APOE and cognition across the lifespan

Jennifer Rusted

University of Sussex

I will cover..

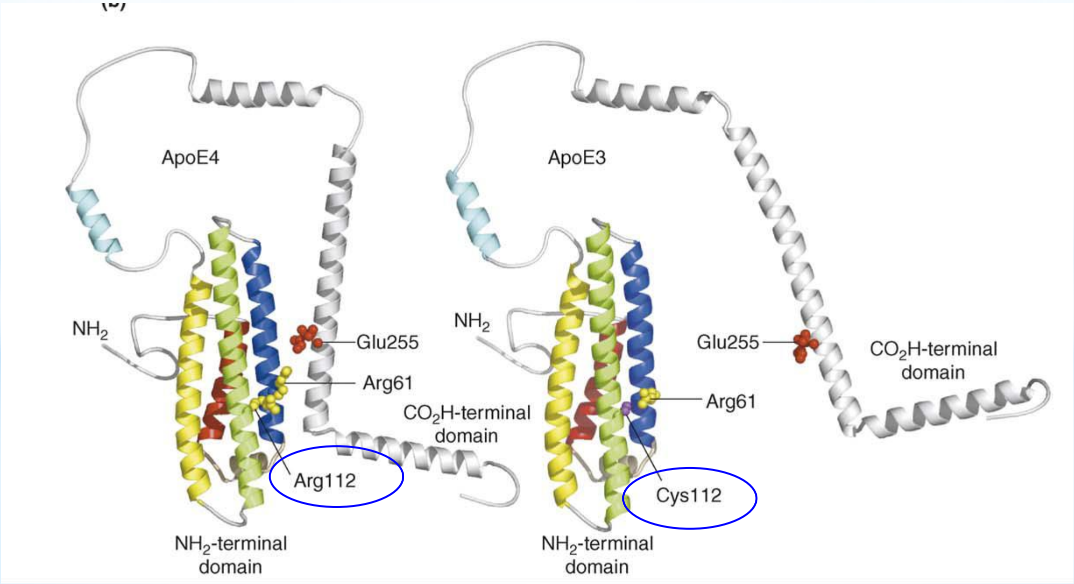
* Alzheimer's Disease: the statistics
* What is APOE
* *APOE4* in older adulthood
* *APOE4* and cognition in young and mid-age adults
  * Impact on performance
  * Impact on brain function
  * Impact on brain structure
* Going forward: an interdisciplinary approach to *APOE4*

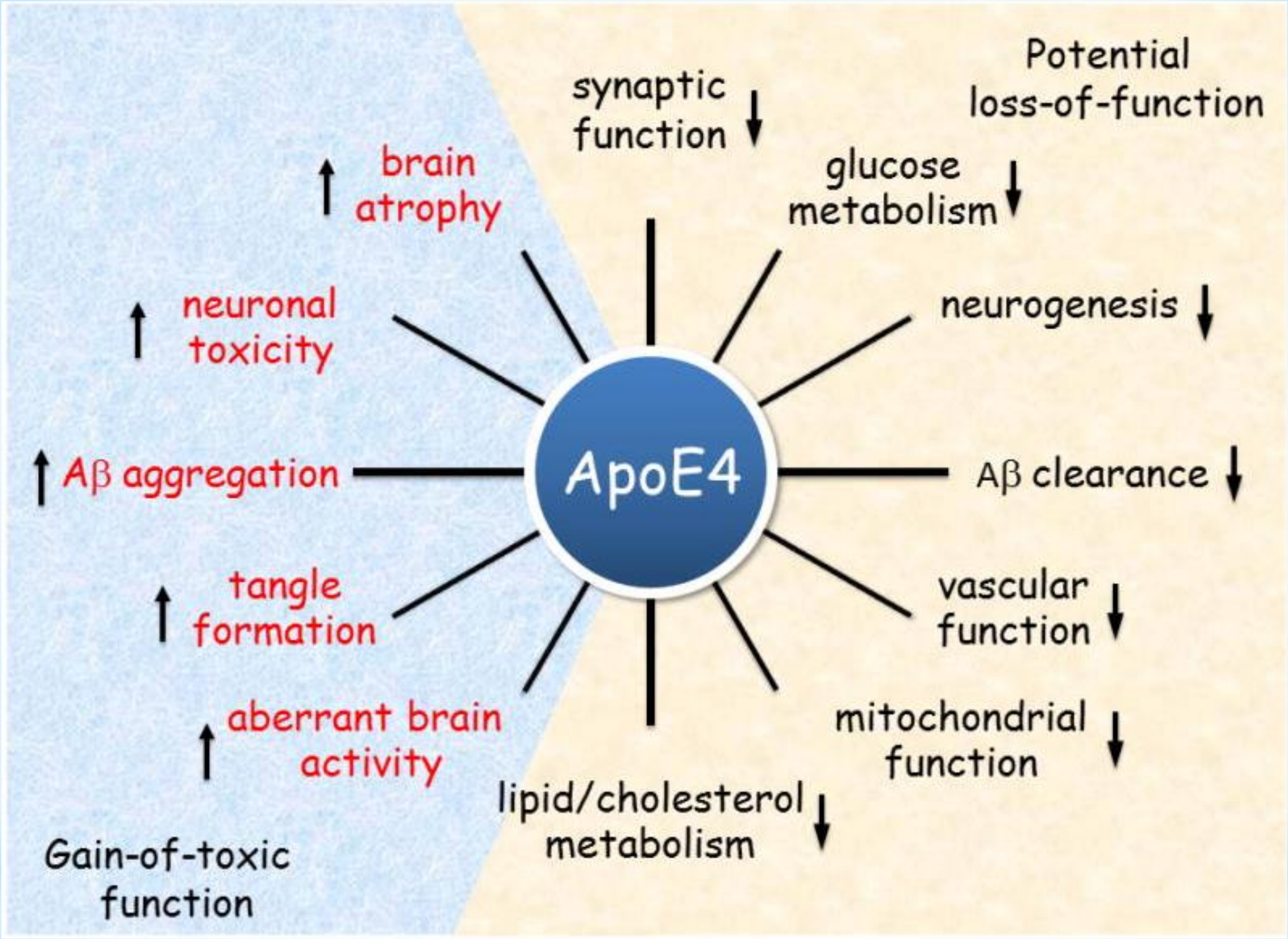
World Alzheimer report 2018

Apolipoprotein (APOE) e4 allele: Largest genetic risk factor for late onset AD

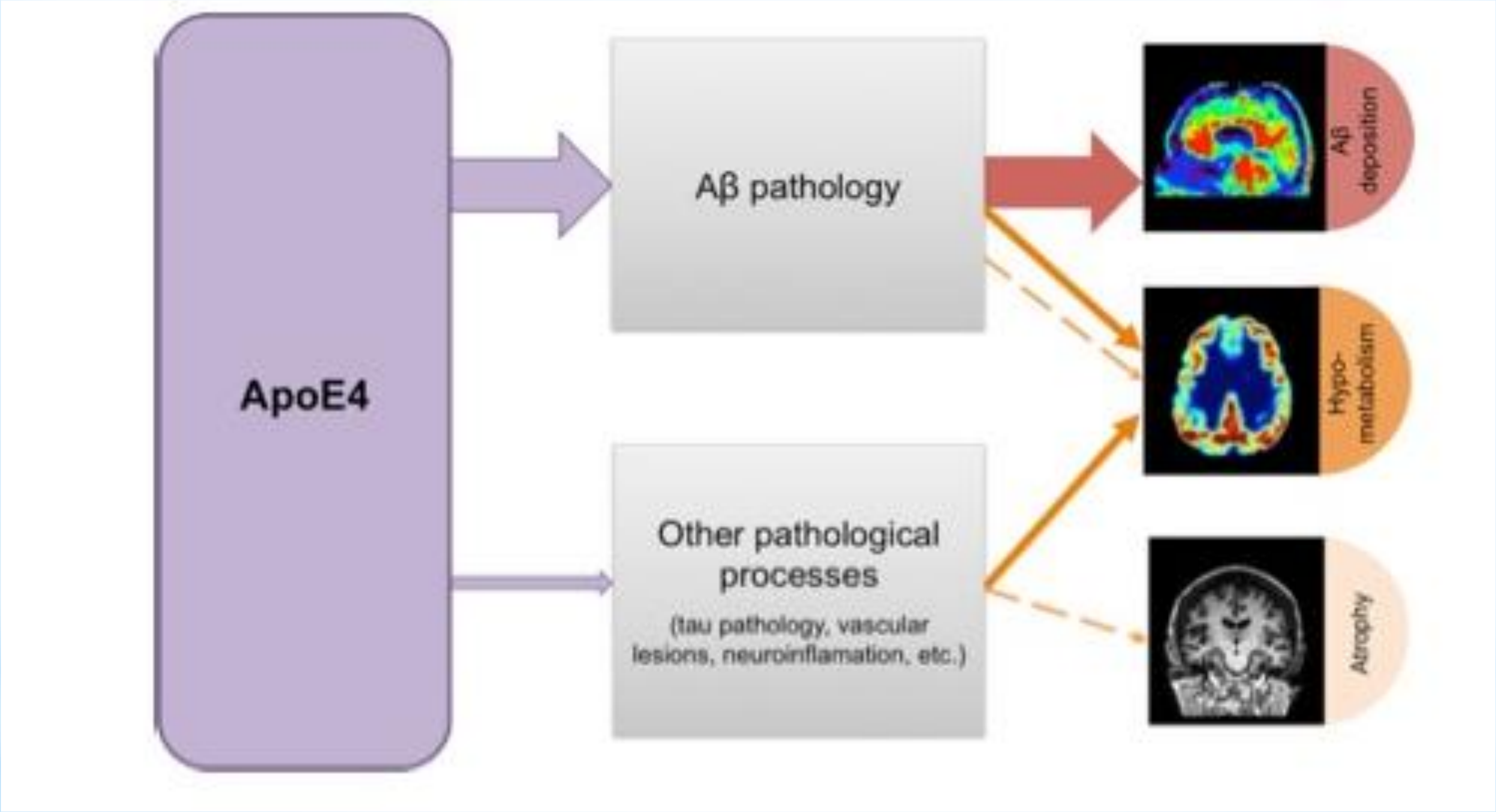
e2 e3 e4

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





Why is the e4 allele a risk factor?



Fouquet et al, 2014

Cognitively healthy older adult e4 carriers

* poorer cognitive performance
* steeper cognitive decline across the lifespan

* reduced brain volume in frontal and medial temporal lobes
* lower brain glucose metabolism
* altered task-related brain activation patterns: posterior-to anterior shift
* altered functional connectivity with hippocampus

Reported cognitive effects in child/adolescent e4 carriers

- higher IQs
  (Yu et al 2000; Oria et al, 2005)
- higher educational achievement
  (Hubacek et al 2001; Taylor et al, 2011)
- higher mental development index scores
  (Wright et al, 2003)
- superior verbal fluency and visual working memory
  (Alexander et al, 2007)
- higher vocabulary scores
  (Acevedo et al, 2010)

Reported cognitive effects in healthy young adult e4 carriers

* superior verbal fluency and visual working memory

  (Alexander et al, 2007)
* better associative memory

  (Mondadori et al, 2007)
* better prospective memory, speed of processing, attention and verbal fluency

  (Marchant et al, 2010)
* better reasoning and arithmetic skills

  (Schultz et al, 2008)
* better spatial memory, object location memory

  (Stening et al., 2016)

APOE-e4 and cognition across the life span

e4 polymorphism confers a disadvantage from the outset

- compensatory activations/overactivation at specific sites in the brain attempt to counteract neurocognitive deficits

(Cabeza et al, 2002; Reiman et al, 2009; Filippini et al, 2010)

e4 polymorphism is associated with cognitive advantages in youth at the cost of disadvantages (eg. poorer ageing) in older adulthood

- reflects structural differences/greater neural efficiency/increased functional connectivity

(Han & Bondi 2008; Han & Tuminello, 2013)

- …an example of antagonistic pleiotropy after Williams (1957)
- "Selection of a gene that confers an advantage at one age and a disadvantage at another"

Our work

- Cognitive assessment:
  Do young adult e4s outperform their e3 peers?

- Brain Imaging:
  Can we see differences in brain structures and brain activation patterns between e4 and e3 young adults?

- What changes at mid-age?

Experimental approach

healthy adult participants

young (18-28 yrs)

mid-age (45-

e4+ | e3/e3 | e4+ | e3/e3

Cognitive Testing

Brain Imaging

- Structural MRI
  DTI +MT + qMT
- NODDI

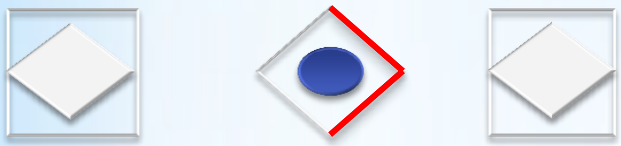
- Functional MRI during selective cognitive tasks

- Cognitive challenge battery

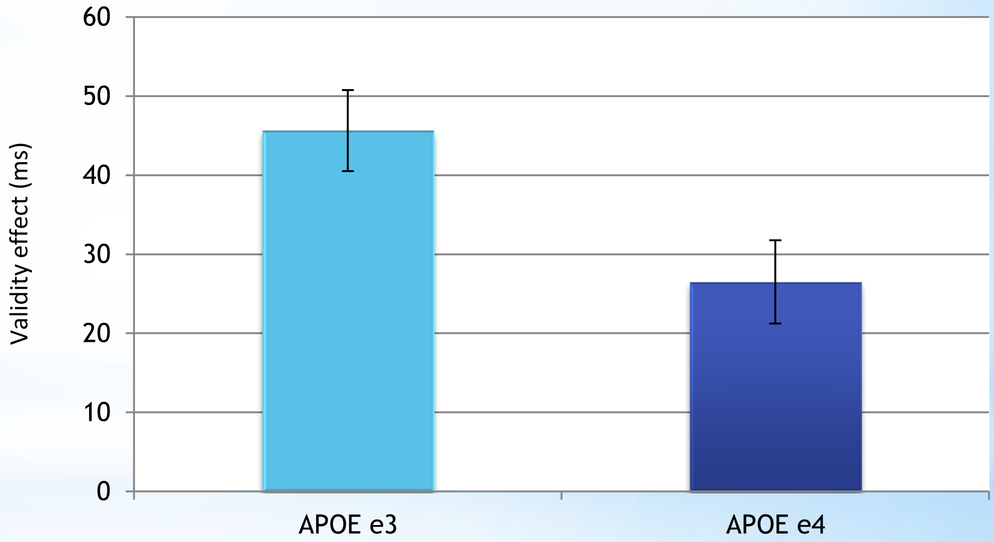
Cognitive profiling - Structural Imaging - Functional Imaging
(- pupillometry - cortisol reactivity - cholinergic system integrity - blood-brain barrier -

Cognitive assessment:
Do young adult e4s outperform their e3 peers?

covert attention task



Validity effect = difference in reaction time to respond to validly cued vs invalidly cued targets



Main effect of genotype

$F_{(3,\ 36)} = 6.79$, $p < 0.01$

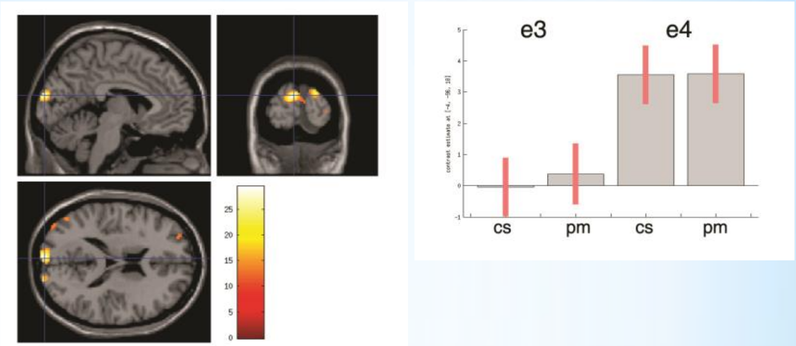
Rusted et al, 2012

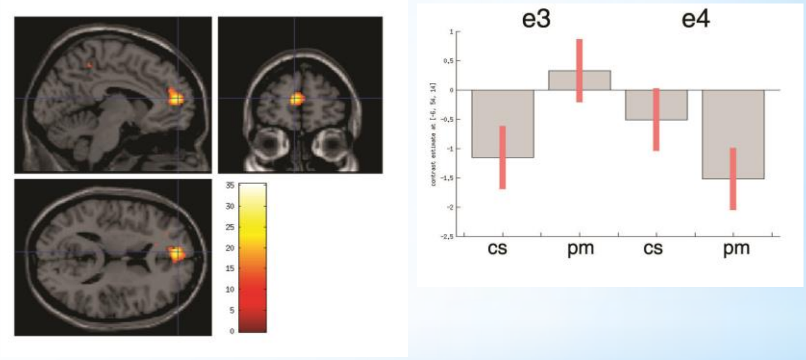
Functional imaging: Are there differences in task-related brain activation patterns between e4 and e3 young adults?

key differences

Memory task

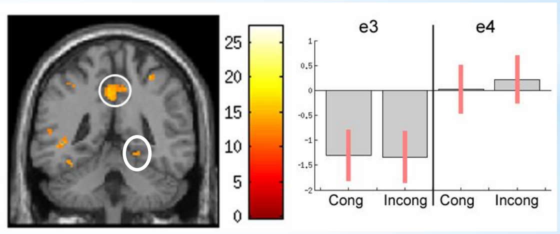
* e4 show heightened activation in early visual cortical areas in response to visual stimuli
* e4 show greater task-specific deactivation in medial frontal cortex (BA10) in response to prospective memory cues





Attention task

* e4 show heightened activation in precuneus bilaterally
* .. and in right hippocampus



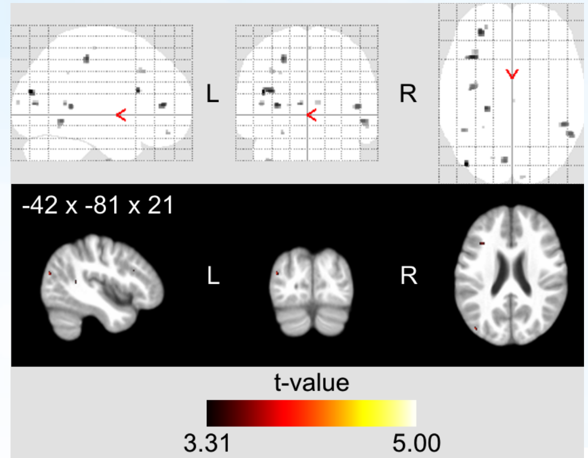
all (p<0.05 FWE-corrected)

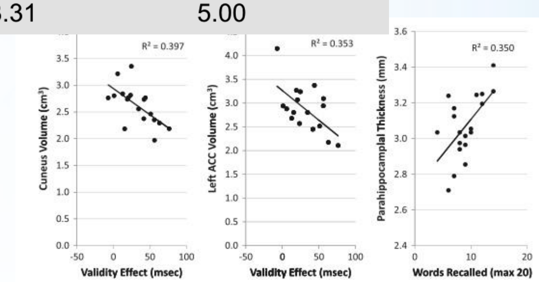
Rusted et al, 2012

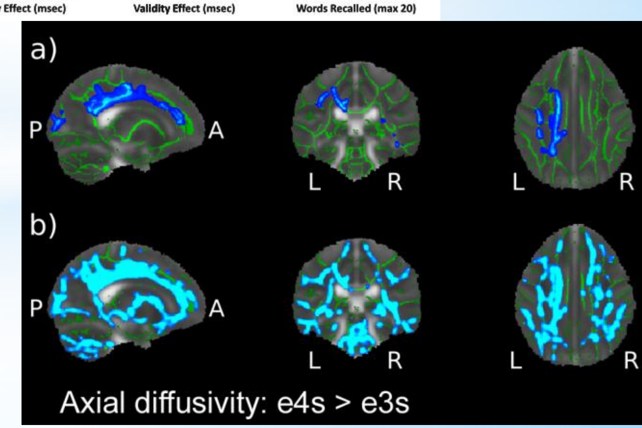
Are there observable differences in brain structures in healthy adult e4s?

Differences in brain volume: young adults

* trend for higher grey matter volume in young e3 carriers
* significantly higher white matter volume in young e4 carriers ($p<0.001$)
* White matter volume correlated with task performance
* DTI axon tract analyses: e4s had significantly increased axial diffusivity (index of neural efficiency) ($p = 0.011$).







Dowell et al, 2013, 2016

Interim summary

* Young adult e4s do outperform e3s on some cognitive tasks

* Significant structural differences are visible in young adult e4 carriers

* Significant differences in brain activations are visible between e4 and e3 carriers

* *distinct patterns of neural recruitment in response to task demands*

what happens in mid-age?

cognitive performance

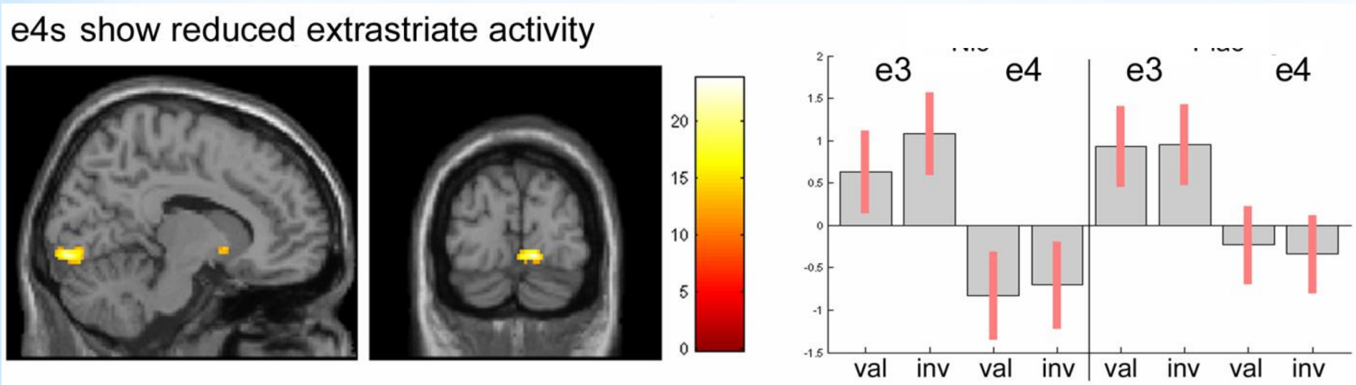
Our Papers	Cognitive task examined and reported
Evans et al (2013b)	No genotype differences in validity effect
Evans et al (2014)	Tendency for e4s to perform better than e3 peers on covert attention, sustained attention task, and more accurate but slower on prospective memory task
Evans et al (2018)	Subsequent memory task: No performance differences between genotypes
Lancaster et al (2017a)	Systematic review of mids literature: Nuanced deficits emerging by 5^{th} decade
Lancaster et al (2016)	Small deficits emerging in error rates on Inhibition and prospective memory tasks
Lancaster et al (2017b)	No genotype differences on dynamic scaling and perceptual capacity tasks: sustained performance relative to e3s

Performance at mid-age: Summary of our findings

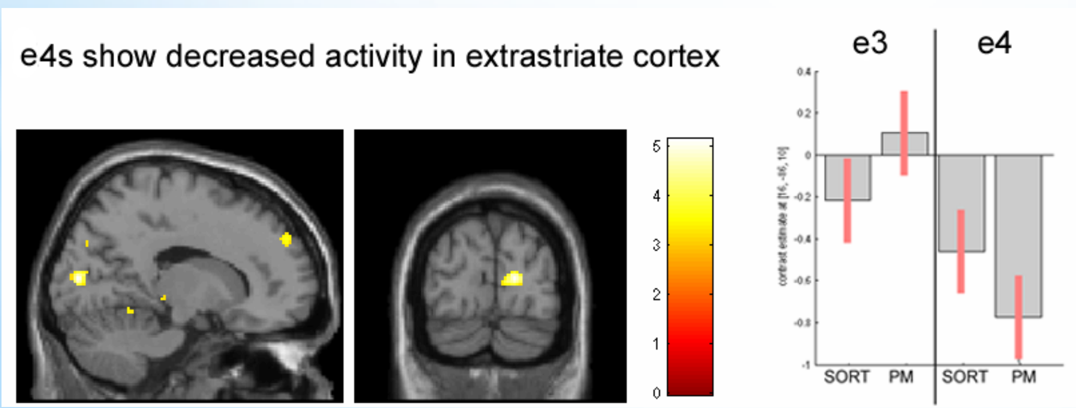
Functional imaging

reduced extrastriate activity in mid-age e4 carriers

* attention task:



* memory task:

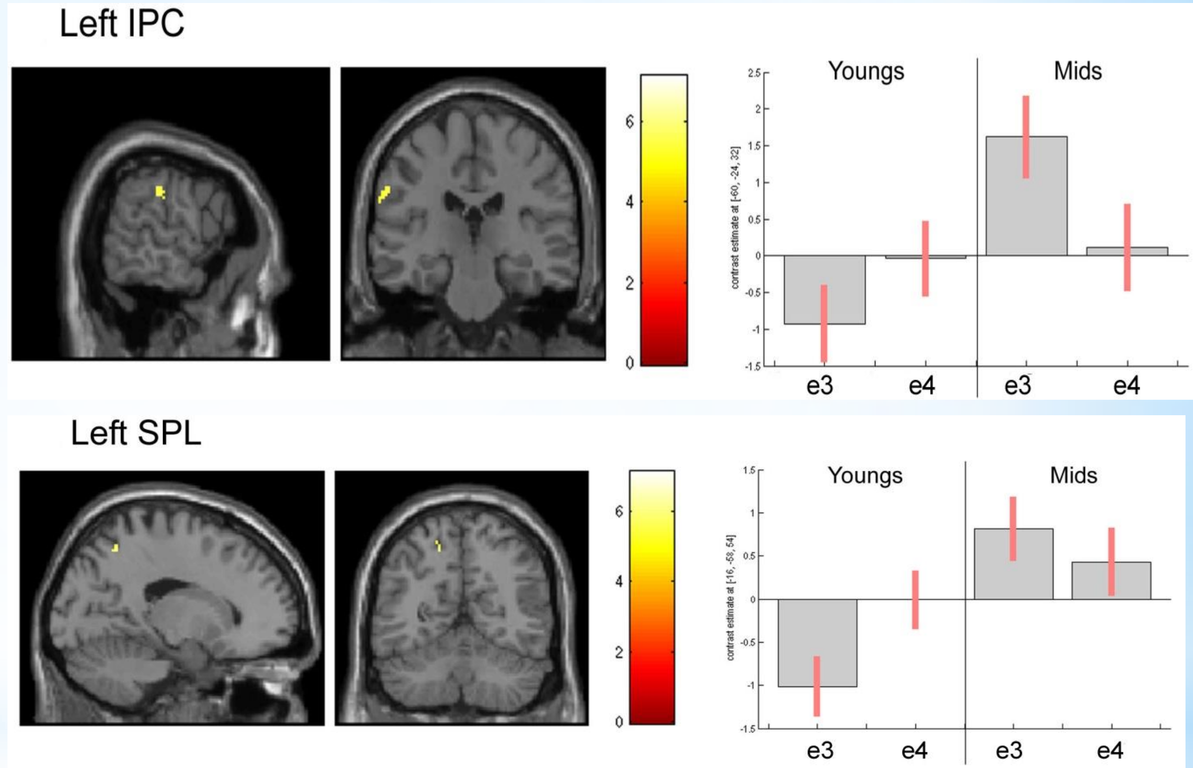


Evans et al, 2014

reduced parietal activation - attention task

Parietal regions

- e3 mids > e3 youngs
- e4s did not show these increases



left IPC: p = 0.021 FWE-corrected

left SPL: p = 0.004 FWE-corrected

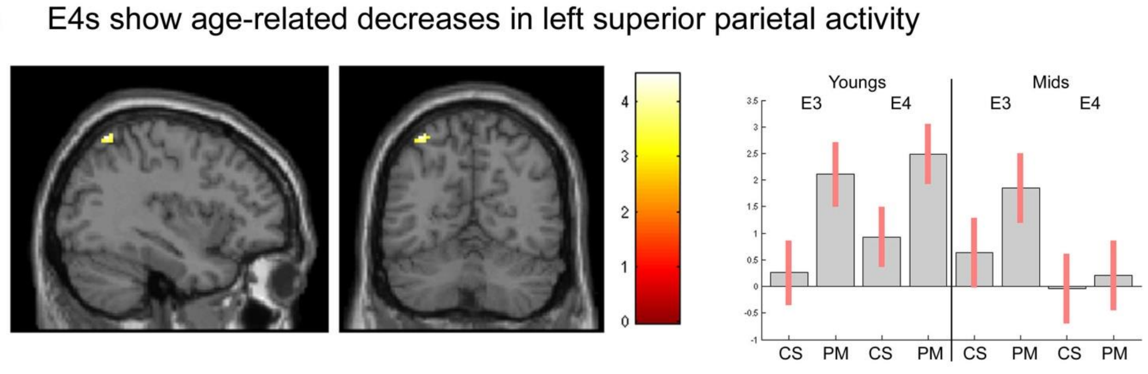
Evans et al, 2014

posterior-to-anterior shift in activity - memory task

left superior parietal:

* mid e4s < young e4s

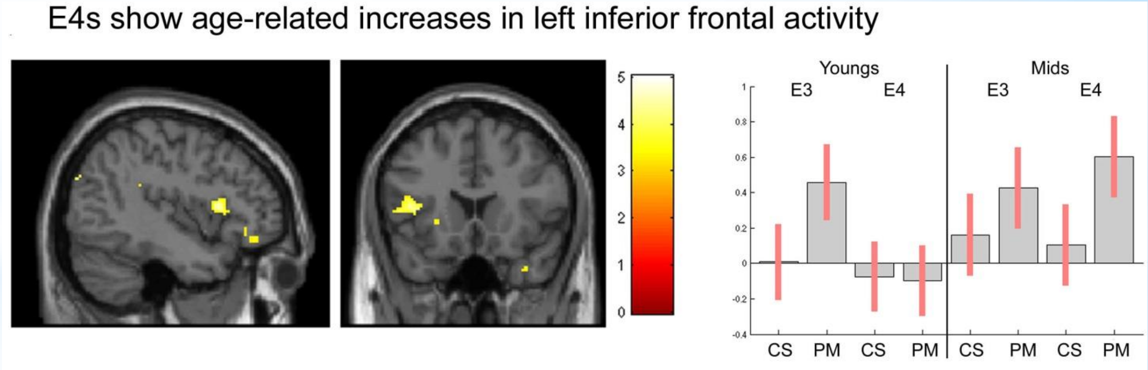
p = 0.018 FWE-corrected after SVC for bilateral SPL



left inferior frontal gyrus:

* mid e4s > young e4s

p = 0.034 FWE-corrected



Evans et al, 2014

Structural imaging

Differences in brain volume: mid age

Brain region	Young			Mid		
	e4+	e3/e3	*p* value	e4+	e3/e3	*p* value
White matter volume ratio ($\times 10^{-3}$)						
Parahippocampus	2.2 (0.3)	2.1 (0.3)	0.396	2.2 (1.5)	2.3 (0.2)	0.389
Cuneus	3.3 (0.3)	2.9 (0.4)	$<$**0.001**	3.2 (0.4)	3.4 (0.4)	0.205
Precuneus	12.6 (1.4)	12.1 (1.7)	0.310	12.9 (1.7)	12.6 (1.5)	0.588
Left anterior cingulate	1.8 (0.3)	1.8 (0.3)	0.668	1.9 (0.2)	1.8 (0.1)	***0.014***
Right anterior cingulate	2.0 (0.2)	1.9 (0.2)	0.850	2.1 (0.3)	2.0 (0.3)	0.611
Posterior cingulate	5.4 (0.4)	5.4 (0.5)	0.508	5.6 (0.5)	5.6 (0.3)	0.937
Cortical thickness (mm)						
Parahippocampus	3.1 (0.2)	3.1 (0.3)	0.698	3.0 (0.1)	2.8 (0.2)	**0.006**
Cuneus	1.9 (0.1)	1.8 (0.1)	0.454	1.8 (0.1)	1.8 (0.1)	0.358
Precuneus	2.6 (0.2)	2.5 (0.1)	0.177	2.4 (0.1)	2.4 (0.1)	0.659
Left anterior cingulate	2.7 (0.2)	2.7 (0.2)	0.938	2.5 (0.1)	2.6 (0.1)	0.244
Right anterior cingulate	2.7 (0.2)	2.7 (0.2)	0.719	2.5 (0.2)	2.5 (0.1)	0.215
Posterior cingulate	2.8 (0.2)	2.9 (0.2)	0.522	2.6 (0.1)	2.7(0.1)	0.473
Hippocampus*	5.6 (0.3)	5.6 (0.6)	0.634	5.6 (0.5)	5.7 (0.4)	0.309

*Hippocampus grey matter volume ratio ($\times 10^{-3}$).

* No correlations with performance

Dowell et al, 2016

BLOOD-BRAIN BARRIER PERMEABILITY IN MID AGE

Aim

- ✓ Assess whether apoe4 status is associated with blood-brain barrier leakage and other subtle structural brain changes in mid age and how this relates to
- ✓ cognition (attention & memory).
- ✓ To correlate findings with blood biomarkers.

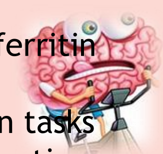
Factors to be measured (+E4 vs -E4)

TECHNIQUE	FACTORS MEASURED
Structural Imaging	(localized) brain volume differences
QSM (Quantitative Susceptibility Mapping)	Microbleed information, iron deposits
Post-Gd T1weighted imaging	(localized) BBB permeability
Prospective Memory Task	Differences in memory and attention
Blood Markers (Plasma & Serum): . C-Reactive Protein . Ferritin level . LRP 1 . NF-Light . MMP-9	. Inflammation . An indication of micro-bleeds .Regulating the pathogenic role of apoE .Reflects axonal damage .BBB Vulnerability & Micro-bleeds

Methods

PHASE 1
Recruiting healthy mid-age adults (42-59) for genotyping.

PHASE 2
1. Blood sample:
 a. Kidney function (for eligibility: Gd contrast agent)
 b. Inflammatory markers in Blood and Serum.
 c. Full blood count
 (for haemoglobin & ferritin levels)
2. Memory & Attention tasks (verbal fluency, prospective memory, switching & reaction time, Memory word list and PRMQ).



PHASE 3
70 minutes 3T MRI scan including Gd contrast agent.

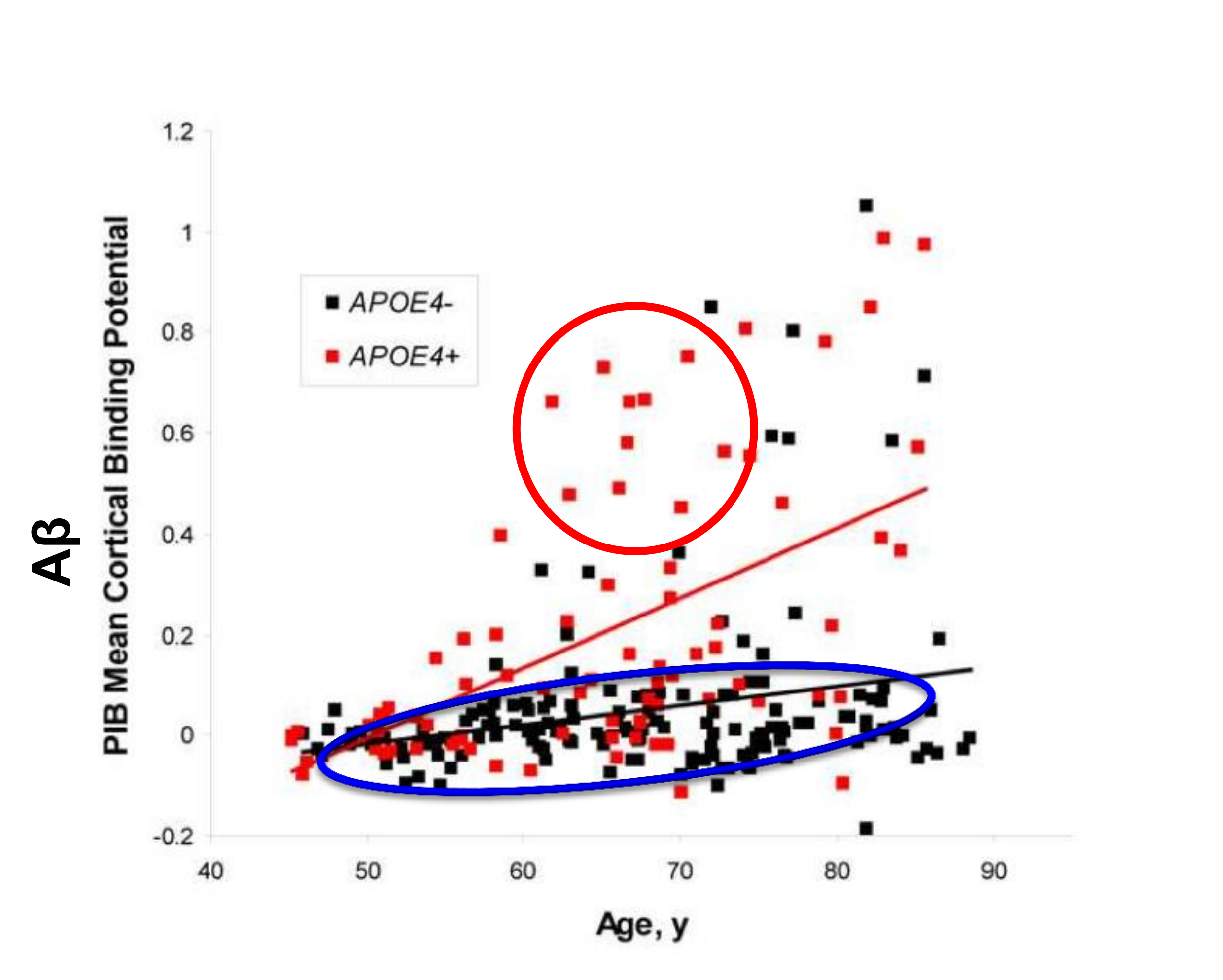
Alruwais et al, in prep

summary

* Evidence for evidence for cognitive, functional and structural differences in young and mid-age e4 carriers compared to their e3 peers

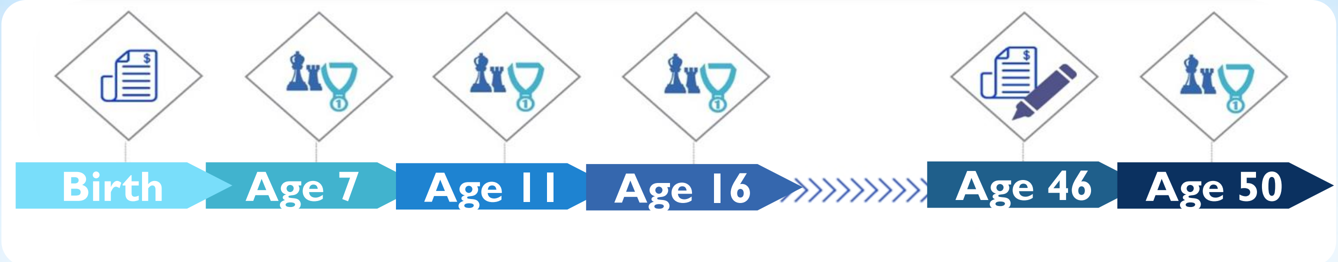
- Subtle structural and functional differences visible between e4 and e3 carriers
- a pattern of *neural* change over 2nd to 5th decade that looks like accelerated ageing in the e4s from an initial position of advantage

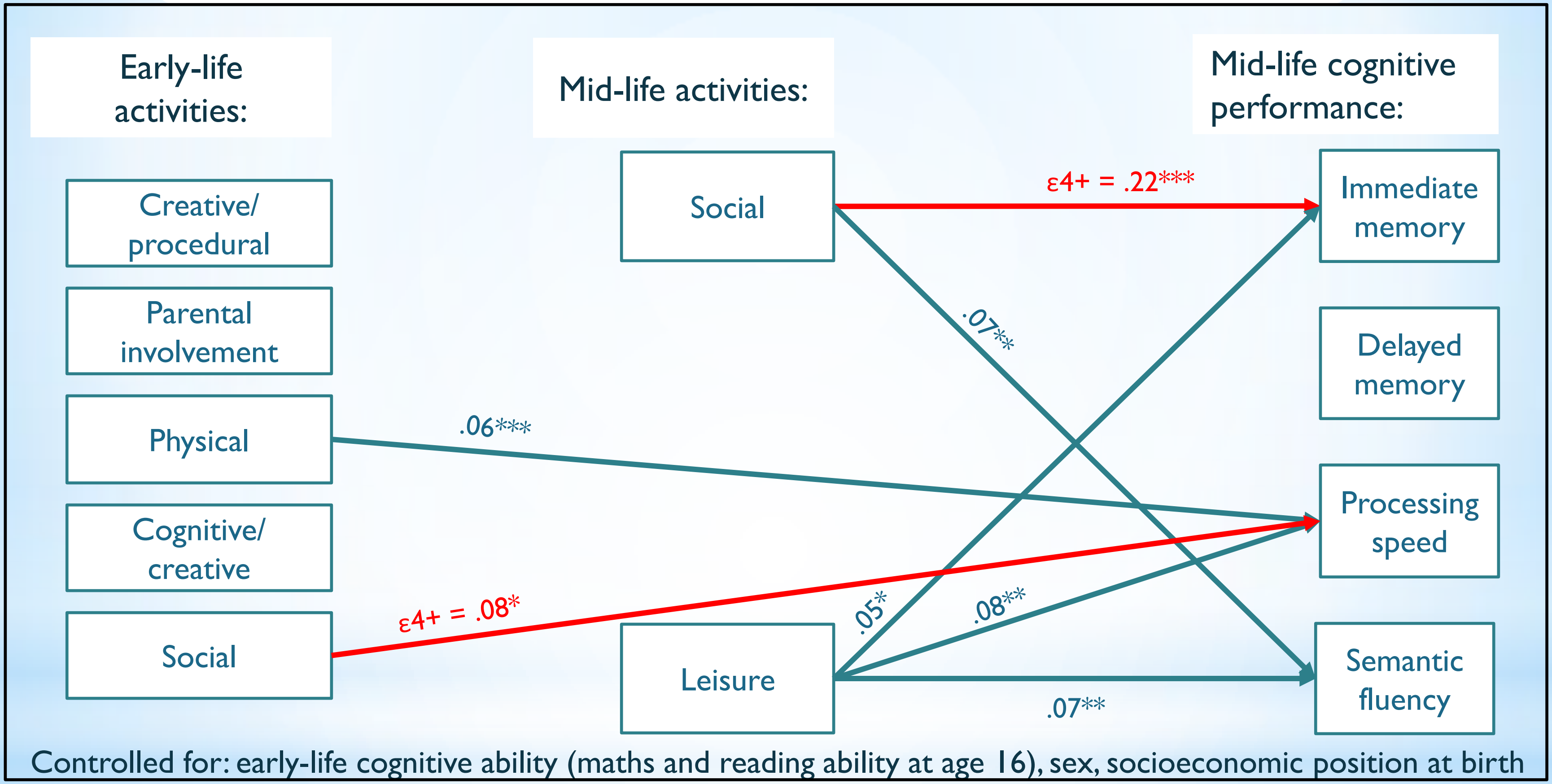
* *enhanced neural efficiency in youth, distinct patterns of neural recruitment in response to task demands*
* *neural compensatory strategies normally employed in response to ageing become exhausted at an earlier age in e4+*
* *evidence for neurogenesis as a compensatory response in mid-age*



Morris et al. *2011*

* Interplay of APOE genotype with environment





Only ε4+ carriers show positive associations between lifetime social activities and cognitive function at age 50

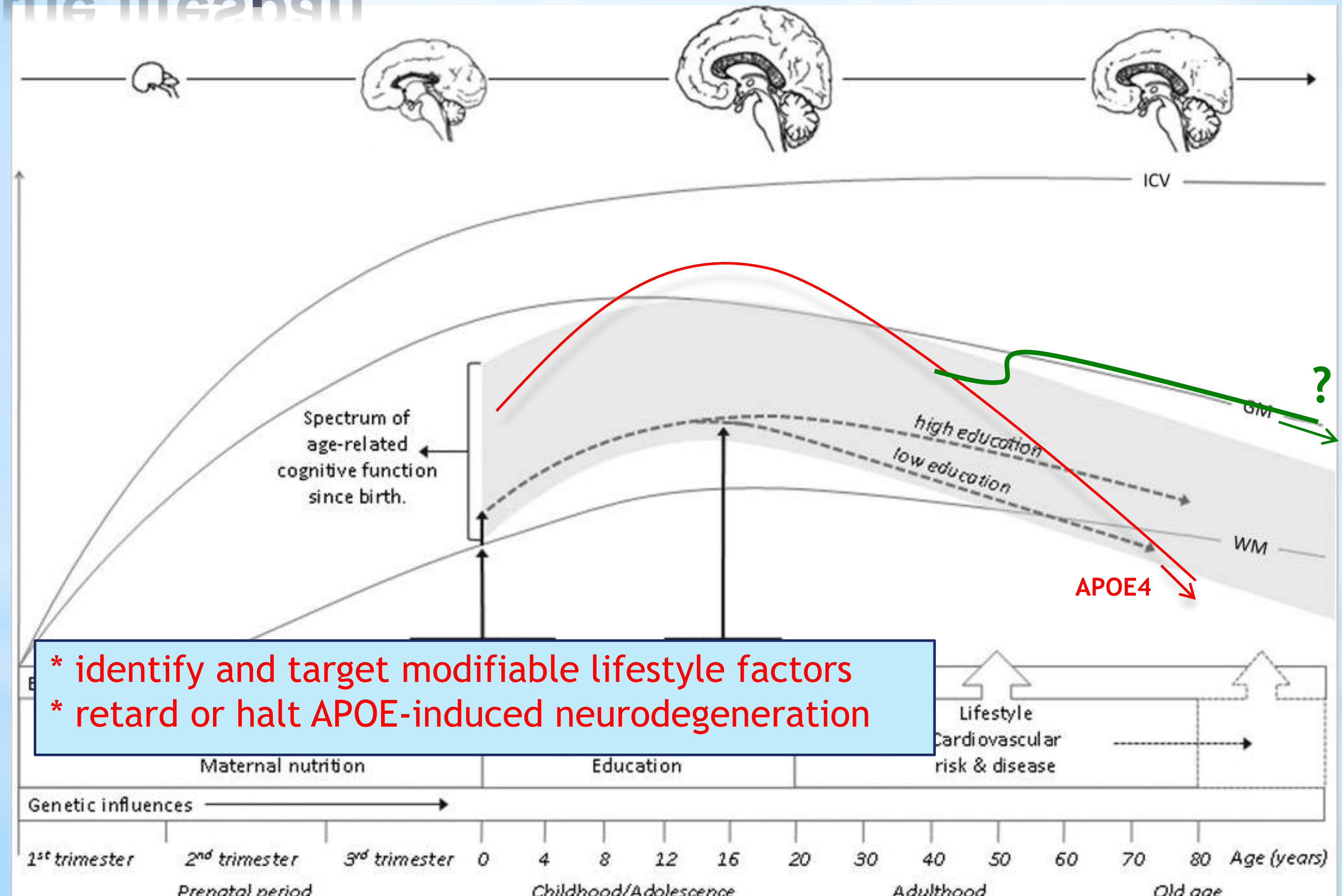
Atkinson et al, in prep

WORLD WIDE FINGERS

* Kivipelto and colleagues, (2013 and continuing)

going forward

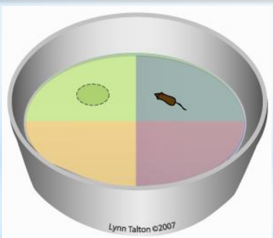
Genetic and environmental impacts across the lifespan



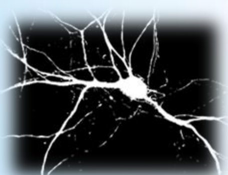
adapted from Muller et al., 2014

Of Molecules, Mice and Men: understanding apolipoprotein E effects across the lifespan

PhD 1. Cognitive outcomes across the lifespan: the brightest candle?



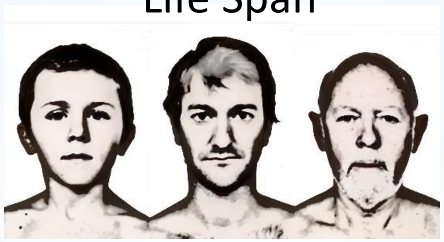
PhD 2. APOE4 Lifespan memory/behaviour (mouse)



PhD 3. Brain cell networks and their function (in vitro)

Directors:
Prof Jenny Rusted
Prof Louise Serpell

Life Span



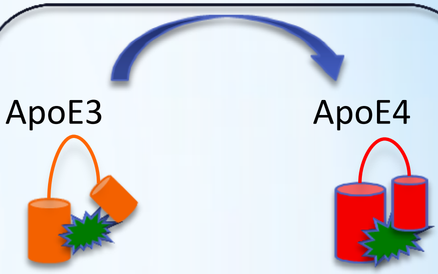
Apo E2	Apo E3	Apo E4

PhD 7. APOE4 effects on synaptic activity

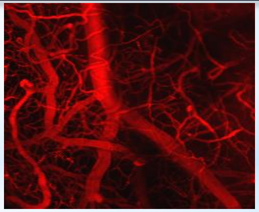
PhD 8. Imaging spatial memory in young APOE4 carriers

University Of Sussex Dementia Research Group Doctoral Training Centre

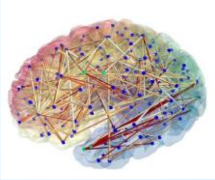
Alzheimer's Society United Against Dementia



PhD 4. Stabilising the structure ApoE4> ApoE3



PhD 5. APOE4, pericyte vulnerability and brain hypoxia (in mouse)



PhD 6. Brain connectivity changes in AD: impact of ApoE4 and environment

* thanks to..

Nick Dowell
Simon Evans
Sarah King
Sam Hutton
Naji Tabet
Sophie Forster

Natalie Marchant
Paul Tofts
Marcus Gray
Torsten Ruest
Louise Serpell

Claire Lancaster
Rebecca Atkinson
Nourah Alruwais
Fenella Prowse
Dan Riley
Jessica Daly
Devin Clarke

BBSRC bioscience for the future

Saudi Government Scholarship Programme

Alzheimer's Society Leading the fight against dementia

E·S·R·C ECONOMIC & SOCIAL RESEARCH COUNCIL

Sussex Partnership NHS Foundation Trust

..and thank you for listening