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A theoretical and empirical modeling of anxiety integrated with RDoC and temporal dynamics

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ABSTRACT

The newly launched Research Domain Criteria (RDoC) emphasize specific mechanisms over diagnostic categories of psychopathology. In our view, RDoC provides a useful heuristic for mental health disorders, but does not capture the complexity of psychological data when proposed mechanisms are viewed as static entities. However, temporal and complex system dynamics may advance RDoC's utility. By investigating temporal patterns within trajectories and the interaction of complex networks, we propose that dynamic modeling provides comprehensive methods with which to investigate the etiopathology and maintenance of mental health disorders. We examine applications of dynamical systems to periphery physiology, an RDoC construct that has been widely used in psychological science. A review of the literature suggests methodological problems with aggregate and reductive models. We present a dynamical systems modeling of anxiety which suggests avenues for future biomarker research. This model appears congruent with RDoC and recent learning theory.

1. Introduction

The *National Institute of Mental Health Strategic Plan* (National Institute of Mental Health [NIMH], 2008) unveiled the Research Domain Criteria (RDoC) as a new platform for investigating mental health. The impetus for this project derived from two core convictions (see Insel et al., 2010; Sanislow et al., 2010). First, NIMH aimed to integrate advances in neuroscience and genomics into mental health research and public health applications. Second, NIMH aimed to foster the collaborative study of psychological and biological processes to create valid phenotypes of mental health disorders. NIMH anticipated an empirically-derived taxonomy of aberrant processes, unrelated to existing mental health disorders (Cuthbert & Insel, 2010). RDoC provided a framework that favored the study of specific mechanisms within mental health deficits (specifically, circuitry and biological units of measure), as opposed to symptoms related to diagnostic criteria (Sanislow et al., 2010). Casey et al. (2013) suggested that much of the literature regarding underlying mechanisms in psychopathology derives from suboptimal methods including cross-sectional and comparative studies. The RDoC initiative opened the door to more sophisticated analysis by favoring collaborative, integrative efforts (Sanislow et al., 2010).

NIMH Strategic Plan (NIMH, 2008) and its successor, *NIMH Strategic Plan for Research* (NIMH, 2015), promoted domains as a new topography of analysis. Categories of investigation included negative affect, positive affect, cognition, social processes, and regulatory systems (Kozak & Cuthbert, 2016; Morris & Cuthbert,2012). The RDoC matrix consists of specific factors (e.g. responses to sustained threat, approach motivation) hierarchically linked to higher-order domains, and proposed units of analysis (genes, molecules, cells, circuits, physiology, behavior, self-report, and paradigms). However, various components are understood to interact (e.g. arousal is concomitant with affect). An important assumption of the RDoC is that psychopathologies are heterogeneous phenomena involving multiple mechanisms, which make them difficult targets for reduction (Cuthbert & Insel, 2013). It was hoped that matrix components would be more accessible to specific mechanisms (Morris & Cuthbert, 2012). Accordingly, several reviews (e.g. Dillon et al., 2014; Meyers, DeSerisy, & Roy, 2016; Schwarz, Tost, & Meyer-Lindenberg, 2016) have proposed RDoC constructs as means to better conceptualize mental health syndromes.

Although it may not come as a surprise to many investigators, not all consider reductionist models of psychopathology to be satisfactory (i.e. ascribing cause solely to biological or psychosocial components; see Kendler, 2012). However, since research domains demonstrate promise as mechanisms, certain methodological complications have been ignored. A review of the literature on one such construct (physiological arousal) reveals a complex and temporally heterogeneous entity (i.e. something dynamical versus static; Voss, Schulz, Schroeder, Baumert, & Caminal, 2009). In what follows, we will propose that RDoC

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constructs serve as valid markers for psychopathology when considered as time-series phenomena. Additionally, we will present an integrated theoretical and empirical model of anxiety using dynamical systems as the mathematical paradigm. For the purposes of this paper, dynamical systems refer to two essential features of data. First, almost all psychological symptoms of interest are not experienced as static unchanging entities, and, consequently, it is of vital importance to examine recurring temporal trajectories which explain how symptoms change within individuals across time. Second, mental health data are produced by complex and elusive networks. Researchers in psychological sciences are in the rudimentary stages of understanding these two features.

In our view, RDoC constructs provide useful heuristics for mental health disorders, but do not capture the complexity of psychological states when assessed as static entities. Typical inferential statistics (e.g. multi-level models, linear models, etc.) assess between and within subject differences for a given domain, but do not assess patterns of change which could be influential (see below). Aggregate differences found in typical analyses might be more or less important from a dynamical systems perspective. For example, observed changes in a treatment study may derive, or be affected by, differential periodicity (e.g. individuals may have similar patterns of change but vary in phase at indexed time points; see Hu, Boker, Neale, & Kump, 2014). In addition, examining fluctuations in continuous biological processes may prove of greater qualitative import than aggregate differences. As in our empirical illustration, such fluctuations may help explain group differences.

For some critics of the RDoC initiative, the dominant ethos created unsubstantiated limitations on research by de facto favoring certain units of analysis over others (see Berenbaum, 2013; Lilienfeld, 2014). There have been recent high profile efforts to fund biologically focused research, such as the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) initiative (Insel, Landis, & Collins, 2013). Calhoun and Craighead (2006) proposed that academic departments would need to re-orient to keep pace with this change towards neuroscience specialization. Conversely, there have been appeals to interpret RDoC through an integrative or inclusive lens (e.g. Schwartz, Lilienfeld, Meca, & Sauvigné, 2016).

Kozak and Cuthbert (2016) suggested that symptoms, the traditional domain of psychiatric diagnoses, should be integrated with other RDoC units of analysis. However, they also noted challenges inherent in analyzing such multi-level data. Therefore, methodological approaches are needed which can link diagnostic understandings (e.g. the Diagnostic and Statistical Manual of Mental Disorders, 5th ed. [DSM–5]; American Psychiatric Association, 2013) and RDoC constructs. Dynamic modeling may be well-suited to provide such a bridge. Specifically, these methods manifest the capacity to model and disentangle continuous biological processes in a manner superior to aggregates.

The purpose of this paper will be to propose that RDoC constructs may best serve as mechanisms for mental health disorders when considered in time-series, optimally assessed through dynamic modeling. In what follows, we limit our attention to peripheral physiology and anxiety symptoms as an exemplar for future biomarker research. This model appears congruent with RDoC and recent learning theory. However, the same approach could be applied to various psychopathological syndromes and RDoC domains (e.g. Wichers, 2014).

2. Dynamic modeling

There is a trend in the literature towards describing change over time based on the awareness that psychological states (e.g. anxious and depressive symptoms) fluctuate within, as well as between, subjects (Biesanz, West, & Kwok, 2003). However, popular modeling techniques such as hierarchical linear modeling and growth curve modeling, which examine trajectories of data, are unable to model fluctuation within trajectories. Thus, methods that average trajectories are incapable of deciphering phasic patterns. Additionally, in cyclical and oscillatory processes, such as those found in psychological data, it is often these individual rather than group differences which are critical (Butner, Amazeen, & Mulvey, 2005). In contrast to popular modeling techniques, dynamic modeling strategies explicitly assess within-person variation by analyzing the rate of change and the speed with which it occurs (see Heath, Heiby, & Pagano, 2007). This modeling focus has unique strengths, allowing researchers to investigate multivariate parameters within cyclical processes and the interaction effects between oscillations (see below; Chow, Ram, Boker, Fujita, & Clore, 2005).

An example of this can be seen in self-regulatory thermostats and the independent oscillator model. Chow et al. (2005) presented emotion as a construct which fluctuates in specific patterns on weekly cycles. Changes in baseline emotion can occur for a variety of reasons (e.g. external and internal stimuli) and in a variety of intensities. Here intensity designates the extent of change (e.g. very sad versus mildly distressed). However, intensity also varies in relation to time. For example, a person may slowly become very depressed or immediately very angry. Finally, there are variations or changes in the rate of change. A person may become very angry quickly but self-regulate, or slow down the acceleration of anger. Such a process could be impacted by a person's phase in a daily or weekly cycle of emotion (i.e. a multivariate parameter within a cyclical process) as well as interaction effects between emotive oscillations. For example, if a person becomes angry with regularity and ease, prior acceleration and intensity may exacerbate future patterns. Chow et al. (2005) employ a dynamical method, the independent oscillator model (see below), to demonstrate these patterns as the effect of emotion regulation (i.e. the 'dampening' on the trajectory and intensity of emotion). This exemplifies a self-regulatory process which occurs in any homeostatic function.

Dynamical methods have been used to model psychological variables including psychiatric symptoms (Odgers et al., 2009), pain prediction (Finan et al., 2010), and substance use recovery (Zheng, Cleveland, Molenaar, & Harris, 2015). Dynamical processes can be analyzed with differential equations in structural equation, multi-level, and state-space models, which detect first and second derivatives as a function of time (respectively, the rate of change and changes in the rate of change), often built around a theorized latent structure. As mentioned, an example exists in the independent oscillator model:

$$Y_i^{''}(t) = \eta Y_i(t) + \zeta Y'(t)$$

Chow et al. (2005) specified the relationship among acceleration (i.e. $Y_i^{''}(t)$; at time t for person i), the rate of change (i.e. $Y'(t)$; at time t for person i), and intensity (i.e. $Y_i(t)$; at time t for person i). This model assumes that variables evolve continuously; the parameter η is set to represent the frequency of oscillation and ζ the time lapse between perturbation and recovery. It is also assumed that an interaction may occur between η and ζ, in which the frequency of oscillations will impact the dampening or amplification of the magnitude of oscillations. Differential equation modeling can assess moderation as well as coupled systems (e.g. unidirectional and bidirectional interaction between multiple variables, such as affect and physiological arousal; Hu et al., 2014). Applied to time-series data, this technique could model idiographic patterns of a given variable in prediction of an outcome (depressive symptoms, anxiety, etc.), along with the perturbations of life factors (e.g. stressors). We propose that temporal dynamics, such as accelerations in negative affect as a response to stressors, could be more salient predictors of psychopathology than aggregates.

In sum, the use of dynamic modeling offers critical distinctions and possible advantages over other statistical methods, including sensitivity to derivatives and the detection of phasic patterns. The following sections will review evidence for the applicability of these approaches to periphery physiology, while attempting to illustrate the appropriateness of using such strategies. Specifically, dynamical methods may resolve certain methodological challenges and optimize physiology as a biomarker. In other words, dynamic models have the potential to detect the within-individual patterns which foster or exacerbate mental health symptoms.

2.1. Arousal

Peripheral physiological measures are often employed as indices in psychological studies. Within RDoC, physiology has been presented as a unit of analysis and mechanism for mental health syndromes. However, whether generalizations can be drawn from aggregates of these metrics remains a matter of debate. In the case of heart rate, a complex set of homeostatic mechanisms, such as the baroreflex, may confound simple comparisons of means (Grossman & Taylor, 2007). In this section, we will discuss the relevance of heart rate to mental health research and present methodological challenges with using this metric as a static biomarker.

States of hyperarousal are characterized by high heart rate and low heart rate variability (HRV; Friedman & Thayer, 1998). These two features have also been associated with trait depression and anxiety (Gorman & Sloan, 2000), as well as state worry (Brosschot, Van Dijk, & Thayer, 2007). Heart rate variability (HRV) refers to cyclic variations in beat-to-beat intervals (RRI). Over time, variations in RRI are assessed as a power spectrum, with power as a function of frequency (i.e. the occurrence of specific variations in heart rate; Task Force of the European Society of Cardiology, 1996). This has been codified into domains, such as high frequency (HF; 0.15–0.4 Hz) and low frequency (LF; 0.01–0.15 Hz) HRV (Thayer, Åhs, Fredrikson, Sollers, & Wager, 2012).

Researchers have proposed HRV as a person-level variable, reflective of parasympathetic (PNS) and sympathetic (SNS) nervous system activity (Butler, Wilhelm, & Gross, 2006; Porges, 2001). Porges (2007) argued that multiple phylogenetic pathways influence heart rate, originating in the nucleus ambiguus and dorsomotor nucleus within the brainstem. Respiratory sinus arrhythmia (RSA), the high frequency variation in heart rate that accompanies breathing, is superimposed upon low frequency variations that stem from tonic vagal control (Lehrer, Vaschillo, & Vaschillo, 2000). Arterial baroreceptors create a feedback loop between blood pressure and heart rate oscillations, fostering homeostasis amidst environmental demands (Vaschillo, Vaschillo, & Lehrer, 2006). Afferents from the facial nerves provide input to the nucleus ambiguus in response to social stimuli (Porges, 2001). Situational changes in RSA have been associated with self-regulatory efforts and executive control (Butler et al., 2006). Therefore, a complex set of mechanisms influence HRV at any given time for any given individual. Measurements could differentially index sympathetic, parasympathetic, respiratory, and vagal influence (Park, Van Bavel, Vasey, & Thayer, 2013; Vaschillo et al., 2006).

With the polyvagal theory, Porges (2001) proposed that the vagal system (i.e. the 'vagal break') generally inhibits sympathetic influence on HRV. The ventral vagal complex (VVC), associated with the nucleus ambiguus, exerts itself when individuals dampen arousal, react to disruptions in homeostasis, and during social engagement (Porges, 2007). According to Porges (2007), RSA offers a reliable index of this influence. The dorsal vagal complex (DVC), on the other hand, reflects tonic control distinct from RSA. When threat is detected (i.e. neuroception), the DVC pathway predominates, fostering an increase in SNS activity and heart rate acceleration (Buss, Davidson, Kalin, & Goldsmith, 2004). Therefore, post-stress return to high RSA is viewed as a psycho-physiological benefit (Butler et al., 2006). In clinical populations, post-stress RSA may reflect low inhibitory control (Sack, Hopper, & Lamprecht, 2004), blunted response to stressors (Karavidas et al., 2007), and poor emotion regulation (Kim et al., 2013).

Such claims are controversial, however, as not all consider RSA a reliable metric of vagal influence (Grossman & Taylor, 2007; Moak et al., 2007). Grossman and Taylor (2007) noted that respiration, tidal volume, physical activity, and sympathetic influence provide substantial confounds for RSA measurement in a variety of ambulatory and stationary tasks. The authors theorized that RSA and vagal influence co-vary or diverge by task, as a means to maximize energy efficiency and promote allostasis. In this view, behavioral changes induced by respiration only confer an adaptive advantage during alert states; thus, in these moments measurement of RSA and vagal tone are associated. Since respiration rate varies in many of the tasks used for psychological assessment, significant changes in RSA may be unrelated to the VVC. Moak et al. (2007) concluded that the LF power domain reflects baroreflex function rather than sympathetic activation. In their study ($n = 98$), persons with low baroreflex function manifested low LF-HRV.

Several counter-arguments have been made. First, the dynamic oscillations of the HRV system promote adaptive regulation; as a particular pattern dominates, the system becomes dysregulated (Thayer, Yamamoto, & Brosschot, 2010). In healthy persons, arterial baroreceptors form a negative feedback loop between heart rate and blood pressure, allowing homeostasis to be maintained amidst changing environmental demands (Vaschillo et al., 2006). Accordingly, dynamical and complex time series analyses seem to be less confounded by respiration than linear models (Denver, Reed, & Porges, 2007; Kettunen & Keltikangas-Järvinen, 2001). For example, Mahananto, Igasaki, and Murayama (2015) found that potentials of unbalanced complex kinetics indexed RRI slope (i.e. the rate of change in 'normal-to-normal' intervals) and slope standard deviation independently from respiration. Additionally, for research designs in which inter-individual differences are the target, respiration should be a function of group or task, as it reflects these differences (see Miller & Chapman, 2001).

2.1.1. Neurovisceral integration

The neurovisceral integration model (Thayer & Lane, 2000) provides an alternate conceptualization for the link between peripheral physiology and mental health. In this model, HRV serves as a marker for the integration of attentional, affective, and autonomic systems. Successful adaptation to changing environmental demands requires flexibility in regulating multiple overlapping processes. Thayer et al. (2012, p 748) suggested, "a core set of neural structures provides an organism with the ability to integrate signals from inside and outside the body and adaptively regulate cognition, perception, action, and physiology." Thus, this regulatory super-system monitors homeostatic processes and external stimuli (i.e. interoceptive and exteroceptive threat) to generate motivation, physiological adjustments, and representations of adaptive responses (via memory, motor function, and perception). In complex dynamical systems, multiple processes interact to create auto-regression (i.e. the extent to which current values are predicted by previous values) and oscillation (Butner et al., 2005; Voss et al., 2009). If these systems are balanced, mutual constraints drive the output towards a limited range of values regardless of the input. For example, a person with neurovisceral integration might adaptively manage internal states regardless of external stress. When unbalanced, a particular process or pattern dominates and the system becomes input-dependent, inflexible, and dysregulated. Thus, a person with neurovisceral disintegration might respond to small stressors with arousal marked by high acceleration, high intensity, and little granularity. Thayer and Sternberg (2006) suggested that human physiology follows these dynamical and complex system patterns.

2.1.2. HRV and anxiety disorders

Newman, Llera, Erickson, Przeworski, and Castonguay (2013) posited that anxiety disorders (AD) are characterized by a reliance on rigid patterns that prevent responsiveness to the environment. Persons with AD evidence lower HRV at baseline (Pittig, Arch, Lam, & Craske, 2013) and lower HF-HRV than controls when confronted with stressors (i.e. a more input-dependent system; Friedman & Thayer, 1998). Pohl and Yeragani (2001) found that persons with panic disorder (PD) exhibited greater heart rate impact from the stimulant isoproterenol. Similarly, participants with PD manifested less HRV than controls after consuming the panicogenic yohimbine (Yeragani et al., 1992). Greater task effects have been observed on HRV in comparison studies, for example when persons with phobia confront phobia-relevant stimuli (Johnsen et al., 2003). While there have been mixed findings (see Aikins and Craske, 2010), mental health patients regularly demonstrate low HRV during relaxation and dysregulated over-reactivity to stressful tasks and stimuli.

As mentioned, there is evidence that HRV may be better suited as a metric for situational integration, rather than person-level (i.e. time and context independent) adaptive ability. However, Park et al. (2013) found that low HRV predicted faster engagement with fearful faces at short stimulus-onset asynchrony (SOA) and slower disengagement at long SOA. This suggests a deficit in both top-down and bottom-up processes. Brain injury and concomitant deficits in executive systems predict HRV dysregulation, poor sympathetic to parasympathetic balance, and disrupted emotion regulation (Kim et al., 2013). Finally, arousal variables are continuous and may have complex lagged associations to affective states (Ram et al., 2014), such as dynamic bidirectional mediation. To the best of our knowledge, these associations have not been fully tested. Thus, aggregate models of HRV in anxiety research may lose critical information on situational context and temporal fluctuation.

While physiological markers relate to state and trait anxiety, there is little overlap between such markers and perceived arousal (Cacioppo, Tassinary, Stonebraker, & Petty, 1987). Thayer (1989) hypothesized that perceived arousal is determined by a person's situational potential to become aroused, rather than objective interoceptive awareness. This could explain why persons with mental health disorders manifest deficits in extinguishing fear expectancies (Blechert, Michael, Vriends, Margraf, & Wilhelm, 2007; Michael, Blechert, Vriends, Margraf, & Wilhelm, 2007). Mental health disorders may reflect lower capacity to regulate aversive reactions. In healthy persons, stress will be met by a balanced neurovisceral system which imposes constraints to produce flexible, complex patterns (i.e. neither stationary nor auto-regressive; Voss et al., 2009). In persons with neurovisceral disintegration, stress produces inefficient energy expenditure, deficient autonomic dampening, and auto-regressive patterns which are largely dictated by external input rather than internal resources. Thayer (1989) hypothesized that perceived danger and energy expenditure during anxious moods overload the system and force attentional shift towards threat (i.e. attentional bias). Notably, Abramovitch, Dar, Hermesh, and Schweiger (2012) proposed a similar executive overload model in OCRD.

In accord with modern learning theory and the inhibitory learning model (Craske et al., 2008; Craske et al., 2014), flexible response to environmental stimuli may promote extinction. For example, inhibiting a conditioned reaction involves an assessment of association contingencies (see Courville, Daw, & Touretzky, 2006), as well as metacognition (e.g. the 'fear of fear'; see Arch & Abramowitz, 2015). Neurovisceral disintegration could disrupt inhibitory learning processes in several ways. First, auto-regressive physiological patterns may prevent new learning (e.g. emphasizing previous input versus momentary experience). Second, stationary patterns could contribute to stimulus generalization, as previous threat dictates perceived ability to become aroused. Third, inefficient energy expenditure may lead to hyperarousal via impaired allostasis. Fourth, deficient dampening may contribute to deficits in fear and arousal termination.

Research employing dynamic modeling strategies might assess such within-individual patterns in the HRV system (for a full review, see Voss, Schulz, Schroeder, Baumert, & Caminal, 2009). Fractal methods, first proposed by Kobayashi and Musha (1982), index the evolving symmetry of patterns seen in HRV data over multiple time-scales. It was subsequently discovered that this self-affinity or frequency dependence cannot be described by a singular exponent (i.e. dimension), but requires multi-fractal scaling to account for coupled feedback loops (Ivanov et al., 1999). As mentioned, dimensional simplicity (versus complexity) in time series measurements are often concomitant with poorer response to environmental demands, making symmetry a useful metric (Heath et al., 2007). Entropy measures, such as multiscale entropy (Costa, Goldberger, & Peng, 2002) and compression entropy (Baumert, Baier, Voss, Brechtel, & Haueisen, 2005), assess randomness (versus auto-regression) in HRV, which could be another proxy for rigidity in response. Symbolic dynamics, a probabilistic approach to short-term pattern analysis, has been used to assess granularity (for example, appropriate intensity in responses; Porta et al., 2001). These methods, although complex, are accessible through statistical programs and online resources.

Aberrant HRV has been proposed as a biomarker of disorder in both physical (Thayer et al., 2010) and psychological health (Wheat & Larkin, 2010). However, HRV data do not present a simplistic portrait of aberrancy. Aggregate methods may be insufficient to investigate arousal as a phenotype for mental health syndromes because complex physiological patterns are time-series phenomena (Voss et al., 2009). Dynamical strategies are relatively new in psychological science, and will likely present their own methodological challenges (e.g. model specification issues, determining the necessary quality and frequency of measurement, etc.). However, these approaches may prove useful in reducing model misspecification and strengthening causal linkages.

3. Anxiety disorders and RDoC

Anxiety research could serve as an exemplar for components within RDoC (McTeague, 2016). Prior research has shown that anxiety may be related to the domains of (1) negative valence systems, (2) positive valence systems, and (3) regulatory processes. Multiple units of analysis have been examined, including physiology, behavior, and self-report. For example, in regards to the physiological domain, abnormal stress sensitivity has been found in clinical populations, including increased somatic arousal (Ravaja, Saari, Kallinen, & Laarni, 2006) and post-stress recovery deficits across a variety of AD (Pittig et al., 2013). Additionally, it is believed that dysregulated positive affect (Eisner, Johnson, & Carver, 2009) and negative affect (Mennin, Heimberg, Turk, & Fresco, 2005) are mechanisms of anxiety (see Walz, Nautaa, & aan het Rot, 2014 and Hofmann, Sawyer, Fang, & Asnaani, 2012 for reviews). Substantial evidence is also accumulating that anxiety and depression may be dynamic bi-directional risk factors for one another over time (Jacobson & Newman, 2016, 2017, 2014, 2012).

A variety of studies have used ecological momentary assessment (EMA) to help elucidate anxiety symptomology. These methods are well-suited to measure temporal change in a person's natural environment and avoid some of the bias inherent in retrospective report (Fahrenberg, Myrtek, Pawlik, & Perrez, 2007). Persons with social anxiety disorder (SAD) manifest higher experiential avoidance (Kashdan et al., 2014) and less differentiation of negative experience in comparison with controls (Kashdan & Farmer, 2014). Likewise, persons with panic disorder (PD) have been found less accurate than controls in self-reported bodily symptoms of anxiety (as indexed by physiological recordings; Hoehn-Saric, McLeod, Funderburk, & Kowalski, 2004). In an investigation of generalized anxiety disorder (GAD) using spectral analysis, oscillations in anxiety symptoms moderated the effect of symptom duration on outcome (Newman & Fisher, 2013). In this study, persons that developed flexible, less predictable responses benefited more from treatment. These findings support the assumption that RDoC constructs have a time-dependent relationship to anxiety symptoms.

In the following section, we will present a dynamic model of anxiety symptoms. This empirical conceptualization is congruent with our review of peripheral physiology as a dynamic biomarker, as well as recent learning theory. In this brief example, temporal dynamics are essential for differentiating complex changes over time for persons with and without an anxiety disorder. Notably, these patterns would not be detectable to aggregate methods. Further, this example demonstrates the necessity for longitudinal analysis of RDoC constructs as mechanisms via complex lagged associations and interactions. For example, to the best of our knowledge, it is unexamined whether oscillatory patterns in arousal differ for persons within various symptom clusters. Additionally, to the best of our knowledge, it is unknown whether temporal dynamics in arousal (i.e. rate of change, and changes in the rate of change) impact symptom severity.

3.1. An integrated dynamical systems modeling of anxiety

Recent conceptualizations of anxiety disorders offer a rich theoretical framework that highlight the importance of applying dynamical systems. The inhibitory learning model posits that after a stimulus has been classically conditioned to produce distress, treatment does not erase this association, but rather forms a second learning pathway to inhibit the evocation of the distress response (Craske et al., 2014). Further, the model suggests that those with anxiety pathology may show deficits in forming new associative learning for the feared stimulus (Craske et al., 2014). This recent model thus may hold important implications toward salience of the trajectory of anxiety over time, with separate trajectories of anxiety for those with or without anxiety pathology. This theory suggests that an elevation in anxiety symptoms among those without anxiety pathology would be followed by a quick and successful inhibitory process. In contrast, for those with anxiety pathology, the model posits that after an increase in anxiety, these persons may show particularly poor regulation or inhibition of the response.

In translating these theories to a dynamical systems conceptualization, those low in anxiety pathology may show a stronger dampening (i.e. inhibition of the response) of the anxiety trajectory following perturbation. In contrast, those with anxiety pathology may show a smaller dampening over time (given that those without anxiety have no regulatory difficulties). These implications of the inhibitory learning model will be tested based on a clinical example.

To provide a concrete illustration, we examined the damped oscillator model. Data was taken from a daily diary study conducted for eight days using a large national sample (N = 1499 persons, 54.1% female, M age = 46.74, age range 20–4) (Almeida, 2015). Anxiety was measured using the following items rated on a 1–5 scale: (1) How much of the time today did you feel restless or fidgety?, (2) How much of the time today did you feel SO restless that you could not sit still?, (3) How much of the time today did you feel nervous?, (4) How much of the time today did you feel so nervous that nothing could calm you down?, (5) How much of the time today did you have a headache, backache, or muscle soreness?, (6) How much of the time today did you have nausea, diarrhea, poor appetite, or other stomach problems?, and (7) How much of the time today did you have any chest pain or dizziness?. This eight item scale had adequate internal consistency (α = 0.70).

For this empirical example, we examined the impact of diagnostic status on daily fluctuations of anxiety. Anxiety disorder diagnoses were measured using the third edition-revised criteria diagnostic and statistical manual (DSM-III-R) assessed through the World Health Organization Composite International Diagnostic Interview for generalized anxiety disorder (N = 34, 2.6%) and panic disorder (N = 114, 7.6%). The purpose of this illustration was to examine (1) whether the duration of anxiety cycles differed among the anxiety disorders group and other participants (for the sake of this empirical example, the non-anxious control [NAC] group), and (2) whether the degree of regulation (i.e. dampening) differed between the anxiety disorders group and the NAC group. Based on the inhibitory learning theory, we hypothesized that there would be differences in the degree of dampening.

Prior to the analyses, all data was person-centered to ensure that all models captured within-person variation. All analyses were performed with *CTSEM* in *R,* modeling continuous time damped oscillator models within a structural equation modeling framework (Driver, Oud, & Voelkle, 2017). All missing data (12.54%) was handled using full information maximum likelihood. Three multi-group continuous time damped oscillator models were examined, (1) a model with no parameters constrained to be equal between the anxiety disorders group and the NAC group, (2) a model with only the oscillating parameters fixed between groups, and (3) a model with only the dampening parameters fixed between groups. Prior to interpreting the model statistics, the differences in fit were examined using log likelihood ratio tests.

The results suggested that there was no significant difference in fit when the oscillatory frequency parameter was constrained to be equal across groups (LL_{diff} = 0.000, p = .999), suggesting that the anxiety disorders group and the NAC group did not have any significant differences in the durations of their anxiety cycles. Nevertheless, constraining the dampening parameter to be equal across groups led to a significantly worse model fit (LL_{diff} = 12.726, p < .001), suggesting that there were significant differences in the dampening parameter between participants NAC and those with clinical anxiety. Thus, the model with only the oscillatory frequency parameter constrained between groups was considered the final model. The final model suggested that the oscillatory frequency was significant (η = −26.708, SE = 0.343, Z = −77.729, p < .001), with an average oscillatory duration of 0.822 days. Note that the dampening parameter was also significant for both the NAC group (ζ = −2.318, SE = 0.112, Z = −20.648, p < .001) and anxiety disorders group (ζ = −1.484, SE = 0.158, Z = −9.413, p < .001), but based on the prior log likelihood ratio test, the NAC group had a significantly more negative dampening parameter.

The results are graphically plotted in Fig. 1. Taken together, these results suggest that the cyclical patterns of anxiety occurred across the same frequency for both the NAC and anxiety disorders group, but the

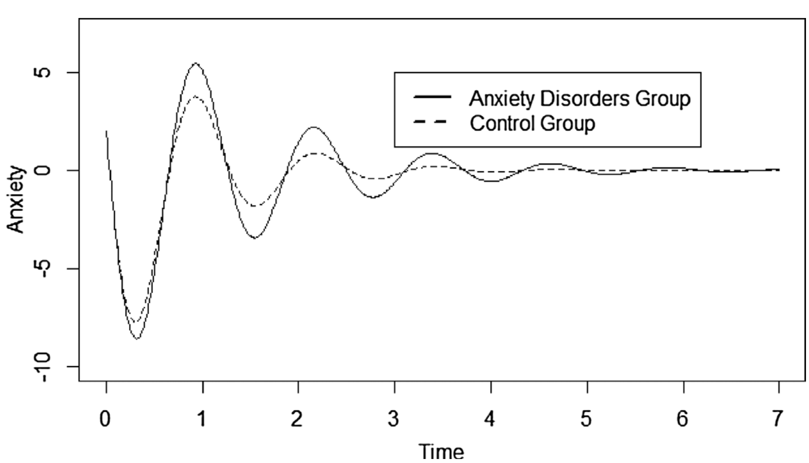

Fig. 1. This figure provides an illustration of the impact of perturbations in anxiety among those with higher anxiety levels compared to those with lower anxiety levels. Time here reflects the number of days. Thus, time zero is set at 2 for both the anxiety disorders (N = 148) and the non-anxious control (NAC) group at 2 units to simulate the oscillations and dampening seen in both the anxiety disorders and NAC group based on the model estimates. As both groups show significant oscillatory cycles at the same period, both groups' anxiety levels immediately drop following an initial peak in anxiety, but the NAC group substantially dampen their anxiety by two days later, suggesting that anxiety is quickly regulated among those in the NAC group. In contrast, it takes several days for those in the anxiety disorders group to fully dampen the impact of one day of high anxiety. To ensure that these results were on the same scale, these results present mean-centered trajectories, but consequently this figure does not present the mean difference in daily anxiety symptoms between the anxiety disorders and the NAC group.

NAC group manifested a strong dampening of anxiety. Consequently, those in the NAC group displayed greater regulatory capacity, such that any anxiety was quickly down-regulated until an equilibrium point had been reached. In contrast, for the anxiety disorders group, it took several days for individuals to reach equilibrium after a minor to moderate rise in anxiety. These results exemplify the power of dynamical systems in connecting (1) complex changes over time and (2) differences between those with and without a diagnostic characterization.

4. Conclusion and future directions

Attempts to isolate and reduce complex phenomena into measurable parameters are necessary for scientific advancement. Translatable goods can be gained by these efforts. This paper argues, however, that RDoC constructs foster and exacerbate psychopathology as oscillatory, multifaceted processes. Analysis of these patterns will provide an essential insight into mental health functioning. Time-independent and reductive approaches will always entail a level of misspecification and stereotype. As has been suggested by Kendler (2012), the weight given to any source of information (e.g. RDoC units of analysis) should be determined empirically, not *a priori*, and may vary across symptom clusters. Dynamic modeling may be useful in assisting these determinations.

Dynamical systems provide methods which could link the RDoC conceptual framework to diagnostic syndromes. Specifically, RDoC constructs are likely mechanisms of mental health symptoms via complex lagged associations and interactions. For example, Wichers (2014) suggested that depression consists of time-lagged associations within a network model of biopsychosocial factors. Anxiety could be similarly conceptualized. In our review, we attempted to demonstrate the relevance of dynamic modeling to periphery physiology as a biomarker for anxiety. Further, we presented an empirical example of anxiety symptoms as determined and exacerbated by system dynamics. In the future, we hope to examine time-lagged associations across various RDoC constructs in persons with anxiety disorders. Modeling these elements will present many challenges, but also opportunities (see Roche, Pincus, Rebar, Conroy, & Ram, 2014; Wichers, 2014). Ram et al. (2014) proposed that intra-individual, time-lagged associations exist between multiple time-scales (i.e. seconds, days, weeks). Recent psychometric evidence suggests that changing temporal patterns in symptom expression manifest in self-report as a function of treatment (Fried et al., 2016). Dynamic modeling may prevent the loss of such crucial information and, therefore, improve model specification.

To test complex models of psychopathology using dynamical systems, intensive data collection will be required, including longitudinal data on mental health symptoms, life stressors, periphery physiology, and other RDoC constructs. Such projects will demand the collaborative, integrative efforts promoted by Sanislow et al. (2010). In the future, new technologies could supplement this foundation, enabling (for example) longitudinal neuroimaging in and outside of the lab. In the short term, researchers should test lagged associations and interactions between RDoC constructs and symptom dynamics wherever feasible. Optimally, multiple time-scales should be used.

In many ways, this is analogous to the situation of physics circa the application of relativity in quantum mechanics. We now know that atoms are not simple building blocks for physical reality, but complex probabilistic and dynamical systems. However, this does not invalidate scientific efforts prior to this discovery, nor render null functional applications of previous work. In a similar way, additional insights into the dynamical nature of RDoC domains, as they relate to psychological phenomena, can lead to concrete directions for future inquiry.

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