

The physiology of transformational experience

a perspective from the human genome

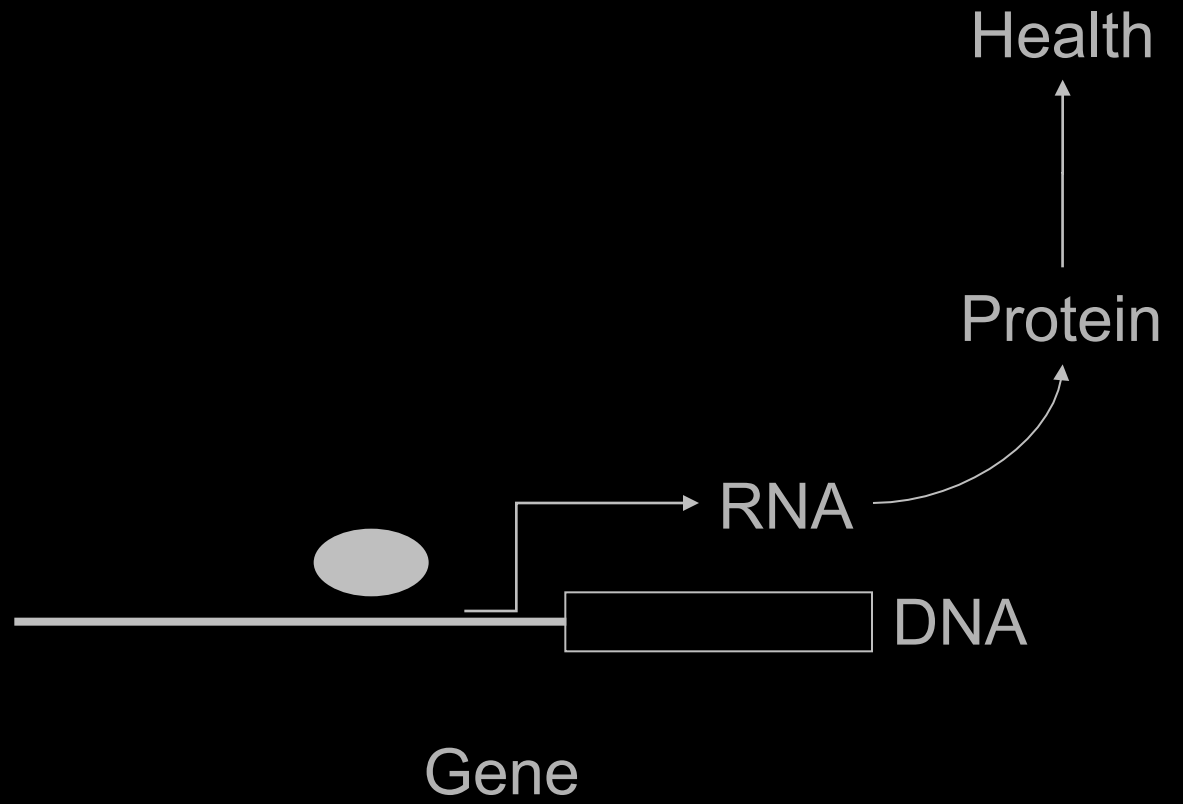
Steve W. Cole, Ph.D.
UCLA School of Medicine
Division of Hematology-Oncology

The experienced self

- stable
- independent

The molecular self

- fluid
- permeable



The experienced self

- stable
- independent

The molecular self

- fluid
- permeable

Environment

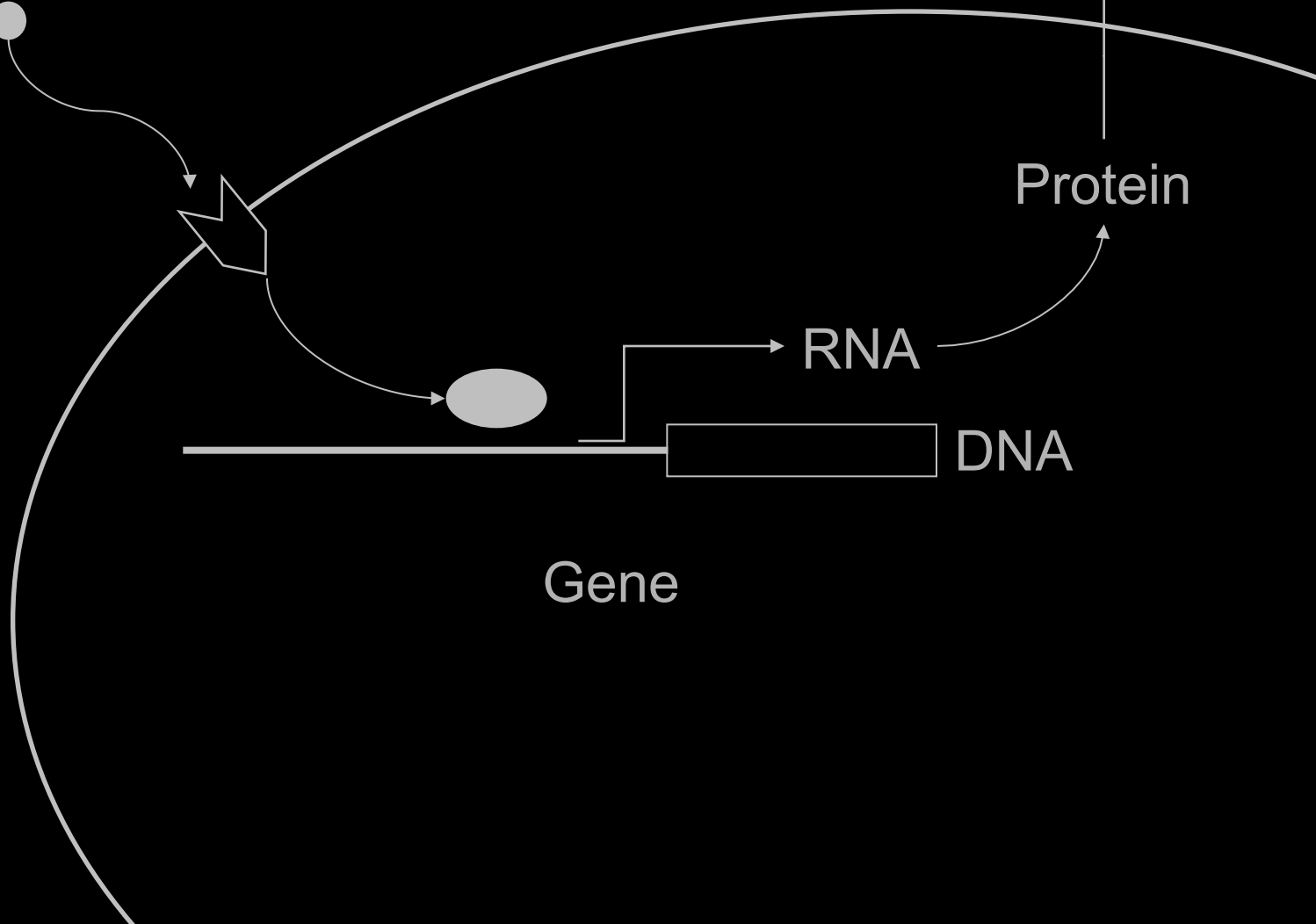
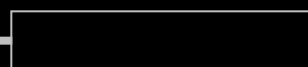
Health

Protein

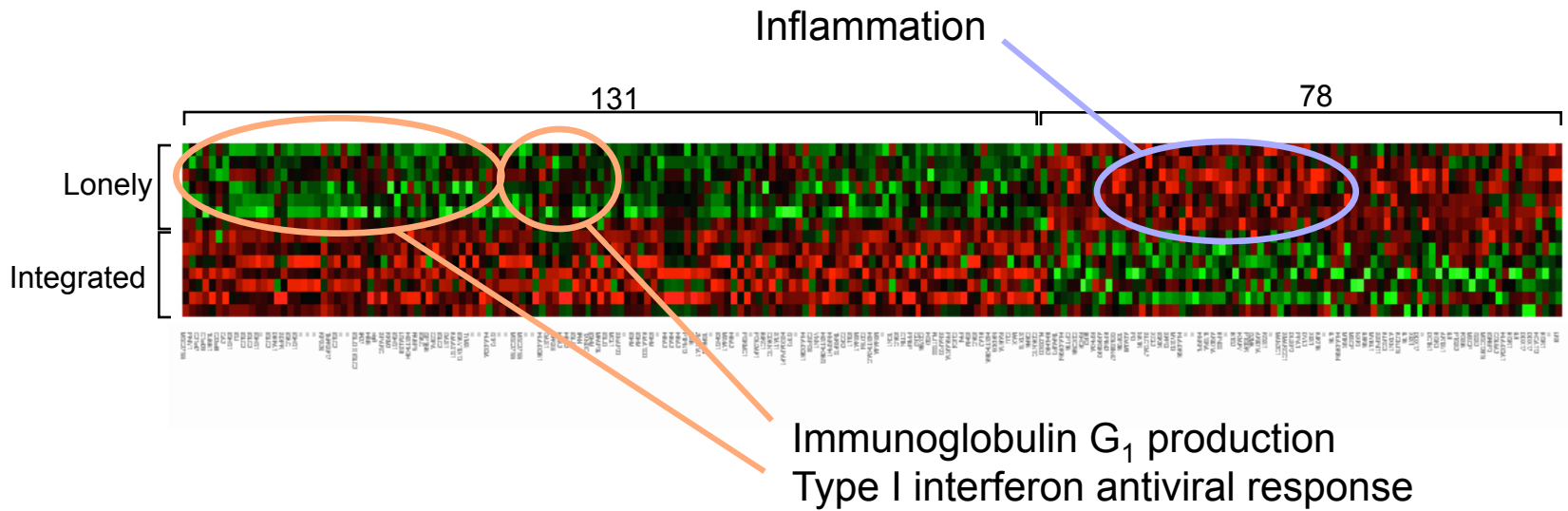
RNA

DNA

Gene



Social isolation



Low SES

Social loss / bereavement

Post-traumatic stress

Cancer diagnosis

Social threat

Loneliness

Social instability

Chronic stress

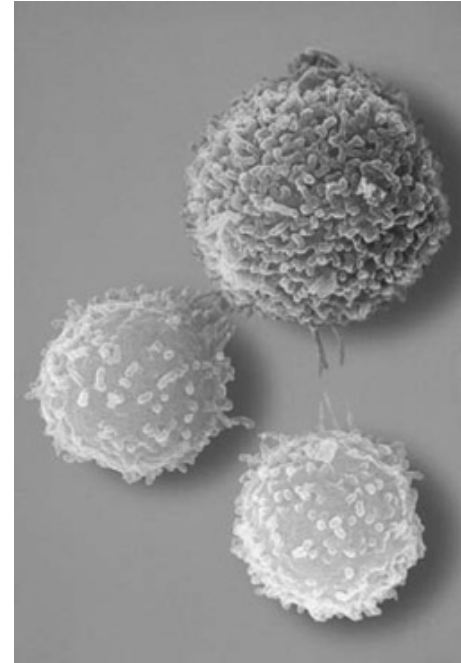
Low social rank

Caregiving for seriously ill

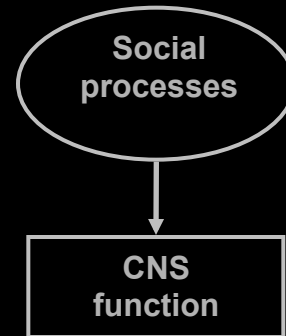
Anxiety

Early life adversity

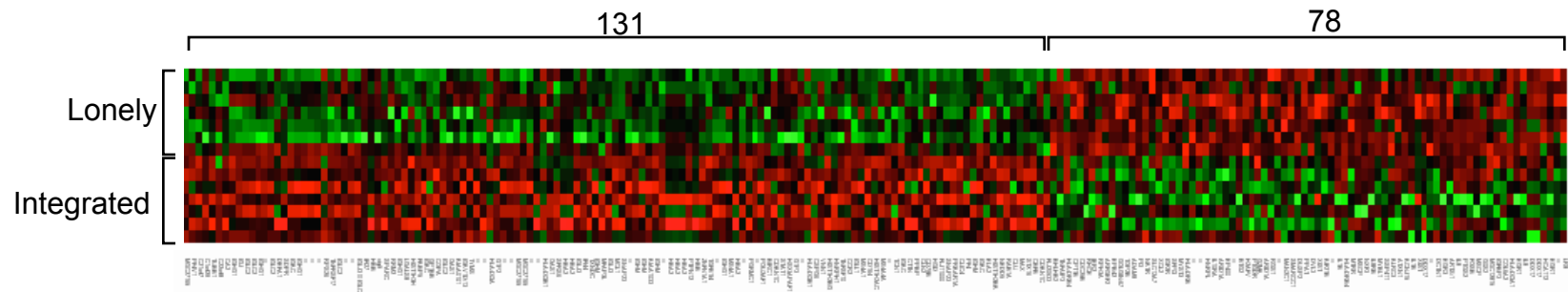
Social instability



Social signal transduction



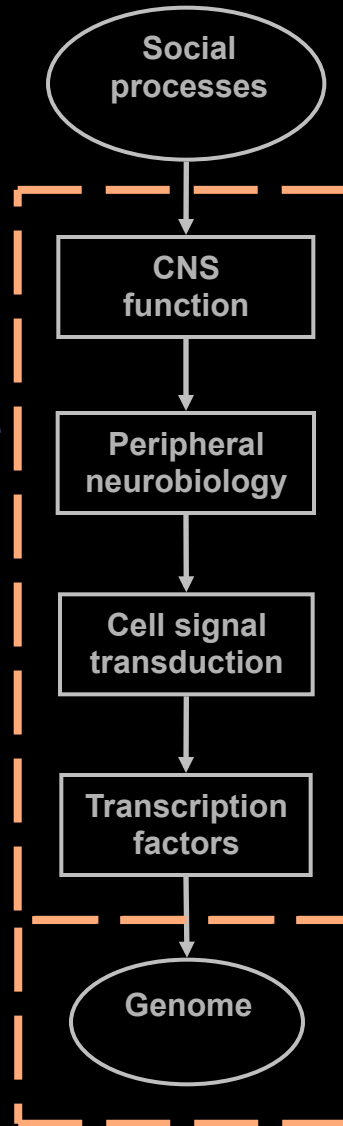
Social isolation

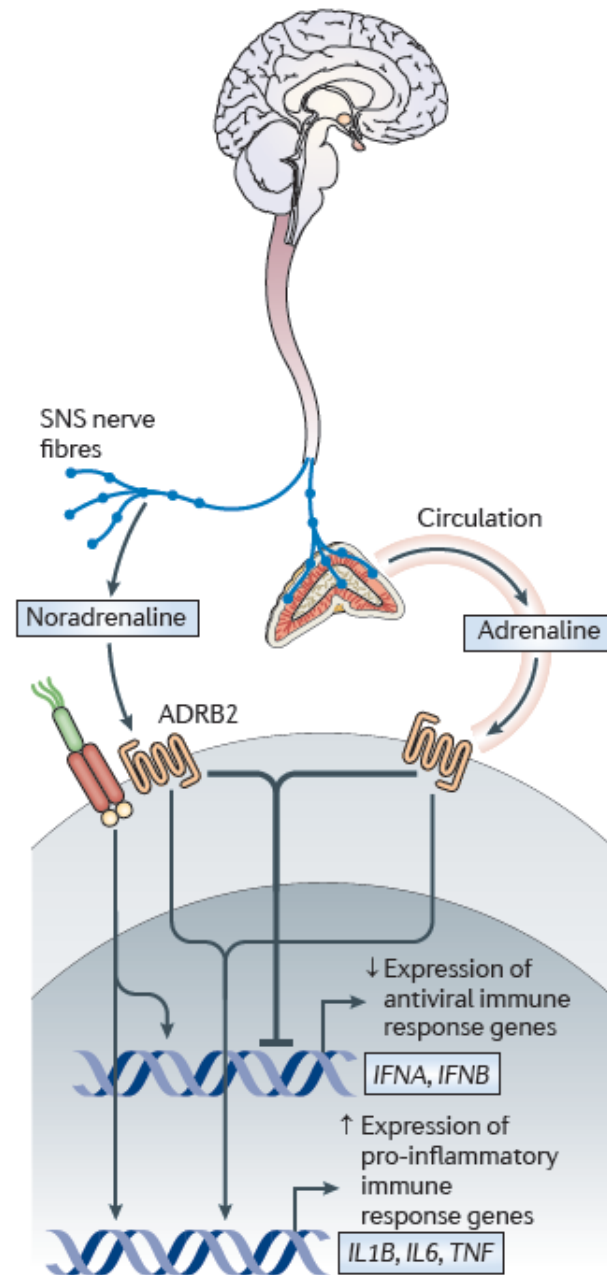


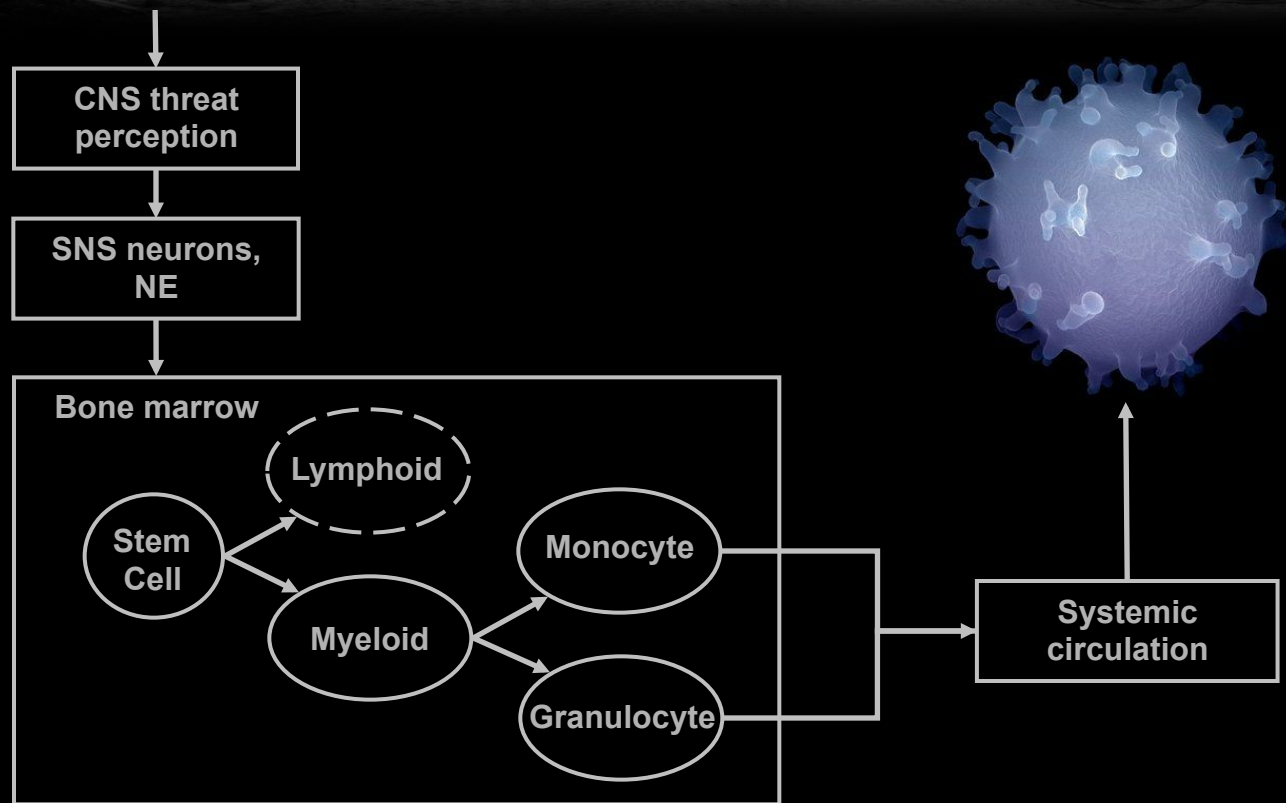
Social signal transduction

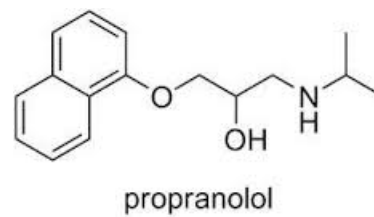
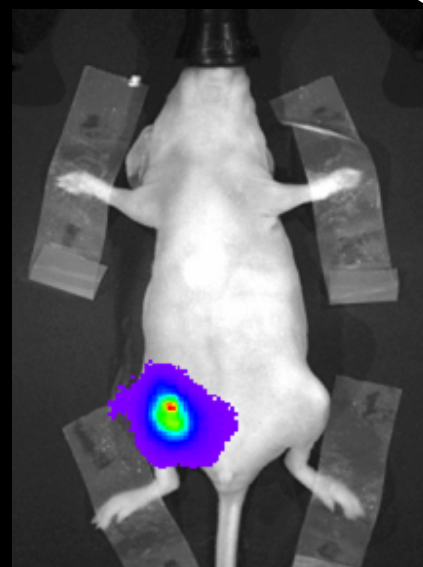
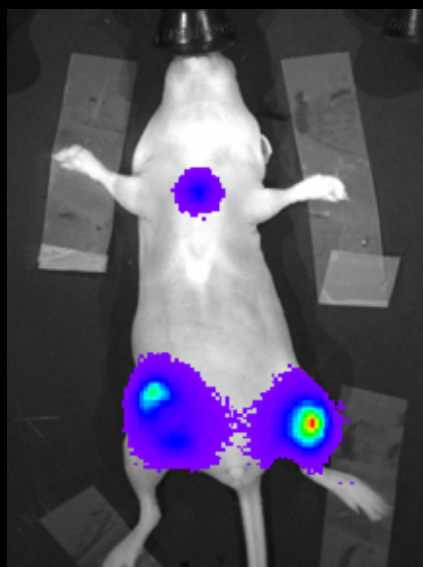
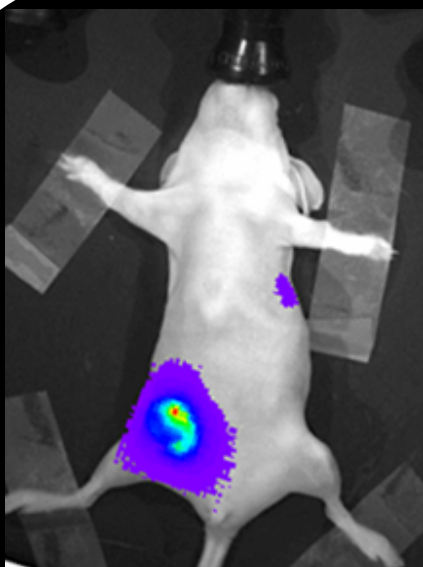
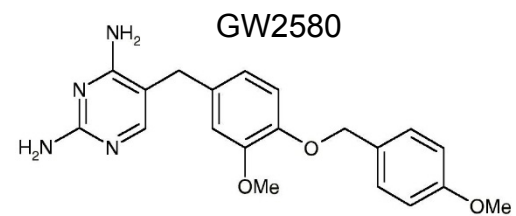
Simple questions

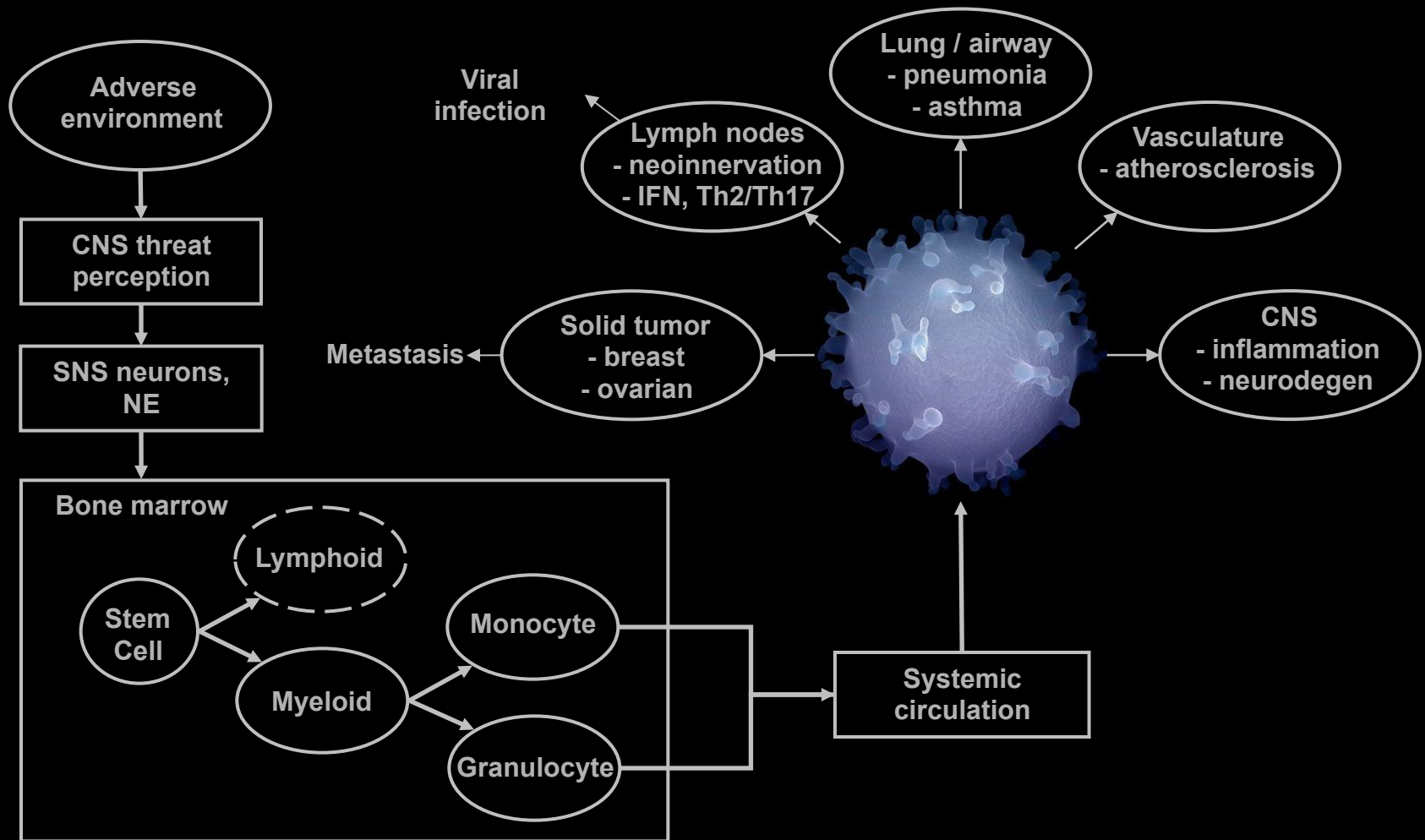
1. Which gene modules are sensitive to social processes?
2. Which transcription control pathways mediate those effects?









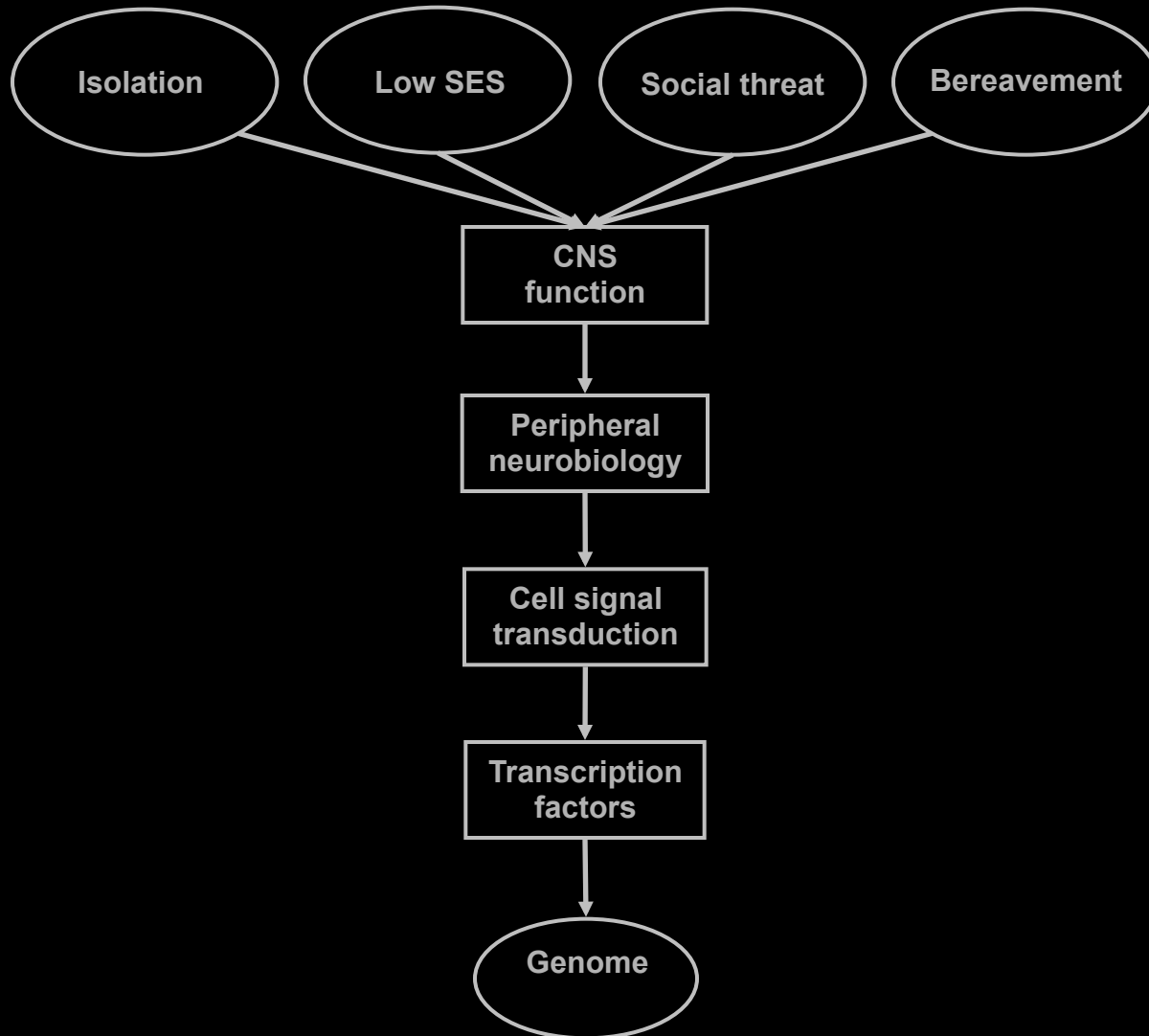


Central nervous system

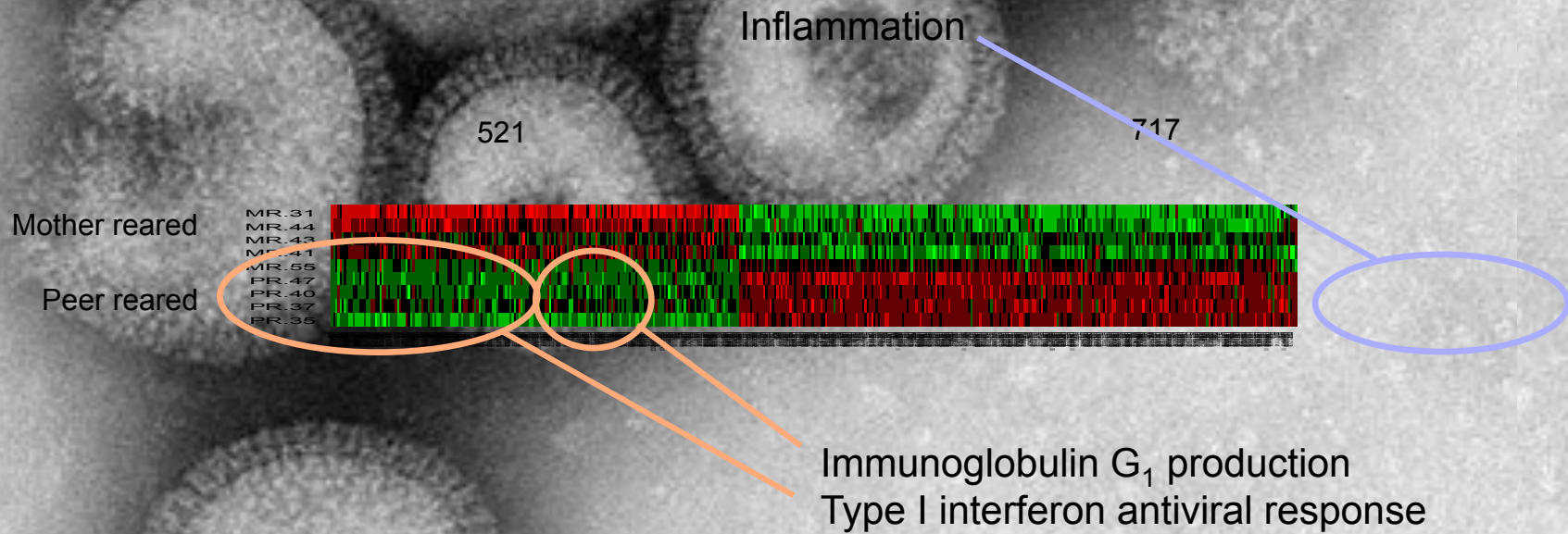


Leukocyte

Social signal transduction



CTRA – conserved transcriptional response to adversity



2 “social genomic programs” in immune cells

safe/attached



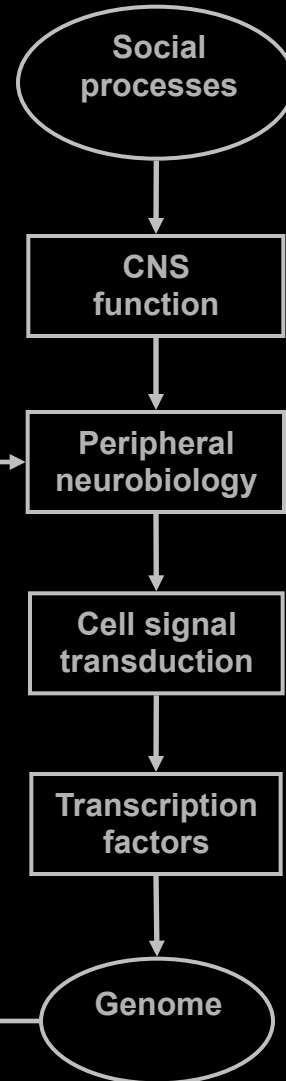
danger/isolated



Social signal transduction

Simple questions

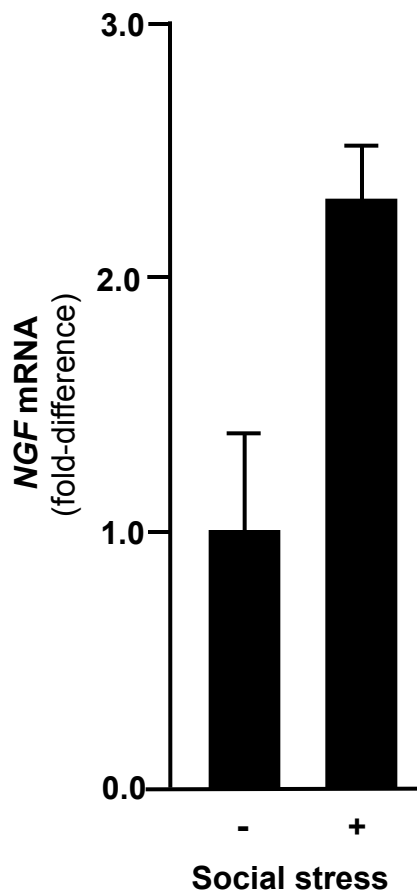
1. Which gene modules are sensitive to social processes?
2. Which transcription control pathways mediate those effects?



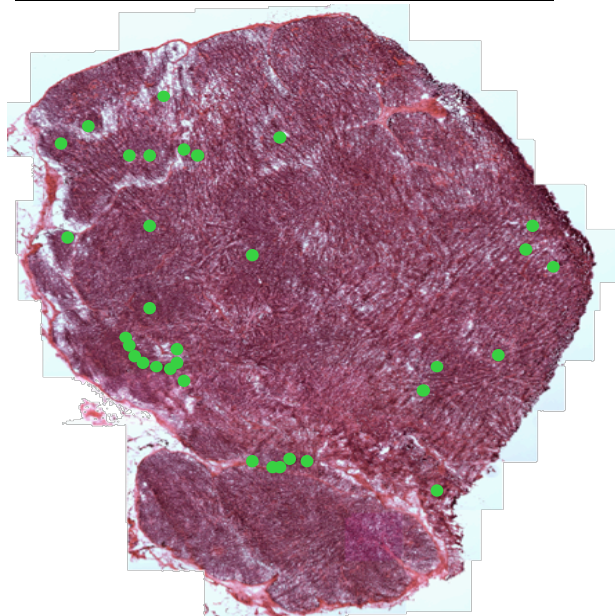
Not-so-simple questions

1. Recursive persistence and environmental embedding

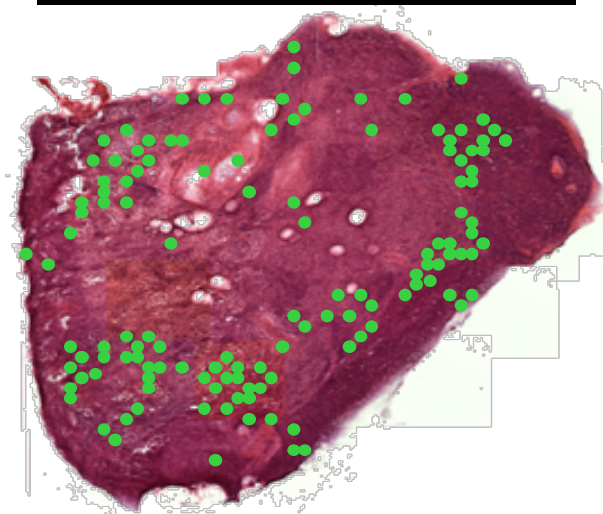
NGF expression



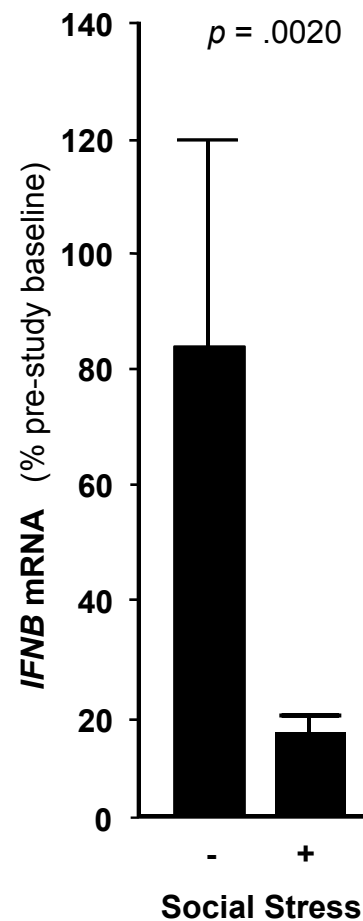
Stable social conditions



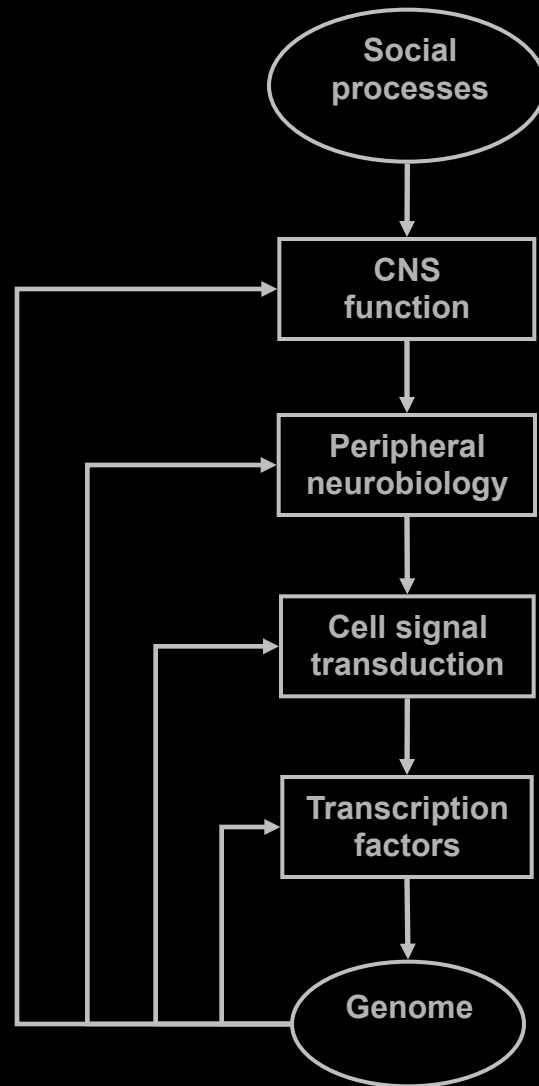
Unstable



IFNB mRNA

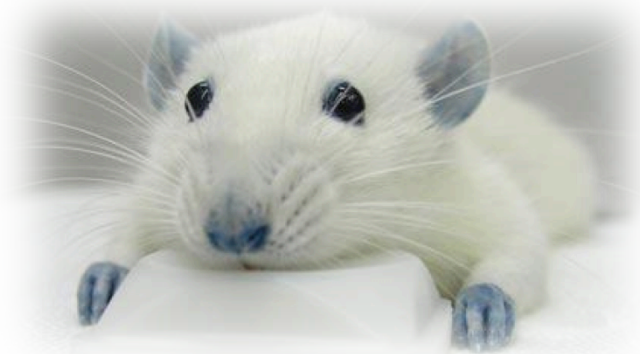
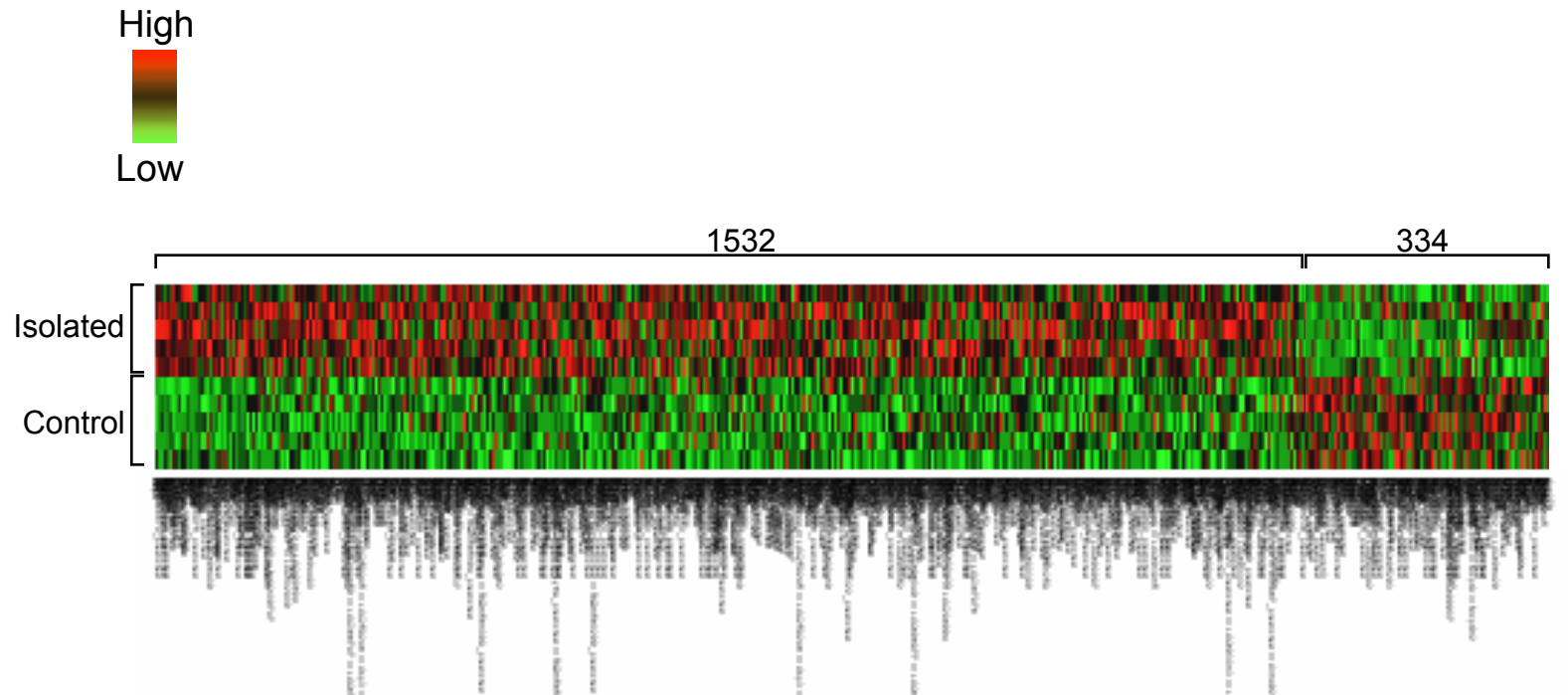


Social signal transduction

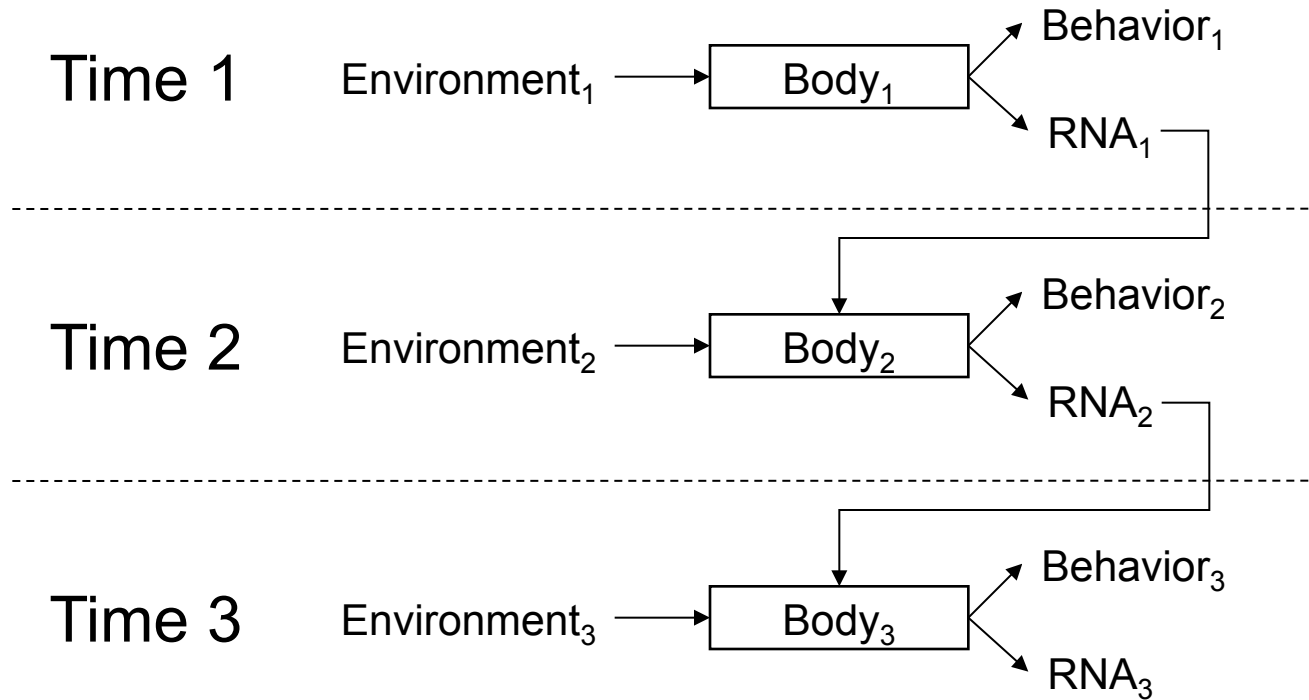


Recursive persistence

Social isolation



Recursive developmental remodeling



RNA = intra-organismic adaptation

Low early-life social class leaves a biological residue manifested by decreased glucocorticoid and increased proinflammatory signaling

Gregory E. Miller^{a,1}, Edith Chen^a, Alexandra K. Fok^{b,c}, Hope Walker^a, Alvin Lim^a, Erin F. Nicholls^a, Steve Cole^{d,e,f}, and Michael S. Kobor^{b,c}

Departments of ^aPsychology and ^bMedical Genetics, and ^cCentre for Molecular Medicine and Therapeutics, Child and Family Research Institute, University of British Columbia, Vancouver, BC, Canada V6T 1Z4; ^dDepartment of Medicine, Division of Hematology-Oncology, University of California, Los Angeles School of Medicine, Los Angeles, CA 90095; ^eMolecular Biology Institute and Jonsson Comprehensive Cancer Center, University of California, Los Angeles AIDS Institute, Los Angeles, CA 90095; and ^fNorman Cousins Center, University of California, Los Angeles, CA 90095

Edited by Burton H. Singer, Princeton University, Princeton, NJ, and approved May 28, 2009 (received for review March 18, 2009)

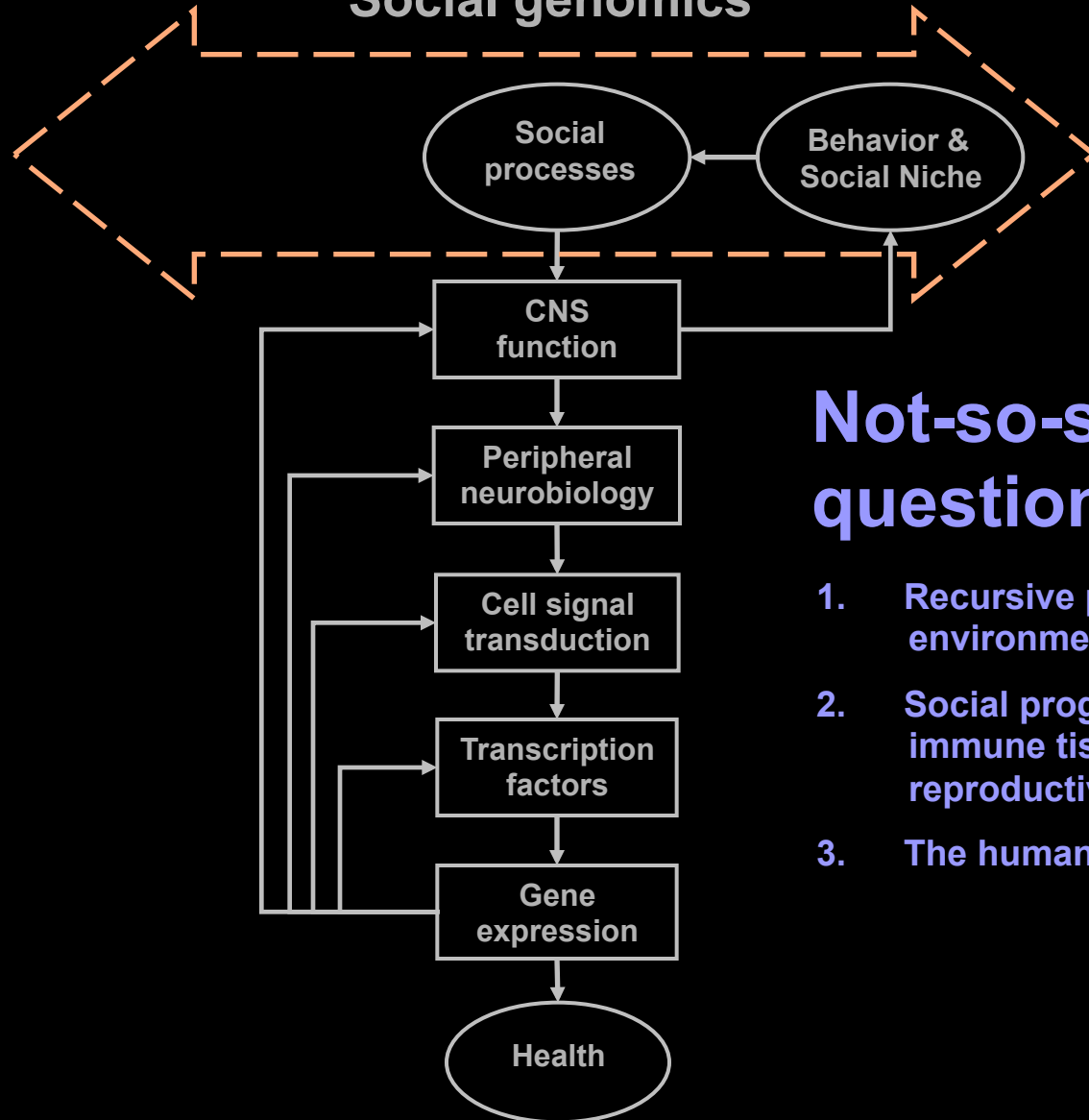
Children reared in unfavorable socioeconomic circumstances show increased susceptibility to the chronic diseases of aging when they reach the fifth and sixth decades of life. One mechanistic hypothesis for this phenomenon suggests that social adversity in early life programs biological systems in a manner that persists across decades and thereby accentuates vulnerability to disease. Here we examine the basic tenets of this hypothesis by performing genome-wide transcriptional profiling in healthy adults who were either low or high in socioeconomic status (SES) in early life. Among subjects with low early-life SES, there was significant up-regulation of genes bearing response elements for the CREB/ATF family of transcription factors that conveys adrenergic signals to leukocytes, and significant down-regulation of genes with response elements for the glucocorticoid receptor, which regulates the secretion of cortisol and transduces its antiinflammatory actions in the immune system. Subjects from low-SES backgrounds also showed increased output of cortisol in daily life, heightened expression of transcripts bearing response elements for NF- κ B, and greater stimulated production of the proinflammatory cytokine interleukin 6. These disparities were independent of subjects' current SES, lifestyle practices, and perceived stress. Collectively, these data suggest that low early-life SES programs a defensive phenotype characterized by resistance to glucocorticoid signaling, which in turn facilitates exaggerated adrenocortical and inflammatory responses. Although these response patterns could serve adaptive functions during acute threats to well-being, over the long term they might exact an allostatic toll on the body that ultimately contributes to the chronic diseases of aging.

cortisol | inflammation | NF-kappa B | socioeconomic status | stress

nurturance or experience prolonged maternal separations can show permanent alterations in stress-related outflow of the autonomic nervous system (ANS) and the hypothalamic-pituitary-adrenocortical (HPA) axis (8–10). These effects are partially mediated by diminished expression of and signaling by the glucocorticoid receptor (GR), a ligand-activated transcription factor that regulates HPA outflow through a hippocampal negative-feedback circuit (11, 12). The effects of early social adversity also extend to the immune system (13). For example, mice that are repeatedly separated from their mothers early in life show an excessive inflammatory response and reduced viral clearance after influenza infection in adulthood (14), an effect that is partially mediated by impaired glucocorticoid regulation of cytokine release.

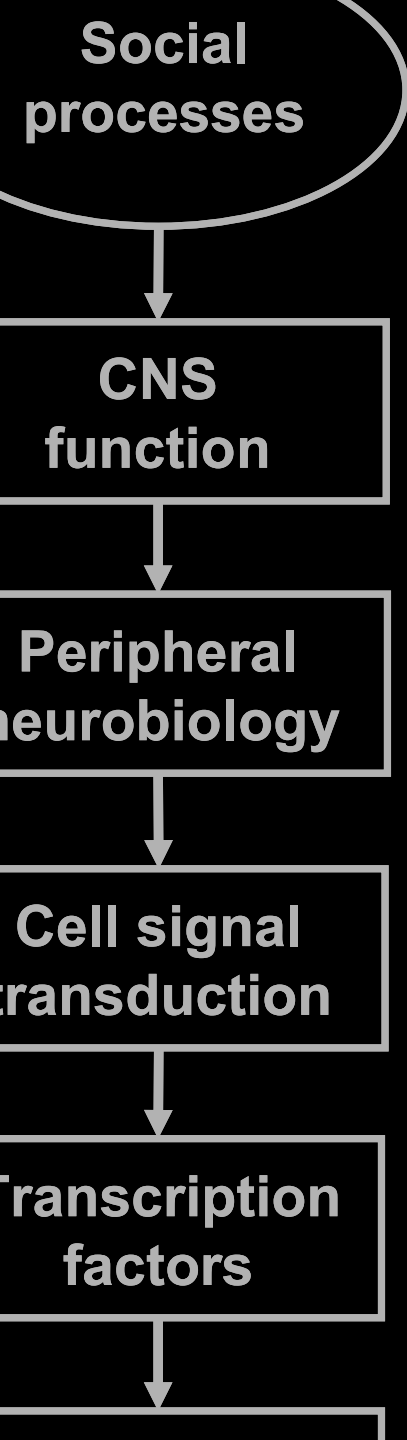
Collectively, these data suggest that repeated social adversity in early life can program a “defensive” phenotype, which is marked by exaggerated adrenocortical and inflammatory responses to challenge (15). Some evidence indicates that this phenotype involves the development of a functional resistance to GR-mediated signaling, which allows cortisol to partially escape inhibition by negative feedback and facilitates the synthesis of proinflammatory mediators by leukocytes. In social contexts where threats like crowding, predation, and conflict are common, these response patterns might confer a survival advantage by helping organisms to rapidly mobilize energy for fighting and fleeing and to mount vigorous immune responses to infection and injury (15). However, in the context of late-life chronic illnesses, dysregulated GR signaling may enable exaggerated inflammatory responses that contribute to the pathogenesis of cardiovascular disease, some types of cancer, and respiratory conditions.

Social genomics

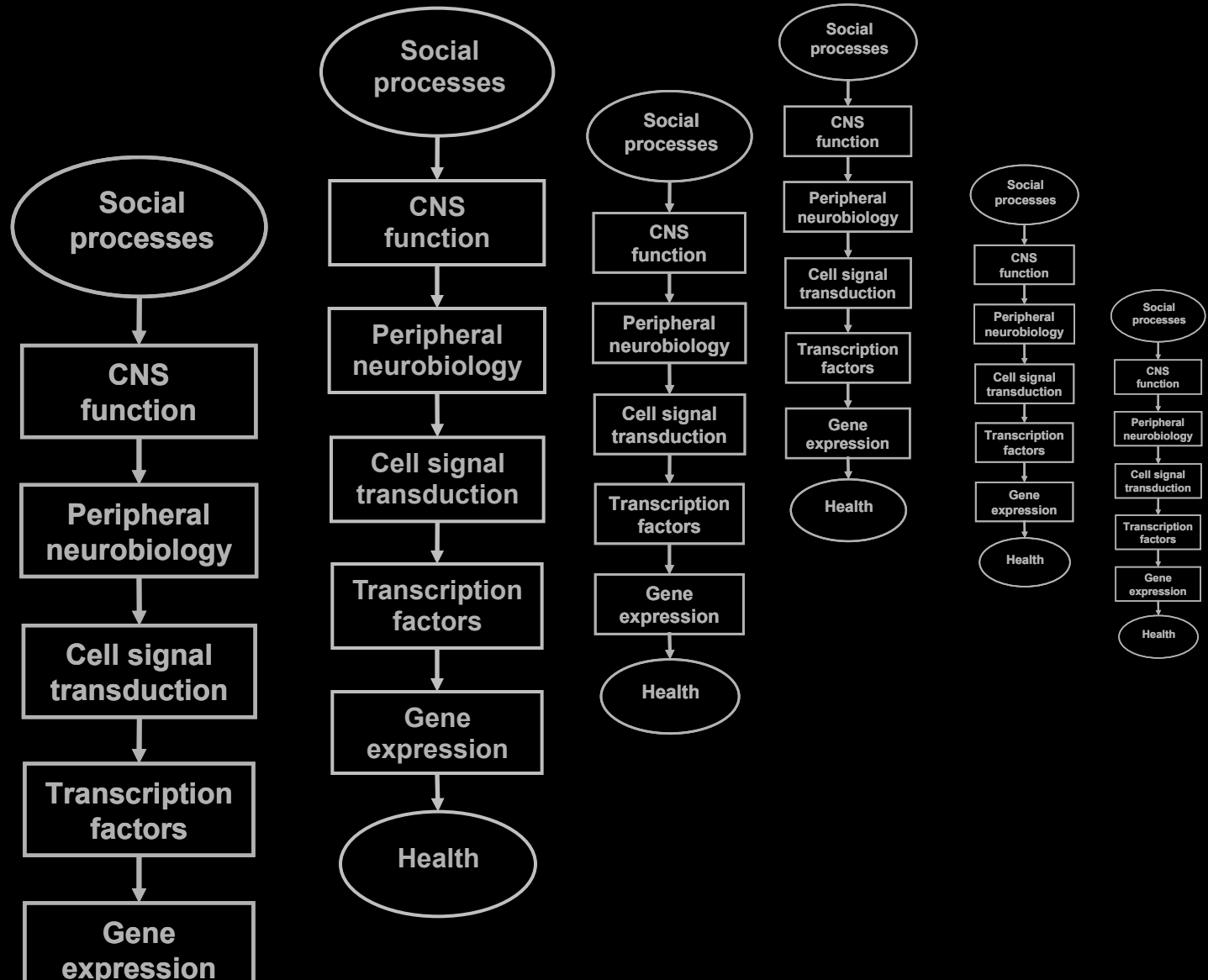


Not-so-simple questions

1. Recursive persistence and environmental embedding
2. Social programming of non-immune tissues (e.g., neural, reproductive)
3. The human metagenome



Social genomics



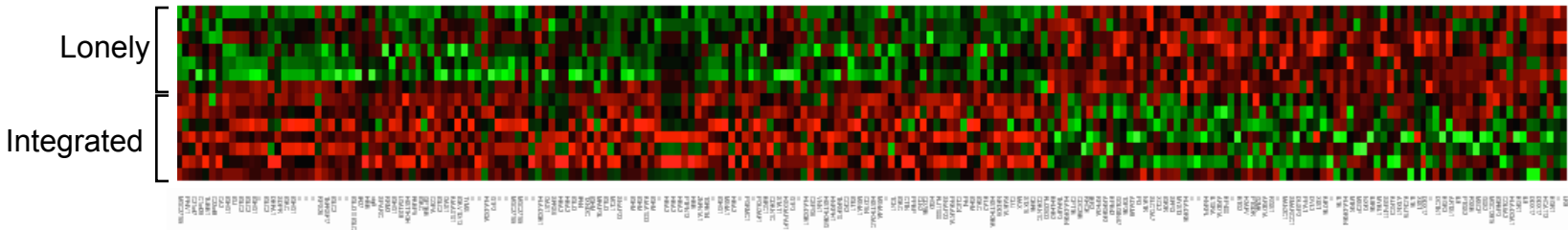
Your experiences today
will influence the molecular composition of your body
for the next 2-3 months

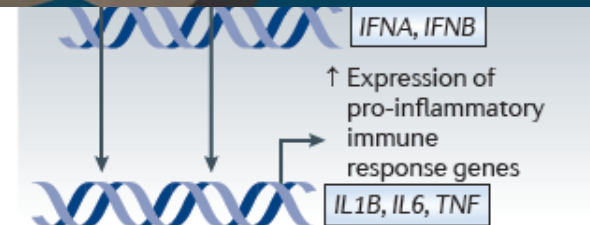
... or perhaps the rest of your life.

Plan your day accordingly.

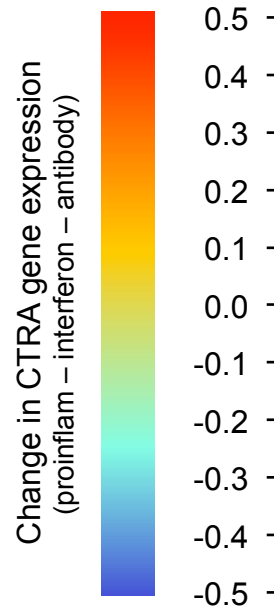
Let's take a break.

How should we divide?





Effect of meditation on CTRA gene expression



UNC SOBC2 study

PI: Dr. Barbara Fredrickson

N = 91, genes = 52

blood sampled in 2013-2014, age 35-67 yrs, 73% female

Chapel Hill adults, UNC staff

Emory CALM study

PIs: Dr. Charles Raison, Tad Pace, Matthias Mehl

N = 119, genes = 41

blood sampled in 2012, age 25-55 yrs, 68% female

Mostly Emory University staff

Contemplative leukocytes

Cognitive-behavioral

Antoni et al. (2012) Biological Psychiatry 71:366–372

Mindfulness

Creswell et al. (2012) Brain, Behavior, & Immunity 26:1095-1101

Relaxation response / mindfulness

Bhasin et al. (2013) PLoS ONE, 8:e62817

Yogic meditation

Qu et al. (2013) PLoS ONE, 8:e61910

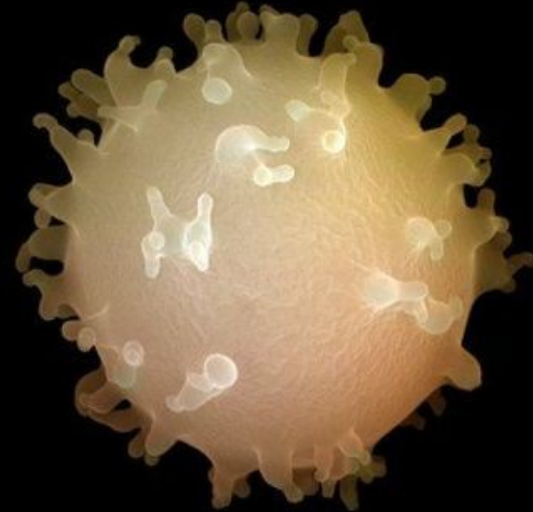
Black et al. (2013) Psychoneuroendocrinology, 38:348-55

Yoga

Bower et al. (2014) Psychoneuroendocrinology, 43:20-29

Tai Chi

Irwin et al. (2014) Journal of the National Cancer Institute, in press.



Attention as a key resource for resilience

Contemplative practices weren't invented to fight cancer or boost performance, but rather to tackle big issues like living **purposefully** and facing death with equanimity.

One fundamental skill they build is **attention**, the simple act of consciously **choosing** what to focus on instead of letting the mind wander.

Having strong attention is an important component of **resilience**, because it develops a sense of **agency** and **choice** in directing one's thoughts and influencing one's inner landscape

– a powerful counterweight to the sense of helplessness or passivity that traumatic stress can produce.

What if you can't stand... medication?

Or meditation?



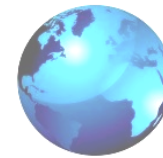
Maybe try just being nice.

How should we live?



Hedonic

How often do you feel **happy**?
How often do you feel **satisfied**?
Keyes MHC-SF - Hedonic

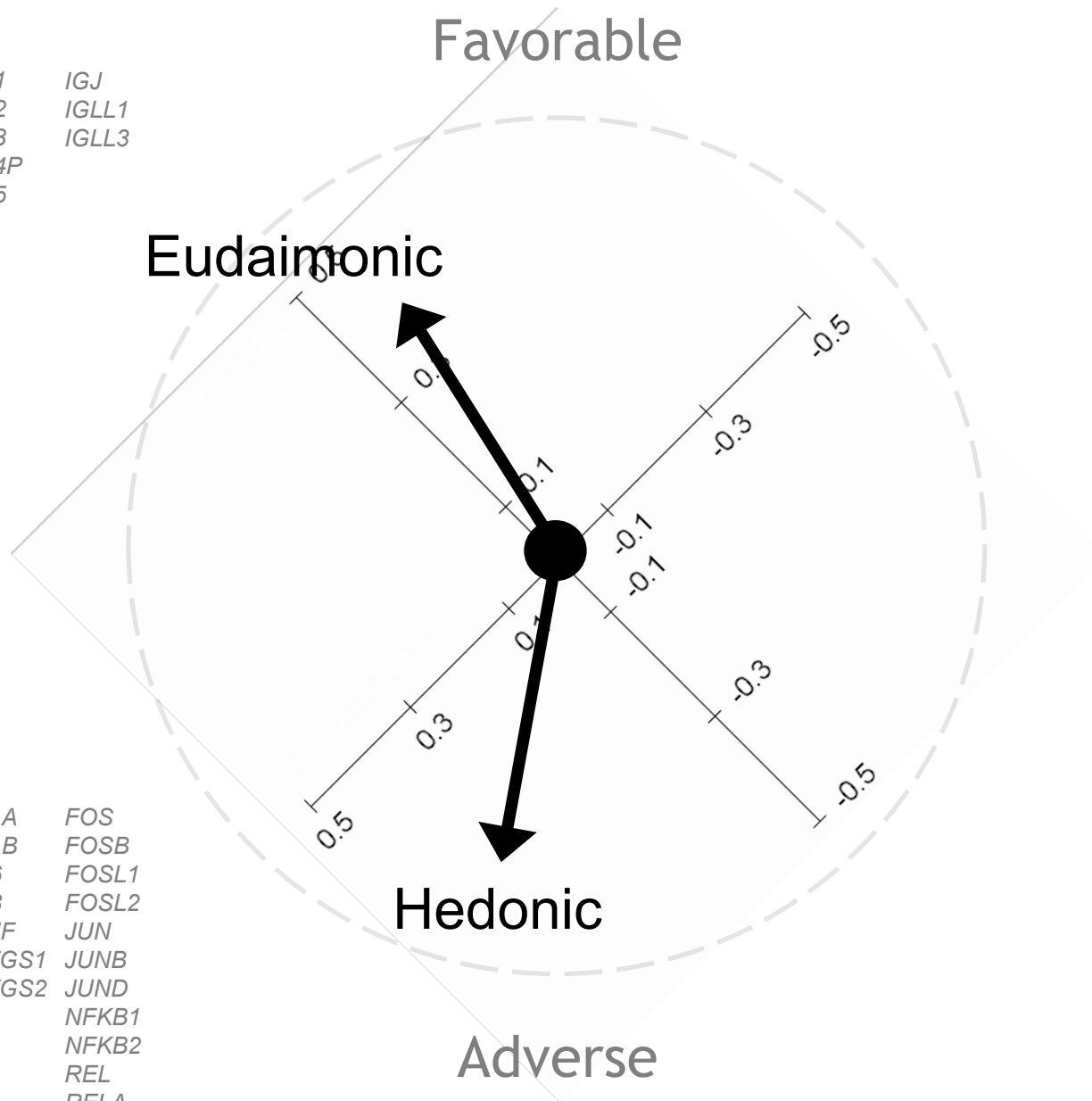


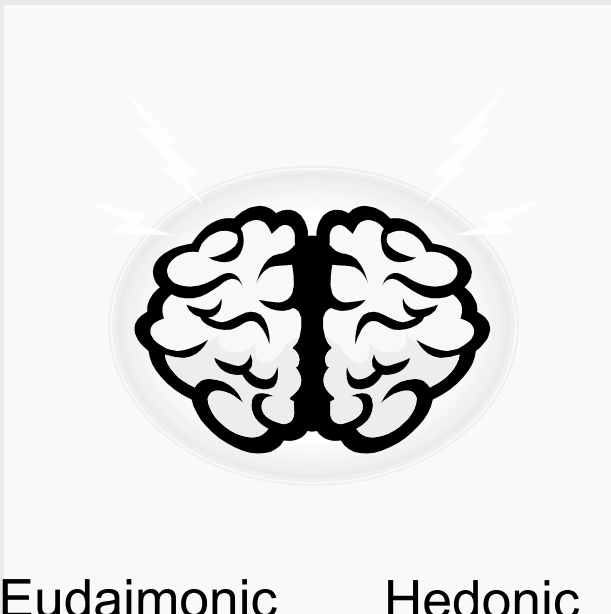
Eudaimonic

Life has **direction** and **meaning**?
Grow and become a **better person**?
Keyes MHC-SF – Eudaimonic

GBP1 IFITM1 IGJ
 IFI16 IFITM2 IGLL1
 IFI27 IFITM3 IGLL3
 IFI27L1 IFITM4P
 IFI27L2 IFITM5
 IFI30 IFNB1
 IFI35 IRF8
 IFI44 IRF2
 IFI44L IRF7
 IFI6 MX1
 IFIH1 MX2
 IFIT1 OAS1
 IFIT1L OAS2
 IFIT2 OAS3
 IFIT3 OASL
 IFIT5

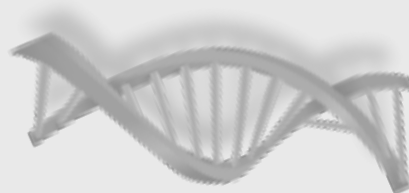
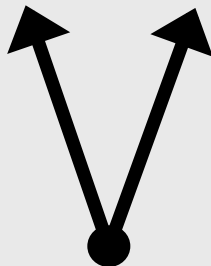
IL1A FOS
 IL1B FOSB
 IL6 FOSL1
 IL8 FOSL2
 TNF JUN
 PTGS1 JUNB
 PTGS2 JUND
 NFKB1
 NFKB2
 REL
 RELA
 RELB





Eudaimonic

Hedonic



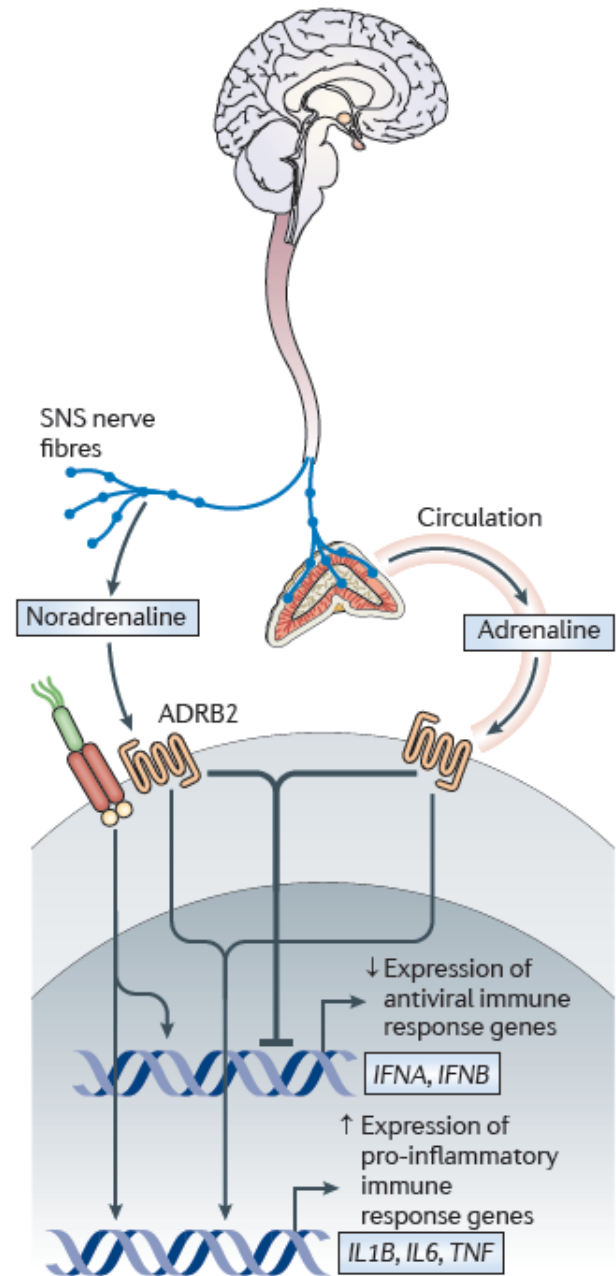
Eudaimonic



Hedonic



Goetz et al., Psych Bulletin, 2010
 Porges, Int J Psychophys., 2001
 Porges, Psychophysiol., 1995



How can we increase eudaimonic well-being?

Attentional path to Eudaimonia: direct attention away from the self, and outward, toward others and the world around us.

Department of Psychology

HOME

UNDERGRADUATE

GRADUATE

FACULTY & RESEARCH

NEWS

TALKS & COLLOQUIA

EMPLOYMENT

CONTACTS

Faculty » Sonja Lyubomirsky

The majority of my research career has been devoted to studying human happiness. Why is the scientific study of happiness important? In short, because most people believe happiness is meaningful, desirable, and an important, worthy goal, because happiness is one of the most salient and significant dimensions of human experience and emotional life, because happiness yields numerous rewards for the individual, and because it makes for a better, healthier, stronger society. Along these lines, my current research addresses three critical questions – 1) What makes people happy?; 2) Is happiness a good thing?; and 3) How can we make people happier still?

Selected Publications

- Lyubomirsky, S. (2013). *The myths of happiness: What should make you happy, but doesn't, what shouldn't make you happy, but does*. New York: Penguin Press. [Visit the book's website](#). [Download the book's full set of references](#).
- Lyubomirsky, S. (2008). *The how of happiness: A scientific approach to getting the life you want*. New York: Penguin Press. [Visit the book's website](#). [Download the book's references](#).
- Nelson, S. K., Kushlev, K., & Lyubomirsky, S. (in press). [The pains and pleasures of parenting: When, why, and how is parenthood associated with more or less well-being?](#) *Psychological Bulletin*.
- Nelson, S. K., Kushlev, K., English, T., Dunn, E. W., & Lyubomirsky, S. (2013). [In defense of parenthood: Children are associated with more joy than misery](#). *Psychological Science*, 24, 10.



Professor

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[Personal website](#)

- Lyubomirsky, S., & Layous, K. (2013). [How do simple positive activities increase well-being?](#) *Current Directions in Psychological Science*, 22, 57-62.
- Layous, K., Nelson, S. K., Oberle, E., Schonert-Reichl, K., & Lyubomirsky, S. (2012). [Kindness counts: Prompting prosocial behavior in preadolescents boosts peer acceptance and well-being](#). *PLOS ONE*, 7, e51380.

[factors against mental health conditions](#). *Journal of Abnormal Psychology*.

- Lyubomirsky, S., Dickerhoof, R., Boehm, J. K., & Sheldon, K. M. (2011). [Becoming happier takes both a will and a proper way: An experimental longitudinal intervention to boost well-being](#). *Emotion*, 11, 391-402.

How can we increase eudaimonic well-being?

Attentional path to Eudaimonia: direct attention away from the self, and outward, toward others and the world around us.

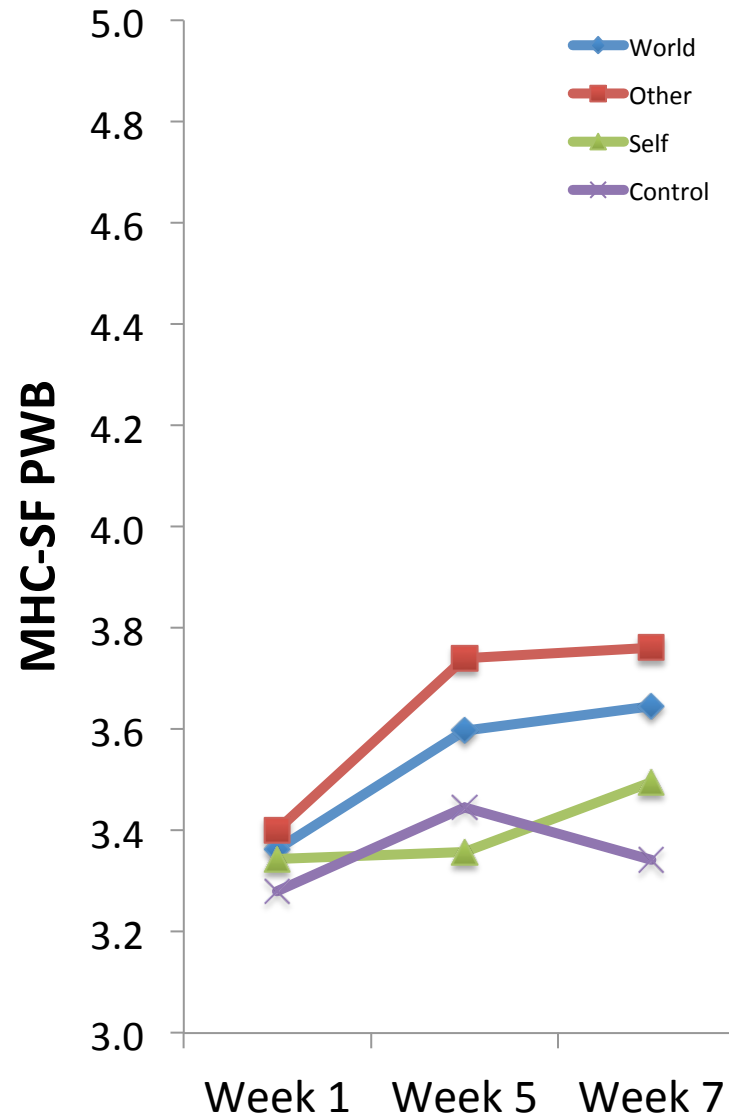
*Tomorrow, you are to perform **three nice things for others**, all three in one day.*

*Tomorrow, you are to perform **three nice things to improve the world**, all three in one day.*

*Tomorrow, you are to perform **three nice things for yourself**, all three in one day.*

*Tomorrow, as you go about your day, please **keep track of your activities**. Do not alter your routine in any way; simply keep track of what you do.*




Eudaimonic well-being





TEXT TO CONNECT


BUILD SKILLS TO CONNECT WITH THE MOST IMPORTANT PEOPLE IN YOUR LIVES.

-  Join a 2-week study: receive daily text messages and complete 2 surveys
-  Compensation rate: Earn up to \$30!
-  Study registration dates: November 14, 2014 – February 14, 2015

STUDIES SHOW:*

1 
Healthy connections can strengthen your heart and may even help you live longer.

(Holt-Lunstad, 2010; Uchino, 2006)

2 
People who feel connected are less likely to get sick, and are more likely to have stronger immune systems.

(Uchino, 2006)

3 
People who feel connected are more likely to be happier, less stressed, and express more meaning in their lives.

(Kraus, 2007; Thoits, 1995)

* Participation in "Text to Connect" does not guarantee these outcomes.



ARE YOU UP FOR IT?

To sign up, please enter the following information:

Age: Primary Language: Country of Residence: Mobile Number:

SIGN ME UP! ▶

Your data will be kept anonymous and we will not sell your information to any outside parties.

[Click here](#) to learn more about our privacy policy.
[Learn more about this project here.](#)





TEXT TO CONNECT

WHILE YOU'RE IN CONNECT WITH THE MOST IMPORTANT

- 1
- 2
- 3

1. Choose a recent deep conversation with someone close to you.
2. Think to yourself: What was important to them?
3. Write a message to them.

STUDIES SHOW

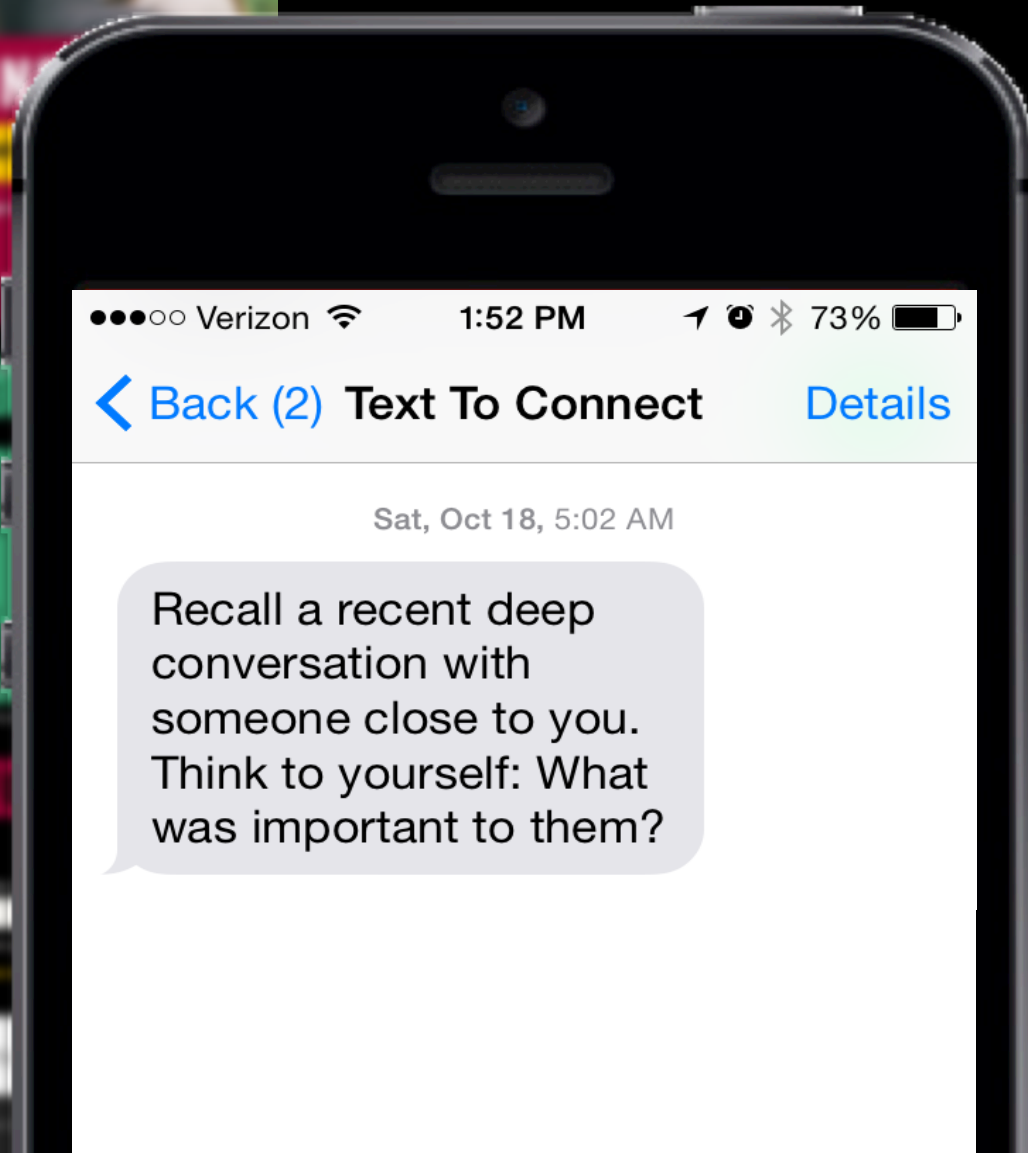
1

2

ARE YOU UP?

1. Choose a recent deep conversation with someone close to you.
2. Think to yourself: What was important to them?
3. Write a message to them.

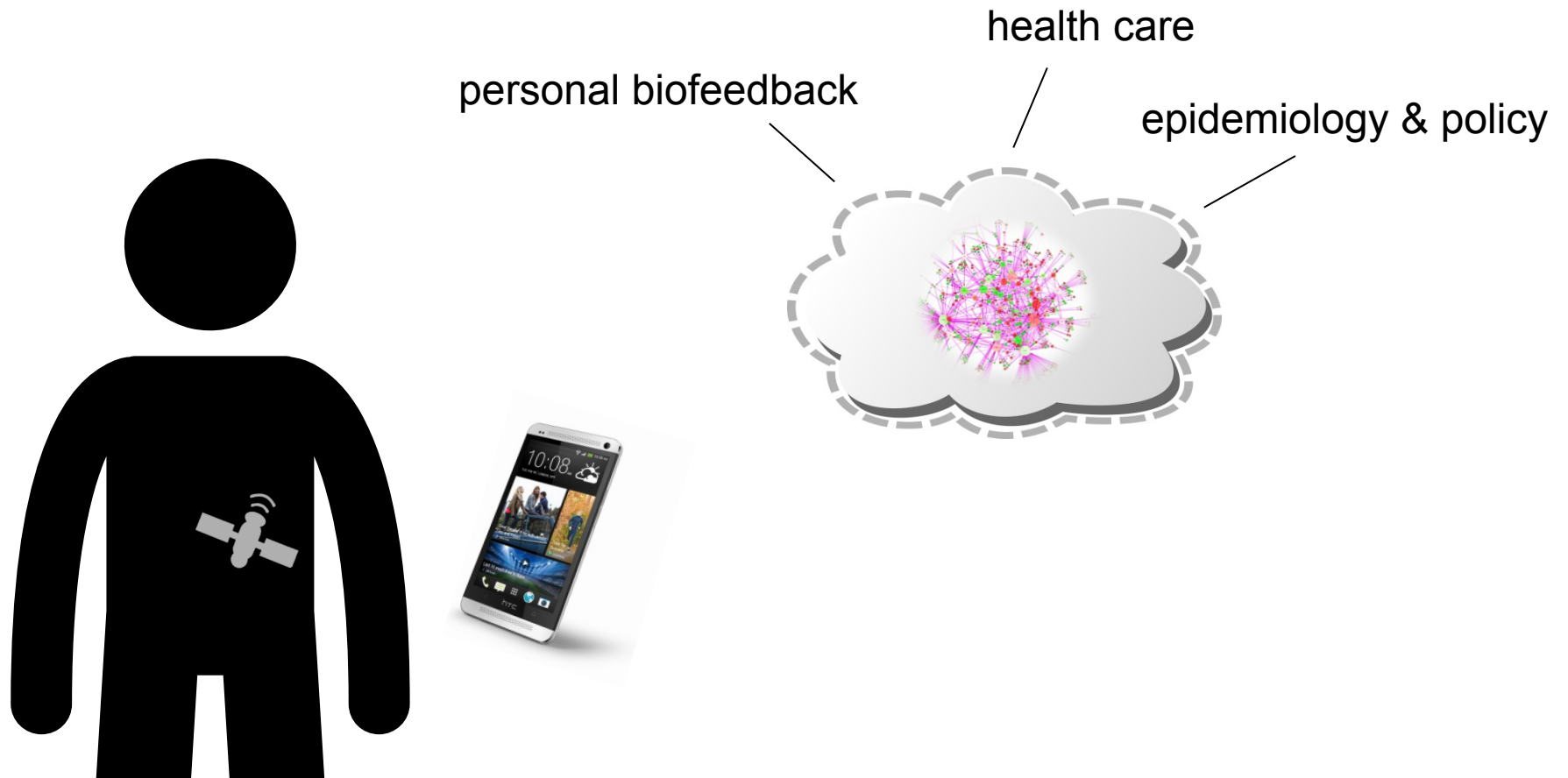
1. Choose a recent deep conversation with someone close to you.
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Attention as a key resource for resilience #2

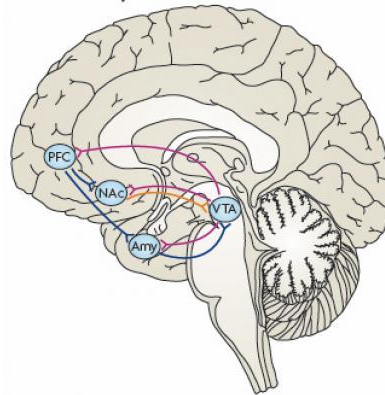
Direct attention toward others, to support empathy, compassion, connection and the good personal health that comes from eudaimonic well-being.

Molecular self-awareness

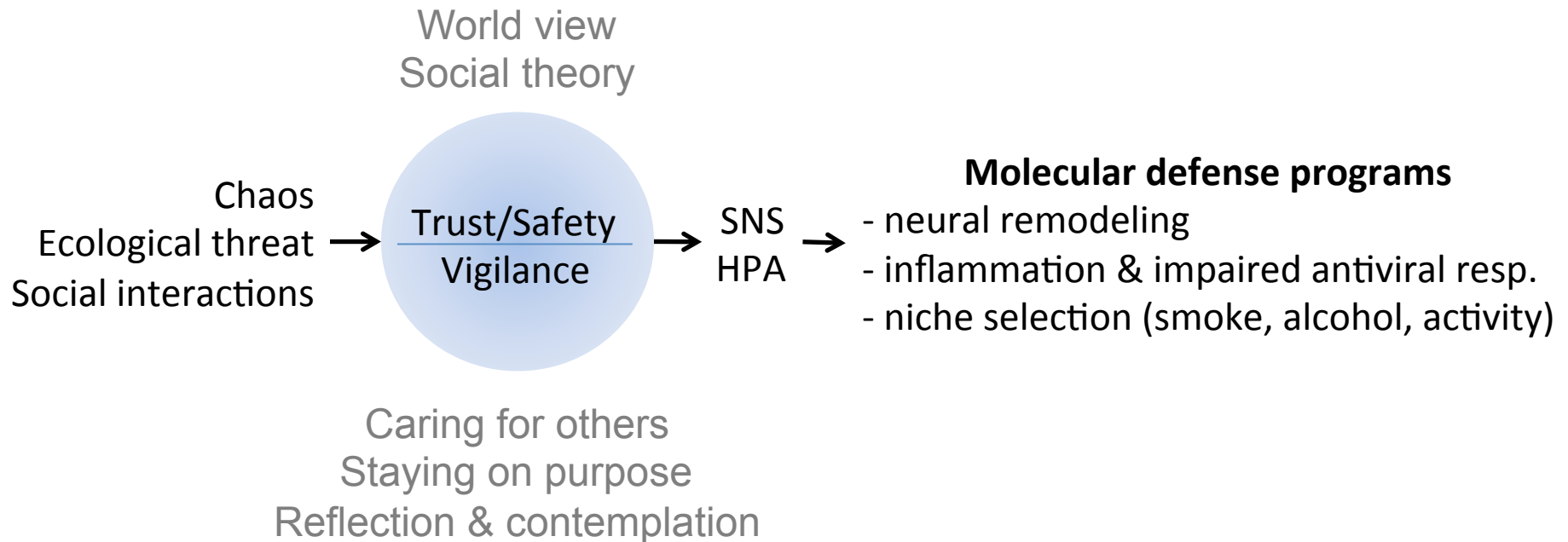




Adversity



Disease



Collaborators

John Cacioppo, Louise Hawkley, Bob Rose
Greg Miller, Edith Chen
Susan Lutgendorf, Anil Sood
John Sheridan, Nicole Powell
John Capitanio, Erica Sloan
Brian Knutson, Scott Hall
Michael Irwin, Patti Ganz, Julie Bower
Margaret Kemeny, Jerry Zack
Teresa Seeman, Andrew Fuligni
Barbara Fredrickson, Karen Grewen

Support

NCI CA116778, CA110793, CA109298
NIAID AI33259, AI36554, AI49135, AI52737
NIA AG107265, AG033590, AG34679
NIMH MH00820, MH15750
NCRR RR020645
UC Universitywide AIDS Research Program
UCLA AIDS Institute
MacArthur Foundation
James Pendleton Charitable Trust
Santa Fe Institute for Complex Systems
Norman Cousins Center

