Advancing the Network Theory of Mental Disorders:

A Computational Model of Panic Disorder

Donald J. Robinaugh[1,2], Jonas M. B. Haslbeck[3,4], Lourens J. Waldorp[4],

Jolanda J. Kossakowski[4], Eiko I. Fried[5], Alexander J. Millner[6], Richard J. McNally[6],

Oisin Ryan[7], Jill de Ron[4], Han L. J. van der Maas[4], Egbert H. van Nes[8], Marten Scheffer[8],

Kenneth S. Kendler[9], Denny Borsboom[4]

[1]Northeastern University
[2]Massachusetts General Hospital
[3]Maastricht University
[4]University of Amsterdam
[5]Leiden University
[6]Harvard University
[7]Utrecht University
[8]Wageningen University
[9]Virginia Commonwealth University

****This is a pre-print version of an article currently undergoing peer-review.****

Author Note

Correspondence concerning this article should be addressed to Donald J. Robinaugh, Department of Applied Psychology, 360 Huntington Ave. Boston, MA 02115. E-mail: drobinaugh@northeastern.edu. This manuscript was supported by a National Institute of Mental Health Career Development Award (K23MH113805) awarded to D. Robinaugh and an ERC Consolidator Grant no. 647209 awarded to D. Borsboom. JMBH has been supported by the gravitation project 'New Science of Mental Disorders' (www.nsmd.eu), supported by the Dutch Research Council and the Dutch Ministry of Education, Culture and Science (NWO gravitation grant number 024.004.016). This paper is solely the responsibility of the authors and does not necessarily represent the views of any funding agency. This work was not pre-registered. Prior iterations of this work were presented in multiple invited talks and conference presentations, including presentations to the Association for Psychological Science and the Transcontinental Computational Psychiatry Workgroup. Prior iterations of this manuscript were archived at: https://osf.io/preprints/psyarxiv/km37w/. The computational model introduced here is available at https://github.com/jmbh/PanicModel. A reproducibility archive for all model simulations and corresponding figures is available at https://osf.io/gpu3v/.

Abstract

The network theory of psychopathology posits that mental disorders are systems of mutually reinforcing symptoms. This framework has proven highly generative but does not specify precisely how any specific mental disorder operates as such a system. Cognitive behavioral theories of mental disorders provide considerable insight into how these systems may operate. However, the development of cognitive behavioral theories has itself been stagnant in recent years. In this paper, we advance both theoretical frameworks by developing a network theory of panic disorder rooted in cognitive behavioral theory and formalized as a computational model. We use this computational model to evaluate the theory's ability to explain five fundamental panic disorder-related phenomena. Our results demonstrate that the network theory of panic disorder can explain core panic disorder phenomena. In addition, by formalizing this theory as a computational model and using the model to evaluate the theory's implications, we reveal gaps in the empirical literature and shortcomings in theories of panic disorder. We use these limitations to develop a novel, theory-driven agenda for panic disorder research. This agenda departs from current research practices and places its focus on (a) addressing areas in need of more rigorous descriptive research, (b) investigating novel phenomena predicted by the computational model, and (c) ongoing collaborative development of formal theories of panic disorder, with explanation as a central criterion for theory evaluation. We conclude with a discussion of the implications of this work for research investigating mental disorders as complex systems.

Advancing the Network Theory of Mental Disorders: A Computational Model of Panic Disorder

In recent years, researchers have persuasively argued that mental disorders arise from systems of interacting components (Borsboom et al., 2022; Fried, 2022; Hayes & Andrews, 2020; Nelson et al., 2017; Olthof et al., 2021). From this perspective, mental disorders are analogous to an ecosystem (van der Maas et al., 2006). They do not appear as a coherent whole because of a shared underlying essence (cf. Wakefield, 1999), but because of a web of causal interactions among the features of the disorder. The network theory of mental disorders - which emphasizes the role of causally interacting symptoms within these systems - has proven especially generative (Borsboom, 2017; Cramer et al., 2010), prompting the development of new methods for assessing the structure of relationships among symptoms (Beltz & Gates, 2017; Borsboom, Deserno, et al., 2021; Bringmann et al., 2022) and a rapidly growing body of empirical studies applying those methods (Contreras et al., 2019; Robinaugh et al., 2020). However, network theory remains abstract. It provides a fruitful conceptual framework but does not posit specific relationships among symptoms. Empirical network studies provide information about these relationships, but cannot, on their own, fully inform a network theory of a given disorder (Haslbeck et al., 2021).

In this paper, we develop such a theory for panic disorder. Panic disorder is well-suited to this effort for two reasons. First, there is strong body of empirical research on the phenomenology, epidemiology, and treatment of panic disorder (Asnaani et al., 2009; Barlow, 1988; Casey, Oei, & Newcombe, 2004; Craske & Waters, 2005; McNally, 1994), providing robust phenomena to explain (Bogen & Woodward, 1988; Haig, 2005). Second, there are well-established cognitive behavioral theories of panic disorder that posit causal relationships among specific symptoms (Barlow, 1988; Beck, 1988; Clark, 1986; Ehlers &

Margraf, 1989; Reiss et al., 1986; van den Hout & Griez, 1983), providing a rich body of work upon which to draw when generating a network theory of panic disorder.

Although cognitive behavioral theories have much to offer a network theory of panic disorder, it is noteworthy that there is a need for further development of cognitive behavioral theories themselves. Leading theories of panic disorder were first proposed more than thirty years ago. They have been unequivocally successful, stimulating a large body of research and laying the groundwork for gold-standard treatments (Barlow, 1988; Clark & Beck, 2011; McNally, 1994). Yet, despite thousands of publications on panic disorder over the past three decades (Asmundson & Asmundson, 2018), there have been few advances in our theories of panic disorder since they were first proposed. In turn, there has been little advancement in our ability to treat of panic disorder since cognitive behavioral treatments were first introduced (Schmidt & Keough, 2010). This stagnation is especially troubling given that roughly half of those who receive these treatments fail to achieve remission (Springer et al., 2018), and recurrence among responders is common (Barlow, 1997; Brown & Barlow, 1995). Panic disorder is not alone in these regards. Despite enormous empirical effort, theories in clinical psychology rarely evolve in a way that would indicate genuine advancement in our understanding of or ability to treat a given condition (Meehl, 1978; Millner et al., 2020).

To address this challenge, we aim to not only propose a theory of panic disorder, but also to lay a foundation for its ongoing development. To do so, we propose a *formal* network theory expressed as a computational model. Most theories in clinical psychology are *verbal* theories expressed only in words. Due to the imprecision of natural language, these theories often contain hidden assumptions, unknowns, and contradictions (Epstein, 2008; Guest & Martin, 2021; Seligman, 1988; Smaldino, 2016). Moreover, it is typically impossible to precisely deduce what verbal theories predict; in part because what they predict depends upon information unspecified in the theory and, in part, because verbal theories provide no

machinery for deducing theory predictions, leaving such deductions to an unspecified, fraught, and idiosyncratic process of mental derivation or simulation. As a result, verbal theories do not lend themselves well to rigorous testing, contributing to their tendency to persist unchanged, neither strongly corroborated nor clearly refuted, and with little guidance for how the theory might be improved (Meehl, 1978; Robinaugh et al., 2021).

In recent years, we and others have argued that formalizing theories as mathematical or computational models can provide much needed support for theory development efforts in psychology (Borsboom, van der Maas, et al., 2021; Fried, 2021; Guest & Martin, 2021; Haslbeck et al., 2021; Millner et al., 2020; Navarro, 2021; Proulx & Morey, 2021; Smaldino, 2017; van Rooij & Blokpoel, 2020; Wang et al., 2023). Although relatively rare in the domains of clinical or counseling psychology (for valuable exceptions in the context of panic disorder, see Fukano & Gunji, 2012; Maisto et al., 2021), formal modeling plays a crucial role in many scientific disciplines and in some areas of psychology (e.g., mathematical psychology and computational psychiatry), equipping researchers in those disciplines and domains to better generate, evaluate, and develop their theories.

Formalizing a network theory of panic disorder serves two key purposes. First, it equips us to evaluate how well our theory achieves its fundamental aim: the *explanation* of panic disorder-related phenomena (van Rooij & Baggio, 2020). To evaluate whether a theory can explain a phenomenon, it is necessary to evaluate whether the phenomenon indeed follows from the theory (van Dongen et al., 2022). Explanation thus relies on our ability to deduce the behavior predicted by the theory. As noted, a theory expressed only in words – as nearly all theories of panic disorder are – is limited in its ability to support deduction and, thus, limited in its ability to demonstrate that the theory indeed explains what it purports to explain (Epstein, 2008; Smaldino, 2017). Formalizing our theory enables us to precisely

deduce what the theory predicts through computational model simulations and, thereby, to rigorously evaluate whether the theory can explain core panic disorder-related phenomena.

Second, formal theories provide a bulwark against theory stagnation by clarifying how the theory can be improved. Most immediately, the specificity required by a formal theory can reveal hidden assumptions and unknowns masked by the imprecision of verbal theories (Epstein, 2008; Guest & Martin, 2021; Smaldino, 2016). Formalization can thus identify opportunities to clarify the theory, uncover aspects of the theory for which there may be fruitful disagreement among theorists, and identify areas in need of further empirical research. More fundamentally, by equipping us to better evaluate what the theory can explain, formal theories can expose a theory's explanatory shortcomings and, by doing so, reveal how the theory can be revised or replaced (Haslbeck et al., 2021; Robinaugh et al., 2021).

The construction and evaluation of our theory will proceed as follows. In Section 1, we propose a formal network theory of panic disorder, expressing the relations among theory components in a set of differential equations. In Section 2, we leverage the deductive power of this formal theory to evaluate whether the theory can explain five robust panic-disorder related phenomena. In Section 3, we propose a theory-driven research agenda that follows from the formal theory. This agenda marks a significant departure from current research practices, emphasizing rigorous descriptive research and ongoing theory development, with explanation as a central evaluative criterion. Finally, we discuss the implications of this work for our understanding of mental disorders as complex systems.

Section 1: A Formal Network Theory of Panic Disorder

The network theory of psychopathology posits that mutually reinforcing relationships among symptoms figure prominently in the etiology of mental disorders. Accordingly, symptoms and the relationships among them will constitute the core structure of our theory. Specifically, we posit that panic disorder arises from three interlocking feedback loops

among symptoms: (a) an amplifying feedback loop between the two core symptoms of a panic *attack* (i.e., arousal and perceived threat), (b) a dampening feedback loop between perceived threat and escape behavior, and (c) a slow amplifying feedback loop among core symptoms of panic *disorder* (see Figure 1). For each, we describe key symptoms, posit causal relationships among those symptoms, and then express those relationships as a set of differential equations. These equations - and their substantive interpretation - constitute the network theory of panic disorder.

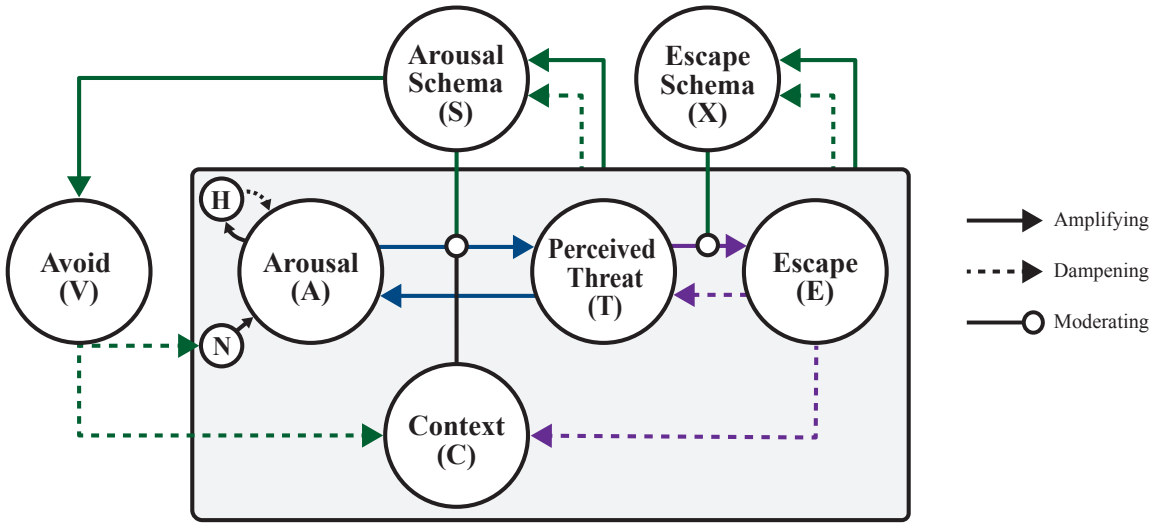

Figure 1. A Causal Diagram of Panic Disorder. The causal diagram depicts the components of the theory and the relationships among them. Components inside the gray box change on a time scale of minutes. The components outside the gray box change on a time scale of days. Arrows indicate causal effects. Solid arrows indicate amplifying (positive) effects. Dashed arrows indicate dampening (negative) effects. Lines ending in an open circle indicate moderation of the causal effects on which they terminate. The paired solid and dashed lines terminating on arousal schema and escape schema indicate an effect that can be either amplifying or dampening. These lines initiate from the grey box designating fast-changing components, rather than any individual component, signifying that this effect is dependent on the aggregate behavior of these components. The system depicted here can be broken down into three interlocking feedback loops: (a) an amplifying feedback loop (depicted in blue) between arousal and perceived threat; (b) a dampening feedback loop (depicted in purple) among perceived threat, escape behavior, and context; and (c) a feedback loop (depicted in green) among arousal schema, escape schema, avoidance, and the aggregate behavior of the fast-moving components depicted in the gray box. This final feedback loop can be amplifying or dampening depending upon the aggregate behavior of arousal, perceived threat, and escape behavior.

Part 1: The Amplifying Feedback Between Panic Attack Symptoms

Theory Components. Recurrent panic attacks are the cardinal symptom of panic disorder and are defined by two criteria: somatic symptoms of autonomic arousal (e.g., heart racing) and fear. These twin criteria are long-established (Frances et al., 1993) but provide a fuzzy delineation of panic phenomenology. The somatic symptoms listed in these criteria include the experience of fear (e.g., the fear of dying) and fear is itself characterized by many of the somatic symptoms (American Psychiatric Association, 1980; Cacioppo et al., 2000). Accordingly, these criteria do not identify fully distinct symptoms for our theory. We will consider the cognitive perception of threat to be the distinctive component of a panic attack identified by the 'fear' criterion and, therefore, will consider ***perceived threat*** and autonomic arousal (hereafter, ***arousal***) to be the core symptoms of a panic attack.

The importance of arousal to panic attacks is established principally by self-reported bodily sensations. Individuals experiencing panic attacks report the sudden onset of heart palpitations, difficulty breathing, dizziness, and faintness (Barlow & Craske, 1988; Brown & Cash, 1990; de Beurs et al., 1994) and other sensations that have long been recognized as products of the autonomic nervous system (Berrios, 1999). Consistent with these reports, panic attacks that occur in the laboratory are associated with increases in autonomic nervous system activity (Cohen et al., 1985; Goetz et al., 1993; Lader & Mathews, 1970). Ambulatory assessments have produced more equivocal findings, a point to which we will return later in this article. These equivocal findings notwithstanding, self-report and laboratory-based data suggest that elevated arousal is a core component of a panic attack.

The importance of perceived threat is similarly established by self-report. From the earliest accounts of panic attacks, researchers have described uncontrollable worry and "ideas

of the extinction of life" (Freud, 1962, p. 93; Leroux, 1889), with thoughts often focused on perceived physical (e.g., heart attack), psychological (e.g., going crazy), or social (e.g., making a fool of oneself) consequences of arousal-related bodily sensations (Hibbert, 1984; Ottaviani & Beck, 1987). Panic patients often fear additional bodily sensations in ways that are in keeping with local understandings of physiology (Lewis-Fernandez et al., 2010). For example, Cambodian refugees with panic disorder commonly dread sensations of orthostatic dizziness, interpreting such symptoms as signaling a potentially lethal episode of *kyol goeu* ("wind overload"; Hinton et al., 2004; Hinton et al., 2001). Although "wind overload" and heart attacks are superficially distinct, they both concern seemingly uncontrollable arousal-related bodily sensations (Marques et al., 2011; Taylor, 1994). Accordingly, perceived threat in panic attacks signifies the appraisal of arousal-related bodily sensations as a source or indicator of threat.

Causal Relationships Between Perceived Threat and Arousal. Numerous theorists have posited an amplifying feedback loop between arousal and perceived threat (Barlow, 1988; Beck, 1988; Clark, 1986; Ehlers & Margraf, 1989; Margraf et al., 1986; Rapee, 1987; van den Hout & Griez, 1983). When arousal is detected and interpreted as a threat (e.g., indicating a heart attack), arousal will increase to prepare the body to respond (e.g., fight or flight; Cannon, 1915). That increase in arousal will further exacerbate perceived threat, creating a "vicious cycle" that culminates in a panic attack (Clark, 1986, p. 463). At their core, these theories suggest two causal effects: an effect of perceived threat on arousal and an effect of arousal on perceived threat.

***The effect of perceived threat on arousal* (*T→A*).** The causal effect of perceived threat on arousal (*T→A*) reflects the body's fight-or-flight response to perceived danger. When a threat is perceived, arousal will increase. For simplicity, we posit that the effect of perceived threat on change in arousal is linear, embodying the position that small and distal

threats prompt minor increase in arousal and large, proximal threats prompt substantial increase in arousal. We will express this effect as a differential equation, characterizing the rate of change of arousal (A) with respect to time (t). This rate of change is denoted mathematically in the derivative of arousal, $\frac{dA}{dt}$, which tells us how arousal will change from its current state as time progresses. If $\frac{dA}{dt}$ is positive, arousal will increase. If $\frac{dA}{dt}$ is negative, arousal will decrease.

We will define $\frac{dA}{dt}$ as a function of the current level of arousal and perceived threat (T), thereby representing the causal effect of perceived threat on arousal. We use a *rate parameter*, denoted α_A, to define the intrinsic rate at which arousal can change, and a *slope parameter*, β_A, which defines the strength of the linear effect of perceived threat on the rate of change in arousal.[1] Accordingly, whereas the rate parameter is a property of arousal itself, the slope parameter concerns the effect of perceived threat on arousal. Together, this yields the equation:

$$\frac{dA}{dt} = \alpha_A(\beta_A T - A) \quad (1)$$

This equation is not intended to represent a fully developed quantitative theory of the body's fight-or-flight system. It is a minimal model: a high-level representation of a process that we posit contributes to panic disorder. Here, we take an additional simplifying step by setting $\beta_A = 1$, conceptualizing $A = 0$ as the within-person equilibrium of arousal and $A = 1$ as the level of arousal elicited by the maximal level of perceived threat ($T = 1$) for a given individual. With this simplifying step, if T is greater than A, then the rate of change for arousal ($\frac{dA}{dt}$) will be positive and arousal will increase. If T is less than A, the rate of change will be negative, and arousal will decrease. If T is equal to A, the rate of change will be zero

[1] Throughout our set of differential equations, we will use α to refer to rate parameters and β to refer to slope parameters, with subscripts denoting the variable whose rate of change is being defined by the equation in which the parameter appears. All equations are unitless.

and arousal will not change. Accordingly, for this simple equation, if we induce a sustained level of perceived threat *T,* then *A* will rise or fall until it is equal to *T*, at which point the rate of change will be 0 and *A* will cease to change. Notably, this also means that if there is an absence of perceived threat (*T*=0), *A* will move to 0, at which point it will cease to change.

The effect of arousal on perceived threat (A→T). The causal effect of arousal on perceived threat (*A→T*) consolidates two processes: the detection of arousal and the interpretation of arousal as a threat. To capture this causal effect, we define the rate of change of perceived threat ($\frac{dT}{dt}$) as a function of the current level of perceived threat (*T*) and arousal (*A*). The processes by which arousal triggers a perception of threat can be thought of as a signal detection process akin to a smoke alarm (Barlow, 1988). For such an "alarm system" to work effectively, low level fluctuations in arousal arising from ordinary activities should have negligible effect on perceived threat. However, beyond a given threshold of normal variation, arousal should begin to elicit perceived threat, with the strength of that effect growing with increasing arousal until tapering as it approaches maximal perceived threat (*T* = 1). A sigmoidal (s-shaped) logistic function allows us to capture these aspects of the *A→T* effect (see Figure 2). Two parameters determine the shape of this sigmoidal effect: λ_T and κ_T. The λ_T parameter controls the mid-point of the s-shaped *A→T* effect. The κ_T parameter controls the slope of the *A→T* effect, with higher values signifying a steeper slope. Together with a rate parameter, α_T, this yields the equation:

$$\frac{dT}{dt} = \alpha_T \left(\frac{1}{1+e^{-\kappa_T(A-\lambda_T)}} - T \right) \quad (2)$$

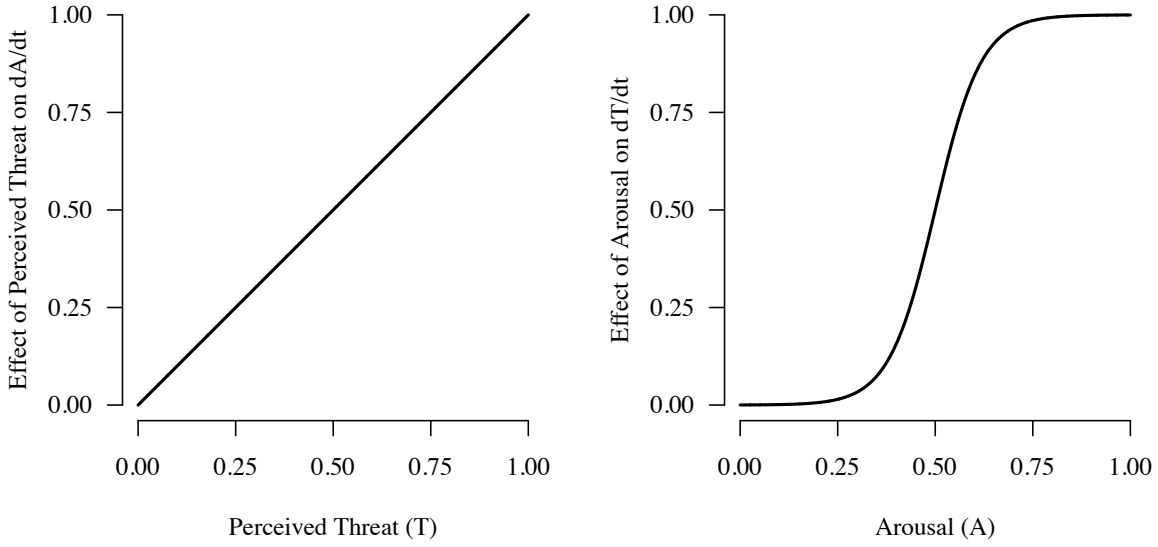

Figure 2. Linear and sigmoidal effects. The effect of perceived threat on the rate of change in arousal ($\frac{dA}{dt}$) is linear. Low levels of perceived threat have a small positive effect on $\frac{dA}{dt}$ and high levels of perceived threat have a large positive effect. In contrast, the effect of arousal on the rate of change in perceived threat ($\frac{dT}{dt}$) is sigmoidal. Here, the parameter controlling the mid-point of the sigmoid, λ_T, is equal to 0.50, meaning that the mid-point of the sigmoid occurs at $A = 0.50$. In this case, low elevations in arousal (e.g., $A < .20$) have negligible effect on $\frac{dT}{dt}$. If the λ_T parameter were raised, the higher mid-point value would shift the sigmoid to the right, and even moderate levels of arousal would have negligible effect on $\frac{dT}{dt}$. Conversely, if $\lambda_T$were lowered, the sigmoid would shift to the left and relatively low elevations in arousal would have a positive effect on $\frac{dT}{dt}$. Accordingly, the λ_T parameter plays an important role in defining the strength of the $A \rightarrow T$ effect.

Arousal schema moderates the effect of arousal on perceived threat (A→T).

Cognitive-behavioral theories posit that the effect of arousal on perceived threat ($A \rightarrow T$) differs across people. For example, Clark and colleagues hold that individual differences in vulnerability to panic attacks arise from an *enduring tendency* to catastrophically misinterpret arousal-related bodily sensations. Consistent with this position, individuals with panic disorder are more likely than those without to negatively interpret arousal-related bodily sensations (Clark et al., 1997). Reiss and McNally (1985) proposed that this enduring tendency could be attributed to one's *beliefs* about arousal. If one believes arousal to be dangerous, a given instance of elevated arousal is more likely to be interpreted as a threat. To

evaluate this hypothesis, they developed the *anxiety sensitivity index*, a measure intended to assess the belief that the bodily sensations that accompany anxiety are dangerous (Reiss et al., 1986) and there is considerable evidence linking scores on the anxiety sensitivity index to the experience of panic attacks (McNally, 2002). Learning theorists have similarly posited that in those with panic disorder, arousal-related bodily sensations have become associated with panic. In other words, small elevations in arousal have become signals of a possible impending attack (Bouton et al., 2001, p. 22), producing a strong $A \rightarrow T$ effect.

Here, we will integrate these three theoretical positions and posit that the 'alarm system' sensitivity embodied in the $A \rightarrow T$ effect is dependent on one's ***arousal schema (S)***. Schemata are cognitive structures: "a relatively cohesive and persistent body of knowledge capable of guiding subsequent perception and appraisals" (Segal, 1988, p. 147). We will consider arousal schema to include beliefs about arousal, as embodied in the concept of anxiety sensitivity, as well as one's learned associations with arousal, as emphasized in learning theories of panic disorder. Arousal schema guides the perception and appraisal of arousal, thereby moderating the relationship between arousal and perceived threat. We will consider arousal schema to be continuous and to range from *0* (indicating an absence of beliefs and learned associations whereby arousal poses or signals danger) to *1* (indicating beliefs or associations in which arousal poses or signals maximal danger).

In our model, arousal schema moderates the strength of the $A \rightarrow T$ effect via its effect on the two parameters that define the $A \rightarrow T$ effect, which we will now denote as $\lambda_T[S]$ and $\kappa_T[S]$ to indicate their dependence on arousal schema. We posit that an increase in arousal schema decreases $\lambda_T[S]$, moving the mid-point of the sigmoidal $A \rightarrow T$ effect to lower levels of arousal (i.e., to the left, in Figure 2), and increases $\kappa_T[S]$, steepening the slope of the sigmoid. The equations implementing this position are presented in Supplementary Materials A. These equations embody three theoretical positions. First, arousal schema is the primary component

determining the strength of the $A \rightarrow T$ effect. Second, because both parameters defining the $A \rightarrow T$ effect depend on S, they move together, precluding some forms of the sigmoidal $A \rightarrow T$ effect (e.g., there will never be an individual for whom both the mid-point and the steepness of the sigmoid are very low). Third, as arousal schema increases, progressively lower levels of arousal become capable of eliciting high levels of perceived threat.

The role of arousal schema in altering the $A \rightleftarrows T$ feedback loop is illustrated in Figure 3. In the language of dynamical systems, when arousal schema is low (left column), the $A \rightleftarrows T$ feedback loop is weak and the $A \rightleftarrows T$ system has a single *stable equilibrium* where arousal is at its within-person equilibrium ($A = 0$) and there is an absence of perceived threat ($T = 0$). If perturbed, the system will return to this stable state. As arousal schema increases (middle and right column), the $\lambda_T[S]$ parameter decreases, moving the sigmoidal $A \rightarrow T$ effect to the left, thereby making lower levels of arousal capable of eliciting perceived threat. In other words, the $A \rightarrow T$ effect becomes stronger. Eventually, this continuous change in arousal schema produces a discontinuous change in the system. The system develops an *alternative stable equilibrium* characterized by substantially elevated arousal and perceived threat (i.e., panic). If sufficiently perturbed, the system can now exhibit runaway amplifying feedback into the alternative stable state of panic. The higher the arousal schema, the more vulnerable the system is to this amplifying feedback. In other words, the higher one's arousal schema, the more vulnerable one is to the experience of a panic attack.

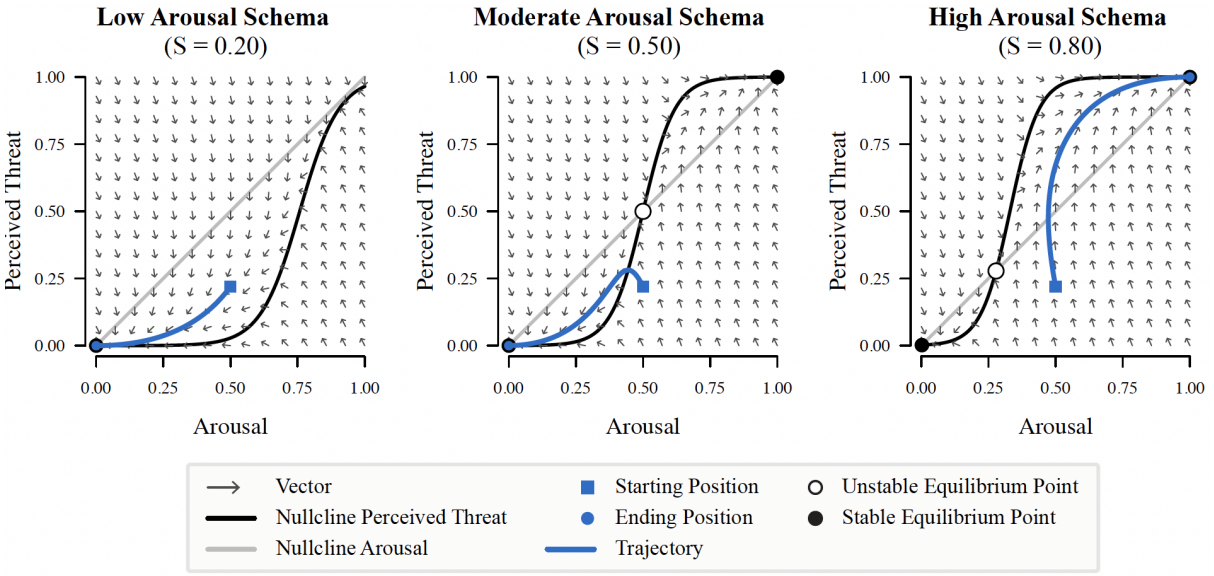

Figure 3. Arousal schema shapes the behavior of the feedback loop between arousal and perceived threat. The phase portraits presented here depict how the simple system of arousal and perceived threat will change over time under conditions of low, moderate, and high arousal schema. The arrows in the background of each portrait are a *vector field*. Each vector (arrow) indicates the direction the system will move next from that point in the state space (i.e., the space defined by arousal and perceived threat) according to Equations 1 & 2. The grey and black lines are "nullclines," identifying where the rate of change for arousal (grey) and perceived threat (black) is equal to zero. The points where these lines intersect are *equilibria* where the rate of change of both components is zero and, therefore, the system will remain fixed. Open circles identify *unstable equilibria* (repellors) from which the system will tend to move away. The filled black circles identify *stable equilibria* (attractors), towards which the system will tend to move. When arousal schema is low (left column), the system always moves toward the sole stable equilibrium: $A = 0.00$ and $T = 0.00$. For example, if the system starts at $A = 0.50$ and $T = 0.20$ (blue square), the system will move through the state space to that single stable equilibrium of $A = 0.00$ and $T = 0.00$ (blue line terminating in a blue circle). As arousal schema increases, there is a qualitative change in the systems dynamics: two new equilibria emerge (one stable and one unstable) and there are now paths through the vector field that lead to an alternative stable state of high arousal and high perceived threat. When arousal schema is high, these paths begin even at moderate levels of arousal. If the system again starts at $A = 0.50$ and $T = 0.20$, it will now end in a state of high arousal and high perceived threat. Accordingly, as arousal schema increases, the system becomes more vulnerable to amplifying feedback between arousal and perceived threat.

Additional Effects on Arousal. Figure 3 depicts the dynamics of the $A \rightleftarrows T$ feedback loop where arousal is influenced only by itself and perceived threat. To better represent all relevant factors affecting arousal, we incorporated two additional assumptions. First, we assume arousal fluctuates over time due to internal physiological processes and from interaction with the environment independent of perceived threat. We model these effects as

stochastic variation (noise; *N*) that perturbs arousal above and below a stable within-person equilibrium ($A = 0$). Second, we assume that the body's regulatory processes (**homeostatic feedback; *H*)** return arousal to equilibrium following extreme perturbations, such as a panic attack. These auxiliary assumptions and the equations defining them are described further in Supplementary Materials A. With these assumptions, the equation defining $\frac{dA}{dt}$ becomes:

$$\frac{dA}{dt} = \alpha_A((\beta_A T + N - H) - A) \quad (3)$$

Together, the equations defining arousal and perceived threat – and their substantive interpretation – represent a minimal model of the feedback loop between arousal and perceived threat.

Part 2: The Dampening Feedback of Escape Behavior.

Theory Components. Although not identified in DSM diagnostic criteria, researchers studying panic attacks commonly describe a third component of panic-attack phenomenology: *escape behavior* (Barlow & Craske, 1988; Salkovskis, 1988; van den Hout & Griez, 1983). The urge to escape is among the more strongly endorsed features of these attacks (Norton et al., 2008) and some researchers have used the desire to escape as a criterion for identifying panic attacks (Chambless et al., 1985). Importantly, escape behavior (also commonly referred to as "safety-seeking" behavior) is not confined to overt efforts to flee a situation. "Patients sit down, hold onto walls… and generally engage in behaviors which they believe may abort imminent disaster" (Salkovskis, 1988, p. 130). Accordingly, escape behavior denotes any behavior aimed at preventing or mitigating the anticipated consequences of currently elevated autonomic arousal (Salkovskis, 1991). We will consider escape behavior to be continuous, signifying the severity of threat that the behavior is intended to mitigate ranging from 0 (an absence of escape behavior) to 1 (escape behavior intended to eliminate or mitigate the highest possible threat).

Relationships Among Perceived Threat and Escape Behavior. Cognitive behavioral theorists have noted that effortful attempts to directly attenuate one's arousal are unlikely to be effective (Clark, 1999). Accordingly, we posit that the effect of escape is on perceived threat: as perceived threat rises, escape behavior is engaged (*T*→*E*); as escape behavior is engaged, perceived threat diminishes (*E*→*T*). We detail these effects below.

The Effect of Escape Behavior on Perceived Threat (E→T). To incorporate the effect of escape behavior on perceived threat, we update the equation that defines perceived threat, adding a negative effect of *E* to the equation that defines the rate of change in *T,* and a parameter β_T that regulates the strength of that effect. This yields an updated equation for *T* that replaces the prior equation for perceived threat (Equation 3) in our model:

$$\frac{dT}{dt} = \alpha_T \left(\frac{1}{1+e^{-\kappa_T[S](A-\beta_T E-\lambda_T[S])}} - T \right) \quad (4)$$

The Effect of Perceived Threat on Escape Behavior (T→E). To embody the proposed effect of perceived threat on escape behavior, we define the rate of change in escape behavior ($\frac{dE}{dt}$) as a function of escape behavior (*E*) and perceived threat (*T*). We define the effect of perceived threat on escape behavior *(T→E)* to be sigmoidal, with the parameters κ_E and λ_E determining the slope and mid-point for this effect, respectively. The sigmoidal effect allows us to embody the theoretical position that small perceived threats may arise without eliciting corresponding escape behavior. Together, this sigmoidal effect and a rate parameter α_E yield the equation:

$$\frac{dE}{dt} = \alpha_E \left(\frac{1}{1+e^{-\kappa_E(T-\lambda_E)}} - E \right) \quad (5)$$

People differ in the threats they can tolerate without escape, and several theorists have posited that one's ability to cope with panic-related threat (i.e., *panic self-efficacy*) may play a significant role in the development and treatment of panic disorder (Beck et al., 1985; Casey, Oei, Newcombe, et al., 2004; Fentz et al., 2013; Gallagher et al., 2013). Casey et al.

(2004) and Sandin et al. (2015) posit that panic self-efficacy is a new path in the vicious cycle of panic attacks, acting as a second mediator (alongside catastrophic misinterpretations) of the effect of arousal on perceived threat. However, as typically characterized and assessed, panic self-efficacy is more dispositional than this account would suggest, reflecting enduring beliefs about one's ability to cope rather than occurrent thoughts about coping in the moment. Moreover, although one's perceived ability to cope with elevated arousal may plausibly affect one's cognitive appraisal of arousal, the concept of self-efficacy has a more behavioral focus, emphasizing the ability to persist in carrying out the behaviors necessary to achieve a particular goal (Bandura, 1977). In the context of panic disorder, this behavioral focus of self-efficacy suggests the role of self-efficacy is not in mediating the appraisal of arousal, but rather in the actions that follow from perceived threat; that is to say, in whether or not to escape.

We adopt this behaviorally focused conception of self-efficacy. We use the term ***escape schema (X)*** to refer to this component to avoid conflating it with work on panic self-efficacy that emphasizes the role of self-efficacy in the appraisal of arousal, which we will consider to be part of arousal schema. We consider escape schema to reflect one's beliefs about the level of perceived threat that one can cope with or tolerate without engaging in escape behavior (thus persisting in their current behavior), ranging from a belief that one cannot cope with or tolerate any threat without escaping (0; no "panic self-efficacy") to the belief that one can cope with or tolerate the highest possible threat without escaping (1; high "panic self-efficacy"). Accordingly, higher escape schema values *raise* the threshold at which perceived threat elicits escape behavior, making escape behavior less likely to occur. To incorporate escape schema, we extend the equation defining escape to include escape schema as follows:

$$\frac{dE}{dt} = \alpha_E \left(\frac{1}{1+e^{-\kappa_E((T-X)-\lambda_E)}} - E_t \right) \quad (6)$$

With this extension, escape behavior develops in response to perceived threat that exceeds one's perceived ability to cope or tolerate (i.e., $T - X > 0$). If X is high, then high levels of T can occur without eliciting escape behavior. Conversely, if X is low, even low T will elicit escape behavior; a tendency that, as described further in the next section, plays a crucial role in the development of panic disorder.

Part 3: The Slow Amplifying Feedback Among Panic Disorder Symptoms

Theory Components. In the DSM-IV, the Panic Disorder syndrome expanded to include three new symptoms: worry about the implications of an attack, persistent concern about additional attacks, and avoidance behavior (American Psychiatric Association, 1994). Worry suggests episodic thoughts about panic attacks and their consequences and such thoughts are endorsed by many who experience panic attacks (Craske et al., 2010). This panic-related worry is readily captured by a component already in the model: perceived threat; specifically, low-level perceived threat outside the context of a panic attack. "Persistent concern" either signifies episodic thoughts about panic attacks and their consequences, rendering it redundant with panic-related worry, or persistent beliefs about the dangerousness of panic-related bodily sensations (Craske et al., 2010, p. 104; McNally, 1994, p. 8). We favor the second interpretation and, hence, consider persistent concern to be captured by an existing model component: "arousal schema." The third symptom, avoidance, denotes behavior aimed at preventing exposure to elevated arousal (e.g., by not drinking coffee) or exposure to situations that heighten the perceived consequences of elevated autonomic arousal (e.g., the middle of a crowded theater). Whereas escape concerns a threat that is already present, avoidance is preemptive, aimed at preventing the threat from arising. Given this distinction, we will incorporate avoidance as a separate component in the theory.

Relationships Among Panic Attacks, Persistent Concern, and Avoidance. In an early contribution to panic disorder theory, Goldstein and Chambless (1978) posited a vicious

cycle that operates, not among the fast-moving symptoms of a panic attack, but rather among the slow-moving symptoms of panic disorder. Panic attacks, they posit, strengthen the belief that arousal is dangerous, thereby both producing avoidance behavior and increasing vulnerability to panic attacks. Reiss and McNally (1985) similarly argue that panic attacks are one path by which an individual may develop the belief that anxiety-related bodily sensations have harmful consequences. Bouton, Mineka, and Barlow (2001) agree, positing that the terror of an initial panic attack establishes an association between certain bodily sensations and full-blown panic such that the former predicts the impending possibility of the latter.

A causal effect of panic attacks on arousal schema could explain how an initial attack may lead to the onset of panic disorder. However, it raises a critical question: why do those who develop panic disorder learn that the bodily sensations associated with a panic attack are dangerous rather than harmless? The repeated failure of a catastrophe to materialize should lead to more accurate beliefs regarding arousal, yet beliefs about their danger arise and persist. Clark and colleagues have posited several processes that maintain such beliefs (Clark, 1999), including the possibility that escape behaviors engaged before or during an attack may shield catastrophic beliefs from refutation (Salkovskis, 1991; Salkovskis et al., 1999). The absence of the feared consequence is attributed to the escape behavior, leaving intact the belief that bodily sensations are dangerous. Learning theorists similarly argue that these behaviors act as inhibitors, predicting an *absence* of the feared consequence. As such, they eliminate the discrepancy between prediction and observation, preventing the individual from learning a more accurate and benign prediction about the consequences of arousal-related bodily sensations (Bouton et al., 2001). Hence, across theories, cognitive and behavioral theorists have argued that escape behavior plays a critical role in determining whether substantially elevated arousal strengthens or disconfirms the belief that arousal is threatening.

The Effect of Panic Attacks on Arousal Schema (P→S). Beliefs about the danger of arousal-related bodily sensations (i.e., arousal schema) do not fluctuate on the same seconds-to-minutes time scale as arousal and perceived threat. Instead, they rise or fall over days or weeks. To accommodate these distinct scales, we divide the components of the model into fast-changing components moving at a time scale of minutes (i.e., arousal, perceived threat, escape) and slow-changing components moving at a time scale of days (i.e., arousal schema, escape schema, and avoidance; see Figure 1).

Although operating on different time scales, the slow- and fast-moving components affect one another. The slow-moving components serve as constants with respect to the fast-changing components, helping to define parameters in the equations that govern their behavior (e.g., see Equations 4 and 5). Conversely, the fast-changing components affect slow-changing components via the ability to learn.

Consistent with prior theories, we posit that what is learned from experiences of elevated arousal and perceived threat depends on the combination of arousal, perceived threat, and escape behavior. To incorporate this effect of panic attacks on arousal schema, we incorporate each of these components, aggregated over time, in the equation defining the rate of change in arousal schema ($\frac{dS}{dt}$). Rate parameters represent the rate at which beliefs and associations are either acquired (α_{S1}) or extinguished (α_{S2}; see Equation 7).

Overall, $\frac{dS}{dt}$ is given by the equation:

$$\frac{dS}{dt} = \begin{cases} 0, & if\ \max(F_{t-\Omega}\,..\,F_t) < \theta \\ \alpha_{S1}(\max(T_{t-\Omega}\,..\,T_t, S) - S), & if\ \max(F_{t-\Omega}\,..\,F_t) \geq \theta,\ \max(E_{t-\Omega}\,..\,E_t) > \mu \\ -\alpha_{S2}\,S, & if\ \max(F_{t-\Omega}\,..\,F_t) \geq \theta, \max(E_{t-\Omega}\,..\,E_t) \leq \mu \end{cases} \quad (7)$$

Three conditional statements determine the appropriate calculation of $\frac{dS}{dt}$. First, the parameter θ is used to determine whether arousal and perceived threat are sufficiently present to allow for learning to occur. To make this determination, we calculate the geometric mean

of arousal and perceived threat ($\sqrt{A \times T}$), which we will refer to as **Fear (*F*)**, taking the position that these are core ingredients of emotion that when jointly present are commonly experienced as fear. The use of the geometric mean embodies the theoretical position that both arousal and perceived threat must be present for this type of learning to occur.

If fear is low (i.e., $max(F_{t-\Omega} .. F_t) < \theta$), there is no opportunity for learning, and arousal schema will not change (see Equation 7). If fear is elevated, there is opportunity for learning, and the lesson learned depends on whether escape behavior was also present. If individuals engage in escape behavior during these episodes (e.g., leave the crowded subway train), they will counterfactually infer that the anticipated consequences of arousal (e.g., fainting on the train) would have occurred if not for the escape behavior. Thus, they will learn that arousal is as dangerous as it was perceived to be during the attack. We represent this learning in our model with a second conditional statement: If the maximum level of escape behavior over a given time period Ω (i.e., $max(E_{t-\Omega} .. E_t)$) exceeds an established threshold (given by parameter μ), then arousal schema will move toward the maximum level of perceived threat during that period of time (i.e., $max(T_{t-\Omega} .. T_t)$, at a rate determined by the growth (or acquisition) parameter α_{S1}. In our implementation of these equations, we will set Ω to 1440 and interpret this time period as 1 day (i.e., 60 minutes x 24 hours).

If an individual experiencing fear does *not* engage in escape behavior, they are able to learn that, even when not engaging in escape behavior, no adverse consequences occur (an effect that, as we will see in Section 2, plays a critical role in cognitive behavioral therapies for panic disorder). For example, if the individual remains on the crowded subway train and observes their surge of arousal pass without consequence, they can learn that escaping the train is unnecessary for arousal to wane without incident. Learning that arousal is *not* dangerous is embodied in the third conditional statement that determines the calculation of

$\frac{dS}{dt}$: if escape behavior is below a given threshold (i.e. $max(E_{t-\Omega} .. E_t) \leq \mu$), then the arousal schema variable will move toward 0 at a rate determined by the decay parameter α_{S2}.

The Effect of Panic Attacks on Escape Schema (P→X). The effect of panic attacks on arousal schema is mirrored for escape schema. If fear is elevated (i.e., $\max(F_{t-\Omega} .. F_t) \geq \theta$), then one has the opportunity to learn. If escape behavior is also present, then one mistakenly concludes that escape behavior helped to stave off perceived threat and, therefore, the level of perceived threat one will tolerate without engaging in escape behavior is reduced. However, if escape behavior is not present, the one is able to learn that escape behavior is not necessary to prevent the perceived threat and, therefore, the level of perceived threat one will tolerate without engaging in escape behavior rises.

$$\frac{dX}{dt} = \begin{cases} 0, & if\ \max(F_{t-\Omega} .. F_t) < \theta \\ \alpha_{X1}(\max(T_{t-\Omega} .. T_t, X) - X), & if\ \max(F_{t-\Omega} .. F_t) \geq \theta, \max(E_{t-\Omega} .. E_t) \leq \mu \\ -\alpha_{X2}\, X, & if\ \max(F_{t-\Omega} .. F_t) \geq \theta, \max(E_{t-\Omega} .. E_t) > \mu \end{cases} \quad (8)$$

The Effect of Arousal Schema on Avoidance (S→V). As beliefs about the danger posed by arousal change, so does one's willingness to engage in activities that elicit arousal or to place oneself in contexts where the consequences of panic attacks may be especially severe. Accordingly, the rate of change in avoidance ($\frac{dV}{dt}$) is a function of the current level of avoidance (V) and of arousal schema (S). As with the effect of perceived threat on escape behavior, we posit a sigmoidal effect, with slope parameter κ_V and mid-point parameter λ_V, bounding avoidance behavior between 0 (an absence of avoidance) and 1 (maximal avoidance) and setting a threshold at which arousal schema begins to lead to avoidance:

$$\frac{dV}{dt} = \alpha_V(\frac{1}{1+e^{-\kappa_V(S-\lambda_V)}} - V) \quad (9)$$

The Effect of Avoidance on Stochastic Variation in Arousal (N) and Context (V→N, V→C). Avoidance has its effect on two fast-changing components. First, avoidance helps define a parameter in the equations that determines the amount of stochastic variation in

arousal (*N*). With higher avoidance, the stochastic variation in arousal is dampened, representing a reduction in activities that elicit fluctuations in arousal, such as drinking coffee or walking quickly up the stairs. Second, avoidance affects the extent to which people are willing to enter a situation in which the perceived likelihood or consequences of a panic attack are heightened (e.g., a crowded theater; Klein & Klein, 1989). Accordingly, we added a binary **context (*C*)** variable to the model that acts as a second moderator of the effect of arousal on perceived threat. The value of *C* (0 or 1) is chosen probabilistically (e.g., 10% likelihood of entering panic-predisposing context [*C*=1]) and, once chosen, remains fixed for a specified period (e.g., 60 minutes), after which it is chosen again. When *C*=1, the effect of arousal on perceived threat is strengthened. With higher avoidance, the likelihood of entering such a context diminishes. The roles of avoidance in the equations determining *N* and *C* as well as the moderating effect of *C* on $A \rightarrow T$ are each described further in Supplementary Materials A.

Summary. The equations presented here, and their substantive interpretation, constitute a formalized network theory of panic disorder: a theory that posits the precise relationships among a set of symptoms and expresses those relationships as set of mathematical equations. We implemented this theory in the software environment R (R Core Team, 2014) as a series of difference equations (see Supplementary Materials A), providing us with a computational model that can precisely deduce the system behavior implied by the theory. This computational model is freely available at https://github.com/jmbh/PanicModel. In the remainder of this paper, we use this computational model as a tool for evaluating whether the theory can explain what it purports to explain (Epstein, 2008; Smaldino, 2017) and, subsequently, for informing how the theory can be improved.

Section 2: Evaluating the Network Theory of Panic Disorder

The ability to explain phenomena is a chief criterion by which psychological theories should be evaluated (van Rooij & Baggio, 2020). A theory explains a phenomenon if one can demonstrate that the phenomenon indeed follows from the theory (van Dongen et al., 2022). In contrast to theories expressed only in words, computational models provide considerable support for evaluating explanation by equipping us to precisely deduce whether a given phenomenon follows from the theory.

In this section, we use the computational model developed in Section 1 to evaluate the network theory of panic disorder, determining whether the theory explains the following five robust panic-disorder related phenomena. First, panic attacks are characterized by a specific phenomenology: a rapid surge of arousal and perceived threat that occurs in the absence of an external threat (Barlow & Craske, 1988). Second, individuals vary in the propensity to experience panic attacks. This is perhaps most clearly illustrated in the biological challenge literature, where the same perturbation to arousal-related bodily sensations elicits panic attacks in some individuals but not others (Clark, 1993; Liebowitz et al., 1984; Rapee, 1995; Woods et al., 1988). Third, recurrent panic attacks are often accompanied by avoidance behavior and persistent beliefs regarding the danger of arousal (Buller et al., 1986; White et al., 2006). That is, these symptoms often cohere as a syndrome. Fourth, panic attacks often occur in the absence of panic disorder. More than a quarter of U.S. adults report having had at least one panic attack over the course of their lives, but lifetime prevalence of panic disorder is only around 3.7% (Kessler et al., 2006). Finally, cognitive behavioral therapy reduces symptoms of panic disorder (Barlow, 1997). An adequate theory must be able to produce these fundamental features of panic attacks and panic disorder. We conducted three simulations to determine whether the network theory can do so. A reproducibility archive for all model simulations and corresponding figures is available at https://osf.io/gpu3v/.

Simulation 1: Biological Challenge

For the first simulation, we simulated perturbations to arousal analogous to biological challenges in which researchers use standard procedures (e.g., CO_2 inhalation) to induce arousal-related bodily sensations (Clark, 1993; Liebowitz et al., 1984; Rapee, 1995; Roberson-Nay et al., 2015; Woods et al., 1988). These simulated challenges induce a moderate level of arousal across all participants and, thus, are an ideal way to evaluate whether the theory can produce our first two phenomena of interest: (a) the basic phenomenology of a panic attack and (b) individual differences in the vulnerability to panic attacks.

We first created a sample of 1,000 simulated individuals, each of whom was assigned a different initial value for two key model components: arousal schema and escape schema. Arousal schema values were drawn from a normal distribution with a relatively low mean (.25) because most individuals endorse minimal beliefs regarding the danger of arousal-related bodily sensations (Deacon et al., 2003). We specified a standard deviation for the distribution (SD = .15) such that the proportion of systems with an alternative stable state in the simple system defined by arousal and perceived threat would be low, given the low lifetime prevalence of having at least one panic attack (Kessler et al., 2006). Escape schema values were drawn from a normal distribution with a mean of (.50) and standard deviation of .15. Together, these distributions can be regarded as auxiliary hypotheses regarding the distribution of beliefs about the danger of arousal and the need for escape behavior in the population prior to any experience of a panic attack (see Supplementary Materials B for further discussion).

With this sample, we evaluated how different individuals respond to the same perturbation. For each individual, we began with arousal equal to 0 and simulated 60 minutes of model behavior, inducing a moderate level of arousal (A=.50) at minute 10. To evaluate the response to perturbation, we calculated two variables of interest: (a) the peak level of fear

experienced in response to the perturbation and (b) the time to recover to the mean level of fear prior to the perturbation. In addition, we evaluated whether each simulated individual exhibited a panic attack in response to the perturbation. In the DSM, panic attacks are defined by "an abrupt surge of intense fear or intense discomfort that reaches a peak within minutes," accompanied by at least four or thirteen cognitive (e.g., fear of dying) or somatic symptoms (e.g., heart pounding, American Psychiatric Association, 2013). In this and all remaining simulations, we implemented these measurement criteria by evaluating (a) whether fear was significantly elevated ($F > 0.50$), (b) whether the maximal level of fear was at least double that of the fear level 10 minutes prior to this peak, and (c) whether arousal was elevated during the experience of fear ($A > 0.25$).

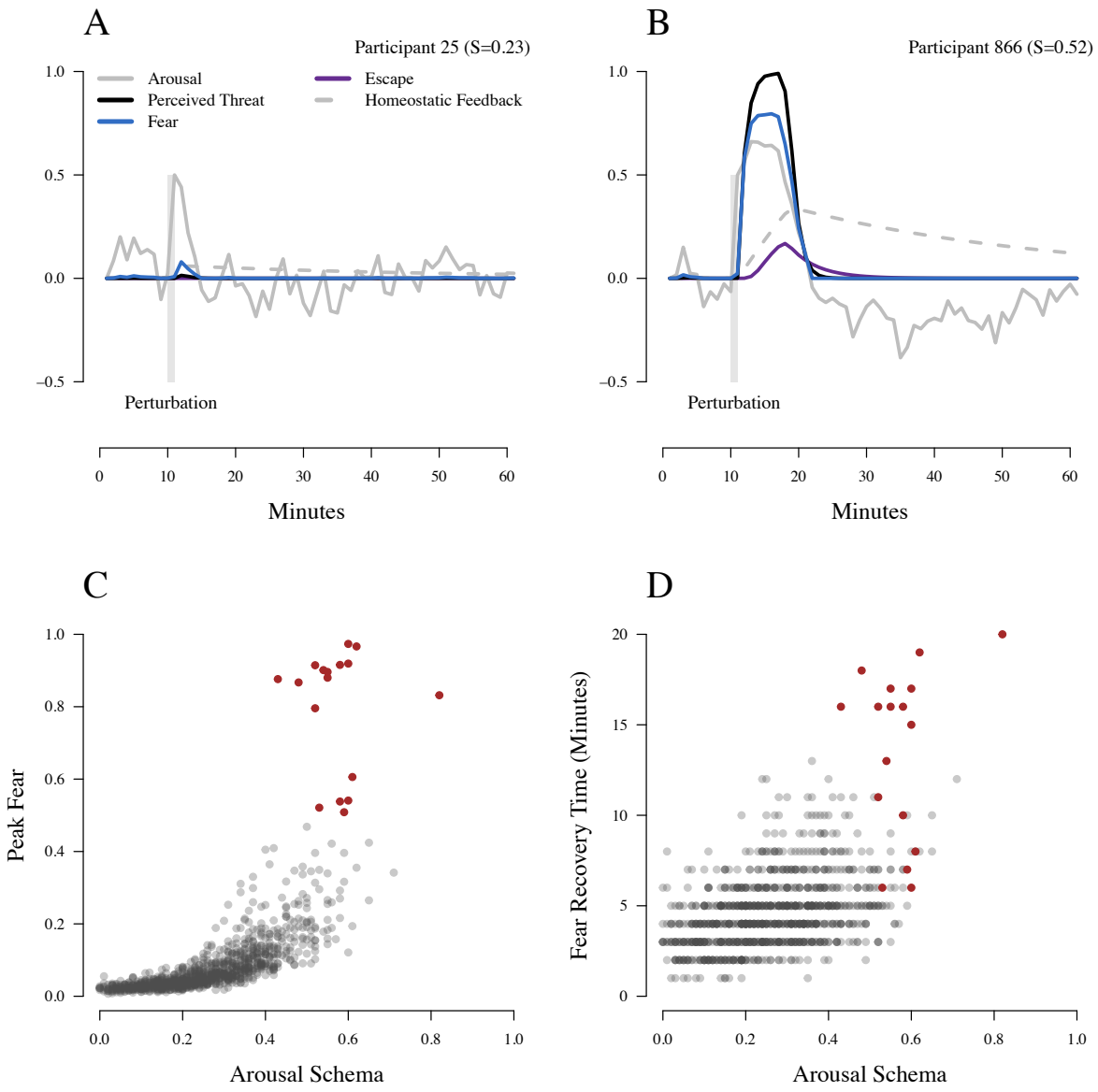

Figure 4. Results of a Simulated "Biological Challenge" Paradigm. *Panel A* depicts the response to an arousal perturbation occurring at Minute 10 for an individual with relatively low arousal schema (*S*=0.23). This individual exhibited only very brief and low-level elevation in fear (defined by the geometric mean of arousal and perceived threat) in response to the perturbation. *Panel B* depicts the response to the same perturbation in an individual with moderately elevated arousal schema (*S*=0.52). This individual experience a surge of fear that peaked within ten minutes of the perturbation. *Panel C* depicts the relationship between arousal schema and peak fear response in the full sample. *Panel D* depicts the relationship between arousal schema and the time to recover to the baseline level of fear in the full sample. In panels C and D, individuals who met criteria for a panic attack are depicted in red.

The results of this simulation are depicted in Figure 4. Although the timing and strength of the perturbation was consistent, responses to the perturbation varied widely. Most individuals exhibited minimal, transient fear in response to the perturbation. In the full

sample, the median peak fear was low (*Mdn* = .05) and the median time to recover was short (*Mdn* = 4 minutes). Panel A depicts a typical example of such a response. However, some individuals exhibited substantially higher fear (maximum peak fear = 0.97) and substantially longer to recover (maximum time to recover = 20 minutes). Panel B depicts a typical example of such a response. As depicted in Panels C and D, respectively, arousal schema was strongly associated with the peak level of fear in response to perturbation (r=.65 [.62, .69], p<.001) and was moderately associated with time to recover from fear (r=.48 [.43, .53], p<.001).

Most individuals in this simulation (98.3%) did not meet criteria for a panic attack, exhibiting only minimal elevations in fear following the perturbation (*Mdn* = .05 among those with no panic attack). However, in response to that same perturbation, a minority (1.7%) did meet panic attack criteria. These individuals exhibited substantial elevations in fear (*Mdn* peak fear = .79 among those with a panic attack). This surge of arousal and fear was followed by a period in which arousal went below its equilibrium for a sustained period (e.g., see Panel B; a phenomenon we discuss further in Section 3). Among those who exhibited a panic attack, 64.7% (1.1% of the full sample) exhibited at least modest escape behavior (E > .1). No escape behavior occurred in those without a panic attack. Arousal schema was elevated in those who exhibited a panic attack relative to those who did not (M=.57 vs. M=.26 in those with and without a panic attack, respectively; Welch's t = 15.27, p<.001). Together, these findings demonstrate that the theory can account for the first two of our phenomena of interest: the basic phenomenology of panic attacks and individual differences in vulnerability to those attacks.

Simulation 2: Natural Variation in Arousal

In Simulation 2, we used the same sample of individuals to examine how the model behaves over 3 months of simulated time. With this longer time frame, Simulation 2 allows us to examine whether the theory can explain our next two phenomena of interest: the

development of panic disorder and the phenomenon of non-clinical panic attacks. We defined panic disorder by the presence of three symptoms: recurrent panic attacks (>1 during the past month), persistent concern (i.e., arousal schema > .50), and persistent avoidance (i.e., avoidance > .50). We defined non-clinical panic attack as the experience of a panic attack that occurred outside the context of panic disorder and without the subsequent development of panic disorder.

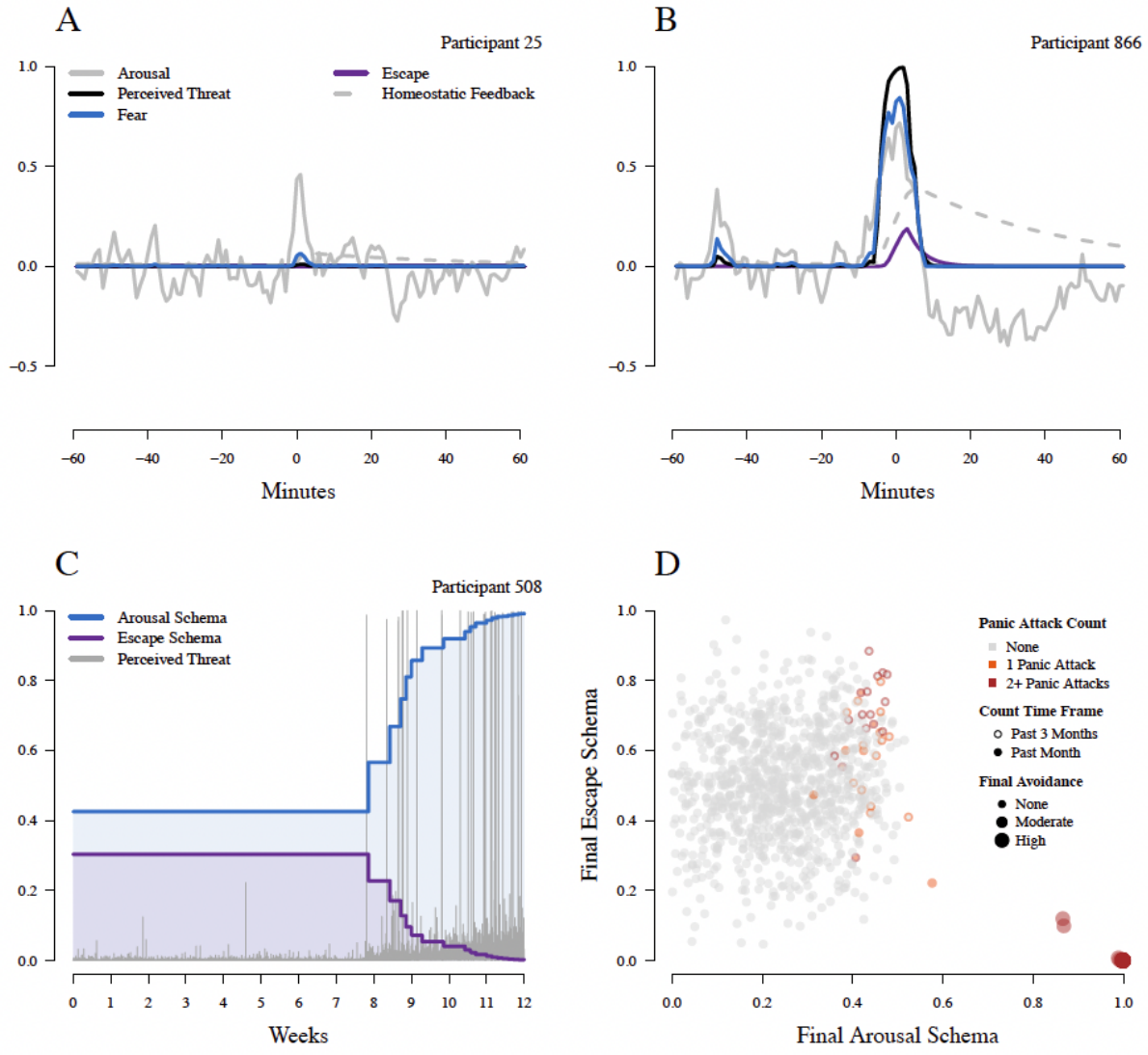

Figure 5. Results of 3-Month Simulation. *Panels A* and *B* depict the 60 minutes before and after the moment of most intense fear reported during the 3-month simulation for participants with low (*S*=0.23) and moderate (*S*=0.52) initial arousal schema, respectively (the same participants depicted in Figure 4). *Panel C* depicts the evolution of arousal schema, escape schema, and perceived threat over the full 3-month simulation for a participant who began with moderate arousal schema (*S*=.43) and later developed panic disorder following a panic attack that occurred in Week 7 of the simulation. *Panel D* depicts the relationships among

arousal schema, escape schema, avoidance, and panic attack frequency at the end of the 3-month simulation. In this panel, individuals depicted in red are exhibiting recurrent panic attacks, persistent beliefs about the danger of arousal, and high levels of avoidance and, thus, would meet criteria for panic disorder. Among these, 40 individuals exhibited maximally severe arousal and escape schema values by the end of the simulation period (i.e., S=1.00 and X=0.00).

The findings from Simulation 2 are depicted in Figure 5. Four phenomena can be seen in these simulation results. First, as with Simulation 1, the theory again produces individual differences in the propensity to experience panic attacks. For most individuals, arousal varies around its within-person mean and elicits minimal levels of perceived threat at any point during the simulation (e.g., Panel A). However, for 7.9% of the simulated sample, that same natural variation in arousal is sufficient to elicit a panic attack at some point during the simulation (e.g., see Panel B). Notably, individual differences in response to the simulated biological challenge in Simulation 1 were predictive of panic-related outcomes in Simulation 2. Peak fear, time to recover, and escape behavior in the biological challenge simulation all predicted both panic attacks (r=.62 [.58, .66], .33 [.28, .39], and .33 [.27, .38], respectively; ps<.001) and panic disorder (r=.43 [.37, .48], .20 [.14, .26], and .21 [.15, .27], respectively; ps<.001).

Second, we again see that the theory produces the basic phenomenology of panic attacks: a surge of arousal and perceived threat that arises in the absence of external threat (see Panel B). Interestingly, the model also suggests why people may perceive panic as being qualitatively distinct from a state of anxiety. In the presence of strong positive feedback, the shift between states does not occur gradually; it occurs as a sudden transition: a catastrophic shift into a state of panic. This categorical shift is noteworthy because it arises from dimensional changes in the components of the positive feedback loop, illustrating a general feature of complex systems: in some conditions (e.g., low arousal schema), complex systems can behave continuously, whereas in others (e.g., high arousal schema) they can only occupy

a limited number of discrete states (Borsboom et al., 2016). Thus, the model may explain why panic attacks are experienced as discontinuous with the normal state of being, even though they key variables involved are all continuous.

Third, the theory produces the emergence of the panic disorder syndrome over time in some individuals (e.g., Panel C). Among those who experienced a panic attack, 55.7% moved into a state in which they would meet diagnostic criteria for panic disorder by the end of the simulation: experiencing recurrent panic attacks, persistent concern, and exhibiting persistent avoidance, giving an overall panic disorder prevalence of 4.4% in the full sample (these individuals are depicted in orange or red in Panel D). For these individuals, initial arousal schema was sufficiently high that there was some vulnerability to a panic attack *and* initial escape schema was sufficiently low that when such an attack occurred, they turned to escape behavior as a way of managing the perceived threat. Consequently, these individuals learned that arousal was dangerous and that escape behavior was effective, initiating a slow vicious cycle in which panic attacks led to greater vulnerability, and greater vulnerability led to more panic attacks. With increasing belief in the danger of arousal, there was a corresponding increase in avoidance behavior, which effectively regulates the frequency of panic attacks, but is insufficient to prevent them entirely and comes at the cost of constraining the system's behavior.

Fourth, the theory produces non-clinical panic attacks. Among those who experienced a panic attack in this simulation, 24.1% experienced only a single attack and 44.3% did not develop panic disorder. For these individuals, initial escape schema values were sufficiently high that they did not engage in significant escape behavior in response to instances of panic (e.g., see Figure 5, Panel B), allowing them to learn that arousal is less dangerous than they perceived it to be at the height of their panic attack and that escape behavior is less necessary in the face of perceived threat than previously assumed.

Simulation 3: Treatment of Panic Disorder

In a final simulation, we evaluated whether the theory accounts for the effects of cognitive behavioral therapy on panic disorder. To do so, we simulated a treatment trial in which 500 individuals with panic disorder received a 5-week cognitive-behavioral therapy intervention and were then followed for 3-months. As in the prior simulations, we began by assigning each participant a different initial value for two key model components: arousal schema and escape schema. Arousal schema values were drawn from a distribution with a high mean (.80) and escape schema values were drawn from a distribution with a low mean (.20), thereby representing a sample that would meet criteria for panic disorder.

Implementing the treatment mathematically forced us to explicitly posit how exactly cognitive behavioral treatments have their effect on panic disorder. We generated these auxiliary hypotheses by reviewing a 5-week cognitive behavioral therapy intervention (Otto et al., 2012; Otto et al., 2010) and positing which model components are targeted by individual components of the therapy (see Figure 6). We identified four treatment components: (a) *psychoeducation*, in which the individual is presented a framework for understanding how cognitions, emotions, and behaviors interact to give rise to panic attacks and panic disorder; (b) *cognitive restructuring,* in which the individual completes exercises that challenge one's beliefs about the likelihood and severity of adverse consequences from arousal-related bodily sensations; (c) *interoceptive exposure*, in which the individual induces elevated levels of arousal while receiving explicit encouragement to refrain from escape behavior during these exercises; and (d) *in vivo exposure*, in which the individual enters situations in which the perceived consequences of arousal are heightened. Notably, these auxiliary hypotheses concern this specific 5-week protocol and may differ when implementing alternative cognitive behavioral treatment protocols. In addition to these posited treatment mechanisms, we made three auxiliary hypotheses: (a) individuals vary in

the extent to which they understand or believe the information provided in psychoeducation and cognitive restructuring; (b) some individuals do not complete all assigned exposure exercises; and (c) some individuals do not fully adhere to the guidance to refrain from escape behavior when perceived threat becomes especially elevated (for further details, see Supplementary Materials B).

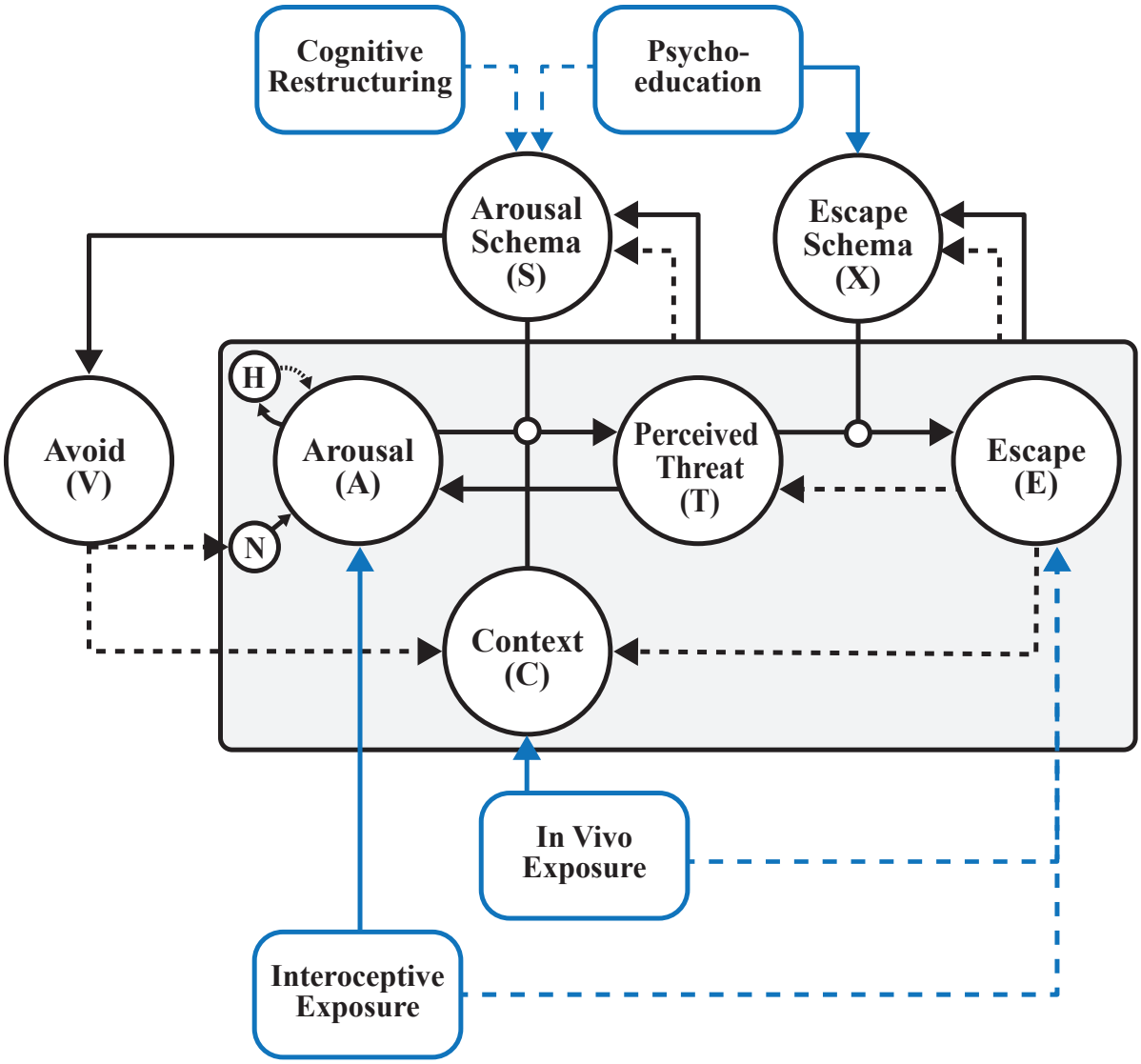

Figure 6. Auxiliary hypotheses regarding the effect of cognitive behavioral treatment of panic disorder. Four therapy components from the 5-week CBT protocol developed by Otto and colleagues (2010, 2012) and their posited effects on the components of the panic disorder model are depicted in blue. *Psychoeducation* in Session 1 aims to decrease the beliefs that arousal is dangerous (arousal schema) and increase confidence in one's ability to cope with perceived threat without engaging in escape behavior (escape schema). *Cognitive Restructuring* in sessions 2 & 3 further targets arousal schema. *Interoceptive exposure* exercises completed daily beginning in session 2 perturb arousal with increasing perturbation strength (A=.25, .50, .75 and 1.00 for the weeks beginning with Sessions 2-5, respectively).

In vivo exposure assigned daily beginning in Session 4 entails entering contexts in which the perceived consequences of a panic attack are heightened and is done in conjunction with interoceptive exposure. Critically, participants are instructed not to engage in escape behavior during any exposure exercises, making exposure a second target of both interoceptive and in vivo exposure.

The results of Simulation 3 are depicted in Figure 7. A successful case of treatment is depicted in Panel A. In treatment Session 1, psychoeducation produces reductions in arousal schema and increase in escape schema, though some of that improvement is lost when a panic attack occurs later in that week. In treatment Session 2 and 3, cognitive restructuring further lowers arousal schema. In addition, beginning in Session 2, daily interoceptive exposure exercises perturb arousal with increasing perturbation strength, sometimes eliciting significantly elevated levels of perceived threat. Because escape behavior was refrained from during these exercises, the individual learned that arousal is not dangerous and escape behavior unnecessary, thereby reducing their beliefs and learned associations concerning the danger posed by arousal (lower arousal schema) and increasing the level of perceived threat they are willing to experience before resorting to escape behavior (higher escape schema). Beginning in Session 4, interoceptive exposure exercises are combined with in vivo exposure exercises, "chaining together" stimuli that lead to heightened perceived threat with the aim of maximizing the opportunity to learn that those stimuli do not pose danger (Powers et al., 2010). Through this combination of *in vivo* and *interoceptive* exposure, further treatment gains are made. Arousal schema steadily decreases while escape schema rises. By the end of treatment, this individual has sufficiently low arousal schema that the system no longer contains an alternative stable state. That is, they are no longer vulnerable to the experience of panic attacks. Accordingly, this simulation demonstrates that the theory can account for the efficacy of cognitive behavioral therapy.

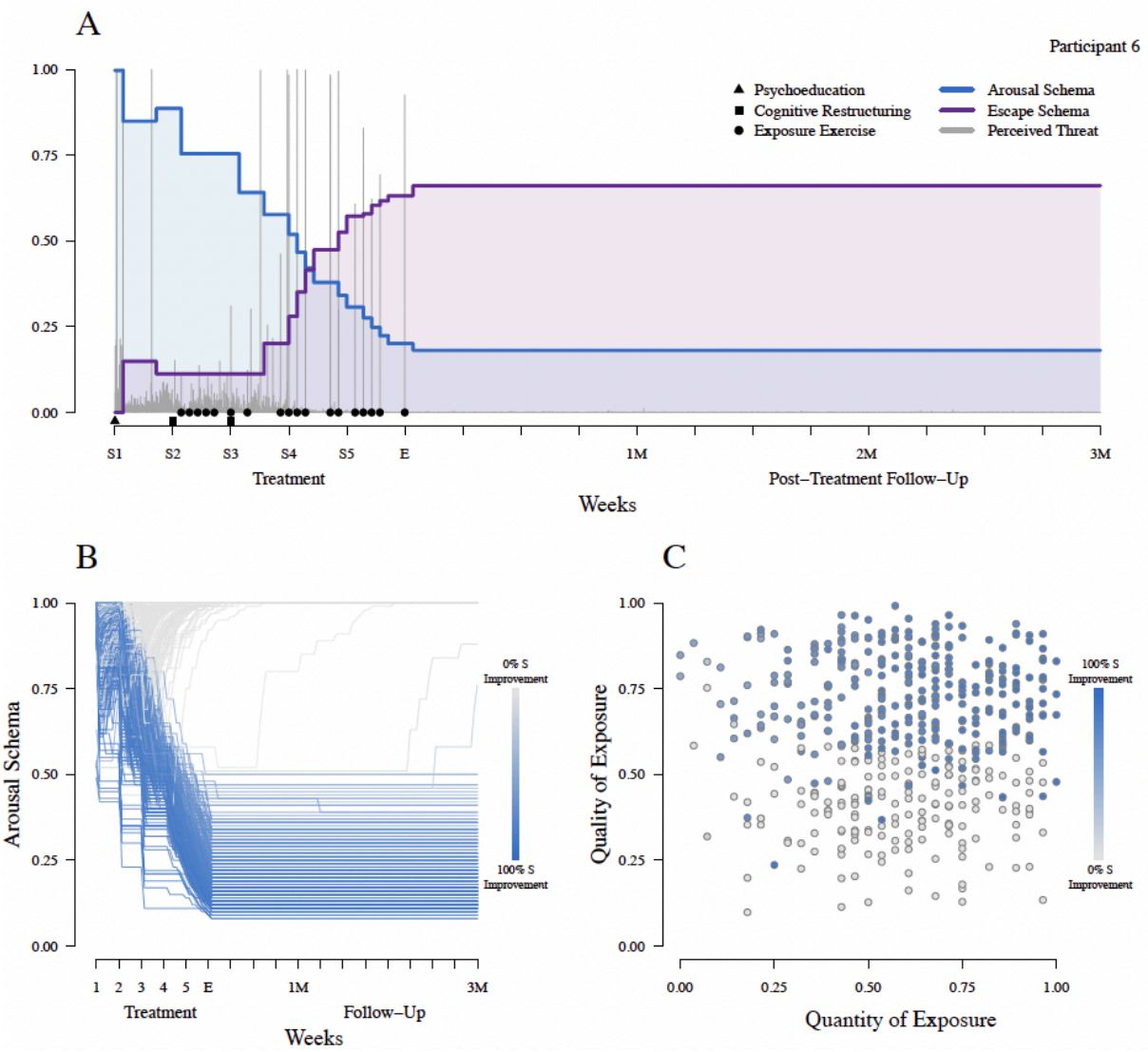

Figure 7. Results of Cognitive Behavioral Treatment Simulation. *S1-S5* = Treatment sessions 1-5. *E* = Treatment endpoint. *Panel A* depicts the effects of treatment for one individual who responded well to the cognitive behavioral treatment. *Panel B* depicts the effects of treatment on arousal schema (*S*) in sample of 500 individuals with a range of treatment adherence parameters. *Panel C* depicts the effects of treatment on arousal schema as function the quantity and quality of exposure exercises.

Not all simulated treatments were so successful. As depicted in Panel B, 36.2% of individuals either failed to respond during the treatment or relapsed during the post-treatment follow-up. Panel C shows that the quality of exposure exercises (i.e., the extent to which individuals responded to the prohibition of escape behavior) was especially important to treatment outcomes. If the quality of exposure exercises was low, it did not greatly matter how many exercises were completed, improvement was minimal. If high, even people who

completed a relatively small number of exposures achieved some reduction in arousal schema. As we discuss further in Section 3, this model prediction has significant implications for how we understand (and, potentially, how we might improve) cognitive behavioral treatments for panic disorder, highlighting the importance of ensuring adequate quality of interoceptive and in vivo exposure.

Summary

The results of our simulations demonstrate that the network theory of panic disorder – and the cognitive behavioral framework upon which it is based – can produce, and thus explain, well-established panic disorder-related phenomena. In future research it will be important to build on this demonstration by evaluating the quality of this explanation. In other words, the theory can explain the phenomenon, but is it a good explanation? Recently, van Dongen et al. (2022) proposed criteria to evaluate explanatory quality. Among these, it will be especially helpful to evaluate *robustness*: the extent to which the phenomena evaluated here are produced across different formalizations that remain consistent with the theory. For example, we specified a perfectly linear effect of perceived threat on the rate of change in arousal, but an alternative monotonically increasing effect in which low levels of perceived threat elicit low levels of arousal and high levels of perceived threat elicit high levels of arousal would also be consistent with the theory. It is therefore important to evaluate the extent to which production of the phenomena is robust to these modeling choices (for a related discussion; see Guest, 2023).

In addition to demonstrating what the theory can explain, the simulations presented here also provide additional insight into the experience of panic disorder (e.g., its tendency to feel abrupt and discontinuous with earlier states) and its treatment (e.g., the critical importance of exposure quality). These insights can motivate future research, providing an opportunity to advance our understanding of panic disorder and its treatment. Just as

importantly, the simulations also identify shortcomings of the theory and, thereby, provide us an opportunity to learn how the theory might be improved . It is these opportunities to which we turn in the next section.

Section 3: A Theory-Driven Research Agenda for Panic Disorder

In this section, we propose an agenda for panic disorder research directly informed by the initial generation and evaluation of the formal network theory of panic disorder. This agenda is rooted in the broad framework of Theory Construction Methodology (Borsboom, van der Maas, et al., 2021; Haslbeck et al., 2021) and is built around three avenues for further research and theory development (see Figure 8). First, constructing the computational model revealed that there is little empirical guidance for specifying many key aspects of the theory, thereby identifying areas in need of further empirical research that would directly inform our understanding of the system that gives rise to panic disorder. Second, because the formal theory allows us to deduce the behavior that should follow from the theory, it makes predictions about phenomena that we should expect to see in the real world, including phenomena not yet well-established by empirical research. Investigating these phenomena would serve to either corroborate or guide the revision of the theory proposed here. Finally, plausible panic disorder-related phenomena remain unexplained by the theory, providing the opportunity to revise the theory through abductive inference with the aim of expanding the theory's explanatory breadth. In the remainder of this section, we propose three concrete areas for future research and theory development in each of these three domains.

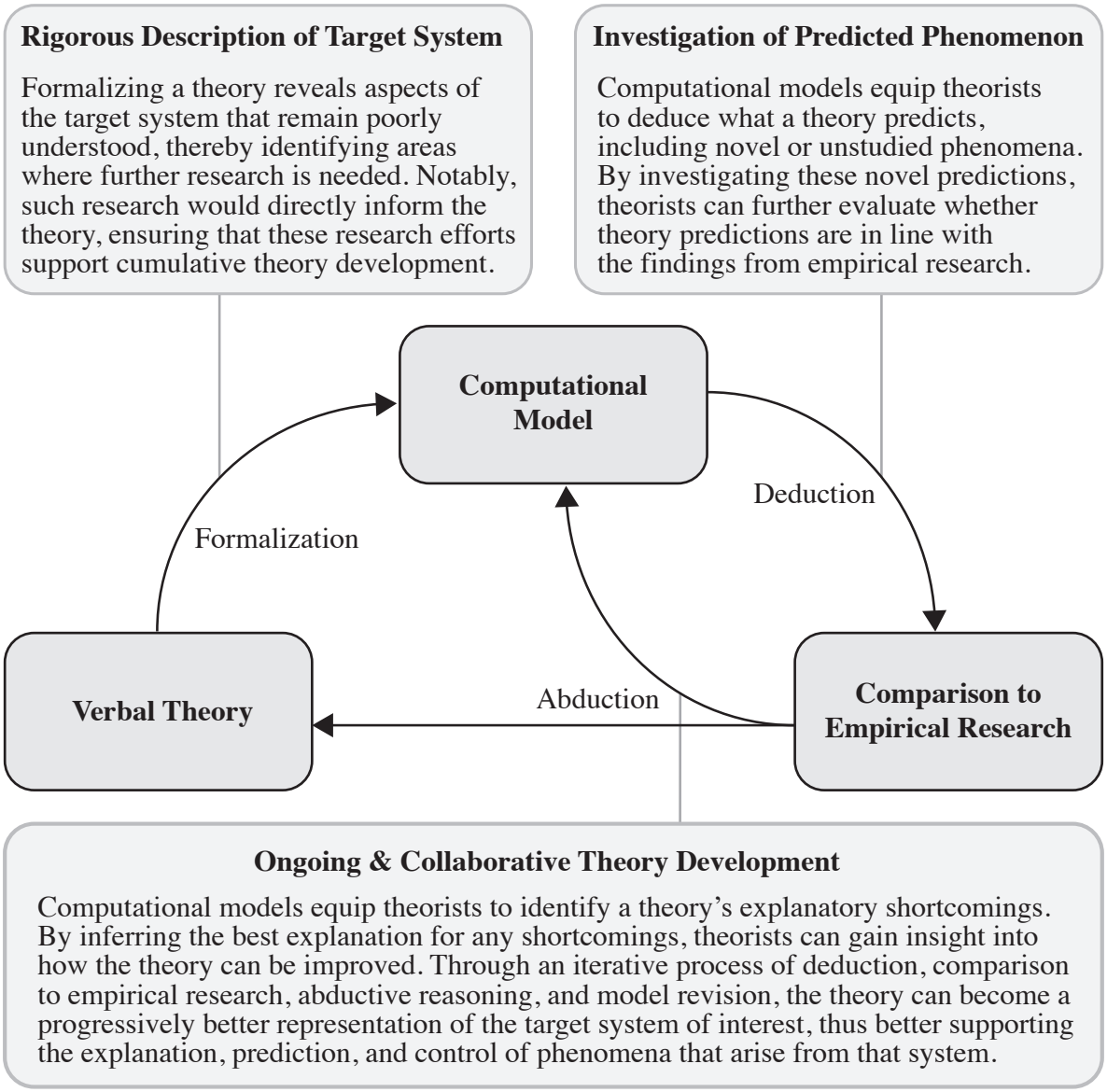

Figure 8. Framework for proposed research agenda. The computational model presented here allowed us to identify areas in need of rich descriptive research, novel phenomena worthy of further study, and phenomena for which the theory cannot account. In this section, we propose a research agenda for panic disorder built on these contributions. The aim of this research agenda is to iteratively refine the computational model, expanding its explanatory breadth and strengthening its practical utility in predicting, preventing, and treating panic disorder.

Rigorously Describe the Target System

The theory generated here aims to represent the system that gives rise to panic disorder (i.e., the "target system"). There are many aspects of this system for which the empirical literature provides minimal insight. To advance theories of panic disorder, it will be

necessary to gather rich descriptive data on each of the individual components of the target system as they evolve over time in relation to one another, across timescales and across a range of conditions. Such data would strongly inform key aspects of the theory, including the functional forms and parameters that define the nature of the posited causal effects. To illustrate, we consider three unknowns identified during the process of generating this initial formal theory and the empirical research that could address them.

What is the Precise Effect of Perceived Threat on Arousal? We posited a linear effect of perceived threat on the rate of change in arousal, based on the assumption that even low levels of perceived threat motivate some preparation for the body to respond and that the need to conserve energy calls for a response that is in proportion to the posed threat. If the functional form of this effect is different than we have posited here, the predictions from this theory could differ substantially (Robinaugh et al., 2021). Experimental studies that manipulate perceived threat and evaluate the corresponding impact on arousal with intensive (ideally, near-continuous) time-series data on relevant model components are needed to clarify the precise nature of this important causal effect and how it differs across people.

What are the Conditions Under Which Learning Occurs? In our model, learning occurs only when there is at least moderately elevated fear. This theoretical position is akin to that made in emotion processing theory (Foa & Kozak, 1986), where learning occurs only when there has been activation of the "fear network." Further research is needed to evaluate whether this thresholding is appropriate or if learning can occur in response to even low levels of arousal and perceived threat. Similarly, it will be important to clarify whether there is a threshold at which the level of fear *impairs* learning. This may again be especially fruitful to evaluate in experimental settings (e.g., following modest perturbation to arousal) as well as in treatment settings following early exposure exercises, ideally leveraging the rich information provided by intensive time series data on relevant model components.

Is Variation in Arousal Under Volitional Control? In our model, avoidance regulates panic attack frequency, in part, by reducing variability in arousal. Although plausible, to our knowledge there is no evidence to suggest that avoidance is indeed successful in controlling arousal in this way. This issue could be readily investigated by asking healthy individuals to avoid arousal-inducing stimuli and activities and evaluating the extent to which these efforts affect objective indices of arousal. If avoidance does not affect arousal, it would mean that the regulatory effect of avoidance either occurs solely through prevention of exposure to panic-predisposing situations or operates through a mechanism beyond those posited by our theory. Accordingly, further research would either support the theory or provide clear guidance for how it should be revised.

Evaluate and Describe Potential New Phenomena

Alongside research on the individual components in the posited target system and the relationships among them, it will also be helpful to investigate phenomena that the theory predicts should arise from this target system. These predicted phenomena can help further clarify whether the theory's predictions are aligned with empirical research and, thus, whether theory is a good representation of the system that gives rise to panic disorder. To illustrate, we consider three such phenomena.

Biological Challenge Response Should Predict Future Panic Attacks. As noted in our discussion of Simulation 2, the model predicts that the time to recover from a perturbation to arousal (i.e., referred to as the system's *engineering resilience* in the dynamical systems literature) and the peak level of perceived threat in response to a perturbation are markers of the system's vulnerability and, thus, should prospectively predict panic attacks. Consistent with this prediction, Schmidt and colleagues have reported that subjective distress (r = .55*)* and self-reported symptoms of arousal-related bodily sensations (r = .47) in response to CO2 inhalation prospectively predict the onset of panic attacks

(Schmidt et al., 2007; Schmidt & Zvolensky, 2007). However, multiple smaller studies have failed to observe these prospective associations (Coryell et al., 2006; Harrington et al., 1996; Perna et al., 1999). Accordingly, additional research – appropriately powered, focused on response indices informed by this model, and, ideally, preregistered – is needed to determine whether this is indeed a robust phenomenon. If so, it would not only provide support for this theory, it would also suggest that perturbations to arousal are a valuable means of detecting risk for panic attacks, thereby enhancing the clinical utility of 'biological challenge' paradigms (Forsyth & Karekla, 2002).

Intervening on Self-efficacy Early in Treatment Should Improve Treatment Outcomes. In our simulated intervention, some individuals failed to respond to treatment. In many cases, this failure occurred because the combination of one's escape schema and one's adherence to the instruction not to escape were insufficiently high to prevent escape (or "safety-seeking") behavior during exposure exercises. These findings suggest that there may be insufficient focus on improving escape schema early in treatment. Consistent with this possibility, Gallagher and colleagues (2013) reported that the largest gains in panic self-efficacy (comparable to our escape schema component) were not made until later in treatment, when the focus of treatment is on exposure exercises. As we demonstrate in more detail elsewhere (Ryan et al., 2023), the model predicts that intervening on escape schema early in treatment, independent of the instruction to refrain from escape behavior during exposure exercises (e.g., by having patients recall life experiences in which escape behavior was not relied upon in the face of perceived threat), will both increase the proportion of people who successfully respond to treatment and reduce the likelihood of relapse after treatment concludes.

Arousal Should Be Diminished Following a Panic Attack. The model predicts that arousal should be below its within-person equilibrium for an extended period following a

panic attack. There are at least two reasons to believe that this is indeed a robust phenomenon. First, following a panic attack it is common for individuals to experience "total exhaustion" (Radomsky et al., 1998; Uhde et al., 1985, p. 42). Second, some individuals report a "panic-safe period" after a panic attack, during which vulnerability to panic attacks is decreased (Radomsky et al., 1998), a possibility that is consistent with diminished arousal. However, further research is needed to determine whether this is indeed a robust phenomenon, work that will clarify not only panic termination, but also the processes that contribute to panic onset.

Iteratively and Collaboratively Develop Panic Disorder Theory

The integrated theory presented here was generated to explain five panic-disorder related phenomena. We selected these phenomena because they were among the most robust phenomena we could identify and because we regard them as central features of panic attacks and panic disorder. As presented in the previous section, our computational model simulations demonstrate that the theory indeed produces those phenomena. It will be critical to evaluate the theory's ability to account for phenomena beyond those examined here. Indeed, the model's ability to account for phenomena beyond those it was initially generated to explain will arguably give the clearest sense of the model's strengths and weaknesses. Yet, even at this stage, the model simulations reveal that there are plausible phenomena for which the theory does not account. These potential explanatory failures suggest there may be shortcomings in how well the theory represents the target system. Far from being a limitation of this modeling effort, we consider the identification of such phenomena to be a significant advantage of the approach taken here as these potential explanatory shortcomings identify areas in need of further empirical research and potential opportunities for theory development. Here, we consider three such potential explanatory failures and theory revisions that could address them.

What Explains Moderate Severity Panic Disorder? Our model predicts that individuals who develop panic disorder will ultimately develop maximally severe panic disorder, a prediction inconsistent with the simple observation that the mean severity of panic disorder typically falls in the moderate range (Furukawa et al., 2009). One of several potential explanations for this explanatory failure lies in the learning that occurs following panic. In the current model, arousal schema moves toward the maximum level of perceived threat experienced during a panic attack. If instead arousal schema moved toward the mean perceived threat during the attack or only the level of threat mitigated by escape behavior (and thus counterfactually inferred to be present), then the rise of arousal schema would be lessened, and panic disorder would be less severe. This possibility underscores the potential value of better grounding the model's learning mechanism in prior models of learning. There are several candidate models. For example, panic theory's emphasis on learning about what it means to be in a state of arousal (arousal schema) and the need to escape (escape schema) parallels the emphasis on learning about states and actions in actor-critic models (Grondman et al., 2012). Alternatively, the tendency in panic disorder for people to infer the presence of an unseen threat (e.g., heart attack) in the face of significant prediction error (e.g., an unexpected discrepancy between predicted and observed levels of arousal) parallels reinforcement learning models that posit learning entails inference about latent state (Gershman & Niv, 2012, pp.; see also Maisto et al, 2021). Grounding the network theory of panic disorder in these learning models would better align the theory with the science of learning, would directly inform specific modeling choices (e.g., whether it is sufficient to model learning on a time scale of days, as we have here, or whether continuous learning is needed), and could potentially help the theory better explain moderate severity panic disorder.

What Explains Elevated Arousal Without Panic Attacks? The model predicts that

significantly elevated arousal will always elicit a panic attack. However, some patients with panic disorder can engage in activities that substantially increase arousal (e.g., exercise) without experiencing panic attacks (Taylor et al., 1987). To account for this phenomenon, it could be helpful to incorporate *expected arousal* in the model, such that perceived threat arises only when arousal exceeds the level of arousal that would be expected given one's current environment or activities (for further discussion of the conditions affecting such expectations, see Bouton et al., 2001; Clark, 1988). This revision may be especially important in cases where arousal-related bodily sensations are perceived as dangerous only in-so-far as they are determined to indicate a potentially serious condition. In such cases, it may only be unexplained arousal that serves as a significant source of distress, distinguishing them from those who believe arousal to be dangerous in and of itself and potentially leading to different theory predictions for these individuals.

What Explains Panic Attacks Without Elevated Arousal? The model predicts that panic attacks are associated with significant elevations in arousal. Although such elevations have been observed in laboratory-based assessments, ambulatory assessments often find that some panic attacks are not associated with increases in objective indices of arousal, such as heart rate (Alpers, 2009). Given the challenges of rigorously assessing psychophysiology with ambulatory methods and the potential confusion of panic with episodes of intense worry, further investigation is needed before concluding that panic without elevated arousal is indeed a robust phenomenon. However, if panic attacks can occur without elevations in autonomic arousal, it would suggest the need for theory revisions. One potential revision would be to separate the detection and interpretation of arousal into distinct processes (Ehlers, 1993). In this case, autonomic arousal leads to somatic sensations through the process of *detection* (interoception) which, in turn, lead to perceived threat through the process of *interpretation*. We can further posit that, as perceived threat increases, attention is

increasingly placed on somatic sensations, strengthening the detection of arousal. As depicted in Supplementary Materials C, this revised model can indeed produce a surge of bodily sensations and perceived threat with only modest elevations in objective indices of arousal. Moreover, distinguishing between autonomic arousal and the somatic sensations associated with arousal may allow the model to better account for the onset of some panic attacks, where somatic sensations initiating the vicious cycle may initially be present for reasons other than elevated autonomic arousal (e.g., hangover; for further discussion, see Clark, 1986). However, as discussed in greater detail in Supplementary Materials C, this potential revision to the model also raises new theoretical challenges that follow from the successful production of this phenomenon (e.g., if not via the regulation of substantially elevated arousal, why do panic attacks end?). Accordingly, if future research establishes that sudden surges in perceived threat and arousal-related bodily sensations can indeed occur in the absence of substantial elevations in autonomic arousal, revisions to the theory proposed in this article will be needed, potentially including to processes central to the vicious cycle between arousal and perceived threat.

Theory Development and Explanatory Breadth. In the preceding paragraphs, we have identified opportunities for theory development stemming from three plausible phenomena that were not produced in our model simulations. As noted, in future research it will be important to evaluate whether the theory accounts for other panic-disorder related phenomena beyond those enumerated here (e.g., the impact of treatments beyond CBT or the high rate of comorbidity between panic disorder and other conditions). There are no established guidelines for selecting the most appropriate phenomena for such efforts. However, it is critical that the chosen phenomena be robust: ideally, consistently observed over time, with multiple methods, and across multiple research groups (Bogen & Woodward, 1988; Haig, 2005, 2013). As the theory's ability to account for these additional phenomena

improves, we can be increasingly confident that the model is a strong representation of the system giving rise to panic disorder and, therefore can be more confident that the inferences form this model will be able to inform the prediction, explanation, prevention, and treatment of panic disorder.

In considering this phenomena-focused approach, the reader may justifiably believe that they can already identify aspects of the model that warrant revision, even without appealing to the explanation of a particular phenomenon. For example, in this model we posited that escape behaviors have some modest effect in reducing perceived threat but have no direct effect on arousal. Although true for some escape behaviors, there may be others that do successfully reduce arousal (e.g., slow breathing) or, conversely, that exacerbate arousal (e.g., rapid breathing) and the model could be revised to represent these distinct types of escape behavior. Similarly, the reader may rightly note that autonomic arousal is not a unitary construct (Blascovich, 1992), suggesting that the model could be revised to better represent the complex and multidimensional nature of autonomic arousal. Although these and other potential revisions would be well-motivated, without anchoring in the explanation of specific phenomena, these revisions risk making the model unnecessarily complex and intractable. We would thus encourage theorists to focus their model revision efforts not only on those changes that expand explanatory breadth but, even further, to reserve model revisions to those instances in which the revision expands the explanatory breadth *beyond* the specific phenomenon it was designed to accommodate (Thagard, 1978, p. 84; see also progressive problem shifts, Lakatos, 1978). By doing so, theorists will be well positioned to balance simplicity and explanatory breadth as they make ongoing improvements to the theory.

Summary

In this section, we have proposed a novel framework panic disorder research, including concrete steps that should be taken for both empirical research and for the ongoing

development of panic disorder theory. The specific steps laid out here are only some of the many ways in which this work can proceed within the framework we have proposed. Formal theories have the advantage of taking a theory out of the hands of individual theorists and into the hands of the broader research community, facilitating collaborative theory development. The model developed here is implemented in freely available software and can be freely accessed at https://github.com/jmbh/PanicModel. Any empirical researcher or theorist may use the model to evaluate this theory for themselves and determine what additional research or theory development is warranted. This is especially important given that the system that gives rise to panic disorder includes components that cut across traditional disciplines, suggesting that contributions across diverse scientific fields will be necessary to fully develop the theory. By better informing empirical research and guiding ongoing and collaborative theory development, we believe the research agenda outlined here - and the model upon which it is built - will equip theorists to advance panic disorder theory in a way that reflects a genuine accumulation of knowledge and moves us towards a theory that can better support the explanation, prediction, and control of panic disorder.

Discussion

In this paper, we have drawn from cognitive behavioral theories to posit a network theory of a specific mental disorder, demonstrated that theory can explain core phenomena associated with that disorder, and used this theory to lay out a research agenda to further advance theories of panic disorder. Alongside these contributions, the formal theory developed here provides several insights into how mental disorders can be conceptualized and studied as complex systems in which a network of causal interactions among symptoms plays a considerable role. We conclude with a discussion of these insights.

Emergence, Equifinality, and Explanatory Pluralism

Our theory illustrates that, from the perspective of network theory, panic disorder is an emergent phenomenon. This can be clearly seen in the simple observation that the most important phenomena produced by our computational model are not explicit components in the model, but rather emerge from interactions among components. “Panic attack” is not a component in the model but rather a specific pattern of system behavior that emerges from the interaction between arousal and perceived threat. Likewise, panic disorder is a state of the system arising from interactions among the elements that define its presence: panic attacks, persistent beliefs about the danger of arousal, and avoidance behavior.

The emergent nature of panic disorder has important implications for how we study it. Emergent phenomena resist reductionist explanations. This suggests that efforts to identify single component-level dysfunction as *the* underlying cause of panic disorder are unlikely to succeed. Indeed, in the model as we have focused on it here, there is no essentially dysfunctional component. On the contrary, each component is necessary for adaptive functioning. If as species we did not react to perceived threat with increased arousal, did not engage in escape behavior in the face of perceived threat, or were incapable of learning that a given stimulus is dangerous, we would surely go extinct. Although the belief that arousal is dangerous may be inaccurate, the system comes by this falsehood honestly, through the appropriate functioning of its ability to learn. Thus, although this is a model of a pathological phenomenon, none of its specific ingredients need be pathological (for similar discussions in the context of addiction, see Pickard, 2022; Ross, 2019).

In place of reductionist simplicity, explanatory pluralism and equifinality - common features of complex systems - are likely to feature prominently (Nolen-Hoeksema & Watkins, 2011; von Bertalanffy, 1972). Factors across levels of analysis operate together in our model to contribute to the development and treatment of panic disorder. Because of the causal relationships among its components, the system arrives at a similar state regardless of the

specific factors that initiate its movement toward that state (cf. Bystritsky et al., 2012, p. 430). That is, whether instigated by alterations in arousal or the receipt of news about one's cardiovascular health, the feedback relationships in the model will ultimately lead the system to a common state of panic disorder. Accordingly, if we are to understand the disorder's etiology, it is not sufficient to understand individual components, we must also understand how they interact with one another (for a similar discussion in the context of brain damage and dyslexia, see Hinton et al., 1993).

The Nature of Mental Health

Together, emergence and equifinality suggest that efforts to define or classify mental disorders based on underlying dysfunction alone are unlikely to be fruitful. Instead, mental disorders may be better characterized as harmful stable states in the dynamical landscape produced by a given target system. For example, panic disorder can be characterized as a system in which there is a harmful stable state characterized by persistent panic attacks, concern about panic attacks, and avoidance. In contrast to current nosologies, this characterization of panic disorder permits diagnosis regardless of whether symptoms are currently present. In other words, it would be possible to identify "silent" panic disorder (a "dormant network" in Borsboom's (2017) network theory), in which the system contains an alternative harmful stable state even when the system is not in that state, thereby allowing for efforts to preemptively remove the stable state through treatment and preventing the subsequent transition (or relapse) into the harmful stable state.

Conversely, this characterization of panic disorder also allows for the possibility of identifying those who do not meet criteria for a disorder despite the presence of transient symptoms. In our model, a healthy and resilient system is one that has a single stable state characterized by an absence of panic attacks, persistent concern, and avoidance. If this system is pushed into a state of elevated symptoms (e.g., a single panic attack), it is perhaps no

longer in a state of mental health, but it is also not in the harmful equilibrium state that characterizes panic disorder. Interestingly, current diagnostic criteria implicitly draw a comparable boundary between transient symptoms and persistent symptoms that do not appear likely to remit naturally (e.g., those that have persisted for at least one month). Accordingly, the characterization of mental disorders as harmful stable states is consistent with current clinical practice but has the considerable advantage of undergirding this practice with a clear theoretical framework.

Transdiagnostic Models of Psychopathology

Although our emphasis in this paper has been on a single disorder, our findings also have implications for transdiagnostic models of psychopathology. In recent years, researchers adopting a transdiagnostic focus have identified robust phenomena regarding the structure of relationships among symptoms of mental disorder, with an emphasis on higher-order subfactors (e.g., fear) and spectra (e.g., internalizing) that represent clustering among syndromes (Conway et al., 2019; Conway et al., 2022; Krueger et al., 2018). Other researchers, including many working from the Research Domain Criteria (RDoC) agenda, have devoted enormous effort to cataloguing components across levels of analysis that may help explain those phenomena (Cuthbert, 2022; Harvey et al., 2004). Yet considerable work remains if we are to move toward the RDoC agenda's aim of understanding of how these various components interact "from an integrative, multi-systems point of view" (Cuthbert & Insel, 2013, p. 4), to give rise to both transdiagnostic and disorder-specific phenomena (Sanislow et al., 2010). As we have argued here, progress toward understanding the function and dysfunction of any system will all but require the development of mathematical or computational models that help us reason about the operation of those systems. We see two clear advantages to computational modeling of complex systems within the transdiagnostic framework.

First, computational models can help identify transdiagnostic *structure*. The core of the system posited here can be understood as a cognition (perceived threat) eliciting an emotion (fear) and prompting behavior (escape behavior) that helps to regulate the emotion in the short-term but only at the cost of heightening vulnerability to the emotion in the long term. Some years ago, Barlow and colleagues observed that this same causal structure is posited in cognitive behavioral models for multiple disorders, with variation only in the specific cognitions, emotions, and behaviors at play and used this insight to develop their transdiagnostic Unified Protocol approach to treatment whereby patients are taught to recognize and intervene upon this causal structure for the cognitions, emotions, and behaviors causing them distress (Barlow, 2011; Barlow et al., 2017; Ellard et al., 2010). Notably, it was only after mapping out causal diagrams and generating treatment protocols for specific disorders that this common causal structure became clear (Mansell et al., 2009). Computational models can facilitate a similar process. By generating computational models for multiple specific disorders, we will be positioned not only to better understand these specific systems, but also identify transdiagnostic structural features that can shed insight into how other disorders may operate and how we might intervene on those disorders within a transdiagnostic framework.

Second, computational models can help identify and evaluate transdiagnostic *components*. In this paper, we have focused on the occurrence of panic attacks within the panic disorder syndrome, but panic attacks are associated with multiple disorders beyond panic disorder alone, including depression, other anxiety disorders, substance use disorders, and posttraumatic stress disorder (Baillie & Rapee, 2005; Kessler et al., 2006; Kessler et al., 1998). Similarly, experiencing fear and anxiety in response to arousal-related bodily sensations strongly predicts anxiety and post-traumatic stress disorders (Chambless & Gracely, 1989; Olatunji & Wolitzky-Taylor, 2009; Taylor et al., 1992) and interoceptive

exposure targeting this fear of somatic sensations is a component of the transdiagnostic Unified Protocol (Barlow et al., 2017; Ellard et al., 2010). Accordingly, there is good reason to suspect that the amplifying feedback loop between arousal and perceived threat, and the arousal schema component that moderates its strength, are transdiagnostic components at play within the systems giving rise to multiple disorders (Boswell et al., 2013; Reiss et al., 1986; Smits et al., 2019). Similarly, avoidance may limit opportunities for positive experiences, prompt feelings of isolation and loneliness, and foster negative information processing biases, thereby feeding into the system that gives rise to depression (Fried et al., 2015; Trew, 2011). The components developed within the context of this model for a specific disorder can, therefore, be connected to or integrated within formal theories for other disorders, allowing us to more rigorously evaluate whether these plausible transdiagnostic components are able to explain the comorbidity among these conditions. In doing so, theorists would also be well equipped to evaluate the conditions under which a common underlying system may produce different mental health conditions, both between individuals (Alice develops panic disorder whereas Bob develops PTSD) and within the same individual over time (Alice develops panic disorder and, later in life, PTSD).

Novel Tools for Clinical Research

Beyond informing our understanding of the nature of mental health and mental disorder, the dynamical systems framework also provides tools with which these disorders can be further studied. For example, in this paper we demonstrated that engineering resilience – a concept drawn from the dynamical systems literature – can quantify vulnerability to panic attacks, an approach that could potentially be used to identify those vulnerable to panic attacks even before any symptoms arise. Relatedly, researchers investigating other dynamical systems, such as ecosystems, have used early warning signals, such as increased autocorrelation among the system's state variables, to detect systems approaching a tipping

point that would push it into an alternative stable (Scheffer et al., 2009). Researchers have begun to use such early warning signals to evaluate whether they portend transitions into or away from mental health (Curtiss et al., 2021; Hasselman, 2022; Schreuder et al., 2022). Although preliminary and likely to face considerable challenges (Dablander et al., 2022; Schreuder et al., 2022), this work suggests that the toolbox used to investigate, anticipate, and control non-linear dynamical systems may be fruitfully applied in psychological and psychiatric research.

Among the tools available in the dynamical systems toolbox, we suspect the greatest utility will be from computational and mathematical models, such as the one developed here. Models are a critical tool in the study of dynamical systems, as the behavior of even relatively simple systems is all but impossible to anticipate through mental reasoning alone. The models and modeling practices from other domains of science (e.g., ecology) can inform efforts to model psychopathology (e.g., de Ron et al., 2022). Prior work on feedback loops may be especially informative (DeAngelis et al., 1986) as we suspect that many emotional disorders arise from the same type of feedback loops present in this model, including amplifying feedback loops (e.g., between rumination and depressed mood; Hosseinichimeh et al., 2018), dampening feedback loops (e.g., between social anxiety and social avoidance), and feedback between fast-changing variables and the slow-changing variables that guide their behavior. The dynamical systems literature provides examples and tools with which to model these relationships and, in doing so, equips us to develop models of how mental disorders operate as complex systems.

Interdisciplinary Collaboration

Although less common in clinical psychology, there is a rich tradition of theory-driven computational modeling in several closely-related disciplines, including computational psychiatry (Huys et al., 2016; Moutoussis et al., 2018), cognitive psychology (Farrell &

Lewandowsky, 2010; Lewandowsky & Farrell, 2011), and mathematical psychology (Estes, 1975; Navarro, 2021). Commonly, these computational models represent specific mental processes (e.g., drift diffusion models of decision making; Fudenberg et al., 2020) and are used to evaluate whether the theory produces phenomena established in experimental tasks (e.g., a speed/accuracy trade-off in decision-making tasks, Milosavljevic et al., 2010) and whether these processes may be aberrant in those with a given mental disorder (e.g., using a drift diffusion model to disaggregate and evaluate distinct aspects of cognition in those with depression; Dillon et al., 2015). Though extremely valuable for understanding these specific mental processes, the full potential of these models for understanding mental health is constrained by the imprecision of the clinical theories that connect these basic mental processes with the broader phenomenon of interest (e.g., symptoms, syndromes, or spectra). By formalizing our clinical theories as computational models and by integrating those formal theories with the computational models developed in related disciplines, we can significantly advance our understanding of mental health.

For example, building from a well-established model of sequential evaluation, Zorowitz and colleagues (Zorowitz et al., 2020) posited that individuals differ in their perceived control over the ability to move toward reward and avoid punishment. They then used a computational model to demonstrate that low perceived control can account for several anxiety and mood-related phenomena and cogently argued that this cognitive process could play a role in a range of anxiety and mood disorders. Panic disorder is among those disorders associated with a low levels of perceived control (Gallagher et al., 2014), with some evidence that avoidance occurs especially for those with a combination of both elevated anxiety sensitivity (cf. arousal schema) *and* low perceived control (White et al., 2006). Accordingly, the model developed by Zorowitz and colleagues could be integrated with the current model of panic disorder (e.g., with perceived control moderating the effect of arousal

schema on avoidance), thereby equipping theorists to evaluate whether this decision theoretic model can help explain individual differences in the panic disorder related phenomena evaluated here, including, for example, whether specific treatment approaches may be more effective than others for those with low perceived control (e.g., requiring greater emphasis on in vivo exposure). In turn, integration with the model developed by Zorowitz and colleagues would allow the model described here to move beyond an abstracted notion of avoidance to a representation of avoidance in physical space, thereby equipping us to determine whether increased arousal schema and diminished perceived control indeed may work together to reduce the amount of physical space in which the potential for reward outweighs the perceived risk of harm, thereby giving rise to agoraphobic avoidance.

A related collection of models that may be especially fruitful in the context of anxiety disorders are models rooted in *active inference* (Friston, 2013; Friston et al., 2017). Active inference models posit that a mental generative model representing statistical regularities in the environment guides both our perceptions and our actions with the aim of minimizing the discrepancy between the predictions from the internal model and the sensory evidence taken in through interoceptive and exteroceptive processes (Parr et al., 2022). With their emphasis on predictive processing and minimization of prediction error (i.e., minimization of uncertainty), active inference models are highly relevant to the domain of anxiety. In a major step forward in bringing together work on active inference and anxiety disorders, Maisto and colleagues used an active inference framework to model the perception of somatic sensations (i.e., heart pounding and breathlessness), inferences about the hidden states producing those sensations (i.e., panic attack or no panic attack), and the actions that follow from those inferences (i.e., take medication or do not; Maisto et al., 2021). The researchers then used this model to demonstrate how individual differences in perception and action can give rise to panic disorder-related phenomena (e.g., persistent use of medication as a means of regulating

panic attacks). Although this iteration of the model focused only on distinguishing between panic and non-panic states and on selecting whether to use medication, the model could readily be extended to include alternative hidden states (e.g., heart attack) and other potential behaviors (e.g., going to the hospital) and integrating such work with the model developed here would allow us to evaluate whether active inference can help us explain a wider range of panic-disorder related phenomena. Moreover, integrating these models would provide a richer description of the core model processes proposed here (e.g., recasting arousal and escape schema as an individual's generative model guiding perception and action) and would confer the substantial advantage of rooting our understanding of clinical phenomena in a "first-principles" model that embodies a leading theory of how the brain and mind operate.

Notably, these are just two examples of how formalized theories of mental disorder could be integrated with well-developed theories of basic mental processes to advance our understanding of mental health. With the growing power and accessibility of modern computing, mathematical and computational models have become an increasingly important tool across domains of science and the number of models that may bear on our understanding of mental health will only continue to grow. By formalizing clinical theories of mental disorder as computational models, we express those theories in language used across scientific disciplines (Muthukrishna & Henrich, 2019), allowing them to be more readily integrated with work in other scientific domains, ensuring that decades of clinical research on mental health are embodied in these integrated computational models and moving us toward a more complete understanding of the many ways in which complex systems of psychological processes can give rise to harmful psychological experiences.

The Treatment of Mental Disorder

From a systems perspective, psychological treatments have their effect by intervening on components of a system (e.g., reducing arousal schema) to a sufficient extent that the

behavior of the system changes (e.g., preventing the amplifying feedback between arousal and perceived threat). To improve treatment, it will be necessary to advance our understanding of these systems and how they respond - or fail to respond - to intervention. As we have discussed, the behavior of complex systems, including how they respond to intervention, is all but impossible to predict without the support of computational or mathematical models. Accordingly, the kinds of computational models that we have developed here have a critical role to play in helping us understand how treatments work, why they sometimes fail, and how they might be improved (for an extended discussion of this potential, see Ryan et al., 2023). Even with these tools, we should not anticipate easy answers or silver bullets (Borsboom et al., 2022). The scientific literature is replete with examples that underscore the challenge of controlling complex systems. Yet with rigorous descriptive research and interdisciplinary collaboration on the generation of models, bringing together expertise from modelers, clinicians, clinical researchers, lay care providers, and those with lived experience of the mental health challenges we seek to explain, there is reason to hope that we can begin to better understand and treat the systems underlying these challenges in all their complexity (Alemu et al., 2023).

Conclusion

In this paper, we posited precisely how a network of causally interrelated symptoms can give rise to a specific disorder. Leveraging the deductive power of the computational model developed here, we demonstrated this theory can produce, and thus explain, panic disorder-related phenomena while also providing new insight into our understanding of the system that gives rise to panic disorder. Just as importantly, we used this computational model to generate a novel research agenda for how theories of panic disorder can be improved. We hope that the approach to theory development taken here will not only advance theories of panic disorder but can also guide similar efforts for other mental disorders and,

ultimately, move the field toward a more fruitful exchange between theory and empirical research in which well-developed formalized theories summarize what is known, reveal what is not, and support the ongoing development of theories of psychopathology.

References

Alemu, R. E. G., Osborn, T. L., & Wasanga, C. M. (2023). The network approach: A path to decolonize mental health care. *Front Public Health*, *11*, 1052077. https://doi.org/10.3389/fpubh.2023.1052077

Alpers, G. W. (2009). Ambulatory assessment in panic disorder and specific phobia. *Psychol Assess*, *21*(4), 476-485. https://doi.org/10.1037/a0017489

American Psychiatric Association. (1980). *Diagnostic and statistical manual of mental disorders : DSM-III* (3d ed.). American Psychiatric Association.

American Psychiatric Association. (1994). *Diagnostic and statistical manual of mental disorders : DSM-IV* (4th ed.). American Psychiatric Association.

Asmundson, G. J. G., & Asmundson, A. J. N. (2018). Are anxiety disorders publications continuing on a trajectory of growth? A look at Boschen's (2008) predictions and beyond. *Journal of Anxiety Disorders*. https://doi.org/10.1016/j.janxdis.2018.05.003

Asnaani, A., Gutner, C. A., Hinton, D. E., & Hofmann, S. G. (2009). Panic disorder, panic attacks and panic attack symptoms across race-ethnic groups: results of the collaborative psychiatric epidemiology studies. *CNS Neuroscience & Therapeutics*, *15*(3), 249-254. https://doi.org/10.1111/j.1755-5949.2009.00092.x

Baillie, A. J., & Rapee, R. M. (2005). Panic attacks as risk markers for mental disorders. *Social Psychiatry and Psychiatric Epidemiology*, *40*, 240-244.

Bandura, A. (1977). Self-efficacy: Toward a unifying theory of behavioral change. *Psychological Review*, *84*(2), 191-215. https://doi.org/10.1037//0033-295x.84.2.191

Barlow, D. H. (1988). *Anxiety and its disorders: The nature and treatment of anxiety and panic*. Guilford Press.

Barlow, D. H. (1997). Cognitive-behavioral therapy for panic disorder: Current status. *The Journal of Clinical Psychiatry*, *58*(2), 32-37.

Barlow, D. H. (2011). *Unified Protocol for transdiagnostic treatment of emotional disorders: Therapist guide*. Oxford University Press.

Barlow, D. H., & Craske, M. G. (1988). The phenomenology of panic. In S. Rachman (Ed.), *Panic: psychological perspectives* (pp. 11-36). Lawrence Erlbaum Associates.

Barlow, D. H., Farchione, T. J., Bullis, J. R., Gallagher, M. W., Murray-Latin, H., Sauer-Zavala, S., . . . Cassiello-Robbins, C. (2017). The Unified Protocol for transdiagnostic treatment of emotional disorders compared with diagnosis-specific protocols for anxiety disorders: A randomized clinical trial. *JAMA Psychiatry*, *74*(9), 875-884. https://doi.org/10.1001/jamapsychiatry.2017.2164

Beck, A. T. (1988). Cognitive approaches to panic disorder: theory and therapy. In S. Rachman (Ed.), *Panic: Psychological perspectives* (pp. 91-110). Lawrence Erlbaum Associates.

Beck, A. T., Emery, G., & Greenberg, R. L. (1985). *Anxiety disorders and phobias: A cognitive perspective*. Basic Books.

Beltz, A. M., & Gates, K. M. (2017). Network mapping with GIMME. *Multivariate Behavioral Research*, *52*(6), 789-804. https://doi.org/10.1080/00273171.2017.1373014

Berrios, G. E. (1999). Anxiety disorders: A conceptual history. *Journal of Affective Disorders*, *56*(2-3), 83-94. https://doi.org/10.1016/S0165-0327(99)00036-1

Blascovich, J. (1992). A biopsychosocial approach to arousal regulation. *Journal of Social and Clinical Psychology*, *11*, 213-237.

Bogen, J., & Woodward, J. (1988). Saving the phenomena. *The Philosophical Review*, *97*(3), 303-352. https://doi.org/10.2307/2185445

Borsboom, D. (2017). A network theory of mental disorders. *World Psychiatry*, *16*(1), 5-13. https://doi.org/10.1002/wps.20375

Borsboom, D., Deserno, M. K., Rhemtulla, M., Epskamp, S., Fried, E. I., McNally, R. J., . . . Isvoranu, A. M. (2021). Network analysis of multivariate data in psychological science. *Nature Reviews Methods Primers*, *1*(1), 1-18.

Borsboom, D., Haslbeck, J., & Robinaugh, D. J. (2022). System-based approaches to mental disorders are the only game in town. *World Psychiatry*, *21*(3), 420. https://doi.org/https://doi.org/10.1002/wps.21004

Borsboom, D., Rhemtulla, M., Cramer, A. O. J., van der Maas, H. L. J., Scheffer, M., & Dolan, C. V. (2016). Kinds versus continua: A review of psychometric approaches to uncover the structure of psychiatric constructs. *Psychological Medicine*, *46*(8), 1567-1579. https://doi.org/10.1017/S0033291715001944

Borsboom, D., van der Maas, H. L. J., Dalege, J., Kievit, R. A., & Haig, B. D. (2021). Theory Construction Methodology: A practical framework for building theories in psychology. *Perspectives on Psychological Science*, *16*(4), 756-766. https://doi.org/10.1177/1745691620969647

Boswell, J. F., Farchione, T. J., Sauer-Zavala, S., Murray, H. W., Fortune, M. R., & Barlow, D. H. (2013). Anxiety sensitivity and interoceptive exposure: a transdiagnostic construct and change strategy. *Behav Ther*, *44*(3), 417-431. https://doi.org/10.1016/j.beth.2013.03.006

Bouton, M. E., Mineka, S., & Barlow, D. H. (2001). A modern learning theory perspective on the etiology of panic disorder. *Psychological Review*, *108*(1), 4-32. https://doi.org/10.1037/0033-295X.108.1.4

Bringmann, L. F., Albers, C., Bockting, C., Borsboom, D., Ceulemans, E., Cramer, A., . . . Wichers, M. (2022). Psychopathological networks: Theory, methods and practice. *Behaviour Research and Therapy*, *149*, 104011. https://doi.org/10.1016/j.brat.2021.104011

Brown, T. A., & Barlow, D. H. (1995). Long-term outcome in cognitive-behavioral treatment of panic disorder: clinical predictors and alternative strategies for assessment. *J Consult Clin Psychol*, *63*(5), 754-765. https://doi.org/10.1037//0022-006x.63.5.754

Brown, T. A., & Cash, T. F. (1990). The phenomenon of nonclinical panic: Parameters of panic, fear, and avoidance. *Journal of Anxiety Disorders*, *4*, 15-29.

Buller, R., Maier, W., & Benkert, O. (1986). Clinical subtypes in panic disorder: their descriptive and prospective validity. *Journal of Affective Disorders*, *11*(2), 105-114. https://doi.org/10.1016/0165-0327(86)90015-7

Bystritsky, A., Nierenberg, A. A., Feusner, J. D., & Rabinovich, M. (2012). Computational non-linear dynamical psychiatry: a new methodological paradigm for diagnosis and course of illness. *Journal of Psychiatric Research*, *46*(4), 428-435. https://doi.org/10.1016/j.jpsychires.2011.10.013

Cacioppo, J. T., Berntson, G. G., Larsen, J. T., Poehlmann, K. M., & Ito, T. A. (2000). The psychophysiology of emotion. In M. Lewis & J. M. Lewis (Eds.), *Handbook of emotions* (pp. 173-191). Guilford Press.

Cannon, W. B. (1915). *Bodily changes in pain, hunger, fear, and rage: An acccount of recent researches in the function of emotional excitement*. D. Appleton and Company.

Casey, L. M., Oei, T. P., & Newcombe, P. A. (2004). An integrated cognitive model of panic disorder: the role of positive and negative cognitions. *Clinical Psychology Review*, *24*(5), 529-555. https://doi.org/10.1016/j.cpr.2004.01.005

Casey, L. M., Oei, T. P., Newcombe, P. A., & Kenardy, J. (2004). The role of catastrophic misinterpretation of bodily sensations and panic self-efficacy in predicting panic severity. *J Anxiety Disord*, *18*(3), 325-340. https://doi.org/10.1016/S0887-6185(02)00257-8

Chambless, D. L., Caputo, G. C., Jasin, S. E., Gracely, E. J., & Williams, C. (1985). The mobility inventory for agoraphobia. *Behaviour Research and Therapy*, *23*(1), 35-44. https://doi.org/10.1016/0005-7967(85)90140-8

Chambless, D. L., & Gracely, E. J. (1989). Fear of fear and the anxiety disorders. *Cognitive Therapy and Research*, *13*, 9-20. https://doi.org/10.1007/BF01178486

Clark, D. A., & Beck, A. T. (2011). *Cognitive therapy of anxiety disorders : science and practice*. Guilford Press.

Clark, D. M. (1986). A cognitive approach to panic. *Behaviour Research and Therapy*, *24*(4), 461-470. https://doi.org/10.1016/0005-7967(86)90011-2

Clark, D. M. (1988). A cognitive model of panic attacks. In S. Rachman & J. D. Maser (Eds.), *Panic: Psychological perspectives* (pp. 71-89). Erlbaum.

Clark, D. M. (1993). Cognitive mediation of panic attacks induced by biological challenge tests. *Advances in Behaviour Research and Therapy*, *15*(1), 75-84. https://doi.org/10.1016/0146-6402(93)90004-L

Clark, D. M. (1999). Anxiety disorders: Why they persist and how to treat them. *Behaviour Research and Therapy*, *37*, S5-S27. https://doi.org/10.1016/S0005-7967(99)00048-0

Clark, D. M., Salkovskis, P. M., Ost, L. G., Breitholtz, E., Koehler, K. A., Westling, B. E., . . . Gelder, M. (1997). Misinterpretation of body sensations in panic disorder. *Journal of Consulting and Clinical Psychology*, *65*(2), 203-213. https://doi.org/10.1037//0022-006x.65.2.203

Cohen, A. S., Barlow, D. H., & Blanchard, E. B. (1985). Psychophysiology of relaxation-associated panic attacks. *Journal of Abnormal Psychology*, *94*(1), 96-101. https://doi.org/10.1037/0021-843X.94.1.96

Contreras, A., Nieto, I., Valiente, C., Espinosa, R., & Vazquez, C. (2019). The Study of Psychopathology from the Network Analysis Perspective: A Systematic Review. *Psychotherapy and Psychosomatics*, *88*(2), 71-83. https://doi.org/10.1159/000497425

Conway, C. C., Forbes, M. K., Forbush, K. T., Fried, E. I., Hallquist, M. N., Kotov, R., . . . Eaton, N. R. (2019). A Hierarchical Taxonomy of Psychopathology Can Transform Mental Health Research. *Perspect Psychol Sci*, *14*(3), 419-436. https://doi.org/10.1177/1745691618810696

Conway, C. C., Forbes, M. K., South, S. C., & Hi, T. O. P. C. (2022). A Hierarchical Taxonomy of Psychopathology (HiTOP) Primer for Mental Health Researchers. *Clin Psychol Sci*, *10*(2), 236-258. https://doi.org/10.1177/21677026211017834

Coryell, W., Dindo, L., Fyer, A., & Pine, D. S. (2006). Onset of spontaneous panic attacks: a prospective study of risk factors. *Psychosomatic Medicine*, *68*(5), 754-757. https://doi.org/10.1097/01.psy.0000232268.00327.b4

Cramer, A. O., Waldorp, L. J., van der Maas, H. L., & Borsboom, D. (2010). Comorbidity: a network perspective. *Behavioral and Brain Sciences*, *33*(2-3), 137-150; discussion 150-193. https://doi.org/10.1017/S0140525X09991567

Craske, M. G., Kircanski, K., Epstein, A., Wittchen, H. U., Pine, D. S., Lewis-Fernandez, R., . . . Dissociative Disorder Work, G. (2010). Panic disorder: A review of DSM-IV panic disorder and proposals for DSM-V. *Depression and Anxiety*, *27*(2), 93-112. https://doi.org/10.1002/da.20654

Craske, M. G., & Waters, A. M. (2005). Panic disorder, phobias, and generalized anxiety disorder. *Annu Rev Clin Psychol*, *1*, 197-225. https://doi.org/10.1146/annurev.clinpsy.1.102803.143857

Curtiss, J. E., Mischoulon, D., Fisher, L. B., Cusin, C., Fedor, S., Picard, R. W., & Pedrelli, P. (2021). Rising early warning signals in affect associated with future changes in

depression: a dynamical systems approach. *Psychological Medicine*, 1-9. https://doi.org/10.1017/S0033291721005183

Cuthbert, B. N. (2022). Research Domain Criteria (RDoC): Progress and Potential. *Curr Dir Psychol Sci*, *31*(2), 107-114. https://doi.org/10.1177/09637214211051363

Cuthbert, B. N., & Insel, T. R. (2013). Toward the future of psychiatric diagnosis: the seven pillars of RDoC. *BMC Med*, *11*, 126. https://doi.org/10.1186/1741-7015-11-126

Dablander, F., Pichler, A., Cika, A., & Bacilieri, A. (2022). Anticipating critical transitions in psychological systems using early warning signals: Theoretical and practical considerations. *Psychological Methods*. https://doi.org/10.1037/met0000450

de Beurs, E., Garssen, B., Buikhuisen, M., Lange, A., van Balkom, A., & Van Dyck, R. (1994). Continuous monitoring of panic. *Acta Psychiatrica Scandinavica*, *90*(1), 38-45. https://doi.org/10.1111/j.1600-0447.1994.tb01553.x

de Ron, J., Deserno, M. K., van der Maas, H. L., Robinaugh, D. J., & Borsboom, D. (2022). Towards a general modelling framework of resource-limited cognitive development. *Child Development*. https://doi.org/https://doi.org/10.1111/cdev.13973

Deacon, B. J., Abramowitz, J. S., Woods, C. M., & Tolin, D. F. (2003). The Anxiety Sensitivity Index - Revised: psychometric properties and factor structure in two nonclinical samples. *Behaviour Research and Therapy*, *41*(12), 1427-1449.

DeAngelis, D. L., Post, W. M., & Travis, C. C. (1986). *Positive feedback in natural systems*. Springer-Verlag.

Dillon, D. G., Wiecki, T., Pechtel, P., Webb, C., Goer, F., Murray, L., . . . Pizzagalli, D. A. (2015). A computational analysis of flanker interference in depression. *Psychol Med*, *45*(11), 2333-2344. https://doi.org/10.1017/S0033291715000276

Ehlers, A. (1993). Interoception and panic disorder. *Advances in Behaviour Research and Therapy*, *15*, 3-21.

Ehlers, A., & Margraf, J. (1989). The psychophysiological model of panic attacks. In P. M. G. Emmelkamp, W. T. A. M. Everaerd, F. W. Kraaimaat, & M. J. M. van Son (Eds.), *Fresh Perspectives on Anxiety Disorders*. Swets & Zeitlinger.

Ellard, K. K., Fairholme, C. P., Boisseau, C. L., Farchione, T. J., & Barlow, D. H. (2010). Unified protocol for the transdiagnostic treatment of emotional disorders: Protocol development and initial outcome data. *Cognitive and Behavioral Practice*, *17*(1), 88-101. https://doi.org/10.1016/j.cbpra.2009.06.002

Epstein, J. M. (2008). Why model? *Journal of Artificial Societies and Social Simulation*, *11*(4), 12.

Estes, W. K. (1975). Some targets for mathematical psychology. *Journal of Mathematical Psychology*, 263-282.

Farrell, S., & Lewandowsky, S. (2010). Computational models as aids to better reasoning in psychology. *Current Directions in Psychological Science*, *19*, 329-335.

Fentz, H. N., Hoffart, A., Jensen, M. B., Arendt, M., O'Toole, M. S., Rosenberg, N. K., & Hougaard, E. (2013). Mechanisms of change in cognitive behaviour therapy for panic disorder: the role of panic self-efficacy and catastrophic misinterpretations. *Behavior Research & Therapy*, *51*(9), 579-587. https://doi.org/10.1016/j.brat.2013.06.002

Foa, E. B., & Kozak, M. J. (1986). Emotional processing of fear: exposure to corrective information. *Psychological Bulletin*, *99*(1), 20-35.

Forsyth, J. P., & Karekla, M. (2002). Biological challenge in the assessment of anxiety disorders. In M. M. Antony, S. M. Orsillo, & L. Roemer (Eds.), *Practitioner's guide to empirically based measures of anxiety* (pp. 31-36). https://doi.org/https://doi.org/10.1007/0-306-47628-2_5

Frances, A., Miele, G. M., Widiger, T. A., Pincus, H. A., Manning, D., & Davis, W. W. (1993). The classification of panic disorders: From Freud to DSM-IV. *Journal of*

Psychiatric Research, *27 Suppl 1*, 3-10. https://doi.org/doi.org/10.1016/0022-3956(93)90013-R

Freud, S. (1962). On the grounds for detaching a particular syndrome from neurasthenia under the description 'anxiety neurosis'. In *The Standard Edition of the Complete Psychological Works of Sigmund Freud* (Vol. 3, pp. 85-115). Hogarth Press. (1895)

Fried, E. (2022). Studying mental health problems as systems, not syndromes. *Current Directions in Psychological Science*.

Fried, E. I. (2021). Lack of theory building and testing impedes progress in the factor and network literature. *Psychological Inquiry*, *31*.

Fried, E. I., Bockting, C., Arjadi, R., Borsboom, D., Amshoff, M., Cramer, A. O., . . . Stroebe, M. (2015). From loss to loneliness: The relationship between bereavement and depressive symptoms. *J Abnorm Psychol*, *124*(2), 256-265. https://doi.org/10.1037/abn0000028

Friston, K. (2013). Active inference and free energy. *Behav Brain Sci*, *36*(3), 212-213. https://doi.org/10.1017/S0140525X12002142

Friston, K., FitzGerald, T., Rigoli, F., Schwartenbeck, P., & Pezzulo, G. (2017). Active Inference: A Process Theory. *Neural Comput*, *29*(1), 1-49. https://doi.org/10.1162/NECO_a_00912

Fudenberg, D., Newey, W., Strack, P., & Strzalecki, T. (2020). Testing the drift-diffusion model. *Proc Natl Acad Sci U S A*, *117*(52), 33141-33148. https://doi.org/10.1073/pnas.2011446117

Fukano, T., & Gunji, Y.-P. (2012). Mathematical models of panic disorder. *Nonlinear Dynamics, Psychology, and Life Sciences*, *16*(4), 457-470.

Furukawa, T. A., Katherine Shear, M., Barlow, D. H., Gorman, J. M., Woods, S. W., Money, R., . . . Leucht, S. (2009). Evidence-based guidelines for interpretation of the Panic

Disorder Severity Scale. *Depression and Anxiety*, *26*(10), 922-929. https://doi.org/10.1002/da.20532

Gallagher, M. W., Bentley, K. H., & Barlow, D. H. (2014). Perceived control and vulnerability to anxiety disorders: A meta-analytic review. *Cognitive Therapy and Research*, *38*, 571-584.

Gallagher, M. W., Payne, L. A., White, K. S., Shear, K. M., Woods, S. W., Gorman, J. M., & Barlow, D. H. (2013). Mechanisms of change in cognitive behavioral therapy for panic disorder: the unique effects of self-efficacy and anxiety sensitivity. *Behaviour Research and Therapy*, *51*(11), 767-777. https://doi.org/10.1016/j.brat.2013.09.001

Gershman, S. J., & Niv, Y. (2012). Exploring a latent cause theory of classical conditioning. *Learning & Behavior*, *40*(3), 255-268. https://doi.org/10.3758/s13420-012-0080-8

Goetz, R. R., Klein, D. F., Gully, R., Kahn, J., Liebowitz, M. R., Fyer, A. J., & Gorman, J. M. (1993). Panic attacks during placebo procedures in the laboratory. Physiology and symptomatology. *Archives of General Psychiatry*, *50*(4), 280-285. https://doi.org/10.1001/archpsyc.1993.01820160050006

Goldstein, A. J., & Chambless, D. L. (1978). A reanalysis of agoraphobia. *Behavior Therapy*, *9*, 47-59. https://doi.org/10.1016/S0005-7894(78)80053-7

Grondman, I., Busconiu, L., Lopes, G. A. D., & Babuška. (2012). A survey of actor-critic reinforcement learning: Standard and natural policy gradients. *IEEE Transactions on systems, man, and cybernetics - Part C: Applications and reviews*, *42*(6), 1291-1307.

Guest, O. (2023). What makes a good theory, and how do we make a theory good? https://doi.org/https://doi.org/10.31234/osf.io/8fxds

Guest, O., & Martin, A. E. (2021). How computational modeling can force theory building in psychological science. *Perspectives on Psychological Science*, *16*(4), 789-802. https://doi.org/10.1177/1745691620970585

Haig, B. D. (2005). An abductive theory of scientific method. *Psychological Methods*, *10*(4), 371-388. https://doi.org/10.1037/1082-989X.10.4.371

Haig, B. D. (2013). Detecting psychological phenomena: Taking bottom-up research seriously. *The American Journal of Psychology*, *126*(2), 135-153.

Harrington, P. J., Schmidt, N. B., & Telch, M. J. (1996). Prospective evaluation of panic potentiation following 35% CO2 challenge in nonclinical subjects. *The American Journal of Psychiatry*, *153*(6), 823-825. https://doi.org/10.1176/ajp.153.6.823

Harvey, A. G., Watkins, E., & Mansell, W. (2004). *Cognitive behavioural processes across psychological disorders: A transdiagnostic approach to research and treatment*. Oxford University Press.

Haslbeck, J. M. B., Ryan, O., Robinaugh, D. J., Waldorp, L. J., & Borsboom, D. (2021). Modeling psychopathology: From data models to formal theories. *Psychological Methods*. https://doi.org/10.1037/met0000303

Hasselman, F. (2022). Early warning signals in phase space: Geometric resilience loss indicators from multiplex cumulative recurrence networks. *Frontiers in Physiology*, *13*, 859127. https://doi.org/10.3389/fphys.2022.859127

Hayes, A. M., & Andrews, L. A. (2020). A complex systems approach to the study of change in psychotherapy. *BMC Medicine*, *18*(1), 197. https://doi.org/10.1186/s12916-020-01662-2

Hibbert, G. A. (1984). Ideational components of anxiety: Their origin and content. *British Journal of Psychiatry*, *144*, 618-624. https://doi.org/10.1192/bjp.144.6.618

Hinton, D., So, V., Pollack, M. H., Pitman, R. G., & Orr, S. P. (2004). The psychophysiology of orthostatic panic in Cambodian refugees attending a psychiatric clinic. *Journal of Psychopathology and Behavioral Assessment*, *26*(1), 1-13. https://doi.org/10.1023/B:JOBA.0000007451.85942.42

Hinton, D., Um, K., & Ba, P. (2001). Kyol goeu (‘wind overload') part I: A cultural syndrome of orthostatic panic among Khmer refugees. *Transcultural Psychiatry*, *38*(4), 403-432. https://doi.org/10.1177/136346150103800401

Hinton, G. E., Plaut, D. C., & Shallice, T. (1993). Simulating brain damage. *Sci Am*, *269*(4), 76-82. https://doi.org/10.1038/scientificamerican1093-76

Hosseinichimeh, N., Wittenborn, A. K., Rick, J., Jalali, M. S., & Rahmandad, H. (2018). Modeling and estimating the feedback mechanisms among depression, rumination, and stressors in adolescents. *PLoS One*, *13*(9), e0204389. https://doi.org/10.1371/journal.pone.0204389

Huys, Q. J., Maia, T. V., & Frank, M. J. (2016). Computational psychiatry as a bridge from neuroscience to clinical applications. *Nature Neuroscience*, *19*(3), 404-413. https://doi.org/10.1038/nn.4238

Kessler, R. C., Chiu, W. T., Jin, R., Ruscio, A. M., Shear, K., & Walters, E. E. (2006). The epidemiology of panic attacks, panic disorder, and agoraphobia in the National Comorbidity Survey Replication. *Archives of General Psychiatry*, *63*(4), 415-424. https://doi.org/10.1001/archpsyc.63.4.415

Kessler, R. C., Stang, P. E., Wittchen, H. U., Ustun, T. B., Roy-Burne, P. P., & Walters, E. E. (1998). Lifetime panic-depression comorbidity in the National Comorbidity Survey. *Arch Gen Psychiatry*, *55*(9), 801-808. https://doi.org/10.1001/archpsyc.55.9.801

Klein, D. F., & Klein, H. M. (1989). The definition and psychopharmacology of spontaneous panic and phobia. In P. Tyrer (Ed.), *British Association for Psychopharmacology monograph, No. 11. Psychopharmacology of anxiety* (pp. 135-162). Oxford University Press.

Krueger, R. F., Kotov, R., Watson, D., Forbes, M. K., Eaton, N. R., Ruggero, C. J., . . . Zimmermann, J. (2018). Progress in achieving quantitative classification of

psychopathology. *World Psychiatry*, *17*(3), 282-293. https://doi.org/10.1002/wps.20566

Lader, M., & Mathews, A. (1970). Physiological changes during spontaneous panic attacks. *Journal of Psychosomatic Research*, *14*(4), 377-382. https://doi.org/10.1016/0022-3999(70)90004-8

Lakatos, I. (1970). Falsification and the methodology of scientific research programme. In I. Lakatos & A. Musgrave (Eds.), *Criticism and the growth of knowledge* (pp. 91-196). Cambridge University Press.

Leroux. (1889). Vertige. In A. Dechambre & L. Lereboullet (Eds.), *Dictionnaire Encyclopedique des Sciences Medicales.* (pp. 146-188). Masson.

Lewandowsky, S., & Farrell, S. (2011). *Computational modeling in cognition: Principles and practice*. Sage Publications.

Lewis-Fernandez, R., Hinton, D. E., Laria, A. J., Patterson, E. H., Hofmann, S. G., Craske, M. G., . . . Liao, B. (2010). Culture and the anxiety disorders: recommendations for DSM-V. *Depression and Anxiety*, *27*(2), 212-229. https://doi.org/10.1002/da.20647

Liebowitz, M. R., Fyer, A. J., Gorman, J. M., Dillon, D., Appleby, I. L., Levy, G., . . . et al. (1984). Lactate provocation of panic attacks. I. Clinical and behavioral findings. *Archives of General Psychiatry*, *41*(8), 764-770. https://doi.org/10.1001/archpsyc.1984.01790190038004

Maisto, D., Barca, L., Van den Bergh, O., & Pezzulo, G. (2021). Perception and misperception of bodily symptoms from an active inference perspective: Modelling the case of panic disorder. *Psychol Rev*, *128*(4), 690-710. https://doi.org/10.1037/rev0000290

Mansell, W., Harvey, A., Watkins, E., & Shafran, R. (2009). Conceptual foundations of the transdiagnostic approach to CBT. *Journal of Cognitive Psychotherapy: An International Quarterly*, *23*, 6-19.

Margraf, J., Ehlers, A., & Roth, W. T. (1986). Sodium lactate infusions and panic attacks: a review and critique. *Psychosomatic Medicine*, *48*(1-2), 23-51.

Marques, L., Robinaugh, D. J., LeBlanc, N. J., & Hinton, D. (2011). Cross-cultural variations in the prevalence and presentation of anxiety disorders. *Expert Rev Neurother*, *11*(2), 313-322. https://doi.org/10.1586/ern.10.122

McNally, R. J. (1994). *Panic disorder: A critical analysis*. Guilford Press.

McNally, R. J. (2002). Anxiety sensitivity and panic disorder. *Biological Psychiatry*, *52*(10), 938-946. https://doi.org/10.1016/S0006-3223(02)01475-0

Meehl, P. E. (1978). Theoretical risks and tabular asterisks: Sir Karl, Sir Ronald, and the slow progress of soft psychology. *Journal of Consulting and Clinical Psychology*, *46*, 806-834.

Millner, A. J., Robinaugh, D. J., & Nock, M. K. (2020). Advancing the understanding of suicide: The need for formal theory and rigorous descriptive research. *Trends in Cognitive Sciences*, *24*(9), 704-716. https://doi.org/10.1016/j.tics.2020.06.007

Milosavljevic, M., Malmaud, J., Huth, A., Koch, C., & Rangel, A. (2010). The drift diffusion model can account for value-based choice response times under high and low time pressure. *Judgement and Decision Making*, *5*, 437–449.

Moutoussis, M., Shahar, N., Hauser, T. U., & Dolan, R. J. (2018). Computation in psychotherapy, or how computational psychiatry can aid learning-based psychological therapies. *Computational Psychiatry*, *2*, 50-73.

Muthukrishna, M., & Henrich, J. (2019). A problem in theory. *Nature Human Behaviour*, *3*, 221-229.

Navarro, D. J. (2021). If mathematical psychology did not exist we might need to invent it: A comment on theory building in psychology. *Perspectives on Psychological Science*, *16*(4), 707-716. https://doi.org/10.1177/174569162097476

Nelson, B., McGorry, P. D., Wichers, M., Wigman, J. T. W., & Hartmann, J. A. (2017). Moving from static to dynamic models of the onset of mental disorder: A review. *JAMA Psychiatry*, *74*(5), 528-534. https://doi.org/10.1001/jamapsychiatry.2017.0001

Nolen-Hoeksema, S., & Watkins, E. R. (2011). A heuristic for developing transdiagnostic models of psychopathology: Explaining multifinality and divergent trajectories. *Perspectives on Psychological Science*, *6*(6), 589-609. https://doi.org/10.1177/1745691611419672

Norton, P. J., Zvolensky, M. J., Bonn-Miller, M. O., Cox, B. J., & Norton, G. R. (2008). Use of the Panic Attack Questionnaire-IV to assess non-clinical panic attacks and limited symptom panic attacks in student and community samples. *Journal of Anxiety Disorders*, *22*(7), 1159-1171. https://doi.org/10.1016/j.janxdis.2007.12.002

Olatunji, B. O., & Wolitzky-Taylor, K. B. (2009). Anxiety sensitivity and the anxiety disorders: a meta-analytic review and synthesis. *Psychol Bull*, *135*(6), 974-999. https://doi.org/10.1037/a0017428

Olthof, M., Hasselman, F., Maatman, F. O., Bosman, A., & Lichtwarck-Aschoff, A. (2021). Complexity theory of psychopathology. *Journal of Psychopathology and Clinical Science*.

Ottaviani, R., & Beck, A. T. (1987). Cognitive aspects of panic disorders. *Journal of Anxiety Disorders*, *1*, 15-28. https://doi.org/10.1016/0887-6185(87)90019-3

Otto, M. W., Tolin, D. F., Nations, K. R., Utschig, A. C., Rothbaum, B. O., Hofmann, S. G., & Smits, J. A. (2012). Five sessions and counting: considering ultra-brief treatment

for panic disorder. *Depression and Anxiety*, *29*(6), 465-470. https://doi.org/10.1002/da.21910

Otto, M. W., Tolin, D. F., Simon, N. M., Pearlson, G. D., Basden, S., Meunier, S. A., . . . Pollack, M. H. (2010). Efficacy of d-cycloserine for enhancing response to cognitive-behavior therapy for panic disorder. *Biological Psychiatry*, *67*(4), 365-370. https://doi.org/10.1016/j.biopsych.2009.07.036

Parr, T., Pezzulo, G., & Friston, K. J. (2022). *Active inference : the free energy principle in mind, brain, and behavior*. The MIT Press.

Perna, G., Cocchi, S., Allevi, L., Bussi, R., & Bellodi, L. (1999). A long-term prospective evaluation of first-degree relatives of panic patients who underwent the 35% CO2 challenge. *Biological Psychiatry*, *45*(3), 365-367. https://doi.org/10.1016/s0006-3223(98)00030-4

Pickard, H. (2022). Addiction and the Meaning of Disease. In N. Heather, M. Field, A. C. Moss, & S. Satel (Eds.), *Evaluating the brain disease model of addiction*. Routledge.

Powers, M. B., Vervliet, B., Smits, J. A., & Otto, M. W. (2010). Helping exposure succeed: Learning theory perspectives on treatment resistance and relapse. In M. W. Otto & S. G. Hofmann (Eds.), *Avoiding treatment failures in the anxiety disorders* (pp. 31-49). Springer.

Proulx, T., & Morey, R. D. (2021). Beyond statistical ritual: Theory in psychological science. *Perspectives on Psychol Science*, *16*(4), 671-681. https://doi.org/10.1177/17456916211017098

R Core Team. (2014). *R: A language and environment for statistical computing.* In R Foundation for Statistical Computing.

Radomsky, A. S., Rachman, S., Teachman, B. A., & Freeman, W. S. (1998). Why do episodes of panic stop? *Journal of Anxiety Disorders*, *12*(3), 263-270. https://doi.org/10.1016/S0887-6185(98)00014-0

Rapee, R. M. (1987). The psychological treatment of panic attacks: Theoretical conceptualization and review of evidence. *Clinical Psychology Review*, *7*, 427-438. https://doi.org/10.1016/0272-7358(87)90020-1

Rapee, R. M. (1995). Psychological-factors influencing the affective response to biological challenge procedures in panic disorder. *Journal of Anxiety Disorders*, *9*(1), 59-74. https://doi.org/10.1016/0887-6185(94)00028-9

Reiss, S., & McNally, R. J. (1985). The expectancy model of fear. In S. Reiss & R. R. Bootzin (Eds.), *Theoretical issues in behavior therapy*. Academic Press.

Reiss, S., Peterson, R. A., Gursky, D. M., & McNally, R. J. (1986). Anxiety sensitivity, anxiety frequency and the prediction of fearfulness. *Behaviour Research and Therapy*, *24*(1), 1-8. https://doi.org/10.1016/0005-7967(86)90143-9

Roberson-Nay, R., Beadel, J. R., Gorlin, E. I., Latendresse, S. J., & Teachman, B. A. (2015). Examining the latent class structure of CO2 hypersensitivity using time course trajectories of panic response systems. *Journal of Behavior Therapy and Experimental Psychiatry*, *47*, 68-76. https://doi.org/10.1016/j.jbtep.2014.10.013

Robinaugh, D. J., Haslbeck, J. M. B., Ryan, O., Fried, E. I., & Waldorp, L. J. (2021). Invisible hands and fine calipers: A call to use formal theory as a toolkit for theory construction. *Perspectives on Psychological Science*, *16*(4), 725-743. https://doi.org/10.1177/1745691620974697

Robinaugh, D. J., Hoekstra, R. H. A., Toner, E. R., & Borsboom, D. (2020). The network approach to psychopathology: a review of the literature 2008-2018 and an agenda for

future research. *Psychological Medicine*, *50*(3), 353-366. https://doi.org/10.1017/S0033291719003404

Ross, D. (2019). Special, radical, failure of reduction in psychiatry. *Behavioral and Brain Sciences*, *42*, e25. https://doi.org/10.1017/S0140525X18001164

Ryan, O., Haslbeck, J., & Robinaugh, D. J. (2023). *Improving Treatments for Mental Disorders using Computational Models.*

Salkovskis, P. M. (1988). Phenomenology, assessment, and the cognitive model of panic. In S. Rachman (Ed.), *Panic: Psychological perspectives* (pp. 111-136). Lawrence Erlbaum Associates.

Salkovskis, P. M. (1991). The importance of behaviour in the maintenance of anxiety and panic: A cognitive account. *Behavioural and Cognitive Psychotherapy*, *19*(1), 6-19. https://doi.org/10.1017/S0141347300011472

Salkovskis, P. M., Clark, D. M., Hackmann, A., Wells, A., & Gelder, M. G. (1999). An experimental investigation of the role of safety-seeking behaviours in the maintenance of panic disorder with agoraphobia. *Behaviour Research and Therapy*, *37*(6), 559-574. https://doi.org/10.1016/S0005-7967(98)00153-3

Sandin, B., Sanchez-Arribas, C., Chorot, P., & Valiente, R. M. (2015). Anxiety sensitivity, catastrophic misinterpretations and panic self-efficacy in the prediction of panic disorder severity: towards a tripartite cognitive model of panic disorder. *Behaviour Research and Therapy*, *67*, 30-40. https://doi.org/10.1016/j.brat.2015.01.005

Sanislow, C. A., Pine, D. S., Quinn, K. J., Kozak, M. J., Garvey, M. A., Heinssen, R. K., . . . Cuthbert, B. N. (2010). Developing constructs for psychopathology research: research domain criteria. *Journal of Abnormal Psychology*, *119*(4), 631-639. https://doi.org/10.1037/a0020909

Scheffer, M., Bascompte, J., Brock, W. A., Brovkin, V., Carpenter, S. R., Dakos, V., . . . Sugihara, G. (2009). Early-warning signals for critical transitions. *Nature*, *461*(7260), 53-59. https://doi.org/10.1038/nature08227

Schmidt, N. B., & Keough, M. E. (2010). Treatment of panic. *Annual Review of Clinical Psychology*, *6*, 241-256. https://doi.org/10.1146/annurev.clinpsy.121208.131317

Schmidt, N. B., Maner, J. K., & Zvolensky, M. J. (2007). Reactivity to challenge with carbon dioxide as a prospective predictor of panic attacks. *Psychiatry Research*, *151*(1-2), 173-176. https://doi.org/10.1016/j.psychres.2006.11.006

Schmidt, N. B., & Zvolensky, M. J. (2007). Anxiety sensitivity and CO2 challenge reactivity as unique and interactive prospective predictors of anxiety pathology. *Depression and Anxiety*, *24*, 527-536.

Schreuder, M. J., Wigman, J. T. W., Groen, R. N., Weinans, E., Wichers, M., & Hartman, C. A. (2022). Anticipating the direction of symptom progression using critical slowing down: a proof-of-concept study. *BMC Psychiatry*, *22*, 49. https://doi.org/https://doi.org/10.1186/s12888-022-03686-9

Segal, Z. V. (1988). Appraisal of the self-schema construct in cognitive models of depression. *Psychological Bulletin*, *103*(2), 147-162. https://doi.org/10.1037/0033-2909.103.2.147

Seligman, M. (1988). Competing theories of panic. In S. Rachman & J. D. Maser (Eds.), *Panic: Psychological perspectives*. Erlbaum.

Smaldino, P. E. (2016). Not even wrong: Imprecision perpetuates the illusion of understanding at the cost of actual understanding. *Behavioral and Brain Sciences*, *39*, e163. https://doi.org/10.1017/S0140525X1500151X

Smaldino, P. E. (2017). Models are stupid, and we need more of them. In R. R. Vallacher, Read, S. J., & Nowak, A. (Ed.), *Computational social psychology* (pp. 311-331). Routledge.

Smits, J. A. J., Otto, M. W., Powers, M. B., & Baird, S. O. (2019). Anxiety sensitivity as a transdiagnostic treatment target. In J. A. J. Smits, M. W. Otto, M. B. Powers, & S. O. Baird (Eds.), *The clinician's guide to anxiety sensitivity treatment and assessment.* Academic Press.

Springer, K. S., Levy, H. C., & Tolin, D. F. (2018). Remission in CBT for adult anxiety disorders: A meta-analysis. *Clinical Psychology Review*, *61*, 1-8. https://doi.org/10.1016/j.cpr.2018.03.002

Taylor, C. B., King, R., Ehlers, A., Margraf, J., Clark, D., Hayward, C., . . . Agras, S. (1987). Treadmill exercise test and ambulatory measures in panic attacks. *American Journal of Cardiology*, *60*(18), 48J-52J. https://doi.org/10.1016/0002-9149(87)90683-7

Taylor, S. (1994). Comment on Otto et al. (1992): Hypochondriacal concerns, anxiety sensitivity, and panic disorder. *Journal of Anxiety Disorders*, *8*(1), 97-99. https://doi.org/10.1016/0887-6185(94)90026-4

Taylor, S., Koch, W. J., & McNally, R. J. (1992). How does anxiety sensitivity vary across the anxiety disorders? *Journal of anxiety disorders*, 249-259.

Trew, J. L. (2011). Exploring the roles of approach and avoidance in depression: an integrative model. *Clinical Psychological Review*, *31*(7), 1156-1168. https://doi.org/10.1016/j.cpr.2011.07.007

Uhde, T. W., Boulenger, J. P., Roy-Byrne, P. P., Geraci, M. F., Vittone, B. J., & Post, R. M. (1985). Longitudinal course of panic disorder: Clinical and biological considerations. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*, *9*(1), 39-51. https://doi.org/10.1016/0278-5846(85)90178-2

van den Hout, M., & Griez, E. (1983). Some remarks on the nosology of anxiety states and panic disorders. *Acta Psychiatrica Belgica*, *83*, 33-42.

van der Maas, H. L., Dolan, C. V., Grasman, R. P., Wicherts, J. M., Huizenga, H. M., & Raijmakers, M. E. (2006). A dynamical model of general intelligence: the positive manifold of intelligence by mutualism. *Psychological Review*, *113*(4), 842-861. https://doi.org/10.1037/0033-295X.113.4.842

van Dongen, N., van Bork, R., Finnemann, A., Haslbeck, J., van der Maas, H. L., Robinaugh, D. J., . . . Borsboom, D. (2022). *Improving psychological explanations*. https://psyarxiv.com/qd69g/

van Rooij, I., & Baggio, G. (2020). Theory development requires an epistemological sea change. *Psychological Inquiry*, *31*(4), 321-325. https://doi.org/https://doi.org/10.1080/1047840X.2020.1853477

van Rooij, I., & Blokpoel, M. (2020). Formalizing verbal theories: A tutorial by dialogue. *Social Psychology*, *51*, 285–298. https://doi.org/https://doi.org/10.1027/1864-9335/a000428

von Bertalanffy, L. (1972). The history and status of general systems theory. *The Academy of Management Journal*, *15*(4), 407-426. https://doi.org/10.2307/255139

Wakefield, J. C. (1999). Mental disorder as a black box essentialist concept. *Journal of Abnormal Psychology*, *108*(3), 465-472. https://doi.org/10.1037//0021-843x.108.3.465

Wang, S. B., Robinaugh, D., Millner, A., Fortgang, R., & Nock, M. K. (2023). Mathematical and computational modeling of suicide as a complex dynamical system. https://doi.org/10.31234/osf.io/b29cs

White, K. S., Brown, T. A., Somers, T. J., & Barlow, D. H. (2006). Avoidance behavior in panic disorder: the moderating influence of perceived control. *Behaviour research and therapy*, *44*(1), 147-157. https://doi.org/10.1016/j.brat.2005.07.009

Woods, S. W., Charney, D. S., Goodman, W. K., & Heninger, G. R. (1988). Carbon dioxide-induced anxiety. Behavioral, physiologic, and biochemical effects of carbon dioxide in patients with panic disorders and healthy subjects. *Archives of General Psychiatry*, *45*(1), 43-52. https://doi.org/10.1001/archpsyc.1988.01800250051007

Zorowitz, S., Momennejad, I., & Daw, N. D. (2020). Anxiety, avoidance, and sequential evaluation. *Computational Psychiatry*, *4*. https://doi.org/10.1162/cpsy_a_00026