The computational psychiatry of major depressive disorder

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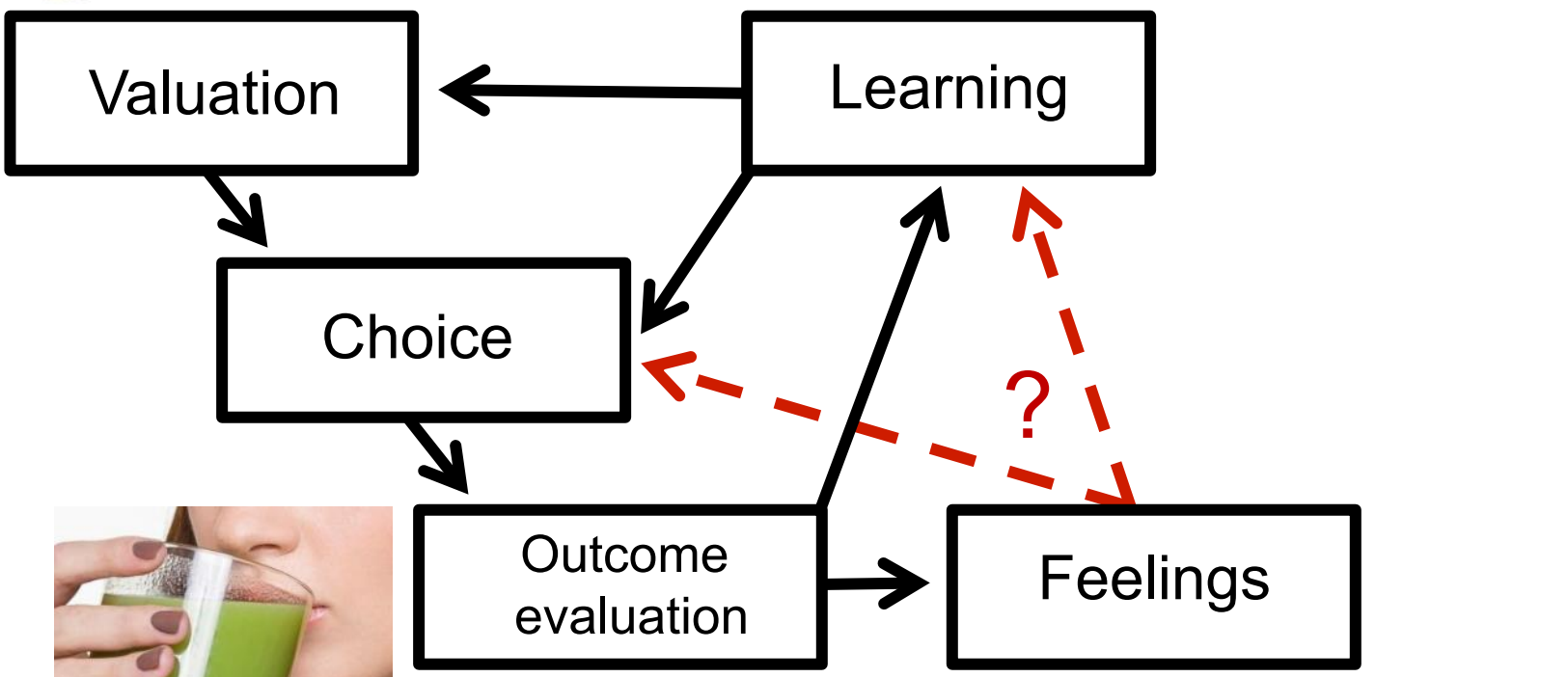
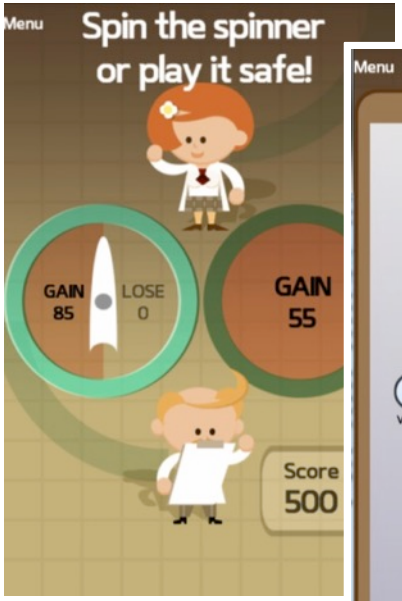
Symposium and Advanced Course on Computational Psychiatry and Ageing Research
Ringberg Castle
13 September 2016

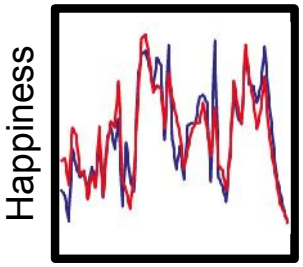
Aim 1: How does mood relate to behaviour?



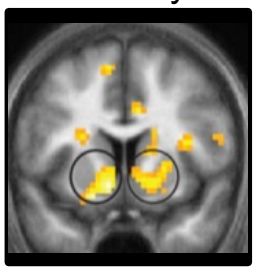
Rutledge et al. (2014) PNAS
Rutledge et al. (2015) J Neurosci
Eldar, Rutledge* et al. (2016) TICS*
Rutledge et al. (2016) Nature Comm

Aim 2: Does depression affect the mood-behaviour relationship?

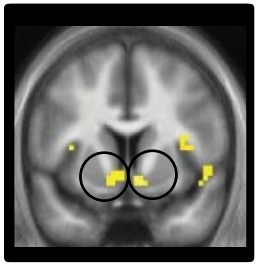


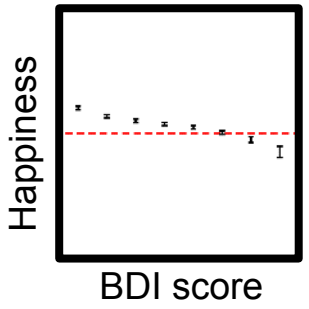


Healthy



Depressed





$$Happiness(t) = w_0 + w_1 \sum_{j=1}^{t} \gamma^{t-j} CR_j + w_2 \sum_{j=1}^{t} \gamma^{t-j} EV_j + w_3 \sum_{j=1}^{t} \gamma^{t-j} RPE_j$$

Certain Reward

Expected Value

Reward Prediction Error
(reward – expectation)

Aim 3: Do antidepressants affect the mood-behaviour relationship?

SSRI

Ketamine

Years	1	2	3	4	5
Development of new tasks & new **computational models**					
Longitudinal **smartphone** data from remitted patients					
Functional MRI of patients & controls					
Pharmacology of standard & fast-acting antidepressants					

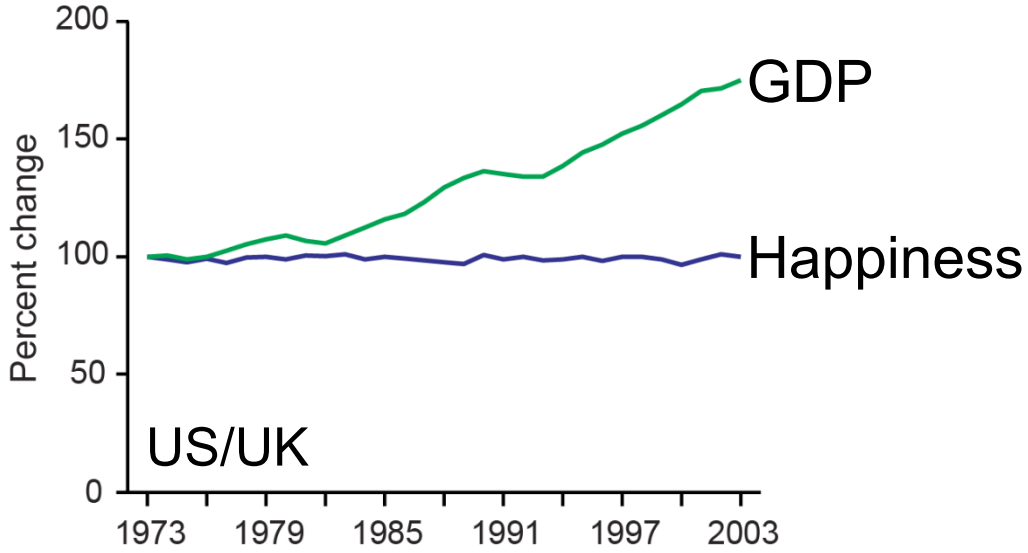
Clinical collaborators

Roland Zahn (King's)

John Krystal (Yale)

How happy are you at this moment?

What determines happiness?



350 million worldwide suffer from depression

Major clinical symptoms:

1) Depressed mood as indicated by subjective report
2) Diminished interest or pleasure as indicated by subjective report

Why do we do the things that we do?
The neuroscience of mood and its relation to choice

How does the brain respond to rewards?

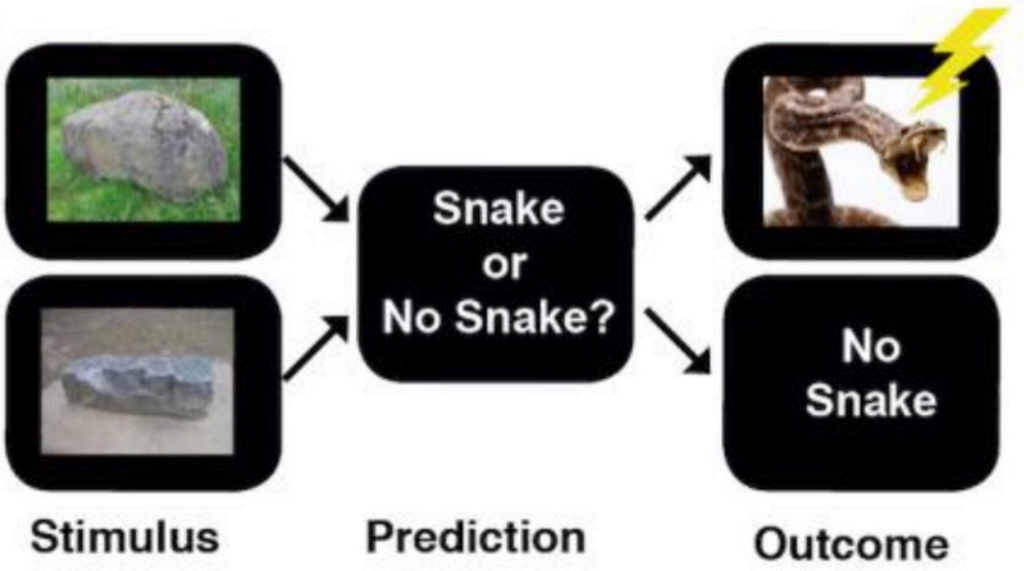
How do rewards relate to subjective feelings?

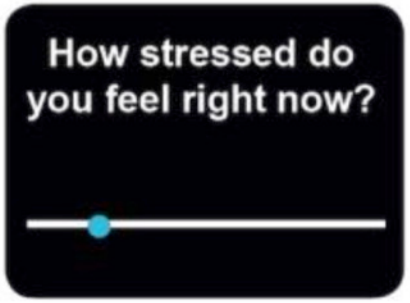
Does dopamine affect feelings and decisions?

Can computational models of feelings and behavior help us to study the neural circuits than link mood and choice?

What determines stress?

Subjective state dynamics depend on the cumulative impact of past events.

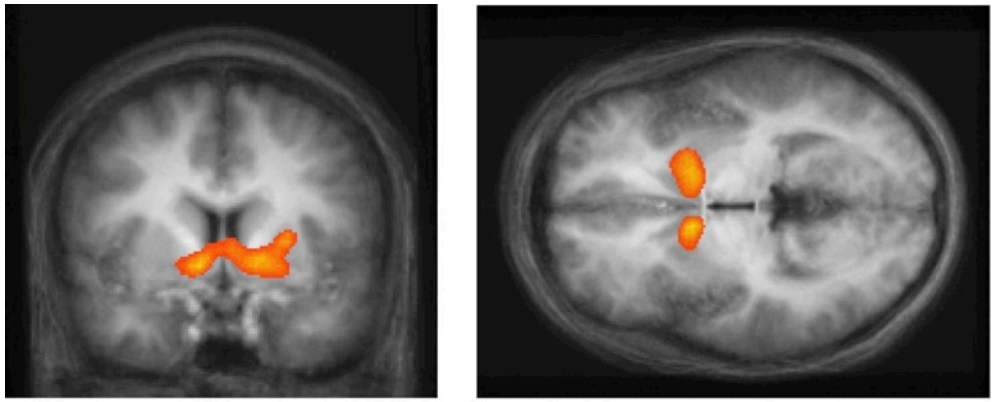




de Berker, Rutledge, et al. (2016) Nature Comm

What determines happiness?

Striatal activity represents RPEs

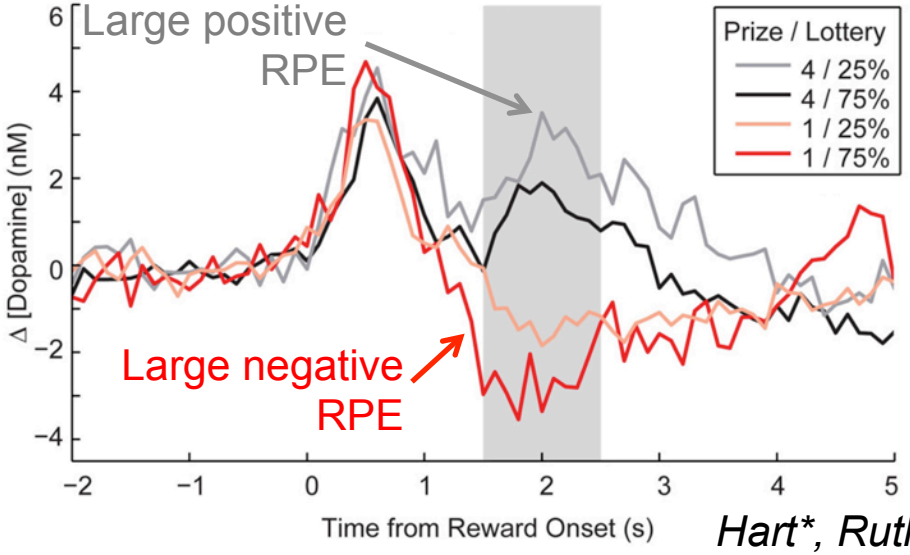


RPE = reward – expectation

Rutledge, Dean, Caplin & Glimcher (2010) J Neurosci

Caplin, Dean, Glimcher & Rutledge (2010) Q J Econ

Striatal dopamine represents RPEs



Hart, Rutledge*, Glimcher & Phillips (2014) J Neurosci*

A framework for value-based decision making

Valuation

Learning

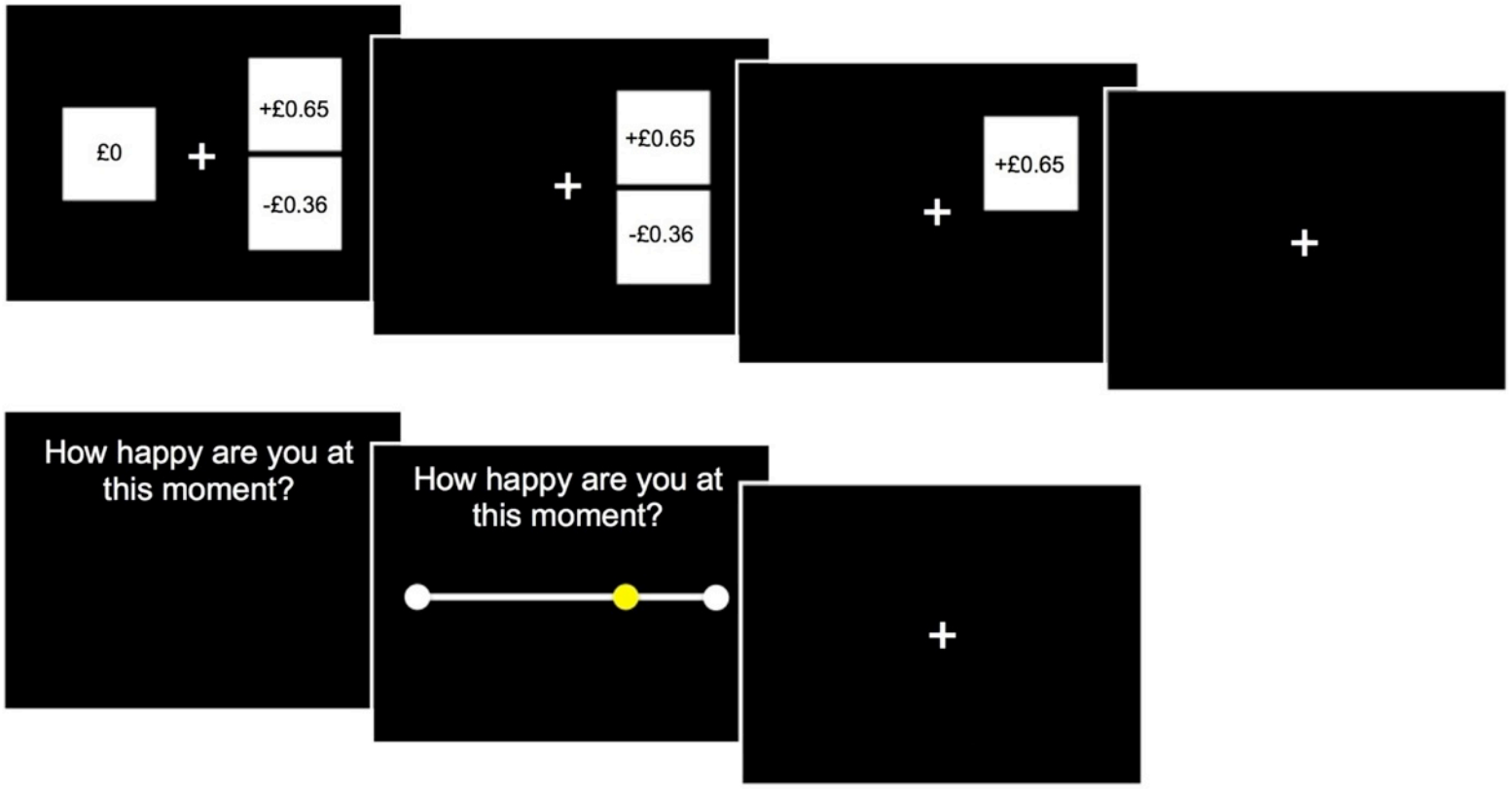
Choice

Outcome evaluation

Feelings?

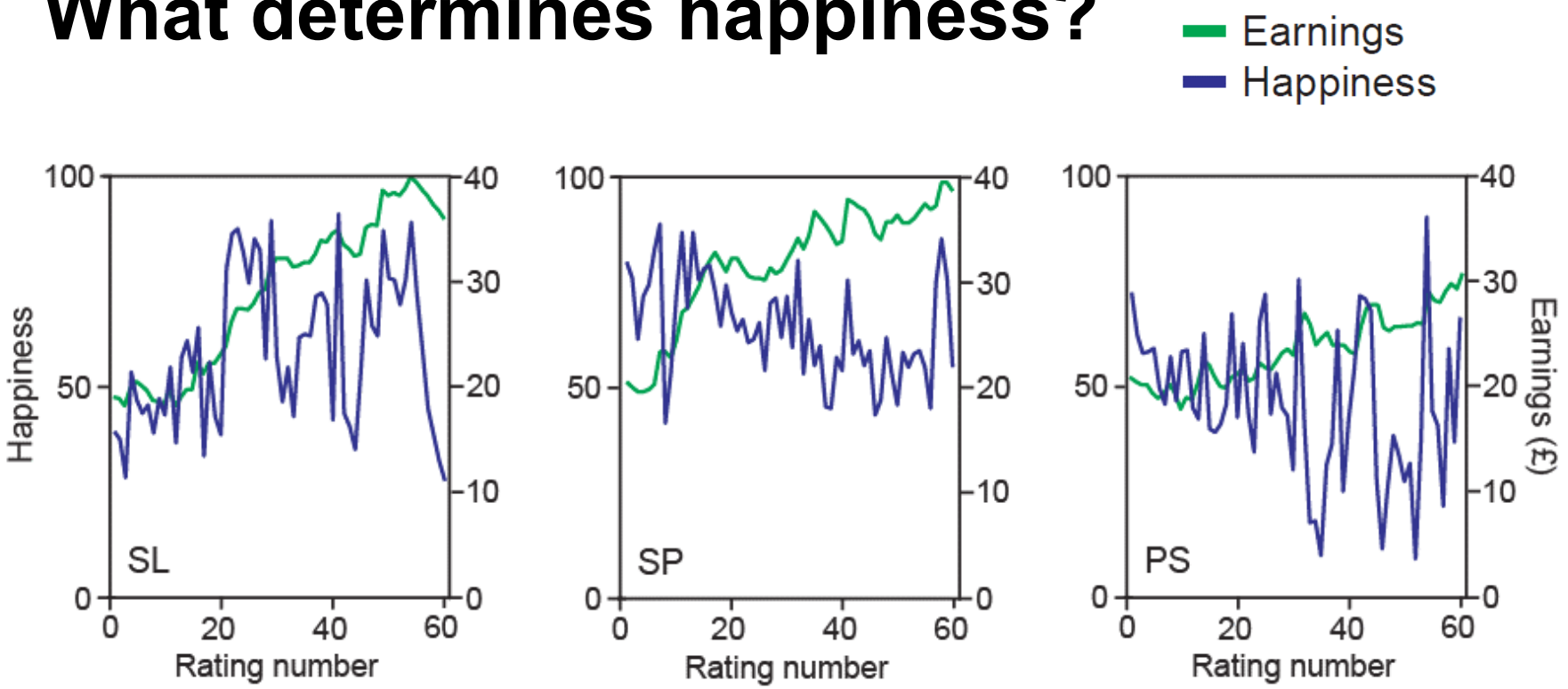
What determines happiness?

What determines happiness?



Rutledge, Skandali, Dayan & Dolan (2014) PNAS

What determines happiness?



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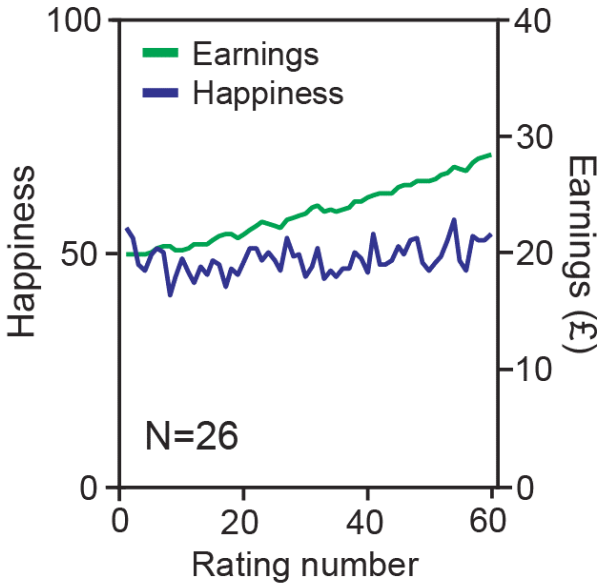
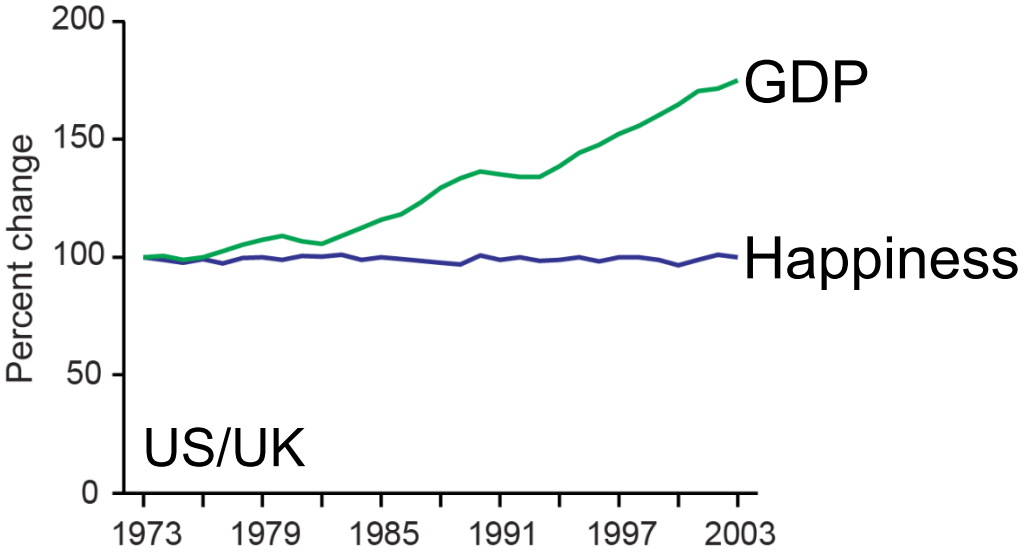




What determines happiness?

"Certain reward" or "Expected value"

"Reward prediction error"

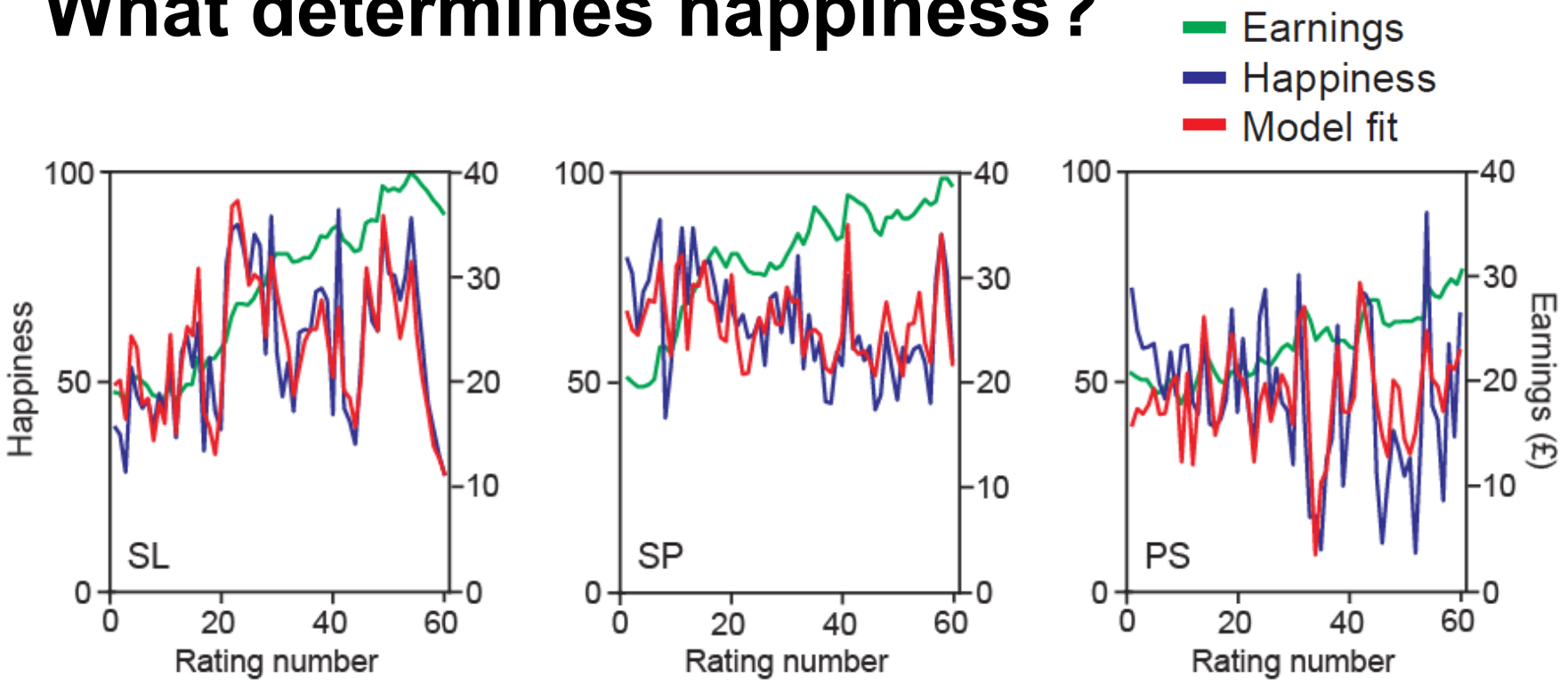
$$Happiness(t) = w_0 + w_1 \sum_{j=1}^{t} \gamma^{t-j} CR_j + w_2 \sum_{j=1}^{t} \gamma^{t-j} EV_j + w_3 \sum_{j=1}^{t} \gamma^{t-j} RPE_j$$

Certain reward

Expected value

Reward prediction error

What determines happiness?



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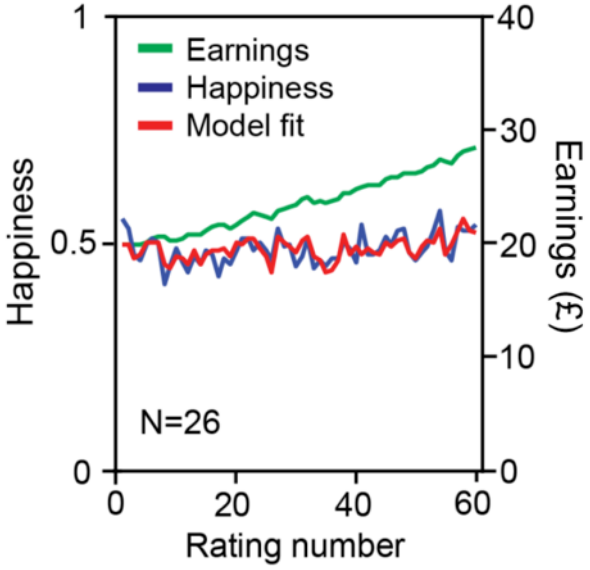
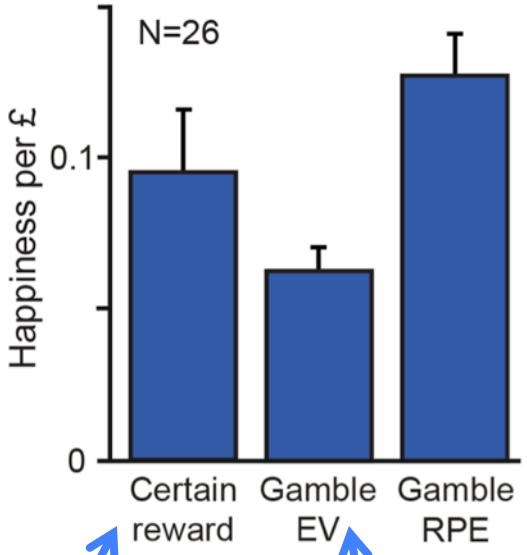
What determines happiness?





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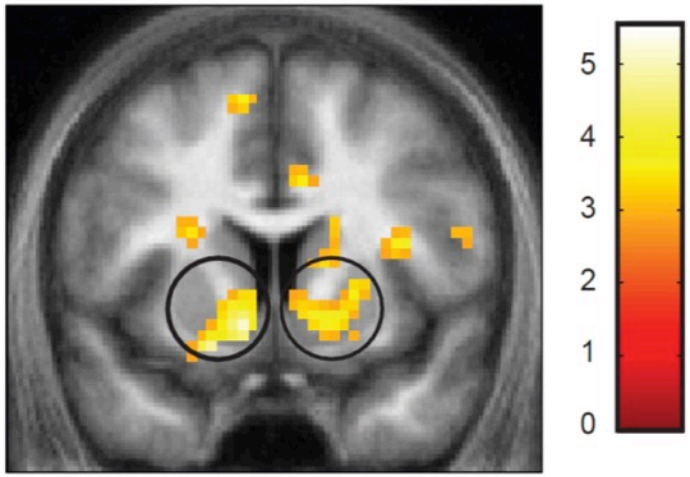
Certain reward

Expected value

Reward prediction error
(reward – expectation)

BOLD activity in ventral striatum is correlated with future happiness ratings



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Certain reward

Expected value

Reward prediction error
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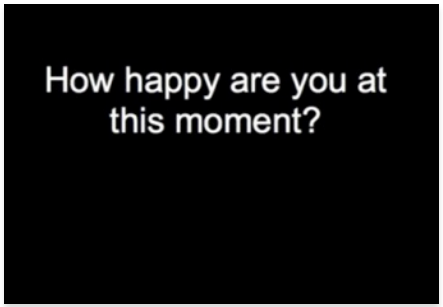
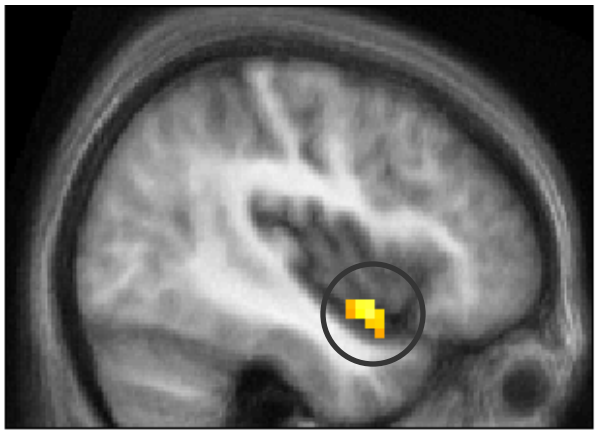
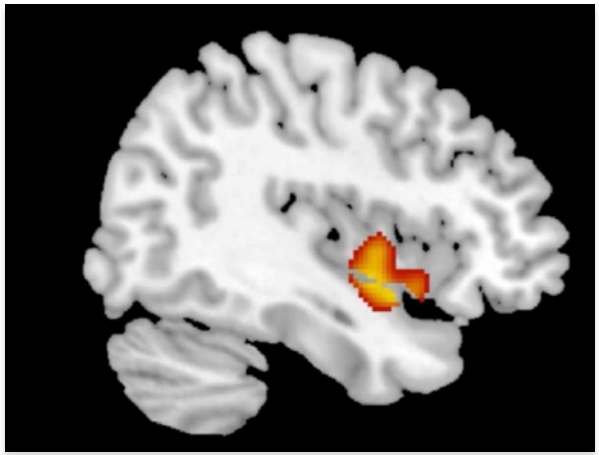
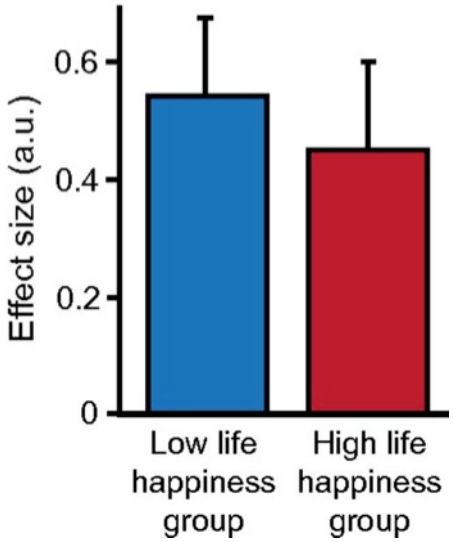
BOLD activity in right anterior insula is correlated with current happiness ratings

$$Happiness(t)$$

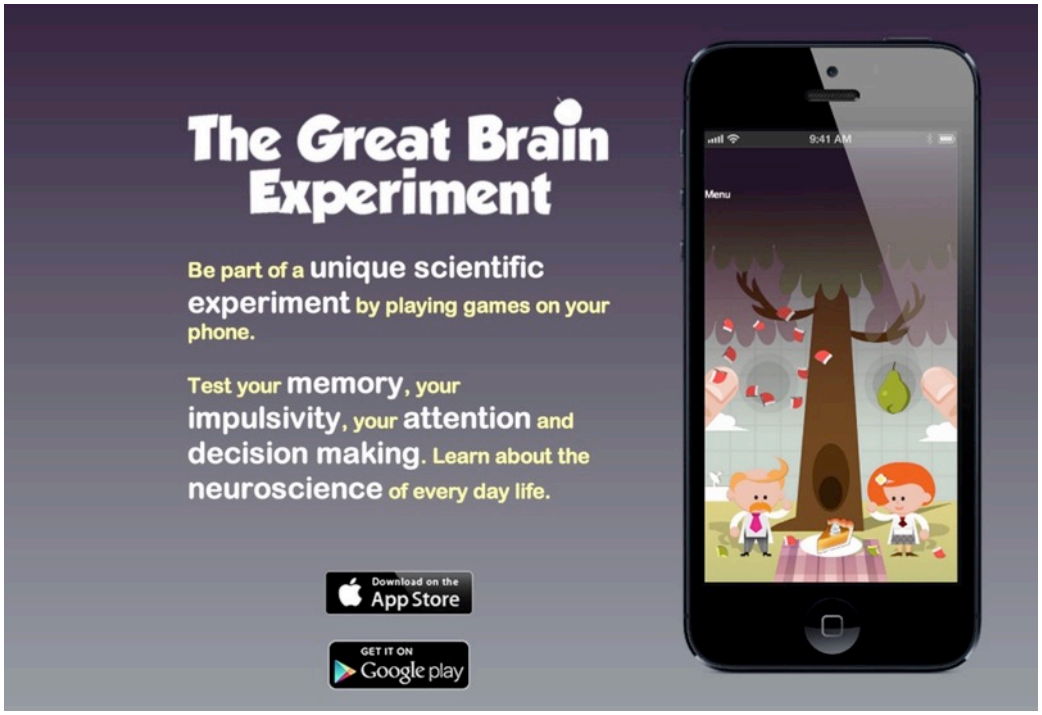








Lower grey matter volume with lower eudaimonic well-being *(Lewis et al., 2013*)



www.thegreatbrainexperiment.com

Core team

Robb Rutledge

Peter Zeidman

Peter Smittenaar

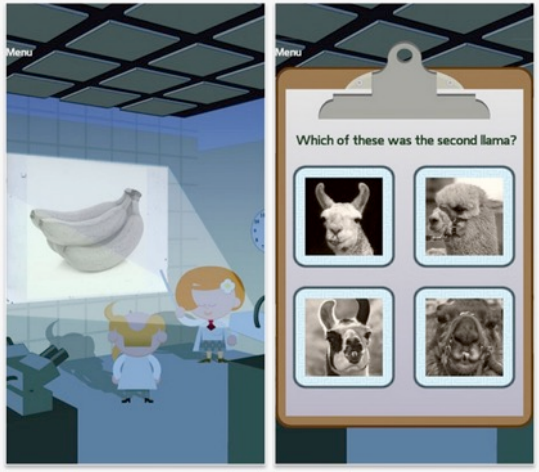
Harriet Brown

Rick Adams

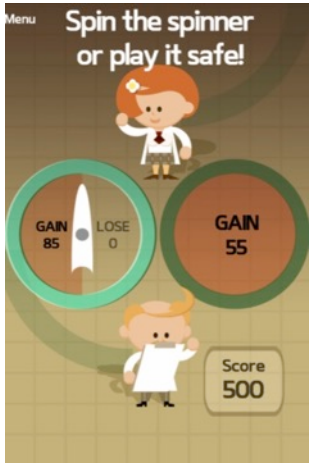
working memory

impulsivity

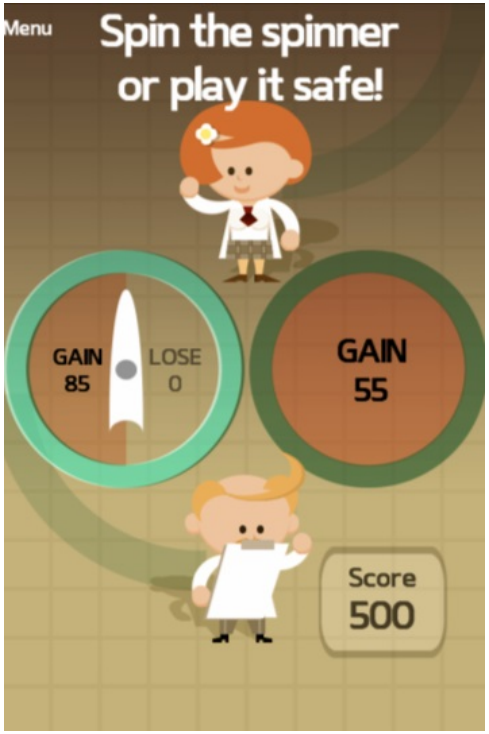
attentional blink

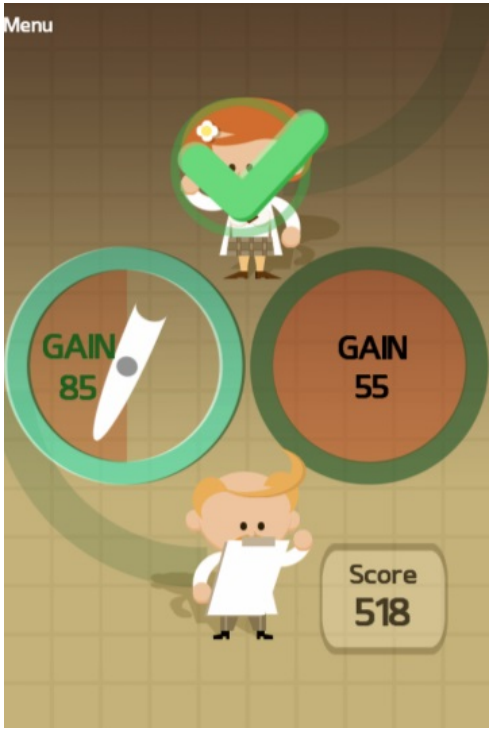


decisions and happiness



The Great Brain Experiment ‘What makes me happy?’



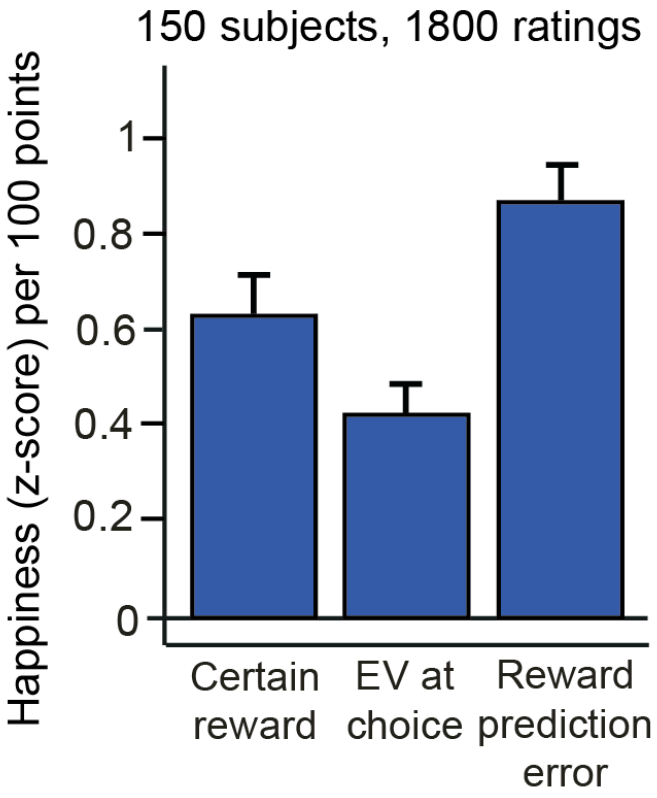


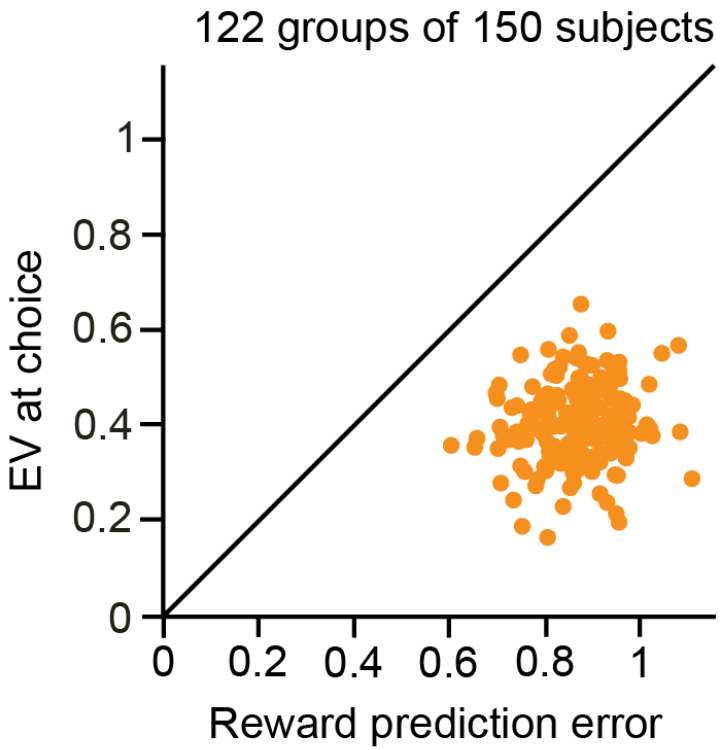
30 choices per play
12 happiness ratings

Rutledge, Skandali, Dayan & Dolan (2014) PNAS

The Great Brain Experiment ‘What makes me happy?’

N=18,420 subjects (221,040 ratings)





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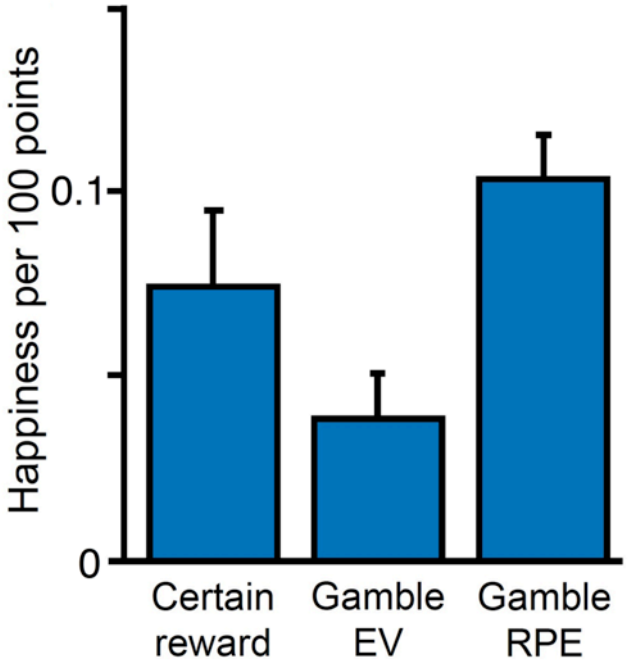
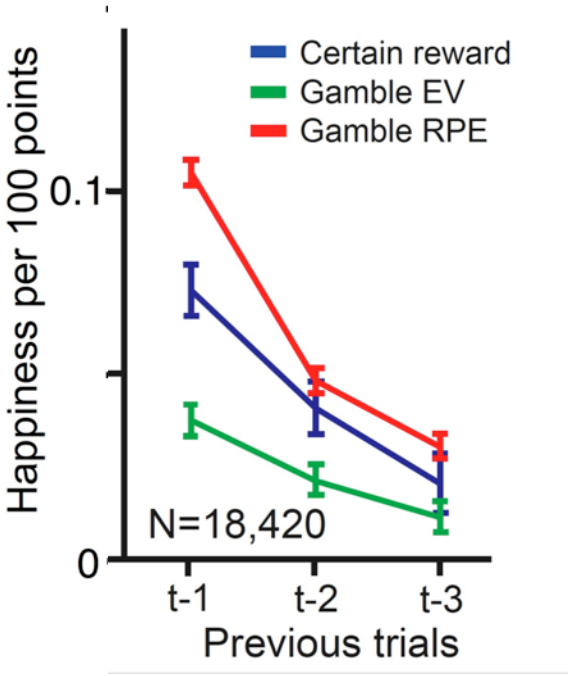
The Great Brain Experiment 'What makes me happy?'

N=18,420 subjects (18,420 ratings)

1 happiness rating
per subject
2-3 trials per subject





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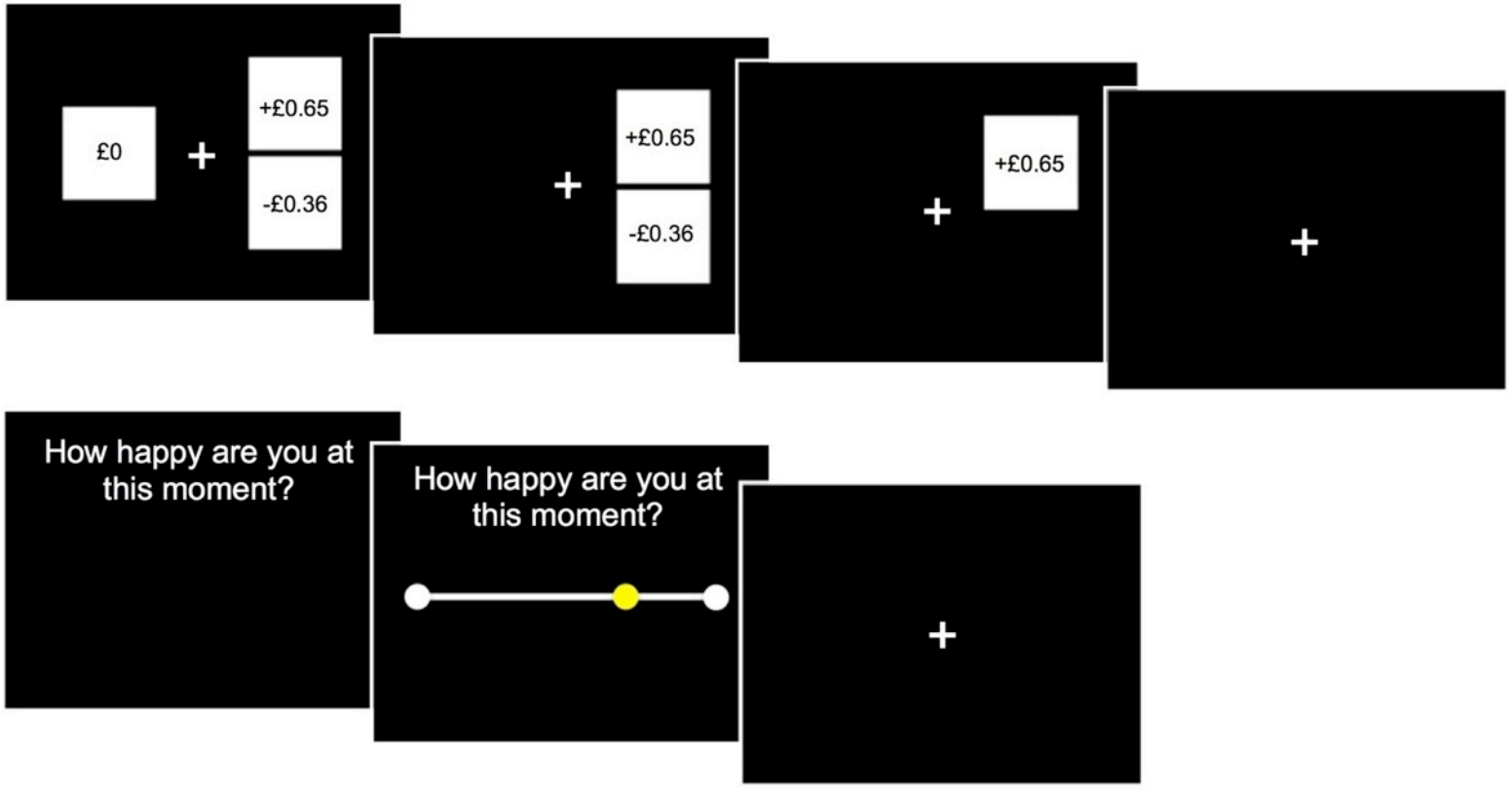
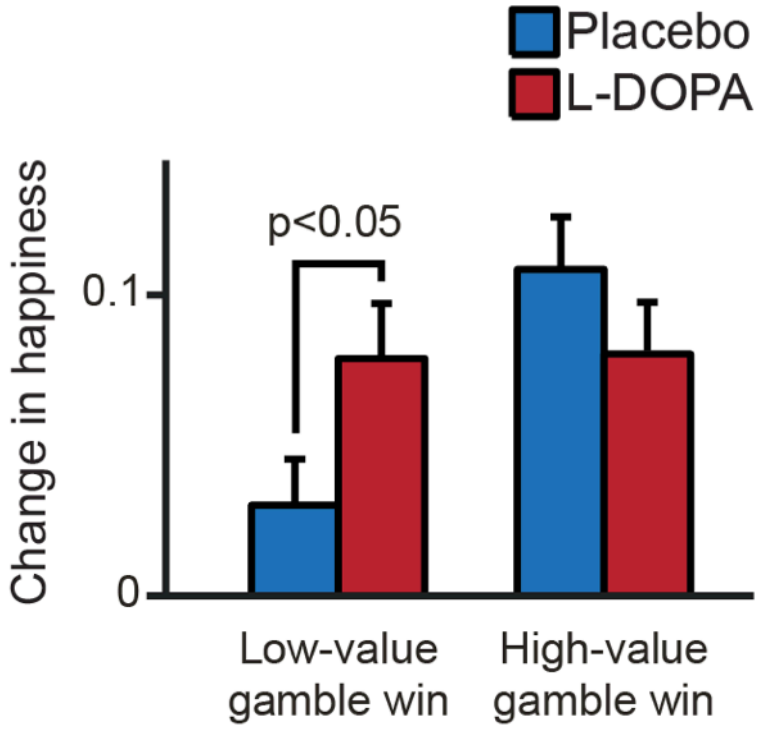
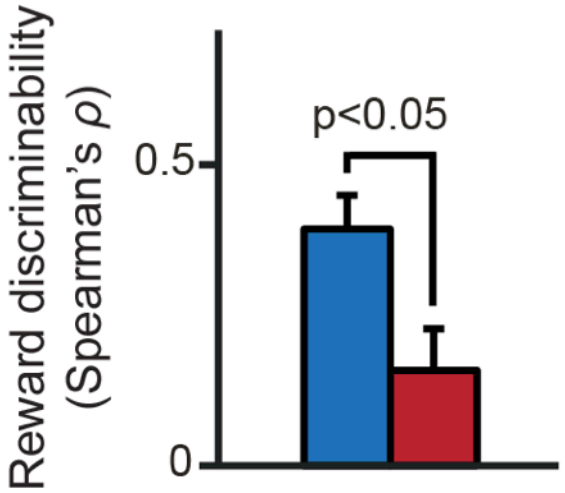
Does L-DOPA affect happiness from rewards?



Rutledge, Skandali, Dayan & Dolan (2015) J Neurosci

Does L-DOPA affect happiness from rewards?

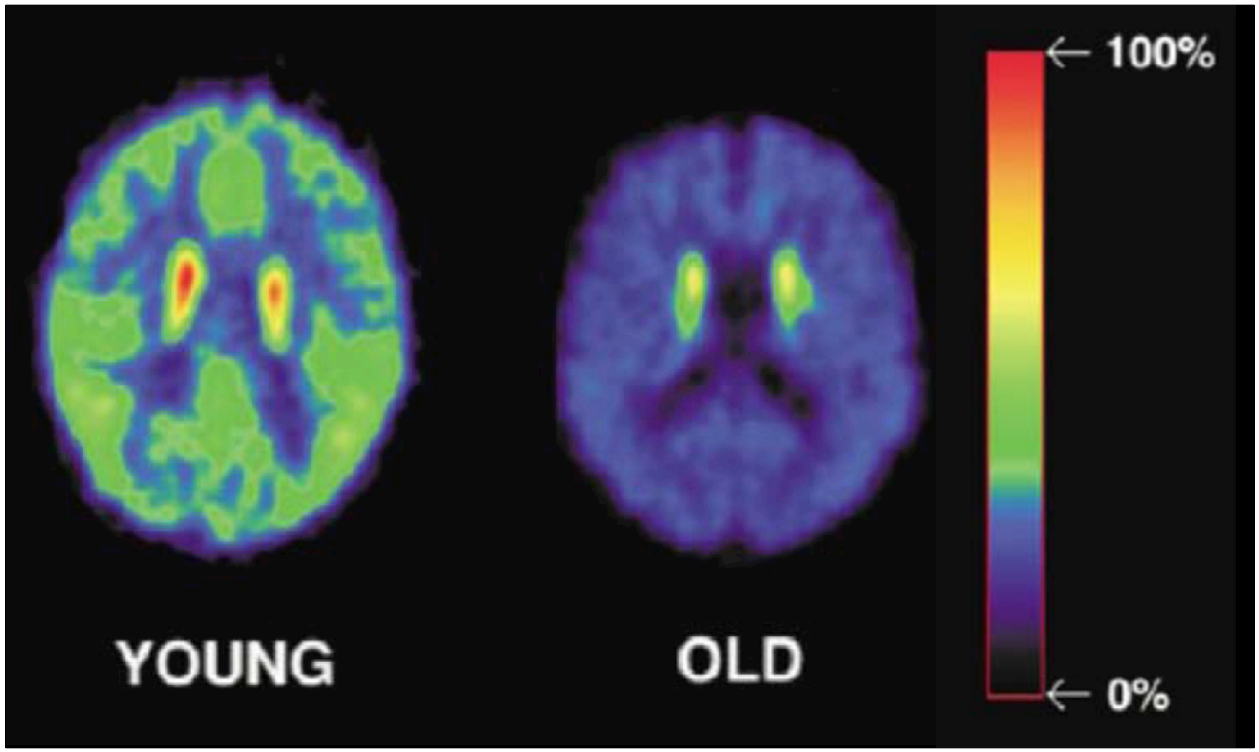




N=30

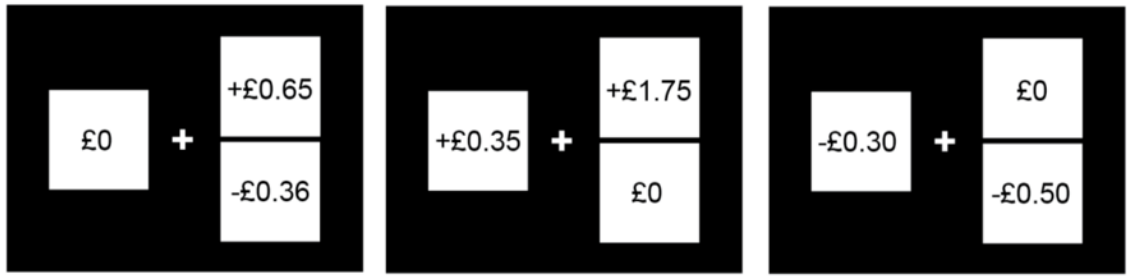
Dopamine declines with age

Economic risk taking decreases over the lifespan *(Dohmen et al., 2005; Deakin et al., 2004; Tymula et al., 2010)*



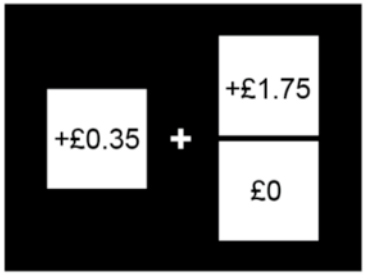
Kaasinen & Rinne (2002)

Does dopamine affect risk taking?

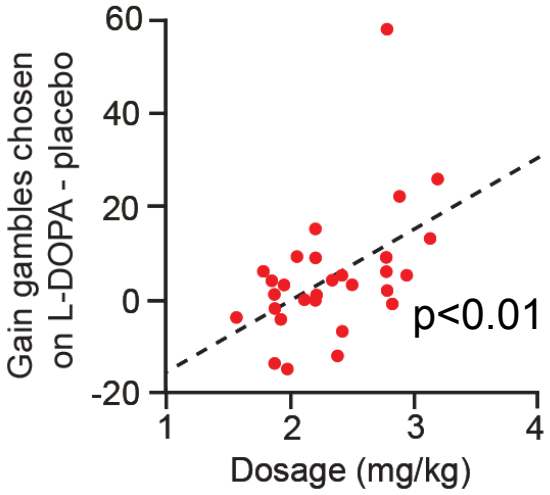


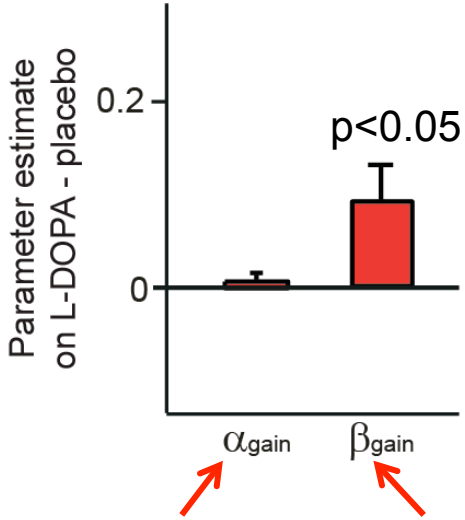
Mixed (n=100) Gain (n=100) Loss (n=100)

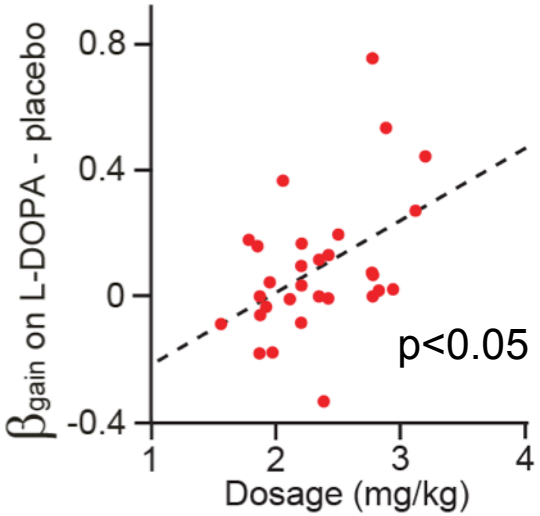
Rutledge, Skandali, Dayan & Dolan (2015) J Neurosci



L-DOPA increases gambling in gain trials







Economic risk preference for gains

Pavlovian approach for gains

Prospect Theory

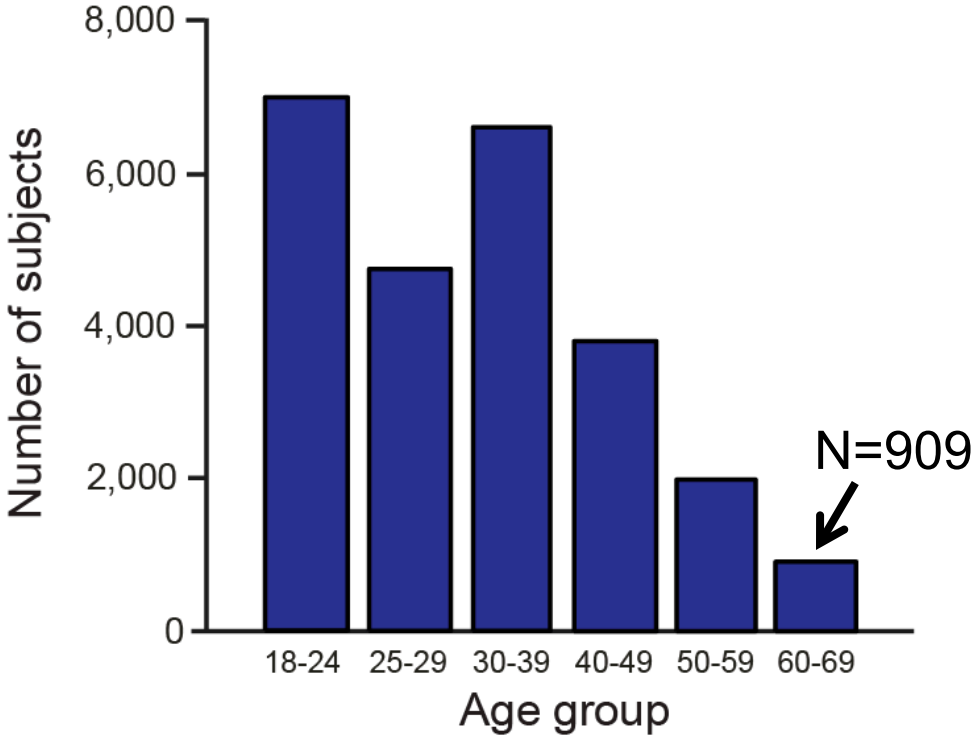
$$U(v) = v^{\alpha_{gain}}$$

Approach-avoidance model

$$P_{gamble} = \frac{(1-\beta_{gain})}{1+e^{\mu(U_{gamble}-U_{certain})}} + \beta_{gain}$$

The Great Brain Experiment ‘What makes me happy?’

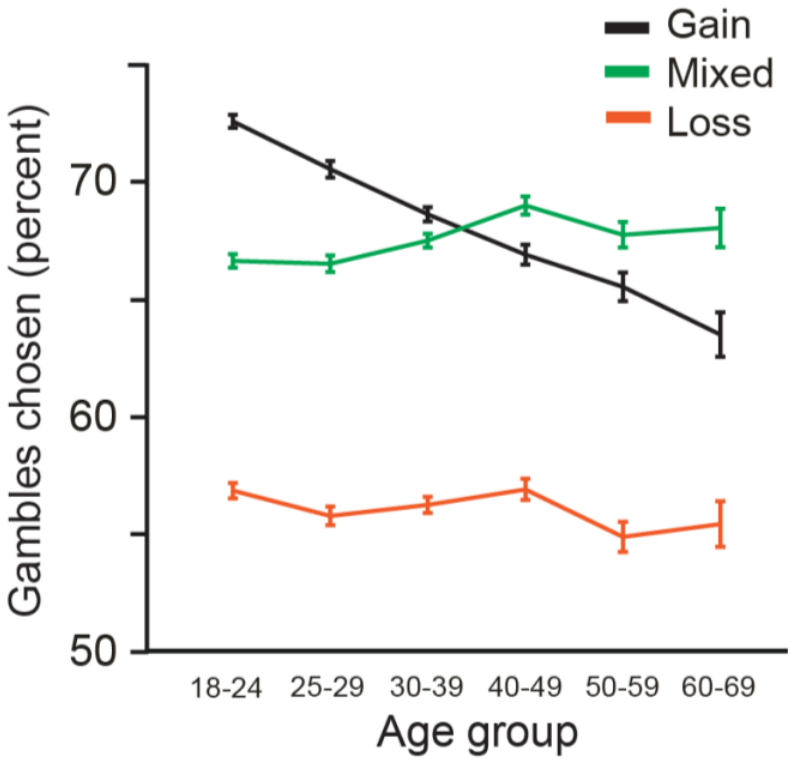
N=24,706 subjects (1,533,450 decisions)

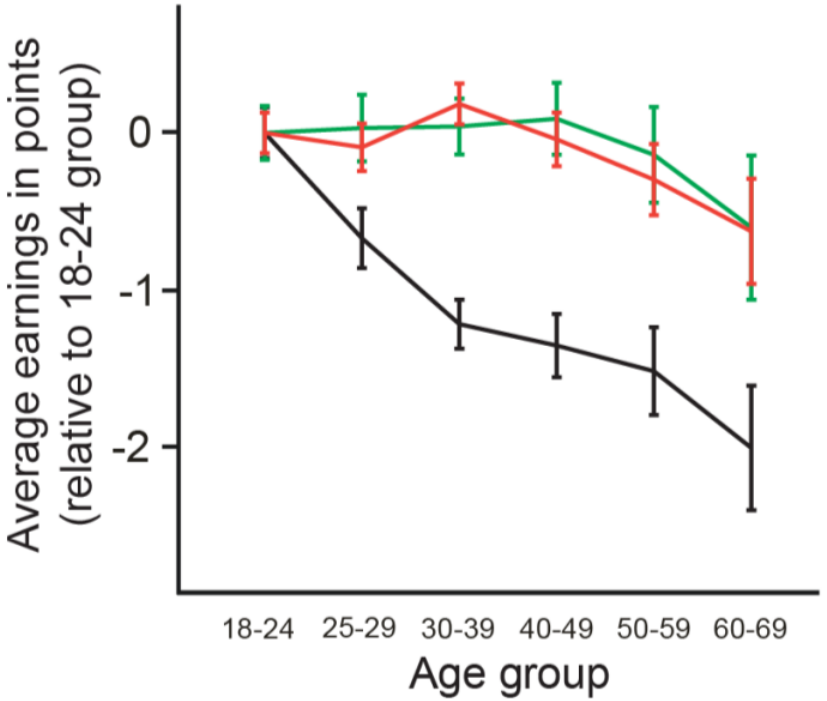


Rutledge, Smittenaar et al. (2016) Current Biology

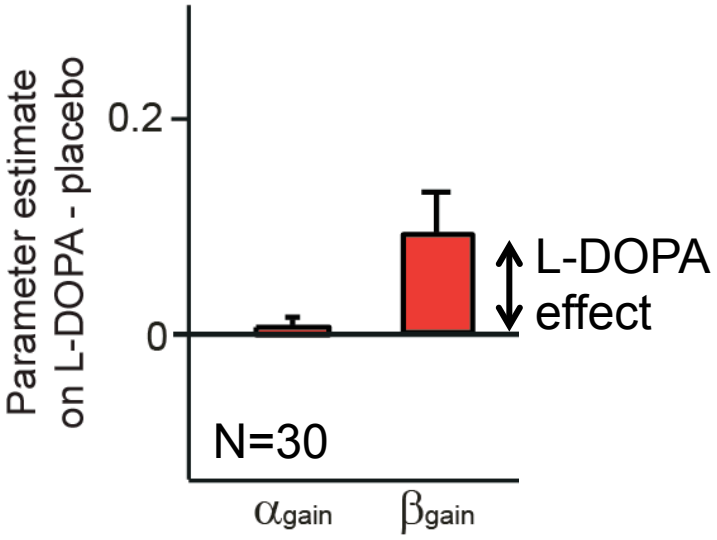
Gambling in gain trials decreases with age

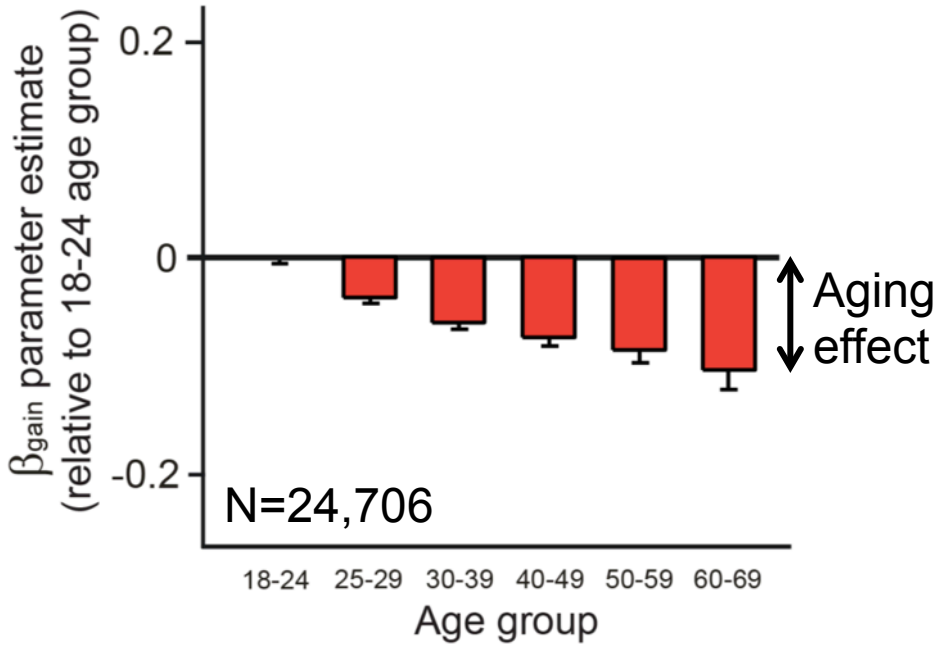
N=24,706

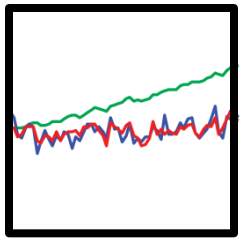




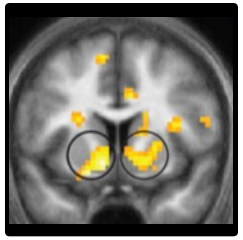
L-DOPA and aging have opposite effects on Pavlovian approach behavior



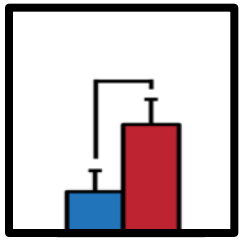




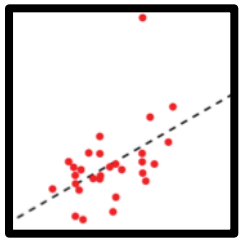
A computational model explains happiness from past expectations and reward prediction errors



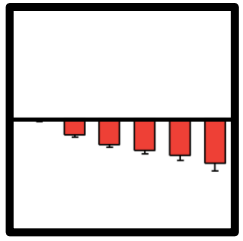
Neural activity in the striatum predicts future happiness ratings



Boosting dopamine increases happiness for small rewards

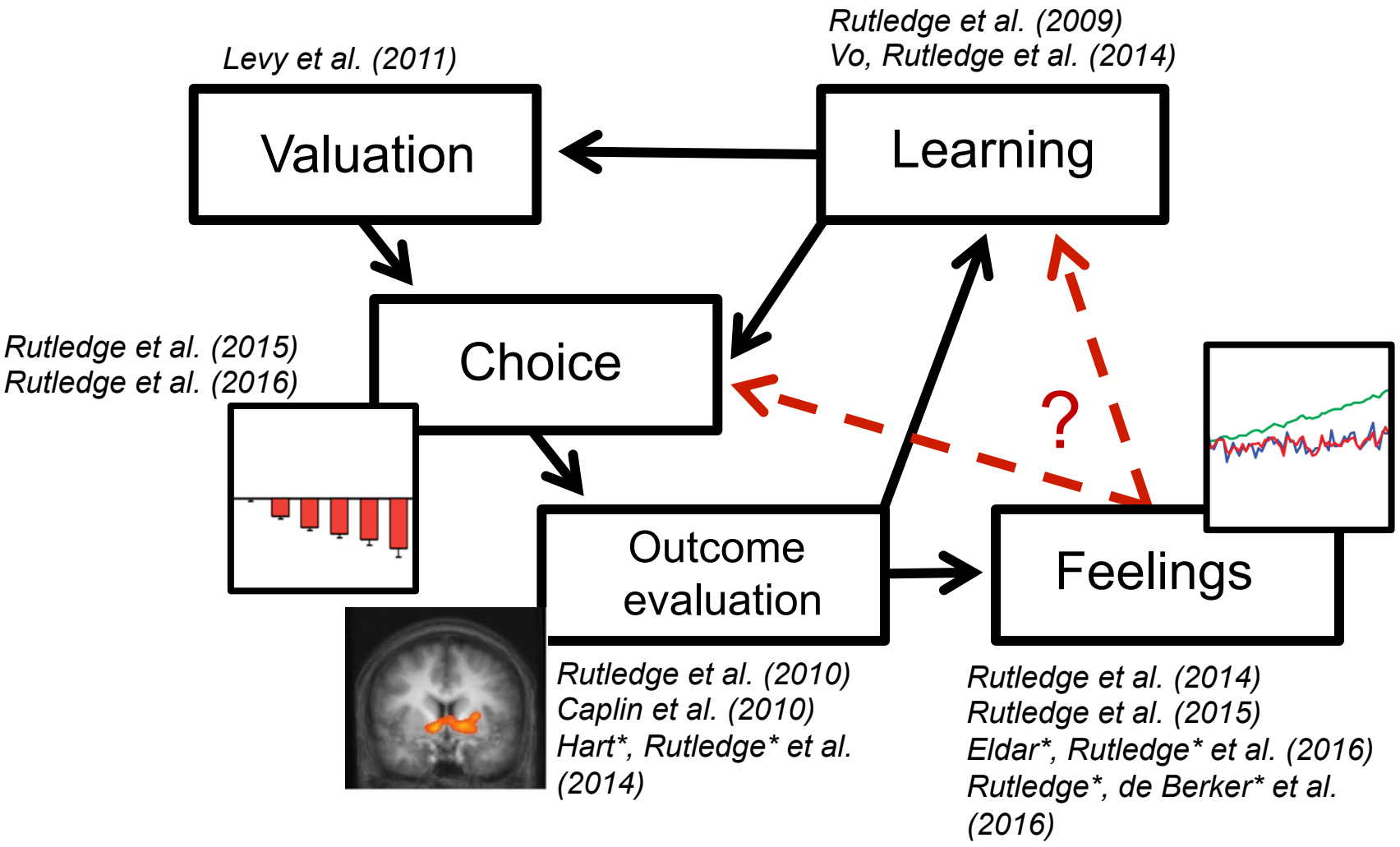


Boosting dopamine increases risk taking for potential rewards

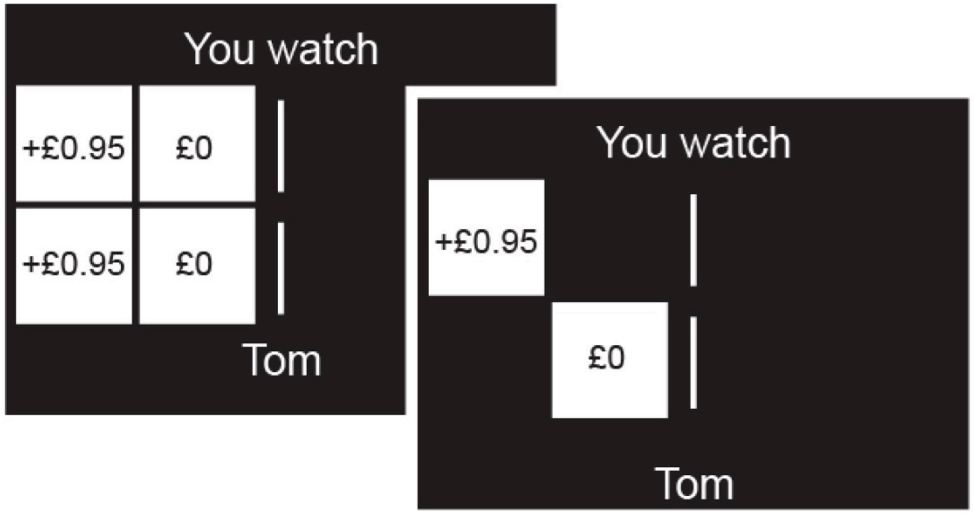


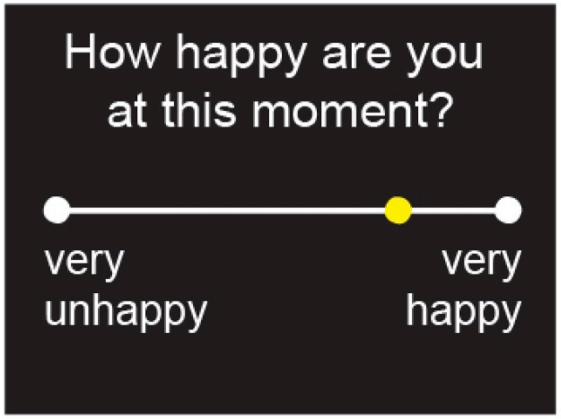
Aging decreases risk taking for potential rewards

A framework for value-based decision making



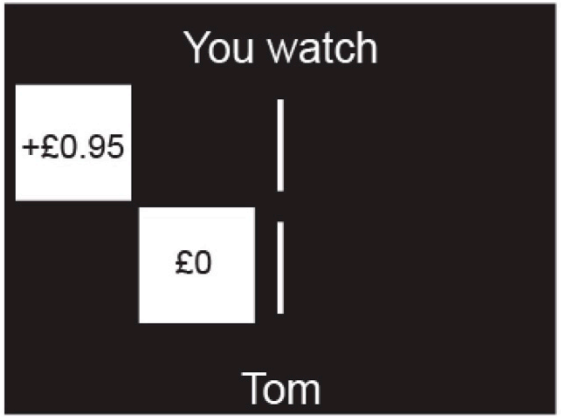
How does inequality impact momentary happiness?

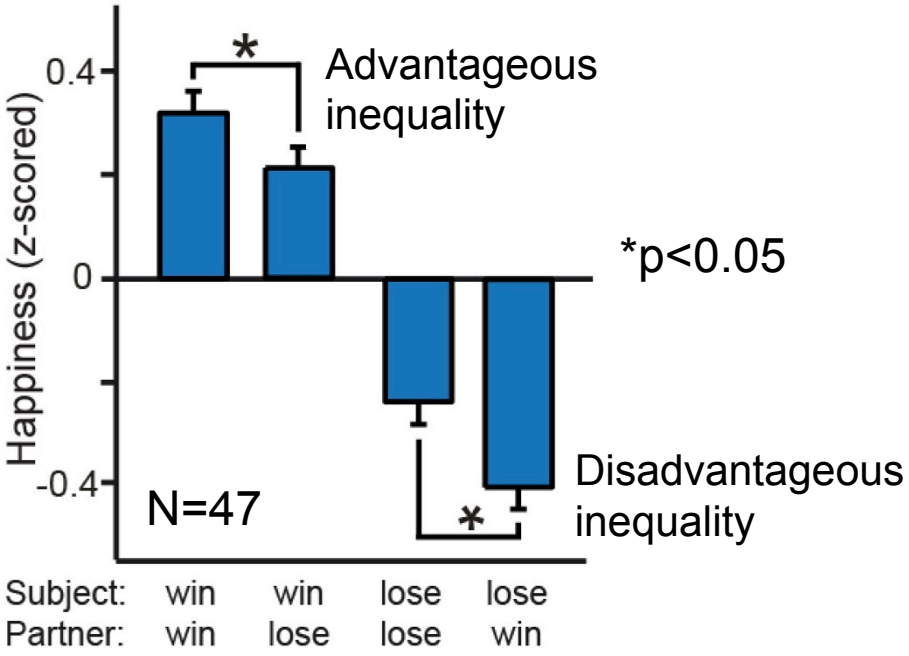




Rutledge, de Berker*, et al. (2016) Nature Comm*

How does inequality impact momentary happiness?



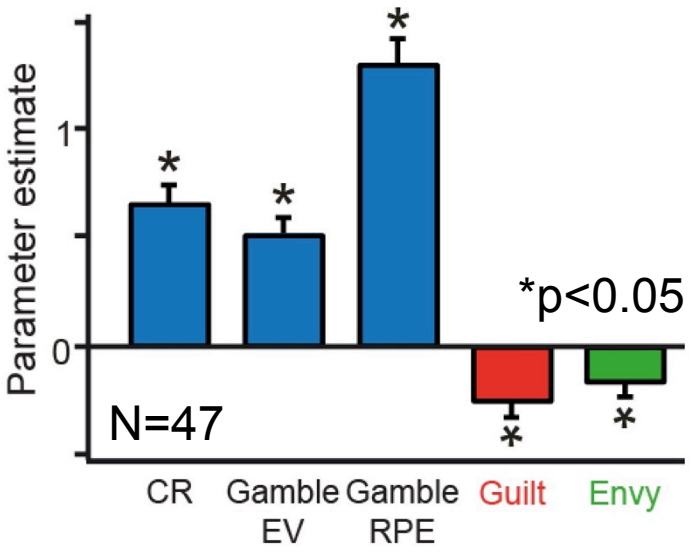


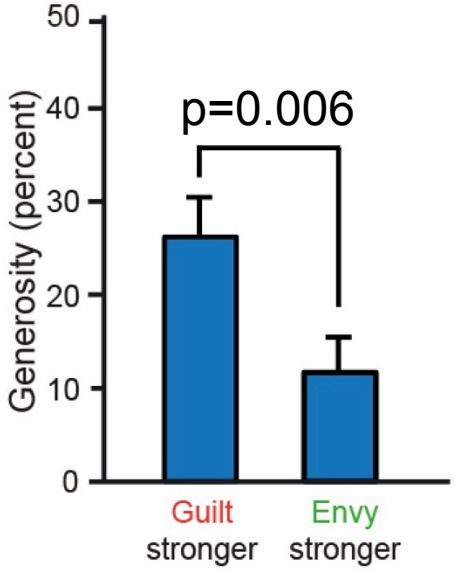
Do inequality impacts relate to altruism?

$$\mathbf{Happiness}(t) = w_0 + w_1 \sum_{j=1}^{t} \gamma^{t-j}\, \mathbf{CR}_j + w_2 \sum_{j=1}^{t} \gamma^{t-j}\, \mathbf{EV}_j + w_3 \sum_{j=1}^{t} \gamma^{t-j}\, \mathbf{RPE}_j$$

$$+w_4 \sum_{j=1}^{t} \gamma^{t-j} \max(\mathbf{R}_j - \mathbf{O}_j, 0) + w_5 \sum_{j=1}^{t} \gamma^{t-j} \max(\mathbf{O}_j - \mathbf{R}_j, 0)$$

Guilt Envy



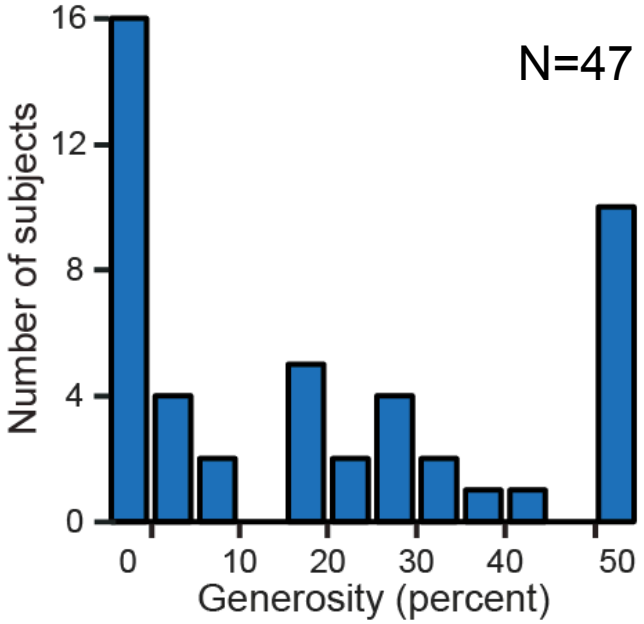


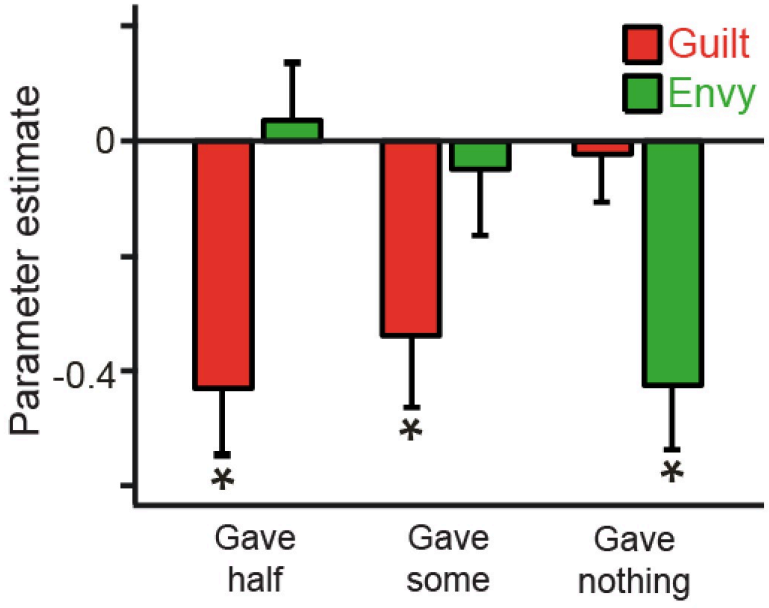
Inequality impacts on happiness predict generosity

$$\mathbf{Happiness}(t) = w_0 + w_1 \sum_{j=1}^{t} \gamma^{t-j}\, \mathbf{CR}_j + w_2 \sum_{j=1}^{t} \gamma^{t-j}\, \mathbf{EV}_j + w_3 \sum_{j=1}^{t} \gamma^{t-j}\, \mathbf{RPE}_j$$

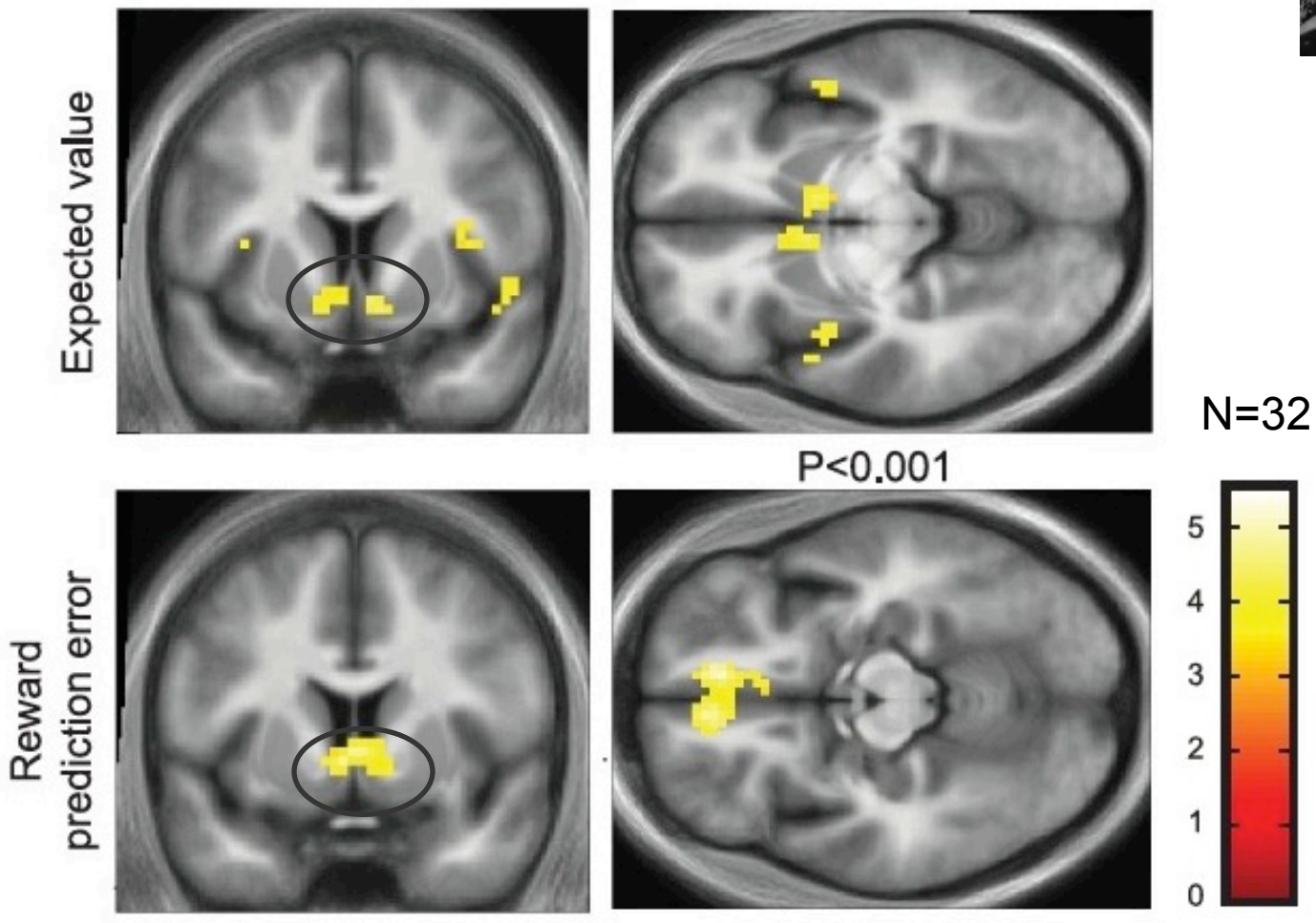
$$+w_4 \sum_{j=1}^{t} \gamma^{t-j} \max\left(\mathbf{R}_j - \mathbf{O}_j, 0\right) + w_5 \sum_{j=1}^{t} \gamma^{t-j} \max\left(\mathbf{O}_j - \mathbf{R}_j, 0\right)$$

Guilt Envy



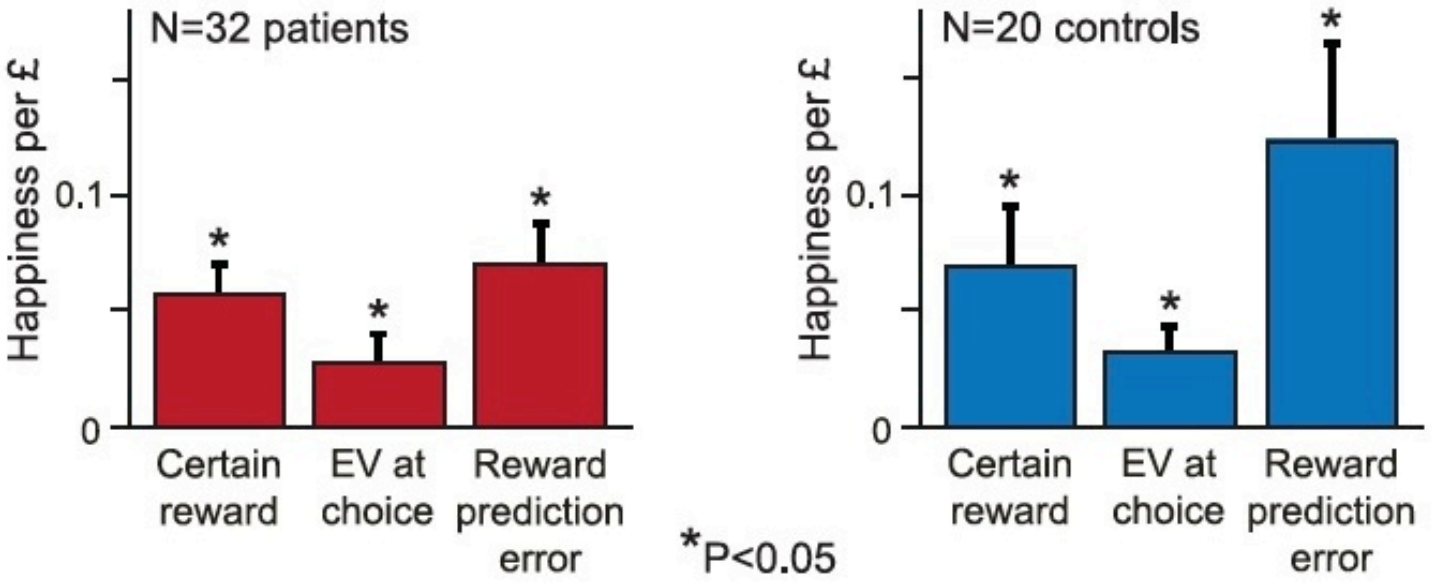


RPEs affect striatal activity in depression



Rutledge, Moutoussis et al. (in prep)

RPEs affect happiness in depressed subjects



$$Happiness(t) = w_0 + w_1 \sum_{j=1}^{t} \gamma^{t-j} CR_j + w_2 \sum_{j=1}^{t} \gamma^{t-j} EV_j + w_3 \sum_{j=1}^{t} \gamma^{t-j} RPE_j$$

Certain reward

Expected value

Reward prediction error
(reward – expectation)

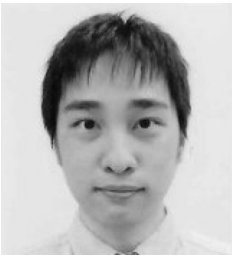
The computational psychiatry of major depressive disorder

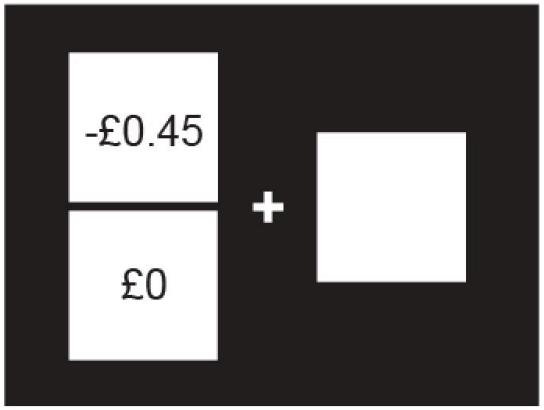
Years	1	2	3	4	5
Development of new tasks & new **computational models**					

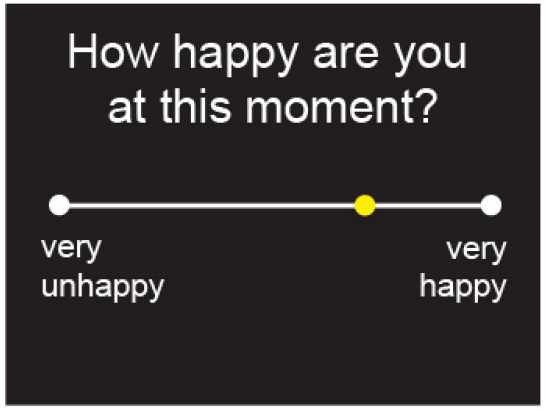
What is the relationship between brain, behavior, and feelings?

1) Task 1: Motivation
2) Task 2: Effort
3) Task 3: Learning

1) Motivation: emotion without choice







2) Effort: how does mood depend on effort?

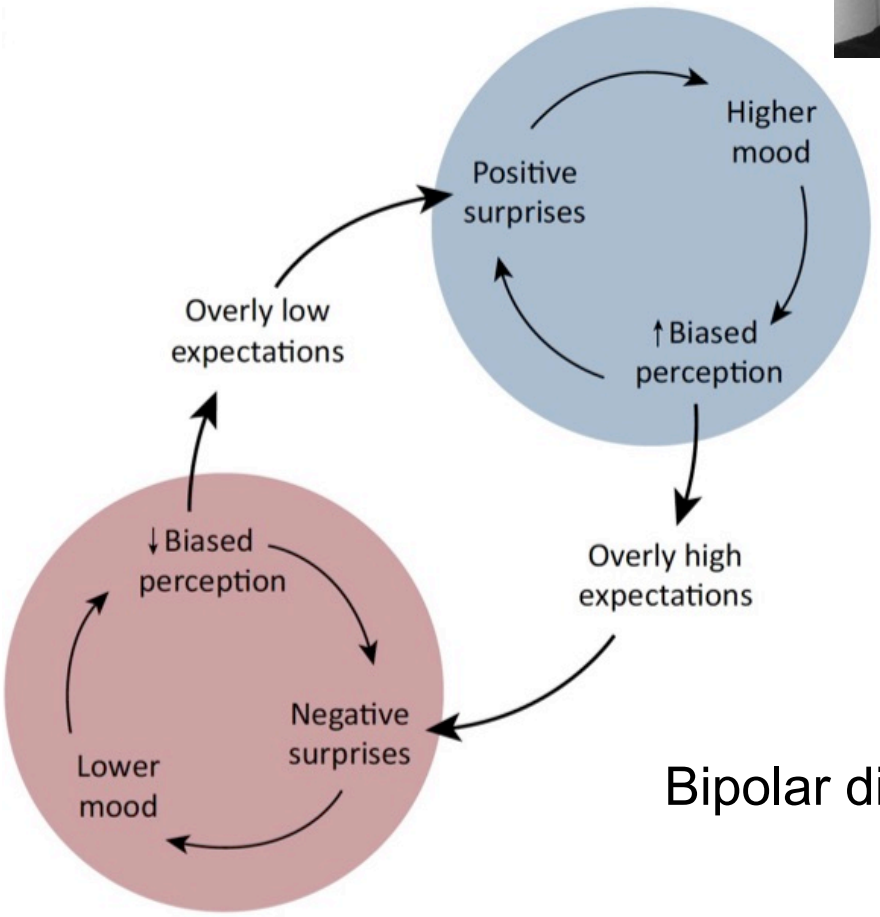
3) Learning: what is the function of mood?

Mood represents the momentum of rewards

Mood biases perception of subsequent rewards

This could ‘correct’ learning when rewards are correlated

Positive feedback dynamics could contribute to mood disorders



Bipolar disorder

Eldar, Rutledge* et al. (2016) TICS*

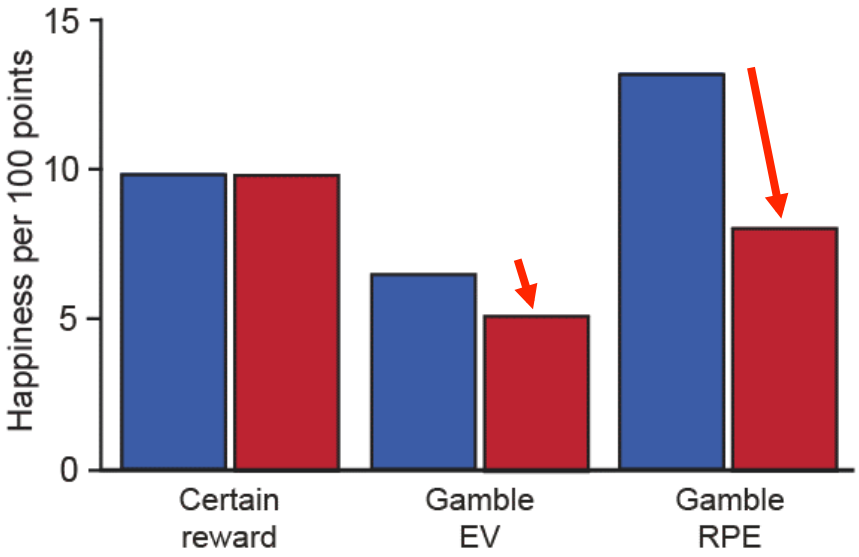
The computational psychiatry of major depressive disorder

Years	1	2	3	4	5
Development of new tasks & new **computational models**					
Longitudinal **smartphone** data from remitted patients					

Can smartphones be used for longitudinal data collection in previously depressed individuals?

50 control subjects and 150 previously depressed subjects. Subjects assessed in the lab, then by smartphone over 14+ months. 30-40% will have relapsed.

Understanding depression



→ Symptoms?

Thank you!

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MRC Medical Research Council

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