

Supplementary Materials A

A Detailed Overview of Model Equations

This supplementary document provides additional details regarding the formalization of our network theory of panic disorder as a set of differential equations, as well as our implementation of that model in *R*. For each theory component (e.g., Arousal; A) we detail the differential equations that define the rate of change in that component (e.g., dA/dt), including the parameter values used in our implementation of the model. We then translate these equations into difference equations, which express the relationships among theory components in discrete time rather than continuous time, and show how we implemented these difference equations in *R*. The step from differential to difference equations was used to solve differential equations numerically. By iterating these difference equations with small time steps we are able to approximate the solutions of the system of differential equations (Atkinson, 2008). Figure A1 presents an annotated causal diagram of our theory, which we will refer to when describing the model equations.

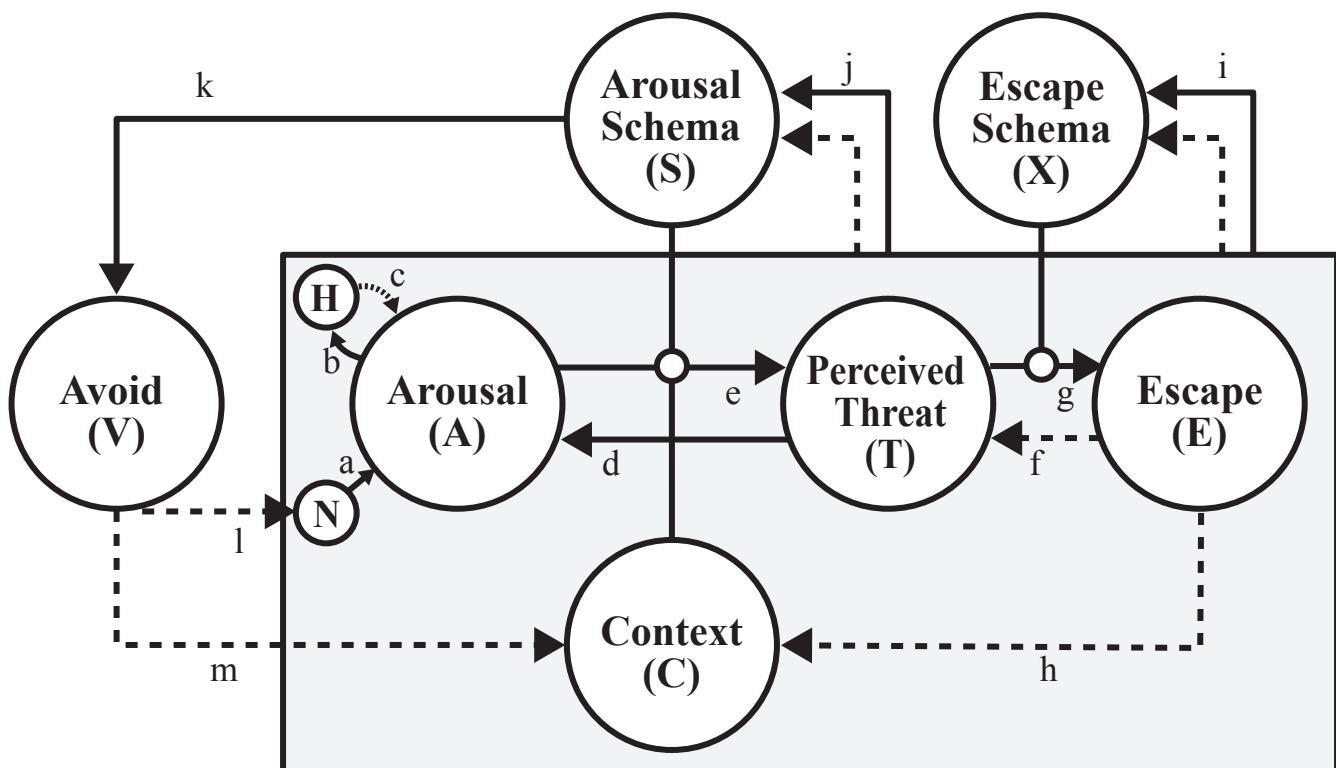


Figure A1. A Causal Diagram Depicting a Network Theory of Panic Disorder. Capital letters are used to identify theory components. Lowercase letters identify the relations among the state variables. Below, we refer to these annotations when detailing the equations in our theory.

AROUSAL

As described in the main text, the rate of change in arousal (A) is a function of itself and three variables: a correlated noise variable that creates variability in arousal (N), homeostatic feedback that contributes to the regulation of arousal when arousal becomes substantially elevated (H), and perceived threat (T). These effects are denoted as “a”, “c”, and “d” in Figure A1. The equations used to define the rate of change in arousal and their implementation in R are detailed below.

Differential Equation: $\frac{dA}{dt} = \alpha_A((\beta_A T + N - H) - A)$

Difference Equation: $A_{t+1} = A_t + \alpha_A((\beta_A T_t + N_t - H_t) - A_t)$

R:

```
dA_dt <- function(A, PT, N, H, r_A, s_PT_A) {  
  r_A * ((s_PT_A * PT + N - H) - A)  
}
```

State Variable	R Code Label	Default Initial Value	Description
A	A	0	Arousal. Autonomic arousal, with 0 indicating the within-person equilibrium of autonomic arousal and positive and negative values indicating arousal above and below that equilibrium, respectively.
T	PT	0	Perceived threat. The perception of threat from arousal ranging from an absence of threat (0) to maximal level of perceived threat (1)
N	N	0	Stochastic Variation (Noise). Natural perturbations to arousal either from the body’s own internal physiological processes or from the environment (e.g., drinking coffee).
H	H	0	Homeostatic Feedback. The body’s regulatory processes that bring arousal back to its equilibrium following significant elevations.

Parameter	R Code Label	Default Value	Description
α_A	r_A	0.50	Rate parameter constraining the rate at which arousal will change
β_A	s_PT_A	1	Slope parameter specifying the strength of the linear effect of perceived threat on the rate of change in arousal.

STOCHASTIC VARIATION (NOISE)

To incorporate stochastic variation in arousal arising from either physiological processes or from the environment, we added a “red noise” variable into the model (Hasselmann, 1976; van Nes & Scheffer, 2004). Conceptually, red noise at time point $t+1$ is generated by adding white noise to the red noise at t . The red noise variable is therefore dependent on the previous time step. Noise that is dependent across time in this way is more realistic than white noise, because it would be unrealistic to assume that the environmental effects on arousal would change erratically on a minute-to-minute basis. The difference equation we used to compute red noise at time step t is given below. In this equation, λ_N gives the approximate period of the noise, N_0 is the approximate mean of the red noise (in this case, 0), β_N is a parameter that expresses deviation, and ε_t is randomly drawn from a standard normal distribution (i.e., white noise). The parameter β_N is defined, in part, by σ (see full equations for β_N and σ below) which, we define as a function of avoidance, thereby formalizing the control of Avoidance or the amount of fluctuation in arousal caused by the environment. Specifically, the effect of avoidance σ parameter is defined as a sigmoid function with slope κ_σ and mid-point λ_σ where ξ defines the lower bound of σ and $\xi + \nu$ defines the upper bound of σ .

Difference equation: $N_{t+1} = \left(1 - \frac{1}{\lambda_N}\right)(N_t - N_0) + N_0 + \beta_N \varepsilon_t$

$$\sigma = \frac{\nu}{1 + e^{\kappa_\sigma(V_t - \lambda_\sigma)}} + \xi$$

$$\beta_N = \sigma \sqrt{\frac{2}{\lambda_N} - \frac{1}{\lambda_N^2}}$$

$$\varepsilon_t \sim N(\mu, \sigma)$$

```
R: sigma <- 0.30 / (1 + exp(1)^(k_V_N * ((V) - h_V_N))) + 0.50
beta <- sigma * sqrt(2/lambda_N - 1/lambda_N^2)
epsilon <- rnorm(daysteps, mean = mu_N, sd = sigma)
for (i in 2:(daysteps+1)){
  Nvec[i] <- (1 - 1/lambda_N) * (Nvec[i-1]) + beta*epsilon[i-1]
}
```

State Variable	R Code Label	Default Initial Value	Description
N	N	0	Stochastic Variation (Noise). Natural perturbations to arousal either from the body’s own internal physiological processes or from the environment.
V	V		Avoidance. Behavior aimed at preventing exposure to arousal or exposure to situations that heighten the perceived consequences of elevated arousal. Default is defined as function of arousal schema (see below).

Parameter	R Code Label	Default Value	Description
λ_N	lambda_N	60	Parameter defining the period of the red noise
μ	mu_N	0	Parameter defining the mean of the red noise
ξ		0.50	Parameter defining the lower bound of σ (which occurs when $V_t = 1$)
ν		0.30	Parameter defining the range of σ , with the upper bound of σ (which occurs when $V_t = 0$) defined by $\xi + \nu$
κ_σ	k_V_N	5	Slope parameter defining the steepness of the effect of avoidance on σ , with higher values indicating a steeper decline with rising avoidance
λ_σ	h_V_N	0.50	Defines the mid-point for the sigmoidal effect of avoidance on σ

HOMEOSTATIC FEEDBACK

The rate of change in homeostatic feedback (H) is a function of itself and arousal (A), as depicted in effect “b” in Figure A1. The equation defining homeostatic feedback is sigmoidal (s-shaped) as this allows us to bound homeostatic feedback (between 0 and 1) and incorporate a threshold at which arousal begins to elicit homeostatic feedback. Accordingly, this component of the model simply represents the auxiliary hypothesis that when arousal becomes significantly elevated it cannot stay that way indefinitely: homeostatic feedback processes are engaged that return arousal to its equilibrium.

Differential Equation: $\frac{dH}{dt} = \alpha_{H1} \left(\frac{1}{1 + e^{-\kappa_H(A - \lambda_H)}} \right) - \alpha_{H2}H$

Differential Equation: $H_{t+1} = H_t + \alpha_{H1} \left(\frac{1}{1 + e^{-\kappa_H(A_t - \lambda_H)}} \right) - \alpha_{H2}H_t$

R:

```
dH_dt <- function(H, A, r_H, k_A_H, h_A_H) {  
  r_H * (1 / (1 + exp(- k_A_H * (A - h_A_H))) - (0.5 * H))  
}
```

State Variable	R Code Label	Default Initial Value	Description
A	A	0	Arousal. Autonomic arousal, with 0 indicating the within-person equilibrium of autonomic arousal and positive and negative values indicating arousal above and below that equilibrium, respectively.
N	N	0	Stochastic Variation (Noise). Natural perturbations to arousal either from the body’s own internal physiological processes or from the environment.
H	H	0	Homeostatic Feedback. The body’s regulatory processes that bring arousal back to its equilibrium following significant elevations.

Parameter	R Code Label	Default Value	Description
α_{H1}	r_H	0.05	Rate parameter constraining the rate at which homeostatic feedback will <i>grow</i> .
α_{H2}		0.50	Rate parameter constraining the rate at which homeostatic feedback will <i>decay</i> .
λ_H	h_A_H	0.40	Midpoint parameter defining the level of arousal needed to elicit half the maximal level of homeostatic feedback (the mid-point of the sigmoid).
κ_H	k_A_H	20	Slope parameter defining the steepness of the slope of the effect of arousal on homeostatic feedback.

PERCEIVED THREAT

The rate of change in perceived threat (T) is a function itself and two other components: arousal (A) and escape (E), depicted as effects “e” and “f” in Figure A1, respectively. Importantly, arousal schema (S) and environmental context (C) also play a role in determining the rate of change in arousal via their effect of arousal on perceived threat, a theoretical position embodied here by having both arousal schema and context as part of the equations that define the parameters $\lambda_T(S, C)$ and $\kappa_T(S, C)$ which, in turn, shape the strength of the effect of arousal on perceived threat. Higher arousal schema leads higher $\kappa_T(S, C)$ (i.e., a steeper sigmoidal curve) and lower $\lambda_T(S, C)$ (i.e., lower levels of arousal are capable of eliciting perceived threat). The effect of arousal schema is specified by the parameters γ_λ and γ_κ (which we assume to be equivalent), ε_κ , and ζ_κ as described below. The effect of context is specified by δ_λ and δ_κ .

Differential Equation:

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

$$\lambda_T[S, C] = \gamma_\lambda^S - \delta_\lambda C$$

$$\kappa_T[S, C] = \varepsilon_\kappa - \zeta_\kappa \gamma_\kappa^S + \delta_\kappa C$$

Difference Equation:

$$T_{t+1} = T_t + \alpha_T \left(\frac{1}{1 + e^{-\kappa_T[S_t, C_t](A_t - \beta_T E_t - \lambda_T[S_t, C_t])}} - T_t \right)$$

R:

```
dPT_dt <- function(PT, A, E, r_PT, k_A_PT, s_E_PT, h_A_PT) {
  r_PT * ((1 / (1 + exp(- k_A_PT * (A - s_E_PT * E - h_A_PT)))) - PT)
}
```

State Variable	R Code Label	Default Initial Value	Description
T	PT	0	Perceived threat. The perception of threat from arousal ranging from an absence of threat (0) to maximal level of perceived threat (1).
A	A	0	Arousal. Autonomic arousal, with 0 indicating the within-person equilibrium of autonomic arousal and positive and negative values indicating arousal above and below that equilibrium, respectively.
E	E	0	Escape. Behavior aimed at mitigating the threat posed by or indicated by arousal, with values defined by the level of threat the behavior is intended to mitigate, ranging from 0 to 1.

Parameter	R Code Label	Default Value	Description
α_T	r_T	1	Rate parameter constraining the rate of change in perceived threat.
$\kappa_T[S, C]$	k_A_PT		Midpoint parameter for the effect of arousal on perceived threat.
$\lambda_T[S, C]$	h_A_PT		Slope parameter for the effect of arousal on perceived threat.
β_T	s_E_PT	0.25	Slope parameter for the linear effect of escape on perceived threat.
γ_λ		0.25	Parameter that defines the impact of S on λ_T .
δ_λ		0.10	Parameter that defines the effect of Context on λ_T .
ε_κ		20	Parameter that defines the upper bound value of κ_T , apart from any additional effect of context.
ζ_κ		10	Parameter that defines the range of κ_T , with $\varepsilon_\kappa - \zeta_\kappa$ giving the lower bound value of κ_T , apart from any additional effect of context.
γ_κ		0.10	Parameter that defines the impact of S on κ_T .
δ_κ		5	Parameter that defines the effect of Context on κ_T .

ESCAPE

The rate of change in escape (E) is a function itself and two other components: perceived threat (T) and escape schema (X), together depicted as effect “g” in Figure A1. If perceived threat exceeds one’s escape schema (i.e., one’s beliefs about the amount of threat that can be tolerated without engaging in escape behavior) then escape behavior will rise. The parameter κ_E specifies the slope of the effect that this excess perceived threat ($T-X$) has on escape behavior and λ_E specifies the mid-point of this effect.

Differential Equation: $\frac{dE}{dt} = \alpha_E \left(\frac{1}{1+e^{-\kappa_E((T-X)-\lambda_E)}} - E \right)$

Difference Equation: $E_{t+1} = E_t + \alpha_E \left(\frac{1}{1+e^{-\kappa_E((T_t-X_t)-\lambda_E)}} - E_t \right)$

R:

```
dE_dt <- function(E, PT, X, r_E, k_PT_E, h_PT_E) {  
  r_E * ((1/(1 + exp(- k_PT_E * ((PT - X) - h_PT_E)))) - E)  
}
```

State Variable	R Code Label	Default Initial Value	Description
E	E	0	Escape. Behavior aimed at mitigating the threat posed by or indicated by arousal, with values defined by the level of threat the behavior is intended to mitigate, ranging from 0 to 1.
T	PT	0	Perceived threat. The perception of threat from arousal ranging from an absence of threat (0) to maximal level of perceived threat (1).
X	X	0.50	Escape Schema. Reflect one’s beliefs about the level of perceived threat that one can cope with or tolerate without engaging in escape behavior.

Parameter	R Code Label	Default Value	Description
α_E	r_E	0.25	Rate parameter constraining the rate of change in escape behavior.
κ_E	k_{PT_E}	10	Slope parameter defining the steepness of the slope of the effect of perceived threat and escape schema on escape behavior.
λ_E	h_{PT_E}	0.50	Midpoint parameter defining the mid-point of the s-shaped curve. That is, the level of perceived threat in excess of escape schema needed to elicit half the maximal level of perceived threat.

AROUSAL SCHEMA

The rate of change in arousal schema (S) is affected by the combination of arousal, perceived threat, and escape behavior. This joint effect is represented by effect “j” in Figure A1, which emerges from the grey box around each of these variables rather than any one variable by itself. As described in greater detail in the main text, the calculation of arousal schema is based on two questions. First, is there sufficient fear (i.e., the combination of arousal and perceived threat) to provide the opportunity for learning to occur? Second, is escape behavior present? As noted in the main text, arousal schema changes on a much slower time scale than the panic attack variables, operating on a time scale of days rather than minutes (i.e., 1,440th the time scale on which of panic attack variables operate). To ease the computational burden of the model, we defined arousal schema to update only every 1,440 time steps. Although reducing computational burden was the primary reason for implementing the model in this way, it is worth noting that sleep plays an important role in the learning that occurs following exposure to a threatening stimulus (Pace-Schott, Germain & Milad, 2015), suggesting there is at least some reason to believe that this day-level updating may be appropriate.

Differential Equation:

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

Difference Equation:

$$S_{t+1:t+\Omega} = \begin{cases} S_t, & \max(F_{t-\Omega} \dots F_t) < \theta \\ S_t - \alpha_{S2} S_t, & \max(F_{t-\Omega} \dots F_t) \geq \theta, \max(E_{t-\Omega} \dots E_t) \leq \mu \\ S_t + \alpha_{S1}(\max(T_{t-\Omega} \dots T_t, S_t) - S_t), & \max(F_{t-\Omega} \dots F_t) \geq \theta, \max(E_{t-\Omega} \dots E_t) > \mu \end{cases}$$

```
R: dS_dt <-function(S, maxE, maxPT, cr_E_S, r_S_a, r_S_e) {
  ifelse(maxE >= cr_E_S,
    r_S_a * (max(maxPT, S) - S),
    - r_S_e * S
  )
}
```

State Variable	R Code Label	Default Initial Value	Description
F	AF		Fear. The geometric mean of arousal and perceived threat ($\sqrt{A \times T}$)
S	S	0.5	Arousal Schema. Beliefs and associations regarding whether arousal poses or signals danger.
E	E	0	Escape. Behavior aimed at mitigating the threat posed or indicated by arousal. Here, the maximum escape behavior during the past day is used.
T	PT	0	Perceived threat. The perception of threat from arousal ranging from an absence of threat (0) to maximal level of perceived threat (1). Here, the maximum perceived threat during the past day is used.

Parameter	R Code Label	Default Value	Description
α_{S1}	r_S_a	0.25	Rate parameter constraining the growth in arousal schema
α_{S2}	r_S_e	0.10	Rate parameter constraining the decay in arousal schema
θ	cr_AF	0.50	Threshold parameter indicating the level of fear needed for learning
μ	cr_E_S	0.25	Threshold parameter indicating the level of escape behavior that delineates whether arousal schema or falls

ESCAPE SCHEMA

Like arousal schema, the rate of change in escape schema (X) is affected by the combination of arousal, perceived threat, and escape behavior. This joint effect is represented by effect “i” in Figure A1. Also, like arousal schema, escape schema is updated only every 1,440 time steps and is based on two conditional statements: is there sufficient fear to provide the opportunity for learning to occur? and is escape behavior present? When escape behavior is present, escape schema will diminish. That is, the individual develops the belief that even low levels of threat cannot be coped with or tolerated without resorting to escape behavior. When escape behavior is absent, escape schema will increase, reflecting the belief that higher levels of threat can be coped with or tolerated without engaging in escape behavior.

Differential Equation:

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

Difference Equation:

$$X_{t+1..t+\Omega} = \begin{cases} X_t, & \max(F_{t-\Omega} \dots F_t) < \theta \\ X_t + \alpha_{X1}(\max(T_{t-\Omega} \dots T_t, X_t) - X_t), & \max(F_{t-\Omega} \dots F_t) \geq \theta \text{ and } \max(E_{t-\Omega} \dots E_t) \leq \mu \\ X_t - \alpha_{X2} X_t, & \max(F_{t-\Omega} \dots F_t) \geq \theta \text{ and } \max(E_{t-\Omega} \dots E_t) > \mu \end{cases}$$

```
R: dX_dt <- function(X, maxE, maxPT, cr_E_X, r_X_a, r_X_e) {
  ifelse(maxE > cr_E_X,
    - r_X_e * X,
    r_X_a * (max(maxPT, X) - X)
  )
}
```

State Variable	R Code Label	Default Initial Value	Description
F	AF	0	Fear. The geometric mean of arousal and perceived threat ($\sqrt{A \times T}$)
S	S	0.5	Arousal Schema. Beliefs and associations regarding whether arousal poses or signals danger.
E	E	0	Escape. Behavior aimed at mitigating the threat posed or indicated by arousal. Here, the maximum escape behavior during the past day is used.
T	PT	0	Perceived threat. The perception of threat from arousal ranging from an absence of threat (0) to maximal level of perceived threat (1). Here, the maximum perceived threat during the past day is used.

Parameter	R Code Label	Default Value	Description
α_{X1}	r_X_a	0.10	Rate parameter constraining the growth in escape schema
α_{X2}	r_X_e	0.25	Rate parameter constraining the decay in escape schema
θ	cr_AF	0.50	Threshold indicating the level of fear needed for learning to occur
μ	cr_E_X	0.25	Threshold that delineates whether escape schema rises or falls

AVOIDANCE

The rate of change in avoidance (V) is a function itself and arousal schema (S), depicted as effect “k” in Figure A1, with the parameters λ_V and κ_V shaping the strength of the effect of arousal schema on avoidance. As with other iterations of the logistic equation used in this model, the κ_V controls the slope of the effect while λ_V controls the mid-point of this s-shaped effect (i.e., the level of arousal schema needed to elicit half the maximal level of avoidance).

Differential Equation: $\frac{dV}{dt} = \alpha_V \left(\frac{1}{1 + e^{-\kappa_V(S - \lambda_V)}} - V \right)$

Difference Equation: $V_{t+1} = V_t + \alpha_V \left(\frac{1}{1 + e^{-\kappa_V(S_t - \lambda_V)}} - V_t \right)$

R:

```
dV_dt <- function(V, S, r_V, k_S_V, h_S_V) {  
  r_V * ((1 / (1 + exp(- k_S_V * (S - h_S_V) ))) - V)  
}
```

State Variable	R Code Label	Default Initial Value	Description
V	V		Avoidance. Behavior aimed at preventing exposure to elevated arousal or exposure to situations that heighten the perceived consequences of elevated autonomic arousal. Initial value is determined by specified initial arousal schema value.
S	S	0.5	Arousal Schema. Beliefs and associations regarding whether arousal poses or signals danger.

Parameter	R Code Label	Default Value	Description
α_V	r_V	1	Rate parameter constraining the growth in avoidance
κ_V	k_S_V	15	Slope parameter defining the steepness of the slope of the effect of arousal schema on avoidance
λ_V	h_S_V	0.75	Midpoint parameter defining the mid-point of the sigmoidal effect of arousal schema on avoidance. In other words, the level of arousal schema needed to elicit half the maximal level of avoidance

CONTEXT

Situational context (C) represents the environment that a person is in and is affected by the two behavioral components in the model - avoidance (V) and escape (E) - as represented by effects “m” and “h” in Figure A1, respectively. In contrast to other theory components, the context component was not developed as a set of differential equations and was, instead, implemented in R using the function `sample()` to randomly select 0 or 1, with probability of selecting the latter determined by π_C . The π_C parameter, in turn, is defined by avoidance, thus giving *avoidance* control over the likelihood of entering a situation in which the perceived threat posed by arousal is heightened. The effect of avoidance on π_C is sigmoidal, defined by the slope parameter κ_π and the mid-point parameter λ_π , with ρ defining the maximum probability of entering a panic-predisposing context, which is reached when there is no avoidance ($V=0$). Together, this provides the equation:

$$\pi_C = \frac{\rho}{1 + e^{\kappa_\pi(V - \lambda_\pi)}}$$

Notably, in contrast to other similar equations used in this model, this equation is monotonically *decreasing*: higher levels of avoidance produce *lower* probability of entering a context that heightens the threat of arousal.

Escape behavior has its effect on situational context more directly. If escape behavior exceeds a given threshold, `cr_E_C`, then the situational context is escaped (i.e., C is set to 0).

```
R: p_C <- 0.1 / (1 + exp(1)^(k_V_C * (V - h_V_C)))
  C <- sample(0:1, size = 1, prob = c(1-p_C, p_C))
```

State Variable	R Code Label	Default Initial Value	Description
C	C		Context. Situation in which the perceived likelihood or consequences of a panic attack are heightened. Initial value is determined by the equation above based on the initial level of avoidance which is, in turn, based on the initial level of arousal schema.
V	V		Avoidance. Behavior aimed at preventing exposure to elevated arousal or exposure to situations that heighten the perceived consequences of elevated autonomic arousal.

Parameter	R Code Label	Default Value	Description
ρ		0.1	Parameter that defines the maximum probability of entering a situational context in which the consequences of elevated arousal or a panic attack are perceived to be heightened.
κ_π	k_V_C	5	Slope parameter that defines the steepness of the sigmoidal effect of avoidance on situational context.
λ_π	h_V_C	0.5	Mid-point parameter that defines the midpoint of the sigmoidal effect of avoidance on situational context.
	C_steps	60	The number of timesteps (i.e., minutes) in which one will remain in the established situational context.
	cr_E_C	.5	The threshold at which escape behavior leads one to escape the current situational context.

References

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