The Role of Dopamine in Cognitive Plasticity

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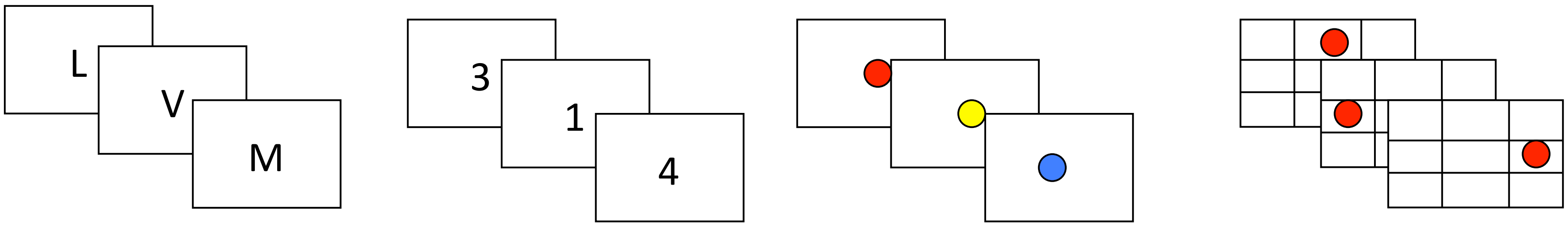
Boosting the Brain, KI, 1-2 September 2011

Executive Training in Young and Old Adults

(Dahlin et al, *Science* 2008)

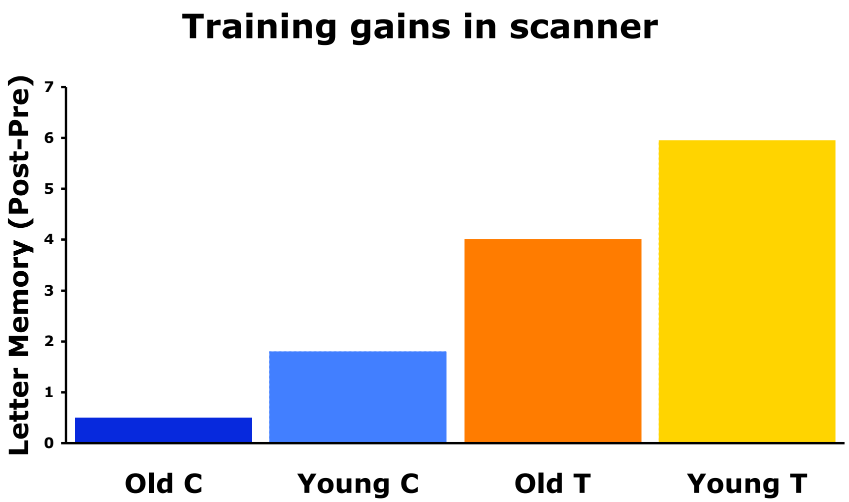
- 24 young and 22 old subjects participated
- Adaptive updating training during 5 weeks (3 sessions x 45 min per week)
- Criterion task: **letter memory**; transfer tasks: n-back and Stroop
- fMRI assessment during criterion and transfer tasks pre and post training

Training of updating



4 versions of updating tasks
Always memorize the last 4 items; report
Adaptive training; increasingly longer lists
Variable list length — 5-15 items
3 levels; all at level 3 week 5

Cognitive and Brain Plasticity



Cognitive and Brain Plasticity

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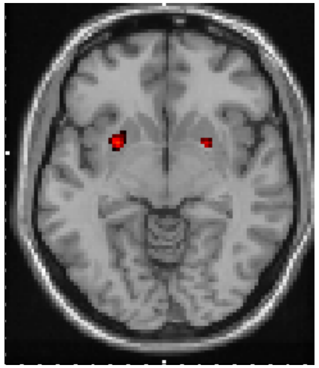

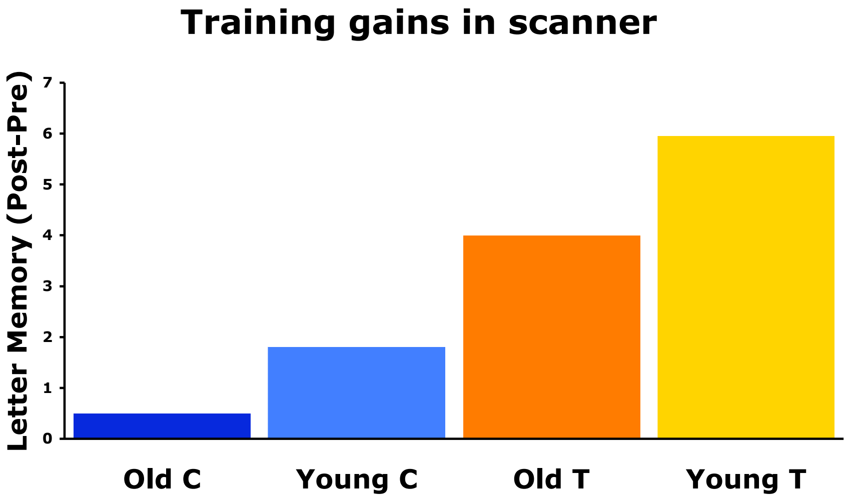

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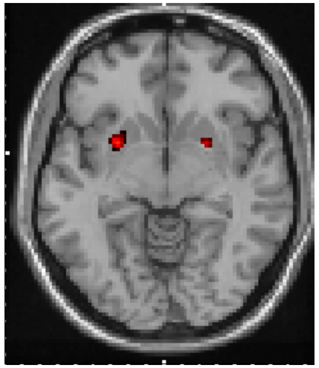

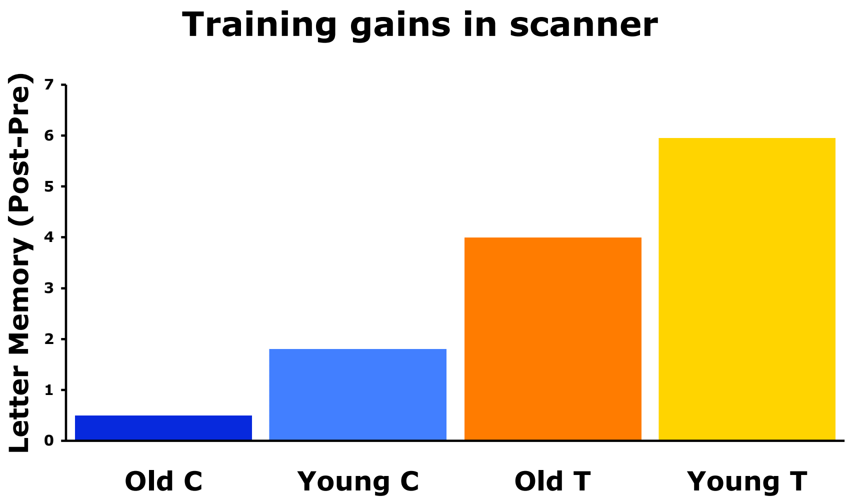

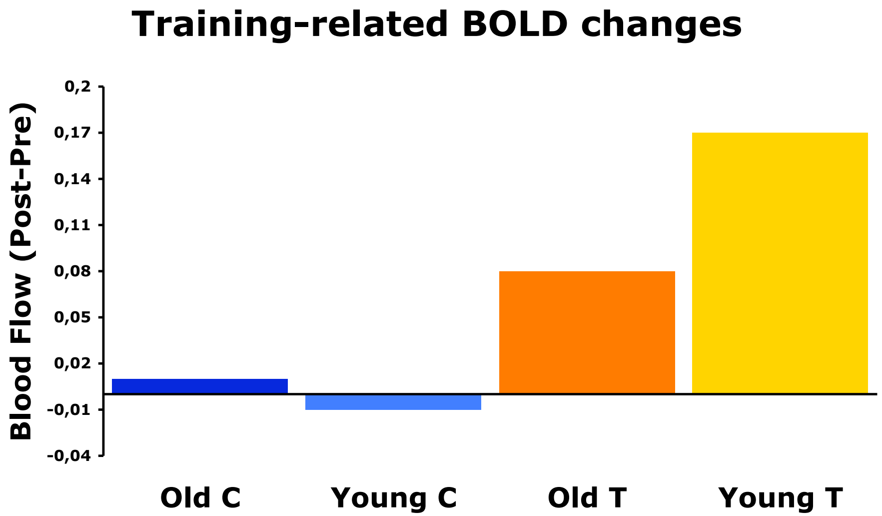

The Caudate and Working Memory

McNab et al. (2004), *Nat Neurosci*, WM training

Dodds et al. (2009), *Psychopharmacology*, DA D2 antagonist

Murty et al. (2011), *Neuroimage*, new WM task

The Functional Significance of Training-Related Increases in Caudate BOLD Signal

(Brehmer et al, *Neuroimage* 2011)

- Five weeks of WM training in older adults using the Klingberg et al. (2002) training regimen

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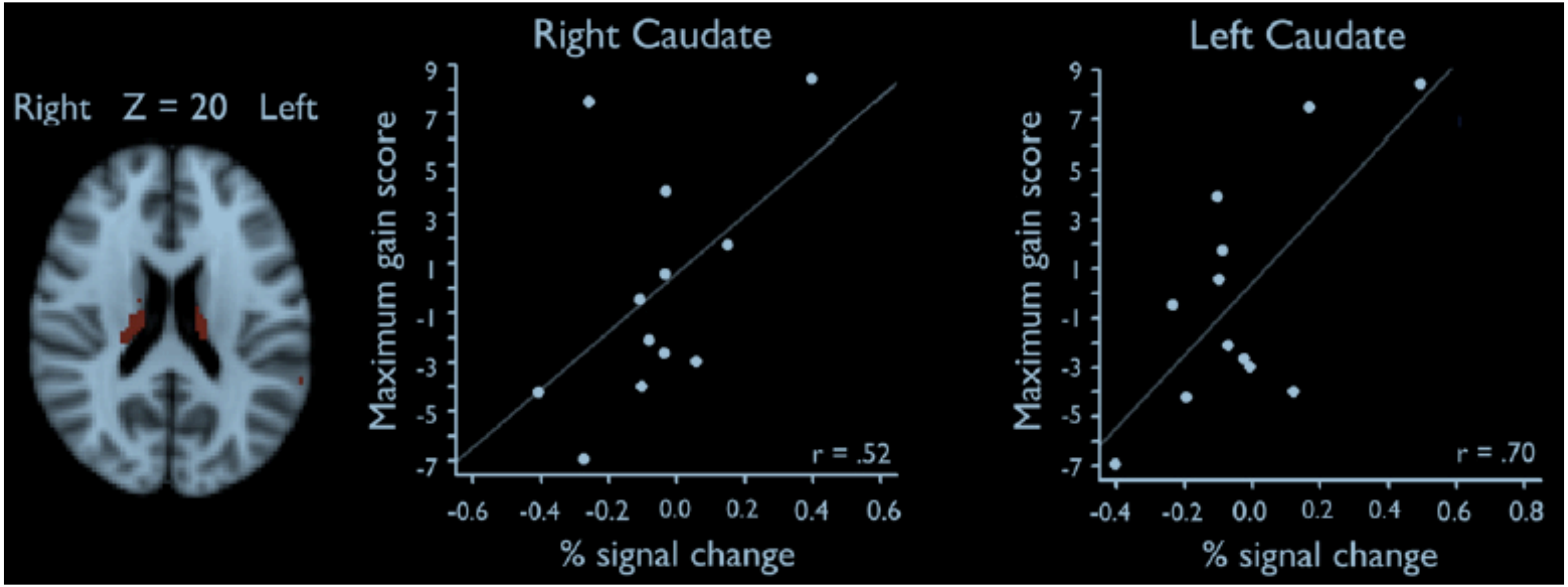
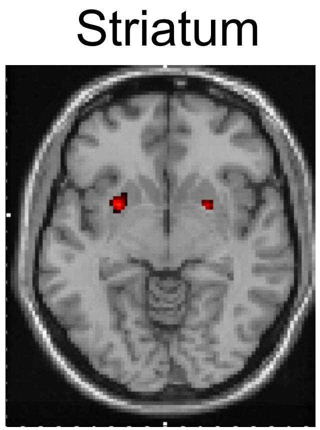
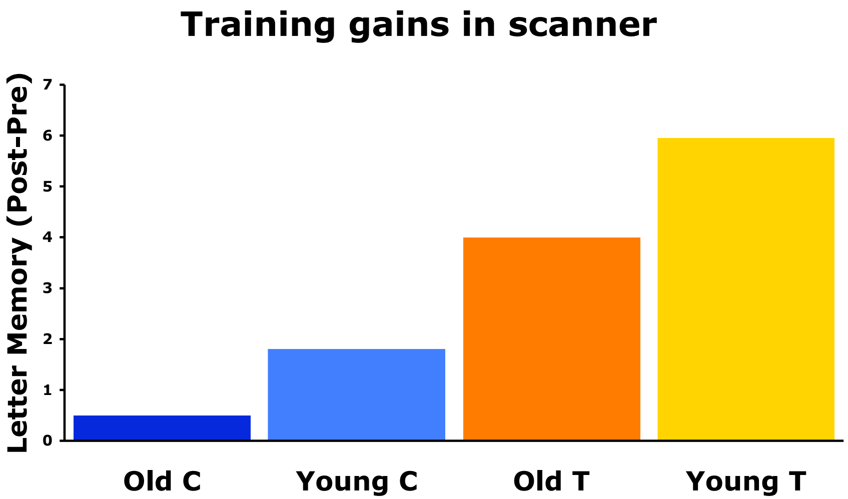
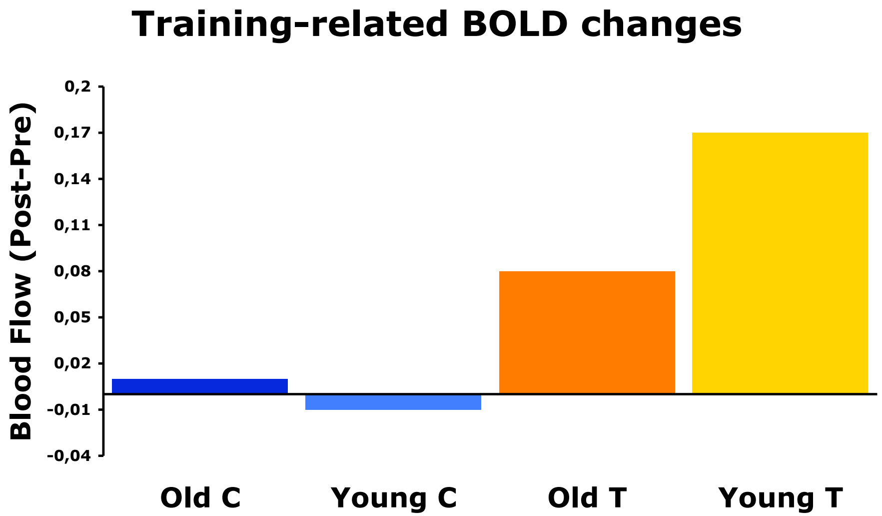


Cognitive and Brain Plasticity



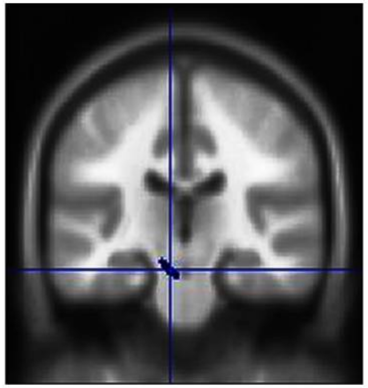




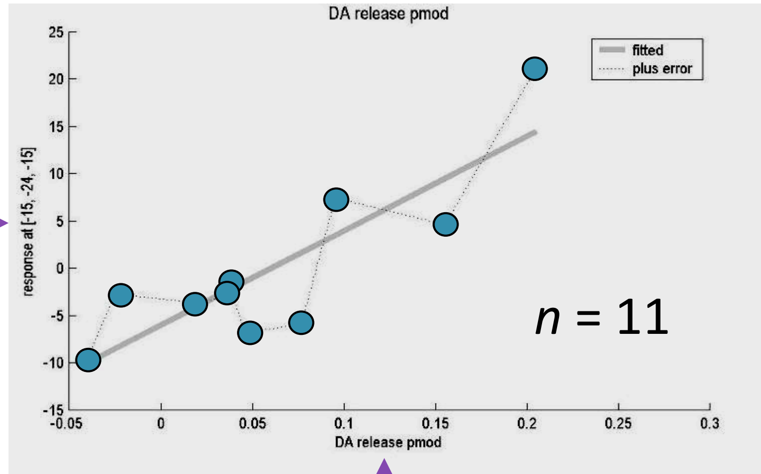
fMRI and PET during reward-related learning

Schott et al, *J Neurosci* 2008

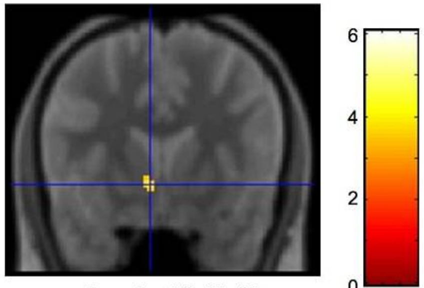
fMRI



[x y z] = [-7 -23 -18]

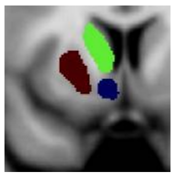


PET



[x y z] = [-6 10 -6]
T = 4.96

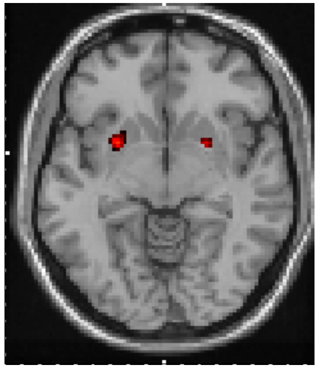
SPM{T_{10}}

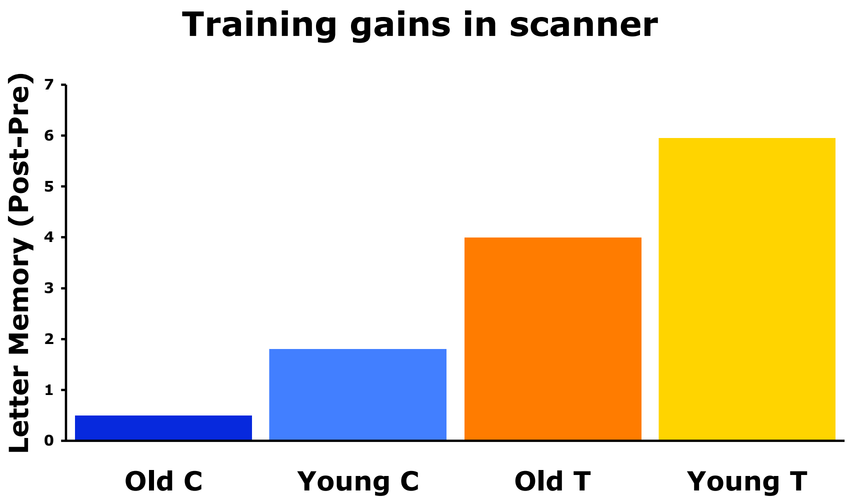


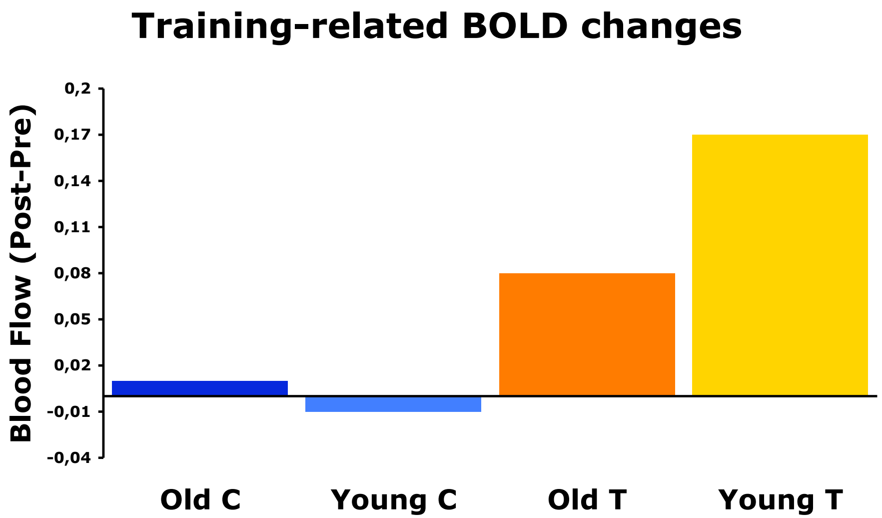
[11C] raclopride displacement

Cognitive and Brain Plasticity

Striatum







Is the enhanced striatal BOLD signal post training associated with an increased release of DA?

Genetics and WM Plasticity: A Detour

- The potential influence of dopamine-related genes on the ability to benefit from WM training

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- The potential influence of dopamine-relevant genes on the ability to benefit from WM training

- Could effects of allelic variations be easier to detect closer to the performance maximum?

The DAT1 Gene

- Homozygosis for the 10-repeat allelle is most common (60%); 30% are heterozygotic (9/10), and less than 10% are homozygotic for the 9-repeat allele

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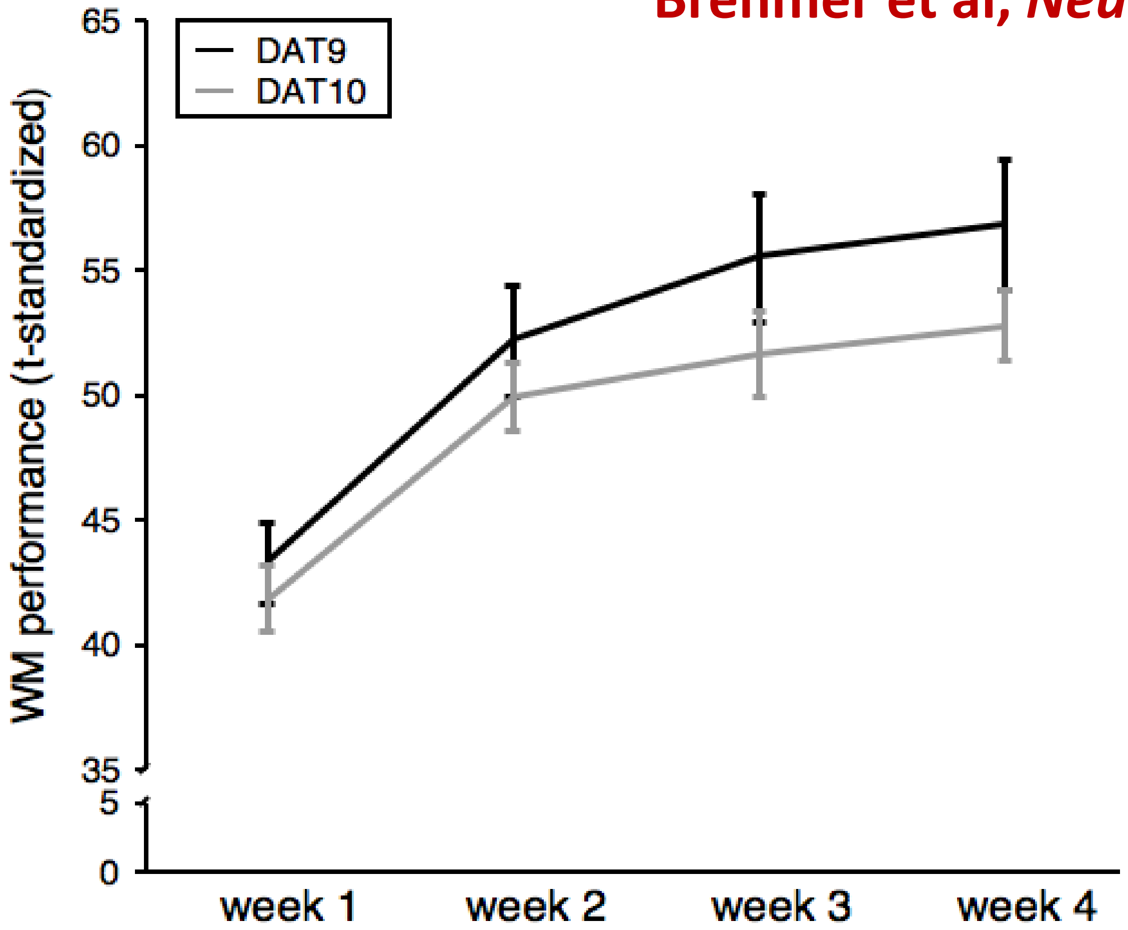
- Greater DAT availability among 10-repeat carriers might translate into lower extrasynaptic dopamine levels

WM plasticity and the DAT1 gene

Brehmer et al, *Neurosci Lett* 2009



- No baseline differences between DAT9 and DAT10 carriers
- DAT9 carriers profit more from training than DAT10 carriers
- No genotype differences on any task in a large NP battery

The LMX1A Gene

- LMX1A is a transcription factor that is critical to the proliferation, differentiation, and maintenance of dopamine-producing neurons in midbrain

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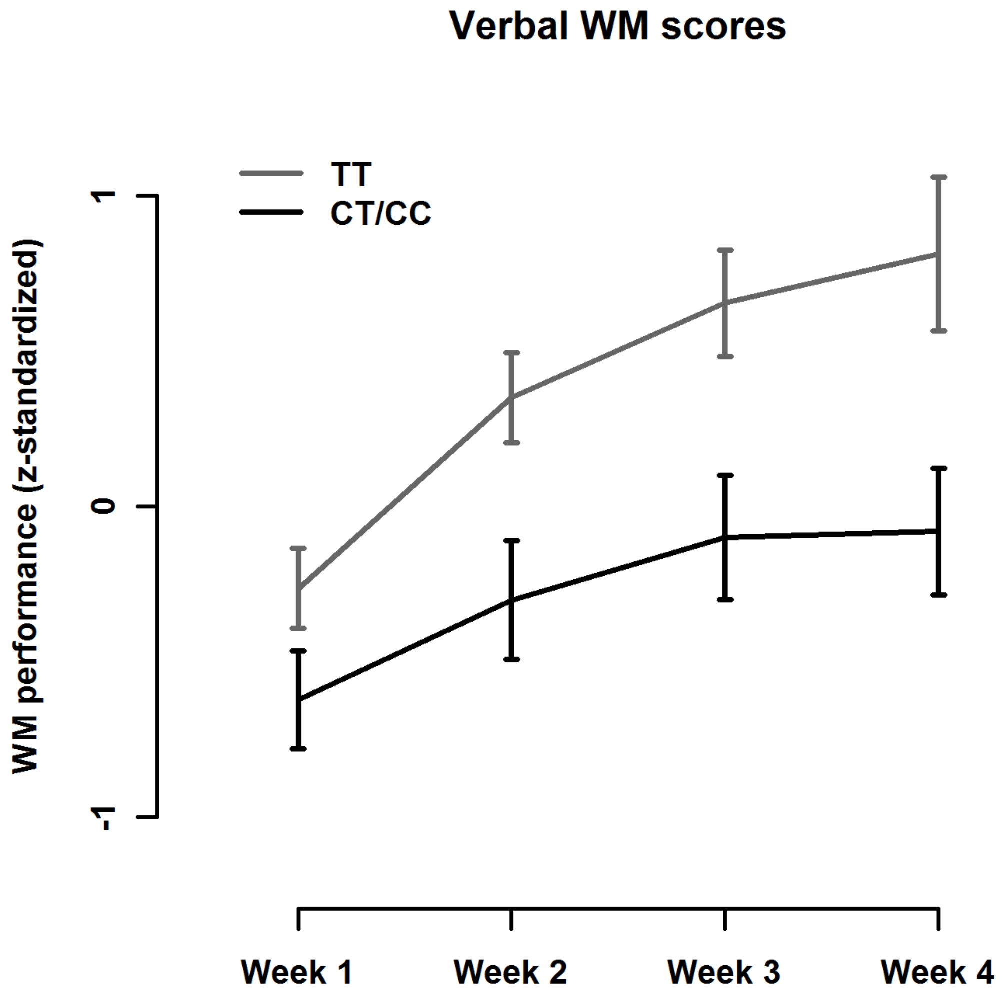
- The LMX1A gene involves 37 SNPs!
- A single study (Bergman et al., 2009; *J Neural Transm*) showed that three LMX1A SNPs are related to PD risk

Bellander et al, *Neuropsychologia* 2011



- No baseline differences between TT and CT/CC carriers
- TT carriers profit more from training than CT/CC carriers
- No genotype differences on any task in a large NP battery

Cognitive and Brain Plasticity

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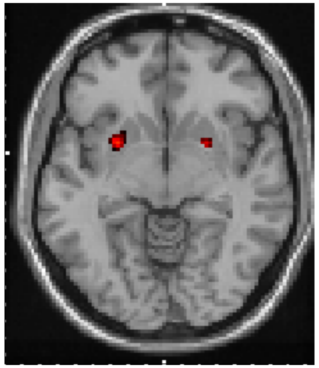
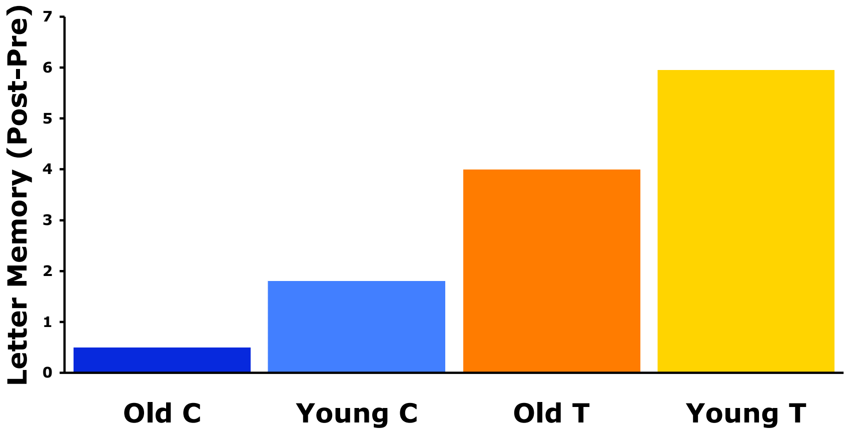
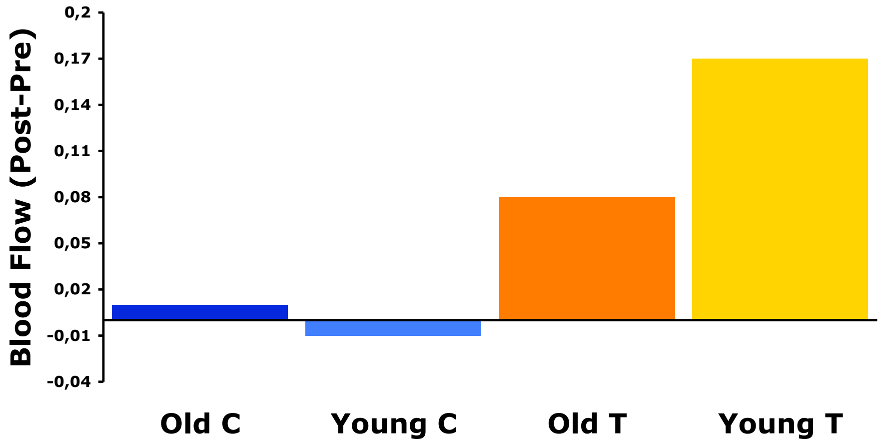


Training gains in scanner



Training-related BOLD changes



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Raclopride – Radioligand for Striatal D2 Receptors

- Of all DA ligands available, raclopride has most consistenly been related to DA release

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- Of all DA ligands available, raclopride has most consistenly been associated with DA release
- Updating is related to transient neural processes linked to striatal D2 receptors

The bolus-plus-infusion technique; Bäckman et al, *Science* 2011

-the tracer (raclopride) is administered as a bolus followed by constant infusion to achieve equilibrium between blood and brain tissue

-the B/I method enables direct measurement of receptor occupancy changes in vivo

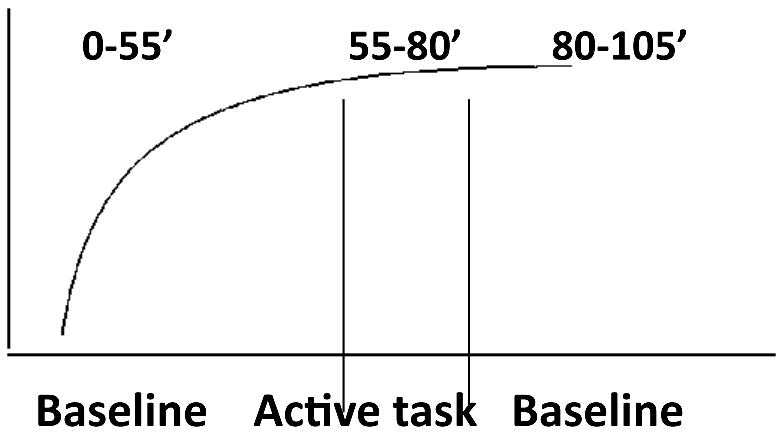
-by maintaining constant plasma radioactivity levels during the stimulus, any confounding effects of dynamic flow changes can be minimized

Baseline: 0-55 minutes post bolus injection performing a task that is similar to the active task but does not tax WM

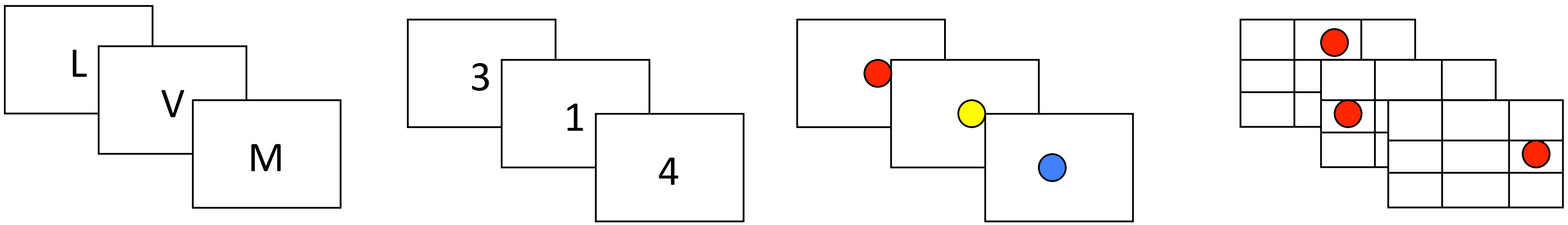
Active task: 55-80 minutes performing a demanding WM updating task (letter memory)

Back to the baseline task for 25 minutes

Task phases and schematic time-activity curve for the tracer



Training of updating



4 versions of updating tasks

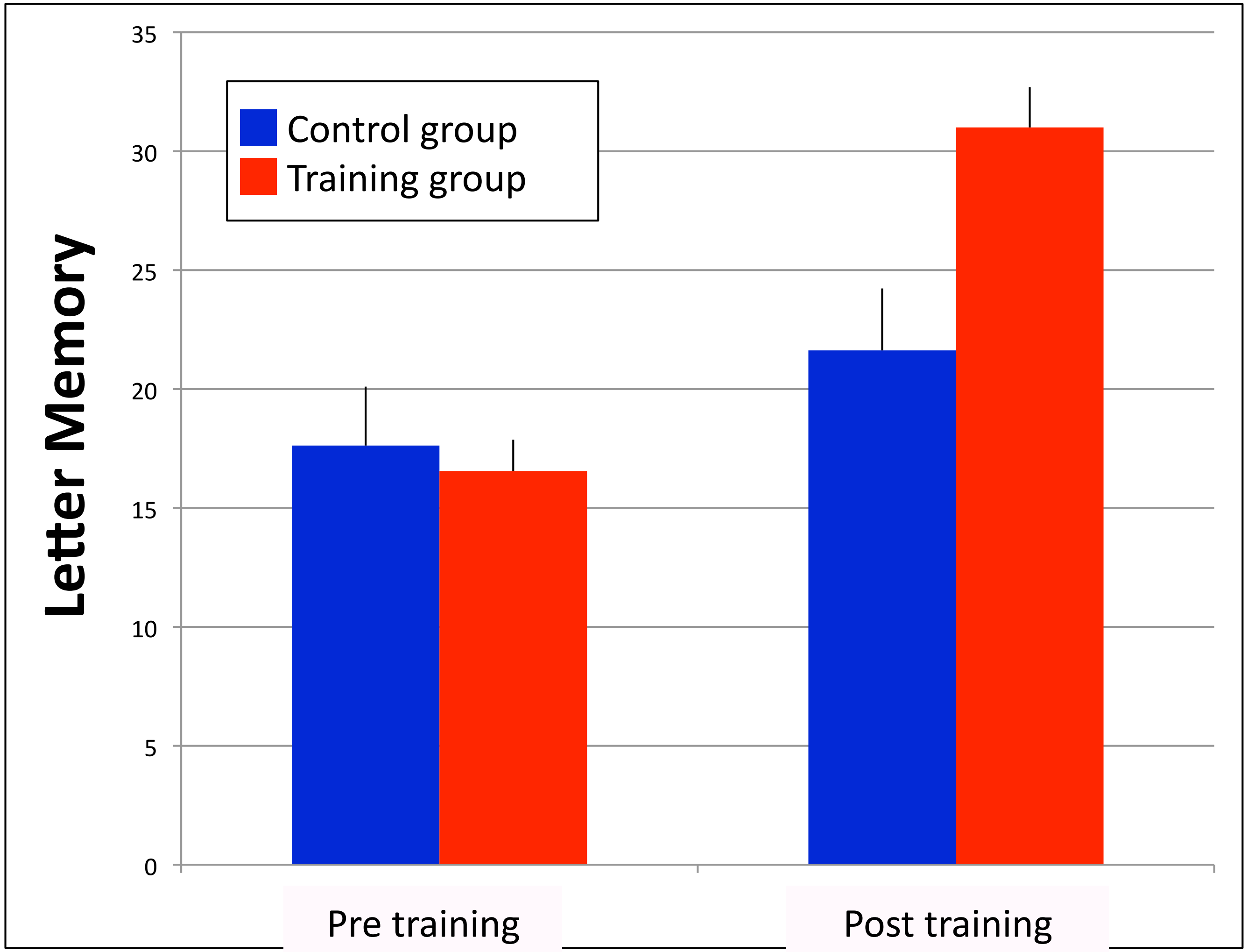
Always memorize last 4 items; report

Adaptive training, increasingly longer lists

Variable list length — 5-15 items

3 levels; all at level 3 week 5

Behavioral Performance



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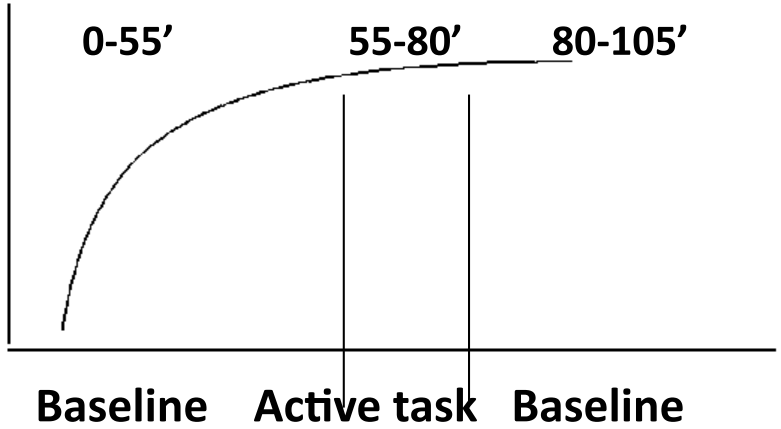
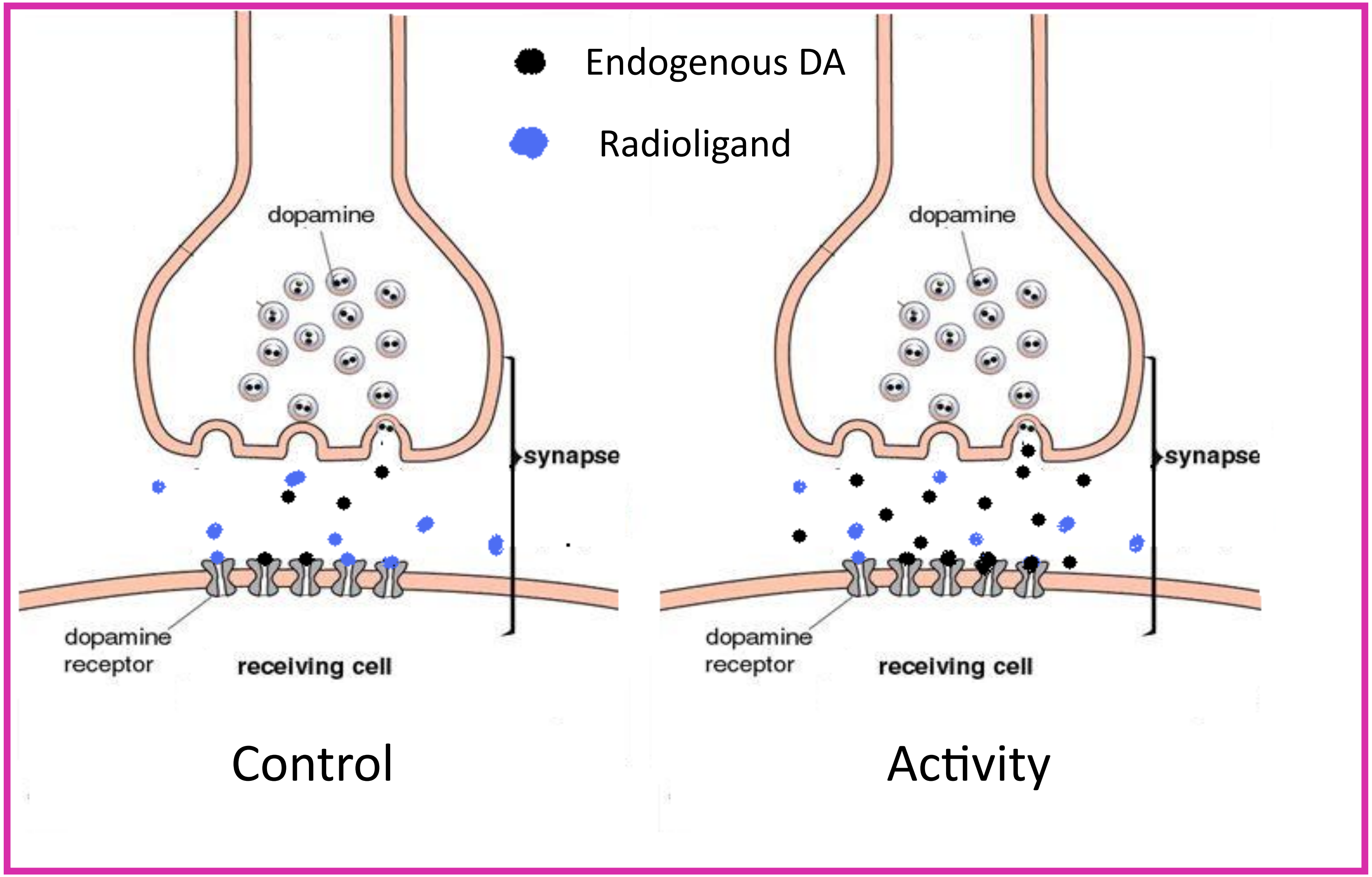


Competition or Displacement Principle



Modulation of DA Binding by Cognitive Activity

Aalto et al. (2005), *J Neurosci*, n-back

Christian et al. (2006), *Neuroimage*, SWM

Monchi et al. (2006), *Neuroimage*, card sorting

Badgaiyan et al. (2007), *Neuroimage*, sequential learning

Garraux et al. (2007), *J Neurosci*, sequential learning

Sawamoto et al. (2008), *Brain*, SWM

Karlsson et al. (2009), *Neuroimage*, interference resolution

Ko et al. (2009), *Neuroimage*, card sorting

Two Predictions

- Increased DA release (i.e., lower D2 binding potential) during updating compared to control task (irrespective of training)

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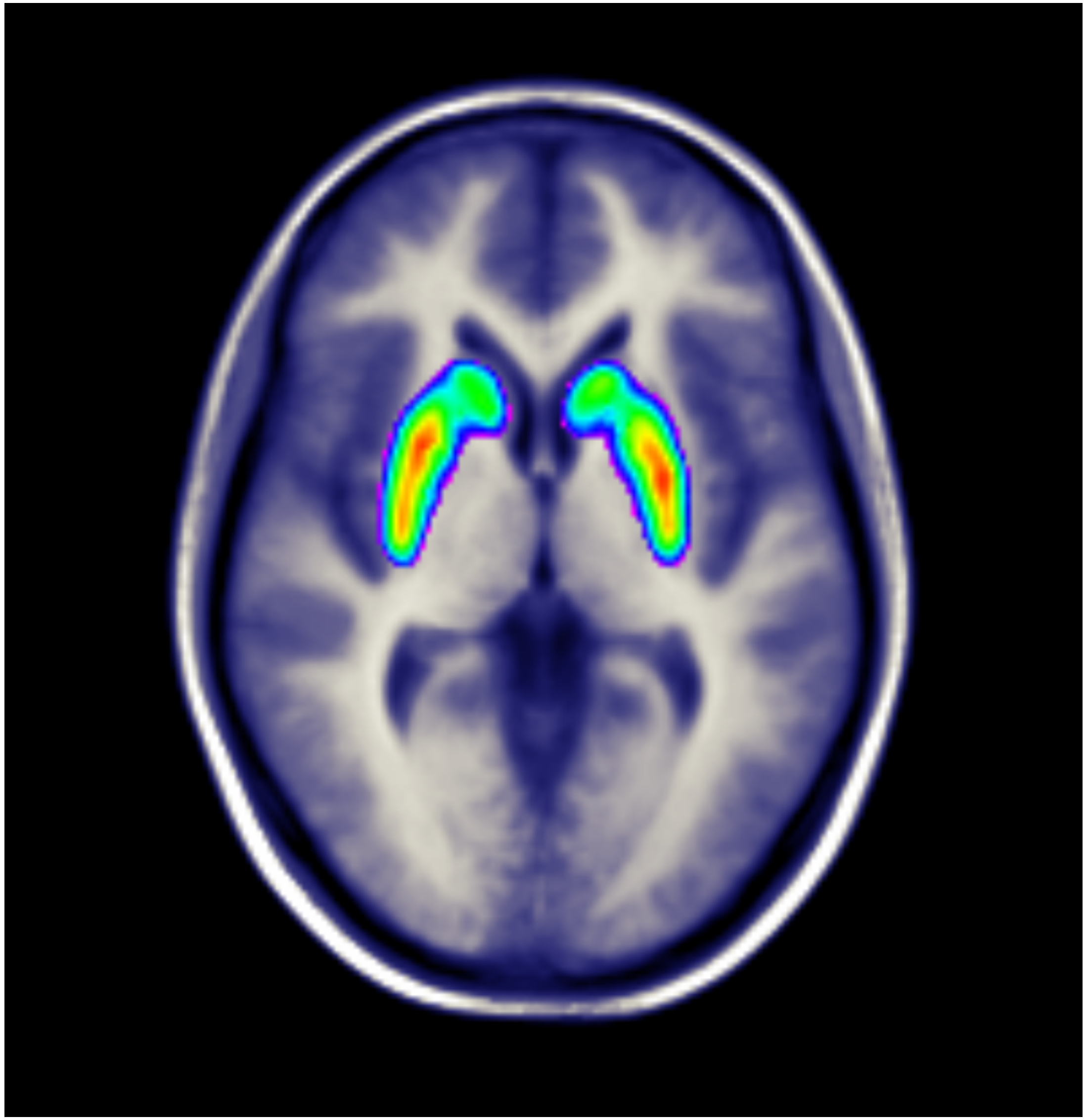
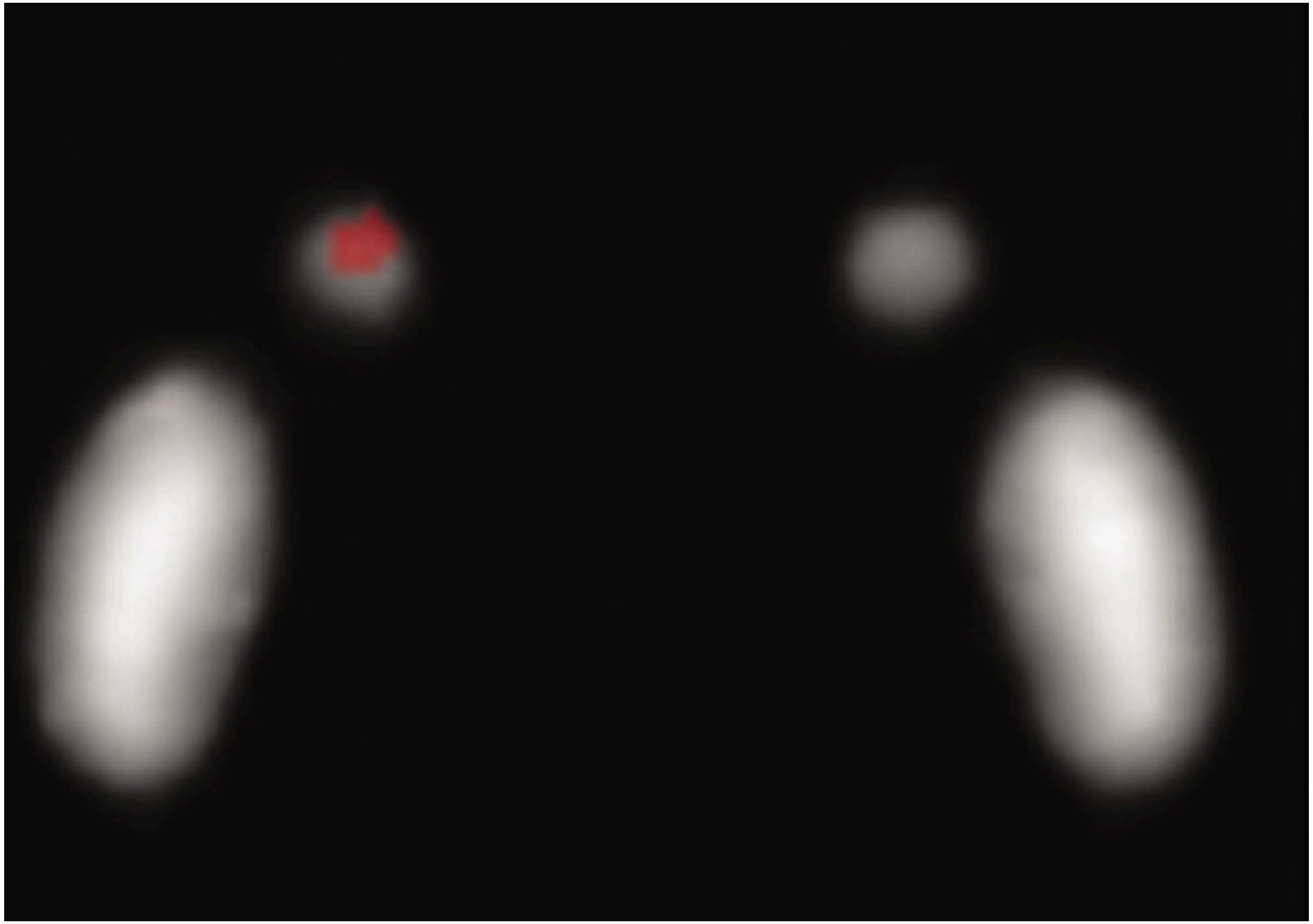
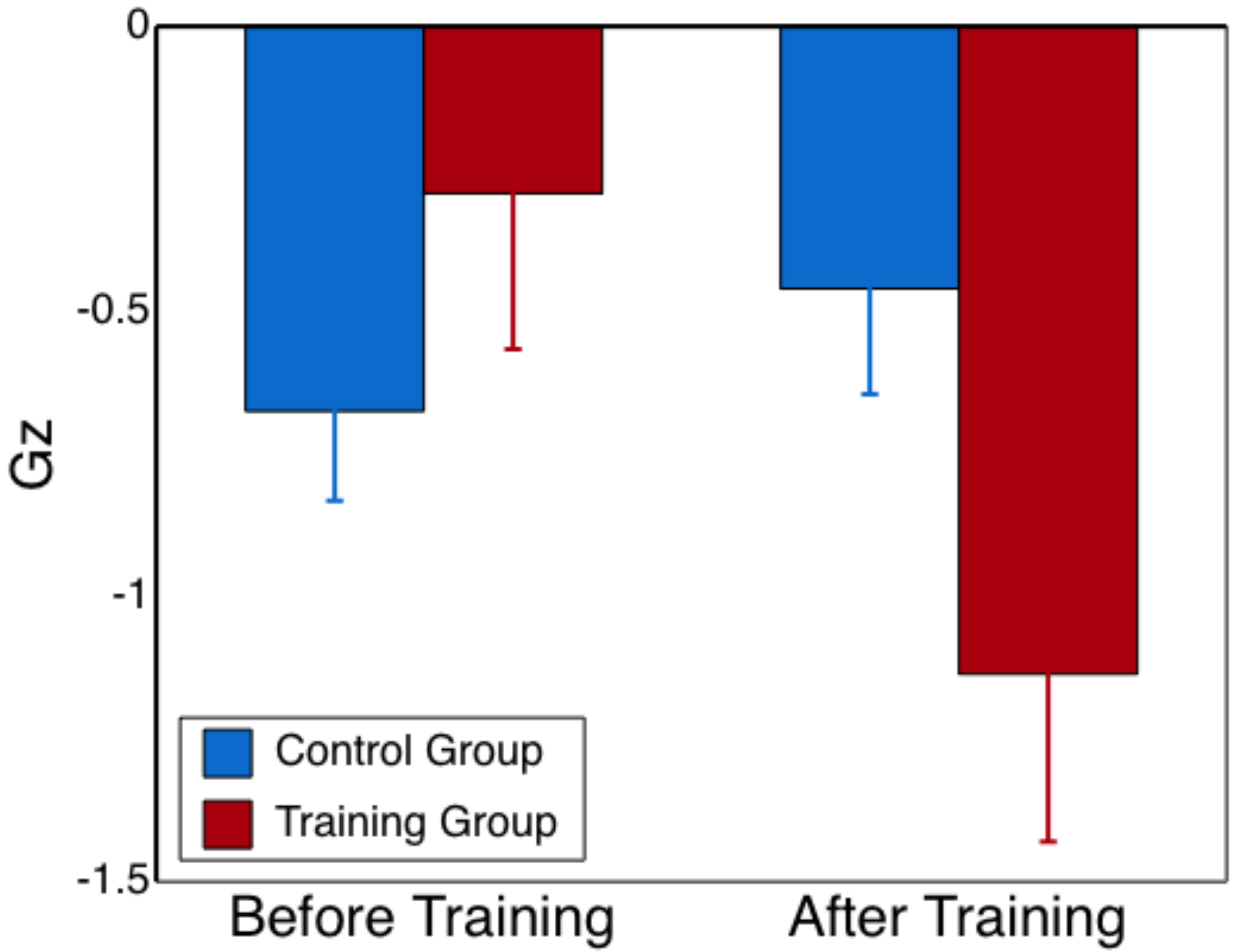
- An additional training-related boost in DA release

DA Release During Updating Before Training



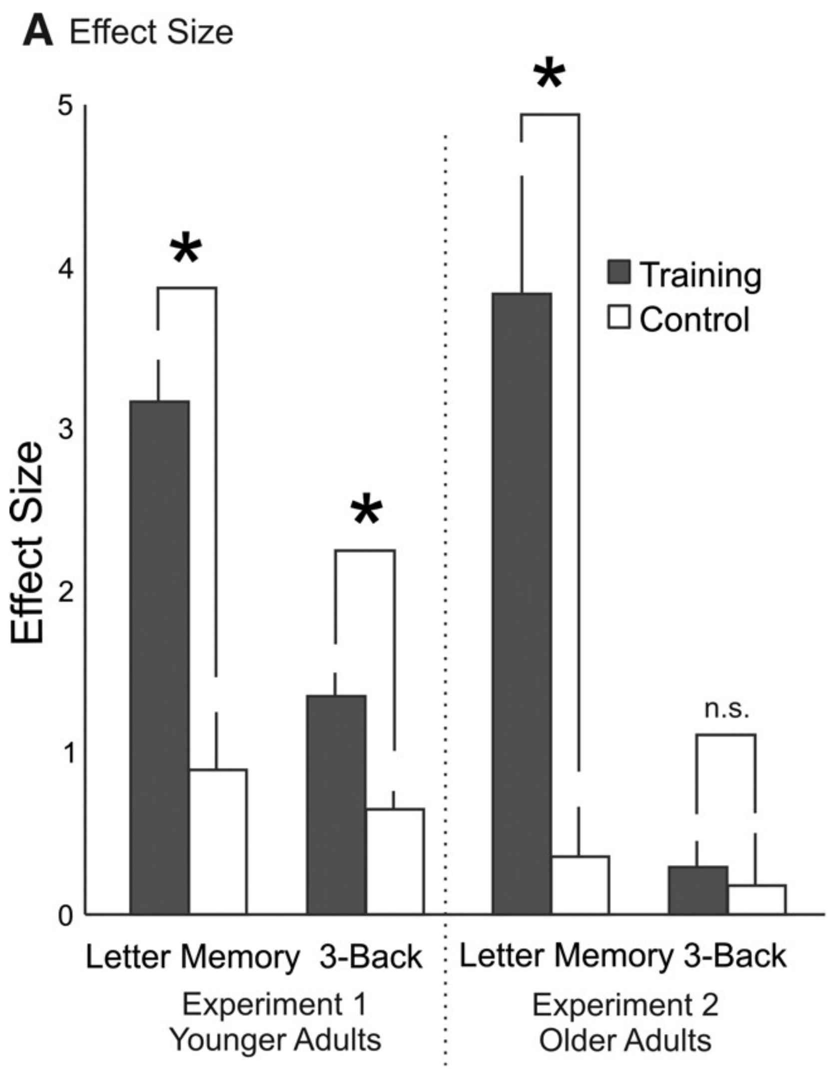



0
-0.5
-1
-1.5
Gz
Control Group
Training Group
Before Training
After Training

Transfer in Dahlin et al. (2008)

- The young showed selective transfer to a structurally dissimilar n-back task that also taxes updating, the old did not (data replicated by Bäckman et al, 2011)

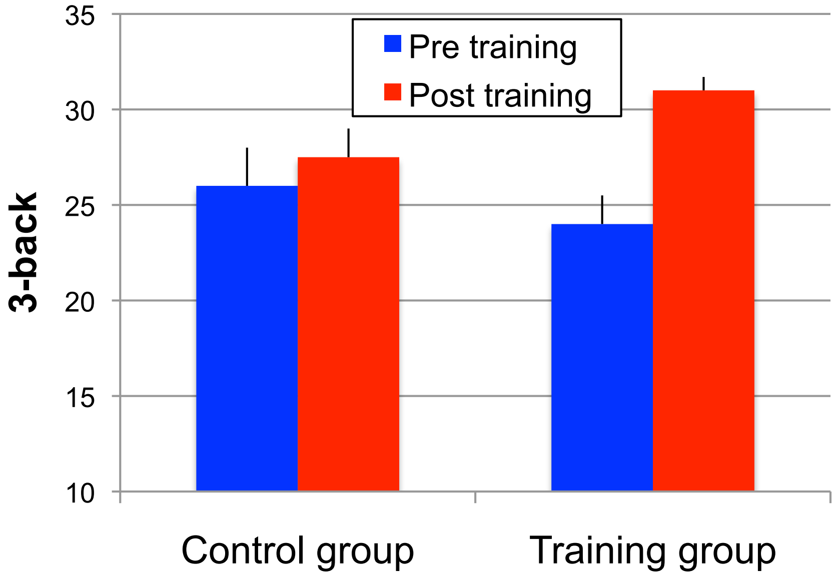
Fig. 1. (A) Letter memory and 3-back performance for training and control groups.



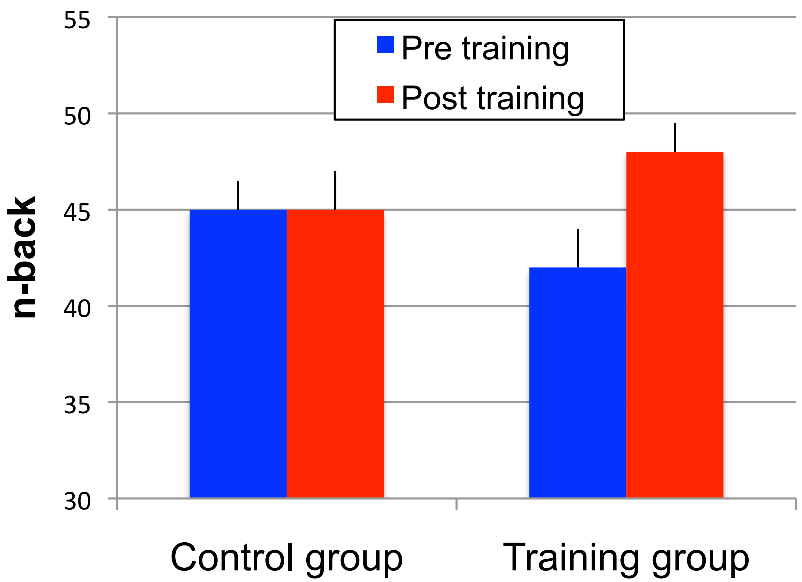
E Dahlin et al. Science 2008;320:1510-1512

Published by AAAS

Dahlin et al, 2008



Bäckman et al, 2011



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- Letter memory – 3-back differences: memorial content, set size, task pacing, response format; brain activation differences before and after training

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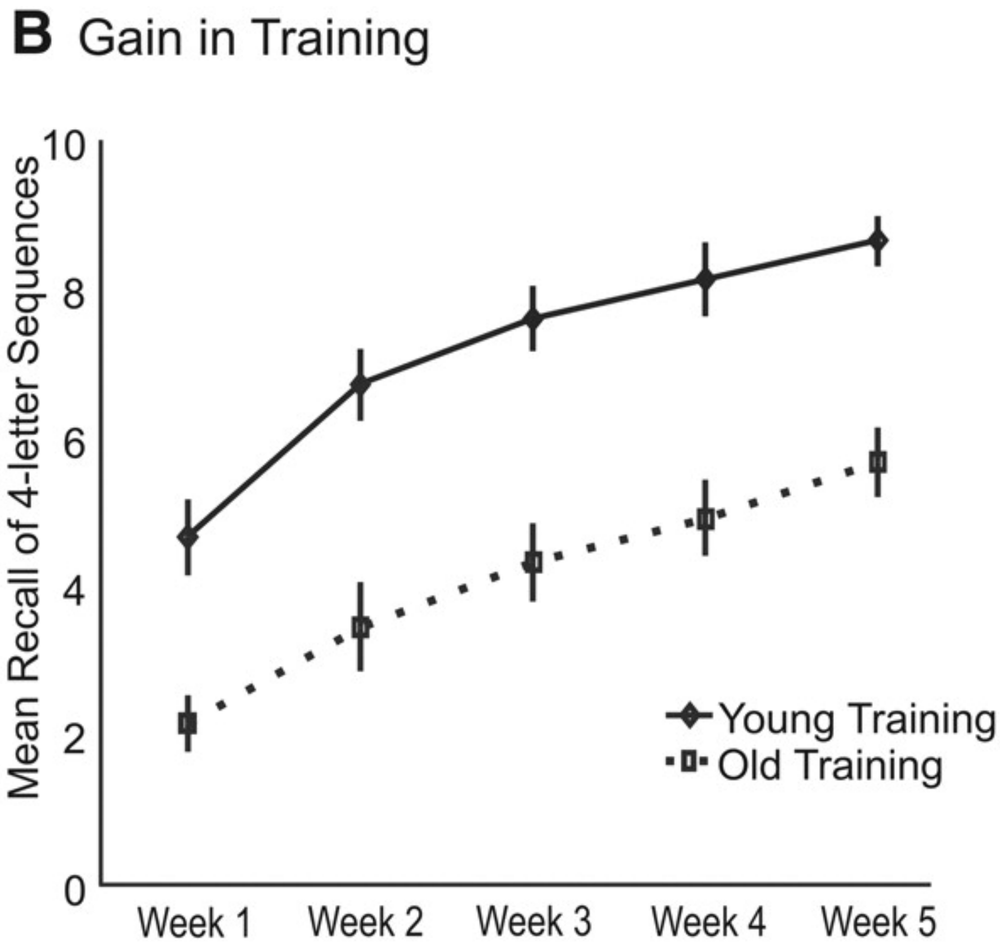
- Letter memory – 3-back differences: memorial content, set size, task pacing, response format; brain activation differences before and after training

- There were overlapping baseline and training-related increases in striatal (caudate) BOLD activity for the young during letter memory and 3-back – a neural substrate of transfer?

Fig. 1. (B) Training-related gains in young and old adults across time



E Dahlin et al. Science 2008;320:1510-1512

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The future?

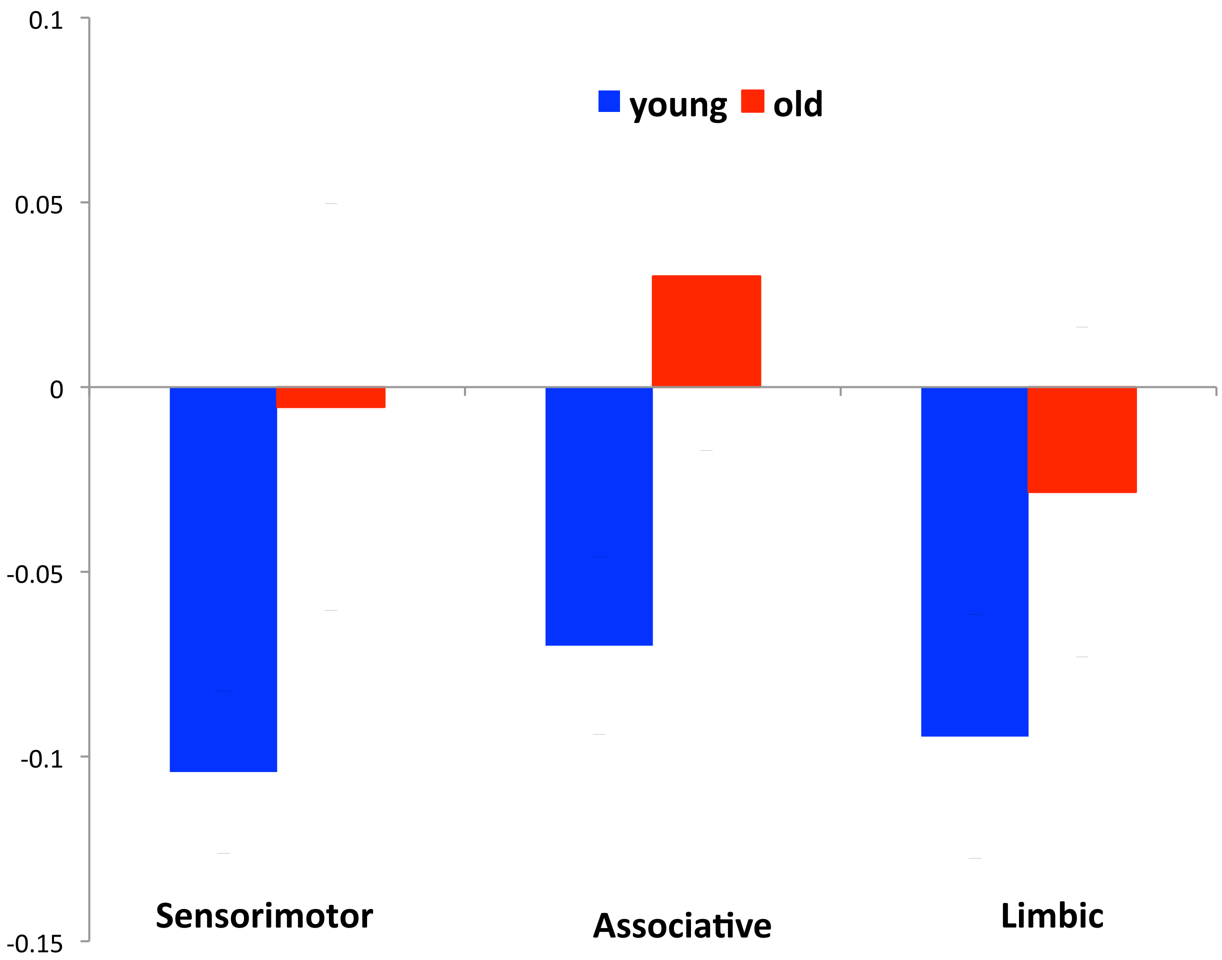
- Is this what there is?

The future?

- Is this what there is?
- Aging

Age-related differences in DA release during a cognitive challenge

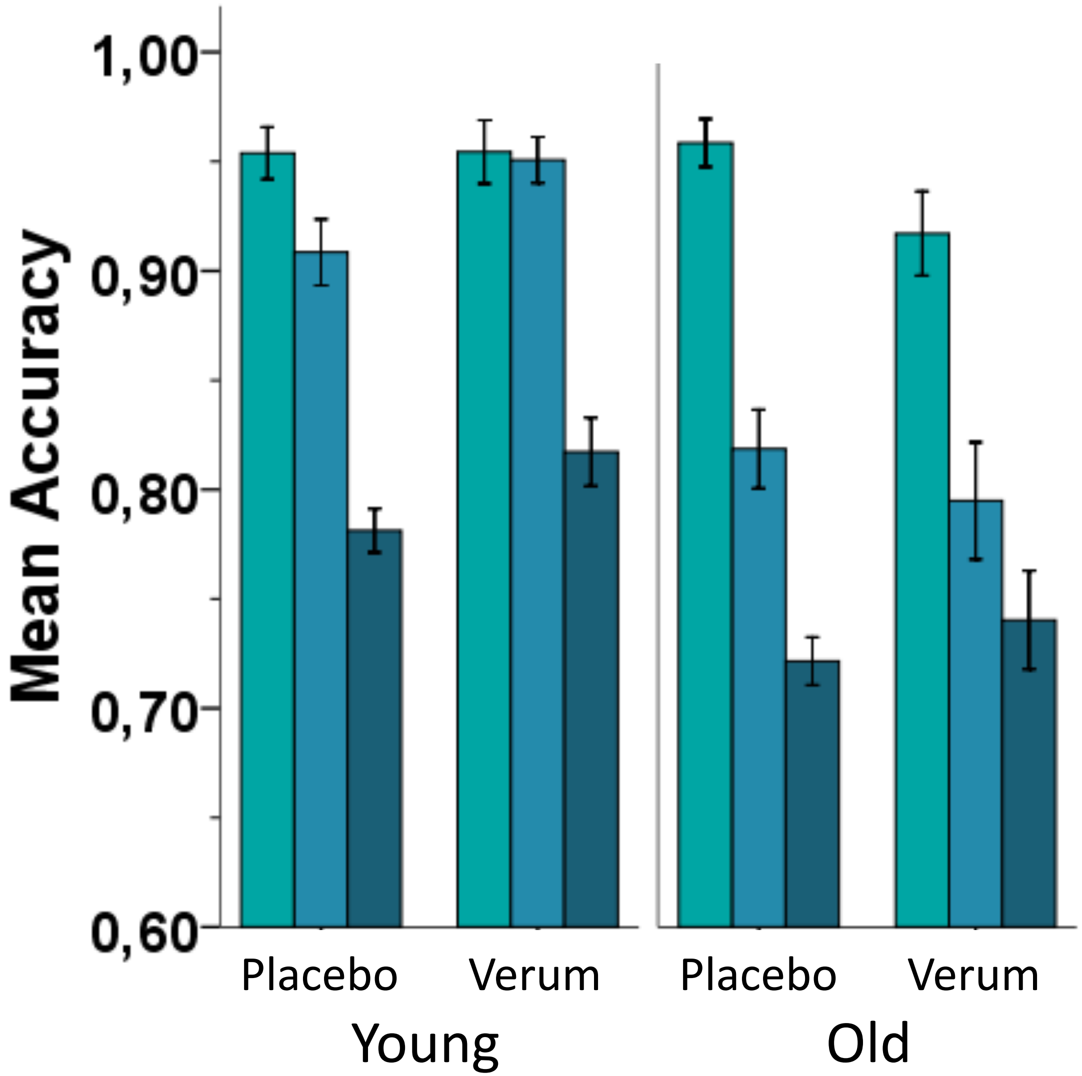
(Karlsson et al, *Neuroimage* 2011)



Large-Scale Study on Amphetamine and WM
(Lindenberger et al, 2011)

- The young showed drug-related improvement in both verbal and spatial WM, the old did not

N-Back Performance by Age, Medication, and Load



Large-Scale Study on Amphetamine and WM
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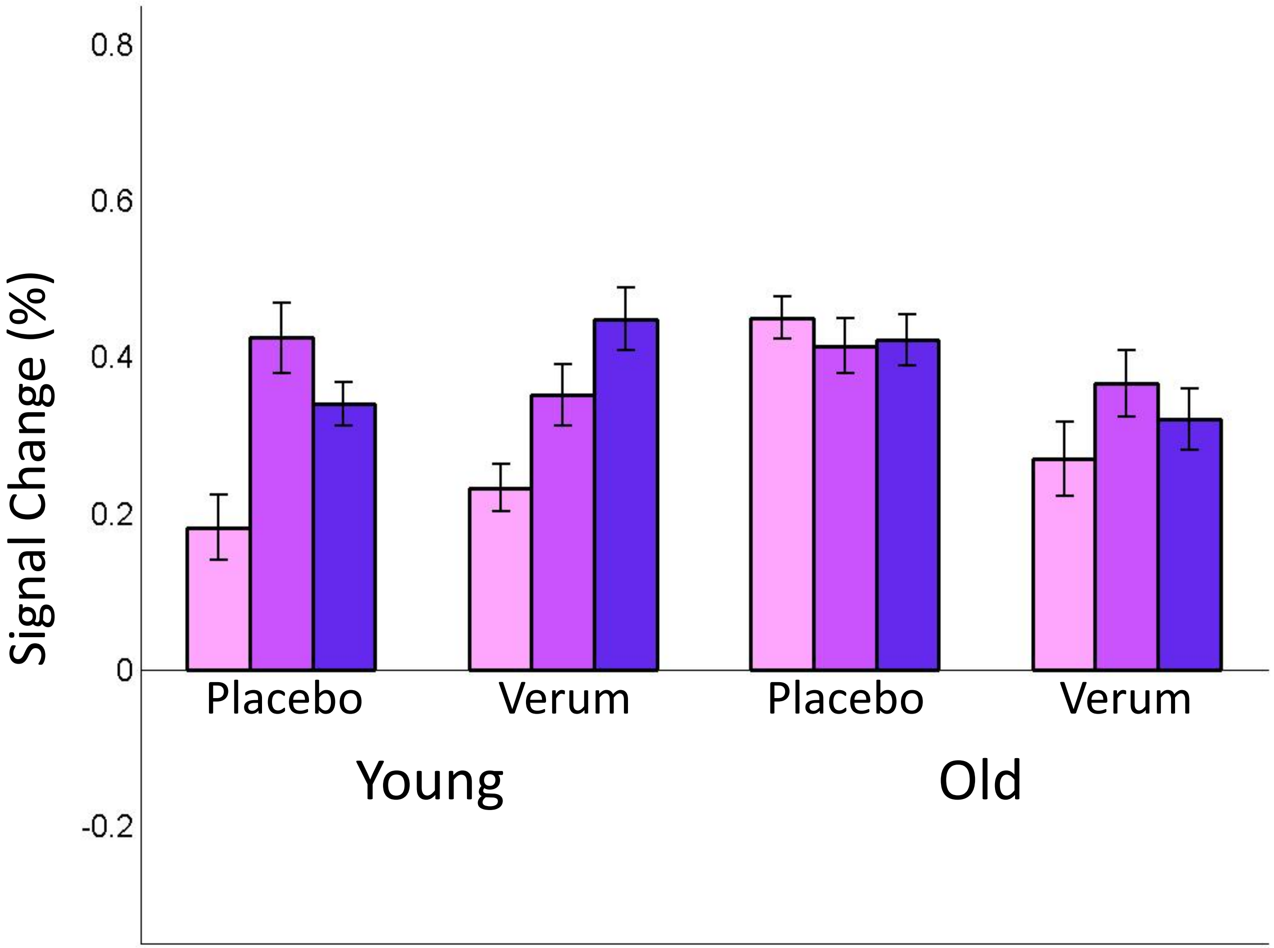
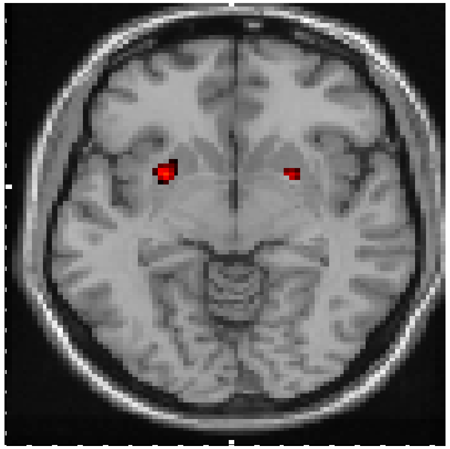
- The young showed drug-related improvement in both verbal and spatial WM, the old did not

- The young also exhibited a drug-related sharpening of the load-dependent BOLD signal, the old did not

Left PPC: BOLD Responsivity to Load

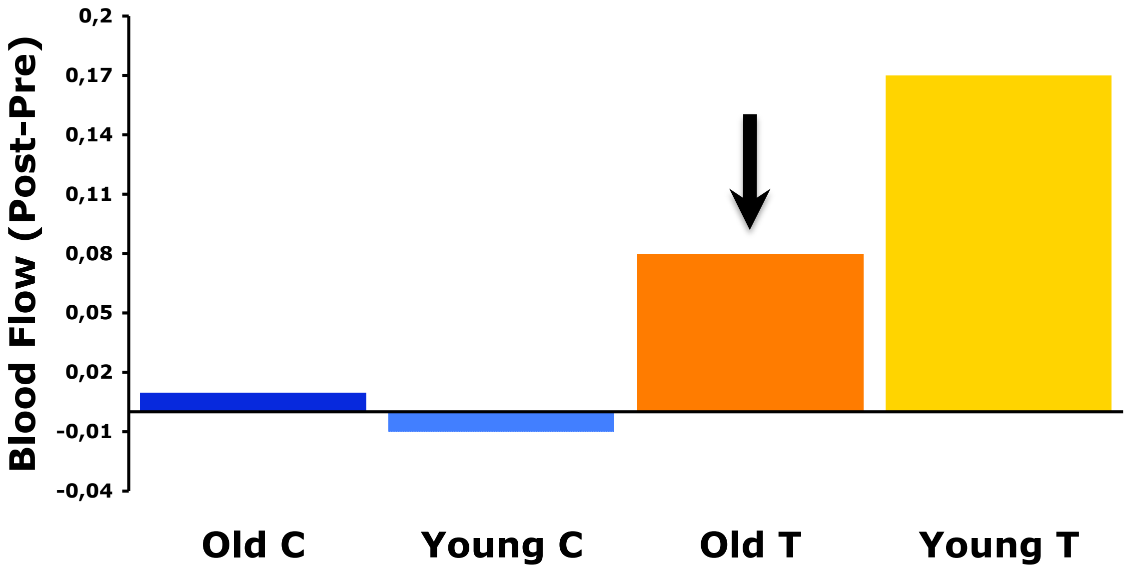


Striatum



Dahlin et al, *Science* 2008

Training-related BOLD changes



The future?

- Is this what there is?
- Aging
- Neurochemical correlates of transfer

The future?

- Is this what there is?
- Aging
- Neurochemical correlates of transfer
- DA release after training of other WM functions (e.g., switching, inhibition)

Key Collaborators

Lars Nyberg, **Medical Biology**, **Umeå University**
Micael Andersson, **Medical Biology**, **Umeå University**
Anna Stigsdotter Neely, **Psychology, Umeå University**
Erika Dahlin, **Medical Biology**, **Umeå University**

Yvonne Brehmer, **Aging Research Center, KI**
Martin Bellander, **Aging Research Center, KI**
Anna Rieckmann, **Aging Research Center, KI**
Sari Karlsson, **Aging Research Center, KI**
Håkan Fischer, **Aging Research Center, KI**
Helena Westerberg, **Aging Research Center, KI**

Matti Laine, **Psychology, Åbo Akademi University**
Anna Soveri, **Psychology, Åbo Akademi University**
Juha Rinne, **Neurology, Turku University**
Jarkko Johansson, **Neurology, Turku University**
Jere Virta, **Neurology, Turku University**

Ulman Lindenberger, **MPI, Berlin**
Hauke Heekeren, **Free University, Berlin**
Shu-Chen Li, **MPI, Berlin**