Earlier Life Influences on Cognitive Function in Aging:

Findings from the Vietnam Era Twin Study of Aging

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Introduction

- Stress has long-term influences on cognition and the brain.

- Management of and adaptation to stress may contribute to cognitive resilience.
Goals of the VETSA Projects

- Examine factors related to cognitive and brain aging and trajectories of change.
  - Cognition
  - Health-related
  - Stress and disadvantage
  - Genes (twin data; GWAS)

- Early identification of risk for mild cognitive impairment (MCI) and Alzheimer’s disease (AD).

- Brain aging: Multi-modal neuroimaging.

- VETSA is well-positioned to accomplish these goals:
  - Baseline when participants were only in their 50s.
  - Large sample with a narrow age range.
  - Data available from earlier periods (e.g., age 20).
- **VETSA Wave 1**
  - Age 56 (51-60)

- **VETSA Wave 2**
  - Age 62 (56-66; 1016 longitudinal)

- **VETSA Wave 3 (in process)**
  - Age 67 (61-71)

- ~1484 MZ and DZ twins (VETSA 1 & 2)
- ~550 with multimodal MRIs
- ~780 with neuroendocrine data (VETSA1)

- Ages 20 38 42 56 62 67
  - Previously collected data
  - VETSA
VETSA 1

Age at military induction: 19.7 yo
Education: 13.8 yrs
Married: 78%
Ethnicity: 88% NHW
All male
**Figure 9**

Conceptual model for VETSA's approach to cognitive aging.
GENETIC VARIATION

ENVIRONMENTAL STRESSORS

CIRCADIAN RHYTHM

Sympathetic Nervous System

Pituitary Adrenal Axis (HPA)

CRH

Catecholamines

Cortisol

INCREASED PHYSIOLOGICAL RISK FACTORS (E.G., Obesity, Insulin Resistance, BP)

Hypertension

Cardiovascular Events

Depression

Cognitive Decline

Figure 1
[based on Rosmond, 2003]
Physiological Influences of Cortisol

- Metabolic Regulation:
  - Mobilize glucose in the liver
  - Increase plasma concentrations of glucose, fatty acids and amino acids
- Maintain cardiovascular responsiveness
- Maintain blood volume
- Anti-inflammatory
- Sustained response to stress
- Down-regulate sympathetic nervous system
Effects of Cortisol Dysregulation in Older Adults

Too much stress can disrupt the Hypothalamic-Pituitary-Adrenal (HPA) axis (“allostatic load”):

- Poorer health: Hypertension, Atherosclerosis
  - Impaired immune function
- Poorer mental health: Depression, PTSD
- Cognitive impairment
- Neurotoxic to brain areas with high concentrations of glucocorticoid receptors: Hippocampus, Prefrontal Cortex

McEwen & Gianaros, 2010
CHILDHOOD ADVERSITY AND LATER LIFE OUTCOMES: Isle of Wight Studies

CHILDHOOD ADVERSITY
- Father low SES
- Mother low education
- Separation from parent(s)
- Large family/overcrowding
- Maternal psychiatric problems
- Father criminal behavior

Rutter 1976; 1977

ADULT OUTCOMES
- Lower education
- Poorer physical and mental health
- Marital & occupational difficulties
- Higher levels of stress
Childhood Disadvantages

- Accumulation of multiple childhood and lifetime hardships is particularly pathogenic.

- Childhood disadvantage disrupts the Hypothalamic-Pituitary-Adrenal (HPA) axis.
  - Contributes to cognitive and brain aging
Childhood Disadvantage in VETSA Participants

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>High risk</th>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Father SES (&lt;32):</td>
<td>9 yrs education; Semi-skilled manual laborers</td>
<td>13 yrs education; Skilled, semi-professional</td>
</tr>
<tr>
<td>Mother education (&lt;12 yrs)</td>
<td>8 yrs</td>
<td>13 yrs</td>
</tr>
<tr>
<td>Family size (#kids&gt;5)</td>
<td>8 kids</td>
<td>4 kids</td>
</tr>
<tr>
<td>Separated from family as child</td>
<td>21%</td>
<td></td>
</tr>
</tbody>
</table>

![Bar chart showing the percentage of VETSA participants with different numbers of familial risks.](chart.png)

- 0 risks: 10% of the sample
- 1 Risk: 20% of the sample
- 2 Risks: 30% of the sample
- 3 Risks: 15% of the sample
- 4 Risks: 5% of the sample
Measures

General Cognitive Ability
- AFQT at age 20, 56, 62

Cognitive Functioning (specific):
- Verbal & Visual-Spatial Ability
- Verbal & Visual-Spatial Memory
- Working Memory
- Executive Functions (Switching/Interference)
- Verbal Fluency
- Abstract Reasoning
- Processing Speed

Basal Cortisol: Cortisol Area under the Curve (3 days avg AUC)
Total effect of Childhood Disadvantage:

direct \([0.08] + \) indirect \([0.04]\)  
\[\beta = 0.12 \ (95\% \ CI: \ 0.05; 0.18)\]
Standardized path estimates: Linear mixed models: adjusting for age, ethnicity, smoking, and depressive symptoms (fixed effects)
Effects on diurnal cortisol

**Familial Risk**

**AFQT Scores**

**Socioeconomic Status**

**Smoking**
Elevated Diurnal AUC Cortisol Significantly Associated with Poorer Cognitive Performance

Type III fixed effects from mixed models controlling for age, ethnicity, cognitive ability at age 20, with assay batch and family ID as random effects

Franz CE et al. (2011)
Age equivalency effects in significant cognitive domains:
Increase in AUC cortisol from 25th to 75th percentile
Are Effects of Childhood SES on Later Adult Cognition Mediated by Adult Resources and Cognitive Ability?
## Total Direct and Indirect Effects from Childhood SES to Cognitive Outcomes at Age 62

<table>
<thead>
<tr>
<th>Effect</th>
<th>Age 62 GCA</th>
<th>Abstract Reasoning</th>
<th>Episodic Memory</th>
<th>Processing Speed</th>
<th>Verbal Fluency</th>
<th>Working Memory</th>
<th>Visual-Spatial Ability</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Effect: Direct+Indirect</strong></td>
<td>0.08</td>
<td>0.17</td>
<td>0.07</td>
<td>0.09</td>
<td>0.08</td>
<td>0.08</td>
<td>0.14</td>
</tr>
<tr>
<td></td>
<td>[0.046, .129]</td>
<td>[0.112, .230]</td>
<td>[0.026, .117]</td>
<td>[0.044, .136]</td>
<td>[0.024, .137]</td>
<td>[0.036, .118]</td>
<td>[0.082, .195]</td>
</tr>
<tr>
<td><strong>Direct Effect</strong></td>
<td>0.01</td>
<td>0.07</td>
<td>0.00</td>
<td>0.03</td>
<td>0.00</td>
<td>0.02</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td>[-0.023, .046]</td>
<td>[0.020, .140]</td>
<td>[-0.040, .056]</td>
<td>[-0.017, .087]</td>
<td>[-0.054, .065]</td>
<td>[-0.016, .064]</td>
<td>[-0.005, .110]</td>
</tr>
<tr>
<td><strong>Total Indirect Effect</strong></td>
<td>0.07</td>
<td>0.09</td>
<td>0.06</td>
<td>0.06</td>
<td>0.07</td>
<td>0.06</td>
<td>0.09</td>
</tr>
<tr>
<td></td>
<td>[0.044, .103]</td>
<td>[0.051, .122]</td>
<td>[0.026, .117]</td>
<td>[0.032, .085]</td>
<td>[0.044, .099]</td>
<td>[0.032, .077]</td>
<td>[0.053, .121]</td>
</tr>
</tbody>
</table>

For 6 cognitive measures, the effect cSES on late midlife cognitive ability was completely Mediated by young adult GCA, adult SES, and CLA.

Overall, cSES influences late midlife cognition primarily through its influence on young adult GCA,
Parental Education, APOE interactions and General Cognitive Ability (GCA)

Parental Education and APOE Interactions and AUC Cortisol (Age 56)

Franz et al. in preparation
VETSA Cognitive Aging Model

Childhood/Adolescence

- Early Family Environment
- Early Cognitive Ability (age 20 AFQT)

Middle Age (and beyond)

- Health/Medical
- HPA Axis
- Life Style
- Midlife Brain Morphology

Genetic Influences

SES
Stress is neurotoxic to the brain.

High glucocorticoid receptor concentrations in both the hippocampus and prefrontal cortex (PFC)

Examined stress exposures and stress responses in relation to brain neurocircuitry
VETSA 1 MRI Methods

- 388 VETSA participants with both cortisol and structural MRI data at 56

- Structural MRI data:
  - Acquired on a 1.5 T scanner
  - Processed using Freesurfer 3.0.1

- Measures:
  - Cortical thickness in 11 prefrontal regions;
  - Hippocampal volume
Summary

- Elevated cortisol associated with:
  - Poorer cognitive performance in multiple domains—including executive functions & visual spatial memory.
  - Thinner cortex in 7 contiguous prefrontal regions
    - Consistent with findings of decreased glucose metabolism in dorsolateral and orbital medial prefrontal cortex when cortisol increased during experimentally induced stress (Kern et al. 2008)
  - No association with hippocampal volume
  - Early stressors influenced later cortisol and cognition.
Trauma Exposure, Post Traumatic Stress Symptoms (PTSD), and Stress Neurocircuitry in the Brain
Vietnam era veterans comprise sizable cohorts of older adults: military service a “hidden” variable in aging research

Military service increases exposure to trauma compared to general population.

Significant, long-lasting repercussions even with below-threshold symptoms

- Increased risk for Alzheimer’s disease;
- Poorer health, wellbeing, quality of life, social functioning.

Veterans in mid-life representative of men their age in most demographic and psychosocial indicators.
PTSD:
-Symptoms triggered by a traumatic event
-Clinically significant if last > 4 weeks, cause distress and/or interfere with work or home life.

4 types of symptoms:

1) Reliving the event/re-experiencing

2) Avoiding situations that remind you of the event (avoidance)

3) Hyperarousal: jittery, on the alert, trouble concentrating or sleeping, angry, irritable, startle easily.

Have more negative beliefs and feelings: lack of enjoyment of activities, lack of trust, guilt, shame, numb, hard to feel happy.

(US DVA website)
VETSA Rates of Lifetime DSM-III-R PTSD Diagnosis by Combat Exposure

<table>
<thead>
<tr>
<th>Combat Exposure</th>
<th>% with PTSD dx</th>
</tr>
</thead>
<tbody>
<tr>
<td>None (72%)</td>
<td>4.4%</td>
</tr>
<tr>
<td>Low (6%)</td>
<td>4.4%</td>
</tr>
<tr>
<td>Medium (7%)</td>
<td>7.7%</td>
</tr>
<tr>
<td>Medium-High (9%)</td>
<td>17.8%</td>
</tr>
<tr>
<td>High (5%)</td>
<td>28%</td>
</tr>
</tbody>
</table>
### Types of Events Resulting in PTSD Diagnosis

<table>
<thead>
<tr>
<th>Event type</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Military combat</td>
<td>49%</td>
</tr>
<tr>
<td>See someone hurt or killed</td>
<td>15%</td>
</tr>
<tr>
<td>News of sudden death or injury</td>
<td>12%</td>
</tr>
<tr>
<td>Sudden injury or accident</td>
<td>9%</td>
</tr>
<tr>
<td>Other event (natural disaster, threat, narrow escape, rape, assault)</td>
<td>15%</td>
</tr>
</tbody>
</table>
Enduring influences: Quality of Life Indicators at Age 56 by Age 38 Post-Traumatic Stress Symptom Clusters

*Higher scores=better QOL/well-being. With exception of SF36 PCS, all clusters within a QOL indicator significantly different

Franz et al., under review
Hippocampus

Inferior Lateral Ventricle (Temporal Horn)

Validated by other groups as an indicator of hippocampal shrinkage/atrophy.

Hippocampal & Amygdala Volumes & Hippocampal Occupancy at Age 56 by PTSD Symptoms at Age 38: Highest vs Lowest Quartile Symptoms

High PTSD n=132; Low PTSD n=138

Hippocampal Volume

-0.3
High
Low

PTSD Symptoms @ 38
$t (268)=-2.29, p=.02$

Hippocampal Occupancy

-0.3
High
Low

PTSD Symptoms @ 38
$t (268)=-3.68, p=.0003$

Amygdala Volume

-0.3
High
Low

$t (268)=-1.24, p=.21$
Timing of Traumatic Event, Hippocampus and Amygdala Volume
# Chronic Posttraumatic Stress Symptoms Predicting Bilateral Cortical and Subcortical Brain Volumes at Age 62

<table>
<thead>
<tr>
<th>BRAIN ROI (AGE 62)</th>
<th>Full Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>t-value</td>
</tr>
<tr>
<td><strong>SUBCORTICAL STRUCTURES</strong></td>
<td></td>
</tr>
<tr>
<td>Hippocampal Volume</td>
<td>2.66</td>
</tr>
<tr>
<td>Hippocampal Occupancy</td>
<td>2.77</td>
</tr>
<tr>
<td>Amygdala</td>
<td>2.06</td>
</tr>
<tr>
<td><strong>PREFRONTAL CORTEX VOLUMES</strong></td>
<td></td>
</tr>
<tr>
<td>Caudal Middle Frontal Gyrus</td>
<td>1.01</td>
</tr>
<tr>
<td>Superior Frontal Gyrus</td>
<td>2.38</td>
</tr>
<tr>
<td>Rostral Middle Frontal Gyrus</td>
<td>2.69</td>
</tr>
<tr>
<td>Pars Orbitalis</td>
<td>-0.61</td>
</tr>
<tr>
<td>Pars Opercularis</td>
<td>-0.50</td>
</tr>
<tr>
<td>Pars Triangularis</td>
<td>2.78</td>
</tr>
<tr>
<td>Medial Orbitofrontal Cortex</td>
<td>-1.33</td>
</tr>
<tr>
<td>Lateral Orbitofrontal Cortex</td>
<td>-1.05</td>
</tr>
<tr>
<td>Frontal Pole</td>
<td>-0.71</td>
</tr>
</tbody>
</table>
Modifiers of Stress: Relationships

- Relationships characterized by safety and trust with another person are both psychologically and physically protective against stress (Bowlby, 1982).
- Quality of relationships ("Secure attachment") should affect coping with stress.
Multiple Mediation of Post-Traumatic Stress Symptoms by Attachment Security Across 24 Years.

Anxious Attachment
Age 56

β = .26 (.17; .34)

β = .19 (.11; .25)

Beta attachment: abandonment fears; co-dependence

Avoidant Attachment
Age 56

β = .17 (.09; .24)

β = .09 (.02; .17)

Beta attachment: fear of intimacy, emotional detachment, lack of trust in others

Implications for Cognitive Resilience

- HPA axis dysregulation an important part of a complex bio-psycho-social evolutionary system. Multiple small disruptions acting additively and/or synergistically can lead to clinically significant dysfunction across the life course.

- Childhood and early adult stress have long-term influences on cognitive and brain outcomes.

- With regard to the brain, this is seen most consistently with regions associated with stress regulation (i.e., the hippocampus) and with areas of the brain important for emotion-regulation.

- There is evidence that the response to stress (i.e., PTSD symptoms; elevated cortisol) not just the event itself that is problematic.

- Early cognitive ability clearly contributed to later outcomes.
  - Still areas for intervention (parental SES, own SES, stress management)
  - Many people exposed to trauma do not develop chronic PTSD symptoms. Search for factors that:
    - make people resilient (i.e., improving childhood conditions, response to stress) and/or
    - may mitigate the influence of stress/trauma (i.e. quality of intimate relationships).
VETSA Aging Model

Childhood/Adolescence

Early Family Environment

Gen’l Intellectual (age 20 AFQT)

SES

Stress exposures

Health/Medical

HPA Axis

Life Style

Middle Age (and beyond)

Midlife Cognitive & Brain Function