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CHAPTER 6

Impulsivity and Vulnerability to Psychopathology

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Terms such as impulsive, disinhibited, and hyperactive have long been used to describe individuals with deficient control over their behaviors. Although some degree of such traits is developmentally appropriate for young children, those who display extreme impulsivity or fail to acquire age-appropriate self-regulation as they mature are vulnerable to a host of maladaptive outcomes. According to developmental psychopathology models of externalizing behavior, extreme impulsivity expressed in the preschool years may represent the first stage in a trajectory that can progress via potentiating and mediating variables to early onset delinquency and other antisocial behaviors (Beauchaine, Hinshaw, & Pang, 2010; Beauchaine, Gatzke-Kopp, & Mead, 2007; Campbell, Shaw, & Gilliom, 2000; Hinshaw, Lahey, & Hart, 1993; Patterson, DeGarmo, & Knutson, 2000). Indeed, trait impulsivity likely underlies a range of disorders falling along the externalizing spectrum, including attention-deficit/hyperactivity disorder (ADHD), conduct disorder (CD), antisocial personality disorder (ASPD), and substance use disorders (see Barkley, 1997; Beauchaine, Klein, Crowell, Derbidge, & Gatzke-Kopp, 2009; Krueger et al., 2002). In other cases, temperamental disinhibition marks the beginning stages of a developmental trajectory that culminates in self-harm, depression, and other forms of internalizing psychopathology (Beauchaine et al., 2009; Hirshfeld-Becker et al., 2002). Thus, impulsivity observed very early in life may indicate considerable risk for a wide range of adverse, multifinal outcomes.

HISTORICAL CONTEXT

As with nearly all psychological phenomena, ideas about the nature and etiology of disinhibition have evolved considerably over the 19th and 20th centuries. Early neurobiological theories of behavioral control focused on frontal regions of the brain. These theories derived largely from observations of altered behavior among those

who suffered from traumatic brain injuries, such as Phineas Gage. In 1848, Gage, a railroad foreman, suffered a severe brain injury when a blasting charge propelled an iron rod through his eye socket and out the frontal part of his skull. Despite full recovery of motor and sensory functions, Gage's personality transformed radically as a result of his injury (Macmillan, 1992). Whereas Gage had been "quiet and respectful" prior to the accident, he became "gross, profane, coarse, and vulgar to such a degree that his society was intolerable to decent people" (Bigelow, 1850, cited in Macmillan, 1992, p. 86). He was further described as "impatient of restraint or advice when it conflicts with his desires, at times pertinaciously obstinate, yet capricious and vacillating, devising many plans of future operation, which are no sooner arranged than they are abandoned in turn for others appearing more feasible" (Harlow, 1868, cited in Macmillan, 2004). Thus, the most striking result of Gage's injuries was marked behavioral disinhibition that contrasted starkly with his socially appropriate demeanor prior to the injury.

Consistent with theories of the time, explanations of Gage's behavior relied on two assumptions. First, particular brain regions located in the frontal lobe were assumed to support specific behavioral traits. When these regions were damaged, those traits were no longer supported. In Gage's case, the shift in behavior was attributed to the rod having injured the "regions of the organs of BENEVOLENCE and VENERATION" (Harlow, 1868, cited in Macmillan, 1992). Second, it was assumed that competing factors were at work within the mind, with behavior resulting from the equilibrium established between them. When this equilibrium was disrupted by damage to parts of the brain, the changing balance affected behavior. In the absence of the inhibiting influence of the damaged areas, the balance between Gage's "intellectual faculties and his animal propensities" was destroyed (Harlow, 1868, cited in Macmillan, 2004), resulting in disinhibited behavior. As later sections of this chapter reveal, this theme—that behavior derives from a relative equilibrium between self-gratifying and cautious motivations—has influenced most major theories of impulsivity and continues to do so today.

Twentieth-century conceptualizations of impulsivity and disinhibition continued to look toward imbalances in competing neurobiological systems. Eppinger and Hess (1915) argued that vagotonia, an imbalance within the autonomic nervous system favoring the parasympathetic over the sympathetic division, accounted for a number of medical and psychological phenomena. They described vagotonia as an "abnormal irritability of all or only a few autonomic nerves" (p. 39), including the 10th cranial (vagus) nerve, and portrayed it as a chronic disposition as opposed to an acute disorder. Occurring more frequently in young individuals, vagotonia was hypothesized to cause neurasthenia, hysteria, and nervousness. Eppinger and Hess described patients with vagotonia as "hasty and precipitous" (p. 40), foreshadowing the links that would later be made between the condition and hyperactivity. Although the vagotonia hypothesis has since been refuted (see Beauchaine, 2001), by the mid-20th century, it was a candidate cause of restlessness and hyperactivity in children, and was considered a possible predictor of later antisocial behavior (e.g., Venables, 1988). More recent sources indicate compromised sympathetic *and* parasympathetic functioning in impulsive children and adolescents (Beauchaine & Gatzke-Kopp, 2012; Beauchaine, Katkin, Strassberg, & Snarr, 2001; Beauchaine et al., 2007; Crowell et al., 2006).

At about the same time the vagotonia hypothesis emerged, the encephalitis epidemics of 1918 yielded a group of children who displayed marked impulsivity, hyperactivity, inattention, aggression, and impairments in judgment (Carlson & Rapport, 1989; Schachar, 1986). Neurologists of the time attributed these behaviors (even in the absence of encephalitic infection) to some kind of underlying neurological disturbance, and the term minimal brain dysfunction (MBD) came to describe such children, as well as those with learning disabilities and other problems (Hässler, 1992). Theories varied with respect to which region(s) of the brain were injured, but it was assumed that impulsivity and hyperactivity resulted from brain damage of some sort, even among children with no documented history of head trauma or illness (Lyon, Fletcher, & Barnes, 2003). Although the problem behaviors included under MBD shifted over the next few decades, variations of the term and concept remained popular until recently (Hässler, 1992). It was not until the *DSM-III* emerged in 1980 that the category of MBD was dropped, and children with learning difficulties were distinguished officially from those with behavioral difficulties (Lyon et al., 2003).

TERMINOLOGICAL AND CONCEPTUAL ISSUES

Despite the centrality of trait impulsivity to current theories of ADHD, conduct disorder (CD), antisocial behavior, and substance use disorders, the construct lacks both a consistent operational definition and a standard method of measurement. Although impulsivity has been defined traditionally by behavioral symptoms, some researchers have attempted to refine these definitions based on results from neuropsychological tests. For example, reaction time during verbal tasks has been used to assess the degree of "short-circuiting of analytic or reflective thought processes" (Oas, 1985, p. 141). Alternatively, errors in maze solving have been suggested to reflect impulsivity, as they may represent poor attention to detail as well as carelessness and lack of planning (Porteus, 1965). Perseverative errors during set-shifting tasks such as the Wisconsin Card Sorting Test have also been attributed to impulsivity (e.g., Avila, Cuenca, Félix, Parcet, & Miranda, 2004), as have errors due to overly quick responding and lack of reflection during match-to-sample tasks such as the Matching Familiar Figures Test (Oas, 1984). Among the most popular measures of impulsivity in neuropsychology are drawing tasks such as the Bender Gestalt (Bender, 1938) and the Draw-A-Person test (Koppitz, 1968). In such tests, impulsivity is assessed by scoring drawings on the basis of variables such as completion time, overall quality, omissions, asymmetry, detailing, and shading (Oas, 1984). Continuous performance tests (e.g., Conners & MHS Staff, 2000; Gordon, 1988) are also purported to assess impulsivity by indexing errors of commission—when participants fail to inhibit inappropriate responses.

Although measures such as these provide various means of operationalizing impulsivity, they do not speak to the neural mechanisms underlying the construct, nor do they fully explain relations between impulsivity and psychopathology (see

Gatzke-Kopp, 2011). Many of these formulations describe impulsivity in highly cognitive terms, likening it to executive functions such as inhibitory control (the ability to interrupt an ongoing action or prevent a prepotent reaction; Kenemans et al., 2005) or effortful control (the ability to control attentional processes and behavior to inhibit a dominant response in favor of a nondominant response; Rothbart & Bates, 1998), two closely related constructs. Although it remains to be determined how cognitive constructs such as these relate to behavioral or trait disinhibition, they are likely to show some overlap, as different measures of inhibitory and effortful control correlate with various facets of impulsivity and problem behavior (e.g., Enticott, Ogloff, & Bradshaw, 2006; Murray & Kochanska, 2002).

More recent cognitive models of disinhibition integrate multiple components of the trait, suggesting several alternative brain mechanisms that may be responsible for impulsive behavior, exemplifying equifinality (see Chapter 1). Nigg (2000, 2005; Chapter 12), for example, has suggested that disinhibition results from dysfunction in at least one of two inhibitory systems. He distinguishes between motivational inhibition, which results from behavioral suppression in the context of anxiety-provoking cues, and executive inhibition, or the deliberate process of stopping or suppressing a response that is prepotent but task-inappropriate. Barkley (1997) has also characterized disinhibition as faulty inhibition, positing a hierarchical inhibitory structure in which behavioral inhibition consists of three subprocesses (inhibition of prepotent responses, halting of ongoing responses, and control of interfering stimuli), each supporting a number of executive functions that allow for effective goal-directed behavior.

Behaviorally, impulsivity has been described as actions that are "socially inappropriate or maladaptive and quickly emitted without forethought" (Oas, 1984, 1985). This behavioral rather than neuropsychological definition has a number of strengths. Although it is distinct from the more heavily cognitive formulations of disinhibition, it does not rule out cognitively mediated mechanisms. Furthermore, it emphasizes disinhibition as a maladaptive trait, distinguishing it from other qualities such as spontaneity that are frequently viewed more positively. Finally, it does not include causal assumptions regarding the etiology of disinhibition, allowing for both psychological and biological contributions.

At present, the most widely used definition of impulsivity/disinhibition is likely that described in the *DSM-IV* (2000). As a component of attention-deficit/hyperactivity disorder (ADHD), impulsivity is demonstrated by "impatience, difficulty in delaying responses, blurting out answers before questions have been completed, difficulty awaiting one's turn, and frequently interrupting or intruding on others" (p. 86). Similarly, Sagvolden, Johansen, Aase, and Russell (2005) describe impulsivity as taking action without forethought and failing to plan ahead, linking it to such related concepts as risk taking, novelty-seeking, sensation-seeking, over-rapid responding, and susceptibility to the pull of immediate rewards (see also Hirshfeld-Becker et al., 2002). These behaviors are considered pathological when they are performed to the point that they interfere with social, academic, and/or occupational functioning, consistent with Oas's (1985) theme of disinhibition as maladaptive and socially inappropriate.

ETIOLOGICAL FORMULATIONS

As should be apparent from this discussion, behavioral (phenotypic) expression of impulsivity may derive from one or more of several sources (see also Sonuga-Barke, 2005). Well-characterized influences on impulsive behavior include brain injuries, which may result from head trauma, hypoxia, or other central nervous system insults (Chapter 10); exposure to teratogens such as alcohol, stimulant drugs of abuse, and/or lead (Chapter 9); early traumatic experiences including social deprivation, child abuse, and neglect (Lucas et al., 2004; Poeggel et al., 1999; Chapter 5); or genetic vulnerabilities that give rise to deficient executive control over behavior (Chapter 12). Although this list is certainly not exhaustive, it illustrates the heterogeneous nature of broad behavioral traits such as impulsivity (see Beauchaine et al., 2010; Beauchaine & Marsh, 2006).

HETEROGENEITY IN THE IMPULSIVITY PHENOTYPE

Rather than describing each of these mechanisms in detail, we begin by focusing on particular neurobiological substrates of disinhibition that (a) give rise to individual differences in impulsivity that are temperamental, present very early in life, and emerge before ADHD can be diagnosed; (b) are supported by voluminous literatures derived from both animal models and humans; and (c) confer vulnerability to externalizing disorders across the lifespan, particularly in the context of high risk environments characterized by violence, trauma, and emotional lability. This focus on temperamental impulsivity is consistent with our main objective in writing this chapter: to describe early-onset impulsivity as a *vulnerability* for later psychopathology. Readers should note, however, that it may be difficult in clinical practice to distinguish between children who are impulsive due to an inherited temperamental trait versus children who are impulsive due to other etiological influences such as prenatal stimulant exposure (see, e.g., Beauchaine, Neuhaus, Zalewski, Crowell, & Potapova, 2011).

Most modern accounts of temperamental disinhibition emphasize structural and functional abnormalities in phylogenetically old brain regions including the mesolimbic dopamine system and the basal ganglia, overlapping neural networks that mature very early in life and are likely to subserve individual differences in impulsivity among young children (see Beauchaine et al., 2001, 2010, 2012; Gatzke-Kopp, 2011; Gatzke-Kopp & Beauchaine, 2007; Sagvolden et al., 2005). Accordingly, heritable compromises in the functioning of these brain regions and associated risk for psychopathology provide the foundations of this chapter. In contrast, frontal theories of disinhibition are not considered "foundational," because these brain regions mature late in adolescence (or beyond) and are therefore less likely to underlie the early expression of trait 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, Neuhaus, Brenner, & Gatze-Kopp, 2008; Sagvolden et al., 2005; see also Shannon, Sauder, Beauchaine,

& Gatzke-Kopp, 2009). In other words, heritable compromises in the functioning of early maturing brain regions that give rise to impulsivity are likely to alter the neurodevelopment of later maturing brain regions that are responsible for executive functioning and planning—especially in high-risk environments. This model highlights the transactional nature of the brain in affecting behavior, and of behavior in affecting subsequent brain development. Recognition and description of such transactions between the individual and the environment are tenets of the developmental psychopathology perspective (see Beauchaine & Gatzke-Kopp, 2012; Cicchetti, 2006; Rutter & Sroufe, 2000; Sroufe & Rutter, 1984; Chapter 1). In later sections, we therefore describe neurodevelopmental mechanisms through which early impulsivity may potentiate vulnerability for deficient executive functioning later in life.

TEMPERAMENTAL IMPULSIVITY AND CENTRAL DOPAMINE FUNCTIONING

Theories advanced to explain individual differences in impulsivity have long focused on the mesolimbic dopamine (DA) system, including the ventral tegmental area and its projections to the nucleus accumbens (Swartz, 1999), and on other dopaminergic networks within the central nervous system (Beauchaine & Gatzke-Kopp, 2012; Castellanos, 1999; Gatzke-Kopp, 2011; Gatzke-Kopp & Beauchaine, 2007, Kalivas & Nakamura, 1999; Sagvolden et al., 2005). Many of these theories follow from seminal research on reinforcement motivation and substance dependence conducted with rodents and nonhuman primates. This research demonstrates that (a) electrical and pharmacological stimulation of dopaminergically mediated mesolimbic structures is reinforcing, such that trained animals will engage in prolonged periods of operant behaviors (e.g., lever pressing) to obtain these incentives (see Milner, 1991); (b) 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; Schott et al., 2008); and (c) DA antagonists attenuate—and in extreme cases block—the rewarding properties of food, water, and stimulant drugs of abuse (e.g., Rolls et al., 1974).

Based on this set of observations, several authors have offered theories of impulsivity and personality that explain individual differences in approach behavior as variations in activity of mesolimbic structures. The most prominent of these theories is that offered by Gray (1987a, 1987b), in which he proposed a mesolimbic behavioral approach system (BAS) as the neural substrate of appetitive motivation. Soon afterward, clinical scientists interested in impulsivity co-opted dopaminergic theories of approach motivation to explain the unbridled reward-seeking behaviors observed in ADHD, CD, and related externalizing disorders (e.g., Fowles, 1988; Quay, 1993; Rogeness, Javors, & Pliszka, 1992).

Although these early theories correctly identified mesolimbic neural structures implicated in the expression of impulsivity, most researchers at the time subscribed to the face-valid assumption that excessive dopaminergic activity led to impulsive behavior. In other words, they assumed a positive correspondence between neural

responding and behavior. This assumption is evident in the formulation of measures such as the BIS/BAS scales (Carver & White, 1994), which presuppose a direct relation between impulsive behaviors and BAS activity (see Brenner, Beauchaine, & Sylvers, 2005). However, several clear and consistent findings present intractable problems for theories linking excessive mesolimbic DA activity to impulsivity.

First, several studies indicate reduced sympathetic nervous system (SNS)-linked cardiac reactivity to reward among impulsive preschoolers, middle-schoolers, and adolescents (Beauchaine et al., 2001, 2007; Crowell et al., 2006). These findings are significant because (a) SNS-linked cardiac reactivity to incentives serves as a peripheral index of central DA responding (Brenner et al., 2005; Brenner & Beauchaine, 2011) and (b) infusions of DA into mesolimbic structures produce SNS-mediated increases in cardiac output (van den Buuse, 1998). Thus, reduced cardiac reactivity to reward among impulsive children is likely to mark attenuated DA responding—directly opposite to expectations based on the excessive DA theory.

Second, studies using both single photon emission computed tomography (SPECT) and positron emission tomography (PET) demonstrate that the primary mechanism of action of methylphenidate and related DA agonists is increased neural activity in the striatum, a structure located within the mesolimbic reward pathway (e.g., Vles et al., 2003; Volkow, Fowler, Wang, Ding, & Gatley, 2002). Thus, pharmacological interventions that *increase* mesolimbic DA activity by inhibiting reuptake *decrease* hyperactivity, impulsivity, and related aggressive behaviors (e.g., Hinshaw, Henker, Whalen, Erhardt, & Dunnington, 1989; MTA Cooperative Group, 1999). Theories of excessive DA as a mechanism of impulsivity predict the opposite effect (i.e., increasing striatal DA activity should exacerbate impulsivity).

Finally, infusions of DA into mesolimbic structures are experienced as pleasurable, and individual differences in central DA expression predict trait positive affectivity (see Ashby, Isen, & Turken, 1999; Berridge, 2003; Forbes & Dahl, 2005). In contrast, PET studies indicate that low levels of striatal DA activity are associated with trait irritability (Laakso et al., 2003). When interpreted in the context of positive relations between externalizing behaviors and both negative affectivity and irritability (e.g., Martel & Nigg, 2006; Mick, Spencer, Wozniak, & Biederman, 2005), these findings suggest diminished rather than excessive DA functioning among at least some impulsive individuals.

These converging sources of evidence for reduced DA functioning as a neural substrate of impulsivity have led to a reformulation of first-generation models. We and others have suggested that underactivation of striatal DA leads to increased behavioral responding, which functions to raise activation levels within the mesolimbic system (Beauchaine et al., 2007; Beauchaine et al., 2012; Gatzke-Kopp, 2011; Gatzke-Kopp & Beauchaine, 2007; Sagvolden et al., 2005; Volkow et al., 2009). Thus, what has been assumed to be reward hypersensitivity is more likely to be reward *insensitivity*, which results in increased impulsive and perseverative responding to up-regulate a chronically aversive mood state—the affective consequence of an underactive mesolimbic DA system (Ashby et al., 1999; Forbes & Dahl, 2005; Laakso et al., 2003). In addition to the literature cited above, this interpretation is supported by research indicating (a) associations between low basal DA activity/blunted DA reactivity

and a propensity to use DA agonist drugs of abuse (De Witte, Pinto, Ansseau, & Verbanck, 2003; Laine, Ahonen, Räsänen, & Tiihonen, 2001; Martin-Soelch et al., 2001; Martinez et al., 2007); (b) significant correlations between blunted DA responses to amphetamine administration and the personality trait of novelty seeking (Leyton et al., 2002); and (c) recent neuroimaging studies indicating reduced striatal activity during reward tasks among children and adolescents with ADHD and CD (Carmona et al., 2011; Durston et al., 2003; Vaidya et al., 1998). Thus, accumulating evidence now supports the hypothesis that trait impulsivity results at least in part from abnormally low central DA activity.

GENETICS AND HERITABILITY

There are two general approaches to studying the genetic bases and heritability of any behavioral trait—behavioral genetics and molecular genetics (see Chapter 3)—each of which contributes differently but significantly to our understanding of impulsivity.

Behavioral Genetics of Impulsivity

Behavioral genetics studies are used to parse variability in a behavioral trait into heritable (both genetic and nongenetic) and nonheritable (environmental) components. Overwhelming evidence indicates that impulsivity is among the most highly heritable of all behavioral traits. Behavior genetics studies comparing concordance rates of impulsivity and ADHD for monozygotic and dizygotic twins produce heritability estimates (h^2) approaching and exceeding .8, indicating that as much as 80% of the variance in impulsive behavior is accounted for by heritable factors (e.g., Levy, Hay, McStephen, Wood, & Waldman, 1997; Price, Simonoff, Waldman, Asherson, & Plomin, 2001; Sherman, Iacono, & McGue, 1997; Willcutt, in press; Wood, Rijsdijk, Saudino, Asherson, & Kuntsi, 2008). Furthermore, Krueger et al. (2002) identified a common vulnerability for a wide range of externalizing symptoms including disinhibition, conduct problems, antisocial personality, alcohol dependence, and drug dependence among a sample of 1,048 participants in the Minnesota Twin Family Study. This latent vulnerability for externalizing disorders, which likely reflects trait impulsivity (Beauchaine & Marsh, 2006), was 81% heritable. Similar findings have since been reported in child samples (Tuvblad, Zheng, Raine, & Baker, 2009). However, each specific category of externalizing behavior was influenced strongly by environmental effects. This finding is important because it demonstrates that a common genetic vulnerability can result in divergent multifinal outcomes depending on environmental experience (Beauchaine et al., 2010; 2012), a point to which we return later.

Molecular Genetics of Impulsivity

Molecular genetics approaches, including both linkage and association studies, are designed to identify specific genes that contribute to the expression of a trait or

disorder (see Chapter 3). Linkage studies search for chromosomal regions that are shared more often than expected among large numbers of families with two or more affected children (Faraone & Mick, 2010). Using this approach, the gene responsible for cystic fibrosis was found by 'linking' the disease to a DNA variant on the long arm of Chromosome 7 within affected families. This discovery was followed by a number of additional linkage studies that specified the location on Chromosome 7 in greater detail (see Bolsover, Hyams, Jones, Shepard, & White, 1997). Because linkage analyses scan broad sections of the genome, the approach works best when very few genes with large effects contribute to a behavioral trait or disease—a rare precondition for psychiatric disorders, which are usually determined polygenically. Nonetheless, a recent genome scan meta-analysis combining 7 datasets supported a significant linkage for ADHD on Chromosome 16, with possible linkages within a number of other regions (Zhou et al., 2008). However, no specific gene has yet been identified through linkage analysis, and failures to replicate plague psychiatric genetics research (see Chapter 3).

In contrast to linkage studies, genetic association studies begin with a candidate gene that is thought to play an etiological role in the expression of a disorder (see Chapter 3). Using this approach, allelic frequencies of specific genetic polymorphisms are compared among those with and without the condition under study. Association studies can be used to detect genes that account for much smaller amounts of variance in behavior. Given well-articulated theories specifying altered DA functioning as a pathophysiological determinant of impulsivity (see above), association studies are well suited for use with this behavioral trait (Galili-Weisstub & Segman, 2003).

Not surprisingly, association studies far outnumber linkage studies of impulsivity and ADHD. Although the consistency of results and effect sizes from these studies have been mixed, meta-analyses suggest a small but significant role for the DRD4 gene (Chromosome 11p15.5), which codes for DA receptors located throughout the central and peripheral nervous systems (Benjamin et al., 1996; Faraone & Mick, 2010; Li, Sham, Owen, & He, 2006). The DAT1, or dopamine transporter gene (Chromosome 5p15.3), regulates synaptic levels of DA, the principal target of psychostimulants used to treat ADHD (Grace, 2002). Although allelic status appears to correlate with volume and activation within mesolimbic structures (Durston, 2010), the precise role of DAT1 in the pathophysiology of ADHD is unclear. Early findings varied considerably across studies and samples (Castellanos & Tannock, 2002; Yang, Chan, Jing, Li, Sham, & Chen, 2007). However, recent data suggest that DAT1 may be more influential in combination with specific environment risk factors such as prenatal substance exposure (Faraone & Mick, 2010; Laucht et al., 2007; Neuman et al., 2007). Other DA genes have been studied as well, but evidence for their roles in the pathophysiology of impulsivity is less consistent (see also Chapter 12).

In addition to genes that are involved directly in DA expression, association studies have also been conducted to evaluate the effects of genes that are involved in the synthesis and metabolism of DA, as these processes also influence synaptic

activity and reuptake. Candidate genes include those that encode for dopamine-β-hydroxylase (DBH), which converts DA to norepinephrine; and both monoamine oxydase (MAO) and catechol-o-methyl transferase (COMT), enzymes involved in DA (and other monoamine neurotransmitter) degradation. Association studies involving these genes have been few and conflicting. With regard to DBH, allelic status has been linked with ADHD within some child and adult samples (Hess et al., 2009), but meta-analyses cast doubt on the reliability and strength of these links (Gizer, Ficks, & Waldman, 2009). Current evidence suggests that polymorphisms in both the MAOA gene (Xp11.23–11.4) and the COMT gene are associated with antisocial behavior among impulsive individuals, particularly in the context of environmental adversity (Caspi et al., 2002; Qian et al., 2009; Thapar et al., 2005). However, direct associations between these genes and ADHD are less consistent in direction and effect size (see Faraone & Mick, 2010), and MAO may have differential effects on impulsivity according to sex (indeed, it is X-linked; see Biederman et al., 2008). Taken together, this set of genes (DBH, MAO, and COMT) may have little effect on the core trait of impulsivity but larger effects on externalizing sequelae, reflecting the effects of Gene × Environment interactions on the development of externalizing behavior (see Beauchaine et al., 2009).

To summarize, behavioral genetics studies of trait impulsivity indicate impressively high heritability estimates and suggest that disinhibition contributes to a number of externalizing behavior patterns. Yet despite this high heritability, candidate genes identified to date account for little variance in impulsive behavior. This state of affairs suggests that considerable work remains in the attempt to understand the genetic bases of impulsivity, which extends to research on most behavioral traits (see Chapter 3).

IMPULSIVITY AND VULNERABILITY TO PSYCHOPATHOLOGY

In developmental psychopathology, a distinction is often made between vulnerabilities and risk factors for psychiatric disorders (e.g., Luthar, 2006; Shannon, Beauchaine, Brenner, Neuhaus, & Gatzke-Kopp, 2007). Vulnerabilities are usually assumed to be biologically based traits that render individuals susceptible to psychopathology, whereas risk factors are environmental influences that interact with vulnerabilities to potentiate psychopathology. For example, it is now known that distressing experiences (risk factors) elicit post-traumatic stress disorder mainly in genetically predisposed (vulnerable) individuals (e.g., Orr et al. 2003; Stein, Jang, Taylor, Vernon, & Livesley, 2002). Although the distinction between vulnerabilities and risk factors breaks down when we consider the interactive roles that genetically determined traits play in eliciting specific environments (evocative effects) and that environments play in the expression of genes (see Moffitt, 2005; Shannon et al., 2007), we maintain traditional use of the terms in upcoming sections, where we outline factors that amplify the likelihood of psychopathology among impulsive and therefore vulnerable individuals.

Before proceeding, however, it should be noted that temperamental impulsivity is usually not enough (except in perhaps the most extreme cases) to result in psychopathology in the absence of additional vulnerabilities and/or risk factors. Research with impulsive preschoolers indicates that at least half progress into later childhood without developing significant behavior problems (see Beauchaine et al., 2010; Campbell et al., 2000). In the sections to follow we summarize several additional vulnerabilities and risk factors that interact with temperamental disinhibition to increase the probability of later psychopathology.

BEHAVIORAL INHIBITION

In addition to impulsivity, a second well characterized temperamental trait is behavioral *inhibition*. This term refers to a general tendency to be wary in novel situations, to be "slow to warm up," and to avoid overly stimulating environments. Kagan, Reznick, and Snidman (1988) identified a group of 3-year-olds who displayed high degrees of behavioral inhibition in unfamiliar laboratory settings. These children avoided approaching and interacting with unfamiliar children and adults, remained in close proximity to their mothers, and ceased vocalizing in the presence of strangers. When they were reassessed at age 7, they remained quiet, cautious, and socially avoidant. Thus, like trait impulsivity, behavioral inhibition can be detected very early in life and is stable (although not invariant) across development. It is also mediated largely by genetic factors (see Chapter 7).

It has often been assumed that trait inhibition and impulsivity mark extremes along a continuum of behavioral control, yet the neural substrates of the two traits are almost completely non-overlapping. In contrast to impulsivity, behavioral inhibition, which renders individuals vulnerable to anxiety disorders, is mediated by the septo-hippocampal system, a primarily serotonergic network (see Gray & McNaughton, 2000). Moreover, the two systems evolved to subserve distinct functions: approach behaviors promote survival by ensuring engagement in activities such as eating, drinking, and copulating; whereas avoidance behaviors promote survival by reducing exposure to danger. In fact, Gray and others (Gray & McNaughton, 2000; McNaughton & Corr, 2004) have argued convincingly that the functional role of the septo-hippocampal system is to *suppress* approach behaviors under conditions of threat.

This conceptualization, in which approach tendencies are actively suppressed by avoidance tendencies, is supported by a large literature on experiments with animals and has direct implications for psychopathology (see Beauchaine, 2001; Beauchaine et al., 2011). Given that the approach and avoidance systems operate with substantial independence, one can be high or low on either or both dimensions. A person who is temperamentally impulsive due to a heritable DA deficiency may be protected from severe psychopathology *if* he or she is also high on behavioral inhibition. Although this might seem implausible at first glance, symptoms of anxiety are surprisingly common among impulsive children with ADHD (Angold, Costello, & Erkanli, 1999; MTA Cooperative Group, 1999), and in the absence of additional comorbidities, such children are more responsive to behavioral interventions than their non-anxious counterparts (Jensen et al., 2001). Furthermore, older externalizing youth with comorbid anxiety are less physically aggressive, regarded less negatively

by peers, and experience fewer police contacts than those without anxiety symptoms (Walker et al., 1991). Such findings are precisely what would be expected from a more responsive septo-hippocampal system. Consistent with this interpretation, in a recent structural neuroimaging study, interactions between trait anxiety and trait impulsivity predicted individual differences in gray matter volumes in both septo-hippocampal and mesolimbic brain regions among children with ADHD (Sauder, Beauchaine, Gatzke-Kopp, Shannon, & Aylward, 2012). Those with ADHD who experienced comorbid anxiety showed normal gray matter volumes in these brain regions compared with controls, whereas those who experienced low levels of anxiety exhibited reduced gray matter volumes.

As this discussion implies, an impulsive person who is low on trait anxiety may be especially vulnerable to developing more serious externalizing disorders. Psychopathy, a behavior pattern characterized by manipulation of others, superficial charm, callousness, and lack of remorse, is probably the most intractable form of externalizing conduct (see Lykken, 2006). As several authors have noted, individuals high in psychopathy exhibit excessive approach behaviors that are *coupled with* a disturbing lack of anxiety and fear (see Fowles & Dindo, 2006). Thus, their impulsive tendencies are not inhibited by impending consequences, presumably because they are very low on behavioral inhibition. As a result, the condition is largely unresponsive to treatment.

Given that temperamental impulsivity and inhibition are both largely heritable, individuals with psychopathy appear to be "doubly vulnerable" to psychopathology. This situation might best be considered a Trait × Trait interaction, with two largely independent heritable attributes contributing to behavioral functioning (see also Derryberry, Reed, & Pilkenton-Taylor, 2003). Although such models are rare in psychopathology research, recent advances in molecular genetics make it much easier to study interactions among underlying genes that potentiate psychiatric morbidity (see, e.g., Beauchaine et al., 2009).

Environmental Risk

There is also considerable evidence that environmental risk can lead to more severe psychopathology among impulsive children, including those with ADHD. These youth are more likely than their non-ADHD peers to develop oppositional defiant disorder (ODD), conduct disorder (CD), and antisocial personality disorder (Barkley, 2003). Longitudinal studies suggest that for many children, hyperactivity/impulsivity constitutes the first stage in a trajectory that progresses via mediating risk factors to antisocial behaviors, eventually culminating in early-onset delinquency (see Beauchaine et al., 2010). We outline some of these risk factors below.

Parenting. One of the most thoroughly studied environmental correlates of externalizing behavior is parenting. Numerous studies have demonstrated that the parents of impulsive and aggressive children are more negative, lax, verbose, and over-reactive in their discipline practices than the parents of control children (Arnold, O'Leary, Wolff, & Acker, 1993; Barkley, Karlsson, & Pollard, 1985). In a longitudinal study of impulsive boys, Patterson et al. (2000) demonstrated that the relation between hyperactivity and antisocial behavior was mediated fully by coercive parental discipline. Thus, hyperactivity led to more serious externalizing behaviors only when parents consistently nagged their children and were explosive in their discipline practices. Similarly, Biederman et al. (1996) demonstrated that hyperactive children who developed conduct disorder were more likely to be reared by antisocial parents than hyperactive children who did not develop conduct disorder. Exposure to parental psychopathology more broadly has a similar effect on emerging externalizing symptoms among children with ADHD (Biederman et al., 1995).

Consistent with these findings, coercive family interaction patterns in which both children and their parents escalate aversive behaviors and negative affect in order to assert their respective wills promote physical aggression, conduct problems, and delinquency (Snyder, Edwards, McGraw, Kilgore, & Holton, 1994; Snyder, Schrepferman, & St. Peter, 1997). Developmental models suggest that these repeated episodes of affective and behavioral escalation, which are enacted thousands of times in the families of at risk children, promote emotion dysregulation and emotional lability, which in turn increase risk for more severe conduct problems (Beauchaine et al., 2007; Crowell, Beauchaine, & Linehan, 2009; Chapter 18). Moreover, interventions that successfully reduce such parenting behaviors also reduce delinquency (e.g., Hartman, Stage, & Webster-Stratton, 2003; Martinez & Forgatch, 2001; Piquero, Farrington, Welsh, Tremblay, & Jennings, 2009). This coercive model has recently been extended to the development of self-inflicted injury, particularly among female adolescents (Beauchaine et al., 2009), which highlights the potential moderating role of sex in the developmental trajectory of impulsivity. Although this body of findings has been interpreted by some as evidence of direct environmental effects, it is possible that heritable genetic vulnerabilities are driving the coercive behaviors observed by both parties (an example of a gene-environment correlation; see Chapter 3). Such genetic versus environmental hypotheses cannot be disambiguated without true experiments in which impulsive children are assigned randomly to coercive and noncoercive caretakers—an ethically indefensible practice. Nevertheless, in a randomized clinical trial, Hinshaw et al. (2000) found that reductions in negative/ineffective discipline in parents of youth with ADHD mediated school-based reductions in disruptive behavior and improvements in social skills, with effects most pronounced for families receiving the multimodal combination of medication and intensive behavior therapy. Similarly, a recent randomized clinical trial demonstrated improved parenting and reduced externalizing behavior among preschool children with ADHD following an empirically supported parent intervention (Webster-Stratton, Reid, & Beauchaine, 2011, 2012).

Child abuse and neglect. Although associated with parenting practices (Azar, 2002), a second risk factor that we consider separately is child abuse and neglect. Those who study child maltreatment have traditionally considered social mechanisms of risk and intergenerational transmission (see Cicchetti & Valentino, 2006). We have therefore included child abuse and neglect under environmental risk factors. However, evidence also suggests that genetic and temperamental factors play roles

in determining who engages in child abuse and neglect, and in influencing the likelihood that a person who experiences abuse will become a future offender (Farrington, Jolliffe, Loeber, Stouthamer-Loeber, & Kalb, 2001; Chapter 5). Although the direction of effects is unclear, maltreated children are more impulsive than nonmaltreated children (Famularo, Kinscherff, & Fenton, 1992), and histories of abuse are associated with higher levels of externalizing symptoms among children with ADHD (Briscoe-Smith & Hinshaw, 2006). Furthermore, behavior genetics studies indicate that physical abuse often plays a direct role in the development of antisocial behavior among children at risk (Trouton, Spinath, & Plomin, 2002). Abuse is also more likely to lead to conduct disorder among children who are genetically vulnerable—as determined in part by impulsive characteristics of family members (Jaffee et al., 2004). Thus, impulsive children may be at higher risk for child abuse and neglect, which then amplifies risk for conduct problems and delinquency. As noted above, one possible mechanism for this effect is a Gene × Environment interaction involving a polymorphism of the MAOA gene, which is associated with high risk for antisocial behavior among males who were maltreated as children (Caspi et al., 2002). This variant in MAOA is likely to affect behavior in part through altered DA turnover.

Neighborhood effects. A third environmental risk factor that interacts with trait impulsivity is neighborhood context. Several studies indicate that impulsive children who are reared in high-risk neighborhoods (typically defined by such factors as low socioeconomic status, high rates of violence and criminality, and low community involvement) are more prone to engage in antisocial behavior than impulsive children reared in low-risk neighborhoods (Meier, Slutske, Arndt, & Cadoret, 2008; Trentacosta, Hyde, Shaw, & Cheong, 2009; Zalot, Jones, Kincaid, & Smith, 2009). For example, Lynam et al. (2000) found that impulsive boys, as assessed by a number of neuropsychological tests and self-report measures, were at higher risk than nonimpulsive boys for engaging in both status offenses and violent crimes, yet only when they lived in neighborhoods of low socioeconomic status and high delinquency. No such effects were observed in high SES neighborhoods (see Zimmerman, 2010, for a different pattern of findings). Taken together, these findings exemplify a Trait × Environment interaction, and illustrate the importance of environmental opportunities in the expression of temperamental risk.

EPIGENETIC AND OTHER EXPERIENCE-DEPENDENT EFFECTS

Epigenetic effects. Epigenetic effects refer to alterations in gene expression that result from changes in DNA structure rather than changes in DNA sequence (Hartl & Jones, 2002; see Chapter 3). Such alterations are mediated by methylation processes that are triggered by environmental events. For example, Weaver et al. (2004) demonstrated epigenetically transmitted differences in the glucocorticoid receptor gene promoter in the hippocampi of rat pups that received high levels of maternal licking, grooming, and arched-back nursing compared with pups that experienced low levels of these maternal behaviors. This epigenetic effect transmits adaptive variations in stress responding to offspring. Rat pups reared in hazardous environments where maternal behaviors are compromised have more reactive hypothalamic-pituitary-adrenocortical (HPA) responses, and are consequently more fearful and wary. Thus, they are better prepared for the hazardous environment that they are likely to face.

Although evidence of epigenetic effects on psychopathology has only begun to emerge, mammals are particularly susceptible to such alterations in gene expression (Hartl & Jones, 2002), and increasingly divergent patterns of DNA methylation emerge over the lifetimes of monozygotic twin pairs (Fraga et al., 2005). Accordingly, several authors have emphasized the importance of epigenetic effects for child psychopathology research (e.g., Beauchaine et al., 2011; Kramer, 2005; Rutter, 2005), and theoretical models of antisocial behavior that include epigenetic effects have begun to appear (Tremblay, 2005).

Several recent empirical findings are relevant to our understanding of these effects with regard to impulsivity. The expression of brain-derived neurotrophic factor (BDNF), which is involved in the differentiation of DA neurons in developing mesolimbic structures and has been implicated in the pathogenesis of impulsivity, may be susceptible to paternally-mediated epigenetic effects (Kent et al., 2005). Similarly, animal studies suggest that prenatal exposure to synthetic glucocorticoids leads to overactivity and ADHD-like behaviors, suggesting such exposure may influence the "programming" of nascent DA systems (Kapoor, Petropoulos, & Matthews, 2008). Moreover, brain tissue from spontaneously hypertensive rats (a well-characterized animal model of ADHD) exposed to polychlorinated biphenyls (PCBs) evidenced differences in mRNA, suggesting an epigenetic effect of PCB on gene expression (DasBanerjee et al., 2008). In addition, although the precise mechanism remains to be described, the DRD4*7 allele, which has been linked with ADHD (see earlier), is less likely to be transmitted to offspring born in the autumn and winter months than to offspring born in the spring or summer (Seeger, Schloss, Schmidt, Rüter-Jungfleisch, & Henn, 2004). In the future, greater understanding of the processes and timing of epigenetic effects may help in formulating targeted interventions for vulnerable children.

Neural plasticity. In addition to epigenetic effects, several other mechanisms of neural programming are relevant for models linking early impulsivity to later psychopathology. Neural plasticity refers to experience-dependent functional changes in neural networks, including their efficiency, sensitivity, and time course of responding (Pollak, 2005). Such experience-dependent changes occur in several neural systems including mesolimbic DA structures (see Beauchaine et al., 2011). For example, Lucas et al. (2004) reported decreased DA transporter densities in mesolimbic brain regions of male rats that were exposed repeatedly to more dominant males in a stress-inducing paradigm. Similarly, repeated episodes of maternal separation early in the lives of rat pups produce long-term decreases in DA transporter expression (Meaney, Brake, & Gratton, 2002). Of particular significance, these effects result in greater sensitivity to the behavioral effects of cocaine and amphetamines later in life. Although similar experiments clearly cannot be conducted with humans, these findings illustrate the exquisite sensitivity of the mesolimbic DA system to early experience and suggest the possibility that experience-dependent changes in DA functioning may predispose affected individuals to stimulant use and/or abuse.

Perhaps more troubling, strong stimulants themselves induce experience-dependent changes in neural function that are similar to those observed following stress exposure. Through this mechanism, alterations in DA expression lead to sensitization and addiction to stimulants including nicotine, amphetamines, and cocaine (e.g., Saal, Dong, Bonci, & Malenka, 2003; Taylor & Jentsch, 2001; Thomas, Beurrier, Bonci, & Malenka, 2001). Chronic elevation of DA neural firing in the nucleus accumbens by strong stimulants has two other problematic effects. First, it down-regulates basal DA activity (Scafidi et al., 1996), which may exacerbate impulsive tendencies that emerge from mesolimbic hypo-responding (see above). Second, it suppresses the strength of connections from the mesolimbic system to the prefrontal cortex (Thomas et al., 2001), which may alter development of executive functioning and long-term planning. In normally developing adolescents, mesolimbic structures are recruited during reward-seeking behaviors in much the same way as observed in children. In contrast, adults depend more on frontal regions in responding to reward (Galvin et al., 2006). This shift reflects a developmental migration from dependence on "bottom-up" neural processing in phylogenetically old limbic structures to "top-down" neural processing in phylogenetically newer cortical structures. Once developed, these frontal (mesocortical) structures inhibit reward-related behaviors when it is advantageous to do so (Taylor & Jentsch, 2001). Environmental risks including stress and drug exposure may prevent this maturational process from unfolding, resulting in an underdeveloped mesocortical DA system that predisposes the individual to further stimulant use and abuse (Prasad, Hochstatter, & Sorg, 1999), and to the potential long-term sequelae of early impulsivity, including conduct problems, delinquency, and antisocial personality development.

It is important to note, however, that sensitization appears to be limited to early exposure to drugs of abuse, and does not extend to the therapeutic use of stimulant medications among children with ADHD. Although animal models prompted suggestions that the use of stimulants such as methylphenidate during childhood might increase the likelihood of substance abuse later in life (Schenk & Davidson, 1997), this has not been supported by analogous research, which has uncovered little evidence of increased risk of substance abuse following stimulant treatment of ADHD (e.g., Barkley, Fischer, Smallish, & Fletcher, 2003; Biederman, Wilens, Mick, Spencer, & Faraone, 1999; Volkow & Swanson, 2008). Instead, increased substance abuse among individuals with ADHD is accounted for by the presence of comorbid antisocial behaviors (Mannuzza et al., 2008), rather than a history of receiving stimulant medications.

IMPLICATIONS FOR LEARNING

As many readers are probably aware, the same mesolimbic and mesocortical structures that have been discussed in this chapter are also recruited for associative learning processes (see Berridge & Robinson, 2003; Sagvolden et al., 2005). Thus, alterations in DA responding that arise from genetic, epigenetic, and experience-dependent effects are likely to influence the efficiency of knowledge acquisition. This might occur through at least three mechanisms: (1) sensation-seeking tendencies that reduce motivation for learning "mundane" information; (2) reduced efficacy of associative learning due to dampened activation of mesolimbic structures; and (3) compromised executive functioning. Although we do not have space to review the learning literature in further detail, these findings underscore the importance of early intervention for impulsive children who may be on an externalizing trajectory.

SYNTHESIS AND FUTURE DIRECTIONS

In this chapter, we have described (a) heritable biological mechanisms of vulnerability that lead to impulsivity among affected children, (b) environmental risk factors that can potentiate vulnerability, leading to more serious externalizing behaviors that are especially difficult to treat, and (c) the potential importance of gene-environment correlations and Gene × Environment interactions in the expression and development of externalizing behaviors among impulsive and therefore vulnerable children. Although discussion of environmental, epigenetic, and experience-dependent risk factors for delinquency is sobering, it is worth repeating that only about half of impulsive preschool children develop more serious externalizing behaviors (Campbell et al., 2000). Furthermore, progress over the past decade in the specification of mechanisms through which impulsive behaviors escalate has been truly astounding.

Modern neuroscientific methods have provided insights into the development of externalizing behaviors that were unimaginable just a few years ago. When considered in conjunction with findings from more traditional approaches, it becomes apparent that some children face a cascade of cumulative vulnerability and risk that is increasingly difficult to reverse across development. In the worst cases, impulsive children are reared by impulsive parents who, in addition to conferring genetic liability, transmit risk through inconsistent and stressful caretaking during infancy, child maltreatment, and coercive, labile parenting (see Beauchaine et al., 2011). Further accumulation of risk may occur via exposure to violence in high-risk neighborhoods, early escalation of substance use, low motivation, and learning difficulties. By middle childhood and adolescence, exposure to stimulant drugs of abuse compromises the development of executive functions and self-regulation, compounding problem behaviors.

In contrast, an impulsive child who is reared in a maximally protective environment faces few or none of these additional risk factors, and may develop both psychological and biological resilience given enriched educational experiences and competent parenting that teaches strong emotion regulation skills (Beauchaine et al., 2007; Raine et al., 2001; see also Chapter 11). Parenting interventions have proven quite effective in reversing risk for conduct problems, especially when delivered early in childhood (Beauchaine, Webster-Stratton, & Reid, 2005; Nock, 2003; Piquero et al., 2009). Thus, there is reason to be optimistic. It is our hope that our knowledge of risk and resilience will continue to grow, and that science will influence public policy such that more children on externalizing trajectories receive preventive services.