Multi-Modal Brain Imaging Studies:

Genetic Risk for Dementia & Age-Related Cognitive Decline

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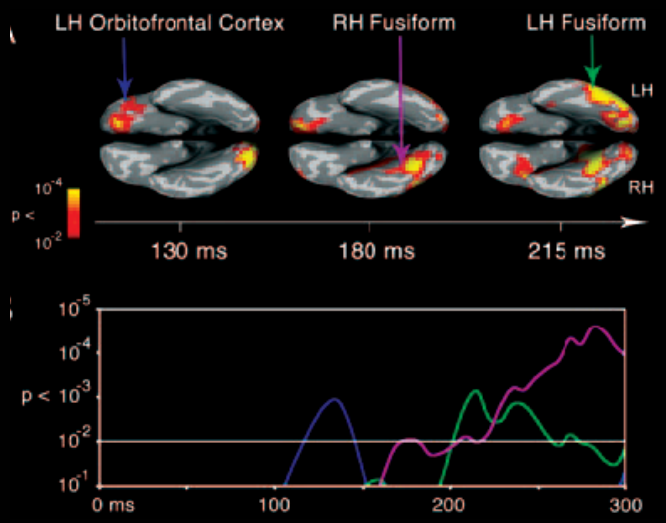
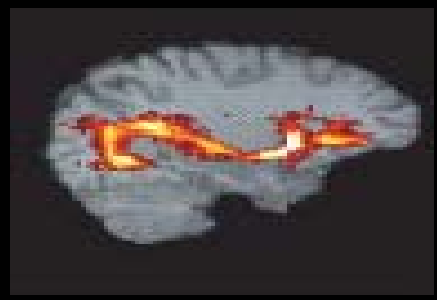
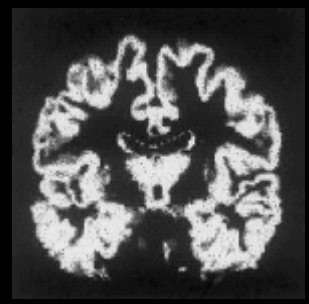
Multi-modal imaging

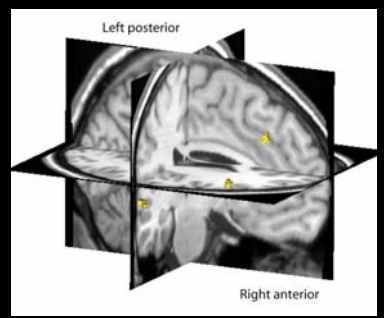
Where & when
(e.g. functional MRI
& EEG/ERP or MEG)



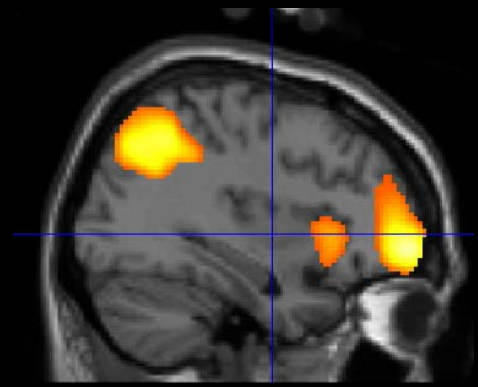
Structure & function
(e.g. Structural & f MRI)

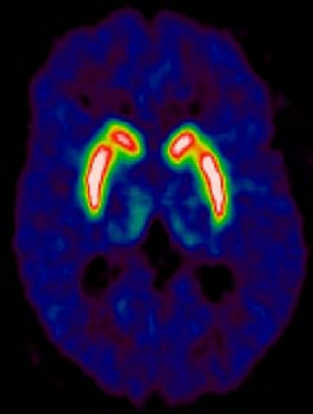






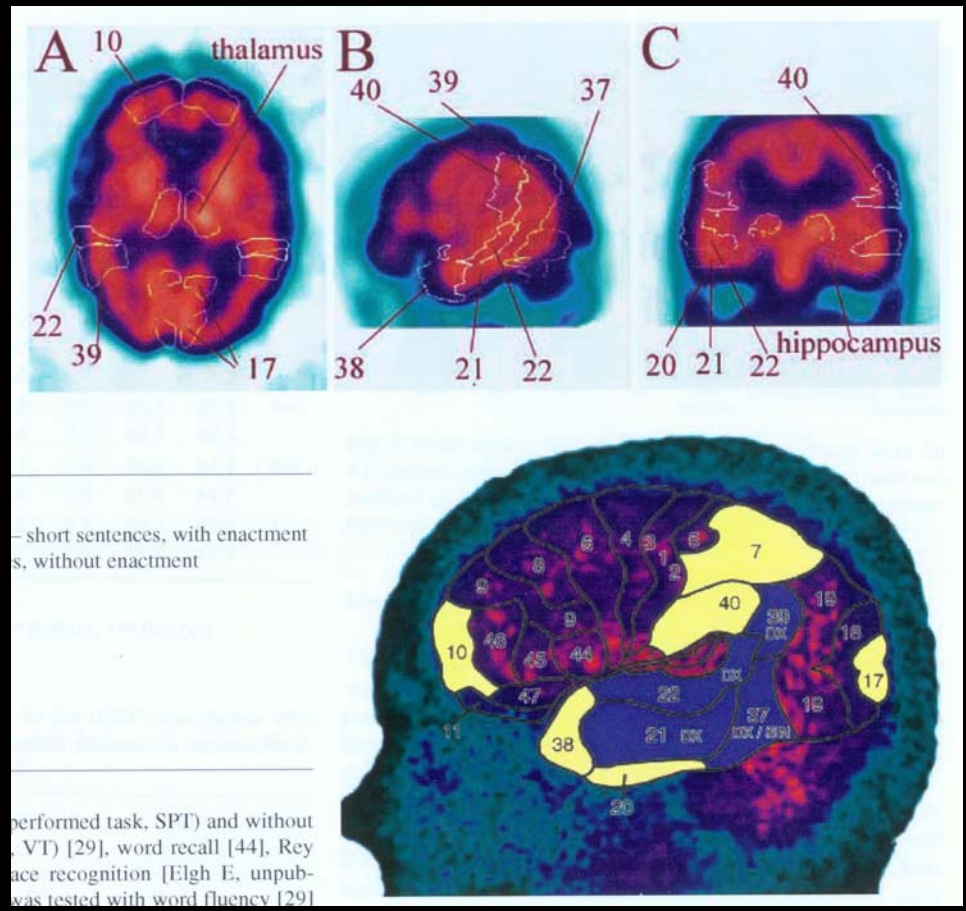
Activity & transmission
(e.g. fMRI & PET/SPECT)





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*)

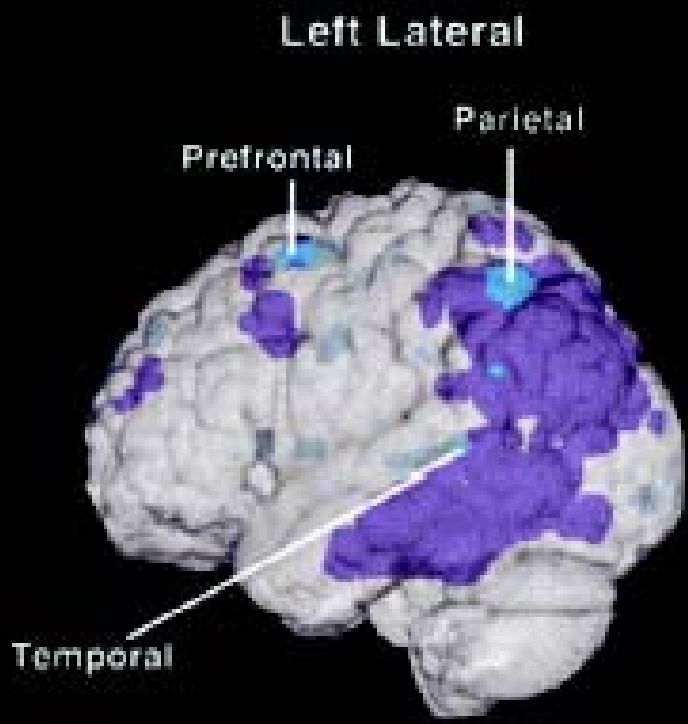


Genetic risk for Alzheimer's Dementia

- Apolipoprotein E (ApoE) gene on chromosome 19:
  - Three alleles: ε2, ε3, ε4
    - 5 common genotypes: ε2/3; ε2/4; ε3/3; ε3/4; ε4/4
      - Presence of ε4 = risk
      - ε44 8 times more likely to develop AD than ε33 persons
- Differences in functional brain activity before disease onset?

Genetic risk and brain function

- *Lowered* resting-state metabolism in ε4 carriers
  - reduced glucose metabolism in fronto-parietal areas (Reiman et al., 2004, *PNAS, 101*, 284)

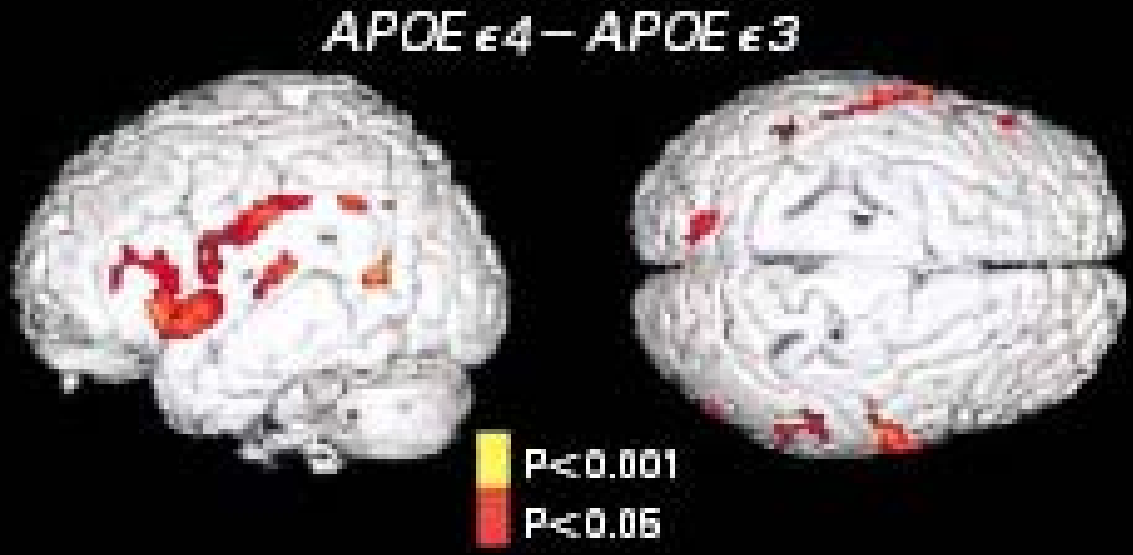


Similar pattern as for AD patients

Genetic risk and brain activity

- *Higher* frontal and parietal brain activity in ApoE ε4 compared with ε3 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

T1: 1988-1990
Test of 1000 subjects
(35-80 years)

→

T2: 1993-1995
Test of 862 subjects
(40-85 years)

→

T3: 1998-2000
Test of 730 subjects
(45-90 years)

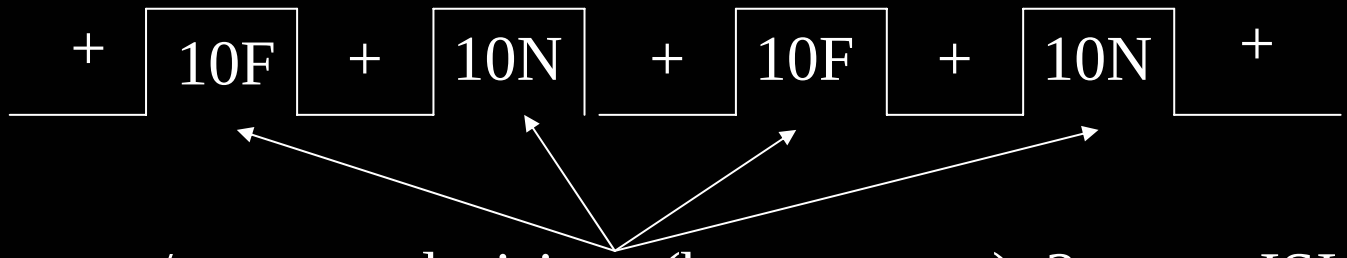
2002-03: MRI testing of 60 ss with longitudinal and genetic data (ApoE)
30 ApoE ε33; 30 ApoEε4 (20 ε34, 10 ε44)

Participants

	ApoE ε3 (30)	ApoE ε4 (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



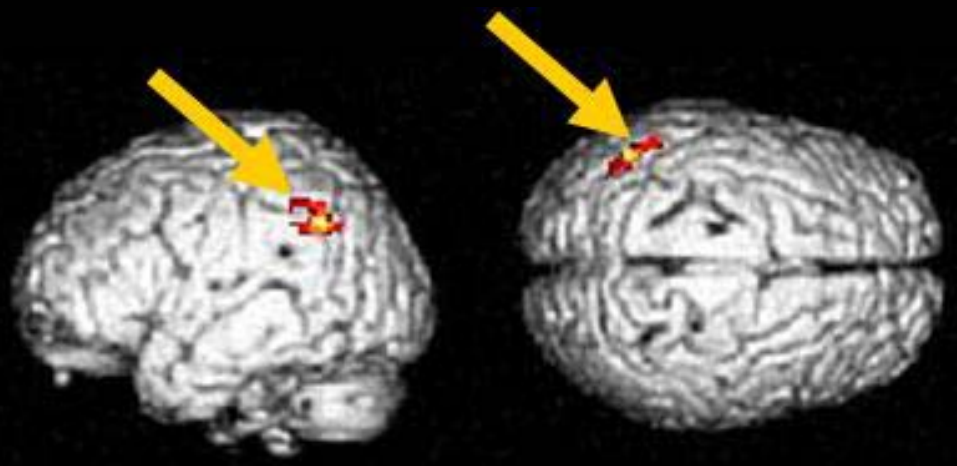
Abstract/concrete decisions (button press), 2 sec + ISI=1 sec

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

Categorization - Rest

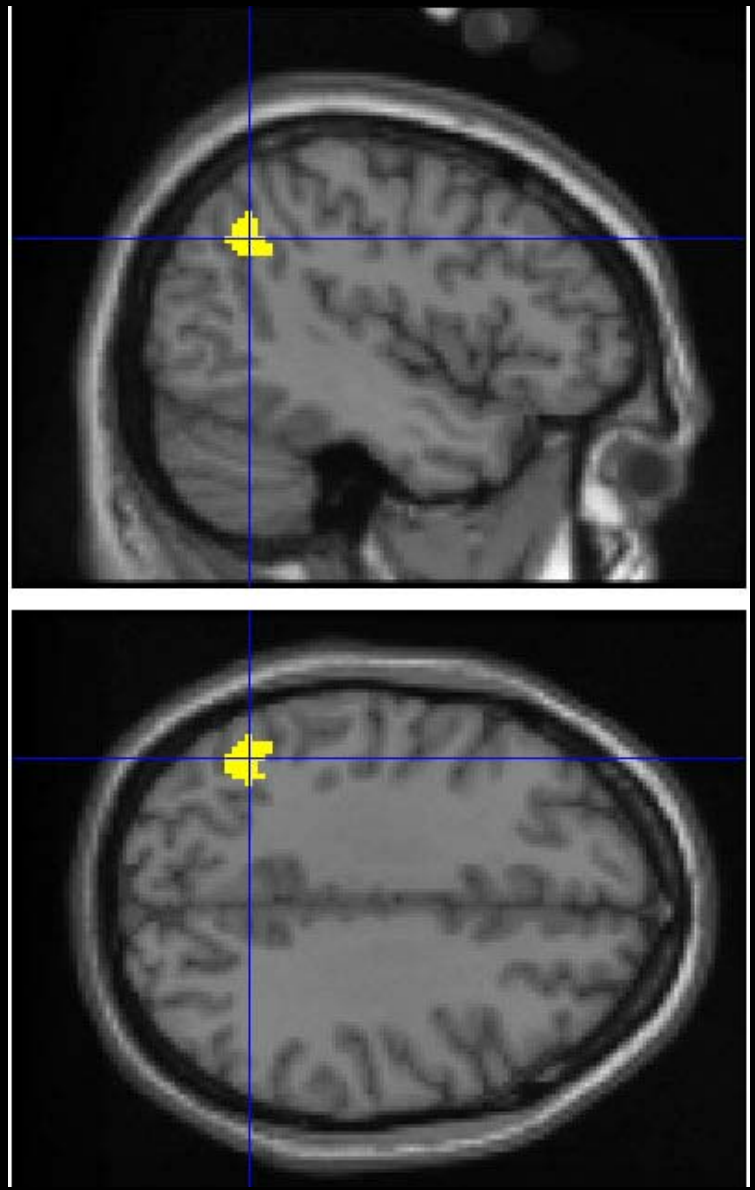
Reduced left parietal activity for high-risk persons

ApoE ε3 (N=30) – ApoE ε4 (N=30)

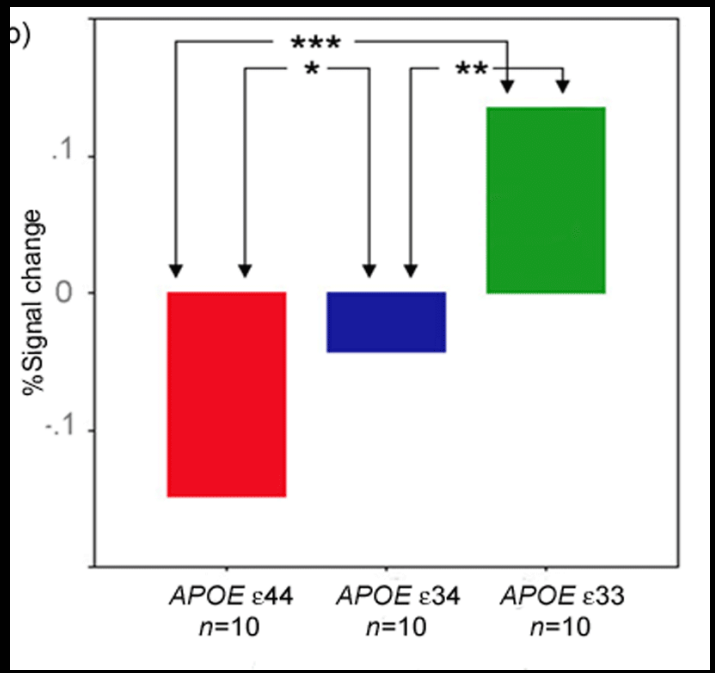


Lind et al (2006)
Brain

Dose effect in parietal cortex

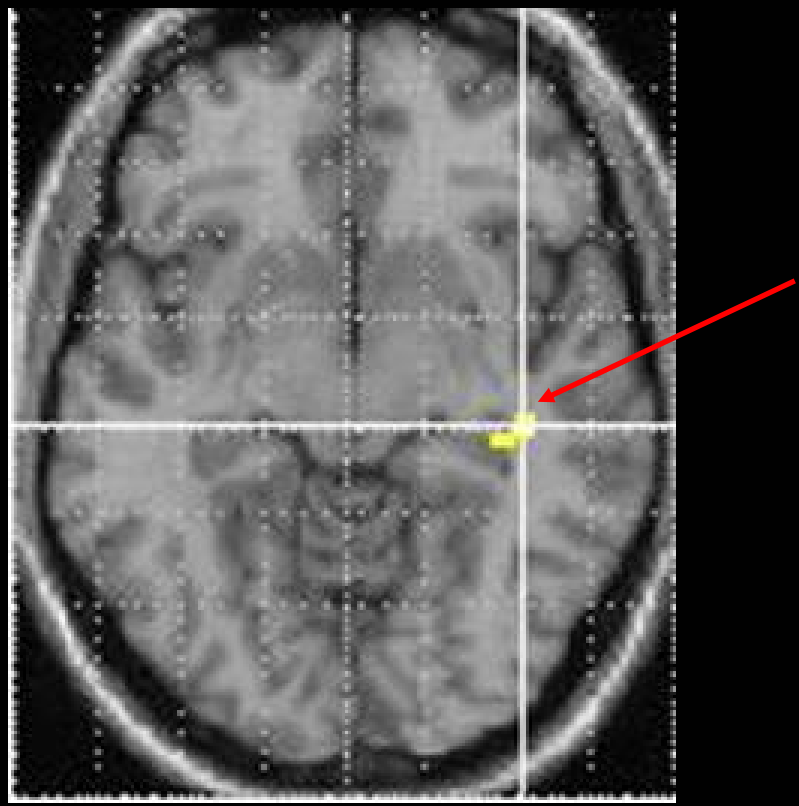


Dose-effect in parietal cortex



(Lind et al, 2006, *Brain*)

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



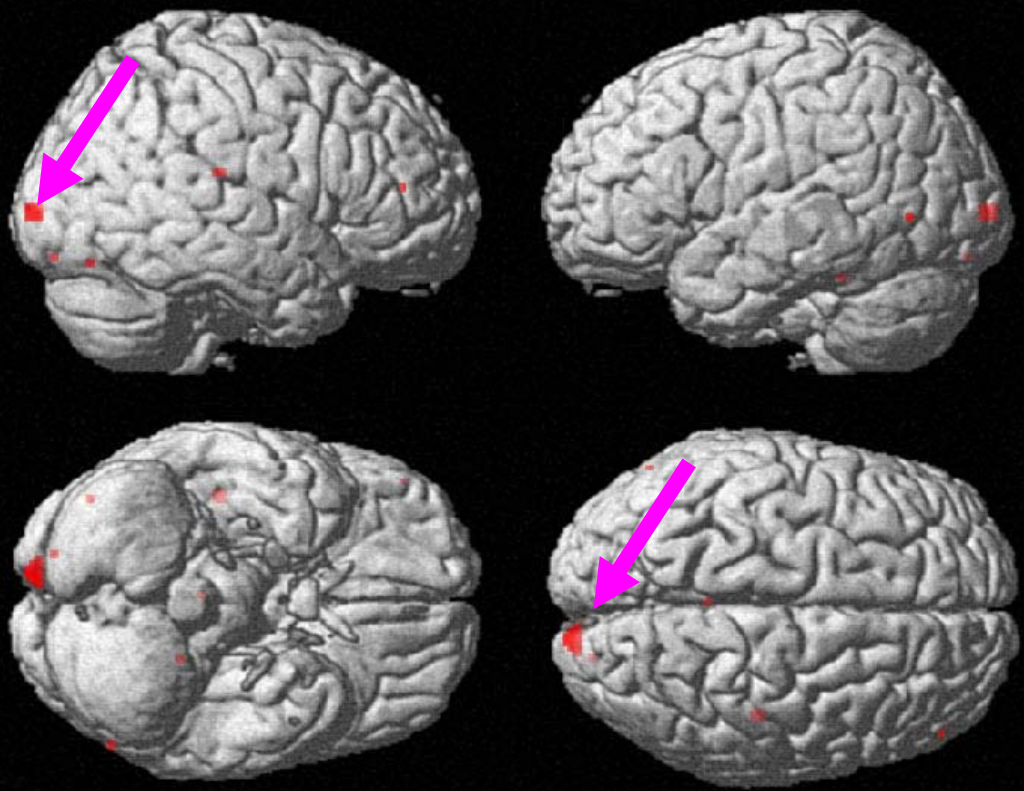
More pronounced novelty effect in right hippocampus for ApoE3

Lind et al (2006)
Brain

Greater activity for ApoE4?

Minimal support for compensation!

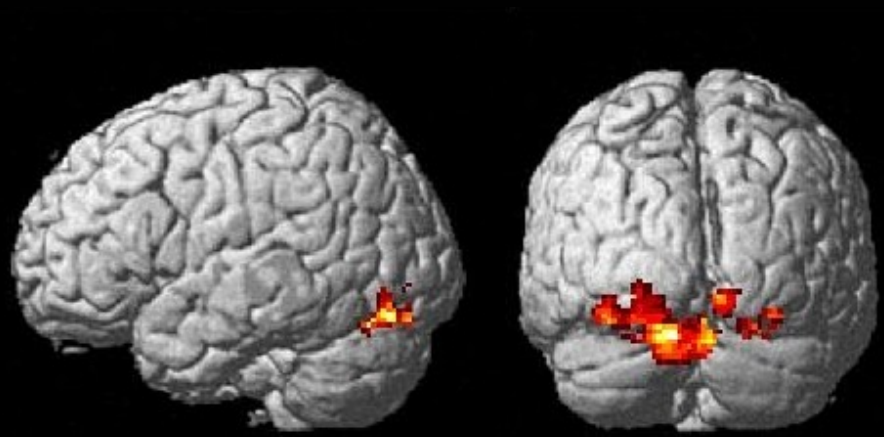
ApoE e4 (N=30) – ApoE e4 (N=30)



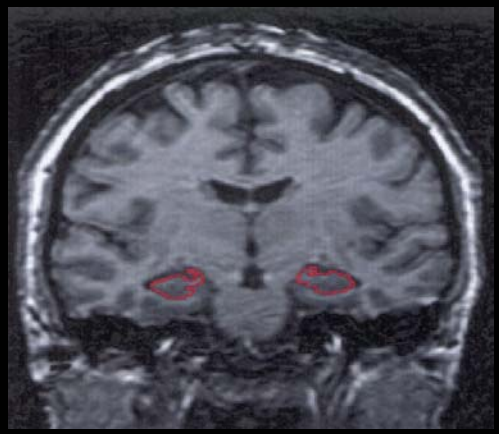
Related observations

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

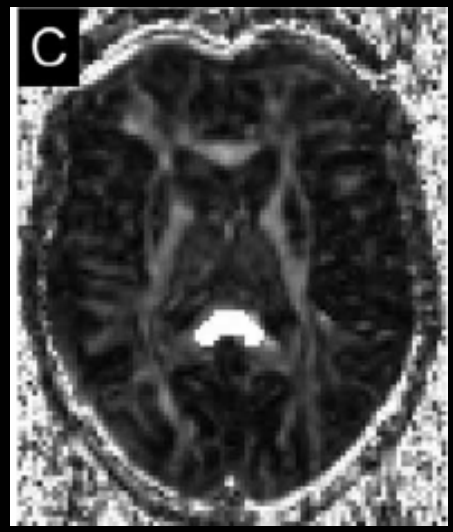
High-risk – low-risk



Genetic risk and structural brain changes



Smaller hippocampus volume for ε4 carriers (Lind et al., 2006, *Neurosci Lett*)

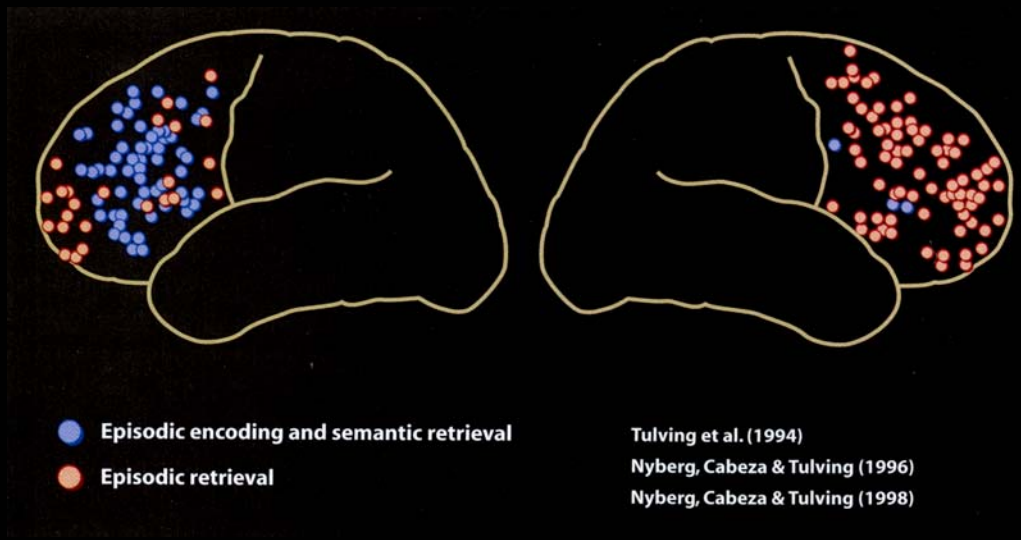


Reduced white-matter in *posterior* corpus callosum (Persson et al, 2006 *Neurology*)

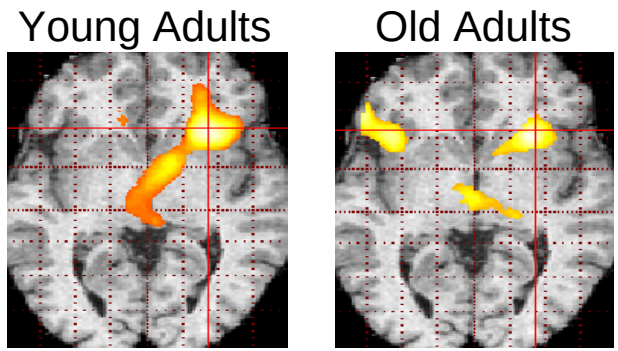
Age-related changes

- Functional imaging studies show that older adults activate some brain regions that younger adults typically *not* activate

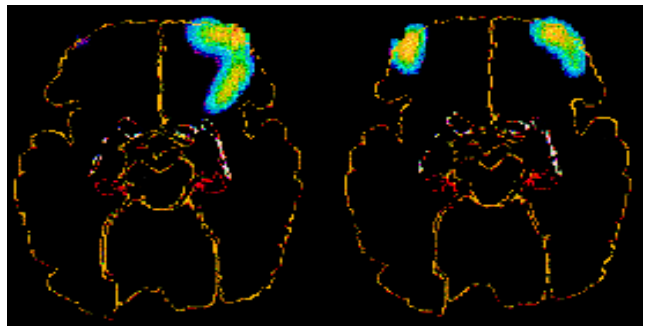
- Episodic memory retrieval: Younger tend to show right-sided frontal activity.



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



Word-Pair Cued-Recall



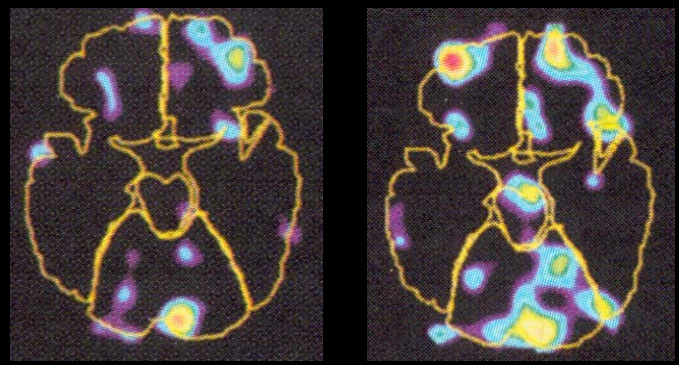
Word-Stem Cued-Recall

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

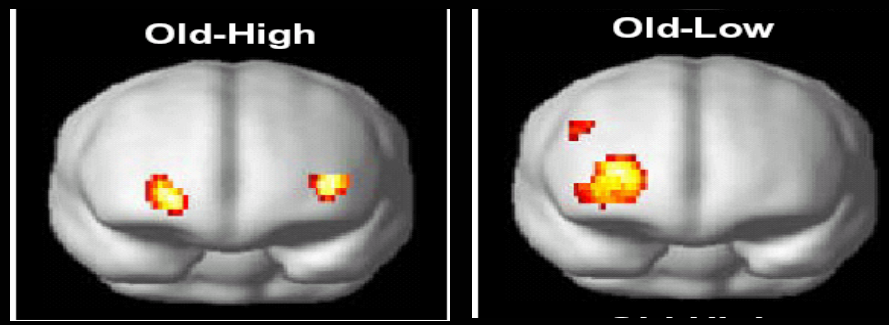
Normal old adults and demented patients



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*)

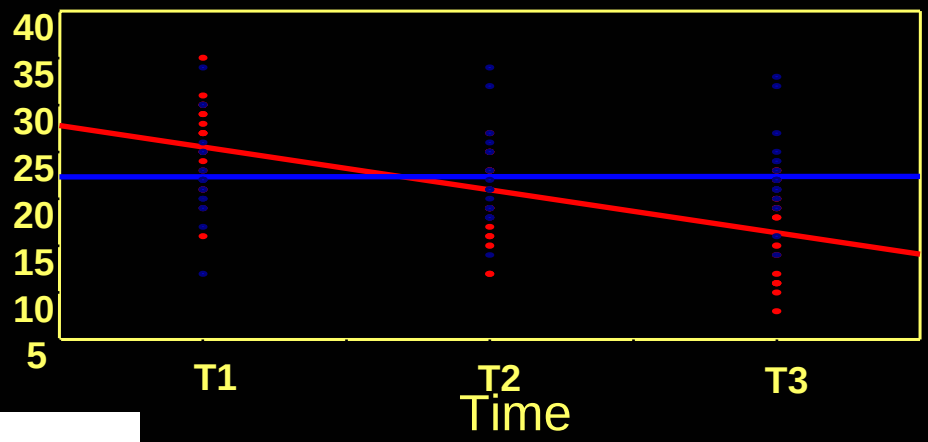


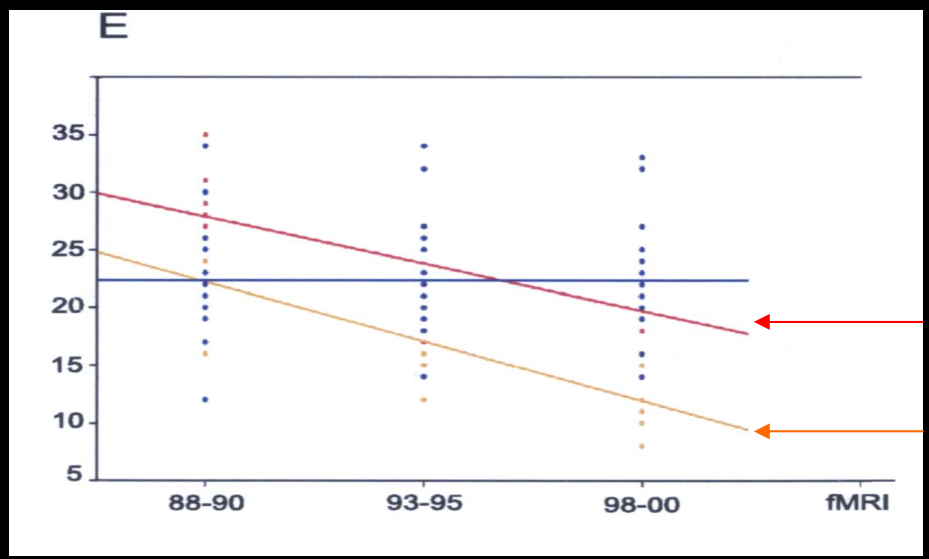
Research Question:

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 stabe/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

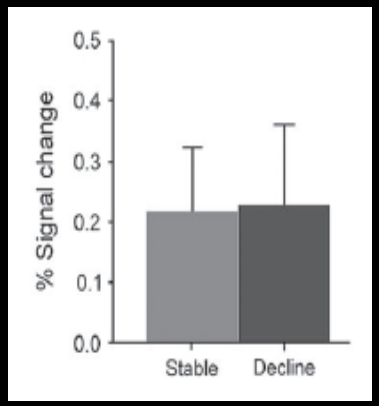
	Stable (20)	Decline (20)
Age	68.2	68.2
Education	10.1	10.7
Female/Male	13/7	13/7
MMSE	28.25	28.35
Vocabulary	22.15	23.75

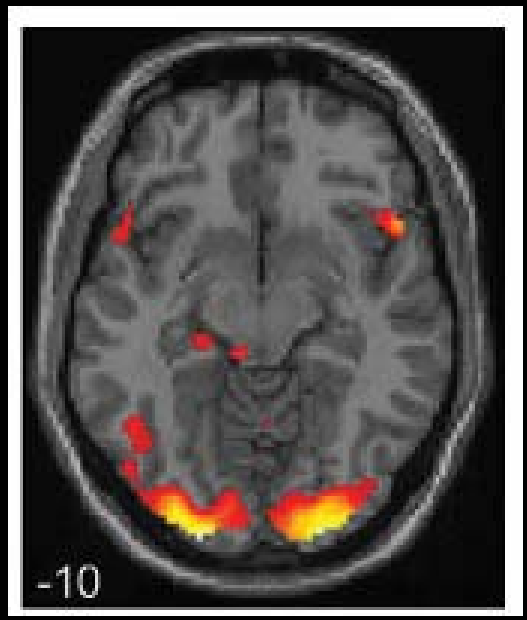
fMRI (categorization), hippocampus volume, DTI (white matter)

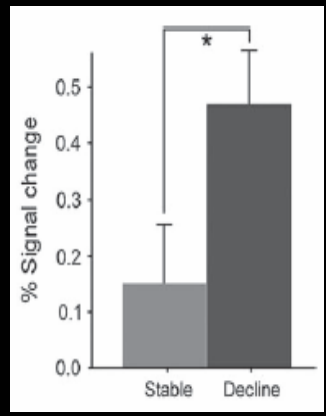
Previous findings in young associate this task with left PFC
- Additional right pFC activity for stable or declining group?

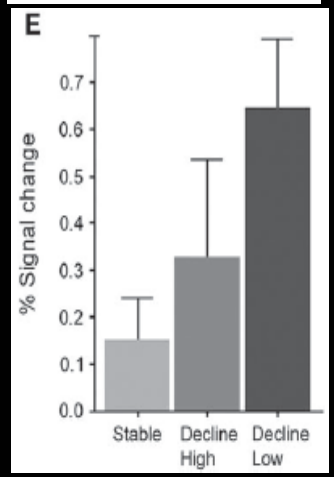
Functional changes
Categorization vs Rest

Overall analysis (N=40) revealed bilateral frontal activity





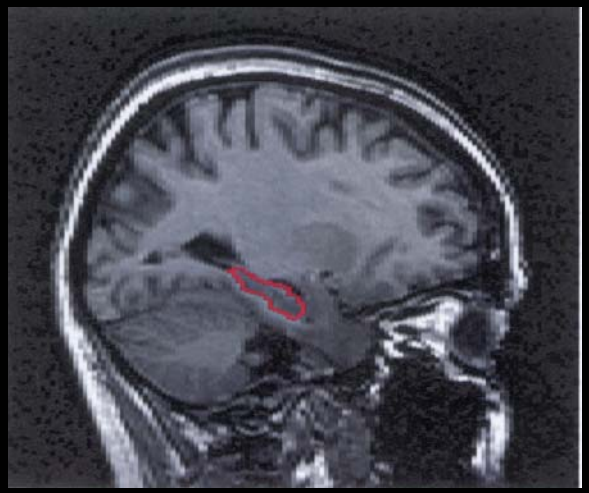




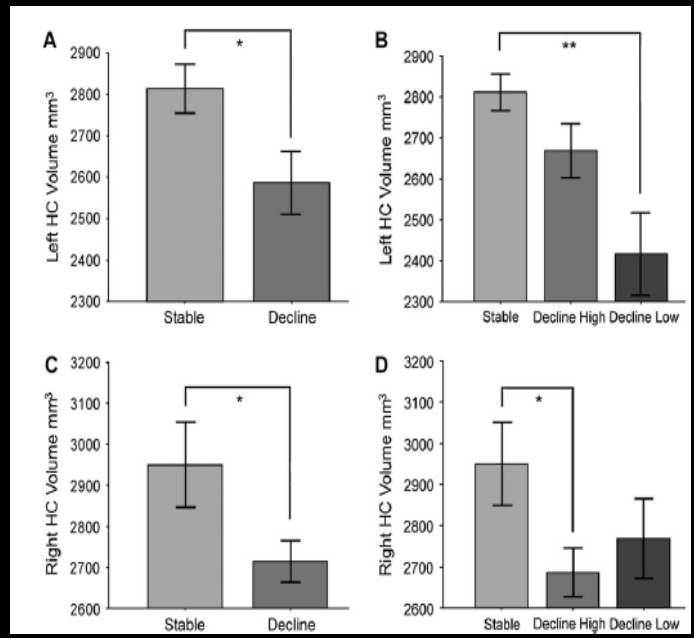
Both groups showed typical left PFC activity

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

Hippocampus volume

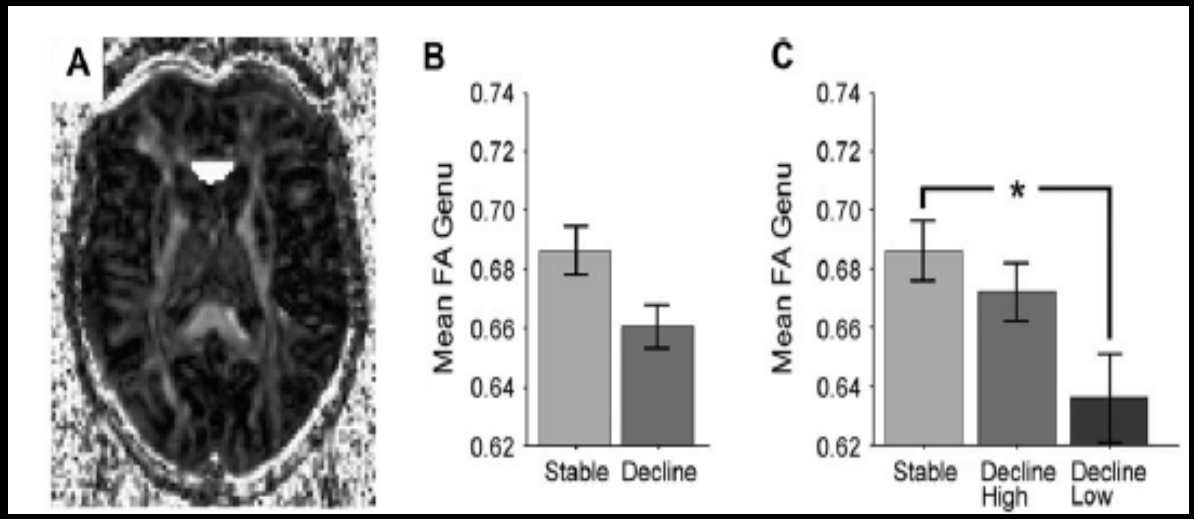


NIH Image 1.6 (see Raz et al, 2004, *Neurology*)



Reduced hippocampal volume for declining group

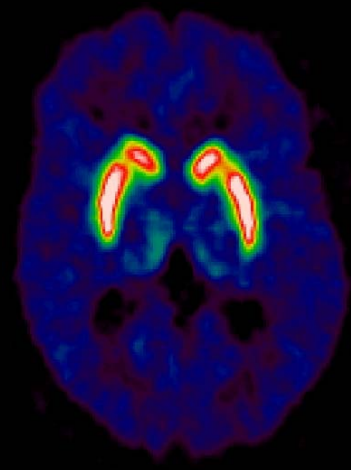
DTI: White-matter integrity

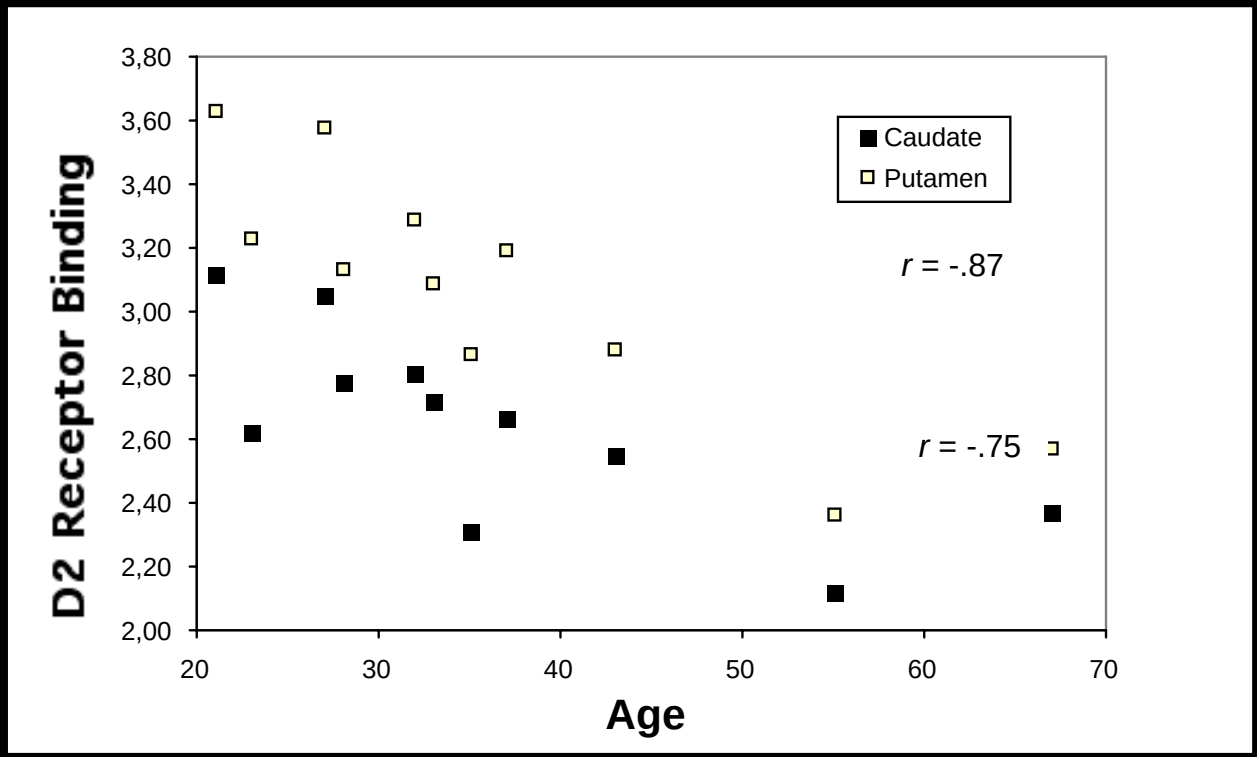


Reducted *anterior* white matter for declining group

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

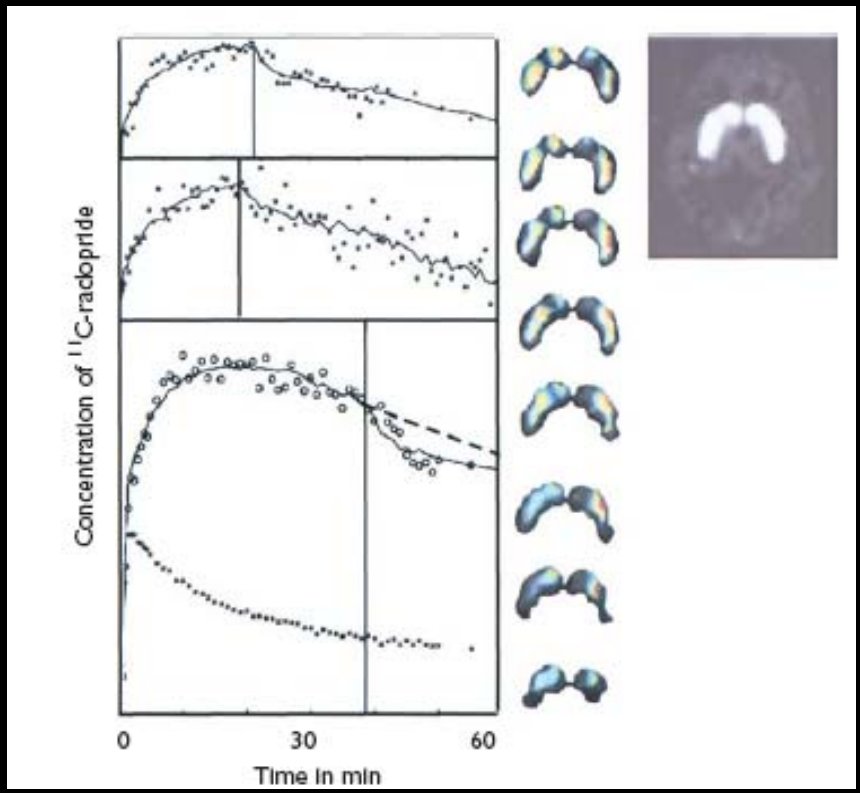
Dopamine Loss Across the Adult Life-Span



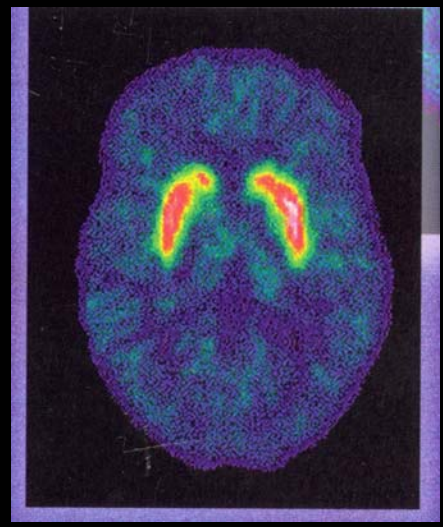


Bäckman et al., Am J Psychiatr, 2000

Bilateral activation in aging: Relation to neurotransmission?



Badgaiyan et al, 2003 *NeuroReport*



Activation studies

Reduced striatal binding during motor task

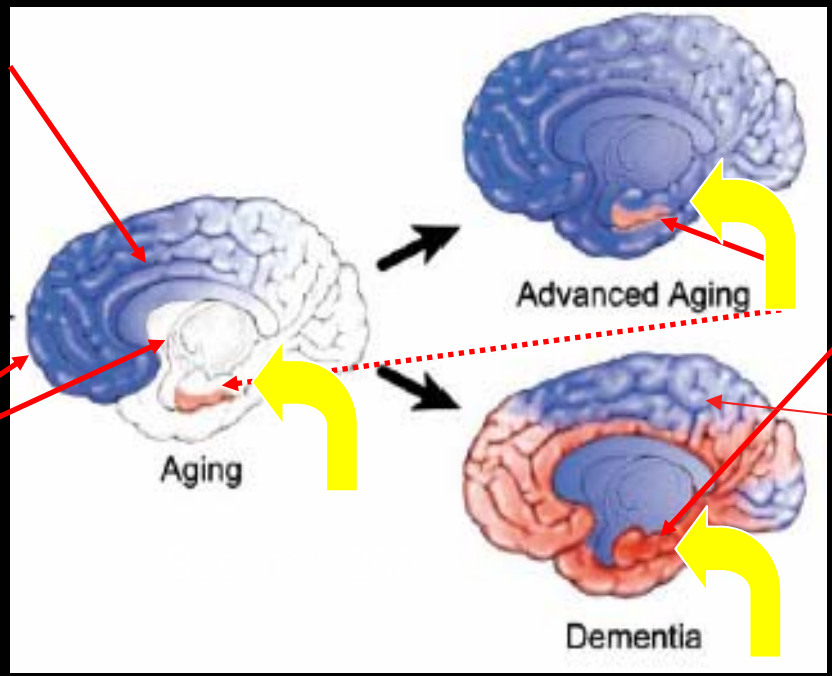
Striatal reduction in [11C] raclopride binding potential during Montreal card-sorting task

(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



Hippocampal volume -preclinical dementia or part of normal aging?

Fronto-striatal volume and activity changes

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