Trait Impulsivity and the Externalizing Spectrum

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Abstract

This article reviews evidence that trait impulsivity—expressed early in life as the hyperactive–impulsive and combined presentations of attention-deficit/hyperactivity disorder (ADHD)—is a bottom-up, subcortically mediated vulnerability to all externalizing disorders. This vulnerability arises from deficient mesolimbic dopamine responding, which imbues psychological states (irritability, discontentment) that motivate excessive approach behavior (hyperactivity, impulsivity). Through complex interactions with (*a*) aversive motivational states that arise from largely independent subcortical systems, (*b*) emotion regulatory mechanisms that arise from top-down, cortical modulation of subcortical neural function, and (*c*) environmental risk factors that shape and maintain emotion dysregulation, trait impulsivity confers vulnerability to increasingly severe externalizing behaviors across development. This perspective highlights the importance of identifying transdiagnostic neural vulnerabilities to psychopathology; dovetails with the hierarchical, latent structure of psychopathology; and suggests that progression along the externalizing spectrum is an ontogenic process whereby a common, multifactorially inherited trait interacts with endogenous and exogenous influences to yield increasingly intractable externalizing behaviors across development.

Contents

INTRODUCTION

Collectively, externalizing spectrum disorders (ESDs), including attention-deficit/hyperactivity disorder (ADHD), oppositional defiant disorder (ODD), conduct disorder (CD), antisocial personality disorder (ASPD), and substance use disorders (SUDs), exact tremendous costs on individuals, families, communities, and society in terms of academic underachievement, underemployment, criminal behavior, incarceration, and other adverse outcomes. In 2010, costs to the US education system for ADHD alone were between $15 billion and $25 billion (Ruland 2012), and state and federal corrections costs—which derive largely from males with CD, ASPD, and/or SUDs (e.g., Teplin 1994)—exceeded $70 billion (Schmitt et al. 2010). Although often underappreciated, almost 1 in 20 adults with ASPD eventually complete suicide, a rate more than 300 times that observed in the general population (Dyck et al. 1988). These statistics suggest that furthering our basic understanding of and formulating more effective treatments for ESDs should be urgent public health priorities.

Traditionally, ESDs have been treated as distinct phenomena. However, high rates of concurrent comorbidity and heterotypic continuity (see Beauchaine & McNulty 2013), as well as common genetic and neural vulnerabilities, suggest shared etiologies (see Castellanos-Ryan &

Séguin 2016, Gizer et al. 2016, Zisner & Beauchaine 2016). Among children, adolescents, and adults with externalizing disorders, exceedingly high rates of concurrent comorbidity are observed in both nationally representative and clinical samples (see, e.g., Gau et al. 2010; Kessler et al. 2006, 2012; Maughan et al. 2004), and heterotypic continuity—defined as sequential development of different externalizing (or internalizing) disorders across the life span—is common. Males who develop ASPD usually traverse a developmental trajectory that begins in preschool with ADHD, followed by ODD, childhood-onset CD, SUDs, and incarceration and recidivism (see Moffitt 1993, Storebø & Simonsen 2016). This developmental pathway may account for most individuals who engage in lifelong delinquent behavior (see Beauchaine & McNulty 2013).[1] However, even though most preschoolers with ADHD continue to exhibit functional impairment into adolescence and adulthood, many do not progress to severe externalizing behavior as they mature (e.g., Lahey et al. 2016). Any developmental model must account for both progression along and desistance from the externalizing spectrum.

Despite these patterns of comorbidity and continuity, largely distinct research and treatment literatures have evolved for ESDs. However, recent conceptualizations of externalizing behavior, which follow from findings presented above and from extensive behavioral genetics research (e.g., Krueger et al. 2002, Lahey et al. 2011), molecular genetics research (see Gizer et al. 2016), and comprehensive literature reviews (e.g., Beauchaine & McNulty 2013), acknowledge common etiological mechanisms among externalizing disorders. The concept of an externalizing spectrum has therefore gained traction in recent years and is consistent with the Research Domain Criteria (RDoC) perspective, which emphasizes transdiagnostic neurobiological vulnerabilities to psychiatric disorders that have traditionally been considered distinct (see, e.g., Beauchaine & Thayer 2015).

In this article, we review evidence that trait impulsivity—an individual difference with well-characterized neurobiological substrates—confers liability to the hyperactive–impulsive and combined presentations of ADHD among children, and is a core predisposing vulnerability to all of the ESDs mentioned above. In sections to follow, we (*a*) outline factor analytic and behavioral genetics findings that suggest a common, latent vulnerability underlies all ESDs; (*b*) propose that this vulnerability is best characterized as trait impulsivity; (*c*) describe how, early in life, trait impulsivity is conferred largely by an underresponsive mesolimbic dopamine (DA) system; (*d*) outline how emotion dysregulation, which derives from inefficient modulation of mesolimbic function by prefrontal networks, takes on increasing importance in the expression of impulsivity by adolescence; and (*e*) describe how, through ontogenic processes, trait impulsivity interacts with various environmental risk factors to alter neurodevelopment of the prefrontal cortex (PFC), canalize externalizing behavior, and pull many impulsive individuals along the developmental trajectory described above.

LATENT STRUCTURE OF THE EXTERNALIZING SPECTRUM

As articulated in the child psychopathology literature, the externalizing spectrum comprises DSM-5 (the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*; Am. Psychiatr. Publ. 2013) syndromes including ADHD, ODD, and CD, and related constructs, including

[1]Several other externalizing pathways are well documented, including those following teratogen exposure, hypoxia, and head injury, as well as fairly normal adolescent-limited engagement in antisociality. Interested readers are referred elsewhere for descriptions of these pathways (e.g., Gatzke-Kopp 2011, Gerring & Vasa 2016, Graham et al. 2016, Moffitt 1993).

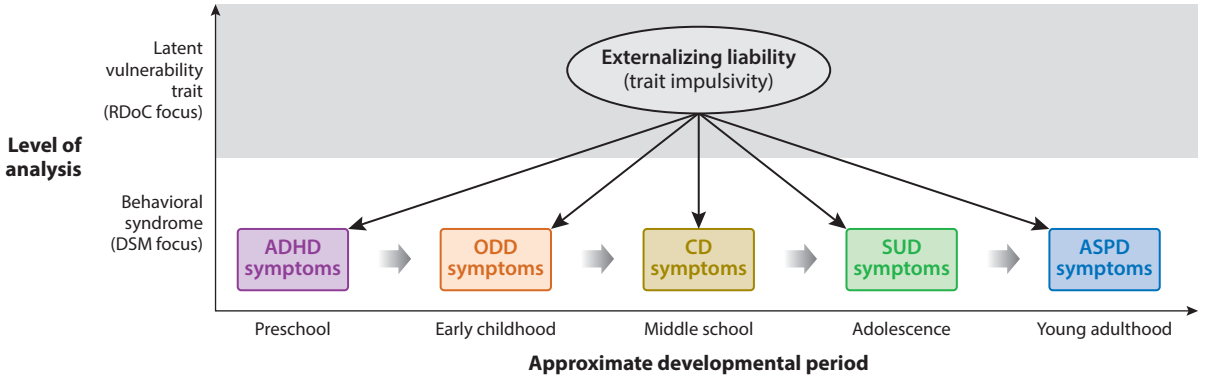

Figure 1

Well-replicated latent structure of the externalizing spectrum. Separate behavioral syndromes load on a single, highly heritable externalizing liability factor. Arrows between syndromes indicate increasingly intractable forms of externalizing behavior that are often observed across development. Figure adapted from Beauchaine & McNulty (2013). Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASPD, antisocial personality disorder; CD, conduct disorder; DSM, *Diagnostic and Statistical Manual of Mental Disorders*; ODD, oppositional defiant disorder; RDoC, Research Domain Criteria; SUD, substance use disorder.

aggression and delinquency.[2] The externalizing spectrum derives from factor analyses of symptoms, which invariably yield a hierarchical latent structure in which a single higher-order factor accounts for much of the covariation among first-order factors, including ADHD, ODD, CD, and related constructs. This factor structure was identified initially by Achenbach & Edelbrock (1991, for example) in foundational studies conducted with children and adolescents, and is observed in both population-based and twin studies. Twin studies in particular yield a largely heritable higher-order externalizing factor (e.g., Lahey et al. 2011).

A well-replicated, parallel latent structure, which also includes a higher-order externalizing factor, is observed consistently by adult psychopathologists, who typically include ASPD and SUDs in their models (e.g., Krueger et al. 2002). The externalizing factor yields heritability coefficients of around .80, and, as in the literature on children, accounts for a preponderance of covariation among first-order factors. The latent structure of the externalizing spectrum is depicted in **Figure 1**, in which behavioral syndromes are specified at the level of analysis of first-order factors and transdiagnostic externalizing liability is specified at the level of analysis of the higher-order factor, consistent with the RDoC perspective.

IMPULSIVITY AS A HIGHLY HERITABLE TRAIT

An obvious question emerges from the factor structure depicted in **Figure 1**. Through what mechanism or mechanisms does a single, highly heritable latent trait confer vulnerability to all externalizing disorders? In a series of papers from our lab published during the past decade (see,

[2] Unlike previous versions of the DSM, DSM-5 no longer includes ADHD among the disruptive behavior disorders, but instead treats it as a neurodevelopmental disorder. This change follows from several considerations, including evidence for dysfunctional neural processing (see, e.g., Nigg 2017), and hope that classifying ADHD as a neurodevelopmental disorder will lead to earlier diagnosis and access to treatment (Tannock 2013). Notably, such considerations could be applied to all externalizing disorders (Gatzke-Kopp 2011), and moving ADHD to a different section of the DSM obscures its etiological connections with other disruptive behavior disorders.

e.g., Beauchaine 2015, Beauchaine & McNulty 2013, Zisner & Beauchaine 2016), we suggest that shared vulnerability to ESDs is conferred by trait impulsivity, an individual difference that at its extreme is expressed as a preference for immediate rewards over larger delayed rewards, as actions taken without forethought, as failures to plan ahead, and as deficiencies in self-control (see Neuhaus & Beauchaine 2017, Sagvolden et al. 2005). Although normal variation in trait impulsivity—which is distributed continuously in the population (see Zisner & Beauchaine 2016)—contributes to core features of personality, such as novelty seeking, sensation seeking, extraversion, and exuberance (e.g., Degnan et al. 2011), extreme impulsivity gives rise to behaviors that are socially inappropriate, maladaptive, and short-sighted (Sagvolden et al. 2005). Operationalized in this way, trait impulsivity is best captured using DSM-derived ADHD hyperactivity–impulsivity scales and closely related measures, and derives from failures in central nervous system (CNS)-mediated self-regulatory processes (e.g., Barkley 2004, Sagvolden et al. 2005).

It is important to acknowledge, however, that alternative definitions of impulsivity abound. These range from more specific operationalizations—such as response inhibition and other metrics of performance on Go/No-go, delay-discounting, reaction time, and related tasks (see Neuhaus & Beauchaine 2017)—to multifaceted personality accounts (e.g., Whiteside & Lynam 2001). Although these characterizations have merit in certain contexts, we prefer to define impulsivity using scores on ADHD hyperactivity–impulsivity scales for three reasons. First, hyperactive–impulsive symptoms of ADHD and closely related constructs, such as self-control, are far more heritable (approximately .80) than tightly circumscribed neurocognitive measures of impulsivity, such as response inhibition (e.g., Beaver et al. 2013, Crosbie et al. 2013, Nikolas & Burt 2010). Notably, such high heritabilities, although common among behavioral traits measured in adulthood, are rarely observed as early in life as they are in ADHD (see Bergen et al. 2007). As a rule, heritabilities rise across development in behavioral genetics research because accumulating but unmeasured gene × environment (G × E) interactions get subsumed into the heritability coefficient (see Rutter 2014). Therefore, by adulthood, many if not most heritability coefficients overestimate pure genetic effects on behavior. Such is not the case for ADHD, which yields exceedingly high and stable heritabilities as early as the preschool years (see Neuhaus & Beauchaine 2017).

Second, when defined by symptoms of ADHD, trait impulsivity is associated with well-replicated molecular genetic and neural substrates, as outlined below in the section titled Molecular Genetics of Trait Impulsivity (e.g., Hart et al. 2012, D. Li et al. 2006, Nigg 2017, Plichta & Scheres 2014). Neural correlates of more circumscribed measures of impulsivity overlap only partially with those of ADHD, and effect sizes linking such measures to neurobiological function tend to be smaller (e.g., Aron & Poldrack 2006, C.R. Li et al. 2006).

Third, although circumscribed measures of impulsivity capture parts of the ADHD phenotype, they are not associated with the same levels of functional impairment or vulnerability to increasingly intractable forms of externalizing behavior across development (see Beauchaine & McNulty 2013, Neuhaus & Beauchaine 2017). These observations form a nomological network that supports the construct validity of trait impulsivity as measured by symptoms of hyperactivity and impulsivity.[3] From this perspective, hyperactive–impulsive symptoms of ADHD are the purest behavioral manifestations of trait impulsivity before it interacts with environmental risk and adversity across development.

[3]We do not include symptoms of inattention in our definition of trait impulsivity. This follows from consistent, accumulating evidence that the inattentive presentation of ADHD is distinct etiologically from the hyperactive–impulsive and combined presentations (see, e.g., Nikolas & Burt 2010).

BOTTOM-UP NEURAL MECHANISMS AND MODERATORS OF TRAIT IMPULSIVITY

Advances in neuroimaging have allowed for sophisticated models of impulsivity and self-regulation to be articulated during the past decade (e.g., Castellanos-Ryan & Séguin 2016, Heatherton 2011, Heatherton & Wagner 2011, Zisner & Beauchaine 2016). Most of these accounts are rooted, at least in part, in theories of approach motivation that derived originally from invasive studies with animals, including single-cell recording and lesion experiments. Such studies, which were conducted in the mid- to late twentieth century, suggest that both subcortical and frontal brain structures are implicated in self-regulation. However, extrapolation to humans could not be confirmed without modern neuroimaging. Since then, imaging studies have established that trait impulsivity is indeed rooted in both subcortical and frontal brain functions and in interconnected neural networks that link these and other brain regions (see, e.g., Casey 2015, Cubillo et al. 2012, Shannon et al. 2009). Nevertheless, when discussing impulsivity and its tertiary outcomes, we find it useful from developmental, phylogenetic, and functional perspectives to distinguish between subcortical emotion-generation systems and cortical emotion-regulation systems, despite their interconnections and reciprocal feedback properties (see Beauchaine & McNulty 2013, Macdonald et al. 2016).

As outlined in the section titled Subcortical Mechanisms of Trait Impulsivity, motivation to engage in intemperate behaviors—the defining feature of impulsivity—is imbued by subcortically generated approach-related affect. However, it cannot be overemphasized that (*a*) behavioral predispositions are also motivated by subcortically generated avoidance-related affect (i.e., trait and state anxiety) and (*b*) neural networks that subserve approach and avoidance functions are modulated by top-down, inhibitory influences of the PFC (see Beauchaine 2015). Accordingly, main effects models that consider function(s) of only one brain region or neural system are insufficient to advance our understanding of psychopathology, its comorbidities, and its tertiary outcomes (Beauchaine & Cicchetti 2016, Casey 2015). In sections to follow, we describe subcortical mechanisms of trait impulsivity and trait anxiety, discuss moderating effects of trait anxiety on impulsivity, and outline how PFC function can regulate or potentiate subcortically mediated propensities toward impulsivity and its adverse sequelae across the lifespan (see also Beauchaine & Zisner 2017).

Subcortical Mechanisms of Trait Impulsivity

Contemporary neural models of trait impulsivity focus primarily on the mesolimbic DA system and its feedforward and feedback projections to and from the mesocortical DA system (e.g., Gatzke-Kopp 2011, Macdonald et al. 2016, Sagvolden et al. 2005). Here we consider the subcortical mesolimbic system. The mesolimbic DA system includes neural projections from the ventral tegmental area to the nucleus accumbens and ventral regions of the caudate nucleus and putamen (Swartz 1999, Voorn et al. 2004). As alluded to above, mesolimbic theories of trait impulsivity derive from foundational research on incentive motivation, incentive salience, and substance abuse and dependence conducted with rodents, nonhuman primates, and humans. This research reveals that (*a*) electrical and pharmacological stimulation of mesolimbic structures is highly reinforcing, as evidenced by trained animals engaging in protracted periods of operant responding to obtain these incentives, often at the expense of consuming primary reinforcers including food and water (see Milner 1991); (*b*) mesolimbic neural activity increases during reward-seeking, reward anticipation, and after delivery of DA agonists (see, e.g., Knutson et al. 2001, Schott et al. 2008); and (*c*) DA antagonists block the rewarding properties of both primary reinforcers and stimulant drugs of abuse, eliminating motivation to approach these incentives (e.g., Rolls et al. 1974). These findings

and others led to several theories in the 1980s that linked impulsivity and related personality constructs, such as reward seeking, extraversion, and novelty seeking, to individual differences in activity and reactivity of mesolimbic structures (e.g., Gray 1987).

Although mesolimbic theories of impulsivity and other externalizing conduct were articulated before modern neuroimaging was available, extensive imaging research conducted since supports the assertion that midbrain DA dysfunction is an etiological factor in many, if not most, externalizing disorders (see Beauchaine & McNulty 2013, Gatzke-Kopp 2011). An impressive body of neuroimaging research conducted during the past 15 years reveals (*a*) reduced mesolimbic or mesocortical reactivity (or both) during the anticipation of incentives among individuals who are impulsive, including those with ADHD (e.g., Dickstein et al. 2006, Plichta & Scheres 2014), CD (e.g., Rubia et al. 2009), SUDs (e.g., Volkow et al. 2004), and antisocial traits (e.g., Oberlin et al. 2012); (*b*) reduced mesolimbic DA transporter function, and reduced D2 receptor or D3 receptor binding (or both) among adults with ADHD (Volkow et al. 2009) and alcoholism (e.g., Laine et al. 2001); and (*c*) compromised functional connectivity between mesolimbic and mesocortical (prefrontal) structures among adolescents with ADHD and CD (e.g., Casey et al. 2007, Shannon et al. 2009). This last finding is significant because mesocortical structures provide top-down inhibitory control over mesolimbic activity and reactivity, especially as individuals mature (see Top-Down Neural Regulation of Trait Impulsivity below). Thus, top-down inhibition of mesolimbic activity and reactivity is a core neural substrate of self-regulation (see Beauchaine 2015, Heatherton 2011).

The mesolimbic DA hypothesis of trait impulsivity is also supported by single-photon emission computed tomography, positron emission tomography, and additional functional magnetic resonance imaging studies of children and adults with ADHD. These studies reveal that DA agonists, such as methylphenidate, increase neural activity in the striatum, part of the mesolimbic reward pathway (e.g., Volkow et al. 2002). In fact, among those with ADHD, methylphenidate normalizes both frontocingulate underactivity (Rubia et al. 2011) and frontostriatal functional connectivity deficits (Rubia et al. 2009).

Finally, individual differences in DA expression correlate with positive affectivity (Ashby et al. 1999), and infusions of DA into mesolimbic structures induce pleasurable affective states (see Berridge 2003). In contrast, low levels of striatal DA are associated with trait irritability (Laakso et al. 2003), which characterizes all ESDs (e.g., Asherson 2005, Martel & Nigg 2006). Deficient mesolimbic DA activity and reactivity produce an aversive, irritable mood state (e.g., Laakso et al. 2003), which provides motivation to engage in reward-seeking and novelty-seeking behaviors to elevate mood through phasic activation of mesolimbic DA neurons (see Zisner & Beauchaine 2016). However, reward seeking produces only transient improvements in hedonic state, so larger and more frequent rewards are sought (Sagvolden et al. 2005). Those with mesolimbic DA deficiency are, therefore, irritable, hyperactive, and impulsive.

Subcortical Moderators of Trait Impulsivity

As alluded to above, trait anxiety is an individual difference that moderates the expression of trait impulsivity. Depending on whether an impulsive individual scores high versus low, respectively, on trait anxiety, their impulsivity may be amplified, resulting in progression to more severe externalizing outcomes, or mollified (see Corr & McNaughton 2016). Like trait impulsivity, trait anxiety is rooted in temperament. Extensive longitudinal research by Kagan and colleagues (as summarized by Kagan 2017) indicates that behavioral inhibition—a temperamental construct characterized by shyness, passive avoidance of real and perceived threat, and wariness of novelty—is heritable and stable, and predicts problems with anxiety, development of anxiety disorders, and neurobiological reactivity to external events across impressively long periods of time.

Trait anxiety also has well-characterized neural substrates (Gray & McNaughton 2000). Importantly, these are largely independent of the neural substrates of trait impulsivity. Trait anxiety arises from patterns of activity and reactivity in a network of neural structures, including the hippocampus, periaqueductal gray, medial hypothalamus, posterior cingulate cortex, amygdala, and the broader septohippocampal system (Corr & McNaughton 2016). According to reinforcement sensitivity theory (RST; see Corr & McNaughton 2012), this network functions to suppress prepotent behaviors in contexts of competing motivational valence (approach–approach, approach–avoidance, avoidance–avoidance). Suppression of ongoing behavior in such situations allows slower neural processes to evaluate potential outcomes, so organisms can choose less risky or less dangerous options.

RST specifies moderating effects of trait anxiety on trait impulsivity. Those who are trait impulsive and, therefore, predisposed to excessive approach behavior should experience worse outcomes if they are also low in trait anxiety because they lack effective motivation to pause for risk assessment. Thus, a strong predisposition to approach is not offset by suppression of ongoing behavior when cues in the environment mark impending danger or punishment. Even a cursory review of the literature supports this notion, with evidence coming from both behavioral and neurobiological levels of analysis.

Behaviorally, both callous–unemotional and psychopathic traits—related constructs that are characterized by low trait anxiety—are associated with poorer concurrent functioning and worse long-term comportment outcomes among externalizing children, adolescents, and adults (e.g., Frick et al. 2014, Kosson et al. 2006, McMahon et al. 2010). In contrast, even though symptoms of anxiety are associated with increased rates of depression and substance use among those on the externalizing spectrum (e.g., Goodwin & Hamilton 2003),[4] they predict better responses to behavioral treatment (Beauchaine et al. 2005) and are associated with less physical aggression, more positive ratings by peers, and fewer police contacts (Walker et al. 1991). Such findings are consistent with RST, which predicts greater sensitivity to punishment among externalizers with comorbid anxiety.

At neurobiological levels of analysis, low trait anxiety, callous–unemotional traits, and psychopathy are all associated with blunted CNS responding to fear-eliciting stimuli, extinction trials, and other forms of punishment within the several brain regions listed above, as well as reduced peripheral nervous system responding to similar stimuli (e.g., Arnett et al. 1993, Blair 2010, Viding et al. 2012). Furthermore, peripheral biomarkers of trait anxiety, including low electrodermal responding, are associated with poorer treatment response among externalizing children (e.g., Beauchaine et al. 2015). Finally, consistent with the protective role of trait anxiety noted above, comorbid internalizing symptoms are associated with less severe structural compromises in several brain regions among externalizing adolescents (Sauder et al. 2012). These findings confirm a moderating role of trait anxiety on trait impulsivity. Thus, motivated behavior is an interdependent by-product of activity and reactivity within dissociable subcortical systems that generate approach- versus avoidance-related affect.

This overview of RST, with a focus on its relevance to externalizing psychopathology, is not a new perspective. RST, which originated in work by Hans Eysenck, Jeffrey Gray, and others (see Beauchaine & Thayer 2015), has long been applied in the personality and psychopathology

[4]Higher rates of substance use among those with comorbid anxiety and externalizing disorders may seem perplexing because substance abuse is usually construed as an externalizing, not internalizing, outcome (see Patrick et al. 2016). Importantly, however, impulsive individuals tend to use substances for their reward properties, which are mediated by the mesolimbic DA system (e.g., Wise & Koob 2014), whereas anxious individuals tend to use substances for their anxiolytic effects (e.g., Conrod et al. 2000). Therefore, individuals who are heterotypically comorbid may be doubly vulnerable.

literatures. Although RST was first derived from factor analytic and animal studies, modern neuroimaging provides overwhelming support for the notions that motivated behaviors emerge from a limited number of subcortical neural networks and that individual differences in functioning of these networks contribute to patterns of personality and, at the extremes, psychopathology.

TOP-DOWN NEURAL REGULATION OF TRAIT IMPULSIVITY

Although we propose here that the subcortical, mesolimbic DA system is responsible for generating impulsivity, a voluminous literature implicates functional subdivisions of the PFC in regulating impulsivity. This literature demonstrates that top-down cortical regulation of impulsivity is effected primarily through orbitofrontal and dorsolateral prefrontal inhibition of striatal (mesolimbic) activity and reactivity (see Heatherton 2011, Heatherton & Wagner 2011). In contrast, top-down cortical regulation of anxiety is effected primarily through lateral and medial prefrontal inhibition of amygdalar activity and reactivity (see Tone et al. 2016). As might be surmised from the above discussion, cortical regulation of anxiety has moderating effects on trait impulsivity. Given space constraints, these effects are not considered further. Rather, we focus on top-down modulatory effects of the PFC on trait impulsivity via reciprocal connections with mesolimbic structures.

Although evidence for prefrontal mechanisms of impulsivity is overwhelming (see, e.g., Castellanos-Ryan & Séguin 2016, Macdonald et al. 2016), few theories effectively integrate subcortical and cortical mechanisms or their interactions, and even fewer consider neurobiological vulnerability × environmental risk interactions across development (for exceptions see Beauchaine 2015, Casey et al. 2007, Nigg 2017, Petrovic & Castellanos 2016, van Leijenhorst et al. 2010). This is a critical oversight given (*a*) clear modulatory effects of the PFC on the mesolimbic DA system (Louilot et al. 1989), which, when disrupted, potentiate impulsivity (see Shannon et al. 2009); and (*b*) the exquisite sensitivity of both subcortical and prefrontal function to environmental insults (see Beauchaine & McNulty 2013, Mead et al. 2010). We describe effects of environmental adversities on PFC development and function below.

Integrating subcortical and cortical mechanisms of trait impulsivity requires that we consider specific functions and developmental trajectories of neural circuits described herein. In doing so, it is important to reemphasize the distinction between trait impulsivity as a by-product of excessive, subcortically mediated approach-related affect versus emotion dysregulation as a by-product of ineffective cortical modulation of subcortical function. These subcortical and cortical systems follow different maturational time courses, which has direct implications for understanding the neural bases of impulsivity across development (see also Brumback et al. 2016). Even though the mesolimbic DA system matures into adolescence (e.g., Galván 2013), its structural and functional development unfolds relatively earlier than (yet overlaps with) development of the PFC (see Brain Dev. Coop. Group 2012, Gogtay et al. 2004). Children and adolescents show stronger striatal responding to incentives than adults do, yet their PFC responding is weaker and more diffuse (see Macdonald et al. 2016). These are likely neural mechanisms of maturational differences in top-down control over incentive responding. Top-down modulation of approach-related affect becomes increasingly important as children's behavior regulation migrates from external sources, such as parents, to internal sources across development (see Beauchaine 2015).

Thus, mesolimbic mechanisms appear to have a relatively larger role in expression of trait impulsivity in childhood, whereas cortical mechanisms take on increasing importance, via emotion dysregulatory effects, into adolescence and adulthood (see Halperin & Schulz 2006). In fact, adolescents with ADHD score higher on measures of emotion dysregulation than children with ADHD (Graziano & Garcia 2016). Emotion dysregulation is also linked with stability of ADHD

and with development of aggressive behaviors across adolescence (Sasser et al. 2016). Furthermore, excessive mesolimbic activity, including that induced by substances of abuse, can alter future PFC development and function in ways that amplify preexisting neural vulnerability (see Environmental Moderation of Genetic Vulnerability below; Hanson et al. 2010). As a result, children who are already impulsive due to heritable individual differences in mesolimbic responding, environmentally induced sensitivity of mesolimbic structures, or both may experience increasing emotion dysregulation across development via feedforward-induced disruptions in PFC function and reduced connectivity between striatal and mesocortical structures (see Shannon et al. 2009). In fact, neurodevelopment of frontal regions—via mechanisms of neural plasticity, programming, and pruning—is affected by environmental experiences that are themselves elicited by impulsive behavior (e.g., Gatzke-Kopp 2011, Sagvolden et al. 2005). Through these mechanisms, disruptions in the function of early maturing brain regions that give rise to impulsivity can alter neurodevelopment of later-maturing brain regions that subserve emotion regulation, especially in high-risk environments.

Prefrontal maturation, as reflected in cortical thinning and reduced gray matter density across late childhood, adolescence, and early adulthood (Gogtay et al. 2004), is a normative neurodevelopmental process that is associated with greater efficiency in several behavioral domains, including emotion regulation (Vijayakumar et al. 2014). This neurodevelopment is disrupted in children with ADHD and CD. Those with ADHD exhibit a significant lag in prefrontal neurodevelopment (Shaw et al. 2012), whereas boys with CD fail to exhibit PFC gray matter reductions from childhood to early adolescence (De Brito et al. 2009). These findings are consistent with the notion that ADHD and CD fall along an externalizing continuum in which CD carries more severe compromises in prefrontally mediated emotion dysregulation, which amplify symptom expression (see Beauchaine & Gatzke-Kopp 2012). Finally, dorsolateral prefrontal volumes measured in early adolescence prospectively predict both externalizing behaviors and binge drinking in later adolescence (Brumback et al. 2016).

This brief review of top-down regulation of trait impulsivity suggests that (*a*) neural substrates of impulsivity and emotion regulation, although functionally interdependent, are dissociable; (*b*) top-down modulation of the subcortical mesolimbic system improves across development in normative samples; (*c*) neurodevelopmental delays in prefrontal maturation are observed among those on the externalizing spectrum; and (*d*) environmental adversities that confer risk for severe externalizing behavior also affect PFC neurodevelopment and function. These findings suggest that heritable trait impulsivity can be regulated, as in cases of uncomplicated ADHD, or dysregulated, as in cases in which ADHD progresses to more severe externalizing behavior through poor top-down modulation of approach-related affect.

MOLECULAR GENETICS OF TRAIT IMPULSIVITY

Consistent with research presented above, molecular genetics studies implicate DA function in vulnerability to trait impulsivity and more severe externalizing behaviors. Although this literature is voluminous and therefore cannot be reviewed comprehensively here, a preponderance of genetic association studies of ESDs focus on genes that affect DA turnover, availability, metabolism, or a combination of these. As is common in molecular genetics research, effect sizes for individual genes are small (see Beauchaine et al. 2017). Nevertheless, significant genetic associations are observed among ADHD, ODD, CD, ASPD, or a combination of them, and the DA receptor D4 gene (*DRD4*), the DA receptor D5 gene (*DRD5*), the DA transporter 1 gene (DAT1), the monoamine oxidase A gene (*MAOA*), and the catechol-*O*-methyltransferase gene (*COMT*) (see

Gizer et al. 2016).[5] Genetic linkages have also been observed between the *DRD2* gene and ADHD (Wu et al. 2012), SUDs (e.g., Gorwood et al. 2012), and ASPD (Hill et al. 1999). Of note, the *DRD2* gene is expressed heavily in mesolimbic structures (see Gizer et al. 2016).

Several studies have also examined relations between externalizing behaviors and genes that affect serotonin neurotransmission. The serotonin system is of interest in impulsivity research for several reasons. Certain serotonin genes influence striatal function, with effects on both incentive processing (e.g., Hayes & Greenshaw 2011) and impulsive aggression (e.g., Seo & Patrick 2008). The *HTR1B* serotonin receptor gene, which is expressed in the striatum, is implicated in ADHD (Gizer et al. 2009), SUDs (e.g., Cao et al. 2013), and in some studies in antisocial behavior (Moul et al. 2013). Several studies have focused specifically on the *5-HTTLPR* gene. Although the *l* allele is associated with ADHD, effect sizes are quite small (Gizer et al. 2009). The *l* allele is also associated with antisocial behavior in some studies (Sadeh et al. 2013).

Even this brief overview indicates that many genes contribute to expression of impulsivity and other externalizing outcomes. Given this, it is unsurprising that impulsivity is a multifactorially inherited trait (see, e.g., Franke et al. 2009). Thus, it is affected by a large number of susceptibility loci and rare structural variants (e.g., Elia et al. 2010), none of which is sufficient, by itself, to eventuate in psychopathology. Rather, multifactorially inherited traits are phenotypic by-products of many genetic susceptibilities, their interactions with one another, and their interactions with other heritable traits and environments (see Neuhaus & Beauchaine 2017). The importance of such interactions in expression of multifactorial phenotypes (e.g., obesity, type II diabetes) has been recognized for decades in other areas of science (see Beauchaine & Cicchetti 2016). In contrast, many psychiatric genetics studies still focus on main effects of single genes on psychopathological outcomes. For multifactorially inherited traits, such as impulsivity, effect sizes for single genes are almost always quite small (often explaining less than 1% of variance in behavioral outcomes), and interactions between genetic susceptibility and environmental risk determine phenotypic expression of vulnerability.

ENVIRONMENTAL MODERATION OF VULNERABILITY

Given that trait impulsivity is so heritable, and emerges consistently as a higher-order liability to all externalizing syndromes (see above; Krueger et al. 2002, Lahey et al. 2011), why do the same, highly correlated first-order factors (ADHD, ODD, CD, SUDs, and ASPD) also emerge consistently across studies? To address this question, two observations should be considered: (*a*) first-order externalizing syndromes are considerably less heritable than higher-order externalizing liability (i.e., trait impulsivity; see Krueger et al. 2002) and (*b*) first-order factors are influenced much more by environment than is externalizing liability (see Burt 2009). Given high rates of comorbidity among externalizing syndromes, correlations among first-order factors are unsurprising. However, greater environmental influence at the externalizing syndrome level requires explanation.

Despite shared vulnerability conferred by heritable trait impulsivity, environmental factors account for much of the variance in specific externalizing syndromes, including ADHD, ODD, CD, SUDs, and ASPD (Krueger et al. 2002, Lahey et al. 2011). In fact, shared and nonshared environmental influences typically contribute more than heritability to specific externalizing outcomes. Although this may seem counterintuitive, environmental risk exposure is a necessary condition

[5] Monoamine oxidase and catechol-*O*-methyltransferase are both enzymes that catabolize DA, among other neurotransmitters. Thus, both affect DA availability.

for the emergence of most highly heritable phenotypes. For example, one who is genetically vulnerable to SUDs will never develop a substance use disorder in the absence of exposure to substances of abuse. This of course implies a strong G × E interaction. As noted above, G × E interactions are not captured in typical behavioral genetics research paradigms (see Rutter 2014). A major thesis of this article is that genetic vulnerability to trait impulsivity, expressed early in life as ADHD, is a necessary but insufficient etiological agent in progression to more serious externalizing disorders across development. Interactions with environments are required (see below).

Consistent with the above discussion, psychiatric molecular genetics research, in which environmental risk factors are measured directly, indicates that (*a*) as in the case of all multifactorially inherited traits, G × E is the rule rather than the exception in the development of psychopathology and (*b*) G × E interactions often account for far more variance in psychopathological outcomes—including ESDs—than do main effects (Beauchaine et al. 2008). These points are exemplified in a highly cited finding by Caspi et al. (2002), who demonstrated that conjoint effects of child maltreatment and a polymorphism in the *MAOA* gene predict both juvenile and adult antisocial behavior. Those who incur maltreatment and inherit the low *MAOA* activity genotype, which affects dopaminergic, serotonergic, and noradrenergic function, are at much higher risk for engaging in serious externalizing behavior than those who experience maltreatment but do not inherit the *MAOA* vulnerability allele. Although the *MAOA* genotype explained less than 1% of the variance in antisocial behavior—a main effect size not uncommon in psychiatric genetics (see above)—the joint effects of maltreatment and genotype explained 65% (Caspi et al. 2002). This finding and others (see Beauchaine et al. 2008) lead to the counterintuitive conclusion that highly heritable vulnerabilities to psychopathology interact more strongly with environments than less heritable vulnerabilities do. We now turn our attention to environmental risk factors that mediate progression along the externalizing spectrum among trait-impulsive and therefore vulnerable individuals.

ENVIRONMENTAL RISK MEDIATORS OF PROGRESSION ALONG THE EXTERNALIZING SPECTRUM

A number of environmental risk factors are associated with progression along the externalizing spectrum. Below we describe specific examples in which environmental effects mediate relations between trait impulsivity, ADHD, and more severe externalizing outcomes. We order our discussion in the developmental sequence of externalizing behavior outlined above.

Ineffective Parenting and Coercive Family Processes

Certain temperamental traits, measured as early as toddlerhood, including inhibitory control and low fear, share conceptual overlap and genetic underpinnings with ADHD (see Beauchaine & McNulty 2013). Longitudinal associations between some of these traits and later ESDs are mediated by ineffective parenting. For example, when subjected to deficits in parenting that are common to maternal depression, 2-year-old boys who are low in fear exhibit increasing conduct problems through age 7 (Shaw et al. 2003). When their mothers are taught to parent effectively, no such association is found (see Dishion & Racer 2013).

Considerably more research exists on environmental mediators of longitudinal associations among ADHD, ODD, CD, and related constructs, such as aggression and delinquency. Foundational studies conducted in the 1980s and 1990s demonstrate that coercive relationship dynamics in which parent–child conflict is negatively reinforced predict longitudinal increases in child

aggression and other conduct problems, which, in turn, generalize to peer groups (e.g., Snyder et al. 1994). Such relationship dynamics are especially predictive of longitudinal increases in delinquency among impulsive children. For example, Patterson and colleagues (2000) found that associations between parents' and teachers' reports of hyperactivity in fourth grade and antisocial or delinquent behavior in ninth grade were accounted for fully by coercive discipline practices. Hyperactive children who experienced effective parenting did not progress to more severe externalizing outcomes, whereas those who experienced explosive, coercive, and nattering parenting did. High rates of parental criticism also mediate associations between ADHD and growth in ODD among 7–13-year-olds (Musser et al. 2016). Similar to research on temperament referred to above, disruptions in parenting that are common to maternal depression mediate longitudinal associations between ADHD in early childhood and conduct problems 2–8 years later, whereas positive parenting offers protection (Chronis et al. 2007). Finally, histories of abuse predict higher levels of externalizing behavior specifically among children with ADHD (Briscoe-Smith & Hinshaw 2006).

Deviant Peer Group Affiliations and Neighborhood Risk

Extrafamilial influences also mediate associations between impulsivity and more severe externalizing outcomes. Coercive peer group involvement predicts longitudinal increases in conduct problems from kindergarten to third and fourth grade, specifically among impulsive children (Snyder et al. 2008). Mediational effects of neighborhood characteristics on the progression of externalizing behavior are also well documented. Compared with their nonimpulsive peers, impulsive adolescents engage in more criminal activity, including violent crimes, only in low socioeconomic status neighborhoods where criminal opportunities are common (e.g., Meier et al. 2008).

Trait impulsivity also predicts early initiation of, and longitudinal increases in, substance use (see Iacono et al. 2008). For example, adolescents and young adults who do not experience normative reductions in impulsivity across development increase their alcohol, marijuana, and cigarette use more rapidly than those whose impulsivity declines with age (Quinn & Harden 2013). Moreover, associations between childhood externalizing behaviors, including ADHD, and symptoms of SUDs are mediated by disruptions in normative social relations and deviant peer group affiliations (Marshal & Molina 2006, Molina et al. 2012).

Finally, although associations between childhood impulsivity/ADHD and adult ASPD are well documented (e.g., Storebø & Simonsen 2016), and although considerable variance in adult antisocial outcomes is accounted for by nonshared environmental influences (e.g., Krueger et al. 2002), specific environmental risk mediators are not well understood. Nevertheless, deviant peer group affiliations appear to play a part (see Dishion & Racer 2013). Thus, environmental risk mediators contribute strongly to progression along the externalizing spectrum among neurobiologically vulnerable, trait-impulsive children, adolescents, and adults.

EXPERIENCE-DEPENDENT EFFECTS ON SUBCORTICAL AND CORTICAL NEURAL FUNCTION

Some have argued that mediational effects of environment on progression along the externalizing spectrum represent active or evocative gene–environment correlation (*r*GE), or both, rather than G × E, as proposed above. Active *r*GE occurs when individuals select specific environments based on heritable attributes, whereas evocative *r*GE occurs when individuals' inherited behavioral propensities elicit systematic responses from others. Although *r*GE is clearly operative in the development of externalizing behavior (for a discussion, see Beauchaine et al. 2017), contemporary models of psychopathology do not force us to choose between the main effects of heritability versus environment or between individual versus parental, peer, or social influences on behavior. Nor

are *r*GE and G × E necessarily independent. In fact, *r*GE and G × E sometimes operate together to promote psychopathology, a point we return to below.

Transactions within and across genetic, neurobiological, and behavioral levels of analysis are the rule rather than the exception in expression of complex, multifactorially inherited traits (see above; Beauchaine & Gatzke-Kopp 2012). Therefore, arguments over directions of effect between individuals and their environments in shaping and maintaining behavior are often misplaced. This is especially apparent when we consider mechanisms through which environmental adversities alter neurobiological structure and function in ways that maintain, amplify, and sometimes canalize vulnerability to psychopathology.

As noted above, childhood adversity, including abuse and neglect, can alter the structure and function of the PFC, with implications for regulation of approach-related affect and impulsivity. In this section, we elaborate on mechanisms of experience-dependent effects on both subcortical and cortical neural systems. Sensitivity of the PFC to structural and functional changes following environmental insults is well documented (see Mead et al. 2010). Orbitofrontal cortex volumes, for example, correlate negatively with levels of physical abuse incurred by children and portend difficulties in socioemotional and executive function (Hanson et al. 2010). Similar effects are observed for other early life stressors (see Beauchaine 2015, Macdonald et al. 2016). Troublingly, being reared in poverty predicts slower development of frontal brain structures among infants and children (e.g., Hanson et al. 2013).

It is also important to restate that neurodevelopment of mesolimbic and prefrontal structures is interdependent. Environmentally induced downregulation of midbrain DA function can alter neuromaturation of the PFC (see Beauchaine et al. 2011). In fact, neurodevelopment of later-maturing brain regions, such as the PFC, may be disrupted if input from early-maturing brain regions, including the striatum, is compromised (see Benes 2006).

Epigenetics and Neural Plasticity

Considerable research has addressed the mechanisms of experience dependence, including epigenesis, maternal programming effects, allostasis, and other forms of neuroplasticity (see, e.g., Gatzke-Kopp 2011). Of note, these mechanisms are often overlapping. For example, allostasis—which refers to long-term functional alterations in operating ranges of neurohormonal and other neurobiological systems—is often effected through epigenetic mechanisms (see Beauchaine et al. 2011). Neuroplasticity—which refers to experience-dependent changes in the efficiency, sensitivity, and time course of responding within and across neural networks (Pollak 2005)—can also be effected epigenetically. Epigenesis occurs when DNA structure is altered by environmental experience, sometimes with implications for behavior. These structural alterations are mediated by DNA methylation, among other mechanisms. Although differences in DNA methylation are observed at selected sites between psychiatric and control groups for a number of disorders (for a discussion, see Beauchaine et al. 2017), including ADHD (e.g., Wilmot et al. 2016), epigenetic influences on behavior are difficult to test among humans with current technologies, partly because we cannot conduct true experiments, and also because we cannot interrogate CNS tissues among live participants. As a result, we often have to assay peripheral targets, such as blood, without fully understanding their validity as markers of CNS processes.

Nevertheless, several findings have emerged that link epigenetic mechanisms to impulsivity. For example, expression of brain-derived neurotrophic factor—which is implicated in differentiation of DA neurons in maturing mesolimbic structures and is likely involved in the pathophysiology of ADHD—is susceptible to environmentally induced epigenetic regulation (Kent et al. 2005). Similar effects in the PFC have been observed among rats (see Hill & Roth 2016). Thus, brain

regions that are implicated in both impulsivity and behavior regulation are affected by epigenetic processes.

Given the difficulties of inferring epigenetic effects on human behavior, animal research is essential. Such research demonstrates that chronically administering alcohol to male mice before they mate induces epigenetically mediated alterations in DA transporter expression in both the striatum and PFC among their offspring (Kim et al. 2014). Similarly, in utero exposure to nicotine and other DA agonists results in long-term downregulation of mesolimbic function among offspring (for reviews, see Beauchaine et al. 2011, Gatzke-Kopp 2011). These effects likely also occur through epigenetic mechanisms (Babenko et al. 2015).

Chronic stress also affects long-term function of subcortical and cortical DA systems. For example, Lucas et al. (2004) found decreased DA transporter densities in mesolimbic structures among male rats that were exposed repeatedly to more dominant males. Frequent episodes of separation from mothers induce similar effects on rat pups and, importantly, result in sensitivity to behavioral effects of amphetamines and cocaine in adolescence (Meaney et al. 2002). If such findings are homologous, they have important implications for development of trait impulsivity and its progression to SUDs among children and adolescents who are reared in stressful and otherwise adverse environments (see also Gatzke-Kopp 2011).

Several findings presented above suggest that certain environmental risk mediators amplify impulsivity by altering bottom-up mesolimbic function and approach-related affect and/or top-down prefrontal function and emotion regulation. Thus, trait impulsivity becomes self-reinforcing through cyclical feedback between neural responding and environmental inputs across time. Nowhere is this more apparent than in the case of heavy substance use.

Substance Use and Exogenous Feedback on Neurobiological Vulnerability

We have already described how trait-impulsive individuals, including those with ADHD, are vulnerable to substance use and abuse (see, e.g., Patrick et al. 2016). Once initiated, use of certain substances—particularly strong stimulants, including cocaine and methamphetamine (DA agonists)—can alter both subcortical and cortical structure and function in ways that amplify trait impulsivity and potentiate emotion dysregulation. Stimulants can be especially appealing to those who are trait impulsive because increased neural firing in the nucleus accumbens and other mesolimbic structures provides temporary relief from the chronically aversive mood state that heritable deficiencies in DA activity and reactivity imbue (see above; Zisner & Beauchaine 2016). However, stimulant-induced elevations in DA neural firing in the nucleus accumbens downregulate its long-term function and suppress the strength of developing connections between mesolimbic structures and the PFC (e.g., Thomas et al. 2001). Self-administration of cocaine among rats increases dendritic branching in the nucleus accumbens, alters neural structure within the PFC, and modifies connective properties between these mesolimbic and mesocortical structures (e.g., Robinson et al. 2001). In turn, use-dependent disruptions in top-down regulation of mesolimbic structures by the PFC facilitate addiction, relapse, and other adverse effects on self-regulation (see Volkow & Morales 2015).

Use of what are often considered to be less neurotoxic substances also affects brain structure and function in ways that exacerbate impulsivity. Alcohol, for example, which has stimulant properties and elicits DA release in the nucleus accumbens (e.g., Boileau et al. 2003), affects both PFC structure and function. Rats submitted to chronic alcohol exposure exhibit deficits in cognitive function that are mediated by disrupted DA signaling in the PFC (Trantham-Davidson et al. 2014). Furthermore, compared with adolescents who rarely use substances, those who regularly

use alcohol and marijuana develop compromised white matter integrity in fiber tracts connecting association areas with frontal structures as they transition into young adulthood (Bava et al. 2013).

As mentioned above, trait impulsivity predicts both initiation and escalation of substance use among adolescents. Findings presented in this section indicate that substance abuse then alters both structure and function of the very neural systems that confer vulnerability to initiating use in the first place. This is likely an example of *r*GE and G × E operating in concert to influence a psychopathological outcome. Individuals who are genetically vulnerable expose themselves to substances earlier (*r*GE) and are more likely to be adversely affected by exposure than their peers (G × E).

THE ONTOGENIC PROCESS PERSPECTIVE AND DIRECTIONS FOR FUTURE RESEARCH

The emergence of substance use and subsequent neural adaptations that feedback onto behavior and amplify trait vulnerability provide a final, salient example of the transactional nature of progression along the externalizing spectrum. Trait impulsivity—which arises from heritable, neurobiological mechanisms and is expressed early in life as ADHD—interacts dynamically with changing environmental risk mediators across development to yield increasingly more severe externalizing conduct. This represents an ontogenic process perspective because progression along the externalizing spectrum can be understood only by considering how individual-level vulnerabilities interact with environmental adversities to change neurodevelopment and behavior across the lifespan. Several important points and directions for future research emerge from the ontogenic process perspective.

The Importance of Development

The externalizing spectrum cannot be understood outside the developmental context. Phenotypic expression of multifactorially inherited traits is a product of complex sets of genetic vulnerabilities, neural vulnerabilities, environmental risk factors, and their past and current interactions. Contrary to common assumption, multifactorially inherited traits interact strongly with environmental risk across development to change symptom expression. This is true for physical as well as mental disorders.

As we have described elsewhere (e.g., Beauchaine & Cicchetti 2016), impaired glucose tolerance, which can interact with environmental risk across development to yield type II diabetes, is a continuously distributed, highly heritable, multifactorial trait (Poulsen et al. 1999). Type II diabetes follows a typical course that begins with insulin resistance, which is followed by a host of increasingly adverse sequelae, including weight gain, elevated triglycerides, high blood pressure, nonalcoholic fatty liver disease, inflammation, ischemic heart disease, kidney failure, retinal damage, and peripheral neuropathy. Thus, observable symptoms increase in complexity over time and are expressed across an ever-broadening number of body systems. However, impaired glucose tolerance may never develop into these adverse tertiary outcomes in protective environments characterized by low stress, exercise, and healthy diet. Similarly, trait impulsivity may never develop into psychopathology, and deficient PFC structure and function may not emerge, in protective environments characterized by secure attachment relationships, effective parenting, neighborhood cohesion, and positive peer groups.

However, in contrast with ESDs, the pathophysiology of type II diabetes is much better understood. Consequently, even though someone in an advanced stage of illness expresses a far more varied and progressive set of symptoms than someone who is earlier in the illness course, we do not attribute differences in symptoms to independent disorders, as we do with heterotypically

continuous externalizing conditions for which etiology is only partly understood and for which we do not acknowledge the role of development in pathophysiology.

Avoiding Biological Reductionism

Few cases of externalizing psychopathology are caused by a single biological vulnerability or environmental risk factor, or by combinations of only biological vulnerabilities or only environmental risk factors (focal lesions provide one exception). Rather, ESDs emanate from sources that span multiple levels of analysis (see Beauchaine & Gatzke-Kopp 2012). Therefore, they cannot be understood through biological reductionism. Although collaboration among geneticists, neuroscientists, neuroendocrinologists, psychologists, psychiatrists, and other mental health professionals has become commonplace, the current zeitgeist favors biological explanations for psychopathology and sometimes eschews environmental context. As outlined above, child abuse and neglect, family coercion, peer contagion, and neighborhood violence and criminality all contribute to progression of ESDs among vulnerable individuals.

Although the RDoC offers a clear advantage over the DSM given its focus on multiple, transdiagnostic vulnerabilities to psychopathology, environmental risk is neither represented in, nor accommodated by, the RDoC matrix. Understanding environmental contributors to illness progression has proved to be essential in reducing morbidity and mortality for a wide range of physical diseases, including coronary artery disease, diabetes, and cancer. Specifying and altering environmental risk factors is no less important for treating and understanding development of ESDs and other forms of psychopathology.

Misguided Searches for Independent Causes

None of the vulnerabilities or risk factors identified in this article operates independently. Many genes interact to affect trait impulsivity. Subcortical neural networks that facilitate approach versus avoidance behaviors and cortical neural networks that facilitate emotion regulation are interconnected and functionally interdependent. Many if not most environmental risk mediators co-occur or overlap. Some of these risk factors take on different forms across development, even though they serve the same or similar functions (e.g., escape from aversive mood states, reinforcement of emotional lability). Thus, the dominant research paradigm in which we evaluate independent effects of one or two variables on externalizing outcomes, while attempting to control for all others, is outdated. We have commented elsewhere on inappropriate use of analysis of covariance to isolate the causal independent variable that produces a given psychopathological outcome while controlling for all others (e.g., Beauchaine et al. 2010). This approach remains common, but fails to carve the complexity of nature at its joints by creating independent variables that rarely exist in reality (e.g., CD without trait impulsivity; see also Lynam et al. 2006, Miller & Chapman 2001).

The next generation of research on ESDs will need to embrace rather than control for etiological and pathophysiological complexity if we wish to advance the science of behavior change. As molecular geneticists have already come to terms with, this will require larger sample sizes, tolerance for overlapping vulnerabilities and risk factors, and analyses of interactions among independent variables.

Problems with Using DSM-Defined Disorders as Starting Points

Despite the ascendance of the RDoC, most basic psychopathology research—including that conducted on ESDs—still compares groups of individuals with DSM-defined disorders in attempts

to specify pathophysiology. This practice has been criticized by many authors, and we will not recount their criticisms here. However, dividing the externalizing spectrum into so-called discrete disorders obscures their etiological connections and fractionates both basic science and treatment literatures (Beauchaine et al. 2008). Moreover, it encourages research aimed at reifying current diagnostic classes by searching for neurobiological differences among them and then interpreting such differences as evidence for existing boundaries. Typically, such research ignores environmental processes that push some individuals along the externalizing spectrum, which alters neurobiological function (see above), and fails to consider the possibility that some ESDs are more advanced manifestations of a common disease process. Future research should focus more on etiology and pathophysiology at the trait level rather than on comparing individuals with different diagnoses in sometimes circular efforts to identify causes of group differences.

Advances in Neuroimaging

Finally, neural systems that give rise to trait impulsivity and development of ESDs are often described as distinct. Even within this review, we refer to the mesolimbic DA system, the septohippocampal system, and prefrontal control networks. Although we explicitly acknowledge that interplay among these networks affects behavior, most neuroimaging studies have focused on single processes when investigating impulsivity. Furthermore, many of the imaging papers cited in this review use region-of-interest approaches in which group differences in regional reactivity are compared between experimental and control groups without evaluating neural connectivity. Although such data provide insights into neural structures that underlie trait impulsivity, they do not characterize how these regions interact.

The development of connectomics, large-scale studies of neural connectivity—along with advances in magnetic resonance imaging (MRI) technology during the past decade—will further our understanding of trait impulsivity and its progression to ESDs. Publicly available databases, such as the Human Connectome Project (Van Essen et al. 2013), leverage recent advances in MRI technology to develop anatomical and functional connectomes, and allow researchers to examine how neural networks vary with individual differences in impulse control. Furthermore, meta-analytic techniques for modeling neural connectivity are well established. Meta-analytic connectivity modeling can combine data from thousands of participants across hundreds of studies, and has been used to characterize functional connectivity among many of the regions discussed here, including the amygdala and nucleus accumbens (e.g., Cauda et al. 2011). Such approaches provide a framework for developing comprehensive network models, which can then be validated on data from the Human Connectome Project and similar initiatives.

CONCLUSIONS

Findings presented above and articulation of the ontogenic process perspective suggest that trait impulsivity, expressed as ADHD very early in life, is highly heritable and, when coupled with environmental adversity, predisposes to progressively intractable ESDs across development. Although the dose of adversity required to push an individual along the externalizing spectrum is unknown, it likely varies from person to person depending on levels of neurobiological vulnerability. Environmental risk operates through multiple mechanisms and often induces neural adaptations that amplify subcortically mediated approach tendencies and interfere with cortically mediated emotion-regulation processes. Affected individuals are, therefore, impulsive and unable to regulate their approach tendencies endogenously. Importantly, this developmental progression

does not characterize all individuals who exhibit externalizing behavior (see Footnote 1). However, the literature review above suggests that it characterizes many.

Consistent with the RDoC perspective, this transdiagnostic approach identifies a limited number of interdependent neural systems that confer vulnerability to ESDs. However, unlike both the RDoC and the DSM, the ontogenic process perspective places strong emphasis on neurodevelopment and on changing environmental risk factors across the lifespan. Furthermore, it accommodates the well-replicated latent structure of psychopathology (see Beauchaine 2015, Beauchaine & Thayer 2015, Beauchaine & Zisner 2017). Subcortical approach and avoidance systems map directly onto, respectively, the broadband externalizing factor (trait impulsivity) and the broadband internalizing factor (trait anxiety). Furthermore, cortical vulnerability maps directly onto the general liability (or p) factor (Caspi et al. 2014). Future research in which progression of trait impulsivity is viewed as an ontogenic process, in which biological, environmental, and developmental determinants are weighted interactively, should advance our understanding of ESDs.

SUMMARY POINTS

1. Trait impulsivity is a highly heritable temperamental trait that confers vulnerability to all externalizing spectrum disorders (ESDs), including attention-deficit/hyperactivity disorder (ADHD), conduct disorder (CD), antisocial personality disorder (ASPD), and substance use disorders (SUDs).
2. Early in life, trait impulsivity arises primarily from low mesolimbic dopamine (DA) activity and inefficient mesolimbic DA reactivity to incentives.
3. Subcortical, mesolimbic DA dysfunction imbues a chronically aversive mood state characterized by discontentment and irritability, which motivates affected individuals to engage in reward-seeking behaviors.
4. Individual differences in trait anxiety, an independent, subcortically mediated temperamental attribute, can amplify or mollify trait impulsivity.
5. Trait-impulsive individuals are vulnerable to developing increasingly intractable ESDs in high-risk environments that promote deficits in top-down (cortical) emotion-regulation systems, which then fail to modulate bottom-up (subcortical) emotion-generation systems.
6. Untoward environmental experiences, including abuse, neglect, and substance use, compromise the structure and function of cortical emotion-regulation systems further, amplifying and canalizing externalizing behavior across development.
7. For most individuals, progression of ESDs can be understood only as an ontogenic process through which a heritable, preexisting neurobiological vulnerability—expressed early in life as ADHD—interacts with other vulnerabilities and environmental risks across development.

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