Parsing Pathways to Health Disparities:

A Mixed-methods, Multi-domain Approach

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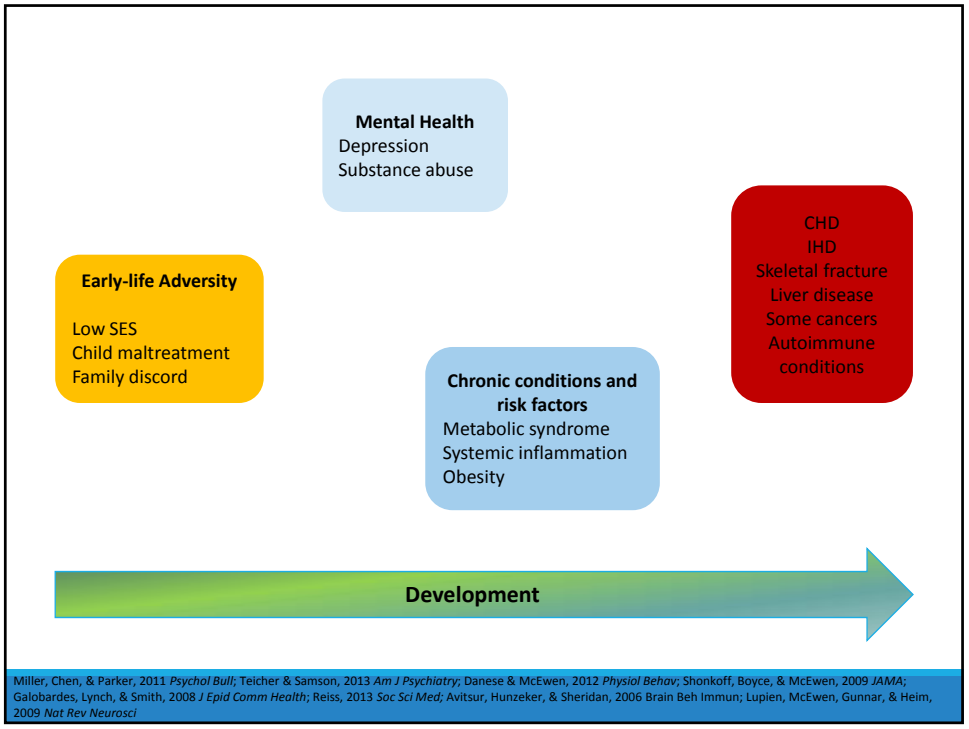
NORTHWESTERN UNIVERSITY

Overview

1. Exposure to adversity and implications for health
   - Mechanistic models incorporating dysregulation across multiple domains
   - Study 1: Socioeconomic status, social-cognitive responses to threat, and obesity in adolescents
2. Ecological approach to adversity in families
   - Study 2: Parent-child conflict, genetic predisposition, brain structure
   - Study 3: Parent-child dynamics, well-being, and immune regulation
3. Optimizing resilience in the face of risk
   - Study 4: Upward social mobility, emotion processing, inflammation
   - Neuro-immune Network Hypothesis



Miller, Chen, & Parker, 2011 *Psychol Bull*; Teicher & Samson, 2013 *Am J Psychiatry*; Danese & McEwen, 2012 *Physiol Behav*; Shonkoff, Boyce, & McEwen, 2009 *JAMA*; Galobardes, Lynch, & Smith, 2008 *J Epid Comm Health*; Reiss, 2013 *Soc Sci Med*; Avitsur, Hunzeker, & Sheridan, 2006 Brain Beh Immun; Lupien, McEwen, Gunnar, & Heim, 2009 *Nat Rev Neurosci*

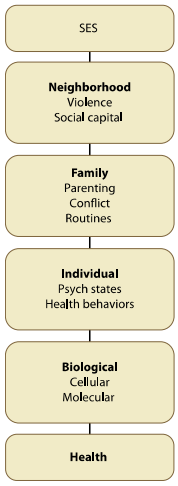


Figure 1

Overview of key pathways at the neighborhood, family, and individual levels linking low socioeconomic status (SES) to poor health.

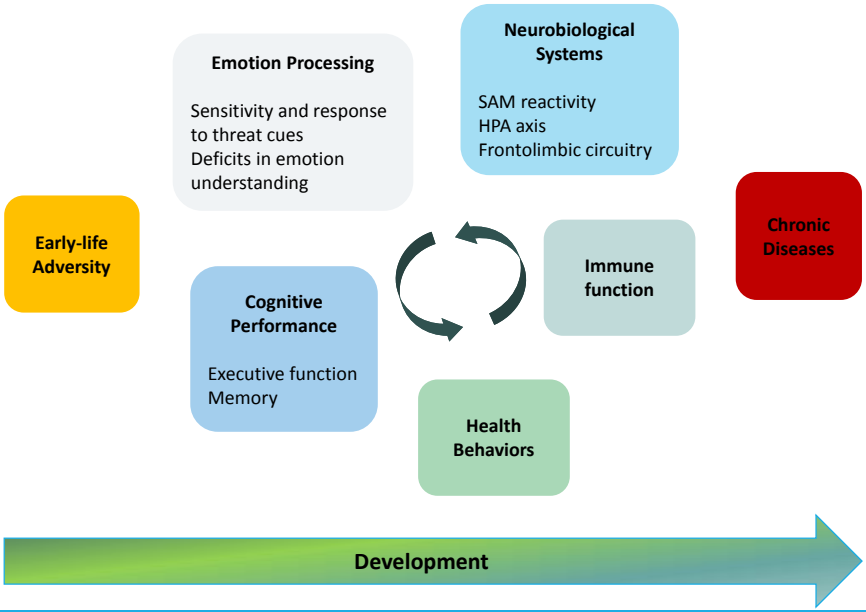
already been conducted, and where relevant, we point readers to these reviews and use them as a foundation from which to synthesize research across a wide variety of multilevel contributors relevant to health disparities.

Chen & Miller, 2013, *Ann. Rev. Clin. Psychol*

How does adversity get under the skin of the developing child?

How does adversity instantiate risk for a heterogeneous set of health problems across the life course?

- Conditions that develop shortly after stressor exposure
  - E.g. depression
- Conditions that manifest decades later
  - E.g. heart disease



Repetti, Taylor, & Seeman, 2002 *Psychol Bull*; Pechtel & Pizzagalli, 2011 *Psychopharm*; Nusslock & Miller, 2015 *Biol Psychiatry*

Psycho-biological Responses to Chronic Stress: The Development of Threat Systems

Threat vigilance

- A heightened attentional bias towards and sensitivity to detecting threats in the surrounding environment
  (Compton, 2003; Gump & Matthews, 1998; Paterson & Neufeld, 1987)
- Examined as an explanation of the wide individual differences typically found in response to identical stressors
  (Paterson & Neufeld, 1987)
- Developed as a result of repeated negative life events
  (Chen & Matthews, 2001; Chen, Langer, Raphaelson, & Matthews, 2004; Flory, Matthews, & Owens, 1998)

Exposure To Adversity and Threat Vigilance

Physically abused youth develop vigilance for facial cues that connote anger (Pollak, 2008; Pollak & Tolley-Schell, 2003; Pollak & Kistler, 2002)

- Abused youth tend to respond aggressively to provocation, even when it is subtle (Dodge, 2006)

Children from low SES families tend to carefully monitor their environment for danger

- Maintain a low threshold for judging ambiguous social situations as threatening (Chen & Matthews, 2003; Chen et al., 2006; Chen et al., 2004)

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Psycho-biological Responses to Chronic Stress: The Development of Threat Systems

Threat systems are mobilized in multiple systems
- Psychosocial responses
- Physiological reactivity
- Health-compromising behaviors

Childhood adversity sensitizes cortico-amygdala neural circuitry, which supports vigilance for, and responses to, threatening stimuli
- Importance of the amygdala and its regulation by the prefrontal cortex
- Enhanced reactivity to threat may stem from inadequate recruitment of prefrontal regions that provide top-down regulation

Davis & Whalen, 2001; Price & Drevets, 2010

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Study 1: Early-life socioeconomic status and implicit threat vigilance

How do early socioeconomic conditions shape sensitivity towards *environment* threat cues?

What is the role of threat vigilance towards environment cues in the context of socioeconomic conditions, health behaviors, and obesity in adolescents?

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Study 1:
Early-life socioeconomic status and implicit threat vigilance

Sample

261 adolescents and a parent

Healthy (free of acute infections 2 weeks prior to study, no history of chronic disorders)

Adolescents aged 13 – 16 (M = 14)
Parents aged 32 – 64 (M = 46)

53.3% female children
75.5% biological mothers
60.2% European-descent

Measures

Implicit threat vigilance

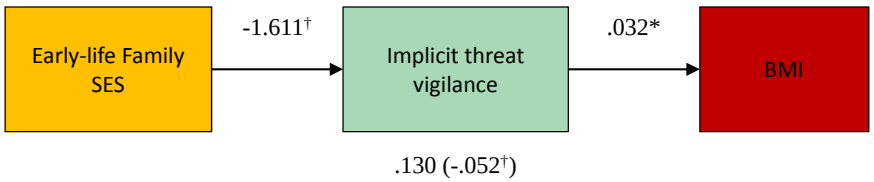
Socioeconomic conditions (early-life and current)
- Income and savings
- Education
- Household crowding

Health behaviors
- Frequency of physical activity

Body composition
- Body Mass Index

Chan, 2015 Dissertation

Study 1:
Implicit threat vigilance partially explained the association between early-life SES and BMI among adolescents



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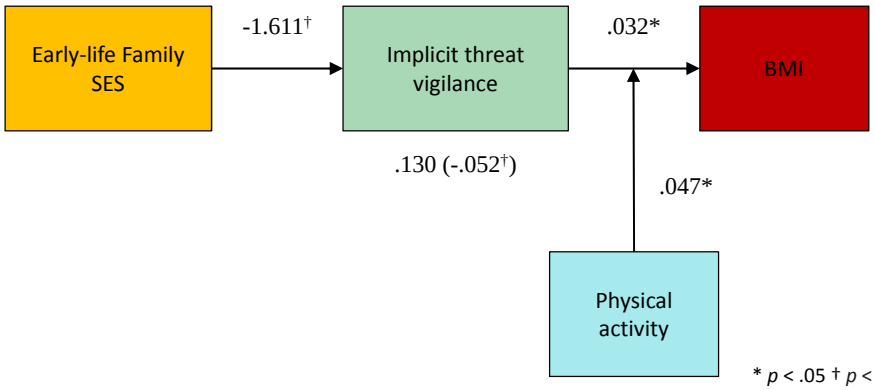

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Study 1 Summary

Consistent with the literature, early childhood socioeconomic conditions was associated with obesity in adolescents as indexed by BMI

This association was at least partially explained by an underlying tendency to be vigilant towards threats in the environment

BMI was highest among those adolescents with heightened vigilance and less frequent physical activity

Adolescents raised in poorer socioeconomic conditions may monitor their environment for potential threat to the extent that this vigilance shapes their physical activity habits

Chan, 2015 Dissertation

Clinical Implications of Threat Vigilance

Sensitivity to threat cues and clinical syndromes
(Calvo & Eysenck, 2000; J. M. G. Williams, Mathews, & MacLeod, 1996)

- Social anxiety, generalized anxiety disorder

Anticipatory threatening or hostile cognitive appraisal process and stress responses

- Heightened cortisol responses to an acute laboratory stress task (Gaab, Rohleder, Nater, & Ehlert, 2005)
- Accelerated cellular aging (O'Donovan et al., 2012)

Preparing for actual threat is adaptive but a consistent elevated state of threat vigilance may take physiological toll (Gump & Matthews, 1998)

Future Directions

What is the optimal level for threat detection and response patterns in different subgroups?

- Discrimination Threat Re-Appraisal Study
  (Levy & Chan, Indiana University, ongoing)
- Can young adults learn to re-appraise previous threat experiences?

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Future Directions

How does dysregulation unfold across threat and response systems?

- Brain, Motivation, and Personality Development (BrainMAPD) Study (Northwestern and UCLA, ongoing)
- Longitudinally examine how exposure to chronic stress predicts changes in multiple systems:
  - Social-cognitive sensitivity to threat
  - Health behaviors
  - Emotion regulation
  - Cortico-amygdala neural circuitry

Functional coupling of prefrontal regulation of amygdala activity is accelerated after exposure to adversity (Gee et al., 2013)

- How would dysregulation in affective, cognitive, and behavioral domains unfold with the coupling of cortico-amygdala activity?

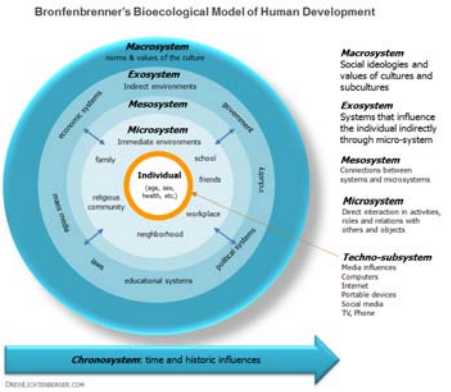
Child maltreatment

Chronic Diseases

Development

Repetti, Taylor, & Seeman, 2002 *Psychol Bull*; Pechtel & Pizzagalli, 2011 *Psychopharm*; Nusslock & Miller, 2015 *Biol Psychiatry*

Child maltreatment



Chronic Diseases

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Study 2:
Parent-adolescent conflict x genetic variation and longitudinal associations with frontal structure

Sample

97 adolescents from tertiary sub-specialty psychiatric clinic
- 55 healthy controls
- 42 with a physician diagnosed mood disorder

Aged 13-20 yrs (M = 16.5)

53% male

6-month period
- Family variables and genetic variation at Time 1
- MRI at Time 2

Measures

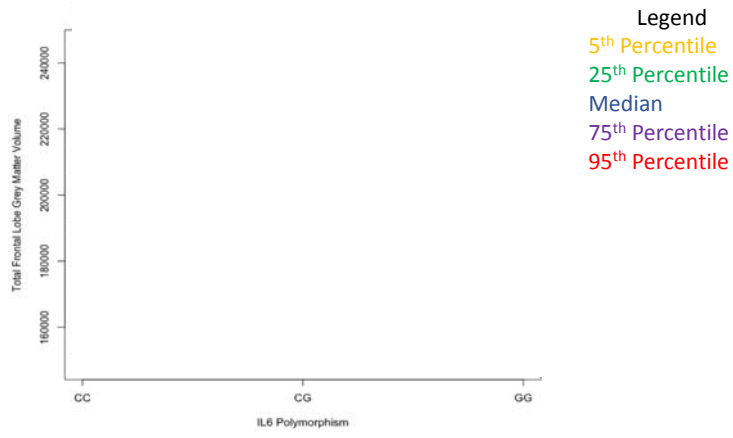
Conflict Behavior Questionnaire (CBQ) with mothers and fathers for the prior 2 weeks at home

Single nucleotide polymorphisms (SNPs) for cytokine genes (IL-1β, IL-6, IL-10, TNF-α) were genotyped with polymerase chain reaction. Venous blood (10-20 ml) was collected, and genomic DNA was extracted using a nonenzymatic, high-salt method

Gray matter (GM) volume of cortical regions previously associated with childhood adversity examined through T1-weighted 3-Tesla magnetic resonance images (adjusted for intracranial volume)

Chan, Collins, Kennedy, MacIntosh, Metcalfe, Korczak, & Goldstein, *under review*

Study 2:
Father-adolescent conflict x genetic variation and longitudinal associations with frontal structure



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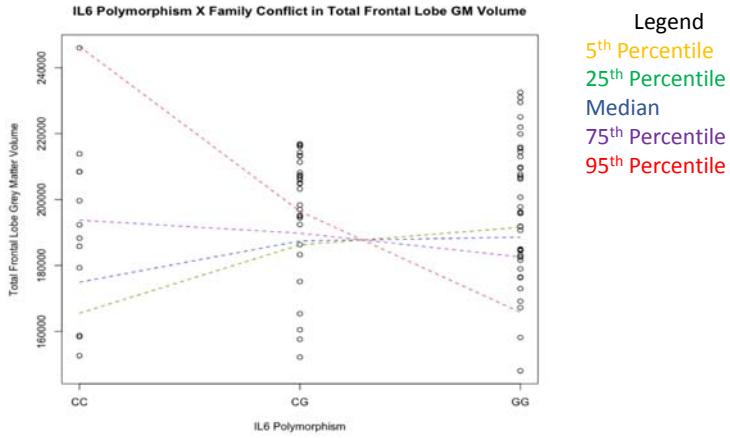

Chan, Collins, Kennedy, MacIntosh, Metcalfe, Korczak, & Goldstein, *under review*

Study 2 Forthcoming Analyses

Previous literature suggests that cortico-amygdala neural circuitry is shaped by childhood adversity

- Child maltreatment
- Maternal deprivation

How about less severe family characteristics like parent-child conflict?

- Longitudinally examine parent-adolescent conflict and functional coupling of prefrontal-amygdala activity

Can family interventions shape brain development among high-risk groups, in addition to targeting clinical symptoms?

- Family-focused Therapy for youth at-risk for a mood disorder (Chan et al., FFT Study, Sunnybrook Health Sciences Centre)

Chan, Collins, Kennedy, MacIntosh, Metcalfe, Korczak, & Goldstein, *under review*

Adversity during Early Stages of Development: The Broader Family Environment and Implications for Chronic Conditions

Hostility and neglect

Conflict and aggression

Parental depression

Parental stress

Child psychopathology

Self-reported physical health complaints

Endocrine functioning

Metabolic syndrome components

Inflammatory dysregulation

Chronic conditions

Repetti, Taylor, & Seeman, 2002; Heim & Nemeroff, 2001; Matthews, 2005; Miller, Chen, & Parker, 2011; Shonkoff, Boyce, & McEwen, 2009

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Ecological Context of Family Interactions

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Micro-level parent-adolescent factors?

Coldness during interactions

Positive parenting behaviors during interactions

Greater daily family conflict

Parent-reported child health

Child-reported health complaints

Metabolic control over diabetes

Systemic inflammation

Repetti, Taylor, & Seeman, 2002; Heim & Nemeroff, 2001; Matthews, 2005; Miller, Chen, & Parker, 2011; Shonkoff, Boyce, & McEwen, 2009

Study 3:
Parental- adolescent understanding of daily demands and health-relevant processes

Having one's experiences, states and traits be accurately perceived by others robustly associated with individual well-being and relationship quality (Kenny & Acitelli, 2001; Funder & Colvin, 1997)

How do parent-adolescent understanding of each other's daily life associate with well-being and health-relevant processes?

Does a parent know when their child has had a bad day?

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Study 3:
Parental- adolescent understanding of daily demands and health-relevant processes

Sample

116 adolescents and a parent

Healthy (free of acute infections 2 weeks prior to study, no history of chronic disorders)

Adolescents aged 13 – 16 (M = 14)
Parents aged 32 – 64 (M = 46)

54.3% female children
81% biological mothers
50.9% European-descent

Daily Measures

2-week diary (self and other report)

- Daily demands
- Positivity of the day together

Lab Measures

Adolescent & parent well-being

- Perceived stress (PSS; Cohen et al., 1983)
- Depressive symptoms (CESD; Radloff, 1977)

Childhood Family environment (Taylor, Lerner, Sage, Lehman, & Seeman, 2004)

Glucocorticoid sensitivity

Human, Chan, DeLongis, Roy, Miller, & Chen, 2014, *Psychosomatic Medicine*;
Human, Chan, Ifthikhar, Williams, DeLongis, & Chen, 2016, Social *Psychological and Personality Science*

Ex-vivo Investigation of Immune Regulation: Glucocorticoid Resistance

Whole blood diluted with saline, co-incubated with 50 ng/ml of LPS and varying doses of hydrocortisone

After 6 hr of incubation at 37 °C in 5% CO2, the supernatants were collected and frozen until assay

Panel of proteins (IL-1β , IL-6, IL-8, tumor TNF-α) were measured in duplicate with Meso Scale Discovery Human ProInflammatory 7-Plex Base Kits on MSD SECTOR Imager 2400 (MSD, Rockville, MD)

Average intra- and inter-assay variability was 6%

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Ex-vivo Investigation of Immune Regulation: Glucocorticoid Resistance

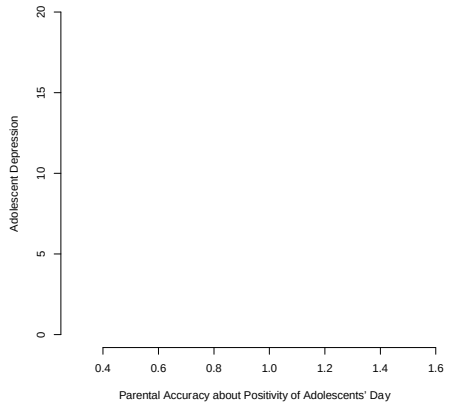
Exposure to LPS should provoke an inflammatory response, but cortisol should inhibit this effect, lowering levels of proinflammatory cytokines

Although an increase in cytokine activity in response to bacterial stimulus is expected and adaptive, an exaggerated response could be problematic

Dose-response curves: Compute concentration of hydrocortisone needed to diminish cytokine production by 50% (i.e., the log inhibitory coefficient-50, or log IC50)

Glucocorticoid resistance: Immune cells are less sensitive or resistant to cortisol's anti-inflammatory signals

Study 3: Parental accuracy about adolescents' positivity of the day associated with lower adolescent-reported depressive symptoms



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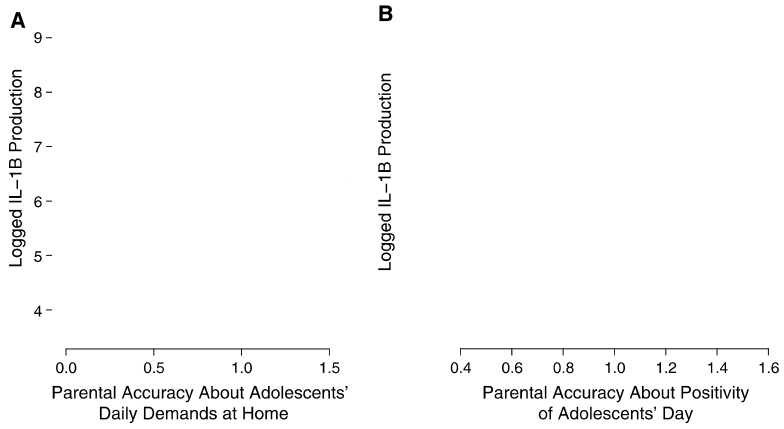
Study 3:
Parental accuracy regarding adolescent daily experiences associated with inflammatory regulation



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Human, Chan, Ifthikhar, Williams, DeLongis, & Chen, 2016, Social *Psychological and Personality Science*

Study 3 Summary

Parental accuracy about adolescents' daily demands was associated with adolescent well-being and immune regulation

- Effects not explained by the positivity of parent perceptions
- Effects held controlling for broad, self-reported measures of family environment and parenting

Parental accuracy regarding demands at school not significantly predictive

- Domain of parental sensitivity and understanding may be important

Human, Chan, DeLongis, Roy, Miller, & Chen, 2014, *Psychosomatic Medicine*;
Human, Chan, Ifthikhar, Williams, DeLongis, & Chen, 2016, Social *Psychological and Personality Science*

Study 3 Future Directions

How do micro-level parent-child dynamics in daily life unfold across different stages of development?

How do these ecological parent-child characteristics co-vary with dysregulation in psychosocial, behavioral, and physiological systems?

Human, Chan, DeLongis, Roy, Miller, & Chen, 2014, *Psychosomatic Medicine*;
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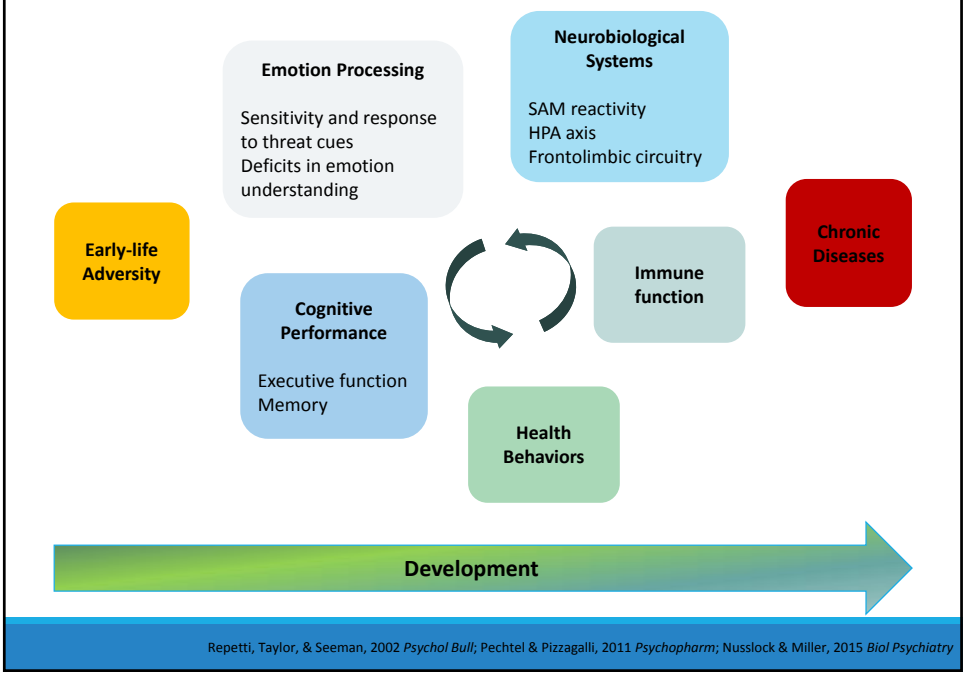

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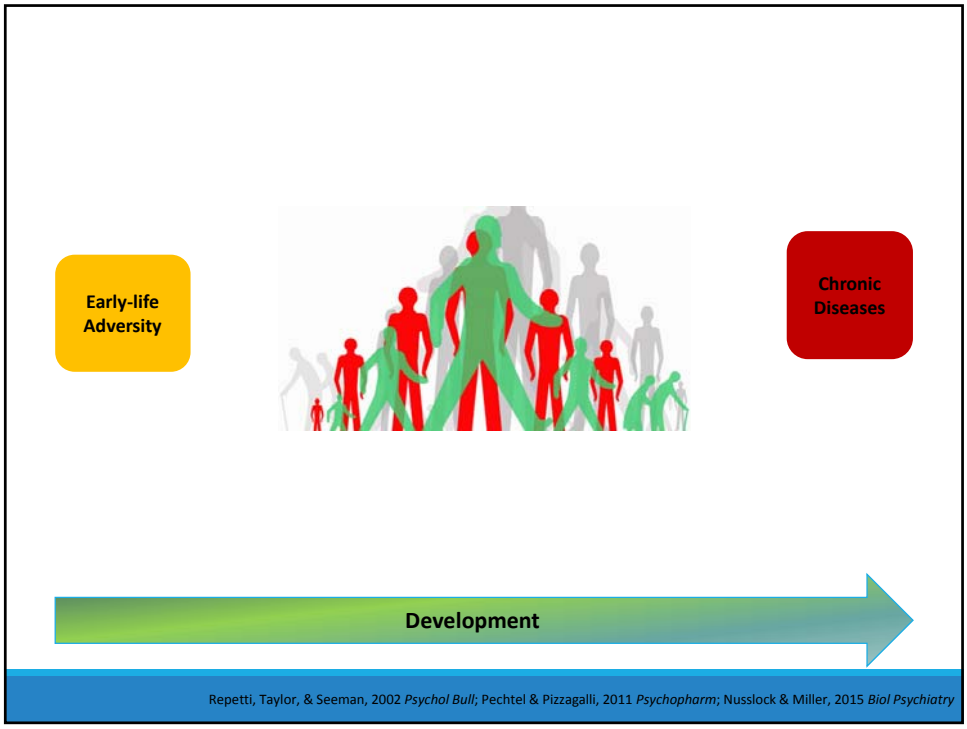

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Models of Risk and Resilience

Common Cold Project (Cohen, Doyle, Turner, Alper, & Skoner, 2004)

- Individuals of different social class backgrounds were intentionally exposed to a virus while quarantined and were followed clinically to track symptoms of the common cold
- Low-SES individuals were three times more likely to develop colds than high-SES individuals
- Despite this relative increase in colds, about 55% of those in the lowest SES category remained cold-free, even though they had all been exposed to the virus

Why do some individuals not get sick despite facing persistent and severe adversity?

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The Possibilities of Resilience

Supportive family relationships are a consistent protective factor for disruptions in children's stress-related regulatory systems

(Masten & Shaffer, 2006; Pettit et al., 1997; Repetti, Taylor, & Seeman, 2002; Cicchetti & Blender, 2006; Gunnar & Quevedo, 2005; Evans et al., 2007)

Maternal care by rat mothers modify offspring expression of genes that regulate behavioral and neuroendocrine responses to stress (Weaver et al., 2004)

Study 4:
Upward social mobility and social capital

Previous models of resilience:

- Tend and Befriend (Taylor et al., 2000)
- Shift and Persist (Chen & Miller, 2012)

In addition to healthy family relationships, what other social capital dimensions need to be built in order to foster upward social mobility in children from disadvantaged backgrounds?

Study 4:
Upward social mobility and social capital

Sample

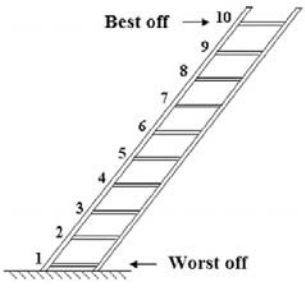
- BrainMAPD Study
- 113 healthy young adults aged 18

Social Capital Measures

- Subjective social status: MacArthur Ladder
- Emotion Regulation Strategies
- Implicit Theories of Emotion Scale
- Parental Bonding Inventory

Biobehavioral Markers

- Obesity indices
- C-reactive protein levels in serum



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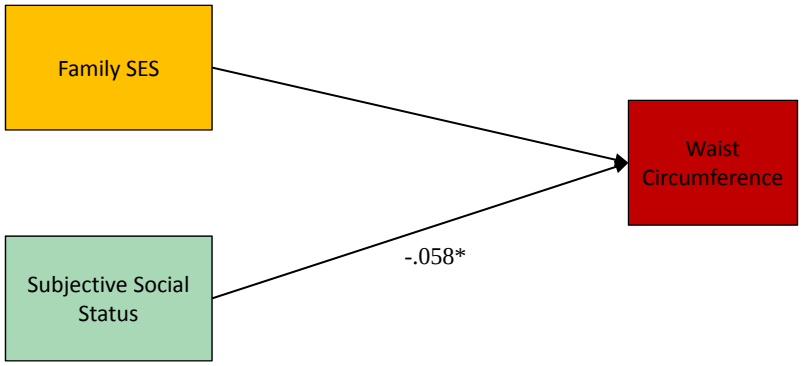

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Chan, Chat, Vinograd, Craske, Nusslock, 2016

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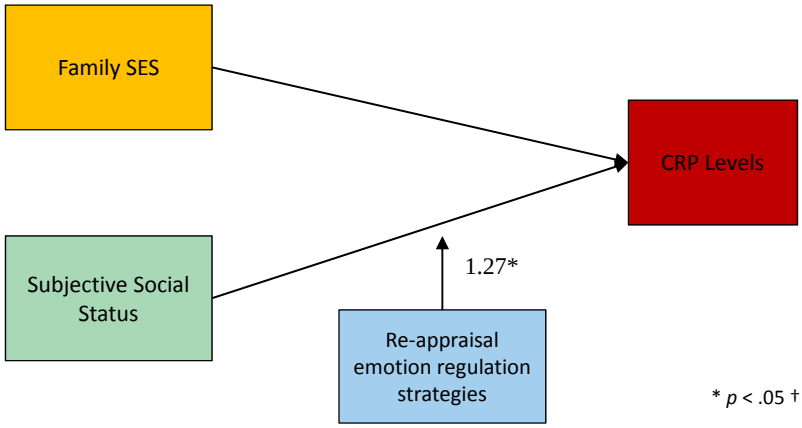

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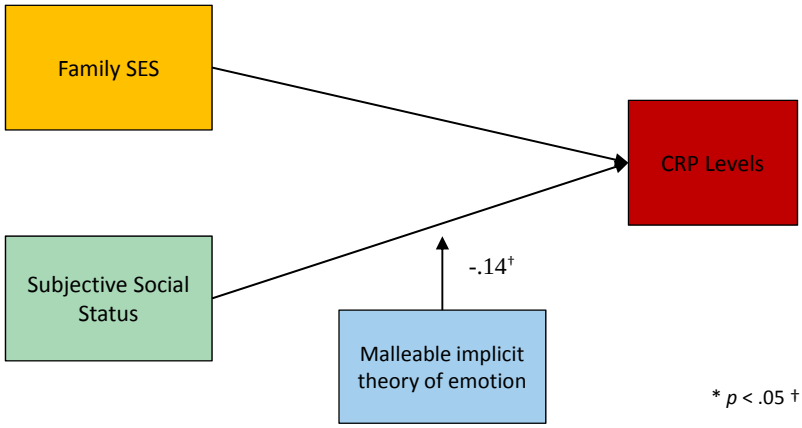

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Chan, Chat, Vinograd, Craske, Nusslock, 2016

Study 4:
Upward social mobility and social capital

Consistent with the Shift and Persist model of resilience

- Individuals who use re-appraisal strategies to cope with chronic stress and those who have malleable theories of emotion may be able to enjoy the health benefits of higher subjective social status

How can we foster adaptive shifting strategies in youth who from disadvantaged backgrounds?

- Youth Engagement Project
  (Chan et al., Ministry of Child and Youth Services 2016)

Chan, Chat, Vinograd, Craske, Nusslock, 2016

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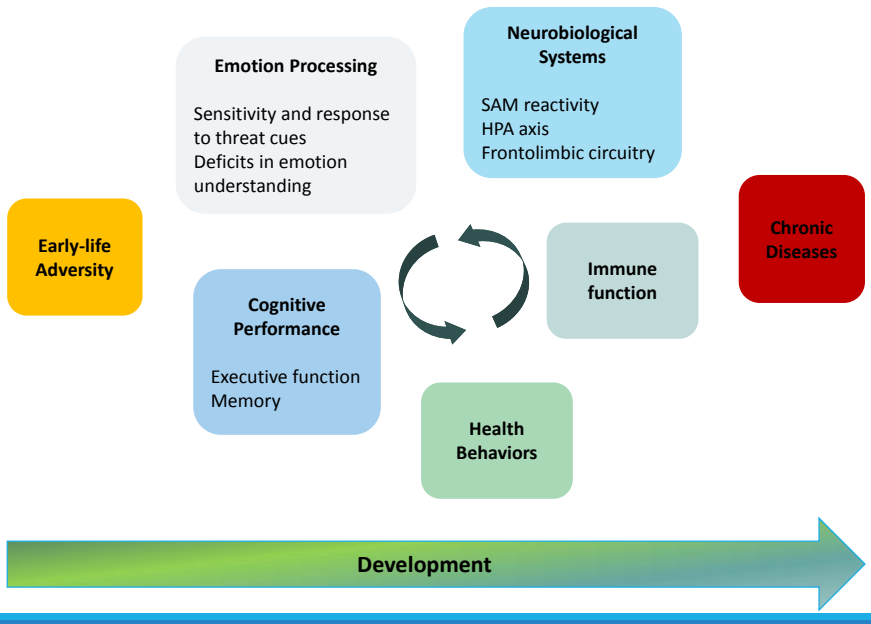
Overall Summary

1. Exposure to adversity and implications for health
   - Mechanistic models incorporating dysregulation across multiple domains
   - Study 1: Early-life socioeconomic conditions and implications for sensitivity to environment threat cues, physical activity patterns, and obesity in adolescents
2. Ecological approach to adversity in families
   - Study 2: Father-child conflict x variation in cytokine genes to predict frontal region structure
   - Study 3: Adolescents whose daily demands were better understood by parents had higher well-being and better inflammatory regulation
3. Optimizing resilience in the face of risk
   - Study 4: Re-appraisal strategies and a malleable theory of emotion may help individuals enjoy the better health outcomes associated with social mobility



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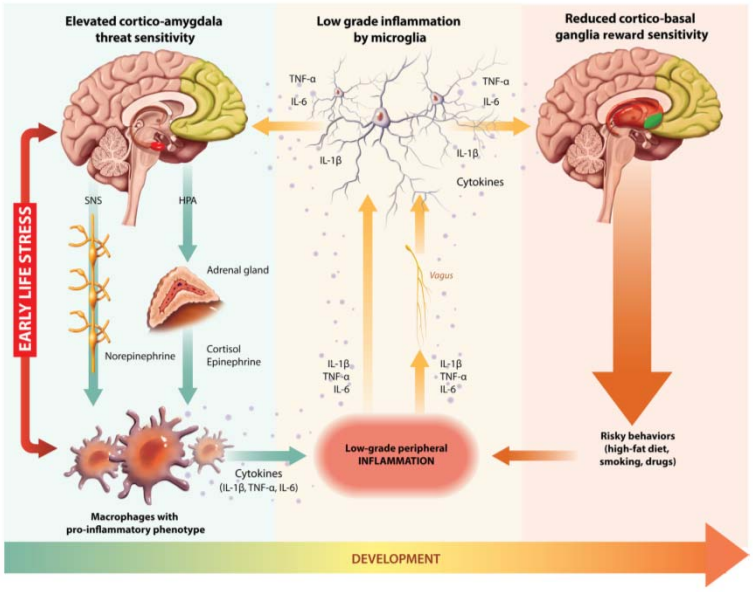

Figure 1. Depiction of neuroimmune network hypothesis. HPA, hypothalamic-pituitary-adrenocortical; IL-1β, interleukin-1β; IL-6, interleukin-6; SNS, sympathetic nervous system; TNF-α, tumor necrosis factor-alpha. Illustration by Chi-Chun Liu and Qingyang Chen.

Nusslock & Miller, 2015 *Biol Psychiatry*

Neuro-immune Network Hypothesis

Heuristic framework for organizing knowledge from disparate literatures and as a springboard for generating integrative research

Drawing on existing data, we argue that childhood adversity amplifies crosstalk between peripheral inflammation and neural circuitries underlying threat-related, reward-related, and executive control-related processes

This crosstalk results in chronic low-grade inflammation, thereby contributing to adiposity, insulin resistance, and other predisease states

In the brain, inflammatory mediators act on cortico-amygdala threat and cortico-basal ganglia reward, circuitries in a manner that predisposes individuals to self-medicating behaviors like smoking, drug use, and consumption of high-fat diets

Acting in concert with inflammation, these behaviors accelerate the pathogenesis of emotional and physical health problems

Nusslock & Miller, 2015 *Biol Psychiatry*

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