



Using functional magnetic resonance imaging to examine memory and ageing

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Research into Ageing, Wellcome Trust, NIMH

Overview

- Cognitive and brain ageing
- Using neuroimaging to study ageing
- Two examples
 - A study of new memory encoding
 - A drug study of new memory encoding
- Conclusions

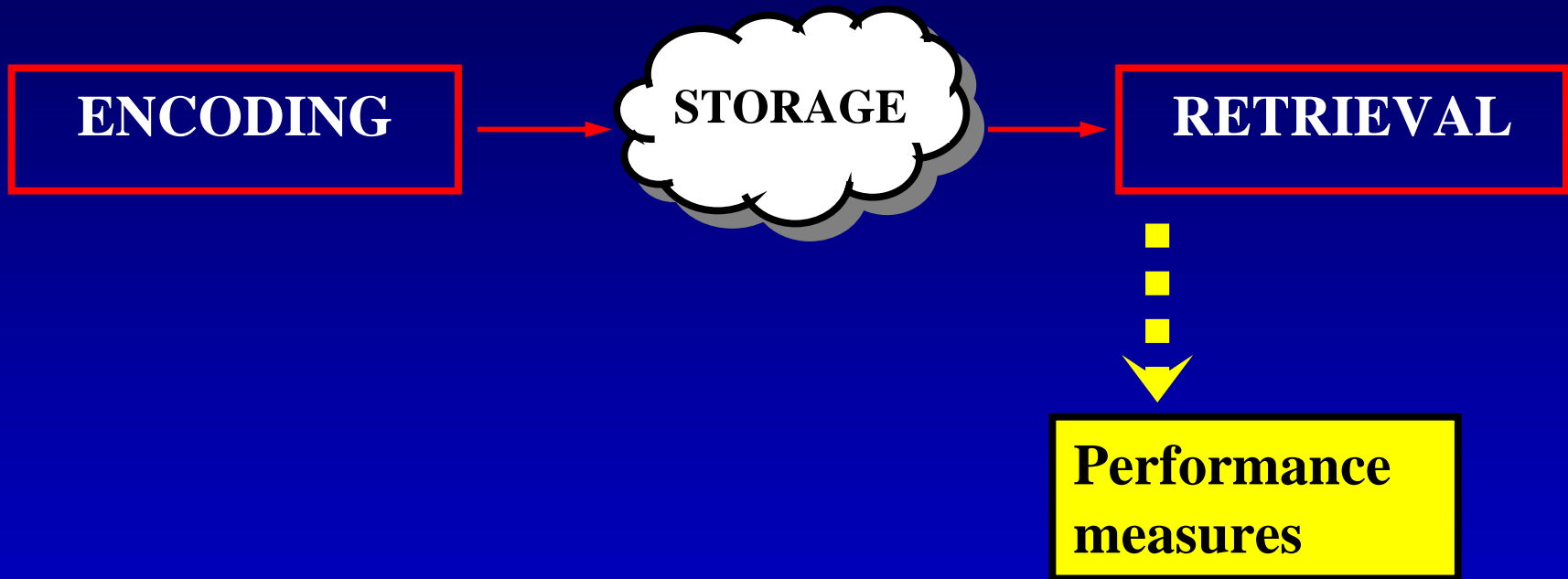
Cognitive ageing

- Does it all go together when it goes?
- Some abilities are more affected
 - Prominent decline in *episodic memory* – specifics of events
 - Increased reliance on a non-specific sense of familiarity
 - Preserved language, knowledge, skills
- Some people are more affected
 - Abilities seem more linked with increasing age
 - *Common cause* or compensation?
 - What characterises ‘successful’ ageing?

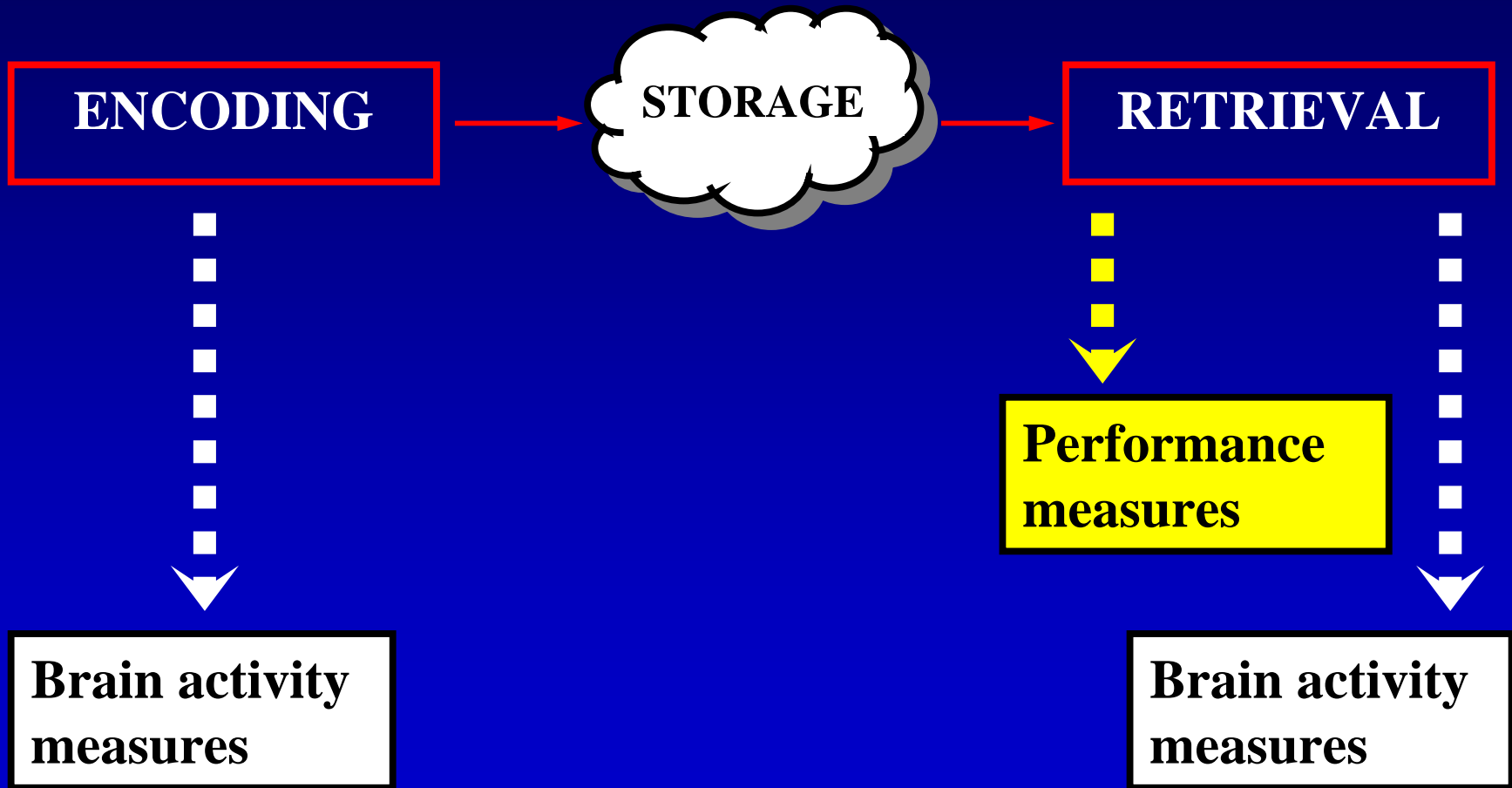
Memory ageing

- How does episodic memory decline in older adults?
- *Encoding* new memories
 - Strategy instructions can help (but don't always)
 - Meaning and relevance can help
- (*Storage* and consolidation of memories)
- *Retrieving* existing memories
 - Information recovered depends on memory test
- Studying the brain can be informative about the mind

Measuring memory



Measuring memory



Brain ageing

- Linking cognitive and brain changes
 - A mechanistic account of memory decline
- Is there uniform loss of function across the brain?
 - Prefrontal cortex
 - Medial temporal lobes
- Can brain changes be linked to chemical systems?
 - Acetylcholine – reduced signalling in Alzheimer's
 - Dopamine – reduced signalling in normal ageing

Ageing and plasticity: the challenge

- Qualitatively different activity in older adults
 - Prefrontal cortex activity bilateral rather than unilateral
 - More prefrontal relative to posterior cortex activity
 - ...does '*over-recruitment*' reflect *decline* or *compensation*?
- Difficult to interpret these patterns because
 - Different levels and kinds of memory in young & old
- If older brains adapt to do the same thing differently, how do we interpret changes in the brain?

Neuroimaging memory and ageing

1. Evidence for plasticity: 'minimal' differences
 - How do age groups differ when 'compare like with like'?
2. Link age differences in activity to processing
 - Do group differences suggest memory differences?
3. Correlate activity with performance
 - Where is activity associated with better memory?
4. Using drugs, see impact of chemical changes
 - Do these suggest mechanisms for age-related differences?

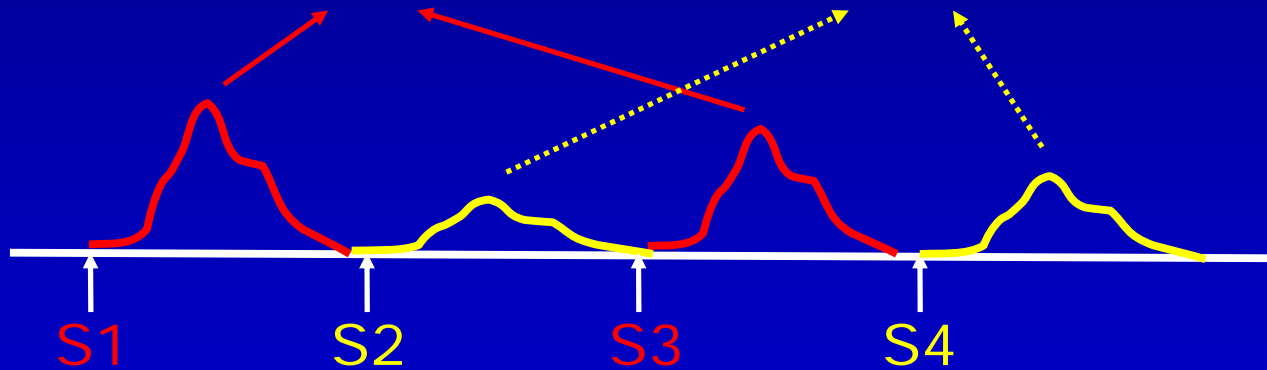
'Subsequent memory' paradigm



Subsequently
Remembered

Subsequently
Forgotten

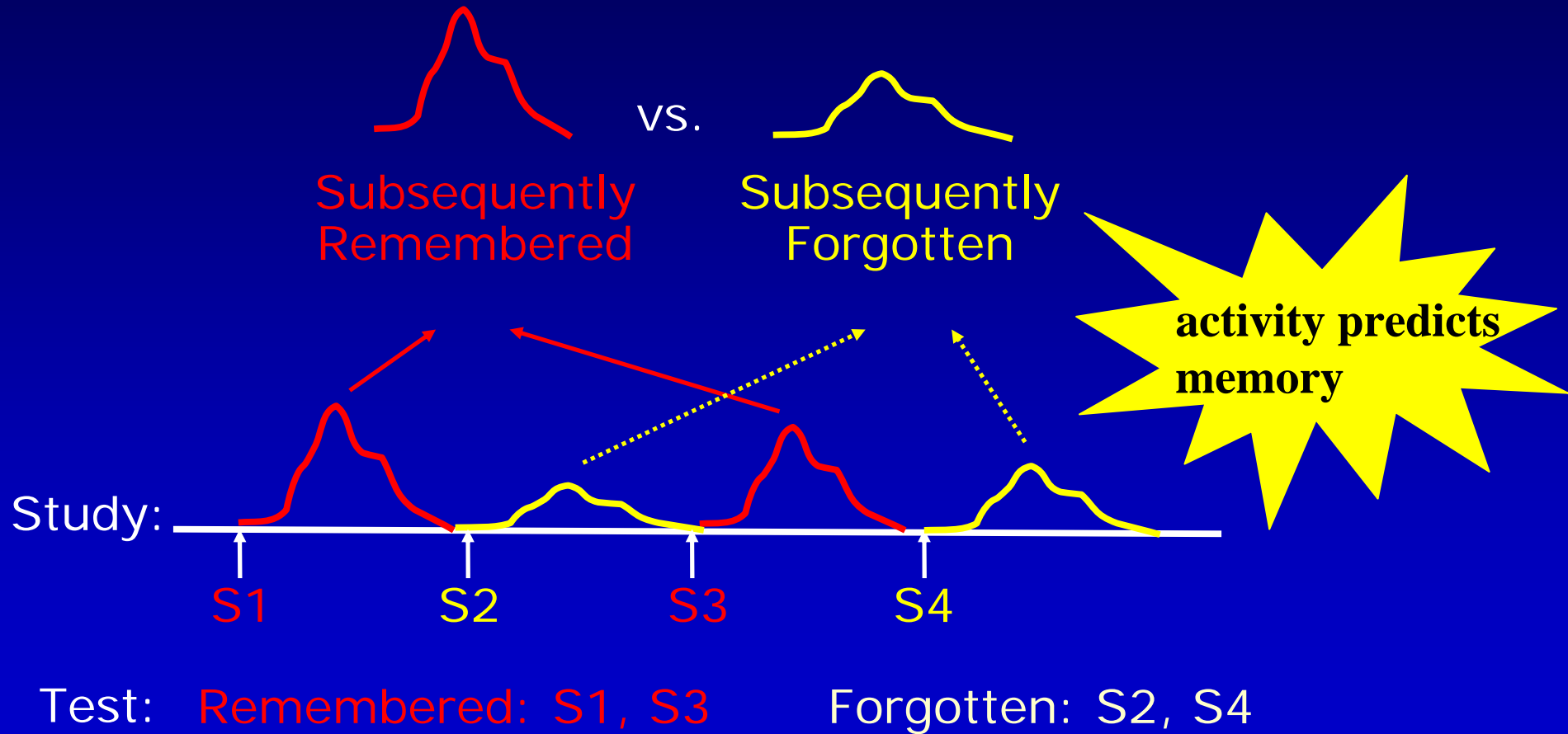
Study:



Test: Remembered: S1, S3

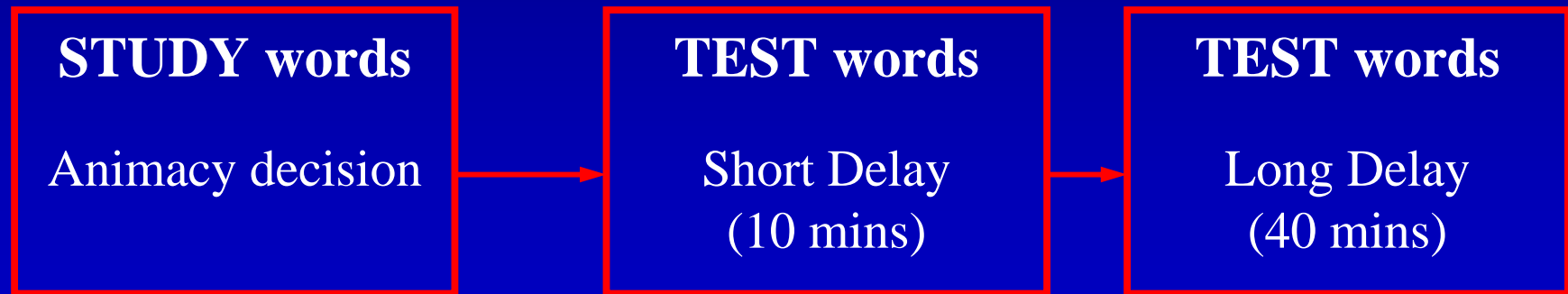
Forgotten: S2, S4

'Subsequent memory' paradigm



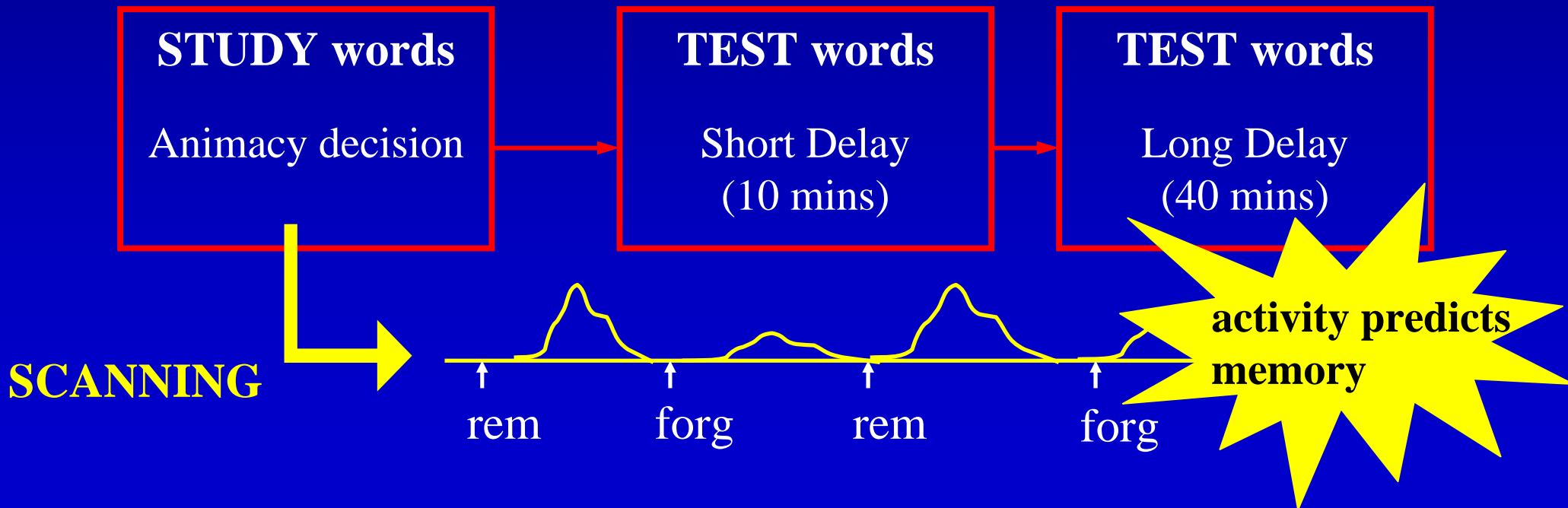
Study 1: ageing and memory encoding

- N = 14/ 14, 18-30 yrs & 63-75 yrs healthy adults
- Meaningful (deep) encoding task, two test delays
- Recognition test with confidence judgement



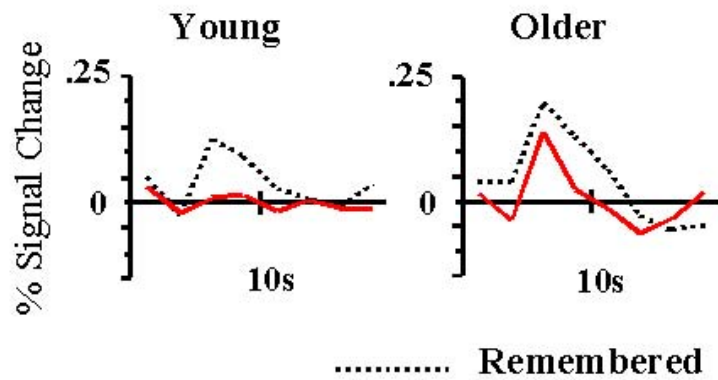
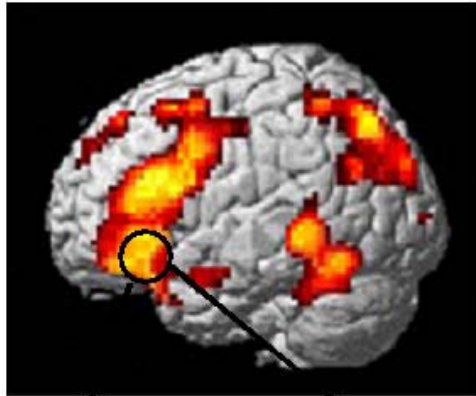
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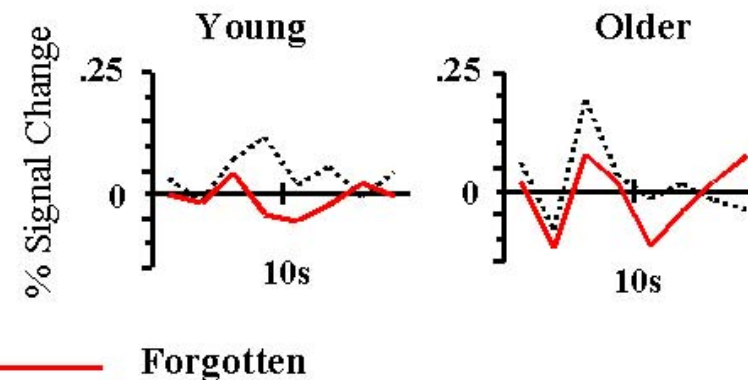
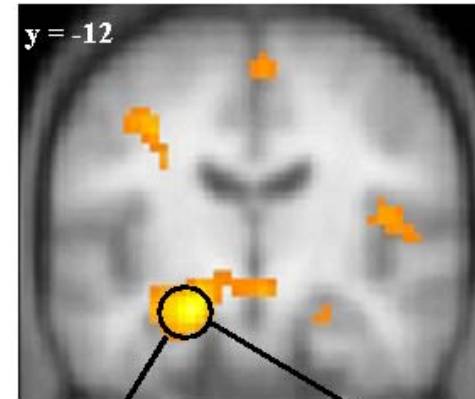


Study 1: Age-invariant effects

Left inferior frontal gyrus

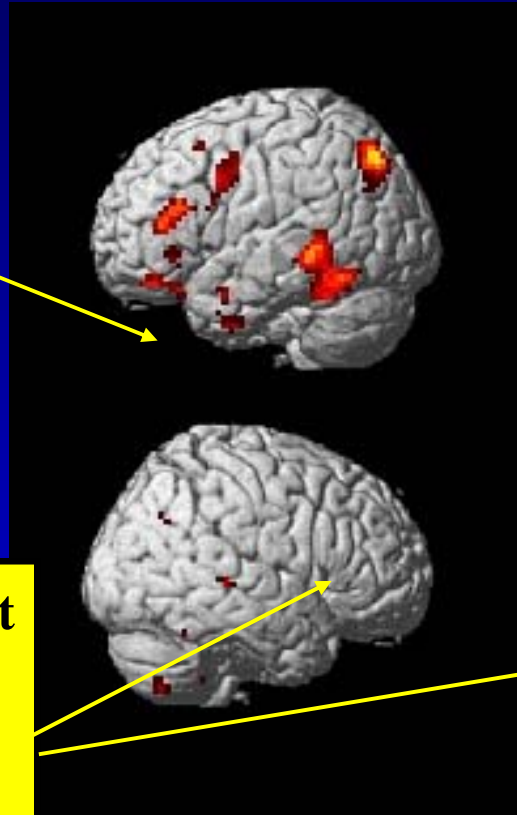


Left medial temporal lobe



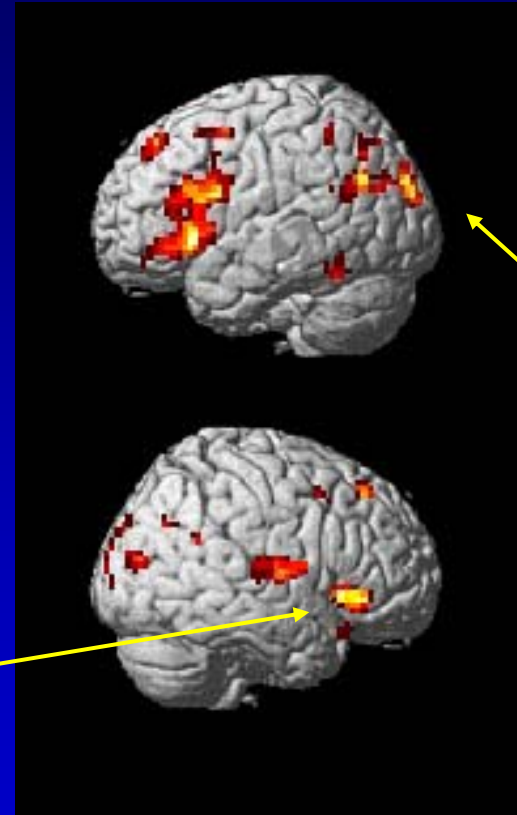
Study 1: Age-related differences

Additional left anterior temporal activity in the younger group



Younger

Additional occipitoparietal effects in the older group



Older

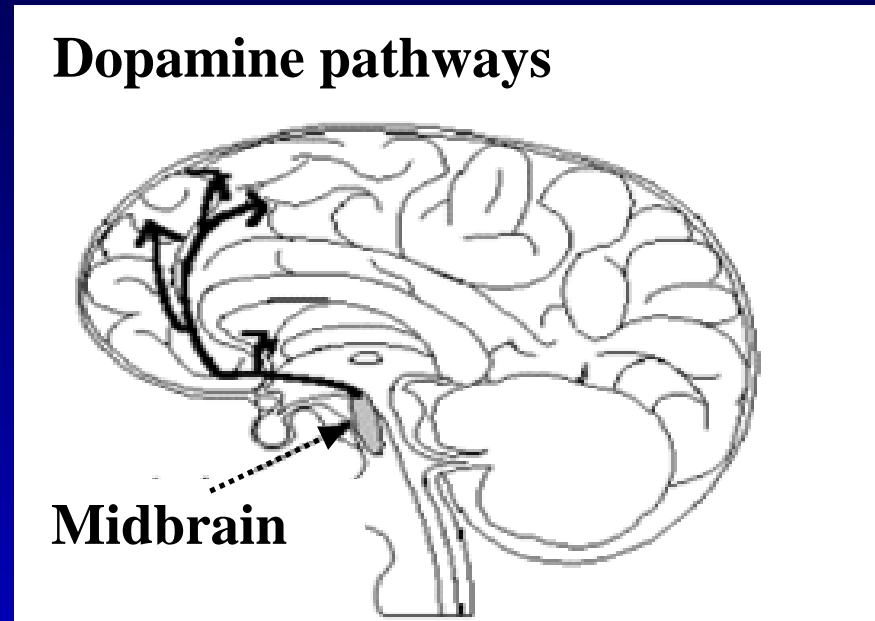
Additional right (as well as left) prefrontal activity in the older group

Study 1: Summary

- No change in key ‘successful encoding’ areas
 - Left inferior lateral prefrontal cortex
 - Medial temporal lobes
- Evidence of ‘over-recruitment’
 - Less lateralised prefrontal activity in older adults
- But processing may still be different in older group
 - Over-recruitment in occipital cortex – more visual contribution to encoding?
 - Under-recruitment in anterior temporal cortex – less ‘elaborate’ encoding for meaning?

Study 2: Dopamine (DA) and encoding

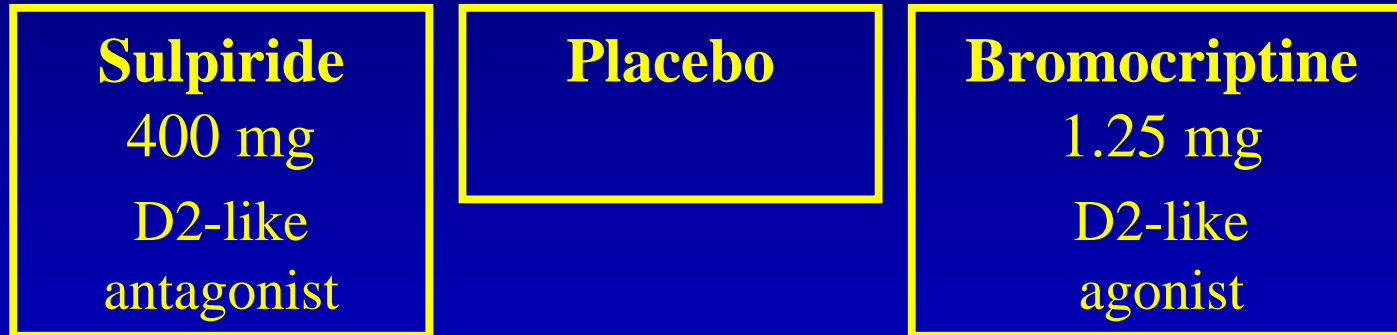
- Modifies neural transmission in networks including
 - Prefrontal cortex
 - Medial temporal lobes (MTL)
- ‘Correlative triad’ of ageing, DA, cognition
 - Decline in DA system markers with age (D2, D1, DAT)
 - Correlates with cognitive decline including memory
 - No specific link as yet



Dopamine acts on networks critical for episodic memory & sensitive to ageing

Study 2: Drugs and design

Increasing signalling at dopamine receptors

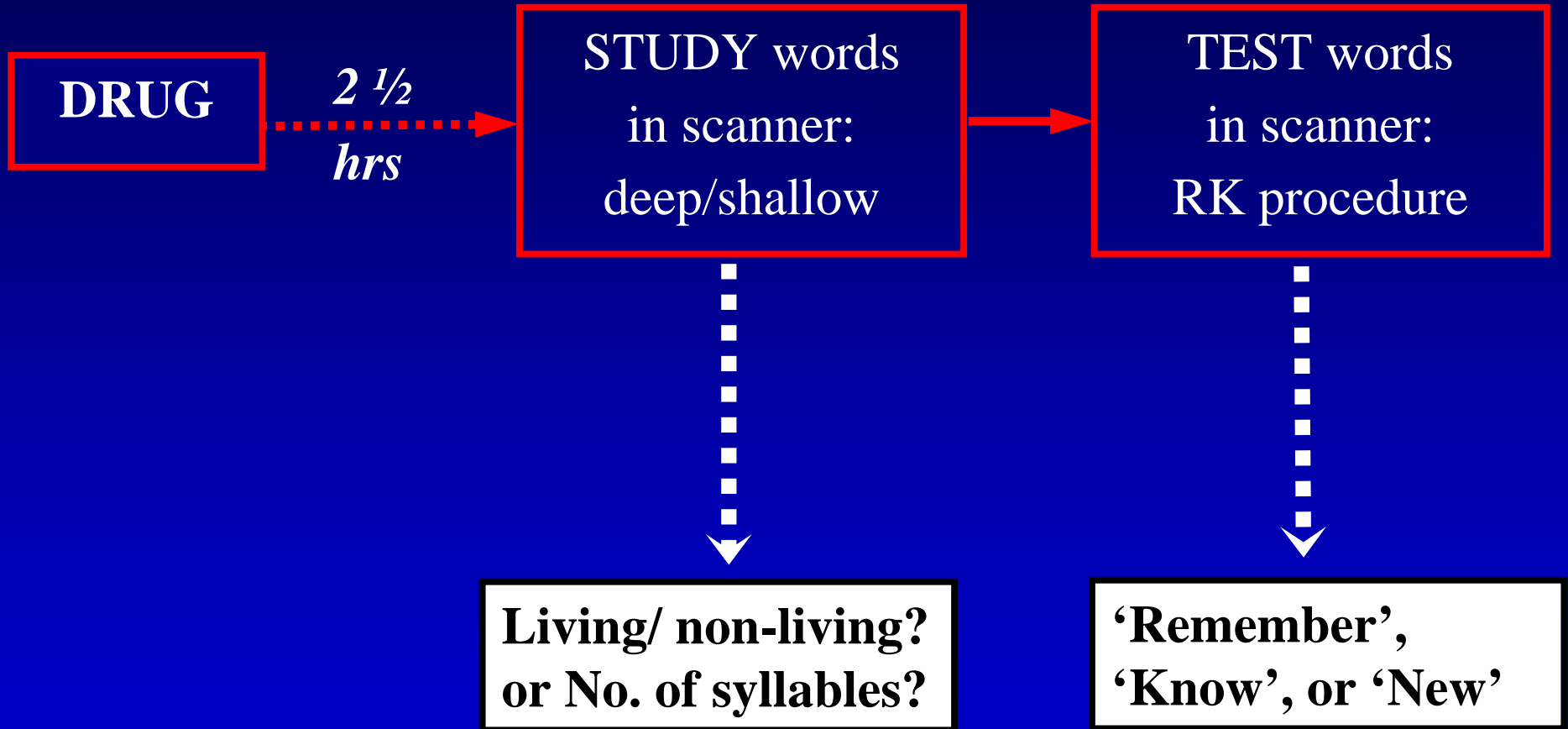


Double-blind crossover design, 3 sessions

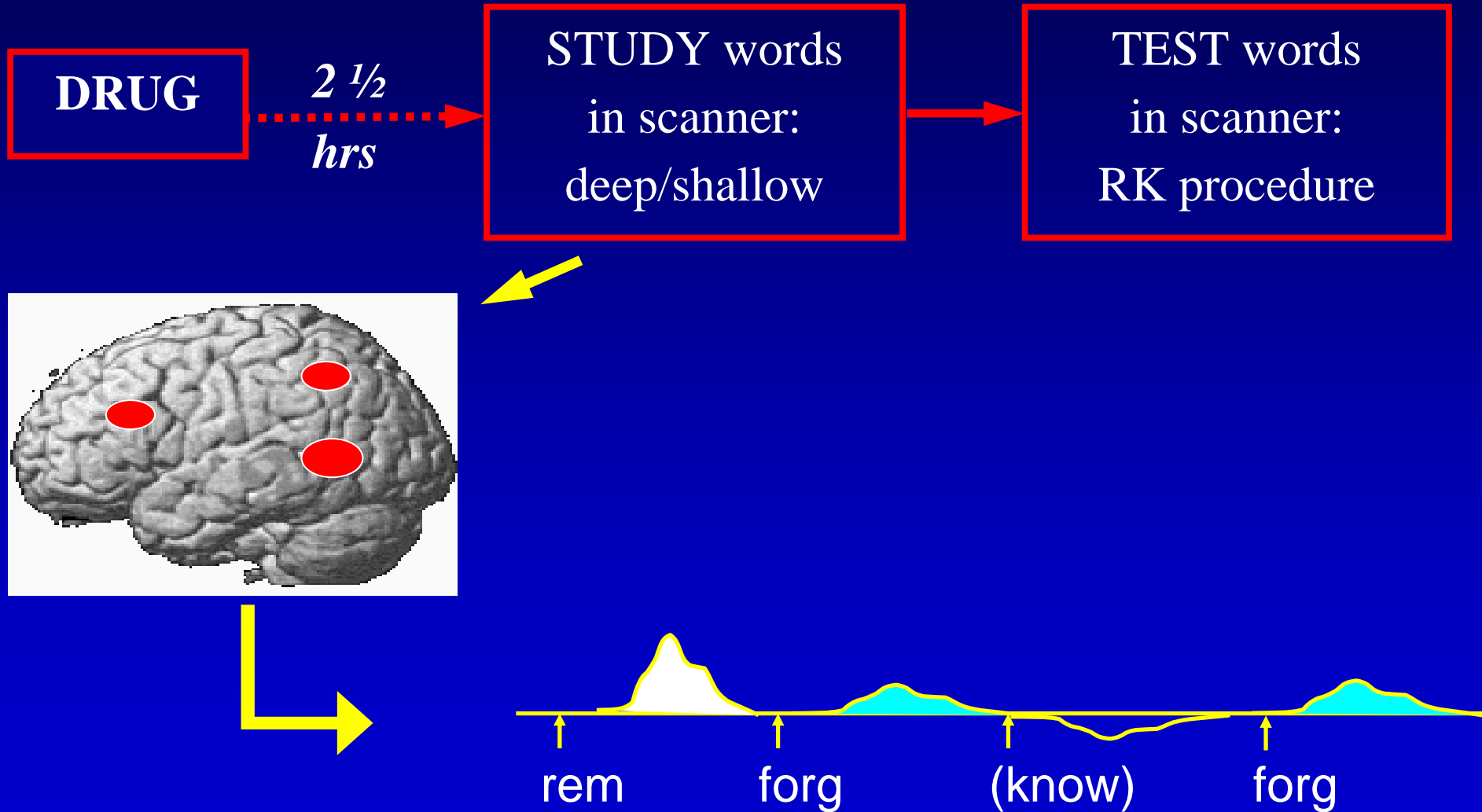
Healthy participants with MMS \geq 28/30

N=15, 12 aged 18-35 and 63-79 yrs

Study 2: Procedure



Study 2: Procedure

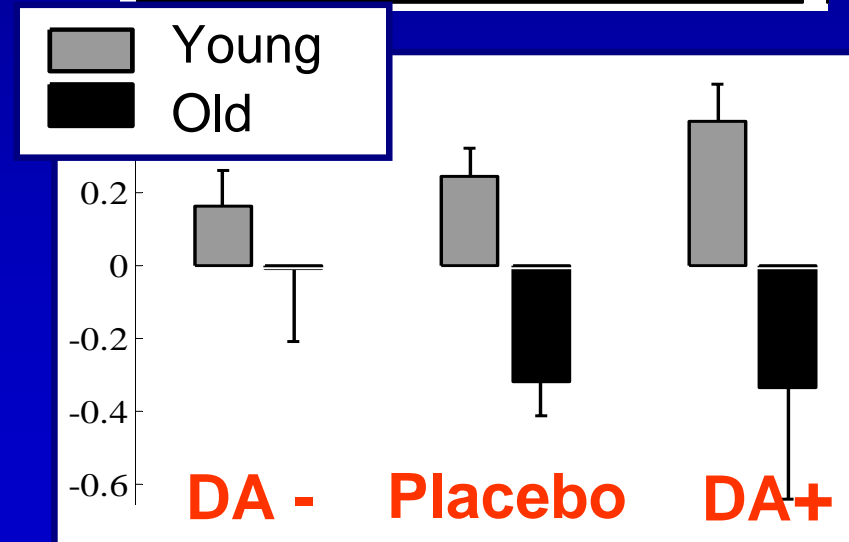
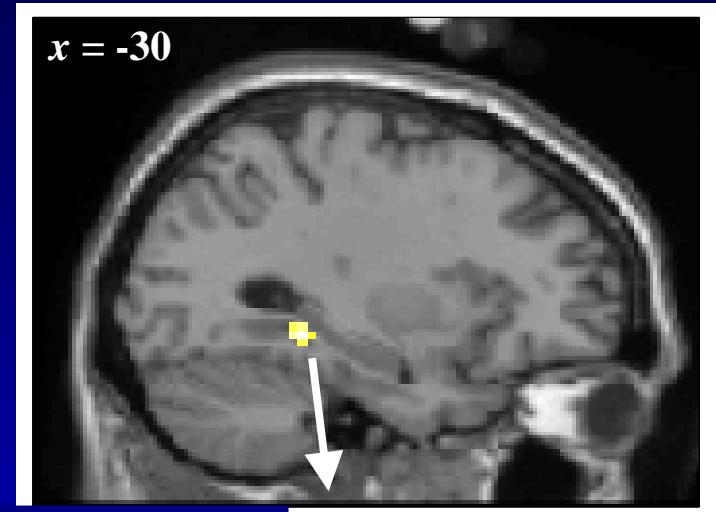


Study 2: memory performance

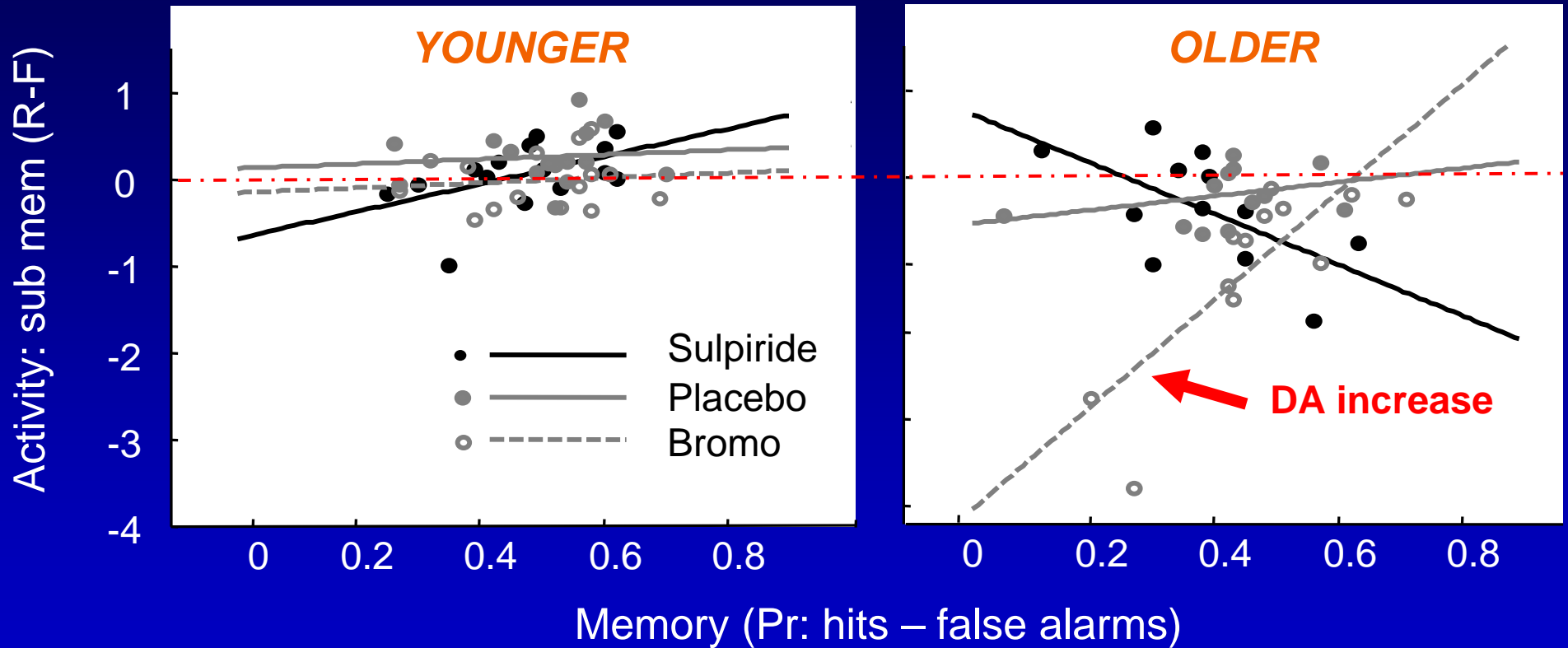
- Good recognition performance in both groups
 - Old slower, slightly poorer memory on average
 - Equivalent rate of correct 'R' judgements
 - Substantial variability in both groups
- No clear memory-specific effects of drugs
 - Some memory improvement with increasing DA
 - More likely to judge items old on sulpiride
 - Responses slower on both drugs
- No age differences in drug effects on memory

Study 2: Medial temporal lobe

- On placebo, groups differ – activity predicts remembering in young, but forgetting in old
- Increased DA signalling emphasises this baseline group difference
- **BUT** the effect depends on individual memory performance



Study 2: medial temporal lobe



- Drugs modulate effects in older group: **poorer performers show (even) 'older' brain activity with DA increase**

Study 2: Further findings

- Similar drug effects seen in other regions
- Importantly – in left inferior lateral PFC
 - On placebo, activity predicts remembering in young, but little impact in old
 - Bromocriptine (DA+) accentuates these differences in older poorer performers

Study 2: Mechanisms?

- Differences between placebo condition and Study 1
 - Under-recruitment in older group in Study 2
 - Do they ‘remember’ less differentiated information?
- Can this account for baseline group differences?
 - Left inferior PFC ‘elaborates’ meaning and this supports recollection
 - MTL binds ‘relational’ information from cortex into memory traces
 - MTL effectiveness depends on pattern separation - poorly differentiated traces may lead to forgetting

Study 2: Questions & caveats

- Direction of drug effects
 - Not consistent with a simple age/ DA-deficiency model
 - DA system ageing may alter its dynamics
 - e.g. relationship between tonic levels and phasic responses
- Encoding-specificity of drug effects
 - Effects on retrieval, or on ‘indirect’ encoding processes
 - Primary action/s may not be where the effects detected
 - Unknown selectivity – effects in non-memory tasks?

Study 2: Summary

- Altering the level of DA signalling alters the pattern of brain activity associated with successful encoding
- This mainly affects older adults and it varies with individual differences in memory
- Provides a direct link in the ‘correlative triad’ between age, dopamine, and cognition
- Further links this with individual differences in ageing memory, brought out by DA system challenge

Future directions

- Further investigations of ‘over-recruitment’
 - Process matching
 - Comparing tasks e.g. ‘spared versus impaired’
- Further investigations of ‘under-recruitment’
 - Which task factors are critical?
- Further investigations of DA and other transmitters
 - How is memory regulated in older (and younger) adults?
 - How selective is the link between DA and neural changes?
- Individual differences: decline vs. compensation...

Thank you.

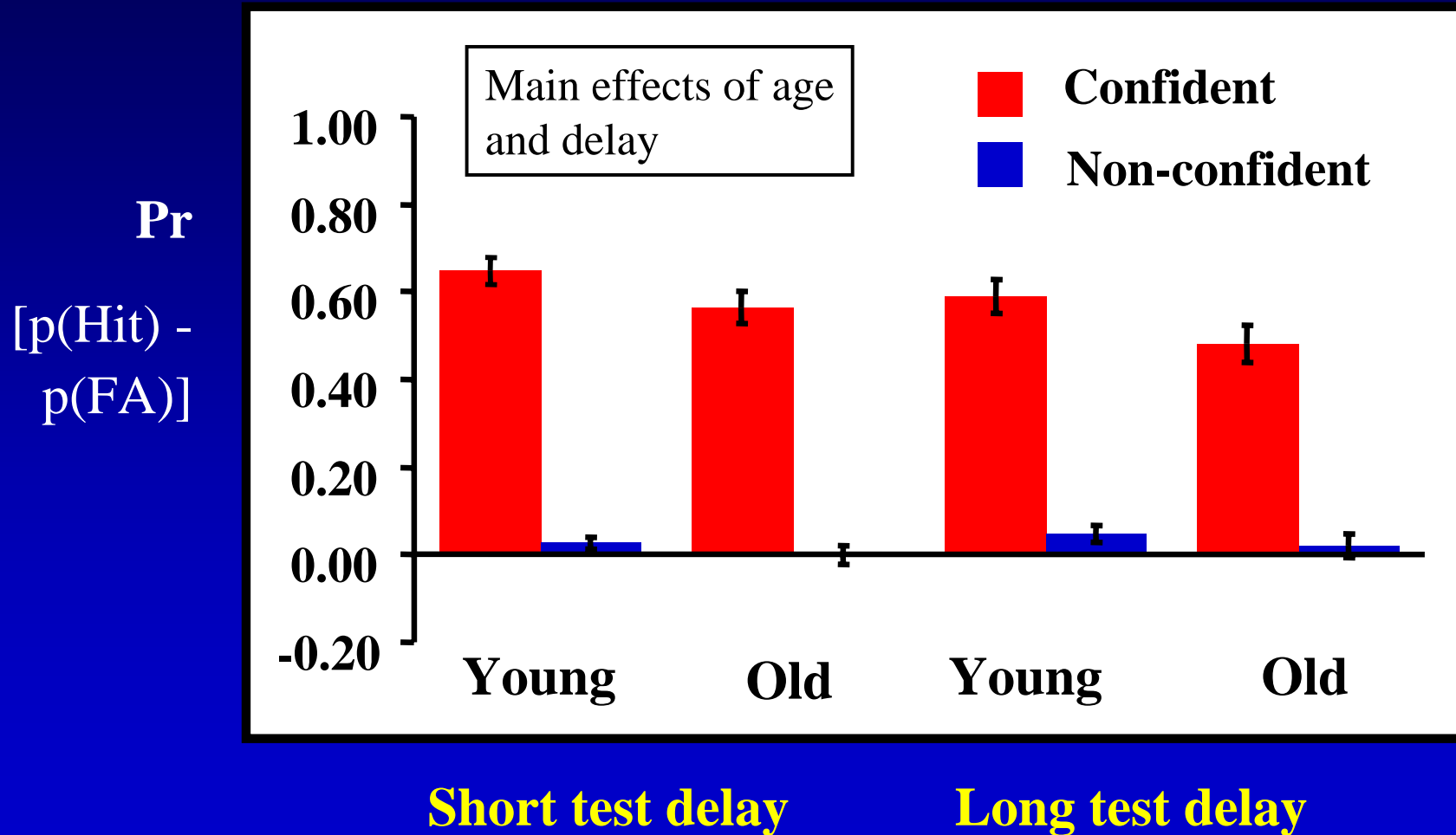
Neuropsychological profile

<i>Mean scores by group</i>	Younger N = 14	Older N = 14
Age	21	68
NART FSIQ estimate	113*	119*
Raven's Advance Progressive Matrices II	11**	9**
Mini Mental State	-	29
Warrington-McKenna Graded Naming	23	25
WAIS digit span	10	9
Verbal paired associates (WMS) – immediate	23*	19*
Verbal paired associates (WMS) – delayed	8**	7**
Short story recall (AMIPB) – immediate	41*	35*
Short story recall (AMIPB) – delayed	39**	30**
FAS verbal fluency	47	51

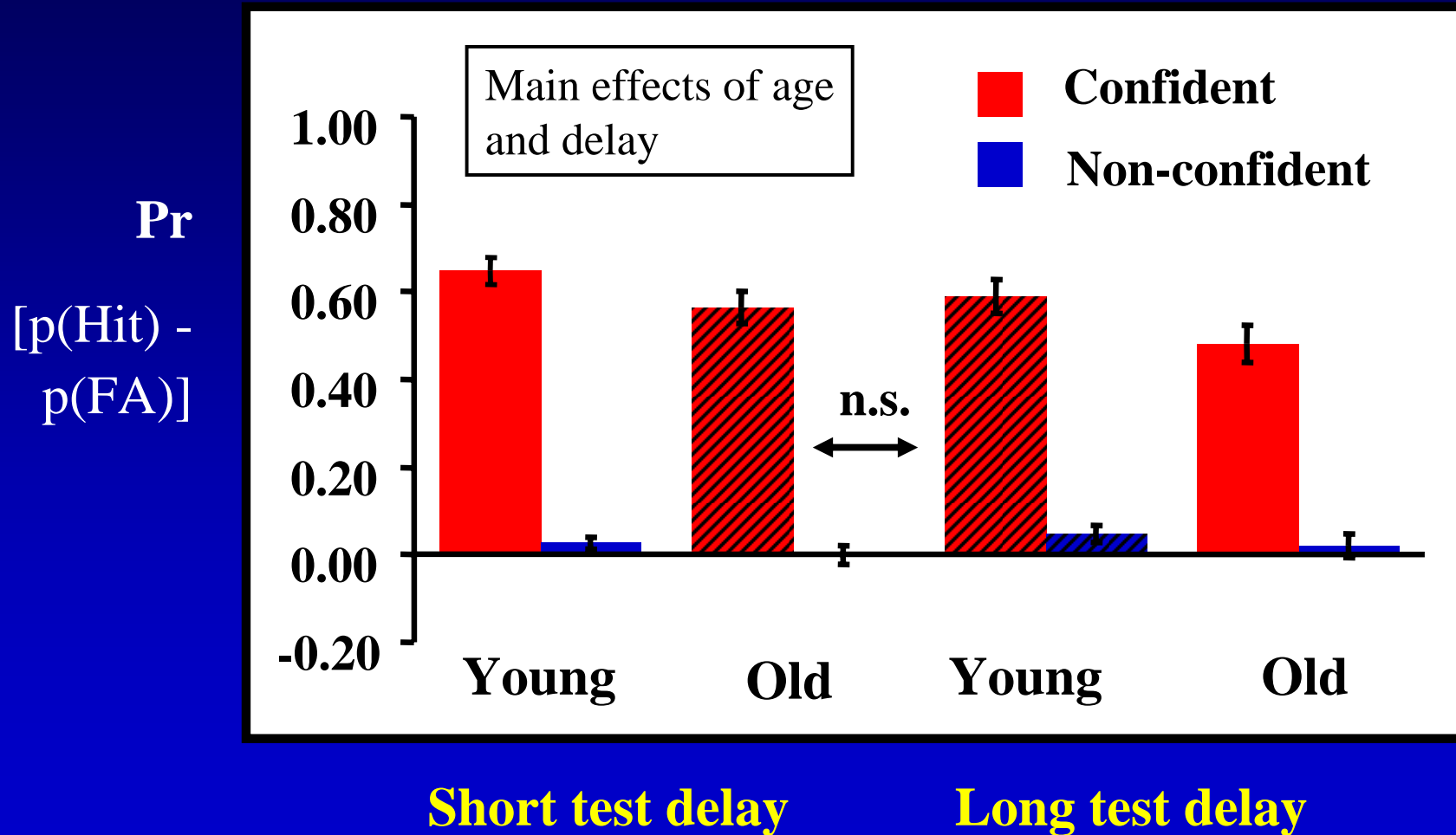
* Groups differ $p < 0.05$

** Groups differ $p < 0.01$

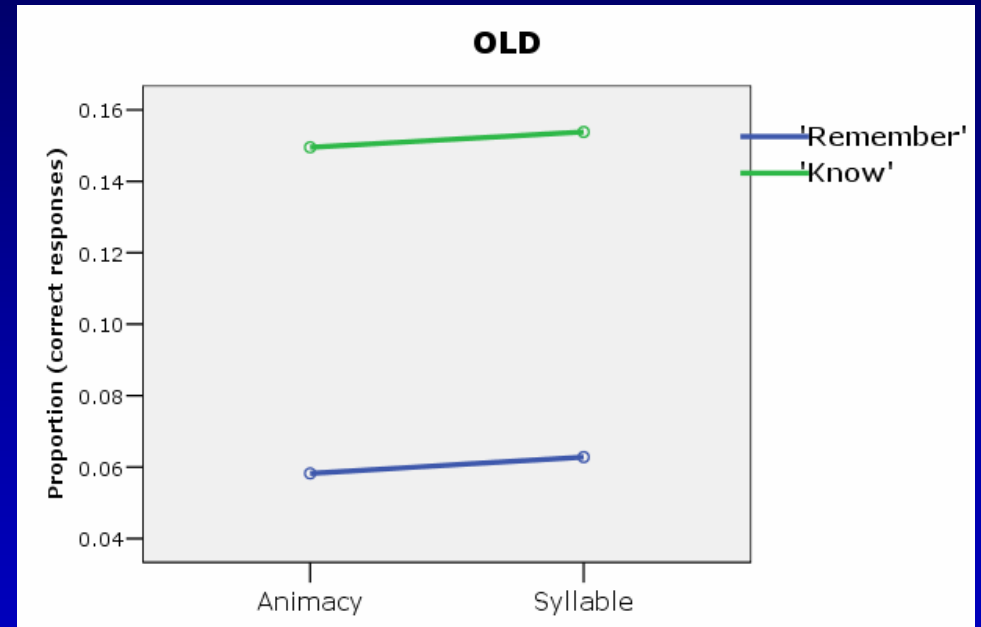
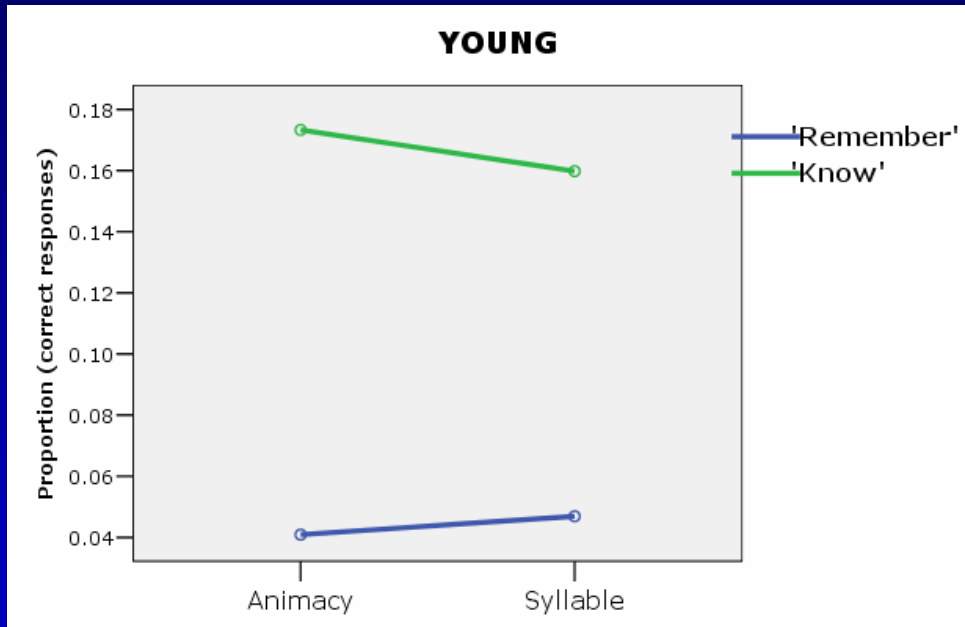
Study 1: performance



Study 1: performance



Study 2: Performance (placebo condition)



Equivalent effects of encoding task on proportions of 'remember' versus 'know' responses in young & older age groups (no effects of drug)