The multiple reserve hypothesis and the salutogenesis of aging

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Disclosures

- No financial conflicts
- Johannesburg, ADI, 1999
H.S. Wang, Dementia in Old Age (Contemp. Neurol. Sci., 1977)
Function is not produced by pathology alone!

- ~1/3 of people > 65 yrs have Abeta plaques on PET
  
  Betriz et al 2013, Aizenstein et al 2008

- Large HC volume protects people with AD pathology
  
  Erten-Lyons et al 2009

- In older persons the relationship between AD pathology and CI is poorer than in young persons
  
  Savva et al 2009
What are the goals for aging?
What are the goals for aging?

1. Not dying
What are the goals for aging?

1. Not dying
2. Not becoming diseased
What are the goals for aging?

1. Not dying (MORTALITY)
2. Not becoming diseased (MORBIDITY)

*Is this the whole story?*
Interim Estimates of 2013–14 Seasonal Influenza Vaccine Effectiveness — United States, February 2014

The 2013–14 seasonal influenza vaccine provides substantial protection against the influenza A (H1N1)pdm09 virus.

In the United States, annual vaccination against seasonal influenza is recommended for all persons aged ≥6 months. Each season since 2004–05, CDC has estimated the effectiveness of seasonal influenza vaccine to prevent influenza-associated, medically attended acute respiratory illness. This report uses data from 2,319 children and adults enrolled in the U.S. Influenza Vaccine Effectiveness Network during December 2, 2013–January 23, 2014, to estimate an interim adjusted effectiveness of seasonal influenza vaccine for preventing laboratory-confirmed influenza virus infection associated with medically attended acute respiratory illness.
What are the goals for aging?

1. Not dying
2. Not becoming diseased
3. Maintaining as high a level of function as possible, enhancing quality of life and resistance to loss of function with aging (FITNESS)
Pathogenesis and Salutogenesis

• Pathogenesis
  - the origination and development of a disease

Princeton Univ. Worldnet

• Salutogenesis
  - a shift from the disease-metaphor to the vision of well-being

Antonovsky, A. Health, Stress and Coping. 1979
Multiple reserve hypothesis

Maintenance and/or enhancement of levels of function enhances resistance to disease and enhance capacities (fitness) with aging:

- Cognitive/cerebral
- Systemic/physical
- Psychological
- Social
Cognitive reserve

- CR is very important but is not the only matter with which we should be concerned.
# Neuronal activity is good for you!

<table>
<thead>
<tr>
<th>Task specific (memory, attention)</th>
<th>Neurogenesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neurotransmitters</td>
<td>Dendritic arborization</td>
</tr>
<tr>
<td>Glucose metabolism</td>
<td>Network complexity</td>
</tr>
<tr>
<td>Blood flow</td>
<td>Development of strategies</td>
</tr>
<tr>
<td>Resistance to excitotoxins</td>
<td>Regulation of the stress response</td>
</tr>
<tr>
<td>Growth factors (BDNF)</td>
<td>Better APP processing</td>
</tr>
<tr>
<td>Protection against free radicals</td>
<td>Less neurofilament phosphorylation</td>
</tr>
</tbody>
</table>
Probability of membership in the case group for men and women as a function of changes from early to middle adulthood in percentage of total hours per month devoted to intellectual activities.

Physical reserve

- Stroke
- Hypertension
- Diabetes
- Kidney, heart, pulmonary disease
- Polypharmacy
- Vision, hearing
- Inflammation
- Nutrition, anemia, others
Microbiota, metagenome

- Collective genome of our indigenous microflora (Lederberg)
- 80-95% of microbes are unclassified and uncultivable
- Mostly anaerobic
- 136 x more genes than the host
- Related to diabetes, heart disease, obesity, arthritis, fatty liver disease, Inflammatory bowel disease, frailty with aging

**Microbiota, metagenome**

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Psychological Reserve

- Depression is a risk factor for AD
- Apathy
- Grief
- Sleep
- Resolved and unresolved conflicts and stress
- Development of strategies

Green et al 2003, Krystal, 1981
Social reserve

- Family resources
- Marriage
- Environmental stimulation, isolation, engagement
- Occupational and recreational tasks
- POVERTY
What life periods are important?

- EARLY LIFE:
  - education
  - Head injury prevention
  - Smoking, drug use
  - Nutrition
  - Occupation, recreational activities

Friedland, Brayne, *Journal of Developmental and Behavioral Pediatrics* 2009
Conclusion

- The absence of disease is not the same as the presence of health, especially with aging.
H.S. Wang, Dementia in Old Age *(Contemp. Neurol. Sci., 1977)*
Alzheimer Disease Process
Alzheimer Disease Process
Alzheimer Disease Process

Cognitive Impairment
Cognitive Reserve

Alzheimer Disease Process

Physical Reserve

Cognitive Impairment
Cognitive Reserve

Physical Reserve

Alzheimer Disease Process

Psychological Reserve

Cognitive Impairment
Alzheimer Disease Process

Cognitive Reserve

Physical Reserve

Social Reserve

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Alzheimer Disease Process

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Cognitive Impairment
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Alzheimer Disease Process

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Cognitive Impairment
Pathogenesis and salutogenesis of brain health with aging

Are influenced by the interplay of disease process with lifestyle factors that

• Determine reserve capacities and influence disease expression

• And influence disease processes directly
Checkmating Dementia

Beatriz Marinello, Michael Glassman, Robert Friedland

To research the effects of chess on the brain and to promote the game of chess and related activities as a way to decrease the risk of age-related dementing disorders.
Recommendations for public policy

- Education, education, education
- Medicare expenses are $10,000 per person
- Every eligible person should be given funds to enhance cognitive, physical, social and psychological reserve
“Since little can be done about brain tissue that has lost its functional capacity, the interaction of these social psychological and somatic factors often becomes the most important determinant of the course and outcome of patients with dementia. Early recognition and correction of these factors may help prevent the development of complications and slow the progression of deterioration.”
The elephant in the room....
Poverty

- Socioeconomic status (SES)
- Every disease is more common in persons of lower SES except....
“New Insights into the Dementia Epidemic” Larson et al, NEJM 2013

- There are more and will be more old people
- Declining age specific prevalence and incidence rates of dementia
- “Knowing about contributing factors is especially important for the study and development of prevention strategies, and prevention is often the key to better control of epidemics, including epidemics of chronic diseases.”
Larsen et al, 2013

### Selected Recent Studies of the Dementia Epidemic

<table>
<thead>
<tr>
<th>Study</th>
<th>Outcome</th>
<th>Data Source</th>
<th>Key Findings</th>
<th>Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manton et al. (United States)¹</td>
<td>Prevalence of severe cognitive impairment</td>
<td>National long-term care survey interviews, 1982–1999</td>
<td>Decline in dementia prevalence among people ≥65 yr of age (5.7% to 2.9%)</td>
<td>Higher educational level, decline in stroke incidence</td>
</tr>
<tr>
<td>Langa et al. (United States)²</td>
<td>Prevalence of cognitive impairment</td>
<td>Ongoing population-based survey of people ≥51 yr of age</td>
<td>Prevalence of cognitive impairment among people ≥70 yr of age (12.2% in 1993 vs. 8.7% in 2002)</td>
<td>Higher educational level; combination of medical, lifestyle, demographic, and social factors</td>
</tr>
<tr>
<td>Schrijvers et al. (Rotterdam)³</td>
<td>Incidence of dementia</td>
<td>Population-based cohort ≥55 yr of age in 1990, extended in 2000</td>
<td>Incidence rate ratios (6.56 per 1000 person-yr in 1990 vs. 4.92 per 1000 person-yr in 2000)</td>
<td>Higher educational level, reduction in vascular risk, decline in stroke incidence</td>
</tr>
<tr>
<td>Qiu et al. (Stockholm)⁴</td>
<td>Prevalence of DSM-III-R dementia*</td>
<td>Cross-sectional survey of people ≥75 yr of age, 1987–1989 and 2001–2004</td>
<td>Age- and sex-standardized dementia prevalence (17.5% in 1987–1989 vs. 17.9% in 2001–2004); lower hazard ratio for death in later cohort suggests decreased dementia incidence</td>
<td>Favorable changes in risk factors, especially vascular risk; healthier lifestyles</td>
</tr>
<tr>
<td>Matthews et al. (England)⁵†</td>
<td>Prevalence of dementia in 3 regions</td>
<td>Survey interviews of people ≥65 yr of age, 1989–1994 (in CFAS I) and 2008–2011 (in CFAS II)</td>
<td>Dementia prevalence (8.3% in CFAS I vs. 6.5% in CFAS II)</td>
<td>Higher educational level, better prevention of vascular disease</td>
</tr>
</tbody>
</table>

* In the study by Qiu et al., dementia was diagnosed according to the criteria provided in the Diagnostic and Statistical Manual of Mental Disorders, third edition, revised (DSM-III-R).
† CFAS denotes Cognitive Function and Ageing Study.
Larsen et al 2013

“Improvement in life expectancy will certainly lead to a net increase in the number of older people who have dementia late in their lives. This fact alone, plus population trends, justifies the value of learning more about lifestyle and risk factors that affect dementia rates. Given recent reports of trends in dementia incidence and prevalence, we believe that research to uncover influences on these trends has great promise.”
Recommendations for public policy

- Education, education, education!

- 2012 Medicare annual expenses per beneficiary are $11,325 per person
  
  2013 Annual Report of the Medicare Trust Fund

- Every eligible person should be given funds to enhance cognitive, physical, social and psychological reserve
Age 82, learning viola da gamba
Everett Poe, age 73, National Pole Vault Champion
Alois Alzheimer and the Southern Bavaria Tennis Champs, 1911
My suggestion to the Communicable Disease Center (CDC) in Atlanta:

*Morbidity, Mortality and Fitness Weekly Report* (MMFWR)
Alzheimer’s Disease Risk Factors

- Age
- Female gender
- Genes (Apo E e4)
- Hypertension, heart disease, stroke
- Diabetes
- High fat diet
- Low intake of vitamin B6, B12, folic acid
- Low intake of alcohol

Kalmijn et al. J Nutr Health Aging. 2000;
Friedland. Arch Neurol. 2003
Reitz et al. Arch Neurol. 2004
Ravaglia et al. Neurology. 2005
Alzheimer’s Disease Risk Factors -2

- Low consumption of fish, fruit, and vegetables
- Obesity
- Low levels of physical and mental activity
- Low levels of education and work complexity
- Head injury
- Smoking
Dementia in Arabs residing in Wadi Ara (1999-present)

- Low prevalence of Apo E ε4 (3-4%)
- High risk of AD (10%) and MCI (32%) > 65
- May be related to smoking, hypertension, diet, physical inactivity, low levels of education, smoking, high serum homocysteine
- Not related to consanguinity
- *Studies did not include neuroimaging or autopsy*

Friedland, Inzelberg, Bowirrat, Masarwa et al, 1999-2012
Medical comorbidity

- Rf for faster progression

- Frailty

- Ad results in porrer health –poorer nutrition, sleep, medication complainse
Salutogenesis of AD: Why don’t we all get it if we live long enough?

- **Genes:** Apo E 2,3
- **Absence of:** head injury
  - high fat diet
  - obesity
  - diabetes (hyperinsulinemia)
  - stroke
  - heart disease, hypertension and smoking
  - chronic inflammation
  - toxic exposures
- **Presence of:** high levels of education and physical and mental activity; fruits, vegetables, fish, intake
  - anti-Ab antibodies
  - alcohol use?
PROTECTIVE FACTORS FOR ALZHEIMER’S DISEASE

Non-modifiable

- young age
- apolipoprotein E-e2 and e3 alleles
- absence of family history of dementia
- absence of mild cognitive impairment
- male gender

Modifiable

- high education and occupational achievement
- vigorous participation in mental and physical activities
- Avoidance of cardiac disease, diabetes & hypertension
- dietary use of antioxidants, B vitamins
- avoidance of high fat diet, obesity, smoking, head injury
- low level of alcohol consumption
AD Progression

- CSF $\beta_42$
- Amyloid imaging
- FDG-PET
- MRI hippocampal volume
- CSF Tau
- Cognitive performance
- Function (ADL)

Patho- and Salutogenesis

- **Pathogenesis**
  the origination and development of a disease

- **Salutogenesis** (lat. salus = health, genere = to create)
  a shift from the disease-metaphor to the vision of well-being

♦ Pathology may be poorly correlated with impairment
Cognitive impairment

- Dementia
- Hallucinations, delusions
- Behavioral manifestations
- Depression
- Agitation
physical

- Most elderly people have more than 2 chronic conditions
Cognitive decline and bone mineral density

- Estrogen replacement therapy is protective against AD (Kawas et al, 1998)

- Women with osteoporosis have relatively impaired cognitive function and increased risk of cognitive deterioration (Yaffe et al, 1999)
# Nutritional properties of Meat

<table>
<thead>
<tr>
<th></th>
<th>Fat (g/100g)</th>
<th>Commercial Meat</th>
<th>Fat (g/100g)</th>
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<tbody>
<tr>
<td><strong>Wildebeast</strong></td>
<td>4.9</td>
<td><strong>Lamb</strong></td>
<td>21.6</td>
</tr>
<tr>
<td><strong>Waterbuck</strong></td>
<td>1.8</td>
<td><strong>Pork</strong></td>
<td>22.6</td>
</tr>
<tr>
<td><strong>Cape buffalo</strong></td>
<td>6.3</td>
<td><strong>Choice beef</strong></td>
<td>23.8</td>
</tr>
<tr>
<td><strong>Eland</strong></td>
<td>4.8</td>
<td><strong>Extra lean</strong></td>
<td></td>
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(ground beef: 17.1)

(adapted from Eaton, 1992)
SYSTEMS WITH FUNCTIONAL AND STRUCTURAL DECLINE DURING AGING

- Central nervous system
- Peripheral nervous system
- Vision
- Audition
- Skeletal
- Gastrointestinal
- Hepatic
- Renal-genitourinary
- Cardiovascular
- Hematologic
- Endocrine
Benjamin Mast, 2011
• Patients with Alzheimer’s disease have reduced activities in midlife compared with healthy control-group members. Friedland RP, Fritsch T, Smyth KA, Koss E, Lerner AJ, Chen CH, Petot GJ, Debanne SM

193 AD and 358 controls

373 total citations

• Environmental enrichment reduces Abeta levels and amyloid deposition in transgenic mice. Lazarov O¹, Robinson J, Tang YP, Hairston IS, Korade-Mirnics Z, Lee VM, Hersh LB, Sapolsky RM, Mirnics K, Sisodia SS.

16 mice (Total) in three groups

566 total citations
What are the goals for aging?

- Many older people do not have major illnesses, but remain limited in their functional capacities.
What are the goals for aging?

- Many older people do not have major illnesses, but remain limited in their functional capacities.
Cognitive reserve

- Related to genes, environment, education as well as occupational and nonoccupational (recreational) activities

“Education is what survives when what has been learned has been forgotten”  
BF Skinner 1964

Friedland, Epidemiology education and the ecology of Alzheimer’s disease, *Neurology*, 1993

Smyth et al, Worker functions and traits associated with occupations and the development of AD, *Neurology*, 2004

88 year old French physician, MMSE 27, mild dementia
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Cognitive reserve
Cerebral reserve
Multiple reserve
Medline/Pubmed
October, 2013

✧ Cognitive reserve  482
✧ Cerebral reserve    52
✧ Multiple reserve    0
Physical inactivity

- May increase risk of AD 80%
  Barnes and Yaffe: “The projected effect of risk factor reduction on AD prevalence” 2011

- Physical activity enhances executive function in APO E4 carriers with MCI
  Baker et al 2013
Polypharmacy

- 51% of NH residents  
  Vetrano et al, 2013

- increased medication burden is be associated with functional decline in community-dwelling older adults with dementia  
  Lau et al 2011

- 42% of 550 subjects with CI were on benzodiazepines  
  Robles et al, 2012
frailty

♦ Associated with CI, MCI, AD, non AD dementia


♦ Cognitive Frailty and Dementia *Journal of Nutrition Health and Aging*, 17:9, 2013
Kidney function

- Chronic kidney disease is associated with white matter pathology and progression on MRI as an independent risk factor

Kuriyama 2013
“Peripheral education of the immune system by colonic commensal microbiota”

“...the efficient peripheral generation of antigen-specific populations of T(reg) cells in response to an individual's microbiota provides important education of the immune system to foreign antigens, thereby providing tolerance to commensal microbiota.”

“Treg induction by a rationally selected mixture of Clostridia strains from the human microbiota”

- Treg cell inducing microbiota enhance Treg cells and anti-inflammatory IL-10 and ICOS, therapeutic for autoimmune disease in mice

Inflammation in AD

- Microglial activation, Cytokines, IL 1Beta
- Oxidative toxicity
- Increased expressions of TLR2 and TLR4 on peripheral blood mononuclear cells

Zhang et al, 2011, Griffin, 2013
Spirituality

- Arab women who pray have a lower risk of cognitive decline
- Spirituality helps to deal with stress and disease

Personality and dementia

- Among cognitively normal 75 and older, 1/3 have sufficient AB plaques/NFTs to fit criteria for AD
- Greater emotional resilience and conscientiousness associated with reduced risk of dementia in subjects with AD neuropathology

Victor Frankl (1905-1997)

“The greatest task for any person is to find meaning in his or her life. This may come from work, family, or endurance of suffering.”

Man’s Search for Meaning, 1946
87 year old, MMSE score 13/30
Social reserve

- Women live longer with daughters and shorter with more sons

Helle et al. 2012, 2013
Isolation

- Social isolation exacerbates memory deficit by increasing Aβ level in mice  
  Hsiao et al, 2011

- Loneliness is a RF for CI  
  Wilson et al 2007; Miller et al 2007

- Large social networks are protective  
  Bennett et al 2006
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“the outcome of social isolation and inactivity regardless of their origin is usually emotional deprivation and an increase in the decline of physical health and self esteem” Wang 1977
AD Progression

Abnormal

- CSF Aβ_{42}
- Amyloid imaging
- FDG-PET
- MRI hippocampal volume
- CSF Tau
- Cognitive performance
- Function (ADL)

Normal

Presymptomatic eMCI LMCI Dementia

Time

CSF Aβ_{42} Amyloid imaging Cognitive performance Function (ADL)

FDG-PET MRI hippocampal volume

CSF Tau

IMPAIRMENT OF BRAIN TISSUE

PHYSICAL ILLNESS
Malnutrition, Lung, Cardiovascular Disease

DECLINE OF BRAIN FUNCTION

PSYCHOLOGICAL REACTION
Depression, Apathy, Grief,

SOCIAL ADJUSTMENT
Isolation, Inactivity, Deprivation, Poverty

BEHAVIORAL MANIFESTATIONS OF DEMENTIA

Adapted from H.S. Wang, 1977
Alois Alzheimer

Is Aging Inevitable?
Alois Alzheimer 1865-1915

Since aging is not inevitable, it must be considered an opportunity.

What are our goals for the opportunity presented by aging?
Cognitive reserve

- “Plasticity” Baltes et al, 1992
- Account for the discrepancy between an individual's measured level of brain pathology and expected cognitive performance
- Katzman and education
- Stern and CR “Efficiency, capacity, compensation, maintenance, plasticity: emerging concepts in cognitive reserve” Barulli, Stern, 2013
Psychological reserve (2)

- Compulsive traits lead to anxiety
- Coping/compensatory mechanisms
- Isolation causes hallucination, delusions, loss of prestige, Loss of emotional gratification, meaning
“What does the pediatrician need to know about Alzheimer disease?”

“It is vital that public policy takes into account the importance of environmental exposures and lifestyle factors beginning in childhood because of their role in influencing neurodegeneration. **Childhood is the period of life when lifestyle patterns are established such as diet, physical and mental activity, and risk behaviors such as smoking.**”