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Heart rate variability as a transdiagnostic biomarker of psychopathology☆

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ABSTRACT

The Research Domain Criteria (RDoC), developed by the National Institute of Mental Health as a neuroscience-informed alternative to traditional psychiatric nosology, is an explicitly *dimensional* system in which classification of psychopathology is derived *inductively* (i.e., from basic science), across *multiple levels of analysis* (e.g., genetic, neural, psychophysiological, and behavioral). Although RDoC is often presented as paradigmatically revolutionary, a review of the history of psychophysiology suggests that roots of RDoC thinking extend at least as far back as the mid-20th Century. In this paper, we briefly and selectively review the historical emergence of neurobiologically-informed dimensional trait models of psychopathology, and we summarize our thinking regarding high frequency heart rate variability (HF-HRV) as a transdiagnostic biomarker of self-regulation and cognitive control. When functional interactions between HF-HRV and systems of behavioral approach and avoidance are considered, diverse patterns of behavioral maladjustment can be subsumed into a single model. This model accommodates the general bifactor structure of psychopathology, and suggests that HF-HRV can be viewed as an autonomic, transdiagnostic biomarker of mental illness.

1. Introduction

The Research Domain Criteria (RDoC) is an explicitly dimensional system in which classification of psychopathology is derived inductively, across multiple levels of analysis spanning genes to behavior. Fundamental objectives of RDoC are to (1) identify core biological systems that are disrupted in different forms of psychopathology, (2) determine how distinct biological systems interact to confer vulnerability to psychopathology, and (3), identify single biological systems that confer transdiagnostic vulnerability to psychopathology. Although RDoC is often presented as paradigmatically revolutionary, a review of the history of psychophysiology suggests that roots of RDoC thinking extend at least as far back as the mid-20th Century. In this paper, we briefly review the historical emergence of neurobiologically-informed dimensional trait models of psychopathology, which have deep roots in psychophysiology research, and we summarize our thinking regarding high frequency heart rate variability (HF-HRV) as a transdiagnostic biomarker of self-regulation and cognitive control. When functional interactions between HF-HRV and systems of behavioral approach and avoidance are considered, diverse patterns of behavioral maladjustment can be subsumed into a single model. This model is fully consistent with the bifactor structure of psychopathology that has emerged from the behavioral genetics literature. In sections to follow, we (1) describe links between HF-HRV and psychopathology, (2) discuss the importance of transdiagnostic vulnerabilities to psychopathology, (3) define subcortical neural circuits that give rise to behavioral approach and avoidance tendencies, (4) consider how these subcortical circuits interact with cortical networks to confer vulnerability to psychopathology, and (5) present a model that integrates biological vulnerabilities with bifactor models of psychopathology.

2. HF-HRV and psychopathology

It has now been about two decades since the first studies emerged in which links between resting HF-HRV and psychological functions—including expression of psychopathology—were described. In general, these early studies, and many that followed, demonstrated that tonic HF-HRV correlates with various positive psychological adjustment outcomes among children, adolescents, and adults, including empathic responding to others who are in distress (Fabes et al., 1993; Liew et al., 2011), social competence (Eisenberg et al., 2008), sustained attention abilities (Suess et al., 1994), executive function (Thayer et al., 2009), temperamental complaisance (Huffman et al., 1998), behavior regulation during social challenges (e.g., Hastings et al., 2008a, 2008b), attachment security (Diamond et al., 2012), and positive social interactions with partners (Diamond et al., 2012).

In contrast, abnormally low resting HF-HRV and large reductions in HF-HRV to assorted challenges—particularly emotion evocation—are

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associated with symptoms of both internalizing and externalizing psychopathology (see Beauchaine, 2001, 2012, 2015a, 2015b; Porges, 2007; Vasilev et al., 2009), and with a wide range of psychopathological syndromes, including anxiety (e.g., Hastings et al., 2008a, 2008b; Thayer et al., 1996; Kemp et al., 2014), phobias (e.g., Ahs et al., 2009), attention problems (see Rash and Aguirre-Camacho, 2012), autism (Neuhaus et al., 2014; Patriquin et al.; 2013), callousness (de Wied et al., 2012), conduct disorder (CD: Beauchaine et al., 2001; Beauchaine et al., 2007; depression (e.g., Rottenberg, 2007; Rottenberg et al., 2002, 2005),[1] non-suicidal self-injury (Crowell et al., 2005), panic disorder (e.g., Asmundson and Stein, 1994), trait hostility (Sloan et al., 1994), psychopathy (Hansen et al., 2007), and schizophrenia (Clamor et al., in press), among others. Furthermore, comorbid internalizing and externalizing symptoms predict greater reductions in HF-HRV during emotion evocation than either internalizing or externalizing symptoms alone (Calkins et al., 2007; Pang and Beauchaine, 2013). This impressively long list suggests that low resting HF-HRV and excessive HF-HRV reactivity to emotional challenge mark one or more core self-regulatory functions that are disrupted across diverse forms of psychopathology (see Beauchaine, 2001, 2015a, 2015b).[2] Understanding the neural bases of HF-HRV, and determining whether neural systems that give rise to the phenomenon exhibit plasticity, may therefore have important implications for treatment, and are consequently core questions in both our research labs as we seek to alter trajectories toward adverse mental health outcomes among vulnerable individuals (see Thayer et al., 2009; Beauchaine, 2015a, 2015b; Beauchaine et al., 2013a, 2013b; Zisner and Beauchaine, in press; Smith et al., 2014).

Below we describe HF-HRV as a transdiagnostic biomarker of self-regulation, and we present a model of vulnerability to psychopathology in which individual differences in approach motivation and avoidance motivation—which derive from subcortical neural circuits—interact with effortful self-regulation—which derives from cortical neural circuits—to affect behavior. Our model integrates traditional dimensional trait conceptualizations of psychopathology, which have been influential historically in the psychophysiology literature, with more recent bifactor models of psychopathology, and suggests that HF-HRV is a peripheral index of psychopathology that is partly heritable and partly socialized, and is associated with global impairment and cognitive dysfunction. In building our model, we first discuss the role of biomarkers in psychopathology research. This discussion is essential given the common misconception that biomarkers must be specific to particular diagnoses to be useful.

3. Pathognomonic signs in psychopathology research

As our first three paragraphs make clear, low tonic HF-HRV and excessive phasic HF-HRV are broad indicators of behavior and emotion dysregulation, and are not specific to any particular disorder or class of disorder. Altered HF-HRV also marks several adverse health outcomes, including cardiovascular disease (e.g., Thayer and Lane, 2007) and diabetes (e.g., Masi et al., 2007) and is more strongly related to self-rated health than a host of other common biomarkers (Jarczok et al., 2015). Historically, very little value has been placed on non-specific biomarkers in psychopathology research. This situation was bemoaned nearly 30 years ago when it was noted that 5-HT disturbances, while non-specific from a nosological perspective, were much more specific from functional and dimensional perspectives (van Pragg et al., 1987). Nevertheless, psychiatry has long venerated *pathognomonic signs* of mental illness, which when present, indicate without a doubt that a person has a specific disorder. The high value placed on pathognomonic signs follows from at least three considerations. The first is psychiatry's adoption of the so-called "medical model" of mental illness, in which discrete psychiatric syndromes, as currently defined, are assumed to arise from independent etiological agents (for further discussion see Beauchaine and Marsh, 2006; Beauchaine et al., 2013a, 2013b; van Praag, 2000, 2004). In medicine, pathognomonic signs, often in the form of laboratory tests, are fundamental to effective diagnosis and treatment. For example, malaria parasite antigens in the blood confirm beyond a doubt that a patient is either currently infected or suffered from a past infection. No other disease entity and no other etiology is possible. Once antigens are identified, antimalarial therapy can be administered to prevent primary or relapse infections. For many years, psychopathologists hoped that pathognomonic signs would also be discovered for psychiatric disorders, but this has proven exceedingly difficult. Psychiatric syndromes that appear at the behavioral level of analysis to be single disorders (e.g., major depression) may be arrived at through multiple etiological pathways (e.g., reduced hedonic capacity, genetic glucocorticoid vulnerability, and ordinary and temporary reactions to adverse life events), a concept termed *equifinality* in the developmental psychopathology literature (Cicchetti and Rogosch, 1996). Thus, hypothalamic pituitary adrenal (HPA) axis dysfunction plays an etiological role in only some depressions, so not everyone who is depressed exhibits abnormal cortisol responses to laboratory challenges (see below; Beauchaine et al., 2015; Beauchaine and Marsh, 2006). Cortisol reactivity is therefore not a pathognomonic sign of *DSM*-defined depression, as was once hoped, and therefore cannot be used for diagnostic purposes.

Second, and relatedly, geneticists have long sought to identify *endophenotypes*, defined as inchoate behavioral signs, neurological indicators, or laboratory markers of genetic vulnerability to psychiatric disorders. Endophenotypes lie along the pathway from genetic vulnerability to disease state. By definition, they are specific to genetic vulnerability (see Gottesman and Gould, 2003; Gould and Gottesman, 2006), even when such vulnerability is not yet, and may never be, manifested in disorder.[3] For example, those who are vulnerable to developing schizophrenia, a highly heritable disorder with clear genetic substrates (see e.g., Allen et al., 2008), exhibit incipient signs, some of which qualify as endophenotypes, including flat affect (e.g., A.R. Tyrka et al., 1995; A. Tyrka et al., 1995); unusual sensory experiences such as perceptual aberration, magical ideation, and referential thinking (e.g, Lenzenweger, 1999; Lenzenweger and Korfine, 1992); specific patterns of responses on objective psychological tests (e.g., Golden and Meehl, 1979); compromised neuromotor performance (e.g., Erlenmeyer-Kimling et al., 1989); and eye-tracking dysfunction (e.g., Levy et al., 2010). In principle, using endophenotypes to identify genetic vulnerability *before* the emergence of psychopathology has major implications for primary prevention,

[1] Although some findings suggest that attenuated HRV among depressed adults results from antidepressant medication (e.g., O'Regan et al., 2015; Kemp et al., 2014), unmediated, physically healthy patients with major depressive disorder also show reductions in HF-HRV (e.g., Kemp et al., 2012).

[2] As we have noted elsewhere (e.g., Beauchaine, 2015a, 2015b; Zisner and Beauchaine, in press), reduced tonic respiratory sinus arrhythmia (RSA), an index of HF-HRV, is almost always observed among samples with *clinical levels* of psychopathology. Similarly, excessive RSA withdrawal is almost always observed among clinical samples when emotion evocation tasks are used. In contrast, in normative and high risk samples, ordinary variation in symptoms sometimes correlates with greater tonic RSA, less RSA withdrawal during assorted lab tasks, or no RSA withdrawal, especially when stimulus conditions are attention demanding rather than emotionally evocative (e.g., Dietrich et al., 2007; Graziano and Derefinko, 2013; Obradović et al., 2010). Although it is beyond the scope of this paper to address findings from non-clinical samples, it is important to note that (1) ordinary (i.e., non-extreme) variation in what we think of as psychiatric symptoms may mark non-psychiatric constructs such as behavioral inhibition, shyness, temperamental exuberance, and adaptive engagement with the environment rather than psychopathology (e.g., Degnan et al., 2011), and (2) alternative biology–behavior relations often exist at the extremes of a distribution vs. the mean (e.g., Plichta and Scheres, 2014).

[3] Some authors use the terms endophenotype and *intermediate phenotype* (Meyer-Lindenberg and Weinberger, 2006) interchangeably. Others, however, argue that intermediate phenotypes are often defined with less precision, and need not be tied directly to genetic vulnerability (Lenzenweger, 2013). Our intent here is not resolve such debates. We use the term endophenotype given its longer representation in the literature (Gottesman and Shields, 1972), and very well defined conceptual and operational criteria (see Beauchaine, 2009; Gould and Gottesman, 2006).

since those at highest risk of developing a disorder can be assigned to treatment (see Beauchaine, 2009; Beauchaine et al., 2008). However, the search for specific endophenotypes of *DSM*-defined syndromes has also proven elusive.[4] As in the case of pathognomonic signs, this is due in part to genetic and neurobiological heterogeneity (equifinality) in almost all major classes of psychiatric disorder (see Beauchaine and Marsh, 2006). Importantly, the endophenotype concept was conceptualized when single-gene models of schizophrenia predominated (e.g., Gottesman and Shields, 1972; Meehl, 1962), yet it is now clear that schizophrenia and most other psychiatric disorders follow multifactorial inheritance patterns, and are therefore influenced by many genes, including both common polymorphisms and rare structural variants (e.g., Allen et al., 2008; Walsh et al., 2008). This makes it far more difficult to identify endophenotypic markers of genetic risk for single disorders, and suggests that it may be useful to (1) search for biomarkers of *quantitative* (i.e., additive) genetic liability burden, and (2) identify susceptibility genes that confer pleiotropic effects across multiple endophenotypes (e.g., Greenwood et al., 2012; Kendler and Neale, 2010).

The third reason that pathognomonic signs have been valued so highly in psychopathology research is that traditionally-defined psychiatric syndromes, such as major depression, schizophrenia, attention-deficit/hyperactivity disorder, etc., are often still assumed to be single disorders with discrete etiologies. This dates back to the beginning of psychiatric nosology when Kraepelin first distinguished manic-depression (bipolar disorder) from what is now known as schizophrenia (see van Praag, 2008 for a historical perspective on psychiatric diagnosis and its shortcomings). However, overwhelming evidence indicates that (1) disorders that have traditionally been defined as distinct, including schizophrenia and bipolar disorder, share common genetic vulnerability (e.g., Lichtenstein et al., 2009; Owen et al., 2007), and (2) traditionally single disorders, such as major depression, are etiologically heterogeneous (see above; Beauchaine and Marsh, 2006). Both of these observations challenge the validity of our current diagnostic system,[5] yet in the history of psychiatry, *DSM*-defined syndromes have been used as gold standards against which biomarkers and putative endophenotypes are evaluated and at times eschewed (van Pragg et al., 1987; van Praag, 2008). For example, the dexamethasone suppression test (DST), which assesses the integrity of HPA axis negative feedback, was once considered a promising biomarker of depression. However, given moderate sensitivity and specificity vis-à-vis the behavioral syndrome, the DST was largely abandoned (Casat and Powell, 1988; Lu et al., 1988). Importantly, however, follow-up studies revealed that depressed patients who exhibit dexamethasone nonsupression are at nearly 10 times the risk of eventual suicide compared with depressed patients who exhibit normal DST results (Coryell and Schlesser, 2001). Thus, abnormal HPA reactivity to the DST marks a more pernicious form of depression, and predicts a critically important clinical outcome. However, rather than entertain the possibility that *behavioral* symptoms lack specificity in identifying distinct *biological* subtypes of depression, use of the DST was abandoned, and an opportunity to refine our diagnostic system by using a relevant biomarker was lost. To this day, psychiatry resists the use of biomarkers in all forms for diagnosis, and every category in the DSM is defined behaviorally—even when carefully chosen biomarkers and endophenotypes would capture genetically and etiologically homogenous subgroups who might benefit from alternative forms of treatment (see e.g., Beauchaine, 2003; Beauchaine et al., 2008; van Pragg et al., 1987; van Praag, 2008; van Praag, 2010).

[4] Although various claims of endophenotypes exist in the literature, close scrutiny reveals that many do not meet specificity requirements, and are therefore better conceptualized as biomarkers. For further discussion of this distinction, see Beauchaine (2009).

[5] Here it is important to distinguish between diagnostic validity (does a disorder, as currently defined, capture a single disease entity) vs. diagnostic reliability (can two observers agree on a single diagnosis). Although reliability of most major *DSM*-defined disorders is adequate to good when structured interviews are used, far less attention has been paid to issues of validity (see Beauchaine et al., 2013a, 2013b).

4. Dimensional trait approaches in psychopathology research

In contrast to categorical approaches to diagnosis, dimensional trait models of psychopathology assume that a very limited number of individual differences interact with one another to affect behavior, and that psychopathology is experienced by those who fall at the extreme end of one or more of these dimensions. Within psychiatry, the strongest proponent of a dimensional—or what he prefers to call functional approach—is van Praag (van Pragg et al., 1987; van Praag, 2000, 2008, 2010). Over nearly thirty years, van Praag has championed the dimensional approach to psychopathology within psychiatry, especially biological psychiatry, with unfortunately little impact on psychiatric diagnosis. For example, his work demonstrates that 5-HT disturbance cuts across nosological categories and that appropriate pharmacotherapy would be better served by attempts to redress these disturbances without regard to nosological categories (van Pragg et al., 1987; van Praag, 2010). Consistent with the RDoc perspective, van Praag has argued that "The search for biological determinants of psychological dysfunctions has indeed been proven to be much more fruitful than the search for the biological cause of a particular nosological entity…" (van Praag, 2010, p. 439).

Within psychology, perhaps the earliest dimensional model of psychopathology stemmed from Eysenck's (1947) two dimensional theory of personality. According to Eysenck, the interaction of two personality traits—extraversion (low to high) and neuroticism (low to high)—affected tendencies toward pessimism, depression, and impulsivity, among many other individual differences. Importantly, Eysenck and other proponents of trait approaches to personality and psychopathology constructed their models *inductively*, using factor analysis and animal models to generate hypotheses, collect data, and offer conclusions about individual differences and their biological substrates. This contrasts with prevailing psychiatric diagnostic systems, in which many disorders are derived *deductively*, through consensus of experts regarding proper categories of psychopathology, often with limited consideration of underlying neurobiology (see Beauchaine et al., 2013a, 2013b; van Praag, 2008, 2010).[6]

Dimensional trait theories have long been used by psychophysiologists to describe personality–physiology and psychopathology–physiology relations. The most notable among these is probably Gray's (1982a, 1982b, 1987a, 1987b) motivational theory (see also Gray and McNaughton, 2000). Gray, a student of Eysenck, proposed three interdependent dimensions of behavior, two of which (behavioral activation and behavioral inhibition) are described by a 30° factor-analytic rotation of Eysenck's original extraversion and neuroticism dimensions (see Matthews and Gilliland, 1999). Importantly, Gray and his colleagues outlined specific evolutionary functions and neural substrates of these individual differences, in extensive detail. According to Gray, the behavioral activation system (BAS); (1) subserves appetitive motivational functions by facilitating both approach toward reward cues and active avoidance of punishment cues; (2) is mediated by the mesolimbic dopamine (DA) pathway, including the ventral tegmental area, the nucleus accumbens, and the ventral striatum; and (3) when activated induces either pleasure during approach or relief during active avoidance. In contrast, the behavioral inhibition system (BIS); (1) subserves aversive motivational functions by facilitating passive avoidance of threat; (2) is mediated by the septo-hippocampal system, including serotonergic projections of the raphe nuclei and noradrenergic projections of the locus ceruleus; and (3) when activated induces anxiety.

[6] Although slow change has been observed in moving the DSM toward a more inductive approach to defining psychiatric syndromes since publication of the Feigner Criteria (Feigner et al., 1972), many disorders are still derived deductively, or by some combination of induction and deduction. Readers who are interested in learning more about the history of the DSM are referred to Beauchaine et al. (2013b).

Theories such as Gray's were an extremely important development in psychopathology research because they enabled psychophysiologists to describe functional relations between core neurobiological systems and individual differences in behavior, including adjustment problems among children, adolescents, and adults. In a highly cited review, Fowles (1980) used Gray's theory to link heart rate reactivity to behavioral activation, and electrodermal reactivity to behavioral inhibition. He then presented evidence that primary psychopaths exhibit normal heart rate reactivity, but low electrodermal responding (EDR), reflecting a core deficiency in septo-hippocampal function. According to this formulation, the approach system of psychopaths is intact, so they obtain normal hedonic value from rewards, but their avoidance system is under-responsive, resulting in deficient anxiety in the face of punishment and extinction cues. Primary psychopaths therefore do not experience punishment as aversive, and take "risks" in approaching stimuli when both reward and punishment outcomes are possible.

4.1. Psychopathology in two-dimensional motivational space

Fowles' (1980) paper suggested that the pathophysiology of primary psychopathy could be understood in terms of dysfunction in one of Gray's (1982a, 1982b, 1987a, 1987b) neurobiological systems of motivation—the septo-hippocampally-mediated BIS. In his 1987 Presidential Address to the Society for Psychophysiological Research, Fowles (1988) extended his theory of psychophysiology–psychopathology relations by considering the *interactive* roles of behavioral activation, behavioral inhibition, and environment on vulnerability to broad classes of psychopathology, including anxiety, depression, psychosis, and externalizing behaviors. Fowles noted that even with only two motivational systems (approach and avoidance), each trichotomized as weak, average, or strong, and two environmental input variables (stimulation and regulation), each trichotomized as present, absent–constantly activated, absent–constantly inactive, a $2 \times 3 \times 3 \times 3$ matrix resulted, and certain forms of psychopathology—at least in theory—were represented in the 54 cells. Fowles emphasized that his depiction was a vast oversimplification, and that (1) in reality, motivational and environmental inputs are continuous, (2) effects of motivation and environment on behavior are not independent, and (3) cognitive factors must also be considered.

It is difficult to overstate the importance of Fowles' 1987 Presidential Address for the emergence of neurobiologically-founded, dimensional trait models of psychopathology that accommodate interactive effects of motivation, environment, and cognition on psychological adjustment. When placed in this context, one can readily see that Research Domain Criteria (RDoC) thinking extends considerably farther back into the history of psychophysiology than is often acknowledged. Indeed, work by Eysenck, Gray, Fowles, and many psychophysiologists who followed in their footsteps laid a rich foundation for the RDoC agenda. Fowles' (1980, 1988) papers in particular created an upsurge of interest in psychopathology research among psychophysiologists, who used his extension of Gray's model to (1) generate and test hypotheses about psychophysiology–behavior relations among children with ADHD and oppositional defiant disorder (ODD; Crowell et al., 2006; Iaboni et al., 1997), adolescents with CD and psychopathic traits (e.g., Beauchaine et al., 2001; Fung et al., 2005), adults with psychopathy (e.g., Arnett and Newman, 2000), and individuals with schizophrenia (e.g., Fowles, 1992); (2) test psychopharmacology–physiology relations during anxiety-provoking tasks (e.g., Landon et al., 1993); and (3) formulate revised theoretical perspectives on the biological bases of both internalizing (e.g., Shankman et al., 2007) and externalizing behavior (e.g., Beauchaine et al., 2007; Quay, 1993). Fowles' formulation continues to inform work by psychophysiologists who use electroencephalography (EEG) and functional magnetic neuroimaging (fMRI) to probe central nervous system reward processing in both internalizing (e.g., Foti and Hajcak, 2009) and externalizing (e.g., Gatzke-Kopp et al., 2009) disorders. This work is central to the RDoC mission.

4.2. Psychopathology in two-dimensional factorial space

In a largely independent methodological tradition, researchers have sought to advance our understanding of psychopathology by factor analyzing symptoms in large population-based samples and twin registries. Krueger (1999), for example, factor analyzed *DSM-III-R* (American Psychiatric Association, 1987) symptoms of a range of mental disorders among participants in the National Comorbidity Survey ($N = 8098$). Across split-half, male only, female only, and treatment-seeking subsamples, two higher-order factors emerged. Consistent with models that existed for some time in the child psychopathology literature (e.g., Achenbach and Edelbrock, 1991), Krueger labelled these factors internalizing and externalizing. The internalizing factor, which could be further divided into two lower-order factors (anxious misery and fear) in the split-half and male/female only subsamples (see Fig. 1), included major depression, dysthymia, generalized anxiety, panic disorder, and phobias. In contrast, the externalizing factor included alcohol dependence, drug dependence, and antisocial personality disorder. Factor analytic work conducted since Krueger's initial study provides strong support for his original findings (e.g., Krueger et al., 2002, 2007), and extends the externalizing factor to include hyperactivity/impulsivity (measured both directly among children and via low constraint among adults), ODD, and CD (e.g., Lahey et al., 2011; Tuvblad et al., 2009). More recent work indicates that, consistent with Eysenck and Eysenck's (1976) and Fowles' (1988) perspectives, thought disorder emerges as a separate higher-order factor when psychotic symptoms are modelled (e.g., Wright et al., 2013), a point we return to below.[7]

Although recent factor analytic models have generally not been informed by neurobiological accounts of psychopathology, some authors, including us, have noted in extensive literature reviews that externalizing spectrum disorders (including ADHD, CD, alcohol and drug dependence, and antisocial personality), of which the externalizing factor is comprised, share a core etiological substrate, a functional deficiency in incentive processing, primarily in the dopaminergically-mediated nucleus accumbens and ventral striatum—Gray's neural substrate of the BAS (see Beauchaine, 2001; Beauchaine et al., 2010; Beauchaine and McNulty, 2013). In fact, extensive neuroimaging research reveals (1) blunted mesolimbic and/or mesocortical reactivity to incentives among those with ADHD (see Bush et al., 2005; Carmona et al., 2011; Dickstein et al., 2006; Durston, 2003), CD (e.g., Rubia et al., 2009), substance use disorders (SUDs; see e.g., Martin-Soelch et al., 2001; Volkow et al., 2004), and antisocial traits (e.g., Oberlin et al., 2012); (2) reduced mesolimbic DA transporter, D2 receptor, and/or D3 receptor binding among adults with ADHD (Volkow et al., 2009) and alcoholism (e.g., Laine et al., 2001); and (3) compromised functional connectivity between mesolimbic and mesocortical structures among adolescents with ADHD and CD during incentive responding (e.g., Shannon et al., 2009).

This dopaminergic deficiency, the likely neural substrate of Krueger et al.'s (2002) highly heritable externalizing factor, gives rise to trait impulsivity, expressed very early in life as ADHD. Trait impulsivity predisposes to progressively more severe externalizing behavior as affected individuals mature, and their temperamental vulnerability interacts with environmental adversities including family coercion, deviant peer group affiliations, neighborhood criminality, alcohol and drug use, and incarceration experiences. Such neurobiological vulnerability × environmental risk interactions may explain the well characterized, heterotypically continuous pathway from ADHD → ODD → CD → SUDs → ASPD, which impulsive individuals often traverse across development (see Beauchaine et al., 2008, 2010). Thus, both factor analytic and recently articulated

[7] In his later work, Eysenck included a psychoticism dimension in his model of personality (Eysenck and Eysenck, 1976), foreshadowing findings from more recent factor analytic studies.

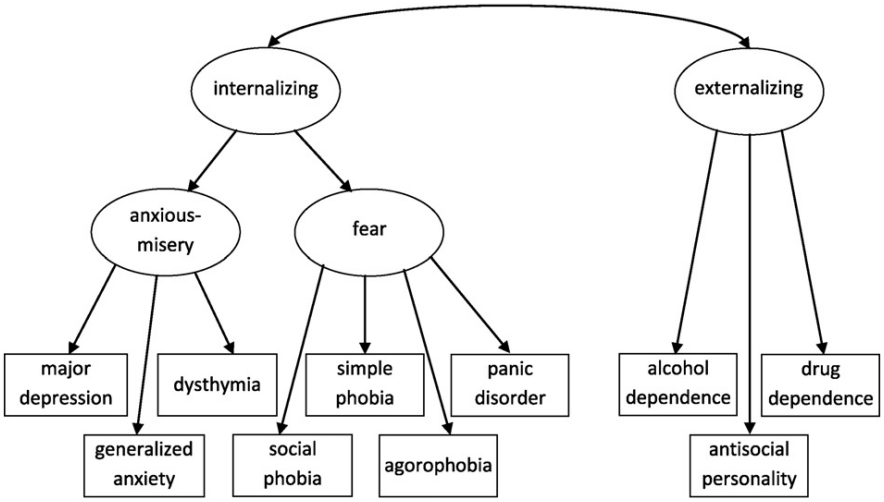

Fig. 1. The general latent structure of psychopathology.
Adapted from Krueger (1999).

ontogenic process models of externalizing psychopathology call into question the notion that the externalizing spectrum marks disorders with discrete etiologies (Beauchaine and McNulty, 2013; Krueger et al., 2002). Rather, central DA dysfunction gives rise to trait impulsivity, which predisposes to a range of externalizing behaviors, the specific nature of which depends heavily on exposure to environmental risk and adversity.

It is important to note that individual differences in central DA expression correlate with trait positive affectivity, and that infusions of DA into mesolimbic structures produce pleasurable hedonic states (Ashby et al., 1999; Berridge, 2003; Berridge and Robinson, 2003; Forbes and Dahl, 2005; Forbes et al., 2009). In contrast, low levels of striatal DA correlate with trait irritability (Laakso et al., 2003). Children, adolescents, and adults with externalizing disorders including ADHD, ODD, and CD score high on measures of trait irritability and negative affectivity (e.g., Asherson, 2005, Martel and Nigg, 2006). Together, these findings provide support for deficient mesolimbic DA function in the pathophysiology of externalizing behaviors (see also Gatzke-Kopp and Beauchaine, 2007), and suggest that excessive behavioral approach tendencies of those who fall on the externalizing spectrum arise from under-responsive central DA systems rather than over-responsive central DA systems, as was once supposed (see e.g., Quay, 1993). Low tonic mesolimbic DA function is experienced as an aversive, irritable mood state (Laakso et al., 2003), which affected individuals attempt to escape through reward-seeking and novelty-seeking behaviors. Such behaviors function to elevate mood through phasic activation of mesolimbic DA neurons. Unfortunately, any associated hedonic value is transient, leading to searches for even larger rewards (see Beauchaine et al., 2007; Gatzke-Kopp, 2011; Gatzke-Kopp and Beauchaine, 2007; Sagvolden et al., 2005). Those with deficient mesolimbic DA function are therefore hyperactive, impulsive, and vulnerable to serious externalizing psychopathology, including drug abuse (see Beauchaine and McNulty, 2013). Important for the present discussion, we and others have also reported that low HF-HRV is associated with impulsivity and addictive behaviors (e.g., Williams et al., in press; Ingjaldsson et al., 2003).

As noted above, a highly heritable internalizing factor also emerges consistently from factor analytic models of psychopathology. Evidence for low HF-HRV in internalizing disorders is abundant though not universal (e.g., Pittig et al., 2013; Kemp et al., 2014; Licht et al., 2009). Notably, moderate to high correlations between the internalizing factor and externalizing factor are observed, reflecting heterotypic comorbidity (e.g., Krueger et al., 2002). Historically, internalizing–externalizing comorbidity has perplexed psychopathologists because symptoms are almost completely non-overlapping across disorders, and because etiological theories have focused on different causal mechanisms (e.g., dopaminergic theories of impulsivity vs. serotonergic and noradrenergic theories of depression). However, work conducted in the last decade suggests that (1) such main effects models are unlikely to account for spectra of psychopathology and their comorbidities, (2) internalizing and externalizing disorders share common neurobiological vulnerability (see below), and (3) multiple neurobiological vulnerabilities often interact to affect behavioral predispositions—the core theme of this article.

Importantly, mesolimbic DA dysfunction is not specific to impulsivity; it is also observed in depression, a disorder that, like externalizing conditions, is characterized by anhedonia, avolition, and irritability (see e.g., Forbes and Dahl, 2005, 2011; Forbes et al., 2009). These symptoms, which are affective consequences of low tonic and low phasic mesolimbic DA function (see above), are *transdiagnostic substrates* of both impulsivity and depression (see Sauder et al., 2012, 2015). Blunted mesolimbic responding to incentives is observed in depressed adolescents and adults (e.g., Forbes and Dahl, 2011; Forbes et al., 2006; Knutson et al., 2008; Smoski et al., 2009), and among asymptomatic daughters of depressed mothers (Sharp et al., 2014). Altered mesolimbic reward processing likely confers risk for heterotypic comorbidity through its effects on positive affectivity and hedonic capacity (Forbes and Dahl, 2005; Neuhaus and Beauchaine, 2013). As noted above, blunted striatal responding to incentives is associated with self-reports of low positive affect in naturalistic settings (Forbes et al., 2009), and low levels of striatal DA predict trait irritability (Laakso et al., 2003). Finally, internalizing × externalizing symptom interactions account for greater reductions in gray matter densities in mesolimbic brain regions than internalizing or externalizing symptoms alone (Sauder et al., 2012).

These well replicated findings of a common neural substrate for impulsivity and depression (Gray's BAS), raise obvious questions about neural systems that differentiate between internalizing and externalizing disorders. As we have described elsewhere, and as we outline above (Neuhaus and Beauchaine, 2013; Sauder et al., 2015), the most notable among these is the septo-hippocampal system (Gray's BIS), the neural substrate of trait anxiety. Sensitization of this largely independent neural network confers vulnerability to depression, but not impulsivity, when coupled with deficient mesolimbic DA function (see Neuhaus and Beauchaine, 2013). In contrast, those with externalizing spectrum disorders tend to experience low trait anxiety (see Corr

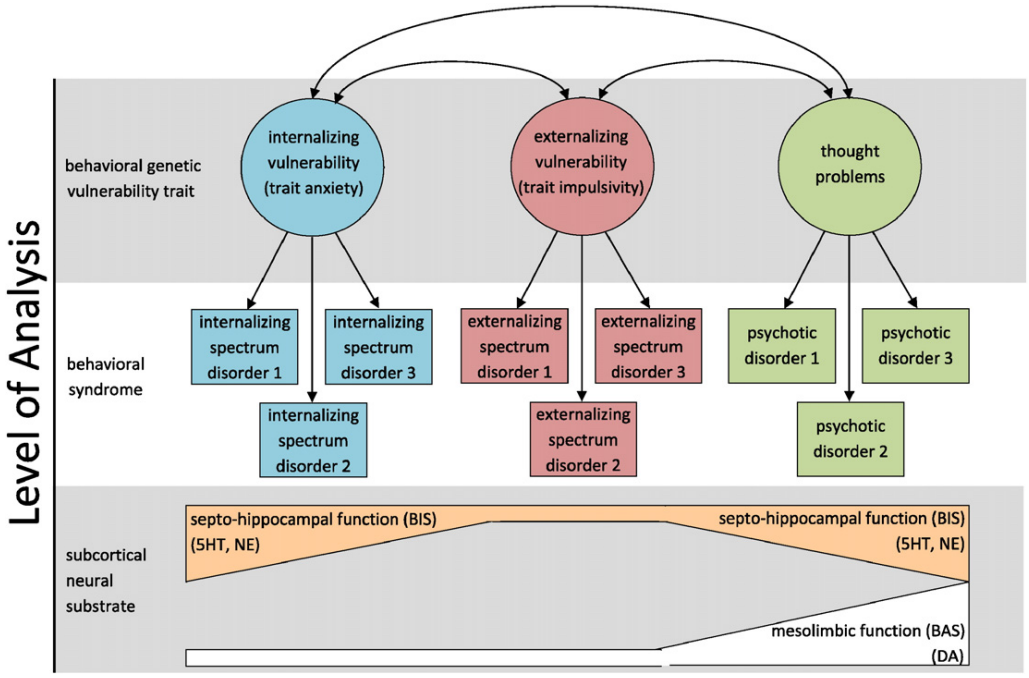

Fig. 2. A multidimensional conceptualization of psychopathology that dovetails motivational and factor-analytic models. Three levels of analysis include (top to bottom) trait vulnerabilities (trait anxiety, trait impulsivity, and thought problems), behavioral syndromes (internalizing, externalizing, and psychotic disorders), and subcortical neural substrates (relative balance of mesolimbic and septo-hippocampal function). Internalizing vulnerability is conferred by a relatively strong BIS and weak BAS. Externalizing vulnerability is conferred by a concurrently weak BIS and weak BAS. Thought disorder is conferred by a concurrently strong BIS and strong BAS. Any comprehensive model of psychopathology of course requires additional levels of analysis (e.g., genetic vulnerabilities, cognitive vulnerabilities, and cortical neural substrates).

and McNaughton, 2015).[8] Thus, at a minimum, two neurobiological systems must be considered when differentiating between impulsivity and depression given both common (mesolimbic) and separate (septo-hippocampal) vulnerabilities (see Sauder et al., 2012). According to this formulation, mesolimbic DA dysfunction and associated anhedonia, irritability, and negative affectivity confer vulnerability to sensation-seeking (i.e., externalizing behaviors) *unless coupled with septo-hippocampally-mediated trait anxiety*. Trait anxiety is therefore a resiliency factor among individuals who are vulnerable to externalizing behavior by virtue of heritable mesolimbic DA dysfunction (see Corr and McNaughton, 2015, Sauder et al., 2012; Walker et al., 1991).

4.3. Integrating motivational and factorial space

In Fig. 2 we present a heuristic model of vulnerability to psychopathology that integrates motivational and factor analytic accounts of internalizing, externalizing, and thought problem dimensions. As noted above, thought problems comprise a separate latent vulnerability in factor-analytic models when psychotic symptoms are included (e.g., Caspi et al., 2014; Wright et al., 2013). This is consistent with Eysenck and Eysenck's (1976) updated theory of personality, and Fowles' (1988) extension of Gray's (1982a, 1982b, 1987a, 1987b) motivational theory to psychopathology. Both approaches acknowledge the importance of a psychosis dimension, the neural substrates of which include excessive mesolimbic DA activity, as suggested by (1) findings of greater striatal responding to incentives in some studies of patients with psychosis (e.g., Nusslock et al., 2012), (2) increased intrinsic striatal connectivity among patients with schizophrenia during active psychotic episodes (e.g., Sorg et al., 2013), and (3) longstanding, subcortical hyperdopaminergic theories of schizophrenia (e.g., see Howes and Kapur, 2009).

Even though Fig. 2 presents a highly simplified characterization of vulnerability to psychopathology, it embodies several important advantages of the RDoC approach. First, it incorporates multiple levels of analysis, including behavioral genetic vulnerabilities (top panel), behavioral syndrome manifestations (middle panel), and subcortical neural substrates (bottom panel). The RDoC initiative was launched following recognition that few forms of psychopathology can be understood by focusing on any single level of analysis (Cicchetti, 2008; Insel et al., 2010; Sanislow et al., 2010), since multiple neurobiological systems *interact* to affect complex human behaviors (Beauchaine, 2001; Beauchaine et al., 2007). Consistent with this perspective, internalizing vulnerability is especially likely when excessive septo-hippocampal activity/reactivity is *coupled with* deficient mesolimbic activity/reactivity; externalizing vulnerability is especially likely when deficient septo-hippocampal activity/reactivity is *coupled with* deficient mesolimbic activity/reactivity; and thought problems are especially likely when excessive septo-hippocampal activity/reactivity is *coupled with* excessive mesolimbic activity/reactivity. In fact, monoamine neural systems (i.e., dopaminergic, serotonergic, and noradrenergic) that govern mood, behavior regulation, and emotion regulation function *interdependently*, so considering single systems in isolation may lead to distorted conclusions about their effects on behavior (see e.g., Beauchaine et al., 2011).

Second, heritable vulnerabilities (e.g., trait impulsivity) and their neural substrates (e.g., mesolimbic DA dysfunction) cut across behavioral syndrome spectra (e.g., externalizing disorders including ADHD, CD, and SUDs), and are not specific to any particular *DSM*-defined diagnosis (see Beauchaine and McNulty, 2013). As discussed above, this is consistent with well-replicated findings from behavioral genetics studies conducted with children, adolescents, and adults (e.g., Caspi et al., 2014; Krueger et al., 2002; Tuvblad et al., 2009; Wright et al., 2013).

[8] We re-emphasize, however, that all of the traits discussed in this article are best represented across dimensions, and that the described tendency toward lower BIS activity among externalizing individuals should not be interpreted as a complete absence of trait anxiety.

Third, heterotypic comorbidity is expected given common neural vulnerabilities across spectrum classes (e.g., externalizing and internalizing). As reviewed above, for example, ADHD and depression share a core neural substrate (deficient striatal responding to incentives), which likely gives rise to common symptoms of anhedonia, avolition, and irritability (see Sauder et al., 2012). Symptoms that differentiate between disorders arise from other neural systems (see Beauchaine and Neuhaus, 2008).

Finally, implicit in Fig. 2 is the importance of translational research in the development of integrative, multiple-levels-of-analysis models of psychopathology such as RDoC. Although Eysenck (1947) theorized that behavioral predispositions toward neuroticism and extraversion were attributable to corresponding individual differences in limbic system function, his original two-factor theory (see above) described human personality strictly at the behavioral level of analysis. Gray (1982a, 1982b, 1987a, 1987b) extended Eysenck's work by identifying specific neural substrates of approach and avoidance motivation. Gray's insights were made possible by advances in technology that facilitated extensive behavioral, single-cell recording, and pharmacological challenge studies with animals (see Gray and McNaughton, 2000). In turn, Gray's theory provided the impetus for psychophysiologists including Fowles (1980, 1988) and others (e.g., Beauchaine et al., 2001; Crowell et al., 2006; Iaboni et al., 1997) to devise paradigms to assess individual differences in approach tendencies, avoidance tendencies, and corresponding vulnerabilities to psychopathology using both peripheral and central nervous system measures (see Brenner and Beauchaine, 2011; Brenner et al., 2005; Harmon-Jones and Allen, 1997; Sutton and Davidson, 1997). Within psychiatry, van Praag has pioneered the dimensional approach based on psychopharmacological analysis as noted above (van Praag, 2008).

The model presented in Fig. 2 demonstrates that dimensional trait models of personality and psychopathology, which have been highly influential in psychophysiology, and factor analytic accounts of psychopathology, which have been highly influential in behavioral genetics, are reconcilable and mutually informative. Higher-order factors comprising trait impulsivity, trait anxiety, and thought problems map onto individual differences in the functioning of subcortical neural circuits that govern approach and avoidance behaviors. As articulated thus far, however, our model is incomplete, for three interrelated reasons. First, it does not describe why some individuals, despite expressing vulnerability to psychopathology by virtue of being trait impulsive and/or trait anxious, do not exhibit impairment (see Beauchaine, 2001). Second, neural vulnerabilities discussed thus far are restricted to subcortical circuits that retain considerable homology across rodent and mammalian species. Although a historical focus on these subcortical circuits is understandable given limitations in technology at the time Gray and others were formulating their theories, we now know much more about the human prefrontal cortex (PFC), which exerts top-down inhibitory control over subcortical circuits involved in trait impulsivity and trait anxiety (see e.g., Beauchaine, 2015a, 2015b; Beauchaine and McNulty, 2013; Goldsmith et al., 2008; Heatherton, 2011; Heatherton and Wagner, 2011). Contemporary models of psychopathology must therefore integrate subcortical and cortical vulnerabilities.

Third, there is a long history of dimensional approaches to psychopathology as revealed by factor analysis within psychology (Krueger et al., 1998; Krueger, 1999; Lahey et al., 2012; Krueger and Markon, 2011; Keyes et al., 2013; Caspi et al., 2014). These studies have consistently identified a hierarchical structure whereby the nosologically defined discrete disorders cluster into correlated higher-order factors of internalizing, externalizing, and thought disorders. These studies, consistent with RDoC, suggest underlying dimensions of biologically-based dysfunction that are better suited to help us understand the etiology, course, and treatment of psychopathology than nosological models. Dimensional models are better able to explain many problems associated with nosological diagnostic models such as co-morbidities and non-specific drug effectiveness. Moreover, their correlated hierarchical structure indicates a superordinate, general psychopathology factor. This has been most clearly articulated by Caspi et al. (2014), who demonstrated a so-called superordinate p Factor that runs in families and is associated with both functional impairment and early life brain dysfunction. In the remainder of this paper, using these dimensional models and the recent Caspi et al. (2014) p Factor as an example, we describe how and why HF-HRV provides a peripheral index of the higher order general psychopathology factor.

5. Hierarchical dimensional models of psychopathology derived from factor analysis

In an early study examining the structure and stability of common mental disorders using the Dunedin Multidisciplinary Health and Development Study ($N = 1037$), a correlated ($r = 0.45$) two-factor model derived from ten common mental disorders (but not thought disorder) was identified, with higher order internalizing and externalizing disorder factors (Krueger et al., 1998). Krueger (1999) replicated this structure using the National Comorbidity Survey sample ($N = 8098$), in which internalizing and externalizing factors correlated at .51 (see Fig. 1). A meta-analysis published in 2006 based on 23,557 participants further support this two-factor model, with internalizing and externalizing factors correlating at .50 (Krueger and Markon, 2006).

In more recent studies, a thought disorder factor has emerged that either stands alone or is subsumed into a higher order internalizing factor. For example, Keyes et al. (2013), using data from the National Epidemiologic Survey of Alcohol and Related Conditions ($N = 34,653$), identified a thought disorder factor that was subsumed with a higher order internalizing factor. Wright et al. (2013), using data from the Australian National Survey of Mental Health and Wellbeing ($N = 8841$), also found inter-correlated internalizing, externalizing, and psychotic experiences factors. Although the correlations among these factors suggest a higher-order general psychopathology factor, no such factor was modelled in these studies. Recently, Lahey et al. (2012), using longitudinal data from the National Epidemiologic Survey of Alcohol and Related Conditions ($N = 34,653$) identified a general psychopathology bifactor. Importantly, they reported that the general psychopathology bifactor accounted for significant variance in future psychopathology, daily functioning, and physical health, independent of variance accounted for by internalizing and externalizing factors.

The bifactor structure of psychopathology, described above, was replicated recently in the Dunedin Multidisciplinary Health and Development Study ($N = 1037$), by Caspi et al. (2014). Caspi et al. used confirmatory factor analysis to test multiple structural models of externalizing, internalizing, and thought disorder symptoms. Included were a correlated factors model, a single factor model, and two bifactor (hierarchical) models (one of which was inadmissible). Among adults who were assessed longitudinally at ages 18, 21, 26, 32, and 38 years, the bifactor measurement model provided a good fit. Although externalizing vulnerability, internalizing vulnerability, and thought disorder were all associated with impairment, as assessed by suicide attempts, psychiatric hospitalizations, social welfare benefit use, and violence convictions, much of this impairment was accounted for by a general vulnerability factor that Caspi et al. labelled p. As noted by the authors, "…in general, people with higher levels of p had the greatest life impairment" (Caspi et al., 2014, p. 127). Furthermore, p, similar to the bifactor model reported by Lahey et al. (2012) and depicted in Fig. 3, was associated more strongly with personal histories of child maltreatment, and with family histories of major depression, anxiety, psychosis, CD, ASPD, and substance dependence than were externalizing or internalizing factor scores. Finally, high p scores were correlated negatively with cognitive function, as assessed by IQ, measures of executive function, attention, and memory—all of which are subserved by the prefrontal cortex (PFC; Stuss and Knight, 2013). In retrospective analyses, some of these impairments were evident between ages 3 and 10 years.

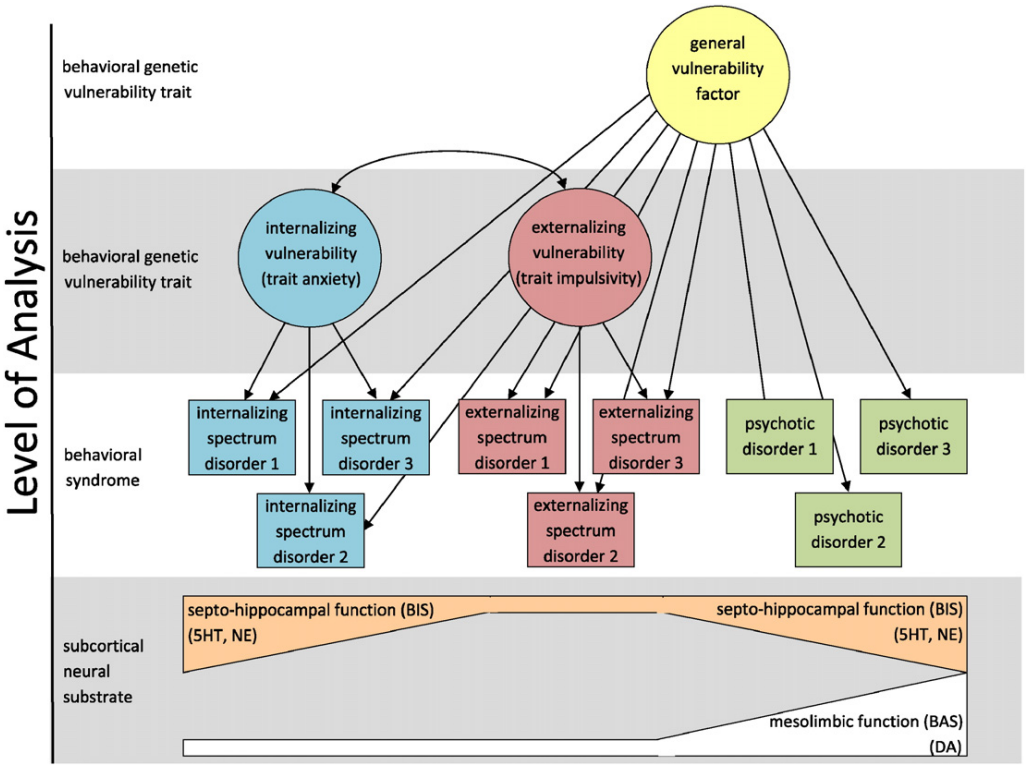

Fig. 3. The bifactor structure of psychopathology, including a superordinate general vulnerability factor (see Caspi et al., 2014; Lahey et al., 2011, 2012).

It is important to restate that low HF-HRV is associated consistently with internalizing disorders (e.g., Pittig et al., 2013; Kemp et al., 2014), externalizing disorders (e.g., Ingjaldsson et al., 2003), and thought disorders (e.g., Clamor et al., in press), independent of medication effects. Thus it is not implausible that HRV might be associated with higher-order factors of internalizing, externalizing, and thought disorders via the same mechanisms proposed to account for a general psychopathology bifactor. The most plausible of these mechanisms is via shared etiology as represented in part by genetic influences (Lahey et al., 2012) and brain integrity (Caspi et al., 2014). Both behavioral and molecular genetics studies find evidence for genetic influences on HRV, with heritability estimates in the .5 range (as reviewed in Thayer and Lane, 2009). Evidence linking HRV to brain integrity is summarized below.

A major implication of these findings is that the traits we have discussed thus far, including trait impulsivity, trait anxiety, and thought problems, are far less functionally impairing in the absence of co-occurring PFC dysfunction, including deficiencies in cognitive control and self-regulation, as represented by a general psychopathology bifactor. Without PFC dysfunction, trait impulsivity and trait anxiety are likely to confer individual differences in personality—not psychopathology—a point we have made elsewhere (Beauchaine, 2001; Beauchaine and Gatzke-Kopp, 2012; Beauchaine et al., 2007).

6. Neurovisceral integration theory, HF-HRV, and general psychopathology

We began this article by describing the wide range of psychiatric disorders and behavioral syndromes that are characterized by low resting HF-HRV and/or excessive HF-HRV reactivity to emotion evocation. Although interactions between neural systems that subserve behavioral approach and behavioral avoidance provide some specificity in differentiating among psychiatric disorders, deficient HF-HRV, like the general bifactor from factor analytic studies, is decidedly non-specific, and thus serves as a transdiagnostic biomarker of psychopathology.

According to neurovisceral integration theory (Thayer et al., 2009), HF-HRV marks general vulnerability to psychopathology because it indexes, albeit peripherally, PFC function, and therefore captures—at the psychophysiological level of analysis—the same vulnerability that the general bifactor captures. The conclusion that HF-HRV marks PFC function is based on three primary considerations, including (1) existence of inhibitory neural efferent pathways from the medial PFC to the parasympathetic nervous system (the autonomic substrate of HF-HRV); (2) positive associations between resting HF-HRV and performance on executive function tasks; and (3) positive correlations between HF-HRV and PFC activity in neuroimaging paradigms.

Inhibitory efferent pathways from the medial PFC to the parasympathetic nervous system have been known for some time (e.g., Barbas et al., 2003; Ter Horst and Postema, 1997; Wong et al., 2007). As described by Thayer et al. (2009), the prefrontal, insula, and cingulate cortices form an interconnected neural network that exhibits feed-forward and feedback connections with the amygdala. Activation of the central nucleus of the amygdala via this network provides inhibition of the nucleus solitary tract, which in turn inhibits vagal motor neurons in the dorsal motor nucleus and the nucleus ambiguus. These structures provide inhibitory input via the parasympathetic nervous system to the sinoatrial node. Through this structural network, efficient PFC function is translated into high tonic HF-HRV, and well regulated phasic HF-HRV. Because most forms of psychopathology are characterized by PFC dysfunction (e.g., Maren et al., 2013; Menon, 2011; Rubia, 2011), they are also characterized by low resting HF-HRV and excessive HF-HRV reactivity—downstream biomarkers of poor executive control (Thayer et al., 2009).

Positive associations between resting HF-HRV and performance on executive function tasks have been reported by our group. For example, Hansen et al. (2003) divided a sample of military personnel based on a median split of HRV. Those in the high HRV group outperformed those in the low HRV group on stimulus detection and addition tasks. This study was replicated and extended in a second sample (Hansen et al.,

2003). More recently, we have reported associations between HF-HRV and executive function tasks among patients with panic disorder (Hovland et al., 2012). In addition, we have recently reported associations between HF-HRV and cognitive control using the think–no think paradigm and a thought suppression paradigm (Gillie et al., 2014, in press).

Perhaps most convincingly, HRV is associated with PFC function as assessed by pharmacological blockade (Ahern et al., 2001), lesion studies (Buchanan et al., 2010), cerebral blood flow using positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) (reviewed by Thayer et al., 2012), and retinal vessel analysis (Schuster et al., 2014). Retinal vessel analysis was used by Caspi et al. (2014) as a surrogate for cerebral blood flow, to assess brain integrity. However, a more direct measure of total cerebral blood flow using pulsed arterial spin labeling, is also associated with HRV (Allen et al., 2015).

Of particular relevance to the present paper, in a series of studies we have shown that HF-HRV is related to activity in the PFC, in part via cortical–subcortical connectivity, and that this relationship is disrupted in patients with major depression (Lane et al., 2013; Smith et al., 2014, in press). Specifically, during an affective set shifting task, HF-HRV, measured in the scanner, was correlated positively with BOLD signal activity in several regions of the PFC in non-depressed participants (see Jennings et al., 2015, for contrary findings). This association was absent in depressed patients (Lane et al., 2013). Over the course of a twelve-week treatment with sertraline, depressed patients' HF-HRV correlation with activity in various regions of the PFC increased from non-significant to significantly positive, and no longer differed from non-depressed participants (Smith et al., 2014). Finally, connectivity between the rostral anterior cingulate and the pons is correlated positively with HF-HRV, and this connectivity is inversely correlated with depression severity (Smith et al., in press). Thus, the ability of the PFC to modulate activity in subcortical circuits, consistent with our proposed model, is disrupted in patients with major depression. These findings further suggest that the HRV-prefrontal relationship is important in understanding both normal and pathological conditions, and is a potential target for intervention.

Furthermore, to clearly show that low HF-HRV is a common vulnerability to psychopathology, other potential biobehavioral pathways should be considered. Whereas a full exploration of these other pathways is beyond the scope of the present paper, several potential alternative pathways such as sleep disturbance, dysregulation of central neurotransmitters, and neuroendocrine dysregulation might need to be considered. Importantly, we have shown that HRV is associated with sleep such that (1) low HRV is associated with poor sleep quality, (2) low HRV before sleep is associated with lower EEG delta power during sleep, (3) low HRV precedes reports of sleep problems, and (4) interventions that increase HRV improve sleep quality (see Hall et al., 2007; Irwin et al., 2006; Cribbet et al., 2014; Hansen et al., 2014a, 2014b, respectively). Similarly, central 5-HT function is related to HRV such that tryptophan depletion in remitted depressives is associated with increased symptoms and decreased HRV (Booij et al., 2006), and twelve-week treatment with sertraline normalizes the association between PFC function and HRV in depressed patients (Smith et al., 2014). In addition, (1) low HRV is associated with higher stress related cortisol responses, (2) low resting HRV is associated with prolonged cortisol responses to mental stress, and (3) low HRV is associated with dysregulated HPA axis functioning (see Looser et al., 2010; Weber et al., 2010; Thayer et al., 2006, respectively). Thus, consistent with the idea that low HRV may be a transdiagnostic biomarker of vulnerability to psychopathology, the final common pathway for these other potential pathways may include HRV.

Neurovisceral integration theory provides an explanation for consistent findings of low tonic HF-HRV and excessive phasic HF-HRV reactivity in psychopathological samples. Non-specific vulnerability to psychopathology is conferred by poor prefrontal control over behavior (Beauchaine, 2015b; Maren et al., 2013; Menon, 2011; Rubia, 2011), which is reflected in measures of HF-HRV given structural and functional connections between the PFC and parasympathetic efferents to the heart. At the factor analytic level of analysis, poor executive control over behavior is captured by the higher-order general psychopathology factor found in numerous studies. Thus, HF-HRV and a general psychopathology factor both index general vulnerability to psychopathology conferred by PFC dysfunction but at different levels of analysis. As detailed in sections above, this account dovetails psychophysiological models of psychopathology with factor analytic models, consistent with the RDoC mission. Importantly, although general vulnerability to psychopathology is conferred by PFC dysfunction, more specific vulnerabilities, which are determined by subcortical neural function (e.g., mesolimbic and septo-hippocampal; see above), determine whether an affected individual is predisposed to externalizing disorders, internalizing disorders, or both.

7. Research implications

Despite its complexity, the model we present oversimplifies the causes of psychopathology. We simply cannot consider all disorders or all neural systems that are implicated in behavioral control. Nevertheless, we hope our article makes clear how important it is to evaluate the interactive effects of multiple neural systems on complex behaviors, including psychopathology. Much if not most psychopathology research is still conducted by analyzing the main effects of single brain systems or responses on behavior. When research is conducted in this way, pathognomonic signs are assigned too much value, as one-to-one correspondences between brain function and behavioral outcomes are sought. Dimensional models, such as those represented by RDoC, afford us the opportunity to break out of this way of thinking (van Praag, 2004). In the future, we look forward to the emergence of a literature in which both cortical and subcortical contributions to psychopathology are evaluated in single studies, and in which the value of transdiagnostic biomarkers such as HRV, become better recognized.

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