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The Research Domain Criteria and Psychopathology Among Youth: Misplaced Assumptions and an Agenda for Future Research

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Abstract

Now over 10 years old, the Research Domain Criteria (RDoC) has gained impressive traction in the adult psychopathology literature, but enthusiasm among child and adolescent psychopathologists lags somewhat behind. We consider possible reasons why RDoC has not been embraced fully in the child and adolescent literatures. We emphasize common, interrelated, and sometimes outdated assumptions that impede scientific progress that RDoC could facilitate. Traditionally, child and adolescent psychopathologists have used behavioral syndromes as gold standards against which biological markers are validated, even though behavioral syndromes are often measured with less precision; sought to identify large main effects of single biological functions on single behavioral syndromes, thereby ignoring (even if implicitly) the overwhelming etiological complexity of psychopathology; expected 1:1 correspondencies between biological functions and behaviors, despite evidence that core biological systems subserving behavior are *functionally interdependent* (i.e., modulate one another); and failed to consider neurobiological mechanisms of homotypic and heterotypic comorbidity and continuity. Using examples from our work, we show how a developmental, RDoC-informed approach to externalizing behavior enriches our understanding of psychopathology. We also provide an agenda for future research, which includes calls to (1) adopt neural-systems-first approaches over disorder-first approaches when studying psychopathology, (2) eschew biological reductionism by integrating environmental risk mediators into our etiopathophysiological models, (3) integrate neural vulnerabilities into the empirical latent structure of psychopathology, and (4) replace null hypothesis significance testing with computational approaches that accommodate etiological complexity by evaluating functional dependencies among RDoC constructs, including positive valence systems (approach), negative valence systems (avoidance), and arousal/regulatory systems (self-regulation).

Keywords

Research Domain Criteria; child; adolescent; externalizing; comorbidity; neuroticism

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The Research Domain Criteria (RDoC), the National Institute of Mental Health's ambitious effort to "develop, *for research purposes* [emphasis added], new ways of classifying mental disorders based on dimensions of observable behavior and neurobiological measures" (NIMH, 2008), recently celebrated its 10-year anniversary. Timing is therefore ripe to consider its merits and limitations, including its usefulness for advancing our understanding of emerging mental health problems among children and adolescents. This special issue is therefore a welcome addition to the literature. Among several relevant matters for discussion are the extent to which RDoC has elucidated etiopathophysiologies of mental disorders, whether the RDoC framework can accommodate ontogenic processes and developmental principles, and whether it is fair to draw hard conclusions about these and other questions given the historical recency of RDoC on the psychopathology research landscape.

In our view, RDoC is yielding important scientific advances and can accommodate developmental mechanisms of psychopathology, even though it remains a work in progress. However, common misunderstandings of core RDoC tenets and outdated assumptions regarding expressions of vulnerability and risk across genetic, neural, hormonal, behavioral, and environmental levels of analysis sometimes yield misguided conclusions about its merits. We consider such misunderstandings below and discuss major advantages of RDoC over traditional approaches to conceptualizing psychopathology. First, however, we place the emergence of RDoC in historical context—a prerequisite for understanding its strengths and limitations.

A BRIEF HISTORY OF RDoC

As most readers are undoubtedly aware, RDoC emerged in part from dissatisfaction with (a) the validity of psychiatric diagnosis when based solely on behavioral symptoms (i.e., without considering etiology or pathophysiology), and (b) the extent to which reliability was emphasized at the expense of validity in the *DSM-IV* and its predecessors (American Psychiatric Association, 2000; see Beauchaine & Klein, 2017). One primary goal of psychopathology research is to specify etiopathophysiology—complex mechanisms through which biological vulnerabilities and environmental risk exposures interact to alter neurodevelopment and behavioral adjustment over time (e.g., Beauchaine & McNulty, 2013; Cicchetti & Cannon, 1999; Hinshaw, 2015). Specifying etiopathophysiology is essential if we wish to improve prevention and intervention programs by targeting mechanisms of psychopathology directly (Beauchaine, Neuhaus, Brenner, & Gatzke-Kopp, 2008). As noted by Thomas Insel, former Director of NIMH and co-founder of RDoC, "symptoms alone rarely indicate the best choice of treatment" (Insel, 2013). This statement follows from appreciation that almost all behavioral syndromes emerge from multiple etiological pathways (known as equifinality in developmental psychopathology and as phenocopies in psychiatry). Mapping these pathways is vital if we wish to maximize treatment effectiveness, an assumption fully consistent with both (a) longstanding efforts in the child and adolescent clinical psychology literatures to identify mediators, moderators, and predictors of intervention response (Beauchaine, Webster-Stratton, & Reid, 2005; Hinshaw, 2007; Owens et al., 2003) and (b) the recent evolution of precision psychiatry (Cuthburt & Insel, 2013; Insel et al., 2010). Both seek to devise more effective treatments that target mechanisms of

psychopathology—whether biological or environmental—for etiologically diverse clients/patients who are currently diagnosed with the same disorder.

With this backdrop in mind, RDoC was initiated as part of the 2008 NIMH Strategic Plan. As envisioned initially by Cuthbert and Insel (2013), RDoC was grounded in seven principles:

1. A strong translational perspective (starting with basic science; inductive not deductive).
2. Explicitly dimensional, with attention to both normal and abnormal.
3. Use and develop reliable *and* valid measures.
4. Reduce heterogeneity of groups of patients.
5. Identify integrative models of neural circuitry and behavior rather than models that focus exclusively on one or the other.
6. Concentrate on constructs with solid evidence to serve as platforms for further research.
7. No ties to existing definitions of disorder.

Although we cannot discuss merits of or ten-year progress toward all of these goals, we note that none is incompatible with objectives of child and adolescent clinical psychology. On the contrary, they instantiate many of our shared values, including appreciation of and advocacy for empirically based assessment; formulation and use of valid constructs and measures; models that integrate biology and behavior; and evidence-based science and practice. Frustrations with RDoC often derive from assertions of biological reductionism, poor mapping of biological elements (genes, molecules, cells, circuits, physiology) onto behavioral and self-report measures, neglect of problems associated with measurement error, and assumptions that the initiative is intended for diagnostic purposes when instead it is explicitly—at least to date—meant to guide basic research on vulnerabilities to and expressions of psychopathology (for further discussion see Franklin, Jamieson, Glenn, & Nock, 2015; Lilienfeld, 2014; Lilienfeld & Treadway, 2016)[1].

These are legitimate concerns. We assert here, however, that RDoC need not be applied in a biologically reductionistic fashion. We further contend that expectations of 1:1 mappings of biological functions onto behaviors are misplaced because they ignore etiological complexities across levels of analysis. In fact, strong associations between single biological functions and behaviors are *precluded* by several factors that RDoC-informed research has elucidated. First, molecular genetic influences on psychopathology are orders-of-magnitude more complex than imagined a decade ago (Beauchaine, Constantino, & Hayden, 2018; Ripke et al., 2013). Second, transdiagnostic neural vulnerabilities to psychopathology are increasingly well-characterized (Beauchaine, 2015; Zisner & Beauchaine, 2016a). These vulnerabilities are often expressed very differently across development given maturational effects on behavior and potentiating influences of environmental risk exposures

[1]Implications for and applications to eventual diagnostic systems may be decades down the road (e.g., Cuthbert, 2015).

(Beauchaine, Hinshaw, & Pang, 2010; Beauchaine, Zisner, & Sauder, 2017). Third, functional dependencies (modulating effects) of biobehavioral systems on one another yield complex patterns of comorbidity that are better captured by advanced computational models than by traditional linear models (Beauchaine, & Cicchetti, 2016; Beauchaine & Tackett, 2020; Corr & McNaughton, 2016; Haines & Beauchaine, 2020).

In the brief sections that follow, we discuss four common, interrelated, and largely outdated assumptions that impede scientific progress that RDoC might otherwise facilitate. These assumptions, which help form the "philosophical backbone" of child and adolescent clinical psychology, too often perpetuate programs of research that are structurally indistinguishable from investigations of decades past, even though new methods and technologies (e.g., genomics, machine learning, neuroimaging) are increasingly used. In short, although many studies in the child and adolescent psychopathology literatures appeal to and reference RDoC, few consistently apply core RDoC principles. Instead, most evaluate biological correlates of traditionally defined DSM disorders using new methods, falling far short of the ultimate goal of elucidating core causal mechanisms. Although once sensible, implicit assumptions underlying this basic approach do not hold up to scrutiny following recent interdisciplinary advances in clinical science. If not challenged, rethought, and modified, these assumptions will hinder desired progress in the field[2].

MISGUIDED ASSUMPTION 1: DSM SYNDROMES ARE PROPER STARTING POINTS FOR RDoC-INFORMED RESEARCH

As outlined above, diagnostic validity concerns were a primary motivating factor toward formulating RDoC. Although invalidity derives from several sources, a major contributor is etiological heterogeneity (Beauchaine & Constantino, 2017; Cuthburt & Insel, 2013; Insel et al., 2010). For example, autism spectrum disorder (ASD) represents numerous phenocopies that emerge from diverse combinations of multifactorial genetic burden including common allelic variation, *de novo* mutations, and copy number variants (De Rubeis & Buxbaum, 2015; Huguet & Bourgeron, 2016). ASD is so etiologically diverse that two people diagnosed with the disorder may share few if any genetic vulnerabilities (Betancur, 2011). Diagnosing ASD and then working backward to infer physiological, neural, and genetic mechanisms is therefore of extremely limited value because heterogeneity precludes specification of any single etiological pathway, unless that pathway is far more common than all others. Similar cases can be made for many DSM disorders (Beauchaine & Constantino, 2017; Beauchaine et al., 2018). This point illustrates the importance of Principle 7 of RDoC (no ties to existing disorders), which has generally not been heeded by child and adolescent psychopathologists. Indeed, a quick review of the Clarkson et al. (2020) meta-analysis (this issue) reveals that almost all of the 33 articles included—despite mentioning RDoC in the abstract, title, and/or keywords—evaluated correlations between measures across various levels of analysis (e.g., physiology, behavior) within or between existing psychiatric disorders for which etiological heterogeneity is considerable (e.g., ASD, ADHD, mood

[2]We are not suggesting that RDoC is without limitations. Such limitations are well documented in this special issue and elsewhere; they need not be recapped here.

disorders). Under such conditions, strong correspondencies across levels of analysis are largely precluded.

Research conducted over the past decade also reveals several transdiagnostic vulnerabilities to psychopathology spanning genetic, neural, and behavioral trait levels of analysis. By definition, these vulnerabilities are not specific to any DSM disorder. At the genetic level of analysis, for example, 22q11.2 deletion syndrome confers vulnerability to schizophrenia-spectrum disorders, mood disorders, stress-related disorders, somatoform disorders, intellectual disability, and ASD (Hoeffding et al., 2017). The same deletion is associated with sleep problems (Kennedy et al., 2014), a transdiagnostic vulnerability to multiple DSM disorders (Harvey, Murray, Chandler, & Soehner, 2011). At the neural level, dampened striatal responding while anticipating incentives is associated with ADHD, other externalizing conditions, unipolar depression, and nonsuicidal self-injury (Beauchaine, Klein, Knapton, & Zisner, 2019; Forbes & Dahl, 2012; Luijten, Schellekens, Kühn, Machielse, & Sescousse, 2017; Plichta & Scheres, 2014; Sauder, Derbidge, & Beauchaine, 2016; Zisner & Beauchaine, 2016a). At the behavioral trait level, negative affectivity/irritability is observed in most DSM internalizing *and* externalizing disorders (Beauchaine & Tackett, 2020; Tackett et al., 2013). Such findings led Skuse (2001) to suggest—well before the advent of RDoC—that "a focus on *traits* [emphasis added], rather than syndromes, is appropriate and could in due course contribute to redefinition of traditional psychiatric syndromes" (p. 395). Such findings also demonstrate that continued studies evaluating neurobiological correlates of existing DSM disorders are unlikely to yield major advances in our understanding of etiopathophysiology.

From a trait perspective, using behavioral syndromes as starting points for RDoC-informed research is also problematic when single vulnerabilities map onto different DSM disorders across development. For example, many adult males who are diagnosed with antisocial personality disorder (ASPD) follow a well-characterized developmental progression through multiple DSM disorders across the lifespan. This developmental trajectory begins with attention-deficit hyperactivity disorder (ADHD)[3], followed in rough temporal sequence by oppositional defiant disorder (ODD), life-course persistent conduct disorder (CD), substance use disorders (SUDs), and ASPD (Beauchaine et al., 2017; Loeber & Hay, 1997; Moffitt, 1993; Robins, 1966). A sizable literature ties all of these disorders to trait impulsivity—a single, highly heritable personality attribute that expresses differently across the lifespan depending on developmental and contextual influences (see e.g., Krueger et al., 2002; Moen Eilertsen et al., 2019).

Although full description of various manifestations of impulsivity across development is beyond the scope of this article, it is often expressed as temperamental surgency and low inhibitory control in toddlerhood (Martel, Gremillion, & Roberts, 2012; Saudino, 2009); as syndromal symptoms of ADHD (e.g., acting without forethought, reward-seeking) in childhood (see Neuhaus & Beauchaine, 2017); as short-sighted decision-making and

[3]Such progression is specific to the hyperactive (HI) and combined (C) presentations of ADHD—not the purely inattentive (IN) presentation (e.g., Ahmad & Hinshaw, 2018). This observation, combined with differentiating factors at neural, behavioral, and treatment-response levels of analysis, suggests a separate etiopathophysiology for ADHD-I (see e.g., Adams, Derefinko, Milich, & Fillmore, 2008; Fair et al., 2013; Stein et al., 2003).

assorted comorbidities in adolescence (e.g. Hurtig et al., 2007); and as employment difficulties, financial distress, and suicide risk in adulthood (e.g., Altszuler et al., 2016; Beauchaine, Ben-David, & Bos, 2020).

Environmentally, progression of trait impulsivity across the temperament → ADHD → ODD → CD → SUDs → ASPD pathway is mediated by various adversities and risk exposures including family coercion abuse, and maltreatment in early childhood (Crowell et al., 2017; Guendelman, Owens, Galan, Gard, & Hinshaw, 2016; Patterson, DeGarmo, & Knutson, 2000; VanZomeren-Dohm, Xu, Thibodeau, & Cicchetti, 2016); peer victimization, deviant peer affiliations, neighborhood risk, and availability of substances of abuse in later childhood and adolescence (Meier, Slutske, Arndt, & Cadoret, 2008; Meza, Owens & Hinshaw, 2016; Snyder, 2016); and criminal justice system involvement in adolescence and adulthood (Gatti, Tremblay, & Vitaro, 2009). Importantly, environments devoid of these risk factors offer partial protection from progression of externalizing conduct. Thus, it is critical to map both occurrences of and developmental timings of risk exposures to understand progression of trait impulsivity and other vulnerabilities to psychopathology. In contrast, assuming independent DSM disorders across development and ignoring potentiating effects of environment obscures etiopathophysiology and the need for prevention early in life (e.g., Beauchaine, Hinshaw, & Bridge, 2019; Beauchaine et al., 2017). For externalizing conduct, acknowledging heightened vulnerability to delinquency among children with ADHD in contexts of risk is essential if we wish to alter this well characterized pathway. Once embedded in family, peer, institutional, and subcultural systems, delinquency is highly resistant to change (e.g., Winiarski, Brown, Karnik, & Brennan, 2020).

Although not the focus of this article, it is noteworthy that similar interactive effects of temperamental vulnerability and environmental risk apply to homotypic progression of internalizing disorders, for which trait anxiety is potentiated by various adversities across development (e.g., Cicchetti & Toth, 1998; Hankin et al., 2016; Klein, Dyson, Kujawa, & Kotov, 2012). Given its importance, we return to homotypic syndrome progression in later sections.

Finally, using behavioral syndromes as starting points for RDoC-informed research effectively renders those syndromes gold standards against which biological markers are validated. In addition to obscuring heterogeneous etiological pathways to psychopathology, as outlined above, this practice is problematic because behavioral syndromes, as assessed by self- and informant-report, are measured with less precision than most (though not all) biological markers. As shown in Figure 1, measurement error typically increases as we move across genetic → neurobiological → behavioral levels of analysis. Allelic variation of common genetic polymorphisms is measured with almost perfect precision, whereas Likert-assessed behavioral constructs contain up to 50% measurement error (Hoyt & Kerns, 1999). Cronbach's alpha, which indexes measurement precision for scales, sets an upper limit on correlation with all other variables, including those measured across levels of analysis. An alpha coefficient of .70, which is acceptable by most any standard, indicates 51% measurement error ($1 - \alpha^2$). The upper bound of variance accounted for in this scale by another variable is therefore 49%.

MISGUIDED ASSUMPTION 2: DSM DISORDERS CAN BE ACCOUNTED FOR BY LARGE, INDEPENDENT MAIN EFFECTS

Historically, psychopathology research was guided by the assumption that large-effect-size, independent causes would eventually be identified for specific DSM disorders (see Beauchaine & Thayer, 2015). Examples include monogenic and oligogenic theories of schizophrenia (Cromwell, & Snyder, 1993) and HPA axis accounts of suicide (Coryell & Schlesser, 2001). For many years, expectations of large-effect-size causes led the field to search for *pathognomonic signs*—markers that indicate presence of disorder with near perfect specificity. When available, pathognomonic signs are fundamental to effective diagnosis because all differentials are ruled out. Prodromal presentations of pathognomonic signs may even aid in prevention.

For psychopathology, searches for pathognomonic signs have failed because almost all mental illnesses are etiologically complex (Beauchaine & Constantino, 2017; Cohen, 2016; Hinshaw, 2017). As outlined above, apparently single syndromes (e.g., ASD, depression) may be arrived at through largely unrelated equifinal pathways. Conversely, common genetic vulnerabilities can express as alternate, multifinal phenotypes through pleiotropy (effects of a single gene on multiple traits), environmental modulation, and other mechanisms (Beauchaine et al., 2018). For example, people from different families with the same copy number variant may show normal intelligence vs. intellectual disability depending on other, within-family genetic influences on intellectual function (Finucane, Challman, Martin, & Ledbetter, 2016).

Despite discovery of extremely few large independent main effects in the history of psychopathology research, they are still being sought and are still assigned high priority in the child and adolescent clinical psychology literatures, often at the expense of mapping transdiagnostic vulnerabilities and etiological complexity. Persistence of this failed approach is likely attributable—at least in part—to prevailing, decades-old statistical models that are insensitive to modulating effects (i.e., functional dependencies) of biobehavioral systems on one other. In fact, classic inferential statistics still dominate the literature despite longstanding recognition of their limitations (for a recent discussion, see Wagenmakers et al., 2018).

One classic inferential method is statistical partialling, which is especially problematic from any transdiagnostic perspective, including RDoC. Partialling approaches, including partial and semi-partial regression, hierarchical regression, ANCOVA, and cross-lag panel models, can obscure and even distort associations between transdiagnostic vulnerabilities and functional behaviors (Beauchaine et al., 2010; Beauchaine & Slep, 2018; McDonough-Caplan, Klein, & Beauchaine, 2018; Miller & Chapman, 2001). Oftentimes, such models are used to assess associations between existing DSM disorders and important clinical outcomes such as suicidal behaviors, controlling statistically for concurrent symptoms of other DSM disorders (comorbidities). This approach is depicted in Figure 2, which illustrates the association between ADHD symptoms and suicidal behaviors, controlling statistically for (partialling out) symptoms of major depressive disorder (MDD) and borderline personality disorder (BPD). This example is instructive because all three disorders share transdiagnostic

neural (striatal dysfunction) and related affective (anhedonia, irritability) vulnerability (Beauchaine & Tackett, 2020; Beauchaine, Klein et al., 2019; Forbes & Dahl, 2012; Plichta & Scheres, 2014; Sauder et al., 2016; Zisner & Beauchaine, 2016a). Importantly, this common neuro-affective vulnerability may contribute to elevated rates of suicide in all three disorders (see Beauchaine, Hinshaw et al., 2019).

As Figure 2 shows, statistical partialling removes important variance attributable to transdiagnostic mechanisms among disorders. In this example, the association (overlap) between ADHD symptoms and suicidal behaviors is misleadingly truncated (right panel) when sources of overlapping variance—*including shared vulnerability*—are partialled out. Such analyses, which are exceedingly common in the child and adolescent psychopathology literatures, can yield incorrect conclusions about etiology. In the example at hand, *a series of three ANCOVAs in which associations between each diagnosis and suicidal behaviors is evaluated, controlling for the remaining two diagnoses, could all be non-significant, even if transdiagnostic vulnerability shared by all disorders is associated causally with suicidal behaviors.* This example lends further support to Principle 7 of RDoC (no ties to existing disorders) and points to the importance of research on transdiagnostic vulnerability traits spanning diagnostic categories. It further suggests that neural functions and biobehavioral traits, which we discuss below, are better starting points for RDoC research than traditional diagnoses (Beauchaine & Constantino, 2017).

MISGUIDED ASSUMPTION 3: BIOLOGICAL FUNCTIONS SHOULD SHOW 1:1 CORRESPONDENCIES WITH BEHAVIORS

A related, often implicit assumption is that correspondencies between biological functions and behaviors should be 1:1, measurement error notwithstanding. This assumption is reflected in research focused either exclusively or primarily on linear associations between biological elements of the RDoC Matrix and behavior, without considering modulating effects of other biological systems (Beauchaine & Constantino, 2017; Corr, & McNaughton, 2016). Models that ignore functional dependencies between biobehavioral systems of approach and avoidance are especially problematic given well-known modulating effects of trait and state anxiety on reward processing and downstream approach behaviors. These modulatory effects are observed in both real-world functional outcomes and carefully designed lab tasks. As described above, for example, impulsive males, who by definition engage in excessive reward-seeking behaviors, are predisposed to externalizing disorders across the lifespan (e.g., conduct problems, delinquency, substance use, criminality; see Beauchaine et al., 2010; 2017; Hinshaw, 2018). However, concurrent symptoms of anxiety predict better functional outcomes, including more positive responses to behavioral treatments (Beauchaine et al., 2005), lower rates of physical aggression, better peer relations, and fewer police contacts (Walker et al., 1991). Conversely, impulsive males who experience little trait anxiety, as indicated by callous-unemotional and psychopathic traits, engage in more concurrent and future antisocial behaviors (Frick, Ray, Thornton, & Kahn, 2014; McMahon, Witkiewitz, Kotler, & the Conduct Problems Prevention Research Group, 2010). In the lab, trait anxiety is associated with better decision-making on delay

discounting tasks among participants who score high on impulsivity, including those with substance abuse problems (e.g., Haines et al., 2020).

Functional dependencies between prefrontal mechanisms of self-control and both impulsivity and anxiety are also well characterized. Voluminous literatures on executive function, emotion regulation, and emotion dysregulation implicate functional subdivisions of the PFC in suppressing strong approach and avoidance tendencies in the service of goal-directed behavior (see Beauchaine & Cicchetti, 2019; Goldin, McRae, Ramel, & Gross, 2008; Zelazo, 2015). Thus, impulsivity can be modulated by neural systems subserving anxiety *and* by neural systems subserving self-regulation (Beauchaine, 2015). A heuristic depiction of functional dependencies among neural systems of approach, avoidance, and self-regulation appears in Figure 3.

More broadly, RDoC does not and should not assume 1:1 correspondencies across levels of analysis given that (1) single genetic vulnerabilities can affect multiple behavioral traits (pleiotropy; see above), (2) single neural circuits often subserve overlapping motivational and emotional functions (see Beauchaine, & Zisner, 2017), and (3) single physiological measures can index multiple neural functions depending on eliciting events. Electrodermal responding (EDR), for example, may index fear in some situations (e.g., public speaking) but more generalized arousal in others (e.g., reward learning). This does not invalidate EDR, which appears in multiple elements of the RDoC Matrix (acute threat, reward prediction error, arousal), as a physiological marker. Rather, stimulus conditions must be considered carefully if one wishes to interpret reactivity of EDR or *any* neural/physiological measure (National Advisory Mental Health Council Workgroup on Tasks & Measures for RDoC, 2016; Zisner & Beauchaine, 2016b).

Consistent with a major theme of this article, this section suggests that human behavioral traits, including psychopathology, are determined by complex, functionally interdependent genetic, neural, and environmental factors, and that 1:1 correspondencies between these factors and behaviors should not be expected (Beauchaine et al., 2017, 2018; Petkus et al., 2017; Sanislow et al., 2010). As a result, multiple interactive functional dimensions of behavior must be modelled to map etiopathophysiology, as we describe in greater detail below.

MISGUIDED ASSUMPTION 4: COMORBIDITIES AND CONTINUITIES CAN BE UNDERSTOOD BY CROSS-TABULATING BEHAVIORAL SYMPTOMS

A final, interrelated issue concerns complex patterns of comorbidity that cannot be accounted for by a diagnostic system that sets boundaries between disorders with limited attention to etiopathophysiology, or by descriptive studies that cross-tabulate overlap among those disorders (see Beauchaine & Cicchetti, 2016). High rates of *homotypic* comorbidity and continuity within the internalizing and externalizing spectra almost certainly derive, at least in part, from shared neurobiological vulnerabilities (genetic, neural, hormonal), which interact with environmental adversities across development to shape and maintain specific expressions of psychopathology (see Beauchaine & Hinshaw, 2016; Hankin et al., 2016; Hinshaw, 2017; Klein et al., 2012). As described above, for example, many externalizing

males traverse a developmental pathway characterized by multiple overlapping DSM diagnoses, including ADHD, ODD, CD, SUDs, and ASPD (Beauchaine et al., 2017). Our work, some of which we describe below, questions the utility of this diagnostic approach, which yields fractionated literatures that (1) are artificially separated by diagnosis, (2) fail to account for well characterized developmental pathways, (3) often ignore important neurodevelopmental influences, and (4) are largely uninformed by one another even though they address common etiopathophysiologies. Diagnosing assumedly discrete disorders across development also de-emphasizes known environmental potentiators of externalizing progression, including coercive and invalidating family processes (Crowell et al., 2017; Patterson et al., 2000), maltreatment (Guendelman et al., 2016; VanZomeren-Dohm, et al., 2016), deviant peer affiliations (Snyder, 2016), peer victimization/rejection (Meza et al., 2016), and neighborhood risk (Meier et al., 2008). As we argue above, understanding homotypic comorbidity and continuity requires a transdiagnostic approach that does not assume independent causes of etiologically related behavioral syndromes, and that embraces rather than obscures interactions between biological vulnerability and environmental risk over time (see Beauchaine et al., 2017; Cicchetti & Toth, 1998; Hankin et al., 2016).

Historically, high rates of *heterotypic* comorbidity and continuity of internalizing and externalizing disorders have been even more perplexing. For example, about half of preschool- and school-age children with ADHD experience comorbid depression (Wilens et al., 2002), and externalizing disorders in childhood predict depression in adolescence and adulthood (Loth, Drabick, Leibenluft, & Hulvershorn, 2014; McDonough-Caplan et al., 2018). Heterotypic comorbidity and continuity cannot be explained by a diagnostic system that defines internalizing and externalizing disorders with fully independent criteria. In contrast, neural vulnerabilities that are common to internalizing and externalizing disorders are increasingly well characterized. As noted above, for example, dampened striatal responding while anticipating incentives characterizes ADHD, other externalizing disorders, unipolar depression, and nonsuicidal self-injury, and is therefore transdiagnostic (Beauchaine, Klein et al., 2019; Forbes & Dahl, 2012; Luijten et al., 2017; Plichta & Scheres, 2014; Sauder et al., 2016)[4].

At the trait levels of analysis, a large literature implicates low tonic and blunted phasic striatal reactivity to a persistent, anhedonic and irritable mood state. This mood state, which is often referred to as negative affectivity or negative emotionality in the child literature and neuroticism in the adult literature (Beauchaine & Tackett, 2020; Tackett & Lahey, 2017), characterizes all of the disorders listed above (e.g., Beauchaine & Constantino, 2017; Laakso et al., 2003). Yet despite transdiagnostic empirical associations between anhedonia/irritability and both internalizing and externalizing disorders (Zisner & Beauchaine, 2016a; Tackett et al., 2013), irritability is not a core symptom of depression, and anhedonia is not a symptom of any externalizing disorder. It is ironic that DSM criterion sets often fail to capture transdiagnostic vulnerabilities that drive comorbidities between the very disorders they describe.

[4]In contrast, amygdala reactivity to fear-eliciting events is high in internalizing disorders but low in externalizing disorders, and is therefore differentiating (see Beauchaine & Constantino, 2017; Beauchaine & Tackett, 2020).

AN AGENDA FOR FUTURE RESEARCH

In our view, RDoC and its principles hold much potential to advance both basic and applied research on child and adolescent psychopathology, provided that we integrate developmental principles and environmental influences into our etiological models. Indeed, research that specifies etiopathophysiological transactions through which biological vulnerabilities interact with environmental adversities across development is essential because it paves the way for prevention and intervention programs that more directly target group- and individual-level mechanisms of psychopathology (see Beauchaine et al., 2008). However, several outdated assumptions, described above, have mired the field in research that, with certain exceptions, is structurally indistinguishable from research of decades past, even though new technologies and methods are often used. Although many articles in the child and adolescent psychopathology literatures reference RDoC, few apply all RDoC principles. Studies of etiopathophysiology that use DSM syndromes as starting points are especially problematic because they presuppose those syndromes are sufficiently homogeneous when many are not, obscure important transdiagnostic vulnerabilities to psychopathology, and obfuscate mechanisms of homotypic and heterotypic comorbidity, including biological vulnerabilities and environmental mediators of internalizing and externalizing progression. In addition, we often expect 1:1 correspondencies between neurobiological functions and behaviors, and the field continues to search for large independent causes of psychopathology where there are few to be found.

In the remainder of this article, we describe how core RDoC principles can be incorporated into a research agenda that addresses these concerns, and we offer specific suggestions for future research. As we have described elsewhere, *developmental principles including ontogenesis, whereby neurobiological vulnerabilities interact with environmental risk factors to alter neurodevelopment over time, are readily accommodated by RDoC-informed research, provided we focus on traits instead of disorders.* This is illustrated in the example of externalizing progression described above and considered in further detail below (e.g., Beauchaine & McNulty, 2013; Beauchaine, Shader, & Hinshaw, 2016). We note, however, that critical developmental influences, environmental risk factors, and their interactions differ substantially across vulnerability traits (e.g., trait impulsivity, trait anxiety, self-regulation). We therefore question the utility of adding development or environment “vectors” to RDoC Matrix, as doing so would oversimplify the complexity of emerging psychopathology. We elaborate on this important point below.

When Possible, Adopt a Neural-systems-first Approach to Studying Vulnerability Traits

As noted above, DSM syndromes are often unfruitful starting points for research aimed at specifying etiopathophysiology given (1) complex equifinal pathways to single disorders via multifactorial genetic liabilities, (2) neural functions that confer transdiagnostic vulnerability to multiple DSM disorders, (3) functional dependencies among neural systems that yield complex patterns of comorbidity, and (4) impinging effects of environment on behavior, among other factors. Measurement precision of behavioral syndromes is also low. As a result, studying neurobiological correlates of single disorders often provides limited, non-specific, and sometimes misleading information about etiopathophysiology (for elaboration

see Beauchaine & Tackett, 2020). Given such limitations, we and others have argued that a "neural-systems-first" approach be adopted, and whenever possible supplant "disorder-first" (i.e., phenotype-first) approaches in studies of etiopathophysiology (Beauchaine & Constantino, 2017).

With a neural-systems-first approach, neural functions serve as starting points from which we simultaneously work backward (toward genes) *and* forward (toward behaviors) to understand etiopathophysiologies of *vulnerability traits* associated with those neural functions, regardless of specific disorder(s). This approach is consistent with core RDoC principles outlined above, especially Principle 5 (identify integrative models of neural circuitry and behavior rather than models that focus exclusively on one or the other). An example appears in the left side of Figure 4, which depicts our neurodevelopmental model of externalizing behavior (see Beauchaine et al., 2017). First, working 'backward' (upward from the neural functions panel), complex determinants of blunted striatal reactivity are identified, including genetic, epigenetic, and neurohormonal (for reviews see Beauchaine & Constantino, 2017; Gatzke-Kopp, 2011). Next, working 'forward' (downward from the neural functions panel), associations between blunted striatal reactivity and transdiagnostic emotional and temperamental predispositions to psychopathology are specified (see e.g., Beauchaine et al., 2017; Laakso et al., 2003). An assumption of this model is that environmental risk factors shape neuro-affective vulnerability into progressively more serious externalizing outcomes over time—an assertion supported by considerable research (e.g., Burt, Krueger, McGue, & Iacono, 2001; Meier et al., 2008).

This approach contrasts with traditional genetics studies in which SNPs, polygenic risk scores, etc., are mapped onto individual DSM disorders—not transdiagnostic neural functions. Disorder-first approaches ignore shared genetic liability across traditional diagnostic categories, and have produced another fractionated literature in which unique SNP, GWAS, and eGWAS profiles are sought (and often assumed) for individual disorders. This despite evidence that externalizing disorders, which we consider here, share considerable overlap in additive molecular genetic vulnerability (see e.g., Gizer, Otto, & Ellingson, 2016)

Although neural-systems-first approaches offer opportunities to identify transdiagnostic neurobiological vulnerabilities to psychopathology, they cannot do so without significant resources and painstaking planning. Large, carefully-ascertained samples must be recruited and undergo neuroimaging protocols designed to engage brain networks subserving core behavioral functions (e.g., motivation, emotion, arousal, social affliation) that are disrupted across various forms of psychopathology. To evaluate effects of environmental risk mediators on behavioral and neural development, participants must undergo repeated assessments (e.g., annually), between which environmental adversities are measured. Multisite collaborative efforts that fit this description are underway, such as the Adolescent Brain Cognitive Development (ABCD) study (see e.g., Casey et al., 2018).

Published findings from large research consortia such as ABCD should avoid two issues discussed herein that plague the literature, including (1) evaluating associations between single DSM disorders and neural functions using statistical partialling, and (2) expecting 1:1

correspondencies between neural functions and behaviors. Given over 10,000 participants, the ABCD Study holds tremendous potential to elucidate transdiagnostic neural correlates of psychopathology, but only if authors avoid these outdated approaches (e.g., Beauchaine, 2020).

Integrate Environmental Risk Mediators Into RDoC-informed Etiopathophysiological Models

Although some consideration of environmental risk and context appears in the RDoC literature (Cuthbert, 2014; Sanislow, Ferrante, Pacheco, Rudorfer, & Morris, 2019), RDoC does not incorporate effects of specific adversities on behavioral adjustment, neurodevelopment, or other forms of vulnerability. This is sometimes levied as a criticism of RDoC (Wakefield, 2014), but no psychiatric nomenclature could account for all forms of and timings of environmental risk exposures across the lifespan. Given the overwhelming ontogenic complexity through which environments shape biological systems throughout development, environmental adversities have extraordinarily diverse effects across people and neural systems. The nature and extent of such effects depends on age at exposure, magnitude and duration of exposure, and moderating influences of individual differences and contextual supports, among other factors (Cicchetti & Cannon, 1999; Lupien, McEwen, Gunnar, & Heim, 2009; Mead, Beauchaine, & Shannon, 2010).

Complex effects of early-life stress on the limbic-hypothalamic-pituitary-adrenal (LHPA) axis provide a salient example. Such effects depend on numerous factors, including the nature of adversity (e.g., loss, maltreatment, abuse), developmental timings of stress exposures (e.g., early childhood, middle childhood, adolescence), heritable trait predispositions toward internalizing vs. externalizing psychopathology, the component of LHPA axis function assessed (e.g., cortisol reactivity, diurnal rhythm, negative feedback integrity), sex, and other individual differences (see Koss & Gunnar, 2018). Taken together, even this oversimplified set of influences yields 108 combinations of effects. The complexity of adversities on LHPA axis function is evident even among resilient adults *without psychopathology*. For example, healthy adults who lost a parent in childhood to either desertion or death show stronger cortisol reactivity to dexamethasone/corticotropin-releasing hormone challenge than controls, except in cases where desertion is accompanied by poor caretaking (Tyrka et al., 2008). In these cases, cortisol reactivity is blunted.

When considering children, adolescents, and adults *with psychopathology*, the complexity of environmental effects on LHPA axis function expands considerably. This is almost certainly a cause of apparent inconsistencies in the literature, including findings of blunted, null, and excessive cortisol reactivity to lab stressors in both internalizing and externalizing samples (Ruttle et al., 2011). Among depressed, maltreated school-age children, downregulation of diurnal cortisol patterns is often observed (Cicchetti, Rogosch, Gunnar, & Toth, 2010). At the same time, both blunted cortisol reactivity and excessive cortisol reactivity to lab stressors are common (Harkness, Stewart, & Wynne-Edwards, 2011; MacMillan et al., 2009). Other findings link withdrawn behavior among maltreated children to higher afternoon cortisol one year later and aggressive behavior to lower morning cortisol one year later (Alink, Cicchetti, Kim, & Rogosch, 2012). Although our intent here is to describe and

not explain the complexity of these findings, age at maltreatment and timing of assessment appear to be important. For example, LHPA axis hyper-activity is often found soon after maltreatment, with downregulation occurring over time through allostatic mechanisms (Rogosch, Dackis, & Cicchetti, 2011). Thus, consistent with a major theme of this article, *effects of environmental risk on behavioral outcomes are complex, multicausal, dependent on age and developmental stage, and moderated by various endogenous and exogenous factors including individual differences and protective influences*. Such effects are therefore extremely heterogeneous.

Despite this heterogeneity in outcomes following adversity, effects on behavior and neuro-development are often widespread and substantial, and therefore cannot be ignored (e.g., Hair, Hanson, Wolfe, & Pollak, 2015). In our view, responsibility for measuring and modeling environmental adversities and their untoward sequelae across development falls on the shoulders of individual research groups, who are in the best positon to decide which risk factors are relevant to their work given (1) the specific RDoC construct(s) under study, (2) developmental stages and age ranges of their samples, and (3) specific adversities participants have incurred or are likely to incur. Common adversities include poverty and its correlates, maltreatment, sexual abuse, marginalization, substance use, head injuries, and teratogen exposures. Few of these are relevant to each-and-every study, and many more could be listed. It is therefore impractical to add development and/or environment 'vectors' to the RDoC Matrix, as some have suggested (Wakefield, 2014; Woody & Gibb, 2015). Although such calls are clearly well-intentioned, doing so would likely compromise modeling precision by vastly oversimplifying the complexity of biology × environment interactions across development (see immediately above). This is one reason why Axis IV—an attempt to quantify effects of widely variegated psychosocial and environmental stressors on mental health—was eliminated from the DSM. Given the complexity of environmental influences on psychopathology across development, Axis IV suffered from low reliability and low validity (Probst, 2014). We are therefore circumspect about formulaic approaches to specifying effects of environmental risk across development. Simply put, *environmental effects on psychopathology across the lifespan differ across trait vulnerabilities and moderated by multiple intervening influences; they are therefore too complex to reduce in this way*. Specific environmental risk factors for psychopathology and effects of timing should therefore be identified for different neurodevelopmental vulnerabilities. Sets of risk factors will only partly overlap across broad dimensions of psychopathology (externalizing, internalizing, psychosis; see Beauchaine et al., 2017; Hankin et al., 2016; Mittal & Wakschlag, 2017).

In our work, we focus on environmental risk mediators with well-characterized effects on progression of externalizing behavior (bottom panel, Fig. 4). These risk factors, which vary markedly across development, include invalidating and coercive family processes (Crowell et al., 2017; Patterson et al., 2000), maltreatment (Guendelman et al., 2016; VanZomeren-Dohm et al., 2016), deviant peer affiliations (Snyder, 2016), peer victimization/rejection (Meza et al., 2016), neighborhood risk (Meier et al., Cadoret, 2008) and exposure to substances of abuse (Gatzke-Kopp & Beauchaine, 2007; Sibley et al., 2014). Several of these risk factors alter prefrontal cortex development, with adverse effects on executive function, emotion regulation, and self-control later in life (see Beauchaine, 2015; Pfefferbaum et al.,

2018; Zelazo, 2015). It bears repeating, however, that precise, prospective prediction of effects of such adversities on behavioral and neural functions for any individual is impossible given differential timings, durations, and intensities of exposures.

In sum, RDoC does not tabulate specific effects of environmental risk factors on behavior or neurodevelopment. Nevertheless, many risk factors associated with progression of internalizing, externalizing, and psychosis are well-known and should be incorporated into RDoC-informed research (Beauchaine et al., 2017; Cicchetti & Toth, 1999; Hankin et al., 2016; Hinshaw, 2018; Mittal & Wakschlag, 2017). Which adversities to measure should not be dictated *a priori* because developmental and contextual factors vary widely across populations and studies. Similarly, specific behaviors to assess across development differ substantially depending on the vulnerability trait under focus. Although such behaviors may include symptoms of DSM disorders (see the behavioral syndromes panel, Fig. 4), DSM disorders should no longer be gold standards against which validities of vulnerabilities to psychopathology (e.g., genetic neural, emotional) are evaluated. Instead, transdiagnostic influences on behavior across development should be emphasized (RDoC panels, Fig. 1).

Finally, when assessing longitudinal effects of environment on behavior and neurodevelopment, it is important to use developmentally sensitive assessments (see Mittal & Wakschlag, 2017; Shader et al., 2018). In our work, we have used various monetary incentive tasks to evaluate sensitivity to rewards among 4- to 20-year-olds (e.g., Crowell et al., 2006; Gatzke-Kopp et al., 2009; Sauder et al., 2016). These tasks are graded in difficulty to ensure sensitivity to impulsive responding among participants who fall along the developmental spectrum of externalizing behaviors depicted in Figure 4. More recently, we have used adaptive design optimization, which alters task difficulty based on individual differences in responding, including individual differences associated with age (see Haines et al., 2020).

Integrate Neural Vulnerabilities Into the Empirical Latent Structure of Psychopathology

An additional source of invalidity for the DSM stems from the traditional practice of rationally deriving discrete categorical disorders (see Beauchaine & Klein, 2017). Many such disorders are carried forward to the DSM 5 from past editions, despite longstanding problems with both construct and discriminant validity, and despite recognition that almost all forms of psychopathology are distributed continuously and therefore do not fit a categorical model (e.g., Kotov et al., 2017). In contrast, hierarchical structural models of psychopathology are derived empirically using factor analysis. They are dimensional by nature because they are based on symptom correlations in large population-based and twin samples of children, adolescents, and adults. Structural models invariably yield separate but correlated second-order internalizing, externalizing, and (when measured) thought problems factors (e.g., Krueger, 1999; Wright et al., 2013). The second-order externalizing factor, which we focus on here, is far more heritable than first-order factors that load on it, including symptoms of ADHD, ODD, conduct problems, and for adults, substance abuse and ASPD (Krueger et al., 2002). Covariation among these first-order factors is accounted for largely by environmental influences (Burt et al., 2001). Thus, *a single, highly heritable trait confers vulnerability to all externalizing disorders, but specific behavioral expressions*

of vulnerability are shaped by environment. This is consistent with the model presented in Figure 4, and helps to explain patterns of both concurrent comorbidity and heterotypic continuity. It also illustrates again why a focus on traits and their interactions with environment is needed to understand etiopathophysiology of externalizing and other psychopathological behaviors (Beauchaine et al., 2017; Skuse, 2001).

More recent *bi-factor* models also reveal a higher-order, general liability factor, often referred to as *p*. In samples of children, adolescents, and adults, second-order internalizing, externalizing, and thought problems factors all load on this higher-order factor (e.g., Caspi et al., 2014; Lahey, Van Hulle, Singh, Waldman, & Rathouz, 2011)[5]. Although the meaning of *p* is currently a topic of debate (e.g., Brandes, Herzhoff, Smack, & Tackett, 2019; Carver, Johnson, & Timpano, 2017), one perspective is that it represents poor top-down executive control over behavior and emotion, a *sine qua non* of psychopathology (e.g., Beauchaine & Zisner, 2017; Caspi et al., 2014). Among children and adolescents, high scores on *p* are associated with family histories of anxiety, depression, CD, substance abuse, ASPD, psychosis, and maltreatment (Laceulle, Vollebergh, & Ormel, 2015).

At present, many adult psychopathologists are gravitating away from the DSM in favor of systems that accommodate the first- (e.g., ADHD), second- (e.g., externalizing), and higher-order (*p*) dimensional latent structure of psychopathology (Kotov et al., 2017; Krueger et al., 2018; Trull & Widiger, 2013). This is consistent with RDoC Principle 2 (construct explicitly dimensional models, with attention to both normal and abnormal). With a few exceptions, however (Lahey, Krueger, Rathouz, Waldman, & Zald, 2017), child and adolescent psychopathologists have been reluctant, continuing to rely on DSM diagnoses in most published research (even when dimensional scores are reported). This is ironic given that factor-analytic, empirically derived assessment was formalized in the child psychopathology literature (see Achenbach, 1966; Achenbach, & Edelbrock, 1983). It is also problematic because it impedes scientific progress by obscuring heterotypic progression of transdiagnostic vulnerabilities to psychopathology that RDoC could help elucidate, as already discussed (see Fig. 4).

Child and adolescent clinical psychology will almost certainly benefit from prioritizing hierarchical dimensional models (e.g., Achenbach, 2009) over DSM diagnoses rather than prioritizing DSM diagnoses over hierarchical dimensional models. Among other advantages already noted, doing so will facilitate development of more integrative approaches that bridge neural and behavioral levels of analysis—a primary objective of RDoC Principal 5 (identify integrative models of neural circuitry and behavior rather than models that focus exclusively on one or the other). Such models should articulate how neural systems of approach motivation (positive valence systems), avoidance motivation (negative valence systems), and self-/emotion regulation (arousal/regulatory systems) map onto the empirically derived latent structure of psychopathology, and how they interact with one another to yield complex patterns of comorbidity (see Beauchaine & Cicchetti, 2016; Beauchaine & Zisner,

[5]New studies call into question the psychometrics of many bifactor models (Burns, Geiser, Servera, Becker, & Beauchaine, 2020; Eid, Geiser, Koch, & Heene, 2017). Nevertheless, such models are of considerable interest to psychopathologists, so we discuss them herein. Importantly, measurement issues in bifactor model-fitting do not invalidate the second-order factor structure of psychopathology (i.e., internalizing, externalizing, thought problems).

2017; Palacios-Barrios & Hanson, 2019). At present, most neuroimaging research—whether region of interest, connectivity, resting state, or connectome-based—is still focused on identifying unique neural "signatures" of DSM disorders, despite empirical evidence for a limited set of neural systems that map more directly onto internalizing liability, externalizing liability, and executive function/emotion dysregulation.

Such evidence includes extensive comparative and psychophysiological research, much of which predates RDoC, that details subcortical neural circuits implicated in appetitive responding, aversive responding, and social affliation. These neural circuits are altered both structurally and functionally by repeated and prolonged stress exposures in ways that compromise adaptive behavioral development (see Beauchaine, Neuhaus, Zalewski, Crowell, & Potapova, 2011; Lupien et al., 2009). A more recent but nevertheless large body of neuroimaging research with humans reveals functional subdivisions of the PFC that provide top-down (cortical) regulation over these subcortical neural systems (see e.g., Beauchaine & Cicchetti, 2019; Heatherton & Wagner, 2011). Consistent with themes of this paper, future research should (1) evaluate patterns of neural reactivity to carefully chosen appetitive stimuli, aversive stimuli, and emotion evocation (e.g., Bas-Hoogendam, van Steenbergen, van der Wee, & Westenberg, 2020); (2) assess correspondencies between such patterns of reactivity, empirically derived transdiagnostic vulnerability traits (impulsivity/externalizing, anxiety/internalizing, behavioral/emotion dysregulation), and connectivity between relevant cortical and subcortical brain regions (e.g., Kujawa et al., 2016; Shannon, Sauder, Beauchaine, Gatzke-Kopp, 2009); and (3) further evaluate longitudinal effects of adversity on these neural systems (e.g., Birn, Roeber, & Pollak, 2017). Application of imaging techniques including resting state connectivity and connectome-based modeling will also be more informative if focused on empirically derived vulnerability traits (e.g., Jiang et al., 2018; Tian, Wang, Xu, Hong, & Ma, 2018). Taken together, such research will yield a more fundamental understanding of adaptive human behavior than continued studies that correlate neural structure and function with DSM diagnoses.

Gravitate Toward Bayesian Models of Functional Dependencies Among RDoC Constructs

A final recommendation for future research that we have also discussed elsewhere is the need to eschew null hypothesis significance testing and statistical partialling procedures (see above) in favor of Bayesian models that accommodate complex modulating effects (functional dependencies) of core neurobehavioral systems on one another (Beauchaine & Tackett, 2020; Haines & Beauchaine, 2020). As noted above, for example, trait impulsive behaviors, which characterize all externalizing syndromes, are magnified by low trait anxiety and mollified by high trait anxiety (see Beauchaine et al., 2017; Walker et al., 1991). Main effects and ANCOVA models often miss such functional dependencies or statistically partial them from variance in outcomes, with considerable potential to oversimplify effects and distort etiology (McDonough-Caplan et al., 2018; see Fig. 2).

Hierarchical Bayesian models offer a partial solution to this problem. These models represent one of several approaches collectively referred to as model-based cognitive neuroscience, computational psychiatry, etc. (Wiecki, Poland, & Frank, 2015). Using carefully designed lab tasks, hierarchical Bayesian models can identify multiple interactive

cognitive and/or neural influences on behavior, including impulsivity, which we consider here (e.g., Sanislow, Ferrante, Pacheco, Rudorfer, & Morris, 2019; Turner et al., 2018). Although mathematical underpinnings of Bayesian modeling are beyond the scope of this paper, some description is warranted. Figure 5 depicts a nested Bayesian hierarchy in which functional behavioral outcomes (e.g., substance abuse, criminal justice contacts) are predicted by decision-making processes measured in the lab. These decision-making processes are affected by state variables such as lab stress, individual differences in trait vulnerabilities, and contextual risk factors. The particular Bayesian hierarchy chosen should be guided by theory to include traits most likely to interact with one another to affect decision-making and functional behaviors across development.

We have applied hierarchical Bayesian modeling to evaluate simultaneous, interactive effects of trait impulsivity and trait anxiety on impulsive decision-making in the lab, using delay discounting tasks (Haines et al., 2020). These tasks, which index propensities to choose smaller-sooner (SS) over larger-later (LL) rewards, are commonly used to quantify impulsivity among those with ADHD, and to evaluate neural correlates of impulsive decision-making (e.g., Peper et al., 2013; Wilson, Mitchell, Musser, Schmitt, & Nigg, 2011). In our recent work with participants at differential vulnerability to externalizing behavior, recovering substance abusers exhibited a functional dependency between trait impulsivity and trait anxiety on their decision-making (Haines et al., 2020). No such effect was observed among undergraduates (bottom panel, Fig. 5). Thus, performance on a laboratory task was associated with an important real-world functional outcome (substance abuse), and identified modulating effects of one transdiagnostic vulnerability trait (anxiety) on another (impulsivity) in affecting decision-making. If replicated, this finding may have important implications for treatment given that successful recovery requires stronger valuations of future incentives (benefits of sobriety) than immediate incentives (benefits of relapse) (see e.g., Stanger et al., 2012).

In sum, hierarchical Bayesian models, which have rarely been used in the child, adolescent, or adult psychopathology literatures, offer considerable advantages over traditional modeling approaches. Most importantly, given substantive theory and precise measurement, they can account for functional dependencies among neurobehavioral traits. This provides a long-needed alternative to traditional null hypothesis significance testing and related statistical partialling procedures, and will facilitate future research on core RDoC constructs and their interactions across levels of analysis.

CONCLUSIONS

In this paper, we considered four outdated assumptions and related problematic research strategies that impede effective RDoC-informed research. These include using behavioral syndromes as gold standards against which biological markers are validated, presupposing and searching for large main effects of single biological functions on single behavioral syndromes, expecting 1:1 correspondencies between biological functions and behaviors, and failing to specify neurobiological mechanisms of homotypic and heterotypic comorbidity and continuity. We then presented corresponding strategies for circumventing these problems. We conclude that RDoC-informed research holds much potential to advance our

understanding of psychopathology if we (1) adopt a neural-systems-first approach over a disorder-first approach to studying vulnerability traits, (2) eschew biological reductionism by integrating environmental risk mediators into our etiopathophysiological models, (3) integrate neural vulnerabilities with the hierarchical latent structure of psychopathology, and (4) when possible, replace traditional null hypothesis significance testing with computational approaches that accommodate etiological complexity among core RDoC constructs. These strategies, combined with sound developmental practices and specification of complex transactions through which different trait vulnerabilities interact with environmental risk to potentiate psychopathology, will advance our understanding of etiopathophysiology. RDoC has 10 years under its belt. We look forward to applying lessons learned during this time in the next decade of RDoC-informed research.

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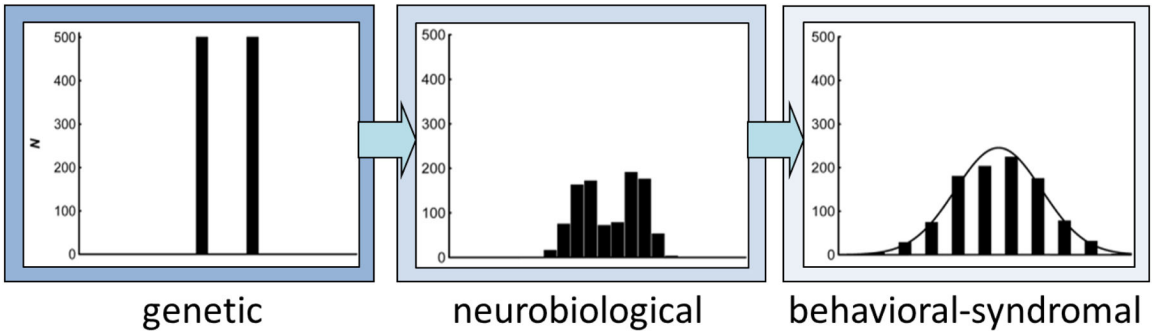

Figure 1.

Differences in measurement precision across levels of analysis spanning genes to behavior. The far left panel depicts perfect measurement precision of a dichotomously distributed allelic vulnerability expressed in equal proportions (50:50) in a sample of *N*=1,000. The middle panel depicts increased measurement error associated with many neurobiological markers of genetic vulnerability. The right panel depicts behavioral-syndromal assessment of genetic vulnerability, including an additional 50% measurement error (see text for details). Most genetic vulnerabilities to psychopathology are multifactorial and therefore far more complex than this simple illustration. Adapted with permission from Beauchaine and Constantino (2017).

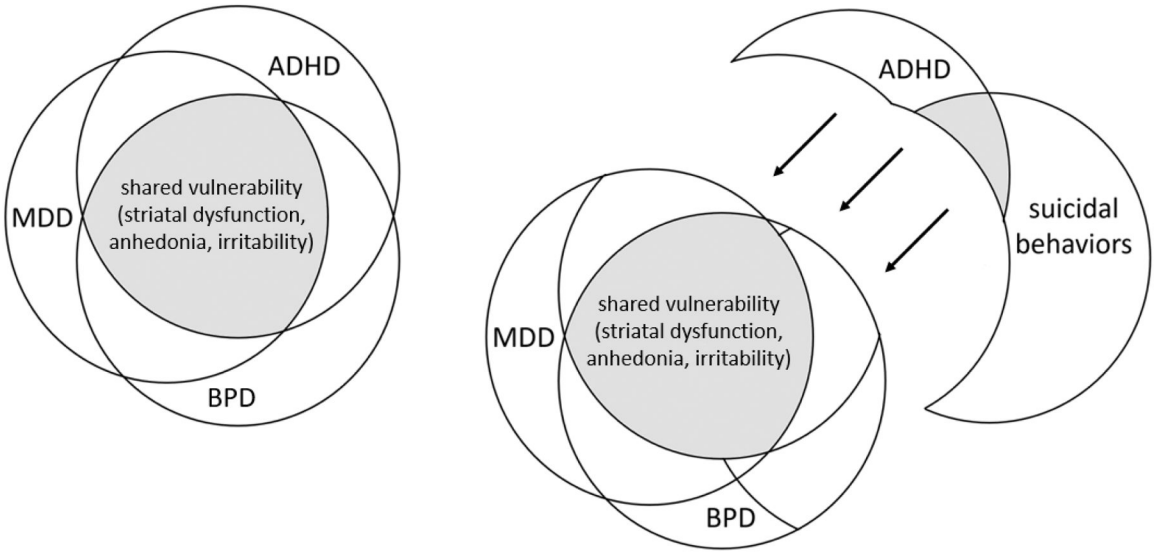

Figure 2.

Prediction to a high-risk clinical outcome (suicidal behaviors) by symptoms of attention-deficit/hyperactivity (ADHD), controlling for symptoms of major depressive disorder (MDD) and borderline personality disorder (BPD). The left panel depicts overlap in variance (concurrent comorbidity) among all three disorders, which share transdiagnostic neural, affective, and temperamental vulnerabilities (see text). The right panel depicts variance removed (i.e., partialled out) when statistically controlling for comorbid conditions. Statistical partialling, including techniques such as ANCOVA, hierarchical regression, and lag correlational designs, remove variance attributable to transdiagnostic vulnerabilities and in doing so create statistical entities that misrepresent and distort etiological relations among disorders.

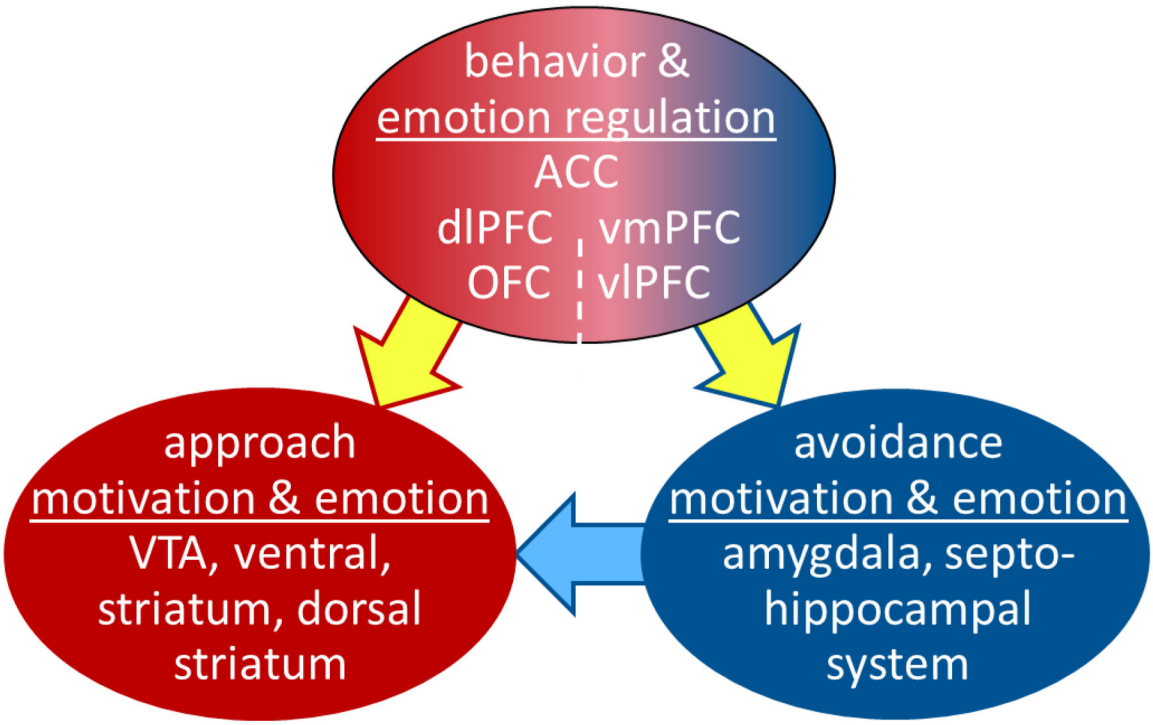

Figure 3.

Heuristic depiction of functional dependencies (modulating effects) among biobehavioral systems of approach, avoidance, and self-regulation. Arrows indicate suppressive effects of neural systems on one another. Following from the example in text, impulsive behaviors can arise from excessive approach motivation, deficient avoidance motivation, deficient self-regulation, or any combinations thereof. As a result, 1:1 correspondencies between neural functions and behavior are unlikely, and inferring neural sources of impulsivity based on behavioral symptoms alone is impossible. ACC=anterior cingulate cortex; dlPFC=dorsolateral prefrontal cortex; OFC=orbitofrontal cortex; vlPFC=ventrolateral PFC; vmPFC=ventromedial PFC; VTA=ventral tegmental area. Some important neural structures are omitted for the sake of simplicity.

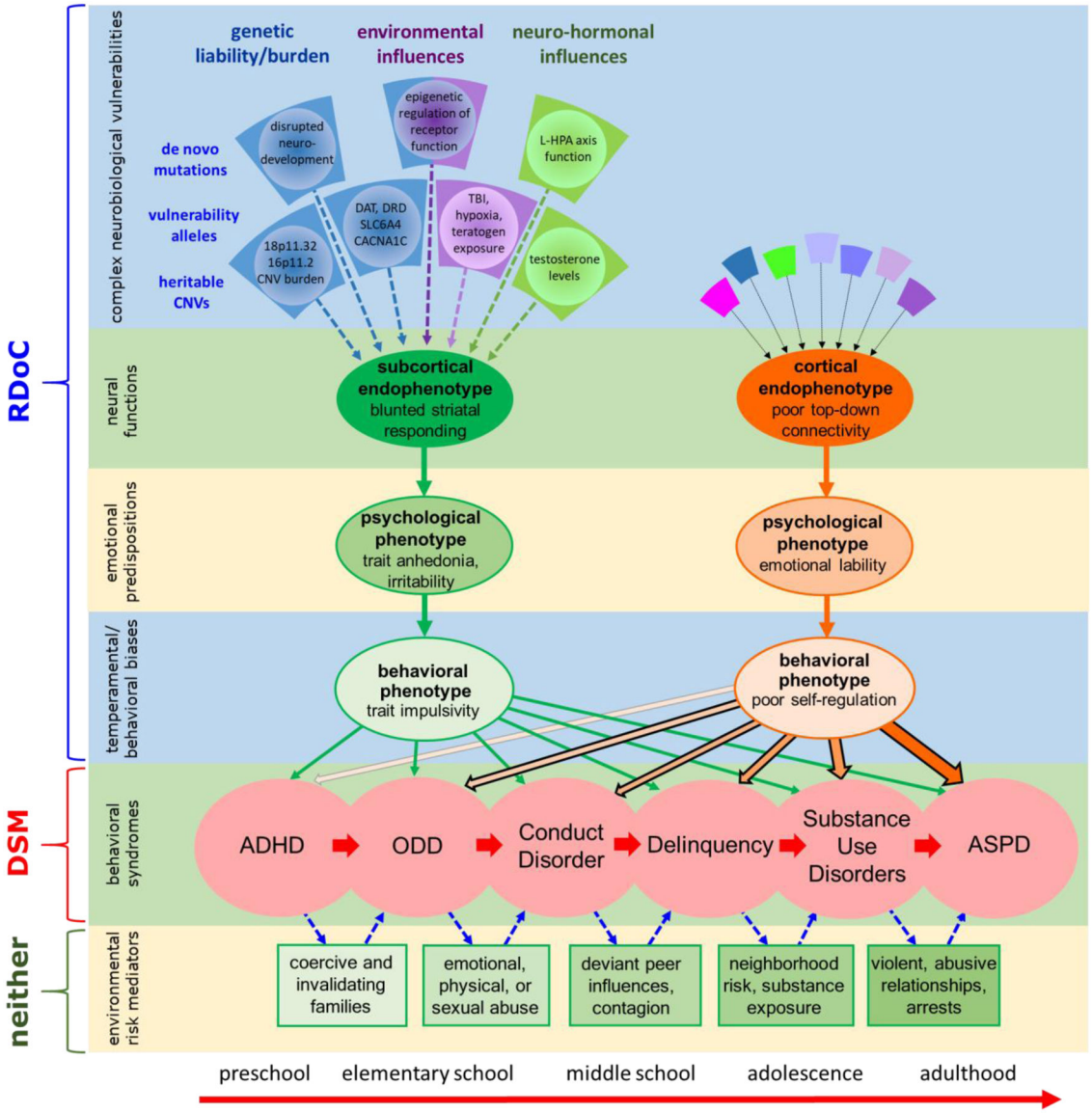

Figure 4.

A neurodevelopmental model of externalizing progression for males. Complex neurobiological vulnerabilities (e.g., multifactorial genetic load, neural functions, neurohormone regulation, epigenetic influences) affect both subcortical (e.g., striatal responding to incentives) and cortical (e.g., top-down regulation of behavior and emotion) neural functions. Blunted amygdalar responding to threat is omitted to simplify presentation, but is an important contributor to externalizing behavior (see text). These neural functions interact with one another to imbue emotional predispositions and temperamental biases, which in turn confer vulnerability to or protection from psychopathology in contexts of environmental risk across development (bottom panel). Whereas RDoC focuses on temperamental, emotional, neural, and neurobiological levels of analysis, the DSM focuses exclusively on behavioral syndromes, which are considered discrete. These diagnostic categories, which in practice overlap considerably, obscure heterotypic progression of

externalizing behavior (red arrows). In contrast, no RDoC principle precludes integrating development into models of psychopathology. Note, for example, increasing influence of poor top-down cortical (frontal) function and associated deficits in self-regulation (widening orange arrows) on progression of externalizing behavior from preschool to adulthood (see Beauchaine & Cicchetti, 2019; Beauchaine et al., 2017; Casey, Oliveri, & Insel, 2014). Greater understanding of etiopathophysiology is facilitated by focusing on traits (e.g., impulsivity, self-regulation) and their neurodevelopment rather than by focusing on diagnostic categories, because many traits transcend diagnoses (Skuse, 2001). Neither RDoC nor the DSM integrate environmental influences on neurobiological functions or behavior (see text). Adapted with permission from Beauchaine and Constantino (2017).

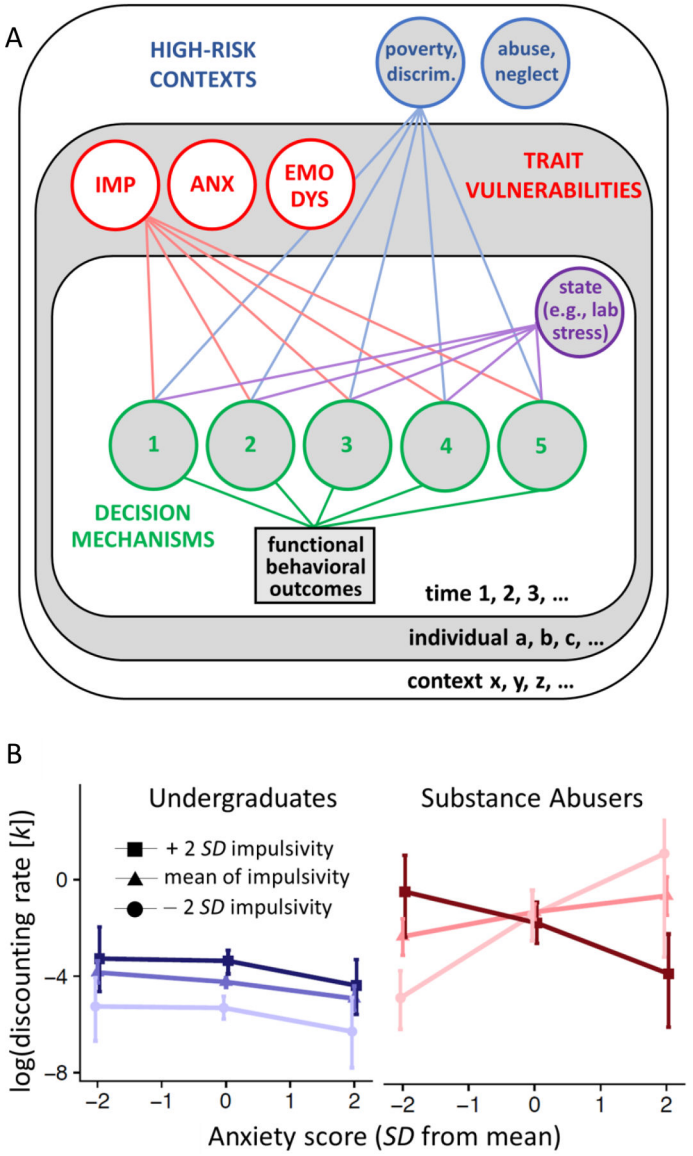

Figure 5.

(**A**) Heuristic depiction of hierarchical Bayesian modeling of functionally dependent influences among multiple trait vulnerabilities (IMP=trait impulsivity, ANX=trait anxiety, EMO DYS=emotion dysregulation) on laboratory task performance (decision mechanisms), which in turn predicts behavioral outcomes. Bayesian models can accommodate high-risk contexts (poverty, discrimination, abuse, neglect) and immediate situational factors (lab stress) into the hierarchy provided they are measured. IMP, ANX, and EMO DYS map onto RDoC constructs of + valence, – valence, and arousal/regulation, respectively, and onto parallel structural dimensions of psychopathology (externalizing, internalizing, general liability [*p*]). All effects flow from top to bottom (arrow heads and effects of abuse, neglect, anxiety, and emotion dysregulation are omitted to simplify presentation (for details see Haines & Beauchaine, 2020). (**B**) Functional dependency between impulsivity and anxiety in predicting choices on a standard delay discounting task (shorter-sooner vs. larger-later

rewards) among undergraduates vs. recovering substance abusers. In addition to a main effect of group (higher discounting rates among substance abusers), an interaction appears whereby discounting rates are highest among substance abusing participants who score high on impulsivity *and* low on anxiety. Most traditional modeling approaches would miss this modulating effect of anxiety on impulsive decision-making. Adapted with permission from Haines et al. (2020).