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Multifinality in the development of personality disorders: A Biology × Sex × Environment interaction model of antisocial and borderline traits

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Abstract

Although antisocial personality disorder (ASPD) is more common among males and borderline PD (BPD) is more common among females, some authors have suggested that the two disorders reflect multifinal outcomes of a single etiology. This assertion is based on several overlapping symptoms and features, including trait impulsivity, emotional lability, high rates of depression and suicide, and a high likelihood of childhood abuse and/or neglect. Furthermore, rates of ASPD are elevated in the first degree relatives of those with BPD, and concurrent comorbidity rates for the two disorders are high. In this article, we present a common model of antisocial and borderline personality development. We begin by reviewing issues and problems with diagnosing and studying PDs in children and adolescents. Next, we discuss dopaminergic and serotonergic mechanisms of trait impulsivity as predisposing vulnerabilities to ASPD and BPD. Finally, we extend shared risk models for ASPD and BPD by specifying genetic loci that may confer differential vulnerability to impulsive aggression and mood dysregulation among males and impulsive self-injury and mood dysregulation among females. Although the precise mechanisms of these sex-moderated genetic vulnerabilities remain poorly understood, they appear to interact with environmental risk factors including adverse rearing environments to potentiate the development of ASPD and BPD.

Antisocial personality disorder (ASPD) and borderline personality disorder (BPD) are among the most costly public health concerns confronting the US criminal justice and healthcare systems. Although ASPD affects only 3–6% of adult males and 1% of adult females (American Psychiatric Association, 2000; Kessler et al., 1994; Robins, Tipp, & Przybeck, 1991), many if not most property offenses and violent crimes are committed by individuals with the disorder. Indeed, lifetime prevalence rates in incarcerated samples approach 50% (Teplin, 1994). Thus, roughly 1 million of the 2.3 million incarcerated individuals in the United States have ASPD. With the cost of imprisoning one person per year at about $25,000, ASPD accounts for $25 billion per year in corrections expenditures alone, which is about $200 for each US taxpayer (Bureau of Justice Statistics, 2007). This of course does not include the costs associated with crimes that led to incarceration.

BPD and its associated features are also quite costly (Bender et al., 2001). According to most estimates, the prevalence rate of BPD is about 2–3% among adult females and 1% among adult males (Swartz, Blazer, George, & Winfield, 1990), although some recent surveys yield slightly higher numbers (Grant et al., 2008). Despite a relatively moderate prevalence rate, however, BPD is the

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most common Axis II disorder observed in inpatient psychiatric settings (Trull, Stepp, & Durrett, 2003; Skodol et al., 2002). Among adolescents with borderline traits, intentional self-injury (a cardinal feature of BPD) costs the US healthcare system $150 million per year in inpatient hospitalization costs alone (Olfson et al., 2005). Moreover, adolescents and adults who engage in self-injury are at high risk for eventual suicide, with an 8–10% lifetime completion rate (e.g., American Psychiatric Association [APA], 2000; Berman, Jobes, & Silverman, 2006).

Although these statistics only partially capture the extent of the personal and societal costs of antisocial personality disorder (ASPD) and BPD, they demonstrate the potential importance of furthering our understanding of both disorders in efforts to mitigate risk. As we outline in later sections, ASPD and BPD are disorders for which biological vulnerabilities interact with potentiating environments to produce debilitating and enduring personality disturbance. Understanding the precise nature of these vulnerabilities and risk factors may provide opportunities for early interventions that alter developmental trajectories toward severe psychopathology. The behavior patterns characteristic of ASPD and BPD are very difficult to treat once canalized (see, e.g., Burke, 2007; Linehan, 1993). Thus, earlier identification of vulnerability may be necessary to prevent the significant costs of ASPD and BPD to individuals, their family members, and society (Crowell, Beauchaine, & Lenzenwger, 2008; Crowell, Beauchaine, & Linehan, 2009).

In this article, we present a common developmental model of antisocial and borderline personality development that captures important biological vulnerabilities and environmental risk factors for both disorders. Although at first glance it might seem odd that we present a single model of two disorders with different symptoms and sex distributions, we are not the first authors to do so. For example, Paris (1997) reviewed a number of common etiological factors and overlapping features of ASPD and BPD, concluding that the two disorders reflect the same underlying trait with different behavioral expressions for males versus females.

Paris' (1997) contention that ASPD and BPD share a common etiology was based on several observations. First, both disorders are characterized by significant risk for depression and suicide. As noted above, 8–10% of those with BPD eventually commit suicide (APA, 2000). Those with ASPD are also at much higher suicide risk than the general population, with a completion rate of approximately 4–5% (Dyck, Bland, Newman, & Orn, 1988; Robins, 1966). Second, ASPD and BPD are both characterized by impulsivity, a trait that is about 80% heritable (e.g., Krueger et al., 2002), conferring general rather than specific risk for psychopathology (see Beauchaine & Neuhaus, 2008; Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008). Finally, ASPD and BPD have similar prevalence rates in the community, and nearly identical sex distributions of about 3–4:1 favoring males for ASPD and females for BPD.[1] This set of observations led Paris to suggest that ASPD and BPD are sex-moderated manifestations of a single underlying pathology (see also Lyons-Ruth, 2008).

In addition to the observations offered by Paris (1997), other findings also point toward a shared etiology for both disorders. For example, ASPD and BPD are highly comorbid in clinical samples (e.g., Becker, Grilo, Edaell, & McGlashan, 2000). Furthermore, affected individuals often come from the same families (Goldman, D'Angelo, & DeMaso, 1993), and increased prevalence of ASPD is observed in the first-degree relatives of those with BPD (Schulz et al., 1989). In addition, disturbed parent–child relationships, disrupted attachment, family discord, and traumatic experiences including abuse are common in the life histories of those with ASPD and those with BPD (e.g., Lyons-Ruth, 2008; Norden, Klein, Donaldson, Pepper, & Klein, 1995).

All of these findings are derived from symptom patterns and life histories of individuals with ASPD, individuals with BPD, and their family members. However, in the last decade much more has been learned about the molecular genetics and neurobiology of ASPD, BPD, and related traits, providing for a more compre-

1. In recent epidemiological studies of BPD, Grant et al. (2008) and Lenzenweger, Lane, Loranger, and Kessler (2007) reported roughly equal prevalence rates for males and females in large community samples. Consistent with previous research, however, the mental and physical health burdens of BPD were considerably higher among women. Furthermore, clinical samples continue to favor females.

hensive account of common vulnerabilities and risk factors for both disorders. Our primary objective in writing this article is to provide an updated model of shared etiology for ASPD and BPD that accounts for both biological vulnerabilities and environmental risk. Taken together, literature addressing the development of these PDs supports the following set of conjectures, which we present here as an organizing framework for the remainder of this article:

1. Both ASPD and BPD are disorders for which trait impulsivity is the principal predisposing vulnerability.
2. Trait impulsivity derives primarily from heritable compromises in central dopaminergic and serotonergic function.
3. For both disorders, impulsivity is potentiated by high risk family environments in which emotional lability is shaped and maintained by operant reinforcement contingencies.
4. Over time, these reinforcement contingencies result in enduring patterns of emotion dysregulation, leading to ASPD and/or BPD in vulnerable individuals.
5. Sex effects moderate the behavioral expression of Biology × Environment interactions to produce ASPD disproportionately in males and BPD disproportionately in females.

In the sections to follow, we present a common developmental model of ASPD and BPD, drawing attention to etiological commonalities across disorders. In doing so, we first discuss several issues and problems associated with classifying and studying PDs, particularly among children and adolescents. Such a discussion is necessary because nosologic and diagnostic conventions affect (a) how atypical personality development is conceptualized, (b) whether diagnoses of PDs are considered in childhood and adolescence, and (c) whether children and adolescents with antisocial and borderline traits are studied in the same way as adults with PDs. Next, we briefly describe different approaches to studying antisocial and borderline pathologies. We then discuss impulsivity as the principal vulnerability to both PDs, before turning to the molecular genetic bases of impulsive behavior. During this discussion, we highlight important Gene × Sex interactions that may confer differential vulnerability to aggression and mood dysregulation among males versus self-injury and mood dysregulation among females. Next, we outline environmental risk factors for antisocial and borderline personality development, again pointing to commonalities across disorders.

Issues and Problems in the Classification of PDs

There are a number of issues in the classification of PDs that have created considerable dissatisfaction and controversy with the current nosology (Clark, 2007; Widiger & Trull, 2007). In this section, we briefly consider these problems and their implications for PDs in youth.

Definition of PD

PDs are defined in the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (*DSM-IV*; APA, 2000) as the following: (a) an enduring pattern of experience and behavior that deviates markedly from societal expectations, which is manifested in at least two of the following domains: cognition, affect, interpersonal functioning, or impulse control; (b) the pattern is inflexible and pervasive across a broad range of situations; (c) it leads to clinically significant distress or impairment in functioning; and (d) it is stable and of long duration, and its onset can be traced back to at least adolescence or early adulthood.

Several aspects of this definition are noteworthy. First, it is not included explicitly in the criteria for individual PD; hence, it is often ignored (Johnson, First, Cohen, & Kasen, 2008). Second, as discussed below, this definition is not specific to PDs; disorders in other sections of the *DSM* also exhibit these features. Third, as will also be discussed, it makes strong assumptions about the age of onset and development of PDs that recent studies have called into question. With the exception of ASPD, which the *DSM* does not permit to be diagnosed before age 18, PDs can be diagnosed in children and adolescents. However, the *DSM* indicates that PDs are unusual in childhood and adolescence, and to rule out transient developmental disturbances, a duration of at least 1 year is required. Contrary to the *DSM* perspective, however, there is growing evidence that PDs (a) can be identified in adolescents (Westen & Chang, 2000); (b) are

generally as common in adolescents as in adults (Grilo et al., 1998); and (c) are largely similar in adolescence compared with adulthood in terms of structure (Westen, Shedler, Durrett, Glass, & Martens, 2003), concurrent validity (Levy et al., 1999), and stability (Johnson et al., 2000).

Distinction between Axis I and Axis II

DSM-III (APA, 1980) introduced a multiaxial system that distinguished PDs from other mental disorders by placing them on separate axes. In part, this was intended to force clinicians to pay greater attention to personality pathology, which is often overshadowed by acute episodes of Axis I psychopathology. This proved highly successful, as the prevalence of PD diagnoses increased dramatically after the introduction of *DSM-III* (Loranger, 1990).

However, the conceptual basis for the Axis I–Axis II distinction has always been problematic (Krueger, 2005; Livesley, 1998; Widiger, 2003). For example, many if not most Axis I disorders (e.g., schizophrenia, dysthymic disorder, obsessive–compulsive disorder, generalized social phobia, substance use disorders, anorexia nervosa, somatization disorder) meet the general criteria for PDs summarized above, with an adolescent or early adult onset, chronic course, and pervasive effects on psychological and social functioning. In addition, at least several PDs appear to have etiological influences that overlap with Axis I disorders, and can be conceptualized as lying on a spectrum that cuts across the Axis I–Axis II boundary (e.g., schizotypal PD and schizophrenia, avoidant PD, and generalized social phobia). From another perspective that will be discussed below, this reflects the significant heterotypic continuity that exists between many PDs and Axis I disorders. As a result of these problems, many investigators have argued that the Axis I–Axis II distinction, at least as currently defined, should be abandoned and PDs should be classified on the same axis as other psychiatric disorders (Clark, 2007; Livesley, 1998; Krueger, 2005).

Dimensional versus categorical classification

Perhaps the strongest criticisms of the *DSM-IV* classification of PDs concern the use of a categorical diagnostic format (Clark, 2007; Widiger & Trull, 2007). As *DSM* itself suggests, most PDs are probably the extreme end of a continuum of normally distributed personality traits. Hence, selecting a boundary between normal and pathological is somewhat arbitrary. Moreover, dichotomizing a continuous variable reduces the amount of information contained within that variable, attenuating reliability (MacCallum, Zhang, Preacher, & Rucker, 2002). Indeed, there is extensive evidence that when the *DSM* PDs are treated as continuous variables by summing criteria, increases are observed in interrater reliability (Zimmerman, 1994), agreement between patients and other informants (Riso, Klein, Anderson, Crosby Ouimette, & Lizardi, 1994), and stability over time (Durbin & Klein, 2006; Grilo et al., 2004).

Following from these and other arguments, a number of dimensional classification systems of PDs have been proposed (Shedler & Westen, 2004; Trull & Durrett, 2005; Widiger & Simonsen, 2005). One of the major approaches uses the "Big Five" taxonomy of general personality dimensions (Widiger & Trull, 2007). At least four of the Big Five dimensions (extraversion, neuroticism, agreeableness, and conscientiousness vs. impulsivity) have theoretically meaningful associations with PDs (e.g., avoidant PD is low on extraversion, borderline PD is high on neuroticism, ASPD is low on agreeableness and conscientiousness, and obsessive–compulsive PD is high on conscientiousness; O'Connor, 2005; Saulsman & Page, 2004). This approach may have limitations, in that it is better at characterizing some PDs than others (Saulsman & Page, 2004) and does not include some clinically relevant features of personality pathology, such as suicidal or self-injurious behavior and unusual perceptual experiences (Shedler & Westen, 2004). However, it underscores the close relationship between normal and abnormal personality processes. Moreover, the associations between these trait dimensions and measures of PDs in adolescents appear to be similar to those observed in adults (DeClerq & DeFruyt, 2007), suggesting that there may be substantial homotypic continuity in the traits that comprise PDs from youth through adulthood.

Diagnostic criteria

There are also a number of problems with specific PD criteria. First, the criteria are a mixture

of specific behaviors (e.g., unable to discard worn out or worthless objects), symptoms (e.g., transient paranoid ideation or severe dissociative symptoms), and traits (impulsivity or failure to plan ahead). As discussed below, this may explain some of the instability in PD diagnoses.

Second, for some disorders (e.g., paranoid PD) the criteria are all variations on a single theme, whereas for other disorders (e.g., borderline PD) the criteria cover widely disparate domains. Third, many of the criteria for specific PDs overlap with other PDs (e.g., inappropriate, intense anger or difficulty controlling anger in BPD and irritability and aggressiveness in ASPD) and with Axis I disorders (e.g., suicidal behavior in BPD and major depressive disorder), inflating estimates of comorbidity and heterotypic continuity.

Fourth, as noted above, the cutoffs are not derived empirically, and are therefore somewhat arbitrary. This is especially problematic because small changes in the criteria sets and/or cutoffs can have dramatic effects on prevalence rates (Blashfield, Blum, & Pflohl, 1992). Fifth and finally, it is unclear whether the specific criteria and cutoffs are appropriate across developmental periods. For example, although there is evidence for continuity between PDs in adolescents and adults, there also appear to be some age-related differences in their manifestations (Becker, Grilo, Edell, & McGlashan, 2001; Durrett & Westen, 2005; Westen et al., 2003).

The DSM clusters

DSM divides PDs into three clusters: Cluster A (schizoid, schizotypal, and paranoid PDs) includes disorders that are characterized by odd or eccentric behavior; Cluster B (antisocial, borderline, histrionic, and narcissistic PDs) by dramatic, emotional, or erratic behavior; and Cluster C (dependent, avoidant, and obsessive–compulsive PDs) by anxious or fearful behavior. Support for the validity of the cluster grouping is limited at best. Although some structural analyses (primarily factor analysis) have found support for the *DSM* cluster framework, many have not, and a variety of different factor structures have been obtained among adolescents as well as adults (Durrett & Westen, 2005; Sheets & Craighead, 2007). Although most PDs are correlated with the other PDs in the same cluster, many also exhibit high correlations with PDs in other clusters. This high within and across cluster overlap is consistent with the evidence regarding comorbidity and heterotypic continuity discussed below.

Assessment

An additional set of concerns involves the assessment of PDs. At present, PDs are typically assessed using either structured interviews with the patient or self-report inventories. One problem is that, unlike Axis I criteria, many of the PD criteria are formulated at a high level of abstraction (e.g., identity disturbance; lack of empathy). This leaves a great deal of room for interpretation by the respondent, and subtle variations in the wording of questions can produce very different responses. As a result, agreement between different PD interviews, different self-report inventories, and between interview and self-report measures of PDs tend to be fairly low (Clark, Livesely, & Morey, 1997; Perry, 1992). Another problem is that individuals' reports of their personality are influenced by their current mood state (and concurrent Axis I disorders; De Fruyt, Van Leeuwen, Bagby, Rolland, & Rouillon, 2006; Hirschfeld et al., 1983). This is particularly problematic for self-report measures, as interviewers can try to focus the participant on periods of euthymic mood (if any; Loranger, Lenzenweger, Garner, & Susman, 1991). An even greater problem is that some PDs, almost by definition, involve limited awareness of one's behaviors and their effects on others. Hence, assessments that rely on the patient to provide accurate information may be of questionable validity (Shedler & Westen, 2004). This is especially problematic for children and adolescents, whose insight and self-awareness may be even more limited than for adults (Westen & Chang, 2000). As a result, many investigators advocate the use of knowledgeable informants, either as a sole source or a supplementary source of data on PDs (Oltmanns & Turkheimer, 2006). Unfortunately, the level of agreement between self- and informant reports is often very low (Klonsky, Oltmanns, & Turkheimer, 2002; Riso et al., 1994), raising questions about which source to rely on or how to combine the data.

Concurrent comorbidity

Another major concern regarding PDs is the high rate of co-occurrence (or comorbidity) among them. Among those with a PD, over 50% meet criteria for multiple PDs (Fossati et al., 2000; Pfohl, Coryell, Zimmerman, & Stangl, 1986). In Zimmerman, Rothschild, and Chelminski's (2005) sample of 859 psychiatric outpatients, 35 of the pairwise odds ratios between specific PDs were 2.0 or greater, and 25 were at least 3.0. Comorbidity among PDs is even greater in community samples (Grant, Stinson, Dawson, Chou, & Ruan, 2005).

As noted above, although there are significant within-cluster associations, there are also associations between PDs in different clusters. For example, in the Zimmerman et al. (2005) study, the median within cluster odds ratios for Clusters A, B, and C were 19.2, 8.8, and 2.0, respectively, whereas the corresponding median across-cluster odds ratios were 4.0, 3.2, and 3.9. The strongest associations between specific pairs of PDs were schizoid–schizotypal, schizoid–avoidant, paranoid–borderline, antisocial–borderline, antisocial–narcissistic, and narcissistic–histrionic.

There are surprisingly few data on co-occurrence between PDs in adolescents, but the available evidence suggests that comorbidity rates may be even greater and the patterns less differentiated than in adults (Becker et al., 2000). The high rate of comorbidity among PDs in adolescents and adults reinforces concerns that the boundaries between PDs do not reflect meaningful distinctions, and it suggests that PDs may be more parsimoniously represented by a smaller number of trait dimensions (Clark, 2007) such as impulsivity and affective lability.

As mentioned earlier, PDs also exhibit significant comorbidity with Axis I disorders. For example, in both clinical (e.g., Zimmerman et al., 2005) and community (Grant, Hasin, et al., 2005) samples, 40–60% of patients with mood, anxiety, and substance use disorders meet criteria for at least one PD. Cluster A PDs exhibit particularly strong associations with psychotic disorders, consistent with evidence of a schizophrenia spectrum that includes schizotypal and paranoid PD (Kendler et al., 1993). However, there are also significant associations between Cluster A PDs and anxiety and mood disorders (Zimmerman et al., 2005). Cluster B PDs have particularly strong associations with substance use disorders, consistent with the notion of an externalizing spectrum characterized by impulsivity (Dolan-Sewell, Krueger, & Shea, 2001; Krueger, Markon, Patrick, Benning, & Kramer, 2007). However, Cluster B PDs are also associated with mood and anxiety disorders, some eating disorders such as bulimia nervosa, and some somatoform disorders such as somatization disorder (Dolan-Sewell et al., 2001; McGlashan et al., 2000; Zimmerman et al., 2005). Cluster C disorders have strong associations with anxiety and mood disorders, as well as eating and somatoform disorders (Dolan-Sewell et al., 2001; McGlashan et al., 2000; Zimmerman et al., 2005).

Stability

One of the defining characteristics of PDs is stability over time. Several recent longitudinal studies have examined the stability of PDs over periods ranging from 2 to 10 years (Durbin & Klein, 2006; Grillo et al., 2004; Johnson et al., 2000; Lenzenweger, Johnson, & Willett, 2004). These studies indicate that the stability of PDs is actually quite modest and not appreciably different from many Axis I disorders (Shea & Yen, 2003). However, the rank-order stability of PD dimensional scores is higher than PD diagnoses and comparable to the stability of general personality traits (Durbin & Klein, 2006). For example, in the Collaborative Longitudinal Study of Personality Disorders, 2-year remission rates of schizotypal, borderline, avoidant, and obsessive–compulsive PDs ranged from 50% to 61%; kappa values for the associations between baseline and 2-year follow-up diagnoses ranged from .35 to .47; and intraclass correlations between baseline and 2-year follow-up dimensional scores ranged from .53 to .67 (Grillo, Becker, Edell, & McGlashan, 2001). Importantly, the stability of PDs in adolescents appears to be comparable to that in adults (Chanen et al., 2004; Grilo et al., 2001; Johnson et al., 2000).

When PDs are examined at the level of individual criteria, most include both stable and unstable features (McGlashan et al., 2005). For example, in BPD, some impulsive and cognitive features, such as self-injury, suicide attempts, and quasi-psychotic thinking resolved relatively quickly,

whereas many affective and interpersonal features such as chronic anger, dysphoria, and emptiness/loneliness, as well as interpersonal features such as dependency and intolerance of being alone were relatively stable (Zanarini et al., 2007). Moreover, change in five-factor model personality traits predicts change in PDs, but change in PDs is not related to change in personality (Warner et al., 2004). Furthermore, impairment associated with PDs appears to be more stable than PD diagnoses themselves (Skodol et al., 2005). These data suggest that current PD criteria are a mixture of stable traits that may be associated with chronic impairment and acute symptoms that resemble Axis I psychopathology and attenuate diagnostic stability (Clark, 2007; McGlashan et al., 2005; Zanarini et al., 2007). As a result, some investigators have argued that PDs should be classified on Axis I and the personality traits that underlie PDs (and many Axis I disorders) should be classified on Axis II (Clark, 2007; Livesley, 1998).

Homotypic/heterotypic continuity

Homotypic continuity refers to the same pattern of symptoms or behaviors being manifested at different points in time. In contrast, heterotypic continuity refers to the association of one pattern of symptoms or behaviors at one point in time with a different pattern of symptoms or behaviors at a later point in time. The research on the stability of PDs and PD dimensional scores discussed above provides evidence of moderate homotypic continuity in PDs. Another approach to homotypic continuity is to examine early behavioral precursors of PDs (DeClercq & De Fruyt, 2007). The extensive literature discussed below on child externalizing problems and adult antisocial PD is an example of this. Unfortunately, data on the behavioral precursors of other PDs, including BPD, are limited.

Information on heterotypic continuity comes from longitudinal studies of the relationships of PDs with other PDs and Axis I disorders over time. Although longitudinal associations between disorders can be explained by a number of mechanisms (Klein & Riso, 1993), heterotypic continuity suggests that the same psychopathological process may be expressed in different forms at different stages of development or different stages of the course of the disorder. This raises concerns about the validity of the current nosology, as disorders that are currently held to be distinct may be better conceptualized as age- or stage-specific manifestations of the same condition (see Beauchaine et al., 2008).

There are surprisingly few data on longitudinal relationships between different PDs. This may be in part because of the reluctance to diagnose PDs in childhood and adolescence and the assumption that PDs are manifest by early adulthood, leaving a very narrow window of time to investigate longitudinal associations between PDs. However, there have been a number of studies of the longitudinal relationship between PDs and Axis I disorders (e.g., Helgeland, Kjelsberg, & Torgersen, 2005; Klein & Schwartz, 2002; Shea et al., 2004). Several studies have reported that Axis I disorders in childhood or adolescence predicted PD diagnoses or traits in adulthood (Helgeland et al., 2005; Kasen, Cohen, Skodol, Johnson, & Brook, 1999; Lewinsohn, Rohde, Seeley, & Klein, 1997; Rey, Morris-Yates, Singh, Andrews, & Stewart, 1995). For example, Kasen et al. (1999) found that disruptive behavior disorders in childhood not only predicted Cluster B PDs in young adulthood (homotypic continuity) but also Cluster A and C disorders (heterotypic continuity). In addition, childhood anxiety disorders predicted subsequent Cluster A and C disorders, and childhood depression predicted later Cluster B and C disorders.

Associations also run in the reverse direction. Using the same sample as Kasen et al. (1999), Johnson, Cohen, Skodol, et al. (1999) reported that Cluster A PDs in adolescence predicted anxiety, mood, and disruptive behavior disorders in early adulthood; Cluster B PDs in adolescence predicted adult mood, disruptive, and substance use disorders; and Cluster C PDs predicted subsequent mood and disruptive behavior disorders.

These associations underscore concerns about the conceptual coherence of the distinction between PDs and Axis I disorders, and suggest that there are broad spectra of psychopathologies that cut across the two *DSM* axes. Moreover, these associations must be viewed within a developmental perspective, as PD traits may be precursors of Axis I psychopathology, and early-onset Axis I disorders may be antecedents of subsequent PDs. An important next step will be

to determine whether there are meaningful patterns of progression from PDs to Axis I disorders and vice versa, and to explore the factors that influence the sequencing of these conditions.

Interim summary

There are a number of problems and issues in the current classification of PDs that must be considered to advance the developmental psychopathology of personality pathology. First, contrary to the *DSM* model, PDs can be identified and are common in adolescents. However, it is still unclear whether there are age-specific manifestations of PDs that require different criteria and cutoffs for different developmental periods, and relatively little is known about the childhood manifestations and precursors of most PDs.

Second, most PDs probably represent extreme ends of a continuum, rather than discrete entities; hence, measurement would be enhanced by using a dimensional rather than categorical approach. Third, the high comorbidity among PDs indicates that the current set of disorders and clusters is not optimal. It is likely that the boundaries between PDs are incorrectly drawn, and that using a relatively independent set of trait dimensions to classify personality pathology would be both more economical and informative.

Fourth, the Axis I–Axis II distinction is highly problematic, as most features assumed to characterize PDs also apply to Axis I disorders. Moreover, the high concurrent and longitudinal comorbidity between PDs and Axis I disorders, together with evidence of shared etiological factors between disorders on different axes, suggest that many PDs are better conceptualized as lying on a spectrum with Axis I disorders.

Fifth, and finally, the criteria for PDs are a mixture of symptoms and traits, contributing to lower stability than the construct of PD has traditionally implied and further blurring the distinction between Axes I and II. A greater emphasis on underlying traits would greatly increase the predictive validity of personality pathology constructs. Recent research on the psychopathology, pathogenesis, and pathophysiology of a handful of PDs, most notably ASPD and BPD, is suggesting new approaches to conceptualizing and understanding the development of personality pathology. With these caveats in mind, we now turn to specific discussion of ASPD and BPD.

Traditional Approaches to Studying Antisocial Behavior

Definitions and developmental issues

Terms such as antisocial behavior, delinquency, criminality, and conduct problems are often used interchangeably in psychological and sociological research. However, there are important distinctions among terms and constructs that must be considered before proceeding.

DSM-IV (APA, 2000) specifies three disruptive behavior disorders including attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), and conduct disorder (CD). These diagnoses are usually restricted to childhood and adolescence, although ADHD can also be diagnosed among adults. In contrast, ASPD and most other PDs are typically (though not always) diagnosed in those over age 18 (see above). However, Robins (1966) noted long ago that a diagnosis of ASPD virtually requires childhood conduct problems. In fact, adults with ASPD almost invariably traversed a developmental pathway that began early in life with the hyperactive–impulsive or combined subtype of ADHD, followed by preschool ODD, preadolescent CD, and late adolescent and adult substance use disorders (Loeber & Hay, 1997; Loeber & Keenan, 1994; Lynam, 1996, 1998). As noted above, this progression from one disorder to others along the externalizing spectrum is an example of heterotypic continuity (see Figure 1). Among children who exhibit CD, earlier age of onset is associated with especially high risk of adult ASPD (Moffitt, 1993, 2003; Ridenour et al., 2002). Any developmental theory of antisocial behavior must account for this life-long pattern of externalizing conduct.

It is also important to note that in our discussion of antisocial personality development we are not referring specifically to psychopathy, although some psychopathic individuals are likely captured by the discussion to follow. Psychopathy has a much lower prevalence rate (0.5–1%) than ASPD (see, e.g., Hare, 1993, 1996), and appears to have a unique genetic loading (Larsson, Andershed, & Lichtenstein, 2006). Although many if

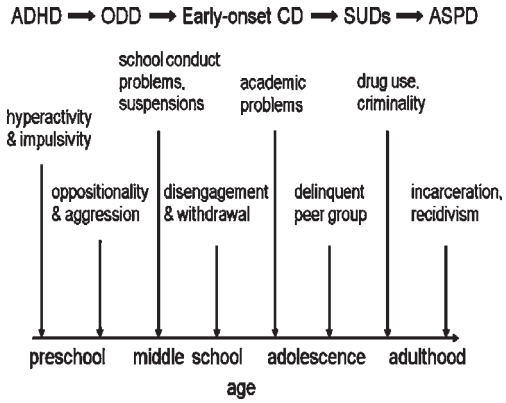

Figure 1. A heterotypically continuous developmental trajectory to antisocial personality disorder (ASPD) that begins with hyperactivity and impulsivity in preschool. ADHD, attention-deficit/hyperactivity disorder; ODD, oppositional defiant disorder; CD, conduct disorder; SUDs, substance use disorders.

not most psychopaths meet criteria for ASPD, most of those with ASPD are not psychopaths. We refer interested readers to Patrick (2005) for detailed discussion of the psychopathy construct.

Biological approaches

Antisocial, aggressive, and criminal behaviors have been studied for well over a century. During this time, most research has assessed the main effects of single variables on antisocial outcomes, an approach that until recently was characteristic of most psychological science (Miller & Keller, 2000; Porges, 2006). Some of the earliest models of delinquency focused on biological vulnerabilities for aggression, criminality, and related constructs. For example, Eppinger and Hess (1910/1915) proposed that an autonomic imbalance favoring the parasympathetic nervous system was the principal biological vulnerability for aggression. This deficiency was the proposed neural substrate of low resting heart rate, which is observed consistently in delinquent, conduct-disordered, and psychopathic samples (see Lorber, 2004). Although the "vagotonia" hypothesis was eventually proven wrong (see Beauchaine, 2001), it spawned several generations of research (including a number of studies in the last decade) leading to more refined models of autonomic and central nervous system liability for conduct problems, delinquency, and antisocial behavior (see, e.g., Beauchaine, Hong, & Marsh, 2008; Beauchaine, Katkin, Strassberg, & Snarr, 2001; Gatzke-Kopp, Raine, Loeber, Stouthamer-Loeber, & Steinhauer, 2002; Raine, 1996; Raine, Venebles, & Mednick, 1997).

Other studies of biological vulnerabilities for antisocial behavior have focused on genetic, neural, and neuroendocrine factors (for reviews, see Blair, 2001; Pliszka, 1999; Raine, 2002a, 2002b; Slutske, 2001). These studies show consistent evidence that antisocial behavior is (a) part of a spectrum of externalizing conduct in which heritable impulsivity is a core predisposing vulnerability (Krueger et al., 2002, 2007); (b) associated with abnormalities in serotonergic and dopaminergic neurotransmission; and (c) linked to functional abnormalities in striatal, orbitofrontal, and anterior cingulate cortex activity (Blair, 2004; Gatzke-Kopp et al., in press; Lee & Coccaro, 2007; Rubia et al., 2008). In sections to follow, we focus on genetic mechanisms of serotonergic and dopaminergic dysfunction. Readers interested in neuroimaging findings on antisocial behavior and related constructs are referred elsewhere (e.g., Durston, 2003; Patrick & Verona, 2007; Pridmore, Chambers, & McArthur, 2005).

Environmental risk approaches

In contrast to biological theories of antisocial behavior, a considerable yet largely separate literature exists on environmental risk factors for conduct problems, delinquency, and criminality. This research follows from seminal work by Glueck and Glueck (1950), who suggested that family environments and broader contextual influences shape antisocial behavior. The environmental risk factors approach is currently instantiated in coercion theory (Patterson, 1982; Patterson, DeBaryshe, & Ramsey, 1989; Patterson, DeGarmo, & Knutson, 2000), which specifies operant reinforcement contingencies through which antisocial behavior is shaped and maintained within families. Other environmental risk approaches include those that emphasize economic disadvantage and neighborhood violence on the development of delinquency, (e.g., Ingoldsby & Shaw, 2002), and experimental work demonstrating that deviant peer group affiliations increase delinquent behavior (e.g., Dishion, McCord, & Poulin, 1999).

Biology × Environment interaction models

More recently, Biological Vulnerability × Environmental Risk models of antisocial behavior have emerged (see, e.g., Hiatt & Dishion, 2008; Tremblay, 2005). These models stem from studies demonstrating joint effects of both classes of variables on antisocial outcomes (see Raine, 2002b). For example, in a landmark molecular genetics study, Caspi et al. (2002) found that the combination of child maltreatment and a polymorphism in the monoamine oxidase A gene (*MAOA*) predicted both juvenile and adult antisocial behavior. Those who experienced maltreatment and inherited the low MAOA activity genotype, which encodes for an enzyme that metabolizes both serotonin (5-HT) and dopamine (DA), were at much higher risk for engaging in antisocial behavior than those who experienced maltreatment but did not inherit the low MAOA activity genotype. Similarly, children who are impulsive, which is a highly heritable trait, are at greater risk for delinquency in neighborhoods high in socioeconomic disadvantage, violence, and crime (Lynam et al., 2000; Meier, Slutske, Arndt, & Cadoret, 2008).

Interaction models of both antisocial behavior and borderline pathologies have revealed that the combined effects of biological vulnerabilities and environmental risk factors are often synergistic rather than additive (Crowell et al., 2008; Raine, 2002b). In fact, significant Biology × Environment interactions are sometimes observed in the absence of main effects (Beauchaine et al., 2008). Thus, it is critical that the joint effects of vulnerabilities and risk factors be explored, even when each in isolation is only weakly associated with adverse outcomes. For example, in the Caspi et al. (2002) study described above, the *MAOA* genotype explained less than 1% of the variance in antisocial behavior. However, the joint effects of maltreatment and genotype explained about 65%. Had only main effects been assessed, the authors would have concluded that the *MAOA* genotype was unrelated to antisocial behavior.

Traditional Approaches to Studying Borderline Pathology

When compared with ASPD, theoretical and empirical work on BPD and its developmental precursors has been relatively limited. Although there were early clinical descriptions of affected individuals (Kernberg, 1967; Knight, 1953; Stern, 1938), the diagnosis was not formally recognized in the *DSM* until its third instantiation, in which BPD was defined as a disorder of late adolescence or (more frequently) adulthood (APA, 1980). According to both past and current diagnostic conventions, a formal diagnosis of BPD is proscribed among younger individuals (APA, 2000). However, diagnostic criteria also require that the individual be persistently and pervasively affected by the disorder for at least 1 year (adolescents) or 2 years (adults), suggesting that there may be impairing precursors to the diagnosis that have not been recognized as such. Thus, as a consequence of diagnostic convention, those studying borderline pathology have often neglected to examine the disorder and its precursors among youth. As discussed below, noteworthy exceptions to this rule have been limited by small sample sizes and reliance on diagnostic criteria that do not translate well to the behavioral repertoires of children and young adolescents. This is in stark contrast with the identification of child-specific criteria for antisocial pathology, as summarized in the above discussion and in Figure 1. For these reasons, much of the relevant developmental research on BPD has emerged only in the past decade, replacing an impoverished literature that neither identified vulnerable youth nor described their development along a potentially devastating behavioral trajectory.

Definitions and developmental issues

The nine diagnostic criteria for BPD can be grouped into four broad areas of dysregulation: emotional, behavioral, interpersonal, and cognitive. For a formal diagnosis of BPD, five of these criteria must be met. However, when considering the application of these symptoms to children, only two are clearly downward extendable (i.e., to children below age 9): (a) affective instability and (b) inappropriate intense affect. Four other criteria could be appropriately modified to fit behaviors typical of young children. These include (c) frantic efforts to avoid abandonment, which could manifest as persistent separation anxiety/worrying; (d) self-damaging

impulsive acts, which might take the form of running into traffic or rough and harmful playground behavior; (e) a pattern of unstable, intense interpersonal relationships, which could manifest as an extremely volatile relationship with one or more primary attachment figures, siblings, or peers; and (f) paranoid ideation or dissociative symptoms, likely in the form of hostile attributional biases and depersonalization (e.g., Crick, Murray-Close, & Woods, 2005). An additional symptom, (g) recurrent suicidal or nonsuicidal self-injurious behaviors, probably emerges in later childhood or early adolescence, with as many as 30% of adults with BPD reporting the initiation of self-injurious behaviors before the age of 12 and another 33% reporting initiation between the ages of 12 and 18 (Zanarini et al., 2006). Finally, (h) chronic feelings of emptiness and (i) identity disturbance are more likely to manifest in late adolescence or adulthood.

Even though it may be possible to modify and apply diagnostic criteria for BPD to children and adolescents, there is considerable debate regarding how to assess emerging borderline features, at what age a formal diagnosis is appropriate, and which of the diagnostic criteria are stable or traitlike and therefore likely to have greater predictive validity (for a review, see Miller, Muehlenkamp, & Jacobson, 2008). As with research on PDs among adults described above, evidence suggests that BPD can be identified reliably among adolescents in single time-point assessments (Becker et al., 1999; Becker, McGlashan, & Grilo, 2006; Blais, Hilsenroth, & Fowlder, 1999; see also Geiger & Crick, 2001), yet longitudinal research indicates considerable instability of the diagnosis over time, with at least 50–70% of adolescents moving to a subclinical levels of symptoms at subsequent assessments (Bernstein et al., 1993; Chanen et al., 2004; Grilo et al., 2001). However, in contrast to symptom-based research, studies examining temperamental or traitlike features of BPD have shown much greater temporal stability (Cloninger, 1987; Crawford, Cohen, & Brook, 2001) as have those following more severely affected individuals (see Levy et al., 1999). This suggests that although diagnostic multifinality may be common, biologically based temperamental vulnerabilities are likely to be more enduring and more predictive of long-term impairment (Lenzenweger & Castro, 2005), consistent with research on other PDs (see above; Clark, 2007).

Existing developmental research can be divided roughly into two broad categories. One line of research is based on the assumption that borderline-like features exist in youth and can be identified and labeled using existing measures. For example, Paris and colleagues have explored "borderline pathology of childhood" (also referred to as multiple complex developmental disorder; Cohen, Paul, & Volkmar, 1987) using a modified version of the Diagnostic Interview for Borderlines (Zanarini, Gunderson, Frankenburg, & Chauncey, 1989). Their findings suggest that affected children are neuropsychologically distinct from controls and likely to have encountered a number of early environmental stressors (Paris, Zelkowitz, Guzder, Joseph, & Feldman, 1999; Zelkowitz, Paris, Guzder, & Feldman, 2001). However, most of their participants have not developed BPD as adults, which may be because of small sample sizes, or because children who meet criteria for BPD are distinct from those who develop the disorder in adulthood (Zelkowitz et al, 2007). Interestingly, and consistent with the multifinality hypothesis set forth in this paper, longitudinal research following those with borderline pathology of childhood indicates that "borderline" males tend to develop ASPD in adulthood rather than BPD (see Lofgren, Bemporad, King, Lindem, & O'Driscoll, 1991). In contrast to research applying the BPD label to children, other work is based on the philosophy that developmental precursors to BPD do not necessarily take the same form as the adult diagnosis. Rather, the development of BPD is likely characterized by Gene × Environment interactions that manifest differently depending on age (e.g., Crowell, Beauchaine, McCauley, et al., 2008; Crowell et al., in press). Thus, research on the development of BPD differs depending on whether one assumes the disorder is characterized by a pattern of homotypic versus heterotypic continuity.

In this article we suggest that, similar to the development of ASPD, the development of BPD is likely characterized by a pattern of heterotypic continuity that is better described in terms of early predisposing traits rather than specific BPD symptoms. Although the exact characteristics of those on a BPD trajectory

are not yet known, there are data to suggest that self-injuring adolescents represent one population at high risk for a later borderline diagnosis (for a review, see Crowell, Beauchaine, & Lenzenweger, 2008). Specifically, as we discuss below, there is a growing body of research indicating that self-injuring adolescents and adults with BPD overlap on a number of biological vulnerabilities and psychosocial risk factors. Among both populations there is now consistent evidence to suggest that comorbidity across both the internalizing and externalizing spectra characterize adults with BPD, self-injuring and suicidal adolescents, and adolescents who eventually meet criteria for BPD (e.g., Crawford et al., 2001; Zelkowitz et al., 2007). This suggests that the combination of poor impulse control and early emotional lability may characterize youth at risk for both self-injurious behaviors and a later BPD diagnosis.

Biological approaches

Although many early accounts of borderline pathology posited an underlying biological substrate (Gunderson & Singer, 1975), empirical evidence has only recently emerged to support this proposition. Research addressing the biology of BPD has focused primarily on behavioral genetics and neuroimaging. As with ASPD, these studies suggest that BPD is (a) partly heritable and (b) linked to functional abnormalities in orbitofrontal and anterior cingulate (as well as amygdala) activity (Ceballos, Houston, Hesselbrock, & Bauer, 2006; Donegan et al., 2003; New et al., 2007; Putnam & Silk, 2005; Silbersweig et al., 2007). In addition, molecular genetics data linking specific susceptibility loci to borderline traits point toward altered dopaminergic and serotonergic functioning. Although we do not review the neuroimaging literature in this article, we elaborate on heritability immediately below, and on molecular genetics in later sections.

Behavioral genetics and family history studies indicate a reliable heritable component to BPD. In a recent twin study, 69% of the variance in BPD symptoms was attributable to additive genetic effects (Torgersen et al., 2000). Slightly smaller estimates have been observed in other samples, with 35–42% of the variance in borderline features explained by heritability (Distell et al., 2007; Livesley, Jang, & Vernon, 1998; Torgeson et al., 2008). Of importance, behavioral genetics research exploring the overlap between ASPD and BPD has revealed that shared genetic and environmental risk factors for the disorders are greater than those common to all four Cluster B PDs (Torgersen et al., 2008). This overlap is likely because of shared vulnerability for impulsivity. Indeed, Nestadt et al. (1994) found that the two disorders overlapped significantly on a factor characterized primarily by impulsivity, substance abuse, and norm violations.

Family studies suggest that two traits, affective instability and impulsivity, likely account for most of the heritability of BPD. These traits are more common among relatives of those with BPD than among those with other PDs (Silverman et al., 1991). Moreover, for individuals with BPD, there is significant familial aggregation of impulse control disorders (White, Gunderson, Zanarini, & Hudson, 2003). Behavioral genetics studies indicate that both emotional lability and impulsivity are largely heritable, with respective heritability coefficients of around 50% and 80% (Livesley & Jang, 2008; Livesley, Jang, & Vernon, 1998; Price, Simonoff, Waldman, Asherson, & Plomin, 2001; Sherman, Iacono, & McGue, 1997; Widiger & Simonson, 2005).

Environmental risk approaches

There are several developmental theories of BPD, each of which outlines potential environmental risk factors for the disorder (Fonagy, Target, & Gergely, 2000; Gunderson & Lyons-Ruth, 2008; Judd & McGlashan, 2003; Kernberg, 1967, 1975, 1976). One of the most thoroughly delineated models (Crowell et al., 2009; Linehan, 1993) proposes that the emotional lability observed in adults with BPD emerges within an invalidating family environment (see also Fruzzetti, Shenk, & Hoffman, 2005). According to this model, vulnerable youth are at increased risk for BPD when placed in an environment characterized by intolerance toward the outward expression of private emotional experiences. Although empirical data testing this model are limited, it nevertheless remains a predominant contemporary theory that

we return to in later sections where we describe our own developmental model.

Much has also been written about the life histories of individuals with BPD. These studies have focused primarily on disturbed parent–child relationships, disrupted attachment, and early traumatic experiences including abuse and neglect (Herman, Perry, & vander Kolk, 1989; Levy, 2005; Paris, Zweig-Frank, & Guzder, 1994; Zanarini, 2000). Unfortunately, most of these studies have been retrospective, with all of the associated caveats vis-à-vis recall biases and reliability. Recently, however, researchers have begun to examine the development of borderline features in longitudinal samples (e.g., Crick et al., 2005), including children at high risk for ASPD and BPD (e.g., Cohen et al., 2008; Lyons-Ruth, 2008; Lyons-Ruth, Holmes, & Hennighausen, 2005) and among the children of parents with the disorder (e.g., Herr, Hammen, & Brennan, 2008; Macfie, 2009). We elaborate on some of these findings in later sections.

Biology × Environment interaction models

To date, although Biology × Environment interaction models of BPD have been articulated (e.g., Crowell, Beauchaine, & Lenzenweger, 2008, Crowell et al., 2009; Putnam & Silk, 2005), data supporting such models have again been limited. In a notable exception, Cloninger and colleagues (Joyce et al., 2003) examined the joint effects of early childhood adversity and temperament on the later development of borderline pathology in a sample of 188 depressed outpatients. The combination of (a) neglect and abuse experiences and (b) temperamental novelty seeking and harm avoidance accounted for significant variance in the development of BPD. Importantly, novelty seeking and harm avoidance are temperamental traits that are rooted in dopaminergic and serotonergic neurotransmission, respectively (see Cloninger, 1987).

In our own research on self-injurious behaviors among adolescent girls, described in detail below, we examined the effects of both peripheral 5-HT and mother–daughter conflict during a discussion task on self-injuring behaviors. Although the main effects of 5-HT and dyadic conflict were modest, their interaction accounted for 64% of the variance in self-injury (Crowell, Beauchaine, McCauley, et al., 2008), providing support for the notion that biological vulnerabilities interact with adverse experiences to potentiate BPD-related behaviors.

Interim summary

A long history of research on conduct problems, delinquency, and related constructs has produced rich theoretical models of biological vulnerabilities and environmental risk factors for antisocial behavior. More recently, Biology × Environment interaction models have emerged following important studies demonstrating how adverse experiences moderate the expression of genetic vulnerability. Thus, it is now clear that antisocial personality development results from the interplay of genes and environment.

In contrast to ASPD, although elaborate theoretical models of the effects of environment on BPD development have long been articulated, empirical studies of etiology have emerged only recently. As with ASPD, these studies suggest that BPD is both genetically and environmentally influenced, and that trait impulsivity confers vulnerability to the disorder. We now turn to a detailed discussion of the role of trait impulsivity in the development of ASPD and BPD.

Impulsivity and Vulnerability to Antisocial and Borderline Pathologies

As stated above, ASPD in adulthood is almost invariably preceded by a developmental progression that begins with hyperactivity–impulsivity very early in life. Thus, impulsivity appears to be the primary vulnerability for the heterotypically continuous pathway depicted in Figure 1. This interpretation is supported by behavioral genetics research indicating that a single latent trait, which is about 80% heritable (Price et al., 2001; Sherman et al., 1997), predisposes to disorders across the externalizing spectrum, including impulsivity, CD, drug and alcohol dependencies, and adult antisocial behavior (Kendler, Prescott, Myers, & Neale, 2003; Krueger et al., 2002; Krueger & Markon, 2006). Similarly, heritable impulsivity appears to be a principal vulnerability to borderline

personality development (Crowell, Beauchaine, & Lenzenweger, 2008, Crowell et al., 2009).[2] In writing this article, we focus on this heritable vulnerability, among other predispositions. We acknowledge, however, that there are multiple equifinal pathways to the impulsivity phenotype that are either partially or fully independent of inherited impulsivity (see Sonuga-Barke, 2005). The origins of such pathways include brain injuries as a result of head trauma, hypoxia, or other central nervous system insults (Gatzke-Kopp & Shannon, 2008), and exposure to teratogenic agents such as alcohol, stimulant drugs of abuse, and lead (Fryer, Crocker, & Mattson, 2008). Such risk factors may produce a phenotype that is indistinguishable from that derived from trait impulsivity. Although we do not wish to minimize the importance of impulsivity derived from these sources, our developmental model begins with heritable vulnerability, expressed early in life as impulsivity, which interacts with environmental risk across the life span to produce ASPD and BPD.[3]

Impulsivity and central DA functioning

Most contemporary accounts of temperamental impulsivity emphasize (a) structural and functional abnormalities in evolutionarily old brain regions including the mesolimbic DA system and/or (b) serotonergic networks including the septohippocampal system (discussed below). The mesolimbic DA network matures very early in ontogenesis, and is a primary neural substrate of disinhibition in both children and adults (see Beauchaine et al., 2001; Castellanos, 1999; Gatzke-Kopp & Beauchaine, 2007; Kalivas, & Nakamura, 1999; Sagvolden, Johansen, Aase, & Russell, 2005). Mesolimbic theories of impulsivity follow from seminal research on learning, motivation, and substance dependence conducted with rodents and nonhuman primates. This research demonstrates that electrical and pharmacological stimulation of dopaminergically rich mesolimbic structures is reinforcing (see Milner, 1991); neural activity increases within mesolimbic structures during both reward anticipation and reward-seeking behaviors and following administration of DA agonists (see Knutson, Fong, Adams, Varner, & Hommer, 2001; Phillips, Blaha, & Fibiger, 1989); and DA antagonists reduce and sometimes block the rewarding properties of food, water, and stimulant drugs of abuse (e.g., Rolls et al., 1974).

Based primarily on these observations, several authors have advanced theories of impulsivity that explain individual differences in approach behavior as variations in activity and reactivity of mesolimbic structures. Perhaps the most famous of these theories is that offered by Gray (1987a, 1987b), who proposed a mesolimbic behavioral approach system as the neural substrate of appetitive motivation. Following from Gray and others who offered similar theories (e.g., Cloninger, 1987), clinical scientists interested in impulsivity turned to dopaminergic accounts of approach motivation to explain the excessive reward-seeking behaviors of children with ADHD, CD, and related behavior disorders (e.g., Fowles, 1988; Quay, 1993).

Although these early theories correctly identified the mesolimbic DA system as a neural substrate of impulsivity, most clinical scientists at the time assumed that excessive dopaminergic activity led to impulsive behavior. However, more recent findings suggest an inverse correspondence between mesolimbic DA activity and impulsivity. For example, studies using positron emission tomography and single photon emission

2. In the adult personality literature, impulsivity is often conceptualized as a combination of extraversion and nonaffective constraint (Tellegen & Waller 1996). Although there is some debate over the neural bases of these traits (see, e.g., Depue & Collins, 2001), dopaminergic substrates have been proposed. Moreover, both ASPD and BPD have been linked with low constraint. However, because the extraversion and constraint constructs are rarely invoked in the child psychopathology literature, we focus instead on trait impulsivity, which most readers are likely to be familiar with.

3. It is important to note that heritable impulsivity may be correlated with environmental risk factors for antisocial behavior such as in utero drug exposure and head trauma. For example, antisocial mothers may be more likely to abuse substances during their child's gestation (a passive gene–environment correlation), and impulsive children may be more likely to engage in behaviors that lead to head injuries (an active gene–environment correlation). Thus, separating children who are impulsive because of trait impulsivity from those who are impulsive, due in part or whole to other etiological factors, may be difficult if not impossible in practice (Beauchaine & Neuhaus, 2008).

computed tomography indicate that the primary mechanism of action of DA agonists such as methylphenidate is increased neural activity in the striatum, a mesolimbic structure (e.g., Vles et al., 2003; Volkow, Fowler, Wang, Ding, & Gatley, 2002). Thus, by increasing mesolimbic DA activity pharmacologically, hyperactivity, impulsivity, and aggression are reduced (e.g., Hinshaw, Henker, Whalen, Erhardt, & Dunnington, 1989; MTA Cooperative Group, 1999).

Furthermore, individual differences in central DA expression correspond with individual differences in trait-positive affectivity, and DA agonists induce pleasurable affective states (see Ashby, Isen, & Turken, 1999; Berridge, 2003; Forbes & Dahl, 2005). In contrast, low levels of striatal DA activity predict trait irritability (Laakso et al., 2003), a common symptom of externalizing psychopathology (Mick, Spencer, Wozniak, & Biederman, 2005), and according to some theorists an alternative manifestation of approach behavioral tendencies (e.g., Harmon-Jones et al., 2002). An inverse correspondence between central DA functioning and impulsivity is also supported by recent neuroimaging studies, indicating reduced mesolimbic activity during reward tasks among children and adolescents with ADHD and CD (Durston et al., 2003; Vaidya et al., 1998). Thus, underactivation of striatal DA leads to increases in impulsive approach behaviors, which function to raise activity within the mesolimbic system (Beauchaine, Gatzke-Kopp, & Mead, 2007; Gatzke-Kopp & Beauchaine, 2007; Sagvolden et al., 2005). In other words, reward insensitivity results in increased impulsive responding to upregulate a chronically aversive mood state, the hedonic byproduct of an underactive mesolimbic DA system (Ashby et al., 1999; Forbes & Dahl, 2005; Laakso et al., 2003).

In addition to mesolimbic theories of impulsivity, much has been written about mesocortical (frontal) substrates of disinhibition (see Gatzke-Kopp & Beauchaine, 2007). We do not consider frontal dysfunction as an early predisposing vulnerability because these brain regions mature very late in adolescence, and are therefore less likely to underlie the early expression of impulsivity (Halperin & Schulz, 2006). Nevertheless, the neurodevelopment of frontal regions may be affected (through mechanisms of neural plasticity, programming, and pruning) by early experiences that are themselves a product of impulsivity (Beauchaine et al., 2008; Sagvolden et al., 2005). Thus, heritable compromises in the functioning of early maturing brain regions that give rise to impulsivity may affect neurodevelopment of later maturing brain regions that are responsible for executive functioning and planning, especially following environmental risk exposure. This conceptualization highlights the interactive nature of the brain in affecting behavior, and of behavior in affecting later brain development. It therefore follows that early vulnerability, expressed as deficient mesolimbic DA functioning, may be compounded in adolescence by mesocortical dysfunction, thereby exacerbating preexisting impulsivity. This may account in part for the increase in ASPD and BPD symptoms in this age range. Interested readers are referred to Halperin and Schulz (2006) and Gatzke-Kopp and Beauchaine (2007) for detailed accounts of later-developing frontal mechanisms of impulsivity.

Given that depression is often comorbid with both ASPD and BPD (see above), it is also important to note that recent neuroimaging studies have revealed reduced reactivity to reward cues in the striatum, a DA-rich mesolimbic structure, in children and adolescents who are depressed (e.g., Forbes, & Dahl, 2005; Forbes, Shaw, & Dahl, 2007). Thus, central DA dysfunction appears to characterize both internalizing and externalizing psychopathology and is a likely neural substrate of low positive affectivity (see above). Furthermore, central DA dysfunction may account for the co-occurrence of both externalizing and internalizing symptoms among comorbid individuals (see Beauchaine & Neuhaus, 2008; Beauchaine et al., 2008).

Impulsivity and central 5-HT functioning

Although it now appears that an underresponsive mesolimbic DA system confers considerable vulnerability to externalizing behavior, central DA dysfunction is not the only route to impulsivity (see, e.g., Beauchaine, 2001; Beauchaine & Neuhaus, 2008), which can also arise from deficient trait anxiety, a personality attribute that is mediated primarily by

central serotonergic networks (Gray & McNaughton, 2000). Normal levels of trait anxiety, or behavioral inhibition, curtail impulsive behaviors. When behavioral inhibition is compromised, impulsivity may emerge even in the absence of central DA dysfunction (see e.g., Beauchaine, 2001; Beauchaine et al., 2001). Accordingly, much has been written about the role of serotonergic functioning in impulsive aggression and antisocial behavior in animals and humans, including several recent reviews (e.g., Gollan, Lee, & Coccaro, 2005; Lee & Coccaro, 2007; van Goozen, Fairchild, Snoek, & Harold, 2007). There is also overwhelming evidence that 5-HT dysfunction is associated with borderline pathology, self-injury, and suicide (Kamali, Oquendo, & Mann, 2002; Joiner, Brown, & Wingate; 2005; Lis, Greenfield, Henry, Guile, & Dougherty, 2007).

Serotonergic projections of the septohippocampal system are involved in the inhibition of prepotent responses, whether approach or avoidance related, when an organism is faced with competing motivational objectives (Gray & McNaughton, 2000). The septohippocampal system induces anxiety, facilitating behaviors aimed at resolving the conflict. The role of the septohippocampal system in anxiety is supported by the finding that anxiolytic drugs (e.g., benzodiazepines) produce behavioral effects in animals that are qualitatively similar to the effects of septohippocampal lesions. Anxiolytics affect the serotonergic system and, of course, decrease anxiety. In contrast to DA-mediated impulsivity, disinhibition among individuals low in trait anxiety derives from a failure to monitor punishment cues and inhibit ongoing behaviors (Beauchaine & Neuhaus, 2008).

Impulsive aggression manifests in ASPD largely in the form of violence and in BPD largely in the form of relational aggression (see, e.g., Crick et al., 2005). Impulsive aggressive behaviors are also observed in many other disorders associated with dysregulated 5-HT function, including substance abuse, mood disorders, and posttraumatic stress disorder (see Gollan et al., 2005). Research with rodents and nonhuman primates indicates that 5-HT depletion leads to aggressive behavior (for review, see Lucki, 1998). Cross-sectional research with humans also links low 5-HT to aggression (Brown, Goodwin, Ballenger, Goyer, & Major, 1979). For example, early research with aggressive children demonstrated reduced levels of the 5-HT metabolite, 5-hydroxyindoleacetic acid (5-HIAA), in cerebrospinal fluid (Kruesi et al., 1990). More importantly, longitudinal studies of at risk children with disruptive behavior disorders implicate reduced 5-HT in later aggressive and antisocial behavior (Kruesi et al., 1992).

In a recent study, reduced 5-HT reactivity to fenfluramine among children predicted antisocial personality traits 9 years later (Flory, Newcorn, Miller, Harty, & Halperin, 2007). Fenfluramine causes synaptic 5-HT release, which results in limbic–hypothalamic release of peripheral prolactin (Pine et al., 1997). Lower levels of peripheral prolactin indicate lower levels of 5-HT release following fenfluramine challenge. In heterogeneous sample of comorbid PD subjects, reduced reactivity to fenfluramine was related to recent impulsive aggression (Coccaro, Kavoussi, & Hauger, 1997). This finding has also been observed in antisocial violent offenders (O'Keane et al., 1992) and nonhuman primates (Botchin, Kaplan, Manuck, & Mann, 1993).

Some researchers believe that impulsive aggression may also be directed at the self and involve similar mechanisms as externalized aggression (Gollan et al., 2005). Consistent with this view, individuals with histories of self-injury have increased levels of sociopathy, anger, and aggression (Simeon & Favazza, 2001). Furthermore, a substantial amount of research relates suicide and self-injury, independent of psychiatric diagnosis, to serotonergic dysfunction (see for a review, Mann, 2003). Many studies have found lower levels of 5-HT and 5-HIAA in the cerebrospinal fluid of suicide victims and attempters. Low levels of this metabolite have been found in suicide attempters, relative to nonattempters with the same psychiatric disorder, including PDs (Mann et al., 1996, 2002).

As with DA, we do not consider frontal dysfunction of 5-HT, despite its relationship to adult impulsive aggression and suicide, to be an early predisposing vulnerability to trait impulsivity because these brain regions mature very late in adolescence. However, 5-HT neurons are likely to influence the development of the frontal cortex (Jacobs & Azmitia, 1992).

Research indicates clearly that 5-HT neurons affect the development of other brain functions, such as GABAergic neurotransmission and anxiety during key stages of development. 5-HT also modulates the activity of other neurotransmitters, including DA (Rogeness, Javors, & Pliszka, 1992).

Like impulsivity derived from central DA dysfunction, trait anxiety is highly heritable (see Derryberry, Reed, & Pilkenton-Taylor, 2003). However, the two traits have dissociable neural substrates, and appear to be largely independent in their heritable contributions to behavior. Thus, an individual may be high or low on either or both traits, with specific implications for behavioral functioning (Beauchaine & Neuhaus, 2008). For example, impulsive children with ADHD and high trait anxiety, the latter reflective of greater sensitivity to environmental cues because of a more responsive septohippocampal system, respond better to treatment than children with ADHD who are low in trait anxiety (Jensen et al., 2001). In contrast, high impulsivity and low trait anxiety may reflect a "double vulnerability" to psychopathology and more serious externalizing behavior as these individuals respond strongly to reward but not to punishment. As noted by several authors, psychopaths exhibit excessive approach behavior coupled with a disturbing lack of anxiety and fear (see Fowles & Dindo, 2006).

Molecular genetics of impulsivity

From the above discussion, it is not surprising that molecular geneticists studying impulsivity have focused on genes that encode for dopaminergic and serotonergic neurotransmission. A brief overview of synthesis and metabolism pathways suggests a number of points at which DA and 5-HT function might be influenced by genes that affect neurotransmitter or conversion enzyme activity (see Figure 2).

Both DA and 5-HT are biogenic amine neurotransmitters. This classification follows from a structural similarity derived from a common amine functional group. DA is synthesized from L-tyrosine, which is converted to L-dihydroxyphenylanaline (L-DOPA) by tyrosine hydroxylase. L-DOPA is then converted to DA by DOPA decarboxylase. In turn, DA is metabolized into other catecholamines (norepinephrine, epinephrine) by DA β-hydroxylase. All catecholamines are degraded by MAO and catechol-*O*-methyltransferase (*COMT*).

In contrast to DA, 5-HT is synthesized from L-tryptophan, which is converted to 5-hydroxy-L-tryptophan by tryptophan hydroxylase. Tryptophan hydroxylase is then converted to 5-HT by 5-hydroxytryptophan decarboxylase. Like DA, 5-HT is degraded by MAO (Figure 2).

These synthesis and metabolism pathways, along with knowledge of receptor densities and subtypes, reveal a number of mechanisms through which individual differences in impulsivity and other personality attributes such as depression and trait anxiety might be conferred (see, e.g., Cloninger, 1987, Cloninger, Svrakic, & Svrakic, 1997). In part because MAO degrades DA and 5-HT, which affects the availability of both neurotransmitters, genes that encode for MAO activity have received considerable attention in research on both externalizing and internalizing outcomes. Genes that encode for COMT activity, which affects the rate of DA metabolism, have also been studied. We therefore begin with brief descriptions of research on these genes, which we follow with discussion of genes that encode for DA and 5-HT receptor and transporter expression. Note that the biochemistry and functions of each gene discussed could be described in a full length article. Because of space constraints, our descriptions are necessarily concise.

MAOA. MAO is an enzyme that catabolizes all biogenic amines, including DA and 5-HT. A long history of research links MAO dysfunction to conduct problems, aggression, substance use, and depression (Reich, Hinrichs, Culverhouse, & Bierut, 1999; Shih & Thompson, 1999). MAO activity is encoded by two subtypes of MAO genes, *MAOA* and *MAOB*. Given the association between *MAOA* and 5-HT function, it is of particular interest in research on antisocial and borderline pathologies. Polymorphisms in the *MAOA* gene (locus Xp11.23–11.4), including a variable number tandem repeat (VNTR) in the promotor region, have been identified. Longer repeats (3.5, 4, and 5) are associated with higher production

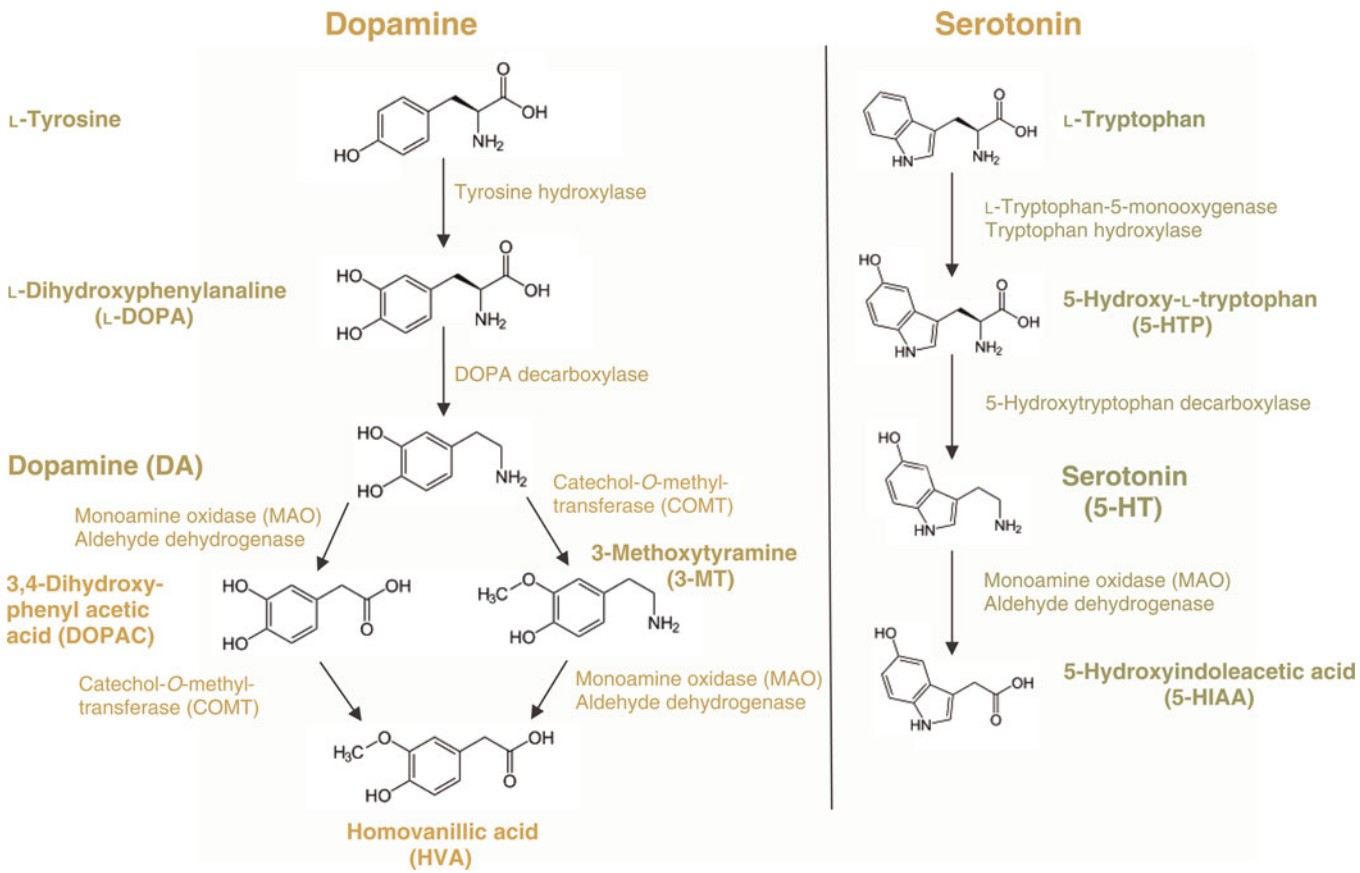

Figure 2. Simplified synthesis and metabolism pathways for (left) dopamine (DA) and (right) serotonin. These pathways suggest a number of points at which dopaminergic and serotonergic function might be affected by, for example, genes that encode for neurotransmitter activity or conversion enzyme activity. DA is also converted into norepinephrine by DA β-hydroxylase, which in turn is converted into epinephrine by phenylethanolamine-*N*-methyltransferase (not shown). [A color version of this figure can be viewed online at journals.cambridge.org/dpp]

of *MAOA*, and thus more efficient clearance of DA and 5-HT, in contrast to the three repeat allele. Variation in this gene has been linked with aggression, antisocial behavior, alcoholism, and depression (Cravchik & Goldman, 2000; Gutierrez, et al., 2004; Rottmann et al., 1999). Knockout mice in which the *MAO* gene is deleted are aggressive, yet their behavior is normalized by restoring *MAO* levels (Cases et al., 1995; Shih & Thompson, 1999).

Research associating the *MAOA* gene with personality and clinical impairment is plagued by inconsistent findings. There are at least three reasons for this. First, *MAOA* gene function is especially sensitive to environmental regulation, highlighting the importance of environmental variables in mapping genotype → phenotype relations. This is illustrated in the recent study by Caspi et al. (2002), who reported no main effect of the *MAOA* VNTR polymorphism on antisocial behavior but reported a significant *MAOA* × Child Maltreatment interaction (see above).

Second, in addition to the effects of environment in moderating genetic risk, vulnerability conferred by *MAOA* gene polymorphisms may also be potentiated by allelic variation in other high-risk genes. For example, Wang et al. (2007) found an *MAOA* VNTR 4-repeat allele × DA receptor D2 (DRD2) A1/A1 allele interaction in predicting alcoholism in males. Although research on Gene × Gene interactions remains limited, such studies are important given that genetic liability to most psychiatric disorders, including ASPD and BPD, is likely to be complex, with many different alleles contributing (see, e.g., Castellanos & Tannock, 2002; Gottesman & Gould, 2003).

Finally, sex appears to moderate vulnerability conferred by polymorphisms in the *MAOA* gene. For example, although neither of the above interactions applied to women, Yu et al. (2005) reported increased frequency of the 4-repeat allele in female patients with major depressive disorder, and better antidepressant (fluoxetine) responses in depressed women who were 3-repeat homozygous. Thus, *MAOA* gene polymorphisms confer vulnerability for psychopathology, which in turn, is moderated by other genes, environmental experiences, and sex. Sex effects, which predispose to externalizing behaviors among males and internalizing behaviors among females, may help to explain why males and females are at differential risk for ASPD and BPD.

COMT. COMT is an enzyme involved in the catabolism of catecholamines, including DA, epinephrine, and norepinephrine. A codon substitution resulting in a replacement of the methonine amino acid with the valine amino acid results in an increase in COMT enzyme activity. Thus, individuals with the val/val genotype (locus 22q11) have significantly higher COMT activity than those who are heterozygous or met/met homozygous (Lotta et al., 1995). This increased COMT efficiency results in lower synaptic DA activity. Val/val homozygotes therefore require excessive DA release to achieve the same level of post synaptic activation as those with at least one met allele.

The *COMT* gene has been implicated in the pathogenesis of both antisocial behavior and depression, which may be linked in part with sex differences in gene expression. High COMT enzymatic activity is observed in depressed women (Puzynski, Hauptmann, & Zaluska, 1983), and the val genotype confers vulnerability to mood episodes following stressful life events (Mandelli et al., 2007). Furthermore, early-onset major depression is characterized by a higher prevalence of the val/val *COMT* genotype (Massat et al., 2005). Finally, researchers recently identified both a main effect for the val/val genotype, and a Gene × Environment interaction with low birth weight (a condition frequently associated with hypoxia) in predicting the severity of antisocial symptoms in a group of 240 mostly male children with ADHD (Thapar et al., 2005). Thus, although evidence remains preliminary, *COMT* polymorphisms may confer vulnerability following environmental risk exposure differentially based on unexplained sex effects.

DRD4. The *DRD4* gene (locus 11p15.5) has well-characterized variants, including the 7-repeat (long) allele. This polymorphism has been linked consistently to ADHD (Faraone, Doyle, Mick, & Biederman, 2001; Swanson & Castellanos, 2002), novelty-seeking (Benjamin, Patterson, Greenberg, Murphy, & Hamer, 1996; Ebstein et al., 1996), blunted responding to DA agonists (Van Tol et al., 1992), and exploratory behavior in animals (Fink & Smith,

1980), effects that may derive from underresponsive postsynaptic receptors (Missale, Nash, Robinson, Jaber, Caron, 1998). Genetic association studies suggest that the 7-repeat allele confers about a 1.5 relative risk for ADHD (Smalley et al., 1998). Thus, although the effects of this polymorphism on impulsivity appear to be modest, they are nevertheless consistent, and may interact with other high risk genes to potentiate risk for psychopathology (see below).

DA transporter (DAT1). An additional candidate gene in the etiology of impulsivity is the *DAT* (locus 5p15.33), which modulates both synaptic and extrasynaptic DA levels, the primary regions at which psychostimulants exert their effects (Grace, 2001). The 10-repeat allele, which reduces the availability of synaptic DA through more efficient reuptake (Swanson et al., 2000), has been linked consistently with ADHD (Swanson & Castellanos, 2002). Neuroimaging studies indicate that this *DAT1* polymorphism exerts its effects on behavior through altered DA activity within the striatum, a mesolimbic structure (Durston et al., 2008). Consistent with the deficient DA hypothesis of impulsivity, methylphenidate downregulates DAT activity, resulting in higher levels of striatal DA (Vles et al., 2003).

There is also evidence of *DAT1* gene involvement in both depression and BPD. For example, Haeffel et al. (2008) reported that *DAT1* polymorphisms interacted with maternal rejection to predict depression in a sample of Russian male juvenile detainees. Furthermore, Joyce and colleagues (2006) found that the nine-repeat allele of the *DAT1* gene was associated with BPD among depressed adults. Within suicidal and nonsuicidal self-injuring populations, however, there is a more reliable association between DA deficiency and self-injurious behaviors (see Pitchot et al., 2001; Ryding, Ahnlide, Lindstrom, Rosen, & Traskman-Bendz, 2006; Sher et al., 2005). However, the precise genetic mechanisms have yet to be elucidated, and this research has largely been conducted among males and with small sample sizes, necessitating further investigation.

DRD2. The DRD2 receptor modulates DA synthesis and regulates DAT activity (Mayfield & Zahniser, 2001). Although relations between the *DRD2* gene (locus 11q23) and ADHD have been inconsistent (see Sagvolden et al., 2005), *DRD2* polymorphisms have been associated with risk for alcoholism, particularly when comorbid with symptoms of CD and/or ASPD (Lu, Lee, Ko, & Lin, 2001). This relationship may be mediated in part by the effects of the *DRD2* A2/A2 allele on reward-related impulsivity (Limosin et al., 2003). Other researchers, however, have implicated the A1/A1 and A1/A2 alleles in sensation seeking and active avoidance of aversive states (Berman, Ozkaragoz, Young, & Noble, 2002). Although these seemingly discrepant findings need to be disentangled in future research, there appears to be some link between the *DRD2* gene and vulnerability to externalizing psychopathology.

5-HT transporter (5-HTT). 5-HT is clearly implicated in the pathogenesis of depression (see above), and manipulation of this neurotransmitter represents the most common pharmacological treatment for mood disorders. 5-HTT is an important protein in the regulation of synaptic 5-HT. Genetic variation in the promoter region of this gene (locus 17q11.2) results in two common variants: short (s) and long (l) alleles. The long allele results in high production of *5-HTT*, which is presumed to induce more rapid turnover, leading to less synaptic 5-HT. The *5-HTT* gene has been associated repeatedly with depression. Those who are s/s homozygous are at increased risk for mood disorders, especially when they encounter adversity and early familial dysfunction (Taylor et al., 2006), indicating an important Gene × Environment interaction (Wilhelm et al., 2006). This vulnerability to depression following stressful life events appears to be much stronger in women than in men (Mandelli et al., 2007).

Violence has also been associated with disrupted 5-HT signaling (see above), and a variant of the *5-HTT* gene has been linked with childhood aggression (Beitchman et al., 2006). Homologous findings have been documented in animals, in which the s/s allele is associated with both excessive anxiety and aggressive behavior in response to novelty among primates with poor maternal caregiving histories (Suomi, 2004). Furthermore, primates with one or two copies of the s allele

exhibit reduced 5-HT turnover following social stress (see Wrase, Reimold, Puls, Keinast, & Heinz, 2006). Among young adult humans, the s allele has been linked to both ASPD and BPD symptoms (Lyons-Ruth et al., 2007). Of importance, males and females with the s allele are reactive to different types of stressors, and these Gene × Stress × Sex interactions result in different symptom profiles (Sjoberg et al., 2006). The association between the *5-HTT* gene and aggression is more prominent in males (Verona, Joiner, Johnson, & Bender, 2006). In contrast, genetically vulnerable females are more likely to engage in self-injury. Some of our research, described both above and below, indicates an interaction between peripheral 5-HT and family dysfunction in predicting self-injury among adolescent girls. Thus, both overt aggression and self-injury must be considered in 5-HT– and *5-HTT*–behavior relations (Courtet et al., 2001).

Replicated associations between the *5-HTT* gene and seemingly disparate behaviors such as aggression and depression indicate that the gene may mark broad vulnerability to psychopathology, perhaps conferred in part through negative affectivity (Perez et al., 2007). Such a model is consistent with recent behavioral genetics conceptualizations of comorbidity, where a single latent liability is expressed in seemingly different ways because of moderating influences (Krueger & Markon, 2006), including sex effects. Viewed in this way, a common vulnerability to negative affectivity may lead to expressions of both depressive affect and aggressive behavior, with sex or sex-specific genetic and/or socialization mechanisms potentiating the particular expression of this trait (see e.g., Beauchaine, Hong, et al., 2008). This provides yet another example of sex effects moderating links between genetic vulnerability and behavior.

Gene × Gene interactions. As alluded to above, recent research has indicated that high risk alleles may interact to increase risk for psychopathology, over and above the main effects of single genes. Schmidt, Fox, and Hamer (2007) assayed both the *5-HTT* and *DRD4* genes in a sample of 108 children who were 7 years old. Those who had a short copy of the *5-HTT* allele and a long copy of the *DRD4* allele scored highest on both internalizing and externalizing behaviors. Given the sex effects discussed above, one question that emerges from this study is whether sex moderated the Gene × Gene interaction effect, with externalizing behaviors more likely among males and internalizing behaviors more likely among females. Unfortunately, the authors did not include sex in their models. In contrast, in a large sample of adults, Mandelli et al. (2007) reported a *5-HTT* × *COMT* interaction in predicting the onset of major depression following exposure to significant life stressors, mainly among women. These findings illustrate the importance of (a) assessing Gene × Gene interactions in characterizing polygenic vulnerability to psychopathology and (b) evaluating the effects of environment on genetic vulnerability.

Interim summary

Trait impulsivity, which derives from both dopaminergic and serotonergic mechanisms, appears to confer vulnerability to both antisocial and borderline pathologies. A number of genes that affect dopaminergic and serotonergic neurotransmission, including *MAOA*, *COMT*, *DRD4*, *DAT1*, *DRD2*, and *5-HTT*, have been implicated in the expression of impulsivity, aggression, anxiety, depression, or some combination of these traits. For several of these genes, phenotypic expression of vulnerability may be moderated by poorly understood sex effects. The *MAOA* polymorphism appears to confer vulnerability to externalizing behaviors among males and internalizing behaviors among females. Similarly, the Val/Val *COMT* genotype, which renders carriers more vulnerable to psychopathology following stressful life events, may be more likely to potentiate antisocial behavior among males versus depression among females. Furthermore, although sex effects have not been reported for the *DAT1* gene, longer repeats have been linked to ADHD, depression, and BPD. Finally, the short allele of the *5-HTT* appears more likely to confer vulnerability to aggression among males and self-injury among females. These Gene × Sex interactions may help to explain why similarly vulnerable males and females develop ASPD and BPD, respectively. However, replications are needed before firm conclusions can be drawn. We now follow up our earlier discussion

by elaborating on the influence of environment on the expression of antisocial and borderline pathologies.

Environmental Risk for Antisocial and Borderline Personality Development

Antisocial behavior

As noted above, there is a long tradition of research addressing environmental risk factors for antisocial personality development. Although much of this research has focused on middle childhood and adolescence, evidence suggests that parent–child relationships are compromised as early as infancy among children at risk for later conduct problems and antisocial behavior (Lyons-Ruth, 2008), and that parents who had CD themselves offer adverse rearing environments for their children, including disrupted parenting, socioeconomic disadvantage, and relationship violence (Jaffee, Belsky, Harrington, Caspi, & Moffitt, 2006). Thus, Gene × Environment correlations are clearly operative in the development of ASPD (Moffitt, 2005).

Research from the Harvard Family Pathways Study (Lyons-Ruth et al., 2005), a longitudinal research project in which participants were followed from infancy to young adulthood, indicates some potential mechanisms through which genetic vulnerabilities and environmental risk factors combine to potentiate the development of antisocial and borderline pathologies. In this study, infants who were referred for home visits because of poor quality of care were more likely than their peers to exhibit antisocial and borderline symptoms as adolescents. In addition, children of mothers who withdrew from attachment cues during lab visits, and children who experienced significant trauma during their upbringing, were more likely to develop antisocial and borderline symptoms (Lyons-Ruth, 2008). Furthermore, participants with two copies of the *5-HTT* s allele had a fourfold risk of antisocial and borderline pathologies as adults (Lyons-Ruth et al., 2007). Thus, consistent with findings summarized above, the s allele conferred particular vulnerability to environmental risk exposure.

In later childhood, coercive family processes contribute to further development and maintenance of externalizing behaviors (Patterson et al., 1989, 2000). In an elegant series of studies, Snyder and colleagues (Snyder, Edwards, McGraw, Kilgore, & Holton, 1994; Snyder, Schrepferman, & St. Peter, 1997) demonstrated that dyadic interaction patterns in the families of aggressive children are characterized by coercive exchanges that negatively reinforce both aggression and emotional lability. In such exchanges, parents of aggressive children tend to match and at times exceed the aversiveness and arousal level of their child, who in turn, matches or exceeds the aversiveness and arousal level of his/her parent. Eventually, this escalation terminates the antagonistic interaction, reinforcing aggression, heightened autonomic arousal, and emotional lability. Such coercive exchanges often begin in the first 5 years of life (Campbell, Pierce, Moore, Marakovitz, & Newby, 1996; Patterson, Capaldi, & Bank, 1991) and are enacted thousands of times over the course of development, producing automated patterns of aversive behavior and negative emotional responding (see Beauchaine et al., 2007). Importantly, both parents and children contribute to the coercive process. Impulsive children elicit reactions from caregivers that exacerbate their preexisting genetic vulnerabilities (O'Connor, Deater-Deckard, Fulker, Rutter, & Plomin, 1998). Such evocative gene–environment correlations occur when children's challenging behaviors are met with ineffective and coercive parenting, which amplifies risk for progression to more serious externalizing behaviors. This process also involves passive gene–environment correlation, as impulsive children are more likely to have impulsive parents who overreact to defiant or provocative behavior.

In addition to the family environment, both peer influences and neighborhood effects contribute to the development and continuance of antisocial behavior (see, e.g., Hiatt & Dishion, 2008). Dishion and colleagues (Nelson & Dishion, 2004; Piehler & Dishion, 2008) have demonstrated powerful longitudinal associations between deviant peer group affiliations in adolescence and later antisocial behavior in adulthood. Importantly, these findings are not merely correlational. Experimental research in which at-risk adolescents are assigned randomly to

group-based interventions often result in *increases* in delinquency among treated participants compared with nontreated controls (Dishion et al., 1999; Dodge, Dishion, & Lansford, 2006).

Finally, impulsive children who are reared in neighborhoods characterized by socioeconomic disadvantage, violence, and crime are at higher risk for delinquency than their peers. For example, Lynam et al. (2000), using both neuropsychological tests and self-report measures, demonstrated that impulsive boys are far more likely than nonimpulsive boys to engage in both status offenses and violent crimes, yet only when they live in low socioeconomic status neighborhoods with high rates of delinquency. No such relation was found in moderate to high socioeconomic status neighborhoods. Given the considerable heritability of impulsivity, this likely reflects a Gene × Environment interaction that has since been replicated in an impressively large sample (Meier et al., 2008).

Following from the above discussion, we have proposed a biosocial developmental model of ASPD that begins with preexisting genetic vulnerabilities, which predispose to trait impulsivity (Beauchaine et al., 2007). In high risk contexts in which coercive family processes are operative, this genetic vulnerability is potentiated, leading to aggression, emotional lability, and significant risk for serious conduct problems. Children along this trajectory are especially vulnerable to the influences of deviant peer groups and high-risk neighborhoods characterized by violence and criminality. Our biosocial developmental model of ASPD is summarized in Figure 3.

Borderline pathology and self-injurious behavior

As noted, the development of BPD has not been studied as extensively as the development of antisocial behavior. Consequently, no clear etiological pathways to BPD have been identified to date. Nevertheless, it is likely that there are impairing precursors to the disorder (Crick, Woods, Murray-Close, & Han, 2007), with emerging evidence supporting a similar developmental progression to that described above for ASPD. Longitudinal studies conducted over impressively long periods of time now indicate that parent–child relationships characterized by early disrupted attachment, poor quality of care, and significant trauma confer risk for the development of borderline symptoms in adulthood (Lyons-Ruth, 2008). Thus, early childhood experiences are similar for those who develop ASPD and those who develop BPD (see above). This confirms earlier retrospective reports (e.g., Norden et al., 1995), and is consistent with the observation that individuals with ASPD and individuals with BPD often are reared within the same families (Goldman et al., 1993).

Limited empirical work has appeared describing risk factors for BPD in middle and later childhood. Nevertheless, evidence suggests that by late childhood and adolescence, borderline features, including hostile attributional styles and relational aggression, can be identified, and are moderately stable (see, e.g., Crick et al., 2005, 2007). Furthermore, heterotypic continuity in symptoms from early childhood to late adolescence and early adulthood has been observed. For example, Caspi and colleagues assessed genetic, temperamental, and environmental risk factors for personality disturbance in a high risk sample (e.g., Caspi, Moffitt, Newman, & Silva, 1996). When participants reached age 18, Caspi and Silva (1995) described a group who were undercontrolled/impulsive as 3-year-olds. As young adults, many of these individuals identified themselves as mistreated or victimized. In addition, they were danger seeking and impulsive, prone to react with negative emotional lability to daily events, and deeply involved in adversarial relationships. In other words, these impulsive and maltreated children later experienced dysregulation across behavior, emotions, cognitions, and interpersonal relations.

As with ASPD, family processes also appear to be important in the development of borderline pathology. Although no empirical data exist describing coercive interaction processes in families of those with borderline features, Linehan (1993) has proposed similar socialization mechanisms. According to her model, emotion dysregulation is socialized through negative reinforcement within an invalidating family context characterized by reciprocal transactions between a challenging child and an ineffective caregiver. More specifically, Linehan proposed

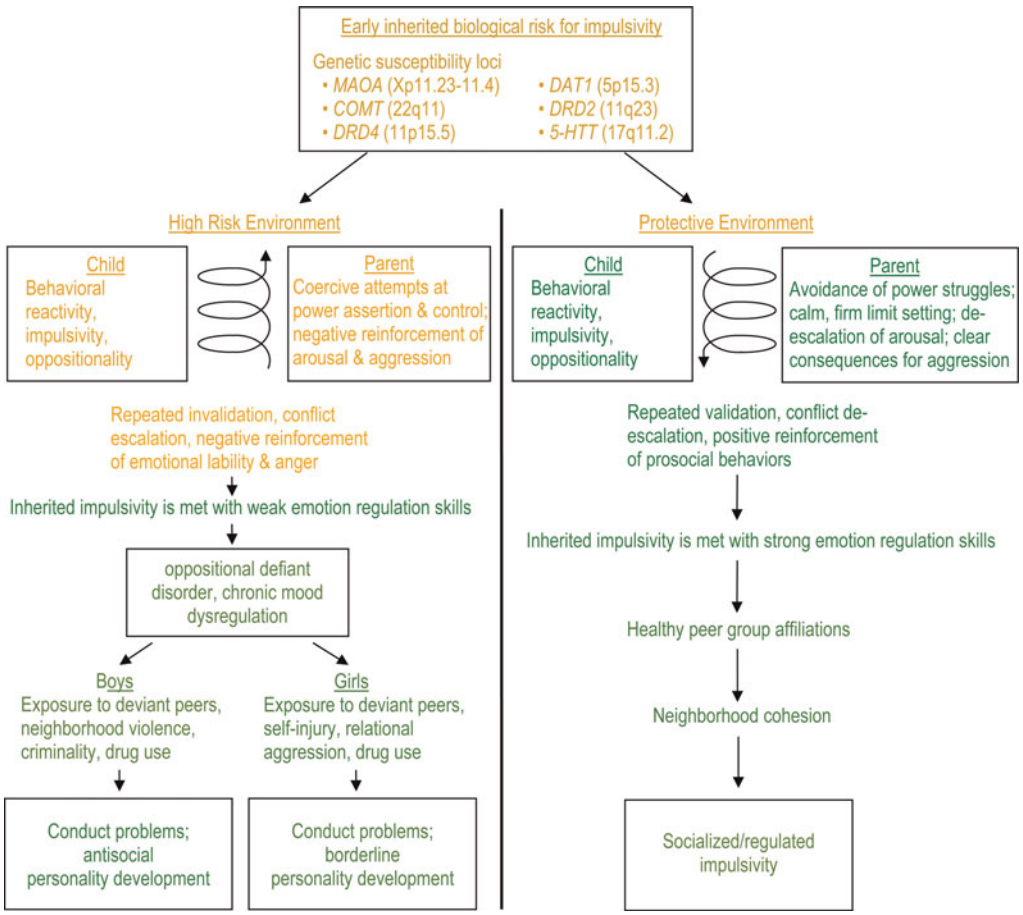

Figure 3. A biosocial model of antisocial and borderline personality development. (Left) Genetic vulnerability interacts with environmental risk to produce oppositional behavior and chronic emotion dysregulation, eventuating in antisocial behavior among boys and borderline traits among girls. (Right) A protective environment buffers vulnerable children from developing emotional and behavioral dysregulation. Adapted from "Polyvagal Theory and Developmental Psychopathology: Emotion Regulation and Conduct Problems From Preschool to Adolescence," by T. P. Beauchaine, L. Gatzke-Kopp, and H. K. Mead, 2007, *Biological Psychology, 74*. Copyright 2007 Elsevier. Adapted with permission. [A color version of this figure can be viewed online at journals.cambridge.org/dpp]

that emotion dysregulation emerges within an environment typified by a lack of tolerance for the outward expression of private emotional experiences (i.e., those that cannot be validated by external events). Within such an environment, vulnerable children are unable to learn appropriate strategies for understanding, labeling, and coping with their emotions. Concurrent with this emotional invalidation, caregivers intermittently reinforce extreme expressions of emotion, communicating to their child that his/her needs are more likely to be met following angry or dysregulated outbursts. Thus, an invalidating family environment reinforces intense emotional displays while simultaneously communicating that such emotions are unwarranted and/or inappropriate. As a consequence, the child struggles with the appropriate expression of emotion and instead vacillates between the extremes of lability and inhibition.

Although longitudinal data testing Linehan's theory have yet to be reported, limited cross-sectional findings are consistent with her model. For example, in the recent study of biological and behavioral correlates of self-injury among adolescent females described above,

we reported that peripheral 5-HT, a putative marker of trait impulsivity (see above), was reduced among self-injuring teens (Crowell et al., 2005). Independently, however, peripheral 5-HT was only a weak predictor of lifetime self-injurious events. Yet in conjunction with observational ratings of negativity and conflict within the mother–daughter dyad, peripheral 5-HT accounted for a remarkable 64% of the variance in self-injurious behaviors (Crowell, Beauchaine, McCauley, et al., 2008). This statistical interaction indicates that the behavioral effects of low peripheral 5-HT are moderated by aversive family interaction patterns. Thus, as with ASPD, biological vulnerabilities to BPD appear to be potentiated by high risk family environments.

Much has also been learned about environmental risk for self-injury. Although not all self-injuring adolescents are on a BPD trajectory, the two populations overlap significantly. As noted above, both conditions are characterized by comorbidity of internalizing and externalizing psychopathology (e.g., Verona, Sachs-Ericsson, & Joiner, 2005). Moreover, there is a high rate of self-inflicted injury among those with BPD, with approximately 40–90% engaging in nonsuicidal self-injury or making a suicide attempt during their lifetime (APA, 2000). Overlapping environmental risk factors include poverty and familial chaos, neglect, and invalidation (Johnson, Cohen, Brown, Smailes, & Bernstein, 2008; Johnson et al., 1999). Self-injurious behaviors are often impulsive, while also serving to regulate overwhelmingly negative mood (Klonsky, 2007).

As with ASPD, peer influences contribute to the development and persistence of self-inflicted injury and suicidal ideation. In a ground-breaking series of studies, Prinstein, Boergers, Spirito, Little, and Grapentine (2000) have demonstrated contagion effects of self-injury and suicidal ideation, which are often learned from deviant peers. Furthermore, many adolescents who engage in self-injury do so in part for social reinforcement purposes (Nock & Prinstein, 2004, 2005). Thus, these borderline features appear to emerge from the combination of trait impulsivity, adverse family contexts, and deviant peer group affiliations.

Following from this discussion, our biosocial developmental model of BPD, which parallels the previously discussed pathway to ASPD, is depicted in the left panel of Figure 3. We propose that trait impulsivity is the primary vulnerability to borderline pathology. Within high risk (i.e., invalidating and coercive) family environments, this vulnerability is potentiated, primarily among girls, through intermittent reinforcement of emotional lability and aggression (physical and/or relational), leading to heightened negative affectivity, interpersonal conflict, and chronic dysregulated mood. Children on a BPD trajectory are also at risk for continued failure to navigate developmental and social challenges, perhaps because of a hostile or paranoid attributional style. By adolescence, the combination of impulsivity, mood symptoms, and disrupted interpersonal relationships, in conjunction with deviant peer group affiliations, increases risk for more extreme maladaptive regulatory behaviors such as self-inflicted injury. Although not all people with BPD engage in self-injury, the function that the behavior serves is common to nearly all adults with BPD. Dysregulated, mood-dependent behaviors (e.g., self-injury, explosive anger, substance abuse) are a primary means of coping among those with the diagnosis.

Interim summary

In addition to the common biological vulnerabilities outlined in earlier sections, risk factors for antisocial and borderline personality development are quite similar. For both disorders, environmental risk, including poor quality of care, disrupted attachment relationships, socioeconomic disadvantage, and abuse and neglect, is often expressed beginning in infancy. By early childhood, coercive and invalidating family processes become operative. These family interaction patterns, which are enacted countless times over the course of development, negatively reinforce emotional lability, aggression, and in some cases interpersonal violence. Thus, at-risk children acquire automated response patterns of emotional dysregulation, which are overlaid onto heritable trait impulsivity. In later childhood and adolescence, deviant peer group affiliations emerge in which boys on an antisocial trajectory learn delinquent behaviors from their friends and in which girls on a borderline trajectory learn self-injurious behaviors from their friends. These

parallel processes can be captured by a single developmental model.

Concluding Remarks

In this article we have proposed a unified theory of antisocial and borderline personality development that accounts for a number of overlapping biological vulnerabilities, environmental risk factors, and outwardly expressed features of ASPD and BPD. To date, the literatures on these two disorders have been largely disconnected, with a few notable exceptions (e.g., Norden et al., 1995; Paris, 1997).

A primary advantage of specifying etiological pathways to psychopathology is the development of targeted interventions that address causal processes directly (see, e.g., Beauchaine & Marsh, 2006). For example, identifying family coercion in the etiology of delinquency (Patterson, 1982) led to more refined interventions for conduct problems that target the specific parent and child behaviors that maintain and advance antisocial behavior patterns (e.g., Webster-Stratton & Hammond, 1997). To our knowledge, comparable middle childhood interventions for borderline personality development do not yet exist. However, if Linehan's (1993) theory of etiology is correct and similar family processes support borderline personality development, interventions can and should be formulated that target the invalidation and negative reinforcement of emotional liability described above. Furthermore, knowledge of the etiology of borderline pathology tells us that girls who live in families with a delinquent boy should not be overlooked when a parent–child intervention targeting the boy is initiated.

It is important to note that several aspects of our theory, especially those specific to BPD development, need to be confirmed through additional studies. As we acknowledge above, much less empirical work has described trajectories to BPD, and Linehan's (1993) invalidation model needs to be verified. Doing so will require painstaking coding of family interactions, similar to the work conducted by Snyder and colleagues describing microsocial behavior patterns in the families of delinquent and aggressive children (e.g., Snyder et al., 1997).

Finally, our shared etiology hypothesis rests on the assumption that at least some high-risk genes confer differential vulnerability to aggression and mood dysregulation in boys versus self-injury and mood dysregulation in girls. Although we provided preliminary support for this assumption, several findings need to be replicated in future studies. Whether or not such replication is realized, we hope that our common theory of antisocial and borderline personality development provides an organizing framework for future studies that advance our understanding of these two very costly mental health conditions.

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