

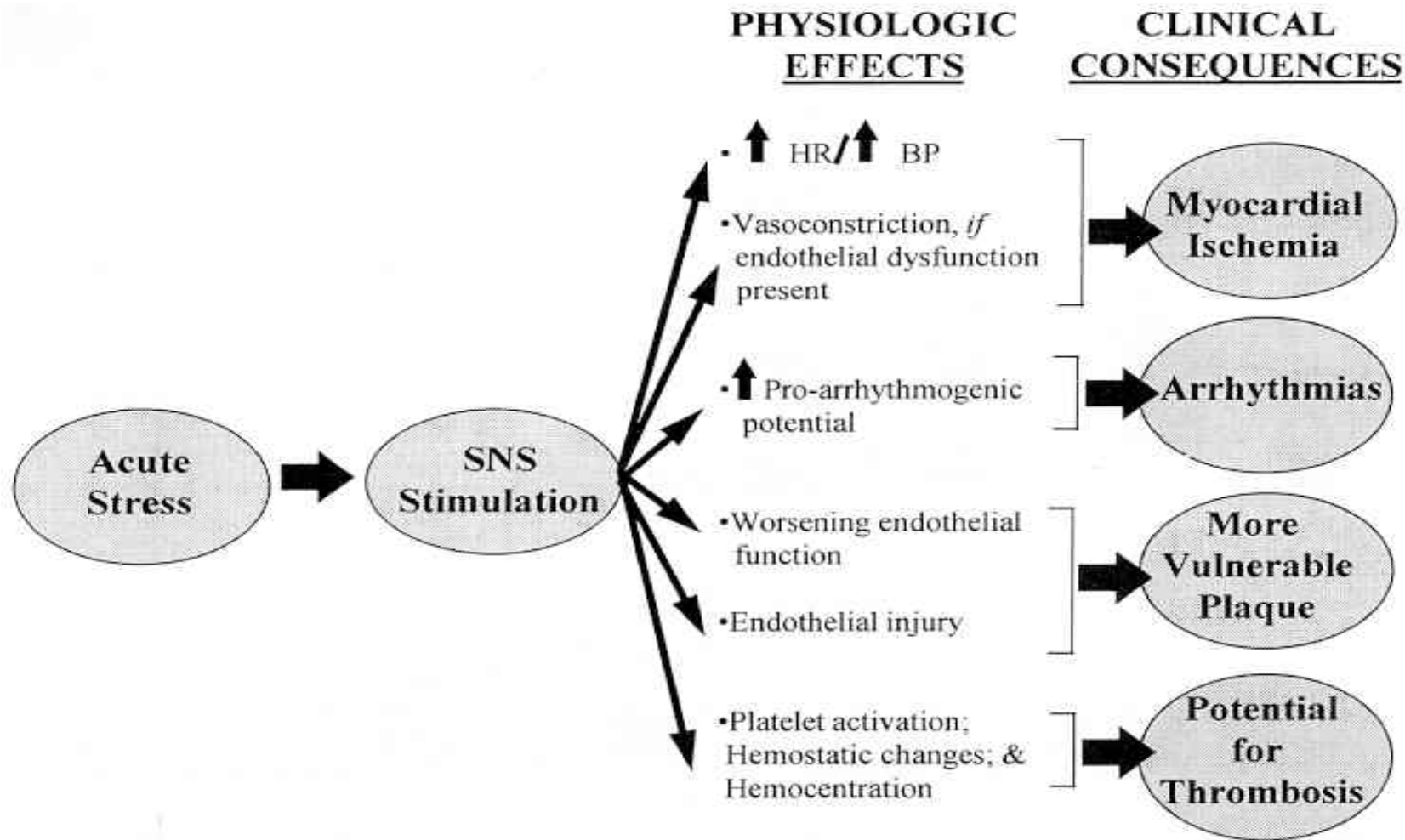
# The body is the shadow of the soul: the science and practice of mind-body medicine

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Pathophysiological effects of acute psychosocial stress.  
 From: Rozanski: Circulation 1999;99:2192-2217

# Psychosocial factors and heart disease

- As a causal factor
  - Type A/hostility (6/14 studies)
  - Depression and anxiety (11/11 studies)
  - Work characteristics (6/10 studies)
  - Social support (5/8 studies)
- As a prognostic factor
  - Type A (0/5 positive studies)
  - Depression and anxiety (6/6)
  - Work characteristics (1/2)
  - Social support (9/10)
    - Hemingway H, Marmot M. BMJ 1999;318(7196):1460-7.

# Psychosocial interventions for CAD

- Meta-analysis of 23 studies
- Overall reduction of odds for new cardiac events if patients get psychosocial intervention as part of care
- Increased risk for those with no psychosocial therapy as a part of management
  - OR 1.70 for mortality
  - OR 1.84 for recurrence
    - Linden W. et al. Arch Int Med 1996;156(7):745-52.

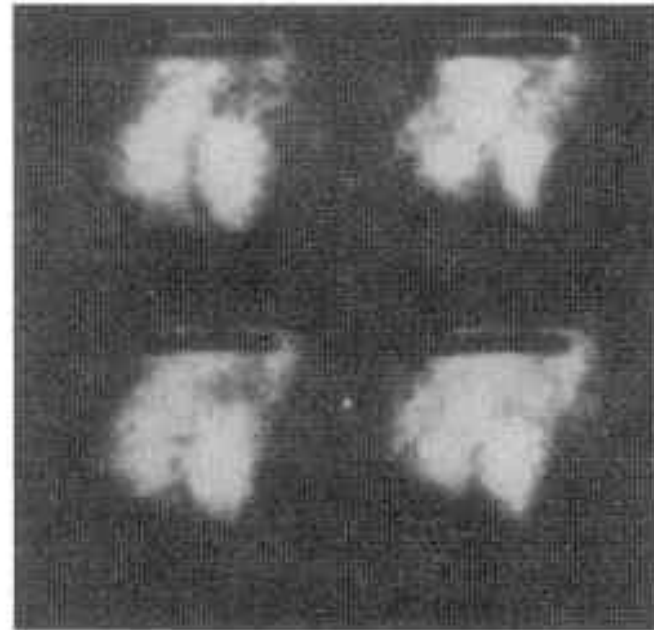
“Man is not disturbed by events, but by the view he takes of them.”

**Epictetus**

Cardiovascular reactivity will be based upon our perception of how threatening the event is

**REST**

**SPEECH**



**ED**

**ES**

**Scintigrams** - radionuclide ventriculography at rest and then during a mental stress task involving a speech task (speaking about feelings of personal stress concerning his problems in caring for his family). During speech patient had worsening of left ventricular segmental wall motion and abnormal outward motion during systole developed in septum. **Rozanski: NEJM**

# Appraisal and the stress response

- Study examined whether reappraising stress-induced arousal could improve cardiovascular outcomes and decrease attentional bias for emotionally negative information
- Participants randomly assigned to either a reappraisal intervention (instructed to treat physiological arousal during a stressful task as functional and adaptive – acceptance) or to 1 of 2 control interventions: attention reorientation and no instructions
- Participants instructed to reappraise arousal exhibited more adaptive cardiovascular stress responses
  - Increased cardiac efficiency, lower vascular resistance, decreased attentional bias
    - Jamieson JP, Nock MK, Mendes WB. Mind over matter: reappraising arousal improves cardiovascular and cognitive responses to stress. *J Exp Psychol Gen.* 2012 Aug;141(3):417-22. doi: 10.1037/a0025719.

# Stress perception and health

- Study examined relationship b/w amount of stress, the perception that stress affects health, and health and mortality outcomes in U.S. adults
  - Controlled for sociodemographic, health behavior, and access to health care factors
- 33.7% of adults perceived that stress affected their health a lot or to some extent
- Both higher levels of reported stress and the perception that stress affects health independently associated with increased likelihood of worse mental and physical health outcomes
- Those who reported a lot of stress and that stress impacted their health a lot had a 43% increased risk of premature death
- Those with high stress but a perception that it had a positive effect had lower rate of premature death than those with less stress but negative perception
  - Keller A, Litzelman K, Wisk LE, et al. Does the perception that stress affects health matter? The association with health and mortality. *Health Psychol.* 2012 Sep;31(5):677-84. doi: 10.1037/a0026743. Epub 2011 Dec 26.



# Stress and MS lesions

- Study on whether different types of stressful events and perceived stress predict the development of MS brain lesions
- 121 patients with MS followed for 48 weeks during an RCT comparing stress management therapy for MS (SMT-MS) to a waitlist control (WLC)
  - MRI scans every 8 weeks to measure brain lesions
  - Monthly interviews measured stressful life events and self-report measures of perceived stress, anxiety and depressive symptoms
  - Participants classified stressful events as positive or negative
- Positive stressful events predicted decreased risk for lesions in the control group (OR 0.53 for each additional positive stressful event) and less risk for new or enlarging lesions regardless of group assignment (OR 0.74)
- Major negative stressful events predicted lesions (OR 1.77) and new or enlarging lesions (OR 1.57) whereas moderate negative stressful events, perceived stress, anxiety and depressive symptoms did not
  - Burns MN, Nawacki E, Kwasny MJ, Pelletier D, Mohr DC. Do positive or negative stressful events predict the development of new brain lesions in people with multiple sclerosis? *Psychol Med.* 2013 May 17:1-11.

# Yogic meditation, genes and immunity

- Study on effect of Yogic meditation on genetic expression
- 68 genes were found to be differentially expressed (19 up-regulated, 49 down-regulated) after adjusting for potentially confounded differences in sex, illness burden, and BMI
- Up-regulated genes included immunoglobulin-related genes
- Down-regulated genes included pro-inflammatory cytokines
  - Black DS, Cole SW, Irwin MR, et al. Yogic meditation reverses NF- $\kappa$ B and IRF-related transcriptome dynamics in leukocytes of family dementia caregivers in a randomized controlled trial. *Psychoneuroendocrinology*. 2013 Mar;38(3):348-55. doi: 10.1016/j.psyneuen.2012.06.011.

# Meditation and inflammation

- Novice meditators' Inflammatory markers (serum interleukin (IL)-6 levels) were 41% higher than those of expert meditators
- The odds of a novice having detectable C-reactive protein (CRP) (a marker of inflammation) were 4.75 times as high as that of an expert
- Differences in stress responses between experts and novices provided one plausible mechanism for their divergent inflammatory response to stress
  - Kiecolt-Glaser JK, Christian L, Preston H, et al. Stress, inflammation, and yoga practice. *Psychosom Med*. 2010 Feb;72(2):113-21. doi: 10.1097/PSY.0b013e3181cb9377.

# Vacations and your heart

- Vacations can be both good and bad for health
- More vacations can protect against AMI (RR 0.71) over 9-year follow-up.
  - Gump BB et al. Psychosom Med. 2000; 62(5): 608-12.
- Higher incidence of AMI associated with vacations during the first 2 days (then protective)
- Significantly higher risk:
  - Lower education
  - Living with a spouse
  - Traveling by car
  - Staying in a tent or mobile home
    - Kop WJ, et al. Psychosom Med. 2003;65(3):396-401.

# TELOMERES

Google Image modified by Vitetta and Sali

Embryonic Stem Cell

Adult Stem Cell

Telomere Long

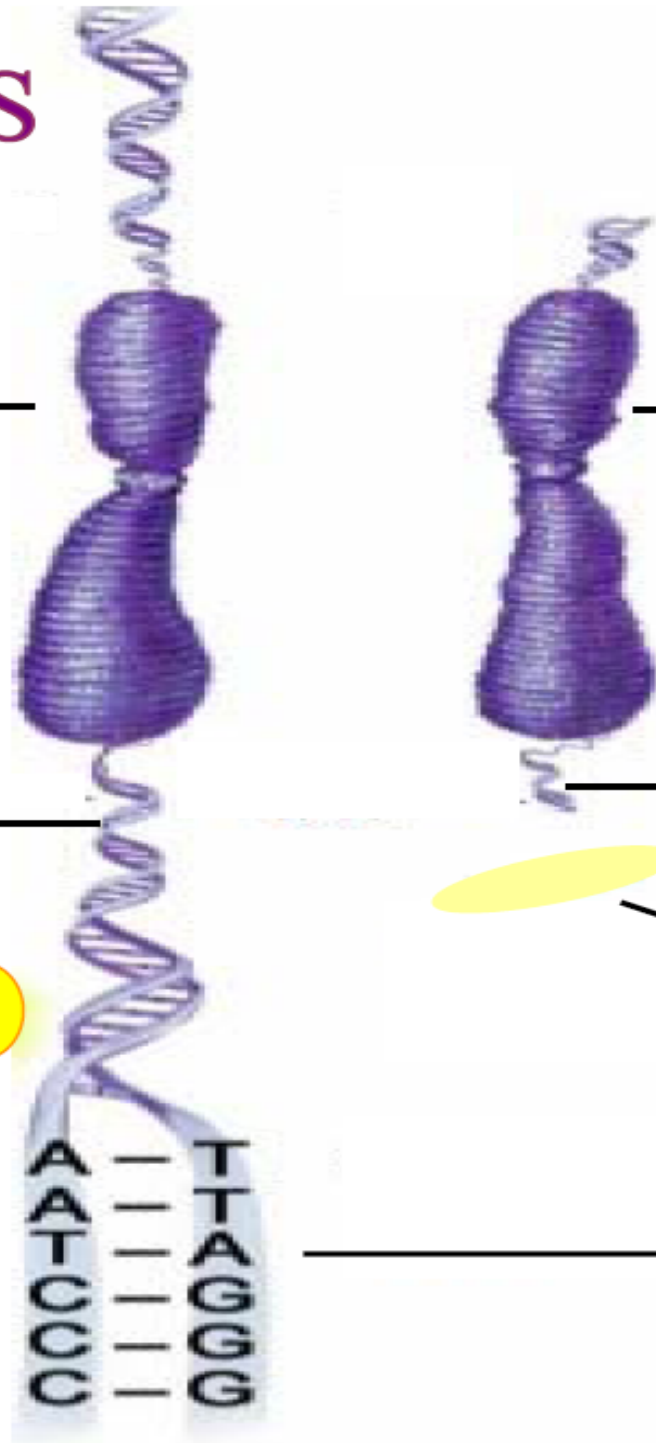
Telomere Short

Telomerase Active

Telomerase Inactive or Absent

A T  
A T  
C C C  
G G G

Telomere is a Repeating DNA Sequence



# Stress and telomere shortening

- Study on healthy premenopausal women showed that psychological stress associated with:
  - higher oxidative stress
  - lower telomerase activity (telomerase repairs DNA telomeres) leading to shorter telomere length
- These are known determinants of cell death/longevity
- Women with highest levels of perceived stress c/w low stress women have shorter telomeres
  - Average equivalent at least 9-17 years of additional ageing
- Implications for how, at the cellular level, stress may promote earlier onset of age-related diseases
  - Epel ES et al. Proc Natl Acad Sci U S A. 2004;101(49):17312-5.

# Intrauterine stress and telomere length

- Telomere Length assessed in 94 healthy young adults
  - 45 were offspring of mothers who had experienced a severe prenatal stress
  - 49 subjects were offspring of mothers who had a healthy, uneventful index pregnancy
- Prenatal stress exposure was a significant predictor of subsequent adult telomere length in the offspring
  - Effect unchanged after adjusting for potential confounders and was more pronounced in women
    - Entringer S, Epel ES, Kumsta R, Lin J, Hellhammer DH, Blackburn EH, Wüst S, Wadhwa PD. Stress exposure in intrauterine life is associated with shorter telomere length in young adulthood. Proc Natl Acad Sci U S A. 2011 Aug 16;108(33):E513-8.

# Mind wandering and ageing

- The greater the level of mind wandering, the greater the level of telomere shortening (a marker of biological age)

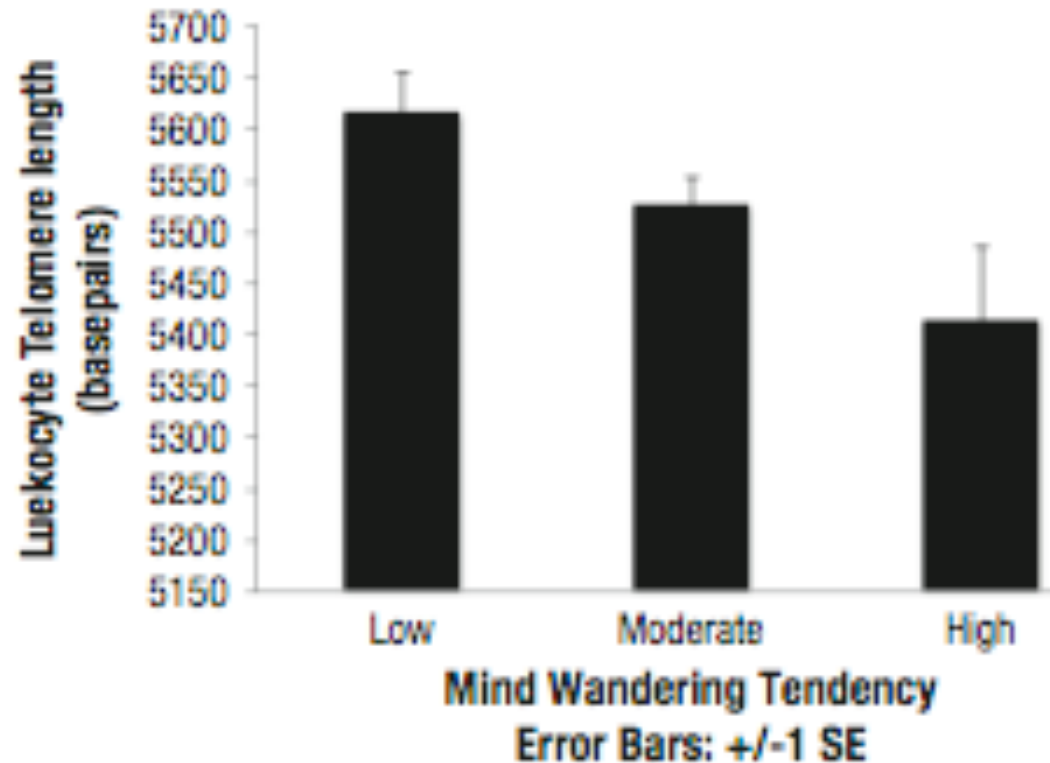


Fig. 1. Leukocyte telomere length by greater mind-wandering group.

Epel ES, Puterman E, Lin J, Blackburn E, et al. Wandering Minds and Aging Cells. *Clinical Psychological Science* 2012, in press.



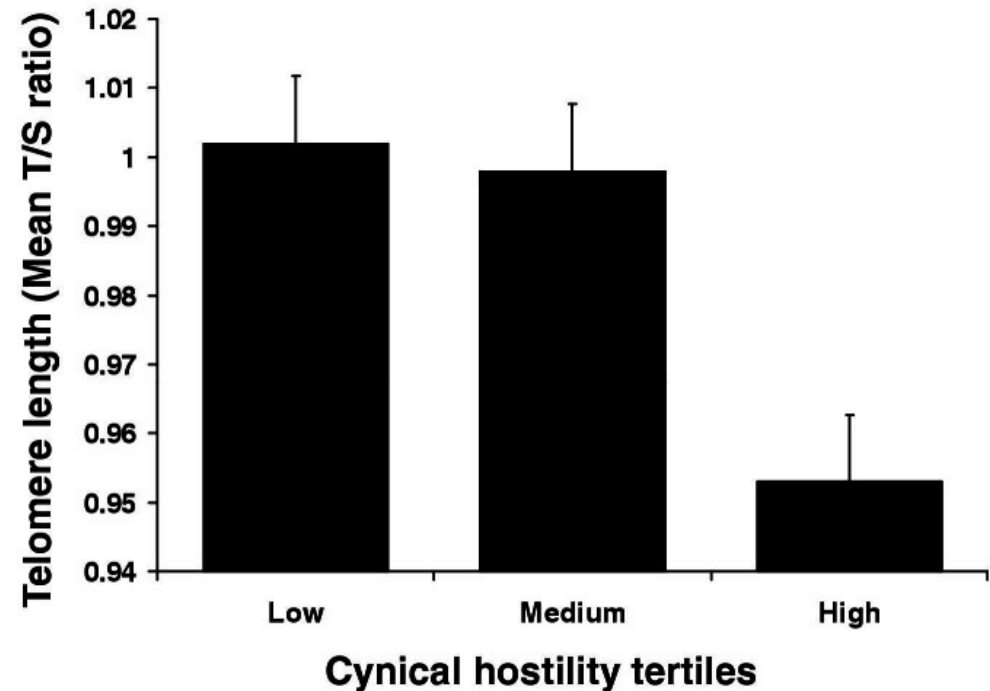
# Depression, ageing and telomeres

- Patients with major depressive disorder (MDD) have increased risk of aging-related illness (e.g. heart disease, diabetes, obesity, cancer)
- Study on whether MDD is associated with accelerated biological aging
  - 1095 current MDD patients, 802 remitted MDD patients and 510 control subjects
- TL shorter among remitted MDD patients and current MDD patients
  - Adjustment for health / lifestyle variables did not reduce associations
- Higher depression severity ( $P < 0.01$ ) and longer symptom duration in the past 4 years ( $P = 0.01$ ) were associated with shorter TL
- Depressed patients show accelerated cellular aging according to a 'dose-response' gradient
  - Verhoeven JE, Révész D, Epel ES, Lin J, Wolkowitz OM, Penninx BW. Major depressive disorder and accelerated cellular aging: results from a large psychiatric cohort study. *Mol Psychiatry*. 2013 Nov 12. doi: 10.1038/mp.2013.151.

# Hostility and telomere length

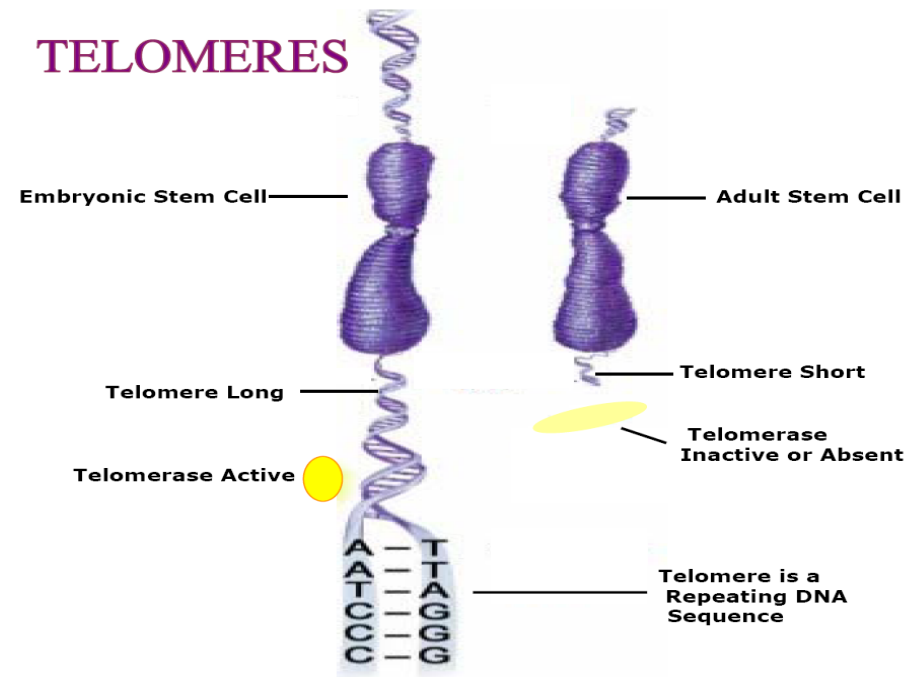
- High-hostile men had significantly shorter leukocyte TL than their low-hostile counterparts
- The relationship between hostility and disease is stronger in men than in women, and men generally have a shorter life expectancy than women

Brydon L, Lin J, Butcher L, Hamer M, Erusalimsky JD, Blackburn EH, Steptoe A. Hostility and cellular aging in men from the Whitehall II cohort. *Biol Psychiatry*. 2012 May 1;71(9):767-73. doi: 10.1016/j.biopsych.2011.08.020.



# Mindfulness and cellular ageing

- Meditation may slow genetic ageing and enhance genetic repair
  - “...we propose that some forms of meditation may have salutary effects on telomere length by reducing cognitive stress and stress arousal and increasing positive states of mind and hormonal factors that may promote telomere maintenance.”
    - Epel E, Daubenmier J, Moskowitz JT, Folkman S, Blackburn E. Can meditation slow rate of cellular aging? Cognitive stress, mindfulness, and telomeres. *Ann N Y Acad Sci.* 2009 Aug; 1172:34-53.



# Meditation, mental health & telomerase

- Study of effect of brief daily yogic meditation on mental health, cognitive functioning, and telomerase activity in family dementia caregivers (mean age 60) with mild depressive symptoms
  - Randomized to Kirtan Kriya vs. listening to relaxation music for 12 min/d for 8 weeks
- Meditation group showed significantly lower levels of depressive symptoms and greater improvement in mental health and cognitive functioning c/w relaxation group
- Meditation group: 43% improvement in telomerase activity c/w 3.7% in the relaxation group
- Improvement in mental health “is accompanied by an increase in telomerase activity suggesting improvement in stress-induced cellular aging.”
  - Lavretsky H, Epel ES, Siddarth P, Nazarian N, Cyr NS, Khalsa DS, Lin J, Blackburn E, Irwin MR. A pilot study of yogic meditation for family dementia caregivers with depressive symptoms: effects on mental health, cognition, and telomerase activity. *Int J Geriatr Psychiatry*. 2012 Mar 11. doi: 10.1002/gps.3790.

# Ornish program for cancer

- 92 men with early prostate cancer who chose to watch and wait
- Randomised to lifestyle (experimental) group vs. usual treatment (control) group
  - Vegan diet
    - Fruits, vegetables, whole grains, legumes and soy
    - 10% calories from fat
    - Supplemented by soy (tofu), fish oil (3gm daily), vitamin E (400IU daily), selenium (200mcg daily), vitamin C (2gm daily)
  - Exercise
    - Walking 30min 6 times weekly
  - Stress management
    - Gentle yoga, meditation, breathing and PMR
  - Support group 1 hour weekly
    - Ornish D. Weidner G. Fair WR. et al. Journal of Urology. 2005;174(3):1065-9.

# Lifestyle change and telomeres

- Telomere shortness is a prognostic marker of ageing, disease, and premature illness
- 5 year follow-up study to investigate long-term effects of lifestyle change on telomere length
- Men who had biopsy-proven low-risk prostate cancer c/w control patients
- Intervention group followed a programme of comprehensive lifestyle changes (low fat vegan diet, exercise, stress management, meditation and social support)
- Control group underwent active surveillance alone
- At 5 years compared relative telomere length and telomerase activity and their relation to the degree of lifestyle change
  - Ornish D, Lin J, Chan JM, Epel E, Kemp C, Weidner G, Marlin R, Frenda SJ, Magbanua MJ, Daubenmier J, Estay I, Hills NK, Chainani-Wu N, Carroll PR, Blackburn EH. Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. *Lancet Oncol.* 2013 Sep 16. doi:pii: S1470-2045(13)70366-8. 10.1016/S1470-2045(13)70366-8

# Lifestyle change and telomeres

- Relative telomere length increased from baseline in the lifestyle intervention group, but decreased in the control group
- Adherence to lifestyle change significantly associated with relative telomere length after adjustment for age and the length of follow-up
  - For each percentage point increase in lifestyle adherence score, T/S units increased by 0.07
- “Our comprehensive lifestyle intervention was associated with increases in relative telomere length after 5 years of follow-up, compared with controls, in this small pilot study. Larger randomised controlled trials are warranted to confirm this finding.”
  - Ornish D, Lin J, Chan JM, Epel E, Kemp C, Weidner G, Marlin R, Frenda SJ, Magbanua MJ, Daubenmier J, Estay I, Hills NK, Chainani-Wu N, Carroll PR, Blackburn EH. Effect of comprehensive lifestyle changes on telomerase activity and telomere length in men with biopsy-proven low-risk prostate cancer: 5-year follow-up of a descriptive pilot study. *Lancet Oncol.* 2013 Sep 16. doi:pii: S1470-2045(13)70366-8. 10.1016/S1470-2045(13)70366-8

# Purpose, happiness, self-gratification, genetics and immunity

- Immune cells in individuals with high levels of hedonic wellbeing (pleasure seeking / gratification) were characterized by:
  - an increased expression of genes involved in inflammation (implicated in diseases such as arthritis and heart disease), and
  - decreased expression of genes involved in antiviral responses
- This immune response (known as CTRA) is also associated with chronic stress and uncertainty
- The opposite effect was found for eudaimonic wellbeing (meaning / engagement)
- Both forms of wellbeing were associated with similar self-reported affect

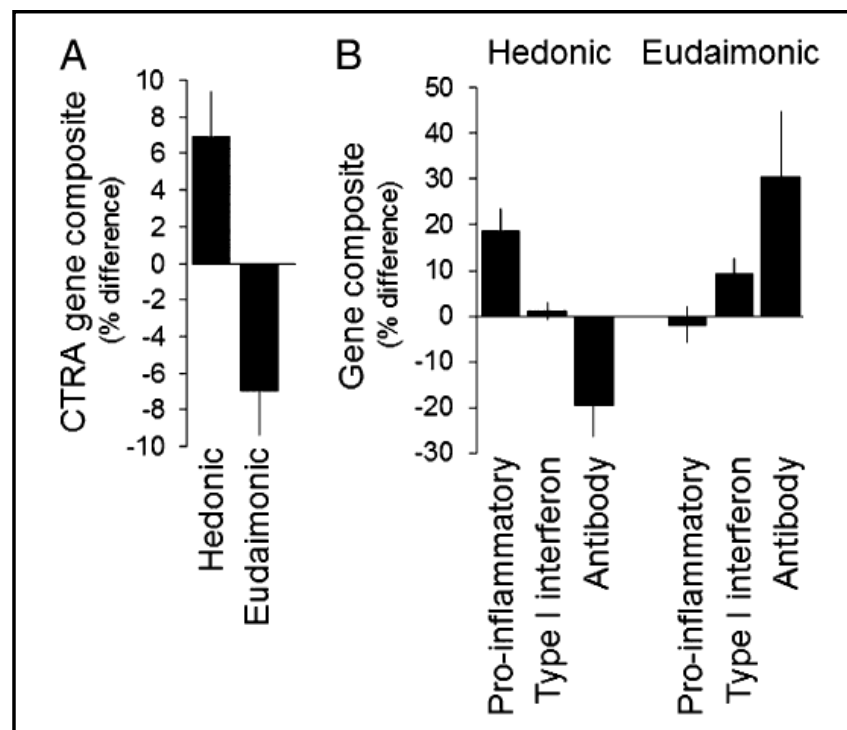


Fig. 2. Expression of the CTRA gene set. (A) Linear model-based estimates of mean difference ( $\pm$ SEM) in expression in a 53-gene CTRA contrast score in PBMCs from individuals with low levels ( $-2$  SD relative to sample mean) vs. high levels ( $+2$  SD) of hedonic well-being and eudaimonic well-being (each adjusting for the other and for demographic and behavioral covariates). (B) Differential expression of CTRA subcomponents: 19 proinflammatory genes, 31 type I IFN response genes, and three antibody synthesis genes.

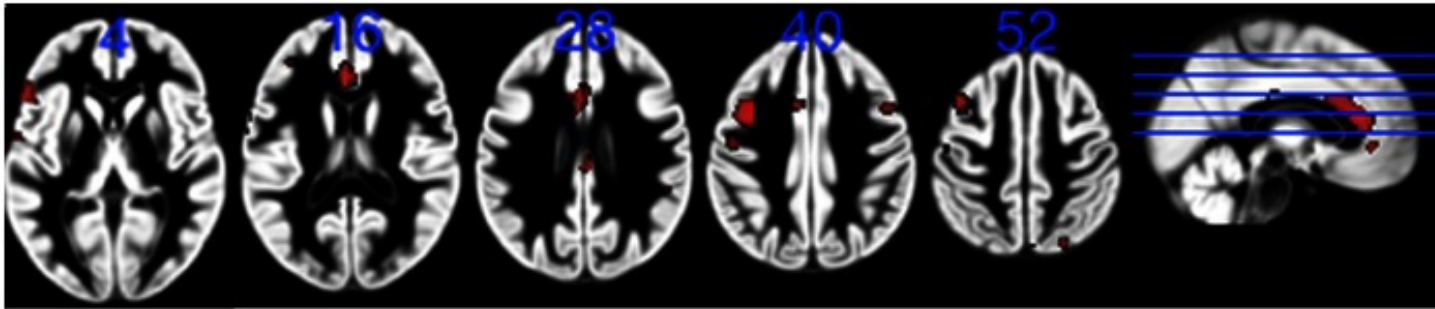
Fredrickson BL, Grewen KM, Coffey KA, et al. A functional genomic perspective on human well-being. Proc Natl Acad Sci U S A. 2013 Jul 29. [Epub ahead of print]



# Giving, stress and mortality

- Study on whether providing help to others predicts a reduced association between stress and mortality
- Participants completed baseline interviews assessing past-year stressful events and whether they had provided assistance to friends or family
- Participant mortality and time to death monitored for 5 years
- Significant interaction between helping behavior and stressful events (HR = 0.58)
- Stress did not predict mortality risk among individuals who provided help to others in the past year (HR = 0.96), but did predict mortality among those who did not provide help to others (HR = 1.30)
- “Helping others predicted reduced mortality specifically by buffering the association between stress and mortality.”
  - Poulin MJ, Brown SL, Dillard AJ, Smith DM. Giving to others and the association between stress and mortality. *Am J Public Health*. 2013 Sep;103(9):1649-55. doi: 10.2105/AJPH.2012.300876.

# Stress and grey matter



- Study on occupational stress on grey matter volume
- Stressed subjects exhibited significant reductions in the GM volumes of the anterior cingulate cortex and the dorsolateral prefrontal cortex, caudate and putamen volumes
- Volumes correlated inversely to the degree of perceived stress
  - Blix E, Perski A, Berglund H, Savic I. Long-term occupational stress is associated with regional reductions in brain tissue volumes. PLoS One. 2013 Jun 11;8(6):e64065. doi: 10.1371/journal.pone.0064065. Print 2013.
- **Figure 2: Reductions in GM volumes in stressed subjects.**
- Significant reductions in the GM (red) in stressed subjects compared with controls. Clusters calculated using peak threshold at  $p=0.001$ , FDR corrected at  $p<0.05$ . All the clusters are superimposed on the GM template from the entire study group. The numbers indicate z-levels in MNI co-ordinates. R=right side.

# Mental stimulation and brain health

- Healthy elderly (av. 76.1yrs) c/w patients with Alzheimer Disease (74.8yrs) and young controls (24.5yrs)
- ‘Brain health’ (amyloid deposits) c/w participation in cognitive activities (e.g. reading, writing, playing games)
- Greater participation in cognitively stimulating activities (particularly in early and middle life) associated with reduced amyloid uptake
  - The top ¼ of older participants for cognitive activity had amyloid uptake comparable to young controls
  - The lowest ¼ for cognitive activity had amyloid uptake comparable to patients with AD
    - Landau SM, Marks SM, Mormino EC, Rabinovici GD, Oh H, O'Neil JP, Wilson RS, Jagust WJ. Association of Lifetime Cognitive Engagement and Low  $\beta$ -Amyloid Deposition. Arch Neurol. 2012 Jan 23. [Epub]

# The Default Brain

- Active tasks
  - Tasks associated with paying attention
  - Brain efficient and quiet
- Default state (mode)
  - Mind is inattentive, distracted, idle, recalling past, daydreaming
  - Areas active in default mode similar to areas affected by Alzheimer's Disease

# Default mode network

- High default mental activity in psychopathology (e.g. depression, anxiety, schizophrenia and autism)
- Default activity decreased or deactivated when paying attention (e.g. experienced mindfulness meditators)
- In experienced meditators even when default network active, regions associated with self-monitoring and cognitive control are co-activated: reduced vulnerability to default thinking
  - Brewer JA, Worhunsky PD, Gray JR, et al. Meditation experience is associated with differences in default mode network activity and connectivity. Proc Natl Acad Sci U S A. 2011 Dec 13;108(50):20254-9.

# Does 'stress' cause cancer?

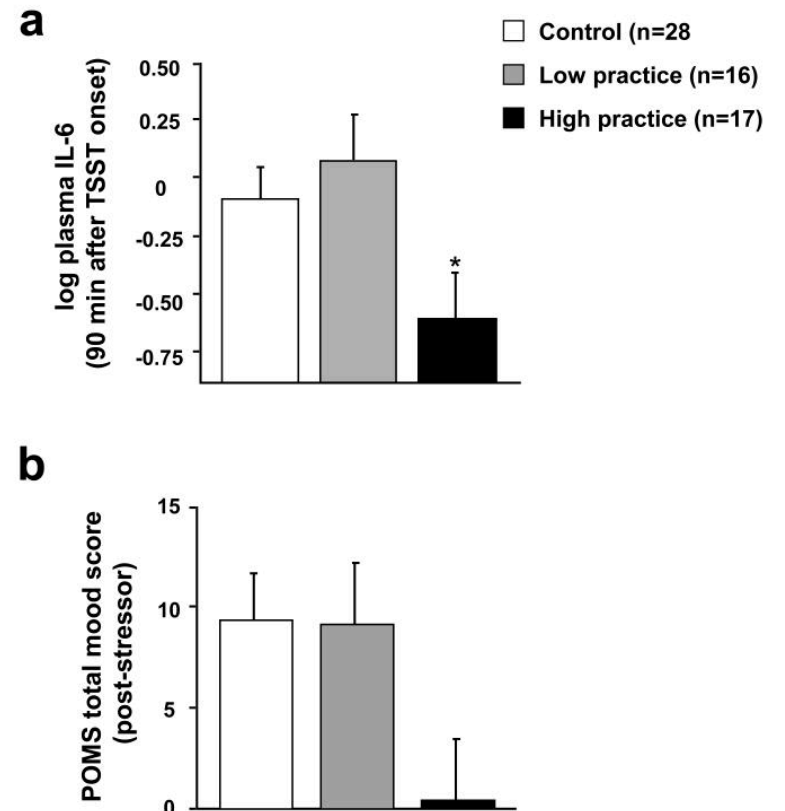
- Yes and no depending on how you define it, measure it and the person experiencing it
- Meta-analysis to verify association b/w stressful life events and primary breast cancer incidence
- 618 studies (1982-2007): 8 case control and cohort studies selected and 3 analyses for Relative Risk
  - Widowhood: RR1.04 (95%CI: 0.75-1.44;  $p = 0.800$ )
  - Divorce: RR1.03 (0.72-1.48; 0.850)
  - Self-rated intensity/frequency of stress: RR1.73 (0.98-3.05; 0.059)
    - Santos MC, Horta BL, do Amaral JJ, et al. Association between stress and breast cancer in women: a meta-analysis. *Cad Saude Publica*. 2009;25 Suppl 3:S453-63.

# Depression and cancer

- Immune activation and inflammation play a role in the pathophysiology of both depression and cancer
- Cancer patients experience a threefold higher rate of depression within the first five years of diagnosis
- Chronic depression associated with increased (approx. doubled) cancer risk and shortened survival
  - Elevated concentrations of proinflammatory cytokines associated with depression may mediate the neuroendocrine, neural, and immune pathways that account for the relationship
  - Proinflammatory cytokines are known to modulate key neurobiological correlates of depression including hypothalamic-pituitary-adrenal (HPA) axis dysregulation, monoamine neurotransmitter metabolism, and limbic system activity
    - Penninx BW, Guralnik JM, Pahor M, Ferrucci L, Cerhan JR, Wallace RB, et al. Chronically depressed mood and cancer risk in older persons. *J Natl Cancer Inst* 1998;90:1888-93.
    - Currier MB, Nemeroff CB. Depression as a Risk Factor for Cancer: From Pathophysiological Advances to Treatment Implications. *Annu Rev Med*. 2013 Nov 11. [Epub ahead of print]

# Compassion meditation, cancer and inflammation

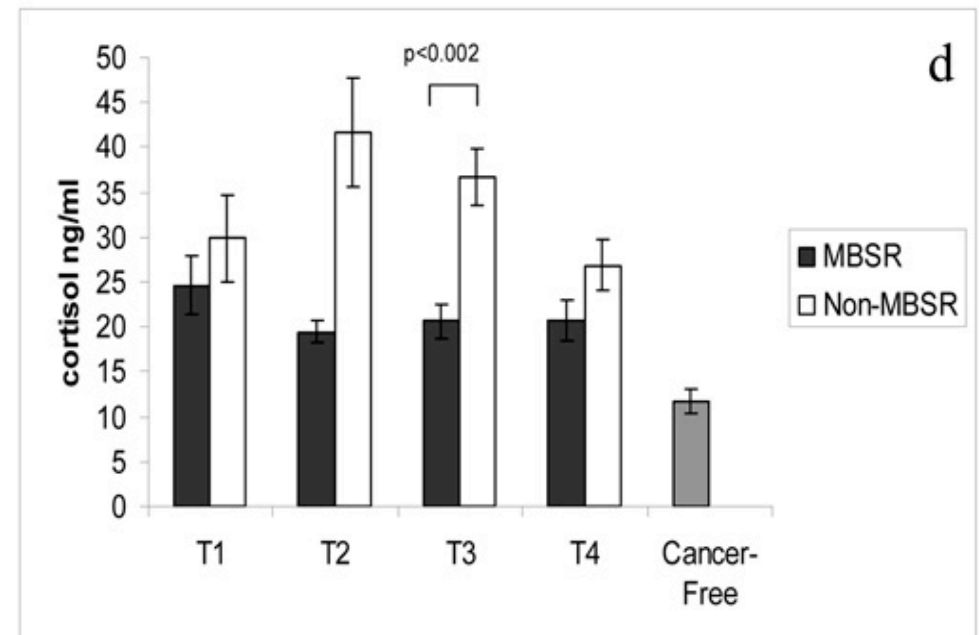
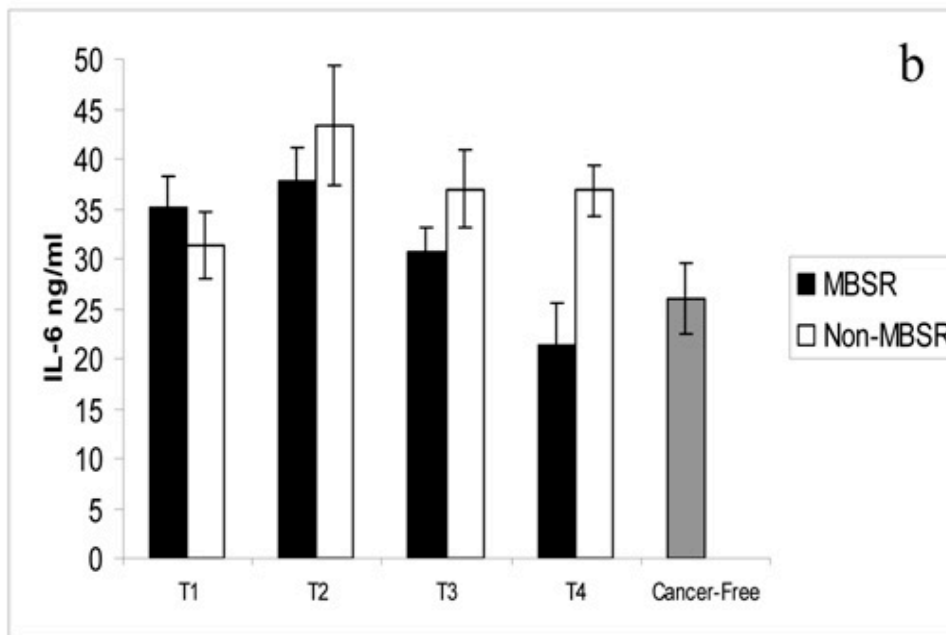
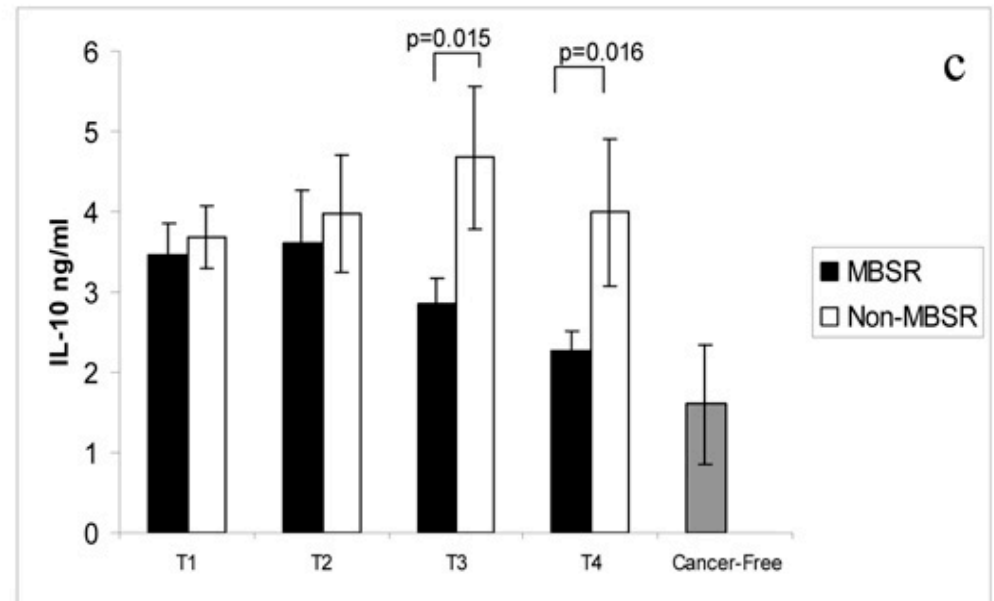
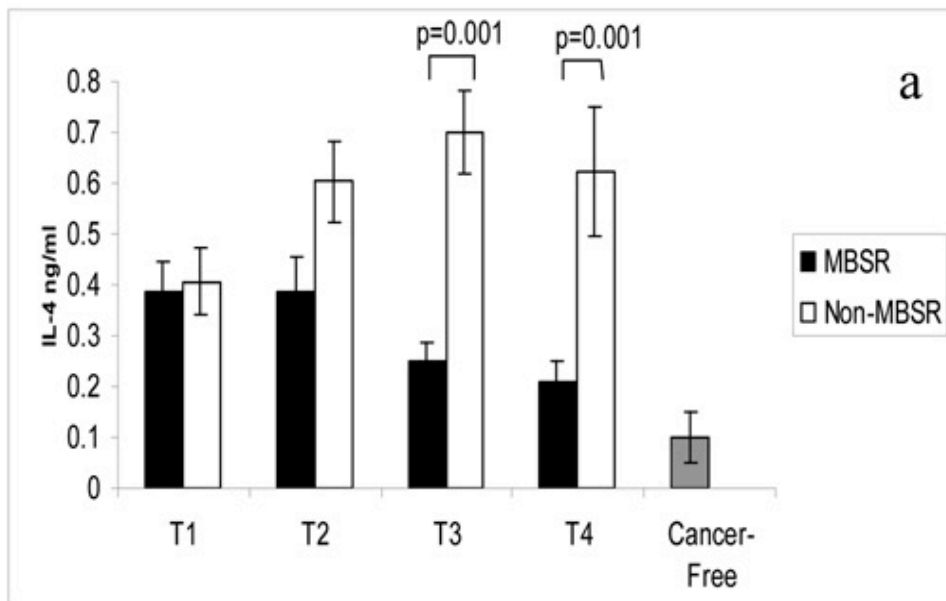
- Study of 61 healthy adults randomized to 6 weeks of training in compassion meditation or participation in a health discussion control group followed by exposure to a standardized laboratory stressor (TSST)
- Within the meditation group, increased meditation practice correlated with decreased TSST-induced IL-6 and POMS distress scores
- Individuals with meditation practice times above the median exhibited lower TSST-induced IL-6 and POMS distress scores compared to individuals below the median, who did not differ from controls
  - Pace TW, Negi LT, Adame DD, et al. Effect of compassion meditation on neuroendocrine, innate immune and behavioral responses to psychosocial stress. *Psychoneuroendocrinology*. 2009 Jan;34(1):87-98. doi: 10.1016/j.psyneuen.2008.08.011.





# Mindfulness and cancer

- Reductions in NK cell activity (NKCA) and IFN-gamma production with increases in IL-4, IL-6, and IL-10 production and plasma cortisol levels observed for breast cancer patients
- Women in the MBSR group
  - Re-established their NKCA and cytokine production levels
  - Reduced cortisol levels
  - Improved QOL, and increased coping effectiveness
- Breast cancer patients in the Non-MBSR group exhibited continued reductions in NKCA and IFN-gamma production with increased IL-4, IL-6, and IL-10 production
  - Witek-Janusek L, Albuquerque K, Chroniak KR, et al. Effect of mindfulness based stress reduction on immune function, quality of life and coping in women newly diagnosed with early stage breast cancer. *Brain Behav Immun.* 2008 Aug;22(6): 969-81. doi: 10.1016/j.bbi.2008.01.012.



# Therapeutic effects of music

- relaxation and better pain management
- reducing cardiac reactivity and improving performance
- reducing anxiety and stress physiological markers
- improved cognitive function (elderly, young adults and children) and mental clarity
- improved mood, cardiac and respiratory function for critically ill patients
- EEG changes and reduced cortisol in depressed adolescents
- increased empathy in children (but increased assertive behaviour with fast tempo music)
- enhanced immunity, reduced inflammation and increased melatonin levels
  - Fancourt D, Ockelford A, Belai A. The psychoneuroimmunological effects of music: A systematic review and a new model. *Brain Behav Immun.* 2013 Oct 21. doi:pii: S0889-1591(13)00513-8. 10.1016/j.bbi.2013.10.014.

# Not all music positive

- Grunge rock was found to have a negative effect on adolescent mental health
  - increased hostility, sadness, tension and fatigue
  - decreased caring, relaxation, mental clarity and vigour
    - McCraty R. et al Alt Therapies in Health and Medicine 1998;4 (1):75-84.

# Music and mental health

- **Pop:** Conformists, overtly responsible, role-conscious, struggling with sexuality or peer acceptance
- **Heavy Metal:** Higher levels of suicidal tendency, depression, drug use, self-harm, shoplifting, vandalism, unprotected sex
- **Dance:** Higher levels of drug use regardless of socioeconomic background
- **Jazz / Rhythm and Blues:** Introverted, misfits, loners
- **Rap:** Higher levels of theft, violence, anger, street gang membership, drug use and misogyny
  - Baker F, Bor W. Can music preference indicate mental health status in young people? *Australas Psychiatry*. 2008 Aug;16(4):284-8.

# Smiling and longevity

- Retrospective study on major league baseball players looking at photos from 1952 baseball register
- 3 kinds of smiles
  - no smile
  - partial smile (only movement of muscles around the mouth)
  - full (Duchenne) smile (movement of muscles around the mouth and corners of the eyes)
    - Abel EL, Kruger ML. Smile Intensity in Photographs Predicts Longevity *Psychological Science* 2010;21(4):542–544.

# Smiling and longevity

- For those who had died, longevity ranged from an average of:
  - 72.9 years (n = 63) for players with no smiles
  - 75.0 years (n = 64) for players with partial smiles
  - 79.9 years (n = 23) for players with Duchenne smiles
- Players with Duchenne smiles were half as likely to die in any year compared with non-smilers (HR = 0.50, p = .006)
  - Abel EL, Kruger ML. Smile Intensity in Photographs Predicts Longevity *Psychological Science* 2010;21(4):542–544.