A Simulation Approach to Assessing the Impact of a Cognitive Intervention on Depression

Andrea Wittenborn
Jennifer Rick
Michigan State University
Niyousha Hosseinichimeh
Virginia Tech
Hazhir Rahmandad
Massachusetts Institute of Technology

Agenda

- Introduction to depression
- Description of
  - Qualitative modeling
  - Estimation process
  - Simulation modeling
- Final remarks

Background

Depression is Remarkably Destructive

- Depression is a leading cause of medical disability (WHO, 2010)
- 1 in 6 U.S. adults will be affected (Kessler et al., 2005)
  - 40-60% of those affected will have more than 1 episode
- The age of onset is decreasing (Kessler et al., 2003)
- Economic burden exceeds $210 billion/year in the U.S. (Greenberg et al., 2015)

Depression is Resistant to Change

- Despite decades of widespread public awareness campaigns, research, and intervention, population-level prevalence rates remain stable (Ferrari et al., 2013)
- Intervention findings
  - Antidepressants have not shown a consistent advantage over placebo pills (Kirsch et al., 2008)
  - Only half of psychotherapy patients recover after their first course of treatment (e.g., Barber et al., 2012)


151mL/H

Depression is Heterogeneous

- Diagnosed when 5 or more of the 9 symptoms are present for 2 weeks
  - Symptoms: depressed mood, diminished pleasure, change in appetite, sleep problems, psychomotor changes, fatigue, worthlessness, inability to concentrate, recurrent thoughts of death
- This equates to 1,497 different symptom combinations (Østergaard, Jensen, & Bech, 2011)

Depression Research is Often Narrowly Focused

- Theories of depressive pathogenesis range from
  - Cognitive theories
  - Hypothalamic-pituitary-adrenal axis dysfunction theory
  - Inflammation theory
  - Neurodegenerative theory
  - Marital discord theory
- Studies are designed to examine one cause of depression

Table 1. *Results of PubMed search for articles on major depressive disorder 1980-2014*

Terms	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Cognitive bias	331													
2. Rumination	11	263												
3. Memory	3	8	296											
4. Social isolation	4	4	1	363										
5. Financial stress	0	0	2	9	280									
6. Immune response	0	0	1	5	0	816								
7. Cortisol	2	3	12	27	2	56	1884							
8. Hippocampus	0	0	3	4	1	2	15	151						
9. Sleep	3	6	4	7	11	43	127	0	2820					
10. Gene	2	5	5	8	2	58	38	10	37	1552				
11. Personality disorder	9	5	3	6	0	3	17	1	19	7	1225			
12. Diet	2	0	0	0	0	24	5	0	11	15	3	294		
13. Exercise	1	0	3	7	2	16	15	0	47	5	0	15	547	
14. Early adverse experiences	6	4	0	2	0	10	21	8	1	40	16	0	1	347

Wittenborn, Rahmandad, Rick, & Hosseinichimeh (2016). Depression as a systemic syndrome: Mapping the feedback loops of major depressive disorder. *Psychological Medicine, 46*, 551-562.

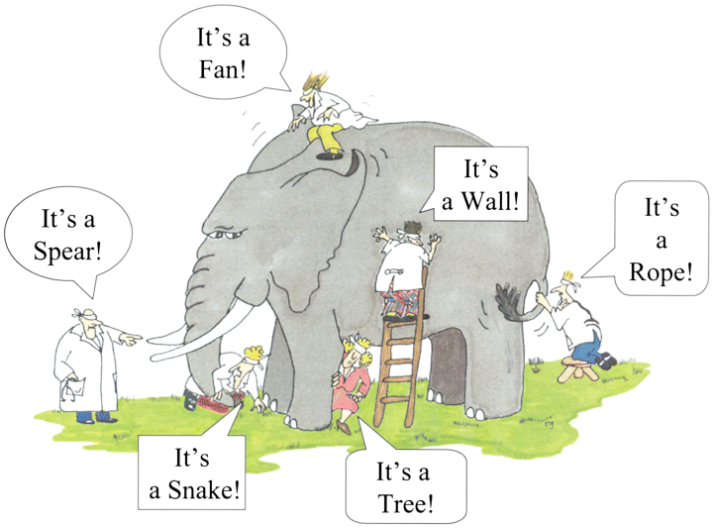
Qualitative Modeling

System Dynamics (SD)

- A computer-aided approach to policy analysis and design that applies to dynamic problems characterized by mutual interaction, accumulation, and information feedback (Mabry et al., 2008; Sterman, 2000).
- Best suited for complex problems that:
  - Are **hard** to capture in **controlled experiments**
  - Lead to **counter intuitive** behaviors and show **policy resistance**
  - Require **understanding/collaboration across disciplinary boundaries**

Why Use SD to Study Depression?

- Depression is
  - A complex public health challenge
  - Heterogeneous
  - Resistant to change
  - A systemic syndrome with multiple diverse drivers, endogeneity, and system delays
  - Previously studied from mostly narrow theoretical perspectives



Qualitative Model of Depression Dynamics

- We created the first depression systems mapping using a wide boundary and structured approach (Hu et al., 2011)
  - Broad scope of causal mechanisms and the interactions among them
  - Continuous definition of depression (Aggen et al., 2005; Hankin et al., 2005)
  - Mapped findings from human models (Seok et al., 2013; Lacro et al., 2014)
  - Mapped reinforcing feedbacks only due to breadth of model
  - Genes, personality, gender, SES, diet, exercise, and other random life events are exogenous variables

Wittenborn, Rahmandad, Rick, & Hosseinichimeh (2016). Depression as a systemic syndrome: Mapping the feedback loops of major depressive disorder. *Psychological Medicine, 46*, 551-562.

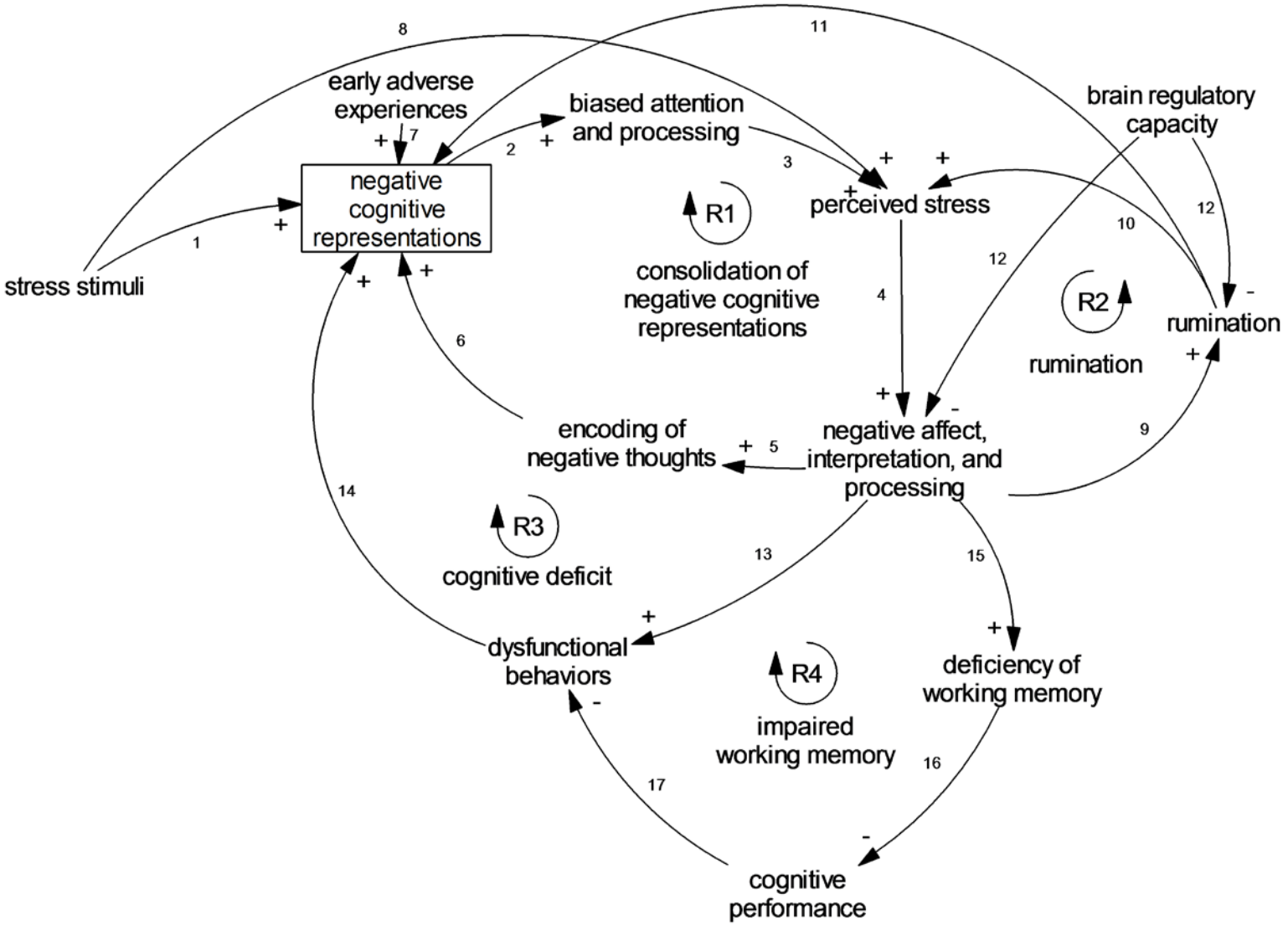


Figure 1. Cognitive dimensions

Wittenborn, Rahmandad, Rick, & Hosseinichimeh (2016). Depression as a systemic syndrome: Mapping the feedback loops of major depressive disorder. *Psychological Medicine, 46*, 551-562.

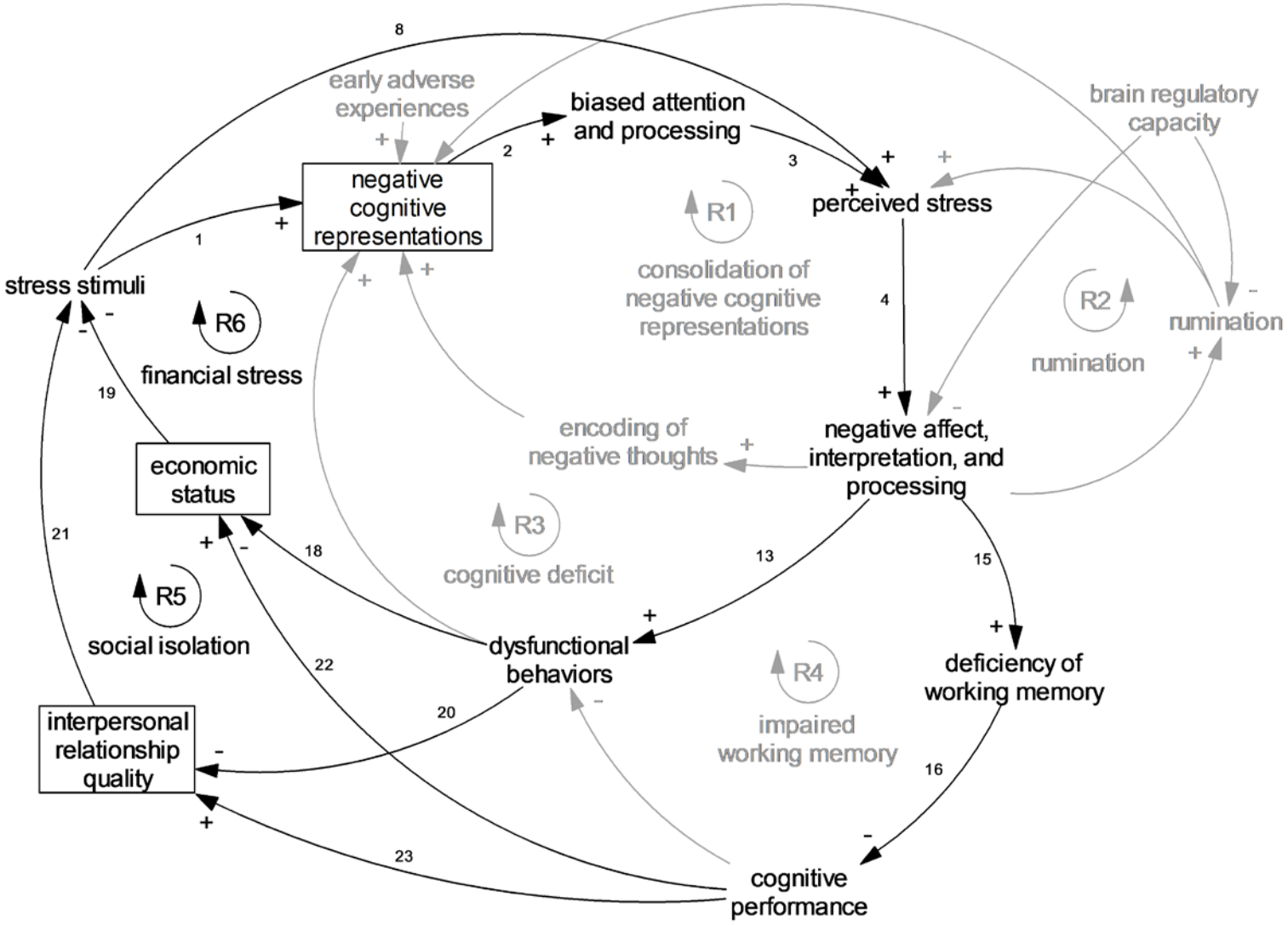


Figure 2. Cognitive, social, and environmental dimensions

Wittenborn, Rahmandad, Rick, & Hosseinichimeh (2016). Depression as a systemic syndrome: Mapping the feedback loops of major depressive disorder. *Psychological Medicine, 46*, 551-562.

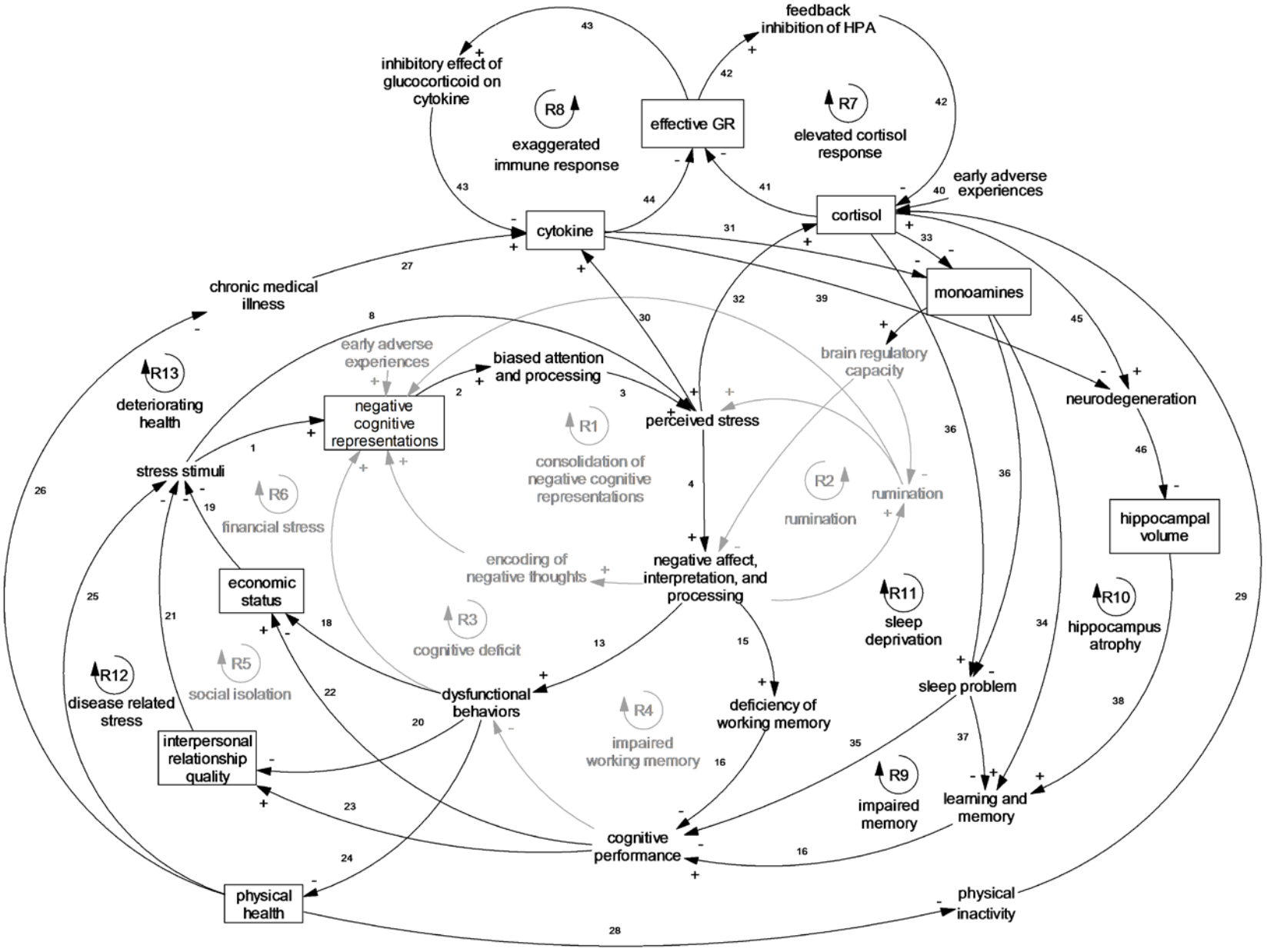


Figure 3. Cognitive, social, and environmental dimensions

Wittenborn, Rahmandad, Rick, & Hosseinichimeh (2016). Depression as a systemic syndrome: Mapping the feedback loops of major depressive disorder. *Psychological Medicine, 46*, 551-562.

Estimating SD Models Using Panel Data

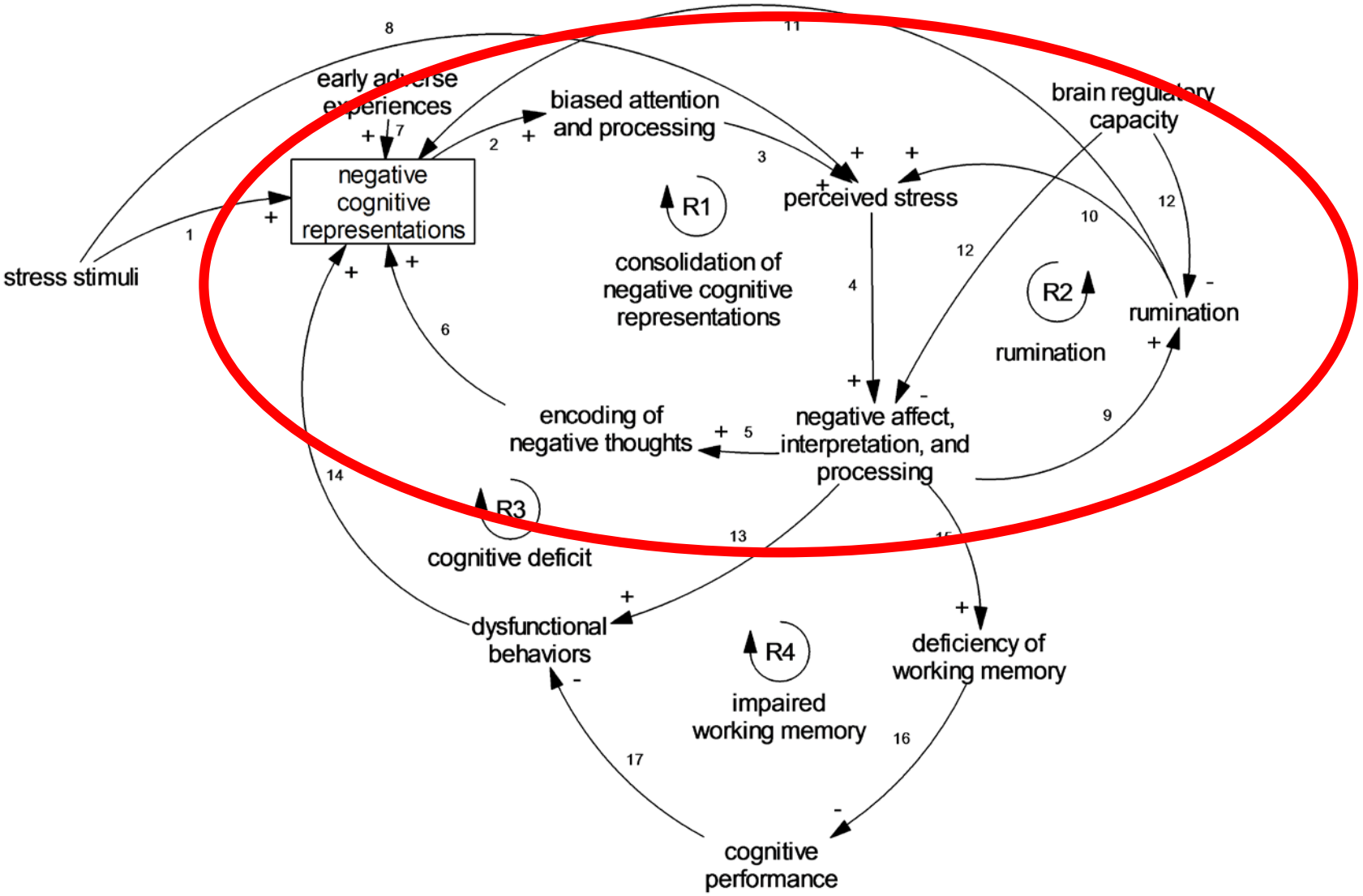


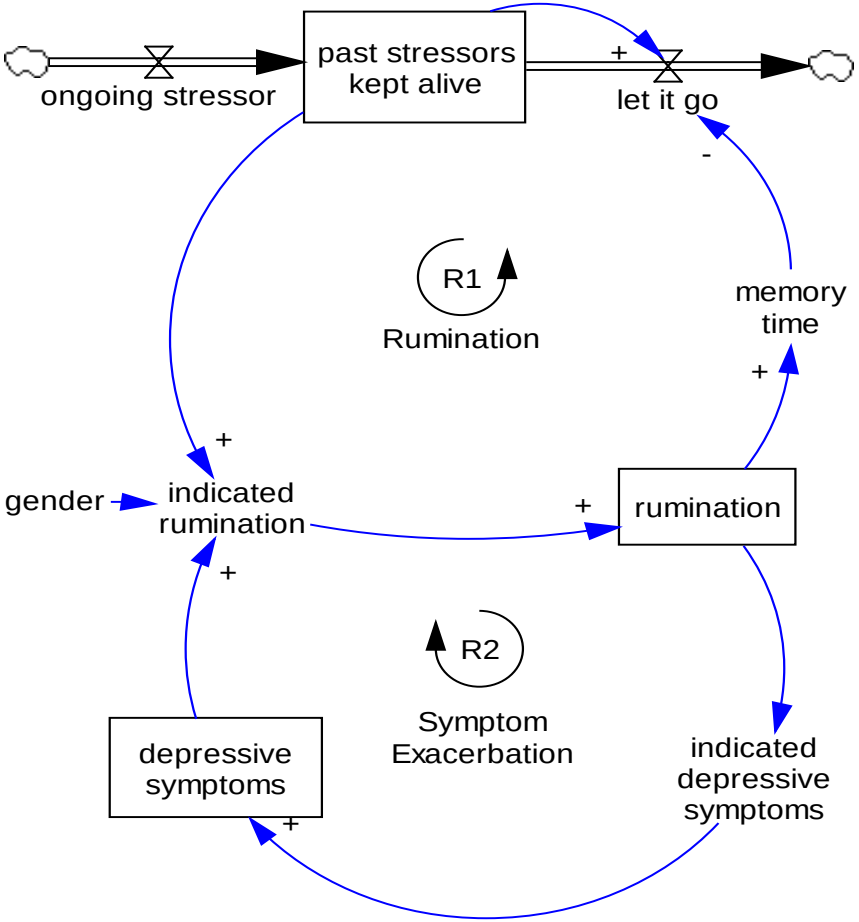
Figure 4. Cognitive dimensions

Wittenborn, Rahmandad, Rick, & Hosseinichimeh (2016). Depression as a systemic syndrome: Mapping the feedback loops of major depressive disorder. *Psychological Medicine, 46*, 551-562.

Modeling Stress, Rumination, and Depression

- Stress increases vulnerability to rumination and subsequent depression
- Little is known about the mechanisms underlying these processes, but they are likely feedback-rich
- We developed an SD model based on the response style theory and built on the hypothesis that rumination contributes to depression by “keeping stressors alive”

A Dynamic Model of Stress, Rumination, and Depression



$$let\ it\ go_t = \frac{past\ stressor\ kept\ alive\ _t}{memory\ time_t}$$

$$memory\ time_t = \theta_9 \times rumination_t$$

$$indicated\ rumination_t = \theta_1 + \theta_2 \times depressive\ symptoms_t + \theta_3 \times gender + \theta_4 \times past\ stressor\ kept\ alive\ _t + \text{Rumination Noise}$$

$$indicated\ depressive\ symptoms_t$$

Hosseinichimeh, N., Rahmandad, H., Jalali, M.S., & Wittenborn, A.K. (2016). *Using indirect inference method for parameter estimation in dynamic models.* Manuscript under review

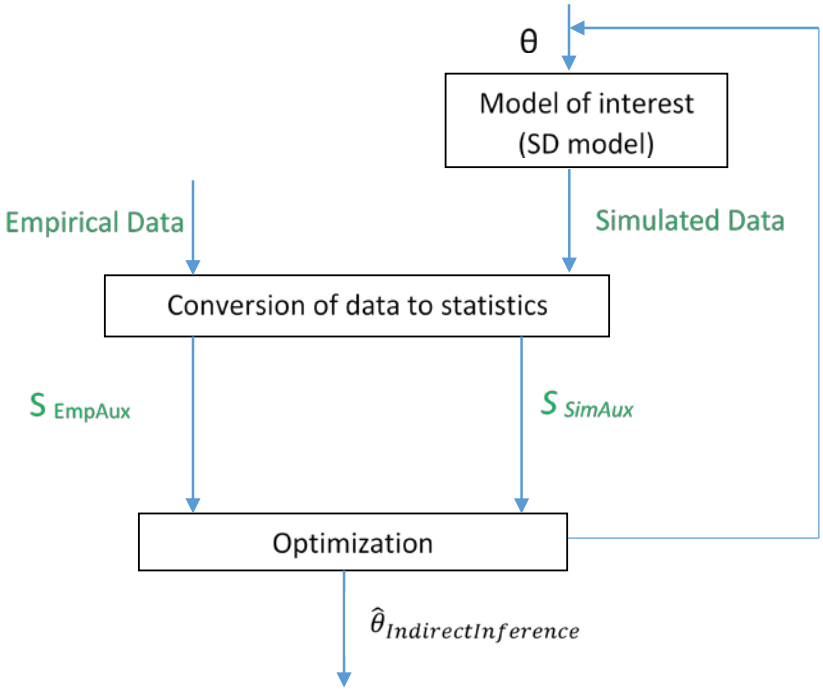
Data

- Survey of 520 female and 545 male adolescents from two middle schools (grades 6-8) in Connecticut (McLaughlin & Nolen-Hoeksema 2012)
  - N=661 after removing missing responses
- 3 assessments
  - Time 1-2 (4 months) and Time 2-3 (3 months)
- Measures
  - **Stressful life events**–Life Events Scale for Children (Coddington, 1972)
  - **Rumination**–Children's Response Style Questionnaire (CRSQ; Abela, Brozina, & Haigh, 2002)
  - **Depressive Symptoms**–the Children's Depression Inventory (CDI; Kovacs, 1992)

Hosseinichimeh, N., Rahmandad, H., Jalali, M.S., & Wittenborn, A.K. (2016). *Using indirect inference method for parameter estimation in dynamic models.* Manuscript under review

Estimation Approach: Indirect Inference

1. Define and estimate a set of empirical-auxiliary statistics
2. Generate the simulated data using the SD model
3. Estimate the simulated-auxiliary statistics using the auxiliary model and simulated data
4. Minimize the difference between the auxiliary-empirical statistics and the auxiliary-simulated statistics



Hosseinichimeh, N., Rahmandad, H., Jalali, M.S., & Wittenborn, A.K. (2016). *Using indirect inference method for parameter estimation in dynamic models.* Manuscript under review

Empirical-Auxiliary Statistics

$$Rum_3 = b_0 + b_1\, MDD_3 + b_2\, gender + b_3\, PerNegStim + b_4\, Rum_2 + b_5\, Rum_1 \quad (1)$$

$$MDD_3 = a_0 + a_1\, Rum_3 + a_2\, MDD_1 \quad (2)$$

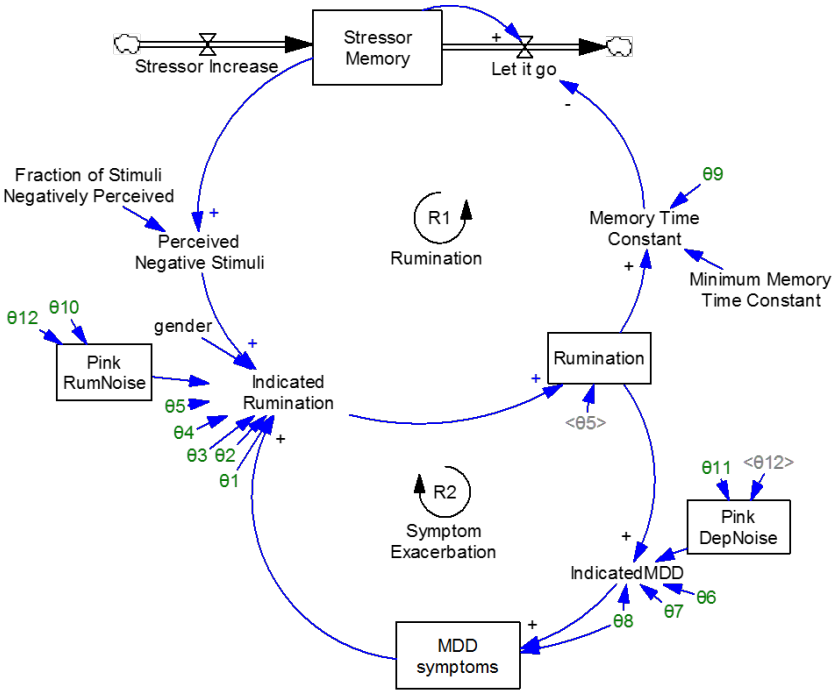
$$(StressorMemory_3 - StressorMemory_1)/7 = c_0 - c_1 \frac{StressorMemory_1}{Rum_1} \quad (3)$$

Regression	Statistic	Empirical-auxiliary Statistic
Equation (1)	b_0	-0.4663
	b_1	0.2313
	b_2	1.2021
	b_3	0.1316
	b_4	0.4548
	b_5	0.1749
Equation (2)	a_0	2.0012
	a_1	0.2526
	a_2	0.5559
Equation (3)	c_0	-0.0201
	c_1	-0.1222
Mean	Mean_MDD at T_3	9.7852
	Mean_Rum at T_2	10.8487
	Mean_Rum at T_3	9.9546

Hosseinichimeh, N., Rahmandad, H., Jalali, M.S., & Wittenborn, A.K. (2016). *Using indirect inference method for parameter estimation in dynamic models.* Manuscript under review

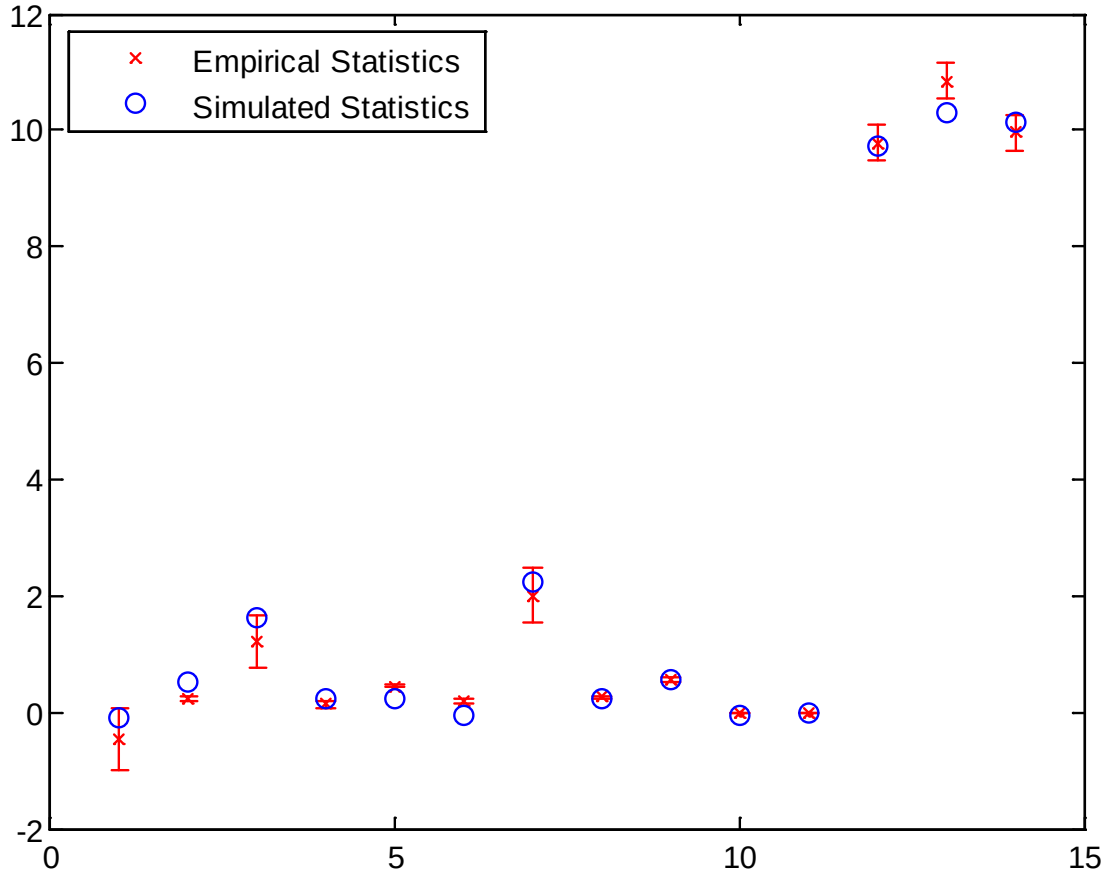
Estimated Parameters

Unknown Parameters	**Estimate (95% conf. intl)**
Rumination Constant (θ_1)	-1.2504 [-3.1920,0.6911]
Depression Effect Coefficient (θ_2)	0.4236 [-0.1661,1.0132]
Gender Coefficient (θ_3)	2.5152 [0.5518,4.4787]
Perceived Stress Coefficient (θ_4)	0.2518 [0.0227,0.4809]
Rumination Coefficient (θ_5)	0.1639 [-0.8064,1.1342]
Depression Constant (θ_6)	0.3730 [0.2968,0.4491]
Rumination Effect Coefficient (θ_7)	0.0699 [0.0638,0.0759]
Depression Coefficient (θ_8)	0.8894 [0.8822,0.8967]
Effect of Rumination on Time Constant (θ_9)	1.4741 [1.3735,1.5747]
RumNoise Standard Deviation ($\theta_{10}=\sigma_r^2$)	7.8735 [-0.1391,15.8861]
DepNoise Standard Deviation ($\theta_{11} = \sigma_d^2$)	0.0002 [-0.0307,0.0311]
Correlation Time (θ_{12})	1.6008 [0.0456,3.1559]



Hosseinichimeh, N., Rahmandad, H., Jalali, M.S., & Wittenborn, A.K. (2016). *Using indirect inference method for parameter estimation in dynamic models.* Manuscript under review

Empirical-Auxiliary Statistics and Simulated-Auxiliary Statistics



Hosseinichimeh, N., Rahmandad, H., Jalali, M.S., & Wittenborn, A.K. (2016). *Using indirect inference method for parameter estimation in dynamic models.* Manuscript under review

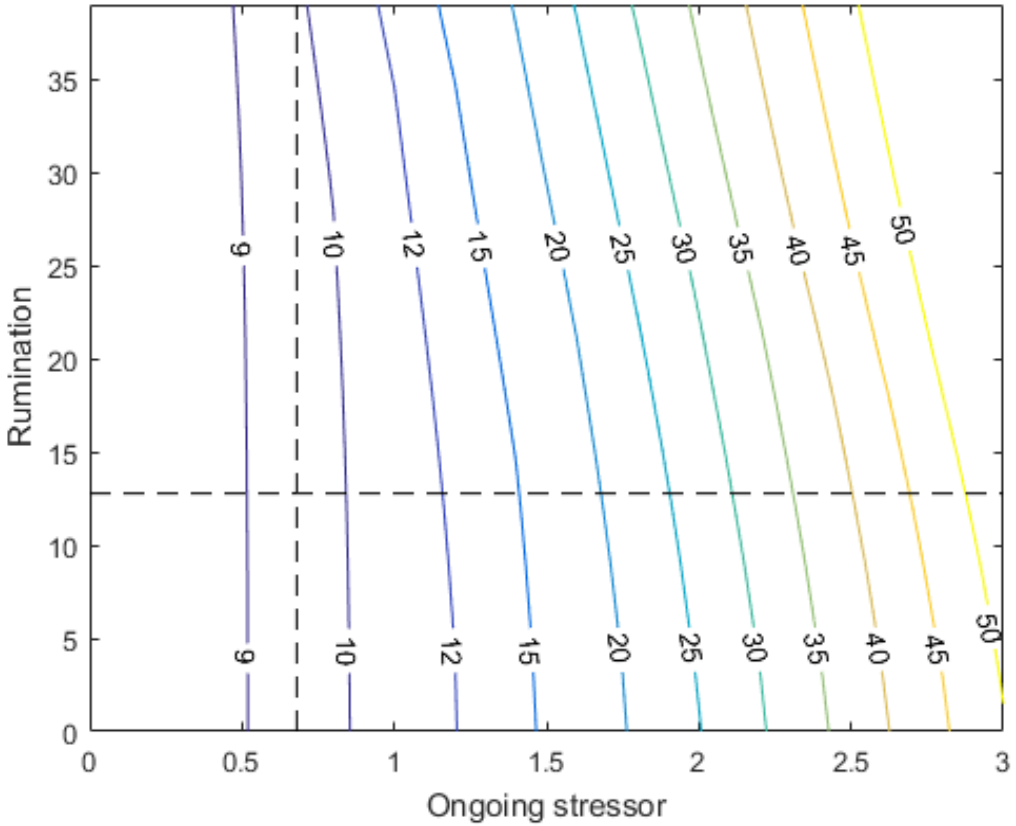
Memory Time by Gender and Rumination Level

Participants	Female	Male	T-test (p-value)
All participants	11.7	6.8	0.00
Depressed individuals with high rumination (Rum_0>mean rumination=11.59)	20.4	19.5	0.10
Moderate or severely depressed patients with low rumination (Rum_0<mean rumination=11.59)	9.3	6.5	0.00

Hosseinichimeh, N., Rahmandad, H., Jalali, M.S., & Wittenborn, A.K. (2016). *Using indirect inference method for parameter estimation in dynamic models.* Manuscript under review

Impact of Initial Rumination Level and Ongoing Stressors in Girls

Depressive symptoms at time 120



Hosseinichimeh, N., Rahmandad, H., Jalali, M.S., & Wittenborn, A.K. (2016). *Using indirect inference method for parameter estimation in dynamic models.* Manuscript under review

Simulation Experiment to Examine Trajectories of Depression

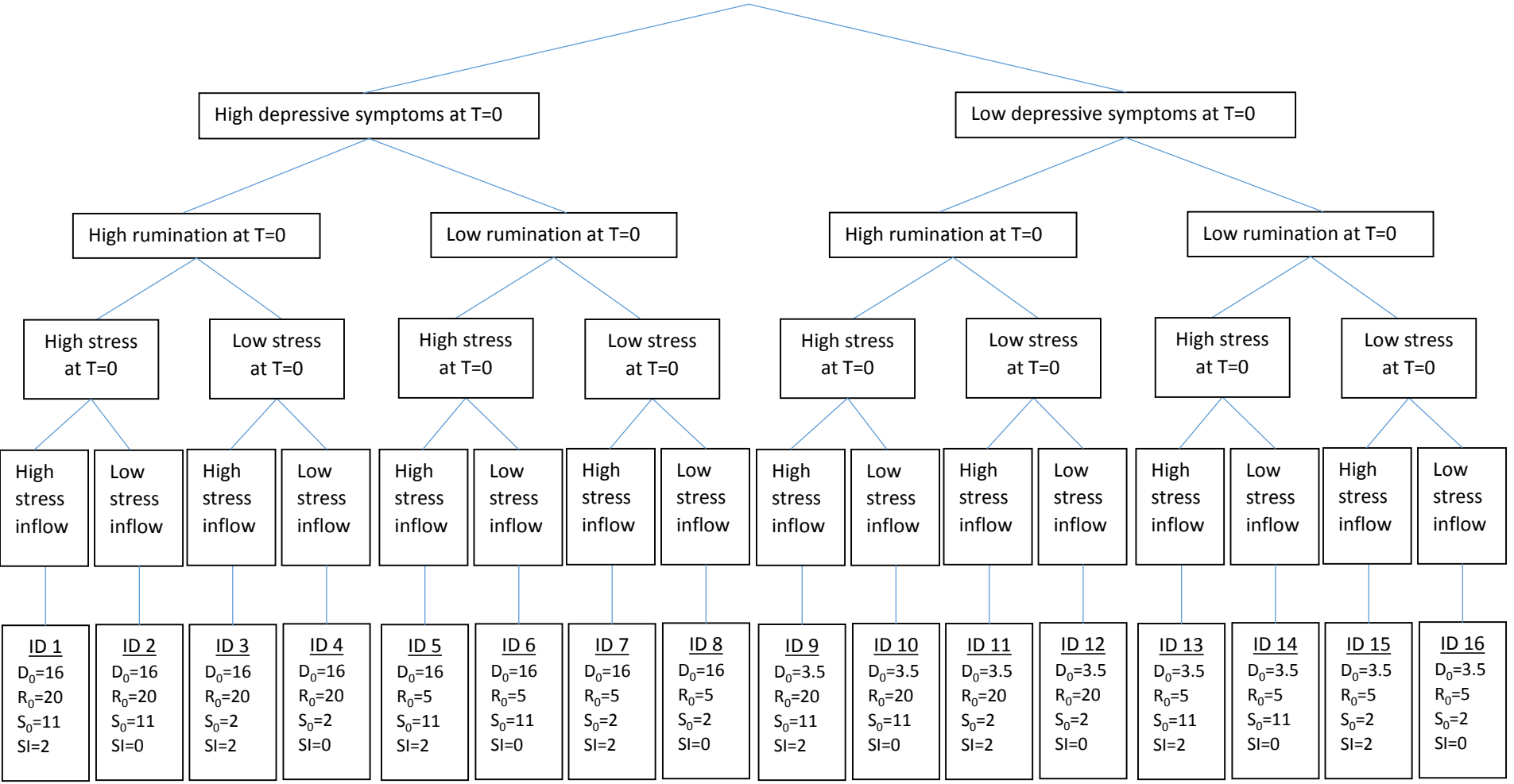


Figure 5. Sixteen categories of female/male participants. D_0, R_0, S_0, and SI represent initial depressive symptoms and rumination, prior stressors, and ongoing stressors respectively.

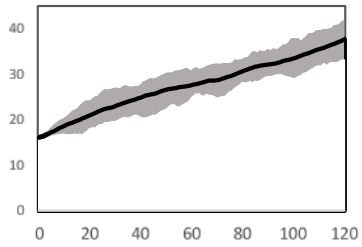
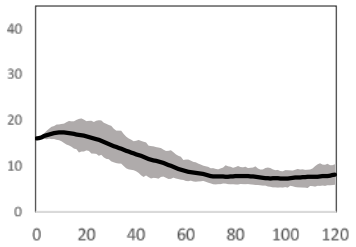
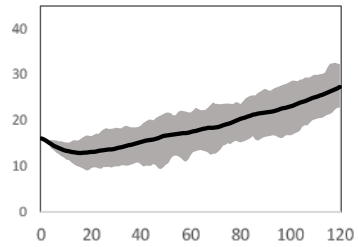
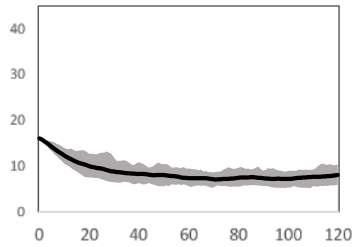
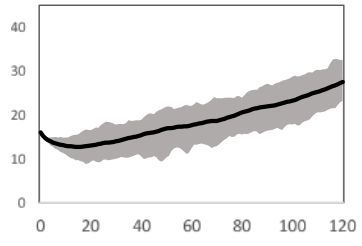
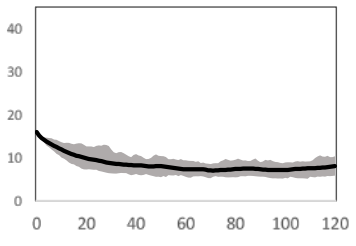
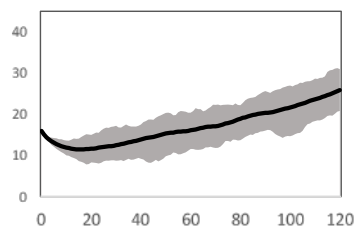
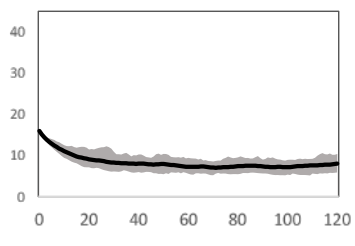
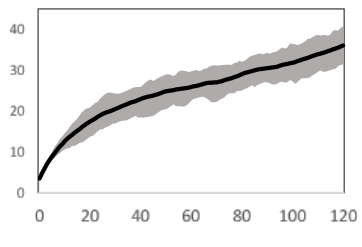
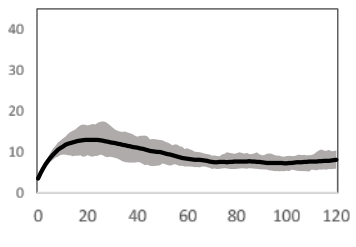
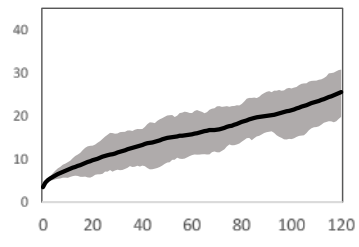
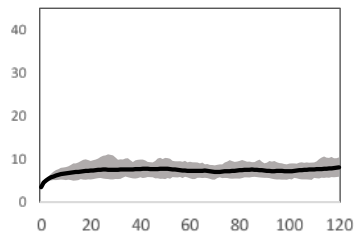
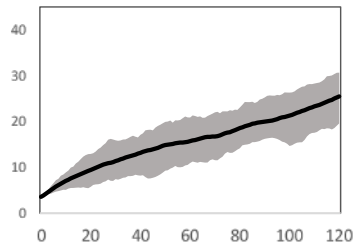
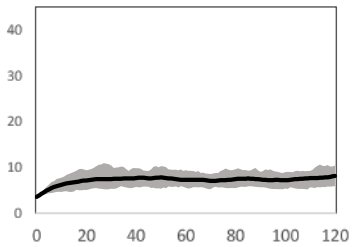
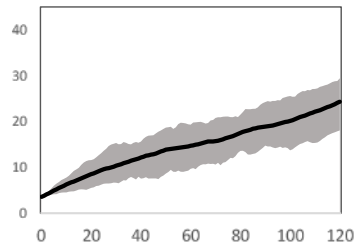
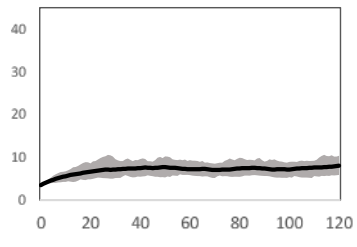
	High prior and ongoing stressors	High prior stressors but no ongoing stressors	Low prior stressors but high ongoing stressors	Low prior and no ongoing stressors
High depressive symptoms and rumination at T=0	 Group 1	 Group 2	 Group 3	 Group 4
High depressive symptoms but low rumination at T=0	 Group 5	 Group 6	 Group 7	 Group 8
Low depressive symptoms but high rumination at T=0	 Group 9	 Group 10	 Group 11	 Group 12
Low depressive symptoms and rumination at T=0	 Group 13	 Group 14	 Group 15	 Group 16

Figure 6. Simulated depressive symptoms over 120 months for 16 female groups with characteristics listed in Figure 5.

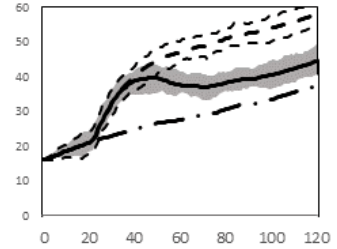
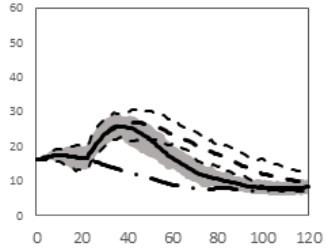
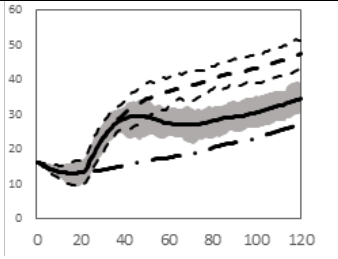
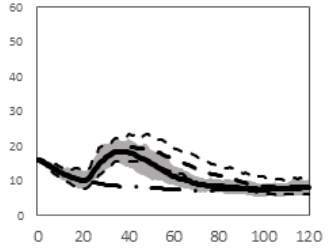
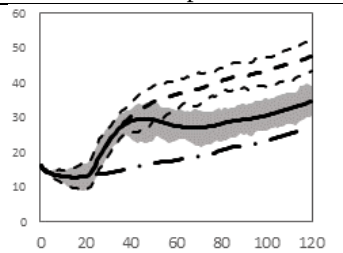
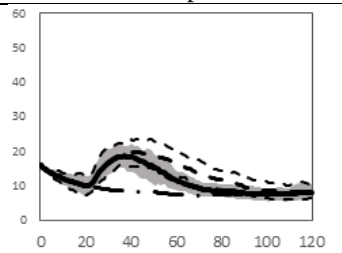
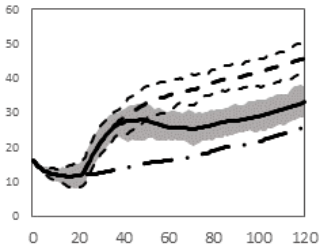
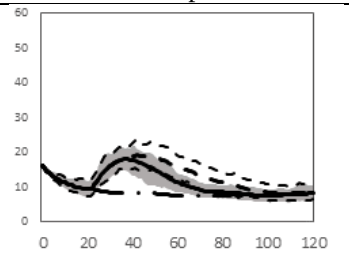
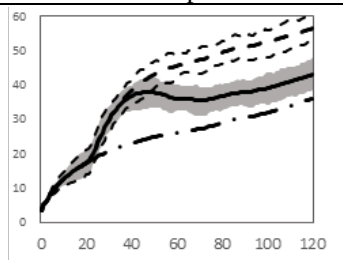
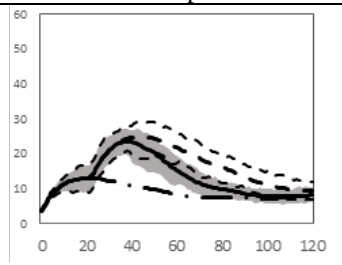
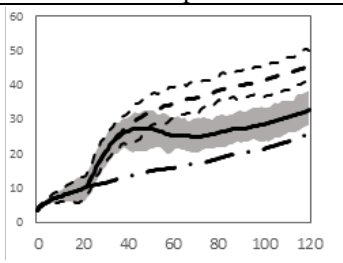
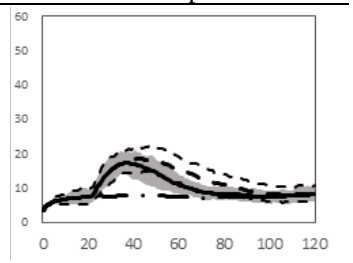
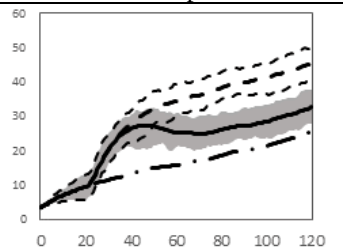
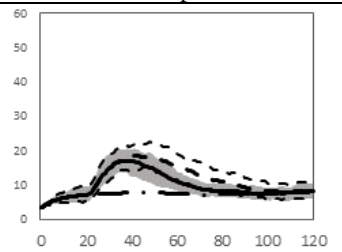
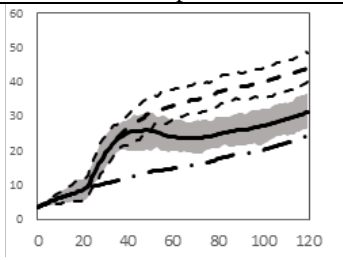
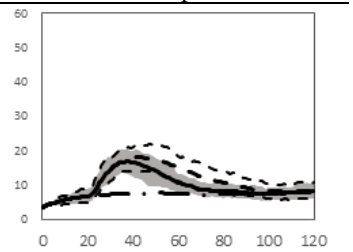
	High prior and ongoing stressors	High prior stressors but no ongoing stressors	Low prior stressors but high ongoing stressors	Low prior and no ongoing stressors
High depressive symptoms and rumination at T=0	 Group 1	 Group 2	 Group 3	 Group 4
High depressive symptoms but low rumination at T=0	 Group 5	 Group 6	 Group 7	 Group 8
Low depressive symptoms but high rumination at T=0	 Group 9	 Group 10	 Group 11	 Group 12
Low depressive symptoms and rumination at T=0	 Group 13	 Group 14	 Group 15	 Group 16

Figure 7. Simulated depressive symptoms for 16 female groups with characteristics listed in Figure 5. The long-dash-dot captures the baseline output. The dashed line depicts the depressive symptoms when girls experience a major event at month 20. The solid line shows the results when they experience a major event at month 20 and then a therapy at month 30.

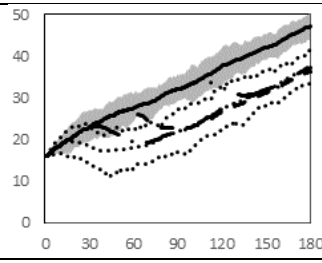
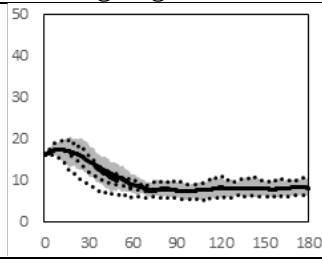
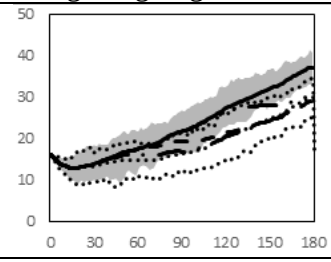
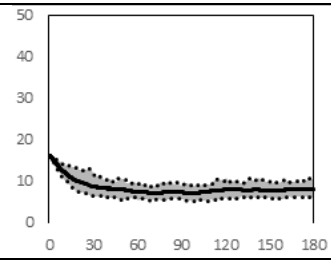
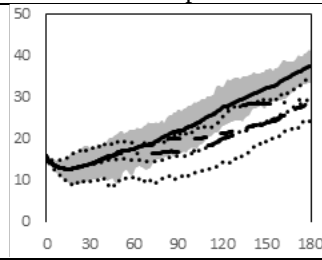
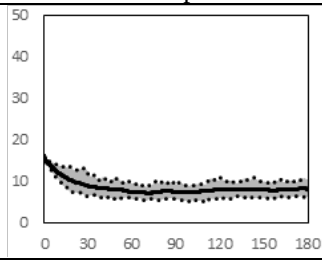
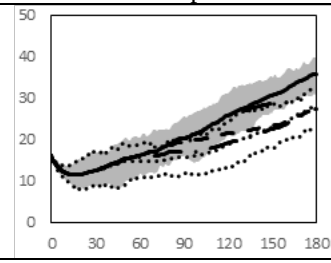
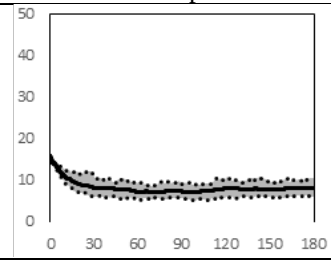
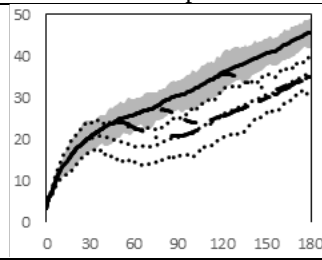
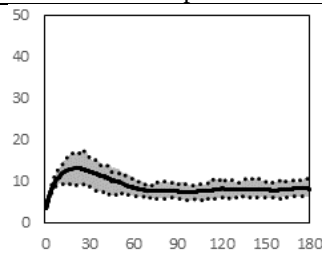
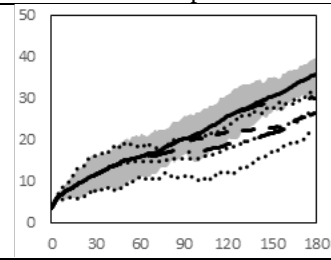
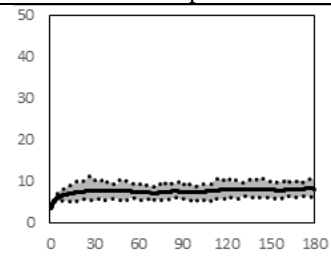
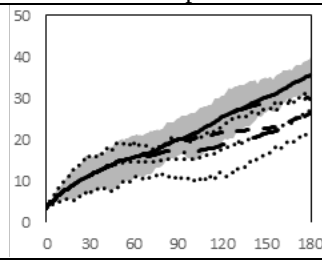
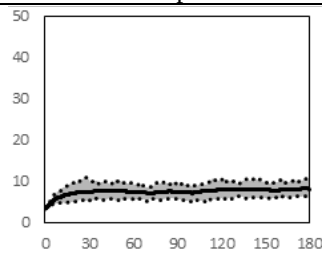
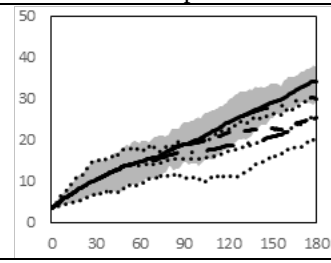
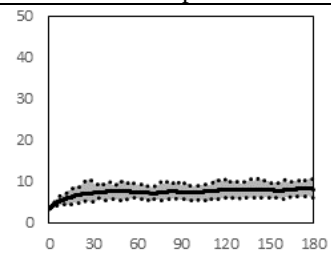
	High prior and ongoing stressors	High prior stressors but no ongoing stressors	Low prior stressors but high ongoing stressors	Low prior and no ongoing stressors
High depressive symptoms and rumination at T=0				
	Group 1	Group 2	Group 3	Group 4
High depressive symptoms but low rumination at T=0				
	Group 5	Group 6	Group 7	Group 8
Low depressive symptoms but high rumination at T=0				
	Group 9	Group 10	Group 11	Group 12
Low depressive symptoms and rumination at T=0				
	Group 13	Group 14	Group 15	Group 16

Figure 8. Simulated depressive symptoms for 16 female individuals described in Figure 5. Solid line captures the baseline, the dot line, long-dash-dot, dashed line, and long-dash-dot-dot depict the depressive symptoms when girls receive the cognitive based therapy 6 months, 2, 4, and 8 years after their first episode.

Discussion

- Innovative method of assessing how a cognitive intervention and its timing impacts depression
- Methodological introduction and application of indirect inference to estimating biological and health models offers new opportunities
- Provides simulation lab for testing the impact of treatment on the depressive symptoms of diverse individuals.
- Implies booster sessions might support change in individuals with high ongoing sessions.

Acknowledgements

Financial Support

NIMH award R21MH100515

Institute for Society, Culture and Environment, Virginia Tech

Collaborators

Hazhir Rahmandad, MIT Sloan School of Management

Niyousha Hosseinichimeh, Virginia Tech

Steve Hollon, Vanderbilt University

Jennifer Rick, Michigan State University