Populations are getting older

2015 vs 2050

Percentage aged 60 years or older:
- 30% or more
- 10 to <30%
- <10%
"The ageing of populations is poised to become the next global public health challenge. During the next 5 years, for the first time in history, people aged 65 years and older in the world will outnumber children aged younger than 5 years."

See Comment page 484
By 2050, the number of people over the age of 80 will triple globally. These demographics could come at great cost to individuals and economies. Two groups describe how research in animals and humans should be refocused to find ways to delay the onset of frailty.
Number of people with Dementia Worldwide

- **2015** → 47 million
- **2030** → 75 million
- **2050** → 131 million

A fast growing epidemic -
A Brief History of Alzheimer’s Disease

On November 25th, 1901, Auguste Deter was admitted to the Frankfurt hospital where she was examined by Dr. Alois Alzheimer. She had a striking cluster of symptoms that included reduced comprehension and memory, as well as aphasia, disorientation, unpredictable behavior, paranoia...
Alzheimer’s Disease 100 years ago

In November 1906, Dr. Alois Alzheimer reported on Auguste Deter. The translated title of his lecture ‘on peculiar disorder of the cerebral cortex’. Subsequently this presenile dementia was designated ‘Alzheimer’s disease’.

In 1907 he reported on the autopsy findings:

→ **TANGLES**: ‘In the core of otherwise almost normal cells there stands out one or several fibrils due to their characteristic thickness and peculiar impregnability.’

→ **PLAQUES**: ‘Numerous small miliary foci are found in the superior layer. They are determined by the storage of a peculiar material in the cortex.’
Clues from the Scene of the Crime

Brain Atrophy

Neuronal Loss

93 year old normal

80 year old AD

Neurofibrillary Tangles

Senile Plaques
**Historical perspective on the AD diagnosis**

**1906 - 1950**
During this period, individuals aged <65 years who developed dementia were diagnosed as having AD or presenile dementia when no other known causes of dementia were present. Individuals with dementia who had a strong history of vascular disease and exhibited executive symptoms were labeled as having multi-infarct dementia, independent of their age. Patients who developed dementia aged ≥65 years and for whom no other cause of this condition was known were diagnosed as having senile dementia. This form of dementia was understood to be vascular and prompted the use of vasodilators.

**1950 - 1980**
In this period, late-onset AD was recognized to be pathologically indistinguishable from the early-onset form of this disease. In addition, the vascular explanation for senile dementia was largely abandoned. Consequently, the age criterion for the label AD was lifted, the term senile dementia was abandoned, and the diagnosis of AD was assigned when all other possible causes of cognitive impairment were excluded. In addition, a key publication by Katzman and colleagues noted the “malignancy” of AD.

*Nature Reviews Neurology 7, 137-152 (March 2011)*
Historical perspective on the AD diagnosis

1980 - present
The vascular component of late-onset AD has again been recognized. In 1984, the National Institute of Neurological and Communicative Disorders and Stroke and Alzheimer's Disease and Related Disorders Association criteria were implemented. The key to these criteria is the linkage of clinical syndromal patterns to neuropathology after death through the use of possible, probable and definite labels for AD.

Nature Reviews Neurology 7, 137-152 (March 2011)
The Story Continues
Pathology of Alzheimer’s Disease

- There are 3 consistent neuropathological hallmarks
  - Neuritic Plaques (Amyloid-rich senile plaques)
  - Neurofibrillary tangles
  - Neuronal degeneration – Synaptic Loss

- These changes eventually lead to clinical symptoms, but may begin years before the onset of symptoms
  - Amyloid plaque formation precedes neurofibrillary tangles, with amyloid accumulation occurring during a long preclinical period lasting years up to 10 – 15 years
  - 20% to 40% show extensive amyloid pathology with minimal or no clinical AD symptoms
Aβ-Amyloid Plaques

- Neuritic Plaques are extracellular
  - Primarily of amyloid
  - Abnormal proteinaceous material
  - Cellular elements

- The form of amyloid in Alzheimer’s brains is Aβ

- Distributed in the cortex and limbic nuclei

- Highest concentration is in the hippocampus

- Aβ in late-onset Alzheimer’s disease may be an imbalanced or ineffective Aβ clearance rather than excess formation
Amyloid Processing

- Amyloid Precursor Protein (APP) is metabolized by intracellular proteases
  - β-secretase cleaves APP at an extracellular site beyond the cell membrane
  - γ-secretase cleaves APP in the transmembrane portion of the protein
    - These cleavages produce β-amyloid peptides and then protofibrils that are neurotoxic
    - After transport to extracellular space the β-amyloid peptides aggregate to form plaques which mature to neuritic plaques
  - APO-ε4 may facilitate accumulation of β-amyloid

Cummings JL: The Neuropsychiatry of Alzheimer’s Disease and Related Dementias. Martin Dunitz; 2003
Neurofibrillary Tangles

- Neurofibrillary tangles are intracellular collections of abnormal filaments, which have a distinct paired helical structure.
  - It is unique to Alzheimer’s disease
  - The neurofibrillary tangles of supranuclear palsy do not have the paired helical structure
- Results from hyperphosphorylation of the microtubule-associated protein tau
- Found throughout the neocortex and limbic nuclei
- Neurophil threads are related.
  - Paired helical filamentous structures clustered among the dystrophic neurites of senile plaques
**Synaptic Loss**

- Oligomers of Aβ are implicated as direct synaptotoxins.

- Neurodegeneration, synaptic loss, and cognitive symptoms are more strongly associated with the formation and extent of neurofibrillary tangles than with amyloid plaque deposition.

- The deep layers of the temporal cortex and the hippocampus sustain the greatest degree of synaptic loss.

- Loss of acetylcholine, serotonin, and norepinephrine inputs to cortex contribute to the cognitive and behavioral symptoms.

The continuum of Alzheimer's disease

Cognitive function

Preclinical

Aging

MCI

Dementia

Years

Model of the clinical trajectory of Alzheimer’s disease (AD). The stage of preclinical AD precedes mild cognitive impairment (MCI) and encompasses the spectrum of presymptomatic autosomal dominant mutation carriers, asymptomatic biomarker-positive older individuals at risk for progression to MCI due to AD and AD dementia, as well as biomarker-positive individuals who have demonstrated subtle decline from their own baseline that exceeds that expected in typical aging, but would not yet meet criteria for MCI. Note that this diagram represents a hypothetical model for the pathological-clinical continuum of AD but does not imply that all individuals with biomarker evidence of AD-pathophysiological process will progress to the clinical phases of the illness.

Hypothetical model of the Alzheimer's disease (AD) pathophysiological sequence leading to cognitive impairment. This model postulates that amyloid beta (Aβ) accumulation is an “upstream” event in the cascade that is associated with “downstream” synaptic dysfunction, neurodegeneration, and eventual neuronal loss. Note that although recent work from animal models suggests that specific forms of Aβ may cause both functional and morphological synaptic changes, it remains unknown whether Aβ is sufficient to incite the neurodegenerative process in sporadic late-onset AD. Age and genetics, as well as other specific host factors, such as brain and cognitive reserve, or other brain diseases may influence the response to Aβ and/or the pace of progression toward the clinical manifestations of AD.
Hypothetical model of dynamic biomarkers of the AD expanded to explicate the preclinical phase: Aβ as identified by cerebrospinal fluid Aβ_{42} assay or PET amyloid imaging. Synaptic dysfunction evidenced by fluorodeoxyglucose (F18) positron emission tomography (FDG-PET) or functional magnetic resonance imaging (fMRI), with a dashed line to indicate that synaptic dysfunction may be detectable in carriers of the ε4 allele of the apolipoprotein E gene before detectable Aβ deposition. Neuronal injury is evidenced by cerebrospinal fluid tau or phospho-tau, brain structure is evidenced by structural magnetic resonance imaging. Biomarkers change from normal to maximally abnormal (y-axis) as a function of disease stage (x-axis). The temporal trajectory of two key indicators used to stage the disease clinically, cognitive and behavioral measures, and clinical function are also illustrated.

Treatment Issues
Current Pharmacotherapy

- Donepezil
- Rivastigmine
- Galantamine
- Memantine

Neurotransmitter based
What is New in Pharmacotherapy?
Amyloid Processing

- Amyloid Precursor Protein (APP) is metabolized by intracellular proteases
  - ß-secretase cleaves APP at an extracellular site beyond the cell membrane
  - γ-secretase cleaves APP in the transmembrane portion of the protein
    - These cleavages produce ß-amyloid peptides and then protofibrils that are neurotoxic
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- Found throughout the neocortex and limbic nuclei
- Neurophil threads are related.
  - Paired helical filamentous structures clustered among the dystrophic neurites of senile plaques
Reduced production of Amyloid

A. BACE 1 Inhibitors
   i. E2609 – 700 subjects - Prodromal AD or Mild AD (2016)
   ii. AZD 3293 – 2200 subjects – MCI due to AD or Mild AD (2019)

B. BACE 1+2 Inhibitor – 1500 subjects
   i. Verubecestat Phase 3 – Prodromal AD (2018)

C. Pioglitazone
   i. (A PPARy agonist that acts as a BACE inhibitor) –Phase 3
   ii. MCI due to AD – 3500 people (2019)
Other Mechanisms of Action


2. **Insulin** – Phase 2/3 – 240 people with MCI or early AD (2016)

3. **Glulisine** – Rapidly acting insulin analogue – Phase 2 – 90 people with MCI or mild AD (2017)

4. **Gllostaza** – PDE3 Inhibitor (it is an antiplatelet drug) – Phase 2 – 200 people with MCI (2018)
Increased Clearance of Amyloid

Monoclonal antibodies - Passive immunotherapy

1. **Solanezumab** - A-4 Study – 1150 people (65-85 years old) with asymptomatic amyloidosis (2020)

2. **Solanezumab** – Early onset familial AD (18-80 years old) – 105 who have APP, PSEN1 or PSEN 2 mutations (DIAN-Tu) (2019)

3. **Gantenerumab** – Phase 2/3 – DIAN-Tu – Early onset familial AD (18-80 years old) – 105 who have APP, PSEN1 or PSEN 2 mutations (2019)

4. **Crenezumab** – Phase 2 – 300 members of columbian families including 200 carriers of PSEN1 mutation (2020)
5. **BI-409306** – PDE9 Inhibitor enhances synaptic plasticity and reduces Amyloid toxicity - Phase 2 - 624 people with MCI due to AD (2016)

6. **Simvastatin** – Cholesterol lowering drug with anti-inflammation properties; can lower Aβ production – Phase 4 – 520 people with amnesic MCI (2018)

7. **VX-745** – P38-MAP kinase inhibitor – modulates inflammation – Phase 2 – 32 people with MCI due to AD or mild AD (2016)
Increased Clearance of Amyloid - continued


9. **BAN 2401** – Phase 2 – 800 people with MCI due to dementia or mild AD (2020)

10. **Intravenous Immuno Globulin** (contains naturally occurring polyclonal anti Aβ-antibodies) – Phase 2 – 50 people with MCI (2017)
Modulation of Neuro Transmission

1. **Atomoxetine** – Phase 2 (Noradrenaline uptake inhibitor) – 40 people with MCI (2017)

2. **Ladosticil (TV 3326)** – Acetyl Cholinesterase inhibitor and MAO inhibitor – Phase 2 – 200 people with MCI (2016)

3. **DAOIB** – NMDA receptor regulator - enhances NMDA receptor mediated Glutamatergic neuro transmission – 50 people with MCI (2016)

4. **PXT 00864** (a combination of Acamposate and Baclophen) Regulates GABA-ergic neuro transmission – Phase 2 – 45 people – 60 years or younger with mild AD (2015)
Hypothetical model of AD pathophysiological cascade

- Age Genetics
- Cerebrovascular risk factors
  Other age-related brain diseases
- Amyloid-β Accumulation
- Synaptic Dysfunction
  Glial Activation
  Tangle Formation
  Neuronal Death
- Cognitive Decline
- Brain and cognitive reserve
  ? Environmental factors

Pathways to sporadic AD

- Cholesterol metabolism
- Glucose metabolism
- Inflammation
- Membrane/vesicle recycling
- Oxidative stress

Treatment approaches

- Preventive strategies
- Modification strategies
  - Breakthroughs from basic research
  - New biomarkers for AD subtypes

Pathways to familial AD

- Aβ accumulation
- Synaptic deficits
  - Tau aggregation
- Neuronal death

- Aβ-modification strategies
  - Immunotherapy
  - Enzyme inhibitors
  - Anti-aggregants

- Tau-modification strategies
  - Immunotherapy
  - Kinase inhibitors
  - Anti-aggregants

- Symptomatic or palliative strategies
Epidemiological and genetic studies of people with non-genetically determined (ie, sporadic) AD have identified mechanisms that might underlie brain Aβ accumulation, neuronal tau hyperphosphorylation, and synaptic deficits, ultimately leading to cognitive impairment and dementia. In familial AD, the disease begins with Aβ pathology. It seems likely that different causative pathways result in distinct disease subtypes, which should be treated differently. The identification of subtypes of patients, with homogeneous pathogenesis and prognosis, will facilitate research and result in more accurate and personalized treatments for sporadic and familial AD.

AD=Alzheimer’s disease. Aβ=amyloid β.
Mitochondrial Dysfunction
Mitochondrial Dysfunction: Common Final Pathway in Brain Aging and Alzheimer’s Disease — Therapeutic Aspects

Walter E. Müller
Anne Eckert
Christopher Kurz
Gunter Peter Eckert
Kristina Leuner
SO WHAT IS REALLY NEW?
Treat Aging
1. Treat aging
   
a. Exercise
   
b. Low calorie diet and intermittent fasting
   
c. Classical yoga with breathing practices and meditation
Fauja Singh, here aged 100, prepares for Britain’s Edinburgh marathon in 2011.
Figure 1. The Seven Pillars of Aging
Cell 159, November 6, 2014 ©2014 Elsevier Inc.
### Table 1. Critical Areas of Aging Research and Important Goals

<table>
<thead>
<tr>
<th>Areas of Aging Research</th>
<th>Important Goals</th>
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</thead>
<tbody>
<tr>
<td>Adaptation to stress</td>
<td>Bridge continuum from psychological to molecular stresses</td>
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<tr>
<td></td>
<td>Differentiate hormesis from toxic stress</td>
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<tr>
<td></td>
<td>Better align human and animal studies</td>
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<tr>
<td>Epigenetics</td>
<td>Biomarker development: chronologic vs. biologic aging</td>
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<tr>
<td></td>
<td>Link age-related environmental inputs to epigenetic signatures</td>
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<td></td>
<td>Test small molecules that regulate enzymes controlling epigenetic events</td>
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<tr>
<td>Inflammation</td>
<td>Differentiate adaptive and maladaptive inflammatory responses</td>
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<td></td>
<td>Define age-related inflammatory sources and their systemic effects</td>
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<td></td>
<td>Determine how obesity and metabolic dysfunction alter inflammation with age</td>
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<tr>
<td>Macromolecular damage</td>
<td>Generate systems-level understanding of the types of macromolecular damage and their roles in chronic disease states</td>
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<td></td>
<td>Understand how stochastic damage influences the variability of aging</td>
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<tr>
<td>Metabolism</td>
<td>Define role of signal transduction pathways linked to metabolism in the aging process</td>
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<td></td>
<td>Understand contribution of circadian clocks to aging and metabolism</td>
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<td></td>
<td>Connect metabolic dysfunction with tissue-specific decline in aging</td>
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<tr>
<td>Proteostasis</td>
<td>Identify proteostatic pathways that are overwhelmed in specific chronic disease states</td>
</tr>
<tr>
<td></td>
<td>Examine crosstalk between proteostasis machineries</td>
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<tr>
<td></td>
<td>Understand non-cell-autonomous signaling and activation of proteostasis pathways</td>
</tr>
<tr>
<td>Stem cells and regeneration</td>
<td>Determine whether declining adult stem cell function drives aging and chronic disease</td>
</tr>
<tr>
<td></td>
<td>Examine how aging and associated disease impair adult stem cell function</td>
</tr>
<tr>
<td></td>
<td>Determine how macromolecular damage accumulates in aging adult stem cell pools</td>
</tr>
</tbody>
</table>
What is Aging?
Aging

• Chronological

• Functional

• Molecular
Chronological Age vs Functional Age

- **Chronological Age** – counting birthdays
- **Functional Age** – how well we are able to do things related to our life experience

« How old would you be if you didn’t know how old you were? »

Satchel Paige, age 47
Pitcher, Cleveland Indians

Ref. APA 2012 Annual Meeting – Course: Depression and Cognitive Impairment in Late Life. Donald Davidoff. PhD
Molecular Aging
Scientists discover DNA body clock
Newly discovered mechanism could help researchers understand ageing process and lead to ways of slowing it down

Horvath looked at the DNA of nearly 8,000 samples of 51 different healthy and cancerous cells and tissues. Photograph: Zoonar GmbH/Alamy
“DNA Methylation age of human tissues and cell types”
Telomeres
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 forestalls telomere shortening and has additional non-telomeric roles in cell survival.
Telomeres are the end caps ("aglets") of our DNA

When telomeres critically shorten, the ends of the DNA are exposed to damage, and the cell dies

Telomere damage increases p53, leading to cellular growth arrest, senescence and apoptosis, and decreases PGC-1α, leading to decreased mitochondrial biogenesis and function and increased ROS.
PBMC Telomere Length and Aging

- On average, healthy adults lose ~30 - 100 base pairs/year. But this is variable, with some people maintaining or even lengthening telomeres over time.

Frenck et al, PNAS 1998

AAGP Annual Conference – O.M. Wolkowitz, MD. – Telomere as a marker of accelerated Aging in Major Depressive Disorder
The association between multivariable adjusted 3MS scores and telomere length tertile. Models were adjusted for age, gender, race, education, and assay variability. *p for trend = 0.98 for baseline and 0.01 for change score.
Gene Expression and the System Biology of Brain Aging

1. Age-related expression changes account for only a small fraction of the genes monitored in gene expression studies in different species.

2. There is an age-associated induction of stress response genes that is common to all the species studied. A significant reduction in the expression of mitochondrial genes was also detected. This may suggest that mitochondrial dysfunction may be a source of increased stress.

3. There is evidence showing that ‘oxidative stress’ contributes to many of these changes.
Can age promote disease?

Can specific diseases stem from age-related pathways?
Figure 2: Evolutionary changes in gene regulation in the brain during ageing.

- **Age-downregulated**
- **Age-upregulated**

- Mouse brain
- Human brain
- Rhesus macaque brain
- Human blood
- Human muscle
- Human kidney

A broad regulatory shift in age-related gene expression appears in the primate lineage. Genes that change with ageing in the human and rhesus macaque cortex are predominantly downregulated (pink), in contrast to the mouse cortex, where most age-regulated genes are upregulated (green). This degree of gene repression is not observed in several other non-neural human tissues, including peripheral blood mononuclear cells (T.L. and B.A.Y., unpublished observations), muscle and kidney.

TABLE 2 - Evolutionary conservation of gene expression changes during brain ageing

<table>
<thead>
<tr>
<th>Gene category</th>
<th>Human brain</th>
<th>Rhesus macaque (brain)</th>
<th>Rat (brain)</th>
<th>Mouse (brain)</th>
<th>Fly (organism)</th>
<th>Worm (organism)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress response</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
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<td>↑</td>
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<tr>
<td>Mitochondria</td>
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<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Neural plasticity/synaptic function</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Inhibitory interneuron function</td>
<td>↓</td>
<td>↓</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Ubiquitin-proteasome pathway</td>
<td>↓</td>
<td>↓</td>
<td>–</td>
<td>↓</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Immune/inflammatory response</td>
<td>↑</td>
<td>–</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td>Metalion homeostasis</td>
<td>↑</td>
<td>–</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Myelin-related proteins</td>
<td>↑</td>
<td>–</td>
<td>↑</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Glial genes</td>
<td>↑</td>
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</tr>
</tbody>
</table>

Some gene categories, such as those involved in stress responses and mitochondrial function, show conserved changes during ageing, whereas others, such as inhibitory interneuron function, exhibit primate-specific changes.

An upward arrow indicates that expression increases with age; a downward arrow indicates that expression decreases with age; and a dash indicates that no change in expression with age is detected in the ageing mouse brain, different subset of mitochondrial genes are either age-upregulated or age-down regulated.

Neural Mechanisms of ageing and cognitive decline
Nicholas A. Bishop, Tao Lu, and Bruce A. Yankner
Published in Nature, Mar 25, 2010; 464 (7288) 529-535
Figure 3: Conserved pathways that regulate organismal and brain ageing.

NATURAL 464, 529-535, March 2010
Shown are mechanisms that involve mitochondrial function, oxidative stress, autophagy, protein homeostasis, TOR signalling, insulin/IGF-1 signalling (IIS), caloric restriction (CR) and sirtuins. Modest concentrations of ROS generated by mitochondria during normal metabolism may induce stress-resistance pathways that scavenge ROS and repair damage. However, progressive mitochondrial damage may lead to pathological concentrations of ROS production, which, in turn, may contribute to further mitochondrial damage. Damaged mitochondria can be cleared by autophagy, which is promoted by CR and inhibited by TOR signalling. CR improves overall mitochondrial function, in part, by promoting mitochondrial biogenesis and reducing ROS production. ROS can damage other crucial macromolecules, such as DNA and proteins. Unrepaired DNA damage may give rise to epigenetic changes and gene silencing and may exacerbate mitochondrial impairment by reducing the expression of nuclear-encoded mitochondrial genes. ROS can also modify proteins, leading to protein unfolding and aggregation. Modified proteins can be removed by a number of degradative pathways, including the ubiquitin–proteasome pathway. Inadequate clearance may lead to the accumulation of toxic protein aggregates. The dynamics of protein clearance and aggregate formation may be modulated by the IIS pathway and by SIRT1 and CR. The accumulation of damaged and toxic proteins may also be modified through the regulation of messenger RNA translation by TOR signalling and CR.

Figure 4: The brain as a potential regulator of organismal ageing.
Fig. 6. Molecular aging is conserved in the prefrontal cortex
Adapted from (Erraji-Benchekroun et al., 2005). An age-related expression cluster representation is depicted for 588 core age-affected genes. Note the continuous progression and similar effects in two areas of the prefrontal cortex (Brodman areas, BA9 and BA47). Each probeset is represented by a row, each array or brain area per subject by a column. Samples are organized left to right by brain area and increasing age. Green and red bars indicate decreased and increased gene expression, respectively, versus the averaged signal for these genes across all samples. Along the Y-axis, probesets are clustered according to similarities in expression profiles across age. In this cohort, a similar number of probesets were downregulated (n=291, upper panel) and upregulated (n=297, lower panel) throughout lifetime. Columns to the right indicate the distribution of genes with glial- (WM) or neuronal-enriched (GM) origin of gene transcripts. Notice the high concentration of glial-enriched genes with increased expression with age, while most, but not all, neuronal-enriched genes appeared to be downregulated with age.
Fig. 7. Molecular age predicts chronological age

Adapted from (Erraji-Benchekroun et al., 2005). The “molecular” age represents a summary number for each individual that is defined by age-regression analysis of expression levels for core age-affected genes when compared to transcript changes in all other subjects. Overall, there is a high correlation between “molecular” and chronological ages (BA9: r=0.65; BA57, r=0.73). A few samples demonstrated larger deviation than average at both young and older ages. These subjects did not correspond to any identifiable clinical, demographic, or experimental parameters.
Table 1: Examples of agreement in directions of changes between age- and disease-related genes

Adapted from (Glorioso et al., 2010). Red or green boxes indicate significant up-and down-regulations (p < 0.05) of mRNA and/or protein levels in disease or during aging. Grey boxes indicate genetic associations with disease with unknown or unclear reports of directionality in disease.
How may normal brain aging contribute to age-gated neurological disease?
Fig. 9. Proposed molecular/cellular pathways underlying molecular aging and its functional Consequences

Modulation of this pathway by genetic and/or environmental factors is hypothesized to underlie molecular mechanism(s) behind the gating of disease onset and variable functional declines by normal brain aging.
Age-upregulated (red) and age-downregulated (blue) gene categories are shown for microarray studies of aging in species from Caenorhabditis elegans to man. The insert shows the phylogenetic relationship and estimated time of the last common ancestor between species in millions of years (green), as previously described (163).

DNA damage and brain aging. Oxidative damage of DNA may be mediated by reactive oxygen species (ROS) derived from aging mitochondria. DNA damage is repaired efficiently in the young adult brain, but persists in the aged brain. During normal aging, this may result in the silencing of genes involved in synaptic plasticity, mitochondrial function, and protein trafficking, potentially contributing to cognitive decline. In neurodegenerative diseases, DNA damage may additionally compromise neuronal survival.

Figure 2
Global impact of mitochondrial aging. In the aging brain, reduced autophagic clearance of degenerating mitochondria and increased mitochondrial DNA (mtDNA) damage may reduce ATP levels and elevate the level of reactive oxygen species. Reactive oxygen species can further damage nuclear and mitochondrial DNA, resulting in reduced transcription, and damage RNA and protein, giving rise to protein misfolding and aggregation. Aggregated proteins may accumulate in the aging brain as a result of inefficient clearance through the autophagic and ubiquitin-proteasome pathways. Toxic protein aggregates may also lower the mitochondrial permeability transition pore (mPTP) threshold for inducing apoptosis.

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Summary - Molecular Aging

- Aging is fundamentally molecular.
- Mitochondrial dysfunction is the primary event.
- Stress causes mitochondrial aging.
  - Reduces ATP and increases ROS.
- Neuronal DNA repair processes are compromised leading to cell death.
So what to do?
Late-onset dementia: a mosaic of prototypical pathologies modifiable by diet and lifestyle

Mark P Mattson
AGING

Impaired bioenergetics
Impaired calcium Handling
Oxidative damage
Impaired autophagy
Inflammation

PROTEIN AGGREGATION/TOXICITY
Aβ
Tau
TDP-43
α-Synuclein

Synapse dysfunction
Synapse degeneration
Neuronal death

DEMENTIA

Impaired adaptive stress responses
Reduced neurotrophic support
FIGURE 2

Generic age-related cellular stress and specific proteopathic abnormalities exert reciprocal cross-amplifying detrimental effects on synaptic plasticity and neuronal viability. During aging, neurons experience reduced energy availability (e.g., mitochondrial dysfunction and reduced glucose transport), increased levels of oxidative stress, perturbed cellular calcium homeostasis, impaired autophagy, and inflammation. The latter adverse changes are exacerbated by a reduced ability of neurons to respond adaptively to stress. The aggregation and associated neurotoxic activities of proteopathic proteins (Aβ, Tau, TDP-43 and α-synuclein) are promoted by metabolic, oxidative and calcium-related stress and impaired autophagy/protein degradation. Thus, cross-amplifying neurodegenerative processes result in synapse dysfunction, degeneration and neuronal death, resulting in dementia.
a

CHALLENGES
Fasting
Exercise
Intellectual
Phytochemicals

RECOVERY
Eating
Relaxation
Sleeping

Enhancement of:
Learning and Memory
‘Cognitive Reserve’
Motor Function
Stress resistance

Calcium
ROS
Energy demand
AMPK, CREB, PGC-1α
Neurotrophic factors
Autophagy
Antioxidant enzymes
DNA repair enzymes

mTOR
Protein synthesis
Mitochondrial biogenesis
ATP
Neurite outgrowth
Synaptic plasticity
Neurogenesis

ROS
Oxidative damage
DNA damage
Protein aggregation

Resistance to ILOD

b

Fast Run Sleep Eat Run Eat Relax Sleep

day night day night
FIGURE 3

Intermittent bioenergetic challenges forestall ILOD by stimulating adaptive stress response pathways. (a) As with other species, humans evolved in environments where there was competition for food, mates and other resources. Accordingly, selection favored individuals whose brains functioned best when they were hungry, physically active and under stress. In response to the challenges (exercise, dietary energy restriction/fasting, intellectual challenges and consumption of noxious phytochemicals) neurons experience mild bioenergetic and oxidative stress. The neurons respond adaptively by activating signaling pathways that improve their ability to cope with more severe stress and resist disease. These neuroprotective pathways are triggered by calcium, reactive oxygen species (ROS) and increased energy demand, and involve kinases such as AMP-activated kinase (AMPK), and transcription factors such as cyclic AMP response element binding protein (CREB). The latter pathways increase autophagy, and induce the expression of genes encoding neurotrophic factors, antioxidant enzymes and DNA repair enzymes. During the challenges there is a reduction of mTOR (mammalian target of rapamycin) activity and protein synthesis. Once the challenge is over (e.g., food has been acquired) there is a recovery period that involves eating, relaxing and sleeping. During the recovery period mTOR activity, protein synthesis and mitochondrial biogenesis increase, and the growth of axons and dendrites, formation of new synapses and neurogenesis (the production of new neurons from stem cells) occur. Because of the adaptive stress responses induced during the challenge period levels of oxidative stress, DNA damage and protein aggregation are reduced. This model predicts that individuals who regularly engage in cycles of challenges and recovery periods during their adult life will exhibit optimal brain function and will be relatively resistant to the development of ILOD. (b) An example of a lifestyle that includes intermittent challenges as a means of optimizing brain health. In this case the person fasts (water or non-caloric beverages only) on the first day, while engaging in intellectual challenges (light bulb) and physical exercise (running). On the next day the subject eats several meals, runs, relaxes and engages in critical thinking.
Purpose in Life
1. Our lifestyle should allow the most advanced part of our brain (prefrontal cortex) to exercise control over the more primitive parts. This results in resistance to stress called “Resilience”. If not, “stress” is the outcome.

- Stress accelerates brain aging

2. Appropriate values & attitudes to life together with the “effort” to put it into practice creates resilience.
What are these Values and Attitudes?
Ryff's model of psychological well-being

- Personal growth
- Self-acceptance
- Autonomy
- Environmental mastery
- Positive relationships
- Purpose in life
"The **THING** is to **UNDERSTAND MYSELF**,  
To see what **GOD** really wishes **ME** to **DO**;  
The **THING** is to **FIND A TRUTH** which is **TRUE** for **ME**,  
To **FIND THE IDEA** for which **I** can **LIVE** and **DIE**."

-Søren Kierkegaard
Social Genomics

Gene Expression profile of ‘Conserved Transcriptional Response to Adversity (CTRA)’
⇒ Leads to Stress and Aging
Psychological Well-Being and the Human Conserved Transcriptional Response to Adversity

Barbara L. Fredrickson, Karen M. Grewen, Sara B. Algoe, Ann M. Firestine, Jesusa M. G. Arevalo, Jeffrey Ma, Steve W. Cole
A functional genomic perspective on human well-being

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Well-Being

Hedonic
Eudaimonic
Hedonic Well-being

Based on the individual’s pleasurable experiences
Eudaimonic Well-being (Aristotle)

- Results from striving towards meaning and a nobler purpose beyond simple gratification
Gene Expression Profile:

Is an opposite direction in the two types of well-being. In the Hedonic well-being, it is in the direction of chronic stress and aging.

In the Eudaimonic well-being, it is in the opposite direction of non-stress, and negative aging.
Conclusion  Greater purpose in life is associated with a reduced risk of AD and MCI in community-dwelling older persons.
Classical Yoga

(Includes lifestyle changes, physical yoga, breath training and meditation)
The default mode networks links the effects of yoga and early AD pathology
Default mode network and Alzheimer’s disease
At rest, but active. fMRI images of a normal human brain at rest. The images reveal the highly organized nature of intrinsic brain activity, represented by correlated spontaneous fluctuations in the fMRI signal. Correlations are depicted by an arbitrary color scale. Positive correlations reside in areas known to increase activity during responses to controlled stimuli; negative correlations reside in areas that decrease activity under the same conditions. (Left) Lateral and medial views of the left hemisphere; (center) dorsal view; (right) lateral and medial views of the right hemisphere. [24 NOVEMBER 2006, VOL 314, SCIENCE, 1249-1250]
Default mode network

- Structural aspects
- Parts of medial prefrontal cortex (Mpfc)
- Posterior cingulate cortex and the cingulate ventral pre-cuneus and parietal cortex
- Lateral temporal & parietal cortex
- Hippocampus
Metabolic reduction in the posterior cingulate cortex in very early Alzheimer's disease.

This study investigated cerebral glucose metabolism in very early Alzheimer's disease, before a clinical diagnosis of probable Alzheimer's disease is possible, using [18F]fluorodeoxyglucose positron emission tomography. First, 66 patients with probable Alzheimer's disease with a spectrum of dementia severity (Mini-Mental State Examination score, 0-23) were recruited and studied. Cortical metabolic activity was analyzed topographically using three-dimensional stereotactic surface projections. Regression analysis was performed for each brain pixel to predict metabolic patterns of very early disease. Predictions were tested prospectively in a group of 8 patients who complained only of memory impairment without general cognitive decline (Mini-Mental State Examination score, 25 +/- 1) at the time of scanning but whose condition later progressed to probable Alzheimer's disease. Both results were compared to cerebral metabolic activity in 22 age-similar normal control subjects. Prediction and analysis of actual patients consistently indicated marked metabolic reduction (21-22%) in the posterior cingulate cortex and cinguloparietal transitional area in patients with very early Alzheimer's disease. Mean metabolic reduction in the posterior cingulate cortex was significantly greater than that in the lateral neocortices or parahippocampal cortex. The result suggests a functional importance for the posterior cingulate cortex in impairment of learning and memory, which is a feature of very early Alzheimer's disease.

Minoshima S(1), Giordani B, Berent S, Frey KA, Foster NL, Kuhl DE. Author information: (1)Department of Internal Medicine, University of Michigan Medical School, Ann Arbor 48109-0028, USA.
Figure 4.
Default mode network (DMN) regions have elevated glycolysis in healthy control subjects and increased glucose metabolism and amyloid binding in Alzheimer’s disease (AD). From left to right: DMN regions have increased aerobic glycolysis DMN regions in the normal brain; DMN regions have decreased glucose metabolism in AD; DMN regions are the first to develop amyloid deposition in AD.

Probing the Molecular Mechanism of Mind-Body Practices with Genomic and Translational Techniques
The Benson-Henry Institute (BHI) is an Independent thematic center at MGH Clinical practice, research and education

“Mind and body practices focus on the interactions among the brain, mind, body, and behavior, with the intent to use the mind to affect physical functioning and promote health”: meditation, yoga, taichi

(http://nccam.nih.gov)
BHI Working Hypothesis

- We look for the common pathway between mind-body techniques and their salutary effects.
- The stress response is a state characterized by sympathetic overdrive (Cannon WB, 1929).
- The relaxation response (RR) is a state, elicited by mind-body techniques, characterized by decreased oxygen consumption, decreased heart rate, and decreased respiratory rate which offsets the effects of stress (Benson, 1971).
- Mind-body techniques can be used to combat stress in a broad array of stress-initiated or exacerbated illnesses.
Healthy Individuals: Matched for age, gender, race, height, weight and marital status

Group **M**: 19 Long-term Practitioners of Daily RR Practice

Group **N₁**: 20 Controls

Group **N₂**: 20 N₁ individuals who completed 8 weeks of RR training
Mind-Body Techniques Used in M Group to Elicit the Relaxation Response

- Vipassana Meditation
- Mantra Meditation
- Mindfulness Meditation
- Transcendental Meditation
- Breath Focus
- Kripalu Yoga
- Kundalini Yoga
- Repetitive Prayer
Findings

- Distinct differences in the gene expression profiles (GEPs) between individuals with many years of practice (group M) and those without such experience (group N₁).
- Significant GEP changes within the same individuals before (N₁) and after 8 weeks of training (N₂).
- Similar changes in GEP found in M vs. N₁, and those of N₂ vs. N₁.
RR Practice enhances expression of gene associated with:

- Energy metabolism
- Mitochondrial function
- Insulin secretion
- Telomere maintenance
- Critical molecules - mitochondrial synthesis and insulin
- Inflammatory response
- Stress related pathways
- Critical pattern - NF-kB Pathway (down regulates)

Altogether these results indicate that Relaxation Response elicitation may evoke its’ downstream health benefits by improving mitochondrial energy production and utilization, and thus promoting mitochondrial resilience through up regulation of ATPase and insulin function. Mitochondrial resilience might also be promoted by RR induced down regulation of NF-kB.
Science Proves: Meditation Reverses Aging Process by Causing the Elongation of Telomeres

REFERENCE: UTKU OGUZ
POSTED ON SEPTEMBER 17, 2014
Meditation can literally change your brain!
Kundalini Yoga Found to Enhance Cognitive Functioning in Older Adults

Vabren Watts

Published online: May 03, 2016

Yoga can do more than reduce stress in older adults, says geriatric psychiatrist Helen Lavretsky, M.D.
Conclusions

1. The current focus on downstream events such as \( \beta \) Amyloid and Tau is not likely to lead to efficient prevention or treatment of AD.

2. Mitochondria are the organs of energy production in the brain and they are intimately involved in brain aging and AD.

3. Exercise and calorie restriction which includes intermittent fasting have been shown to reverse the aging and stress effects on mitochondria.

4. In studies on social genomics, purpose in life has also been shown to be an important contributor towards protection against the stress induced aging effect in the brain.

5. Yoga and meditation have also shown to be effective in reversing aging in general (telomeres) and brain aging in particular.

6. However, these programs need to be implemented in a large scale in order to have an impact on this “rising tide” or “tsunami” called Alzheimer’s disease.
Medical Education
- Emphasize prevention
- Courses on energy restriction and exercise

Biomedical Research
- NIH
- Foundations
- Others

Government
- Federal
- State
- Local

Education
- Primary
- Secondary
- College

Physicians
- Pediatricians
- General practice
- Psychiatrists
- Disease specialists

BRAIN-WASTING FORCES
- Food Industry
- Pharmaceutical Industry
- Agriculture
- Effort-sparing technologies

Diagnosis and Treatment
- Prescriptions
- Energy restriction plans
- Exercise plans
- Rehabilitation Facilities
  - 3 – 4 week intervention
  - Intermittent ER
  - Daily Exercise
  - Monthly Follow-Up

Families
- Parents lead by example

Media
- Internet
- Television
- Newspapers
THANK YOU!