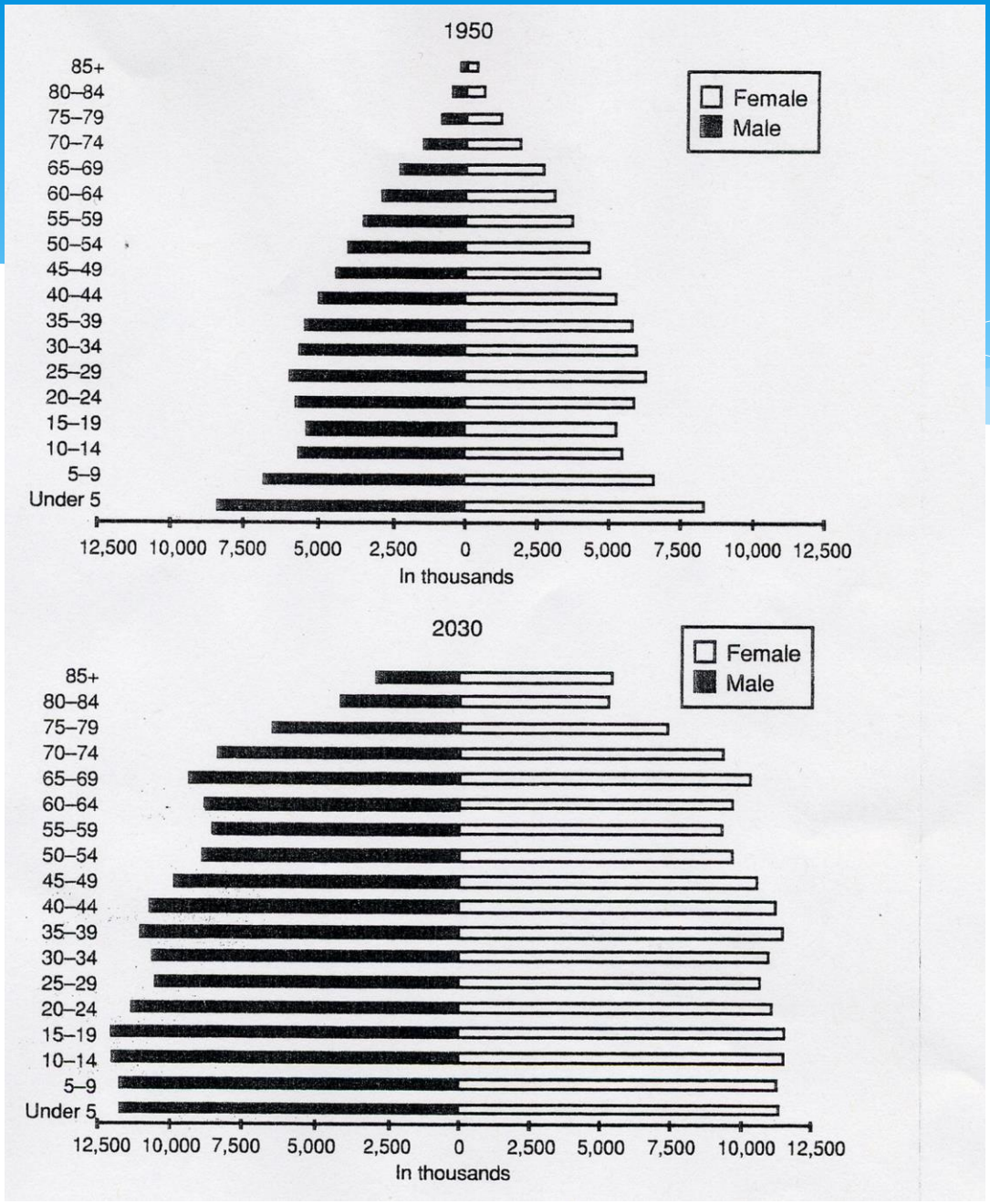
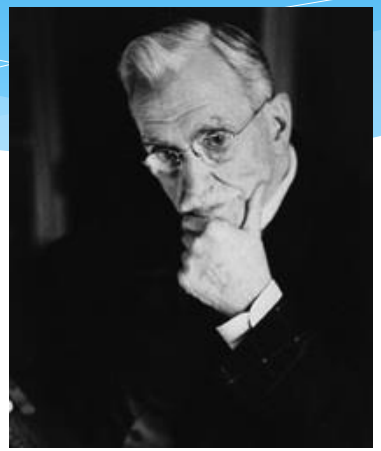
Psychobiology of cognitive ageing and dementia

Aims of this workshop

* To provide some examples of age-related change in cognitive performance and how we test them
* To provide an overview of brain changes associated with ‘normal’ and with pathological ageing
* To provide an overview of techniques for imaging brain structure
* To provide an overview of biological risk factors
* To consider some of the implications of knowing our genetic risk score
* To consider lifestyle factors to counter brain changes


1950
85+
80–84
75–79
70–74
65–69
60–64
55–59
50–54
45–49
40–44
35–39
30–34
25–29
20–24
15–19
10–14
5–9
Under 5
Female
Male
12,500 10,000 7,500 5,000 2,500 0 2,500 5,000 7,500 10,000 12,500
In thousands
2030
85+
80–84
75–79
70–74
65–69
60–64
55–59
50–54
45–49
40–44
35–39
30–34
25–29
20–24
15–19
10–14
5–9
Under 5
Female
Male
12,500 10,000 7,500 5,000 2,500 0 2,500 5,000 7,500 10,000 12,500
In thousands

* Emmet Reid
  Professor of Chemistry
  Hopkins University



* First book at 86
* Second book at 98
* Autobiography at 100… "*My First One Hundred Years: An Interim Report*"

why are people so different in the way they and their cognitive skills age?

why do some experience pathological change – resulting in a dementia - when others do not?

Ageing in three dimensions

* social
* psychological
* biological

Social ageing

- social habits and the roles of individuals in relation to the expectations of various groups and of society

- SOCIAL maturation begins at birth and continues throughout the lifespan

Biological ageing

* nearness to death - the position of an individual relative to his/her potential lifespan

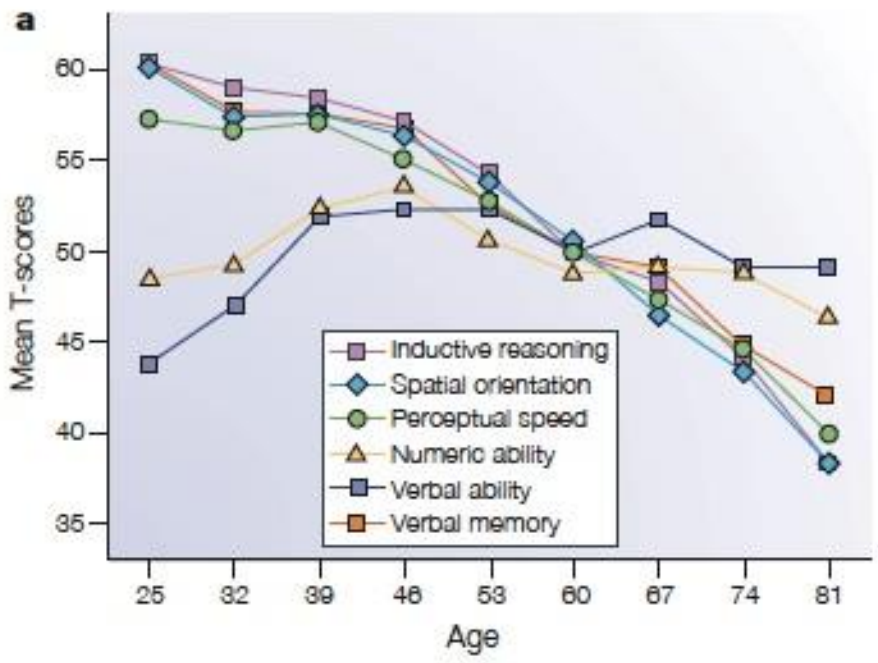
* biological DEVELOPMENT occurs until an individual attains physical maturity
* biological AGEING occurs from mature adulthood

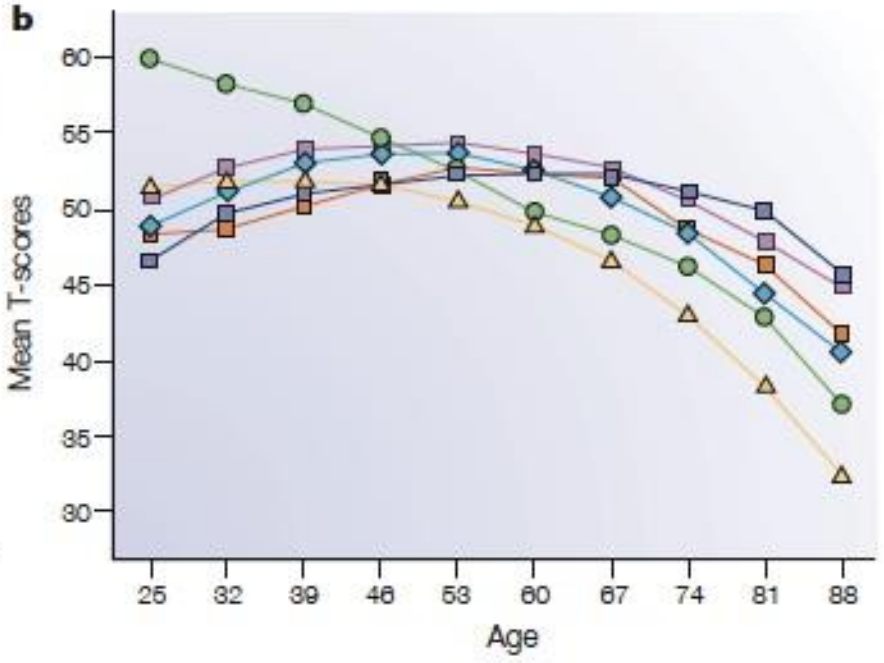
* by definition, then, a period of decline…?
* all biological ageing involves decrements or changes in the direction of less capacity

Psychological ageing

* adaptive capacity of an individual in terms of behavioural response, subjective reactions and awareness
* different aspects begin at different time points in a person's life
* includes the possibility of stability and increment as well as decline

Cognitive ageing: Schaie 1996





cross sectional data

longitudinal data

cognitive slowing - reduced processing speed

* Ageing is accompanied by slowed responding on almost every task in which response speed is assessed
* Salthouse et al, 1988, 1998, 2003..

reduced working memory capacity

* Working memory (WM) …

"a short term memory system that holds on to small amounts of information while you use them in ongoing activities" - "online processing"

* Baddeley & Hitch, 1986; Schacter, 2001

* linked to…
  * deficits in multitasking
  * reduced capacity/processing resource
  * deficits in effective encoding of new material

reduced ‘executive control’

- Executive control processes ….
- “high level functions that encompass organisation, sequencing and regulation of processes for everyday behaviours that require planning, holding open of multiple goals or maintaining cognitive flexibility”

- Linked to.. SHIFTING… UPDATING… INHIBITION
- Miyake (2002)

…needed for inhibitory control, cognitive flexibility, dual task performance, working memory

Task-switching paradigms:
requirement for high cognitive flexibility
stretches
executive processes

Older adults show poorer cognitive flexibility and inhibitory control

Gazzaley et al (2005)

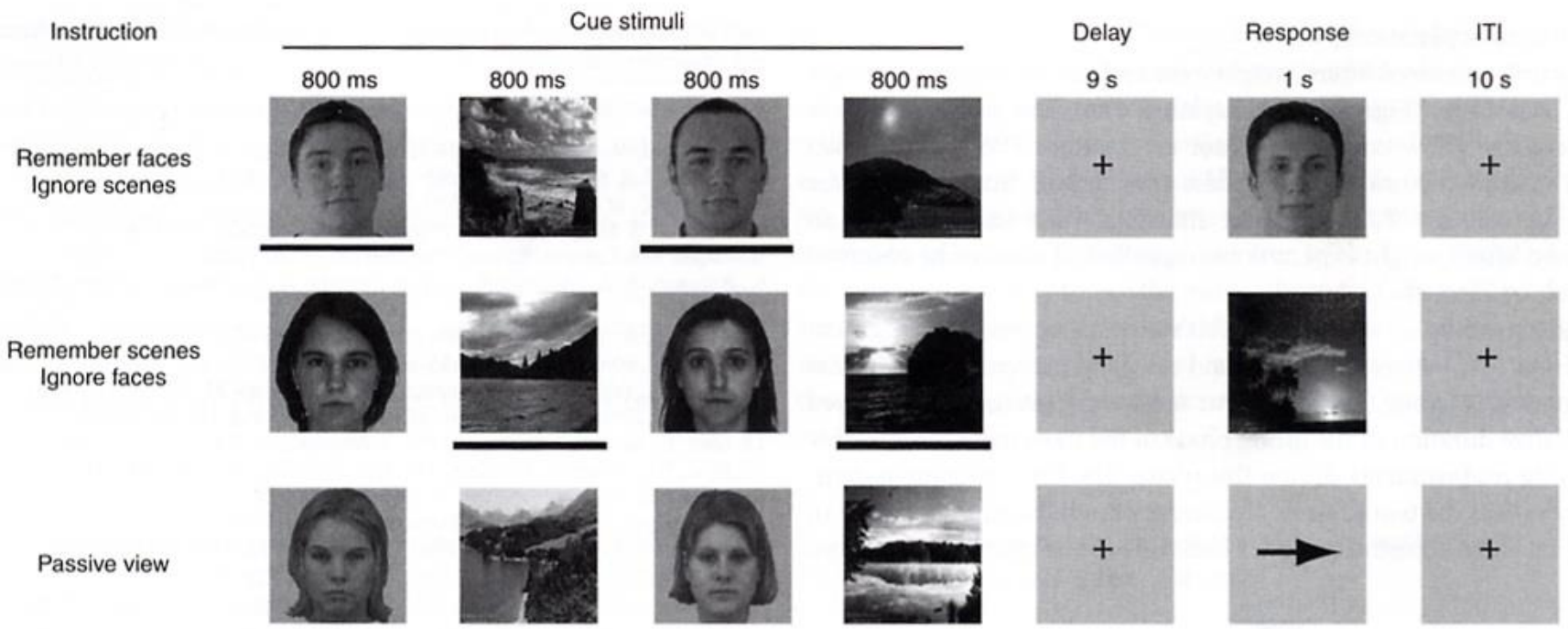
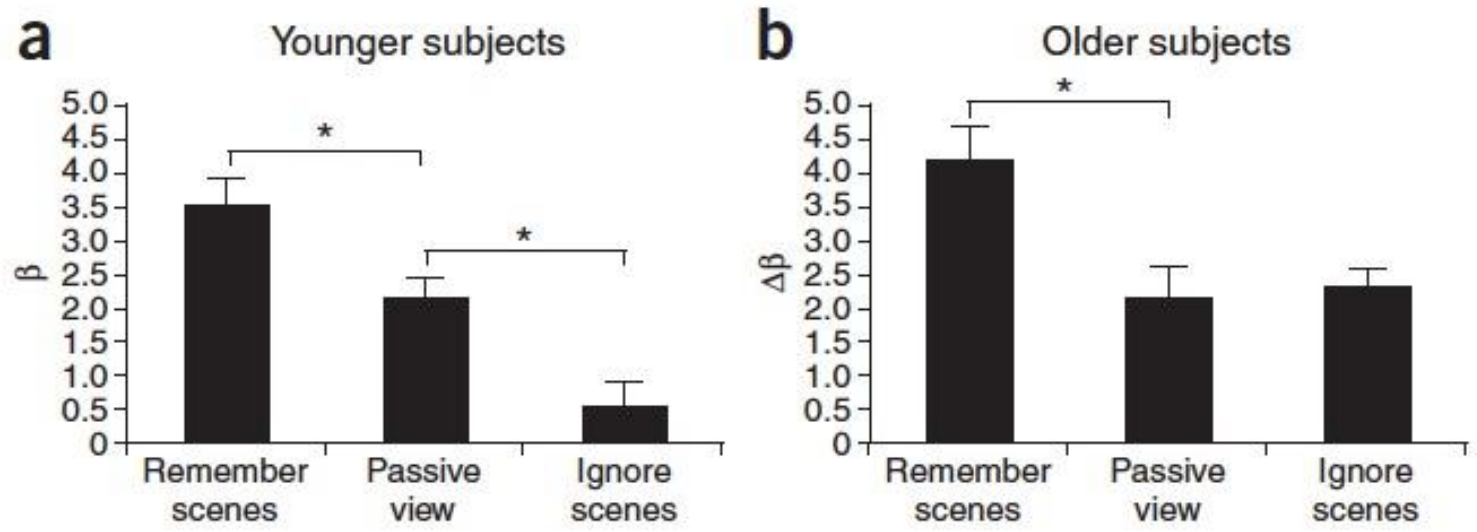


Figure 1 Experimental framework. The three tasks differ only in the instructions given at the beginning of each run, instructing the participant which, if any, stimuli they should attempt to remember over a 9-s delay, and in the response requirements. In the response period of the two memory tasks, a face or scene stimulus was presented (corresponding to the relevant stimulus class), and participants were required to report with a button press whether the stimulus matched one of the previously presented stimuli. In the 'passive view' response period, an arrow was presented, and participants were required to make a button press indicating the direction of the arrow. The lines below the stimuli are used to highlight task relevance in this illustration and were not present in the actual task.



Gazzaley et al, (2005)

Dual task paradigms:
dividing attention across 2 tasks
stretches
working memory

Older adults are impaired when attention/executive resources have to be shared between tasks

Einstein et al (1998)

* Standard single task condition: remember to press a designated key once and once only during each of 11 successive 3-minute tasks

* Divided attention condition: volunteers simultaneously listen for targets (two odd digits in a row) in a continuous stream of digits presented aurally

Design and results

* 2 x 2 design
* Younger/Older adults (mean 19.8 vs 70.7 yrs)
* Standard/Divided attention conditions
* Measure: number of errors (pressing designated key more than once per task)

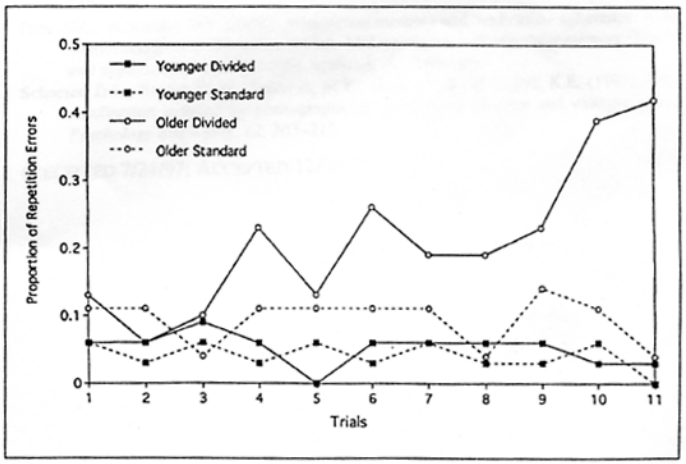


Fig. 1. Mean proportion of repetition errors as a function of age (younger vs. older adults) and attention conditions (divided vs. standard). For ease of apprehension, the results are collapsed over the cue variable.

VOL. 9. NO. 4. JULY 1998

Cognitive slowing, executive inhibition and Prospective Memory

..not always performance penalties

* Shift with age from fast, novel processing to reliance on accumulated knowledge

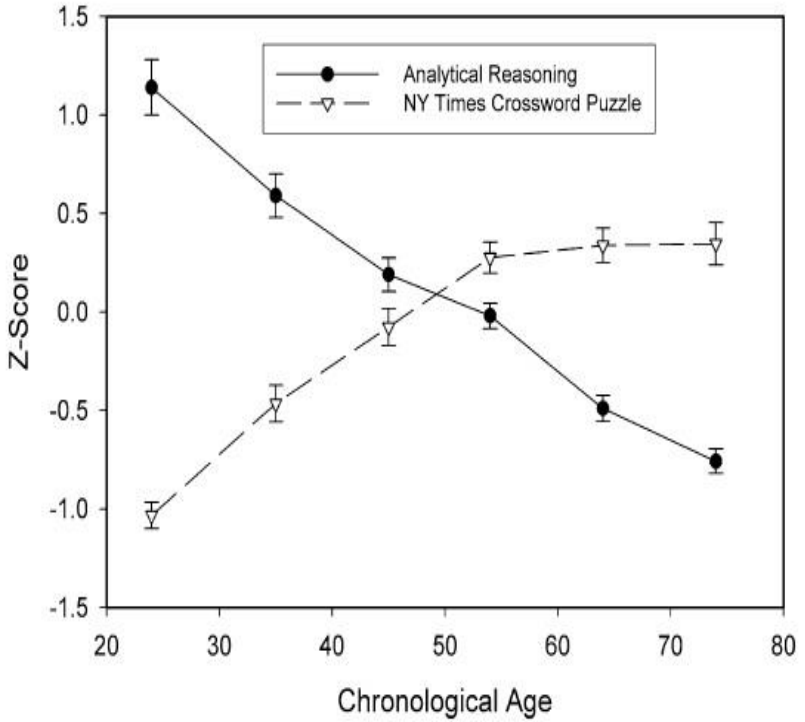


Figure 4

Means (and standard errors) of performance on an analytical reasoning test and on a crossword puzzle test from studies by Salthouse and colleagues.

Salthouse 2012

Biological ageing in BRAIN

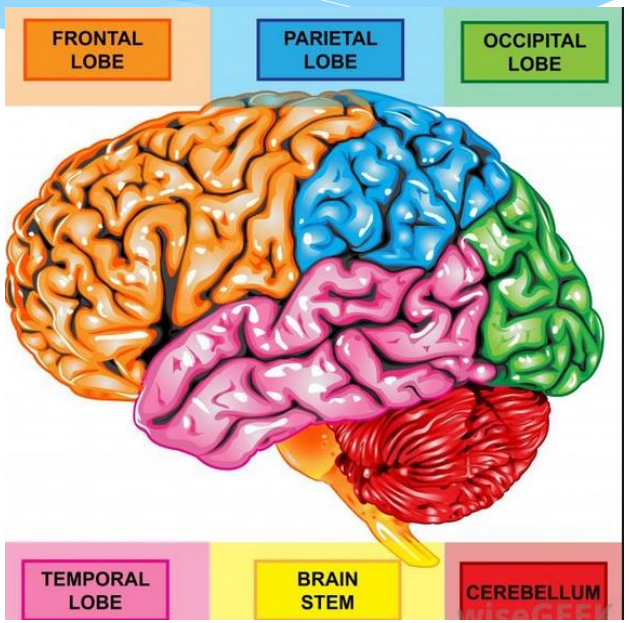
* cell death - reduced brain volume
* loss of dendritic branching - reduced efficiency in communication between neurons
* increases in abnormal deposits/structures ..
  * beta amyloid
  * senile plaques
  * lewy bodies
  * neurofibrillary tangles
  * white matter hyperintensities
* reduced neurotransmitter activity
* cerebrovascular damage

‘Normal’ brain ageing

Atrophy (cell loss)

in 4 key brain regions

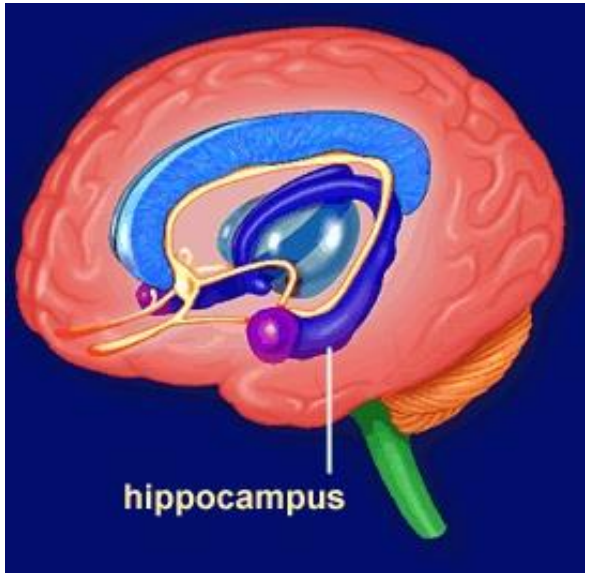
* Cerebellum
* Frontal lobes
* Temporal lobe
* Hippocampus



* Purjinke cell loss in cerebellar cortex: 25-44% over 5 decades
* Frontal lobe: 17% - 23% reduction beyond 6th decade
* Temporal lobes: up to 40-50% reduction in volume through 7th decade

Hippocampus

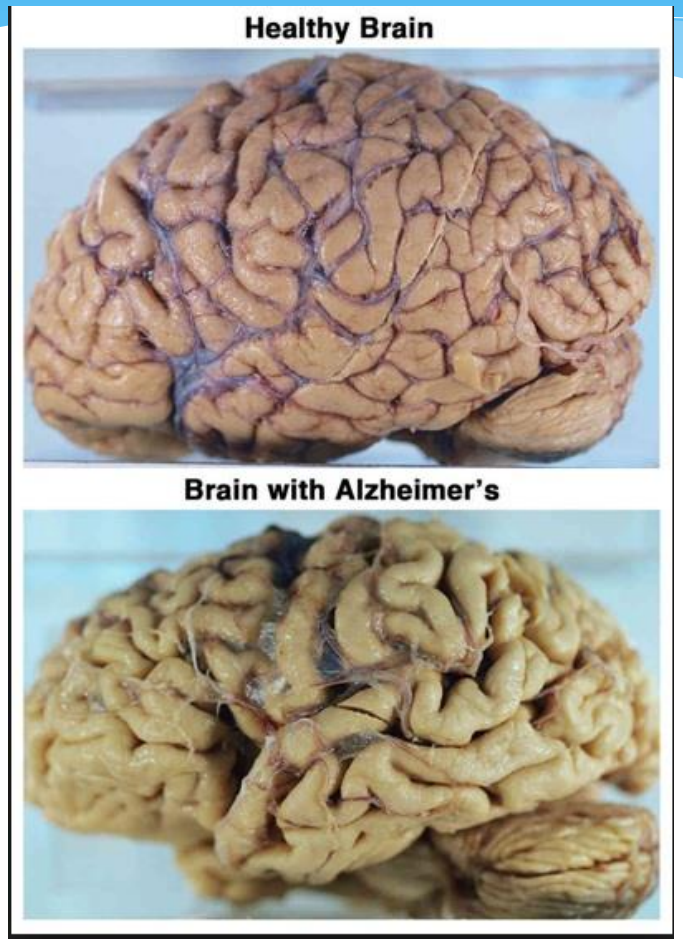
* Age-related loss in hippocampus
* 15-20% reduction in volume through 7th decade

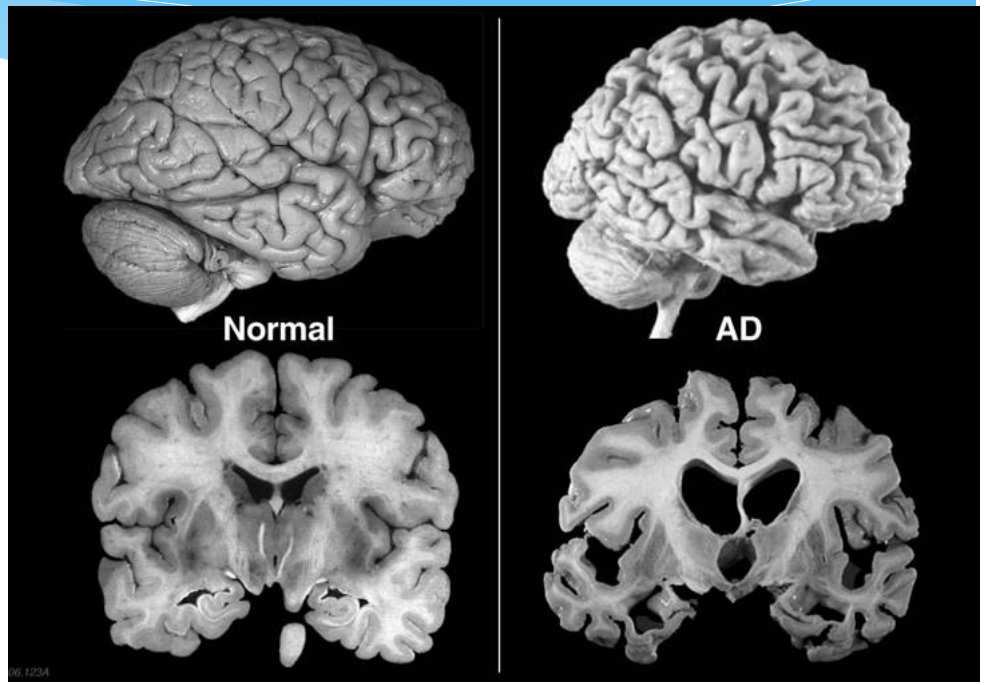


implicated in deficits in…

* episodic memory formation
* retrieval from memory
* associative memory
* spatial memory

Pathological change



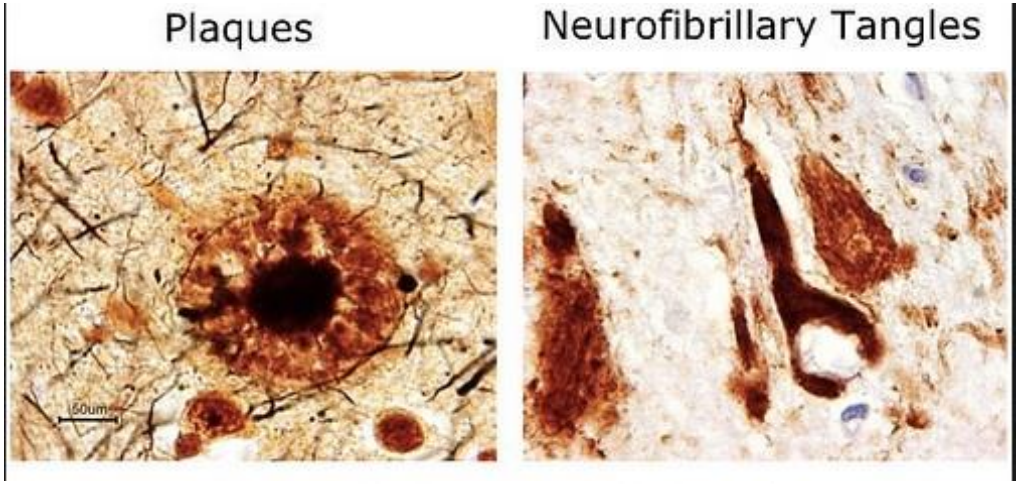


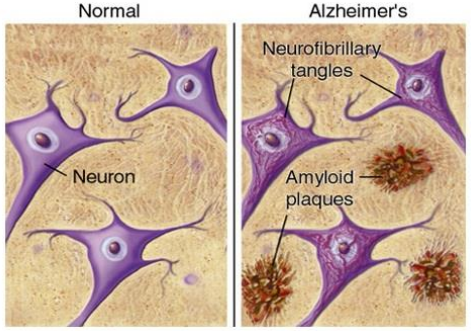
Significant tissue loss, including frontal lobes

Alzheimer type dementia defined by presence of 'Braak pathology'

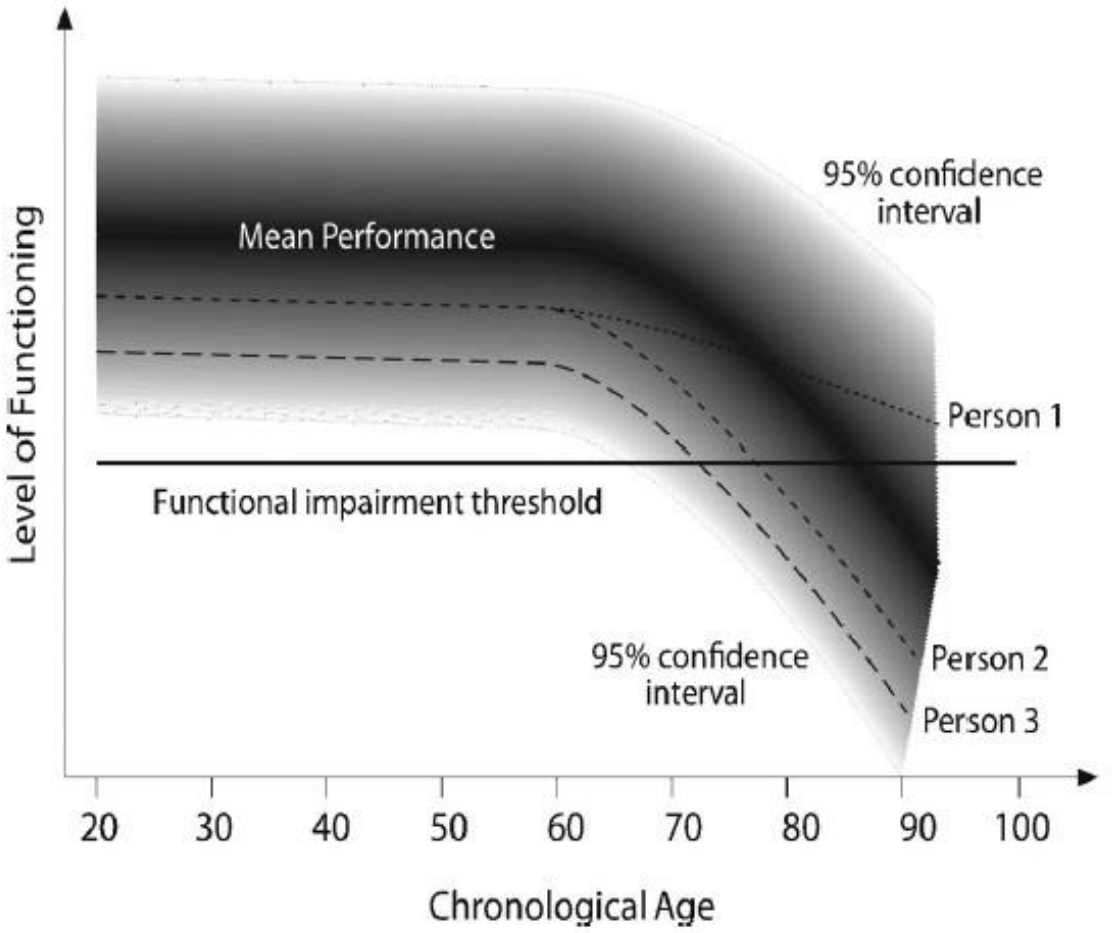
Senile plaques:
excess β-amyloid (Aβ) protein

Neurofibrillary tangles:
misformed tau protein





* Functional consequences of age-related biological changes vary across individuals



Lovden et al, 2010

cognitive flexibility

* The inherently adaptive and variable nature of cognitive and brain functioning..

* The range of existing (and novel) cognitive states/processes available and the ability to rapidly adapt these to environmental demands

plasticity

* the capacity for reactive change in flexibility (in response to new demands, including to perform complex cognitive processes)

  ..occurring at a level of:

* individual neurons – eg. change in neuronal firing rate (in response to pharmacological agents, or when new learning takes place)
* morphological changes - eg. increased dendritic branching in the cortex of older animals exposed to enriched environments

compensation

* the capacity to recruit additional neural tissue from specific sites to counteract neurocognitive deficits in response to loss or deficiency
* functional reorganisation observed after lesion or stroke.. .but also in normal ageing
* can involve profound adaptation/ reorganisation of brain function

Seeing the changes in the brain: Imaging techniques

Structural Magnetic Resonance Imaging (MRI)

* uses magnetic fields and radio waves to excite hydrogen molecules in the brain and generate maps of different tissue types based on the relaxation properties of the hydrogen atoms.
* Estimating volume of brain tissue across white and grey matter separately by aligning all sample brains and computing volume on a voxel-by-voxel basis

vascular (multi-infarct) dementia

* BRAIN INFARCTs result in death of region of brain to which blood supply is blocked
* Multiple small strokes eventually result in sufficient loss of tissue to produce dementia syndrome
* More common in males
* Onset may be abrupt
* unequal distribution of deficits in cognitive function
* 10-30% of dementias
* most common type in some countries e.g. Japan, China & Sweden

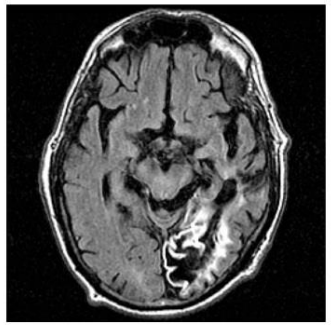


Figure 1. MRI scan (axial T1 sequence) showing large cortical infarcts in the dominant (left) hemisphere consistent with multi-infarct dementia.

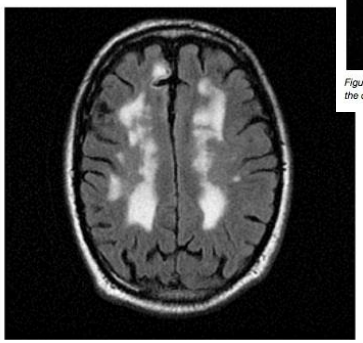
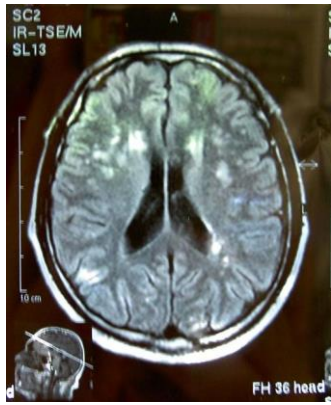
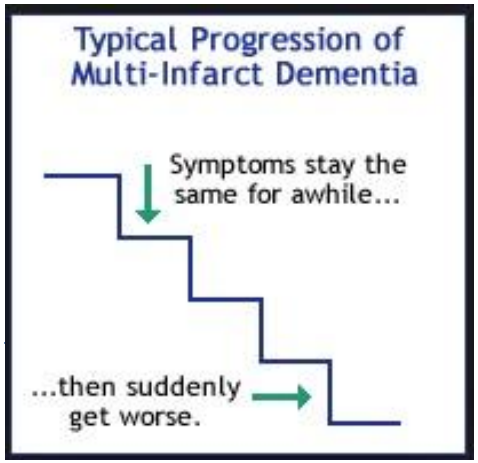


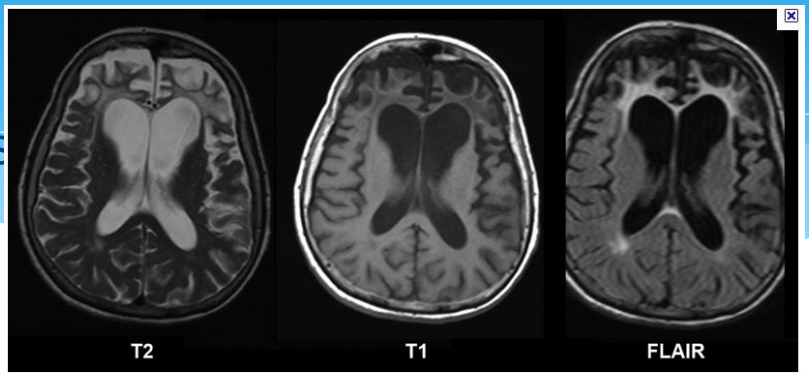
Figure 2. MRI scan (axial fluid-attenuated inversion recovery sequence) showing extensive white-matter lesions consistent with subcortical ischaemic vascular dementia.



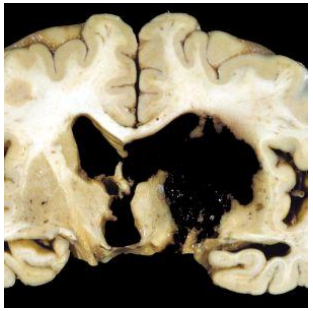


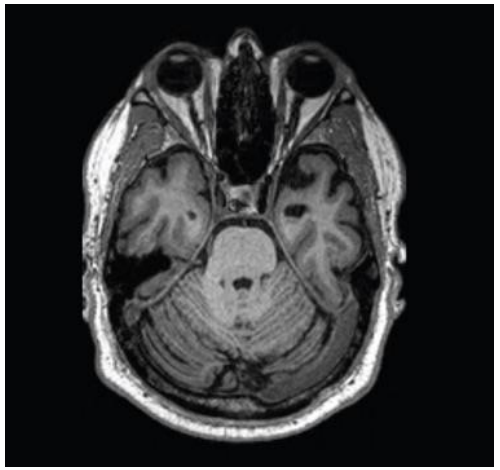
Fronto-temporal dementia

* Includes Pick's disease
* Linked to chromosome 17 abnormalities and tau pathology
* Large proportion of <65 yr dementias
* No obvious memory problems



* Two clinical presentations:
* Behavioural: impulsive, disinhibited or blunted, social and personal neglect, repetitive behaviour, lack of social tact and empathy





* Language: disturbed understanding and generation of language, behavioural problems also

AD is a progressive brain disease

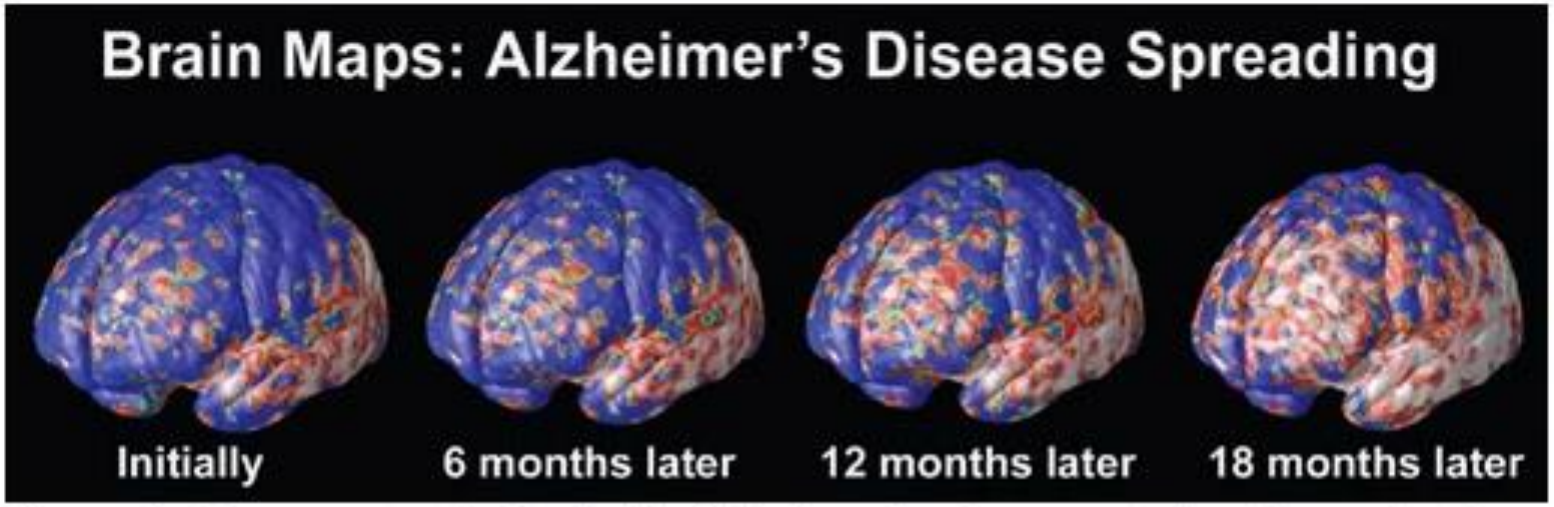
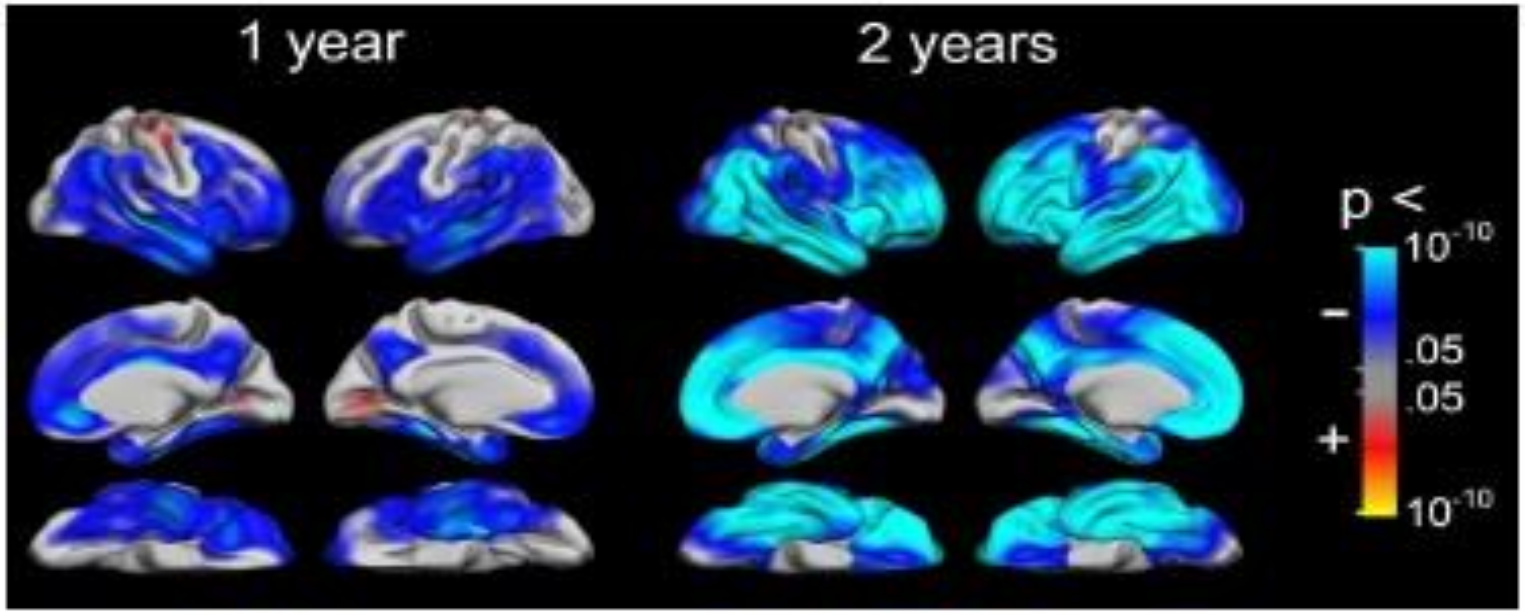


Figure 1: Damage to the brain in Alzheimer's disease. - Time lapse brain scans show healthy brain activity (red and blue areas) and rapidly spreading areas of cell death (gray areas) in someone with Alzheimer's disease. About 5 percent of brain cells die each year in someone with Alzheimer's, compared to less than 1 percent in a senior who is aging normally.

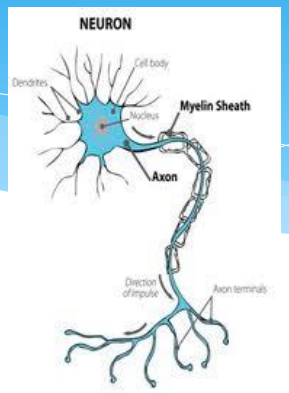
Fjell (2009): Gross volumetric changes

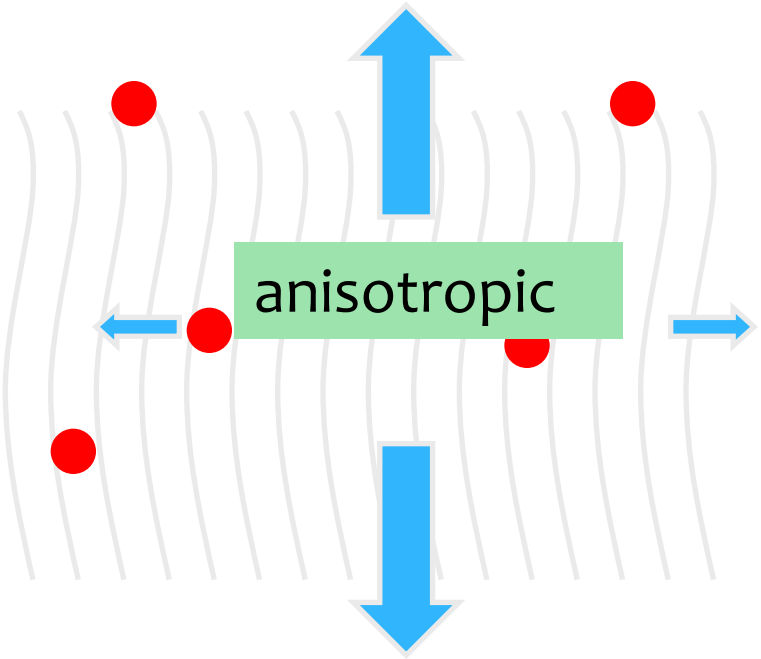
* 142 healthy elderly (range 60-91yrs)
* 0, 12 and 24 month scans
* Significant atrophy - 0.5% loss of volume - at 1 yr
* greatest in fronto-temporal regions
* accelerating function with age



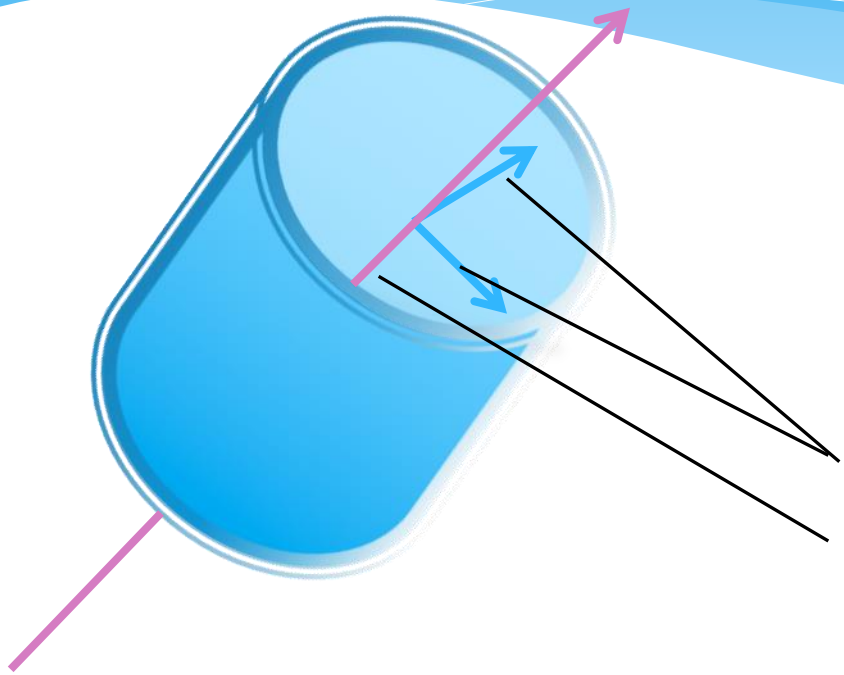
Diffusion tensor imaging (DTI)

* Based on the movement of water molecules within the axons
* The direction of water diffusion is influenced by surrounding tissue e.g. damage to myelin sheaths in white matter axonal tract will affect direction of diffusion of molecules within it
* So DTI detects subtle changes in the structural integrity of the myelin sheath of the axons –
* proxy measure of neural health and efficiency





Fractional Anisotropy (FA)



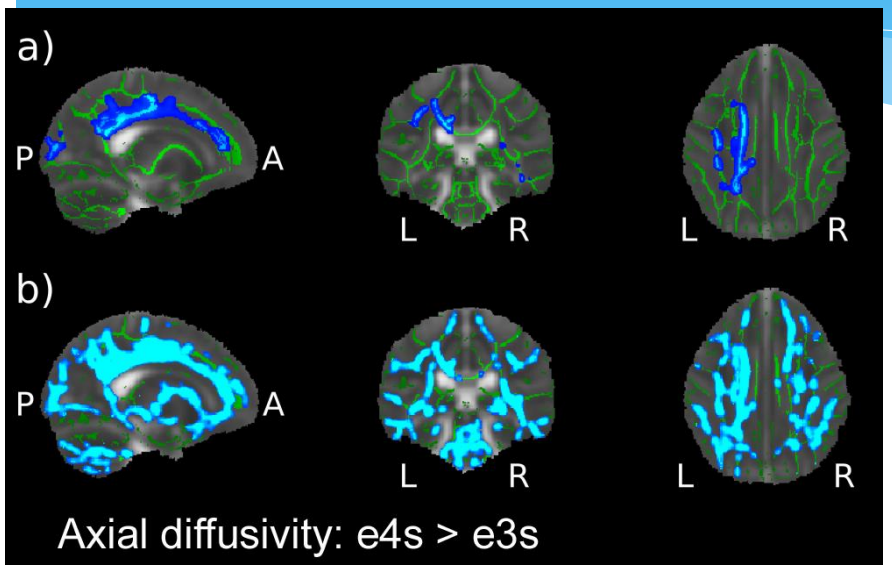
Composite of eigenvalues in 3 dimensions

Eigenvalues for individual components..

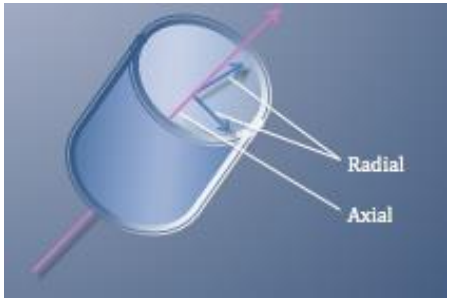
Radial
Axial

NODDI: neurite orientation dispersion and density imaging
..differentiates neurite density (NDI) from orientation dispersion (ODI
..so separating the 2 key factors contributing to changes in FA and providing a more accurate story of WM microstructure.

Diffusion Tensor Imaging – genotype differences



* Whole brain analyses also showed e4s had significantly increased axial diffusivity (diffusion along the tract) (p =0.011).
* Regional analysis (TBSS): significantly higher in left hemisphere (corrected for multiple comparisons) - (a)
* underlying trend points to widespread differences - (b)



* Suggests improved axonal microstructure and improved white matter fibre organisation (coherence) in young adult e4s, as well as greater overall white matter volume

functional MRI (fMRI)

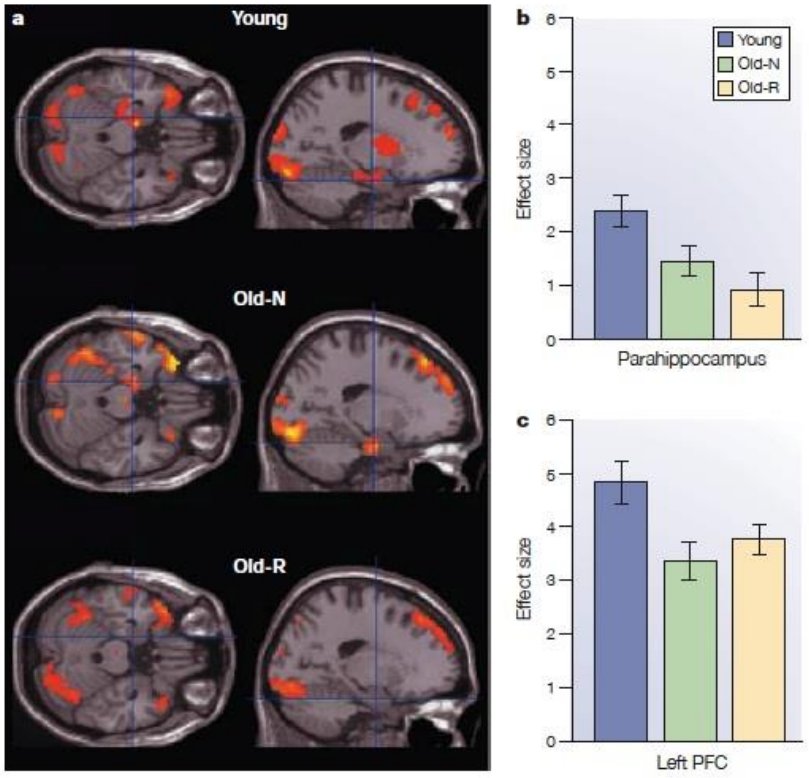
* Functional Magnetic Resonance Imaging
* measures haemodynamic response reflecting neural activity in the brain which uses oxygen
* deoxygenated haemoglobin = index that neuron has been active: BOLD signal
* Blood
* Oxygen
* Level
* Dependent contrast

* *proxy measure of brain activity*

Compensatory recruitment of frontal regions

* HAROLD -

hemispheric asymmetry reduction in older age



- Recall task
- fMRI shows age-related differences
- and differentiates good from poorer performers in the older age group

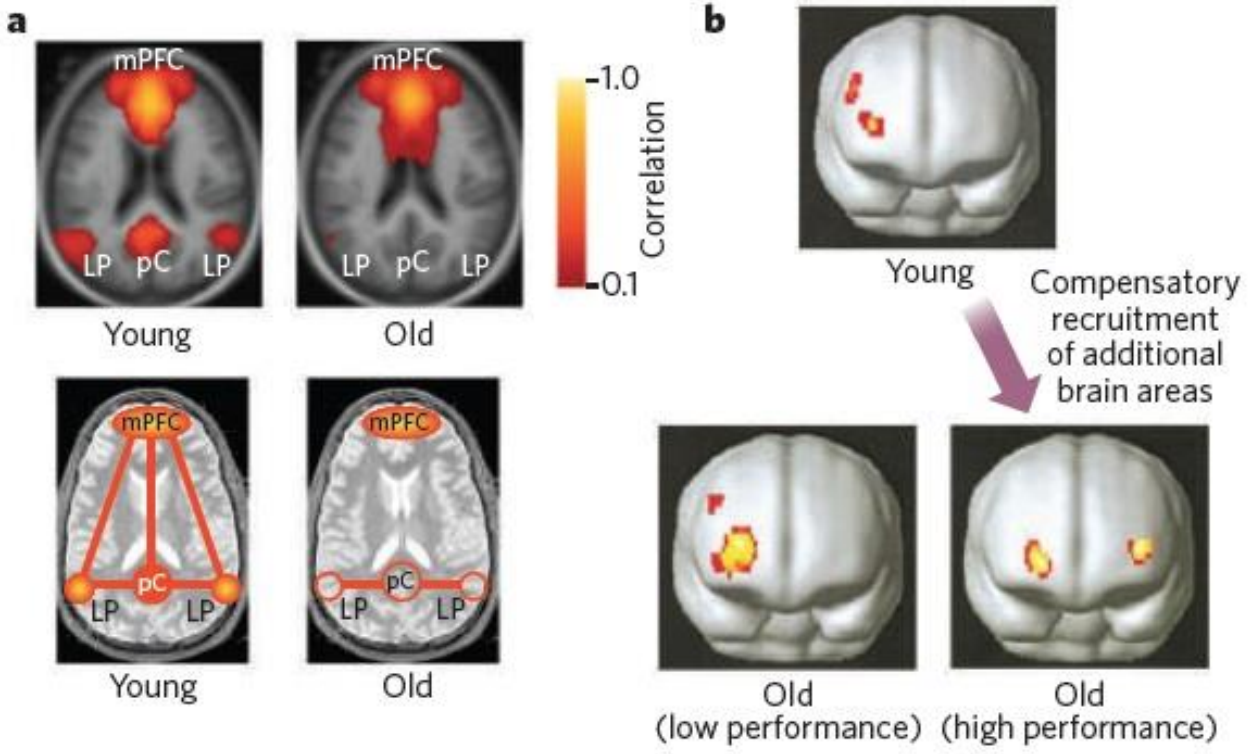
Daselaar et al 2003

Compensatory recruitment of frontal regions..

* PASA –

posterior-anterior shift with age

- reduced occipital coupled with increased frontal activity



Cabeza 2002

Scaffolding hypothesis

* As neural structures naturally decline with age, other structures in both proximal and distal regions are recruited to preserve function

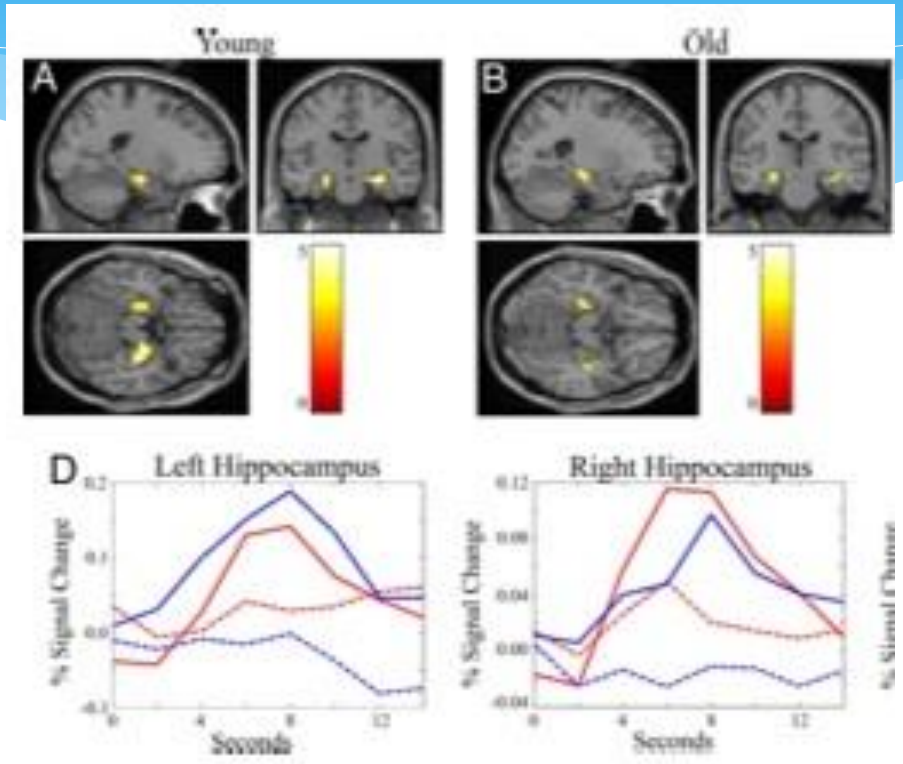
* CRUNCH: Compensation-Related Utilization of Neural Circuits Hypothesis
* Reuter-Lorenz & Cappell (2008)

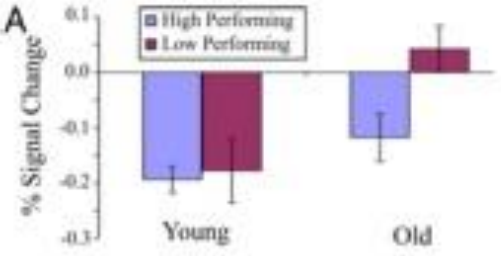
* effective only at lower levels of task demand
* training, exercise, and other interventions may increase compensatory potential

Complex patterns of change

* Miller et al (2008)
* memory failures associated with comparable levels of hippocampal activation …

* BUT poorer parietal *de*activation at the point of encoding…



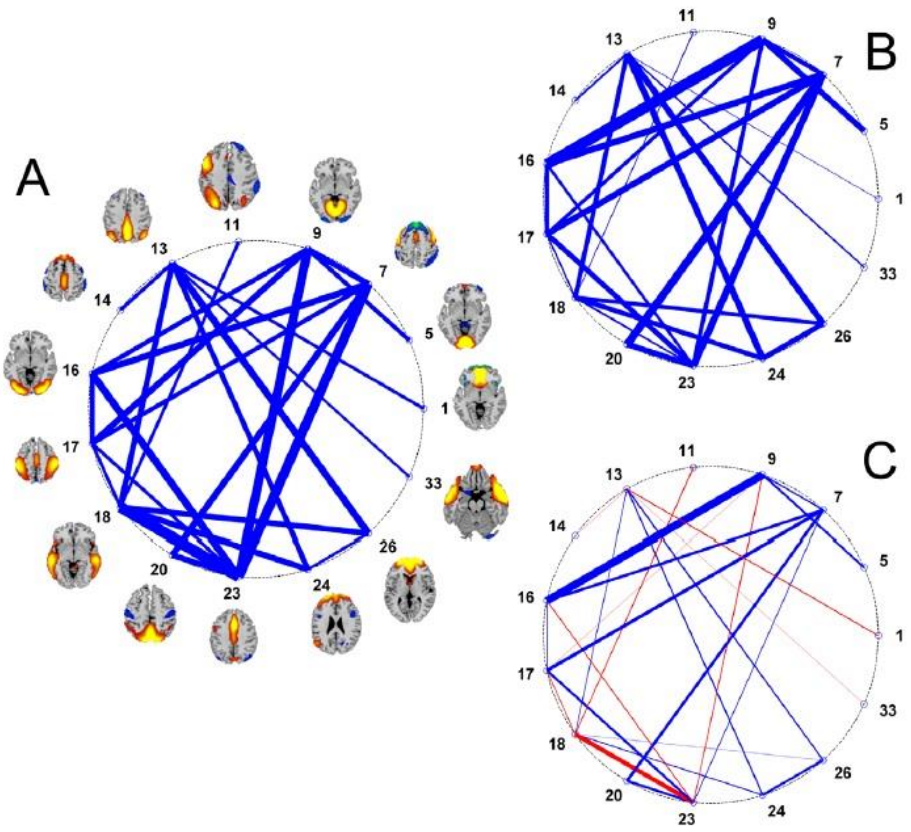


Connectivity differences

* Steffener et al 2012

* A= connectivity analysis of brain regions active during a verbal delayed recognition task.
* 71 yr (c) vs 24 yr (b) of age
* Age-related performance differences correlated with connectivity differences

* Brain volume lower in older volunteers … *but connectivity differences independent of volumetric differences*



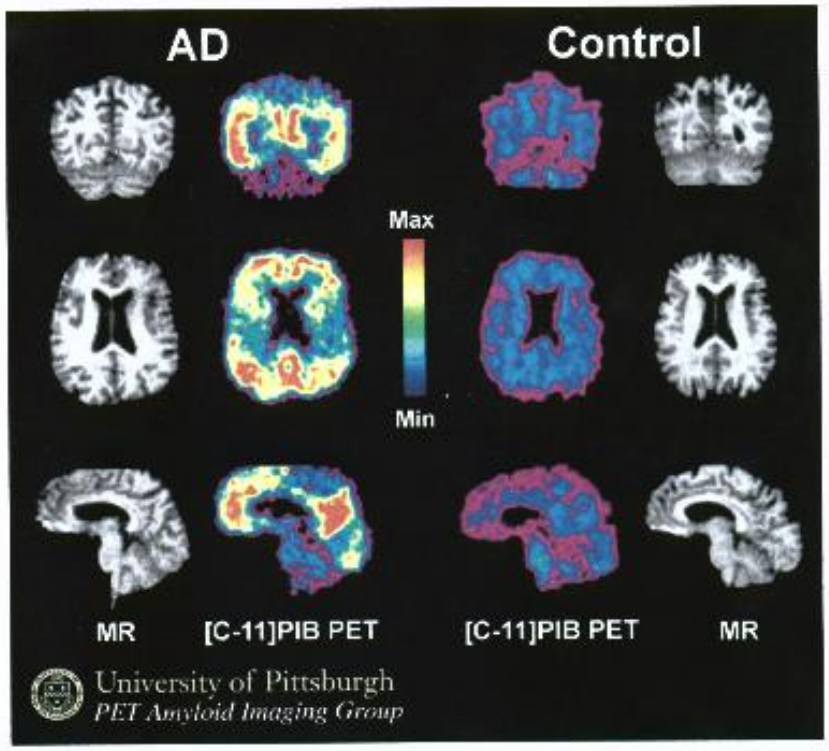
Summary..

* Cognitive skills change with age – many decline, some remain stable, a few improve
* Functions showing decline with age include:
    * response speed
    * on-demand retrieval
    * new learning
    * cognitive flexibility and attention
    * inhibitory capacity and working memory
* The brain is an organ and ages like other parts of the body
* There is evidence for neural adaptation by the ageing brain

..and emerging complexities

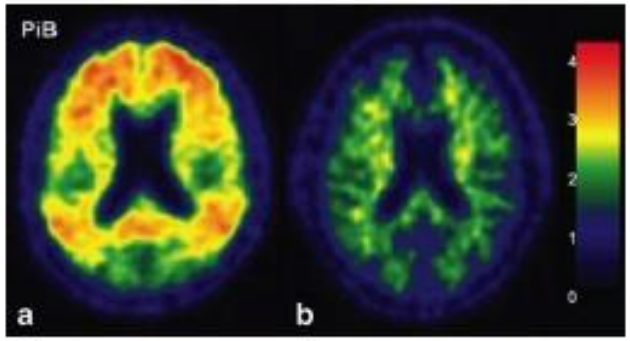
* Dedifferentiation of brain activations with age is associated with performance change: "difficulty in engaging specialized neural mechanisms"
* Compensation – associated with positive outcomes, or at least maintained performance: "recruitment of additional neural tissue from specific sites to counteract neurocognitive deficits"
  * contralateral recruitment
  * unique recruitment
  * Substitution
* Task-related *decreased* activations as important as *increased* activations
* White matter changes are important, as well as cortical (grey matter) neuronal changes

imaging β amyloid in vivo - Pittsburgh compound B (PIB)



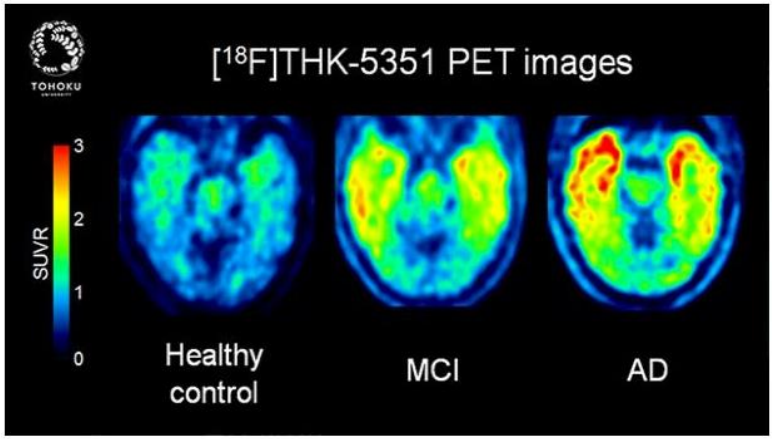
Nichols et al, 2006

- β-amyloid deposition can occur without clinical signs of dementia
- 25-30% of healthy older adults have diagnostically significant levels

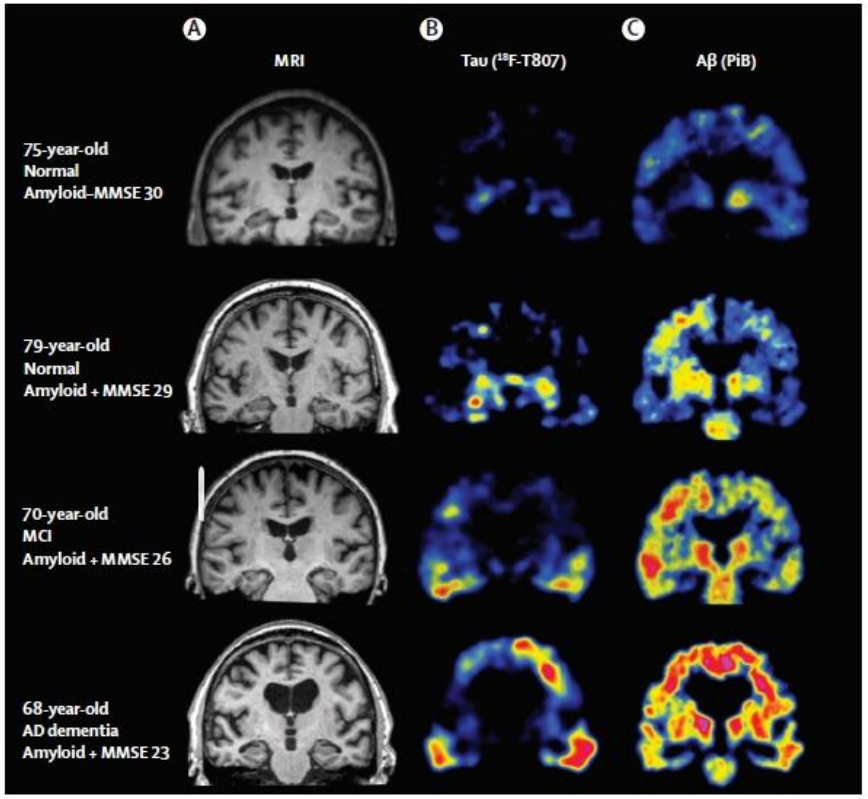


Jack et al 2009: β-amyloid in healthy brains

Imaging p-tau in vivo



- Density of NFTs (tau) correlates better with memory loss than does β-amyloid deposition
- Co-occurrence of β-amyloid and tau deposits necessary for progression to Alzheimers DIsease



Villemagne et al, 2015

Two examples of what we can ‘see’ with these tracers

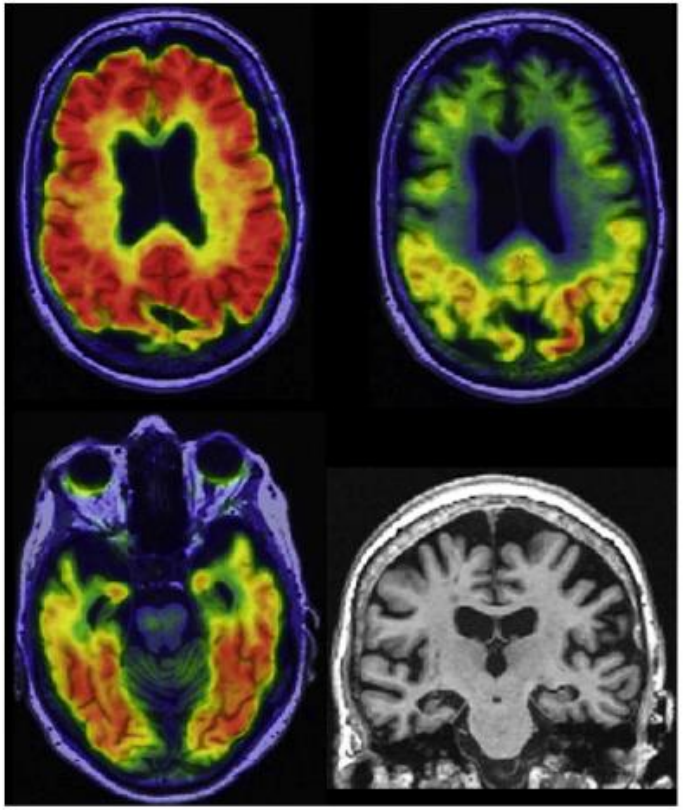


Fig. 1. Alzheimer’s disease with dementia. A 75-year-old woman with amnestic multidomain dementia. Participant in the Mayo Alzheimer’s Disease Research Center. Abnormal amyloid PET with Pittsburgh compound B (top left), tau PET with flortaucipir (top right and bottom left), and atrophy on MRI (bottom right). Biomarker profile A+T+(N)+.

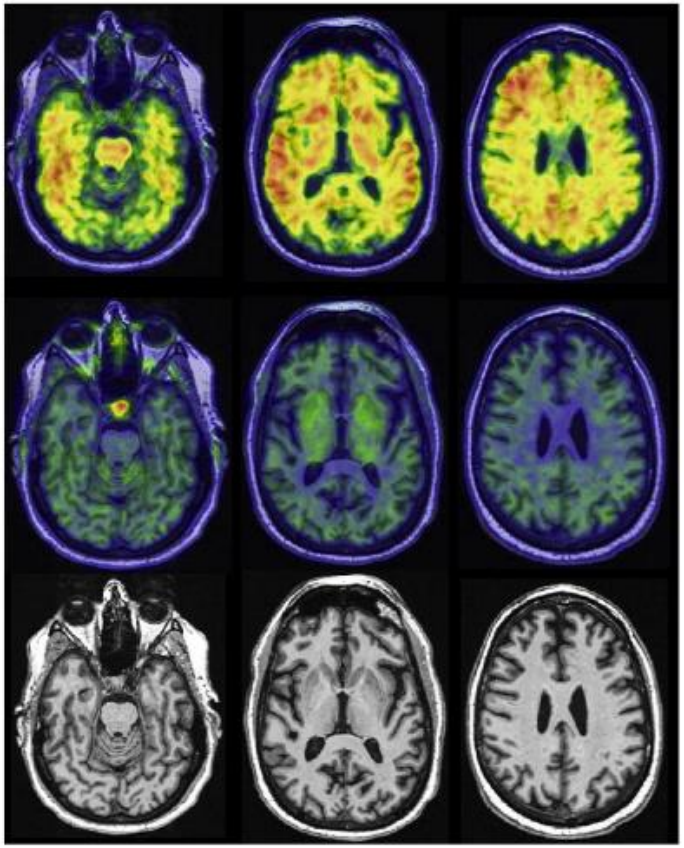


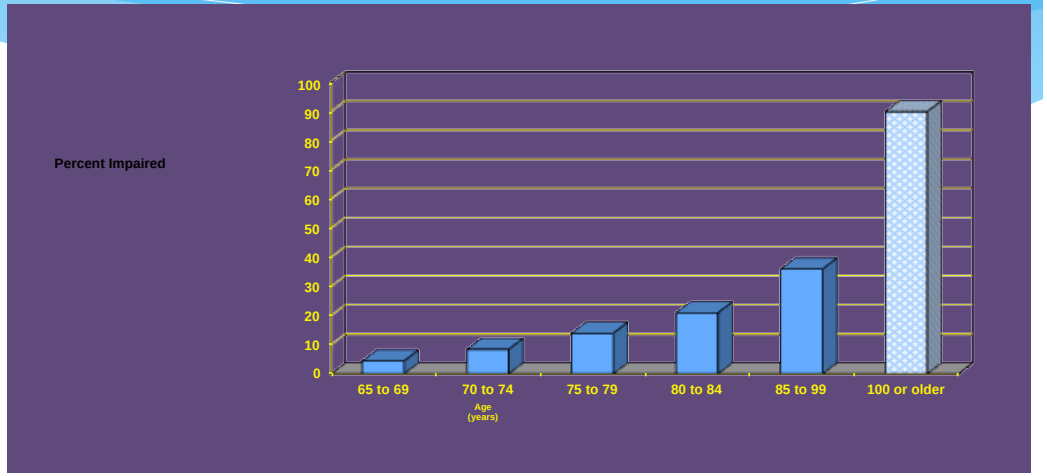
Fig. 2. Preclinical Alzheimer’s pathologic change. A cognitively unimpaired 67-year-old man. Participant in the Mayo Clinic Study of Aging. Abnormal amyloid PET (Pittsburgh compound B, top row), no uptake on tau PET (with flortaucipir, middle row), no atrophy on MRI (bottom row). Biomarker profile A+T−(N)−.

Jack et al, 2018

Risk factors for cognitive ageing and dementia

In order, the two biggest risk factors for Alzheimer type dementia..

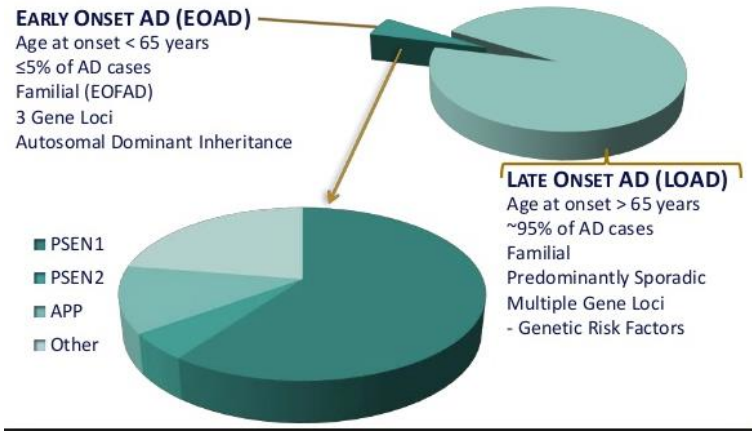
* Your age



* Your genes

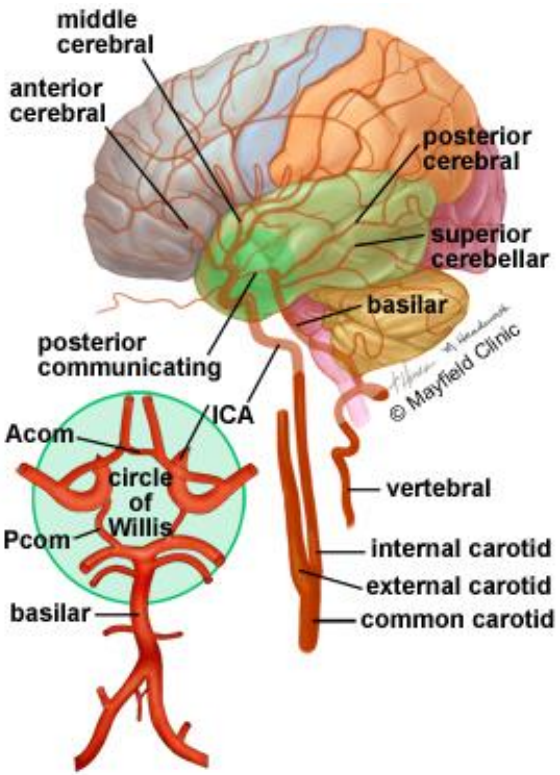
IDENTIFIED links

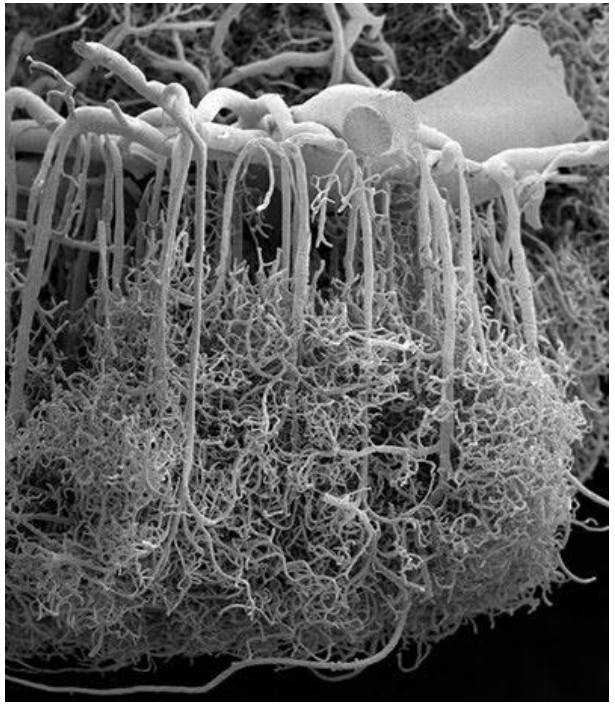
* Chr 21 (Aβ protein overexpression)
* Chr 14 +1(presenilin protein mutations)
* Chr 19 (apolipoprotein E polymorphisms)



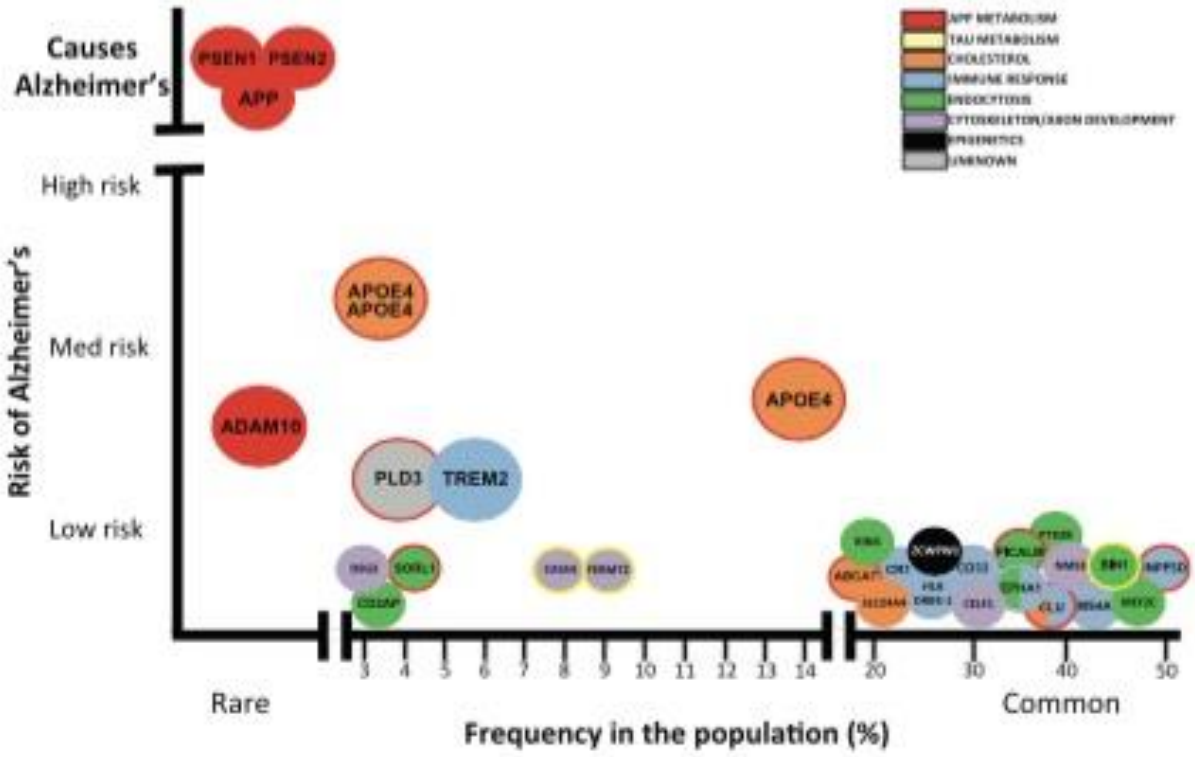
Cardiovascular risk factors

* Role of brain's vasculature:
* Provide substances to brain (e.g. oxygen and glucose)
* Clearance of unwanted substances (e.g. CO_2, Aβ)
* Protect brain from circulating toxins or infection (e.g. bacteria)





Rare and common gene variants identified in genome-wide associated studies (GWAS)



Karch & Goate, 2015

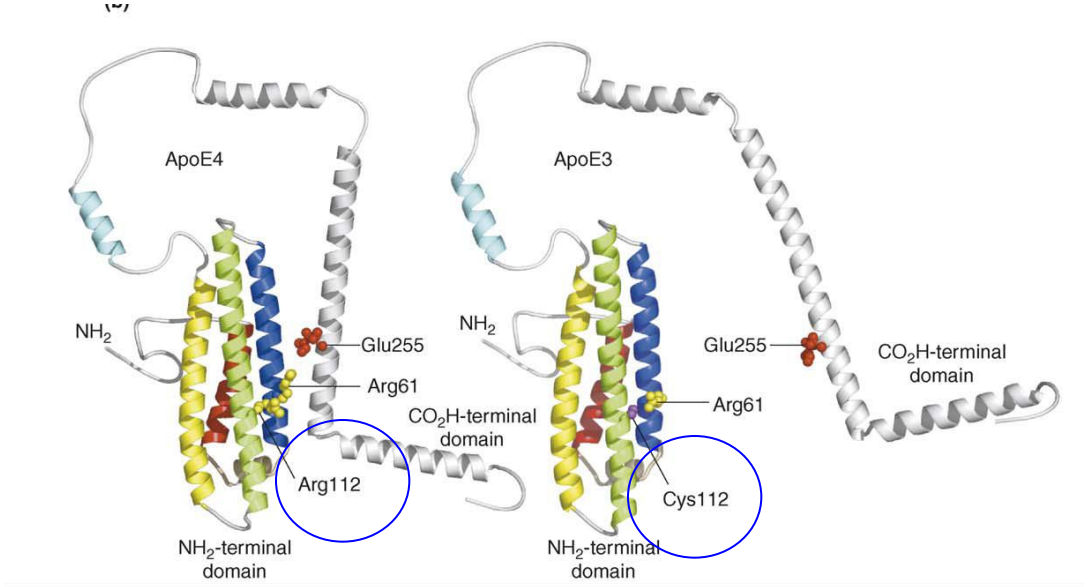
* Recent interest..
* TREM2
* SORL1
* CLU, CR1, KLOTHO, PICALM

Chromosome 19: APOE

Apolipoprotein E:
associated with regulation of cholesterol levels

(epsilon) e2 e3 e4

e2/e2 e2/e3 e2/e4 e3/e3 e3/e4 e4/e4



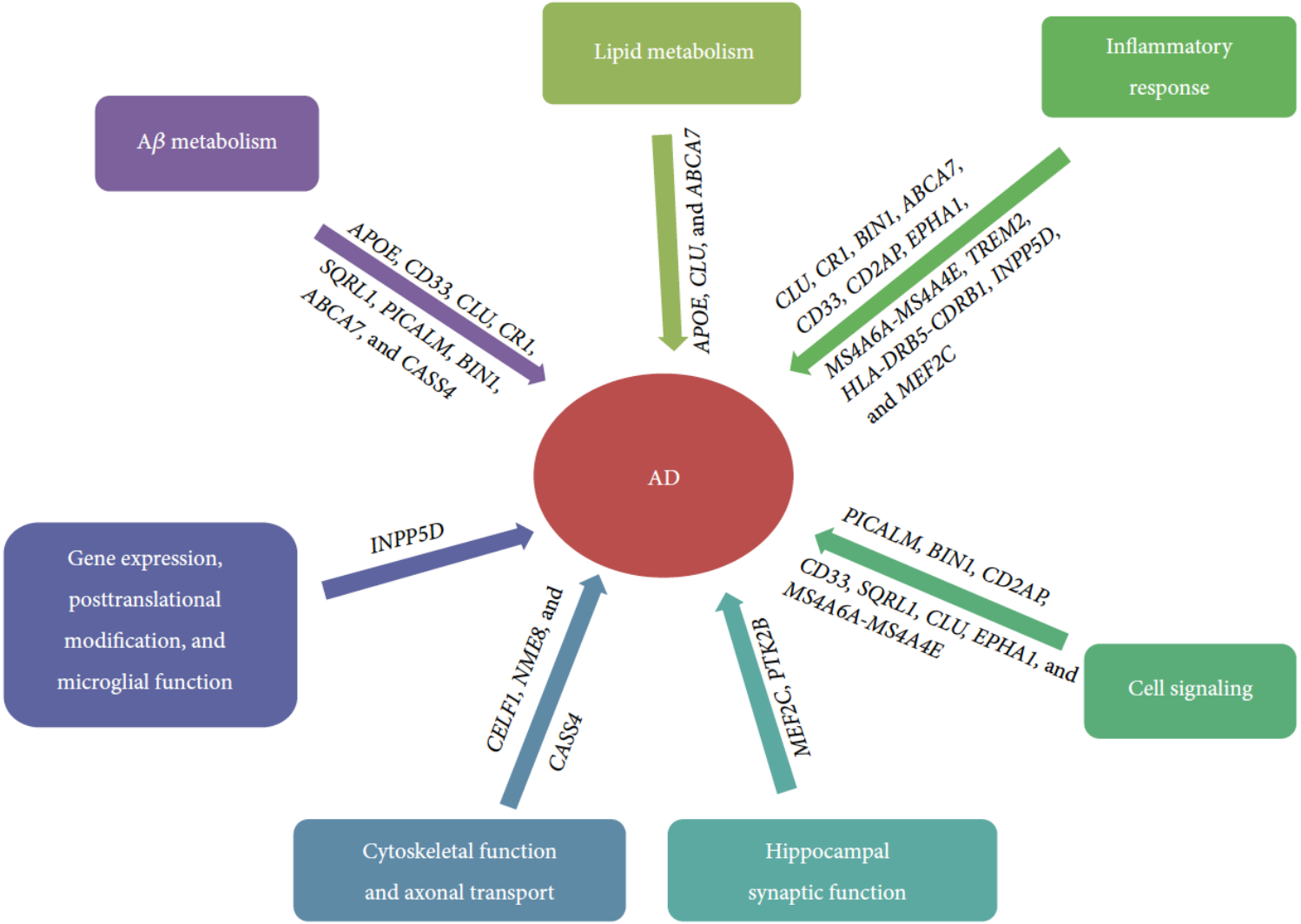


FIGURE 1: Potential pathways of susceptibility genes involved in the pathogenesis of AD.

Zou et al, 2014

Polygenic risk score

* Desikan et al (2017): statistically derived *Polygenic Hazard Score*

* based on age and GWAS studies that isolated the top 31 AD-associated SNPs from 17,000 cases and 37,000 controls

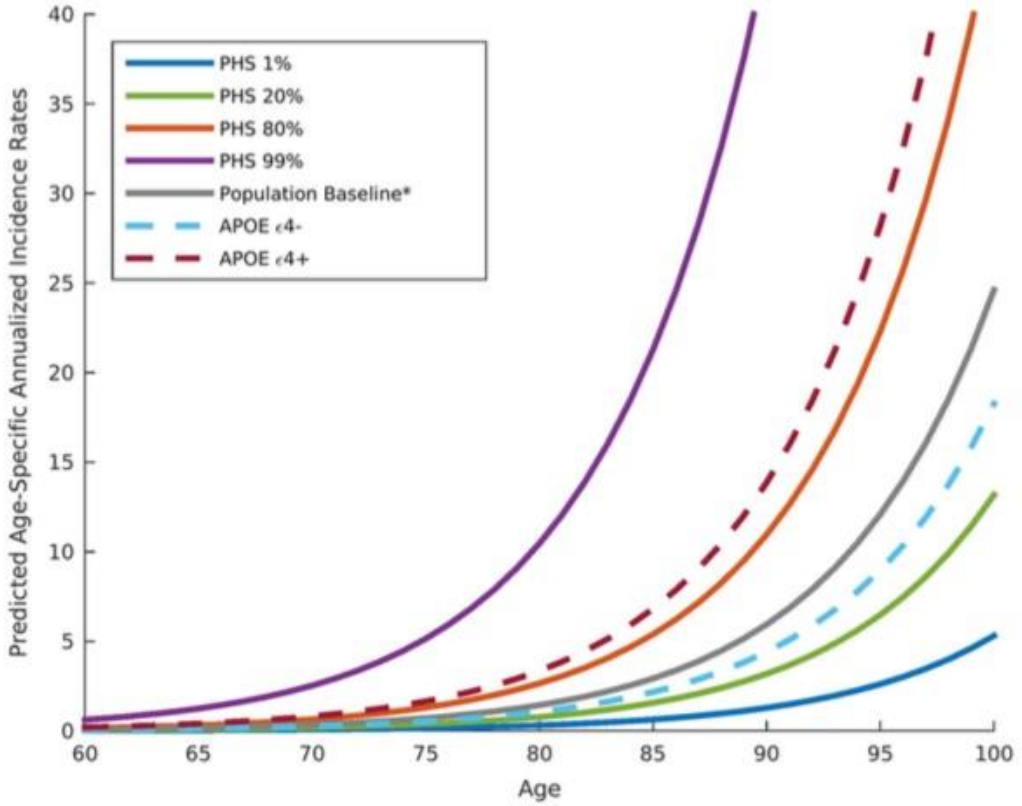


Fig 4. Annualized incidence rates showing the instantaneous hazard as a function of polygenic hazard score percentile and age. The gray line represents the population baseline estimate. Dashed lines represent incidence rates in *APOE* ε4 carriers (dark red dashed line) and non-carriers (light blue dashed line) not associated with a PHS percentile. The asterisk indicates that the baseline estimation is based on previously reported annualized incidence rates by age in the general US population [18]. PHS, polygenic hazard score.

Desikan et al, 2017

Susceptibility testing? The value of disclosure

Susceptibility testing

* Apolipoprotein E (*APOE*) testing for risk of AD –

* Roberts et al (2011) examined "the process and impact of disclosing genetic susceptibility for a prevalent, severe and incurable neurological condition."

Table 1. Overview of REVEAL clinical trials

Trial	Dates	Site locations	Study sample	Main question(s)
REVEAL I	2000–2003	Boston Cleveland New York City	162 Adult children of people with AD	What is the psychological impact of disclosure of genetic risk for AD?
REVEAL II	2003–2006	Boston Cleveland New York City Washington, DC	280 First-degree relatives of people with AD	Can genetic risk for AD be disclosed safely and effectively using a condensed protocol?
REVEAL III	2006–2009	Boston Cleveland Washington Ann Arbor, DC	257 Adults with and without immediate AD family history	What is the impact of disclosure of pleiotropic disease risks associated with *APOE*? Can results be disclosed safely and effectively via phone?
REVEAL IV	2010–present	Boston Philadelphia Washington Ann Arbor, DC	Persons with amnestic MCI and their study partners	What is the impact of disclosing *APOE* to a population at imminent risk of AD?

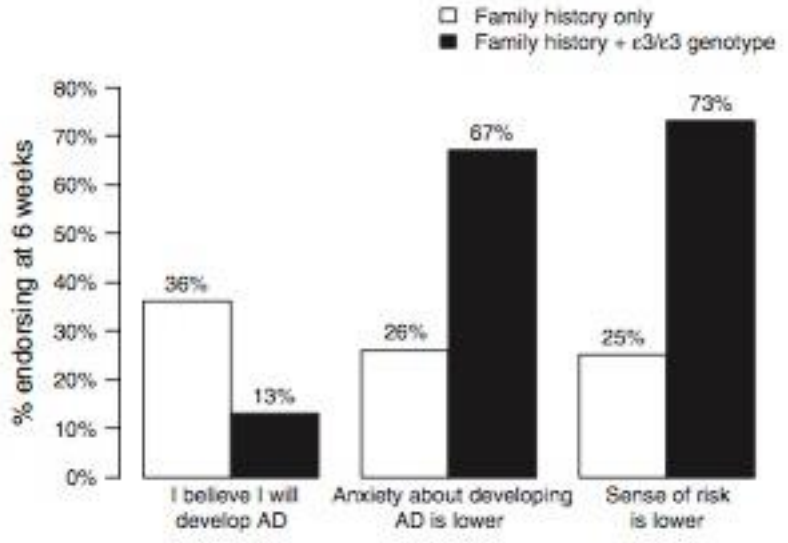
AD, Alzheimer's disease; *APOE*, apolipoprotein E; REVEAL, Risk Evaluation and Education for Alzheimer's Disease.

* Roberts (2011)
* Interest in being tested:
* < 60 yrs; 79% college educated; 79% female
* Perceived utility of testing:
* arranging personal affairs, informing long-term decisions (eg. insurance), preparing the family, emotional relief if found to be at lower risk.
* Risk recall and perceptions:
* many could not recall their lifetime risk information at a 6-week follow-up, but the vast majority knew their APOE status

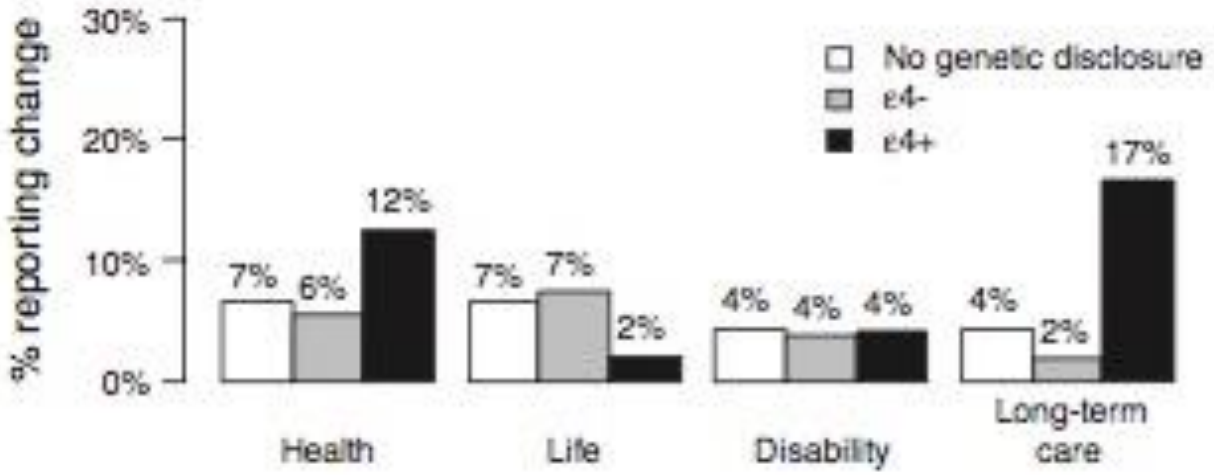
"..genotype information has an outsized influence on risk perceptions, even when offered within a multi-factorial risk assessment.."

- ε4- participants - 2 groups
- both groups received the same message about lifetime risk of AD (29% probability), but one group were not disclosed their APOE status
- the ε4-negative ‘disclosed’ women perceived their risk as lower, reported testing as having a more positive impact, endorsed less strongly the belief that they might develop AD, and reported a greater reduction in anxiety about AD

No difference in anxiety, depression or ‘distress’ scores assessed at 1 yr follow-up

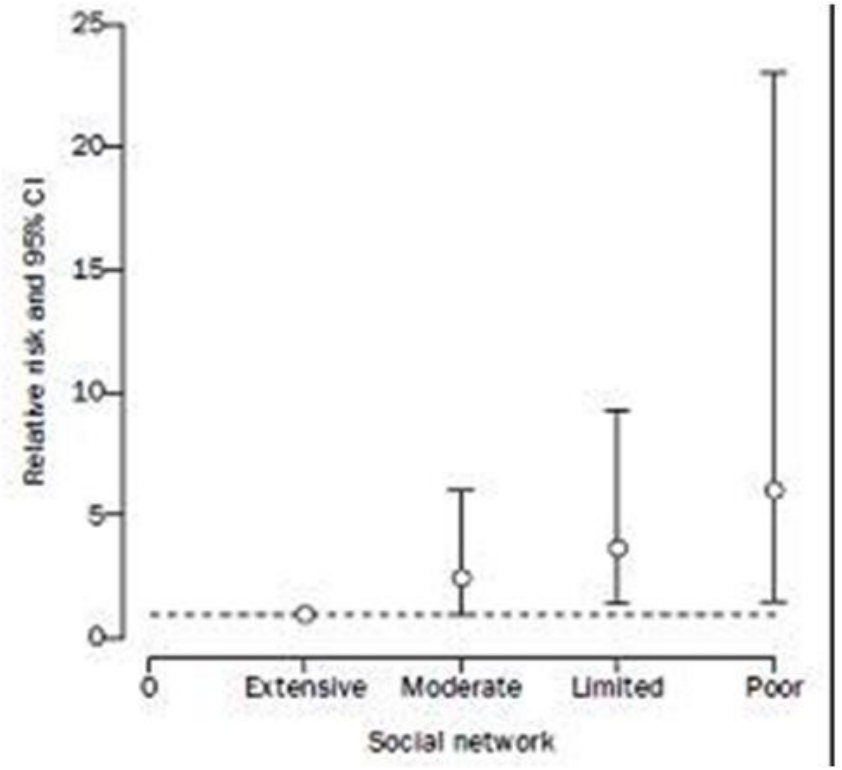


* Behavioral impact of disclosure
* ε4-positive participants were approximately four times more likely than controls to report LTC insurance changes during the 1-year follow- up



Lifestyle factors that reduce dementia risk

SOCIAL ENRICHMENT



Wang et al, 2002

- **Fratiglioni et al (2000)**
- being both single & living alone almost doubled the risk
- the lower the frequency of social contact the higher the risk
- having children with frequent but unsatisfying contact = increased risk.
- **Amieva et al(2010)**
- quality of relationships the only emerging predictive risk factor

COGNITIVE RESERVE

* “the capacity of the mature adult brain to sustain the effects of disease or injury sufficient to cause clinical dementia in an individual possessing less cognitive reserve”

* In persons with AD who have comparable neuropathology, higher cognitive reserve is associated with fewer behavioural consequences - reduced clinical severity

Stern (2002) Barulli & Stern (2013)

* *active* and *passive* components affect brain reserve
* *Active*: cognitive software
* moderated by
  * level of education
  * occupations requiring continuing education
  * sustained intellectual engagement requiring mental effort
* *Passive*: brain structures
* determining
  * basic capacity to efficiently process and retrieve information
  * capacity to respond to insult - plasticity and compensation
  * ‘neural reserve’ - individual differences in network efficiency

McDowell et al (2007)

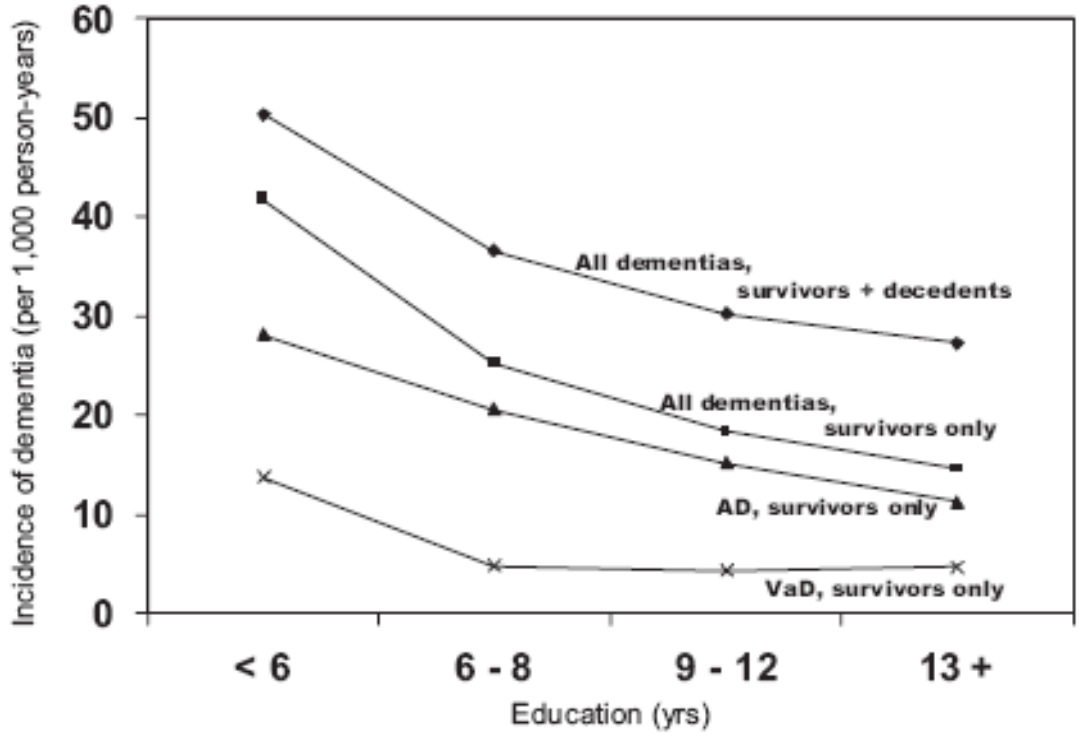
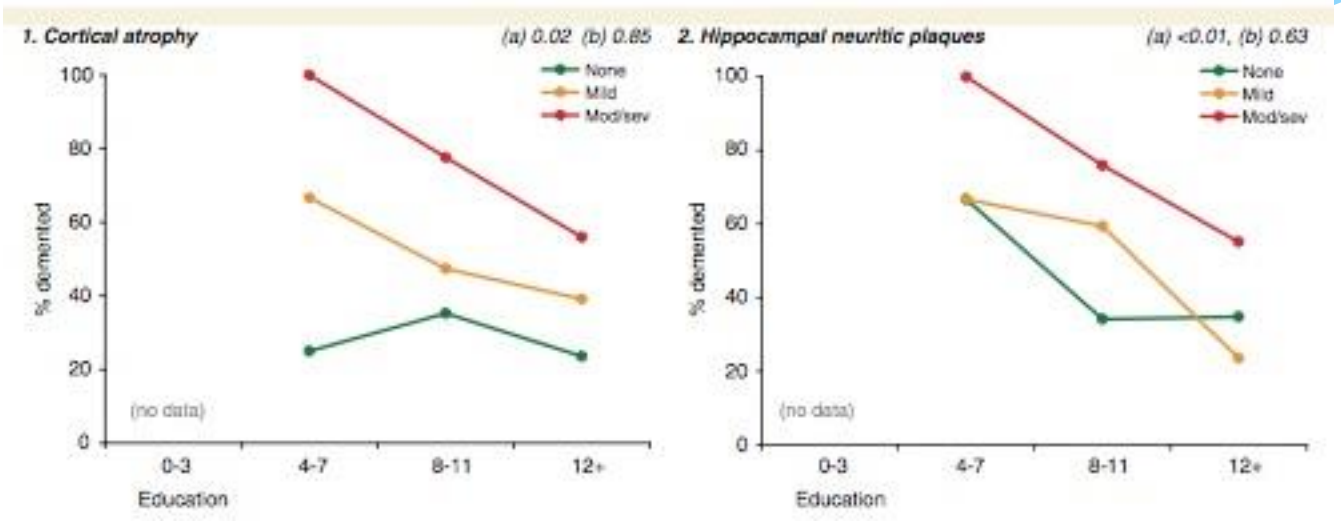


Figure 1. Age- and sex-standardized ten-year cumulative incidence of dementia (all types, Alzheimer's disease and vascular) per thousand, by educational level.

Brayne et al (2010)

182 HE
232 Dementia

PM data
Median age:87

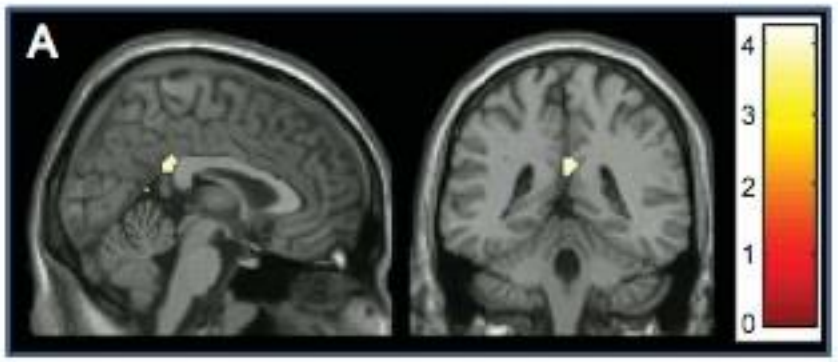


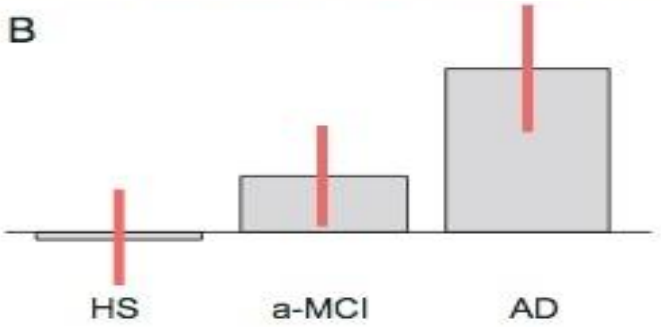
- Education did not protect individuals from developing neurodegenerative and vascular neuropathology but reduced the impact of pathology (delayed clinical expression of dementia) before death.

..education offers **functional protection** in the presence of pathology

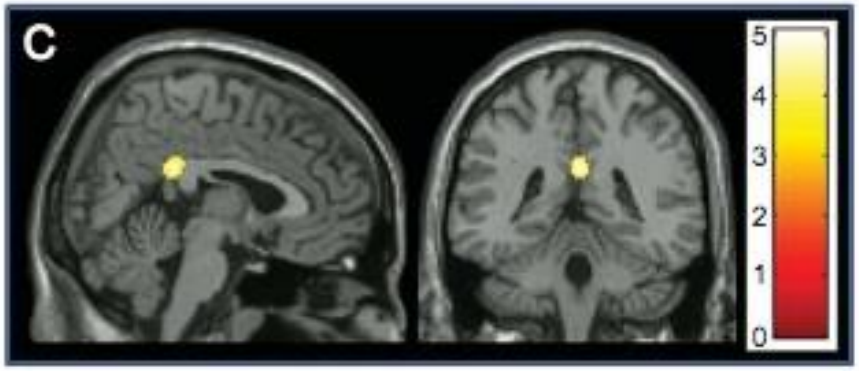
Bozzali et al (2015)

* Imaging CR effects
* A) Positive association: Education modulates functional connectivity in the posterior cingulate cortex, which is one of the most critical brain 'hubs'



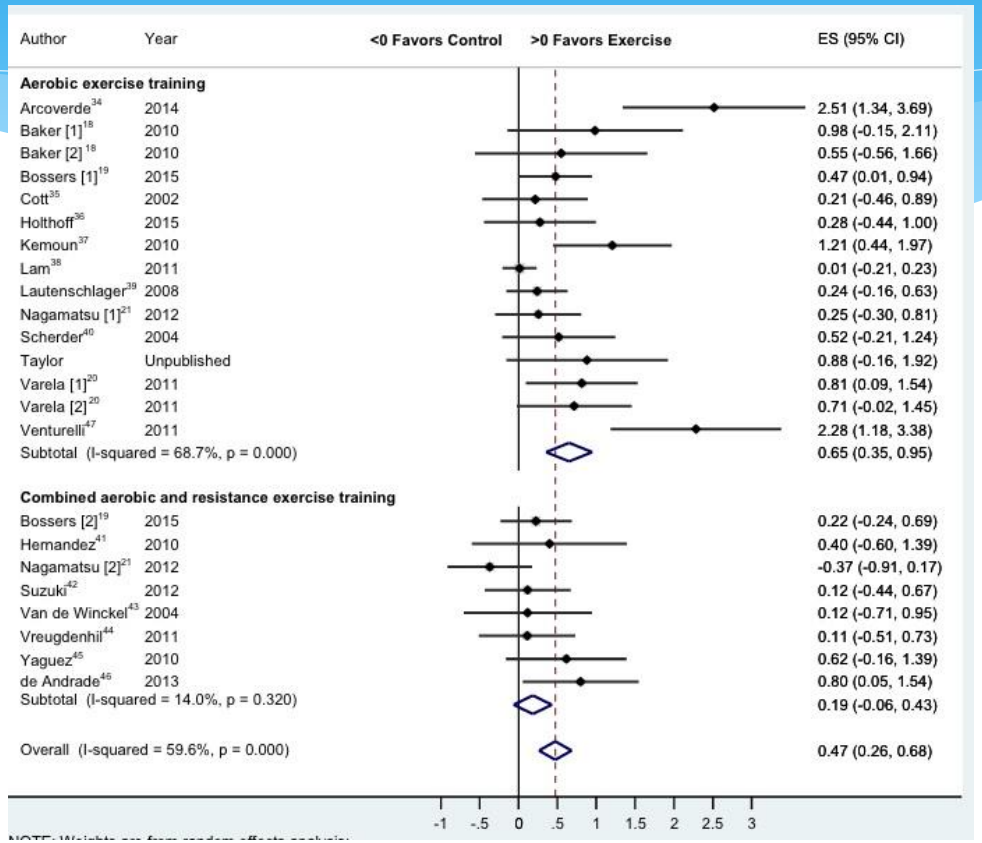


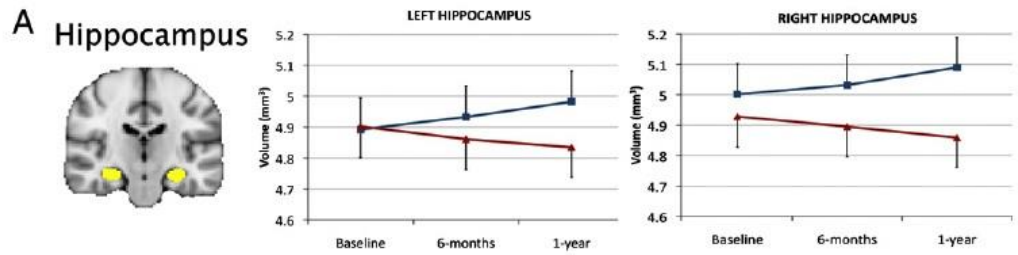
* B) Plot showing the degree of association in each group separately, indicating that the result shown in A is driven by patients with AD.
* C) Positive association in patients with AD only



Positive effects of exercise

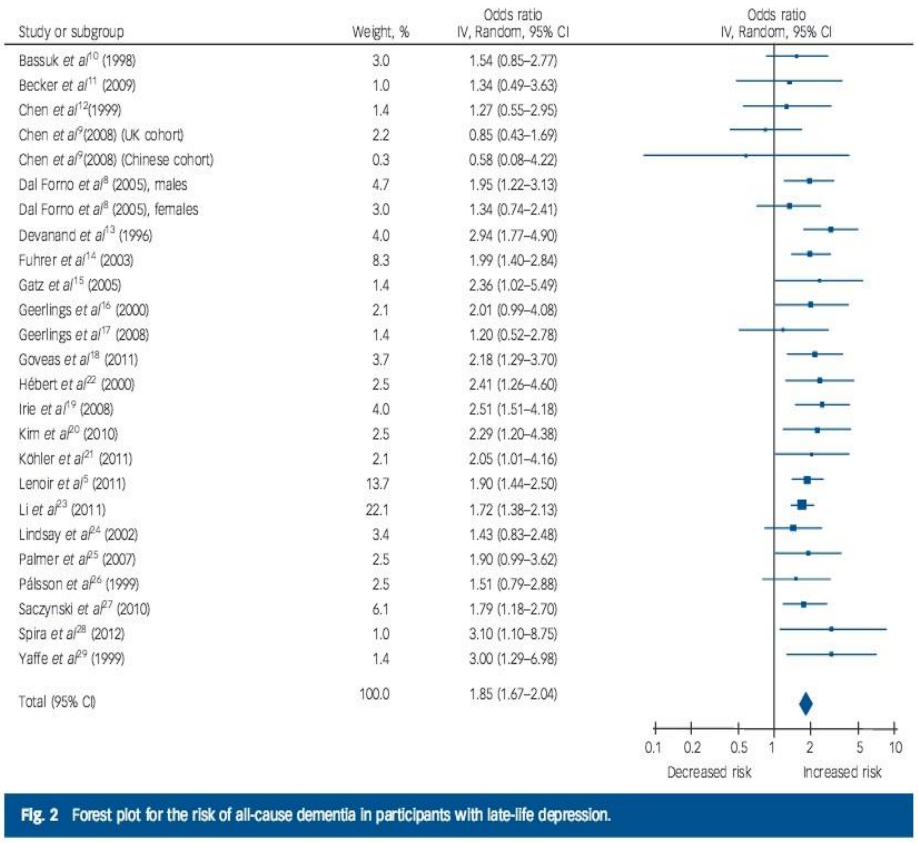
* Panza et al, 2018: Nineteen studies with 23 interventions
* 1,145 participants; mean age of 77 years (64% already showing symptoms of memory impairment)
* Effects reflect link between cardio- and cerebro-vascular health





Erickson, 2011

Psychological factors: depression



Study or subgroup	Weight, %	Odds ratio IV, Random, 95% CI
Bassuk *et al*[10] (1998)	3.0	1.54 (0.85–2.77)
Becker *et al*[11] (2009)	1.0	1.34 (0.49–3.63)
Chen *et al*[12](1999)	1.4	1.27 (0.55–2.95)
Chen *et al*[9](2008) (UK cohort)	2.2	0.85 (0.43–1.69)
Chen *et al*[9](2008) (Chinese cohort)	0.3	0.58 (0.08–4.22)
Dal Forno *et al*[8] (2005), males	4.7	1.95 (1.22–3.13)
Dal Forno *et al*[8] (2005), females	3.0	1.34 (0.74–2.41)
Devanand *et al*[13] (1996)	4.0	2.94 (1.77–4.90)
Fuhrer *et al*[14] (2003)	8.3	1.99 (1.40–2.84)
Gatz *et al*[15] (2005)	1.4	2.36 (1.02–5.49)
Geerlings *et al*[16] (2000)	2.1	2.01 (0.99–4.08)
Geerlings *et al*[17] (2008)	1.4	1.20 (0.52–2.78)
Goveas *et al*[18] (2011)	3.7	2.18 (1.29–3.70)
Hébert *et al*[22] (2000)	2.5	2.41 (1.26–4.60)
Irie *et al*[19] (2008)	4.0	2.51 (1.51–4.18)
Kim *et al*[20] (2010)	2.5	2.29 (1.20–4.38)
Köhler *et al*[21] (2011)	2.1	2.05 (1.01–4.16)
Lenoir *et al*[5] (2011)	13.7	1.90 (1.44–2.50)
Li *et al*[23] (2011)	22.1	1.72 (1.38–2.13)
Lindsay *et al*[24] (2002)	3.4	1.43 (0.83–2.48)
Palmer *et al*[25] (2007)	2.5	1.90 (0.99–3.62)
Pálsson *et al*[26] (1999)	2.5	1.51 (0.79–2.88)
Saczynski *et al*[27] (2010)	6.1	1.79 (1.18–2.70)
Spira *et al*[28] (2012)	1.0	3.10 (1.10–8.75)
Yaffe *et al*[29] (1999)	1.4	3.00 (1.29–6.98)
Total (95% CI)	100.0	1.85 (1.67–2.04)

Fig. 2 Forest plot for the risk of all-cause dementia in participants with late-life depression.

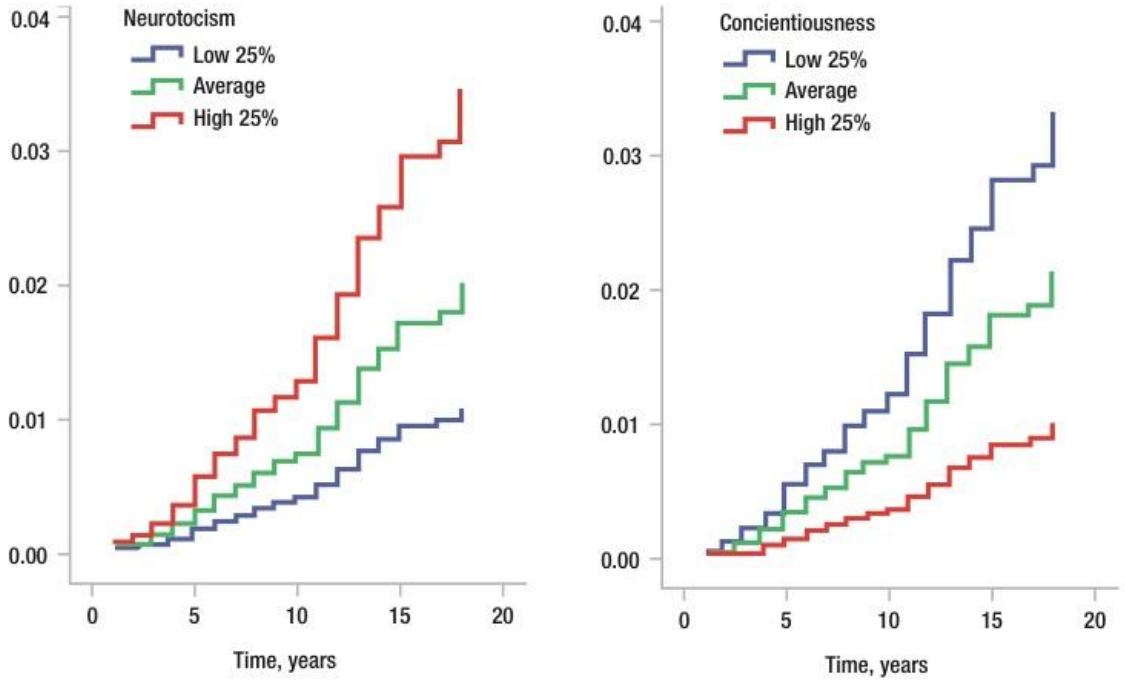
Diniz et al, 2013

* John et al (2018)
* Modelling data collected over 30 years from 18,558 individuals al born in one week in 1958
* Demonstrated cumulative consequences of repeated affective episodes at 23, 33, 42 years on cognitive performance at 50 yrs of age

Psychological factors: neuroticism and conscientiousness

Figure 3.3

Mid-life personality and risk of Alzheimer's disease (AD) in the Baltimore Longitudinal Study of Aging (BLSA)[64] (n = 1,671). High neuroticism and low conscientiousness increased AD risk more than 12 years later

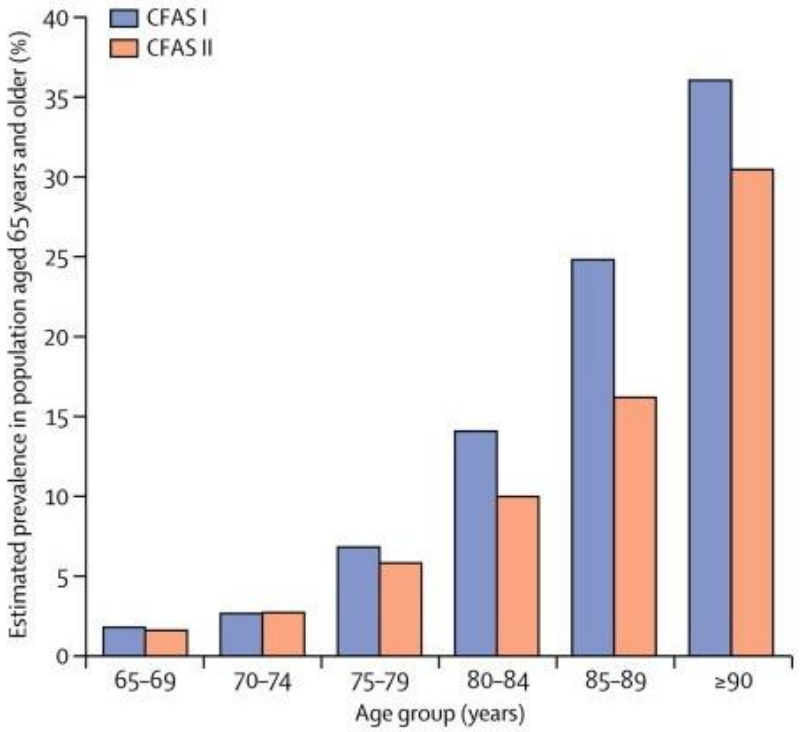


Cumulative hazard of incident Alzheimer's disease clinical dementia associated with the low 25% and high 25% on neuroticism and conscientiousness, adjusted for age, sex, ethnicity and education. The group with average scores (25%-75%) was included in the analyses but is not shown in the figure. For neuroticism, the low 25% was n=405 and the high 25% was n=436. For conscientiousness, the low 25% was n=422 and the high 25% was n=393.

Terracciano et al, 2014

Matthews et al - 2013

Figure 1

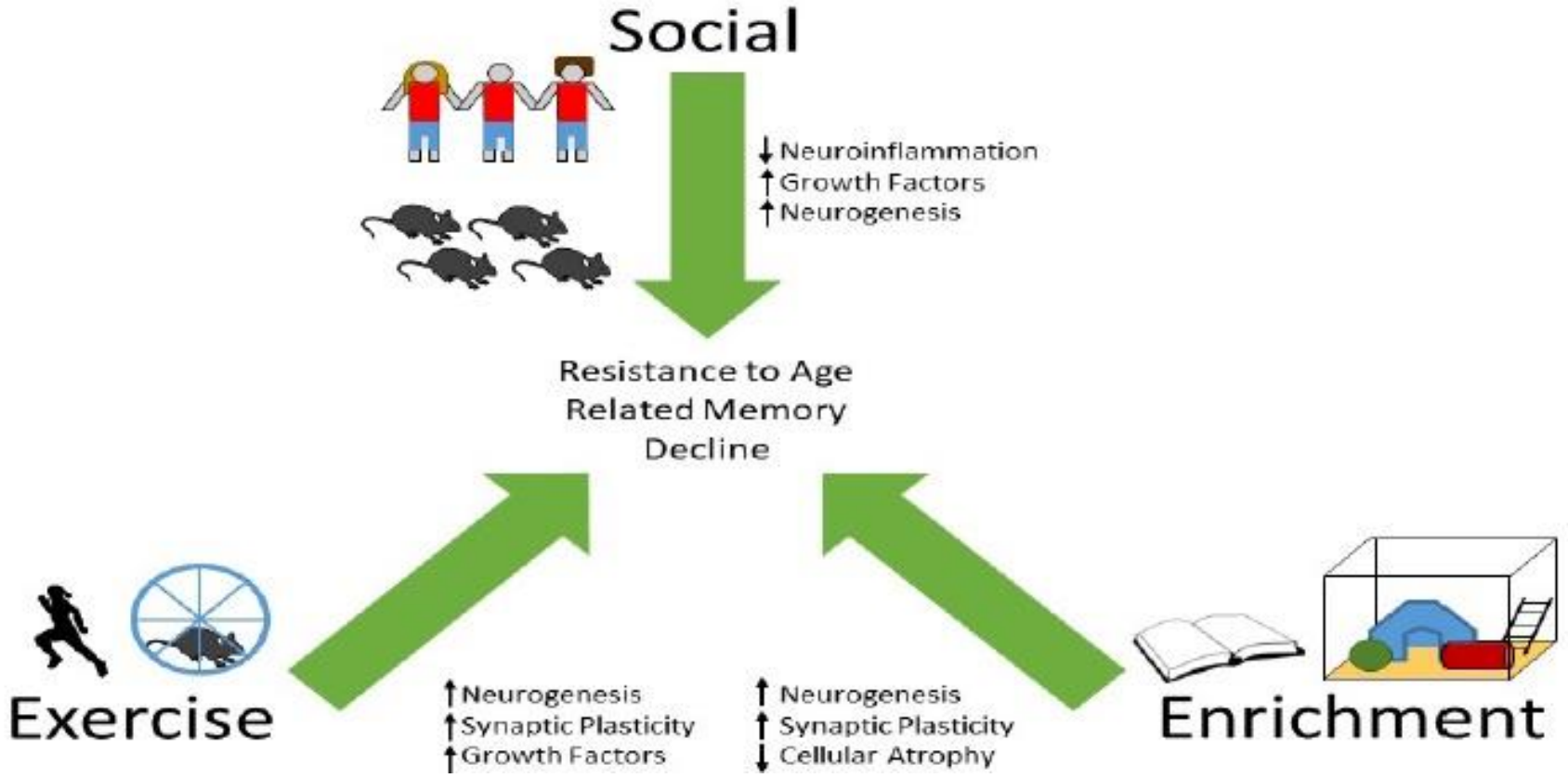


CFAS I and CFAS II age-specific dementia prevalence

CFAS=Cognitive Function and Ageing Study.

* Predictive comorbidities in order of increased risk: Vascular disease ..TIA… stroke..Parkinson's
* No increased risk with diabetes in CFAS
* protective effect of yrs of education,
* increased risk with social deprivation and class
* increased risk for single over married persons
* NB: together CFAS measured risk factors explain less than 50%

Dause & Kirby 2019



Lifestyle adjustments: what would you propose?

FINGER studies

* Kivipelto (2013)
* 1200 older adults recruited to a “multidomain intervention” trial:
* nutritional guidance
* exercise
* cognitive training
* social activities
* management of vascular and metabolic risk factors (weight, BP)

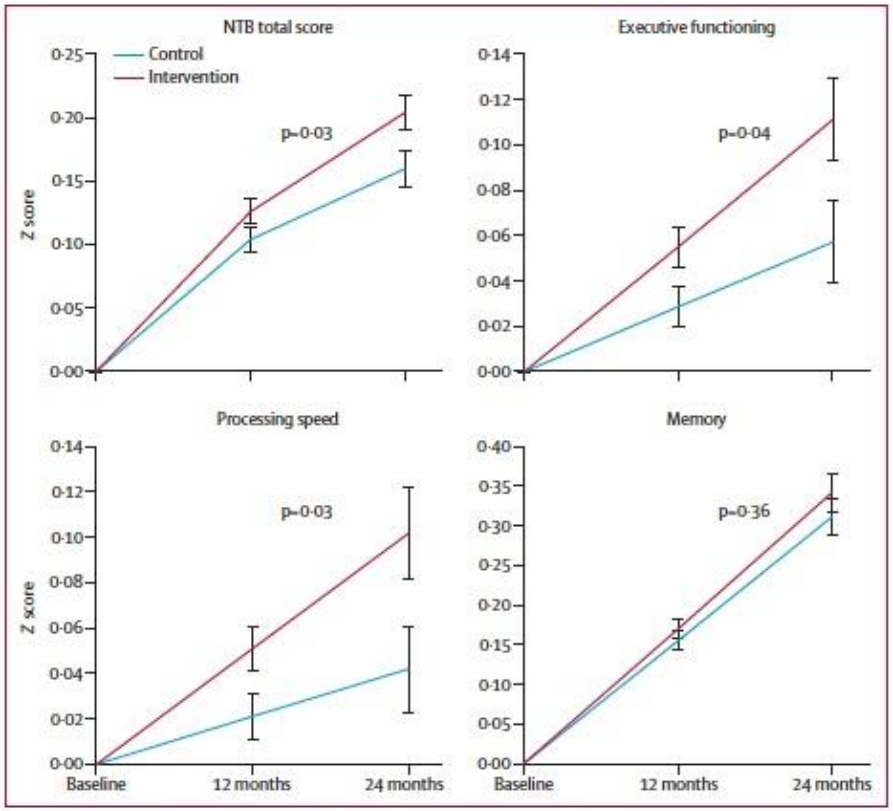


Figure 2: **Change in cognitive performance during the 2 year intervention**
Figure shows estimated mean change in cognitive performance from baseline until 12 and 24 months (higher scores suggest better performance) in the modified intention-to-treat population. Error bars are SEs. Mixed-model repeated-measures analyses were used to assess between-group differences (group x time interaction) in changes from baseline to 24 months based on data from all participants with at least one post-baseline measurement. NTB=neuropsychiatric test battery.

Ngandu et al (2015)

WORLD WIDE FINGERS

5 SIMPLE THINGS THAT YOU CAN START NOW

LOOK AFTER YOUR HEART

Smokers have a 45% higher risk of developing dementia than non-smokers

BE PHYSICALLY ACTIVE

Walking is fun and a great way to keep fit and healthy. Build walking into part of your daily routine by downloading an app like 'Ground Miles' and keeping track of your steps.

FOLLOW A HEALTHY DIET

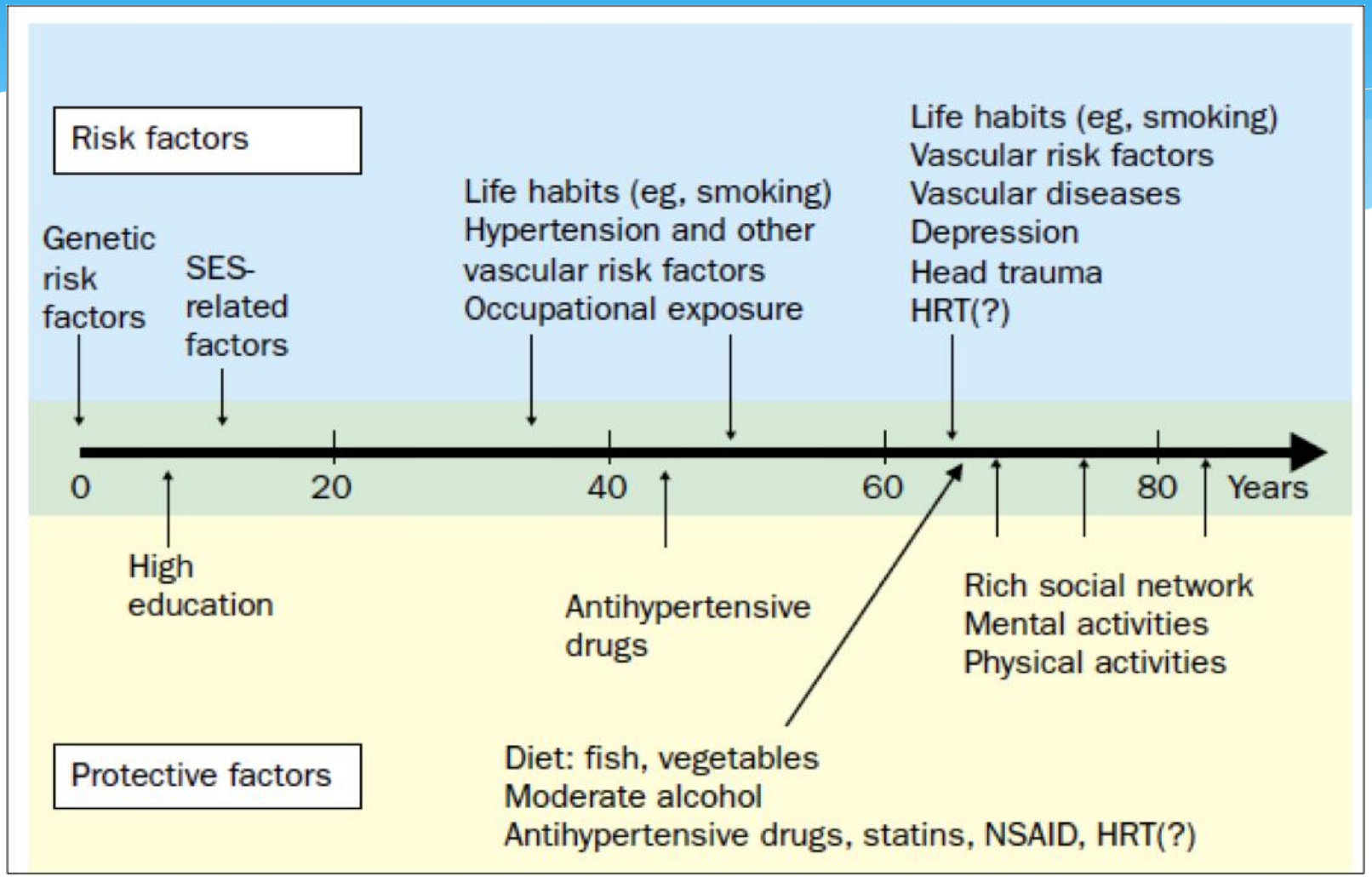
A healthy diet high in cereals, fish, legumes and vegetables could help to reduce your risk of dementia

CHALLENGE YOUR BRAIN

Lots of mental activity is linked to less shrinkage of the hippocampus, a part of the brain critical for memory and often the first to be damaged by Alzheimer's disease, the most common form of dementia

ENJOY SOCIAL ACTIVITY

This is one of the most enjoyable things you can do that could reduce your risk of developing dementia - and yet only 17% of the people we surveyed around the world knew about it*



Fratiglioni et al (2004)

Aims of this workshop

* To provide some examples of age-related change in cognitive performance and how we test them
* To provide an overview of brain changes associated with ‘normal’ and with pathological ageing
* To provide an overview of techniques for imaging brain structure
* To provide an overview of biological risk factors
* To consider some of the implications of knowing our genetic risk score
* To consider lifestyle factors to counter brain changes