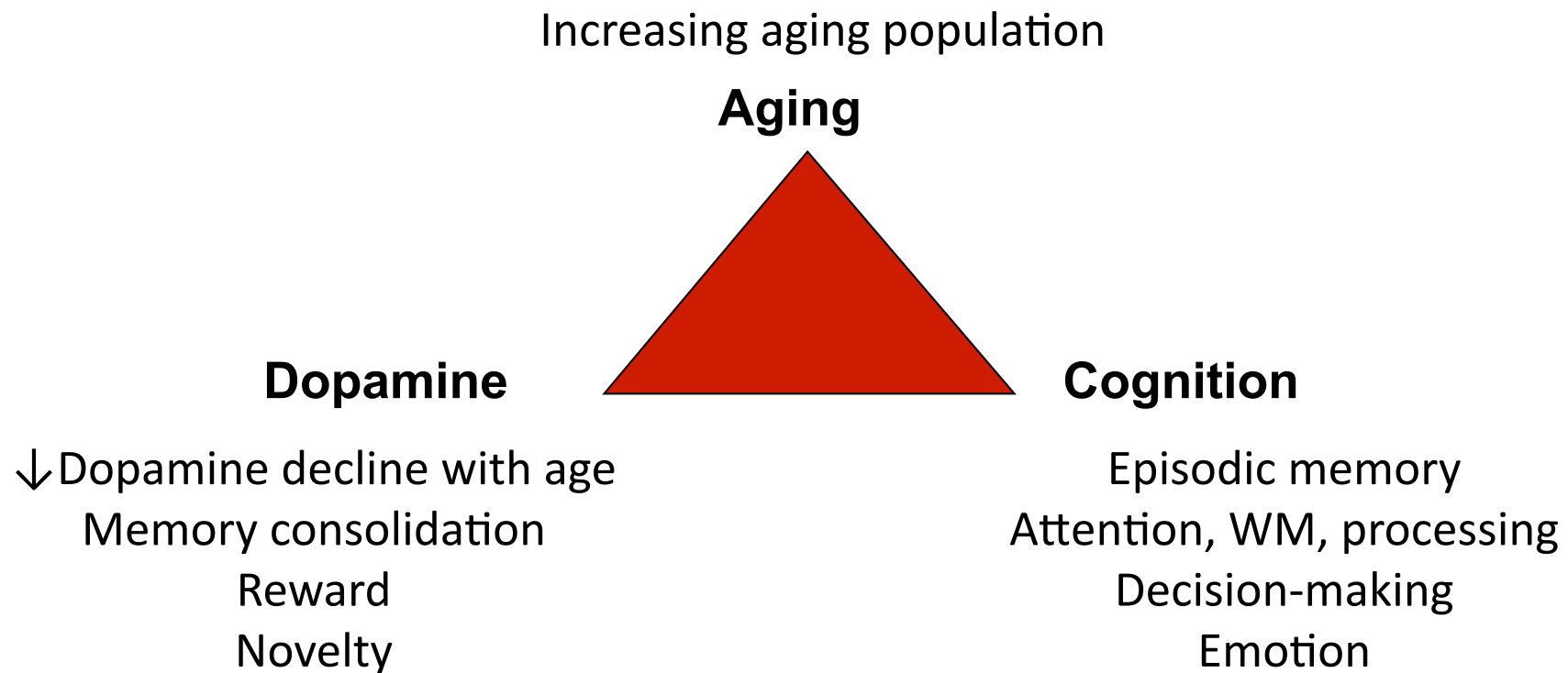


Dopamine and episodic memory in healthy aging

Rumana Chowdhury, Marc Guitart-Masip, Nico Bunzeck, Jasmine Medhora, Laura Sasse,
Ray Dolan, Emrah Düzel

Boosting the Brain Symposium, Karolinska Institutet
September 2011

Background

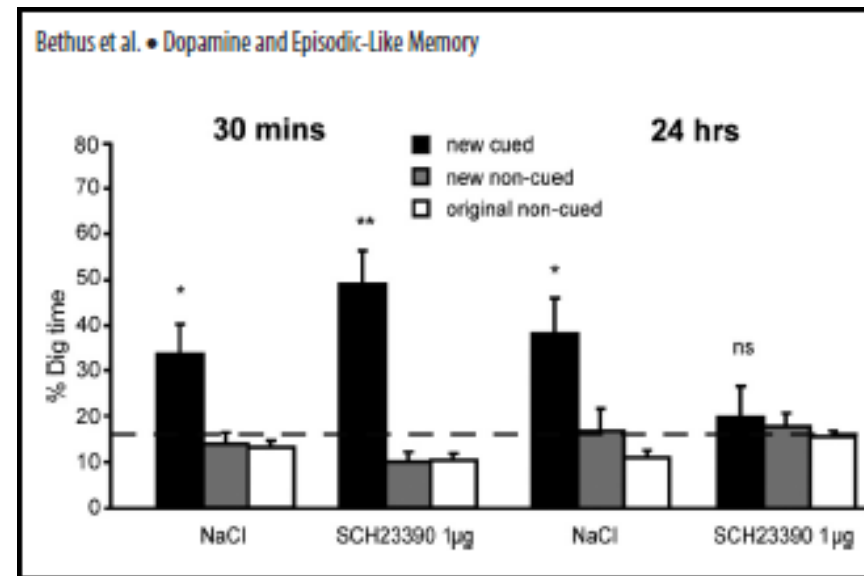


“Correlative triad” (Backman et al., 2006)

Dopamine & delayed episodic memory

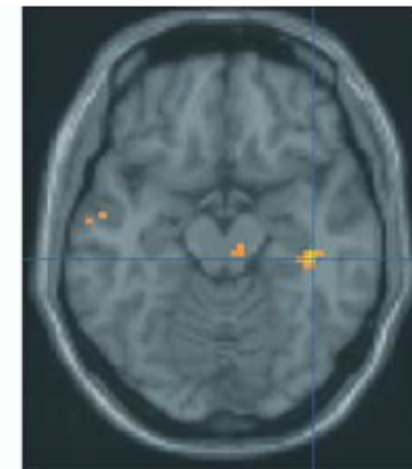
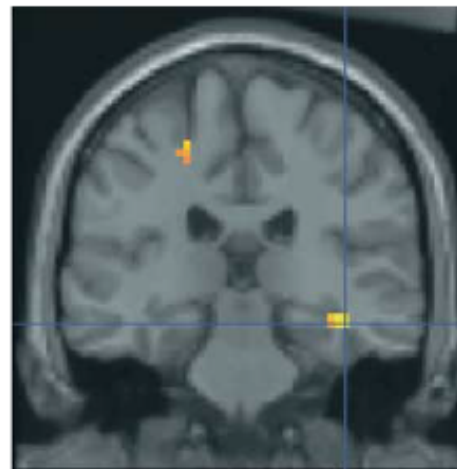
Animal studies (Bethus et al., 2010)

- Dopamine at encoding critical for delayed memory



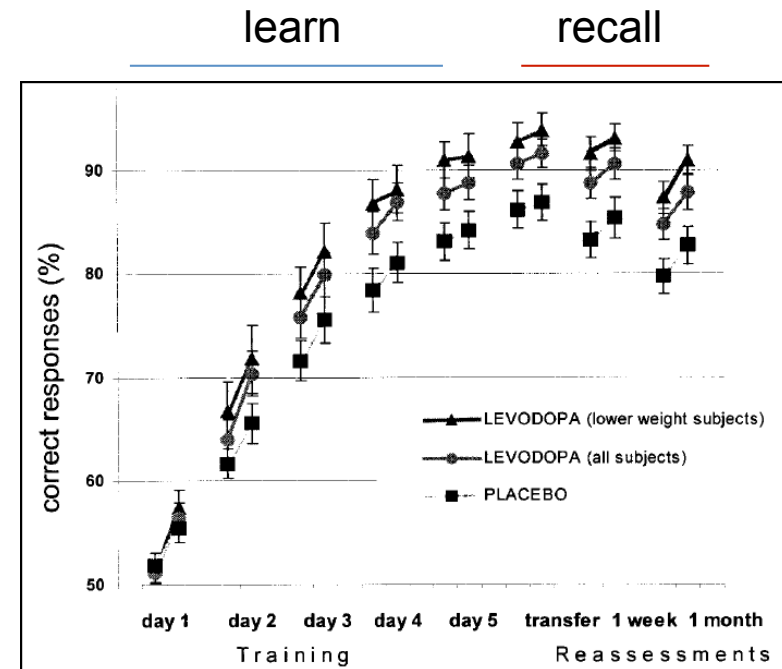
Young adults (Wittman et al., 2005)

- Better delayed memory for reward-predicting items
- SN/VTA & hippocampal activation

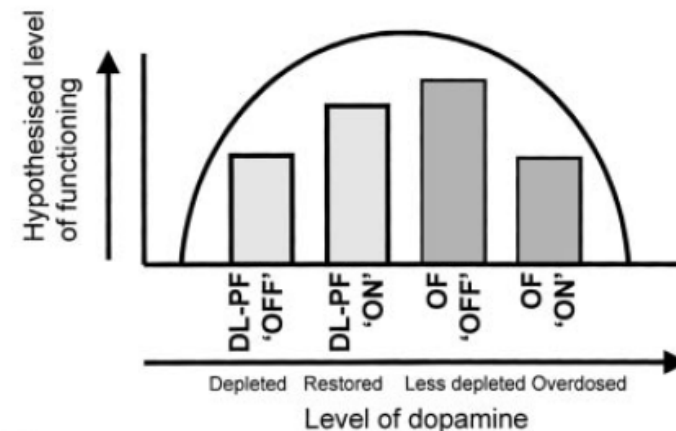


Effect of dose

- Dose-dependent enhancement of learning and recall in young adults (Knecht et al., 2004)



- ‘Inverted u-shape’ relationship with working memory (Goldman-Rakic et al., 2000; Cools et al., 2001)



Questions

- In healthy older adults who have a dopamine decline, can dopamine improve episodic memory?
 - effect of reward versus no-reward
 - effect of pharmacological manipulation (L-DOPA)
- Is the relationship linear or non-linear?

Participants

- n=30, age 65-75 yrs
- Within-subject design: 2 days (L-dopa / placebo), 1 week apart
- Healthy, 97% non-smokers, 93% normotensive
- Normal neuropsychological test profile

	Mean (SD)
Age, yrs	70.17 (3.26)
Gender M:F	11: 19
Education, yrs	16.27 (2.97)
National Adult Reading Test IQ	122 (6.00)
Body Mass Index	26.7 (4.5)
Mini-Mental State Examination score	29.9 (0.4)
Geriatric Depression Scale score	1.6 (2.1)

Paradigm

Early: 2 hrs (minimise confounding state effects)

Delay: 6 hrs

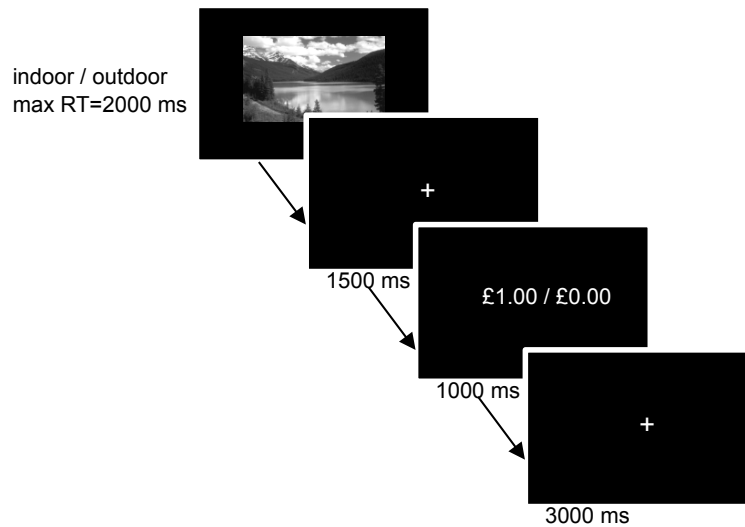
90 mins →

Brief training:
10 trials

DRUG
150mg L-DOPA

or
PLACEBO
Orange juice

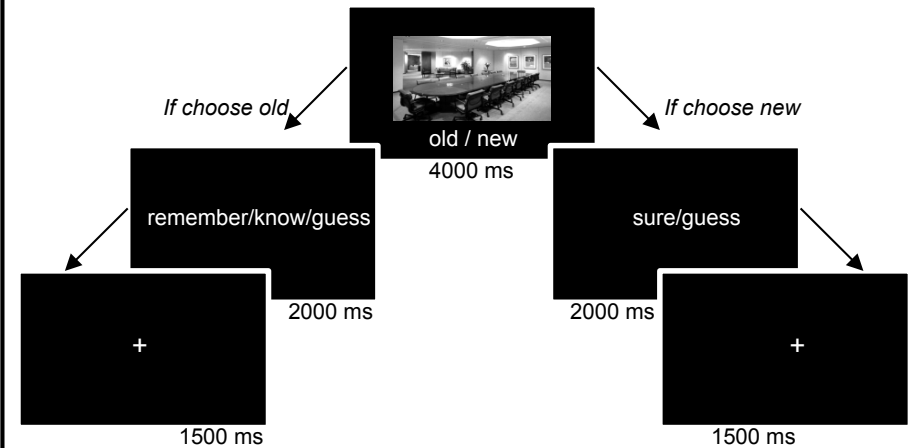
Encoding task



- 120 trials
- One category: images predict reward
- High accuracy level

Recognition task x2

Remember/know paradigm



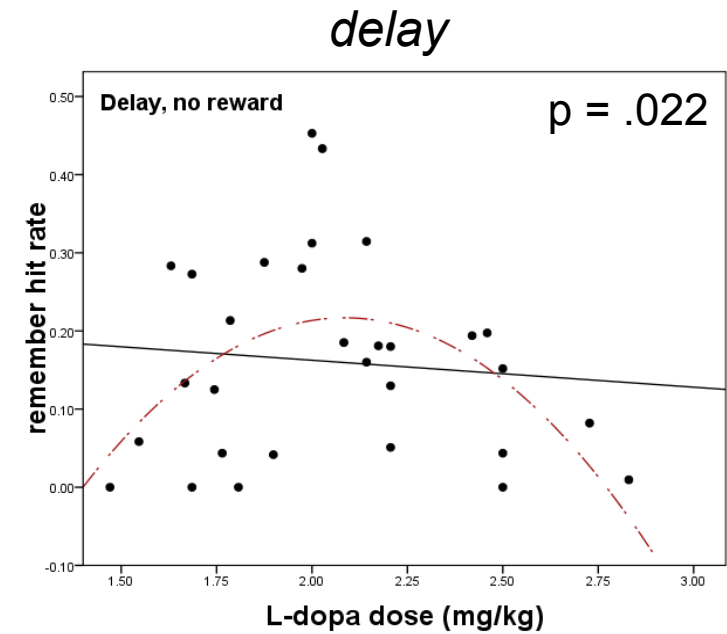
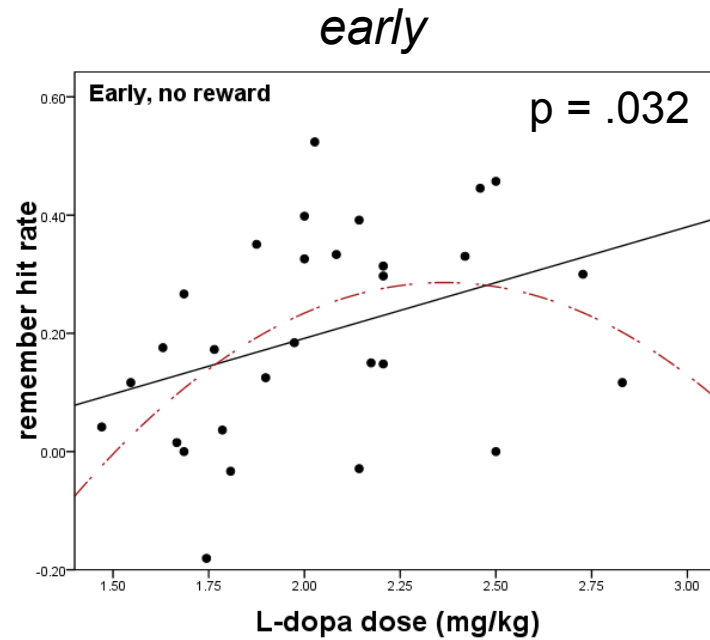
- 60 old + 30 distractors for each task

Measures

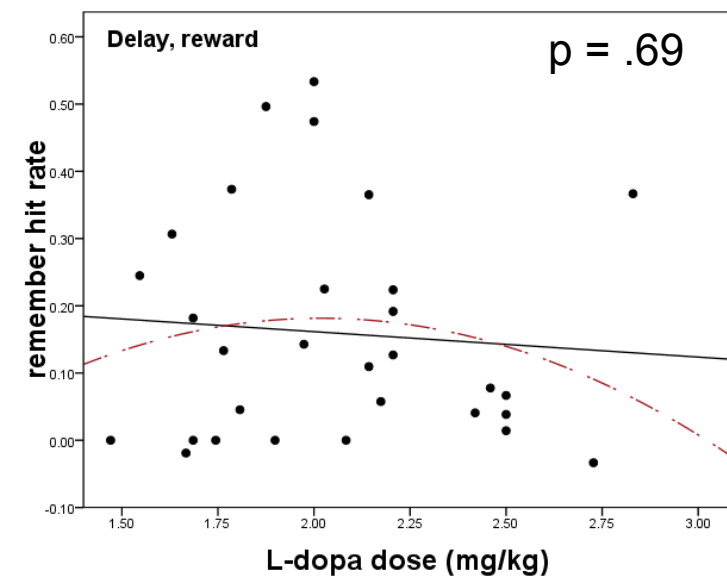
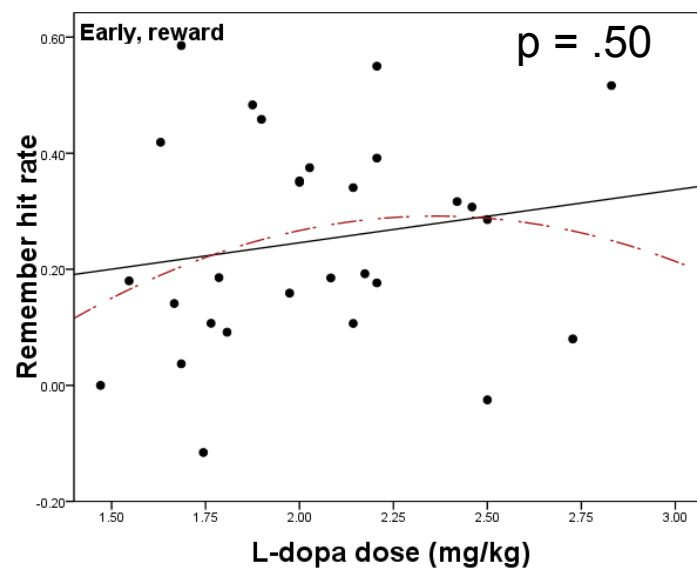
- Rates as a proportion of number of correctly encoded items
- Corrected remember rate: *remember hits – remember false alarms*
- Corrected know rate: $\frac{\textit{know hits}}{1 - \textit{remember hits}} - \frac{\textit{know false alarms}}{1 - \textit{remember false alarms}}$
- *Weight-adjusted l-dopa dose: 150 / body weight (mg/kg)*

Quadratic effect of l-dopa on non-reward 'remember' responses

no reward



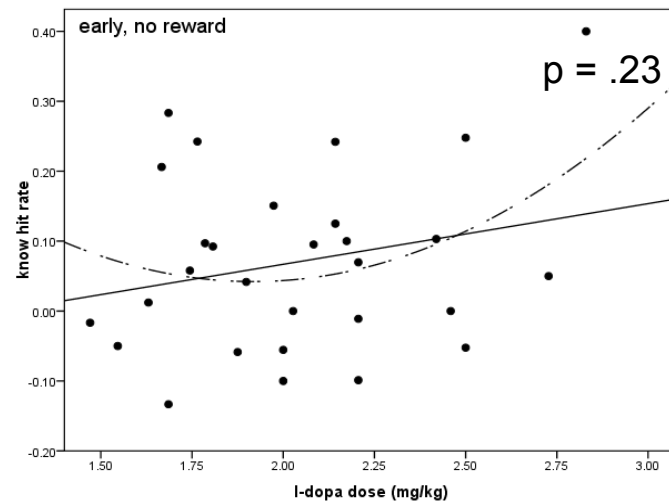
reward



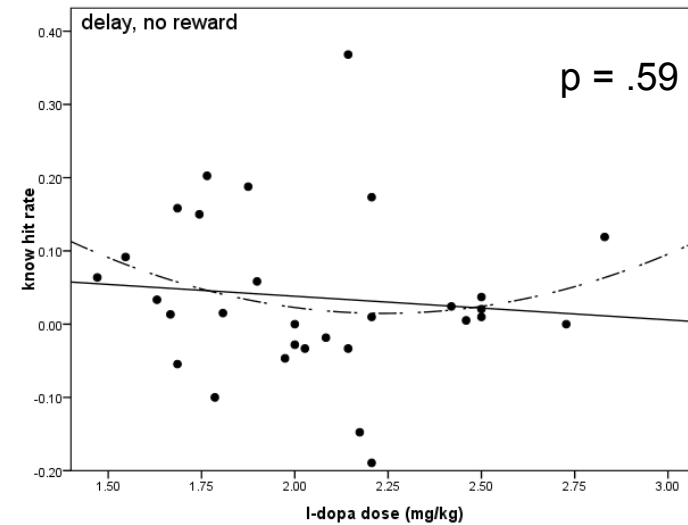
No linear or quadratic effect of L-dopa on 'know' responses

no reward

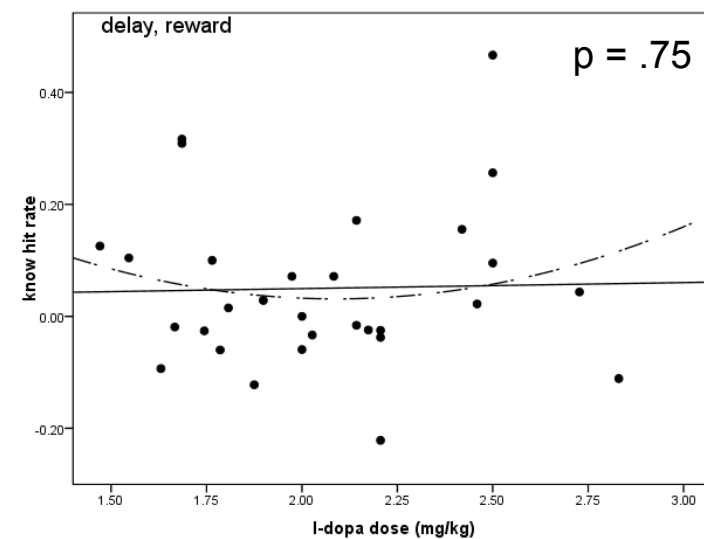
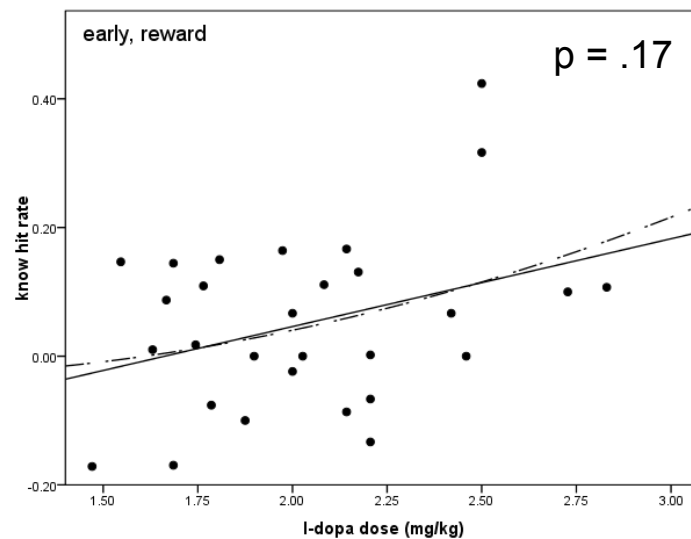
early



delay

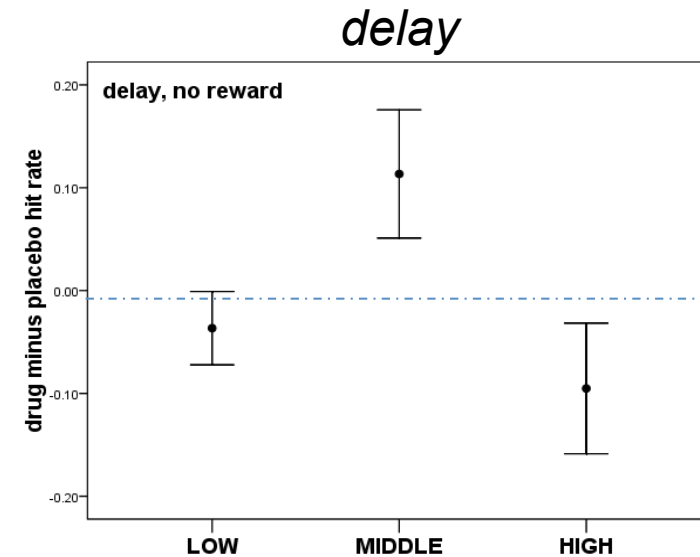
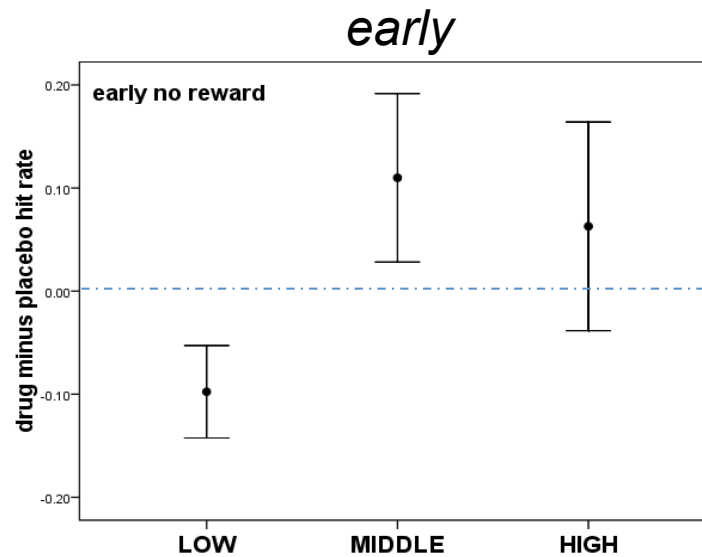


reward

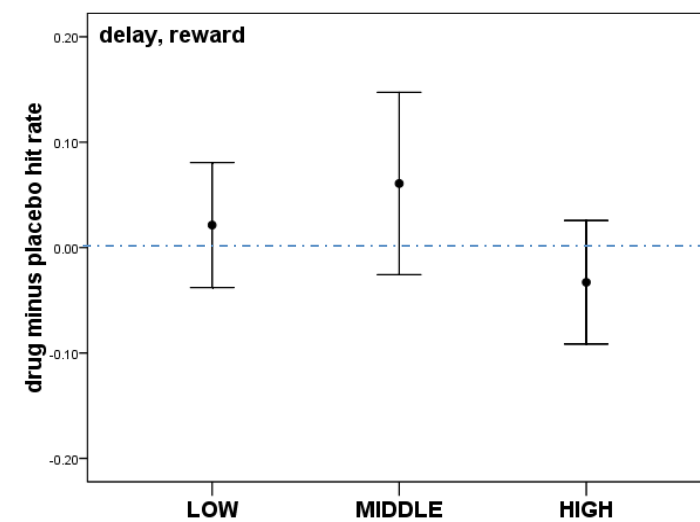
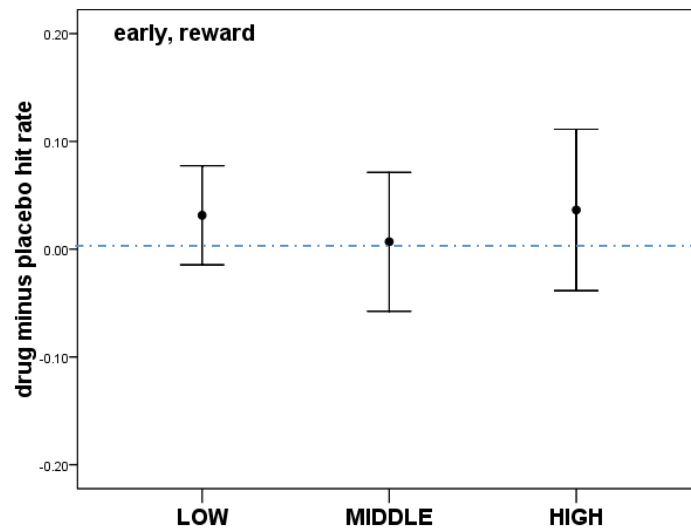


Inverted u-shape relationship between delayed remember responses for non-rewarding images & L-dopa

no reward



reward



Discussion

Dopamine modulates episodic memory in healthy older adults:

- Specific effect on remember responses (hippocampal dependent)
- Inverted u-shape effect – middle dose improves & higher dose impairs, especially delayed memory
- Dissociation between effect of l-dopa on rewarding vs. non-rewarding cues

Variable dopamine decline with age

Future studies to quantify underlying dopamine reserve (e.g. PET, structural imaging) may help understand dose-response relationship

Acknowledgements

- The Wellcome Trust
- All participants

Any questions?

"The afternoon of life must have a significance of its own and cannot be merely a pitiful appendage of life's morning," – Carl Jung

Extra slides

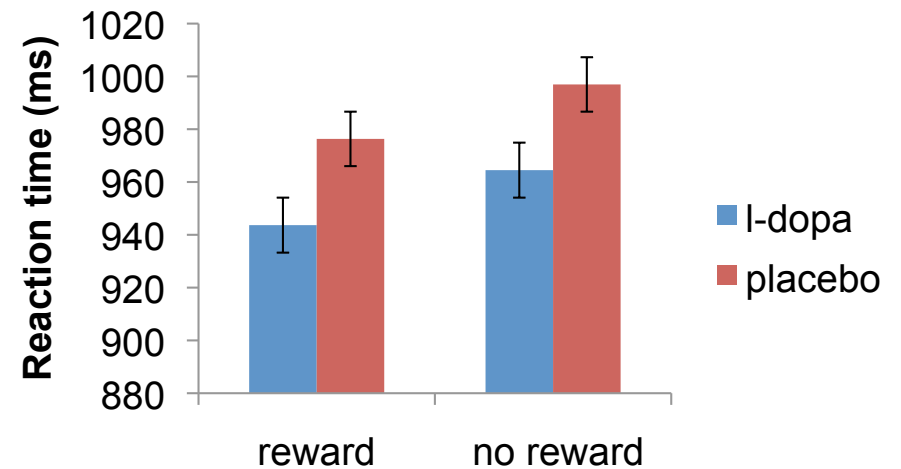
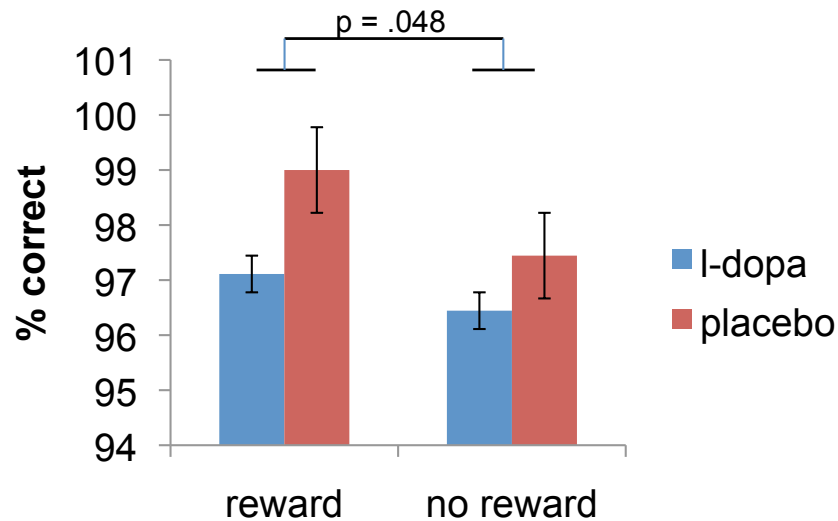
Participants

- 32 healthy older adults age 65-75yrs
- No neurological/psychiatric/cardiovascular/endocrine conditions
- Normal neurological examination
- Normal performance neuropsychological tests:

<u>Domain</u>	<u>Test</u>
IQ	NART
Declarative memory	RAVLT
Semantic Memory	“FAS”, animals
Working Memory	Backward Digit Span, Trail Making B
Processing speed	Forward Digit Span, Trail Making A
Attention	D2
Visuo-spatial	VOSP number location

- Within-subject design: 2 days, 1 week apart
- 150mg L-DOPA and placebo (counterbalanced)

Encoding



- Overall high accuracy (97.5% correct indoor/outdoor classification)

remember

know

