Sadness and the Cell: Is Depression in Your Body, or is it All in Your Mind?

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Disclosures

- I have no relevant financial relationships to disclose
Is depression actually a whole body disease, one manifestation of which is depression?

- Depression is the leading cause of disability in North America and is projected to become the second leading cause of disability worldwide by 2020.

- If depression is purely a “mental illness” or even a “brain disease,” why do depressed individuals have a significantly increased rate of physical diseases usually associated with advanced age*?:
  - Heart disease and Stroke?
  - Dementia?
  - Obesity, Diabetes, Osteoporosis and Metabolic syndrome?
  - Immune dysfunction?
  - Premature death (even controlling for suicide)?

*Adjusted for age, HTN, diabetes, smoking, perceived health and cognitive function
Physical Disease Burden in Major Depression

Mortality from specific causes in depressed compared with nondepressed patients

<table>
<thead>
<tr>
<th>Cause</th>
<th>HR*</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular disease</td>
<td>1.8</td>
<td>1.2 - 2.5</td>
</tr>
<tr>
<td>CHD</td>
<td>1.7</td>
<td>1.0 - 3.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.7</td>
<td>0.8 - 3.5</td>
</tr>
<tr>
<td>CHF</td>
<td>3.2</td>
<td>1.3 - 8.0</td>
</tr>
<tr>
<td>Other CV disease</td>
<td>3.2</td>
<td>1.1 - 9.0</td>
</tr>
<tr>
<td>Cancer</td>
<td>1.0</td>
<td>0.6 - 1.7</td>
</tr>
<tr>
<td>Other causes</td>
<td>1.8</td>
<td>1.2 - 2.7</td>
</tr>
</tbody>
</table>

*Hazard ratio adjusted for age, MI, stroke, COPD, HTN, diabetes, smoking, perceived health and cognitive function

Mortality Among Men with Severe Mental Disorders Who Reach Old Age

![Graph showing mortality rates](image)

Figure 1. Survival over a follow-up period of up to 14.7 years of a community-representative sample of older men with and without serious mental health disorders. The age-adjusted mortality hazard was 2.0 (95% CI = 1.8, 2.2) for depression, 1.5 (95% CI = 1.3, 1.9) for CHD, 1.3 (95% CI = 1.2, 2.5) for CHF, and 1.2 (95% CI = 1.1, 2.8) for men with a past diagnosis of schizophrenia spectrum disorder (Schizophrenia-S), bipolar disorder, depression and alcohol-induced disorders.

doi:10.1371/journal.pone.0118822.g001
Can “Cell Aging” in Stress and Depression Help Explain Medical Illnesses?

Underlying dysregulated stress & endocrine systems?

Slide by Barbara Penninx, MD
Simplified Hypothetical Model of Some Protective and Damaging Factors in Stress and Depression

- STRESS AROUSAL
  - ↓ BDNF
  - ↑ NEUROSTEROIDS
  - ↑ CORTISOL
  - ↑ INFLAMMATION
  - ↑ OXIDATIVE STRESS
  - ↑ CELL AGING (TELOMERES)


Hypothetical Model of Some Protective and Damaging Factors in Stress and Depression

- STRESS AROUSAL
  - ↓ PNS
  - ↓ BDNF
  - ↓ NEUROSTEROIDS, ANTI-OXIDANTS, ANTI-INFLAMMS
  - ↑ CORTISOL
  - ↑ INFLAMMATION
  - ↑ SNS
  - ↑ EXCITOTOXICITY, OXIDATIVE STRESS
  - ↑ CELL AGING (TELOMERES)

Not Illustrated: Genetics, Epigenetics

 Protective Factor
 Damaging Factor
Oxidative Stress Damages Cells

DNA (and telomeres in particular) is highly sensitive to oxidative damage. Once a cell becomes pre-apoptotic, mitochondrial free radical release increases, forming a vicious cycle.

Inflammation

Chronic Stress → Increased Cortisol → Down-regulated Lymphocyte Glucocorticoid Receptors → Disinhibited Peripheral Cytokine Release

Increased SNS/ Decreased PNS → Increased Inflammatory Cytokine Release

Miller, Maletic, & Raison, *Biological Psychiatry*, 2009
Telomeres and Telomerase

- **Telomeres** are non-coding sequences capping DNA ends that can shorten with somatic cell divisions and serve as a “senescence clock” (a marker of biological age).
- **Telomerase** is a cellular enzyme that rebuilds telomeres and has additional non-telomeric roles in cell survival.

Telomeres are the end caps ("aglets") of our DNA

Each time a cell divides, its telomeres *may* shorten. When telomeres critically shorten, the ends of the DNA are exposed to damage, and the cell may die.
Telomeres May be Our Body’s Canaries in the Coal Mine

Telomere shortening may directly cause cell damage and sickness, or-

Telomeres can index our cumulative exposure to inflammation, oxidative stress and other toxic cellular environments.

A Possible Conduit by Which Stress Impairs Health

The relationship of telomere length to aging, longevity and physical and mental illness
WBC Telomere Length and Aging

- On average, healthy adults lose ~30-60 base pairs/year. But this is variable, with some people maintaining or even lengthening telomeres over time.

Valdes AM, et al., Lancet, 2005

Does Length Really Matter?

Short Leukocyte Telomeres…

Are Associated with:

- Coronary Artery Disease
- Diabetes
- Dementia
- Immunosenescence

Predict Subsequent Mortality

Cawthon et al., 2003
Baseline and *Prospective Change* in Telomere Length Predict Mortality

**Baseline**

**Change Over 2½ Years**

*Figure 1.* Those with shorter (below median) telomere length at baseline (dashed line) had 2.3 times greater likelihood of mortality over the following 12 years compared to those with longer telomeres (solid line).

*Figure 2.* Those with telomere shortening over a 2.5 year period (dashed line) had 3.0 times greater likelihood of mortality over the 12 years since the baseline blood draw, compared to those without telomere shortening (solid line).

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**Accelerated telomere shortening in response to life stress**

Elissa S. Epel, Elizabeth H. Blackburn, Jue Lin, Firdaus S. Dhabhar, Nancy E. Adler, Jason D. Morrow, and Richard M. Cawthon

*PNAS, 2004*

**Women Caregiver Study Design:**

- 39 mothers of chronically ill children
- 19 mothers of healthy children (control group)
- Ages 20-50 y.o. All analyses controlled for age.
- Telomere length and telomerase activity assayed in pooled peripheral blood mononuclear cells (PBMCs)

Elissa Epel, PhD
Elizabeth Blackburn, PhD
Jue Lin, PhD
High stress women had cell aging comparable to non-stressed women ~13 years older.

Longer duration of stress = Shorter telomeres

Perceived stress, independent of Group, accounted for telomere shortening.
Psychological Mediation of Telomere Length

O’Donovan et al., 2012

Chronic Major Depression

Simon et al., 2006

MDD Subjects showed an average of 10 years accelerated telomere aging

Note: Average lifetime duration of depression: 25.7 ± 12.1 years
**Telomere Shortening is Not Specific to Major Depression**

*Other Psychiatric Conditions May, on Average, Have Shortened Telomere Length. This is Still Under Investigation:*

- Chronic Psychological Stress
- Childhood Depression
- Adolescents at Risk for Depression
- Schizophrenia?
- Early Life Adversity?
- Others: PTSD?, Bipolar?

*Hypothesis: Telomere shortening is related to biochemical mediators (e.g., cortisol, catecholamines, oxidation and inflammation), genetic factors or environmental insults that traverse traditional psychiatric diagnoses.*

**Summary: What Causes Short Telomeres?**

- ↑Oxidative Damage
- ↑Inflammation
- ↑Cortisol
- ↑Stress-Related Adrenaline
- ↓Telomerase
- Chronic viral infections
- Early Life Adversity

*Take Home Message:*

*It is “possible” (but unproven) that intervening in these pathways could delay cell aging and improve health*
How Early Can Telomere Shortening Be Seen in Depression? Which Comes First: Depression or Short Telomeres?

Telomeres in First Episode Depressed Adolescents (Eva Blom and Tony Yang, UCSF)

Telomeres in Never-Depressed Girls at Risk for Developing Depression (Ian Gotlib, Stanford)

Tom Insel, NIMH Director’s Blog: “Depression, Daughters, and Cellular Aging,” Oct. 23, 2014: “Beyond suggesting a risk biomarker for early identification of depression, this finding indicates a troubling early sign of risk for premature biological aging and possibly age-related chronic diseases, such as cardiovascular disease. Investigating the cause and timing of decreased telomere length—to what extent it may result from abnormalities in stress responses or is genetically influenced, for example—will be important for understanding the relationship between cellular aging, depression, and other medical conditions.”

Early Life Adversity And Cell Aging in Adults

Is there a scar that goes unhealed?
Definition of “Adverse Childhood Experience” (ACE) Scores

ACE score = number of categories endorsed (0-8)

1. Emotional Abuse
2. Physical Abuse
3. Sexual Abuse
4. Household Substance Abuse
5. Household Mental Illness
6. Mother Treated Violently
7. Incarcerated Household Member
8. Parental Separation

(Anda et al., 2005)

Adverse Childhood Events (ACE) and Adult Psychiatric and Medical Morbidity

ACE and Depression

ACE and Other Co-Morbid Physical Outcomes

From Anda et al., 2005

Fig. 1 The mean number of combined outcomes in the study sample was 3.1 (range 0-14) cases are adjusted for age, sex, race, and educational attainment. The trend in the means is significant (P < 0.0001); vertical error bars represent 95% confidence intervals.
Adverse Childhood Events and Inflammation
Kiecolt-Glaser et al., 2011

Multiple childhood adversities were associated with significantly shorter TL and with significantly increased IL-6 (correlations between IL-6 and TL were not reported).

Telomeres are shorter in those with Adverse Childhood Events
Kananen et al., 2010
Q: How Early in Life Can Adverse Events Affect Adult Telomere Length?

Answer: In the Uterus
Stress exposure in intrauterine life is associated with shorter telomere length in young adulthood

Maternal Psychosocial Stress During Pregnancy is Associated with Newborn Leukocyte Telomere Length (cord blood) - Entringer et al., 2013

P< 0.05, controlling for birth weight, early life adversity and current stress

Telomeres in the prenatal stress group were shorter by an average of 178 base pairs, indicating approximately 3.5 years of accelerated biological aging.

Scatterplot of association between maternal pregnancy-specific stress and newborn (cord blood) telomere length (R^2 = 0.25). T/S ratio is adjusted for covariates (newborn gestational age at birth, weight, sex, and exposure to antepartum obstetric complications).
In Addition to Preserving and Lengthening Telomeres, Telomerase May Have Direct Antidepressant and Neurotrophic Effects

Cell Aging by Telomere Loss Can Be Reversed with Telomerase

“Recently in Nature, Jaskelioff et al (2011) demonstrated that multiple aging phenotypes in a mouse model of accelerated telomere loss can be reversed within 4 weeks of reactivating telomerase. This raises the major question of whether physiological aging, likely caused by a combination of molecular defects, may also be reversible.”

Commentary by Bernardes de Jesus and Blasco, 2011
Telomerase Activity in Depression is Directly Related to Hippocampus Size

Data represent depressed subjects. Relationship was weaker in controls.

\[ r = 0.51, p = 0.03, df = 16 \]

Wolkowitz et al., 2012 Ann Conf, ISPNE

- So what’s the good news?
Telomere Length and/or Telomerase Activity are Associated with Lifestyle*

* (Associations do not necessarily suggest causality)

Possibly Favorable Regulators:
- Exercise
- Dietary restraint
- Multivitamin intake (Vit C, D and E)
- Folate
- Omega-3 fatty acids
- Social support
- Stress management
- Statins
- Estrogen

Possibly Unfavorable Regulators:
- Fruits and vegetables
- Meditation
- Sleep
- TA-65/ Telomerase Activators (Astragalus membranaceus)
- Antidepressants


Multisystem Resiliency Moderates the Major Depression/ Telomere Length Association

Figure adapted from: Puterman E, et. al, 2013

Multisystem Resiliency” defined as healthy emotion regulation, strong social connections and good sleep and exercise patterns
Telomeres Can Lengthen!

Telomeres lengthen in ~1/4th of adults (MacArthur Aging Study, analysis of high functioning 70 – 79 year olds) over a 2.5 year period

Epel et al, Aging, 2009

Dean Ornish Lifestyle Study

• Telomerase was measured at baseline and after 3 months

Mean telomerase activity in 30 men with low-risk Prostate CA

Meditation Retreat Study

3 months of Meditation for 8-10 hr/ day in a retreat setting, vs. Wait-list control

![Meditation Retreat Study Image]

Figure 2. Post-retreat telomerase activity was significantly greater in the retreat group ($p < .05$). Error bars: ± 1SEM (Jacobs et al., 2011)

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Well Being: Purpose in Life

**High scorer:** Has goals in life and a sense of directedness; feels there is meaning to present and past life; holds beliefs that give life purpose; has aims and objectives for living.

**Low scorer:** Lacks a sense of meaning in life; has few goals or aims; lacks sense of direction; does not see purpose of past life; has no outlook or beliefs that give life meaning.
Provisional Interpretations, I:

- Telomere shortening observed with chronic stress and in several psychiatric disorders is not a specific diagnostic biomarker, but it may point to the presence of specific pathologies or risk factors.
- It may be more pronounced with longer disease exposure (a “dose-response relationship”)
- It may be result from cumulative exposure to oxidation, inflammation, catecholamines or cortisol, which are often elevated in these conditions.
- Telomerase diminution or activation may occur. The latter may be a compensatory attempt. This may have prognostic and therapeutic implications.
Provisional Interpretations, II:

- Certain diseases now considered “mental illnesses” may be re-conceptualized as systemic bodily conditions, albeit with prominent behavioral manifestations.
- Understanding cell aging in stress and psychiatric disorders may explain the high medical co-morbidity and should lead to new treatment targets for both the psychiatric and physical illnesses.
- Lifestyle factors may be important modifiable risk factors.

“Every stress leaves an indelible scar, and the organism pays for its survival after a stressful situation by becoming a little older.”

-Hans Selye
For more information on our studies or to schedule an eligibility screen, please contact us at:

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Questions?