The Aging Brain
“One of the greatest success stories of modern times is the increasing number of people living into old age.

However this triumph of humanity is also one of our greatest challenges.”

Kofi Annan – 2000
Nobel Peace Prize Winner - 2001
Secretary General United Nations 1997-2007
Aging population

- Economic
- Social
- Health Care
- Planning
- Research
- Prevention
- Intervention
- Treatment

2050 almost $\frac{1}{2}$ population of Europe $> 60$
Cognitive Impairment

- Quality of Life
- Disability
- Neuropsychiatric
- Dementia
- Health Care
Dementia

Prevalence of Cognitive Impairment and Dementia, by Age (ADAMS)

- 16.2 MILLION

Dementia > Stroke + Cardiac + Cancer
Dementia will overwhelm world health services

(Ferri et al, 2006 Lancet)
Biological Aging

- Skin/Hair
- Musculoskeletal
- Senses
- Cardiovascular
- Respiratory
- Endocrine
- Gastrointestinal
- Immune
Cognitive Aging

Doctor, Doctor, I keep forgetting things.
When did this start?

Memory Function
Processing Speed
Executive Function
Cognitive Decline

- Cognitive Decline
  - Age-Determined
  - Pathological

- Differential Decline
  - Inter-individual variability
    - Nature
    - Severity

- Preserved Function
Is Cognitive Decline Inevitable?

Nola Ochs
BA
Aged 95

Bernard Herzberg
MA
Aged 96

Michael Cobb
PhD
Aged 91
Individual Difference

- Inevitable?
- Heterogeneity?
- Source?
- Multiple factors
  - age-intrinsic
  - age-extrinsic
Multiple Factors

- Age Intrinsic
  - Cognitive Decline
  - Age Extrinsic
- Disease
- Non-Disease
- Degenerative Psychiatric Somatic Vascular
- Education Economic Environment Genetic Lifestyle Social
Dynamic Interaction

Cognitive Decline

- Education
- Economic
- Genes
- Environment
- Health
- Lifestyle
- Social
Research

- Usual
- Successful
- Pathological
- Markers
- Predict
- Prevent
- Intervention
- Rehabilitation

Picasso - Painter – Aged 74
Brain Ageing

- Brain Volume reduction
- Ventricular enlargement
- Regional neuronal loss
- Axons & dendrites
- Neurotransmitters
- Cerebral blood flow
- Cerebral metabolic rate
- Senile plaques
- Neurofibrillary tangles
Brain Volume Reduction
Ventricular Enlargement

- Young / Old differences
- Begin Early
- Across Lifespan
- Grey matter
- Not pathological
- Acceleration
Brain Volume Reduction
Ventricular Enlargement

- Adults 0.2% per year
- Seniors 0.5% per year
- Double in AD
- Volume losses 30-90
  - 14% cerebral cortex
  - 35% hippocampus
  - 26% white matter

- Regional differences
  - 1% temporal parietal occipital
  - 10-17% frontal cortex
  - 8% striatum
  - 22% prefrontal 5th-7th decade
  - 43% prefrontal after 65
Brain Volume Reduction
Ventricular Enlargement

- Subarachnoid space
- Ventricles
- Sulci & Gyri
- Frontal Cortex
Reduced volumes in the hippocampus in the aged brain.
White Matter

Communication Channels

Nerve Fibres

Grey Matter

Information Processing

Diffusion Tensor Imaging

Changes with Age
White Matter

young/old
ty young/AD
old/AD
Cognitive Aging

“Against the backdrop of generalized age-related deterioration, numerous differential changes loom, like multiple islands of relative preservation and decline” Raz, 2000

- Decline
  - Processing speed
  - Episodic Memory
  - Executive /Attention

- Preserved
  - Semantic Memory
  - Autobiographical Memory
  - Emotional Processing
  - Implicit Memory
  - Procedural*
  - Short-term*
Figure 1. Mean performance as a function of age in tasks assessing episodic memory, semantic memory, short-term memory and the perceptual representation system.
Education Protects Against Alzheimer’s Disease?
Demented Identical Twin

Non-demented Identical Twin

Left school legal minimum age

Stayed on in school
Education is not just noise....

Dementia Rating Scale

Alzheimer cells

healthy cells

Education Builds a Better Connected Brain

More able to cope with disease?
But so do other types of engagement....

Bennet et al, Lancet Neurology
Enrichment selectively increases NA


Enrichment’s memory and neurogenesis effects mediated by novelty.

Novelty mediated by NA.

Veyrac et al (2008), Neuropsychopharmacology
“LC-NE activation affects synapses throughout the CNS, suppressing most, but permitting or even accentuating activity in those that are transmitting novel or significant stimuli...this favours the development of persistent facilitatory changes in all synapses that are currently in a state of excitation” (Kety, 1972)
‘The only major region that does not receive input from the LC is the area that contains the basal ganglia’ (Sara (2009) Nat Rev Neuroscience)
Human noradrenergic Markers?

Rajowksi et al 1993

Murphy, Robertson and O’Connell 2012
NOVELTY
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Sustained Attention Performance and Noradrenaline in ADHD

Greene et al, 2011, Bellgrove et al, 2009
Cognitive Reserve and Pupil Dilation (IQ/Education)

BORTEMANN et al 2010

Van der Meer et al, 2010
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More Education linked to bigger pupil dilation

Challenging mental tasks dilate pupils

Other people dilate pupils

Actively remembering things dilates pupils

NOVELTY dilates pupils
EDUCATION TRIGGERS MULTIPLE NA INFUSIONS, INCREASING BRAIN CONNECTIVITY

MENTALLY CHALLENGING ACTIVITIES AND JOBS DO THE SAME

ENGAGING WITH OTHER PEOPLE SIMILAR EFFECTS

THIS LIFETIME OF BOOSTED NORADRENALINE ACTIVITY MAY AFFECT THE DISEASE PROCESS ITSELF

WE CAN NOW MEASURE THESE EFFECTS
Reduced Risk of AD

BRAIN MECHANISMS

DISEASE COMPENSATION
INCREASED CORTICAL VOLUME
INCREASED CORTICAL CONNECTIVITY
NEUROGENESIS
SYNAPTOGENSES
BDNF INCREASE

DISEASE MODIFICATION
ANTI-INFLAMMATORY
REDUCED AMYLOID BURDEN,
PLAQUE SIZE
and AGGREGATION
RESCUES CHOLINERGIC &
DOPAMINERGIC CELLS

NORADRENALINE

EDUCATION
IQ
MENTAL ACTIVITY
SOCIAL ENGAGEMENT
ENVIRONMENTAL ENRICHMENT
NOVELTY

Modifiable Variables

COGNITIVE RESERVE
Brainstem Nuclei (LC, DRN, SN, VTA) and Cognitive Decline
(Wilson et al, 2013, Neurology)
Successful Aging

Protective APOE 2/2 allele, 'longevity genes'

APOE, presenilin risk for other diseases

Cardiovascular training, caloric restriction

Hypertension, diabetes

Compensation, functional plasticity

Atrophy, white matter damage, neurotransmitter dysfunction

Cognitive training programs, active involvement

‘Use it or lose it’ social and cognitive isolation after retirement

Positive emotional bias

Depression, personality changes in dementia

Dementia and decline
Additional Reading
