Chronic Stress: Implications for Memory and Emotional Regulation

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Outline

Introduction

- What is Stress? Physiological & psychological stress
- Stress, the brain and memory
- Stress, emotions and memory
- Stress & Aging: From normal to pathological aging
- Role of the testing environment
- Stress and psychiatric conditions
- Current projects
What is Stress?
Stress: Popular definition

Children & older adults

Time Pressure
The recipe for stress

- Novelty
- Unpredictability
- Threat to the ego
- Sense of low control

Mason, 1968
## Acute vs. Chronic Stress

### Acute stress

An **adaptive** response, where the system responds to the perceived threat, allows for **energy mobilization**, and then it returns to its basal levels.  
(Fight or Flight)

### Chronic stress

When one is faced by prolonged stress. The over-activation of the stress system causes **dysregulations** in the multiple systems as well as structural **brain changes**.
The Hypothalamic Pituitary Adrenal (HPA) axis

1936: The body’s response
1968: The brain’s response
Cortisol Circadian Rhythm

24-hour circadian profile of cortisol
How can stress be measured?

- Blood
- Urine
- Saliva
- CSF
Stress, the Brain & Memory
Cortisol and the Brain

Cortisol is lipophilic, so it has the capacity to easily cross the Blood Brain Barrier.
Cortisol & Hippocampal Volume

Longitudinal data

Cortisol effects on the Hippocampus

**Direct effects**
- On HC neurons
- Interfere with LTP -> impair learning & memory
- Neurogenesis (Alasdair et al., 2008; Stranahan, 2008)

**Indirect effects**
- Hippocampal glucose metabolism (de Leon et al. 1997)
- Sensitize neurons to metabolic & neurochemical challenges such as:
  - glutamate excess
  - oxidative stress
  - disrupted calcium homeostasis (Herbert et al., 2006)
Cortisol & Memory

Biphasic modulation of memory formation by GCs

Lupien et al., 2007
Stress, Emotions & Memory

Hormonal Implications
Differences between STRESS & EMOTION

Differences
- Stress: Always causes an emotion
- Emotion: Not necessarily stressful

Similarities
- The source can be identified
- Lasts for short periods
- Create physical reactions

Laboratory:
- Emotion: images, words, etc.
- Stress: public speaking
...EMOTION...

Surprise

Consequentiality

Adrenaline

Conscience

Passivity
... STRESS...

- Novelty
- Unpredictability
- Cortisol
- Sense of control
- Spy
2 Main effects

1. Forgetting something due to stress. e.g. wedding anniversary

2. Sharp memory of an emotional situation e.g. car accident
Memory: develops over time

- Vigilance
- Attention

ENCODING  Consolidation  RECALL

Attention: Allows for elaboration
...better elaboration >> better recall
Immediate memory vs. deferred of emotional events.

Study by Cahill et al., 1998: 2 groups of healthy subjects

Task 1: 12 neutral slides
Task 2: 12 slides, the 4 middle slides (5-8) are emotional

Neutral  Emotional  Neutral
Memory of an emotional event

Cahill et al., 1998

Elevated Valence: Augmented Attention

Better encoding… Better recall later
The *Flashbulb Memory* phenomenon

- … 25 February 2007

**Emotion ↑ Attention**

↑ Attention = ↑ Elaboration
The *Flashbulb Memory* phenomenon
Memory of an emotional event

‘weapon-focus’ phenomenon

Studies on trauma victims:
- Excellent memory of the traumatizing event
- Poor memory of peripheral environment
Memory of an emotional event

Biological explanation

- Cardiac rhythm
- Respiration
- Tremor

Release of Adrenaline & noradrenergic activation of the amygdala

Consolidation of emotional information

McGaugh 2013
Emotional memory: Neurological Mechanisms

Role of the amygdala: Structure for fear learning

Effects of chronic stress on amygdala
- increases its volume
- Increases length & complexity of its dendrites
- Causes hyperactivity
- -> so increases fear learning (adaptive mechanism)

Even after cessation chronic stress stress, changes in amygdala are not necessarily irreversible

e.g. following early adversity or trauma

McGaugh 2013
Summary: Cortisol & Noradrenaline

In summary, glucocorticoids...

- Are necessary for learning & memory
- Are involved in the consolidation of neutral and emotional information

In summary, noradrenaline...

- Is necessary for learning & memory
- Is involved in the consolidation of emotional information
Stress & Aging: From Normal to pathological Aging
Older adults show substantial inter-individual variability regarding biological and cognitive manifestations of aging (standard deviation greater than among young adults)

« Differential aging »

Q: Are there biological or social determinants for this large variability?
Memory & Cortisol

Older adults with high current cortisol levels that are increasing annually show impaired cognitive performance (Lupien et al., 1996)

Elevated basal cortisol is associated with cognitive impairment (Lee, 2007)
How does cortisol manifest in healthy aging?

Sindi et al., 2013
Cortisol: Mild Cognitive Impairment & Alzheimer’s Disease

Alzheimer’s Disease

- High basal cortisol levels in AD (Martignoni, 1990; Popp, 2007)

- In AD, higher cortisol associated with more rapid disease progression (Csernansky 2006)

Mild Cognitive Impairment

- MCI associated with ↑ Cortisol Awakening Response, but normal basal cortisol (Lind, 2007)

- In MCI, ↑ Cortisol associated with ↓ memory for paragraph recall (Wolf, 2002)
Additional underlying mechanisms: Preliminary evidence

Experimental AD models

↑ GCs generate oxidative stress

which is associated with:

- accelerated Aβ production,
- decreased Aβ degradation & tau hyperphosphorylation

(Green, 2006; Lee, 2009)
Another determinant of cognitive performance

The role of stressful testing environments
Testing Conditions Favouring Young vs. Older adults

Location of Testing

Age of Research Assistant

TIME of Testing

Task Instructions & Content

Sindi et al., 2013
Website for the guidelines:


Or simply go to humanstress.ca
Stress, Psychiatric Conditions & Allostatic Load
How does cortisol manifest in different psychiatric conditions?
How does cortisol manifest in different psychiatric conditions?

- **Burnout**

  

- **Depression**

  

Juster 2011
Other effects of chronic stress

“Allostatic load” Model

Chronic elevated Cortisol interacts with cytokines & catecholamines, creating a *domino effect* & impacting multiple systems

**Immune**
- Fibrinogen
- C-reactive protein (CRP)

**Cardiovascular**
- Systolic & diastolic blood pressure

**Metabolic**
- Insulin
- Glucose
- Cholesterol
- triglycerides
- visceral fat depositing

McEwen 2008, 2012; Juster 2010
Other effects of chronic stress

- **Brain**: atrophy of brain regions, cognitive impairment

- **Cardiovascular**: atherosclerosis, left-ventricular hypertrophy, clotting factors, homocysteine, oxidative stress markers

- **Immune system**: impaired wound healing, retarded immunization response, suppressed delayed-type hypersensitivity, chronic pain and fatigue (→ imbalance of immune system regulators in the CNS)

- **Metabolic**: glycosylated hemoglobin, HDL:LDL, cholesterol, abdominal fat deposition (waist–hip ratio), bone mineral density

McEwen 2008, 2012; Juster 2010
Current Projects

Stress & Sleep
STOCKHOLM
Karolinska Institutet
• KI-CAR
• ARC
Karolinska University Hospital
• Memory Clinic

HELSINKI
National Institute for Health and Welfare

KUOPIO
University of Eastern Finland
(1) Work-Related Stress (CAIDE)

Midlife work-related stress in the Cardiovascular Risk Factors, Aging and Incidence of Dementia study (CAIDE)

- Dementia (Sindi et al. Journals of Gerontol. 2016)
- Cognition (Sindi et al., submitted)
- MRI (Sindi et al., submitted)
Co-STAR
Cortisol and Stress in Alzheimer’s Disease

Investigation of stress-related clinical and biomarker profiles and their association with cognition/dementia and neuroimaging correlates, in a population of memory clinic patients at the Karolinska University Hospital (Huddinge) Memory Clinic

**Clinical profiles:**
- prevalence of:
  - burn-out
  - levels of experienced stress
  - anxiety and depressive symptoms;
  - psychological characteristics

**Biomarkers:**
- salivary cortisol
- APOE genotype
- CSF biomarkers
- MRI measurements
- Blood biomarkers: Allostatic load
(3) Multi-centre sleep study

The project combines four Nordic population-based studies (From Sweden and Finland) to assess the associations between sleep and:

- Dementia (Sindi et al., submitted)
- cognition (Including cognitive domains) (Sindi et al., submitted)
- MRI measures
- CSF Aβ
- Physical functioning & frailty
Current Projects

Dementia:
• Risk Detection
• Prevention
• Implementation of Interventions
FINGER is the first multi-domain lifestyle RCT intervention, showing improvements or maintenance of cognitive functioning among older adults at risk for dementia.

The role of telomere length (TL) in the FINGER study:

- Does baseline TL impacts the cognitive response to the intervention? (Sindi et al., submitted)
- Does the intervention alter TL? (Sindi et al., in preparation)
- Is TL associated with lifestyle factors and biomarkers?
The goal is to identify effective prevention strategies for dementia based on experiences/data from 5 ongoing European dementia prevention trials. For the first time, a pilot trial will test a multimodal preventive intervention among patients with prodromal Alzheimer’s disease (AD).

**Microbiome-Gut-Brain Axis: sub-study**
- (Baseline): How does the microbiome of AD patients differ from healthy age-matched controls?
- (Post-intervention): Does the multi-domain intervention impact the microbiome among AD patients?

http://www.mind-ad.eu/
(6) MULTI-MODE
Multimodal strategies to promote a healthy brain in aging: Innovative evidence-based tools

Aims to produce & commercialise 2 evidence-based, e-health tools to predict dementia risk and prevent cognitive decline/dementia for use by citizens/health care staff
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