, 188–205.

Francis, D. D., Diorio, J., Plotsky, P. M., & Meaney, M. J. (2002). Environmental enrichment reverses the effects of maternal separation on stress reactivity. *The Journal of Neuroscience*, *22*, 7840–7843.

Gardner, D. L., & Cowdry, R. W. (1985). Suicidal and parasuicidal behavior in borderline personality disorder. *Psychiatric Clinics of North America*, *8*, 389–403.

Gardner, D. L., Lucas, P. B., & Cowdry, R. W. (1990). CSF metabolites in borderline personality disorder compared with normal controls. *Biological Psychiatry*, *28*, 247–254.

Garnet, K. E., Levy, K. N., Mattanah, J. J., Edell, W. S., & McGlashan, T. H. (1994). Borderline personality disorder in adolescents: Ubiquitous or specific? *American Journal of Psychiatry*, *151*, 1380–1382.

Gerra, G., Zaimovic, A., Avanzini, P., Chittolini, B., Guicastro, G., & Caccavari, R. (1997). Neurotransmitter–neuroendocrine responses to experimentally induced aggression in humans: Influence of personality variable. *Psychiatric Research*, *66*, 33–43.

Giedd, J. N., Blumenthal, J., Jeffries, N. O., Castellanos, F. X., Lui, H., & Zijdenbos, A. (1999). Brain development during childhood and adolescence: A longitudinal MRI study. *Natural Neuroscience*, *2*, 861–863.

Gould, M. S., Velting, D., Kleinman, M., Lucas, C., Graham Thomas, J., & Chung, M. (2004). Teenagers' attitudes about coping strategies and help-seeking behavior for suicidality. *Journal of American Academy of Child and Adolescent Psychiatry*, *43*, 1124–1133.

Green, A. H. (1978). Self-destructive behavior in battered children. *American Journal of Psychiatry*, *135*, 579–582.

Greenberg, M. T., Speltz, M. L., & DeKlyen, M. (1993). The role of attachment in the early development of disruptive behavior problems. *Development and Psychopathology*, *5*, 191–213.

Grilo, C. M., Becker, D. F., Fehon, D. C., Walker, M. L., Edell, W. S., & McGlashan, T. H. (1996). Gender differences in personality disorders in psychiatrically hospitalized adolescents. *American Journal of Psychiatry*, *153*, 1089–1091.

Gross, C., Zhuang, X., Stark, K., Ramboz, S., Oosting, R., Kirby, L., et al. (2002). Serotonin 1A receptor acts during development to establish normal anxiety-like behavior in the adult. *Nature*, *416*, 396–400.

Grube, M. (2004). Which types of aggressive behavior are associated with suicidal and self-injurious behavior at the time of admission? *Psychopathology*, *37*, 41–49.

Gunnar, M. R. (2003). Integrating neuroscience and psychological approaches in the study of early experiences. *Annals of New York Academy of Sciences*, *1008*, 238–247.

Halasz, J., Liposits, Z., Meelis, W., Kruk, M. R., & Haller, J. (2002). Hypothalamic attack area-mediated activation of the forebrain in aggression. *NeuroReport*, *13*, 1267–1270.

Halperin, J. M., Sharma, V., Siever, L. J., Schwartz, S. T., Matier, K., Wornell, G., et al. (1994). Serotonergic function in aggressive and nonaggressive boys with

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

attention deficit hyperactivity disorder. *American Journal of Psychiatry*, *151*, 243–248.

Handlesman, L., Holoway, K., Kahn, R. S., Sturiano, C., Rinaldi, P. J., Bernstein, D. P., et al. (1996). Hostility is associated with a low prolactin response to *meta*-chlorophenylpiperazine in abstinent alcoholics. *Alcohol: Clinical Experimental Research*, *5*, 824–829.

Harlow, H. F., & Harlow, M. K. (1971). Psychopathology in monkeys. In H. D. Kimmel (Eds.), *Experimental psychopathology: Recent research and theory* (pp. 203–229). San Diego, CA: Academic Press.

Heim, C., Newport, D. J., Bonsall, R., Miller, A. H., & Nemeroff, C. B. (2001). Altered pituitary–adrenal axis responses to provocative challenge tests in adult survivors of childhood abuse. *American Journal of Psychiatry*, *158*, 575–581.

Herpertz, S. C., Dietrich, T. M., Wenning, B., Krings, T., Erberich, S. G., Willmes, K., et al. (2001). Evidence of abnormal amygdala functioning in borderline personality disorder: A functional MRI study. *Biological Psychiatry*, *50*, 292–298.

Higley, J. D., Mehlman, P. T., Taub, D. M., Higley, S. B., Suomi, S. J., Vickers, J. H., et al. (1992). Cerebrospinal fluid monoamine and adrenal correlates of aggression in free-ranging rhesus monkeys. *Archives of General Psychiatry*, *49*, 436–441.

Huttenlocher, P. R. (1984). Synapse elimination and plasticity in developing human cerebral cortex. *American Journal of Mental Deficiency*, *88*, 488–496.

Johnson, H., Halit, H., Grice, S., & Karmiloff–Smith, A. (2002). Neuroimaging of typical and atypical development: A perspective from multiple levels of analysis. *Development and Psychopathology*, *14*, 521–536.

Johnson, J. G., Cohen, P., Skodol, A. E., Oldham, J. M., Kasen, S., & Brook, J. S. (1999). Personality disorders in adolescence and risk of major mental disorders and suicidality during adulthood. From a community based longitudinal study of 717 youths. *Archives of General Psychiatry*, *56*, 805–811.

Karkanias, G. B., Li, C. S., & Etgen, A. M. (1997). Estradiol reduction of alpha-2-adrenoceptor binding in female rat cortex is correlated with decreases in alpha2A/D-adrenoceptor messenger RNA. *Neuroscience*, *81*, 593–597.

Kasen, S., Cohen, P., Skodol, A. E., Johnson, J. G., Smailes, E., & Brook, J. S. (2001). Childhood depression and adult personality disorder. Alternative pathways of continuity. *Archives of General Psychiatry*, *58*, 231–236.

Kaufman, J., Birmaher, B., Perel, J., Dahl, R. E., Moreci, P., Nelson, B., et al. (1997). The corticotropin-releasing hormone challenge in depressed abused, depressed non-abused, and normal control children. *Biological Psychiatry*, *42*, 669–679.

Kaufman, J., & Charney, D. S. (1999). Neurobiological correlates of child abuse. *Biological Psychiatry*, *45*, 1235–1236.

Kernberg, P. F. (1982). Update of borderline disorders in children. *Psychiatric Hospital*, *13*, 137–141.

Kingston, L., & Prior, M. (1995). The development of patterns of stable, transient, and school-age aggressive behavior in young children. *Journal of American Academy of Child and Adolescent Psychiatry*, *34*, 348–358.

Kraemer, G. W., Schmidt, D. E., & Ebert, M. H. (1997). The behavioral neurobiology of self-injurious behavior in rhesus monkeys: Current concepts and relations to impulsive behavior in humans. In D. M. Stoff & M. J. John (Eds.), *The neurobiology of suicide: From the bench to the clinic. Annals of the New York Academy of Sciences* (vol. 836, pp.12–38). New York: New York Academy of Sciences.

Kruk, M. R., Halasz, J., Meelis, W., & Haller, J. (2004). Fast positive feedback between the adrenocortical stress response and a brain mechanism involved in aggressive behavior. *Behavioral Neuroscience*, *118*, 1062–1070.

Ladd, C. O., Huot, R. L., Thrivikraman, K. V., Nemeroff, C. B., Meaney, M. J., & Plotsky, P. M. (2000). Long-term behavioral and neuroendocrine adaptations to adverse early experience. *Progress in Brain Research*, *122*, 81–103.

Lee, R. J., Geracioti, T. D., Kasckow, J. W., & Coccaro, E. F. (2005). Childhood trauma and personality disorder: Positive correlation with adult cerebrospinal fluid corticotropin releasing factor concentrations. *American Journal of Psychiatry*, *162*, 995–997.

Lenzenweger, M. F., Clarkin, J. F., Fertuck, E. A., & Kernberg, O. F. (2004). Executive neurocognitive functioning and neurobehavioral systems indicators in borderline personality disorder: A preliminary study. *Journal of Personality Disorders*, *18*, 421–438.

Lenzenweger, M. F., Johnson, M. D., & Willett, J. B. (2004). Individual growth curve analysis illuminates stability and change in personality disorder features: The longitudinal study of personality disorders. *Archives of General Psychiatry*, *61*, 1015–1024.

Lenzenweger, M. F., Loranger, A. W., Korfine, L., & Neff, C. (1997). Detecting personality disorders in a nonclinical population. Application of a 2-stage procedure for case identification. *Archives of General Psychiatry*, *54*, 345–351.

Lewis, D. A., Cruz, D., Eggan, S., & Erickson, S. (2004). Postnatal development of prefrontal inhibitory circuits and the pathophysiology of cognitive dysfunction in schizophrenia. *Annals of the New York Academy of Science*, *1021*, 64–76.

Leyton, M., Okazawa, H., Diksic, M., Paris, J., Rosa, P., & Mzengeza, S. (2001). Brain Regional alpha-[^{11}C]methyl-L-tryptophan trapping in impulsive subjects with borderline personality disorder. *American Journal of Psychiatry*, *158*, 775–782.

Lieb, K., Zanarini, M. C., Schmahl, C., Linehan, M. M., & Bohus, M. (2004). Borderline personality disorder, *Lancet*, *364*, 453–461.

Lincoln, A. J., Bloom, D., Katz, M., & Boksenbaum, N. (1998). Neuropsychological and neurophysiological indices of auditory processing impairment in children with multiple complex developmental disorder. *Journal of American Academy of Child and Adolescent Psychiatry*, *37*, 100–112.

Links, P. S., Heslegrave, R., & Vanreekum, R. (1998). Prospective follow-up study of borderline personality disorder: Prognosis, prediction of outcome, and axis II comorbidity. *Canadian Journal of Psychiatry*, *43*, 365–370.

Linnoila, V. M., & Virkkunen, M. (1992). Aggression, suicidality, and serotonin. *Journal of Clinical Psychiatry*, *53*, 46–51.

Lipschitz, D. S., Winegar, R. K., Nicolaou, A., Hartnick, E., Wolfson, M., & Southwick, S. M. (1999). Perceived abuse and neglect as risk factors for suicidal behavior in adolescent inpatients. *Journal of Nervous and Mental Disease*, *187*, 32–39.

Liu, D., Caldji, C., Sharma, S., Plotsky, P. M., & Meaney, M. J. (2000). Influence of neonatal rearing conditions

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

on stress-induced adrenocorticotropin responses and norepinephrine release in the hypothalamix paraventicular nucleas. *Journal of Neuroendocrinology*, *12*, 5–12.

Loeber, R., & Hay, D. (1997). Key issues in the development of aggression and violence form childhood to early adulthood. *Annual Review of Psychology*, *48*, 371–410.

Lofgren, D. P., Bemporad, J., King, J., Lindem, K., & O'Driscoll, G. (1991). A prospective follow-up study of so-called borderline children. *American Journal of Psychiatry*, *48*, 1541–1547.

Lopez, N. L., Vazquez, D. M., & Olson, S. L. (2004). An integrative approach to the neurophysiological substrates of social withdrawal and aggression. *Development and Psychopathology*, *16*, 69–93.

Lopez–Ibor, J. J., Saiz–Ruiz, J., & Perez de los Cobos, J. C. (1985). Biological correlates of suicide and aggressivity in major depressions (with melancholia). *Neuropsychobiology*, *14*, 67–74.

Low, G., Jones, D., MacLeod, A., Power, M., & Duggan, C. (2000). Childhood trauma, dissociation, and self-harming behaviour: A pilot study. *British Journal of Medical Psychology*, *73*, 269–278.

Luna, B., & Sweeney, J. A. (2004). The emergence of collaborative brain function: fMRI studies of the development of response inhibition. *Annals of the New York Academy of Sciences*, *1021*, 296–309.

Lyoo, I. K., Han, M. H., & Cho, D. Y. (1998). A brain MRI study in subjects with borderline personality disorder. *Journal of Affective Disorders*, *50*, 235–243.

Mann, J. J., Brent, D. A., & Arango, V. (2001). The neurobiology and genetics of suicide and attempted suicide: A focus on the serotonergic system. *Neuropsychopharmacology*, *24*, 467–477.

Mann, J. J., Waternaux, C., Haas, G. L., & Malone, K. M. (1999). Toward a clinical model of suicidal behavior in psychiatric patients. *American Journal of Psychiatry*, *156*, 181–189.

Matsuzawa, J., Matsui, M., Konishi, T., Noguchi, K., Gur, R. C., Bilker, W., et al. (2001). Age-related volumetric changes of brain gray and white matter in healthy infants and children. *Cerebral Cortex*, *11*, 335–342.

McBride, P. A., Tierney, H., DeMeo, M., Chen, J. S., & Mann, J. J. (1990). Effects of age and gender on CNS serotonergic responsivity in normal adults. *Biological Psychiatry*, *27*, 1143–1155.

McBurnett, K., Lahey, B. B., Rathouz, P. J., & Loeber, R. (2000). Low salivary cortisol and persistent aggression in boys referred for disruptive behavior. *Archives of General Psychiatry*, *57*, 38–43.

Meaney, M. J., Diorio, J., Francis, D., Widdowson, J., LaPlante, P., Caldji, C., et al. (1996). Early environmental regulation of forebrain glucocorticoid receptor gene expression: Implications for adrenocortical responses to stress. *Developmental Neuroscience*, *18*, 49–72.

Moffitt, T. E. (1993). Adolescence-limited and life-course-persistent antisocial behavior: A developmental taxonomy. *Psychological Review*, *100*, 674–701.

Molcho, A., Stanley, B., & Stanley, M. (1991). Biological studies and markers in suicide and attempted suicide. *International Clinical Psychopharmacology*, *6*, 77–92.

Moss, H. B., Yao, J. K., & Panzak, G. L. (1990). Serotonergic responsivity and behavioral dimensions in antisocial personality disorder with substance abuse. *Biological Psychiatry*, *28*, 325–338.

Mueller, R. A., Rothermel, R. D., Behen, M. E., Muzik, O., Chakraborty, P. K., & Chugani, H. T. (1997). Plasticity of motor organization in children and adults. *NeuroReport*, *8*, 3103–3108.

New, A. S., Buchsbaum, M. S., Hazlett, E. A., Goodman, M., Koenigsberg, H. W., Lo, J., et al. (2004). Fluoxetine increases relative metabolic rate in prefrontal cortex in impulsive aggression. *Psychopharmacology (Berlin)*, *176*, 451–458.

New, A. S., Trestman, R. l., Mitropoulou, V., Benishay, D. S., Coccaro, E., Silverman, J., et al. (1997). Serotonergic function and self-injurious behavior in personality disorder patients. *Psychiatry Research*, *69*, 17–26.

Nigg, J. T. (2003). Response inhibition and disruptive behaviors: Toward a multiprocess conception of etiological heterogeneity for ADHD combined type and conduct disorder early-onset type. *Annals of the New York Academy of Sciences*, *1008*, 149–159.

Nordstrom, P., & Åsberg, M. (1992). Suicide risk and serotonin. *International Clinical Psychopharmacology*, *6*, 12–21.

Novak, M. A. (2003). Self-injurious behavior in rhesus monkeys: New insights into its etiology, physiology, and treatment. *American Journal of Primatology*, *59*, 3–19.

O'Keane, V., Loloney, E., O'Neil, H., O'Connor, A., Smith, C., & Dinam, T. B. (1992). Blunted prolactin responses to d-fenfluramine challenge I sociopathy: Evidence for subsensitivity of central serotonergic function. *British Journal of Psychiatry*, *160*, 643–646.

Ogawa, J. R., Sroufe, L. A., Weinfeld, N. S., Carlson, E. A., & Egeland, B. (1997). Development and the fragmented self: Longitudinal study of dissociative symptomatology in a nonclinical sample. *Development and Psychopathology*, *9*, 855–879.

Pandey, G. N., Pandey, S. C., Dwivedi, Y., Sharma, R. P., Janicak, P. G., & Davis, J. M. (1995). Platelet serotonin-2A receptors: A potential biological marker for suicidal behavior. *American Journal of Psychiatry*, *152*, 850–855.

Paris, J., Zelkowitz, P., Gudzer, J., Joseph, S., & Feldman, R. (1999). Neuropsychological factors associated with borderline pathology in children. *Journal of the American Academy of Child and Adolescent Psychiatry*, *38*, 770–774.

Pattison, M. E., & Kahan, J. (1983). The deliberate self-harm syndrome. *American Journal of Psychiatry*, *140*, 867–872.

Patton, J. H., Stanford, M. S., & Barratt, E. S. (1995). Factor structure of the Barratt impulsiveness scale. *Journal of Clinical Psychology*, *51*, 768–774.

Pavic, L., Gregurek, R., Petrovic, R., Petrovic, D., Varda, R., Vukusic, H., et al. (2003). Alterations in brain activation in posttraumatic stress disorder patients with severe hyperarousal symptoms and impulsive aggressiveness. *European Archives of Psychiatry and Clinical Neuroscience*, *253*, 80–83.

Pereira, M. E., & Fairbanks, L. A. (1993). What are juvenile primates all about? In M. E. Pereira & L. A. Fairbanks (Eds.), *Juvenile primates* (pp. 3–12, 367–415). New York: Oxford University Press.

Petitto, J. M., Quade, D., & Evans, D. L. (1992). Relationship of object loss during development to hypothalamic–pituitary–adrenal axis function during major affective illness later in life. *Psychiatry Research*, *44*, 227–236.

Pine, D. S., Wasserman, G., Coplan, J. D., Fried, J. A., Huang, Y., Kassir, S., et al. (1996). Platelet 5-HT2A

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

characteristics and rearing factors in boys at risk for delinquency: A preliminary report. *American Journal of Psychiatry*, *153*, 538–544.

Pine, F. (1986). On the development of the "borderline-child-to-be." *American Journal of Orthopsychiatry*, *56*, 450–457.

Plotsky, P. M., & Meaney, M. J. (1993). Early postnatal experience alters hypothalamic corticotropin-releasing factor (CRF) mRNA, median eminence CRF content and stress-induced release in adult rats. *Brain Research. Molecular Brain Research*, *18*, 195–200.

Rakic, P., Bourgeois, J. P., & Goldman–Rakic, P. S. (1994). Synaptic development of the cerebral cortex: Implications for learning, memory, and mental illness. In J. Van Pelt, M. A. Corner, H. B. M. Uylings, & F. H. Lopes da Silva (Eds.), *Progress in brain research, The self-organizing brain: From growth cones to functional networks* (pp. 227–243). Amsterdam: Elsevier.

Rhoades, R. W., Bennett–Clarke, C. A., Chiaia, N. L., White, F. A., McDonald, G. J., Haring, J. H., et al. (1990). Development and lesion induced reorganization of the cortical representation of the rat's body surface as revealed by immunocytochemistry for serotonin. *Journal of Comprehensive Neurology*, *293*, 190–207.

Rinnes, T., De Kloet, E. R., Wouters, L., Goekoop, J. G., DeRijk, R. H., & Van den Brink, W. (2002). Hyperresponsiveness of hypothalamic–pituitary–adrenal axis to combined dexamethasone/corticotropin-releasing hormone challenge in female borderline personality disorder subjects with a history of sustained child abuse. *Biological Psychiatry*, *52*, 1102–1112.

Rusch, N., Tebartz van Elst, L., Ludaescher, P., Wilke, M., Huppertz, H. J., Thiel, T., et al. (2003). A voxel-based morphometric MRI study in female patients with borderline personality disorder. *Neruoimage*, *20*, 385–392.

Rutter, M., Graham, P., Chadwick, O. F. D., & Yule, W. (1976). Adolescent turmoil: Fact or fiction? *Journal of Child Psychology and Psychiatry*, *16*, 35–56.

Rutter, M., Petersen, A. C., Compas, B. E., Brooks–Gunn, J., Stemmler, M., Ey, S., & Grant, K. E. (1993). Depression in adolescence. *American Psychologist*, *48*, 155–168.

Rutter, M., & Sroufe, L. A. (2000). Developmental psychopathology: Concepts and challenges. *Developmental Psychopathology*, *12*, 265–296.

Schaffer, C. B., Carroll, J., & Ambramowitz, S. I. (1982). Self-mutilation and the borderline personality. *Journal of Nervous and Mental Disease*, *170*, 468–473.

Schmahl, C. G., McGlashan, T. H., & Bremner, J. D. (2002). Neurobiological correlates of borderline personality disorder. *Psychopharmacology Bulletin*, *36*, 69–87.

Shearer, S. L. (1994). Phenomenology of self-injury among inpatient women with borderline personality disorder. *Journal of Nervous and Mental Disease*, *182*, 524–526.

Sibille, E., Pavlides, C., Benke, D., & Toth, M. (2000). Genetic inactivation of the Serotonin(1A) receptor in mice results in downregulation of major GABA(A) receptor alpha subunits, reduction of GABA(A) receptor binding, and benzodiazepine-resistant anxiety. *Journal of Neuroscience*, *20*, 2758–2765.

Siever, L. J., Buchsbaum, M. S., New, A. S., Spiegel–Cohen, J., Wei, T., Hazlett, E. A., et al. (1999). *d,l*-Fenfluramine response in impulsive personality disorder assessed with [^{18}F]fluorodeoxyglucose positron emission tomography. *Neuropsychopharmacology*, *20*, 413–423.

Siklich, L., Hickock, J. M., & Todd, R. D. (1990). 5-HT1A receptors control neurite branching during development. *Development and Brain Research*, *56*, 269–274.

Simeon, D., & Favazza, A. R. (2001). Self-injurious behaviors: Phenomenology and assessment. In D. Simeon & E. Hollander (Eds.), *Self-injurious behaviors: Assessment and treatment* (pp. 1–28). Washington, DC: American Psychiatric Press.

Simeon, D., Stanley, B., Frances, A., Mann, J. J., Winchel, R., & Stanley, M. (1992). Self-mutilation in personality disorders: Psychological and biological correlates. *American Journal of Psychiatry*, *149*, 221–226.

Skodol, A. E., Gunderson, J. G., Pfohl, B., Widiger, T. A., Livesley, W. J., & Siever, L. J. (2002). The borderline diagnosis I: Psychopathology, comorbidity, and personality structure. *Biological Psychiatry*, *51*, 936–950.

Skodol, A. E., Stout, R. L., McGlashan, T. H., Grilo, C. M., Gunderson, J. G., Shea, M. T., et al. (1999). Co-occurrence of mood and personality disorders: A report from the collaborative longitudinal personality disorders study. *Depression and Anxiety*, *10*, 175–182.

Soloff, P. H., Lynch, K. G., Kelly, T. M., Malone, K. M., & Mann, J. J. (2000). Characteristics of suicide attempts of patients with major depressive episode and borderline personality disorder: A comparative study. *American Journal of Psychiatry*, *15*, 601–608.

Soloff, P. H., Lynch, K. G., & Moss, H. B. (2000). Serotonin, impulsivity, and alcohol use disorders in the older adolescent: A psychobiological study. *Alcoholism: Clinical and Experimental Research*, *24*, 1609–1619.

Spear, L. P. (2000). The adolescent brain and age-related behavioral manifestations. *Neuroscience and Biobehavioral Reviews*, *24*, 417–463.

Sroufe, L. A. (1990). Considering normal and abnormal together: The essence of developmental psychopathology. *Development and Psychopathology*, *2*, 335–347.

Sroufe, L. A., Egeland, B., & Carlson, E. (1999). One social world: The integrated development of parent–child and peer relationships. In W. A. Collins, & B. Laursen (Eds.), *Relationships as developmental context*: *The 30th Minnesota Symposium on Child Psychology*. Hillsdale, NJ: Erlbaum.

Stein, D., Trestman, R. L., & Mitropoulou, V. (1996). Impulsivity and serotonergic function in compulsive personality disorder. *Journal of Neuropsychiatry Clinical Neuroscience*, *8*, 393–398.

Steinberg, L. R., Dahl, D., Keating, D., & Masten, A. S. (2004). The study of developmental psychopathology in adolescence: Integrating affective neuroscience with the study of context. In D. Cicchetti & D. Cohen (Eds.), *Handbook of developmental psychopathology* (2nd ed.). New York: Wiley.

Stevenson, J., Meares, R., & Comerford, A. (2003). Diminished impulsivity in older patients with borderline personality disorder. *American Journal of Psychiatry*, *160*, 165–166.

Suominen, K. H., Isometsa, E. T., Henriksson, M. M., Ostamo, A. I., & Lonnqvist, J. K. (2000). Suicide attempts and personality disorder. *Acta Psychiatrica Scandinavica*, *102*, 118–125.

Swartz, M., Blazer, D., George, L., & Winfield, I. (1990). Estimating the prevalence of borderline personality disorder in the community. *Journal of Personality Disorders*, *4*, 257–272.

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press

Tebartz van Elst, L., Hesslinger, B., Thiel, T., Geiger, E., Haegele, K., Lemieux, L., et al. (2003). Frontolimbic brain abnormalities in patients with borderline personality disorder: A volumetric magnetic resonance imaging study. *Biological Psychiatry*, *54*, 163–167.

Torgersen, S., Kringlen, E., & Cramer, V. (2001). The prevalence of personality disorders in a community sample. *Archives of General Psychiatry*, *58*, 590–596.

Towbin, K. E., Dykens, E. M., Pearson, G. S., & Cohen, D. J. (1993). Conceptualizing "borderline syndrome of childhood" and "childhood schizophrenia" as a developmental disorder. *Journal of American Academy of Child and Adolescent Psychiatry*, *32*, 775–782.

Veenema, A. H., Meijer, O. C., de Kloet, E. R., & Koolhaas, J. M. (2003). Genetic selection for coping style predicts stressor susceptibility. *Journal of Neuroendocrinology*, *15*, 256–267.

Verney, C., Berger, B., Adrien, J., Vigny, A., & Gay, M. (1982). Development of the dopaminergic innervation of the rat cerebral cortex. A light microscopic immunocytochemical study using anti-tyrosine hydroxylase antibodies. *Developmental Brain Research*, *5*, 41–52.

Vythilingam, M., Heim, C., Newport, J., Miller, A. H., Anderson, E., Bronen, R., et al. (2002). Childhood trauma associated with smaller hippocampal volume in women with major depression. *American Journal of Psychiatry*, *159*, 2072–2080.

Wiederman, M. W., Sansone, R. A., & Sansone, L. A. (1999). Bodily self-harm and its relationship to childhood abuse among women in a primary care setting. *Violence Against Women*, *5*, 155–163.

Windle, R. C., & Windle, M. (1995). Longitudinal patterns of physical aggression: Associations with adult social, psychiatric, and personality functioning and testosterone levels. *Development and Psychopathology*, *7*, 563–585.

Yates, T. (2004). The developmental psychopathology of self-injurious behavior: Compensatory regulation in posttraumatic adaptation. *Clinical Psychology Review*, *24*, 35–74.

Yehuda, R., Halligan, S., & Grossman, R. (2001). Childhood trauma and risk for PTSD: Relationship to intergenerational effects of trauma, parental PTSD and cortisol excretion. *Stress and Development*, *13*, 731–751.

Yen, S., Shea, M. T., Sanislow, C. A., Grilo, C. M., Skodol, A. E., & Gunderson, J. G. (2004). Borderline personality disorder criteria associated with prospectively observed suicidal behavior. *American Journal of Psychiatry*, *161*, 1296–1298.

Zanarini, M. C., Frankenburg, F. R., Vujanovic, A. A., Hennen, J., Reich, D. B., & Silk, K. R. (2004). Axis II comorbidity of borderline personality disorder: Description of 6-year course and prediction time-to-remission. *Acta Psychiatrica Scandinavica*, *1*, 1–5.

Zweig–Frank, H., & Paris, J. (2002). Predictors of outcome in a 27-year follow-up of patients with borderline personality disorder. *Comprehensive Psychiatry*, *43*, 103–107.

https://doi.org/10.1017/S0954579405050546 Published online by Cambridge University Press