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Neural substrates of trait impulsivity, anhedonia, and irritability: Mechanisms of heterotypic comorbidity between externalizing disorders and unipolar depression

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Abstract

Trait impulsivity, which is often defined as a strong preference for immediate over delayed rewards and results in behaviors that are socially inappropriate, maladaptive, and short-sighted, is a predisposing vulnerability to all externalizing spectrum disorders. In contrast, anhedonia is characterized by chronically low motivation and reduced capacity to experience pleasure, and is common to depressive disorders. Although externalizing and depressive disorders have virtually nonoverlapping diagnostic criteria in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders*, heterotypic comorbidity between them is common. Here, we review common neural substrates of trait impulsivity, anhedonia, and irritability, which include both low tonic mesolimbic dopamine activity and low phasic mesolimbic dopamine responding to incentives during reward anticipation and associative learning. We also consider how other neural networks, including bottom-up emotion *generation* systems and top-down emotion *regulation* systems, interact with mesolimbic dysfunction to result in alternative manifestations of psychiatric illness. Finally, we present a model that emphasizes a translational, transdiagnostic approach to understanding externalizing/depression comorbidity. This model should refine ways in which internalizing and externalizing disorders are studied, classified, and treated.

In child and adolescent psychopathology research, most psychiatric disorders are classified as either internalizing syndromes, including depressive and anxiety disorders, or externalizing syndromes, including attention-deficit/hyperactivity disorder (ADHD), disruptive behavior disorders, and substance use disorders (SUDs). The internalizing/externalizing distinction follows from a long tradition of empirically based taxonomy in developmental psychopathology (see Beauchaine & Klein, in press). In such research, factor analysis consistently parses behavioral symptoms of psychopathology into broadband internalizing and externalizing dimensions (e.g., Achenbach, 2011; Achenbach, & Edelbrock, 1983).

More recent structural analyses of symptoms expressed among both twin samples and population-based samples of adults confirm the internalizing/externalizing distinction. These analyses invariably yield a hierarchical latent structure of psychopathology in which (a) higher order internalizing and externalizing factors account for much of the covariation among specific lower order syndromes (i.e., disorders), and (b) higher order internalizing and externalizing factors are themselves correlated (e.g., Kendler et al., 2011; Krueger, 1999; Krueger et al., 2002; Lahey, Van Hulle, Singh, Waldman, & Rahouz, 2011; Tuvblad, Zheng, Raine, & Baker, 2009; Wright et al., 2013). This pattern emerges regardless of the age of participants.

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Population-level covariation among syndromes within the internalizing and externalizing spectra suggests that comorbidity of disorders at the individual level should be common (see, e.g., Angold, Costello, & Erkanli, 1999; Beauchaine, Hinshaw & Pang, 2010; Beauchaine & McNulty, 2013; Klein & Riso, 1993). *Homotypic comorbidity* refers to cases in which an individual experiences two or more internalizing disorders, or two or more externalizing disorders. Given results from factor analyses, and given substantial overlap in criterion sets, homotypic comorbidity has proved to be the rule rather than the exception in child, adolescent, and adult psychopathology research, both in the United States and abroad (see, e.g., Angold et al., 1999; Ferdinand, Dieleman, Ormel, & Verhulst, 2007; Gau et al., 2010; Kessler, Chiu, Demler, & Walters, 2005; Kessler et al., 1994; Maughan, Rowe, Messer, Goodman, & Meltzer, 2004).

In contrast to homotypic comorbidity, *heterotypic comorbidity* refers to cases in which an individual experiences at least one internalizing disorder and at least one externalizing disorder (Angold et al., 1999). Even though internalizing and externalizing disorders comprise largely nonoverlapping criterion sets, heterotypic comorbidity is exceedingly common (e.g., Costello, Mustillo, Erkanli, Keeler, & Angold, 2003; Gilliom & Shaw, 2004; Keiley, Bates, Dodge, & Pettit, 2000; Marmorstein & Iacono, 2003). For example, up to half of preschool and school-age children with ADHD experience a comorbid mood disorder (Wilens et al., 2002), and externalizing disorders in childhood predict depression in adulthood (Loth, Drabick, Leibenluft, & Hulvershorn, 2014). Furthermore, wor-

sening externalizing problems across time predict worsening internalizing problems, particularly among children with high baseline levels of psychopathology (Gilliom & Shaw, 2004; Keiley et al., 2000). However, heterotypic comorbidity is not a transient phenomenon of childhood, and is also observed in adolescent, young adult, and adult samples (see Biederman et al., 2008; Chan, Dennis, & Funk, 2008; Kessler et al., 2005; Krueger, McGue, & Iacono, 2001).

Artifactual, Spurious, and True Comorbidity

From a validity standpoint, sources of comorbidity can be divided into three overarching categories (see, e.g., Angold et al., 1999; First, 2005; Klein & Riso, 1993; Lilienfeld, 2003). These include *artifactual comorbidity*, which occurs when one disease entity is mistakenly split into multiple diagnoses; *spurious comorbidity*, which occurs when distinct disease entities are assigned shared diagnostic criteria; and *true comorbidity*, which occurs when an individual suffers from separate disease entities. To date, most research on comorbidity has focused either on tabulating symptoms to determine whether rates of diagnostic co-occurrence exceed chance levels (see Angold et al., 1999; Kessler et al., 1994, 2005), or on evaluating patterns of symptoms among large population-based and twin samples using advanced statistical modeling (e.g., Krueger & Markon, 2006; Tackett, Waldman, Van Hulle, & Lahey, 2011).

Although these approaches yield important descriptive information about diagnostic co-occurrence and about heritabilities of comorbidity, they provide no information about neurobiological mechanisms. This is a significant limitation because etiology-based diagnosis is often a precondition for determining whether apparent comorbidity is artifactual, spurious, or true (see Beauchaine & Marsh, 2006; First, 2005; Jensen, 2003; Preskorn & Baker, 2002). Lacking specification of etiology, we must infer psychopathology solely from symptoms, which are often nonspecific, insensitive markers of disease state (see Beauchaine, Lenzenweger, & Waller, 2008; Meehl, 1995).

Advances in behavioral genetics, molecular genetics, and neuroimaging have led to significant progress in identifying etiological underpinnings of many mental disorders, and have produced key insights into possible mechanisms of both homotypic and heterotypic comorbidity (see, e.g., Baskin-Sommers & Foti, 2015; Beauchaine et al., 2010; Beauchaine & McNulty, 2013; Rhee, Lahey, & Waldman, 2015). Such efforts lend increasing support to a neuroscience-informed, trait-based approach to characterizing psychopathology in which patterns of functional interaction among a limited number of brain systems give rise to internalizing and externalizing vulnerability (see, e.g., Beauchaine, 2001, 2015a; Beauchaine & Thayer, 2015). For example, high trait impulsivity, which has well characterized neural substrates, confers vulnerability to all externalizing syndromes, including the hyperactive/impulsive and combined presentations of ADHD, oppositional defiant disorder (ODD), conduct disorder (CD), SUDs, and antisocial personality disorder (ASPD; see Beauchaine & McNulty, 2013; Neuhaus, & Beauchaine, in press). Trait impulsivity is therefore a primary vulnerability to homotypic comorbidity among externalizing disorders (Beauchaine, Zisner, & Sauder, in press).

Objectives

Other behavioral traits are *transdiagnostic* vulnerabilities to both internalizing and externalizing syndromes (see Beauchaine, 2015b; Beauchaine & Thayer, 2015). For example, *emotion dysregulation*, often defined as the inability to modulate affective states in the service of adaptive behavior, is observed across a wide range of psychiatric disorders, including major depressive disorder (MDD; e.g., Ehring, Tuschen-Caffier, Schnülle, Fischer, & Gross, 2010), externalizing spectrum disorders (e.g., Beauchaine, Gatzke-Kopp, & Mead, 2007), and anxiety disorders (e.g., Mennin, Heimberg, Turk, & Fresco, 2005), to name but a few. We and others have summarized the role of emotion dysregulation in conferring transdiagnostic vulnerability to psychopathology in recent reviews (Beauchaine, 2001, 2015a; Beauchaine & Thayer, 2015). The purpose of this paper is to describe how mesolimbic dopamine (DA) dysfunction confers transdiagnostic vulnerability to both externalizing spectrum disorders and unipolar depression.[1] We synthesize accumulating research on common neural substrates of trait impulsivity, anhedonia, and irritability, and present several interpretations of relations among these tendencies. As we demonstrate in sections to follow, considerable evidence now supports the following set of conjectures:

1. Trait impulsivity, anhedonia, and irritability (hallmarks of externalizing spectrum disorders and depression) derive from chronically low tonic mesolimbic DA activity and blunted phasic DA responding during anticipation of incentives.
2. A primary route to heterotypic comorbidity is through this transdiagnostic neural vulnerability in incentive processing.
3. Hypofunctioning of the mesolimbic DA system affects approach motivation, producing a chronically aversive mood state characterized by low positive affectivity and irritability, which are common to both externalizing disorders and unipolar depression.
4. At the neural level of analysis, externalizing disorders and unipolar depression are distinguished from one another by individual differences in activity and reactivity of other neural systems.

1. Although we restrict our discussion of internalizing disorders primarily to unipolar depression given space constraints, we acknowledge high rates of comorbidity between unipolar depression and anxiety (see, e.g., Hankin et al., 2016). We do not consider bipolar depression, which is distinct etiologically from unipolar depression, and is characterized by different patterns of heritability and central nervous system function (e.g., Cuellar, Johnson, & Winters, 2005).

In sections to follow, we contend that the neural basis of heterotypic comorbidity between externalizing spectrum disorders,[2] including the hyperactive/impulsive and combined presentations of ADHD[3] and unipolar depression, is shared neural vulnerability in the mesolimbic DA system. We content further that behavioral differences between these disorders arise from impairments in other neural circuits that interact with the mesolimbic DA system to affect behavior. One such circuit is the septohippocampal system, including the amygdala, a region that is hyperresponsive to negatively valenced stimuli among those with depression. We argue that deficient lateral prefrontal regulation of the amygdala portends risk for depression, whereas deficient orbitofrontal and dorsolateral prefrontal regulation of mesolimbic reward circuitry[4] portends risk for externalizing spectrum disorders. Both of these regulatory mechanisms may be disrupted within an individual, giving rise to heterotypic comorbidity. We recognize that other central DA systems and other neurotransmitter systems affect mood state, and interact functionally with the mesolimbic DA system to confer vulnerability or resilience to psychopathology, including both homotypic and heterotypic comorbidity (e.g., Corr & McNaughton, 2016). We and others have considered such relations elsewhere (e.g., Beauchaine, 2001; Beauchaine, Neuhaus, Zalewski, Crowell, & Potapova, 2011; Beauchaine & Thayer, 2015; Sauder, Beauchaine, Gatze-Kapp, Shanon, & Aylward, 2012). Our primary objectives in writing this paper are to describe the role of mesolimbic DA circuitry in conferring vulnerability to trait impulsivity and anhedonia, and to a chronically aversive mood state characterized irritability, which is common to both externalizing spectrum disorders and unipolar depression.

Key Terms and Concepts

The term *temperament* refers to emotional and behavioral predispositions that are expressed very early in life and arise from heritable individual differences in brain structure and function (see, e.g., Kagan, in press; Rothbart, & Bates, 1998). According to prominent developmental models, temperamental predispositions interact with environmental influences throughout childhood and adolescence to eventuate in adult personality (e.g., De Pauw & Mervielde, 2010; Goldsmith, Lemery, Aksan, & Buss, 2000; Rothbart, 2007). Adult personality traits are "relatively enduring patterns of thoughts, feelings, and behaviors that distinguish individuals from one another" (Roberts & Mroczek, 2008, p. 31; see McCrae & Costa, 2003). Temperament and personality both reflect quantifiable, continuously distributed individual differences in the population (see Haslam, Holland, & Kuppens, 2012; Nettle, 2006). Extreme levels of certain temperament and personality traits (e.g., impulsivity, inhibition, and neuroticism) can confer vulnerability to psychopathology (see Beauchaine & Neuhaus, in press; Kagan, in press), especially when coupled with deficiencies in emotion regulation (see Beauchaine, 2015a; Beauchaine & Thayer, 2015). Extreme variation in temperament and personality usually does not reflect qualitative differences between affected individuals and others in the general population (e.g., Clark, 2005; Livesley & Jang, 2005; Miller, Lyman, Widiger, & Leukefeld, 2001). Because temperament and personality traits are distributed along continua, setting boundaries for what is considered to be clinically elevated symptom expression can be challenging and is somewhat arbitrary.

Trait impulsivity

Conceptualizations of the neurobiological basis of impulsivity have evolved over time (see Neuhaus & Beauchaine, in press). Hippocrates viewed impulsive tendencies as the product of excessive yellow bile (Titchener, 1921). In the 18th century, Franz Joseph Gall argued based on phrenology that the absence of the mental faculty of "cautiousness" resulted in impulsivity (Spurzheim, 1834). In the 19th century, John Harlow provided a detailed account of perhaps the most famous head injury of all time: that suffered by Phineas P. Gage (Harlow, 1848). His observations of Gage were consistent with assumptions of brain–behavior relationships that were popular at the time. In particular, specific regions of the frontal cortex were believed to underlie precautious motivations, with damage to these regions resulting in disinhibition. Many also assumed that behavior was the outcome of competing mental forces. Among healthy individuals, more primitive urges were effectively constrained by inhibitory control mechanisms. Thus, damage to brain regions responsible for inhibiting impulses created disequilibrium, so "animal propensities" prevailed (Harlow, 1948).

The notion that adaptive behavior derives from a relative equilibrium between self-gratifying and restrained motivations pervades major theories of impulsivity. For example, Eppinger and Hess (1910/1915) asserted that *vagotonia*, a term used to describe an imbalance in the autonomic nervous system favoring the parasympathetic over the sympathetic division, was used to explain a range psychological and medical phenomena, including neurasthenia, hysteria, nervousness, and impulsive tendencies.

Several more recent theories of impulsivity posit that individual differences in approach behavior derive from activity and reactivity of mesolimbic structures. For example, in his

2. A core tenet of developmental psychopathology is that multiple etiological pathways can lead to phenotypically similar, equifinal outcomes (Cicchetti & Rogosch, 1996). The model elaborated herein is not intended to explain all cases of heterotypic comorbidity; rather, it describes one common pathway (see Beauchaine et al., in press).
3. We exclude the inattentive presentation of ADHD given consistent evidence that it is distinct etiologically from the hyperactive/impulsive and combined presentations (see, e.g., Diamond, 2005; Lee, Burns, Beauchaine, & Becker, 2015; Milich, Balentine, & Lynam, 2001). Thus, throughout this article ADHD refers to the hyperactive/impulsive and combined presentations.
4. Herein, reward circuitry is restricted to discussion of networks that respond to incentives. Although brain regions implicated in punishment overlap with those for reward, punishment is not an emphasis of this work.

prominent neurobiological theory of personality, Gray (1987a, 1987b) proposed a mesolimbic DA behavioral approach system as the neural substrate of appetitive motivation. Subsequently, DA theories of approach motivation were used to explain impulsive, reward-seeking behaviors often observed in ADHD, CD, and other externalizing disorders (e.g., Fowles, 1988; Quay, 1993). Although these early theories correctly attributed impulsivity to mesolimbic neural dysfunction, they incorrectly assumed that *excessive* DA activity predisposed affected individuals to impulsive behavior. As described in detail here and elsewhere, subsequent research reveals that externalizing spectrum disorders are characterized by low rather than high mesolimbic DA activity and reactivity (see Beauchaine & Gatzke-Kopp, 2012; Beauchaine & McNulty, 2013; Gatzke-Kopp & Beauchaine, 2007; Zisner & Beauchaine, 2015).

Contemporary accounts of impulsivity operationalize the construct in a number of ways. In its most general sense, impulsivity refers to deficiencies in self-control over behavior (see, e.g., Zisner & Beauchaine, 2015). The extent to which one exhibits impulsive tendencies varies continuously across the population, and normal variation in this trait is not maladaptive. Rather, normal variation in trait impulsivity is reflected in core aspects of personality, including novelty seeking, sensation seeking, extraversion, and exuberance, all of which may foster adaptive functioning, including creative and flexible thinking (see, e.g., Degnan et al., 2011; Sagvolden, Johansen, Aase, & Russell, 2005).

In contrast, excessive trait impulsivity, the focus of this paper, confers vulnerability to clinically significant psychopathology. As noted above, high trait impulsivity is expressed as a preference for immediate, smaller rewards over larger, delayed rewards, and often results in behaviors that are socially inappropriate, maladaptive, and short-sighted (see Neuhaus & Beauchaine, in press; Zisner & Beauchaine, 2015). As we discuss in detail below, such behaviors reflect an overarching problem with effectively anticipating rewards and optimizing goal-directed behavior (Sagvolden et al., 2005).

In discussing trait impulsivity, it is important to note that others conceptualize the construct without a clinical aspect in mind. For example, Whiteside and Lynam (2001) attribute four etiologically distinct personality facets, including urgency, lack of planning, lack of perseverance, and sensation seeking to impulsive behavior, and Patton, Stanford, and Barratt (1995) distinguish between motor impulsiveness (actions without forethought), nonplanning impulsiveness (overemphasis on the present), and attentional impulsiveness (difficulty maintaining focus on stimuli). In addition, impulsivity is sometimes operationalized as behavioral performance on circumscribed tasks, such as go/no-go (continuous performance), stop-signal, choice serial reaction time, delay-discounting, and cost/benefit decision-making tasks (e.g., Bezdjian, Baker, Lozano, & Raine, 2009; Bickel, Odum, & Madden, 1999; Dimoska & Johnstone, 2007). Go/no-go, stop-signal, and choice serial reaction time tasks may best capture inattentiveness and impulsive action (i.e., premature responding and/or failure to inhibit responses), whereas other behavioral tasks, such as delay-discounting and cost/benefit decision-making tasks, may best capture impulsive choice. However, common self-report and behavioral measures of impulsivity capture only partially overlapping, and in some cases more distinct, aspects of impulsivity (Reynolds, Ortengren, Richards, & de Wit, 2006; Robinson et al., 2009).

Given heterogeneity in definitions of and approaches to measuring impulsivity, a well-supported case for a particular operational definition is crucial. We prefer to operationalize impulsivity for human participants using ADHD hyperactive–impulsive scale scores over other measures for three primary reasons: (a) hyperactive–impulsive symptoms of ADHD are highly heritable (e.g., Faraone et al., 2005), far more so than most alternative measures of impulsivity (73%–85% of the variance in ADHD symptoms is explained by heritability; Nikolas & Burt, 2010; Willcutt, in press); (b) trait impulsivity among those with ADHD is associated with well-replicated physiological and neural substrates (e.g., Beauchaine, Katkin, Strassberg, & Snarr, 2001; Crowell et al., 2006; Hart, Radua, Mataix-Cols, & Rubia, 2012; Plichta & Scheres, 2014); and (c) ADHD predicts functional outcomes including academic and occupational underachievement, and confers vulnerability to other externalizing spectrum disorders across development (see Beauchaine & McNulty, 2013; Beauchaine et al., 2010; Neuhaus & Beauchaine, 2013; Zisner & Beauchaine, 2015).

Anhedonia

Anhedonia, a term that derives from ancient Greek (ἀν- an-, "without" + ἡδονή hēdonē, "pleasure"), was formally coined by Théodule-Armand Ribot to describe an inability to experience pleasure (Ribot, 1896). Even before the term emerged, diminished response to pleasure was considered to be a significant if not essential presenting feature of depression (Bevan, 1899; Bucknill & Tuke, 1874; Clouston, 1896), and it was incorporated into early influential theories of schizophrenia (Bleuler, 1911; Kraepelin, 1919). Interest in the role of anhedonia in psychopathology dwindled in the first half of the 20th century; but it was revitalized in the 1960s by the psychoanalyst Sandor Rado, who posited that anhedonia was one of two key symptoms that marked genetic vulnerability to schizophrenia. Rado (1956, 1962) suggested that anhedonia could be transmitted genetically, and that it interfered with normal living among individuals with schizophrenia, and among their family members who did not experience psychotic features. Paul Meehl (1962, 1973) expanded on this work by suggesting that low hedonic capacity is a characteristic of and heritable trait vulnerability to both depression and schizophrenia.

Anhedonia became a defining feature of mood disorders following Donald Klein's conceptualization of endogenous depression. He asserted that for some, depression is a biologically derived pathology, with onset of anhedonia being the first observable sign of a depressive episode (Klein, 1974). Klein's work contributed to inclusion of anhedonia

as a criterion for major depressive disorder, beginning with DSM-III (American Psychiatric Association [APA], 1980).

Klein (1974), DSM-III (APA, 1980), and many others describe anhedonia as diminished interest or capacity to experience pleasure in response to stimuli that are ordinarily rewarding. However, "diminished interest" implies that hedonic capacity must change from high to low over some interval of time (e.g., during a major depressive episode). In contrast, we and others assert that for some, anhedonia is both traitlike and state dependent. We therefore define trait anhedonia as a relatively stable personality attribute, characterized by chronically low motivation, and inability to experience pleasure (e.g., Loas, 1996; McCabe, 2014; Shankman, Nelson, Harrow, & Faull, 2010). However, we recognize that anhedonia captures partly dissociable processes that may be compromised differentially. These include anticipatory versus consummatory responses to reward, social versus physical (sensory) anhedonia, differences between interest/motivation to seek rewards versus pleasure derived from rewards, and differential responding to distal versus proximal reinforcers (see Shankman et al., 2014). As elaborated in later sections, the aspect of trait anhedonia that is of greatest interest here is diminished positive affect in anticipation of rewards, a deficit related directly to reduced interest in and motivation to seek pleasurable stimuli.

Like trait impulsivity, anhedonia is operationalized in a number of ways. Common measures include the original and revised Chapman Physical and Social Anhedonia Scales (Chapman, Chapman, & Raulin, 1976), the Snaith–Hamilton Pleasure Scale (Snaith et al., 1995), and the Fawcett–Clark Pleasure Scale (Fawcett, Clark, Scheftner, & Gibbons, 1983), which provide some convergent psychometric properties (Leventhal, Chasson, Tapia, Miller, & Pettit, 2006). Anticipatory and consummatory aspects of anhedonia are distinguished from one another using the Temporal Experience of Pleasure Scale (Gard, Gard, Kring, & John, 2006). Examples of common laboratory-based indices of anhedonia include self-report, psychophysiological, and hemodynamic responses to tasting sucrose and chocolate (e.g., Berlin, Givry-Steiner, Lecrubier, & Puech, 1998; Chentsova-Dutton & Hanley, 2010), and to hearing pleasant musical stimuli (e.g., Keller et al., 2013), as well as behavioral responses, such as developing a response bias toward more frequently rewarding stimuli (Pizzagalli, Jahn, & O'Shea, 2005).

As a general rule across self-report and laboratory-based measures, high anhedonia scores capture low positive affectivity, a collection of emotions related to low levels of joy, energy, excitement, and confidence (Watson, 2002). This contrasts with the personality characteristic of negativity affectivity, which manifests as a general tendency to experience distress, nervousness, and hostility, which may or may not co-occur with low positive affectivity (Watson & Tellegen, 1985).[5]

Here, we operationalize trait anhedonia as deficits in incentive processing prior to the experience of reward (i.e., low interest and motivation to expend energy to receive rewards; diminished anticipatory responses to rewards). However, we recognize that the term anhedonia conventionally encapsulates deficiencies relating to both obtaining and directly experiencing rewarding stimuli, and that one or both of these functions can be affected within individuals.

DA neural circuitry

DA system organization. DA is a monoamine neurotransmitter that is implicated in neural processing of motivation, incentive salience, learning, and movement, among other functions. DA projections are traditionally divided into four primary neural systems, including the mesolimbic, mesocortical, nigrostriatal, and tuberoinfundibular pathways, which ascend from the midbrain or hypothalamus (Beaulieu & Gainetdinov, 2011; Björklund & Dunnett, 2007; Taber, Black, Porrino, & Hurley, 2012). Although these pathways are far more interconnected, both structurally and functionally, than originally thought, it is still useful to subdivide DA neural circuits for heuristic purposes (Björklund & Dunnett, 2007; Tisch, Silberstein, Limousin-Dowsey, & Jahanshahi, 2004; Wise, 2009).

The two DA projections that are of greatest relevance to trait impulsivity and anhedonia are the mesolimbic and mesocortical pathways, both of which contain neurons that ascend from the ventral tegmental area (VTA) of the midbrain. In the mesolimbic pathway, the medial forebrain bundle connects the VTA to the ventral striatum (VS), including the nucleus accumbens (NAcc; both the core and shell) and ventral regions of the caudate nucleus and putamen (Voorn, Vanderschuren, Groenewegen, Robbins, & Pennartz, 2004). This pathway is associated most strongly with motivation, incentive salience, and impulsivity, and is implicated in the pathogenesis of all externalizing spectrum disorders, including ADHD, ODD, CD, substance abuse disorders, and ASPD (see Beauchaine et al., 2010, in press; Beauchaine & McNulty, 2013; Beauchaine, Neuhaus, et al., 2016; Gatzke-Kopp & Beauchaine, 2007; Shannon, Sauder, Beauchaine, & Gatzke-Kopp, 2009; Zisner & Beauchaine, 2015). The mesocortical pathway includes DA projections from the VTA to cortical regions, including the prefrontal, orbitofrontal, and

5. Although older conceptions of positive and negative affectivity implied/proposed that the constructs represent poles of a single dimension, neuroscientific evidence suggests that the brain comprises broad systems that engage flexibly to process valence-non-specific content, and that no single affect-processing region responds exclusively to positive or negative stimuli (Lindquist, Satpute, Wager, Weber, & Barrett, 2015). Instead, certain brain regions/subregions, and individual neurons, may exhibit some degree of relative preference for valence-specific stimuli (Bartra, McGuire, & Kable, 2013; Chikazoe, Lee, Kriegeskorte, & Anderson, 2014; Morrison & Salzman, 2009). Inclusion in the positive and negative valence systems of the Research Domain Criteria highlights the importance of fine-tuning models of emotion across multiple levels of analysis to determine relationships between positive and negative affect (National Institute of Mental Health, 2014).

cingulate cortices. This pathway, which is associated with error monitoring, executive functions, evaluating incentive magnitude, and maintenance of goal-directed behaviors, exerts increasing top-down control over the mesolimbic DA system as the frontal cortices mature across development (see, e.g., Beauchaine, 2015a; Beauchaine et al., in press; Beauchaine & McNulty, 2013; Casey, 2015; Macdonald, Goines, Novacek, & Walker, 2016 [this issue]). Due to extensive feedforward and feedback connections between the mesolimbic and mesocortical pathways, they are sometimes referenced jointly as the mesocorticolimbic pathway. However, we prefer to retain a conceptual distinction between the two pathways. This is because top-down inhibitory control of mesolimbic circuitry by cortical regions differs depending on the region and strength of functional connectivity between cortical and subcortical sites (Lodge, 2011). The complex relationship between the mesolimbic and mesocortical pathways suggests that it may be best to regard the pathways as influenced by one another instead of as a single dopaminergic pathway. Pharmacologically induced elevations in prefrontal DA levels decrease DA activity in mesolimbic structures, whereas decreases in prefrontal DA increase DA activity in mesolimbic structures (Louilot, LeMoal, & Simon, 1989). Disruption in this feedback/feedforward system, as evidenced by altered functional connectivity, may be one neural substrate of impulsivity (e.g., Shannon et al., 2009; Tisch et al., 2004).

The third DA pathway, the nigrostriatal pathway, projects from the substantia nigra pars compacta to the dorsal striatum, including dorsal portions of the putamen and caudate. This pathway is most commonly associated with movement, including motoric dysfunction (e.g., Parkinson disease). However, it also plays a role in habit formation and addiction (Everitt & Robbins, 2013). Finally, the tuberoinfundibular pathway contains DA projections from the hypothalamus to the pituitary gland.

DA receptors. DA binds to G-coupled protein receptors that are present in the central nervous system and other locations throughout the body. DA receptor subtypes are grouped as either D1-like (comprising D1 and D5 receptors) or D2-like (comprising D2, D3, and D4 receptors) and are differentiated on the basis of structural, biochemical, and pharmacological properties (Beaulieu & Gainetdinov, 2011). Receptor activation and subsequently elicited responses are functions of a number of factors, including variation in receptor genes, differences in receptor densities between different brain regions and across individuals, and whether receptors are located on presynaptic or postsynaptic neurons (Kelly et al., 1998; Volkow et al., 1999; see Beaulieu & Gainetdinov, 2011). Depending on DA levels that derive from opposing functions and differing ligand affinities of different receptors, DA and its agonists can elicit opposite behavioral effects (e.g., stimulating vs. inhibiting locomotor activity, heart rate, and pain sensitivity; Calabrese, 2001). Responses to DA agonism can be biphasic, such that low doses induce different or opposing effects compared to high doses (e.g., Strömbom, 1976).

DA and reward processing

Reward processing encompasses both endogenous and exogenous responses to reinforcers, including neural responding, and how reward contingencies are used to predict, assess, and guide goal-directed behavior. The role of the mesolimbic DA system in reward processing was first studied in the mid-1950s by Olds and Milner, who demonstrated that rats implanted with stimulating electrodes in regions of this system, including the VTA and striatum, habitually self-stimulate, sometimes to the point of death (Olds & Milner, 1954; see Milner, 1991). Later animal studies, some of which we describe below, expanded this work, and identified midbrain DA function as fundamental in processing incentives, and in guiding future, goal-directed behaviors. These findings and others that followed provide the basis for conceptualizing the mesolimbic DA system as the brain's primary reward circuit and provide a compelling neurobiological explanation for the relationship between reward and motivation.

Incentive processing includes both anticipatory and consummatory phases of reward responding. During reward anticipation, an organism is motivated to approach potential reinforcers. During reward consummation, the organism experiences some degree of pleasure/satisfaction from receiving reinforcement.[6] To maximize access to reinforcers, organisms must learn to anticipate them accurately based on potentially dynamic and ambiguous reward contingencies, a process known as reward learning. The distinction between reward anticipation and receipt has received considerable support from animal and neuroimaging work (discussed below; see Berridge & Kringelbach, 2015; Berridge & Robinson, 1998; O'Doherty, 2004), and emerges in multiples lines of research. For example, separating reward anticipation from receipt parallels the concepts of "wanting" (motivation to pursue rewards) versus "liking" (satisfaction from receiving rewards) described by Robinson and Berridge in their highly influential incentive salience theory of addiction (1993, 2008; Berridge & Kringelbach, 2015). According to incentive salience theory, wanting (anticipating) is mediated by the NAcc core among other regions, whereas liking is mediated by neural processes in the NAcc shell (e.g., Berridge & Kringelbach, 2015; Berridge & Robinson, 2003; Saddoris, Cacciapaglia, Wightman, & Carelli, 2015).

6. Incentives can be primary reinforcers, such as food and sex, which relate directly to survival and procreation, or secondary reinforcers, such as money, beauty, and social approval, which do not relate directly to survival (Krach, Paulus, Bodden, & Kircher, 2010; Kühn & Gallinat, 2012; Liu, Hairston, Schrier, & Fan, 2011). Like primary reinforcers, secondary reinforcers elicit activation in the VS and other brain regions implicated in reward processing, including the OFC and cingulate cortex. Neural processing of social reward is more complex (see Krach et al., 2010) and is not considered in this article.

The computational task of accurately anticipating reinforcers is accomplished in part through appropriate tonic (low-amplitude, baseline) and phasic (high-amplitude, event-related) activity of midbrain DA neurons (Schultz, 1998). For example, unexpected rewards elicit burst firing of DA neurons that project to the NAcc in the VS (Tremblay, Hollerman, & Schultz, 1998). The magnitude and time course of this spike in DA provides a temporal window for an organism to learn which behaviors increase the likelihood of receiving rewards, resulting in reinforcement of these behaviors (i.e., motivated responses; Sagvolden et al., 2005). Once the organism can predict, based on cues, the probability and magnitude of an impending reward, phasic DA reactivity shifts forward from occurring during consummation of the reinforcer to the temporal interval between cue and reward (Bressan & Crippa, 2005). However, phasic DA responding continues to occur during receipt of rewards that are unexpected, or are larger in magnitude than expected. In contrast, phasic DA responding dampens following receipt of rewards that are worse than expected, or expected but absent (Bressan & Crippa, 2005; Schultz, 1998). During reward anticipation, midbrain DA neurons encode relative value of expected rewards (magnitude of the reward weighted by probability and delay), such that large, immediate, and highly probable gains elicit the most robust neural firing (Kobayashi & Schultz, 2008; Tobler, Fiorillo, & Schultz, 2005). The VS, which receives direct input from midbrain DA neurons, and from other structures implicated in reward processing, including the amygdala, insula, and orbitofrontal cortex (OFC), also indexes the relative value of predicted rewards (Knutson, Adams, Fong, & Hommer, 2001), whereas reduced activation signals reward devaluation (Gottfried, O'Doherty, & Dolan, 2003). Thus, DA-mediated activity of the VS and other structures is integral to associative learning, and associative learning is reflected in the ability to anticipate future rewards.

Phasic changes in mesolimbic neural responding have been assessed directly in animals (e.g., Tremblay et al., 1998) and indirectly through functional neuroimaging with humans. One type of functional magnetic resonance imaging task commonly used with humans is the monetary incentive delay task, adapted from tasks used in primate research to study reward processing (Knutson et al., 2001; Schultz, Dayan, & Montague, 1997). Parameters of the monetary incentive delay task vary across studies, but the basic framework is as follows: for each trial, participants are presented with an incentive cue that signals the possibility of winning money, avoiding losing money, or no change during that trial. Participants are then challenged to respond to a target quickly, and their performance determines the monetary outcome for that trial. This paradigm is advantageous because it separates reward anticipation from reward receipt, and has been used widely to investigate neural correlates of reward processing in clinical and nonclinical samples (e.g., Forbes et al., 2006; Knutson, Bhanji, Cooney, Atlas, & Gotlib, 2008; Lutz & Widmer, 2014; Sauder, Derbidge, & Beauchaine, 2016).

Although phasic DA responding has received considerable attention in research on reward processing, tonic levels of DA in the mesolimbic system also play a role in evaluating and responding to incentives (Goto, Otani, & Grace, 2007; Sagvolden et al., 2005). Tonic levels of DA, as assessed through DA concentrations in extrasynaptic space, are normally insufficient to stimulate postsynaptic DA receptors (Grace, 2001). However, tonic DA modulates phasic DA activity (Bressan & Crippa, 2005). For example, tonic DA can bind to DA terminal autoreceptors and other receptor sites in the extrasynaptic space, inhibiting phasic release of DA (Grace & Bunney, 1995). Through such processes, excessively high or low tonic DA can compromise reward learning by altering the relative strength of phasic signals to reinforcers (see Sagvolden et al., 2005; Schultz, 1998).

As alluded to above, incentive processing is related closely to motivation, defined as the degree to which an organism will exert energy in goal-directed behaviors. Like reward processing, motivation derives in part from tonic and phasic DA in the VS, and communication among structures in the mesolimbic DA circuit, including the VS (see Niv, 2007). For example, chronically elevated extracellular DA is associated with enhanced motivation (Cagniard, Balsam, Brunner, & Zhuang, 2006), whereas DA depletion and DA receptor blockage in the VS are associated with reduced motivation (Salamone, Cousins, & Bucher, 1994). Thus, intact ability to neurally encode the relative value of rewards and anticipate future rewards is important for stimulating motivated behaviors in order to obtain rewards that are "worth" the effort.

Several key takeaways from research on incentive processing are worth noting before we move forward in our discussion: (a) effective reward processing is contingent on tonic levels of DA, and on phasic modulation of DA in mesolimbic structures; (b) reward anticipation and reward consummation are dissociable, and reward anticipation may be compromised in organisms that possess intact consummatory responses; and (c) the ability to appraise reward value and anticipate future rewards influences motivation to engage in goal-directed behaviors.

Neural Responding to Incentives and Trait Impulsivity

Contrary to some early accounts, which erroneously attributed pathologically impulsive behavior to excessive mesolimbic DA activity and reactivity (for a review, see Brenner, Beauchaine, & Sylvers, 2005), research conducted in the past 10–15 years identifies chronically low tonic DA and diminished DA reactivity to incentives in the VS as important neural substrates of clinically expressed impulsivity (e.g., Scheres, Milham, Knutson, & Castellanos, 2007; Volkow et al., 2007; see also Gatzke-Kopp, 2011; Gatzke-Kopp, & Beauchaine, 2007; Neuhaus & Beauchaine, 2013; Sagvolden et al., 2005; Zisner & Beauchaine, 2015). Low phasic DA responding is associated with impaired reward processing, which manifests in a number of ways, including compromised ability to differentially respond to rewards based on

their frequency and magnitude (Luman, Van Meel, Oosterlaan, Sergeant, & Geurts, 2009), failure to establish associative learning contingencies (Gatzke-Kopp & Beauchaine, 2007; Sagvolden et al., 2005), and prolonged extinguishing of previously rewarded behaviors (Gatzke-Kopp et al., 2009). As described below, impaired associative learning caused by a hypofunctional mesolimbic DA system is a critical factor underlying poor impulse control.

Animal studies

Converging evidence from comparative studies suggests that impulsive behavior is associated with deficiencies in mesolimbic DA function (see Gatzke-Kopp, 2011; Sagvolden et al., 2005). Selective lesioning of the NAcc core, a DA-rich area of the VS, increases impulsive choice in rats (Cardinal, Pennicott, Lakmali, Robbins, & Everitt, 2001). Similarly, overexpression of the DA transporter in the NAcc, which results in reduced levels of extracellular DA in this region, is associated with both increased impulsive choice (greater preference for immediate, smaller rewards over larger, delayed rewards), and risk proneness (greater preference for large, uncertain rewards over small but likely rewards; Adriani et al., 2009).

The role of DA neurocircuitry in impulsivity is especially evident in animal studies that select and compare groups based on (a) differences in inherent VS responding and (b) baseline differences in impulsive behaviors. Both impulsive choice and impulsive action (failure to inhibit behavior when it is advantageous to do so) are associated with abnormally low DA release in the VS in response to electrical stimulation (Diergaarde et al., 2008). Among laboratory animals that are highly impulsive, as assessed by poor behavioral inhibition on the stop-signal task, DA agonism shortens reaction time to inhibit action and thereby improves impulse control (Eagle, Tufft, Goodchild, & Robbins, 2007; Feola, de Wit, & Richards, 2000). In contrast, among animals with fast reaction times at baseline (high impulse control), studies by Eagle et al. and Feola et al. demonstrate that DA agonism either exhibits no effect on impulse control or lengthens reaction time.

Impulsive animals also exhibit an increased proclivity to engage in drug use. For example, inherently low D2/3 receptor availability in the NAcc is associated prospectively with higher rates of cocaine self-administration (Dalley et al., 2007). Combined, such findings suggest low tonic and phasic DA release are associated with impulse control problems.

It is important to note that relations between DA and impulsivity may be obscured entirely when inherent individual differences in mesolimbic function are not considered, because these individual differences modulate effects of DA-acting drugs. Studies that do not consider individual differences in baseline impulsivity overwhelmingly associate DA agonism with *increases* in impulsive action, which is in direct contrast with well-replicated findings linking low DA to impulsivity among highly impulsive animals (see D'Amour-Horvat & Leyron, 2014). In addition to individual differences in DA neurocircuitry function, other factors relating to dosing and drug administration schedules should be considered when conducting and interpreting studies concerning pharmacological manipulation of DA in animals.[7]

It is important to note that there is still uncertainty regarding the precise nature and causes of DA deficiency associated with trait impulsivity. A number of possible mechanisms exist, including abnormalities attributed to DA release, density, and function of the DA transporter and/or DA receptors, and functional connectivity between regions among and outside central DA systems, as well as effects of particular stimulus conditions. In all likelihood, more than one such factor drives behavioral effects, and factors underlying impulsive tendencies may differ among individuals (see Beauchaine et al., in press; Dalley, Mar, Economidou, & Robbins, 2008). Molecular genetic accounts suggest that trait impulsivity and its various behavioral manifestations across development are inherited multifactorially. Because many genes are involved, which interact with one another and with environment to affect behavior, no single genetic locus is necessary or sufficient to confer clinically expressed impulsivity (e.g., Gizer, Otto, & Ellingson, 2016).

Neuroimaging research with humans

Findings from neuroimaging studies among humans with ADHD and other externalizing spectrum disorders who exhibit clinically significant impulsivity parallel and in some cases clarify findings from animal studies. Single photon emission computed tomography, positron emission tomography (PET), and magnetic resonanc imaging studies implicate compromised mesolimbic and/or mesocortical DA function in ADHD (e.g., Ludolph et al., 2008; Vles, Feron, & Hendrikson, 2003; Volkow et al., 2007, 2009), CD (e.g., Rubia, Smith, et al., 2009), SUDs (e.g., Martin-Soelch et al., 2001; Volkow, Fowler, & Wang, 2004), and antisocial traits (e.g., Oberlin et al., 2012). Children with ADHD exhibit smaller

7. Pharmacologic agonism and antagonism of DA has produced equivocal behavioral and neurobiological results, often complicating interpretations of the relation between midbrain DA function and impulsive behavior. One way to reconcile these findings is to consider differences between acute and chronic administration of pharmacologic agents. For example, a single, large dose of amphetamine *increases* D1 receptor binding in the rat striatum, whereas chronic amphetamine administration *decreases* D1 receptor binding in the same region (Howlett & Nahorski, 1979). Another consideration concerns dose dependency. For example, low versus high doses of the DA agonists, including d-amphetamine and methylphenidate, elicit opposing effects on neural firing rates in the caudate nucleus/putamen of the striatum (Rebec & Segal, 1978). Furthermore, factors related to administration scheduling and dose can interact to produce additional complexities. Following administration of chronic low-dose amphetamine, acute increases in amphetamine elicit either depressed or enhanced neural firing in the caudate nucleus/putamen, whereas administration of chronic high-dose amphetamine followed by acute increases in amphetamine elicit neural excitation in this region (Kamata & Rebec, 1983). Such factors, in addition to individual differences among animals (see text), and inherent difficulties measuring impulsivity in animal models, must be considered.

VS volumes, which correspond with severity of hyperactive/impulsive symptoms (Carmona et al., 2009; Sauder et al., 2012). Individuals with ADHD also demonstrate reduced striatal responding to smaller, immediate rewards and larger, delayed rewards in functional magnetic resonance imaging (fMRI) studies (e.g., Plichta et al., 2009).[8] Furthermore, those with ADHD (e.g., Carmona et al., 2012; Furukawa et al., 2014; Hoogman et al., 2011; Scheres et al., 2007; Ströhle et al., 2008), early-onset criminal offending (Cohn et al., 2015), and SUDs (Beck et al., 2009; Wrase et al., 2007) all exhibit VS hypoactivation during reward anticipation and/or reward outcome compared with controls. These findings are consistent with hypofunctionality of DA circuitry observed in impulsive animals.

No clear evidence has emerged from animal research to describe the relationship between phasic DA responses to immediate rewards and impulsivity (Luman, Tripp, & Scheres, 2010), and competing theories suggest that such responses are suppressed (e.g., Sagvolden et al., 2005) or unaffected (e.g., Tripp & Wickens, 2008). In some neuroimaging research, ADHD is associated with similar or perhaps even greater VS responses to reward outcomes (as opposed to reward anticipation), compared with controls (Furukawa et al., 2014; Scheres et al., 2007; Wilbertz et al., 2012). This is consistent with theories that link timing and duration over magnitude of DA responding to ADHD (see also Sagvolden et al., 2005).

Some of the strongest neuroimaging evidence for deficient mesolimbic responding as a neural substrate of impulsivity derives from studies that assess neurobiological consequences of DA agonists among those with ADHD. DA agonists, including methylphenidate, increase extracellular DA levels in the striatal pathway (e.g., Volkow, Fowler, Wang, Ding, & Gatley, 2002). Among both children and adults with ADHD, methylphenidate normalizes (a) attenuated striatal responses to reward (Vles et al., 2003; Volkow et al., 2002), (b) frontocingulate underreactivity during error processing (Rubia, Halari, Mohammad, Taylor, & Brammer, 2011), and (c) functional connectivity deficits between mesolimbic and mesocortical brain regions (Rubia, Halari, Cubillo, Mohammad, & Taylor, 2009). Thus, DA agonists, which increase availability of DA in the striatum, decrease impulsive behaviors by increasing DA availability to levels experienced by individuals without these symptoms (e.g., Hinshaw, Henker, Whalen, Erhardt, & Dunnington, 1989; MTA Cooperative Group, 1999; see Beauchaine & McNulty, 2013).

Translational models of externalizing behavior

As described above, the strength of a given reinforcer to motivate future behaviors is dependent on several factors, including the magnitude and predictability of the reinforcer and the interval between rewarded behavior and receipt of the reinforcer (see Sagvolden et al., 2005). These factors are coded by phasic neural firing in the VS and interconnected brain regions, which signal relative values of expected reinforcers. Associative learning is affected adversely when tonic DA firing is suppressed (Tripp & Wickens, 2008). Under such conditions, an organism is less able to predict and assign value to reinforcers, because the temporal window within which reward learning can occur is narrowed. As a result, larger and more frequent incentives are required to form behavior–reward associations, and to predict future reward outcomes (Sagvolden et al., 2005). It should be noted that more frequent trials of nonreward may also be required for extinction of learned behavior–reward associations.

It follows from patterns of neural activity and reactivity described above that impulsivity emerges as a preference for immediate over delayed incentives given a general failure to associate behaviors with rewards that are temporally distant from one another (see Sagvolden et al., 2005). Thus, immediate but smaller rewards are appealing compared to larger delayed rewards, because immediate choices are more easily associated with reward and therefore reinforced. Impulsive action may reflect slower learning of which behaviors to select in order to progress toward one's goals (i.e., maximize reward yields). For example, the go/no-go task requires the organism to respond to presentation of "go" cues and withhold responses following "no-go" cues. Failure to inhibit "no-go" responses may occur when responses for "go" cues are sufficiently reinforced, but extinction processes for erroneous, ineffective, or insufficient behavior are impaired. This leads to less differential responding between cue types. Consequently, an organism may exhibit generalized responding to cues regardless of type, and fail to withhold responses appropriately (see Sagvolden et al., 2005). This is consistent with neuroimaging research demonstrating a failure to migrate neural activity from mesolimbic structures to the anterior cingulate when previously rewarded behaviors are extinguished among boys with ADHD and/or CD (Gatzke-Kopp et al., 2009).

Contemporary ontogenic process models assert that heritable trait impulsivity is a transdiagnostic vulnerability to all externalizing spectrum disorders (Beauchaine et al., 2010, in press; Beauchaine & McNulty, 2013; Beauchaine, Shader, & Hinshaw, 2016). As noted above, children, adolescents, and adults with ADHD, which often begins a developmental trajectory to more severe externalizing conduct, exhibit diminished DA reactivity to incentives (see Plichta & Scheres, 2014; Rubia, 2011). This hypofunctionality may emerge at least in part through low tonic DA (e.g., Vles et al., 2003; Volkow et al., 2007; see Sagvolden et al., 2005). Although impulsive, reward-seeking behaviors upregulate DA levels temporarily, with associated increases in positive affect, they do so only transiently, and do not address underlying DA deficiency (Gatzke-Kopp & Beauchaine, 2007; Sagvolden et al., 2005). Thus, low tonic DA, combined with low phasic responding to reward cues, may lead to a disproportionately high preference for immediate over delayed rewards and diminished ability to act with foresight.

8. It is important to note that fMRI does not assess neurotransmitter function, whereas PET and single photon emission computed tomography do.

In addition to providing a neurobiological explanation for impulse control problems, the DA deficiency model of impulsivity may also account for mechanisms that underlie responses to certain interventions. For example, raising intrinsically low levels of tonic DA via administration of DA agonists improves associative learning among those with ADHD by extending the interval during which behavior–reward contingencies are encoded (see Gatzke-Kopp & Beauchaine, 2007). DA agonists may also reduce novelty- and sensation-seeking behaviors by diminishing an organism's dependence on immediately available rewarding stimuli to increase striatal activation (Arnsten, 2006). Other neural processes, such as error detection, may also improve when reinforcement contingencies are presented sufficiently close together to accommodate a shorter window for associative learning (see Luman, Oosterlan, & Sergeant, 2005). For example, providing immediate, performance-based rewards is associated with improved task accuracy and increased neural responding to error and task-relevant stimuli among children with ADHD (Rosch & Hawk, 2013). It is also a core component of effective treatments for more severe conduct problems (e.g., Ialongo, Poduska, Werthamer, & Kellam, 2001).

Interim conclusions

Considerable evidence from animal research and neuroimaging studies with humans suggests that for many individuals, trait impulsivity derives from chronically low tonic DA and diminished DA reactivity to incentive cues in the VS and other mesolimbic structures (see Gatzke-Kopp, 2011). As a result, trait impulsive individuals exhibit deficits in associative learning and a preference for immediate but small rewards over larger delayed rewards. This preference for immediacy also manifests in reduced motivation to engage in tasks that require sustained effort, and tasks that are not intrinsically motivating (see Sagvolden et al., 2005). Raising DA to normal levels improves impulse control by facilitating associative reward learning, increasing positive affect (see Ashby, Isen, & Turken, 1999), and reducing reliance on external reinforcers that are immediately available.

Neural Circuitry of Anhedonia

Support for midbrain DA deficiency as a neural basis of anhedonia is also extensive, and derives from animal studies, human neuroimaging experiments, and behavioral studies conducted with both subclinical and clinically depressed samples (Gorwood, 2008). Findings from these studies indicate that anhedonia is characterized by DA deficiencies in associative reward learning and diminished motivation to exert effort to obtain incentives. Some, including Eisenberg et al. (2010), even operationalize anhedonia as diminished VS activation during reward anticipation, highlighting the importance of DA neural circuitry in expression of this trait.

Animal studies

Because animals cannot self-report state or trait anhedonia, it must be inferred from behavior under carefully controlled experimental conditions. For example, anhedonia is sometimes operationalized as aberrantly low likelihood of seeking pleasurable stimuli despite intact motor function. Animal models suggest that DA is neither necessary nor sufficient for experiencing pleasure from *consuming* appetitive stimuli (i.e., liking), but may be involved critically in *motivational* aspects of reward processing (i.e., wanting). Manipulating mesolimbic DA through pharmacological agonism/antagonism, electrical stimulation, and lesions induced by neurotoxins, such as 6-hydroxydopamine, alters an animal's propensity to expend energy to gain rewards, but does not influence hedonic effects of rewards, such as food palatability (see Berridge & Robinson, 1998). For example, mice that are engineered genetically to have synaptic DA levels that are 70% higher than normal expend more energy to obtain sweet rewards, but are no more likely to derive pleasure from sweets themselves, as assessed through orofacial reactions (Peciña, Cagniard, Berridge, Aldridge, & Zhuang, 2003). Similarly, mice that are engineered genetically to be incapable of producing DA exhibit a preference for sucrose and saccharin over water, just as control mice, but initiate licking behavior for the sweet-tasting substances less frequently (Cannon & Palmiter, 2003). The authors suggest that DA is not required to develop a taste preference for sweets, but may be involved in goal-directed behavior to obtain sweets. This parallels findings among depressed humans, who experience hedonic effects of sweet tastes similarly to healthy controls (Dichter, Smoski, Kampov-Polevoy, Gallop, & Garbutt, 2010).

Animals with deficient mesolimbic DA levels also exhibit a preference for low-cost/low rewards when high-cost/high rewards are available, which is sometimes considered to be a behavioral indicator of anhedonia (see Salamone, Correa, Farrar, & Mingote, 2007). This preference is maintained when reward delays are made equivalent across high- and low-cost reward trials (Floresco, Maric, & Ghods-Sharif, 2008), and disappears when low and high rewards require equal energy expenditure (Denk et al., 2005). Thus, animals understand reward contingencies yet choose options that require less effort. Correa, Carlson, Wisniecki, and Salamone (2002) also reported that animals with selective DA lesions in the NAcc are just as likely as controls to exert effort for rewards that require one lever press, but respond less frequently when rewards require five lever presses. Such findings implicate low DA in diminished motivation, or reduced goal-directed behaviors to receive reward.

Neuroimaging research with humans

Anhedonia is often viewed as a core component of depression and schizophrenia, and like impulsivity, is expressed along a continuum in the population (Keller et al., 2013). Nonpathological anhedonia involves both reduced ability to anticipate

and adapt one's behavior to obtain incentives and reduced motivation to work for incentives. For example, Pizzagalli et al. (2005) reported that undergraduates with high self-reported anhedonia failed to show increases in response bias for rewards, whereas participants with low self-reported anhedonia exhibited this response bias. Thus, the high anhedonia group failed to adjust their behavior based on prior rewarded experiences, suggesting deficient ability to anticipate rewards to maximize gains. Pizzagalli et al. propose that this behavioral pattern may reflect the anhedonic phenotype of depression. Undergraduate students with higher self-reported anhedonia are also less willing to expend effort to receive rewards in laboratory-based tasks that are designed to evaluate reward motivation (Treadway, Buckholtz, Schwartzman, Lambert, & Zald, 2009).

To our knowledge, only two studies have assessed the relationship between anhedonia and neural responding to incentives in nonclinical, non–high-risk samples. Both studies used versions of the monetary incentive delay task. The first study, conducted by Wacker, Dillon, and Pizzagalli (2009), included a predominately nonclinical sample ($N = 28$). Reduced NAcc volumes and diminished activation in the NAcc to monetary incentives were both associated with anhedonia (as assessed by the anhedonic depression subscale of the Mood and Anxiety Symptom Questionnaire; Watson et al., 1995), but not with other symptoms of depression and anxiety. The authors failed to find compromised activation to reward cues, which is more consistent with the anhedonia literature. However, their paradigm allowed for monetary gains on 50% of reward trials. This reward schedule is lower than that used in similar tasks from other studies (e.g., ~66% of trials were rewarded in Knutson et al., 2001). Thus, participants were less able to predict reward outcomes, which, as described above, results in elicitation of greater phasic NAcc firing during reward receipt, but not during presentation of reward cues. Wacker et al. (2009) acknowledge that this difference in methods complicates interpretation of their findings. It is therefore unclear whether anhedonia involves dysfunctional neural responding to anticipatory, consummatory, or both phases of reward processing.

The second study was performed by Eisenberger et al. (2010), who, unlike Wacker et al. (2009), excluded participants with a current DSM-IV Axis I diagnosis. Participants ($N = 39$) were randomly assigned to placebo or a low-dose injection of the endotoxin *Escherichia coli*. Endotoxin was administered to induce an inflammatory response, because inflammation is implicated in onset and maintenance of depression (Miller, Maletic, & Raison, 2009). Compared with placebo, endotoxin exposure was associated with both blunted VS activation to reward cues (but not reward receipt) and increased self-reported and observer-assessed depressed mood.[9] Group differences in VS activation mediated the relationship between endotoxin exposure and increases in observer-rated depressed mood. Although the purpose of this study was to investigate the role of inflammation in depression, findings support a functional relationship between blunted VS responses to reward cues and depressive symptoms.

Two other neuroimaging studies have investigated anhedonia among healthy adults without past or current mental illness, but neither included functional tasks that assessed reward responding to incentives. The first study, conducted by Harvey, Pruessner, Czechowska, and Lepage (2007), required participants to view images of positive, negative, and neutral valences. Among other findings, higher anhedonia scores, as measured by the Chapman Revised Physical Anhedonia Scale, were associated positively with activation in the right ventromedial prefrontal cortex (vmPFC), and negatively with anterior caudate volumes, which extended to the VS in a less stringent follow-up analysis. Although the researchers' hypotheses of enhanced vmPFC activation and reduced striatal volumes were supported by their findings, they did not identify reduced VS activation to pleasant stimuli as predicted.

The second study, conducted by Keller et al. (2013), investigated the relationship between trait anhedonia (measured using the positive affect factor of the Mood and Anxiety Symptom Questionnaire—Short Form) and neural responding to musical stimuli. Trait anhedonia was associated with reduced pleasantness ratings of stimuli, and with hypoactivation of the right NAcc, basal forebrain, bilateral hypothalamus, and cortical regions, including orbitofrontal, anterior, and posterior cingulate, and ventromedial prefrontal cortices. Trait anhedonia correlated negatively with effective connectivity between mesolimbic and paralimbic regions, including the bilateral insula and the OFC.

Anhedonia in MDD

As noted above, anhedonia characterizes several psychiatric disorders, including major depression, schizophrenia, and Parkinson disease (Winograd-Gurvich, Fitzgerald, Georgiou-Karistianis, Bradshaw, & White, 2006). Although anhedonia is not required for a DSM-5 diagnosis of major depression, anhedonia and depressed mood are the two core diagnostic features of the disorder (APA, 2013). Reported estimates of clinically significant anhedonia among adults with major depression vary widely from 37% to 92% (Buckner, Joiner, Pettit, Lewinsohn, & Schmidt, 2008; Lemke, Puhl, Koethe, & Winkler, 1999; Pelizza & Ferrari, 2009). Similarly, estimates of anhedonia among depressed children and adolescents range from 10% to 57% (Luby, Mrakotsky, Heffelfinger, Brown, & Spitznagel, 2004; Yorbik, Birmaher, Axelson, Williamson, & Ryan, 2004). Such large discrepan-

9. Eisenberger et al. (2010) operationalized anhedonia as reduced VS activation during reward anticipation, and did not quantify anhedonia through self-report and/or observer ratings. Instead, participants reported the extent to which they felt unhappy, blue, lonely, gloomy, and worthless, and observers rated the extent to which participants appeared unhappy and gloomy.

cies may be attributable to use of different measures of anhedonia, different thresholds for determining clinical significance, and differences in symptom presentation and severity among study samples. Regardless, these findings indicate that anhedonia is a common but not ubiquitous feature of depression.

Because anhedonia is so common to major depression, disentangling state-dependent effects of mental illness from trait anhedonia in psychiatric populations remains a challenge. Nevertheless, mesolimbic DA dysfunction in depression is reported widely (e.g., Lambert, Johansson, Ågren, & Friberg, 2000; Meyer et al., 2001). Striatal hypoactivation to positively valenced stimuli is a well-replicated finding among depressed adolescent and adult samples (e.g., see Forbes & Dahl, 2011; Forbes et al., 2006, 2009; Groenewold, Opmeer, de Jonge, Aleman, & Costafreda, 2013; Morgan, Olino, McMakin, Ryan, & Forbes, 2013). For responses to incentives more specifically, current depression is associated with failure to develop a response bias toward rewarding stimuli (e.g., Henriques, Glowacki, & Davidson, 1994; Pizzagalli, Iosifescu, Hallett, Ratner, & Fava, 2008), impaired reward-based reversal learning (Robinson, Cools, Carlisi, Sahakian, & Drevets, 2012), and blunted VS responses to anticipation and receipt of monetary incentives (e.g., Forbes et al., 2009; Pizzagalli et al., 2009; Smoski et al., 2009). Pizzagalli et al. (2009) also demonstrated that anhedonic symptoms and depression severity correlate negatively with smaller caudate volumes. The one exception to this body of literature is a study by Knutson et al. (2008), who found that NAcc activation did not differ between depressed participants and controls during reward anticipation or receipt. The authors suggest that their sample of depressed adults may not have exhibited VS hyporeactivity during reward anticipation as they predicted specifically because anhedonic features were not sufficiently prominent.

The null finding by Knutson et al. (2008) should not be considered anomalous. As presented above, anhedonia in depression is common, but not universal. A large body of research indicates that depression emerges from a multitude of equifinal pathways involving genetic-, neural-, neuroendocrine-, and trait-level vulnerabilities that interact with environmental risk factors, including adversity in childhood, ongoing stressors, and social instability (see Charney & Manji, 2004; Kendler, Gardner, & Prescott, 2002; Kim, 2008; Klein, Kotov, & Bufferd, 2011). Trait anhedonia may be a characteristic feature of a subpopulation of individuals with major depression, which may account for why only a subset of depressed individuals exhibit mesolimbic DA dysfunction when *interindividual* variability in reward responding is considered (Foti, Carlson, Sauder, & Proudfit, 2014). Accordingly, greater attention to the extent to which individual differences in reward processing predict alternative phenotypic presentations of illness and treatment response may be especially valuable (see Forbes et al., 2009; e.g., Morgan et al., 2013). The importance of identifying clinical subgroups on the basis of etiological vulnerabilities and not collections of behavioral symptoms is revisited multiple times in this article.

Anhedonia in populations at high risk for major depression

Anhedonia may be present prior to and/or after major depressive episodes, and thus may be best characterized as a traitlike vulnerability (McCabe, 2014). Self-reports of anhedonia predict the onset of major depression 1 year later (Dryman & Eaton, 1991), and undergraduate students and individuals with histories of depression report individual differences in hedonic capacity that are stable across long periods of time (Clark, Fawcett, Salazar-Grueso, & Fawcett, 1984; Shankman et al., 2010; Watson & Walker, 1996). Anhedonia is also experienced both during and between major depressive episodes (Schrader, 1997). Despite such findings, and a long-established theoretical argument for anhedonia as a trait vulnerability to depression, very few laboratory-based studies have investigated prospective links between anhedonia and depression, and studies of anhedonia in cases of remitted depression cannot rule out scarring effects.

Remitted depression. Select studies have included samples of individuals with remitted depression to investigate possible traitlike features associated with susceptibility. Compared to healthy controls, individuals with remitted depression may be less able to modulate their behavior based on reinforcement history (i.e., develop a response bias to rewarding outcomes), reflecting deficient reward learning (Pechtel, Dutra, Goetz, & Pizzagalli, 2013). Furthermore, using fMRI, McCabe, Cowen, and Harmer (2009) reported reduced activation in the VS and anterior cingulate cortex (ACC) to a pleasant stimulus (chocolate taste) among individuals with remitted depression compared to healthy controls, suggesting mesolimbic dysfunction may persist following depressive episodes. These results are compatible with those obtained by Hasler et al. (2008), who induced acute catecholamine depletion, including DA, via oral administration of α-methyl-paratyrosine among adults with a history of major depression and healthy controls. Using PET, Hasler et al. compared neural glucose activity before and after depletion, and anticipated increased glucose metabolism in regions implicated in depression due to the inhibitory role of striatal DA projections on glutamate release. Consistent with their hypotheses, depressive and anhedonic symptoms (assessed by the Montgomery–Asberg Depression Rating Scale and the Snaith–Hamilton Pleasure Scale, respectively) increased to a greater extent in the remitted depressed group than in the control group. Furthermore, PET revealed an association between catecholamine depletion and increased metabolic activity of glucose in the VS across groups. Anhedonic symptoms also correlated with heightened metabolic activity in the VS following catecholamine depletion. Hasler et al. suggest that individuals with a history of major depression may be more vulnerable to experiencing depressive and anhedonic symp-

toms due to greater sensitivity of reward circuitry to catecholamine reduction.

The aforementioned studies by McCabe et al. (2009) and Hasler et al. (2008) both implicate VS function in remitted depression, but neither investigated reward anticipation specifically. Dichter, Kozink, McClernon, and Smoski (2012) investigated neural responding to both reward anticipation and outcomes among individuals with remitted major depression using a monetary incentive delay task and failed to find VS hypofunctionality. Instead, they reported hyperactivation in the pregenual ACC, right midfrontal gyrus, and right cerebellum to reward anticipation, and hypoactivation in the OFC, right frontal pole, left insular cortex, and left thalamus. The authors interpret these findings as evidence of aberrant frontostriatal responding due to connectivity among these regions, which are directly or indirectly implicated in reward processing.

Individuals with familial risk for depression. Another approach to investigating anhedonia as a vulnerability to major depression is to study individuals with a family history of the disorder (Rice, Harold, & Thapar, 2002; Weissman et al., 2006). High internalizing symptoms predict reduced neural responding to reward among siblings, over and above ratings of positive and negative affect (Weinberg, Liu, Hajcak, & Shankman, 2015). In addition, across studies, children of depressed parents exhibit hypofunctionality in neural reward circuitry (McCabe, Woffindale, Harmer, & Cowen, 2012; Olino et al., 2014; see Proudfit, 2014). For example, youth with strong familial vulnerability to depression (but not a personal history of depression) exhibit diminished activation in the VS specifically to anticipation of incentives (Olino et al., 2014). In addition, the few longitudinal studies that have investigated depression among vulnerable youth samples report that diminished reward-seeking behavior and aberrant neural reward processing are associated prospectively with depressive symptoms, and may predict later emergence of depression (e.g., Bress, Meyer, & Proudfit, 2015; Bress, Smith, Foti, Klein, & Hajcak, 2012; Rawal, Collishaw, Thapar, & Rice, 2013). These results suggest that youth with family histories of depression exhibit similar neural reward circuitry deficits seen in depression, and that these deficits may reflect an underlying vulnerability for developing the disorder.

Anhedonia, self-inflicted injury (SII), and borderline personality disorder

As summarized above, both anhedonia, assessed via self-report, and blunted VS responding to incentives, assessed through neuroimaging, are exhibited by vulnerable and currently depressed samples. Another subpopulation of interest for the present discussion is individuals with a history of SII, including those who have attempted suicide and/or engage in nonsuicidal self-harm (see Crowell et al., 2008; Kaufman, Crowell, & Stepp, 2016; Nock, 2010). Individuals who engage in these behaviors are *both* trait impulsive and anhedonic, and lie at the nexus of internalizing and externalizing psychopathology (see Beauchaine, Klein, Crowell, Derbridge, & Gatzke-Kopp, 2009; Crowell, Derbidge, & Beauchaine, 2014; Crowell, Kaufman, & Beauchaine, 2014). Anhedonia predicts suicidal ideation (Winer et al., 2014) and violence toward self and others (Fawcett et al., 1990; Nordström, Schalling, & Asberg, 1995; Sadeh, Javdani, Finy, & Verona, 2011). Furthermore, as with other groups characterized by anhedonia, those who have attempted suicide exhibit deficits in reward processing, including impaired reward/punishment-based reversal learning (Dombrovski et al., 2010), a high preference for immediate over delayed rewards, and difficulties anticipating positive future events (see van Heeringen, Bijttebier, & Godfrin, 2011).

Research on the neural substrates of reward responding in SII is still in its infancy, but structural brain alterations in mesolimbic circuitry are implicated in major depression among individuals with a history of suicide attempts (Jia et al., 2010), and those at high risk for suicide based on family history (Wagner et al., 2011). A history of self-harm is also associated with reduced functional connectivity in striatal circuitry, both during depressive episodes and in remitted depression (Marchand, Lee, Johnson, Thatcher, & Gale, 2013; Marchand et al., 2012). In the only study to date that has specifically evaluated neural correlates of reward responding among self-injurers, adolescents who engaged in SII exhibited less striatal activation in anticipation of incentives compared with controls (Sauder et al., 2016).

Although depressed adolescents who engage in SII share many similarities with other depressed groups (e.g., high negative affectivity; low positive affectivity), they are more likely to follow a developmental course toward borderline personality disorder (BPD; see Beauchaine et al., 2009; Crowell, Beauchaine, & Linehan, 2009; Crowell, Kaufman, & Lenzenweger, 2013), and to engage in suicidal behaviors, gestures, and threats (diagnostic criteria of the disorder; APA, 2013). Although emotion dysregulation is regarded as a core feature of BPD (see Crowell et al., 2009; Linehan, 1993), trait impulsivity and anhedonia are also common, and correlate with severity of symptoms (Crowell et al., 2009; Marissen, Arnold, & Franken, 2012). In the only study to date to investigate reward responding in BPD, participants with BPD or ASPD exhibited blunted prefrontal and striatal responding to monetary incentives (Völlm et al., 2007), suggesting deficient neural reward processing.[10]

Interim conclusions

The construct of anhedonia typically encompasses reward processing related to both anticipatory/motivational and consummatory aspects of incentives. It is likely that some anhe-

10. Although a sample consisting of BPD-only participants is preferable for the present discussion, BPD and ASPD share core etiological substrates, and may reflect sex-specific manifestations of a common pathophysiology (see Beauchaine et al., 2009). Thus, collapsing across these groups may still yield interpretable findings for BPD.

donic individuals have deficiencies in both domains, whereas others have deficiencies restricted to only one or the other. However, findings from behavioral neuroscience and human neuroimaging studies suggest that distinguishing between motivation and the experience of pleasure is warranted, and that DA neurotransmission may be more critically involved in the former component. From this perspective, growing evidence suggests that high trait anhedonia may reflect poor associative reward learning and diminished motivation to exert effort to obtain rewards, both of which are mediated by a hypofunctioning mesolimbic DA system. These findings parallel research on the neural bases of trait impulsivity, described above. Major depression is a heterogeneous construct, and anhedonia is not equivalent to, or a necessary component of, depression. Additional research on anhedonia in the context of clinical, high-risk, and nonclinical populations, as well as disentangling the neural substrates of different aspects of depression, including anhedonia, may help to further clarify relationships between DA neural circuitry responding and trait anhedonia.

Trait Irritability as an Aversive Mood State

Emotions are often described as valenced responses to stimuli, whereas mood is described as a slower moving, longer lasting pattern of affective responding that is less tied to discrete events (Rottenberg & Gross, 2003; Watson, 2000). Multiple neurotransmitter systems, including serotonin, norepinephrine, and DA, are associated with mood modulation (see, e.g., Beauchaine et al., 2011; Ruhé, Mason, & Schene, 2007). Here, we emphasize tonic mesolimbic DA dysfunction as an important neural substrate of trait irritability, a tendency to be easily and excessively annoyed, angered, inpatient, and aggressive (see Bettencourt, Talley, Benjamin, & Valentine, 2006; Leibenluft & Stoddard, 2013). Although trait irritability refers to a negative mood state, it is exhibited through emotional outbursts and disproportionately intense aggressive acts to provocations. Thus, trait irritability is closely related to the concepts of emotion/mood dysregulation and emotional lability (Shaw, Stringaris, Nigg, & Leibenluft, 2014; Snaith & Taylor, 1985). However, it is worth noting that trait irritability is a mood state that is largely heritable, whereas emotion (dys)regulation is affected much more strongly by socialization mechanisms (see Beauchaine, 2015a; Beauchaine et al., in press; Goldsmith, Pollak, & Davidson, 2008).

With the exception of ODD and ASPD, irritability is not a diagnostic feature of externalizing disorders or adult major depression (APA, 2013). However, irritability often co-occurs with trait impulsivity and anhedonia and is frequently experienced by those with externalizing and depressive disorders, as discussed below. We argue that low tonic and low phasic mesolimbic DA is a neural substrate of trait irritability, which is experienced as a persistent aversive mood state. Furthermore, we assert that trait irritability has transdiagnostic neural substrates that link it to *both* trait impulsivity *and* anhedonia based on a common etiology (i.e., mesolimbic DA dysfunction), which helps to account for higher than expected rates of comorbidity between depression and externalizing disorders.

Neural bases of trait irritability

Compromised mesolimbic DA function, including low tonic and diminished anticipatory responses to incentives, is a core neural substrate of anhedonia and chronic irritability among both clinical and nonclinical populations (e.g., Beauchaine et al., 2007; Shaw et al., 2014; Yamawaki, Okada, Okamoto, & Liberzon, 2012). PET studies demonstrate that low tonic midbrain DA activity is associated with trait irritability among healthy individuals (Laakso et al., 2003), whereas high DA activity is associated with a pleasant mood state and high hedonic capacity (see, e.g., Ashby et al., 1999; Depue, Luciana, Arbisi, Collins, & Leon, 1994). Thus, tonic DA hypofunctioning affects how incentives are experienced subjectively (i.e., liking), which in turn affects behavior (Berridge & Kringelbach, 2015; Blum et al. 2000, 2008; Sagvolden et al., 2005). Among healthy individuals, the magnitude of DA release in the VS in response to DA agonism correlates with hedonic responding (Drevets et al., 2001), and upregulating DA availability increases hedonic expectations for positive future life events (Sharot, Shiner, Brown, Fan, & Dolan, 2009). Such findings suggest that raising mesolimbic DA levels is associated with improved mood and hedonic capacity.

It is interesting to note that some individuals report an unpleasant subjective reaction to DA agonism, which may reflect individual differences in tonic mesolimbic DA function (Volkow et al., 1999). Healthy individuals who report liking the effects of infusions of methylphenidate, a DA reuptake inhibitor, have fewer D2 receptors in the striatum compared to those who report disliking the experience, and more D2 receptors correlate with greater intensity of unpleasantness (Volkow et al., 1999). Because D2 receptors are autoreceptors, a lack of this receptor type may reflect compensation for diminished DA activity in reward circuitry (Blum et al., 2000). Thus, Volkow et al. (1999) conclude that DA agonism among individuals with intrinsically low mesolimbic DA activity is more likely to be experienced as pleasant because it raises DA levels to within an optimal range for enjoying the experience. In contrast, those with intrinsically higher mesolimbic DA activity are more likely to find the experience aversive because DA agonism pushes activity outside an optimal range of function. In addition, depressed individuals also rate subjective effects of DA agonism as more pleasant than healthy controls, and exhibit comparatively low mesolimbic functioning following dextroamphetamine administration (Tremblay et al., 2005). Low DA synthesis capacity in the striatum and midbrain is also associated with aggressiveness (Schlüter et al., 2013), which, as noted above, is often observed with irritability. Collectively, these findings lend further support to the supposition that low tonic and low phasic DA contribute to trait irritability and altered responses to reinforcers.

Contribution to externalizing disorders

Several contemporary models of ADHD assert that chronic irritability motivates hyperactivity and excessive reinforcement-seeking behavior, hallmarks of the combined and hyperactive–impulsive presentations (Blum et al. 2000, 2008; Sagvolden et al., 2005). Sagvolden et al. (2005) assert that reinforcement-seeking behaviors provoke phasic DA release, which serves to temporarily reduce feelings of irritability, anhedonia, and boredom caused by low tonic DA activity. As noted above, however, any hedonic value gained from these behaviors is transient, and does not address the underlying DA deficiency. Thus, searches for more frequent and larger incentives are undertaken to alleviate the aversive mood state (see Beauchaine et al., 2007; Gatzke-Kopp, 2011; Gatzke-Kopp & Beauchaine, 2007; Sagvolden et al., 2005).

Contribution to depression and SII

Although depression can result from interactions among a multitude of biological vulnerabilities and environmental risk factors, a core etiological factor for many with the disorder is hypofunctioning DA-mediated reward processing. Deficient neural responding to incentives is a neural substrate of low positive affectivity, anhedonia, and irritability (see Forbes & Dahl, 2005, 2011; Nestler & Carlezon, 2006). Lower striatal responding in anticipation of monetary incentives is associated with lower positive affect in real-world settings (Forbes et al., 2009), and predicts increases in depressive symptoms over time (Morgan et al., 2013). Dampened VS activation to reward is also associated with impaired mood reactivity to positive events (Foti et al., 2014). Like anhedonia, irritability is particularly relevant to certain subpopulations with depression, including those with notable mood/emotion dysregulation and emotional lability. Irritability is associated with histories of suicidal ideation, suicide attempts, and nonsuicidal self-injury (e.g., Conner, Meldrum, Wieczorek, Duberstein, & Welte, 2004; Ernst et al., 2004; Herpertz, 1995; Pendse, Westrin, & Engström, 1999; Stålenheim, 2001). Individuals who repeatedly engage in SII are likely to experience negative/irritable mood states and use self-harm as a coping strategy to mitigate emotional distress (Brown, Comtois, & Linehan, 2002; Crowell et al., 2009; Nixon, Cloutier, & Aggarwal, 2002; Nock, Prinstein, & Sterba, 2009; Taylor, Peterson & Fischer, 2012). Trait irritability may also help to explain the high co-occurrence of self-harm and aggression directed toward others (Leibenluft & Stoddard, 2013; O'Donnell, House, & Waterman, 2015).

Vulnerability to externalizing disorders, depression, and heterotypic comorbidity

Trait irritability is common among individuals who are impulsive and anhedonic, and confers vulnerability to externalizing spectrum disorders and depression. Seroczynski, Bergeman, and Coccaro (1999) reported that impulsivity and irritability share overlapping genetic influences, a relationship that is stronger than that linking impulsivity and physical aggression. Greater irritability correlates with greater severity of hyperactive–impulsive ADHD symptoms (Sobanski et al., 2010), and raising mesolimbic DA levels via psychostimulant administration improves irritability among children with ADHD (de la Cruz et al., 2015). Such findings have led some to suggest that chronic irritability is a core feature of ADHD (e.g., Downson & Blackwell, 2010; Skirrow, McLoughlin, Kuntsi, & Asherson, 2009).

Irritability is also associated with more severe anhedonia among depressed adolescents (Gabbay et al., 2015), and is a common experience during major depressive episodes among adults, even when excluding for bipolar spectrum features (Fava et al., 2010; Judd, Schettler, Coryell, Akiskal, & Fiedorowicz, 2013; Perlis et al., 2009). Trait irritability and depression share significant heritability, and irritability in childhood predicts depression in early adulthood (Savage et al., 2015). Of note, irritability concurrent with all major depressive episode criteria except sad mood or anhedonia is exceptionally rare, which suggests it is linked closely to core features of major depression (Fava et al., 2010; Kovess-Masfety et al., 2013).

We discuss irritability here because it frequently co-occurs with both externalizing spectrum disorders and depression, and because it is likely an important vulnerability to heterotypic comorbidity. Irritable children and adolescents with ADHD have significantly higher rates of depressive disorders compared to those who are not irritable (Ambrosini, Bennett, & Elia, 2013; Sobanski et al., 2010). Similarly, chronic but not episodic irritability in early adolescence predicts ADHD and ODD during late adolescence, as well as MDD in early adulthood (Leibenluft, Cohen, Gorrindo, Brook, & Pine, 2006). Moreover, irritability in adolescence is associated with concurrent ADHD, mood disorders, ODD, and CD, and predicts MDD and dysthymia 20 years later (Stringaris, Psych, Cohen, Pine, & Leibenluft, 2009). Finally, irritability is associated with high rates of comorbidity of impulse-control disorders and depression among adults (Fava et al., 2010), and may mark more severe psychopathology (Judd et al. 2013; Perlis et al., 2009; Sobanski et al., 2010).

Interim conclusions

Trait irritability, which is the tendency to be annoyed, angered, and impatient, is an aversive mood state that is characterized by low tonic mesolimbic DA activity and low phasic mesolimbic DA responding to incentives. Therefore, it shares neural bases with both trait impulsivity and anhedonia. As a transdiagnostic, trait-level vulnerability to psychopathology, irritability is often experienced by individuals with ADHD and individuals with major depression and appears to be especially likely among individuals comorbid for both disorders. Among those with ADHD, irritability may serve as a motivator to engage in hyperactive and reward-seeking be-

haviors, which elicit mesolimbic DA release, temporarily improving a chronically aversive mood state.

Neural Accounts of Heterotypic Comorbidity

Higher than expected rates of comorbidity between externalizing spectrum disorders and unipolar depression are difficult to explain when considering that the two classes of psychopathology have almost no overlapping diagnostic criteria, and are often ascribed different etiological bases, with dopaminergic theories predominating for impulse-control disorders and serotonergic and noradrenergic theories predominating for depression. Here, we offer a framework to help explain, at least in part, high rates of heterotypic comorbidity between externalizing disorders and unipolar depression by suggesting that low tonic mesolimbic DA, and low phasic responding during reward anticipation, comprise core neural substrates of trait impulsivity, anhedonia, and irritability, all of which are vulnerabilities to both externalizing disorders and unipolar depression, as described above.

It is important to note that midbrain DA dysfunction does not invariably result in psychopathology, but rather interacts dynamically with other subcortical neural systems, with cortical neural systems, and with environmental risk factors to shape and maintain patterns of behavior (see Beauchaine, 2015a; Beauchaine et al., in press; Beauchaine & McNulty, 2013; Beauchaine & Thayer, 2015). According to this view, externalizing spectrum disorders and unipolar depression share mesolimbic DA dysfunction, yet have other, nonoverlapping neural substrates (e.g., serotonergic and noradrenergic; discussed below). Moreover, midbrain DA dysfunction is especially likely to eventuate in psychopathology when coupled with compromised prefrontally mediated emotion regulation capabilities (Beauchaine, 2015a; Beauchaine et al., 2007).

Subcortical moderators of midbrain DA activity and heterotypic comorbidity

Although externalizing spectrum disorders and unipolar depression are both characterized by anhedonia, avolition, and irritability, they differ in at least one important way: those with externalizing disorders exhibit excessive approach behavior (e.g., novelty, sensation, and reward seeking), whereas those with depression and oft co-occurring anxiety exhibit passive avoidance behavior (i.e., withdrawal; see, e.g., Beauchaine, 2001; Corr & McNaughton, 2016). At the symptom level, this difference is difficult to reconcile with the high rates of heterotypic comorbidity described above. However, the apparent discrepancy can be resolved by differentiating between neural substrates of approach and passive avoidance tendencies. Toward this end, it is important to consider that complex human behaviors are subserved by multiple neurobiological systems that interact functionally with one another (see, e.g., Beauchaine et al., 2011; Zisner & Beauchaine, 2016).

Here we consider how one such network, the septohippocampal system, interacts with midbrain DA function to affect behavior. The septohippocampal system includes extensive serotonergic (5-HT) projections from the raphe nuclei, and noradrenergic projections from the locus ceruleus, to a number of brain regions, including limbic structures (e.g., amygdala and hippocampus), the anterior cingulate cortex, and more frontal regions (Gray & McNaughton, 2000; McNaughton & Corr, 2004). The septohippocampal system and the amygdala[11] (Gray's behavioral inhibition system) is a phylogenetically old neural system that responds to competing motivational objectives (i.e., approach-approach, approach-avoidance, and avoidance-avoidance). When such situations are encountered, septohippocampal activation promotes passive avoidance until the organism decides what action to take. Individual differences in activity and reactivity of this system give rise to corresponding individual differences in trait anxiety (Corr & McNaughton, 2016; Gray & McNaughton, 2000; McNaughton & Corr, 2004). More broadly, the septohippocampal system helps us narrow attention, assign emotional significance to events, and encode them into memory (see Phan, Wager, Taylor, & Liberzon, 2002; Phelps, 2004). Excessive septohippocampal activity confers vulnerability to anxiety disorders and depression (Gray & McNaughton, 2000), whereas deficient septohippocampal activity potentiates vulnerability to externalizing behavior (see Corr & McNaughton, 2016). McNaughton and Corr (2004) conceptualize depression in particular as a behavioral manifestation of excessive septohippocampal system activity, which results in maladaptive responses to threat under circumstances in which the most appropriate response is to approach threat in order to obtain incentives. Instead, those who are depressed fail to approach because aversive outcomes of approach behavior are perceived as unavoidable, and outweigh any possible gains that could be obtained through action.

Single disorders. Low midbrain DA responding to reward, *coupled with* low septohippocampal system activity/reactivity to negatively valenced stimuli, confers vulnerability to externalizing disorders, normal midbrain DA responding to reward, *coupled with* excessive septohippocampal system activity/reactivity to negatively valenced stimuli, confers vulnerability to internalizing disorders (Beauchaine, 2001,

11. The amygdala, also called the amygdaloid complex, comprises distinct groupings of cells, including the basolateral and central nuclei, which serve specific, but related functions related to emotion processing (Sah, Faber, Lopez de Armentia, & Power, 2003). The basolateral amygdala, which has received the most attention in the depression literature thus far, may best be conceptualized as the amygdala itself, with projections to target regions that enable more specialized functions (Davis & Whalen, 2001). For example, the basolateral amygdala projects to the striatum, leading to instrumental approach behaviors, whereas its projections to the central amygdala are involved in attending to salient information and generating fear responses (Davis & Whalen, 2001). Although these functional differences are relevant, the amygdala is not typically subdivided into specific nuclei in human neuroimaging, and thus is not specified in the present work unless relevant for discussion.

2015a; Beauchaine et al., 2007; Beauchaine & Thayer, 2015; Corr & McNaughton, 2016; Gray & McNaughton, 2000; McNaughton & Corr, 2004). This assertion is supported by findings from both peripheral psychophysiological and neuroimaging studies. For example, externalizing symptoms correspond with diminished septohippocampal function, as evidenced by (a) morphological abnormalities in limbic regions, including the hippocampus, parahippocampal gyrus, and amygdala (e.g., Benegal, Antony, Venkatasubramanian, & Jakakumar, 2007; Plessen et al., 2006); (b) blunted amygdalar reactivity to fearful expressions (e.g., Marsh et al., 2008; see Marsh & Blair, 2008); and (c) low electrodermal responding (e.g., Gao, Raine, Venables, Dawson, & Mednick, 2010; Isen, Iacono, Malone, & McGue, 2012), which serves as an index of septohippocampal function in appropriately designed experiments (Fowles 1980, 1988).

In the absence of externalizing symptoms, internalizing psychopathology, including anxiety and unipolar depression, is characterized by excessive septohippocampal system activity/reactivity to negatively valenced stimuli (Beauchaine, 2001, 2015a; Beauchaine et al., 2007; Beauchaine & Thayer, 2015; Gray & McNaughton, 2000; McNaughton & Corr, 2004). For example, depression is associated with morphological abnormalities in the amygdala (Hamilton, Seimer, & Gotlib, 2008) and smaller hippocampal volumes (Campbell, Marriott, Nahmias, & MacQueen, 2004). A number of studies indicate that depression is characterized by heightened activation to negative stimuli in the amygdala, anterior cingulate cortex, and prefrontal regions (see Hamilton et al., 2012; Kerestes, Davey, Stephanou, Whittle, & Harrison, 2014). Furthermore, nonsuicidal depression, depressive symptoms, and trait neuroticism are often associated with normal or heightened electrodermal responding (e.g., Norris, Larsen, & Cacioppo, 2007; Papousek & Schulter, 2001; Thorell et al., 2013), suggesting high septohippocampal system reactivity in this subpopulation (Fowles, 1980, 1988). Such findings support excessive septohippocampal system activity/reactivity as a partial neural substrate of unipolar depression.

Heterotypic comorbidity. Given opposing roles of the septohippocampal system in internalizing versus externalizing disorders, a logical next question is, "How do neural correlates of heterotypic comorbidity differ from those for single disorders along the internalizing and externalizing spectra?" This question is especially pertinent given high prevalence rates of heterotypic comorbidity and evidence from nonhuman research suggesting that these systems interact functionally (e.g., the basolateral amygdala has direct projections to the NAcc, which can influence impulse control and reward-seeking behaviors; Stuber et al., 2011; Winstanley, Theobald, Cardinal, & Robbins, 2004). However, few neuroimaging studies have evaluated associations between Internalizing × Externalizing symptoms and neural function. One notable exception is a neuroanatomical analysis by Sauder, Beauchaine, Gatzke-Kopp, Shannon, and Aylward (2012), who determined that, among adolescent males with ADHD and/or CD, comorbid internalizing symptoms correlated negatively with gray matter volumes in anterior cingulate, mesolimbic, and septohippocampal regions compared to adolescent males without internalizing symptoms. Similarly, reduced hippocampal volumes are associated with depressive symptoms, but not ADHD symptoms, among children with ADHD (Posner et al., 2014). Adolescents with ADHD and CD also display increased amygdalar activation to negative stimuli relative to controls (Herpertz et al., 2008), suggesting aberrant emotional responding among comorbid externalizers. Among adults with ADHD, depressive symptoms correlate with larger amygdala volumes (Frodl et al., 2010), and a history of major depression is associated with smaller hippocampal volumes (Onnink et al., 2014). Such findings provide preliminary support for a pattern of septohippocampal functioning more typical of internalizers among externalizers with internalizing symptoms compared to individuals with externalizing psychopathology alone.

Similarly, compared to individuals with internalizing symptoms alone, individuals with BPD and/or those who engage in self-injury score high on both internalizing and externalizing symptoms (Allely, 2014; Beauchaine et al., 2009; Crowell et al., 2005, 2009, 2012; Derbidge & Beauchaine, 2014; Eaton et al., 2011), and exhibit patterns of neural and psychophysiological responding that are similar to those of externalizers (e.g., Crowell et al., 2012; Vasilev, Crowell, Beuchaine, Mead, & Gatzke-Kopp, 2009; see Beauchaine, 2001, 2012; Zisner & Beauchaine, 2015). As described above, these subgroups also exhibit aberrant mesolimbic DA functioning to incentives similar to those with externalizing psychopathology (Sauder et al., 2016).

Functional outcomes

The research presented above suggests that heterotypically comorbid internalizing and externalizing symptoms are associated with co-occurring functional impairment in neural systems that differentiate between pure disorders. At the behavioral level of analysis, anxiety confers some protective effects among those with externalizing psychopathology. For example, those with ADHD and comorbid anxiety are less impulsive and exhibit a less severe response inhibition deficit than those with ADHD alone (see Shatz & Rostain, 2006). Furthermore, children and adolescents with CD and comorbid anxiety are less physically aggressive, regarded less negatively by peers, and experience fewer police contacts than youth with CD alone (Walker et al., 1991). Externalizing youth with comorbid anxiety are also more sensitive to punishment, and therefore more concerned with negative consequences of their behavior compared to nonanxious externalizing youth, which likely accounts for why this externalizing subgroup exhibits fewer behavior problems and better responses to behavioral treatment (e.g., Beauchaine, Neuhaus, et al., 2016; Jensen et al., 2001). Other research, however, suggests that externalizers with internalizing symptoms exhibit more severe conduct problems and greater risk

of long-term social and academic impairment than noncomorbid individuals (Biederman et al., 2008; Blackman, Ostrander, & Herman, 2005; Daviss, 2008; Ezpeleta, Domènech, & Angold, 2006).

Comorbid internalizing and externalizing psychopathology shape the ways in which disorders present in other ways as well. Anhedonia in BPD is related to poor impulse control, and excessive approach behaviors, but anhedonia among healthy controls is associated with the opposite pattern: withdrawal behaviors (Marissen et al., 2012). Compared to depression, BPD is associated with elevated risk for suicide attempts, but comorbidity between BPD and depression is associated with more serious and more frequent suicide attempts than depression or BPD alone (Soloff, Lynch, Kelly, Malone, & Mann, 2000). High trait impulsivity is a known vulnerability to self-harm (Allely, 2014; Crowell et al., 2009), and some have suggested that ASPD and BPD may reflect sex-moderated manifestations of a single core vulnerability (see Beauchaine et al., 2009; Crowell et al., 2009; Paris, 1997; Phillipsen, 2006).

Interim conclusions

Thus far, we have demonstrated that high trait impulsivity, conferred by low tonic and low phasic mesolimbic DA function, is an important vulnerability to externalizing spectrum disorders, whereas high trait impulsivity combined with high trait anxiety (subserved by excessive septohippocampal and amygdalar activity/reactivity) is implicated in comorbid externalizing and internalizing conditions. Trait anhedonia and irritability, which emerge from the same subcortical, mesolimbic substrates as trait impulsivity, are transdiagnostic vulnerabilities to both externalizing and internalizing spectrum disorders, and thus, heterotypic comorbidity.

Although chronic dysfunction in mesolimbic circuitry versus septohippocampal circuitry confer vulnerability to distinct trait-level predispositions (trait impulsivity and trait anxiety, respectively), functional interactions between neural systems affect how these vulnerabilities present (e.g., anhedonia in externalizing disorders contributes to excessive approach, whereas anhedonia in internalizing disorders contributes to passive avoidance). Investigations into neural correlates of Internalizing × Externalizing interactions are only beginning to emerge, and should shed light on how interdependent neural circuits influence one another in both clinical and healthy populations.

Cortical Moderators of Midbrain DA Activity

Until now, we have emphasized the roles of subcortical mesolimbic and (to a lesser extent) septohippocampal systems in conferring vulnerability to psychopathology. It is important to note, however, that many individuals who are high on trait impulsivity, anhedonia, and/or trait anxiety do not exhibit functional impairment (e.g., Beauchaine, 2015a; Beauchaine & Thayer, 2015; Dimoska & Johnstone, 2007; Karcher, Martin, & Kerns, in press), and therefore do not meet diagnostic criteria for any psychiatric disorder (e.g., Bar-Haim et al., 2009; Harvey et al., 2007).

These subcortical circuits have been conceptualized as bottom-up, *emotion generation* systems, which mediate approach- and avoidance-related affect. In contrast, inhibitory control over subcortical activity and reactivity is effected through prefrontal, top-down, *emotion regulation* systems. In order for approach and passive avoidance to become clinically problematic, they must occur in conjunction with poor cortically mediated emotion regulation (see, e.g., Beauchaine, 2015a; Beauchaine et al., 2007, in press; Beauchaine & Thayer, 2015). Cortical regions of particular interest include (a) the ACC, which subserves conflict and performance-monitoring functions, including error detection and generation of regulating emotional responses (Botvinick, Cohen, & Carter, 2004; Etkin, Egner, & Kalisch 2011; Hajcak, McDonald, & Simons, 2004); (b) the OFC, which monitors affective value of incentives, subserves reward- and emotion-related decision-making functions, and overlaps structurally with portions of the ventromedial PFC (described below; Kringelbach, 2005; Koenigs & Grafman, 2009); (c) lateral regions of the PFC, including the ventrolateral PFC, which is involved in selecting and retrieving information, as well as volitional response inhibition, and the dorsolateral PFC (dlPFC), which is involved in higher order executive functions, such as working memory, integrating multiple sources of information, and organizing goal-directed behavior (Leung & Cai, 2007; Tanji & Hoshi, 2008); and (d) the ventromedial PFC, which is associated with top-down emotion processing, including emotional reappraisal, expression, and regulation (Etkin et al., 2011). These regions either directly or indirectly modulate mesolimbic and septohippocampal function, and are therefore implicated in both externalizing and internalizing psychopathology.

Externalizing psychopathology

Volitional regulation of impulsivity requires modulation of the striatum by interconnected neural systems including the anterior cingulate, orbitofrontal, and dorsolateral prefrontal cortices (see Beauchaine, 2015a; Heatherton, 2011; Heatherton & Wagner, 2011). When mesolimbic DA dysfunction is combined with deficient functioning of these cortical regions, externalizing psychopathology, beginning with ADHD and progressing to more severe externalizing disorders in high-risk environments, is especially likely (Beauchaine & McNulty, 2013; Beauchaine et al., 2010, in press; Beauchaine, Neuhaus, et al., 2016; Zisner & Beauchaine, 2015). This pattern of neural dysfunction is frequently exhibited among externalizers. For example, in addition to striatal abnormalities, which are widely reported in ADHD (see above), the disorder is also associated with ACC abnormalities, including hypofunctionality across a range of tasks (see Bush, Valera, & Seidman, 2005), reduced volumes (Frodl & Skokauskas, 2012; Makris et al., 2007; Seidman et al., 2006), and reduced connectivity

between the ACC and striatum (e.g., Shannon et al., 2009). In addition, individuals with ADHD often display diminished error-related negativity, an electrophysiological signal generated by the ACC that reflects error monitoring (Shiels & Hawk, 2010). Given the crucial role of this region in performance- and goal-related processing, disruptions in the ACC may contribute to altered ability to adjust one's behavior based on feedback, an ability that is compromised in ADHD and other externalizing disorders (e.g., Bush, 2011; Gatzke-Kopp et al., 2009).

Higher order processing of incentives is mediated in large part by the OFC, a region that is also compromised in externalizing disorders. For example, individuals with ADHD have smaller OFC volumes (Hesslinger et al., 2002), but exhibit stronger functional connectivity between OFC, striatum, and ACC (Tomasi & Volkow, 2012). This is compatible with functional evidence from reward-based tasks suggesting that individuals with ADHD may also have OFCs that fail to differentiate between rewards of differing value (Wilbertz et al., 2012), and are hyperresponsive to certain types of gains (Ströhle et al., 2008). Orbitofrontal dysfunction may contribute to increased saliency of rewards once those rewards are of sufficient magnitude to initiate mesolimbic reactivity.

Internalizing psychopathology

As discussed above, the vmPFC, OFC, and ACC are implicated in both reward processing and top-down emotion regulation. Unipolar depression is associated with dysfunctional reactions to emotion-evoking stimuli in regions related to affective processing, including the vmPFC, OFC, and ACC (e.g., see Kerestes et al., 2014; Koenigs & Grafman, 2009; Murray, Wise, & Drevets, 2011; Stuhrmann, Suslow, & Dannlowski, 2011). However, it is important to note that motivated/volitional regulatory control of emotions occurs through inhibition of the amygdala by lateral regions of the PFC (see Buhle et al., 2014; Clauss, Avery, & Blackford, 2015; Heatherton, 2011; Heatherton & Wagner, 2011). The lateral PFC, primarily implicated in cognitive control, does not project directly to the amygdala, but rather exerts inhibitory effects though its connections with medial regions of the PFC, which have dense projections to and from the amygdala (Johnstone, van Reekum, Urry, Kalin, & Davidson, 2007; Öngür & Price, 2000; Urry et al., 2006). For example, cognitive reappraisal of affective stimuli is associated with activation of the lateral PFC and deactivation of the amygdala (see Buhle et al., 2014), whereas unsuccessful cognitive reappraisal (increased negative emotion) may reflect failure of the lateral PFC to suppress amygdala responding (Wagner, Davidson, Hughes, Lindquist, & Ochsner, 2008).

Depression may involve failure of the lateral PFC to suppress the amygdala via the medial PFC (Johnstone et al., 2007), an assertion supported by hypofunctionality of the lateral PFC and reduced functional connectivity between the dlPFC and the amygdala among depressed individuals (see Koenigs & Grafman, 2009; e.g., Dannlowski et al., 2009; Johnstone et al., 2007; Siegle, Thompson, Carter, Steinhauer, & Thase, 2007). Given the role of these lateral regions in regulating emotions, appraisals and attributions initiated by the dlPFC to dampen effects of negative, emotionally evocative stimuli among healthy individuals may not be applied effectively among those who are depressed, contributing to rumination and heightened negative affect (see Gotlib & Hamilton, 2008; Hamilton et al., 2012).

Emotion regulation

Emotion regulation refers to processes that guide the experience and expression of emotions to facilitate adaptive behavior (Thompson, 1990). Emotion regulation skills, subserved by effective cortical regulation of subcortical emotion generation circuits, protect against development of psychopathology (see Beauchaine, 2015a; Beauchaine et al., 2007; Beauchaine & Thayer, 2015). As noted above, subcortical vulnerabilities to trait impulsivity, anxiety, and anhedonia are necessary but insufficient to produce functional impairment. Rather, the combination of subcortical dysfunction and deficient top-down modulation of subcortical systems makes psychopathology most likely (Beauchaine, 2001, 2015; Beauchaine & Gatzke-Kopp, 2012; Beauchaine et al., 2007; Fineberg et al., 2010). This reflects a primary role of the prefrontal cortex: to appropriately modulate/inhibit responses in the service of effective behavior and emotion regulation (see, e.g., Dillon & Pizzagalli, 2007; Etkin et al., 2011; Schore, 1996).

Developmental and environmental considerations

The brain undergoes profound structural changes during development, with cortical regions reaching maturity comparatively later than phylogenetically older, subcortical structures (Gogtay et al., 2004; Toga, Thompson, & Sowell, 2006). Among typically developing individuals, peak volume of the PFC occurs around ages 10–11, and neural maturation into adulthood includes cortical thinning in the parietal and right dorsal frontal areas, and cortical thickening in language-processing areas in the frontal and temporal lobes (see Lenroot & Giedd, 2006; Toga et al., 2006). Adolescence in particular is a developmental period marked by a number of neural changes, including enhanced DA innervation of the frontal cortex and increased DA concentrations in cortical and subcortical regions (Wahlstrom, Collins, White, & Luciana, 2010).

Underdevelopment of prefrontal regions that subserve self-regulatory functions, combined with low mesolimbic DA activity/reactivity, is a shared vulnerability to impulsivity and anhedonia in internalizing and externalizing disorders across the life span (see Beauchaine et al., in press). For example, in adolescence, the absence of fully intact self-regulatory regions, which continue to develop into adulthood (Lenroot & Giedd, 2006), combined with normal upregulation of DA functioning, lead to increased saliency of and motivation to seek rewards that then manifest as increased risk-taking

and novelty-seeking behaviors (see Chambers, Taylor, & Potenza, 2003; Wahlstrom et al., 2010). Thus, among typically developing adolescents, impulsive tendencies are subserved by DA hyperresponsivity to reward unchecked by inhibitory mechanisms. Similarly, Forbes and Dahl (2012) suggest that adolescents with low reward responding are vulnerable to depression because of imbalances in frontostriatal reward circuitry, which are especially discrepant compared with those of typically developing individuals during adolescence. In other words, a trajectory toward depression may be more likely among individuals with inherent mesolimbic DA vulnerability, coupled with underdevelopment of higher order cortical regions involved in self-regulation and emotion regulation.

Like depression, externalizing vulnerability results at least in part from underdevelopment of frontostriatal circuitry (see, e.g., Cubillo, Halari, Smith, Taylor, & Rubia, 2012). Although ~65% of adults who experienced childhood ADHD maintain at least some symptoms into adulthood (Faraone, Biederman, & Mick, 2006), individuals with ADHD whose symptoms remit with age may gain self-regulatory skills that match their unaffected peers through eventual maturation of frontostriatal circuitry and/or recruitment of alternative circuitry to compensate for enduring frontostriatal deficits (Vaidya, 2012). For example, the medial PFC, which has direct projections to the striatum, develops more slowly among children with ADHD, and children with more impairing and persistent ADHD-related impairment have medial PFCs that are and remain thinner into adolescence compared to those with better outcomes and controls (Shaw et al., 2006, 2012). Similarly, fronto-striato-parietal dysfunction among adults with persistent ADHD correlates negatively with the severity of ADHD symptoms (Cubillo et al., 2012; Schneider et al., 2010). Finally, among boys with CD, most of whom experience homotypic comorbidity with other externalizing disorders, normal maturation (gray matter pruning) of the PFC is not observed in late childhood/early adolescence (De Brito et al., 2009). Thus, failures of prefrontal maturation influence the presence, persistence, and severity of symptoms of both internalizing and externalizing disorders.

Given the significance of bottom-up and top-down neural function in the expression of psychopathology, it is important to address environmental influences on prefrontal and subcortical neurodevelopment. Early-life adversity, including child abuse and neglect, malnutrition, and prenatal exposure to neurotoxins, substances of abuse, and high maternal stress, are associated with epigenetic changes that can have profound effects on neural development and function (see Archer, Oscar-Berman, Blum, & Gold, 2012; Gatzke-Kopp, 2011). For instance, the structure and function of DA pathways are altered by both chronic and acute stress, possibly through physiological responses enacted by the hypothalamus–pituitary–adrenal (HPA) axis (Pani, Porcella, & Gessa, 2000). Environmental insults can result in hyper- and hypofunctioning of DA neural circuitry, depending on the severity and chronicity of insult, and are associated with increased risk for psychopathologies characterized by aberrant motivation/reward-processing, including ADHD, substance abuse, and depression (see Beauchaine et al., 2011; Gatzke-Kopp, 2011).

Physical abuse in childhood predicts smaller OFC volumes, which in turn are associated with social difficulties with peers and executive functioning deficits (Hanson et al., 2010). In addition, adversity accrued across childhood is associated with smaller PFC volumes (Hanson et al., 2012), as is being raised in poor neighborhoods (Hanson et al., 2013). Moreover, neglect in childhood is associated with more diffuse frontal white matter organization (Hanson, Adluru, et al., 2013), and chronic exposure to stress results in less dendritic branching and lower neural spine densities in the PFC among rodents (e.g., Holmes & Wellman, 2009).

Neural vulnerabilities to psychopathology that emerge early in development may be exacerbated by environmental stress to make psychopathology more likely. For example, among rodents, a history of chronic stress predicts functional alterations in neural, behavioral, and pharmacological responses to acute stress (e.g., Finlay, Zigmond, & Abercrombie, 1995; Isgor, Kabbaj, Akil, & Watson, 2004; Katz, Roth, & Carroll, 1981). Similarly, among humans, exposure to childhood trauma predicts aberrant tonic HPA axis functioning and physiological sensitization to stress, which in turn predict symptoms of depression (see Heim & Binder, 2012; Heim, Newport, Mletzko, Miller, & Nemeroff, 2008). Such findings suggest that early-life stressors can elicit neural and physiological changes that affect responses to acute stressors, which may then increase risk for the emergence of psychiatric symptoms (Beauchaine, Neuhaus, Zalewski, Crowell, & Potapova, 2011).

Neural vulnerabilities for psychopathology that emerge early in development can also be exacerbated by the psychopathology that they portend once psychiatric illness develops. As reviewed above, for example, low mesolimbic function, an important neural substrate of trait impulsivity, confers vulnerability to all externalizing disorders, including SUDs (Zisner & Beauchaine, 2015). Strong and recurrent exposure to stimulants provokes downregulation of tonic DA activity in the NAcc, but sensitized phasic DA release specifically to these stimulants (see Thomas, Beurrier, Bonci, & Malenka 2001; Vezina, 2004). These changes, combined with the diminished PFC regulatory functioning that occurs in addiction, lead to greater impulsive decision making and higher risk of relapse (see Goldstein & Volkow, 2011; Kalivas, 2008; Schoenbaum & Shaham, 2008). Among individuals with tonic DA levels that are inherently low, neural dysfunction elicited by substance dependence may be particularly devastating.

Interim conclusions

Heterotypic comorbidity emerges at least in part from a common neural vulnerability (low tonic DA and blunted DA-mediated responses to anticipation of incentives) with concurrent impairments in other neural circuits (e.g., hyperresponsitivity of the septohippocampal system to negative

stimuli), which manifest as both overlapping and independent psychopathological symptoms. However, subcortically mediated deficits in approach and avoidance behavior are not necessarily impairing in the absence of co-occurring PFC dysfunction given critical roles of specific PFC regions in self-regulation and emotion regulation. Without PFC dysfunction, individual differences in trait impulsivity produce ordinary variation in personality, not psychopathology (Beauchaine, 2001, 2015a; Beauchaine & Gatzke-Kopp, 2012; Beauchaine et al., 2007). Similarly, trait anxiety and negative affectivity, which are vulnerabilities to unipolar depression, are less likely to result in functional impairment in the presence of strong emotion regulation capabilities. Furthermore, cumulative effects of neurobiological vulnerabilities, such as the degree to which an individual produces blunted mesolimbic responses or excessive septohippocampal responses, within the context of environmental risk factors, such as childhood trauma and substance abuse, influence the ways in which such neural deficits develop, manifest, and are maintained (see Beauchaine, 2015a; Beauchaine et al., in press; Beauchaine & McNulty, 2013; Sauder et al., 2012; Shannon, Beauchaine, Brenner, Neuhaus, & Gatzke-Kopp, 2007).

Implications

Advances in neuroscience provide increasing support for transdiagnostic approaches to psychopathology (see, e.g., Beauchaine & Thayer, 2015; Insel et al., 2010). The framework presented here implies that diagnosing psychiatric illness purely on the basis of behavioral symptoms (e.g., inattention, hyperactivity, anhedonia, or depressed mood) obscures common etiological mechanisms among what have traditionally been classified as distinct diagnostic entities. For example, low tonic mesolimbic DA and diminished phasic responding to incentives are neural substrates of both externalizing spectrum disorders and unipolar depression, and contribute to heterotypic comorbidity. This may help to explain why externalizing disorders confer vulnerability to later depression (e.g., Chronis-Tuscano et al., 2010; Meinzer et al., 2013; Seymour, Chronis-Tuscano, Iwamoto, Kurdziel, & MacPherson, 2014).

Failure to distinguish between heterogeneous subgroups, such as depressed adolescents who engage in SII versus those who do not, may also obscure important etiological substrates of psychopathology (see, e.g., Crowell et al., 2012). Heterogeneity within current diagnostic classes is an ongoing challenge in molecular genetics research on all psychiatric disorders (see, e.g., Beauchaine, Gatzke-Kopp, & Gizer, in press). Behavioral genetics studies yield strong evidence for heritable influences on psychopathology, including externalizing disorders, unipolar depression, and their comorbidity, yet molecular genetics research explains very little of this heritability by specific alleles (Faraone & Mick, 2010; Sullivan, Neale, & Kendler, 2000; Wray et al., 2012). In the spirit of the Research Domain Criteria initiative (e.g., Insel et al., 2010), greater attention to common genetic, biological/physiological, and trait-level vulnerabilities that span across diagnoses, instead of searching within single, behaviorally heterogeneous diagnoses, is expected to provide greater insight into etiological underpinnings of mental illness.

Issues of group heterogeneity also emerge when we fail to consider that multiple combinations of vulnerabilities and risk factors can produce equifinal outcomes. With regard to the framework described herein, we emphasize the importance of distinguishing between bottom-up, emotion-generation processes versus top-down emotion-regulation processes. Subcortical mesolimbic DA function confers individual differences in trait impulsivity, trait anhedonia, and trait irritability, which may be expressed as psychopathology when coupled with anterior cingulate and prefrontal cortex functional deficiencies.

Greater appreciation for etiological similarities and differences between complex psychological and behavioral phenomena has meaningful implications for research and clinical practice (for a detailed discussion, see Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008). For instance, when individuals are studied on the basis of their etiological similarities instead of behavioral/diagnostic similarities, more homogeneous research samples may be obtained. This reduces interindividual variability and increases statistical power, allowing for easier detection of interactions among variables. Furthermore, when relevant biological vulnerabilities are similar across diagnostically distinct groups, other variables, such as environmental risk factors, can be studied more closely to identify how specific factors transact with biological vulnerabilities to protect against or potentiate psychopathology. For example, environmental risk factors, including coercive/ineffective parenting, deviant peer group affiliations, and neighborhood criminality, all mediate the relationship between ADHD and more severe externalizing comportment across development (Beauchaine et al., 2009, in press; Beauchaine & McNulty, 2013). In the absence of these risk factors, ADHD may not progress to more serious externalizing disorders.

Finally, individuals with incipient or existing psychopathology will be more easily identified when reliable, predictive biomarkers and risk factors are found. Such advances can also guide prevention and treatment programs that target specific deficits and needs of individuals with or at elevated risk for psychiatric illness, and restrict these programs to only individuals who are likely to benefit from them.

Artifactual, Spurious, and True Comorbidity Revisited

Despite largely nonoverlapping diagnostic criteria, externalizing spectrum disorders and unipolar depression frequently co-occur. Historically, this has been perplexing, especially considering that these disorders are commonly attributed to different neural substrates. Here, we assert that high rates of heterotypic comorbidity between externalizing disorders and unipolar depression can be accounted for in part by a common neural substrate: low tonic mesolimbic DA and attenuated DA responses to anticipation of reward, which

are associated with trait-level vulnerabilities (high impulsivity, anhedonia, and irritability) common to a number of psychiatric syndromes spanning diagnostic boundaries.

At the beginning of this article, we outlined three subtypes of comorbidity, including (a) artifactual (mistakenly splitting one disease entity into multiple diagnoses), (b) spurious (assigning shared diagnostic criteria to distinct disease entities), and (c) true (when an individual suffers from separate disease entities). When we consider psychopathology from a transdiagnostic perspective in which neural vulnerabilities cut across traditional psychiatric boundaries, heterotypic comorbidity between externalizing disorders and unipolar depression, at least for some individuals, is likely more artifactual than real. Behavioral genetics studies indicate shared heritability, and mesolimbic neural response patterns that give rise to trait impulsivity, anhedonia, and irritability, are shared, not distinct. The convergence of findings from the externalizing and depression literatures, across multiple levels of analysis, supports common trait-level vulnerabilities as substrates for heterotypic comorbidity, and contributes to growing support for translational and transdiagnostic perspectives in psychopathology research.

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