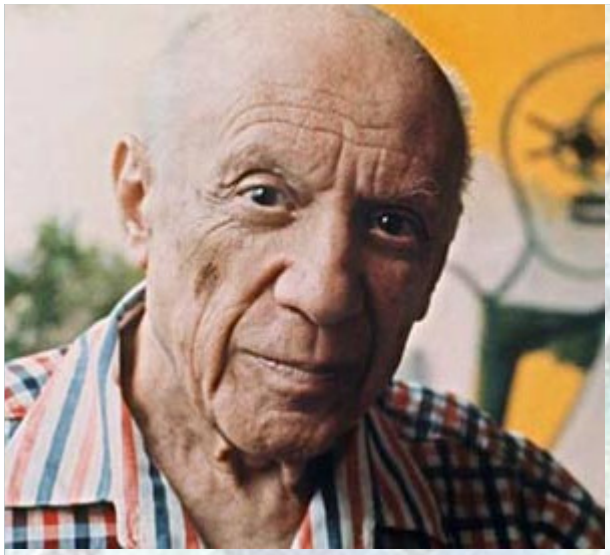

Pablo Ruiz Picasso
October 25, 1881 –
Died April 8, 1973.

Cognitive changes in the ageing brain –
the metabolic substrates

Dr. Emil C. Toescu
Division Medical Sciences,
University of Birmingham

e.c.toescu@bham.ac.uk

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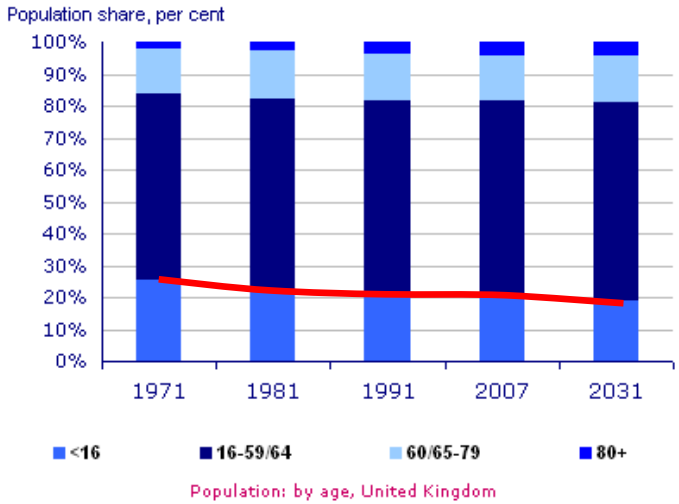
Ageing

More pensioners than under-16's for first time ever



Population: by age, United Kingdom

The percentage of the population aged under 16 has been declining since 1995 and, for the first time ever. has dropped below the percentage of the population of state pensionable age. Average growth in the population aged over state pensionable age between 1981 to 2007 was less than one per cent per year, however, between 2006 and 2007 the growth rate was nearly 2 per cent.

Published on 21 August 2008 at 9:30 am

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THE INDEPENDENT

The population timebomb

There are now more pensioners in Britain than under 16s – with explosive consequences for NHS and pensions

By Ben Russell and Cahal Milmo
Friday, 22 August 2008

Age and incidence of strokes

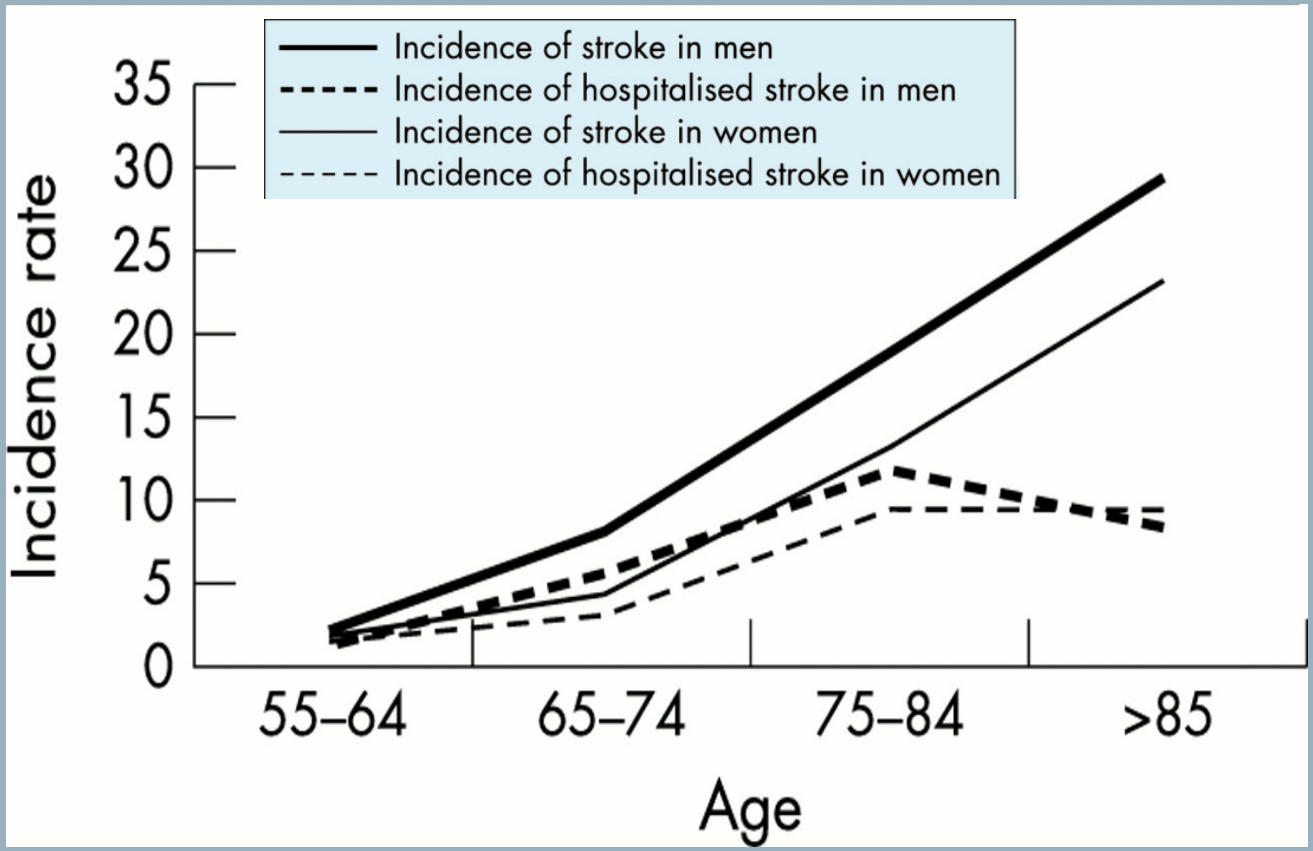
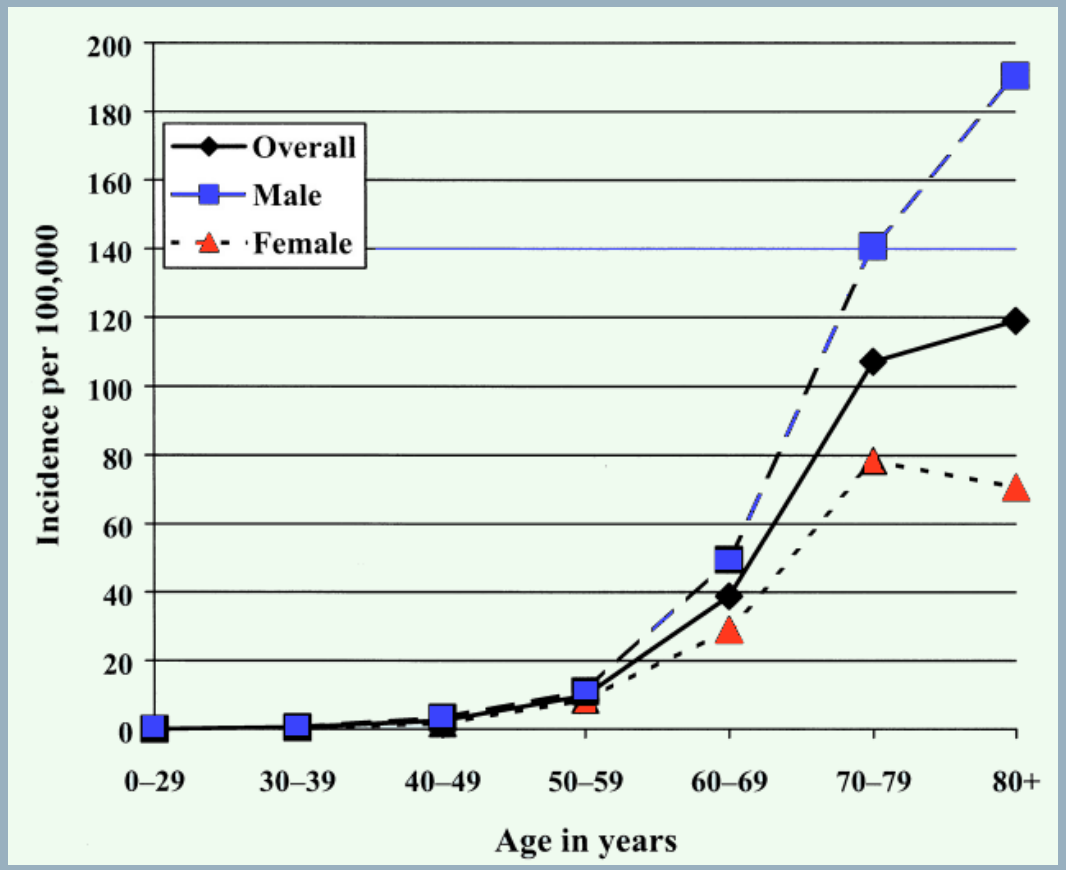


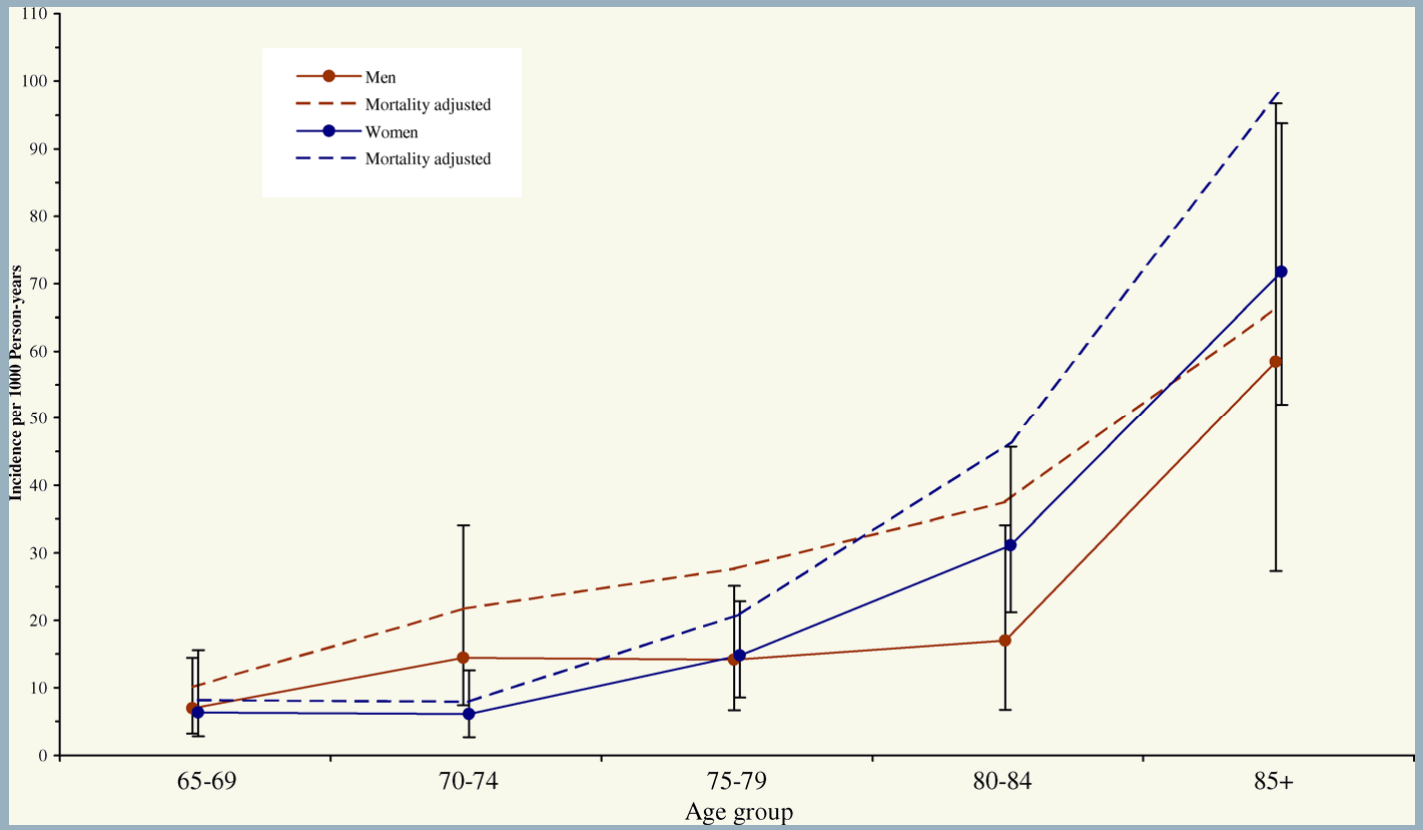
Figure 1 Incidence rate per 1000 person years for stroke and hospitalised stroke in relation to age in men and in women. **Hollander, M et al. J Neurol Neurosurg Psychiatry 2003;74:317-321**

Age and Parkinson's disease



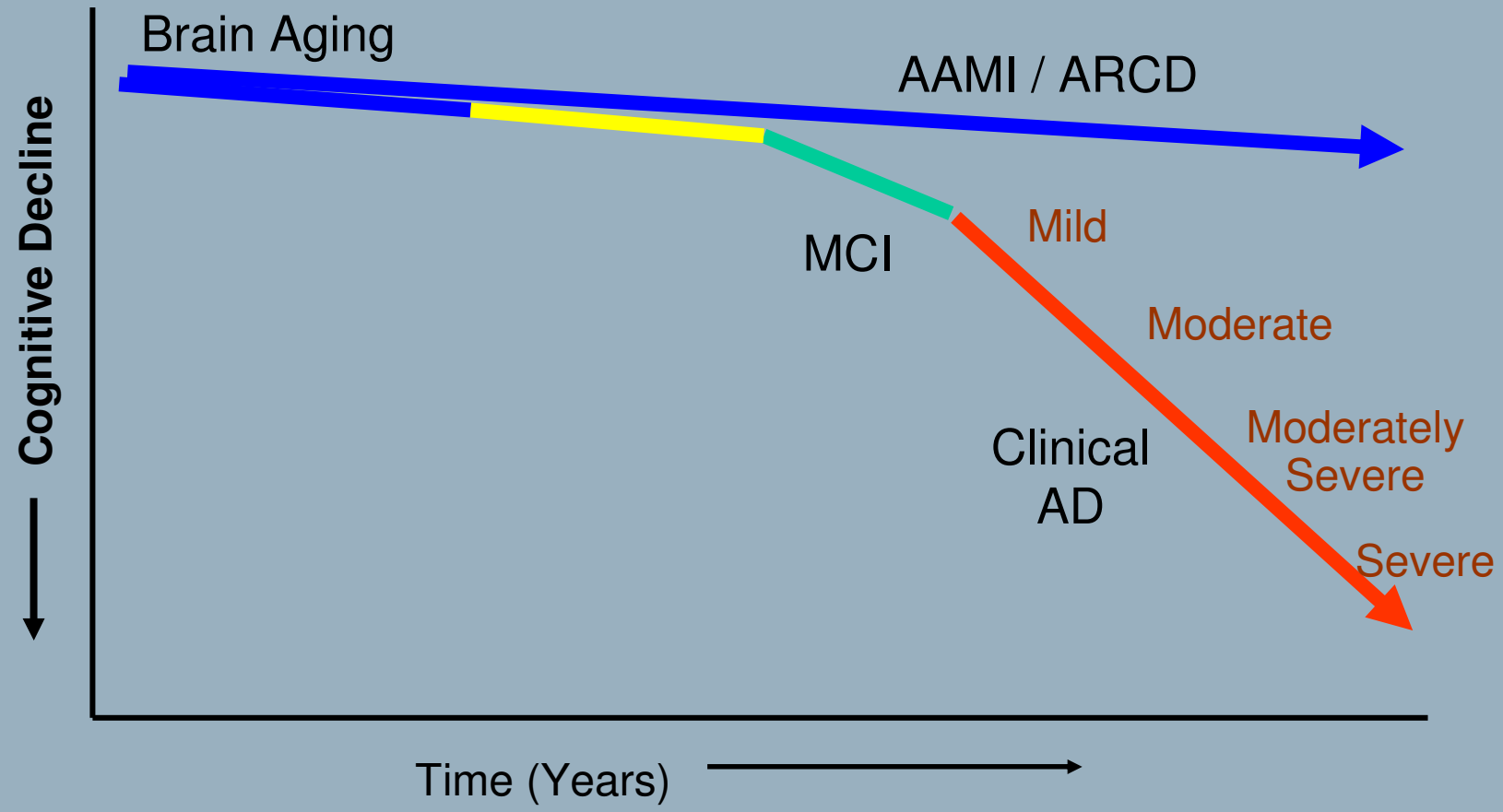
Van Den Eeden, S. K. et al. Am. J. Epidemiol. 2003 157:1015-1022; doi:10.1093/aje/kwg068

Age and Incidence of Dementia in England and Wales



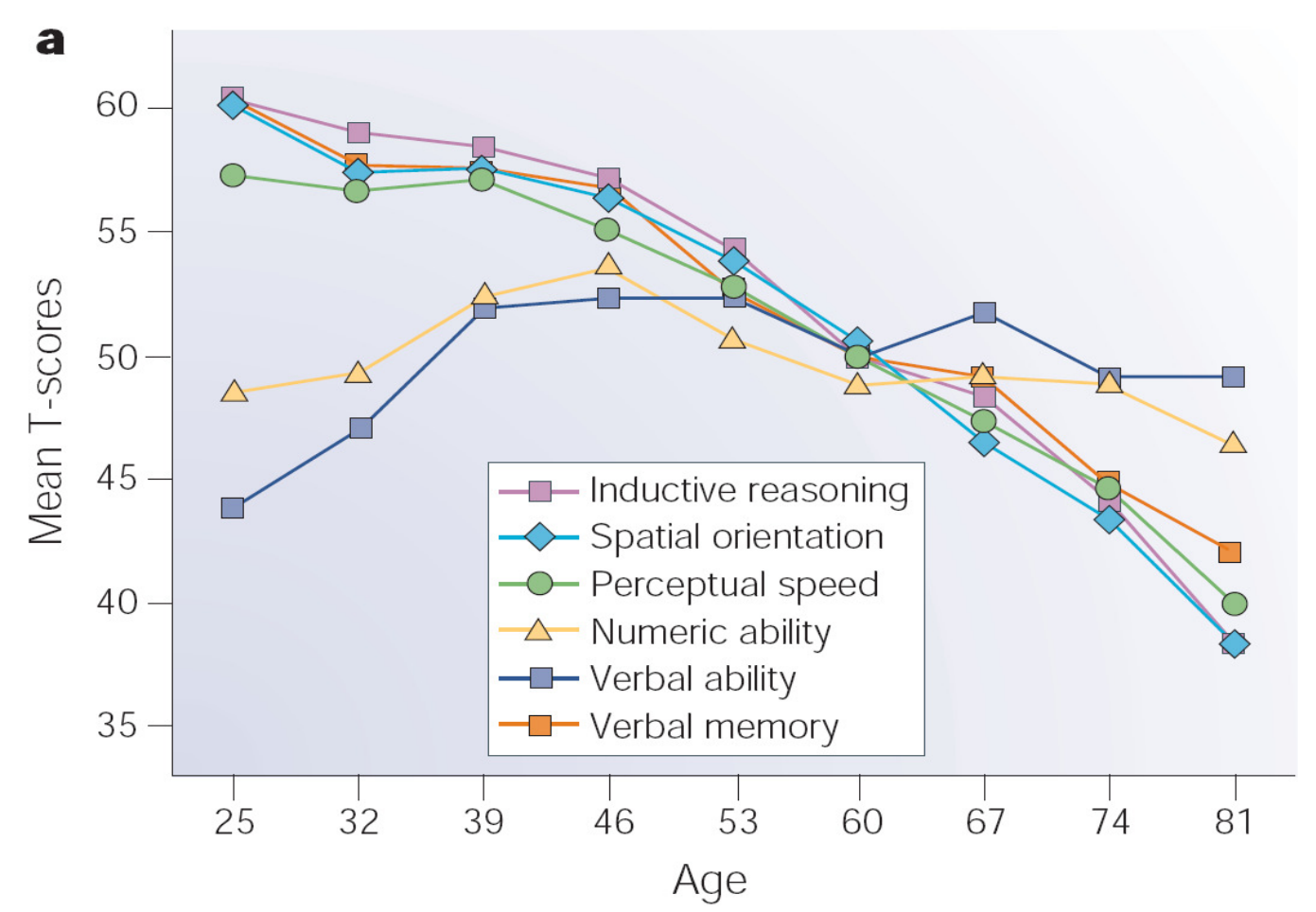
From: [The Incidence of Dementia in England and Wales: Findings from the Five Identical Sites of the MRC CFA Study] Matthews F, Brayne C, 2005 *PLoS Medicine* Vol. 2, No. 8, e193 doi:10.1371/journal.pmed.0020193

Course of Aging, MCI and AD



Human cognitive ageing varies according to ability domain

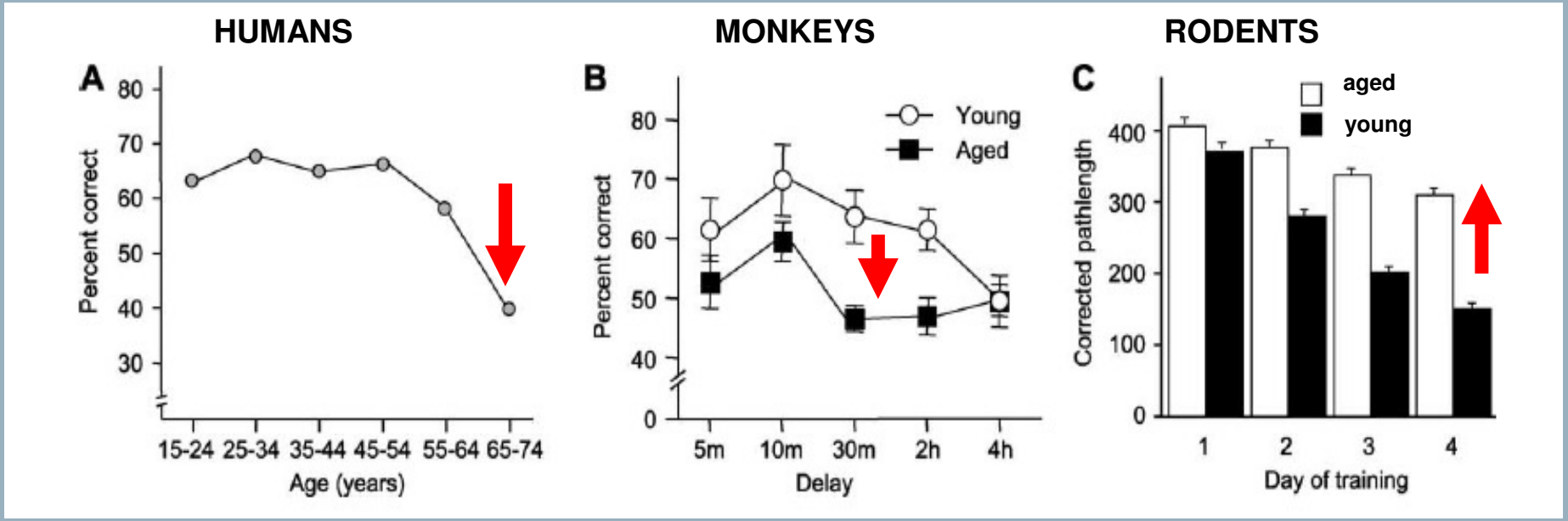
Seattle Longitudinal Study



Hedden & Gabrieli (2003) *Nature Reviews Neuroscience*, *5*, 87-96.

Normal Cognitive Ageing

Testing episodic/spatial memory



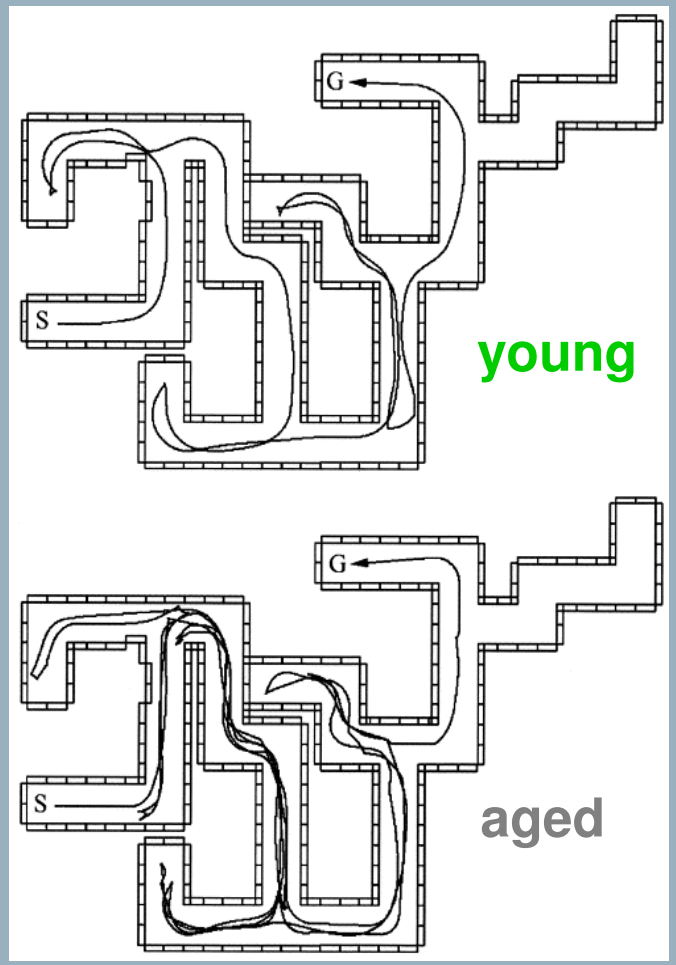
"Pictures at an exhibition" **"Food in the pen"** **Water maze (Morris)**

From Erickson & Barnes (2003) – Exp. Gerontol. 38:61

Normal ageing: spatial memory impairments

Age-related memory impairments:
Impaired hippocampal function?

Is hippocampal function impaired in aged mice?



Moffat et al (2001) *Neurobiol. Aging* **22**, 787-96

Effect of ageing on hippocampal spatial memory function

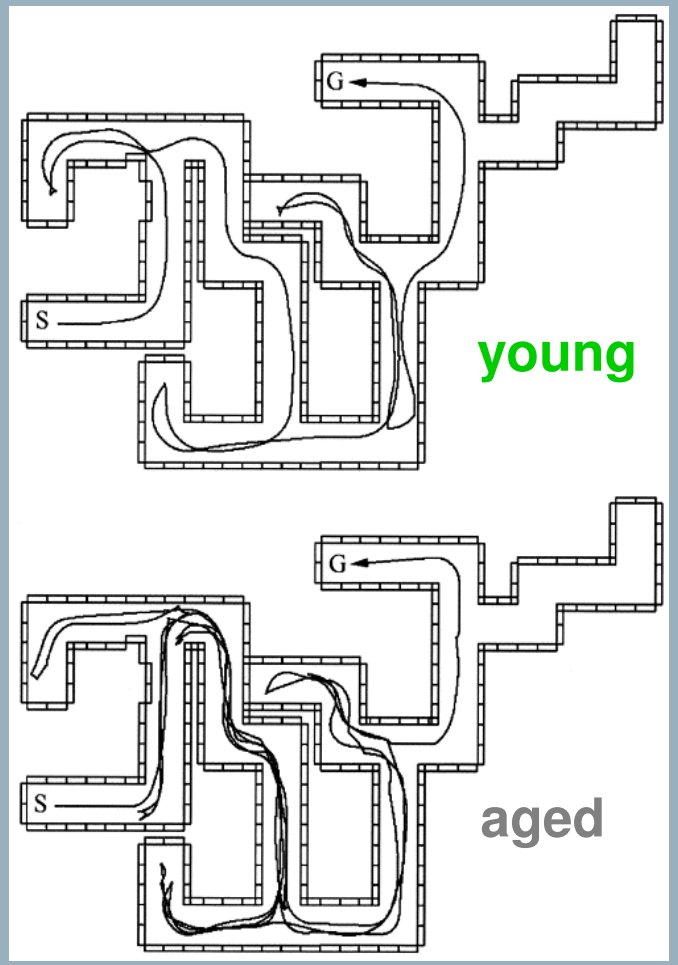
Set of unpublished data showing that, in the Barnes circular maze, ageing impairs, in the mice, the spatial memory on a number of criteria.

Normal ageing: spatial memory impairments

Age-related memory impairments:
Impaired hippocampal function?

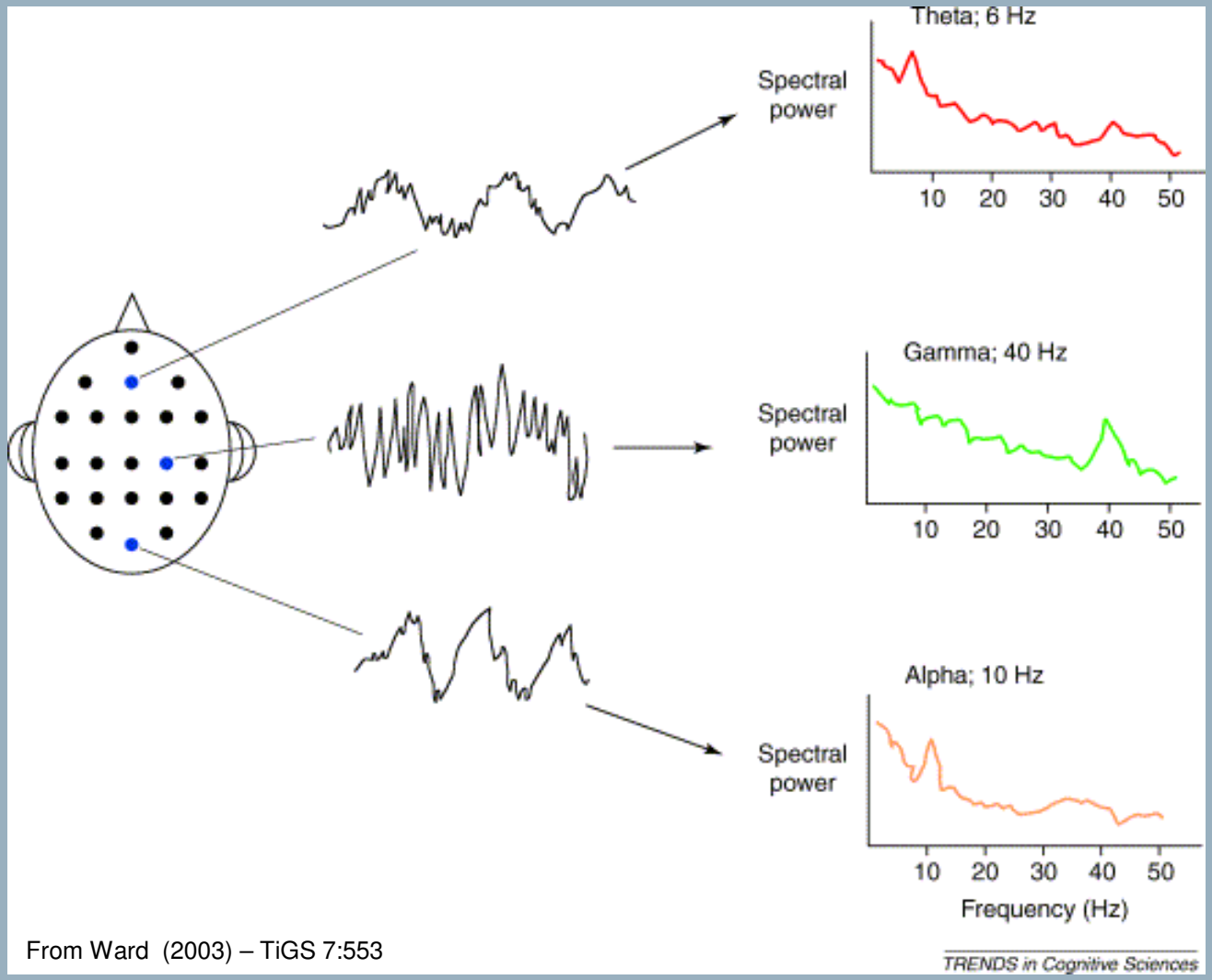
Is hippocampal function
impaired in aged mice?

Is hippocampal neuronal network
function impaired in aged mice?



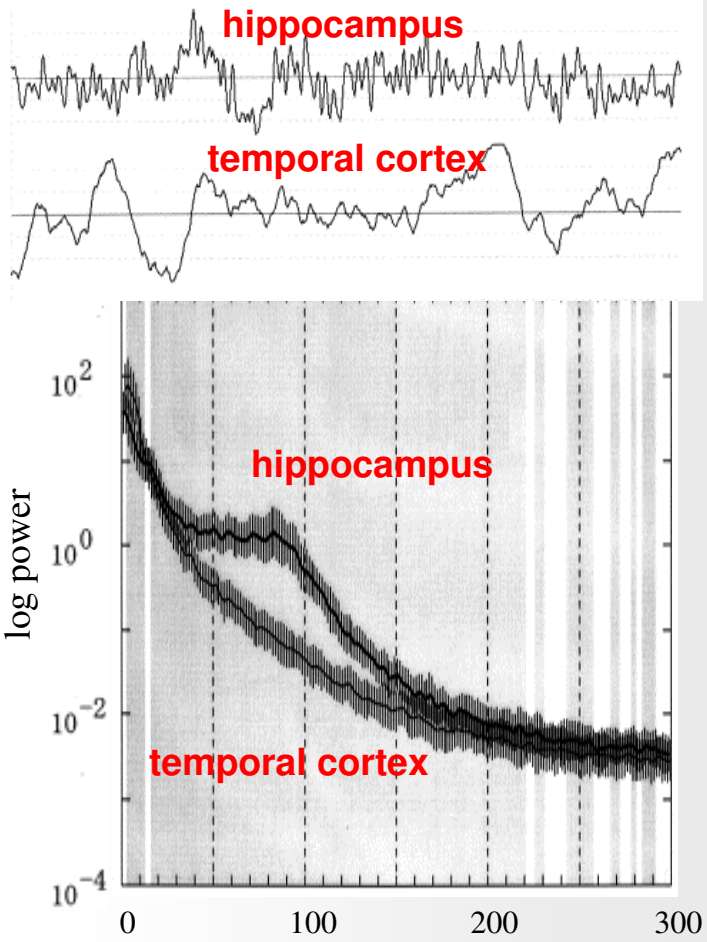
Moffat et al (2001) *Neurobiol. Aging* **22**, 787-96

Oscillatory electrical activity in the brain

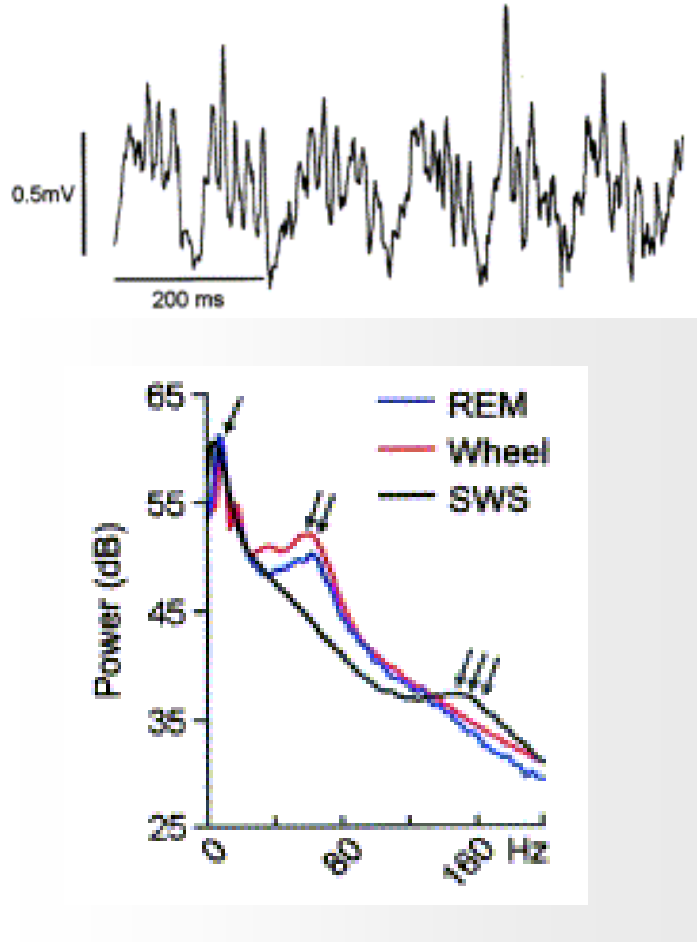


From Ward (2003) – TiGS 7:553

Fast oscillations – Gamma

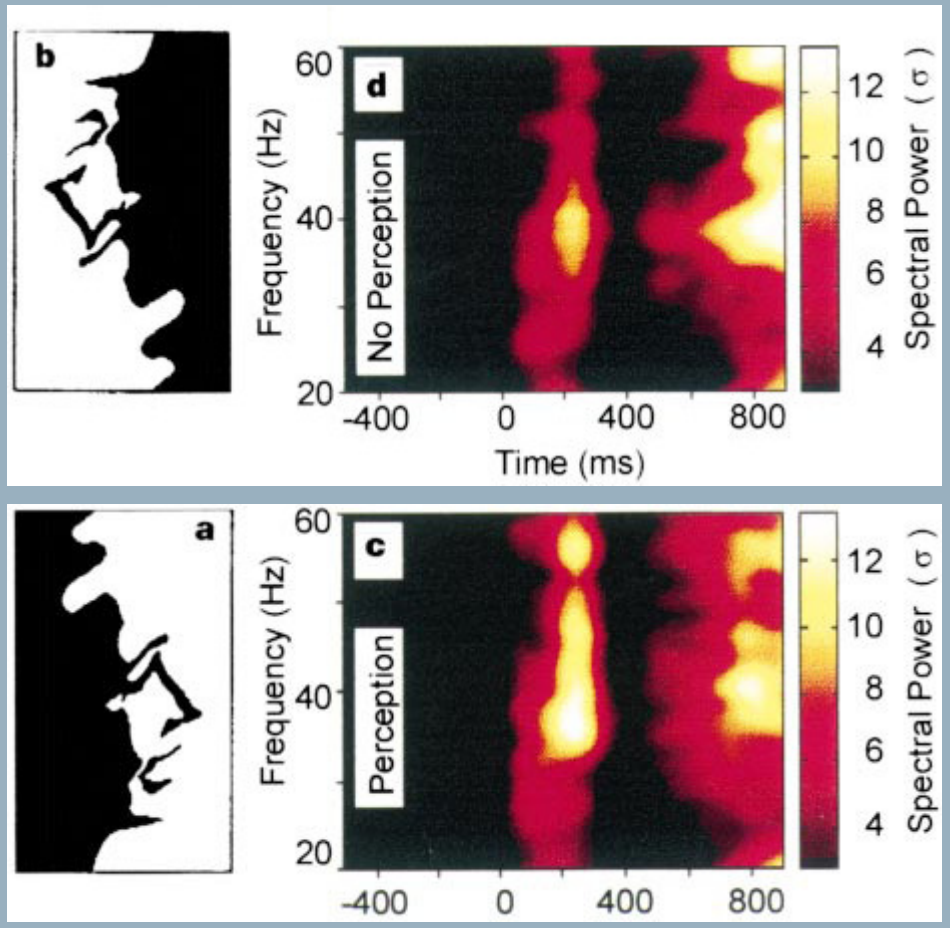


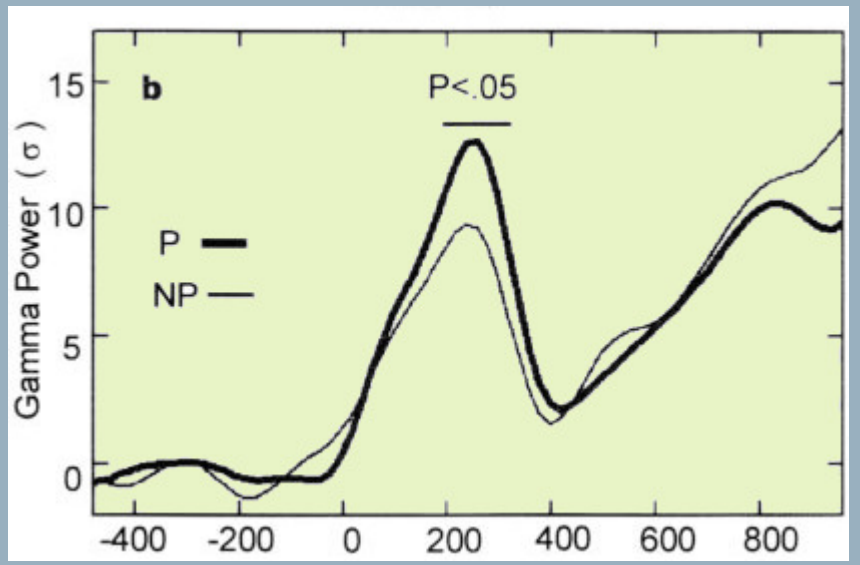
Hirai et al (1999) Neuroscience 90, 1149-55



Buzsaki *et al* (2003) *Neuroscience* **116**, 201-211

Gamma oscillations: involved in cognitive functions

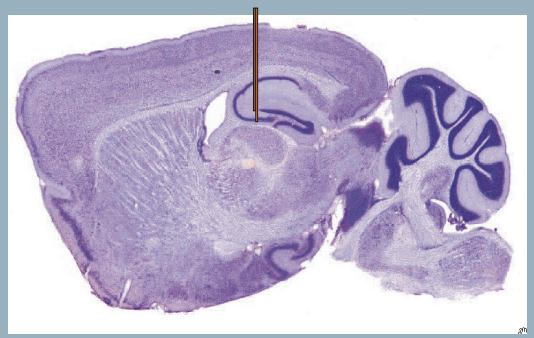




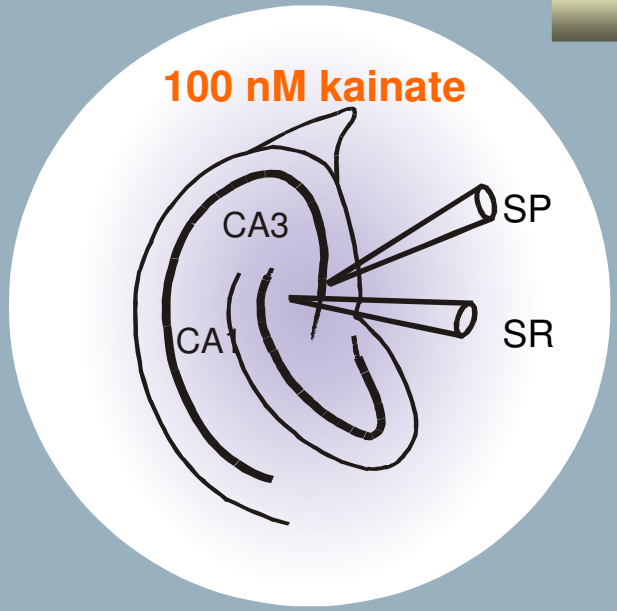
Rodrigues et al. (1999) *Nature* 397: 430-3

Ageing changes in vivo gamma

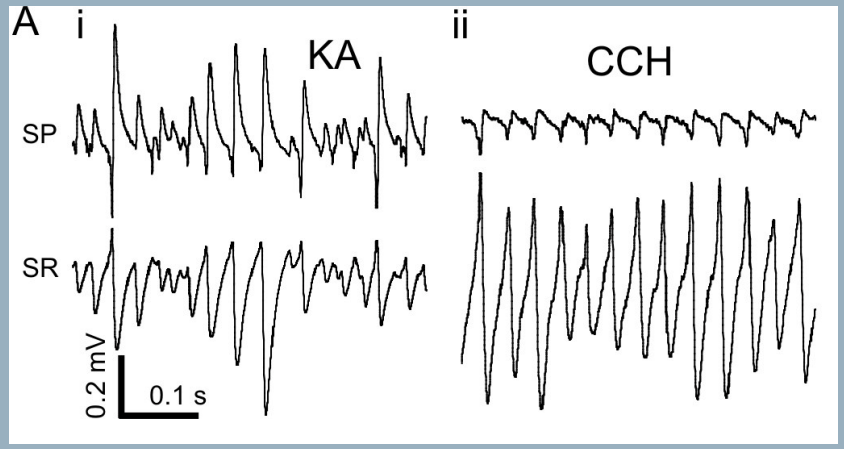
Set of unpublished data, obtained through electrodes impaled in the hippocampus of behaviourally characterised mice, showing decrease in the activation-induced gamma activity in the aged animals.



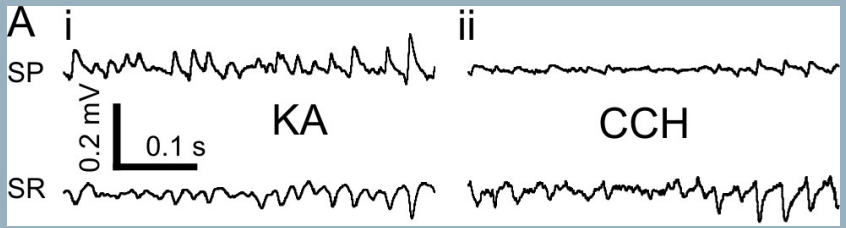
Effect of age on gamma-oscillations

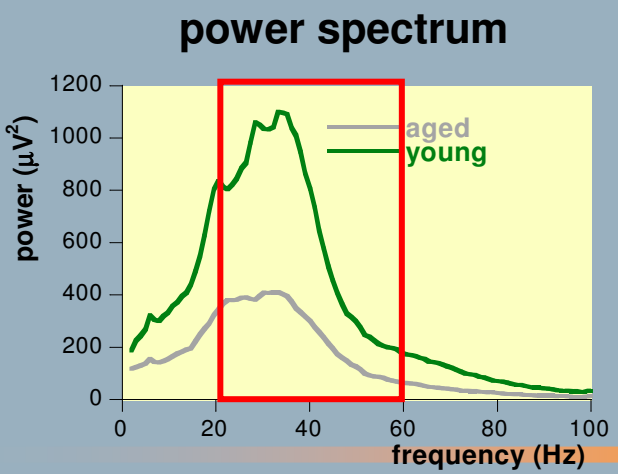


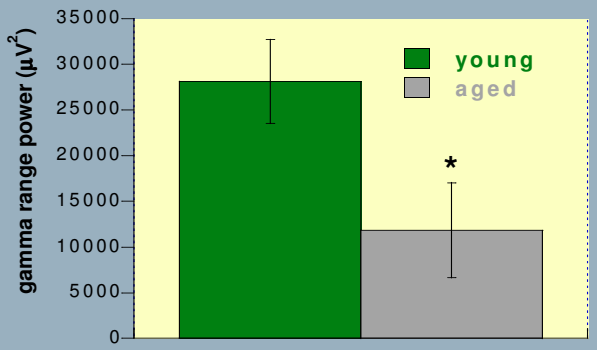
Young



Aged







Vreugdenhil & Toescu (2005)
Neurosci 132:1151-60

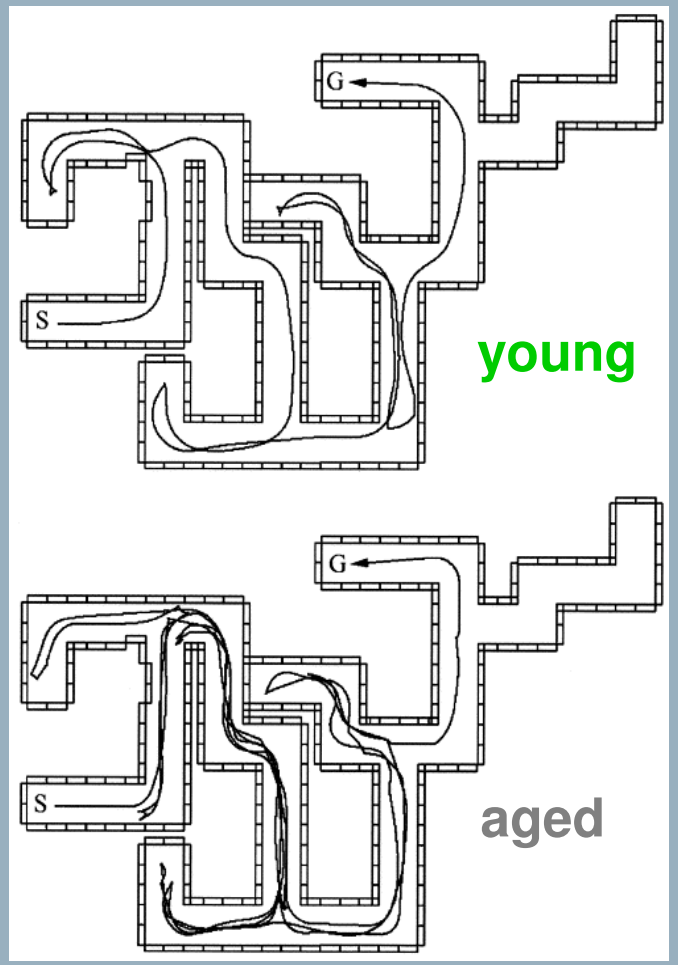
Normal ageing: spatial memory impairments

Age-related memory impairments:
Impaired hippocampal function?

Is hippocampal function
impaired in aged mice?

Is hippocampal neuronal network
function impaired in aged mice?

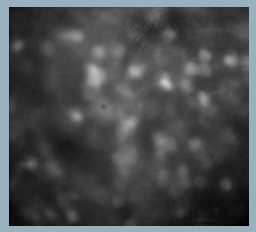
Is cellular function changed in
neurons from aged mice?



Moffat et al (2001) *Neurobiol. Aging* **22**, 787-96

Dual staining for $[Ca^{2+}]_i$ and mitochondrial membrane potential

380 nm image

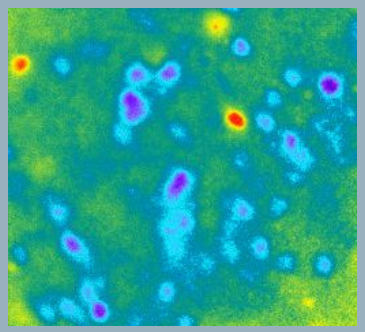


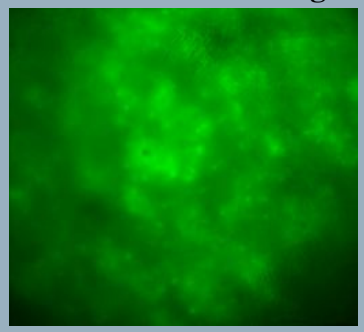
Cerebellar slice,
Granular layer

Fura2 AM staining

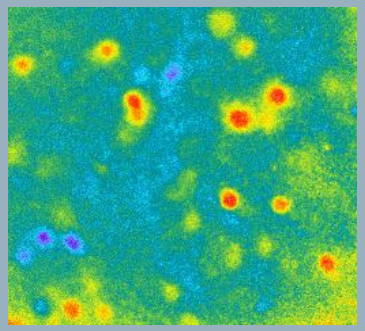
Rhodamine 123 staining

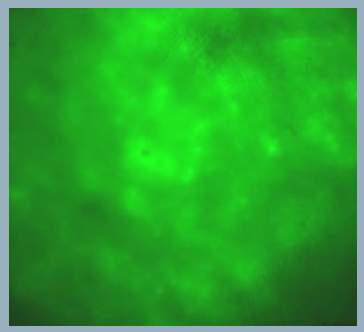
REST





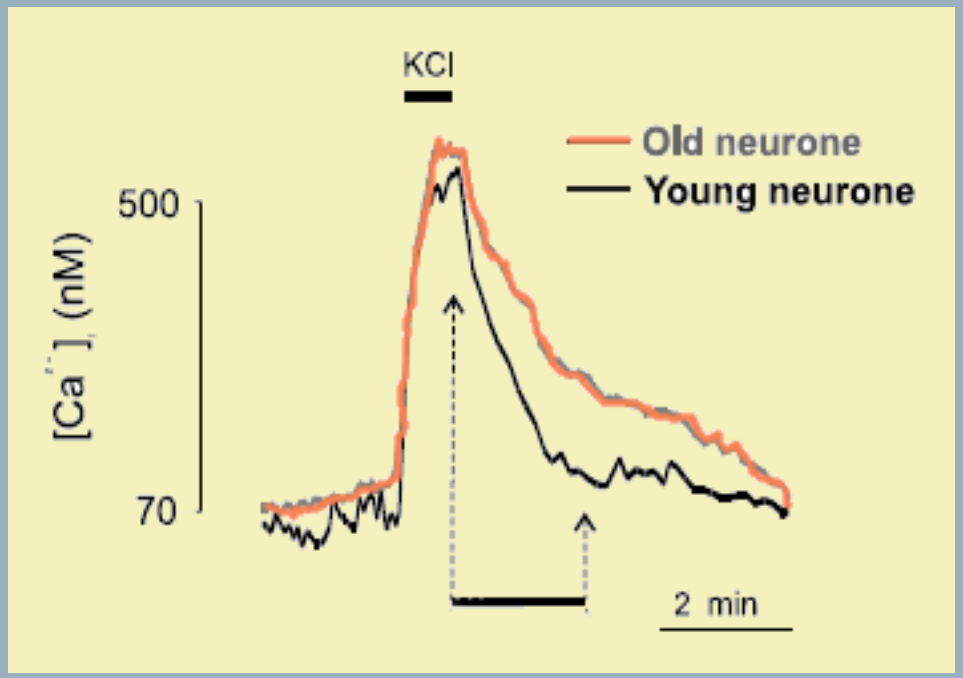
MAXIMAL STIMULATION



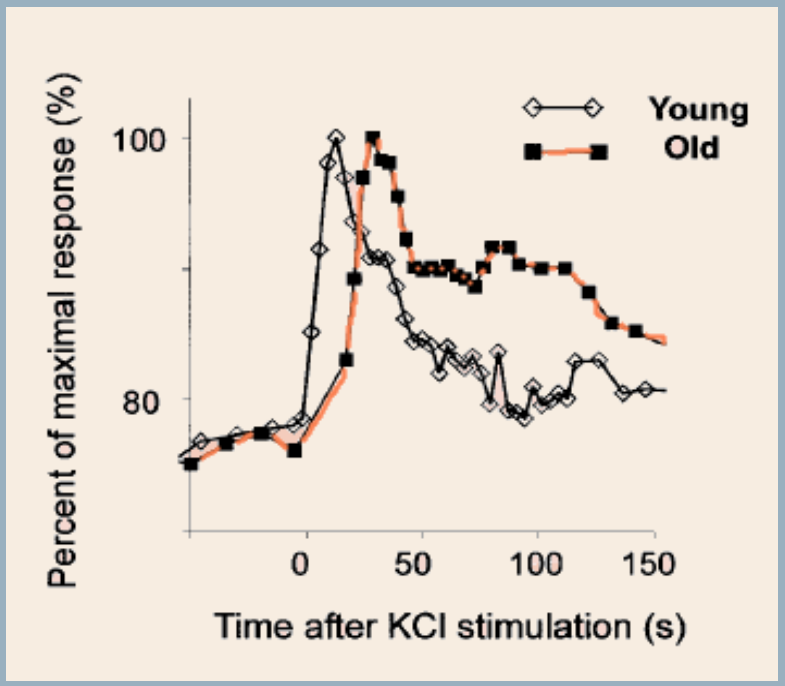


Simultaneous measurements of Ca signal and mitochondrial depolarization

Ca^{2+} measurements

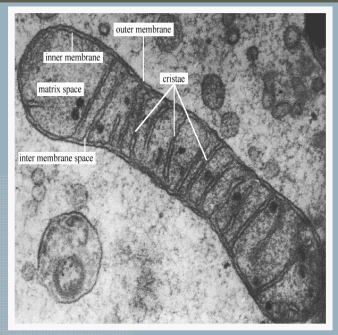


Rhodamine measurements

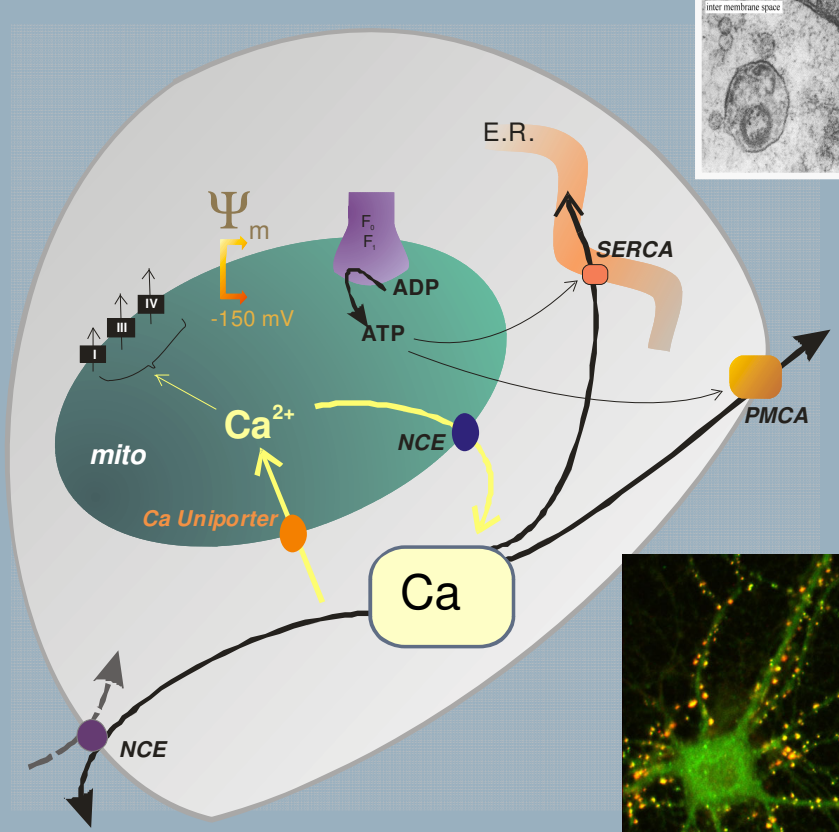


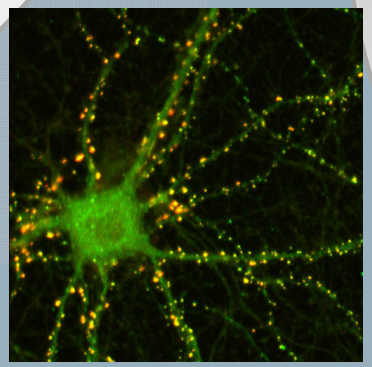
From Xiong et al – J.Neurosci (2002) 22:10761

Mitochondrial functions

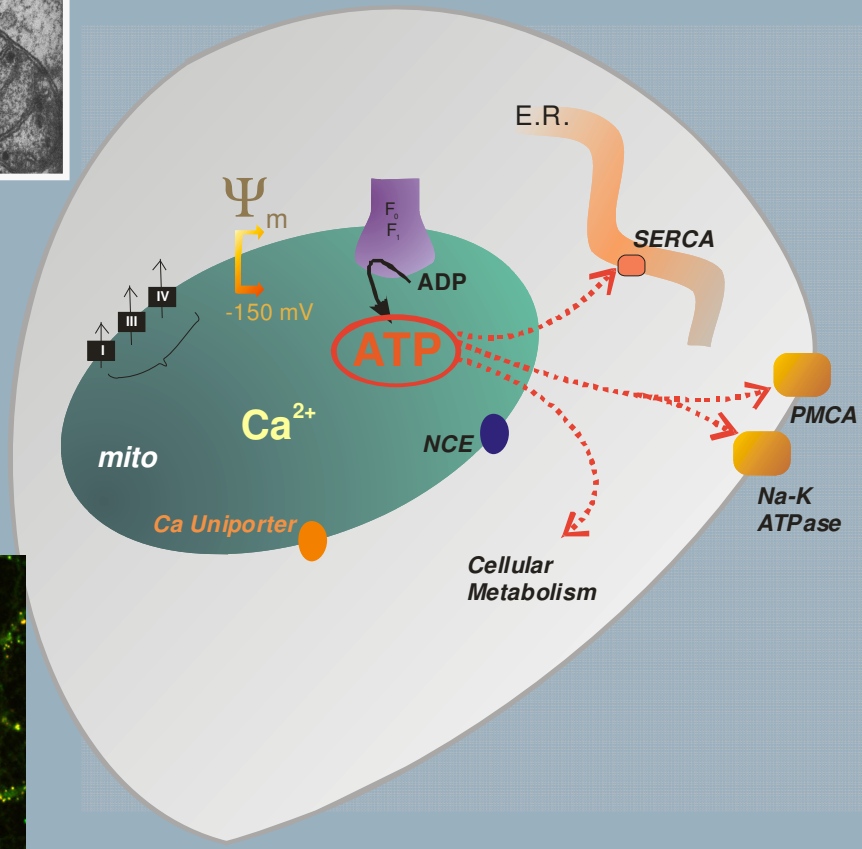


Single mitochodrion

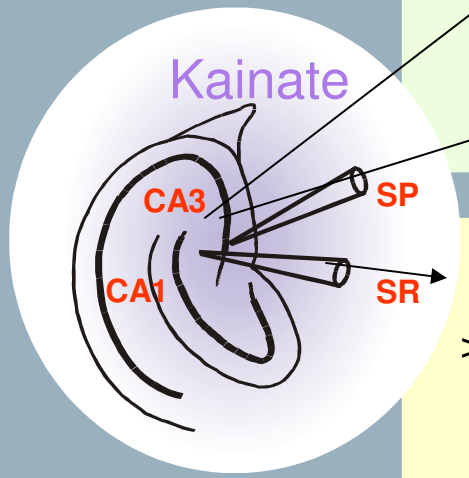


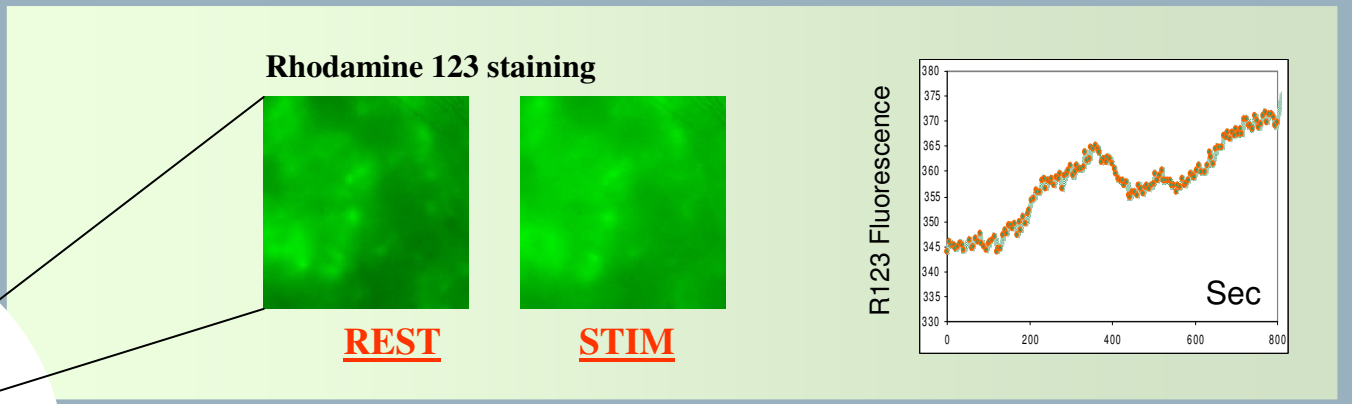


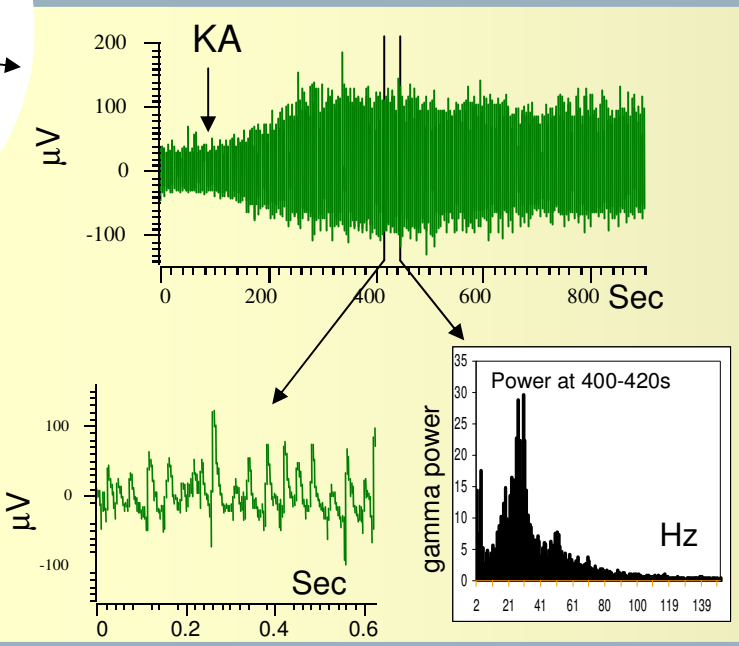
Mitochondrial distribution

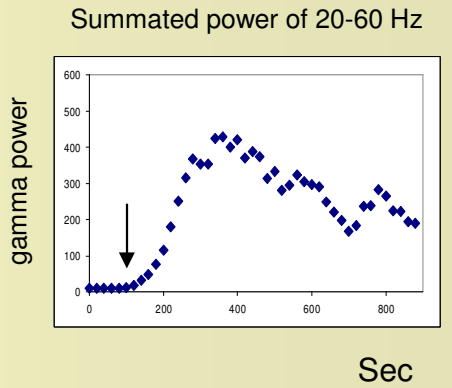


Experimental Protocol









Gamma activity and mitochondrial response

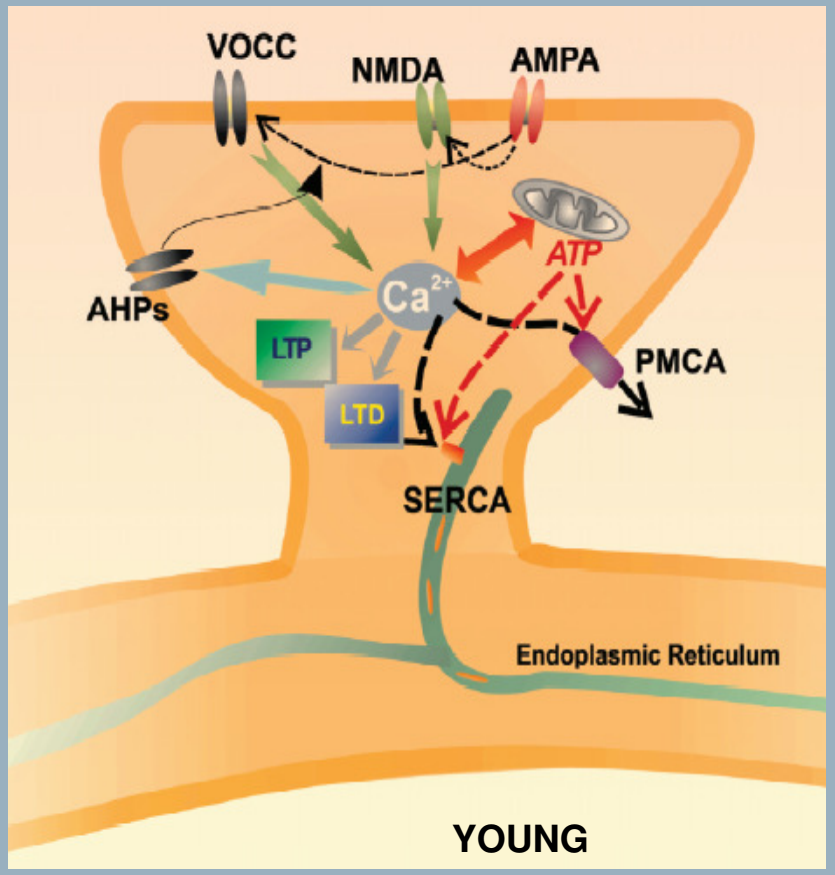
Set of unpublished data showing the difference in gamma activity and mitochondrial response between Young and Old slices.

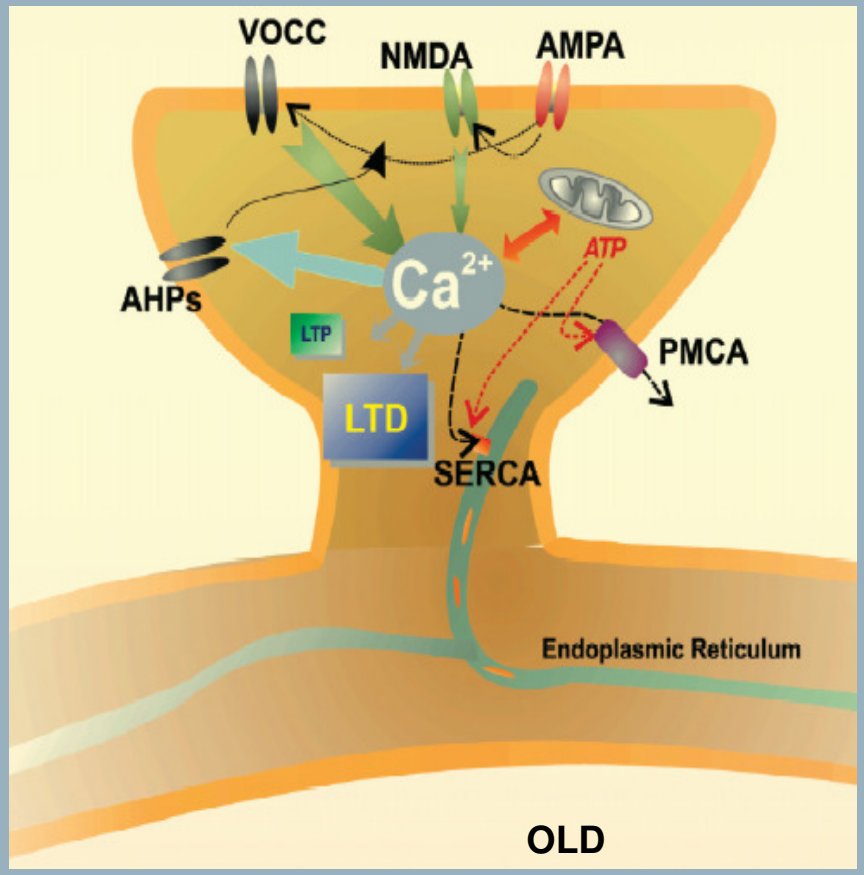
Overall, in the young there is a large gamma, with a small mitochondrial response, developing late. In the old, there is a much smaller gamma, but with a significantly larger mitochondrial depolarization .

Firing-induced $[Ca^{2+}]_i$ transient is increased with ageing

Set of unpublished data showing the difference between Young and Old slices in responding to stimulation protocols with increasing numbers of action potentials. Measurements performed using fura-2 signal, with the die loaded through a patch pipette.

$[Ca^{2+}]_i$, mitochondria and slow AHP





Toescu and Verkhratsky (2004) J.Cell.Mol.Med. 8: 181

Slow after-hyperpolarisation is increased with ageing

Set of unpublished data showing the differences recorded in neurones from Young and Old slices in respect to the functional characteristics of the Ca-activated slow afterhypolarization K current (I_{sAHP}) that could explain the differences in excitability

Features of the process of normal (physiological) ageing

RESTING STATE: - "normal"

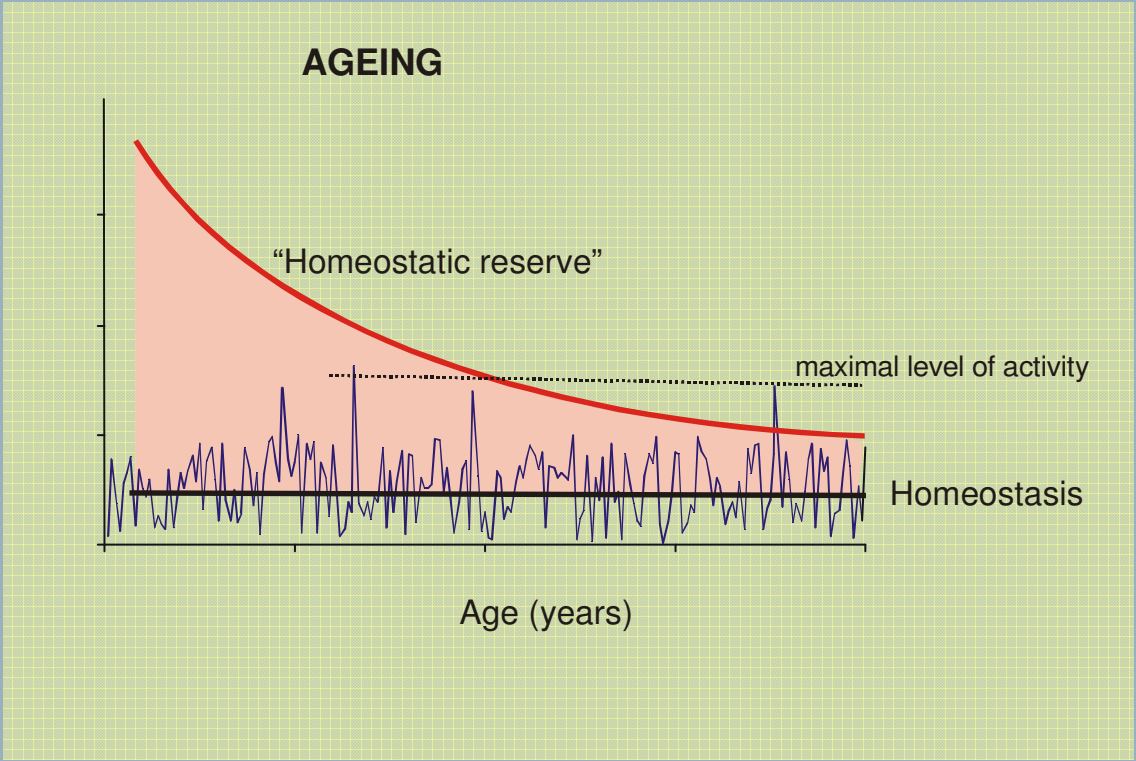
During MAXIMAL STIMULATION – deficits in $[Ca^{2+}]_i$ recovery

- ***ATP supply (?)***
- ***Ca^{2+} - mitochondria interface (?)***
- ***mitochondrial deficits (?)***

Decrease in **HOMEOSTATIC RESERVE**

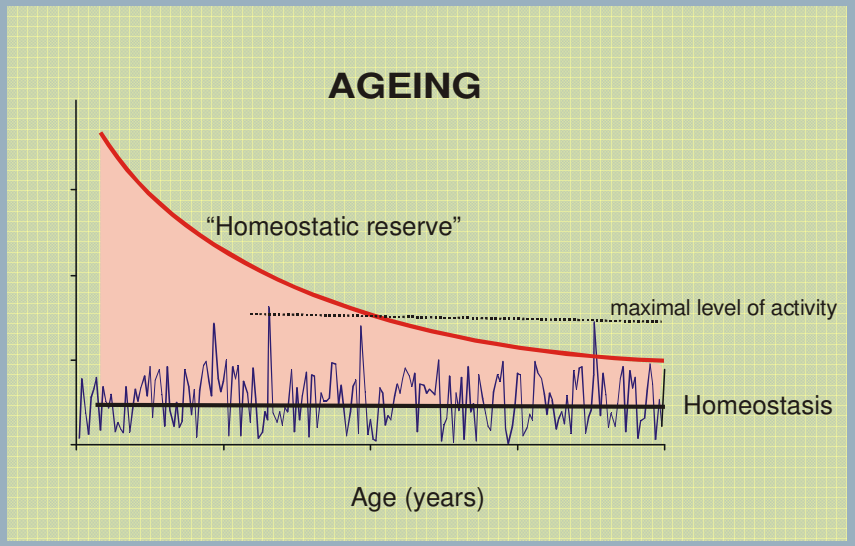
Concept of **Homeostatic Reserve**

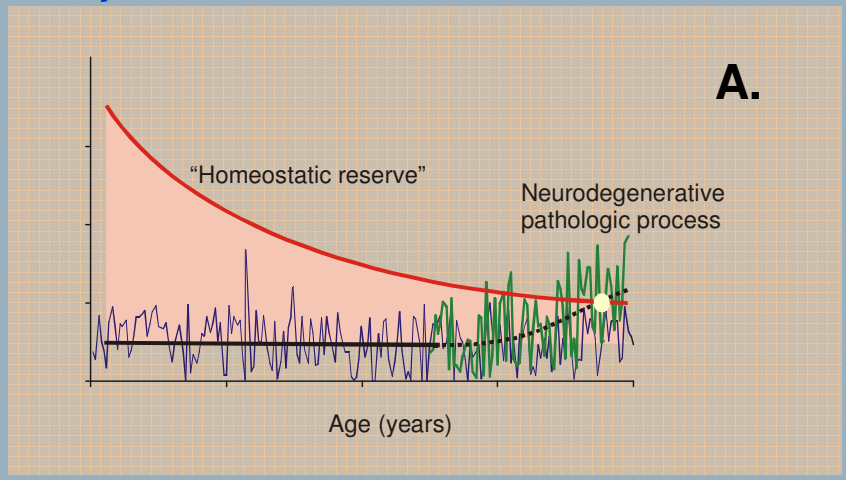
Toescu (2004) – Phil.Trans.Royal Soc B 360:2195

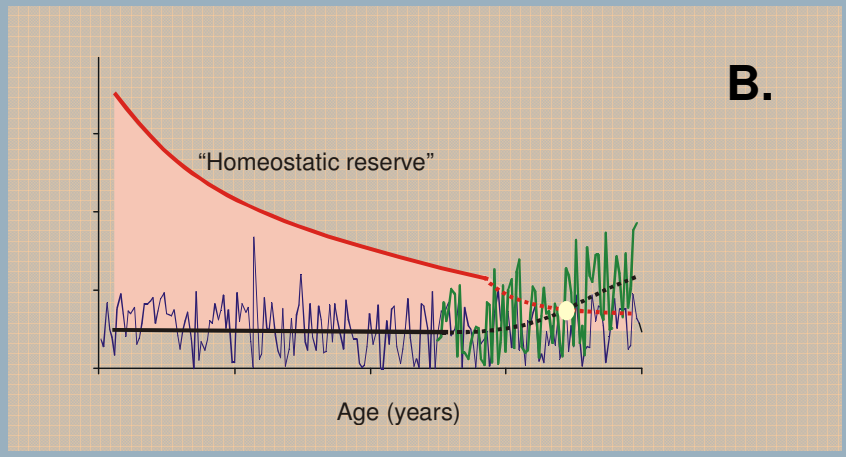


Aging *vs.* Neurodegeneration

Toescu (2004) – Phil.Trans.Royal Soc B 360:2195







Collaborators and co-workers

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Dr. Cheng Lu
John Reynolds

Prof. Janet Lord
Dr. Prem Kumar
Prof. Ann Logan

Manchester

Prof. Alex Verkhratsky

Dr. Natalya Solovievna