

The Importance of Stress Adaptation for Healthy Aging: The Case of Family Caregivers

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Associate Chief of Research, Division of Geriatrics & Aging*

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I have no financial conflicts

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Learning Objectives

- Identify the impact of chronic stressors, including caregiving for a family member with dementia, on accelerated aging (*immune aging, cognitive aging*).

Chronic Stressors

Stressors that are ***demanding, distressing, and ongoing*** (e.g., 6 months or more).

Epel et al., 2018, *Frontiers in Neuroendocrinology*.

Learning Objectives

- Identify the impact of chronic stressors, including caregiving for a family member with dementia, on accelerated aging (*immune aging, cognitive aging*).
- Describe biopsychosocial underpinnings of stress adaptation and resilience being tested in clinical trials.
- Apply evidence-based interventions to promoting informal and formal caregivers' stress resilience and well-being.

CAREGIVING in the U.S. 2020

More Americans caring for someone with Alzheimer's disease or dementia.



More family caregivers report their own health is fair to poor.



23% OF AMERICANS SAY CAREGIVING HAS MADE THEIR HEALTH WORSE.

National Alliance on Caregiving in collaboration with AARP, 2020 Report)

Differences Between Caregivers and Noncaregivers in Psychological Health and Physical Health: A Meta-Analysis

Martin Piquart
Friedrich Schiller University

Silvia Sörensen
University of Rochester

Compared to noncaregivers, dementia caregivers experience:

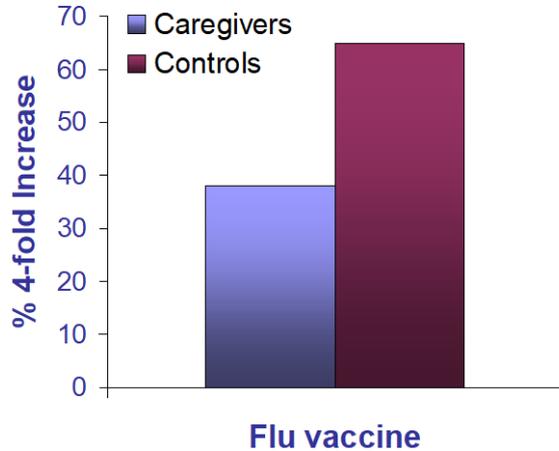
- More perceived stress
- More depression
- Worse subjective well-being
- Worse physical health

Caregiving and Accelerated Aging

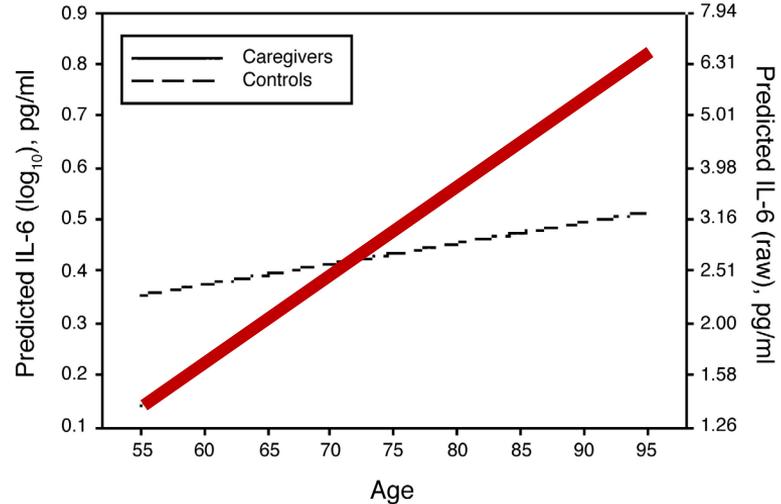
Caregivers of a family member with dementia experience **accelerated immune system aging**



Family Caregivers and Immune Aging



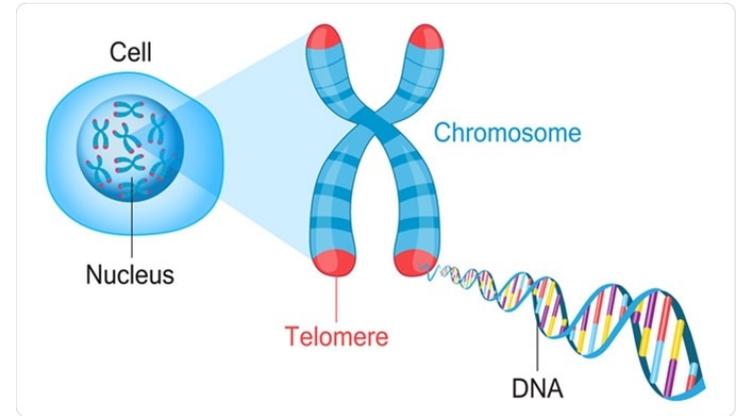
Kiecolt-Glaser et al. (1996). *Proc Natl Acad Sci*



Kiecolt-Glaser et al. (2003) *Proc. Natl. Acad. Sci.*

Caregiving and Cellular Aging - Telomeres

- Caps on the end of our chromosomes made of repetitive sequences of non-coding DNA that protect the chromosome from damage.
- Each time a cell divides, the telomeres become shorter, until the cell can no longer divide.
- The shortening of telomeres is directly linked to the aging of living organisms.
- Telomere shortening can also cause other health complications → cardiovascular and neurological conditions.

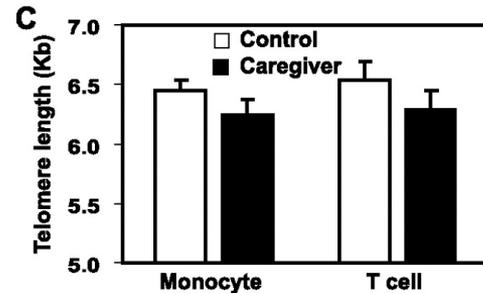
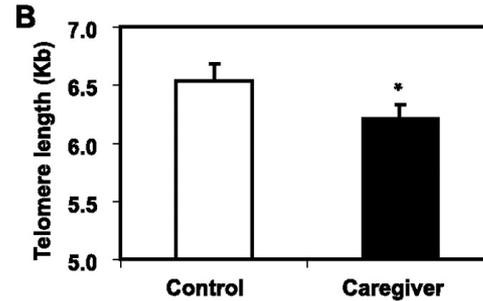


Caregiving is Associated with Cellular Aging - Telomeres

B. Caregivers have shorter telomere length of PBMC* (lymphocytes, monocytes) than controls.

C. Caregivers have shorter T cell and monocyte telomere length than controls

*PBMC = peripheral blood mononuclear cell



Damjanovic et al., 2007, *J Immunol*

Caregiving and Aging-Related T-Cell Profiles

- T cells are responsible for adaptive immunity
 - Naïve T cell – no experience yet with antigen
 - Effector memory T cell – response upon re-exposure to specific antigen
- With normal aging, there is a progressive shift in T cell populations – declines in naïve T cells, increases in effector memory T cells

Caregivers: Mothers of a Child with Autism Spectrum Disorder

Differences in T-cell Composition between Caregivers and Noncaregivers

	Caregivers (High stress)	Controls (Low stress)	F-value	p-value	Effect size ^a
<i>Adjusted for covariates</i>					
CD4+ cells (%)					
Naïve	17.56(0.86)	19.88(0.87)	3.50	0.063	0.29
Effector memory	10.13(0.61)	7.65(0.62)	7.82	0.006	0.43
CD8+ cells (%)					
Naïve	8.49(0.74)	11.20(0.75)	6.44	0.012	0.39
Effector memory	6.20(0.48)	4.65(0.48)	5.06	0.026	0.35

Prather et al. *Brain Beh Immun*, 2019

Stress of family caregiving for persons with dementia has been shown to impact a person's immune system for **up to three years** after their caregiving ends thus increasing their chances of developing a chronic illness themselves.

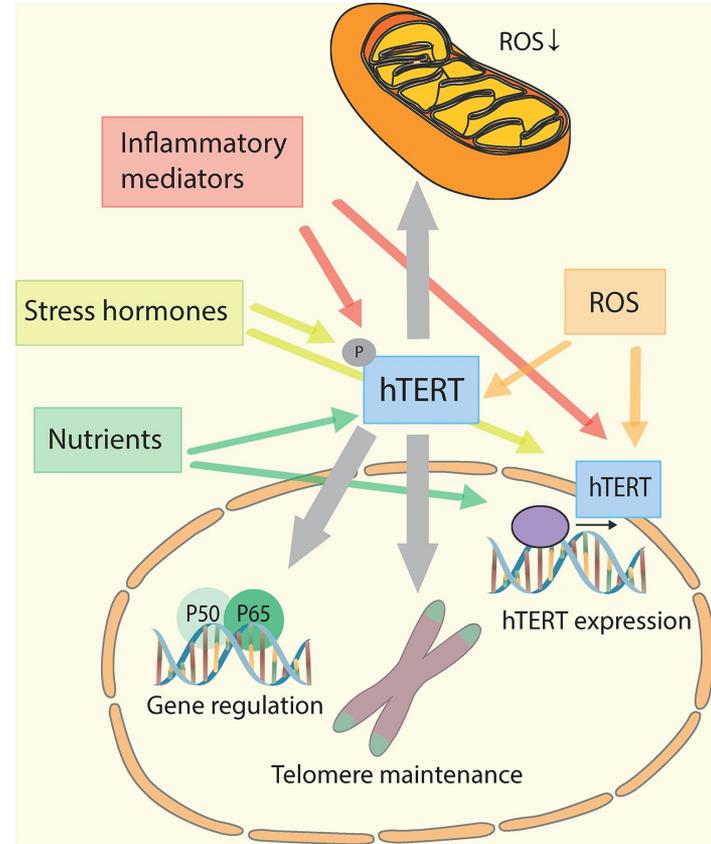
*Drs. Janice-Kiecolt Glaser and Ronald Glaser,
"Chronic stress and age-related increases in the proinflammatory cytokine
IL-6." Proceedings of the National Academy of Sciences, June 30, 2003.*

Candidate Pathways

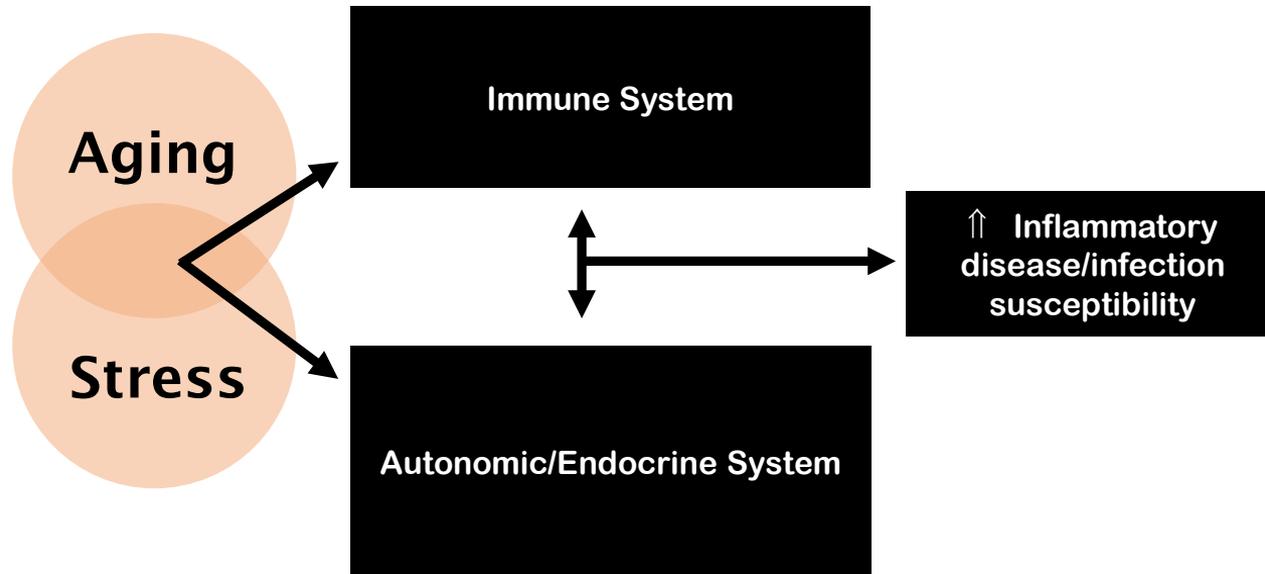
Stress hormones, inflammation in response to chronic stress leads to “aged” immune cell profiles:

- Poor antibody response to vaccine
- Shorter telomeres
- Low numbers of naïve T cells and accumulations of effector memory cells

Immune cell exhaustion



Vulnerability in Older Adulthood



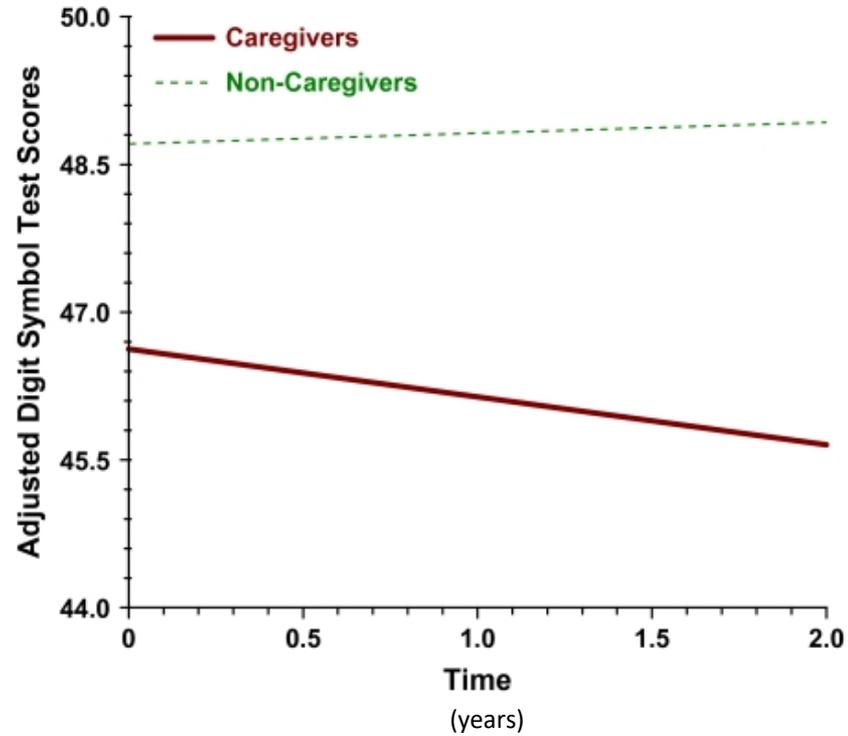
Adapted from: Heffner, K. L. (2011). Neuroendocrine effects of stress on immunity in the elderly: Implications for inflammatory disease. *Immunol Allergy Clin N Am*, 31, 95–108.

Caregiving and Accelerated Aging

Caregivers of a family member with dementia experience **accelerated cognitive aging**

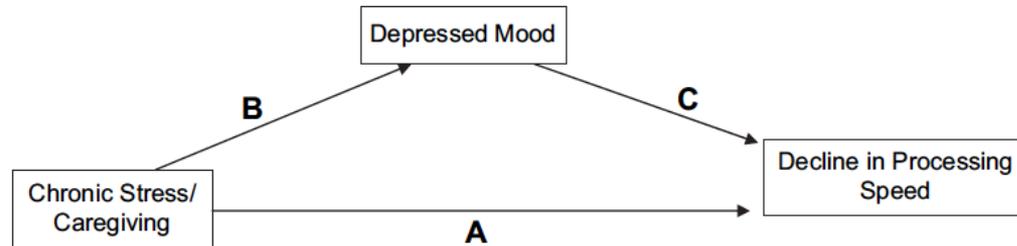


Measure of
processing speed



Vitaliano et al, 2009, The Gerontologist

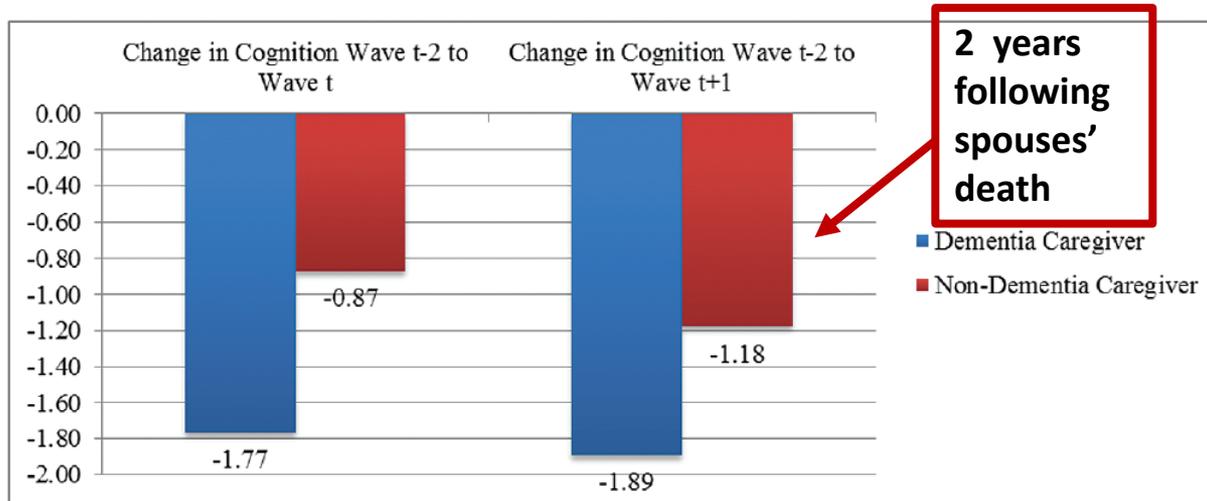
Depressed Mood Mediates Decline in Cognitive Processing Speed in Caregivers



Vitaliano et al, 2009, The Gerontologist

Does Caring for a Spouse With Dementia Accelerate Cognitive Decline? Findings From the Health and Retirement Study

Kara Bottiggi Dassel, PhD,^{*.1} Dawn C. Carr, PhD,² and Peter Vitaliano, PhD³



The Gerontologist, 2017

Neuropsychological Impact of Informal Caregiving

- “...most of the cross-sectional studies reviewed [n=38]...concluded that informal caregivers reported a **generalized cognitive deterioration**, especially memory dysfunctions (i.e. learning verbal, visuospatial, and digit information).
- ...presented **low selective attention, inhibition, and slow processing speed**.
- Longitudinal studies confirmed that caregivers whose care situation was more prolonged showed a **marked deterioration in their overall cognitive state, memory, processing speed, and vocabulary richness.**”

Romero-Martínez, 2020, *Aging & Mental Health*

Caregiving and Accelerated Aging

How can we slow this accelerated aging in stressed caregivers?



How Can We Build Stress Resilience?

The ability or capacity to adapt well or “successfully” in the face of adverse circumstances

Adaptive capacity...

The ability to respond flexibly and adaptively to environmental stressors

...is increasingly recognized as a critical contributor to healthy aging.



How Can We Build Stress Resilience?

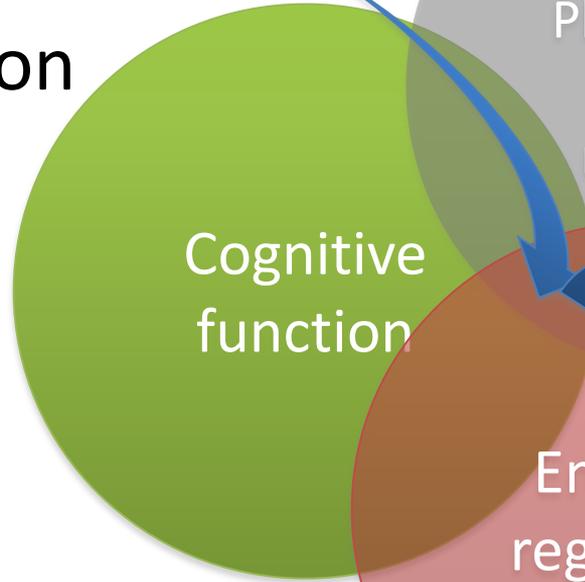
Our Central Hypothesis

Strengthening cognitive function in older caregivers will strengthen overall capacity to adapt to stressors, thereby reducing the impact of caregiving on immune aging.

Rationale: Why Target Cognitive Function for Immune Health?

- Aging-related deficits in cognitive function are linked to poor physiological and emotion regulation → poor stress adaptation & health risks
 - Strength and Vulnerability Integration Model (SAVI) (Charles, 2010)
- Cognitive function, stress physiology, and emotion are regulated by shared neural pathways
 - Cognitive Control Model (Mather & Carstensen, 2005)
 - The Aging-Brain Model (Cacioppo et al., 2011)
 - Neurovisceral Integration Model (Thayer & Lane, 2009)

Cognitive
Intervention

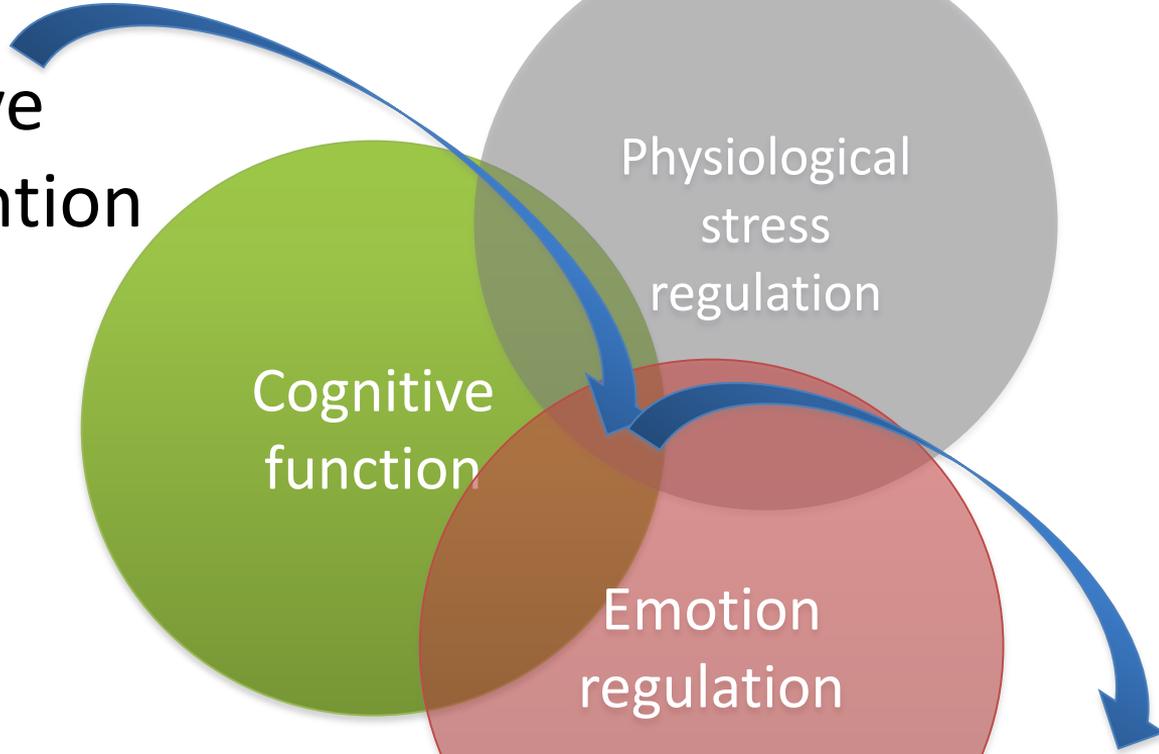


Physiological
stress
regulation

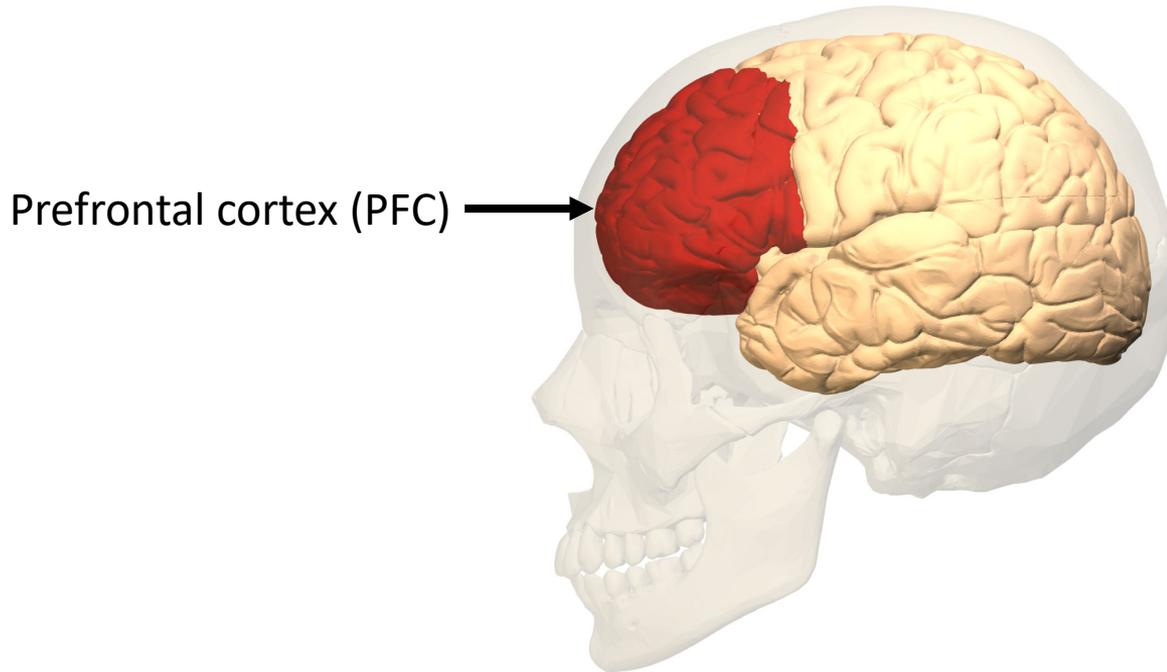
Cognitive
function

Emotion
regulation

Immune
Aging

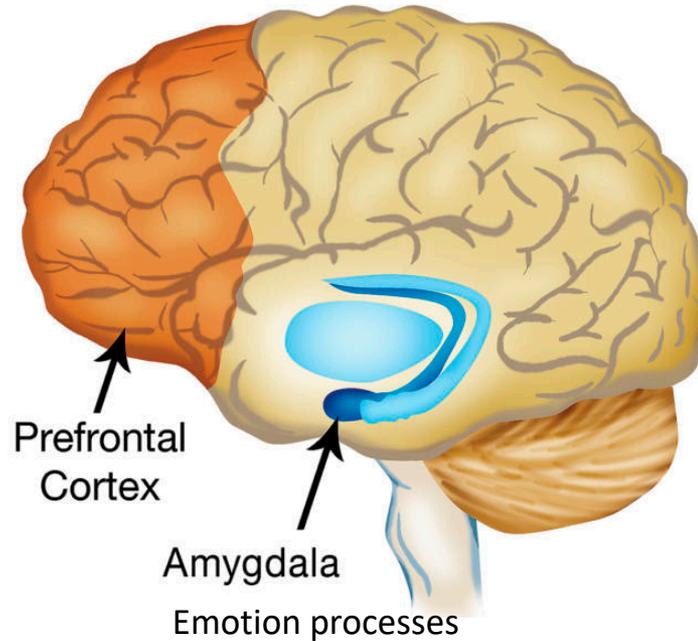


Cognition, Emotion, & Stress Physiology: Neural & Functional Connections



A “hub” for cognitive, emotion, and physiological regulation

Cognitive-Emotion Regulation Links: Frontal Connectivity to Amygdala



The PFC regulates the amygdala
- Cognitive control of emotion

The cognitive control of emotion

Kevin N. Ochsner¹ and James J. Gross²

¹Department of Psychology, Columbia University, Schermerhorn Hall, 1190 Amsterdam Avenue, New York, NY 10027, USA

²Department of Psychology, Stanford University, Building 420, Stanford, CA 94305-2130, USA

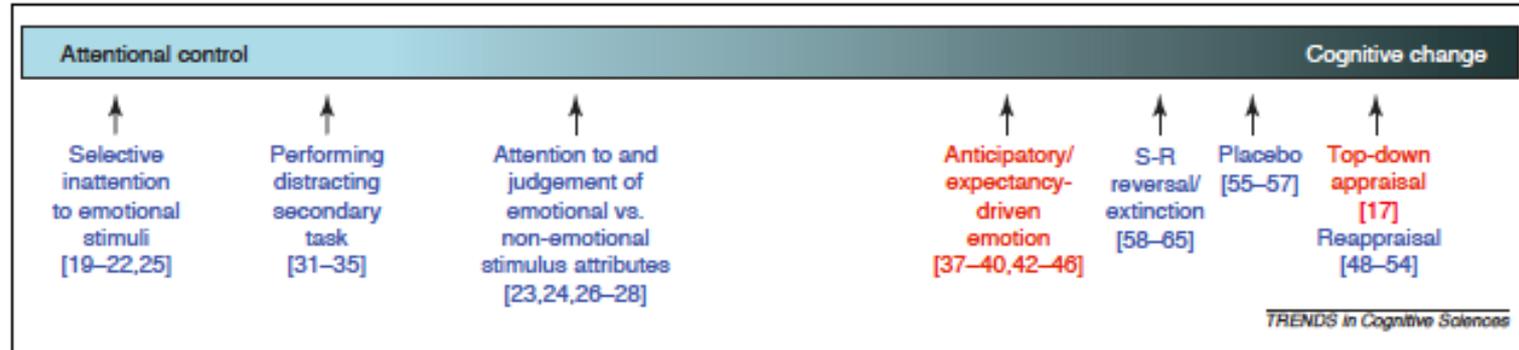


Figure 1. Hypothetical continuum illustrating relationships among the forms of cognitive control of emotion described in this review. The left and right anchors for the continuum represent the exclusive use of attentional control or cognitive change, respectively, to modulate emotion perception and/or responses. Red and blue text denote strategies for controlled emotion generation and regulation, respectively. Relevant citations for each strategy are shown in brackets. This continuum is intended to serve a heuristic function, helping the reader to visualize relationships among control strategies (see text).

PFC and Emotion Regulation: Frontal-amygdala connectivity & anxiety symptoms

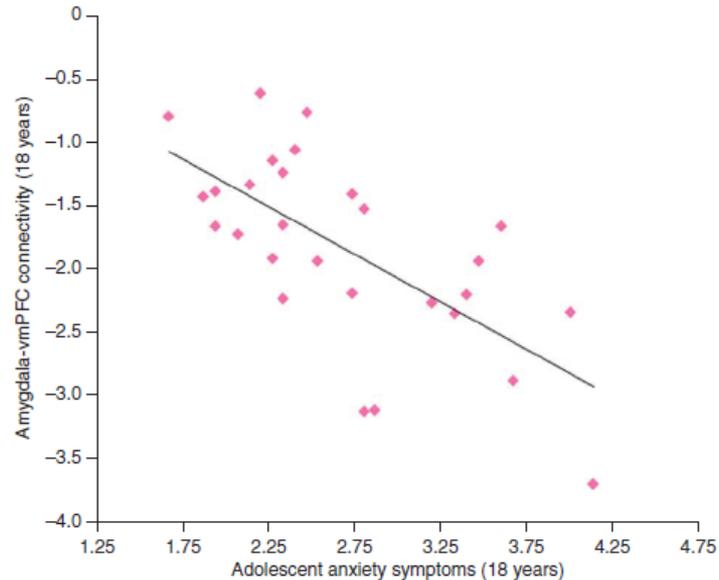


Figure 4 Partial correlation between resting-state left amygdala-vmPFC rs-FC and concurrent self-reported anxiety symptoms in adolescent females, controlling for concurrent symptoms of depression and externalizing behaviors ($R^2 = 0.31$, $P = 0.004$).

Burghy, C., Stodola, D., Ruttle, P. et al., *Neuroscience*, 2012

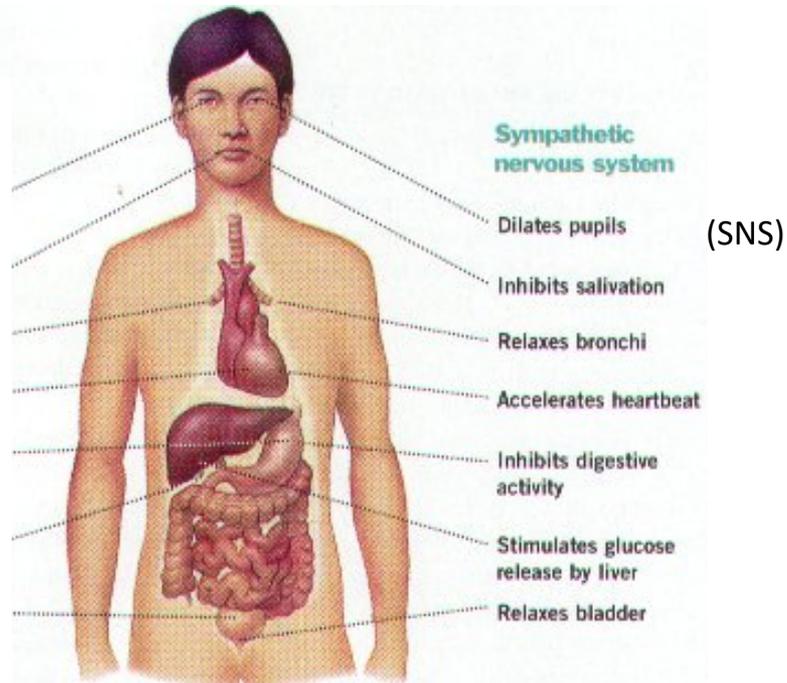
Ageing Effects on PFC

- One of the first regions to show aging-related declines
- Declining cognitive capacities supported by PFC (attentional control, processing speed, executive function) can reduce emotion regulation capacity (Mather & Carstensen, 2005)
- Suggests targeting cognitive function to improve emotion regulation.

Cognitive-Physiological Regulation Links

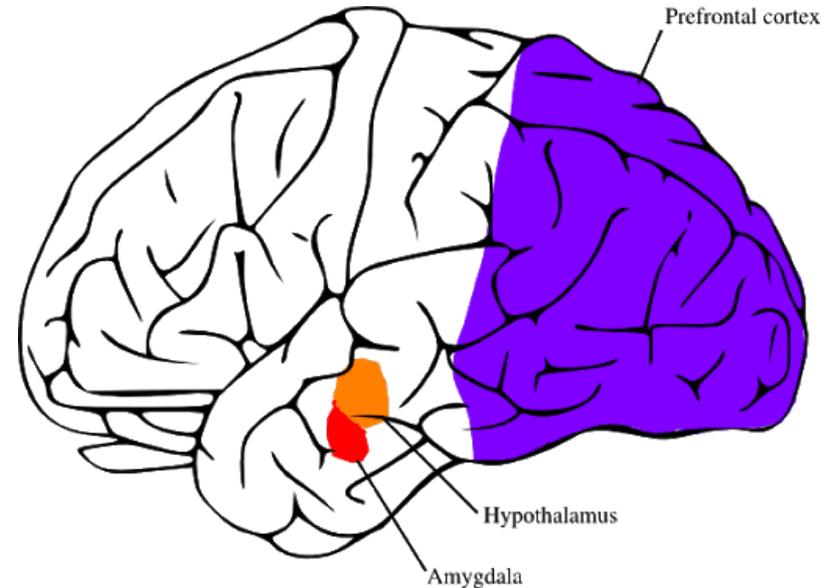
- Neurovisceral Integration Model (Thayer, et al., 2000)
 - Prefrontal cortex serves as a “hub” for regulation of cognition but also for autonomic regulation
 - Capacity for adaptation – responding flexibly to the environment -- is dependent upon the integrity of the PFC and its neural connectivity to the brain structures that regulate autonomic nervous system (ANS)
 - Hypothalamus is the source of ANS activation

The Stress Response: Autonomic (ANS)



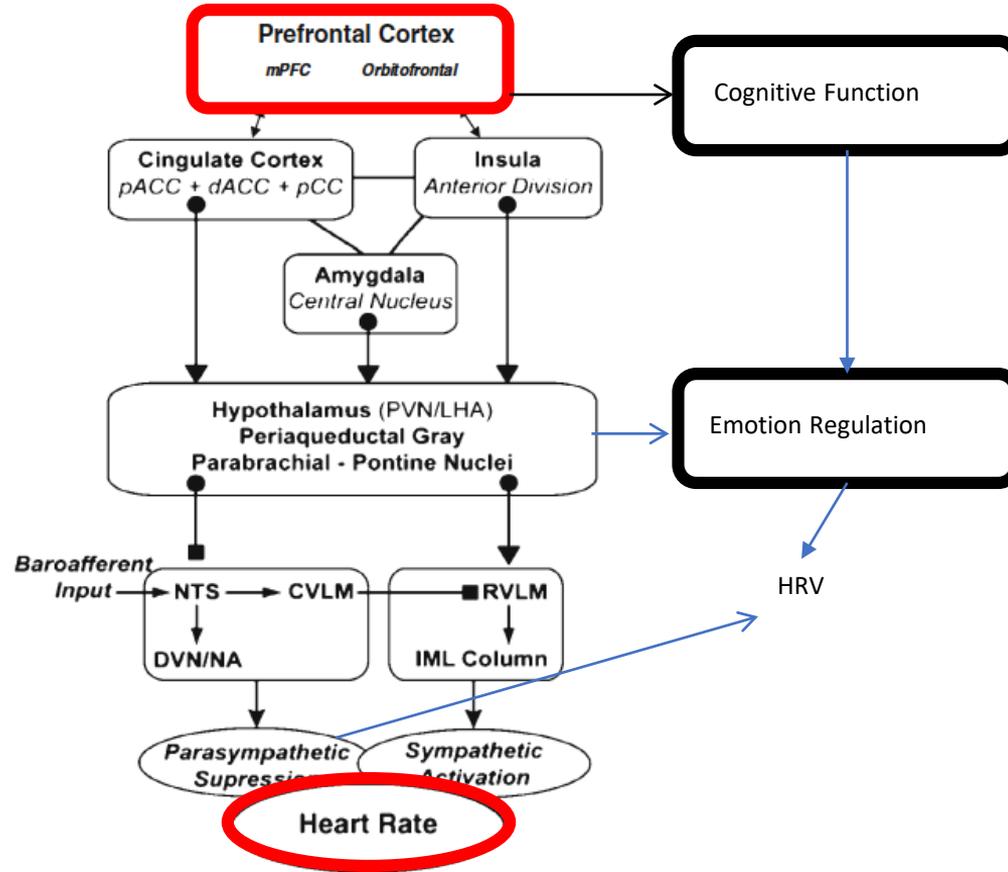
“Fight or flight”

PNS is responsible for flexible responding to environmental changes, ...which helps regulate changes in heart rate (measured as heart rate variability) to meet metabolic demands of the situation



Compromise of PFC structure and function will necessarily impact emotion regulation and ANS function.

Capacity for adaptation, including physiological, cognitive and emotion regulation capacity, is reflected in HRV



Thayer et al, 2009, Ann Beh Med

Adaptive Capacity: Building Blocks

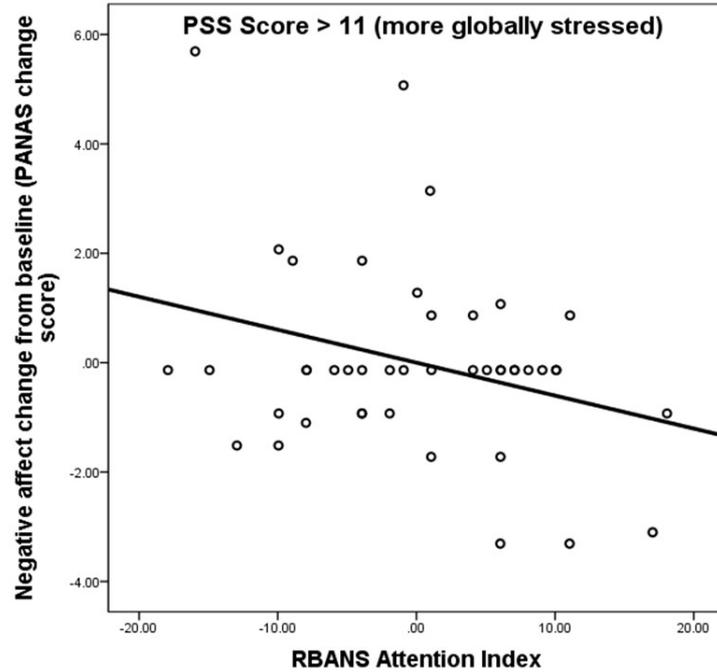
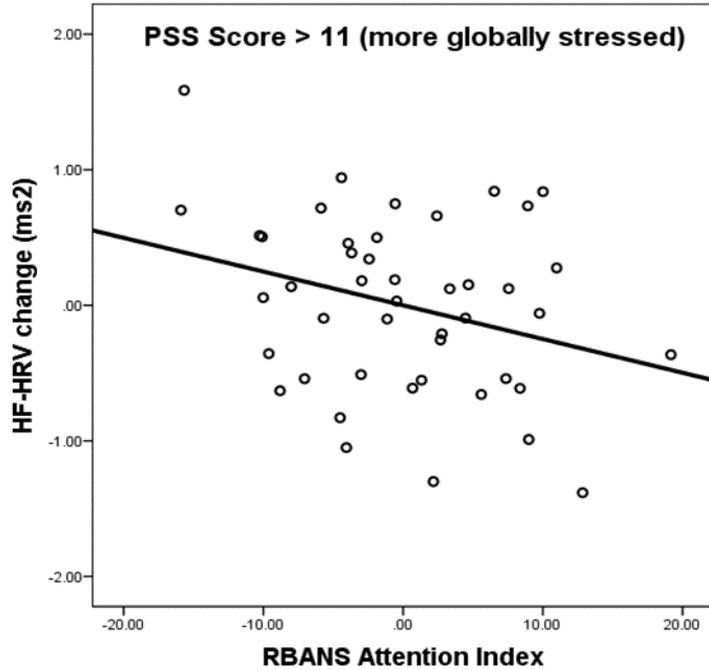
- Cognitive Function
- Emotion Regulation
- Physiological stress system regulation

Adaptive Capacity: Mechanisms & Intervention Targets

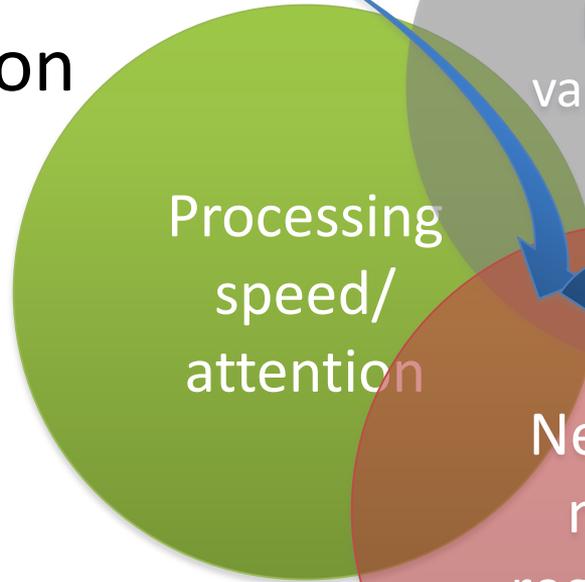
- Cognitive Function
 - Fluid cognitive ability (attention, processing speed)
- Physiological stress system regulation
 - HRV
- Emotion Regulation
 - Less negative affect response to stressors
 - Less depressive and anxiety symptoms



Preliminary Support



Cognitive
Intervention



Heart rate
variability (HF-
HRV)

Processing
speed/
attention

Negative
mood
regulation

**“Younger” T-cell
profiles, less
inflammation**

Cognitive Training → Depressive Symptoms

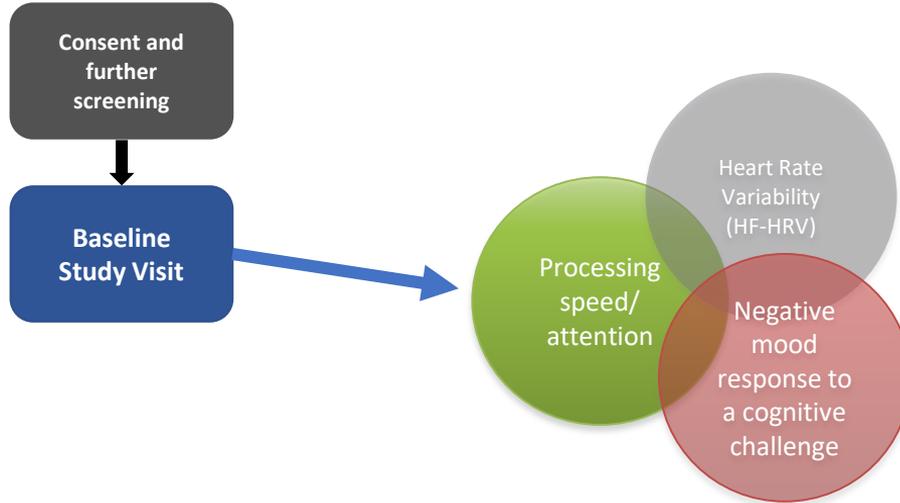
- Advanced Cognitive Training for Independent and Vital Elderly (ACTIVE) Trial
- Speed of processing training was associated with reduced depressive symptoms in depressed older adults over time...
- Reduced incidence of depression in non-depressed older adults
(Wolinsky et al., 2009a; 2009b)

The Current Trial

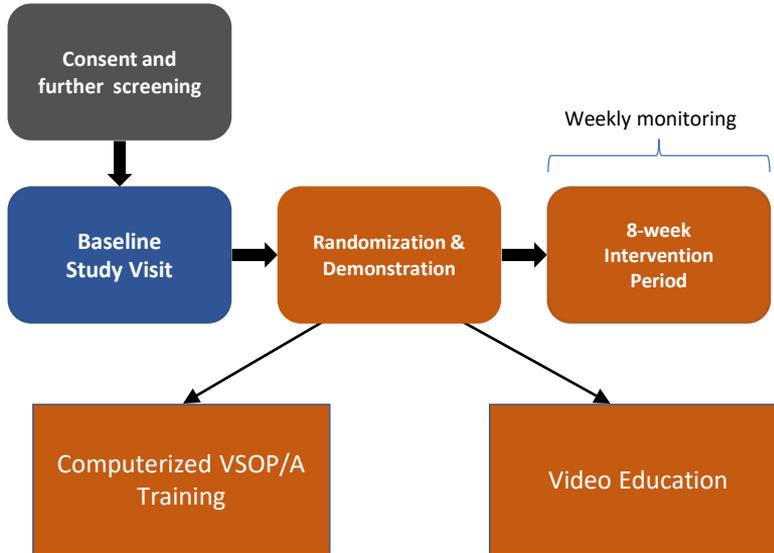
- Stressed and burdened adults, 55-85 years of age, caring for a family member with Alzheimer's Disease (AD) or AD-related dementia
 - No evidence of major depression at enrollment
 - No major immune-related or cardiovascular diseases

(R01AG049764; Heffner, PI)

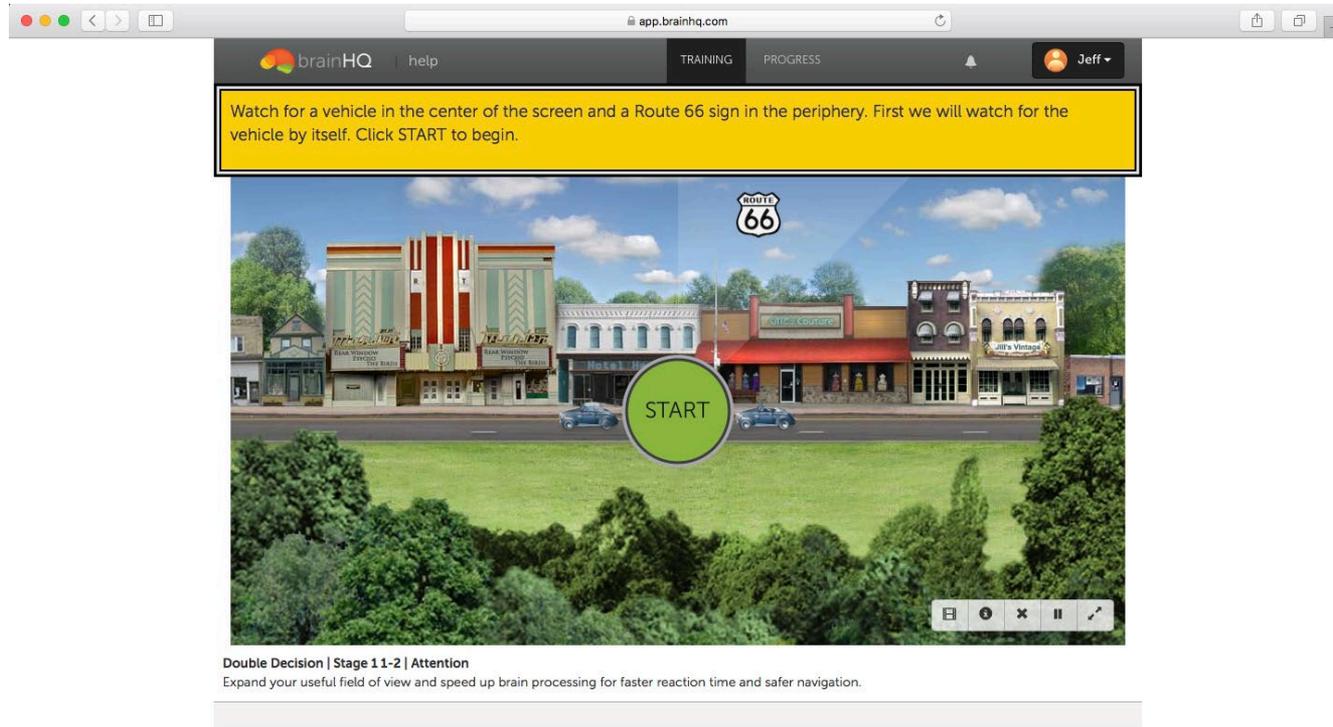
Enrollment Period Timeline



Enrollment Period Timeline



Brain Training: Computerized Cognitive Training



The screenshot shows a web browser window with the URL `app.brainhq.com`. The page header includes the brainHQ logo, a help link, and navigation tabs for TRAINING and PROGRESS. A user profile for 'Jeff' is visible in the top right. A yellow instruction box reads: "Watch for a vehicle in the center of the screen and a Route 66 sign in the periphery. First we will watch for the vehicle by itself. Click START to begin." The main visual is a 3D-rendered street scene with a Route 66 sign in the upper right. A green circular button with the word "START" is overlaid on the road. A video player interface is at the bottom right of the scene.

brainHQ | help TRAINING PROGRESS Jeff

Watch for a vehicle in the center of the screen and a Route 66 sign in the periphery. First we will watch for the vehicle by itself. Click START to begin.

START

Double Decision | Stage 11-2 | Attention
Expand your useful field of view and speed up brain processing for faster reaction time and safer navigation.

Brain Training: Video Education

<https://research.son.rochester.edu/braintraining/>

Brain Training to Promote Health in Spousal Dementia Caregivers

Self-Guided Video Education

Arts

- A Reason to Dance (0:56:46)
- August Wilson: The Ground on Which I Stand (1:24:40)
- Guy Kemper: Painting with Glass (0:56:30)
- Icons Among Us: Jazz in the Present Tense (1:27:16)
- Janis Joplin: Little Girl Blue (1:42:36)
- Let This Be A Lesson: Heroes, Heroines, and Narrative in Paintings at Yale (12 videos)
- Paint with Kevin (24 videos)
- Painting with Wilson Bickford (13 videos)
- Roman Architecture (23 videos)
- Shakespeare Uncovered: A Midsummer Night's Dream with Hugh Bonneville (0:53:04)
- Shakespeare Uncovered: Antony and Cleopatra with Kim Cattrall (0:53:05)
- Shakespeare Uncovered: King Lear with Christopher Plummer (0:53:04)
- Shakespeare Uncovered: Othello with David Harewood (0:53:05)
- Shakespeare Uncovered: Romeo and Juliet with Joseph Fiennes (0:53:05)
- Shakespeare Uncovered: The Taming of the Shrew with Morgan Freeman (0:53:04)

Cooking

- American High Tech Barbecue Cooking (0:43:27)
- Bringing It Home With Laura McInroth (13 videos)
- Cooking on the Wildside (24 videos)
- Cooking with Chef David McCampbell (0:58:35)
- Cooking with Julie Tebouille (15 videos)
- Fit to Eat (35 videos)
- Gourmet Cooking with Earl Peyroux (27 videos)
- Kevin Dundon's Modern Irish Food (17 videos)
- Mike Colameco's Real Food (21 videos)

Culture

- GPB Originals (0:57:50)
- Treasures of New York (0:56:20)
- University Place (0:47:54)
- WPT Documentaries (2 videos)

Economics

- Financial Theory (26 videos)

Gardening

- Alan Titchmarsh's Garden Secrets (3 videos)
- Ask an Expert: Gardening (0:57:58)
- Ask an Expert: Gardening and Landscaping (0:57:17)
- Gardening Documentary Series (5 videos)
- Miniature Gardening: Proper Lawn Care (0:56:51)

Brain Training: Video Education

Brain Training Topics Search for videos Submit Welcome back, Kathi Heffner Log-out

All Categories

Nature - Wild Alaska - Wild Alaska

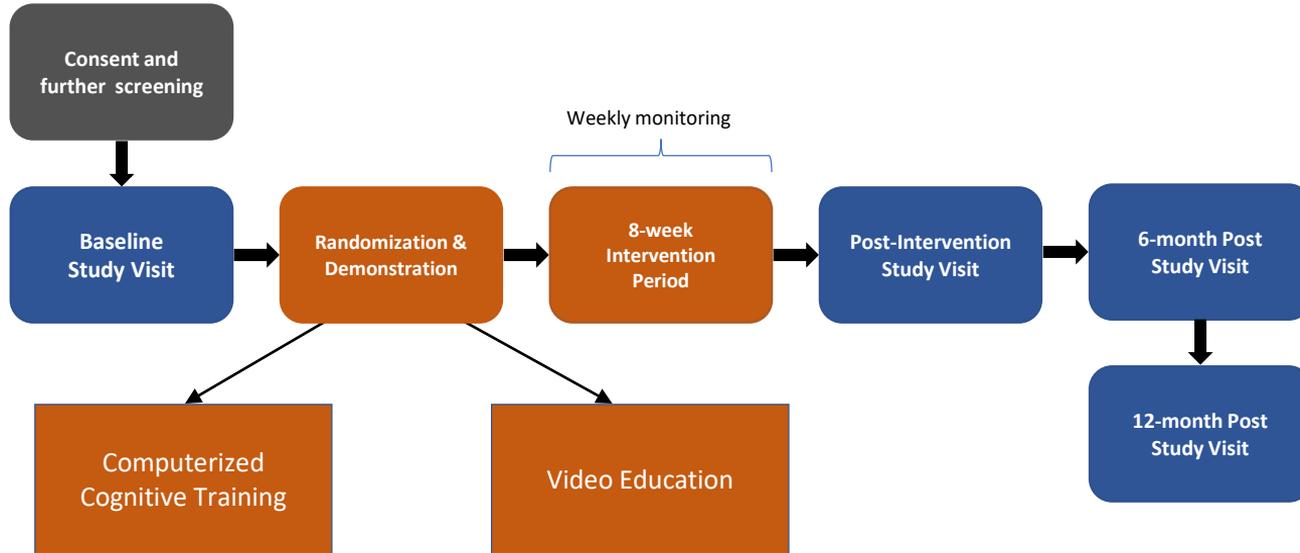


Alaska is a U.S. state situated in the northwest extremity of the North American continent. Bordering the state to the east are the Canadian territory of Yukon and the Canadian province of British Columbia; to the north are the Chukchi and Beaufort Seas, southern parts of the Arctic Ocean. To the west and south is the Pacific Ocean, with Russia (specifically, Chukotka Autonomous Okrug and Kamchatka Krai) farther west across the Bering Strait. Alaska is the largest state in the United States by area, the 3rd least populous and the least densely populated of the 50 United States. Approximately half of Alaska's residents (estimated at 738,432 by the Census Bureau in 2015) live within the Anchorage metropolitan area. Alaska's economy is dominated by the oil, natural gas, and fishing industries, resources which it has in abundance. Tourism and military bases are also a significant part of the economy. Although it had been occupied for over ten thousand years by indigenous peoples, from the 18th century onward, European powers considered the territory of Alaska ripe for exploitation and trade. The United States purchased Alaska from the Russian Empire on March 30, 1867, for 7.2 million U.S. dollars at approximately two cents per acre (\$4.74/km²). The area went through several administrative changes before becoming organized as a territory on May 11, 1912. It was admitted as the 49th state of the U.S. on January 3, 1959.

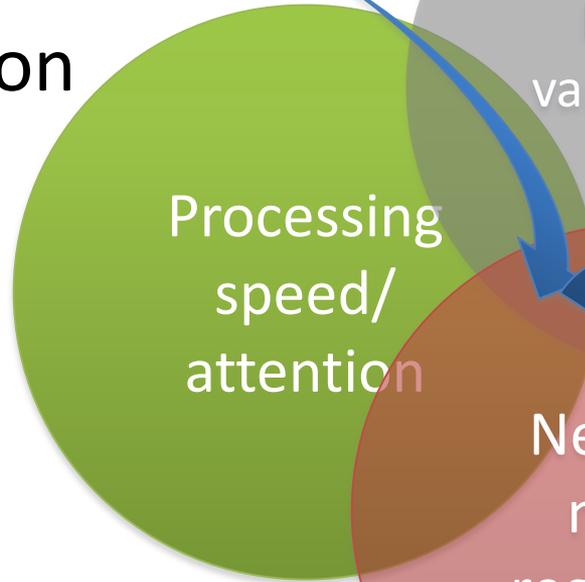
Restart Video Go back 60 seconds

Previous in Series Next in Series

Enrollment Period Timeline



Cognitive
Intervention



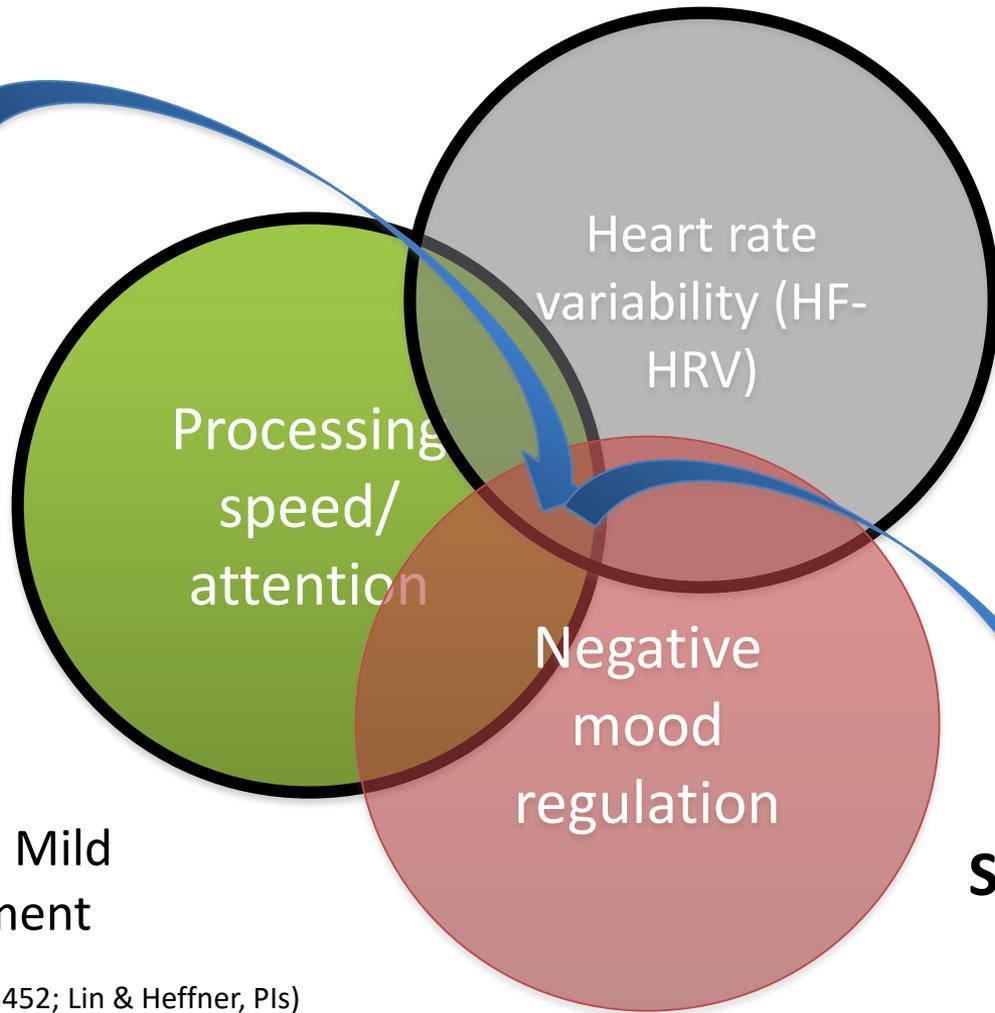
Processing
speed/
attention

Heart rate
variability (HF-
HRV)

Negative
mood
regulation

**“Younger” T-cell
profiles, less
inflammation**

Cognitive
Intervention
+
HRV
intervention

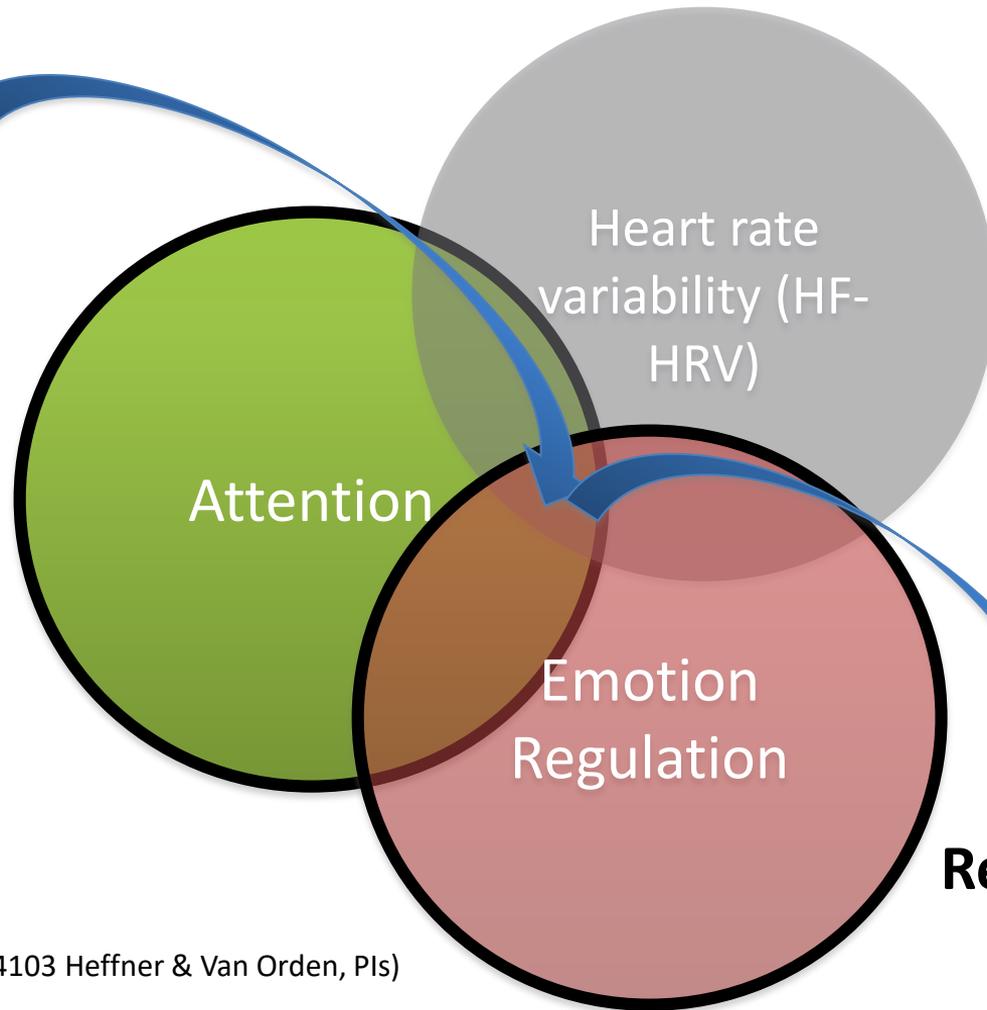


Older Adults with Mild
Cognitive Impairment

**Slower cognitive
decline**

NINR-funded RCT (R01NR015452; Lin & Heffner, PIs)

Mindfulness
Intervention
(Gallegos, PI)



Heart rate
variability (HF-
HRV)

Attention

Emotion
Regulation

Reduce Loneliness

Lonely Caregivers

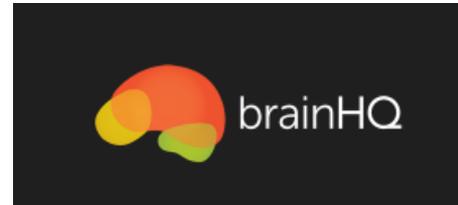
NIA-funded Center (P30 AG064103 Heffner & Van Orden, PIs)

Key Takeaways so far...

- Stress adaptation is a key contributor to healthy aging
- Basic human neuroscience research → behavioral interventions that can more directly target the mechanisms of successful stress adaptation
- These trials are intended to advance evidence-based approaches that effectively increase the healthspan of caregivers (REACH II)
- Evidence-based, self-care tools for promoting adaptation and emotional well-being

Visual Speed of Processing Training

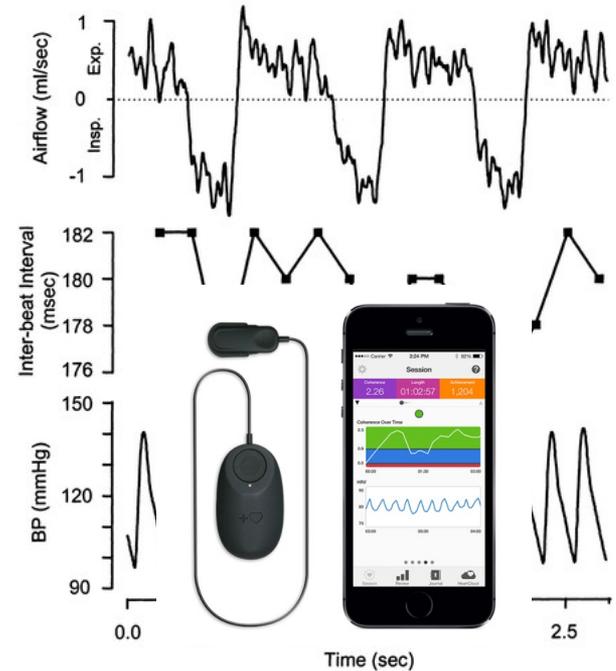
- Highly effective for improving speed of processing and attention
- <https://www.brainhq.com/> *



**I declare no conflict of interest or commercial interests*

Heart Rate Variability Biofeedback

- Guided, paced breathing at “resonance frequency”
- Evidence supports effects on HRV, depressive and anxiety symptoms
- <https://www.heartmath.com/> *



**I declare no conflict of interest or commercial interests*

Mobile Mindfulness Training

- Exercises to train attention and non-judgment and acceptance of emotional experience
- <https://headspace.com/> *

**I declare no conflict of interest or commercial interests*

Thank you: Funder, Collaborators, & Doers

- Hugh Crean, PhD
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- Carol Podgorski, PhD
- Maria Quiñones, PhD
- Silvia Sörensen, PhD
- Mia Weber, PhD
- Kimberly Van Orden, PhD
- National Institute on Aging (NIA)
- National Institute of Nursing Research (NINR)
- Kelly Bellenger-Fedele, MS
- Elizabeth Gajary-Coots, RN
- Dina Johnson
- Kate Kondolf
- Jamil Lane
- Jeff Swan, MS
- Matthew Tansey, MS
- Christopher Lane
- SON Biomolecular Lab (Groth)
- URMC Clinical Trials Processing Lab
- Alzheimer's Association
- Lifespan
- UR Home Medicine

Key Takeaways

- Stress adaptation is a key contributor to healthy aging
- Basic human neuroscience research → behavioral interventions that can more directly target the mechanisms of successful stress adaptation and resilience
- These trials are intended to advance evidence-based approaches that effectively increase the healthspan of caregivers (REACH II)
- Evidence-based, self-care tools for promoting adaptation and emotional well-being