

Multi-Modal Brain Imaging Studies:

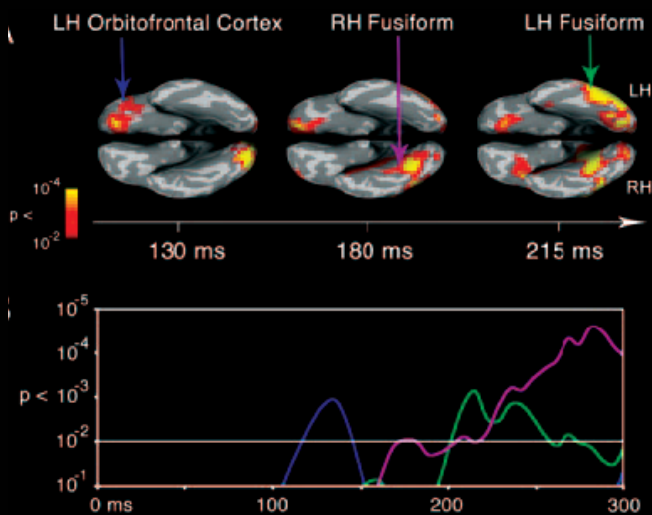
Genetic Risk for Dementia & Age-Related Cognitive Decline

Lars Nyberg

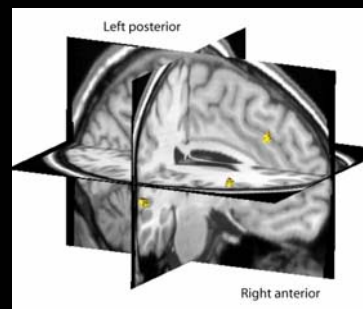
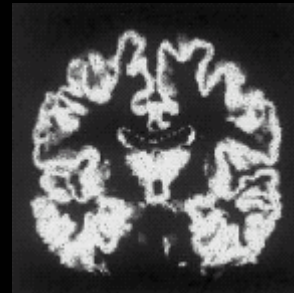
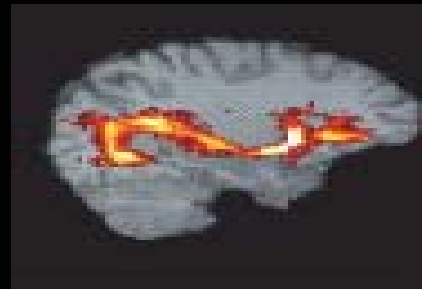
Umeå University, Sweden

Multi-modal imaging

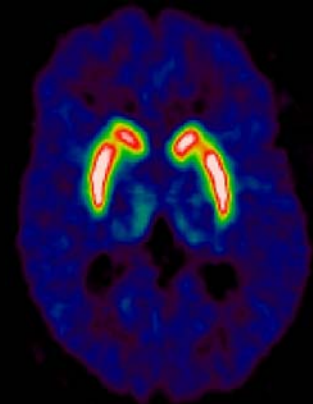
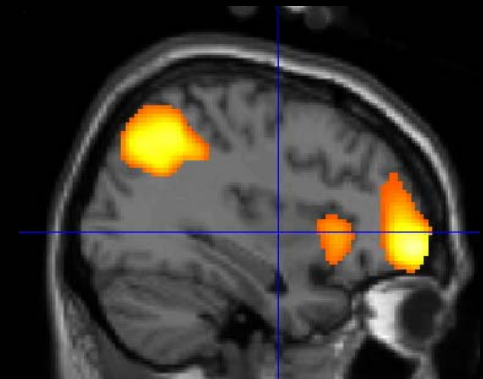
Where & when
(e.g. functional MRI
& EEG/ERP or MEG)



Structure & function
(e.g. Structural & fMRI)



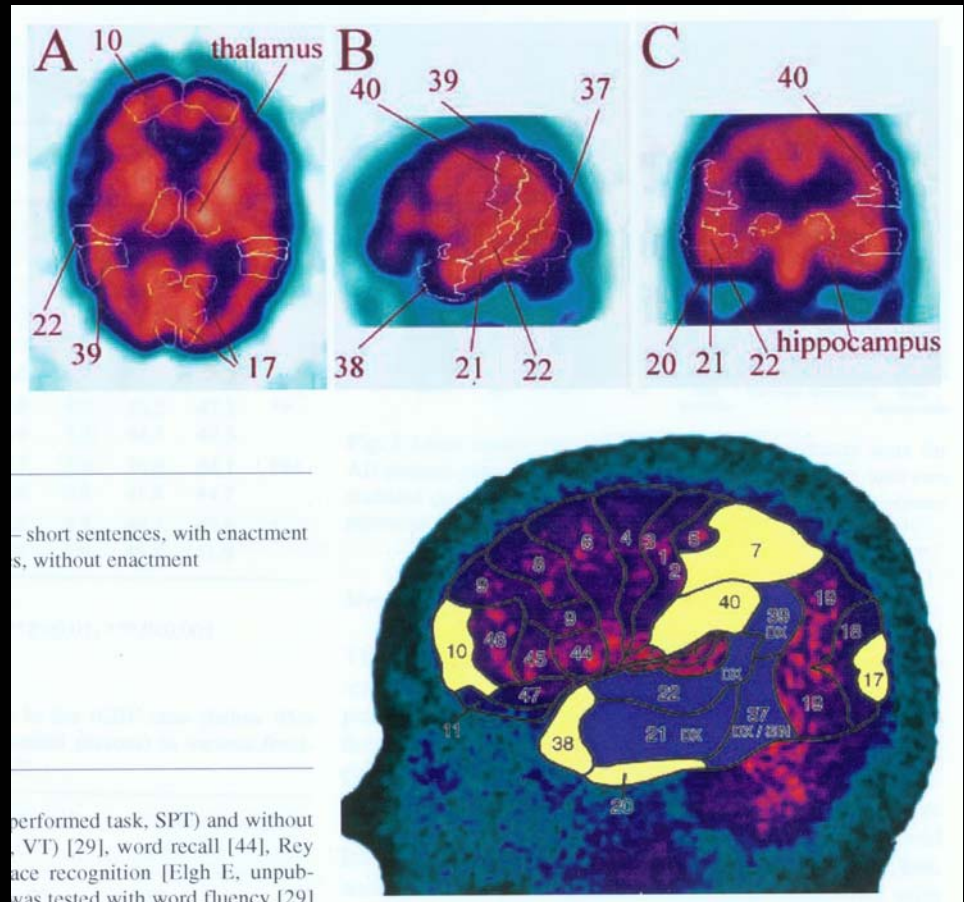
Activity & transmission
(e.g. fMRI & PET/SPECT)



Alzheimer's Dementia:

Reduced hippocampal & temporo-parietal rCBF

- 14 AD-patients & 15 controls
- resting-state SPECT study of rCBF
- Patients showed reduced rCBF in temporo-parietal cortex and left hippocampus
- Reduced episodic memory in AD-patients
- Correlation rCBF & episodic memory performance (Elgh et al. 2002, *EJNM*)

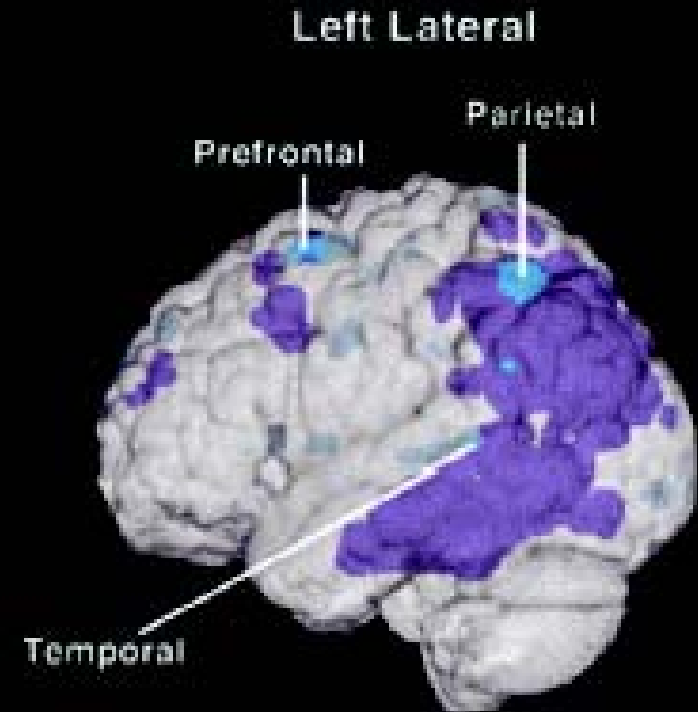


Genetic risk for Alzheimer's Dementia

- Apolipoprotein E (ApoE) gene on chromosome 19:
 - Three alleles: $\epsilon 2$, $\epsilon 3$, $\epsilon 4$
 - 5 common genotypes: $\epsilon 2/3$; $\epsilon 2/4$; $\epsilon 3/3$; $\epsilon 3/4$; $\epsilon 4/4$
 - Presence of $\epsilon 4$ = risk
 - $\epsilon 4/4$ 8 times more likely to develop AD than $\epsilon 3/3$ persons
- Differences in functional brain activity before disease onset?

Genetic risk and brain function

- *Lowered* resting-state metabolism in $\epsilon 4$ carriers
 - reduced glucose metabolism in fronto-parietal areas (Reiman et al., 2004, *PNAS*, 101, 284)

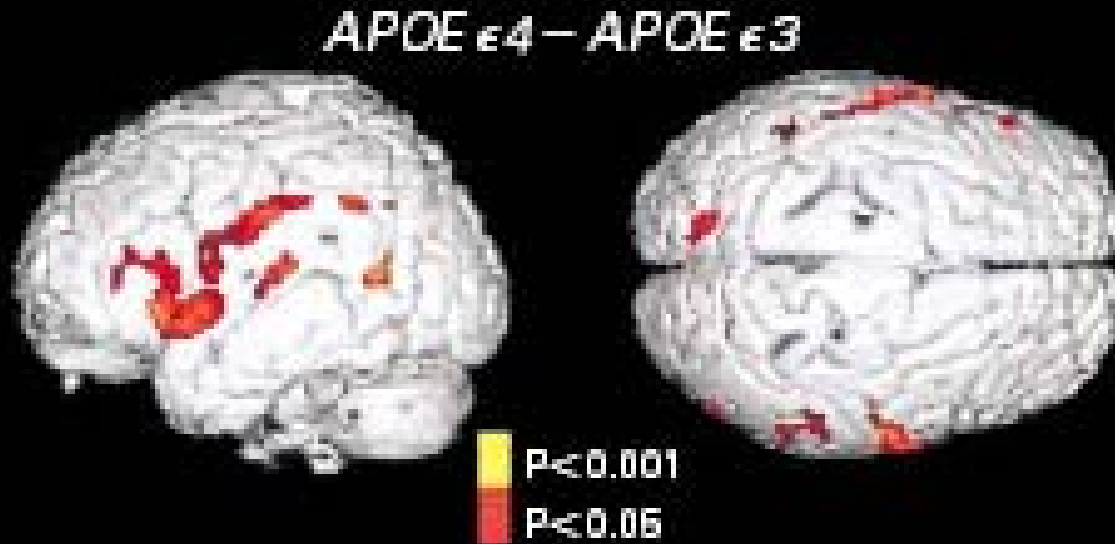


Similar pattern as for AD patients

Genetic risk and brain activity

- *Higher* frontal and parietal brain activity in ApoE ϵ 4 compared with ϵ 3 persons (memory task)
 - “In persons at risk for AD, increased brain activity may serve a compensatory role”

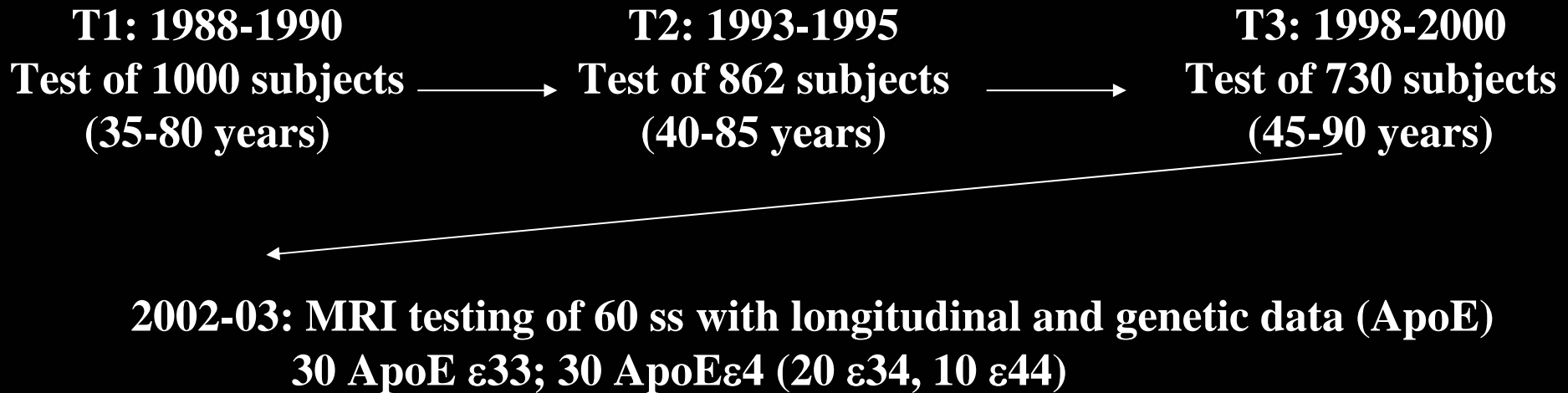
(Bookheimer et al., 2000, *New England J. Medicine*, 343, 450)



Research Questions:

1. Is genetic risk associated with increased or decreased functional brain activity
2. How does genetic risk relate to structural brain changes?

Data from the Betula Study

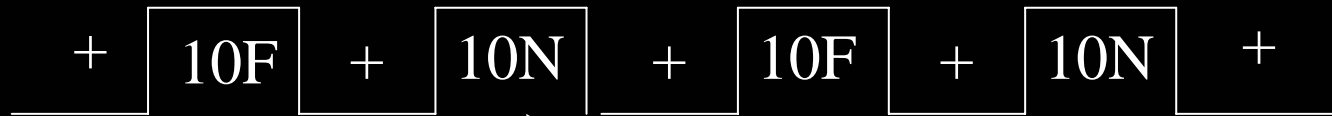


Participants

	ApoE ϵ 3 (30)	ApoE ϵ 4 (30)
Age	66.6	65.6
Education	10.0	10.9
Female/Male	19/11	19/11
MMSE	28.2	28.6
Vocabulary	21.6	24.0

Methods

- Prefamiliarization of 80 words prior to functional scanning
 - Once prior to entering scanner; once during structural scan



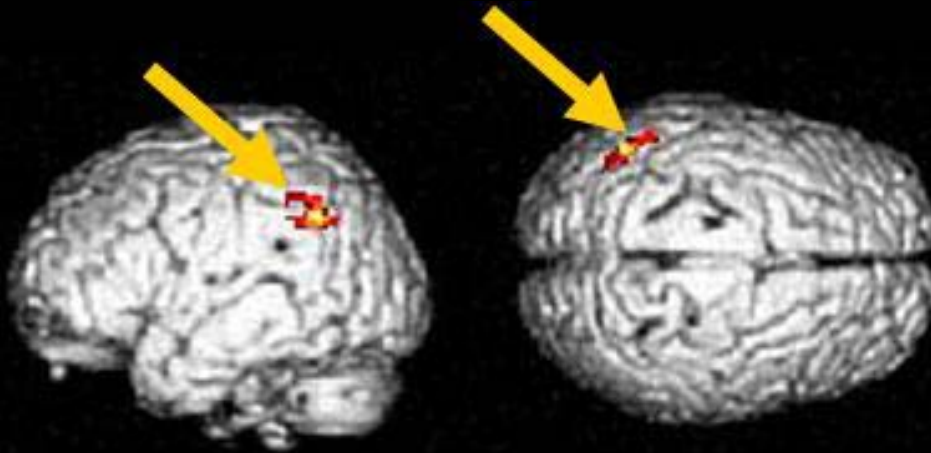
Abstract/concrete decisions (button press), 2 sec + ISI=1 sec

Volumetric (grey matter) and DTI (white matter) scanning

Categorization - Rest

Reduced left parietal activity for high-risk persons

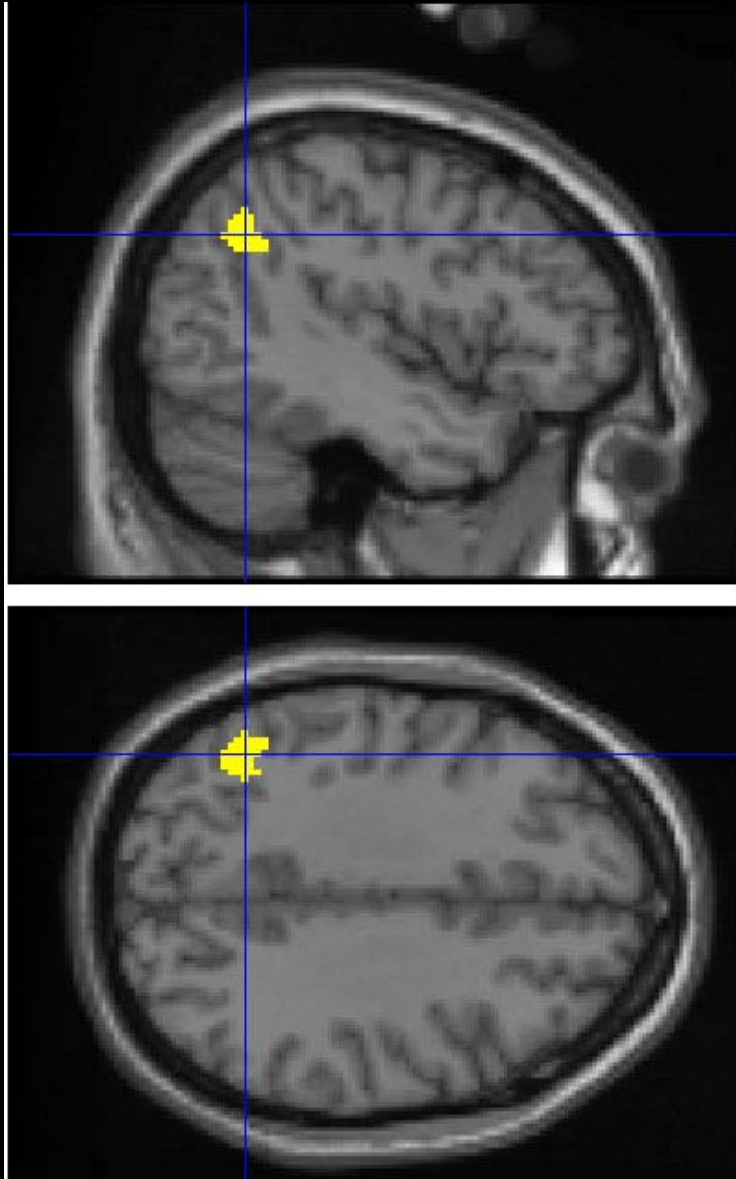
ApoE ϵ 3 (N=30) – ApoE ϵ 4 (N=30)



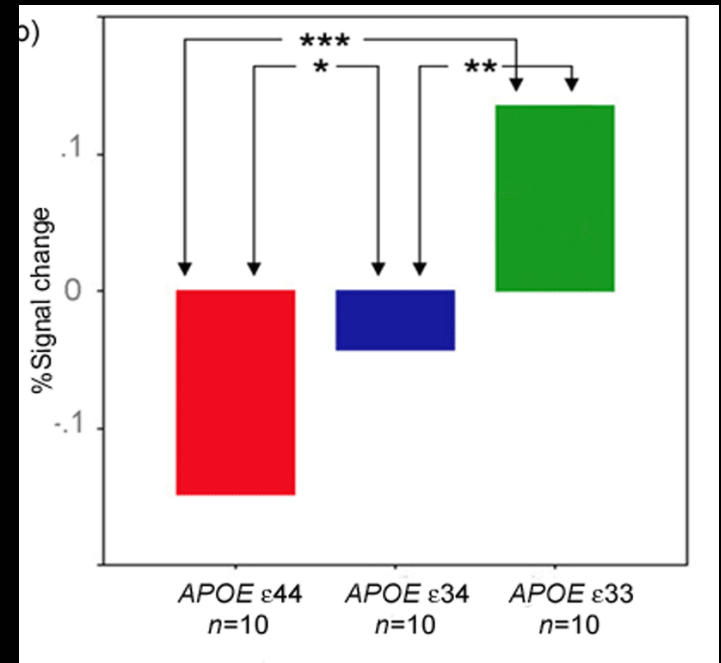
Lind et al (2006)

Brain

Dose effect in parietal cortex

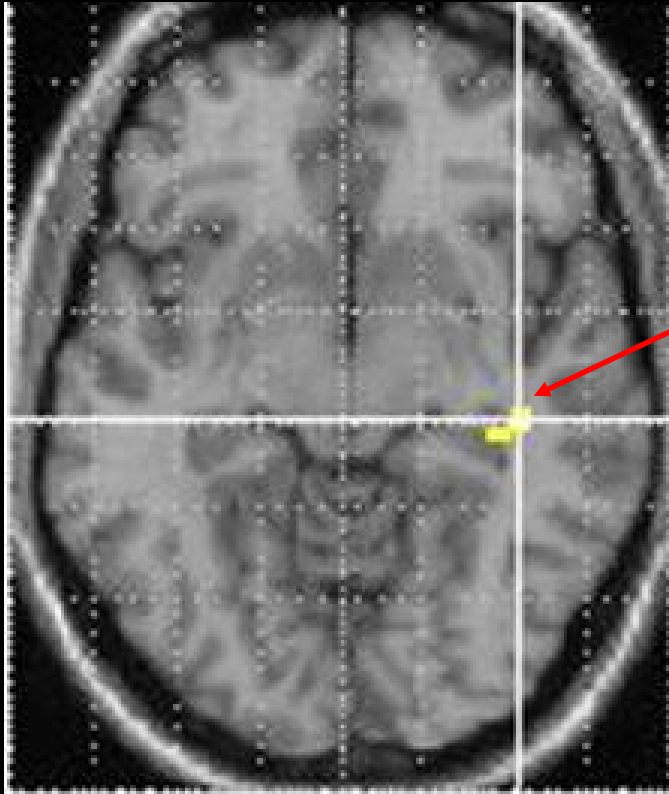


Dose-effect in parietal cortex



(Lind et al, 2006, *Brain*)

Novel > Familiar: Group difference (ApoE e3 > ApoE e4)



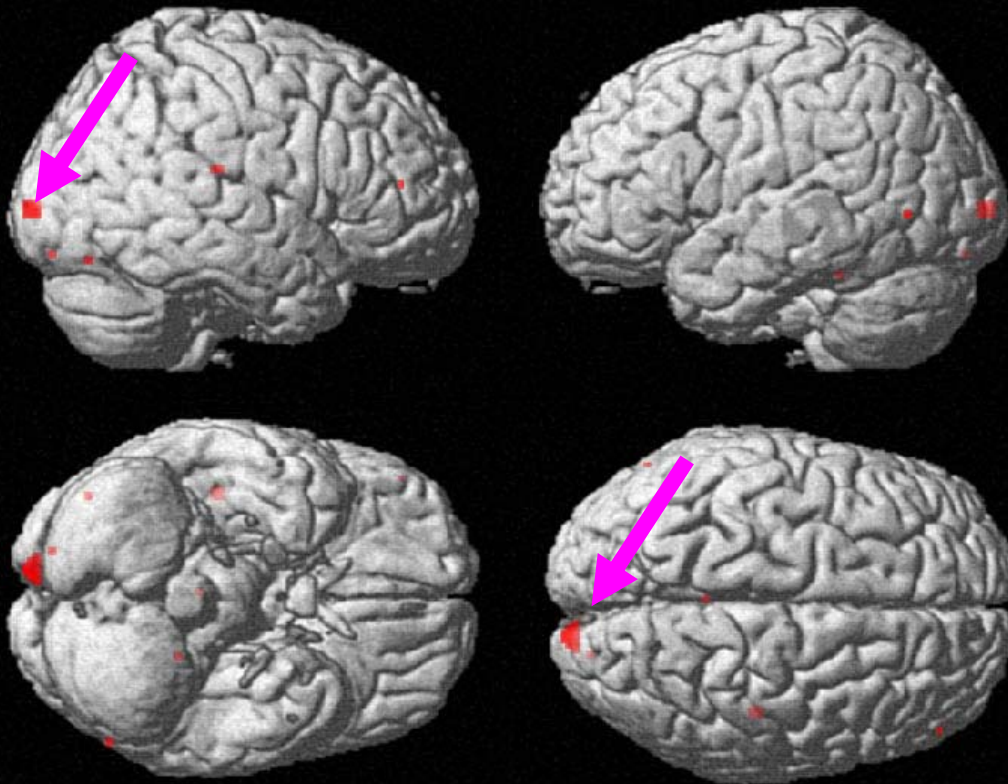
More pronounced novelty effect
in right hippocampus for ApoE3

Lind et al (2006)
Brain

Greater activity for ApoE4?

Minimal support for compensation!

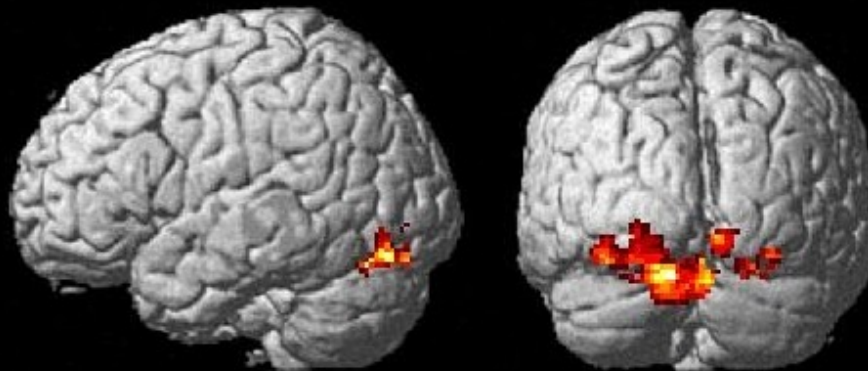
ApoE e4 (N=30) – ApoE e4 (N=30)



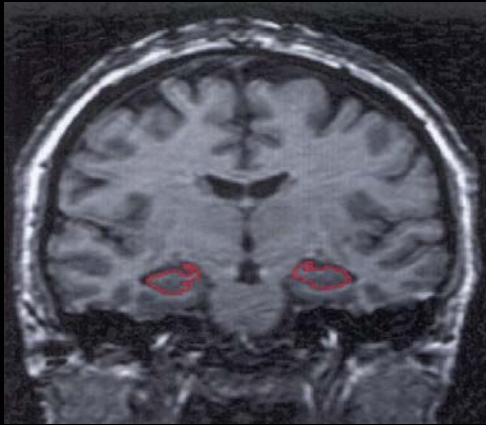
Related observations

Risk for AD based on neurocognitive screening (*7-minute test*)
(Elgh, Larsson, Eriksson & Nyberg, 2003, *Int. Psychoger.* 15, 121)

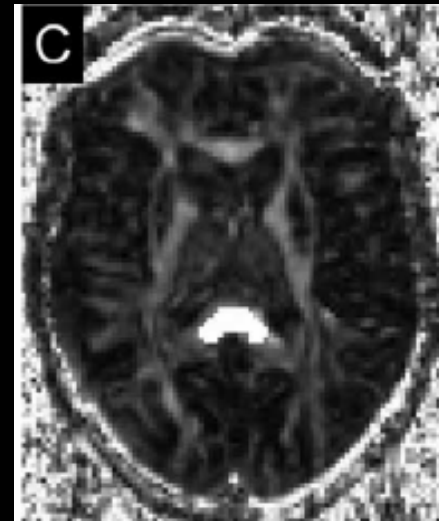
High-risk – low-risk



Genetic risk and structural brain changes



Smaller hippocampus volume for $\epsilon 4$ carriers
(Lind et al., 2006, *Neurosci Lett*)

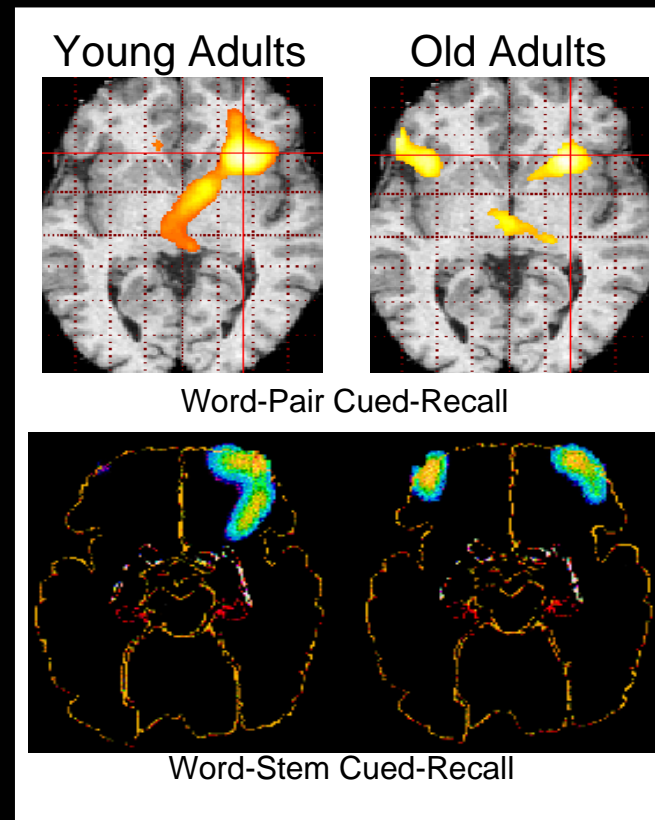
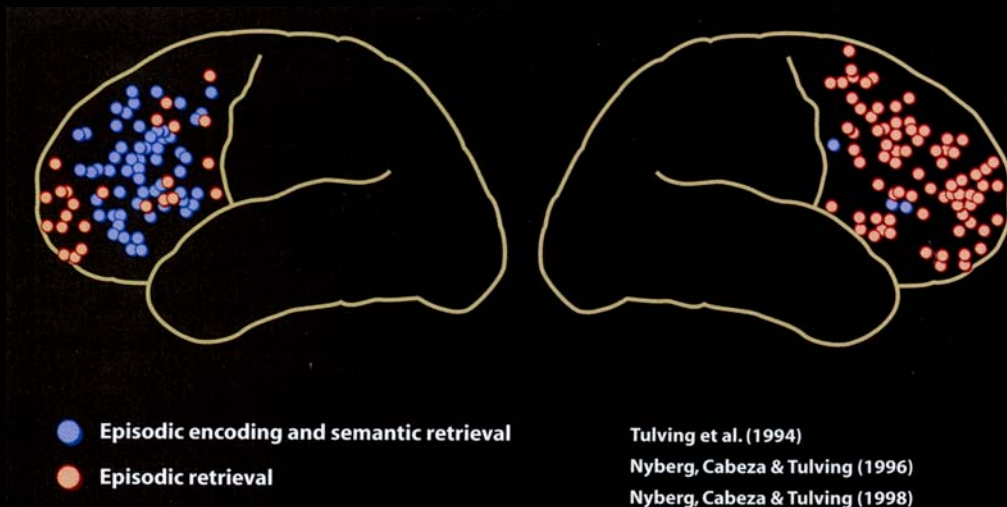


Reduced white-matter in *posterior* corpus callosum
(Persson et al, 2006 *Neurology*)

Age-related changes

- Functional imaging studies show that older adults activate some brain regions that younger adults typically *not* activate
- Episodic memory retrieval: Younger tend to show right-sided frontal activity.

Older adults additionally activate left frontal regions (Cabeza, 2002).



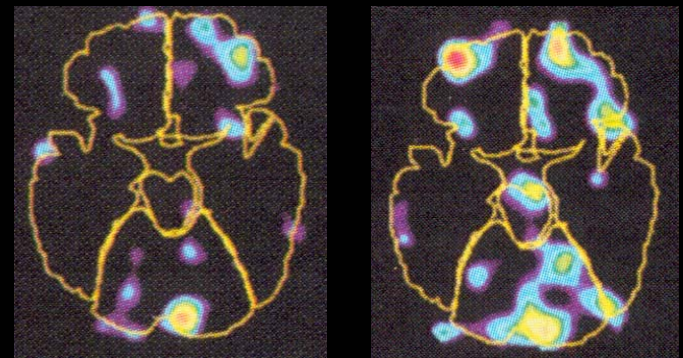
Basis for altered brain activity

- Increasing age -> brain changes -> cognitive changes -> additional brain activity
 - Need for compensation

”left prefrontal activity in AD may reflect a compensatory response triggered by problems in retrieving the target information”

Bäckman, Andersson, Nyberg et al., (1999), *Neurology*, 52, 1861-70

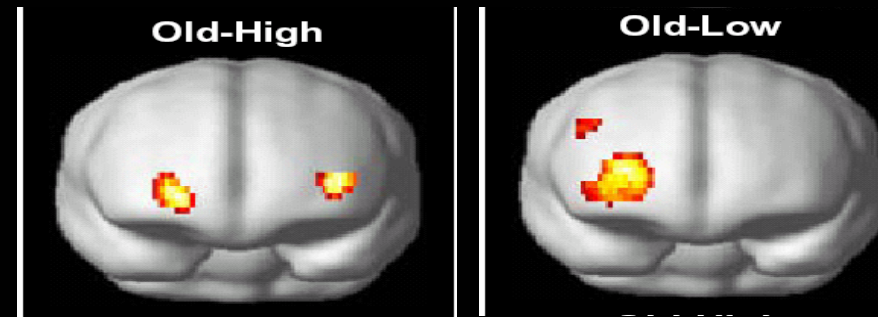
Normal old adults and demented patients



Basis for altered brain activity II

- Increasing age -> brain changes -> additional brain activity -> no cognitive change
 - “Preventive” compensation

Old high-performers show more bilaterality than old low-performers (Cabeza et al. 2003, *NeuroImage*)

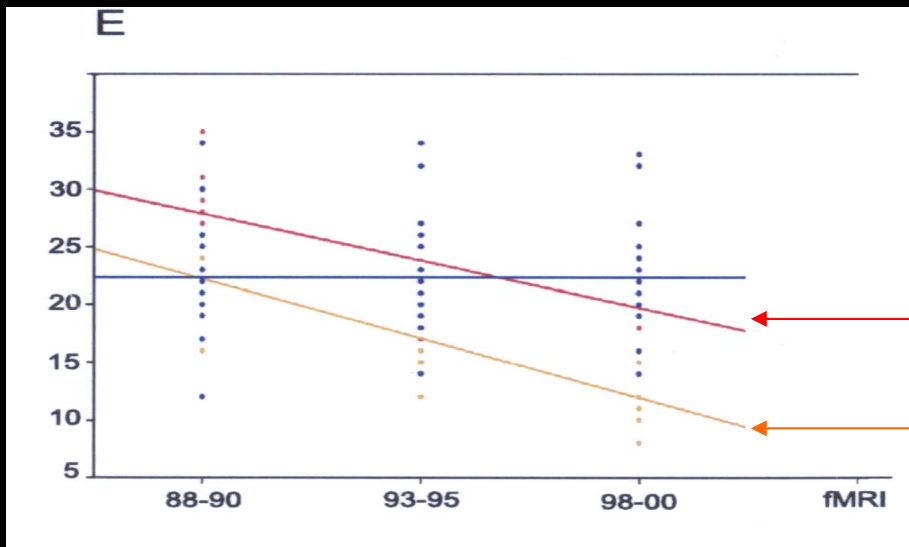
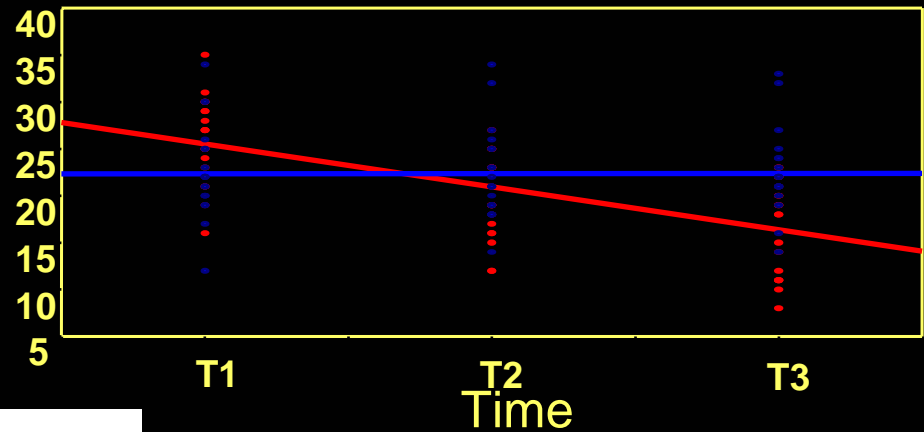


Research Question:

1. Does additional/atypical brain activity correlate with a stable or declining pattern of memory performance over time?
2. How does declining memory relate to structural brain changes?

Identifying stable/declining groups based on the Betula study

Determined the longitudinal pattern of memory change (based on 3 episodic tests)
N = 40



Decline High

Decline Low

Persson et al (2006)
Cerebral Cortex

Methods

	Stable (20)	Decline (20)
Age	68.2	68.2
Education	10.1	10.7
Female/Male	13/7	13/7
MMSE	28.25	28.35
Vocabulary	22.15	23.75

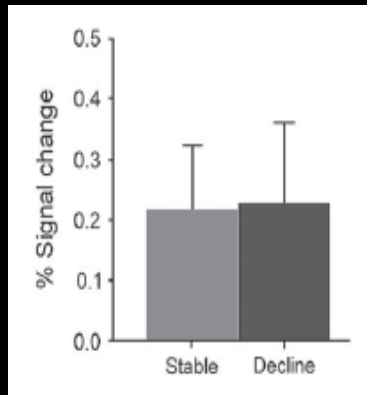
fMRI (categorization), hippocampus volume, DTI (white matter)

Previous findings in young associate this task with left PFC

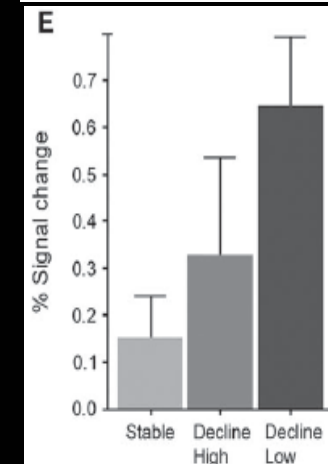
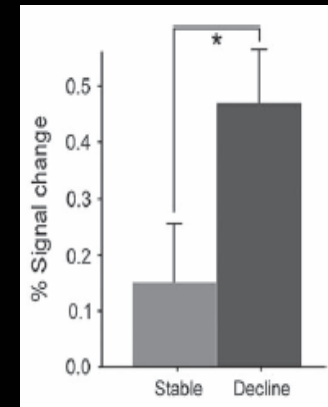
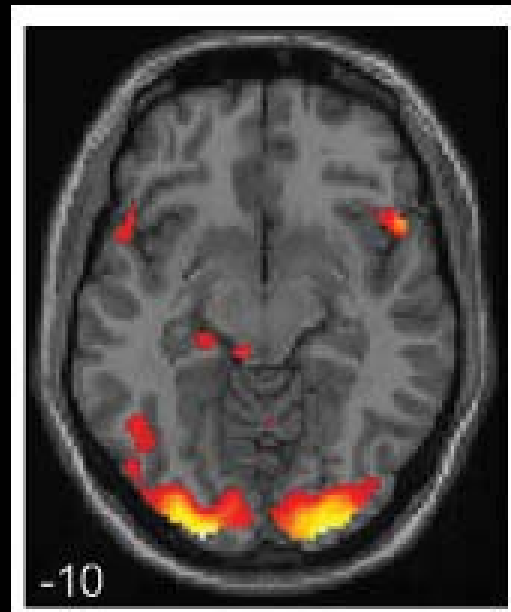
- Additional right pFC activity for stable or declining group?

Functional changes Categorization vs Rest

Overall analysis (N=40) revealed bilateral frontal activity

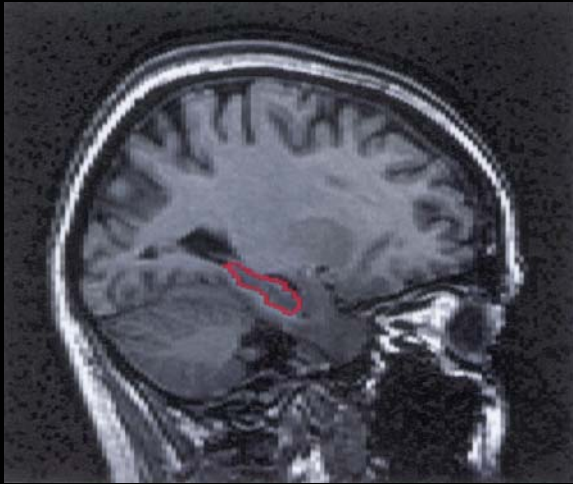


Both groups showed typical left PFC activity

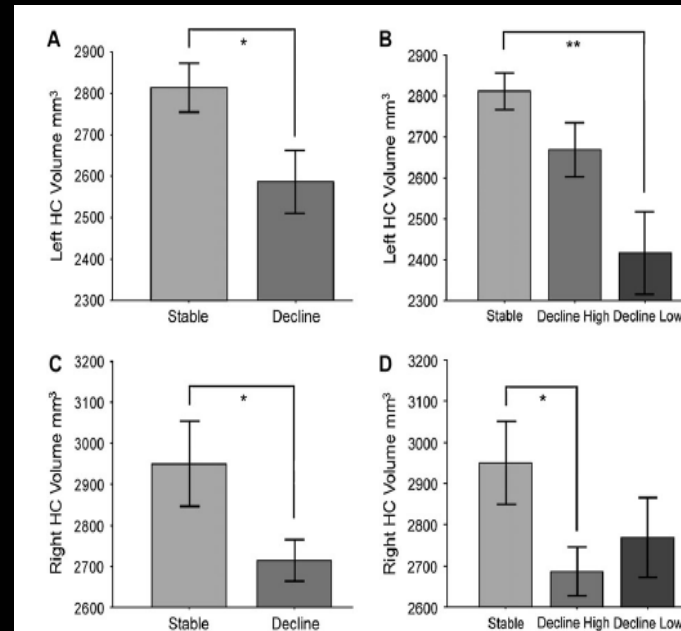


Atypical right frontal activity driven by declining elderly
- Functional compensation for structural changes?

Hippocampus volume

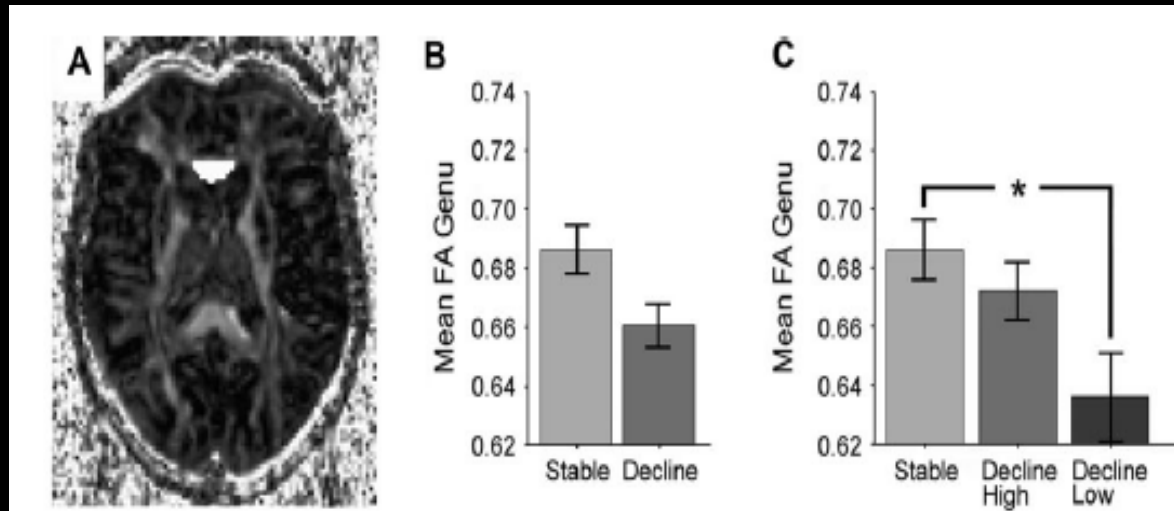


NIH Image 1.6 (see Raz et al, 2004, *Neurology*)



Reduced hippocampal volume for declining group

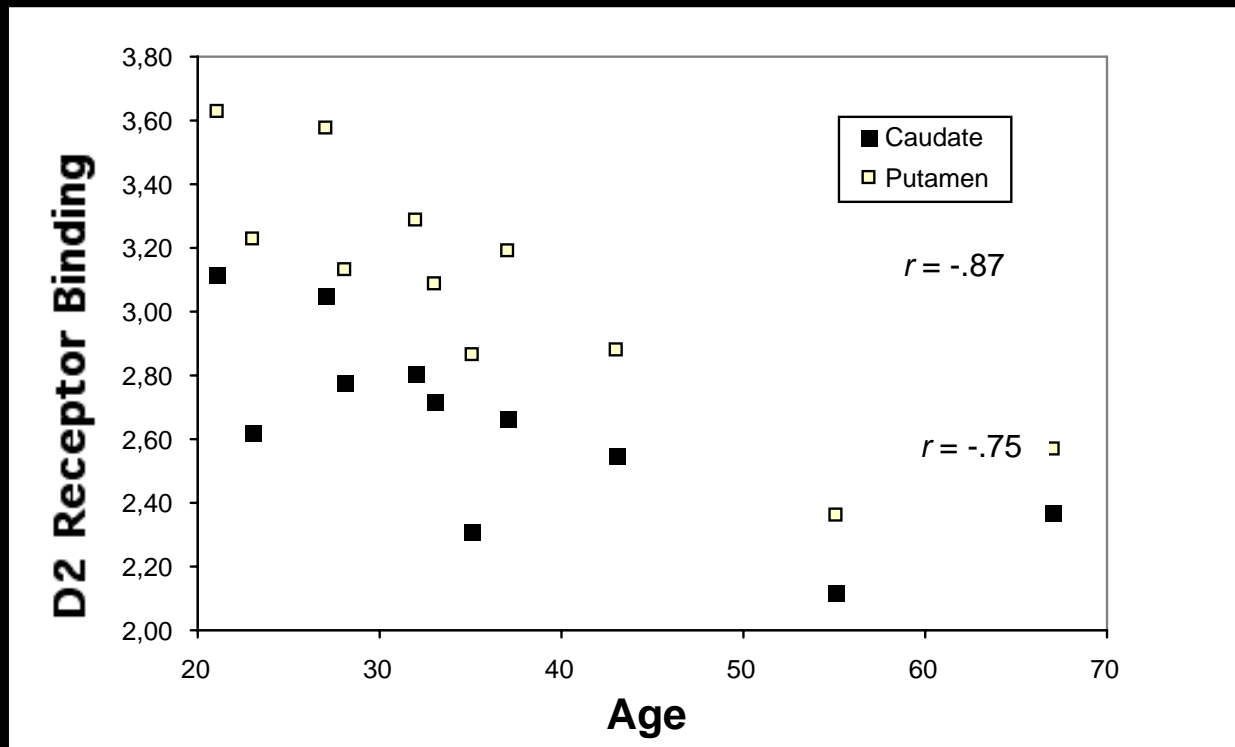
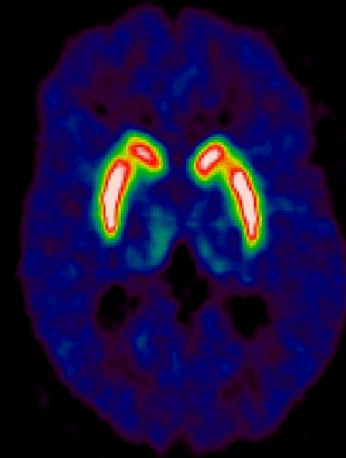
DTI: White-matter integrity



Reduced *anterior* white matter for declining group

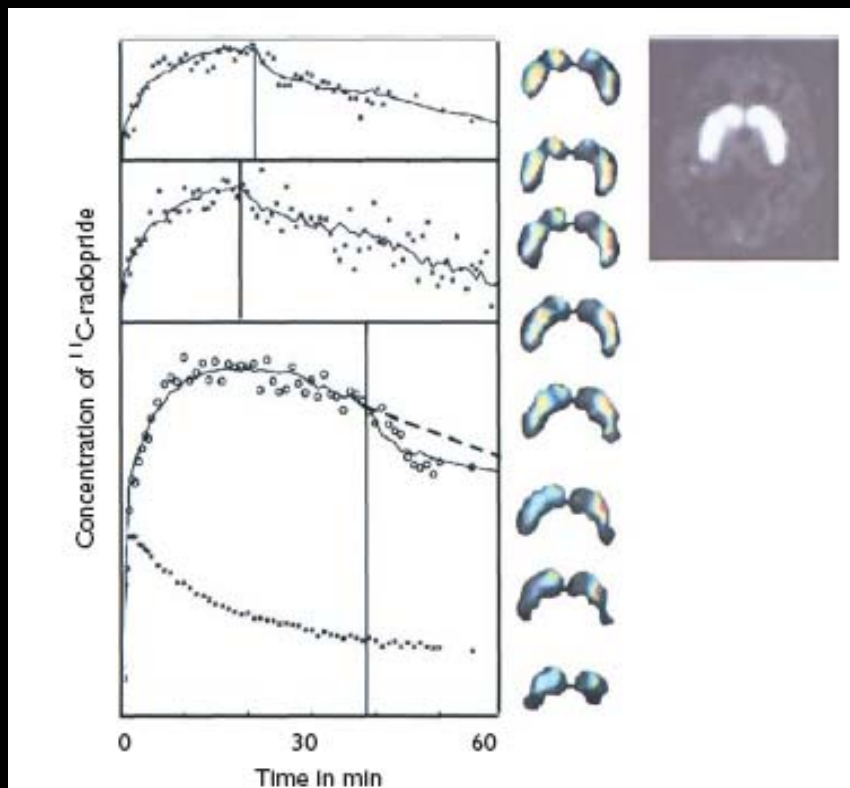
Age-comparative studies found anterior-posterior gradient (e.g. Pfefferbaum, 2000; O'Sullivan, 2001; Head et al., 2004)

Dopamine Loss Across the Adult Life-Span

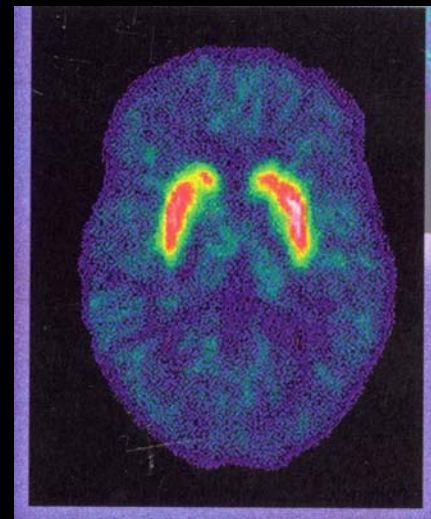


Bäckman et al., Am J Psychiatr, 2000

Bilateral activation in aging: Relation to neurotransmission?



Badgaiyan et al, 2003 *NeuroReport*



Activation studies

Reduced striatal binding during motor task
Striatal reduction in [¹¹C] raclopride binding
potential during Montreal card-sorting task

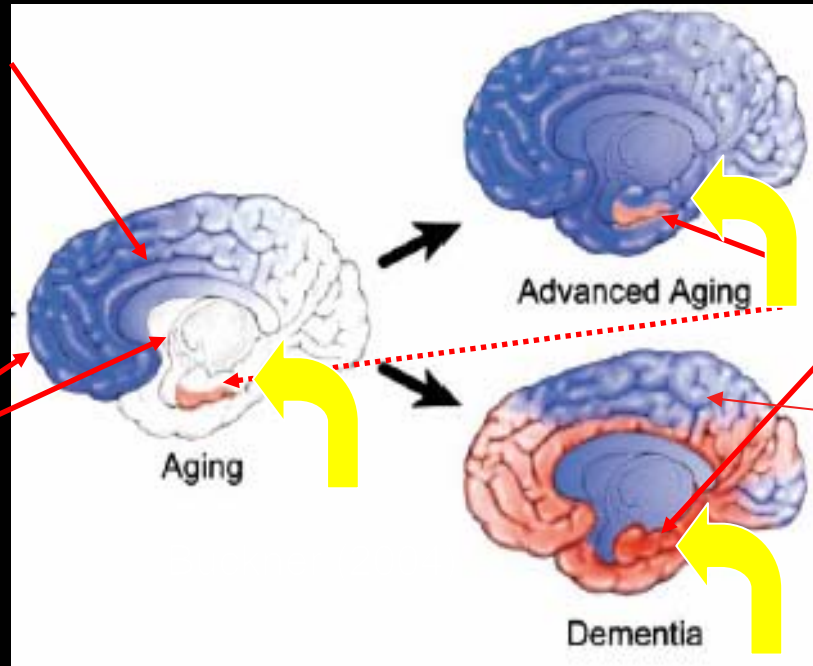
(Monchi et al., 2006, *NeuroImage*)

Ongoing: PET dopamine activation study & fMRI activation study in
younger and older adults

Multiple-factor account of brain-cognition functions in aging and dementia

White-matter frontal changes
-- disconnectivity

Fronto-striatal volume and activity changes



Hippocampal volume
-preclinical dementia or
part of normal aging?

Reduced parietal activity
White-matter posterior changes

Buckner (2004)

Nigro-striatal dopamine (DA) system

Striatal DA-system part of fronto-striatal network (Bäckman & Farde, 2001)

Thank you!

L-G Nilsson
Lars Bäckman
Jonas Persson
Randy Buckner
Johanna Lind
Anne Larsson
Eva Elgh
Lars Farde
Martin Ingvar

