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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