

Caregiver Stress, Cognitive Function and Alzheimer's Disease

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Pertl et al (in prep)

- 205 Irish spousal caregivers of people with dementia followed up over 18 months
- 79.3%, 199/252) rated their current emotional/mental health as 'good', 'very good', or 'excellent'.
- Over 18 months, significant drop in executive function, visual memory and processing speed
- No relationship whatsoever between stress levels and these changes in cognitive function.



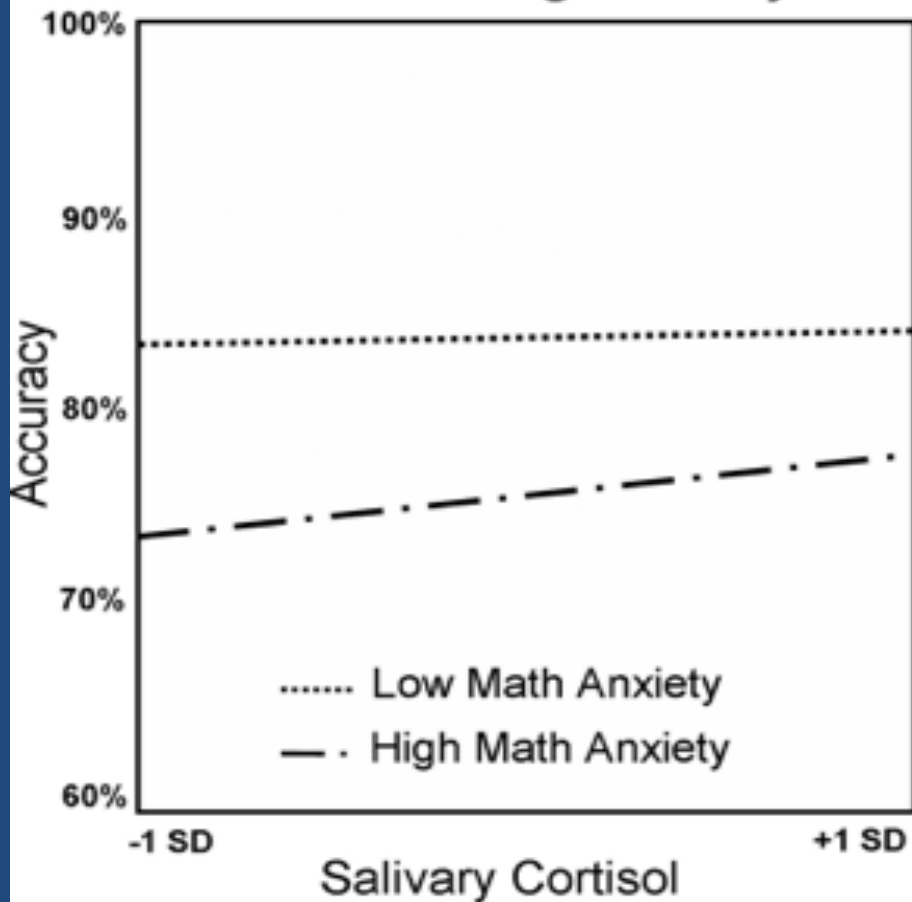


Question 1

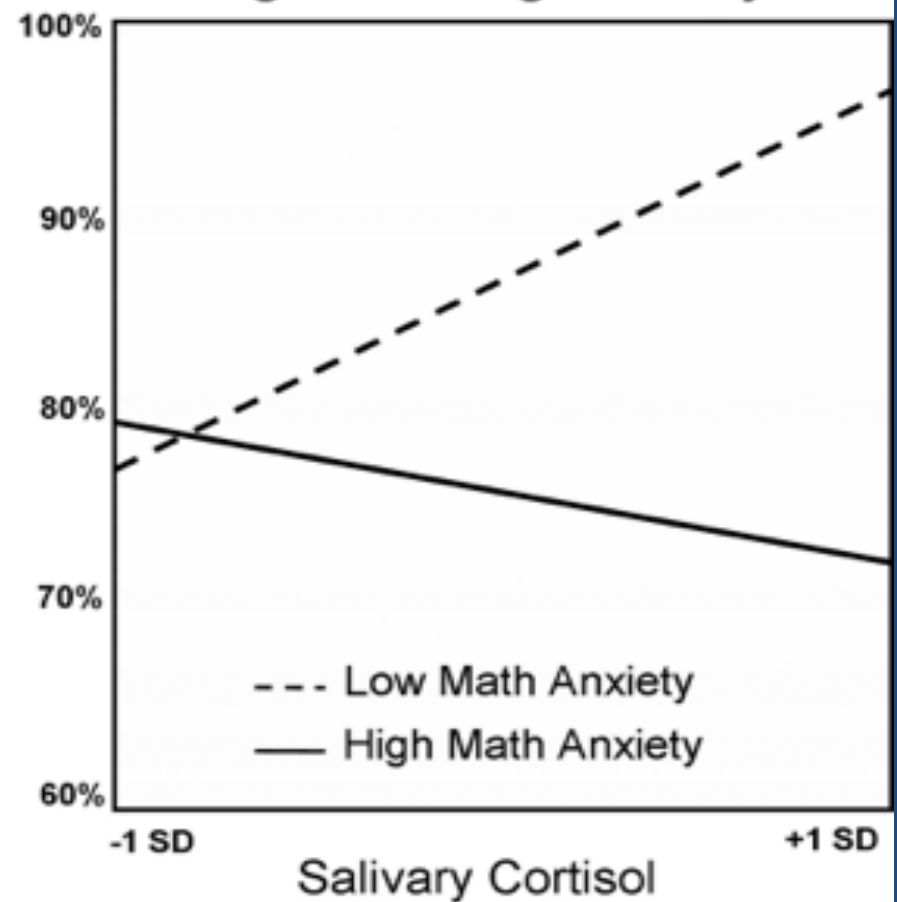
Why do civil engineers build bends in roads where there is no physical need to do so?

Mattarella-Micke et al (2011) *Emotion*

Low Working Memory



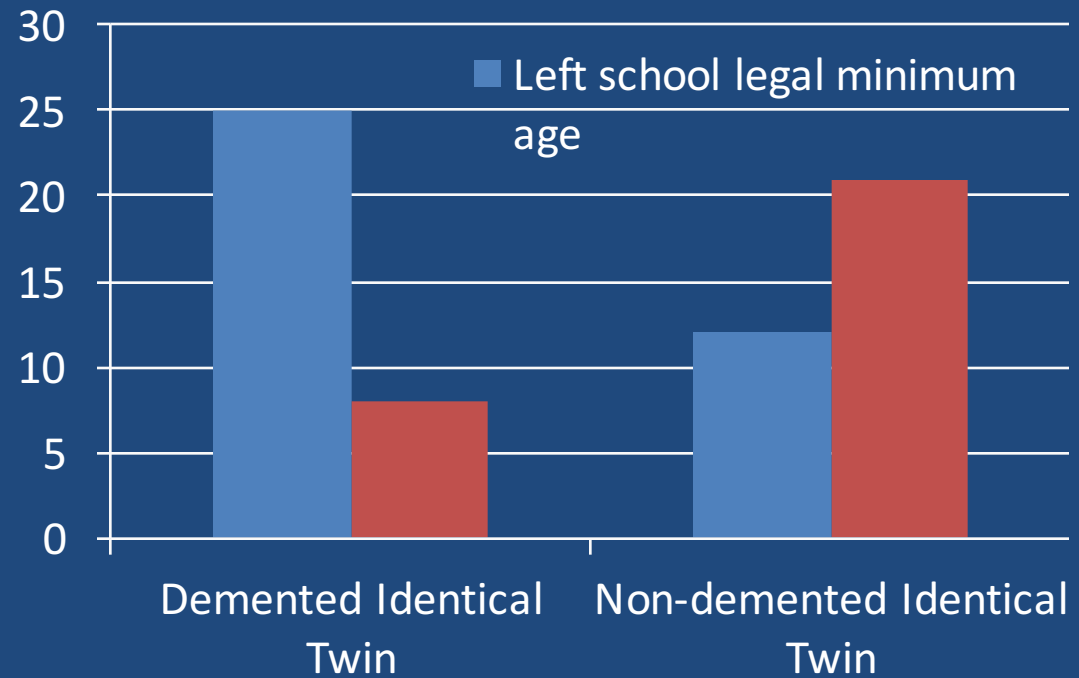
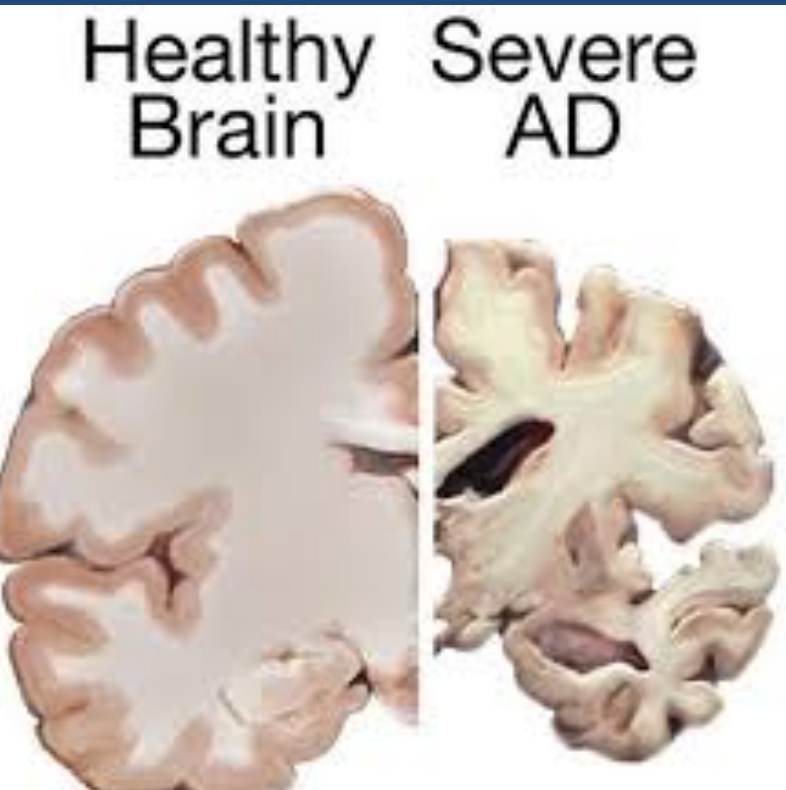
High Working Memory



Question 2

Why is higher cortisol associated with *better* performance in low maths anxiety students and with *worse* performance in high maths anxiety students?

Gatz et al, Physiology and Behaviour, 2007



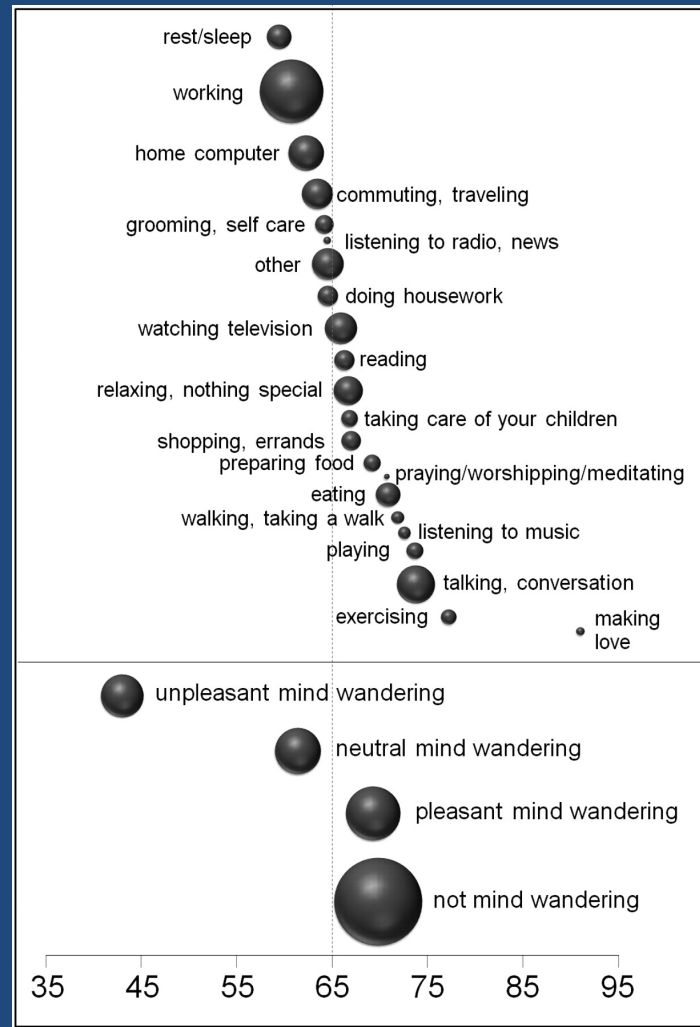
Question 3

Why does education protect against Alzheimer's Disease?

Robertson et al (1997) Neuropsychologia

1 2 ₃ 4 5 6 7 8 9 1 2 ₃ 4 5 6 7 8 9 1 2 ₃

A Wandering Mind is An Unhappy Mind



Matthew A. Killingsworth, and Daniel T. Gilbert *Science* 2010;330:932

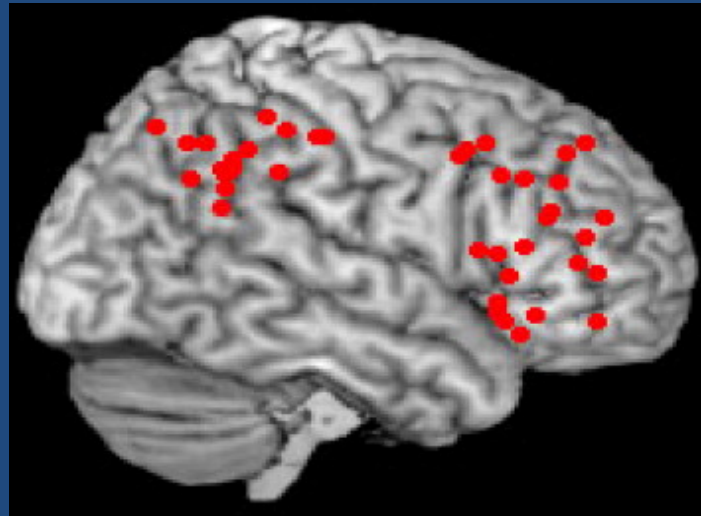
What is sustained attention?

Smilek et al (2010) Neuropsychologia

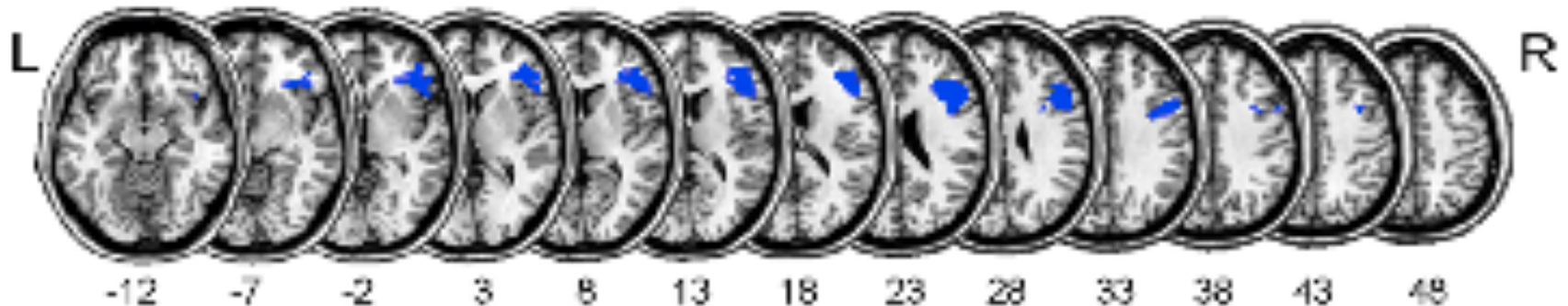
*Failures of sustained attention in life, lab, and brain:
Ecological validity of the SART*

SART predicts everyday mind-wandering

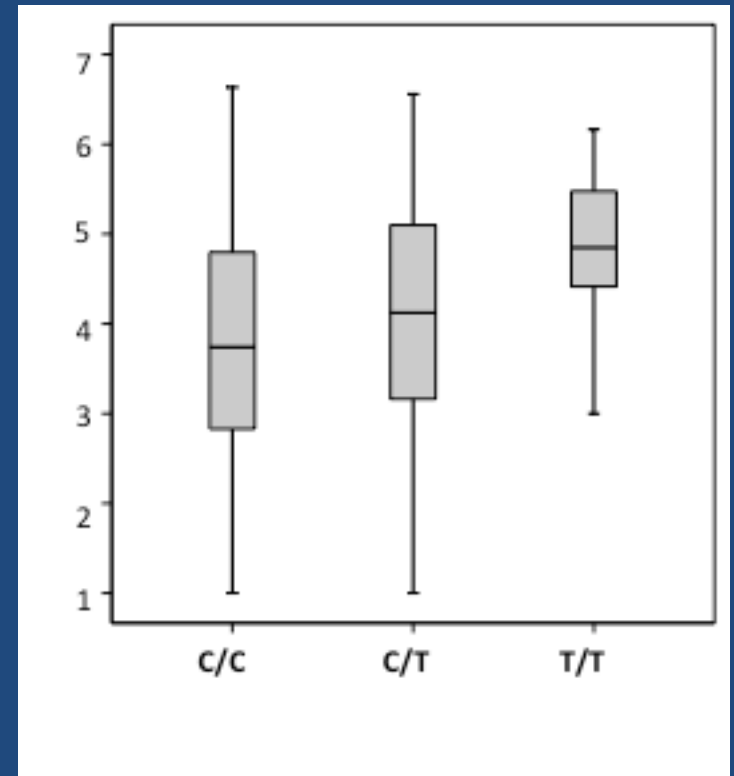
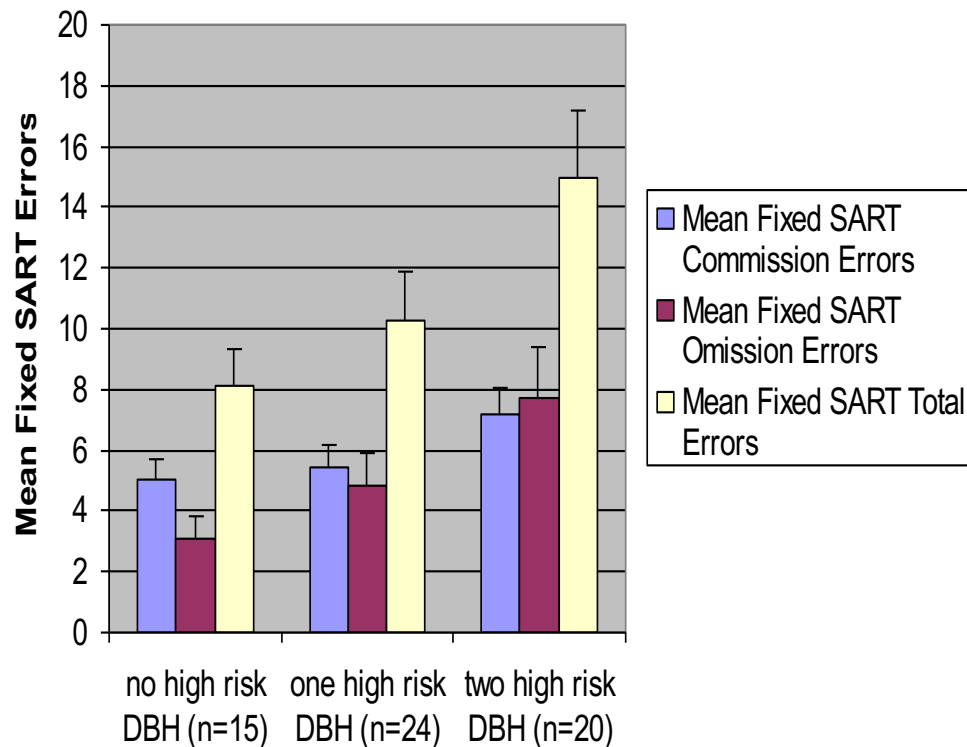
Singh-Curry and Husain (2009) Neuropsychologia; Mohlenbergs (2009) Neuropsychologia



A. VLSM map. Input: Individual numbers of commission errors



Sustained Attention is strongly Noradrenaline/Norepinephrine linked

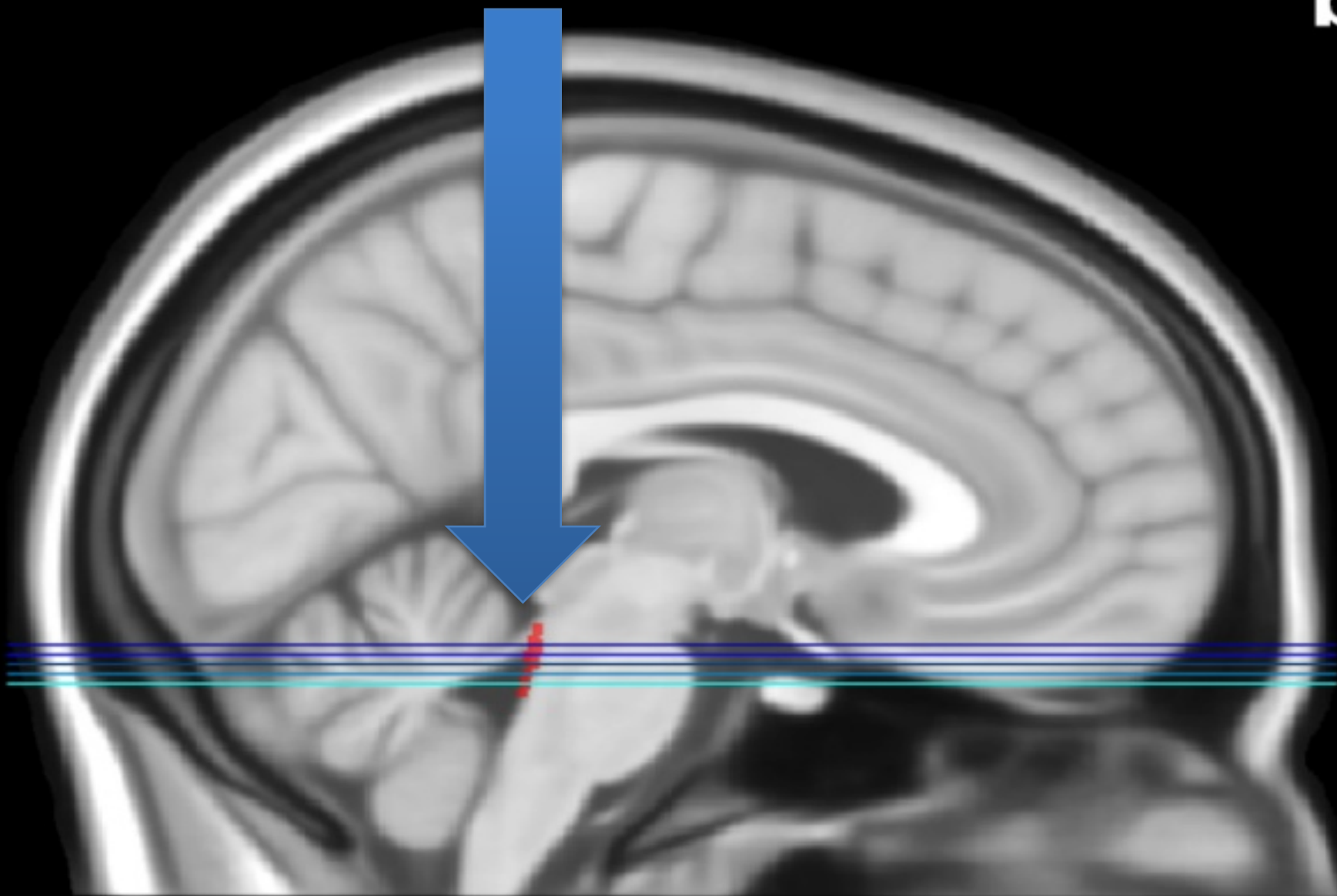


Bellgrove, Robertson (2009) Cortex; Greene et al (2009)

Noradrenergic Upregulation Selectively Activates Right Prefrontal Regions

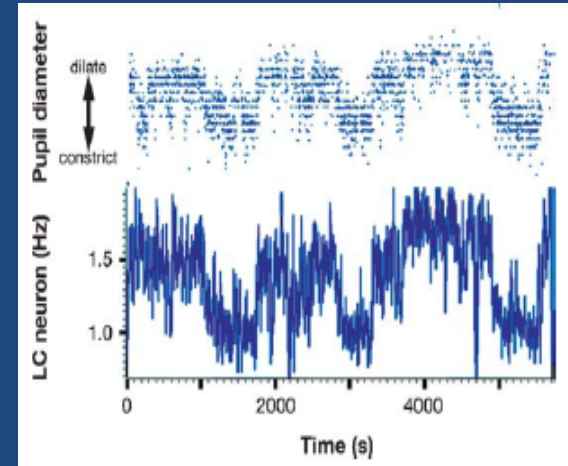
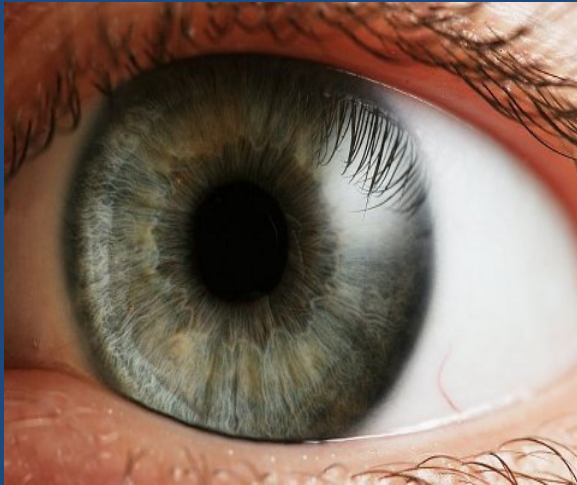
- Bush et al (2012) Psychiatry Research
- Grefkes et al (2009) Cerebral Cortex
- Chamberlain et al (2009) Biological Psychiatry

b

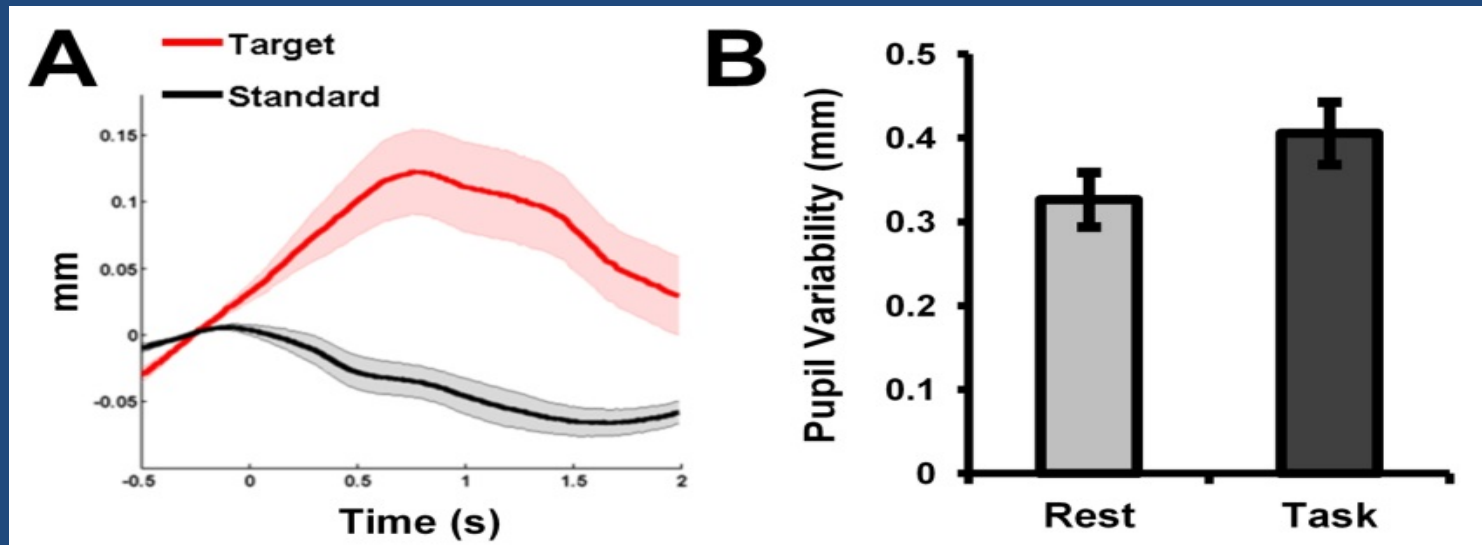


$x = 5$

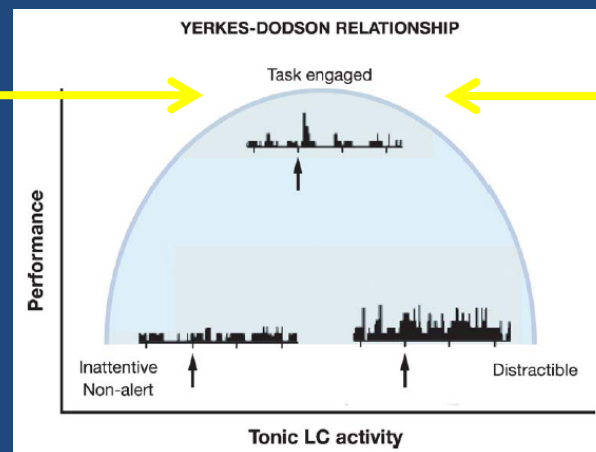
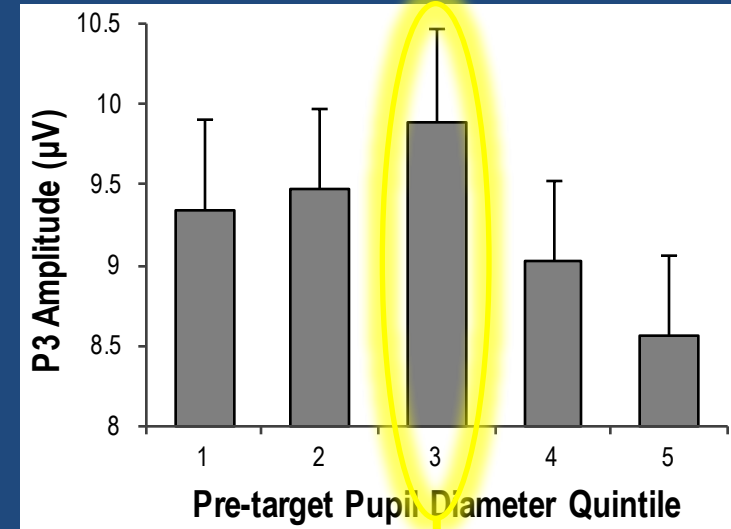
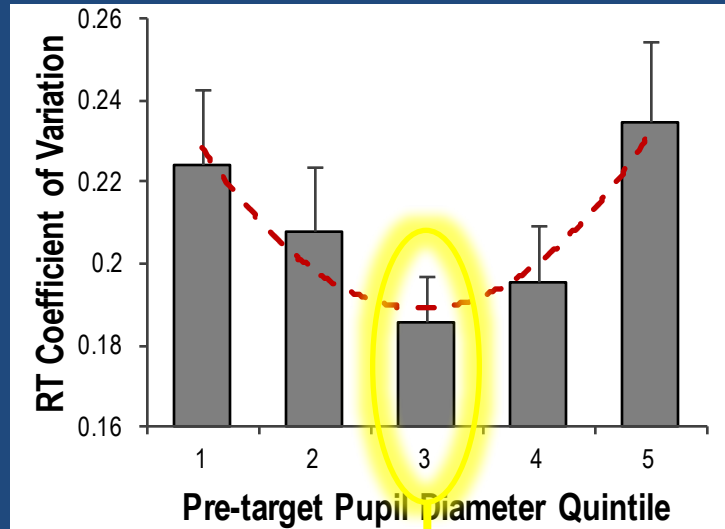
Human noradrenergic Markers?



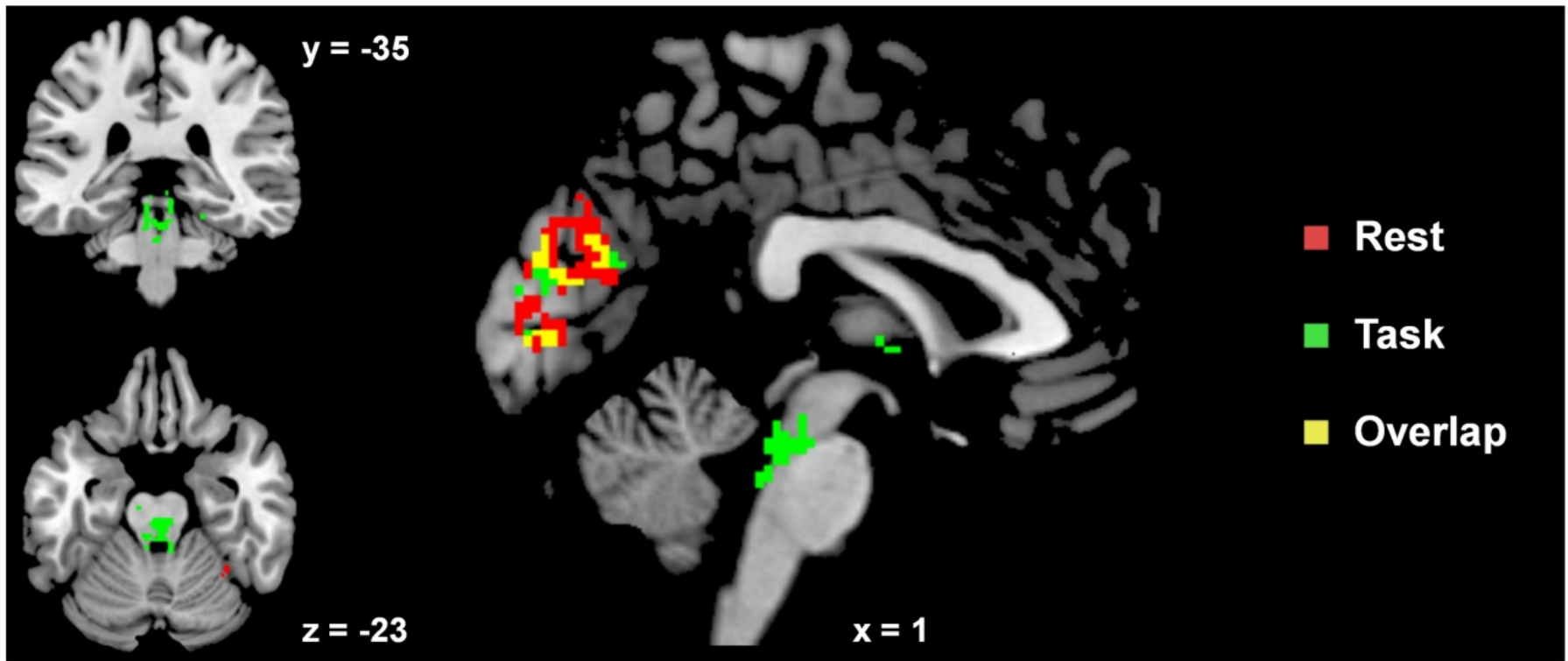
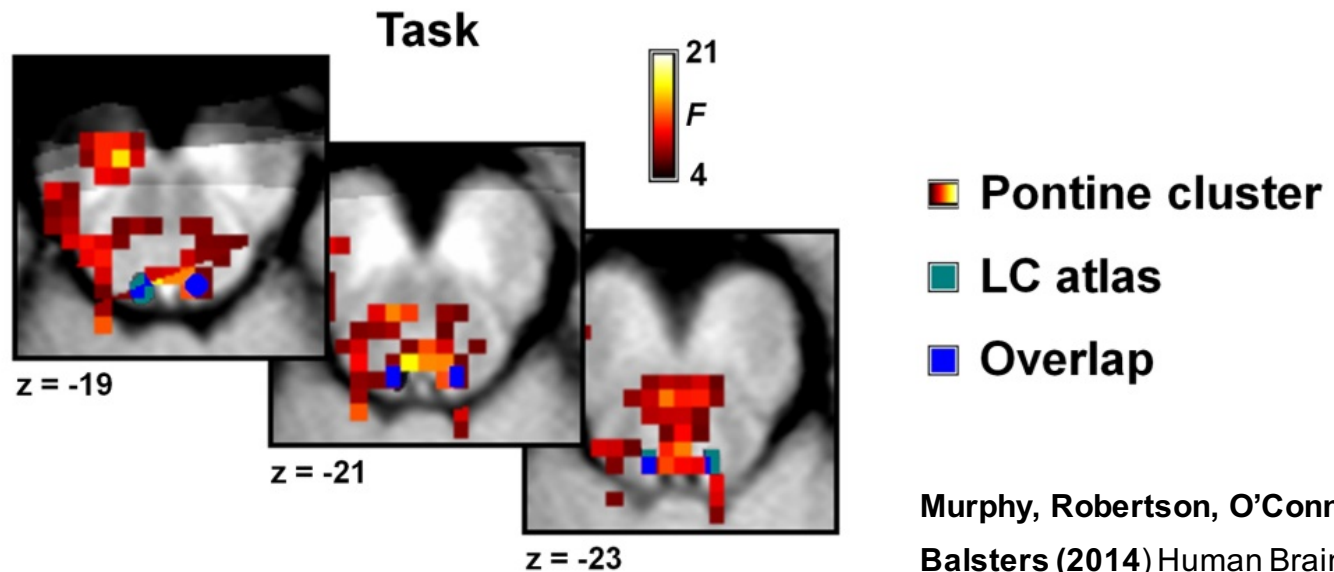
Rajowski et al 1993



Murphy, Robertson and O'Connell 2012



Murphy et al (2011) Psychophysiology.

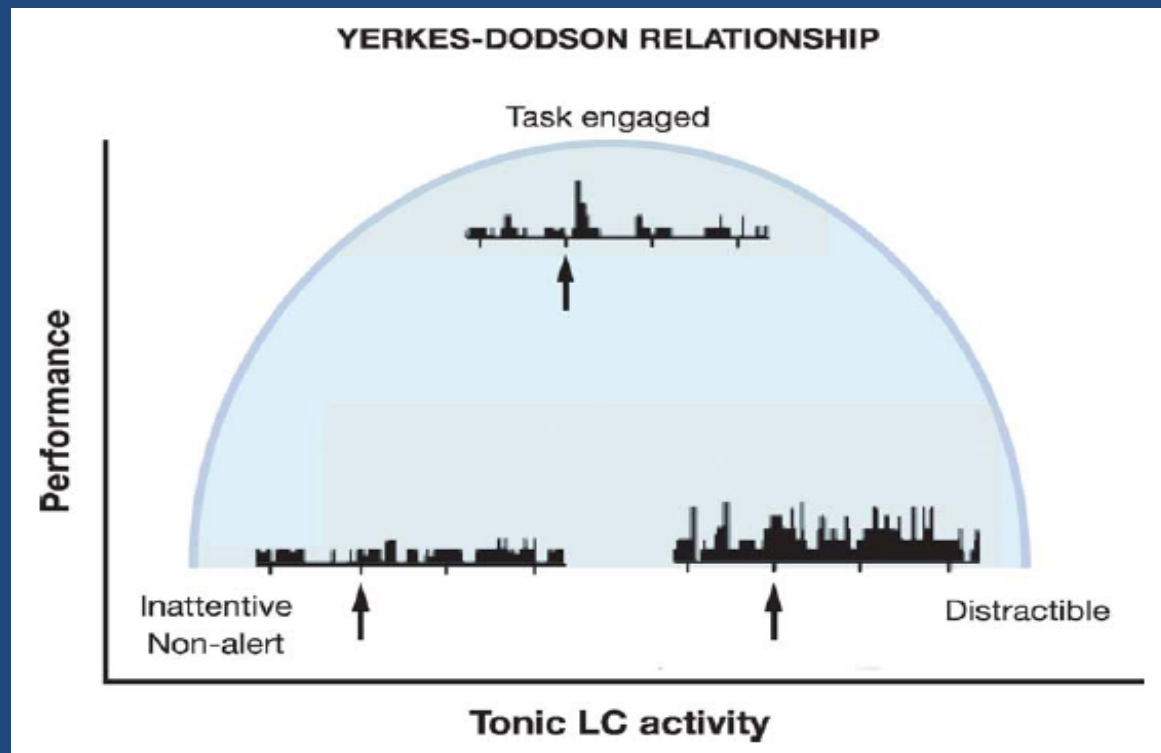
A**B**

Murphy, Robertson, O'Connell and Balsters (2014) Human Brain Mapping

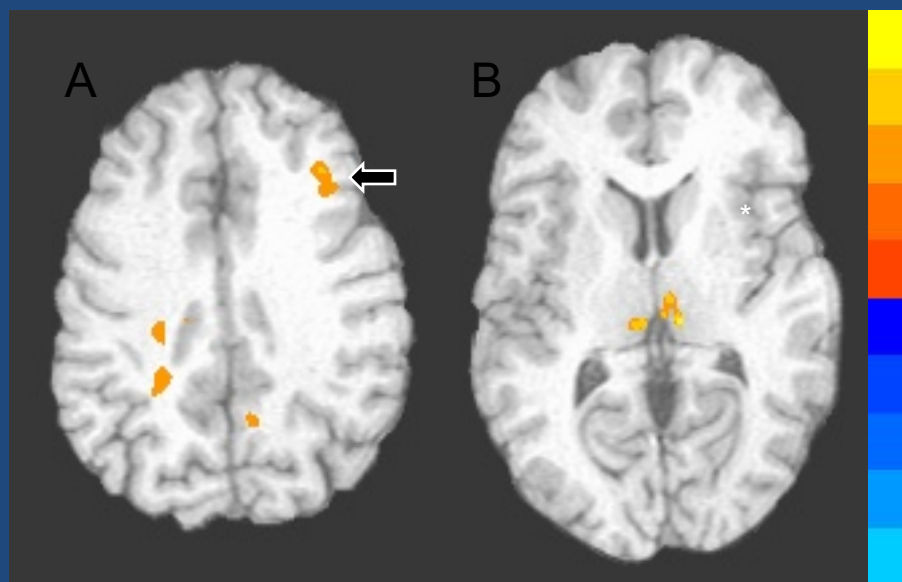
Question 1

Why do civil engineers build bends in roads where there is no physical need to do so?

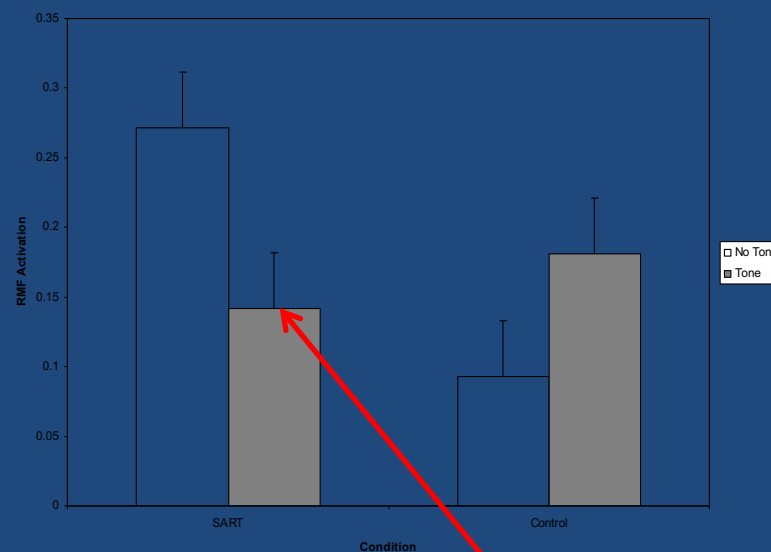
Because the brain needs
challenge to sustain attention in
the absence of external demand



Effects of External Alerting on SART performance – REDUCES right dorsolateral prefrontal cortex activation

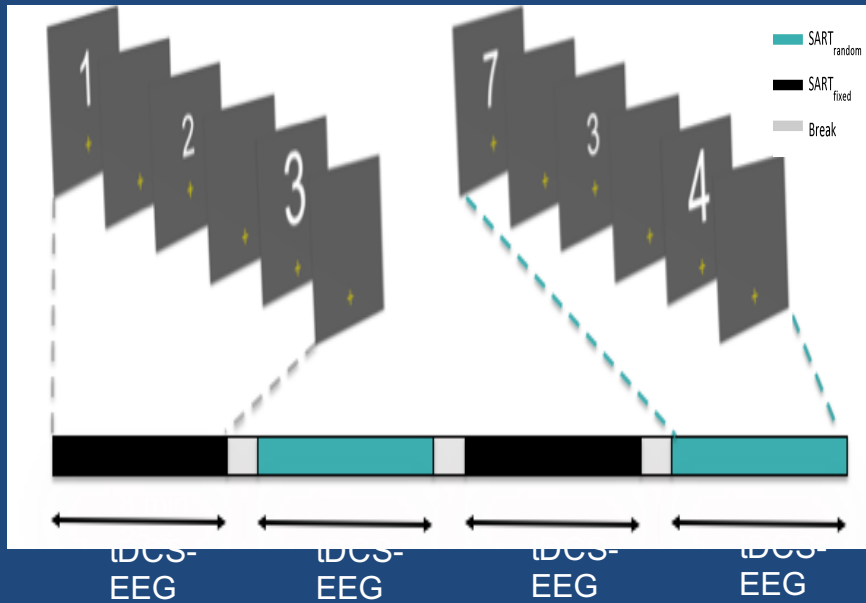


significant activations associated with SART condition compared to Control condition, including (A) right middle frontal gyrus (B) bilateral thalamus.

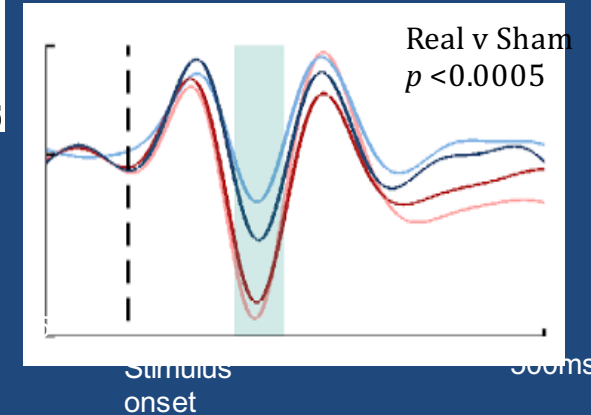
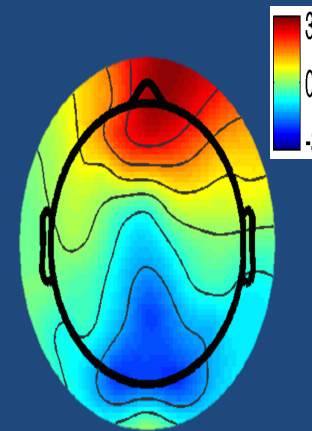


During SART, irrelevant alerting tone DECREASES RIGHT FRONTAL ACTIVATION

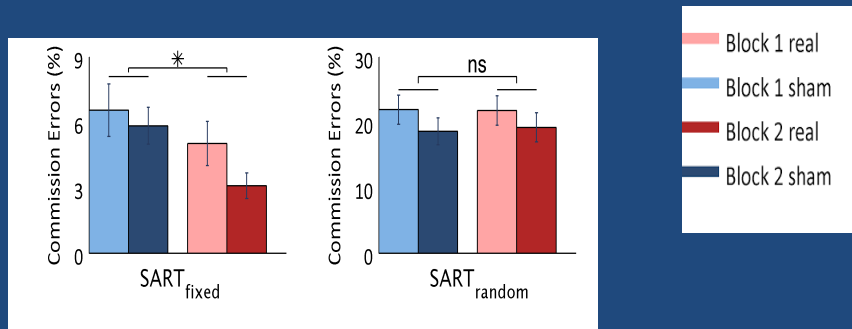
Experimental Design



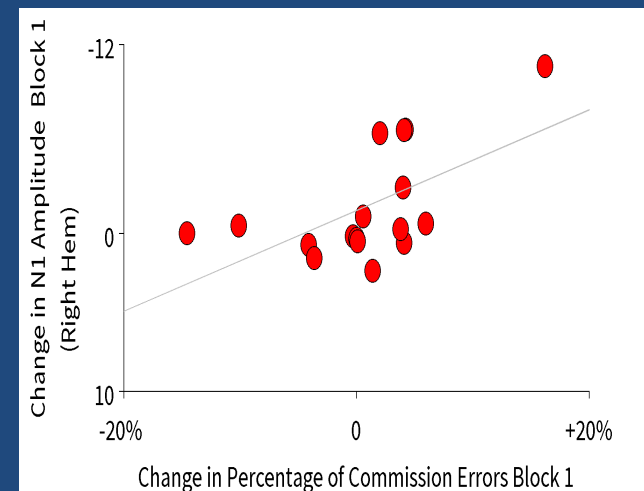
Enhanced N1 component during real stimulation



Reduction in Commission Errors during SART_{fixed} and not SART_{random}



Neurobehaviour relationship



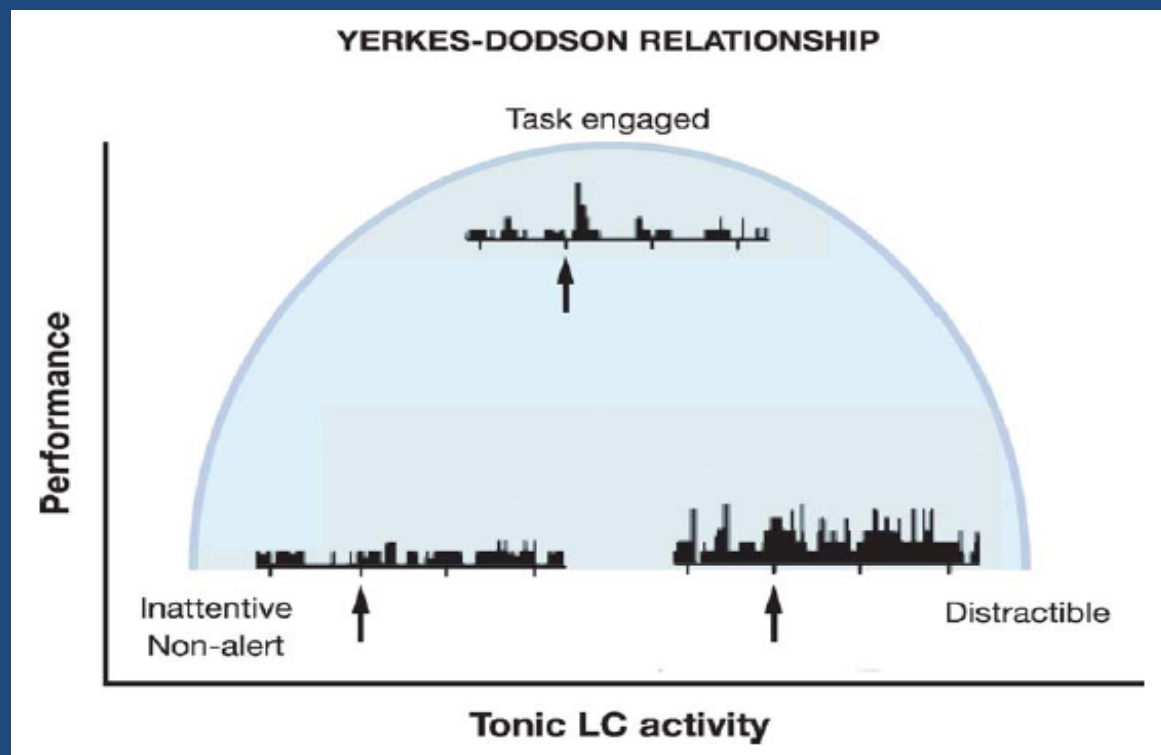
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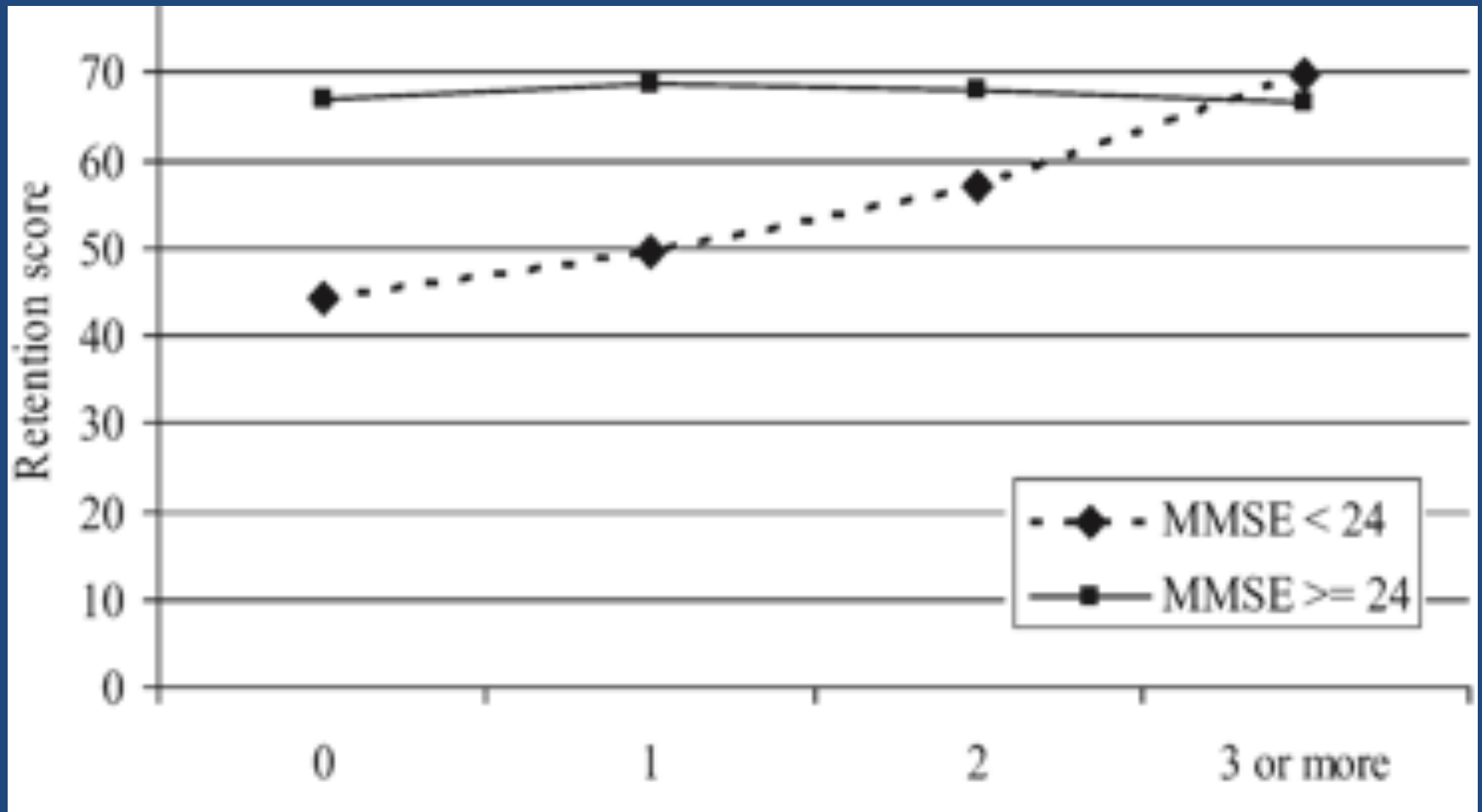
Roozendal et al (2006) PNAS

- Blockade of Noradrenergic Activity Prevents Corticosterone Effects on Memory Enhancement
- Pharmacologically Induced Noradrenergic Activation Mimics the Effect of Emotional Arousal in Enabling Corticosterone Effects on Memory Enhancement

Optimal NA levels needed – too high may disrupt as much as too low.



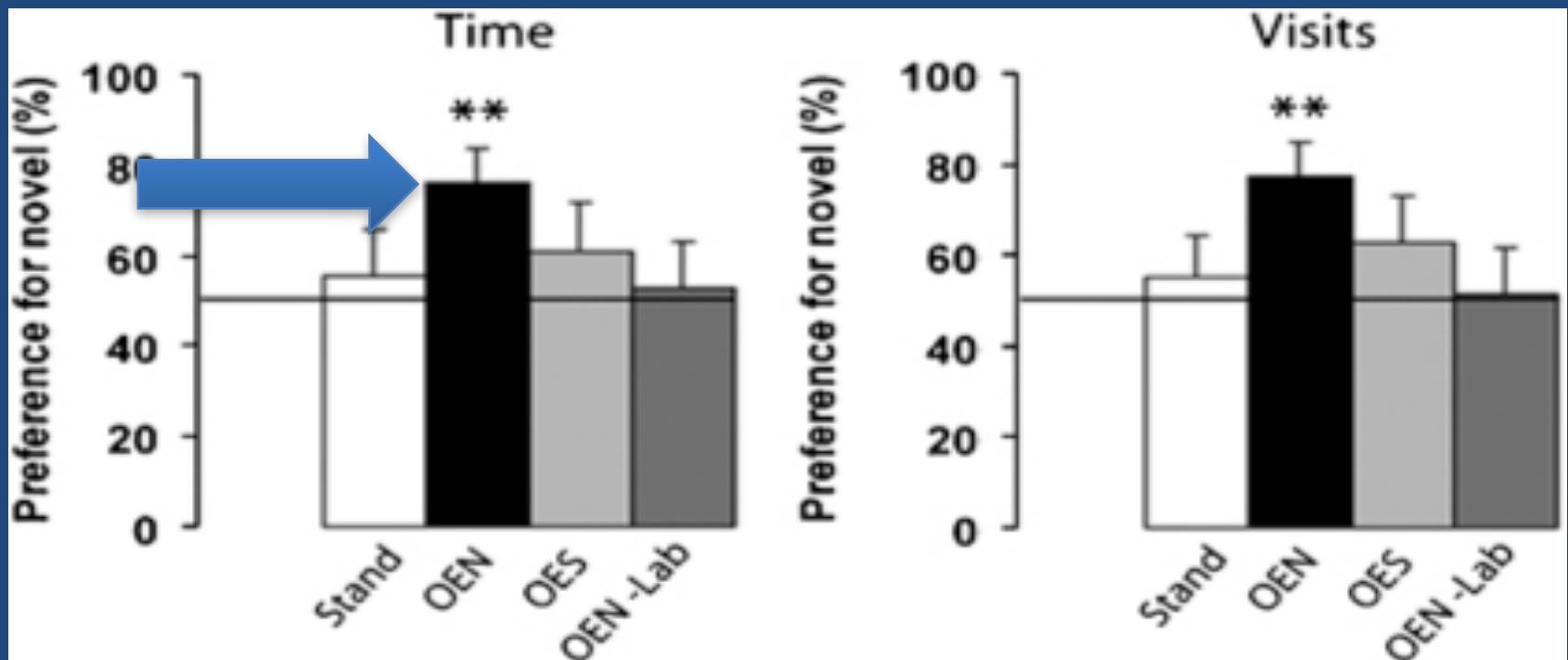
Comjis et al (2011) The Journals of Gerontology
70-somethings who have *more* stressful life events over the next
3 years show *less* cognitive decline.



Question 3

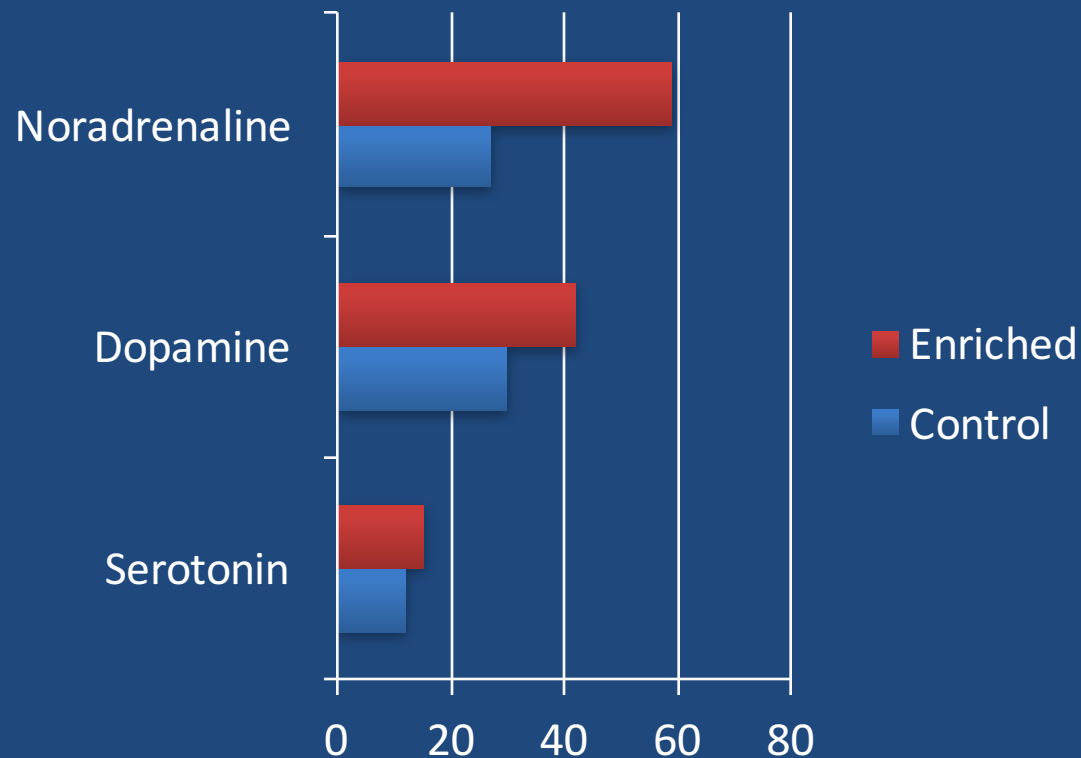
Why does education protect against Alzheimer's Disease?

ENVIRONMENTAL ENRICHMENT IMPROVES BRAIN FUNCTION IN ANIMALS VIA NUMEROUS MECHANISMS INCLUDING NEUROGENESIS



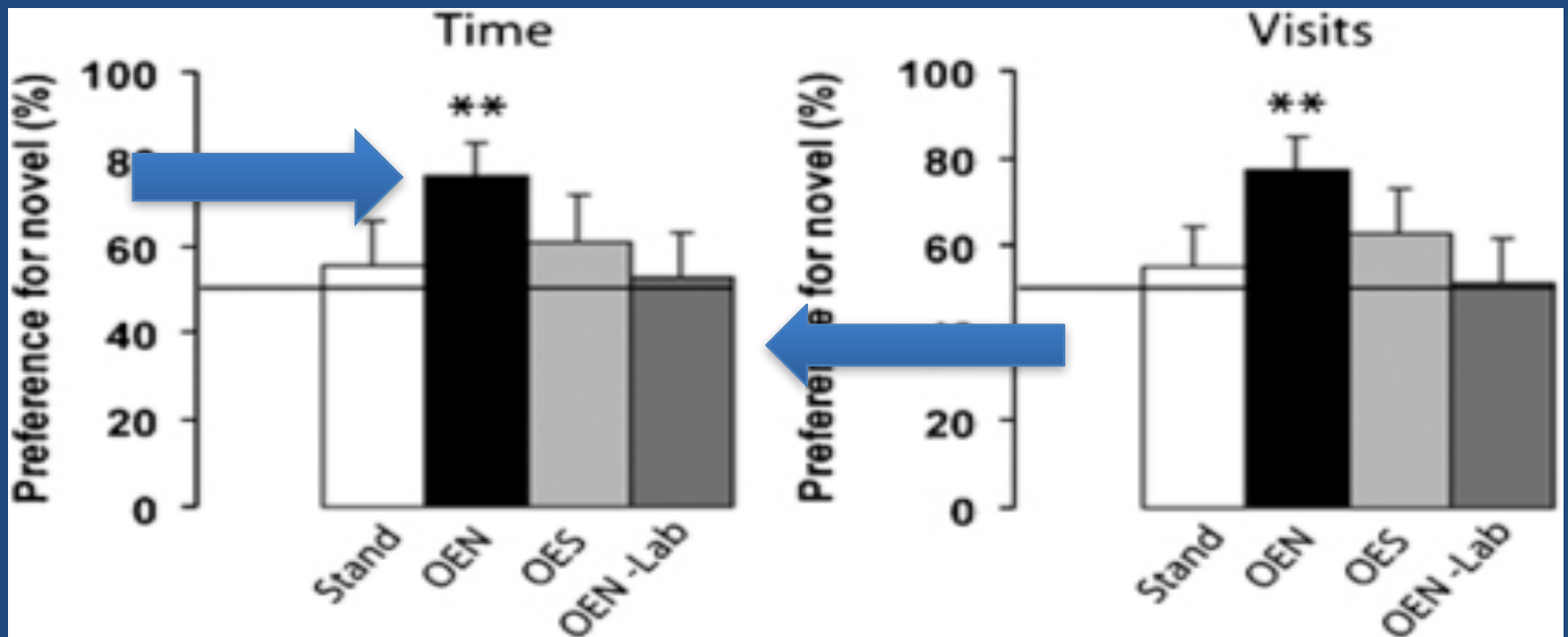
Veyrac et al (2008), Neuropsychopharmacology

ENVIRONMENTAL ENRICHMENT SELECTIVELY INCREASES NOREPINEPHRINE ACTIVITY IN MICE BUT NOT DOPAMINE OR SEROTONIN ACTIVITY



•Naka et al (2002) *Brain Research* 924, 124-6

THE NEUROGENESIS EFFECTS OF ENVIRONMENTAL ENRICHMENT ARE MEDIATED BY NORADRENALINE



Veyrac et al (2008), Neuropsychopharmacology

... which in turn depends on

NOVELTY



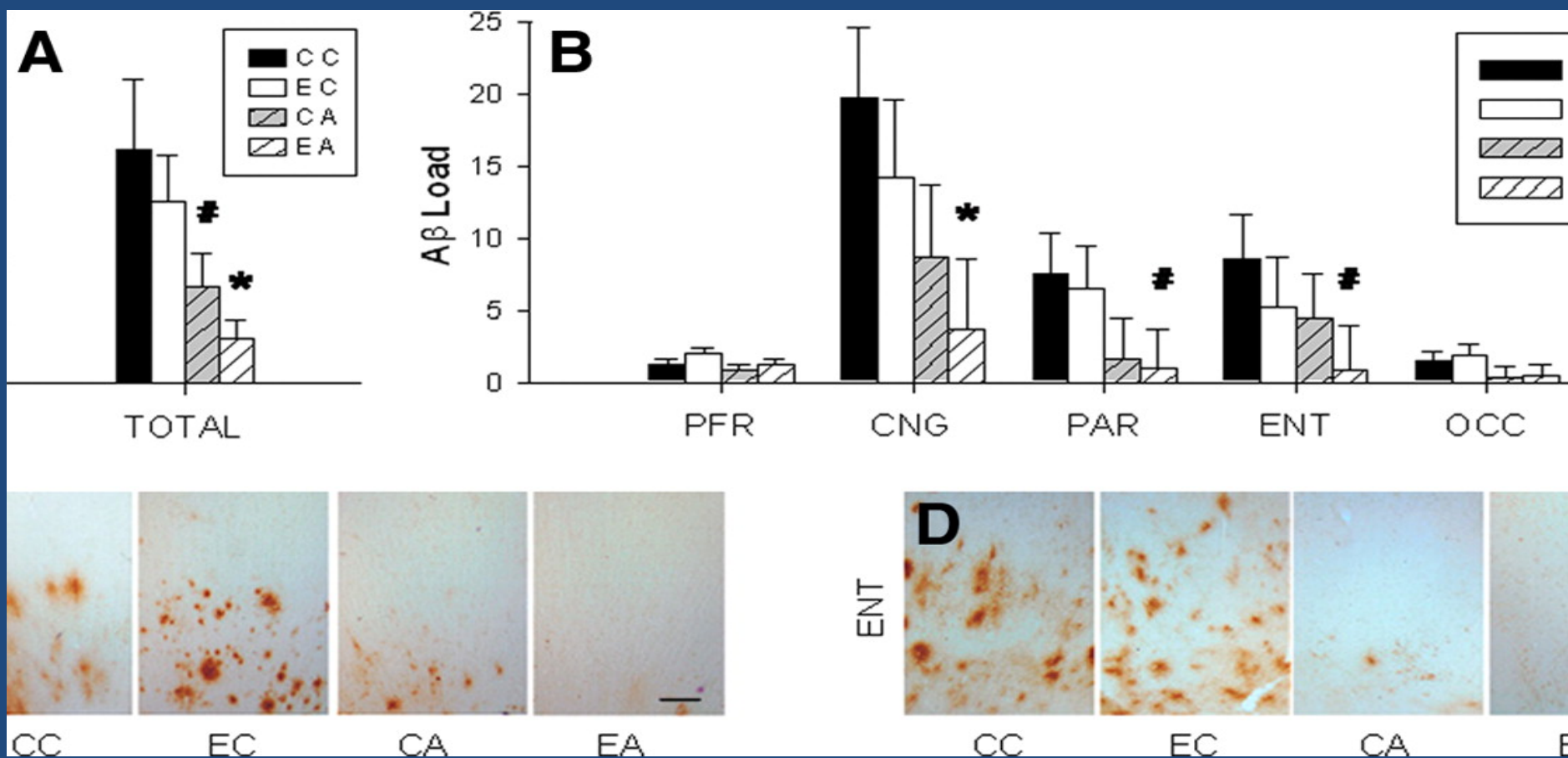
Novelty Determines the Effects of Olfactory Enrichment on Memory and Neurogenesis Through Noradrenergic Mechanisms

Alexandra Veyrac^{1,2}, Joëlle Sacquet^{1,2}, Véronique Nguyen³, Marc Marien³, François Jourdan^{1,2} and Anne Didier^{*1,2}

Veyrac et al (2008), Neuropsychopharmacology

“LC-NE activation affects synapses throughout the CNS, suppressing most, but permitting or even accentuating activity in those that are transmitting novel or significant stimuli...this favours the development of persistent facilitatory changes in all synapses that are currently in a state of excitation”
(Kety, 1972)

ENVIRONMENTAL ENRICHMENT REDUCES AMYLOID PLAQUE BURDEN IN DOGS



Also.... norepinephrine reduces
amyloid toxicity in vitro ..

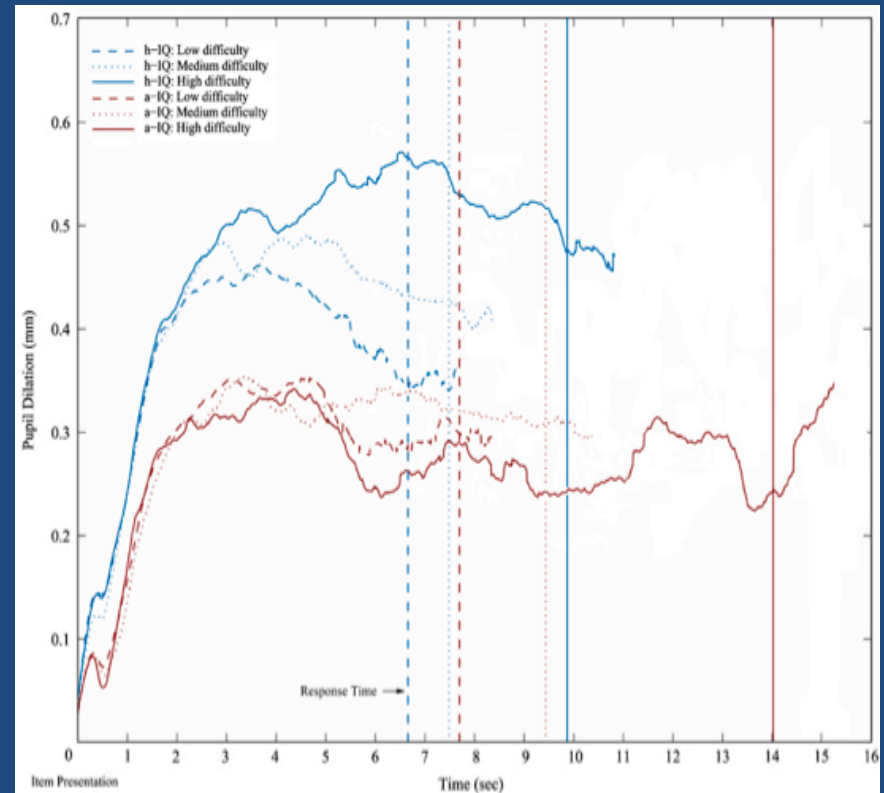
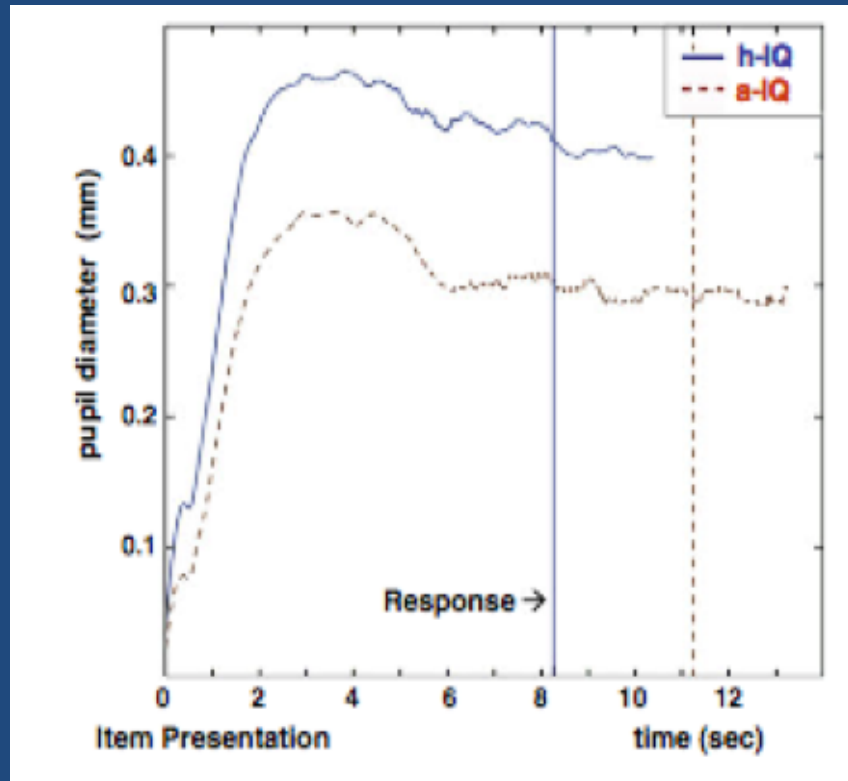
And also rescues cholinergic and
dopaminergic cells.

COGNITIVE RESERVE

A case of Human

Environmental Enrichment?

Cognitive Reserve and Pupil Dilation (IQ/Education)

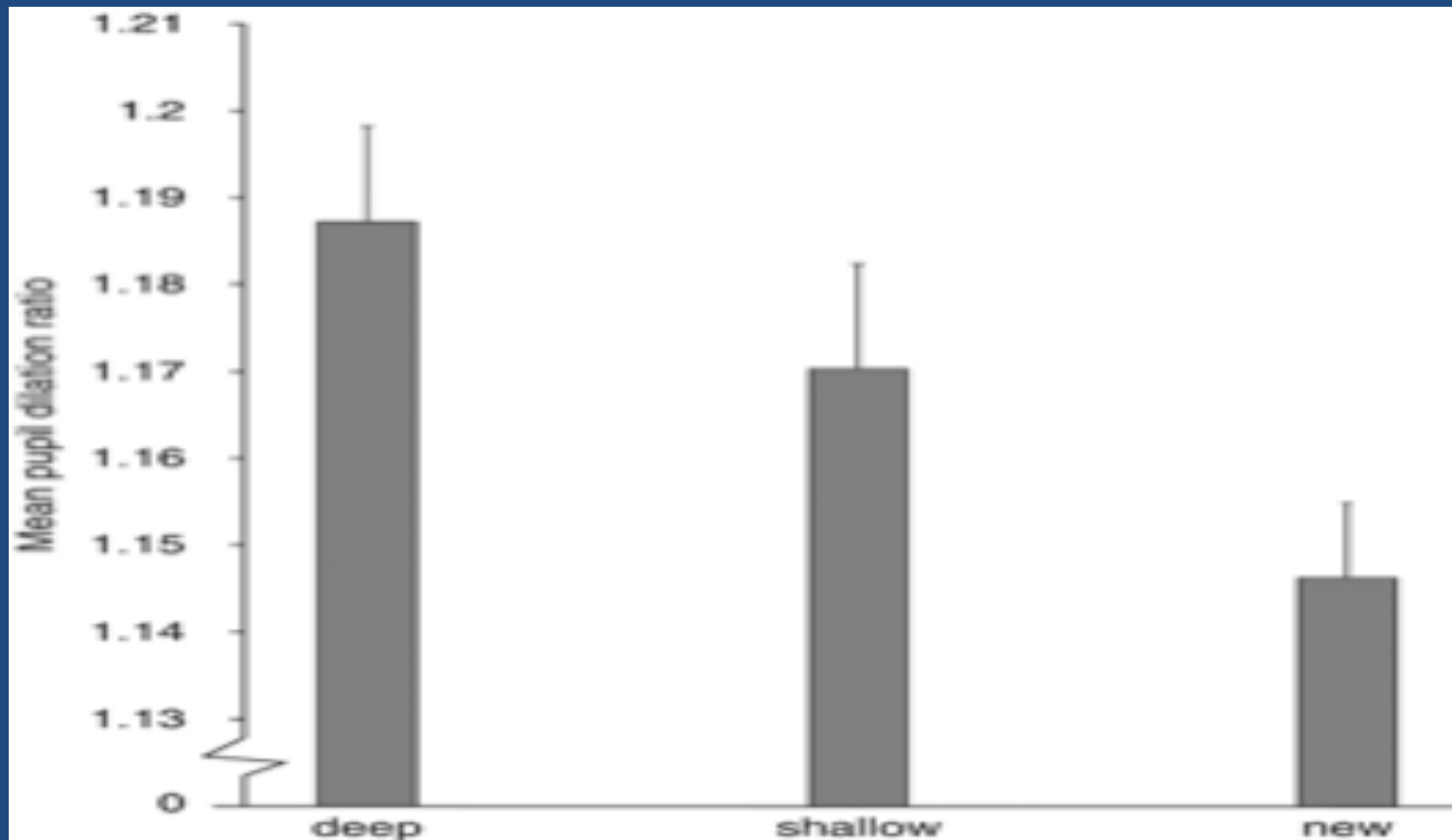


BORNEMANN et al 2010

Van der Meer et al, 2010

Cognitive Reserve and Pupil Dilation (Cognitive Demands – eg Memory)

Recognition Memory





More Education linked to
bigger pupil dilation



Challenging mental tasks dilate
pupils



Other people dilate pupils



Actively remembering things
dilates pupils



NOVELTY dilates pupils



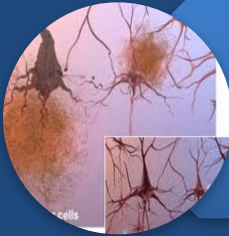
EDUCATION TRIGGERS MULTIPLE NA
INFUSIONS, INCREASING BRAIN
CONNECTIVITY



MENTALLY CHALLENGING ACTIVITIES AND JOBS
DO THE SAME



ENGAGING WITH OTHER PEOPLE SIMILAR
EFFECTS



THIS LIFETIME OF BOOSTED
NORADRENALINE ACTIVITY *MAY* AFFECT
THE DISEASE PROCESS ITSELF



WE CAN NOW MEASURE THESE EFFECTS

Brainstem Nuclei (LC, DRN, SN, VTA) and Cognitive Decline

(Wilson et al, 2013, Neurology)

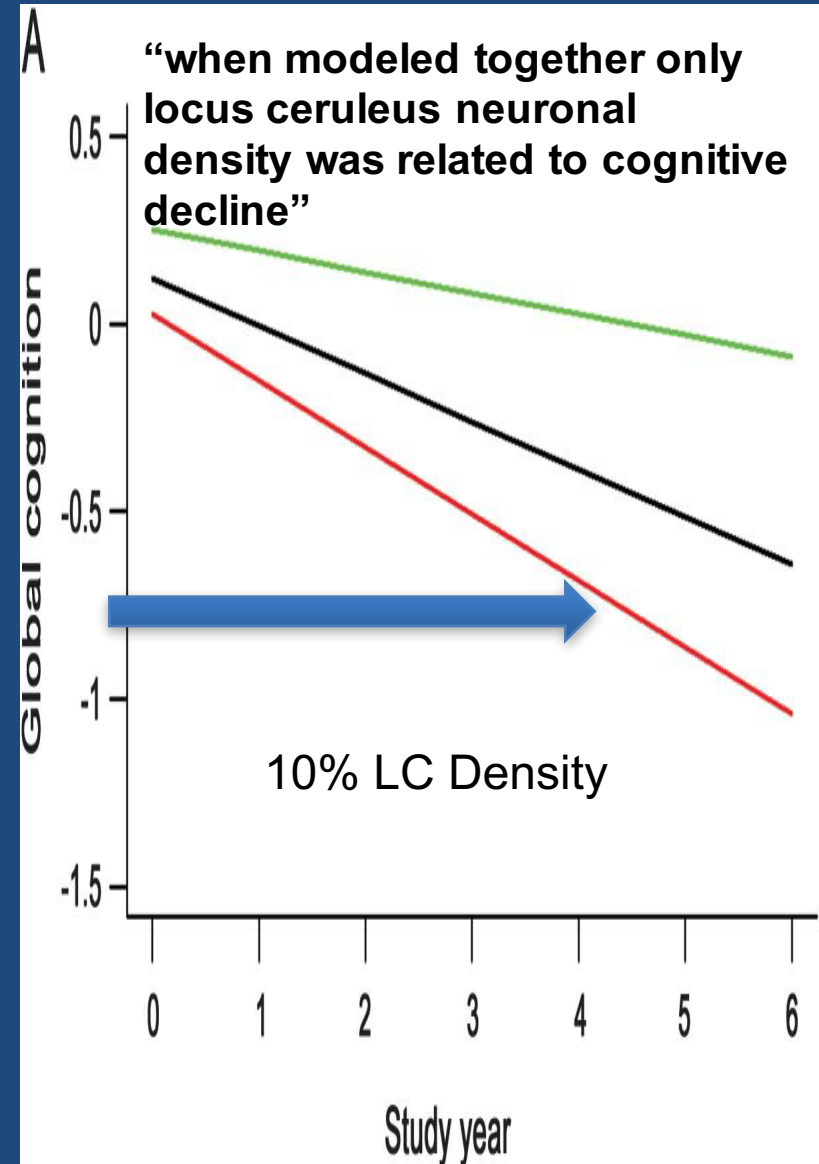
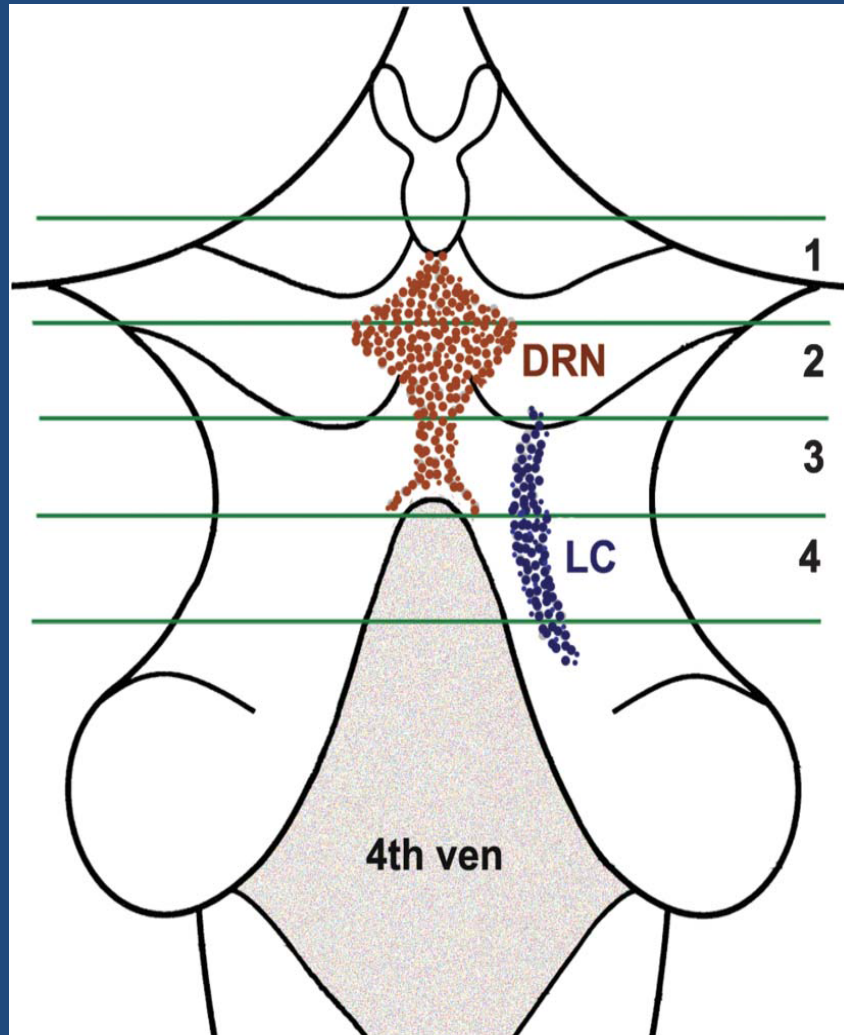


Fig. 2

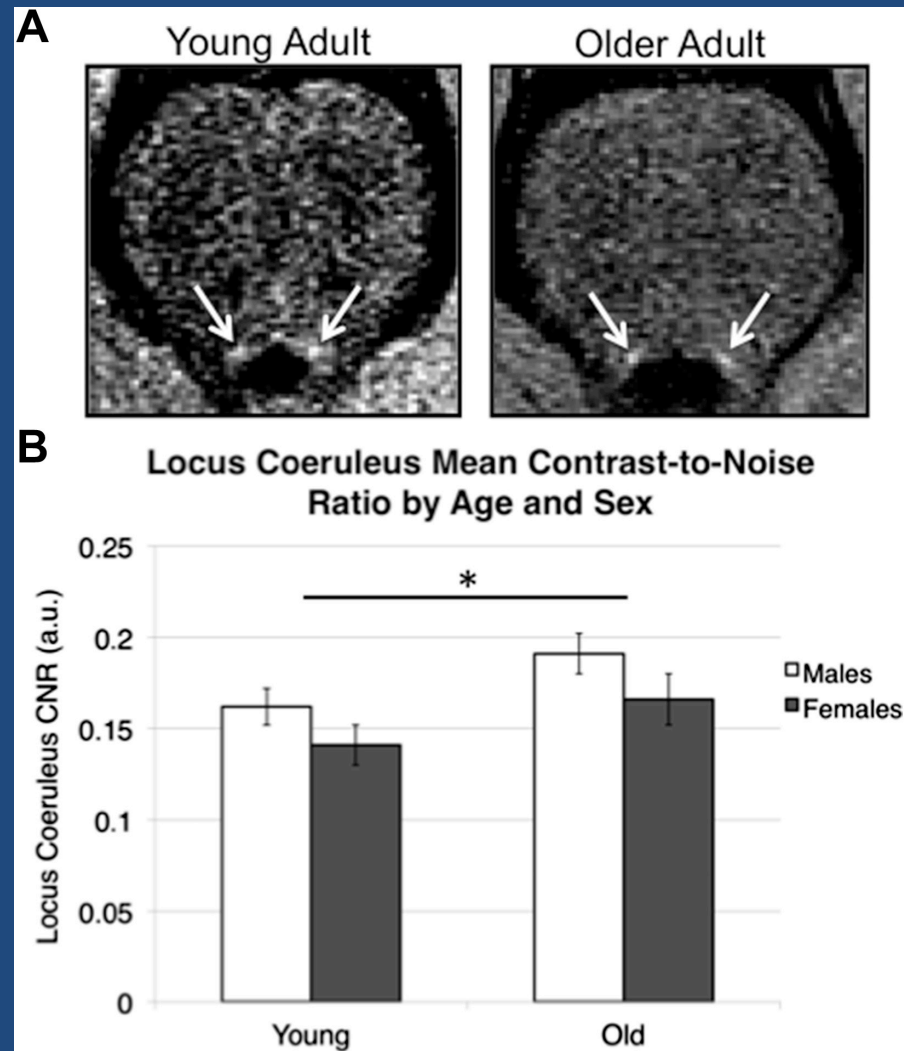
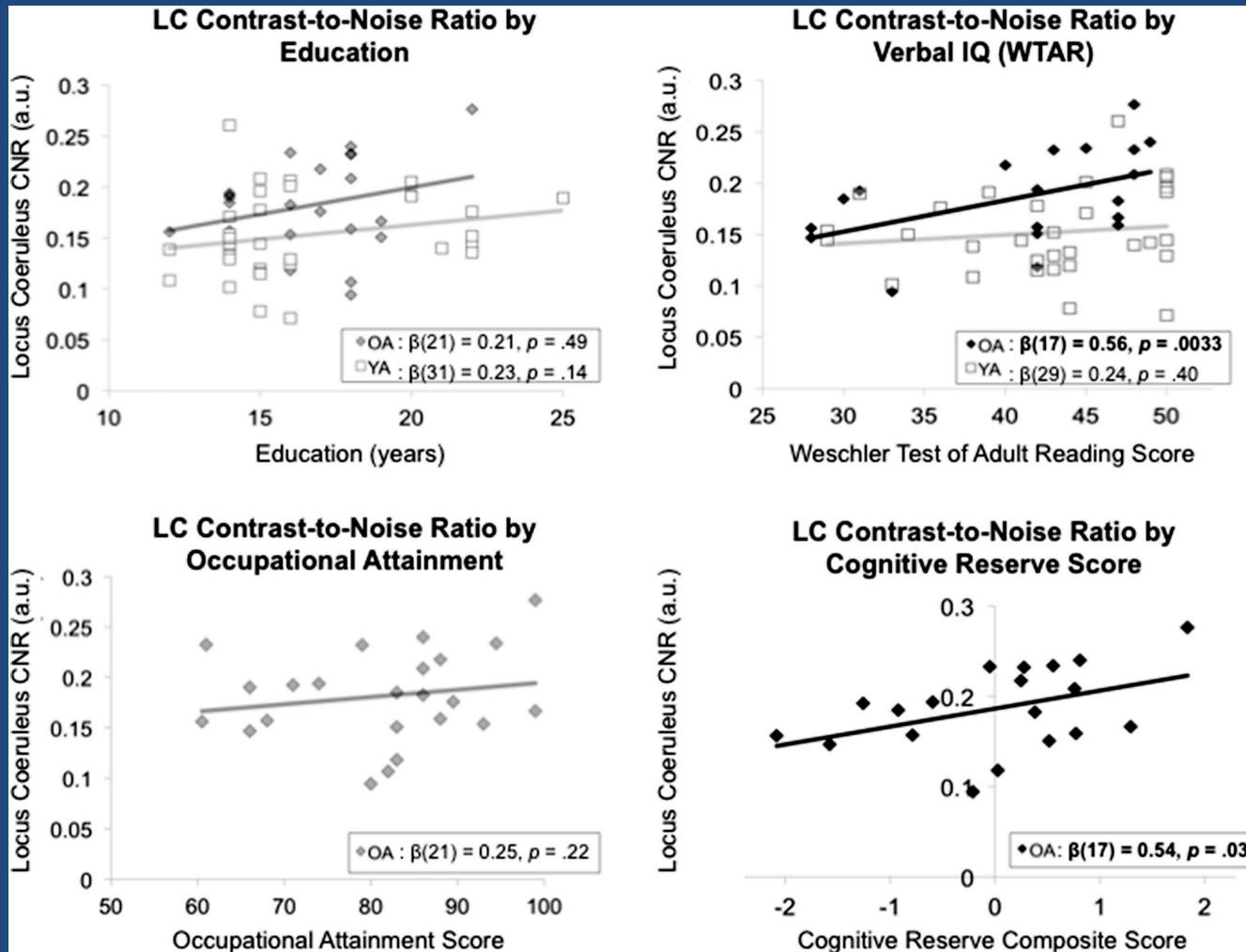


Fig. 3



2 year follow up cognitive function

Pupillary Function

- Correlation with age:

Mean baseline diameter $r(56) = -.347, p = 0.008$.

Mean dilation $r(56) = -.299, p = 0.023$.

Dilation variability $r(56) = -.243, p = 0.066$.

- Age corrected association between Dilation Variability and Education Grp

$F(1,57) = 4.077, p = 0.048$

Results - Cognition

Partial Correlations (df = 48/49)

	Immediate Recall	Delayed Recall	FSCRT Free Recall	Recognition	Memory Discrepancy	Category Fluency	MMSE
Mean Dilation	-0.094	-0.290*	0.040	-0.183	0.271+	-0.145	-0.141
Dilation Variability	0.512***	0.427**	-0.070	0.310*	-0.409**	-0.102	-0.065
Mean Baseline Diameter	0.183	0.219	-0.003	0.102	-0.161	-0.037	-0.115
Baseline Variability	0.165	0.056	-0.014	0.167	0.017	-0.010	0.171

*Note: Partial correlations controlled for Age, Education Group, Sex, Use of Cardiovascular Medications, Smoking status, Problem Drinking and Time of Test; The WMS IV Logical Memory Task was not completed by one participant; *** $p < .001$; ** $p < .01$; * $p < .05$, + $p < 0.1$; All other p values > 0.125 .*

Yerkes-Dodson (1908)



Many Thanks To:

- Maria Pertl
- Josh Balsters
- Jessica Bramham
- Meadhbh Brosnan
- Paul Dockree
- Tom Manly
- Redmond O'Connell
- Michael O'Sullivan
- Simona Salomone