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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).