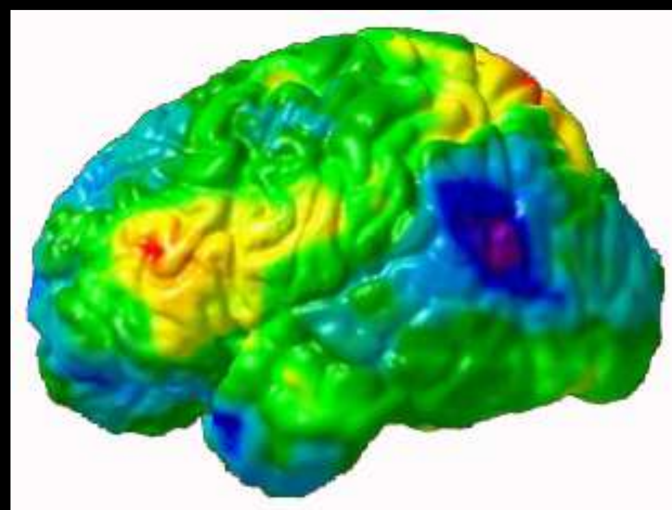
Etudes par imagerie cérébrale de la prise de décisions et du système de récompense chez l'homme

Jean-Claude Dreher

Equipe « Prise de décisions et récompense »
Centre de Neurosciences Cognitives, CNRS, Lyon



INSTITUT FRANÇAIS DE L'ÉDUCATION

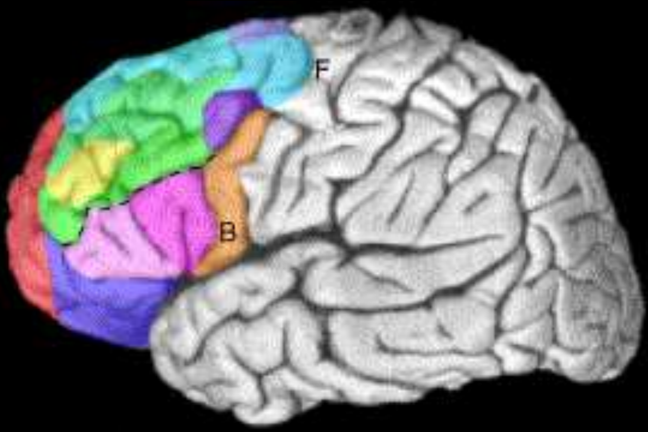
Formavie 2012
5-6 Avril 2012
Ifé / ENS de Lyon

General goal:

Understand the normal and pathological neural mechanisms of decision making and reward processing

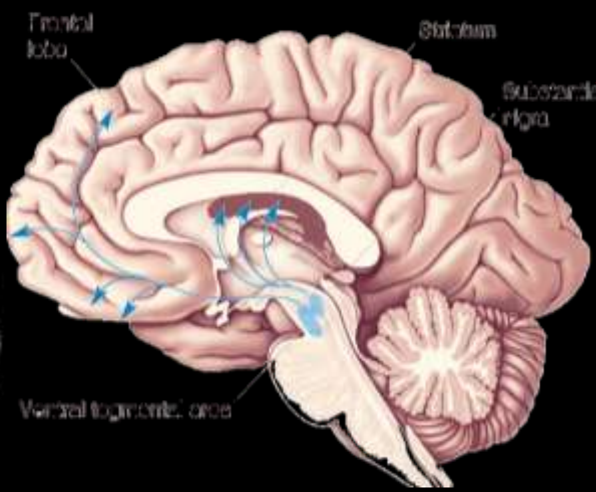
Three axes of research:

I.
Functional organization of the prefrontal cortex



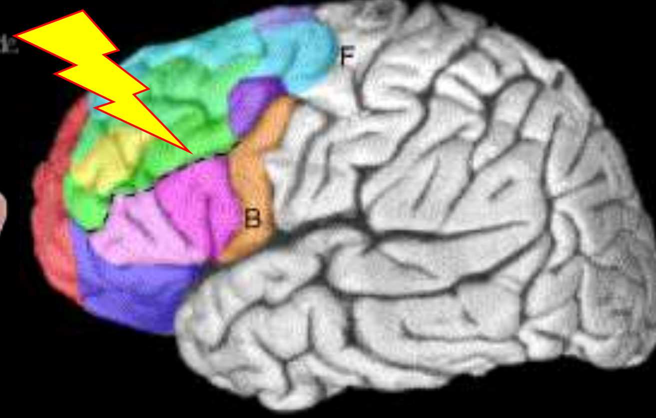
Decision making

II.
Study of the dopaminergic system



Reward system

III.
Dysfunctions of the prefrontal cortex and the dopaminergic system



Schizophrenia,
Parkinson’s disease,
Lesions of the PFC,
Pathologic gambling,
Anorexia,
Healthy aging

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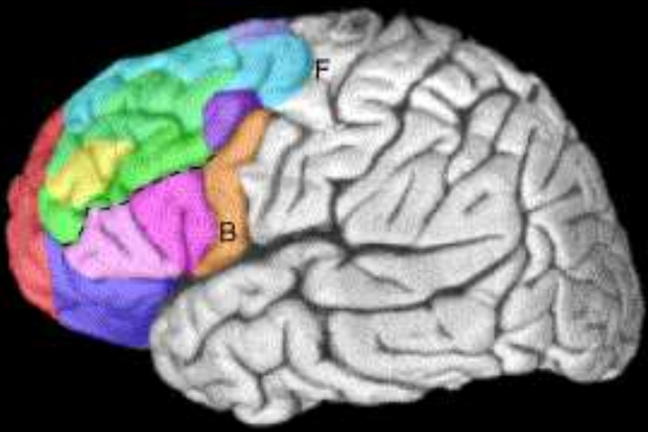

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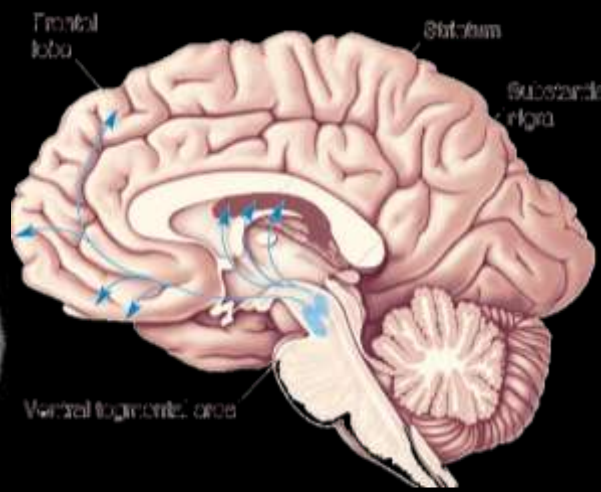

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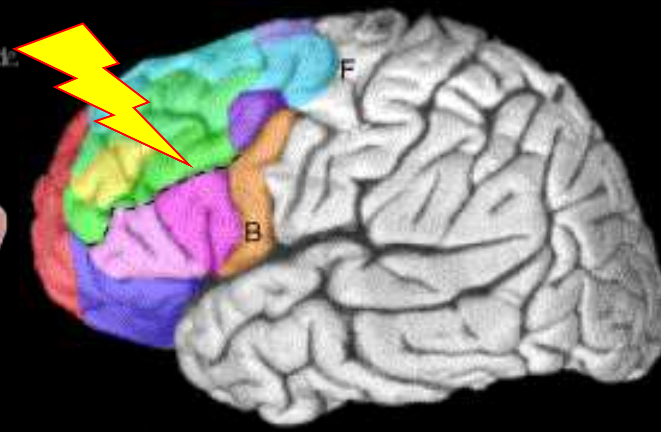

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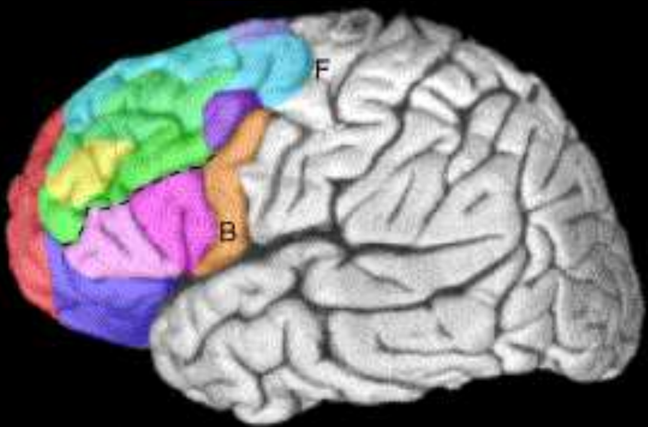

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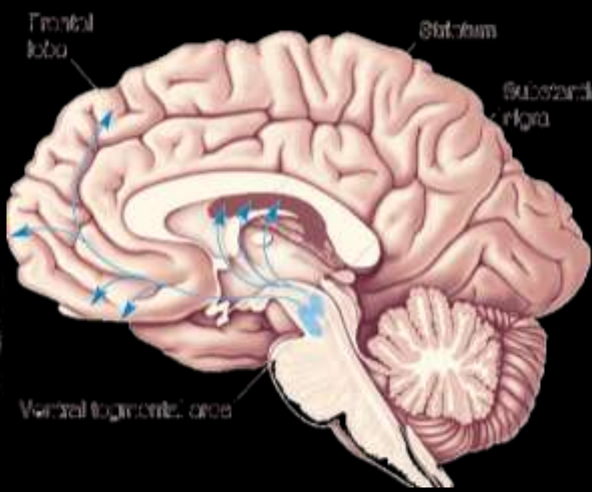

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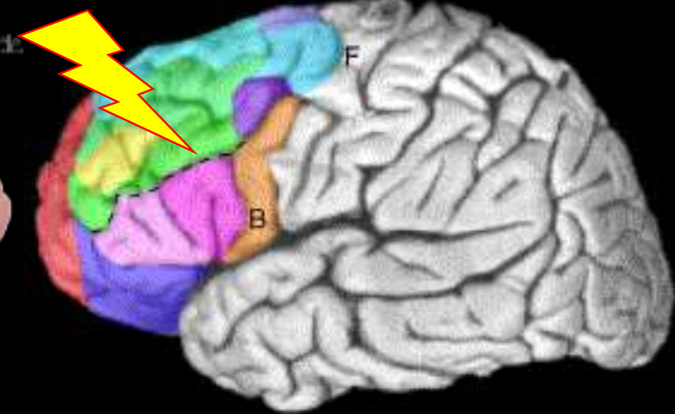

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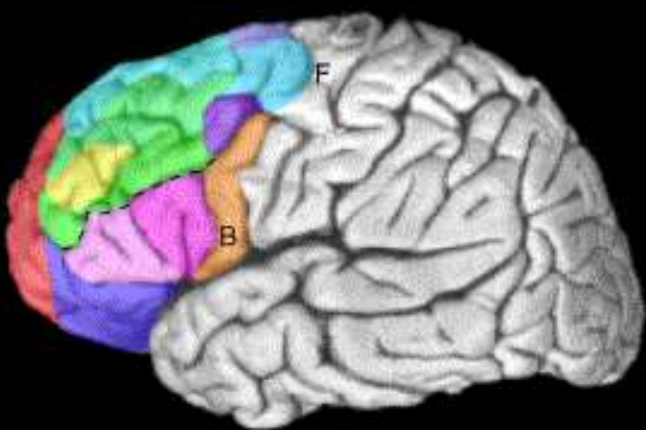
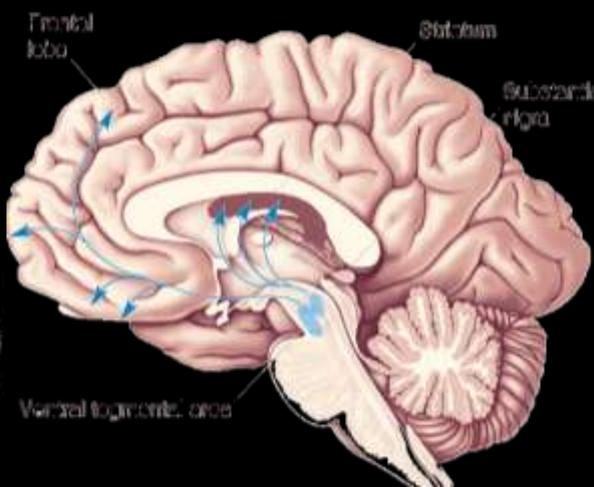
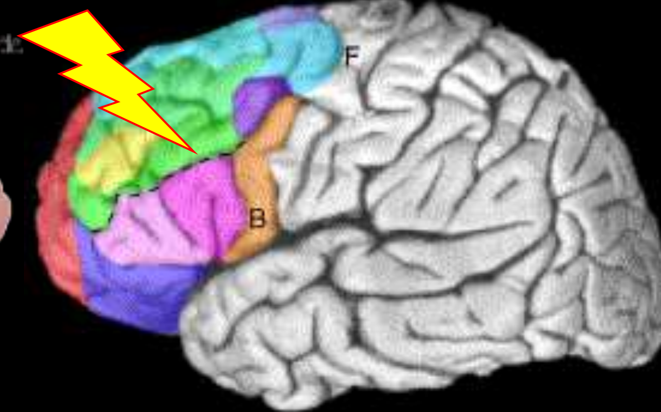






Decision making | **Reward system** | **Clinical Populations**

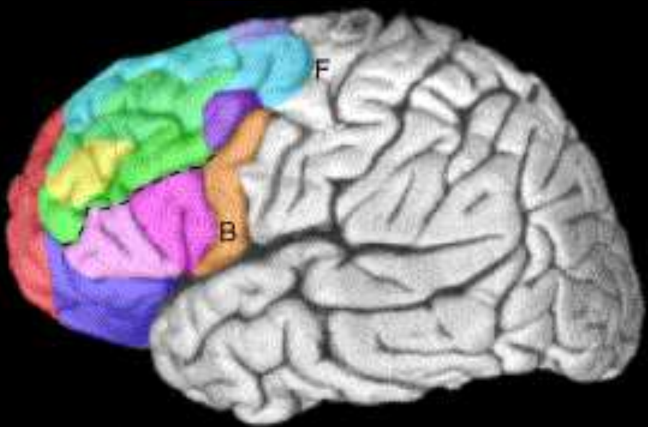
Imaging Methods: fMRI, MEG and intra-cranial recordings in humans

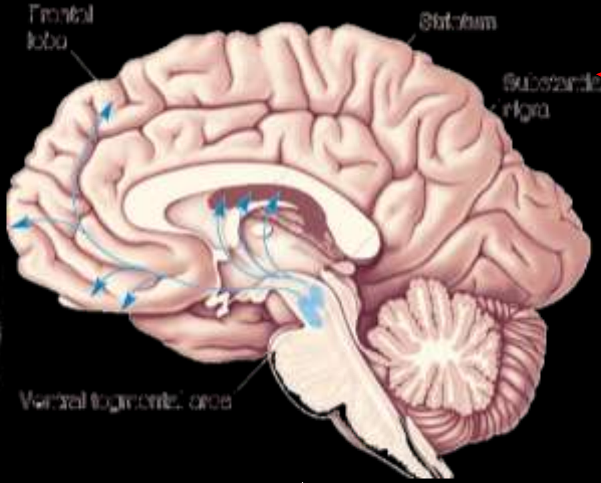
Fourth axis of research:

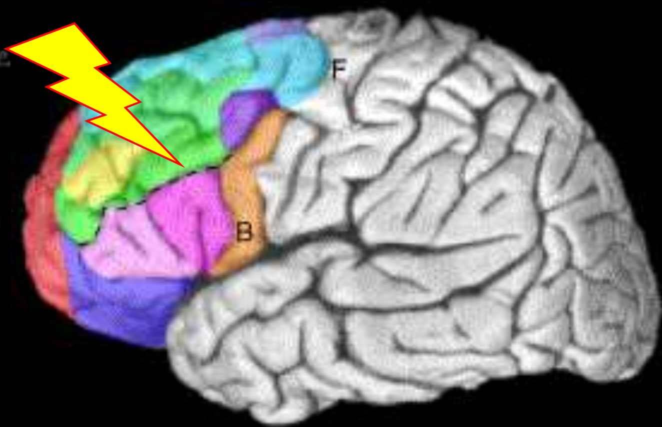
I.
Functional organization of the prefrontal cortex

II.
Study of the dopaminergic system

III.
Dysfunctions of the prefrontal cortex and the dopaminergic system





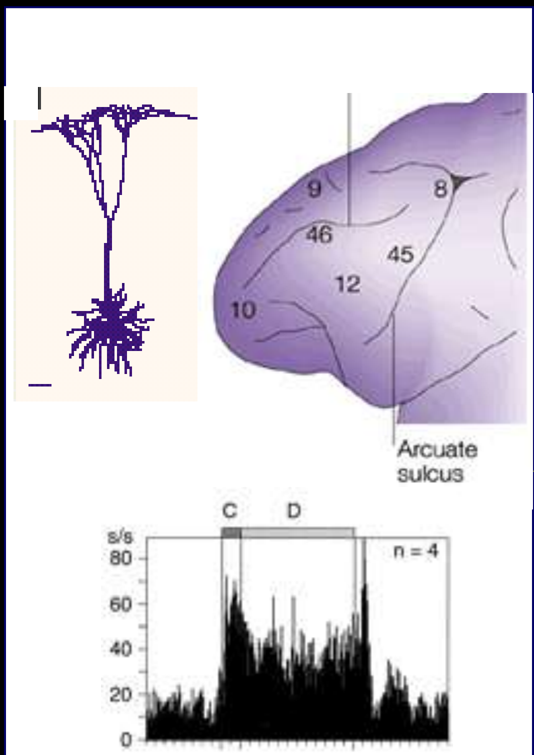


Decision making **Reward system** **Clinical Populations**

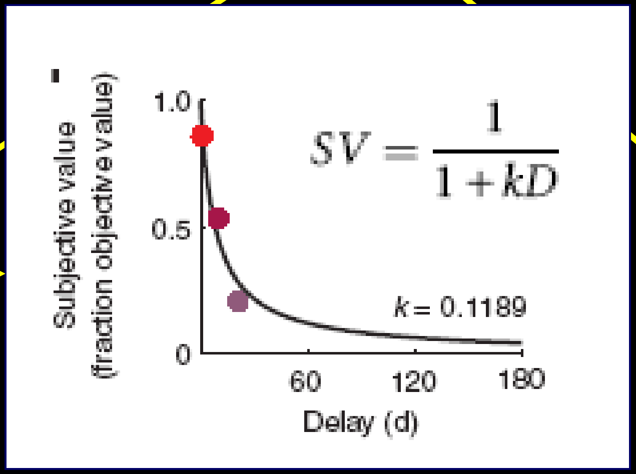
Genetic and gonadal steroid hormones influences ?

General approach: Links between cerebral activation, neurophysiological mechanisms and processes involved in decision making and reward processing

Behavioral performance



Electrophysiology
(monkeys, Intra-cranial human recordings)

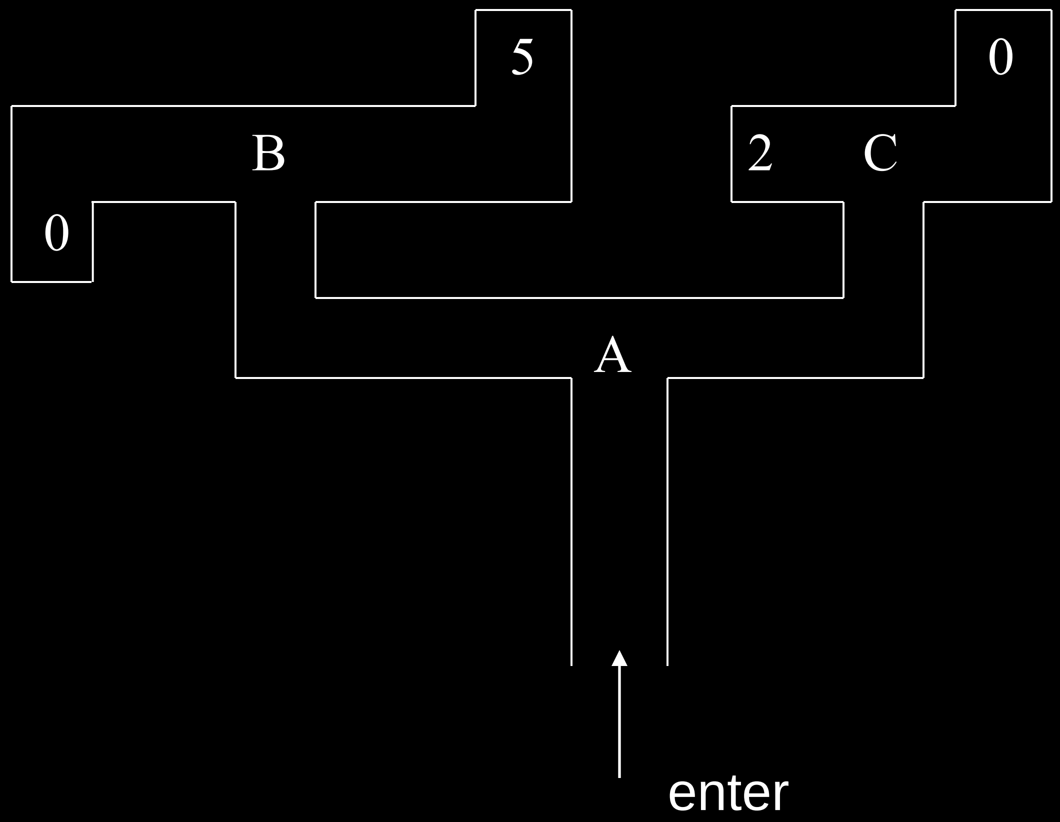


Neurocomputational models

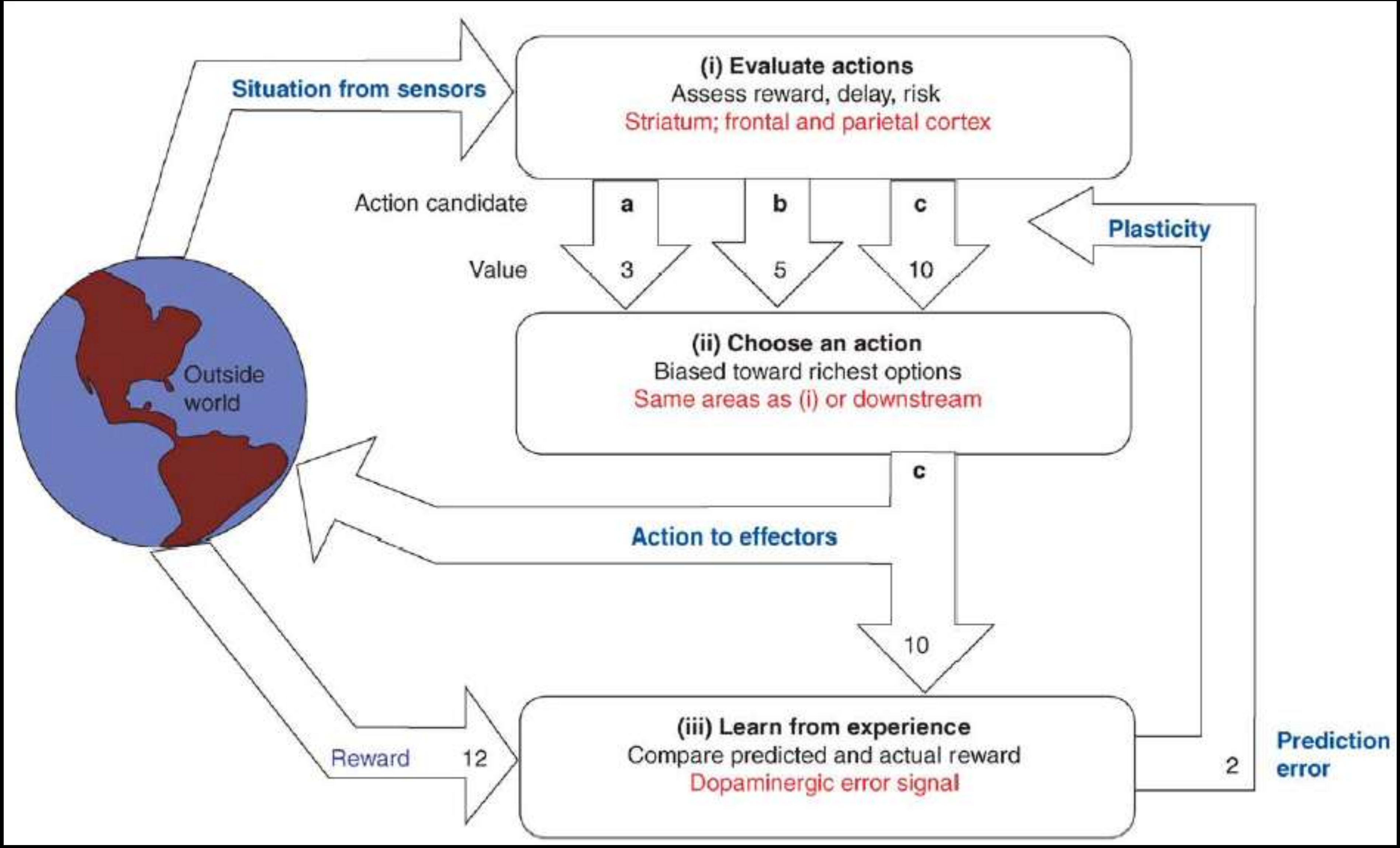
Cerebral activation
(fMRI)

Sequential actions choice

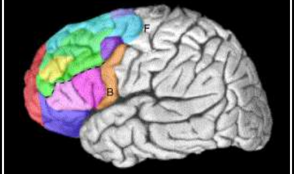
How do we learn to choose actions on the basis of immediate and delayed information about the consequences of those actions?



Basic stages of reinforcement learning models accounts of learned decision-making



Axis I.



Functional organization of the prefrontal cortex

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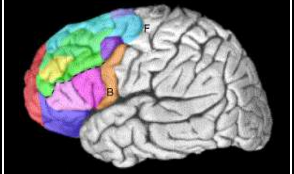

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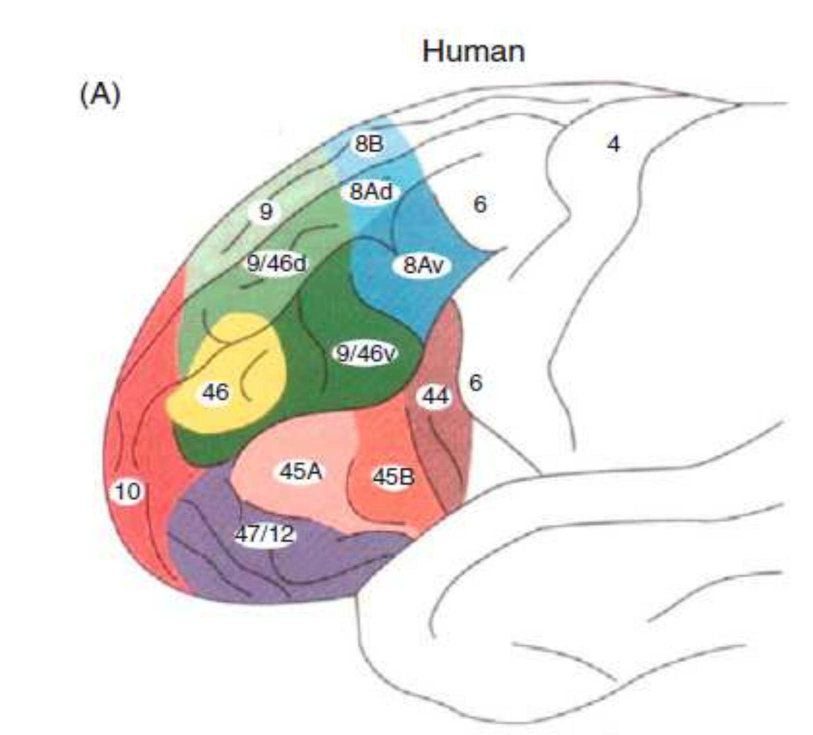

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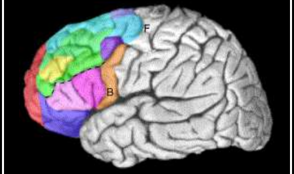

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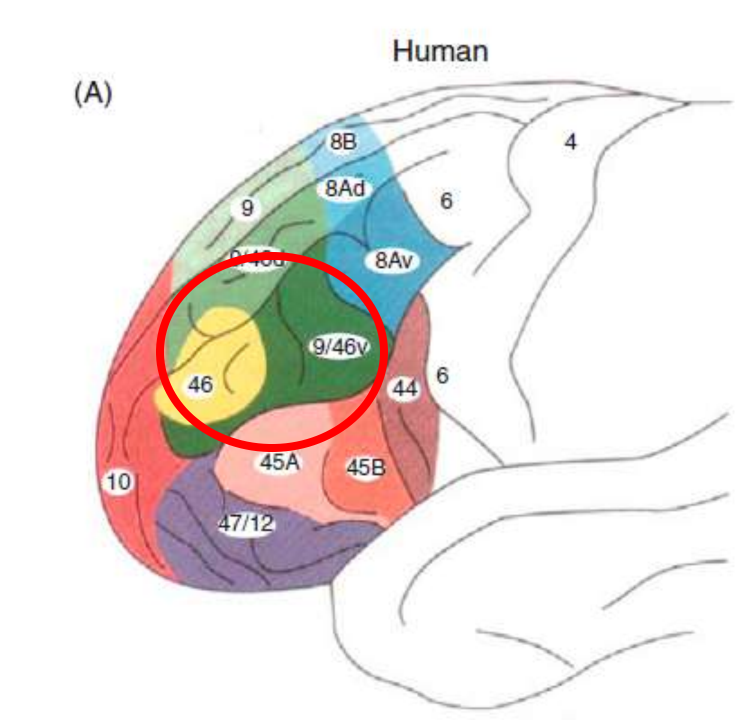
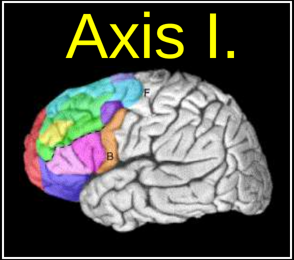


Cognitive functions associated to the Dorsolateral Prefrontal Cortex (BA 9/46):
Working memory, task switching



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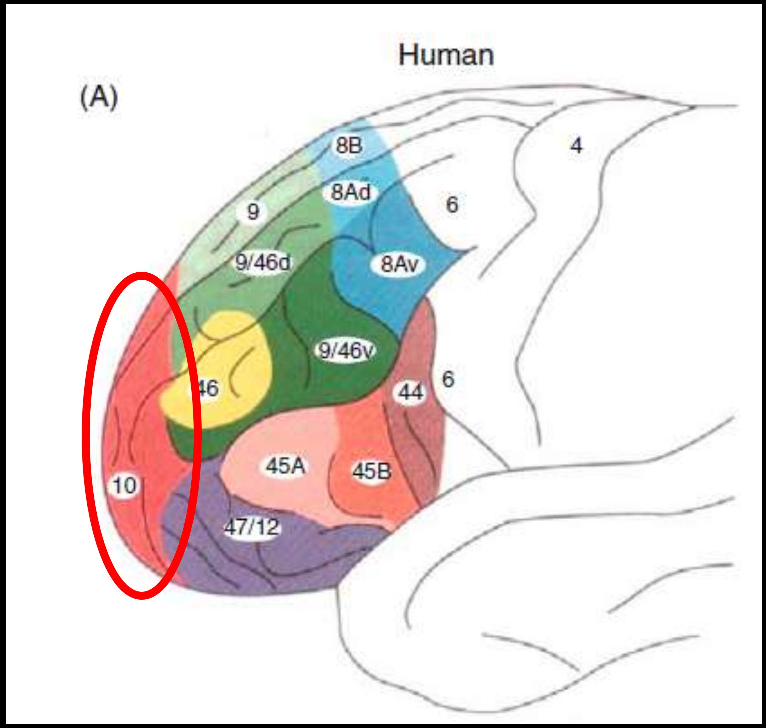
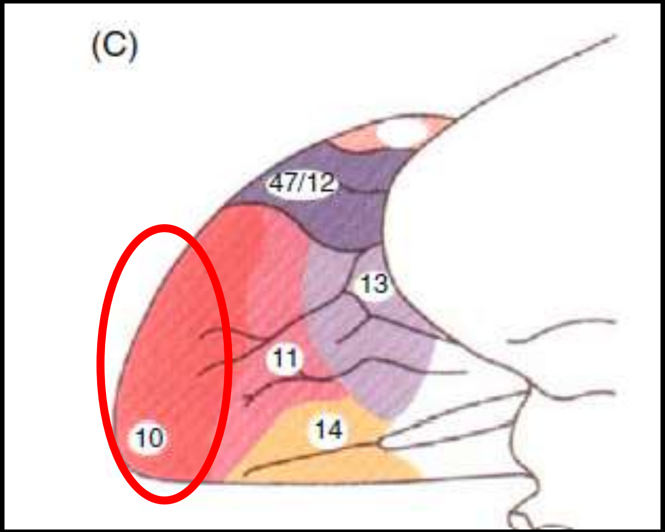
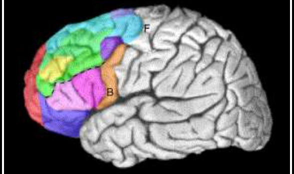


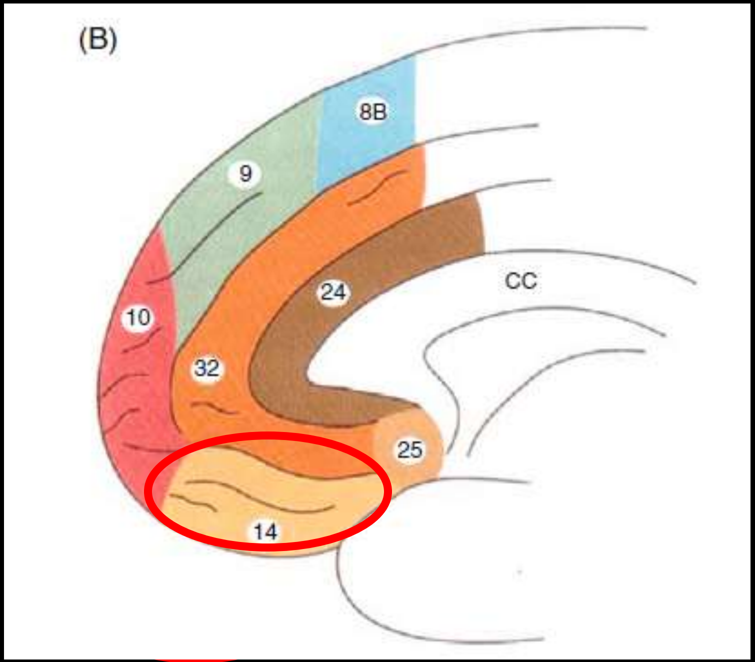


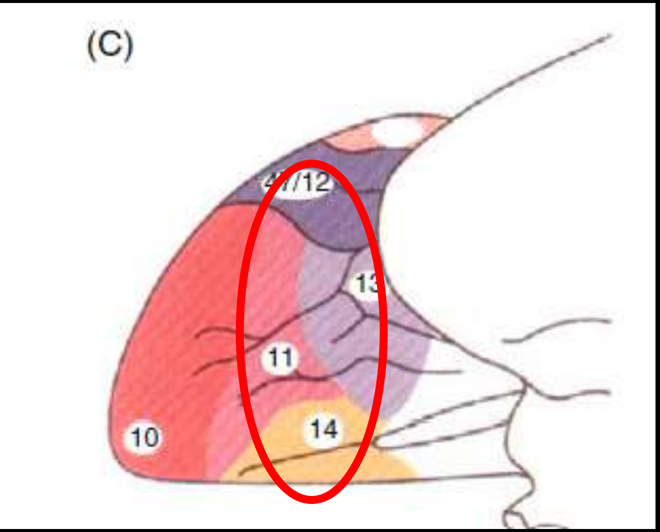
Cognitive function associated to the fronto-polar cortex (BA 10): Planning, Branching (combination of working memory and task switching)

Axis I.



Functional organization of the prefrontal cortex



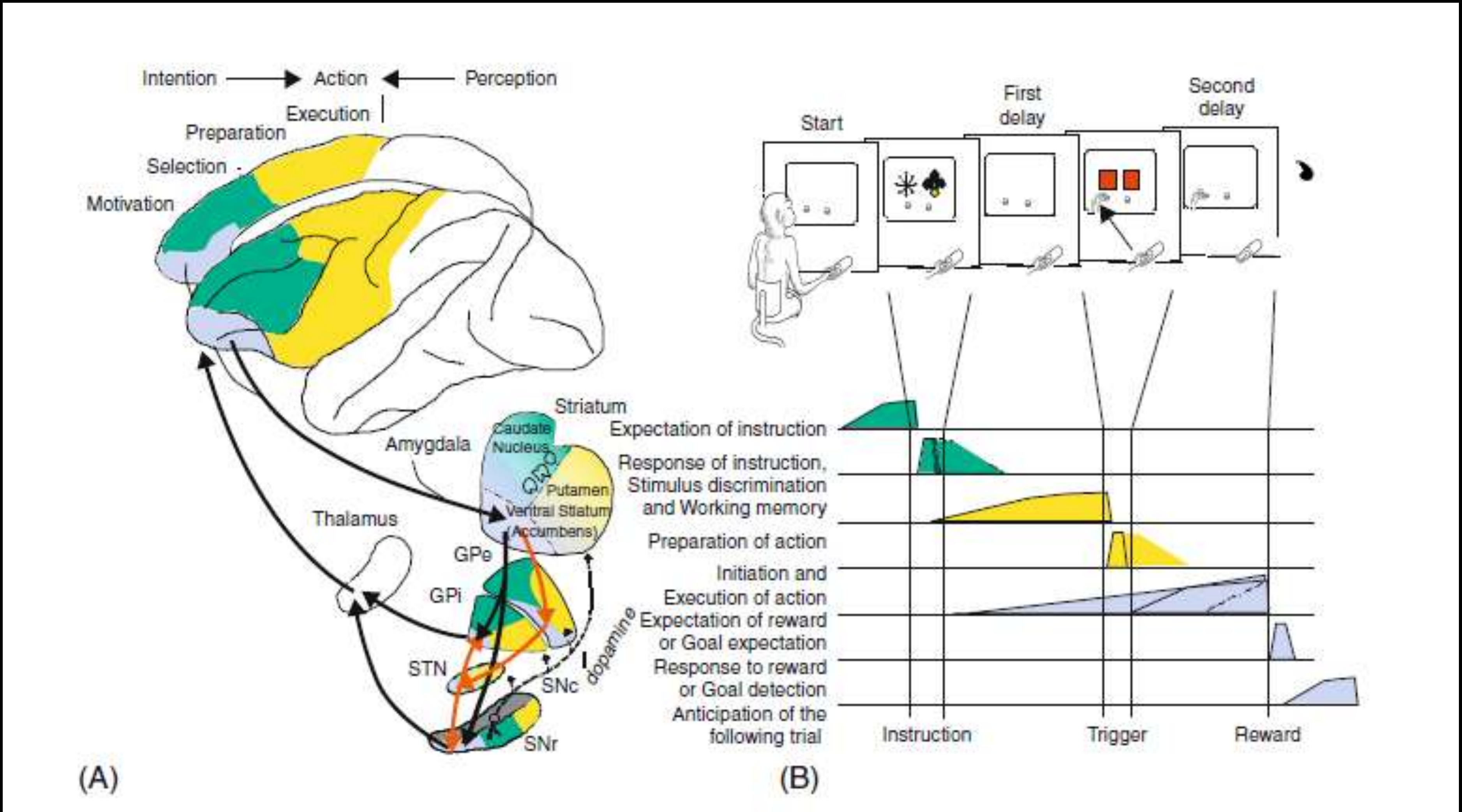


Cognitive function associated to the orbitofrontal cortex (BA 11, 12, 14): reward processing, emotion and motivation

Destruction of the OFC through brain injury typically leads to a pattern of disinhibited behaviour. Examples include swearing excessively, hypersexuality, poor social interaction, compulsive gambling, drug use (including alcohol and tobacco) and poor empathising ability

Functional dissociation of the OFC in humans ?

Striato-frontal loops



Adapted from Tremblay, *Handbook of Reward and Decision making*, 2009

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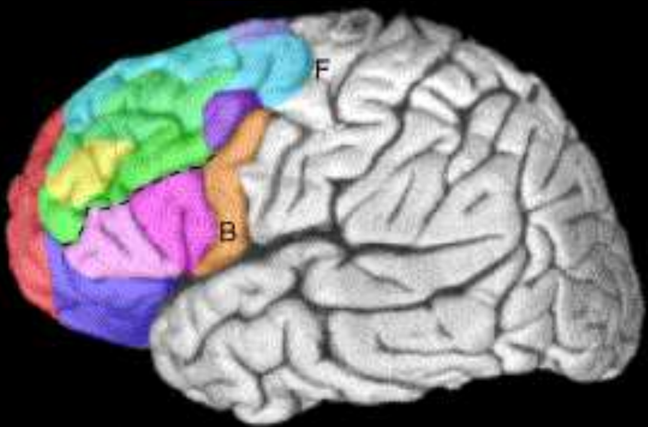
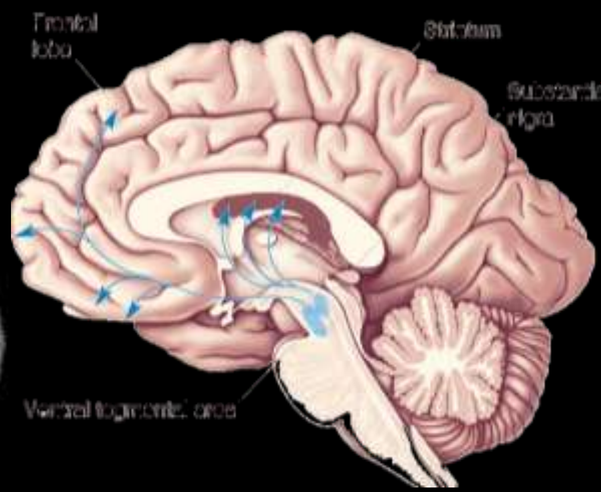


Decision making

II.
Study of the dopaminergic system



Reward system

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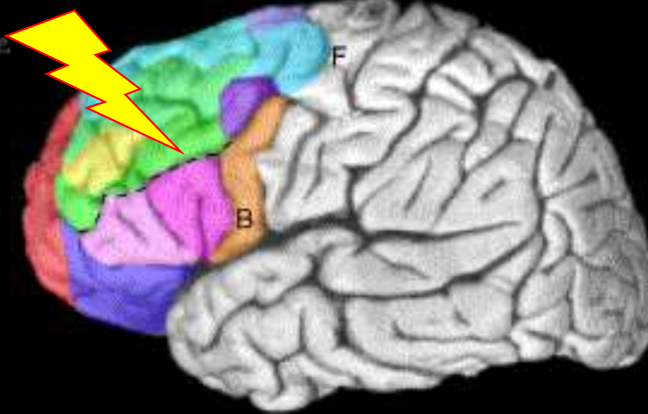

Schizophrenia,
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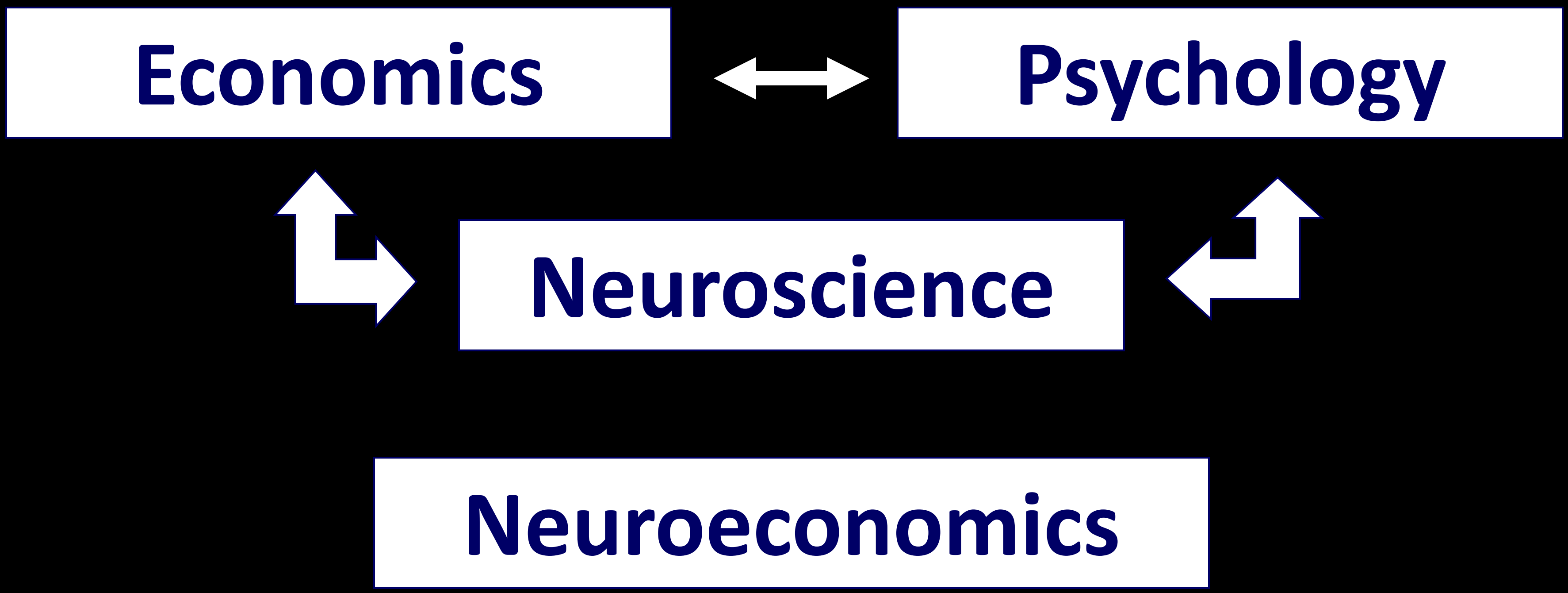
What is a reward?

- A reward is anything that an animal will work to attain -> concepts of motivation and effort
- Rewards are motivating - elicit approach and consummatory behaviour.
-> distinct representation in time: anticipation and reception
- Rewards elicit learning and are often probabilistic
- Some rewards are primary reinforcers i.e. have innate value and have not acquired their reinforcing properties through learning

  Examples of primary rewards include: tastes, odours, sex, grooming, social affiliation (see Rolls, 1999)
  -> One or several reward systems?

- In humans, rewards have an associated subjective state
- The reinforcing properties of rewards depend on the animal's internal motivational state
- Choice between rewards: relationship between decision making and rewards: preferences

Neuro-economics: A map of the problematic



Study of the neurobiological and computational basis of value-based decision making.

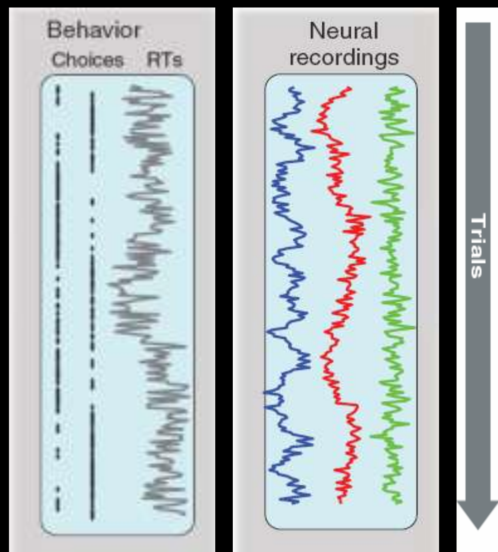
Combines behavioral models of judgment and decision making under risk and uncertainty and neuroimaging

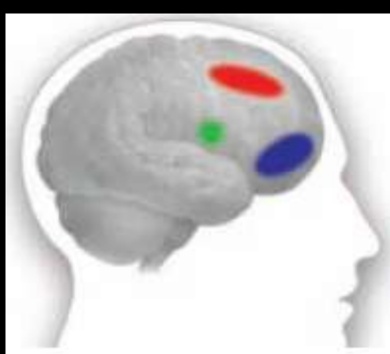
General problem:

Links between behavior and neurophysiological mechanisms involved in decision making and reward processing

Method: model-based fMRI approach

Behavioral and fMRI Data





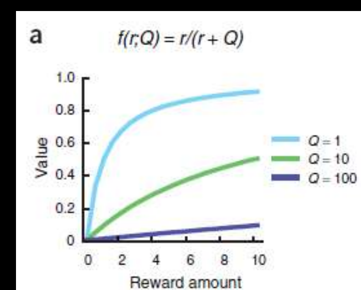
Observed data

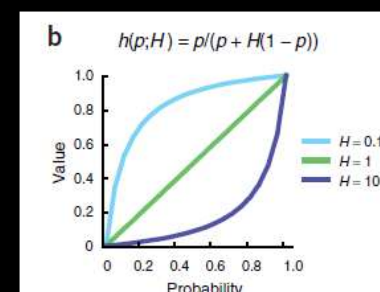
Computational Models

- Models of evaluation of amount, delay and probability/uncertainty of reward.

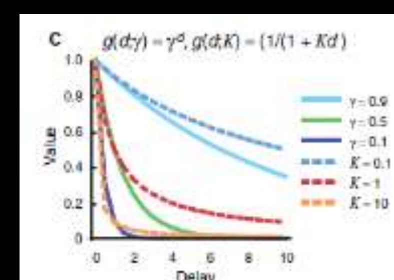
Reward value V:

$$V = f(\text{amount}) \times g(\text{delay}) \times h(\text{probability})$$

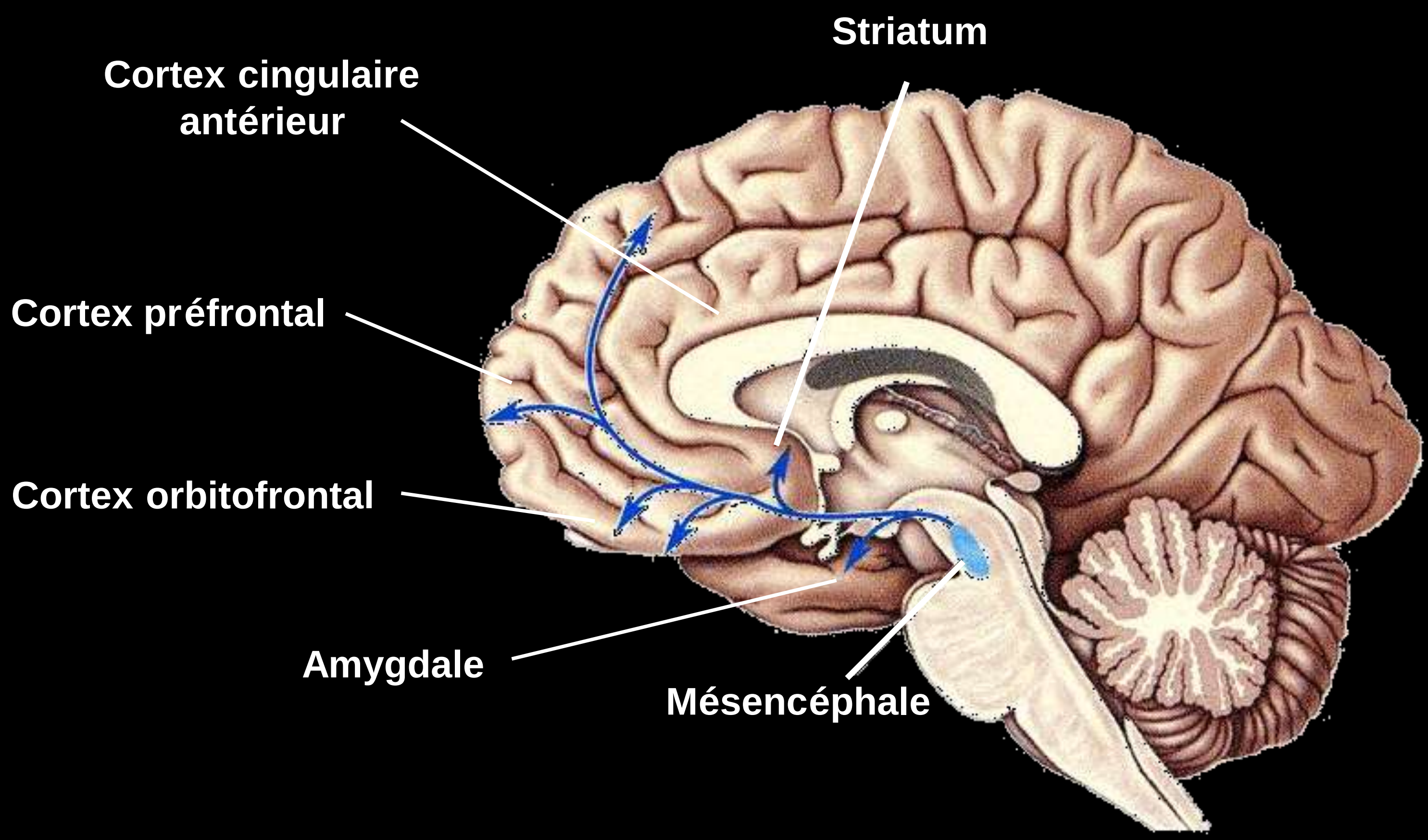




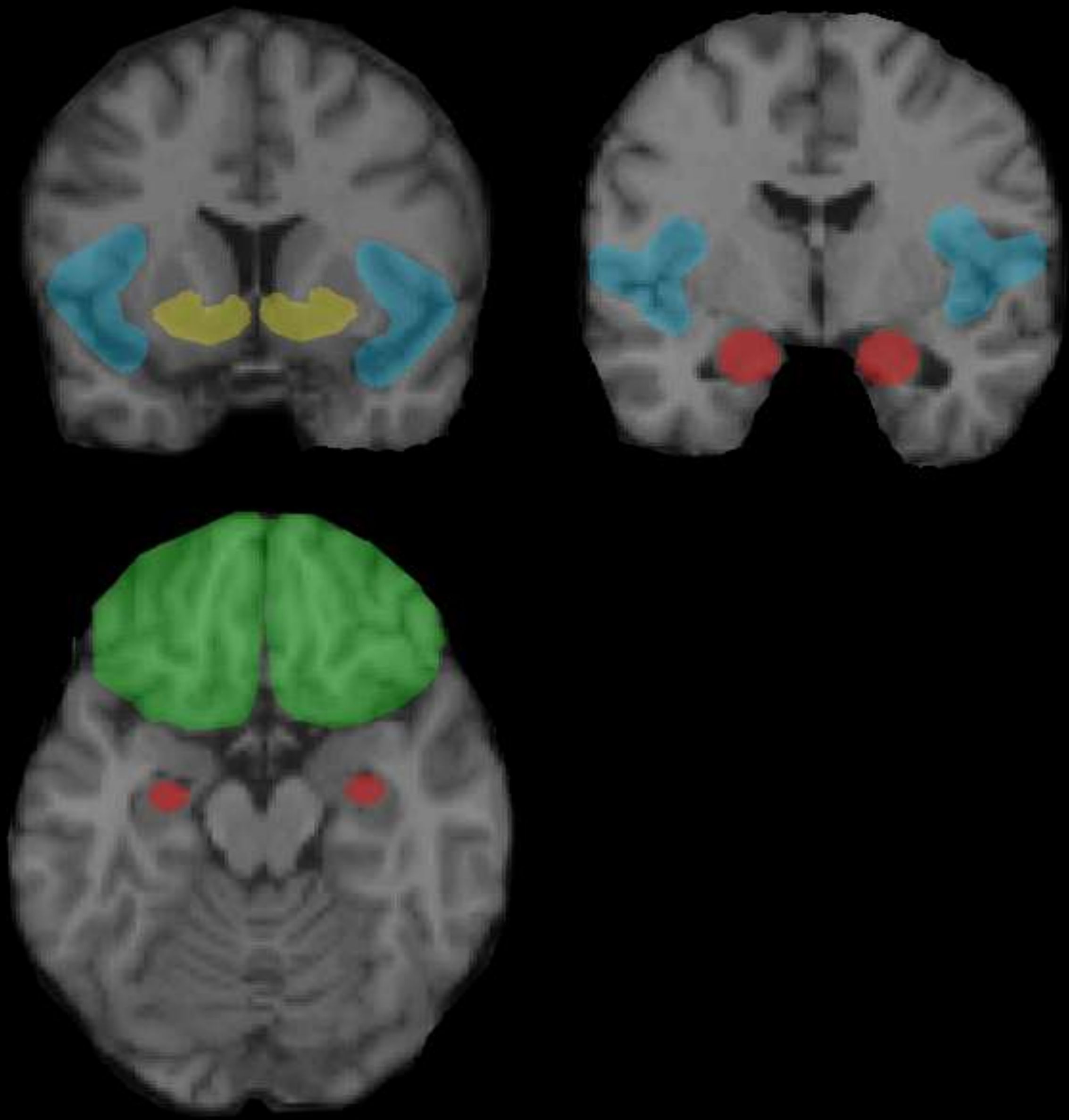
Model prediction



Anatomy: reward system



Reward structures in the human brain



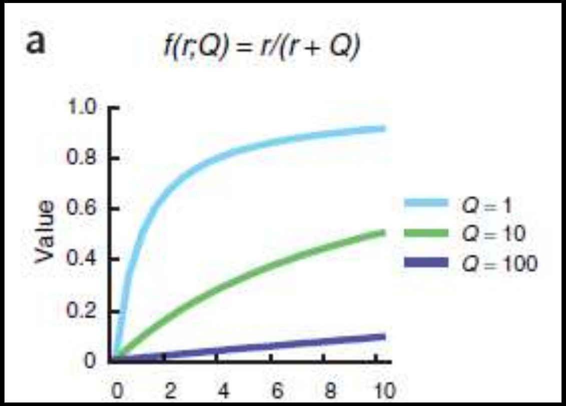
How does the brain computes values ?

Questions

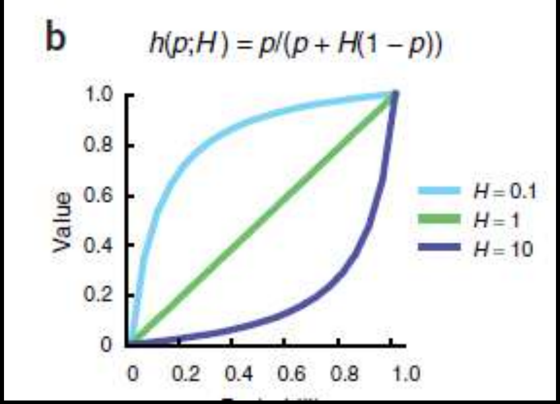
How are factors such as reward amount, probability or uncertainty represented in the brain?

Reward value V:

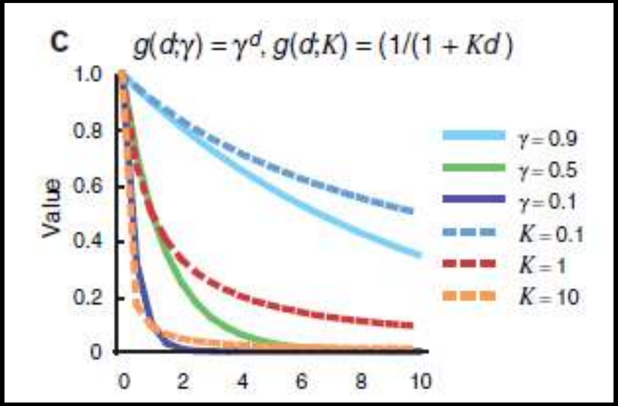
V= f(amount)*g(delay)*h(proba)



Reward amount



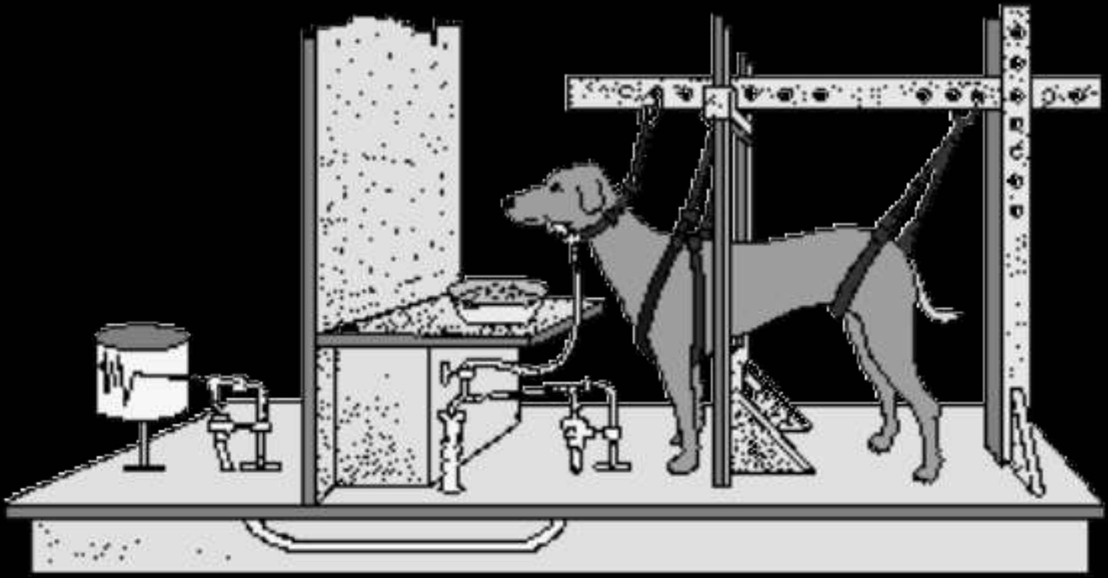
Reward probability



Delay

Pavlovian conditioning

Ivan Pavlov (1849-1936)



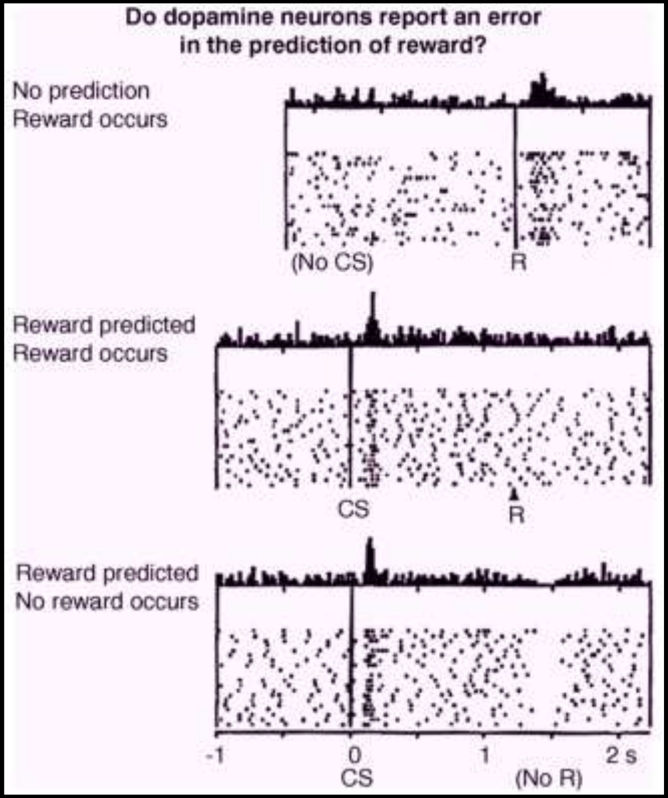
Reward Learning:
Pavlovian Appetitive Conditioning

Single unit recordings from dopamine neurons revealed that these neurons produce responses consistent with TD - learning (Schultz, 1998):

(1) Transferring their responses from the time of the presentation of the reward to the time of the presentation of the CS during learning.

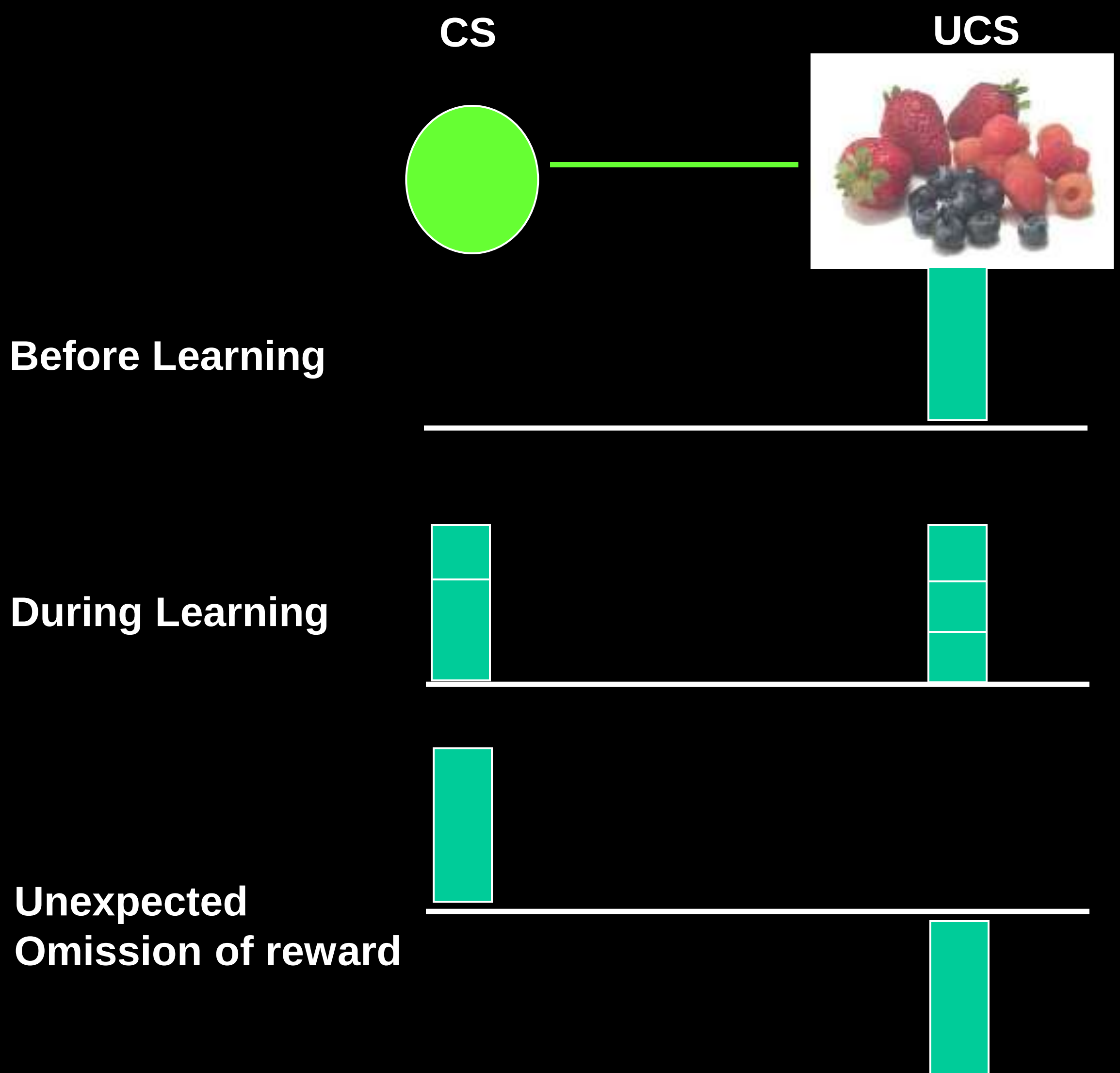
(2) Decreasing firing from baseline at the time the reward was expected following an omission of expected reward.

(3) Responding at the time of the reward following the unexpected delivery of reward

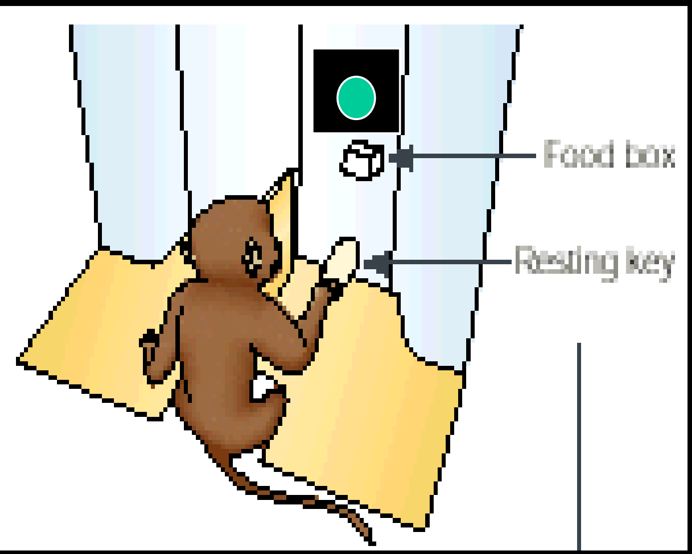


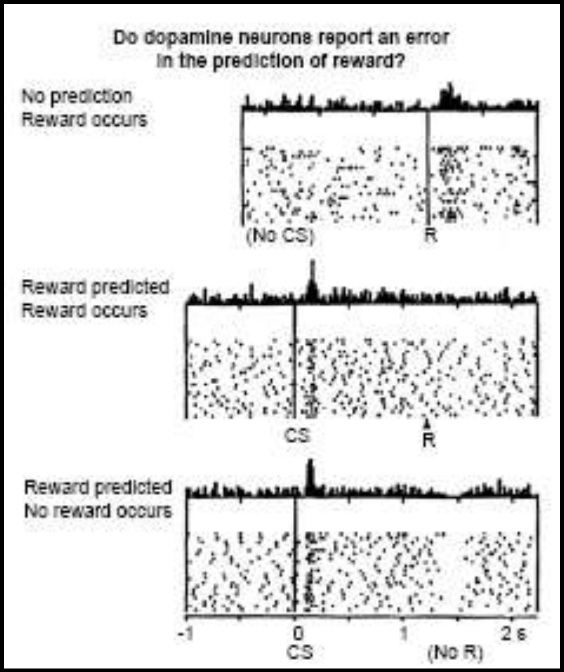
From Schultz, Montague and Dayan, 1997

Temporal difference learning model

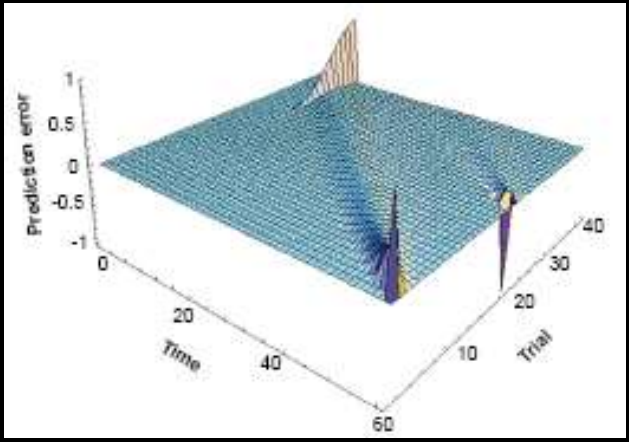


Predicting future events:
Phasic properties of dopaminergic neurons during learning





Phasic changes in dopamine neurons code an error in the prediction of appetitive events



Development of prediction error signal through training, as predicted by temporal difference learning models

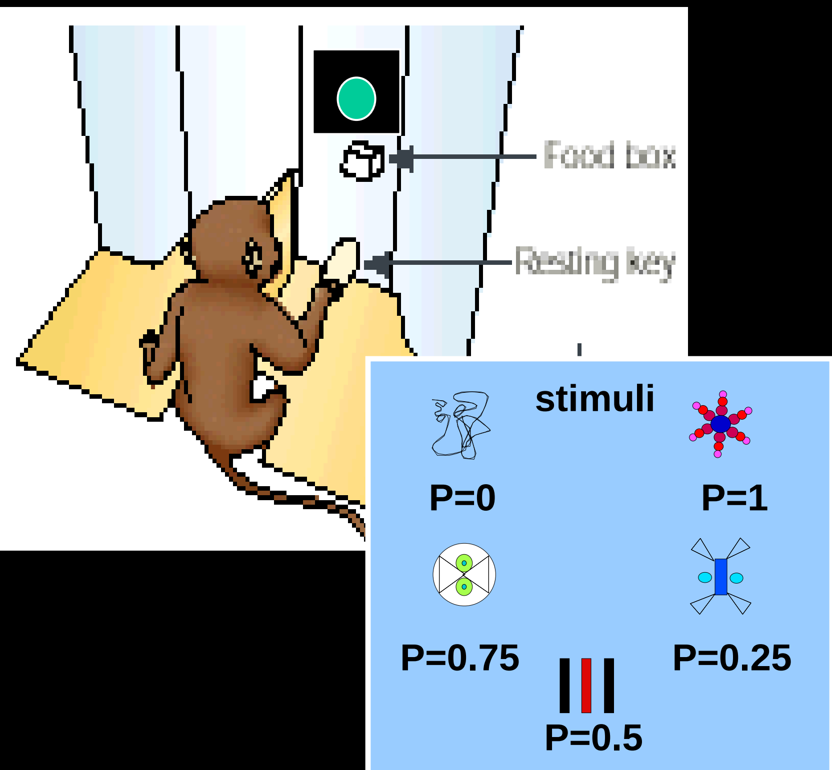
• Learning is mediated by a prediction error (Rescorla and Wagner, 1972; Pearce & Hall, 1980):

$$\delta(t) = r(t) + \gamma\hat{V}(t+1) - \hat{V}(t)$$

(Schultz et al, *Science*, 1997)

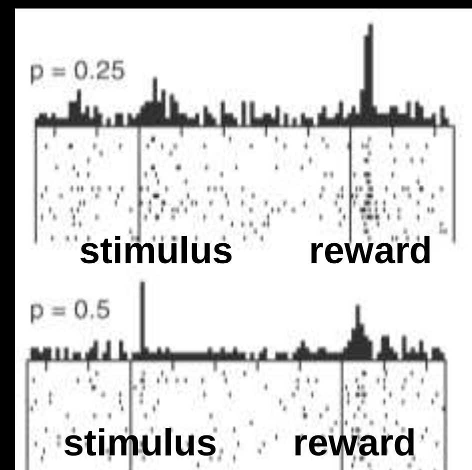
II. Study of the reward system

Electrophysiological properties of dopaminergic neurons

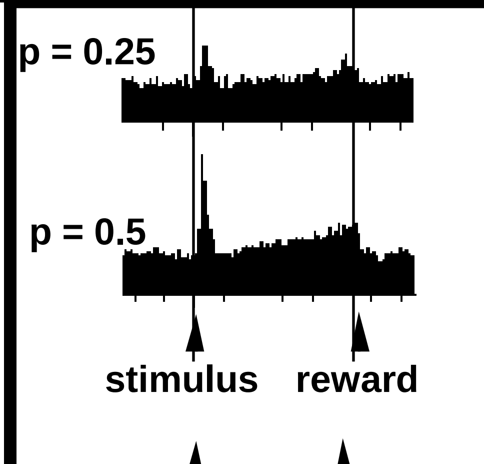


Conditioned Stimulus predicts reward with Probability P

Two modes of firing of DA neurons:



Phasic discharge
Error prediction



Sustained mode
Maximal with P=0.5

(Fiorillo et al., *Science*, 2003)

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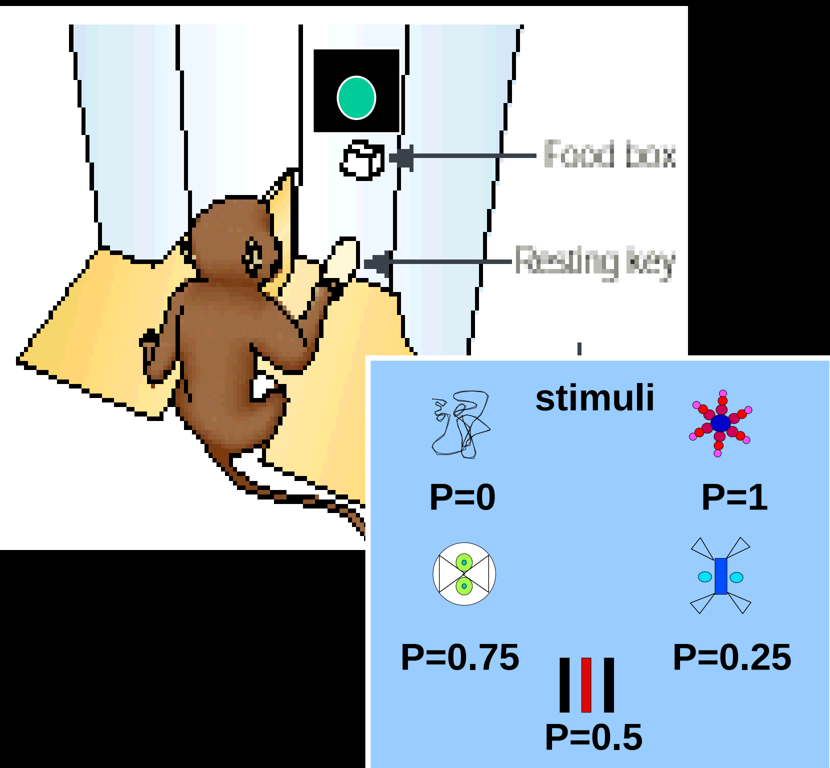
Electrophysiological properties of dopaminergic neurons



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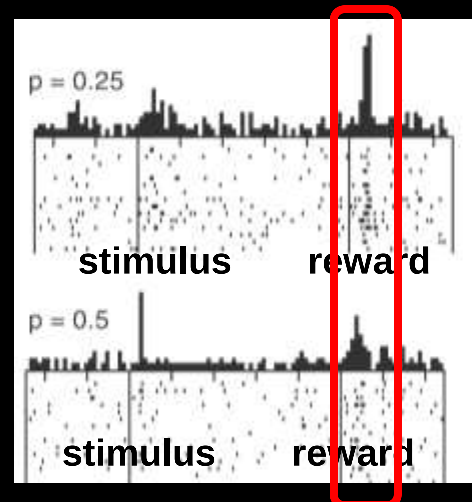
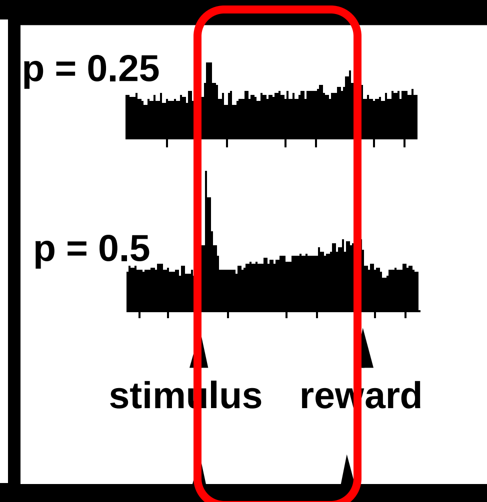
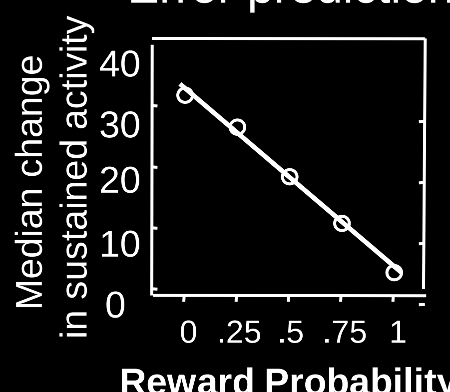
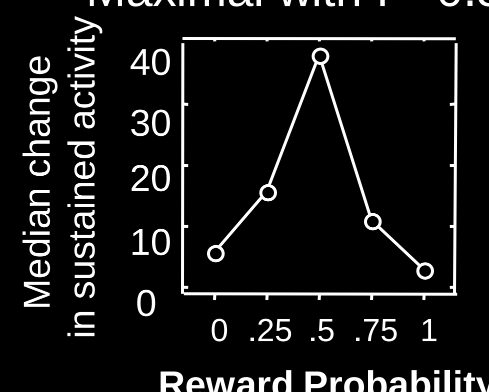




Phasic discharge
Error prediction

Sustained mode
Maximal with P=0.5

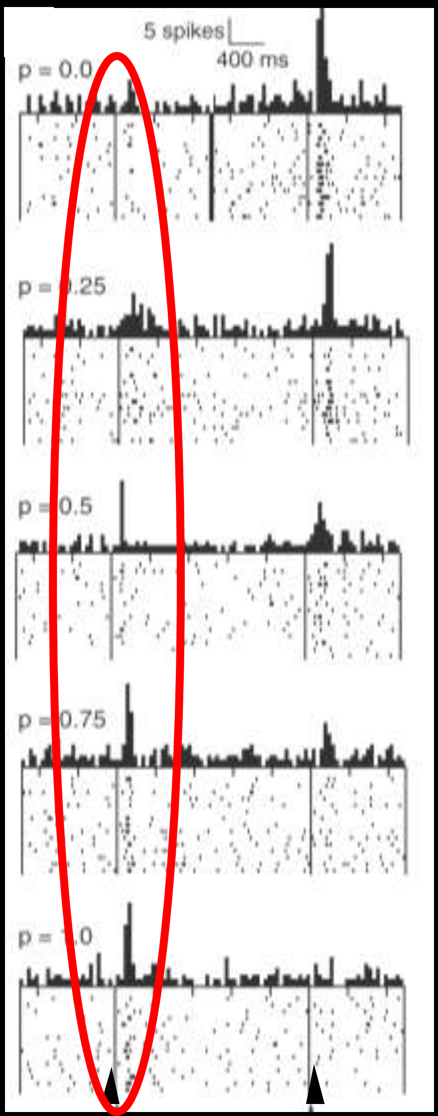




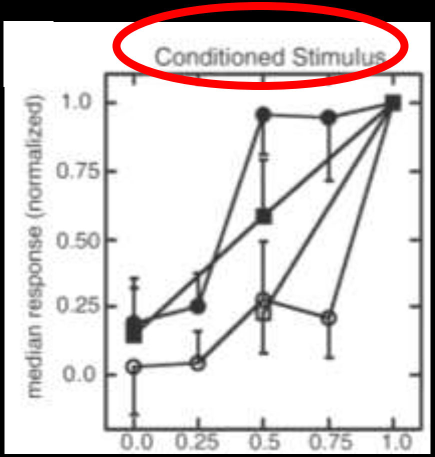
(Fiorillo et al., *Science*, 2003)

INFLUENCE OF REWARD PROBABILITY ON PHASIC AND SUSTAINED DOPAMINERGIC RESPONSES

PHASIC RESPONSES



stimulus reward



Reward probability

(Fiorillo et al., *Science*, 2003)

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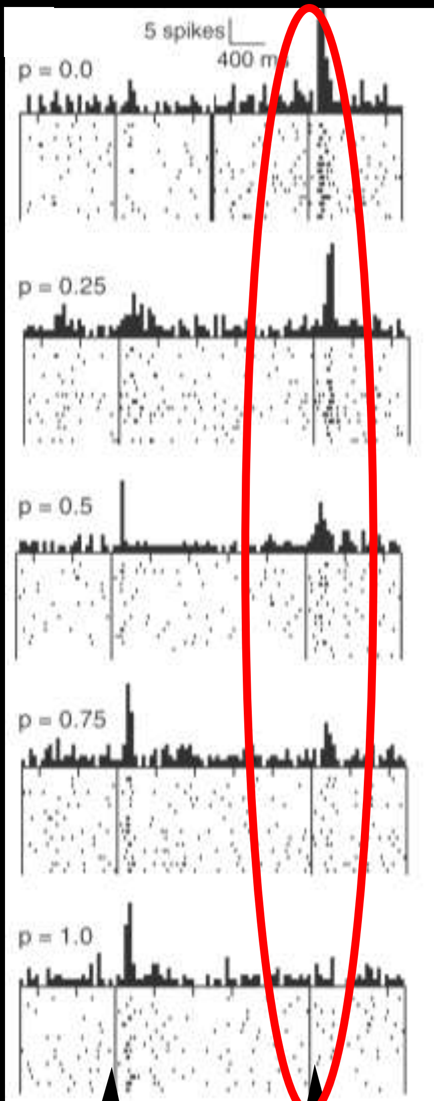
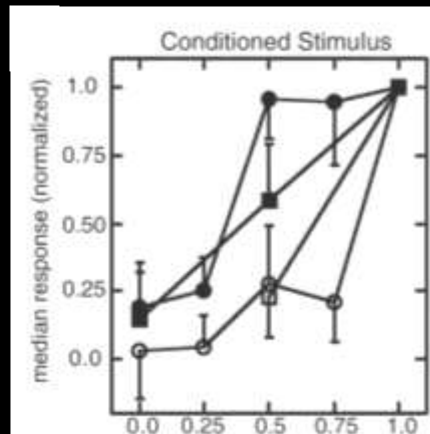
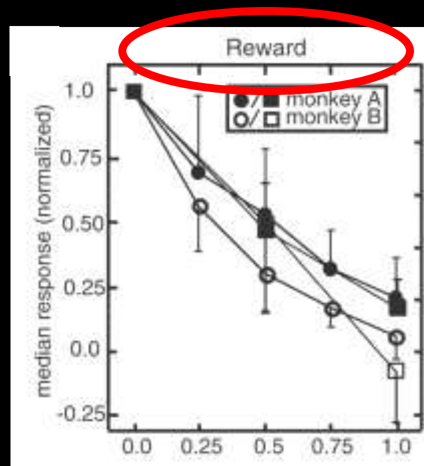
PHASIC RESPONSES





Reward probability



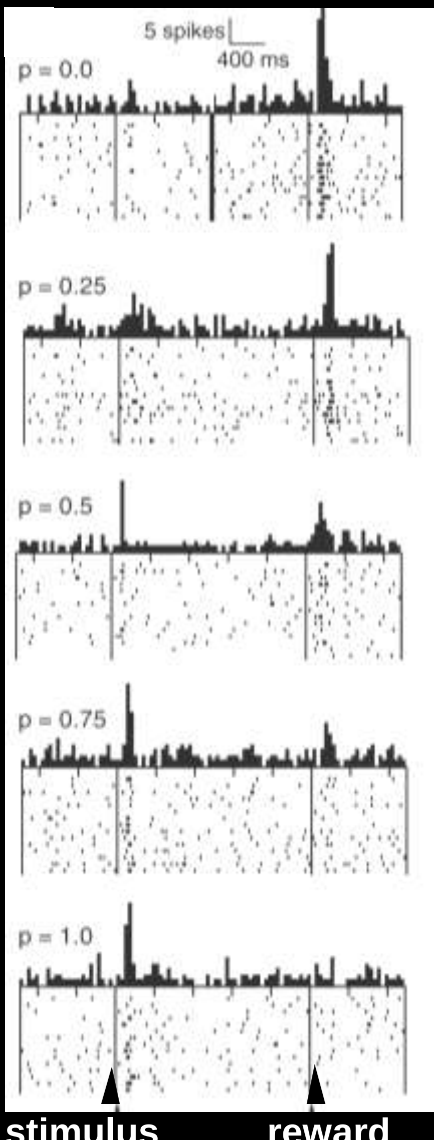
Reward probability

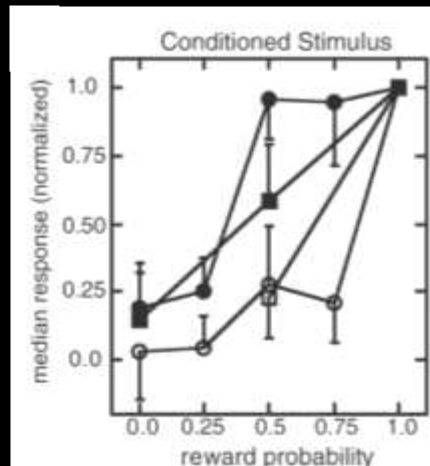
stimulus **reward**

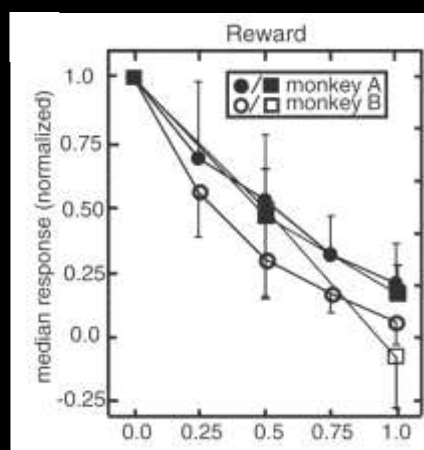
(Fiorillo et al., *Science*, 2003)

INFLUENCE OF REWARD PROBABILITY ON PHASIC AND SUSTAINED DOPAMINERGIC RESPONSES

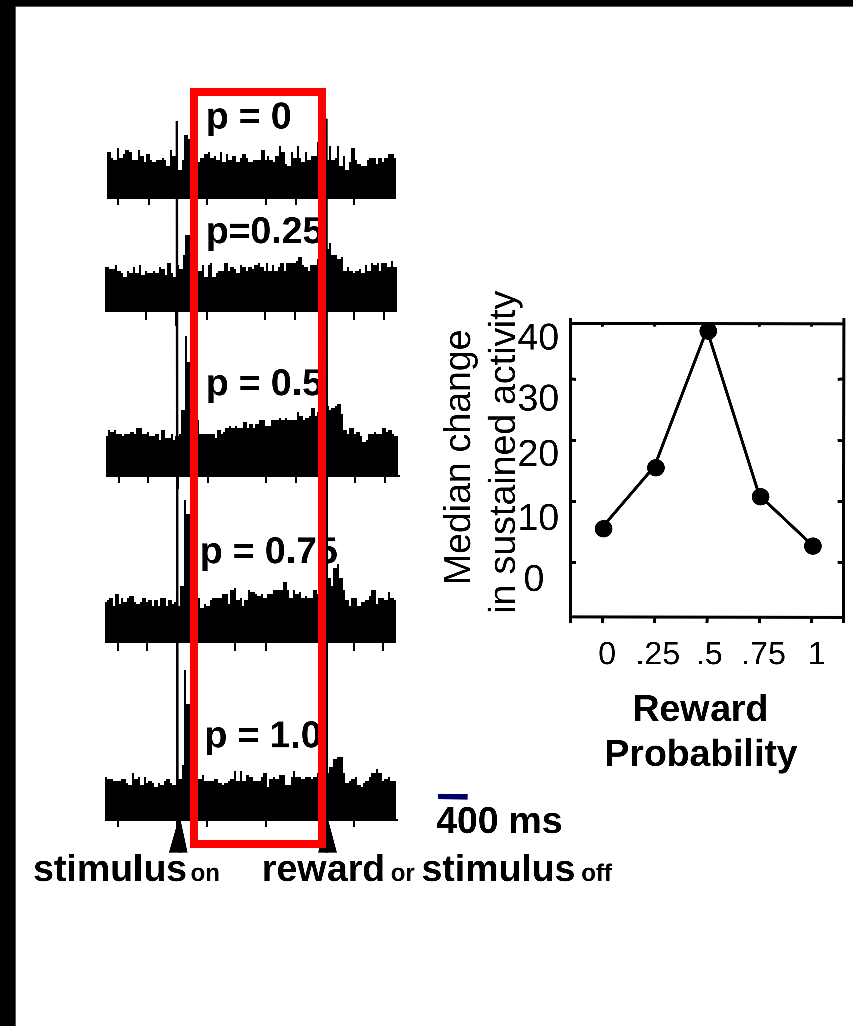
PHASIC RESPONSES





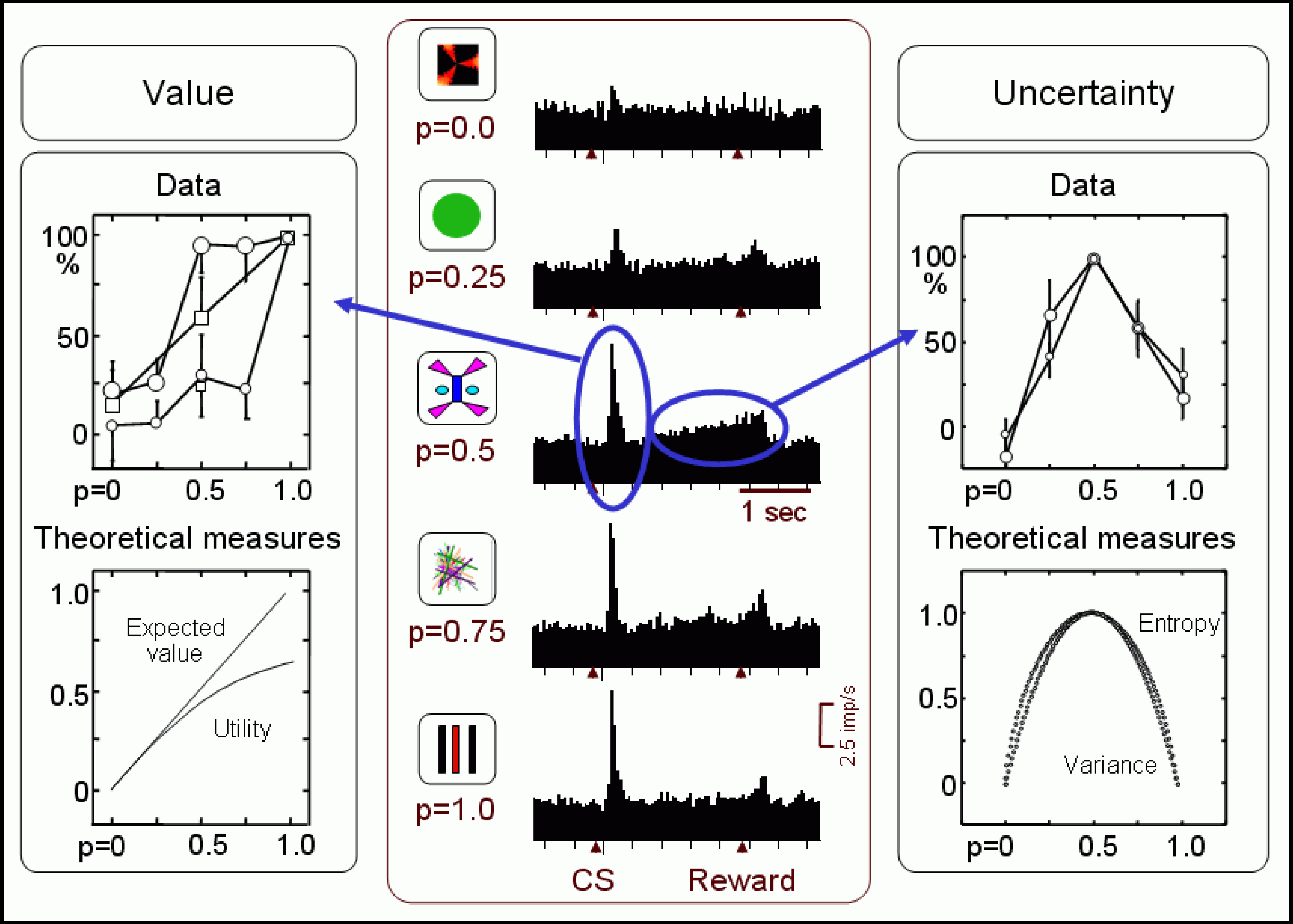


SUSTAINED RESPONSES



(Fiorillo et al., *Science*, 2003)

Tonic dopaminergic activity and Uncertainty



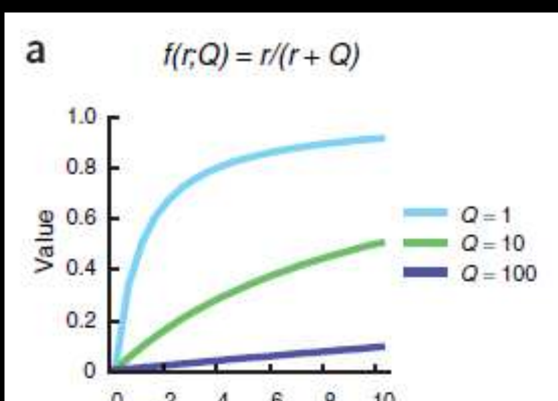
Fiorillo *et al*, Science 2003

Questions

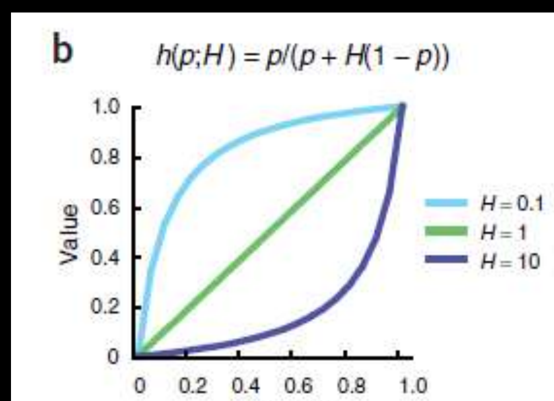
How are factors such as reward amount, probability or uncertainty represented in the brain?

What are the neural representations of different type of rewards (eg. Primary vs secondary)?

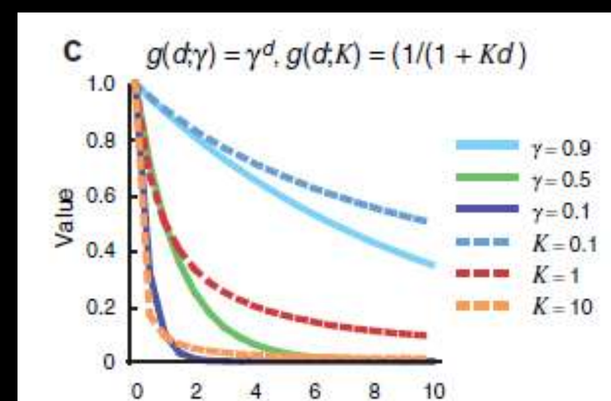
Reward value V:
V= f(amount)*g(delay)*h(proba)



Reward amount



Reward probability



Delay

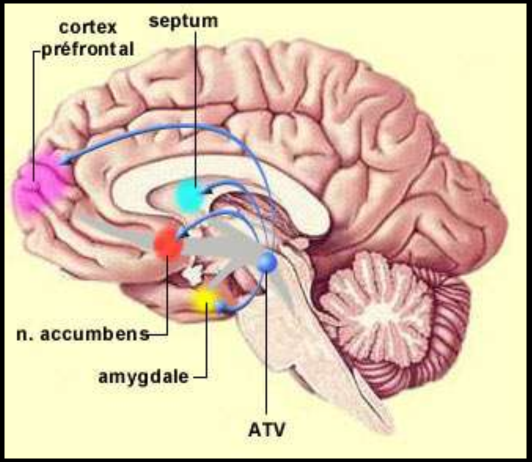
Neural substrate of the phasic and sustained modes of activities in healthy humans

Questions:

(1) Can transient and sustained midbrain activities dynamics be observed in humans ?

(2) Are there distinct brain regions involved with the phasic (at the time of the conditioned stimulus and reward) and with the sustained mode of DA activities ?

-> Role of monetary reward probability and magnitude on brain activity



(Dreher et al., *Cerebral Cortex*, 2006)


CHANCE TO WIN
$ 20 :


CHANCE TO WIN
$ 20 :


CHANCE TO WIN
$ 10 :


CHANCE TO WIN
$ 0 :

Different reward probabilities, equal reward magnitude.

Different reward magnitudes,
equal reward probability.

Equal expected reward value (product probability*magnitude), different reward probabilities and magnitudes.


CHANCE TO WIN
$ 20 :


CHANCE TO WIN
$ 20 :

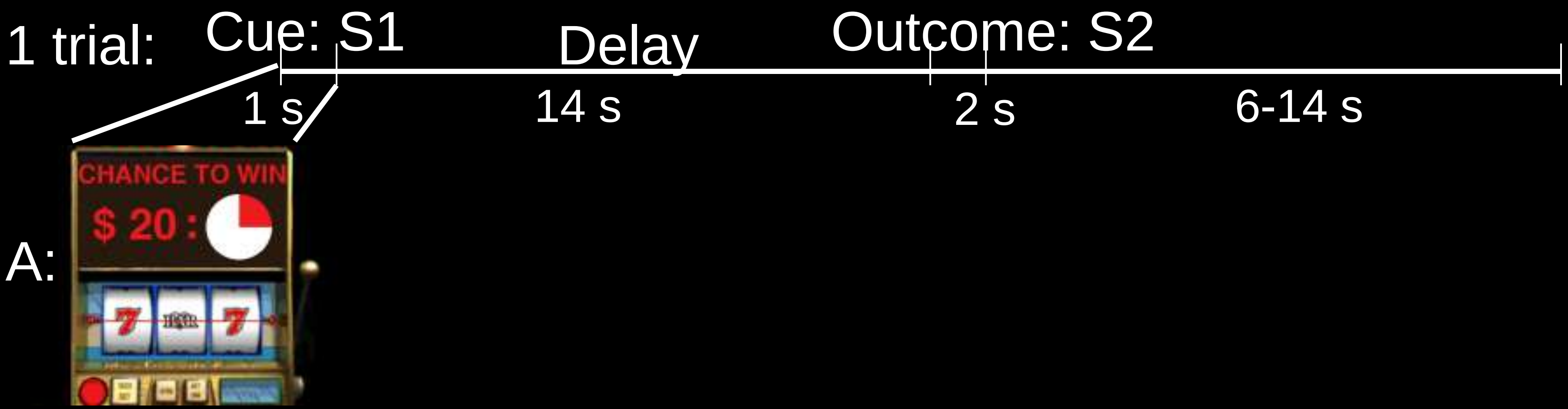

CHANCE TO WIN
$ 10 :


CHANCE TO WIN
$ 0 :

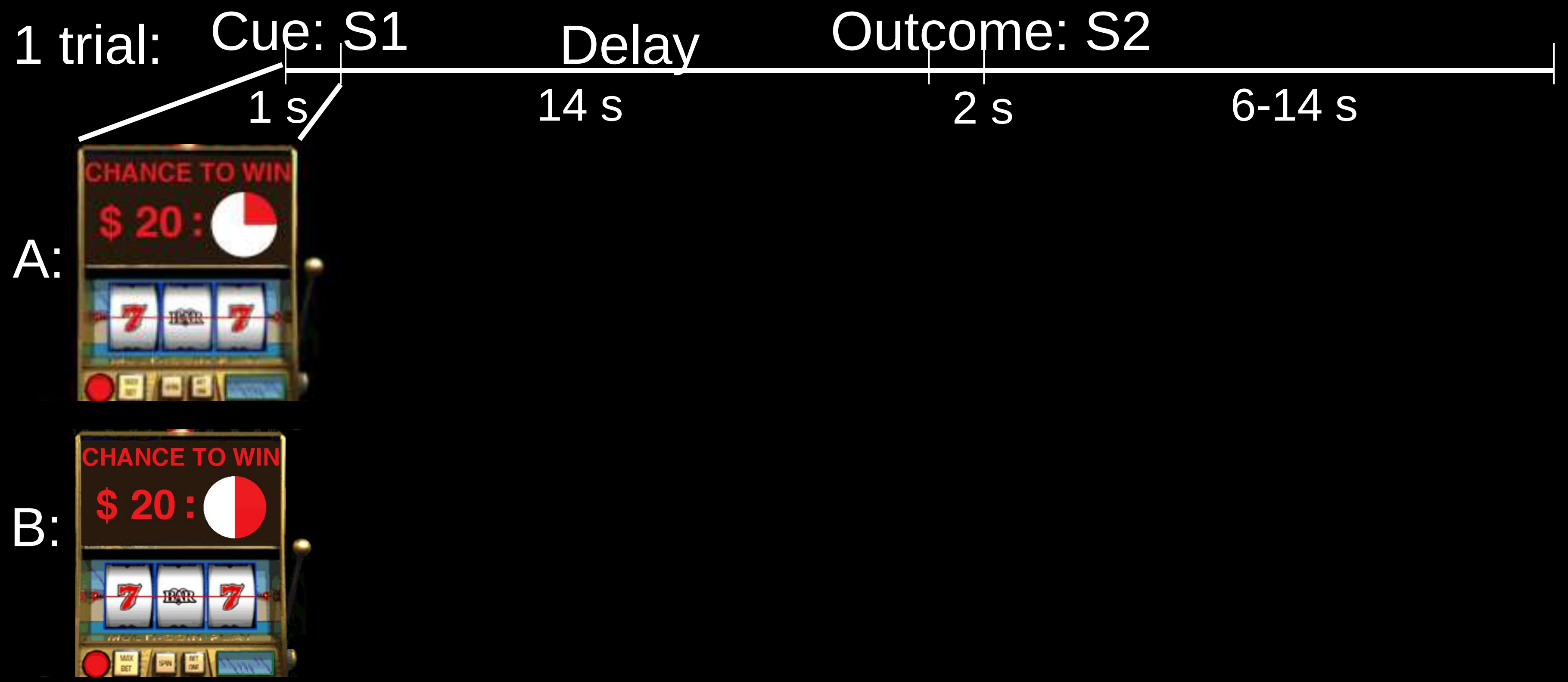

10
FEDERAL
RESERVE NOTE
10
BE 89388421 A
E5
THE UNITED STATES
OF AMERICA
TEN
BE 89388421 A
TEN
DOLLARS


FEDERAL
RESERVE NOTE
CB58417223A
B2
THE UNITED STATES OF AMERICA
CB58417223A

$ 0



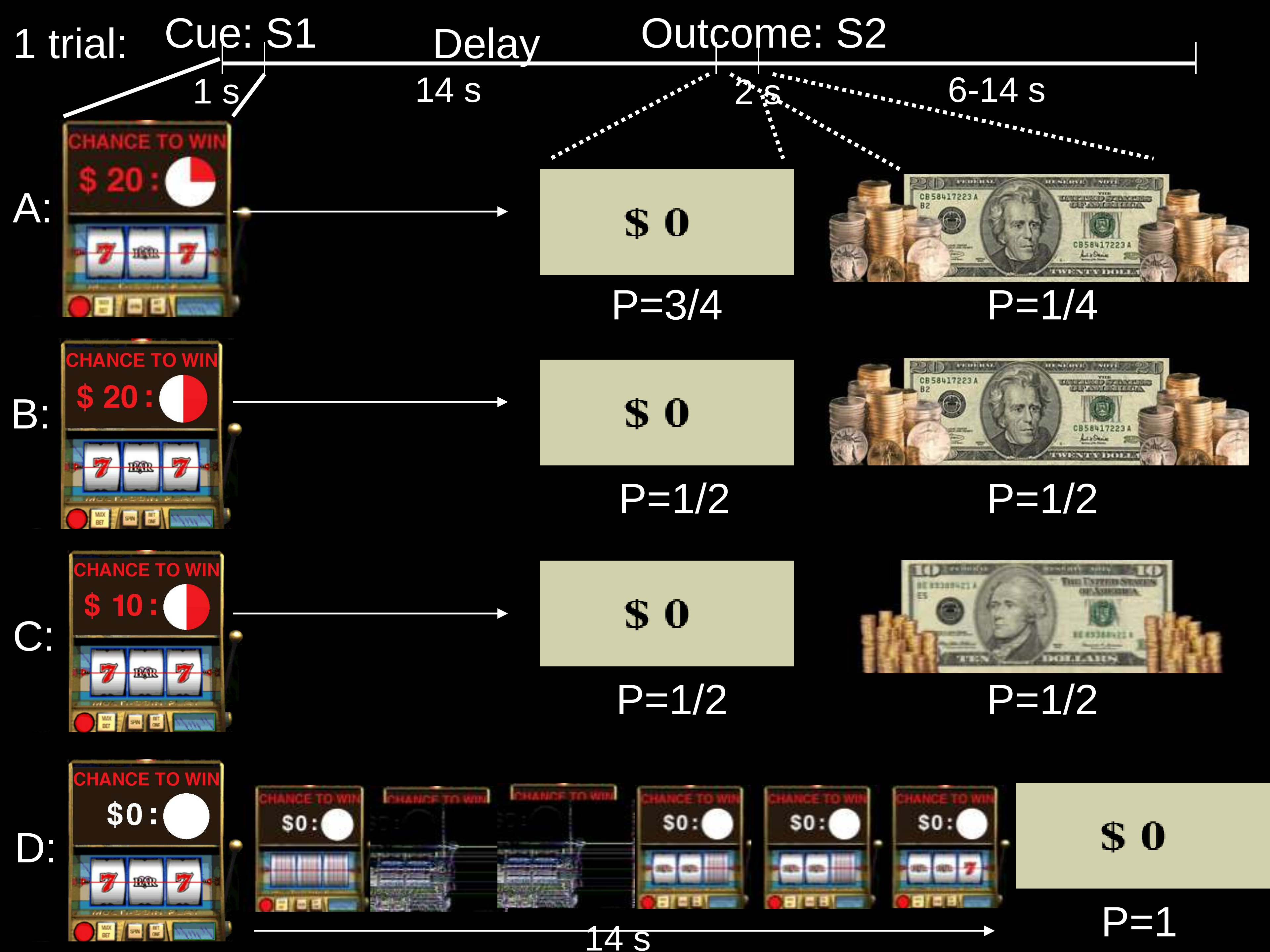
1 trial:
Cue: S1
Delay
Outcome: S2
1 s
14 s
2 s
6-14 s
A:
CHANCE TO WIN
$ 20 :


1 trial:
Cue: S1
Delay
Outcome: S2
1 s
14 s
2 s
6-14 s
A:
CHANCE TO WIN
$ 20 :
B:
CHANCE TO WIN
$ 20 :

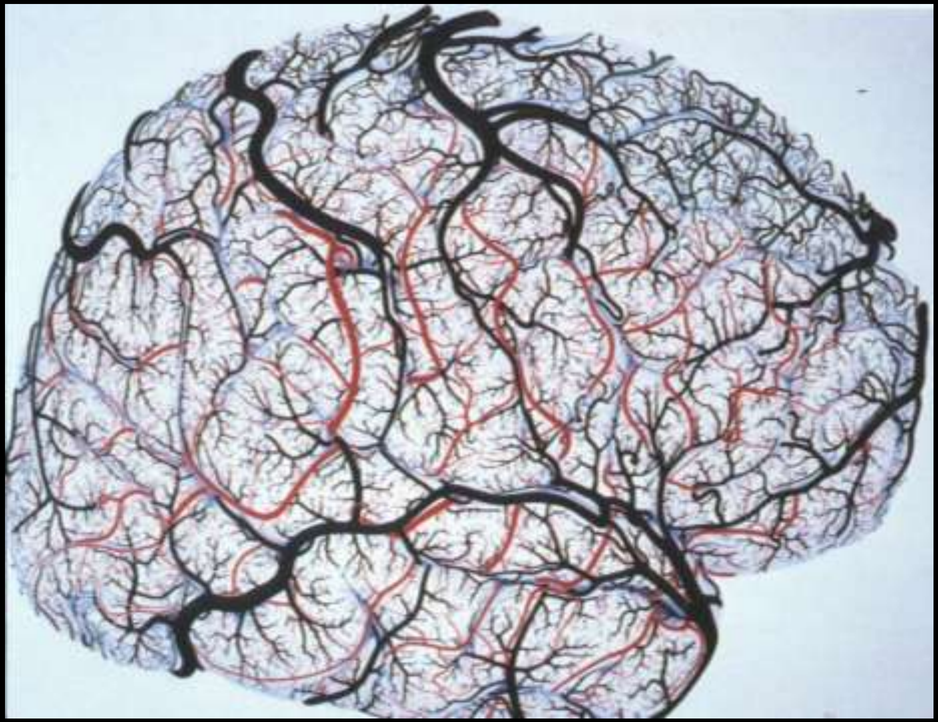

1 trial:
Cue: S1
Delay
Outcome: S2
1 s
14 s
2 s
6-14 s
A:
CHANCE TO WIN
$ 20 :
B:
CHANCE TO WIN
$ 20 :
C:
CHANCE TO WIN
$ 10 :


1 trial:
Cue: S1
Delay
Outcome: S2
1 s
14 s
2 s
6-14 s
A:
CHANCE TO WIN
$ 20 :
B:
CHANCE TO WIN
$ 20 :
C:
CHANCE TO WIN
$ 10 :
D:
CHANCE TO WIN
$0 :


1 trial:
Cue: S1
Delay
Outcome: S2
1 s
14 s
2 s
6-14 s
A:
CHANCE TO WIN
$ 20 :
B:
CHANCE TO WIN
$ 20 :
C:
CHANCE TO WIN
$ 10 :
D:
CHANCE TO WIN
$0 :
14 s


1 trial:
Cue: S1
Delay
Outcome: S2
1 s
14 s
2 s
6-14 s
A:
CHANCE TO WIN
$ 20 :
$ 0
P=3/4
P=1/4
B:
CHANCE TO WIN
$ 20 :
$ 0
P=1/2
P=1/2
C:
CHANCE TO WIN
$ 10 :
$ 0
P=1/2
P=1/2
D:
CHANCE TO WIN
$0 :
$ 0
P=1
14 s

What do we measure with fMRI?

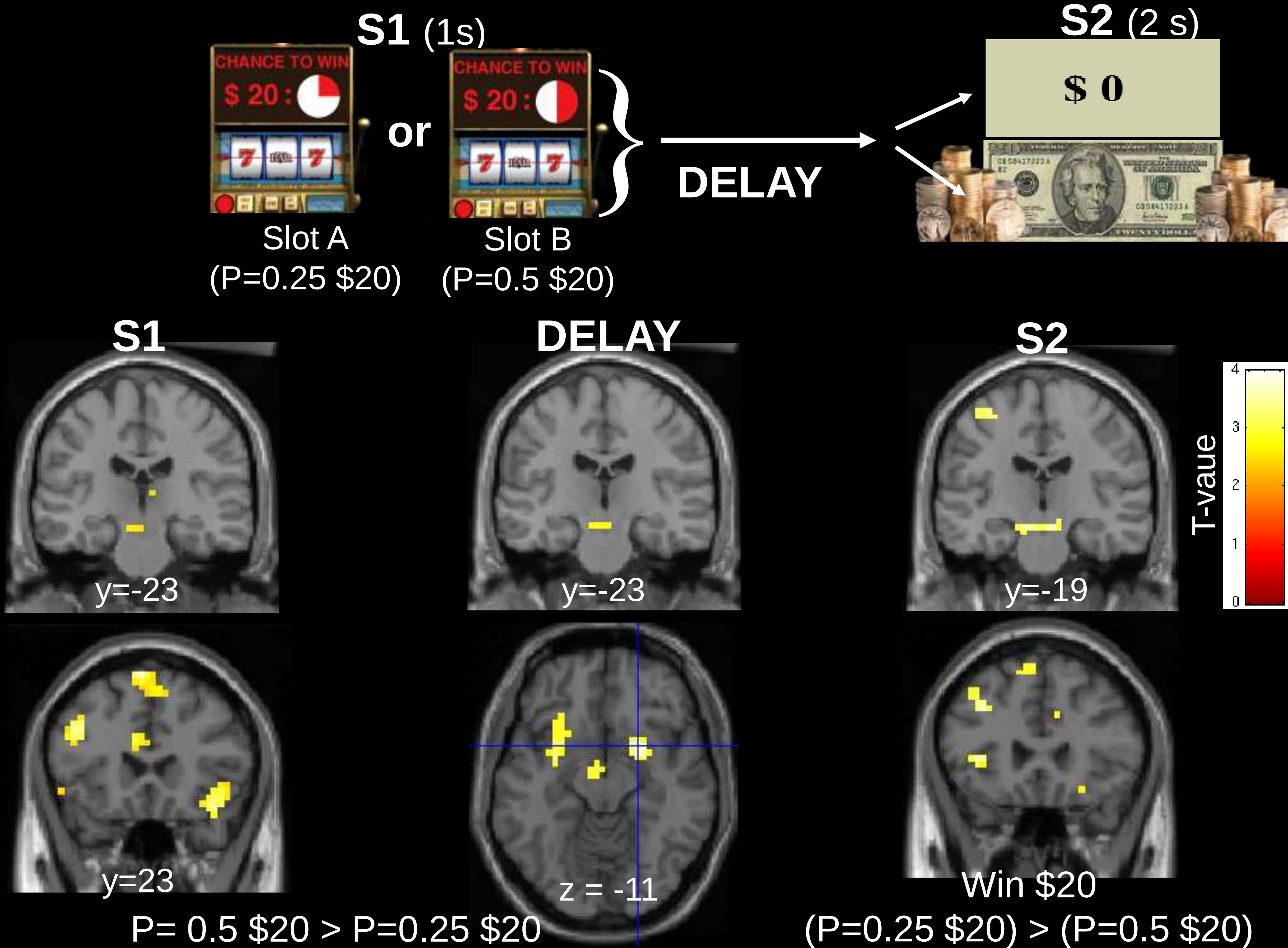


Vasculature of the Human Brain

Neuronal Activity → Hemodynamic Response → Measured fMRI Signal

- fMRI tracks changes in oxygen levels in the blood in response to stimuli
- Blood Oxygenation Level Dependent (BOLD) signal reflects the input and intracortical processing of a given area rather than its spiking output

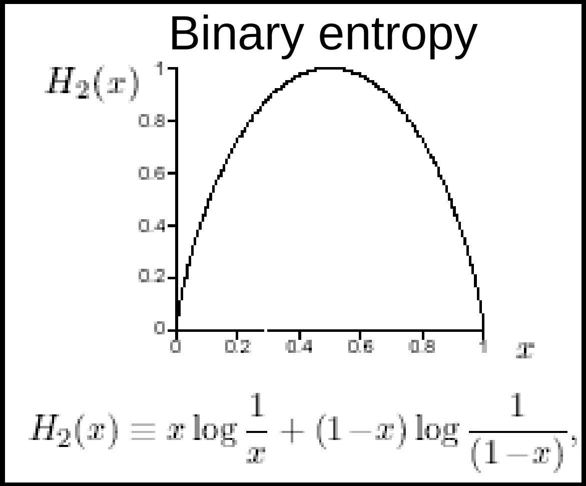
fMRI results

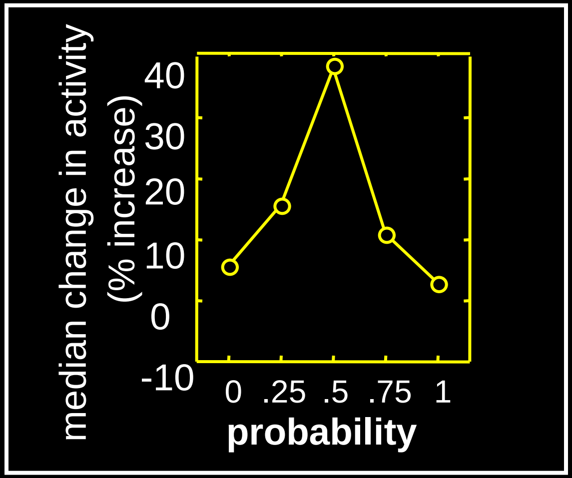


POSSIBLE FUNCTIONS OF DOPAMINERGIC PROJECTION SITES

- The DLPFC may generate or maintain the prediction of potential rewards.

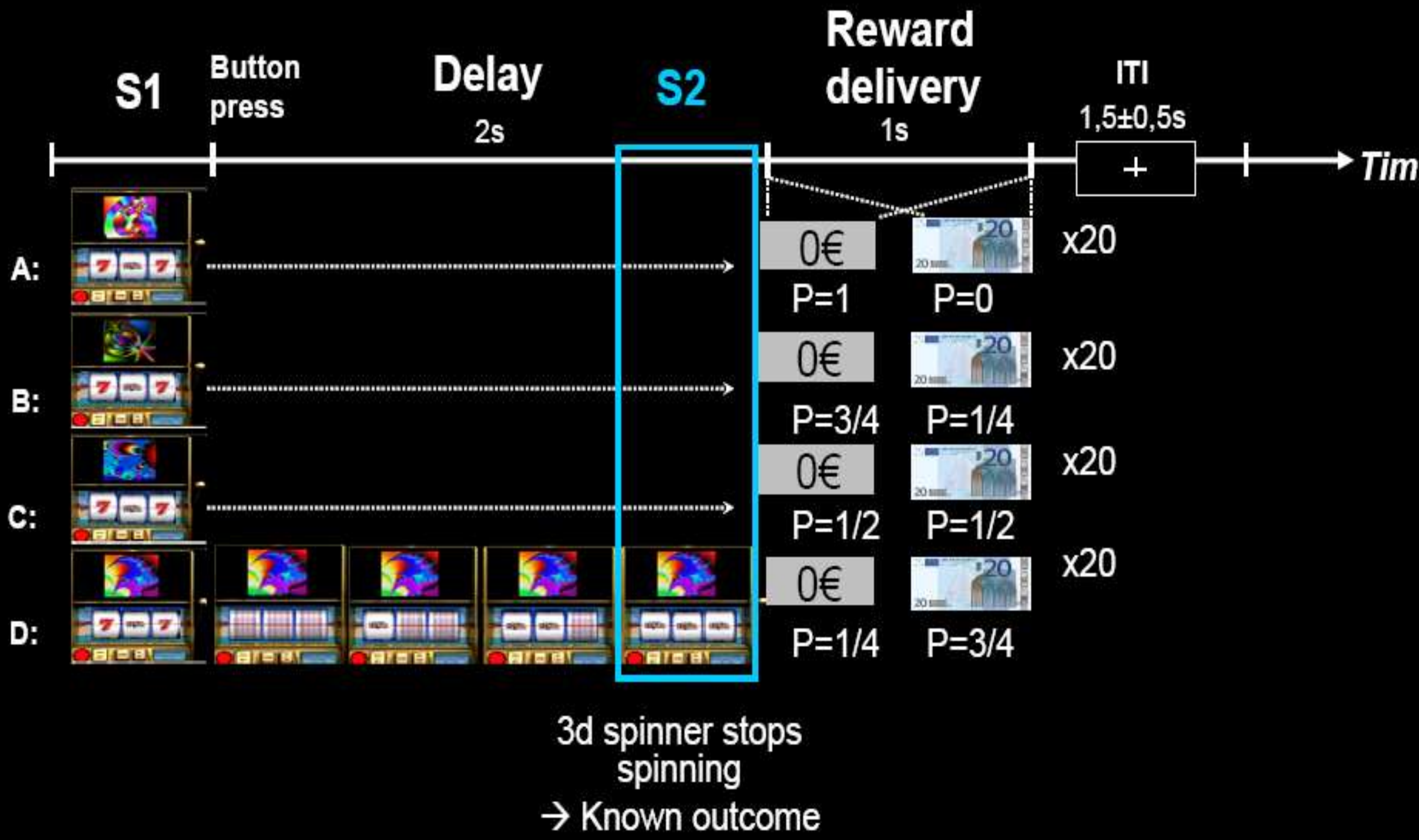
- The ventral striatum activation may reflect the expectation of reward information in terms of information theory (the more uncertain the outcome, the more information it conveys).





• This function may be useful for promoting exploratory behavior in the balance that an organism must exert between exploring the environment to gain new information and exploiting existing knowledge to obtain a reward.

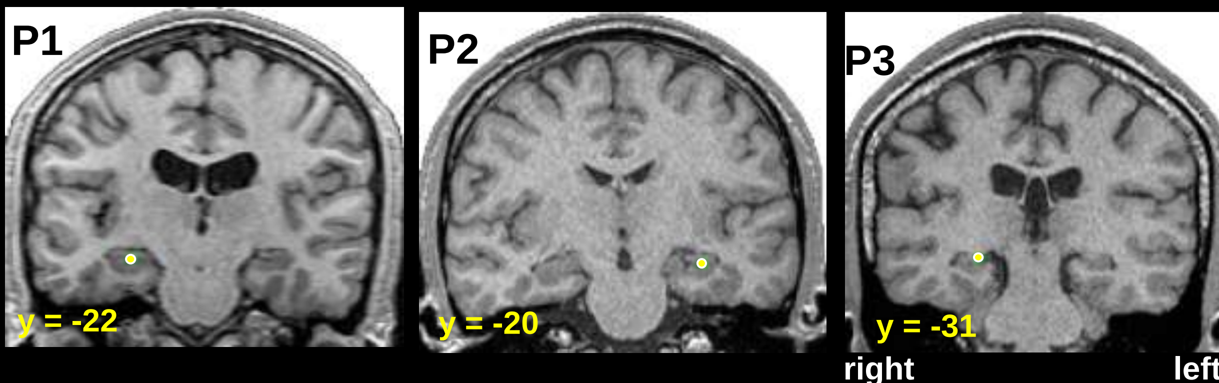
Intra-cranial EEG study of the reward system in humans

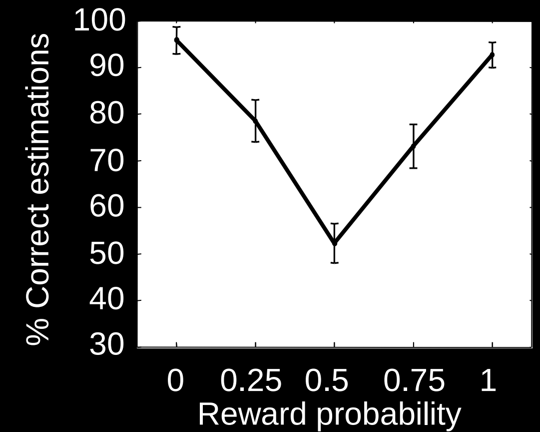


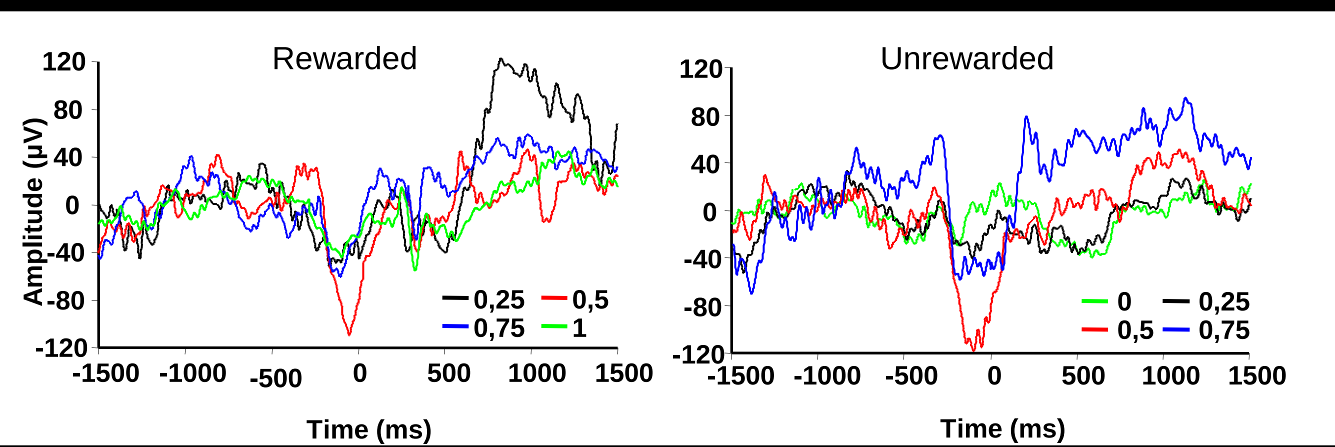
Vanni-Mercier et al., *J. Neurosci*., 2009

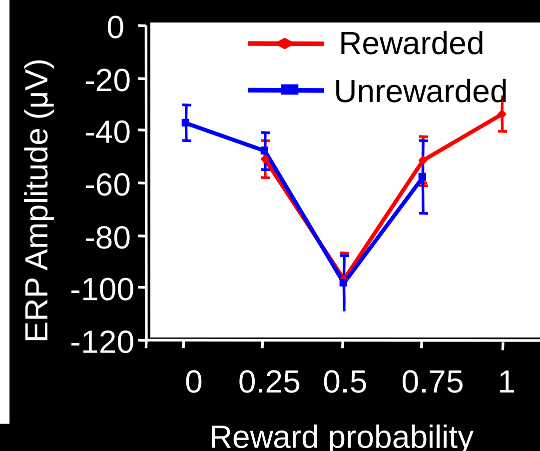
Intra-cranial EEG study of the reward system in humans

Local field potential recorded in the hippocampus for different reward probabilities









Vanni-Mercier et al., *J. Neurosci*., 2009

CONCLUSION:
Reward probability and uncertainty coding

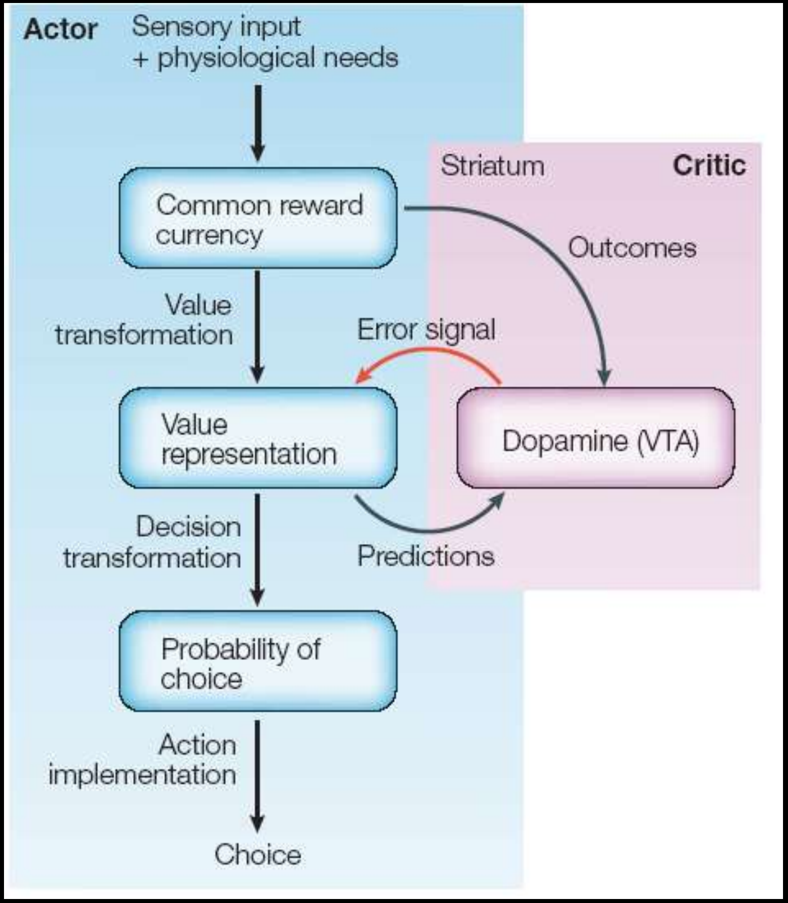
- Our findings extend in humans the distinction between a transient and a sustained mode of midbrain activity found in monkeys.

- Different projection sites, such as the frontal cortex and the ventral striatum respond preferentially to the phasic and sustained modes of activity.

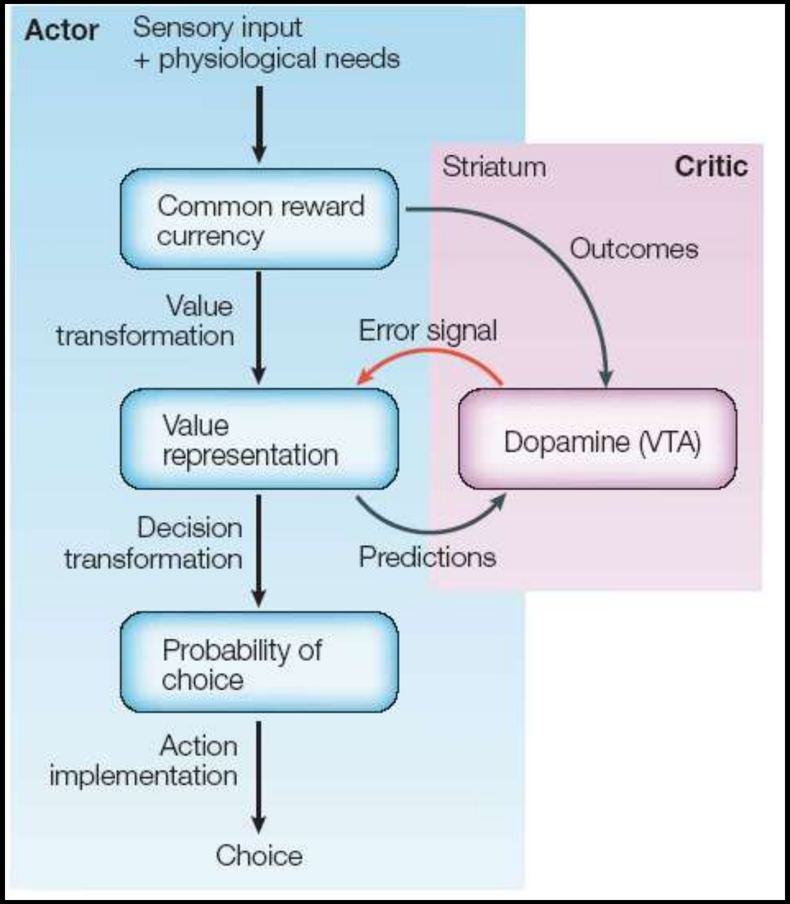
- In the hippocampus, uncertainty is coded at the time of the outcome in a transient fashion.

- These results indicate distinct roles for different dopamine-related networks in processing different reward information signals.

Distinguishing common and specific neural substrates for different types of rewards

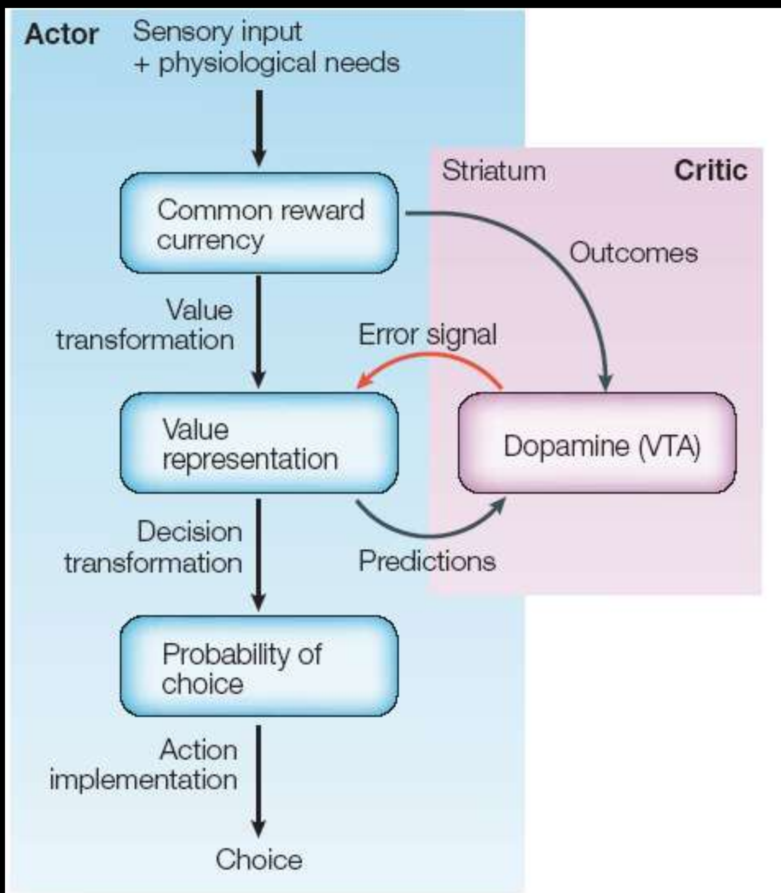


Distinguishing common and specific neural substrates for different types of rewards



Drink (liquid reward)

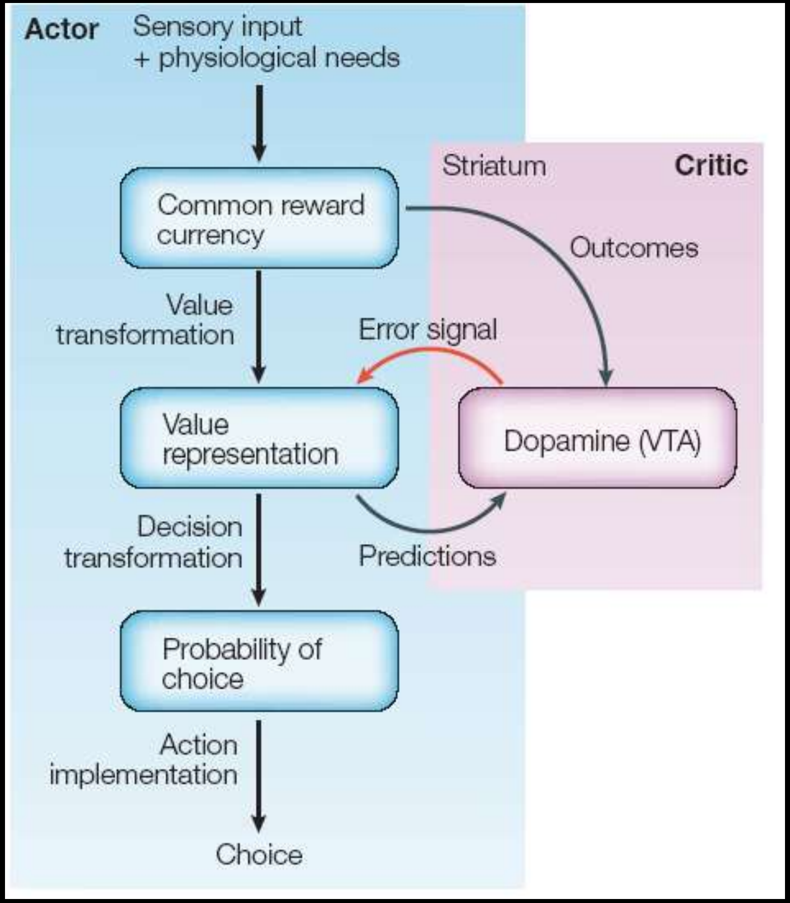
Distinguishing common and specific neural substrates for different types of rewards



Drink (liquid reward)

Monetary reward

Distinguishing common and specific neural substrates for different types of rewards



Drink (liquid reward)

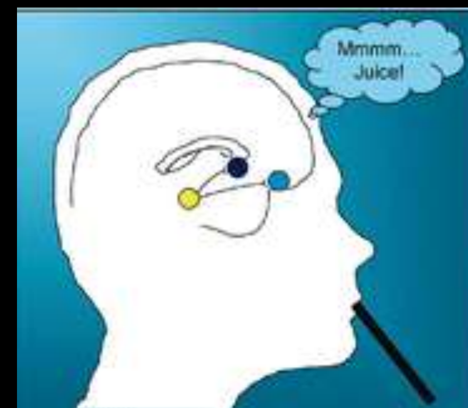
Erotic stimuli

Monetary reward

Distinguishing common and specific neural substrates for different types of rewards

Influence of specific motivational dysfunction on other types of rewards:

- Pathological gamblers
- Anorexia
- Men with Hypoactive Sexual Desire Disorder



Drink (liquid reward)

Erotic stimuli

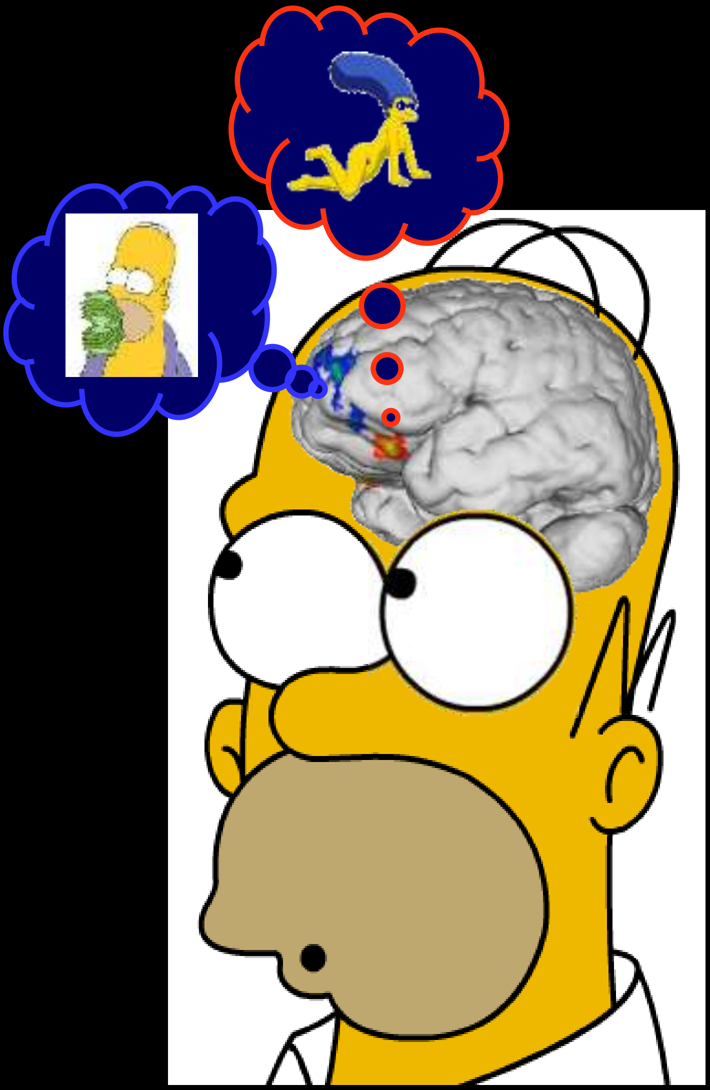
Monetary reward

Distinguishing common and specific neural substrates for different types of rewards

- Are there common / distinct neural networks for rewards of different nature?

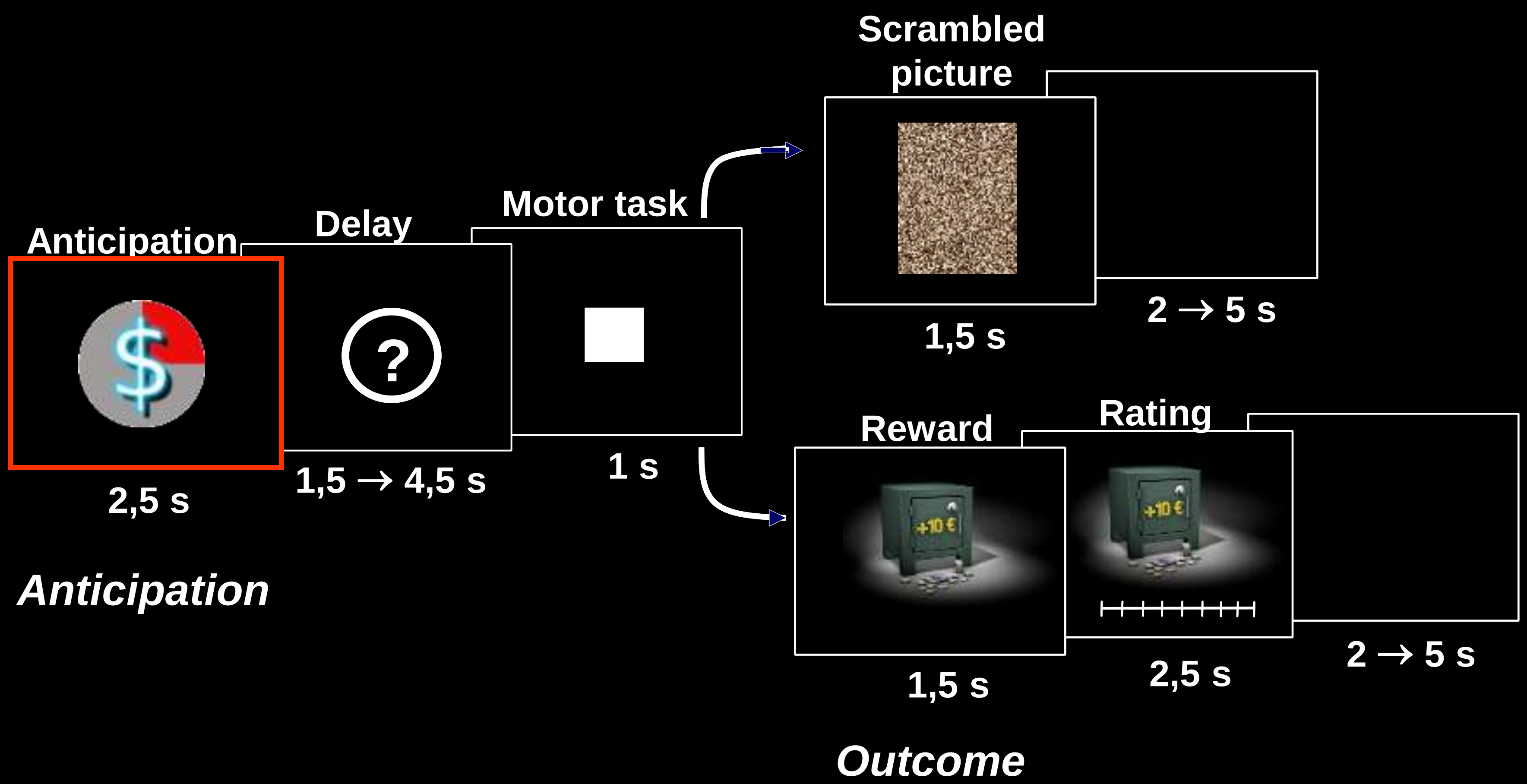
Sescousse et al., *J. Neurosci.*, 2010

Distinguishing common and specific neural substrates for different types of rewards

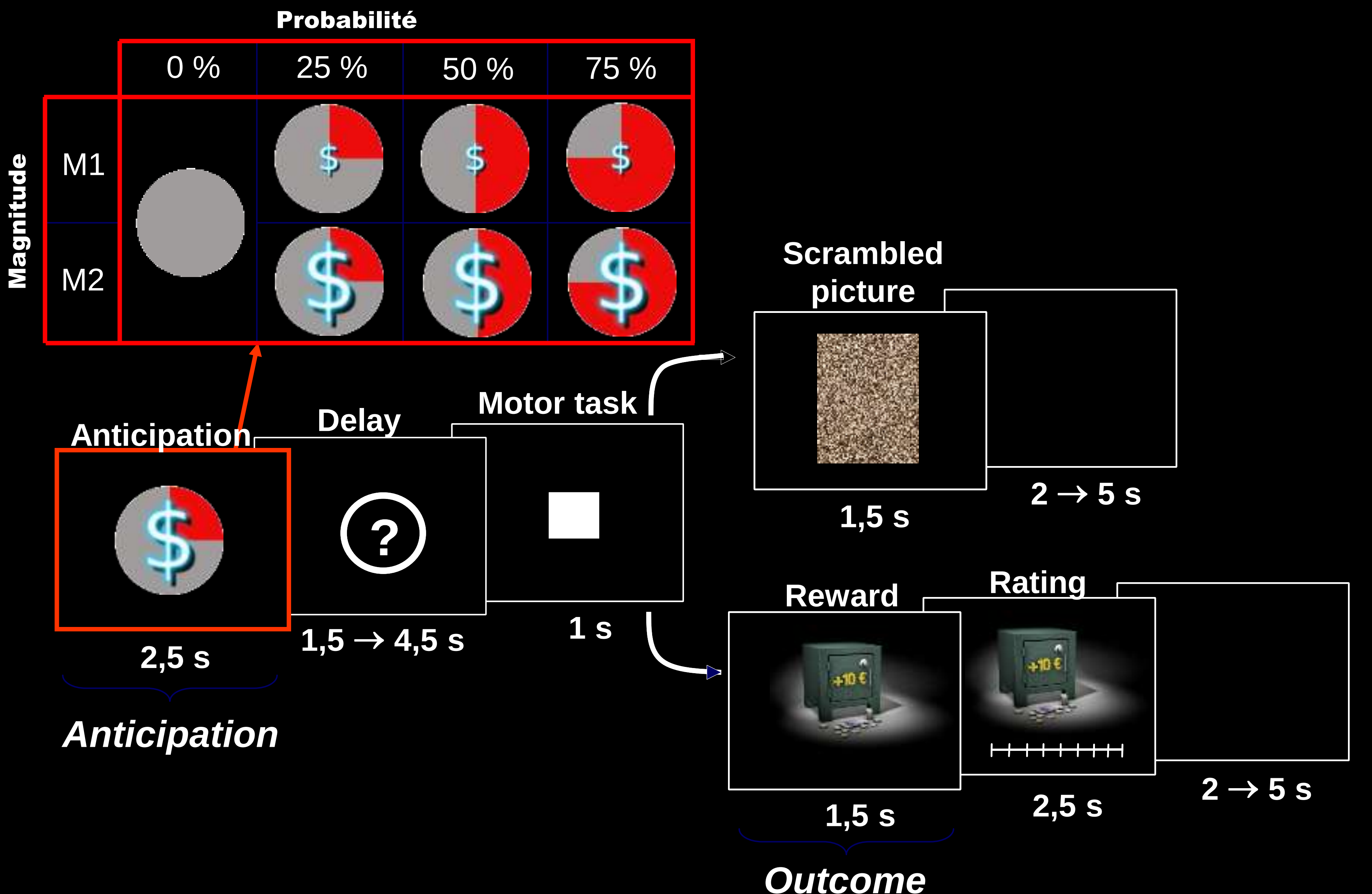


Sescousse et al., *J. Neurosci.*, 2010

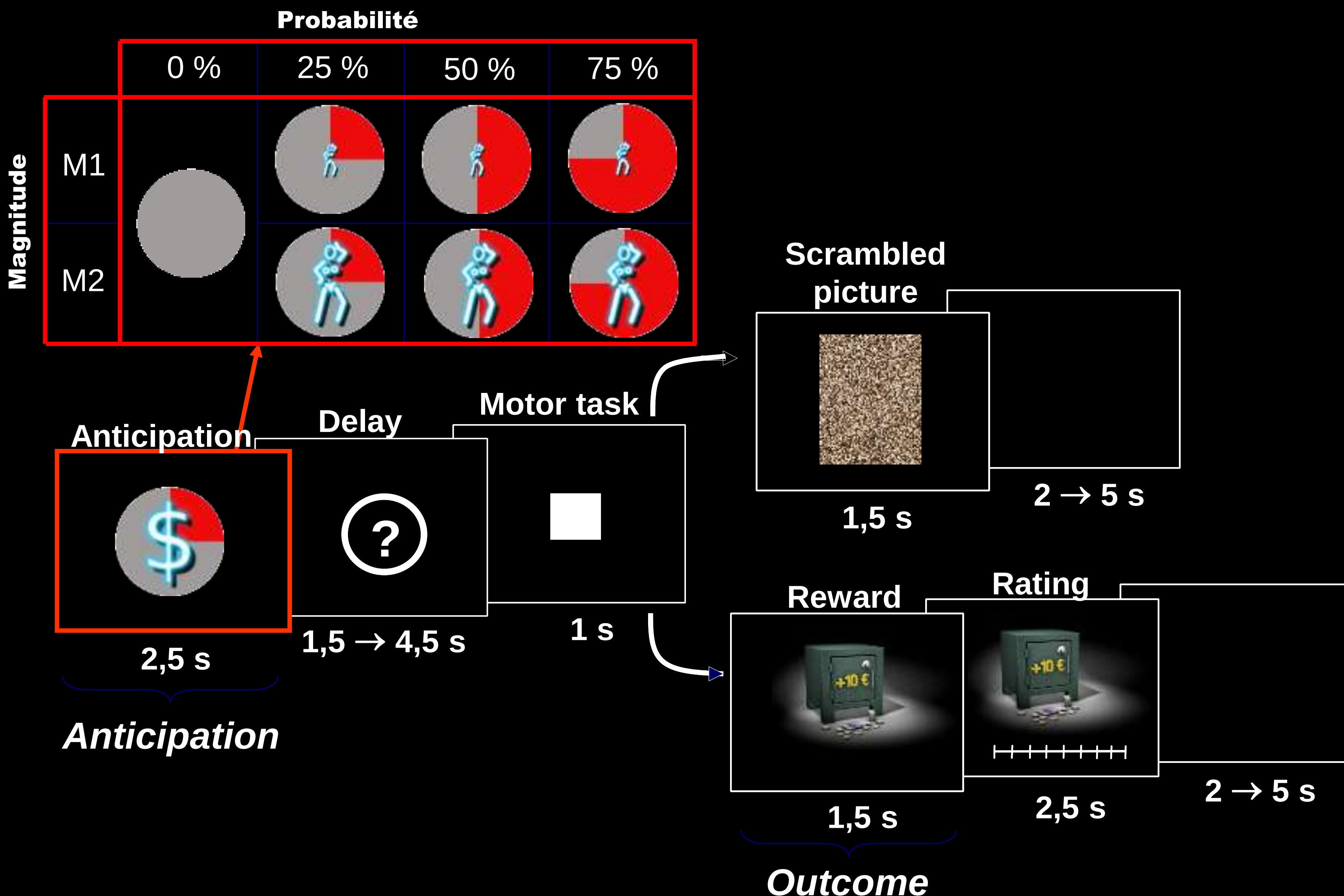
fMRI primary/secondary reward task



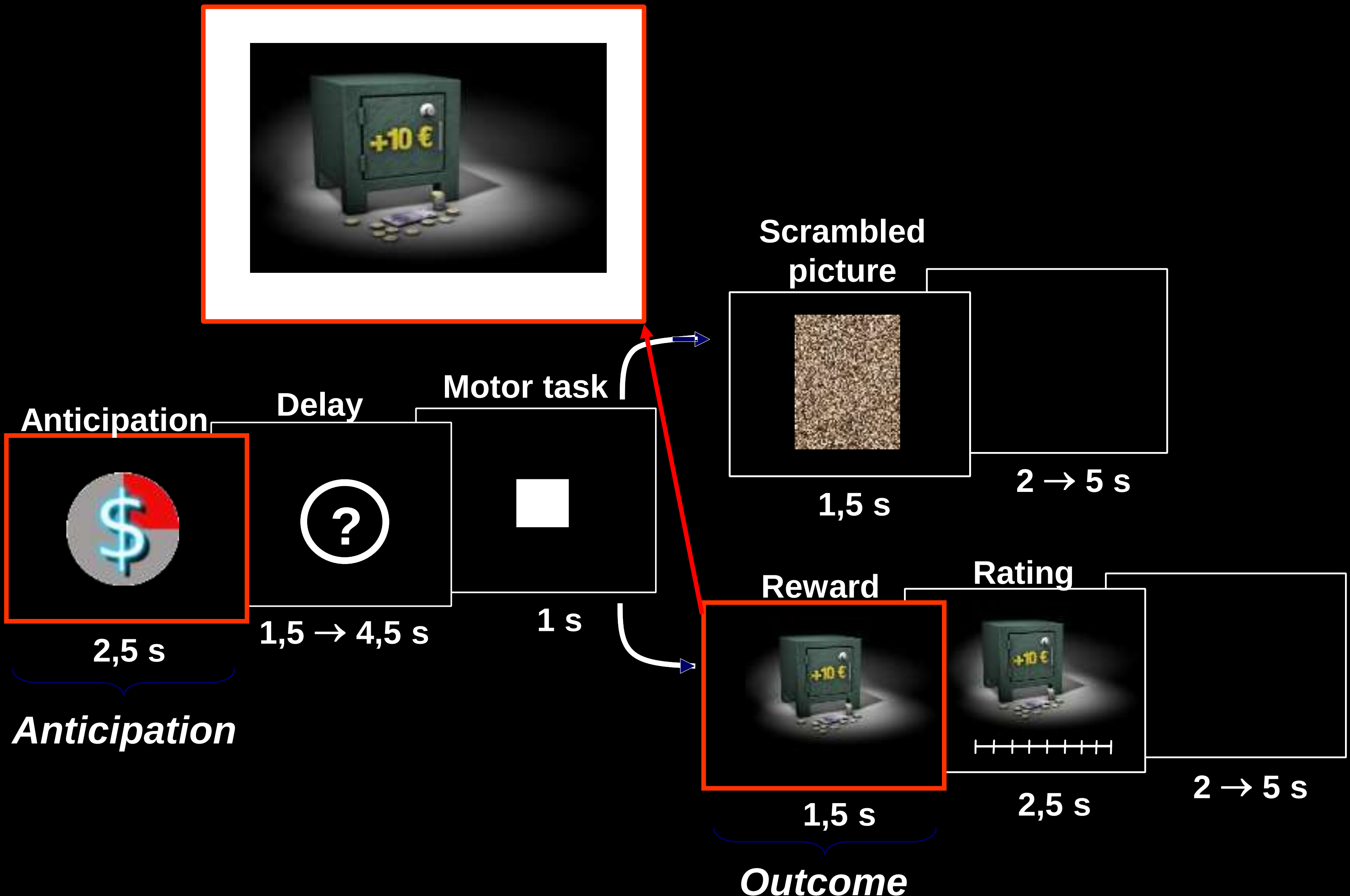
fMRI primary/secondary reward task



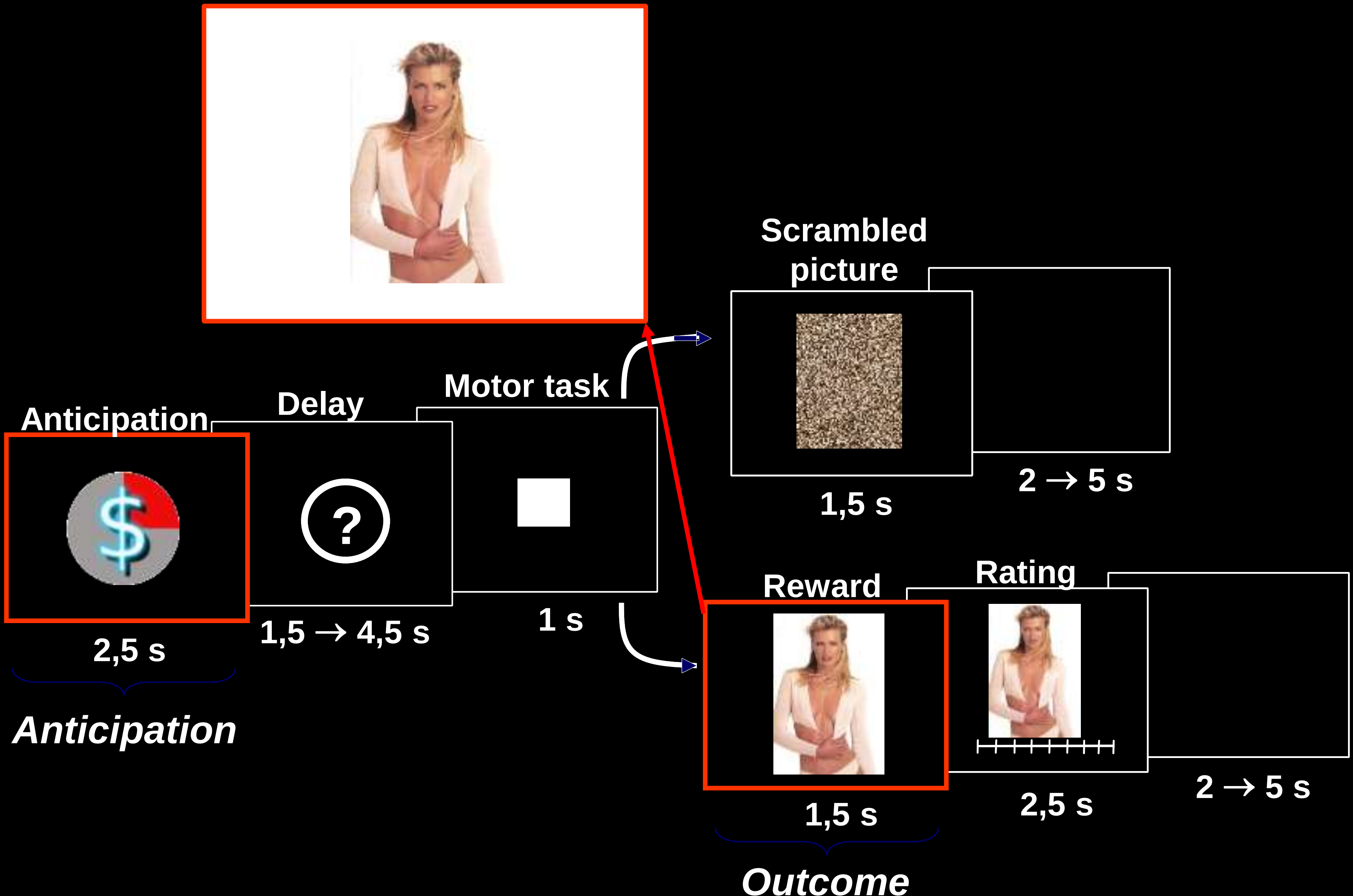
fMRI primary/secondary reward task



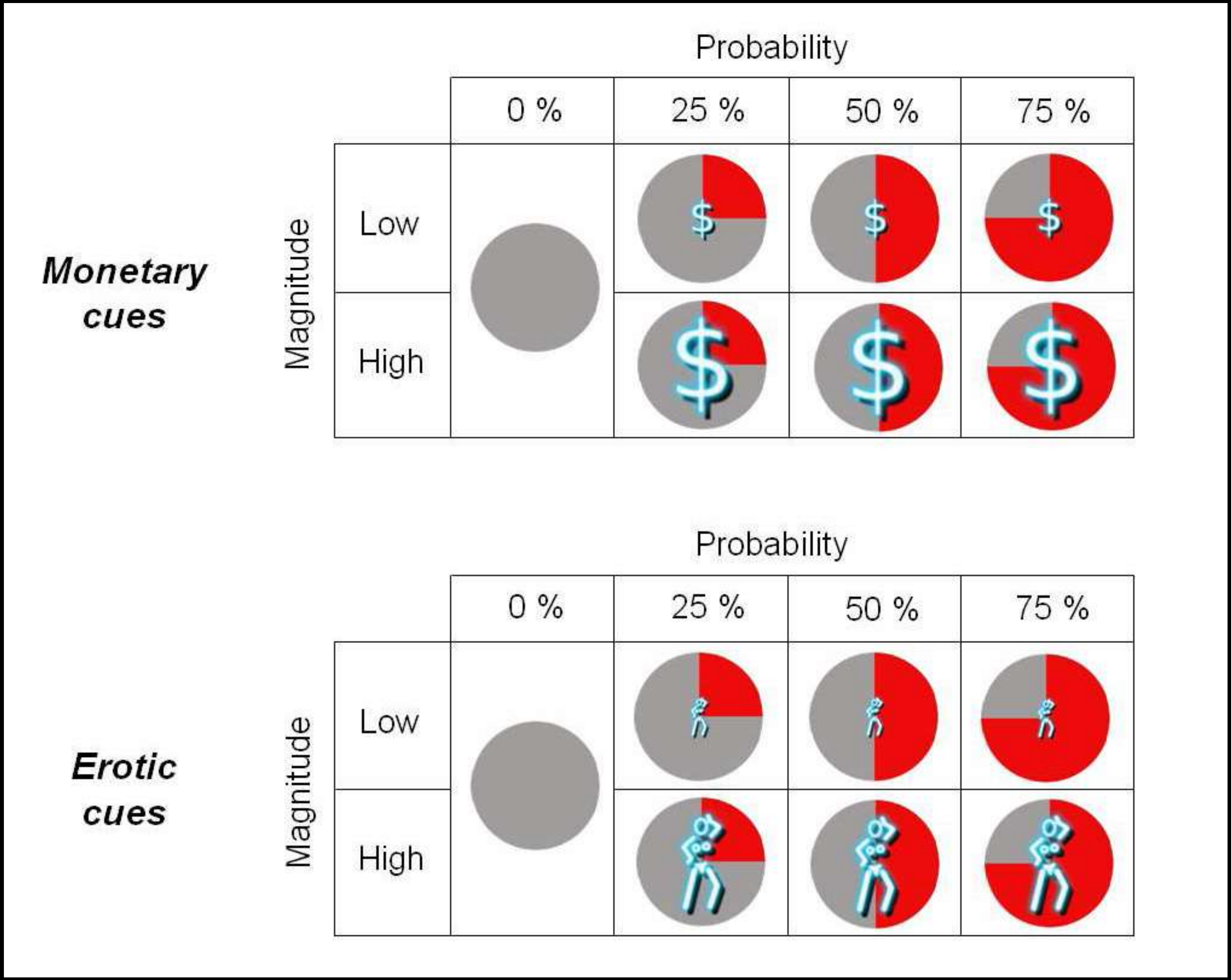
fMRI primary/secondary reward task



fMRI primary/secondary reward task



fMRI primary/secondary reward task



Methods

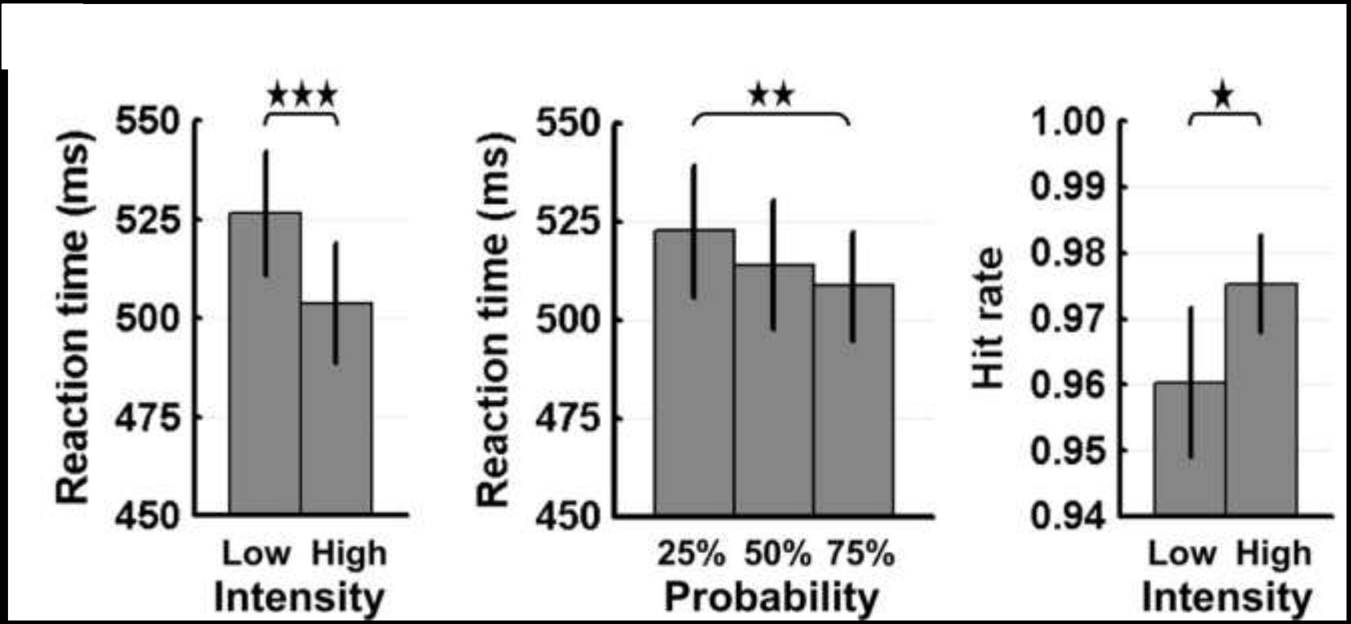
• 18 young, healthy, heterosexual men (mean age: 24 ± 3.3 years)

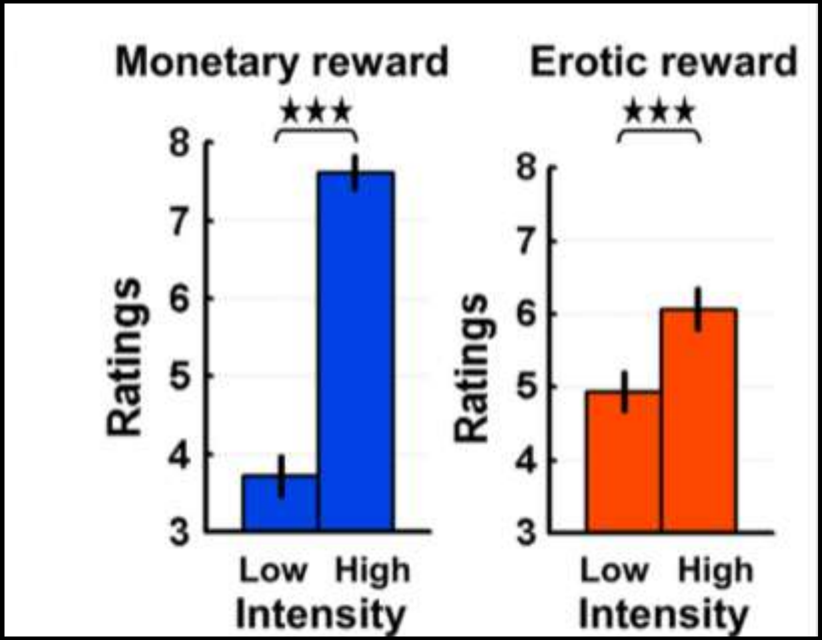
• Subjects' sexual orientation assessed using the french analysis of sexual behavior questionnaire (Spira et al., 1993) and sexual arousability was measured with the Sexual Arousability Inventory (SAI) (Hoon and Chambless, 1998), which ensured that subjects showed a "standard" sexual arousability

• Right-handed, as assessed by the Edinburgh Handedness Questionnaire

• No history of psychiatric or neurological illness

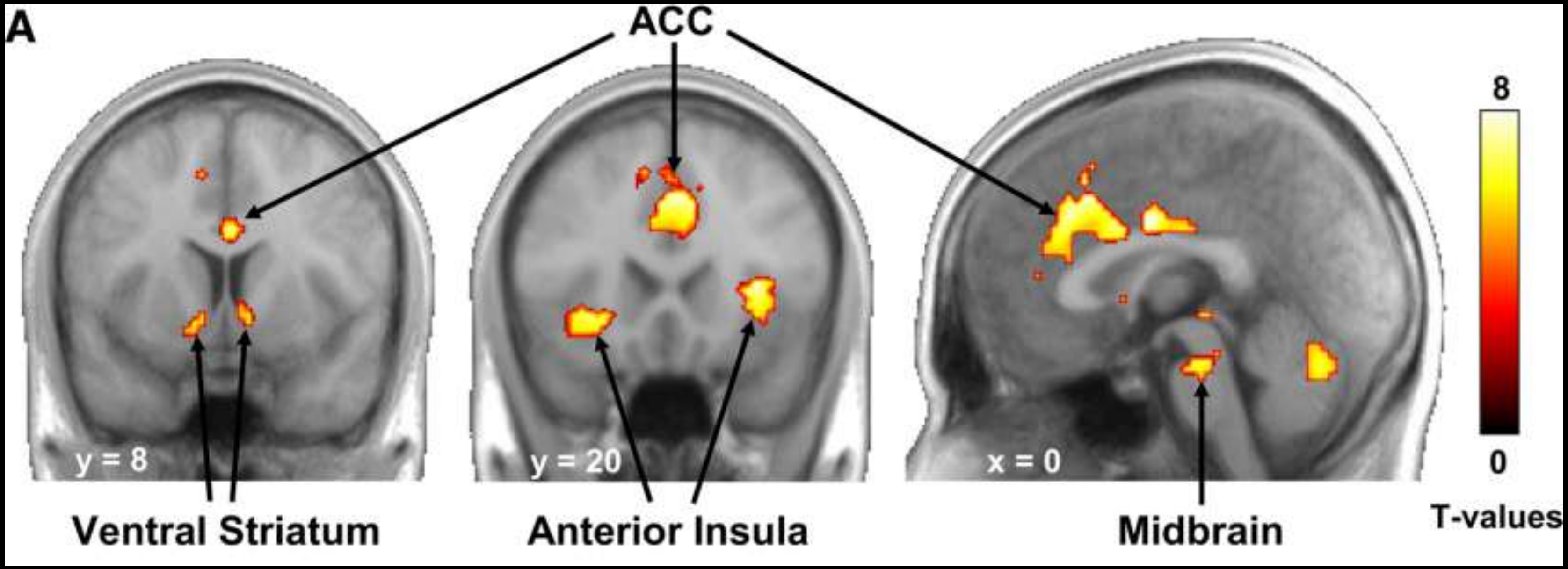
Behavioral results





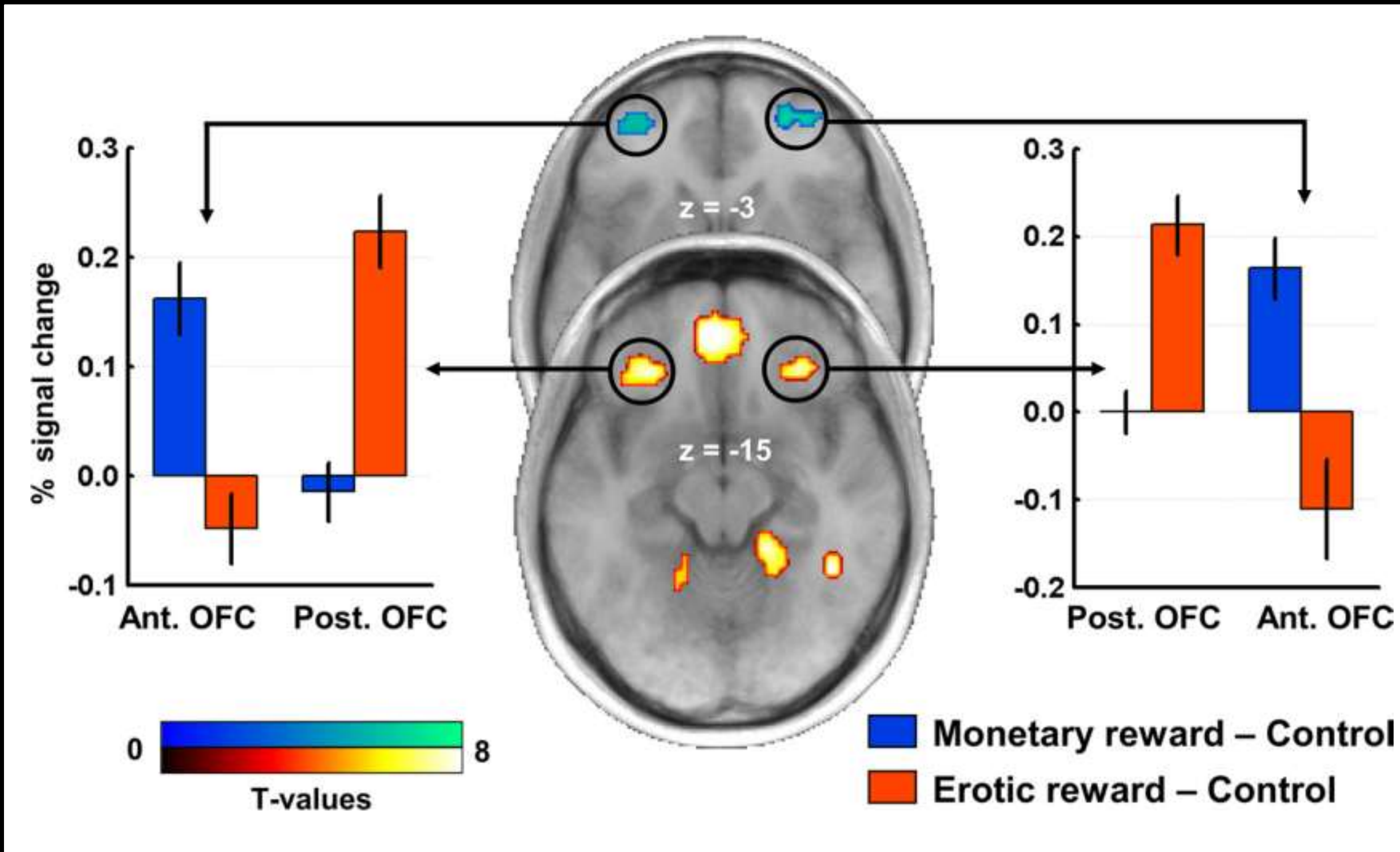
Common brain network for rewards of different nature

and

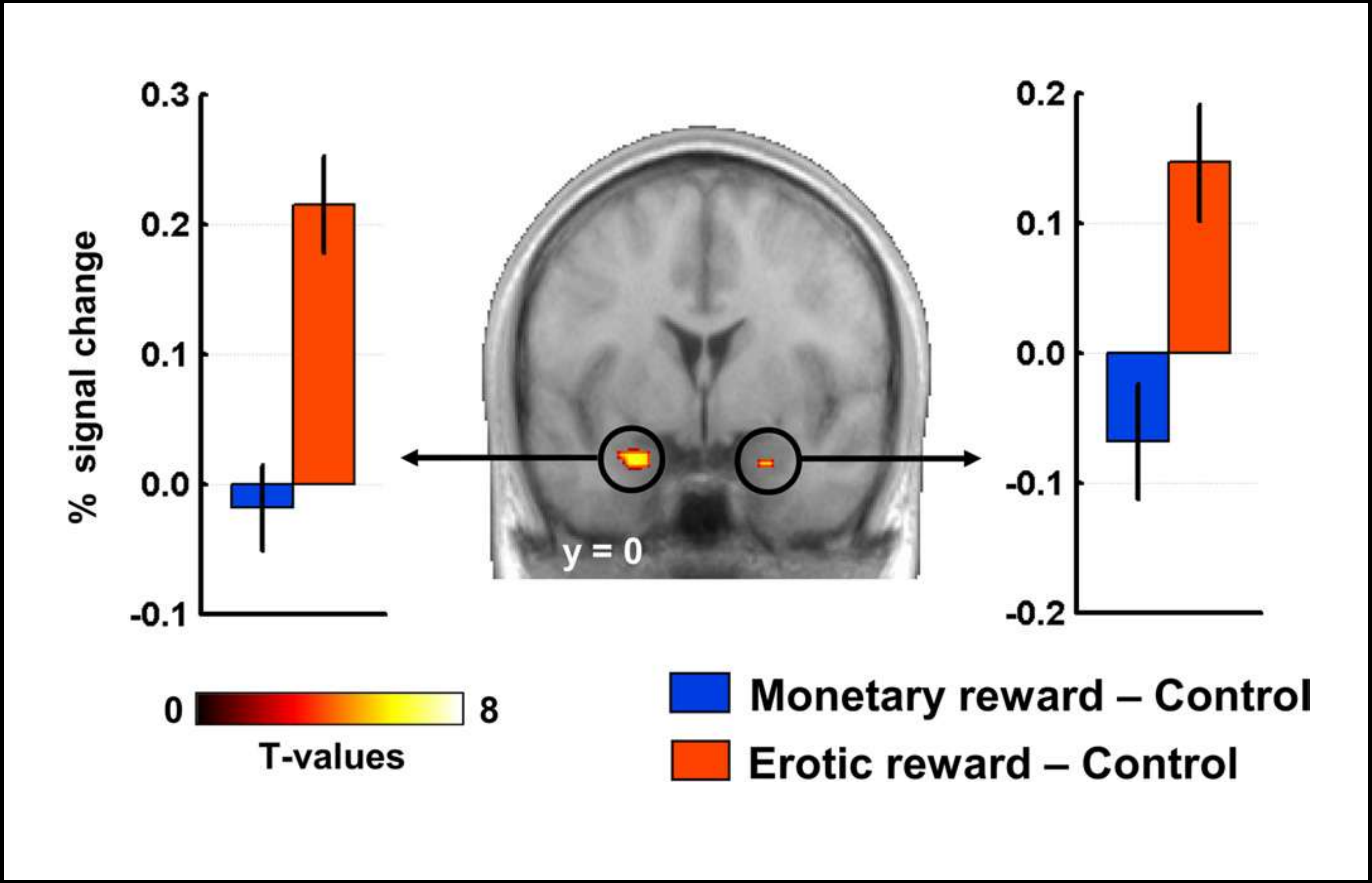


CONJUNCTION of (moneywin > control) & (sexwin > control)

Antero-posterior dissociation in the orbitofrontal cortex according to reward nature



Amygdala is more activated for erotic rewards than for monetary gains



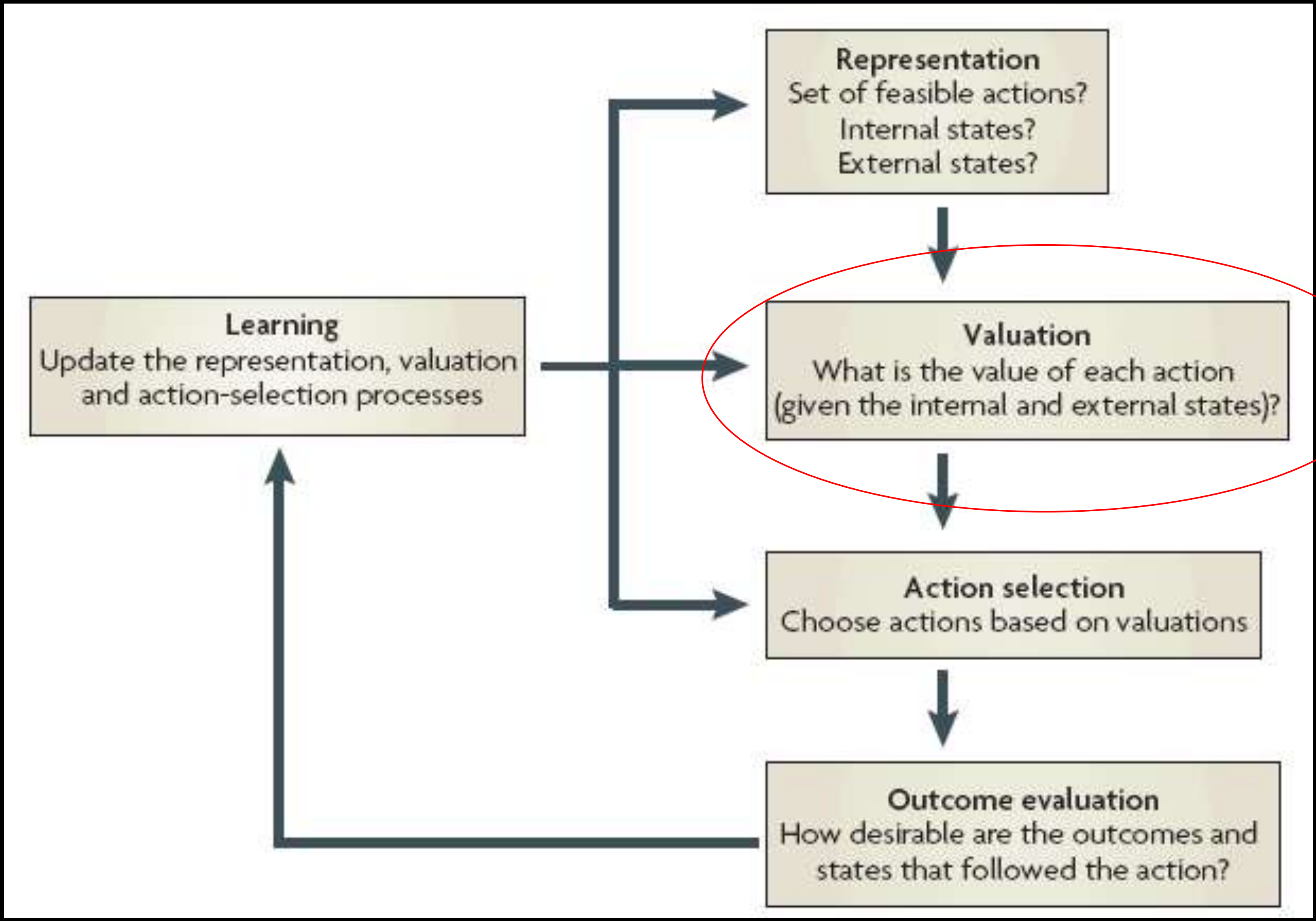
Conclusion

- The anterior lateral OFC, a phylogenetically recent structure, processes secondary rewards, while the posterior lateral OFC, phylogenetically and ontogenetically older, processes primary rewards.

- A set of neural structures encode the subjective value of rewards regardless of their type, consistent with the computation of a common neural currency.

- Supports a unified modular view of reward value coding in the brain, and propose a novel framework describing the functional organization of the human lateral OFC which has basic implications for integrative theories of prefrontal cortex functions.

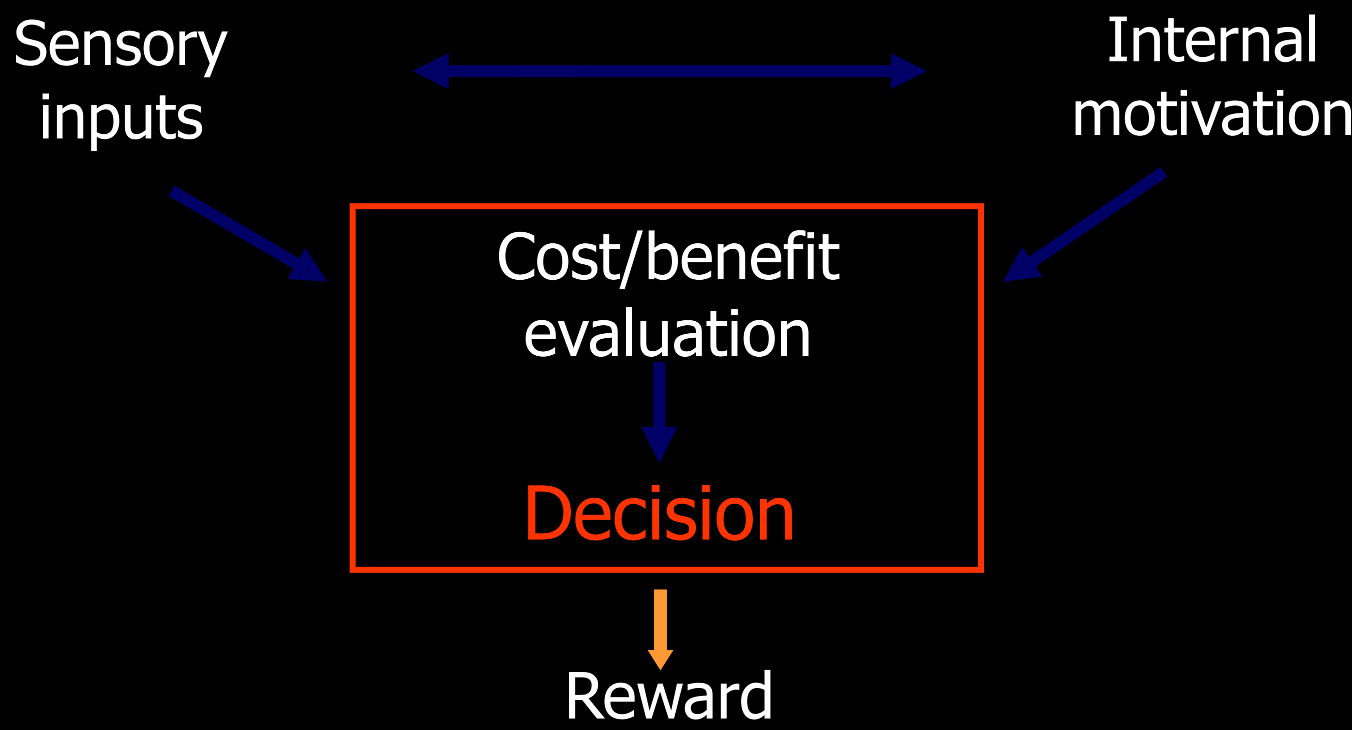
Value-based decision making



Rangel et al., *Nat. Rev. Neurosci.*, 2008

Value-based decision making

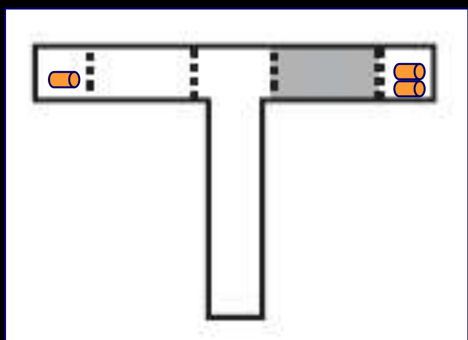
What are the neural substrates underlying our motivated decisions?



- Standard theories of economic decision making do not distinguish between decisions related to different types of costs, such as delay or effort costs
- A choice is made after a valuation stage, regardless of the nature of the cost
- Unclear which frontal regions are involved for different decision costs in humans

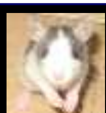
Separate neural pathways process different decision costs (in rats)

- Functional dissociation between the anterior cingulate cortex and the orbitofrontal cortex in rats

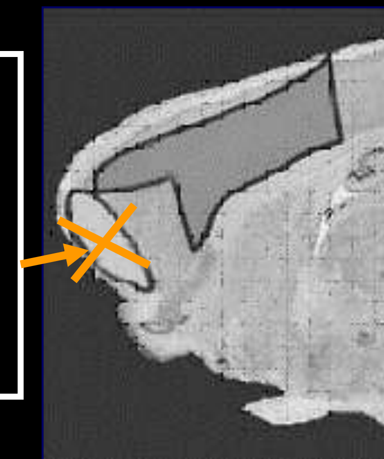


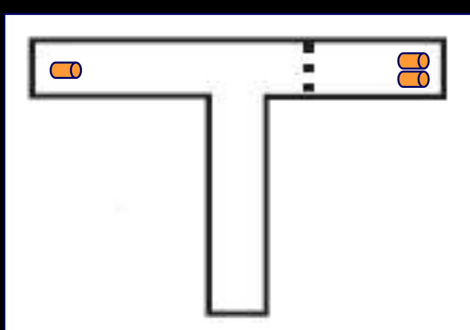
← delay: 15 s

← start



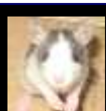
lesion of the orbitofrontal cortex -> affect how long rats decide to wait for rewards





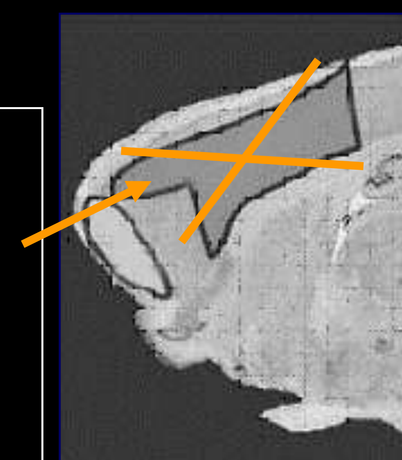
← barrier

← start



lesion of the anterior cingulate cortex

-> affect how much effort rats decide to invest for rewards



Rudebeck et al, Nat.Neurosci., 2006

Delay discounting in the human brain

• Neuroimaging studies of decision-making have generally related neural activity to objective measures (such as reward magnitude, probability or delay), despite choice preferences being subjective.

• However, economic theories posit that decision-makers behave as though different options have different subjective values.

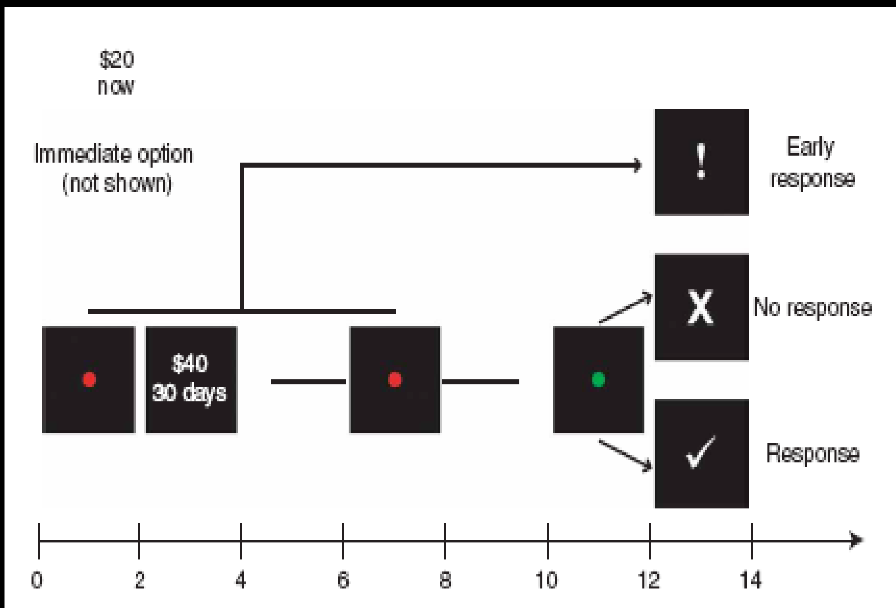
Many decisions involve the evaluation of rewards and costs that arrive with different delays.

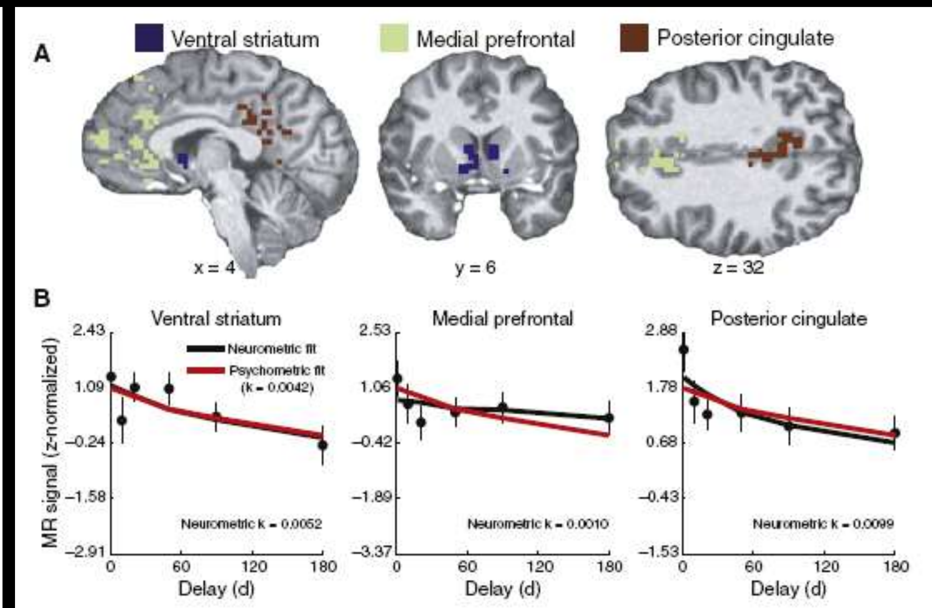
Thus, the valuation systems require a mechanism for incorporating the timing of rewards into their computations.

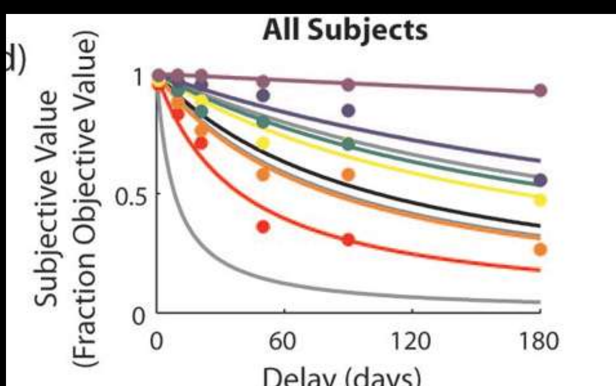
Temporal modulators of value in the goal-directed system

Delay discounting in the human brain

- Subjective value = 1/kD, k:subject specific constant, D: Delay







- Subjective utility theories: rational decision makers choose the option with the highest subjective value

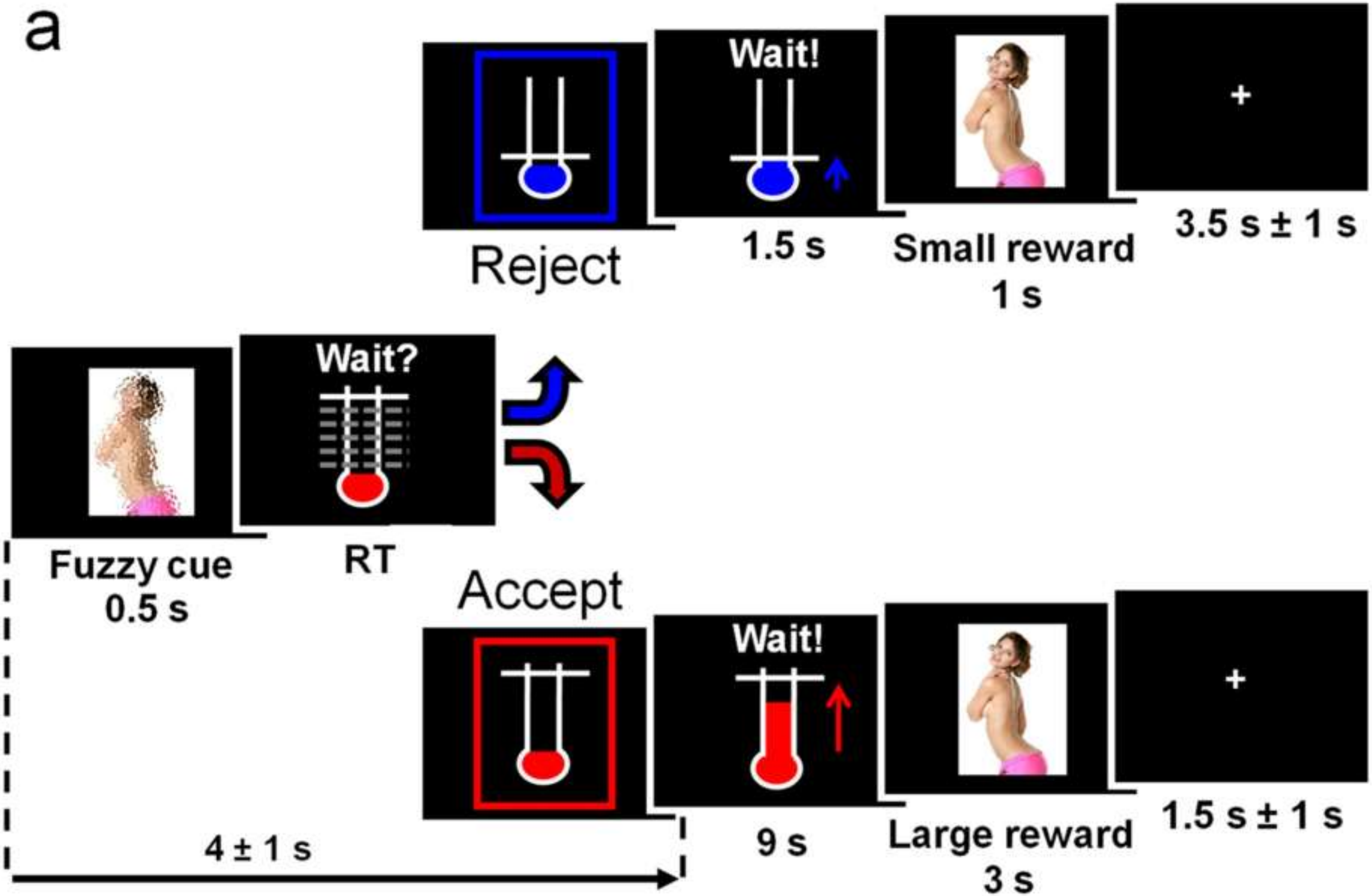
Kable and Glimcher, *Nat. Neurosci.* 2007

Distinct valuation subsystems in the human brain for effort and delay decision costs

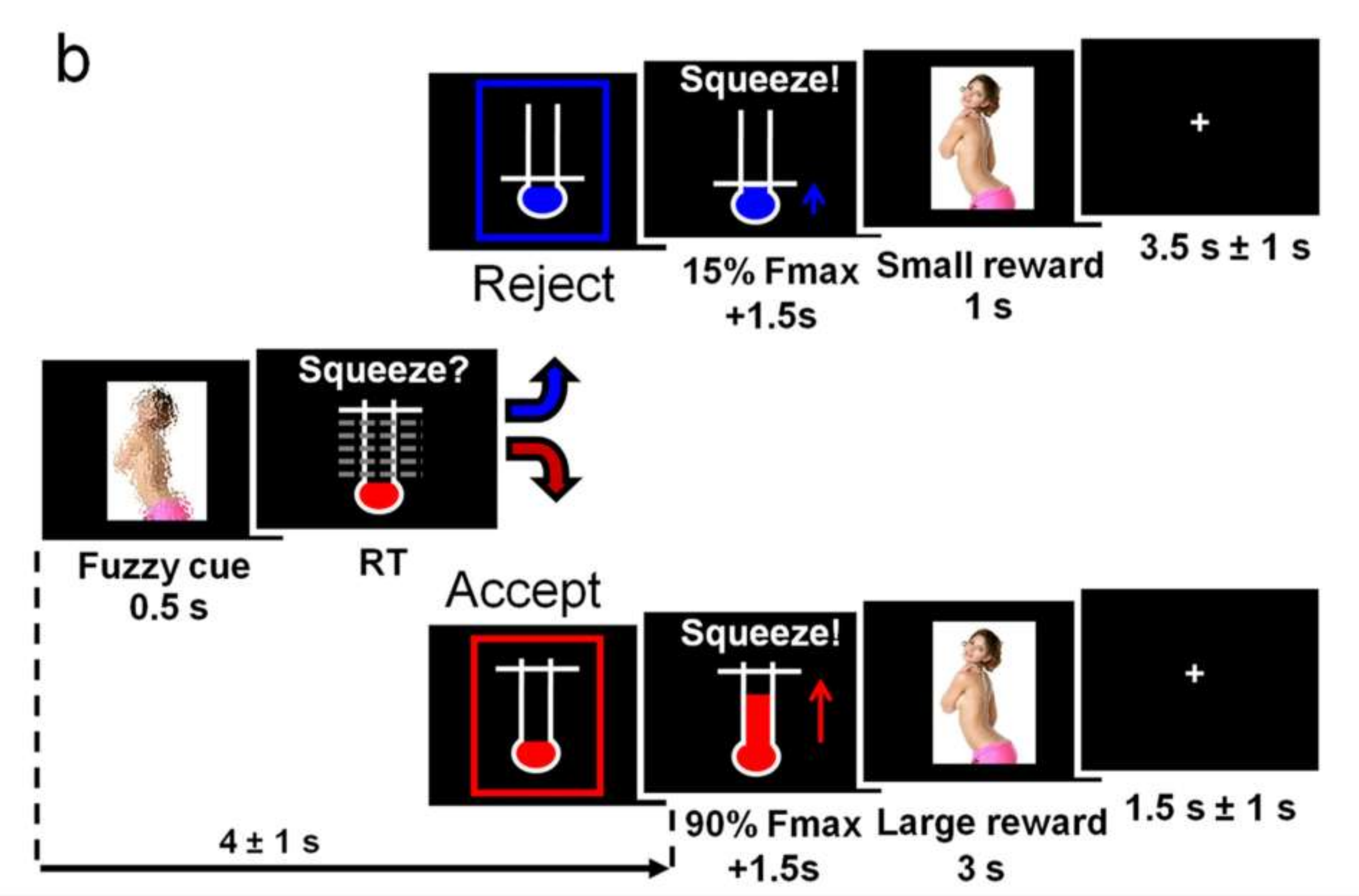
• QUESTION: Unclear whether the human brain uses a single valuation system to compute the subjective value of rewards associated with different types of costs, such as delay or effort.

Prévost et al., *Journal of Neuroscience*, 2010

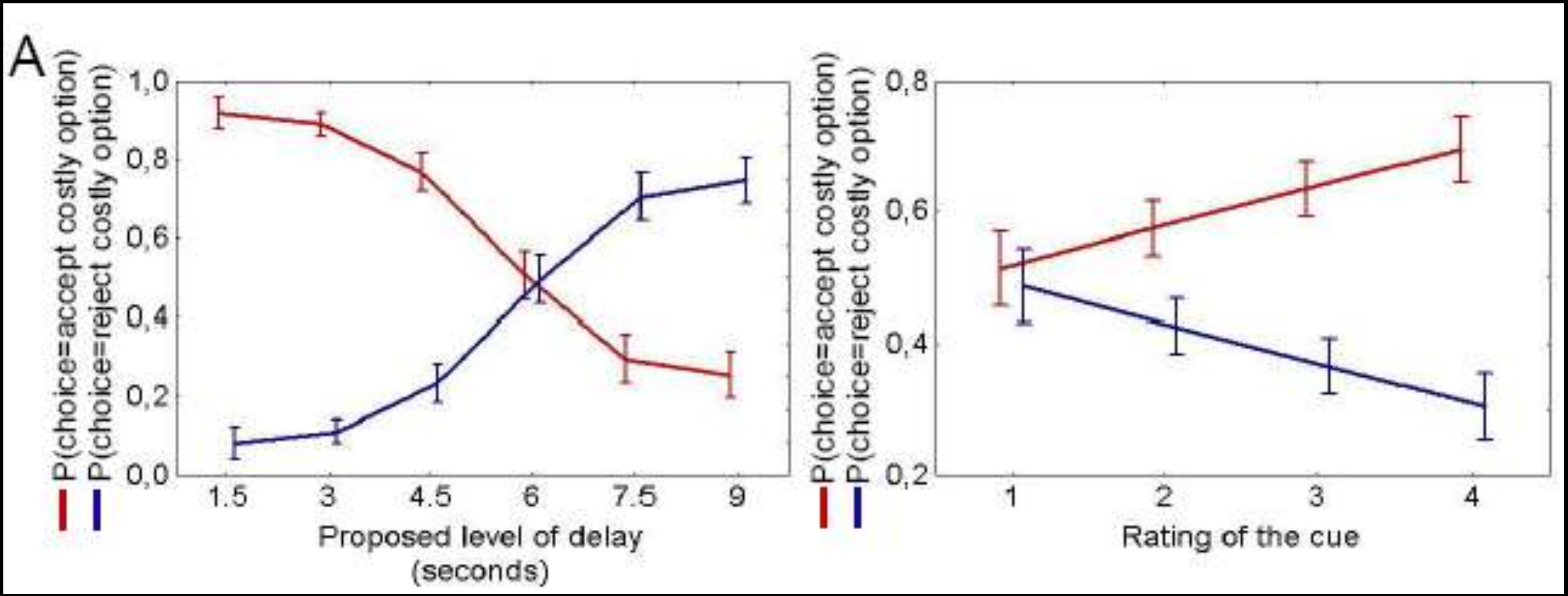
Delay-discounting task



Effort-discounting task

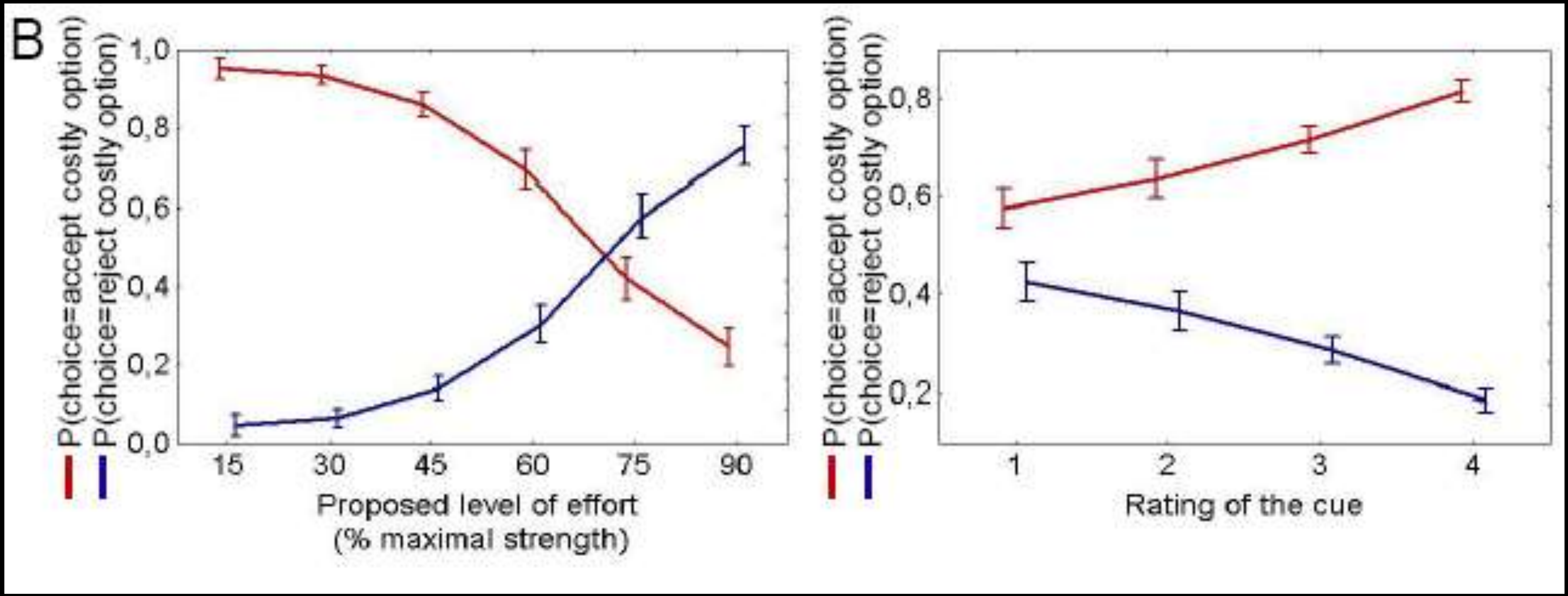


Behavioral results: delay condition



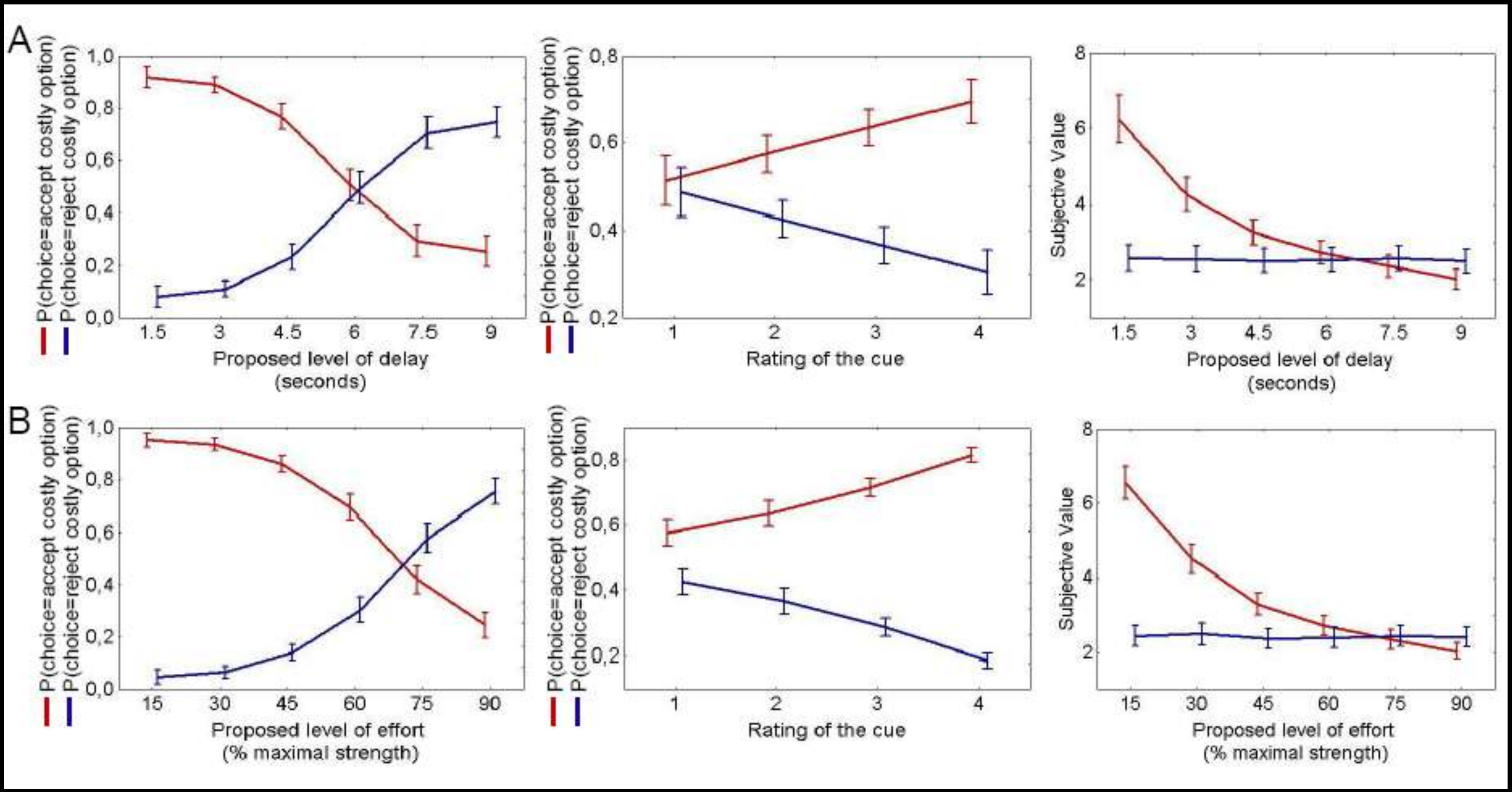
- Subjects integrated in their decision both the benefit associated with the cue and the cost indicated by the proposed level of delay

Behavioral results: effort conditon



• Subjects integrated in their decision both the benefit associated with the cue and the cost indicated by the proposed level of effort

Behavioral results

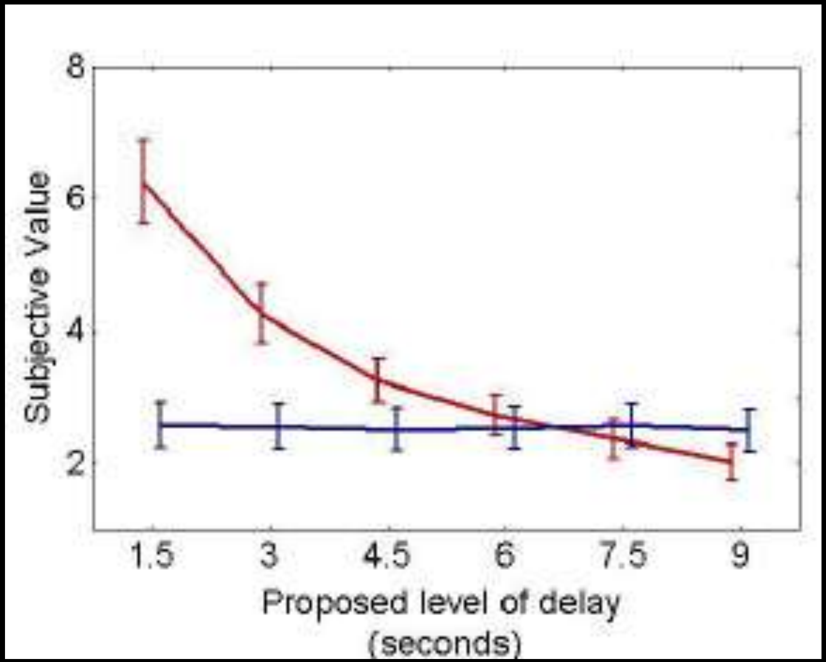


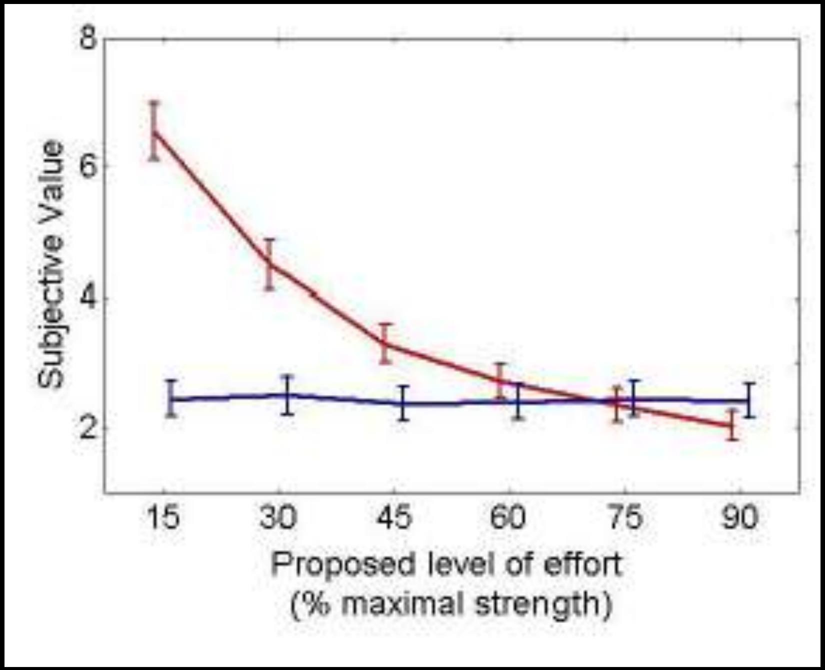
Proposed level of Cost

Rating

SV ~ Incentive / Cost (Hyperbolic function)

Behavioral model of subjective value





$SV_D = A_D * x_D / (1 + C_D * k_D)$
$SV_E = A_E * x_E / (1 + C_E * k_E)$

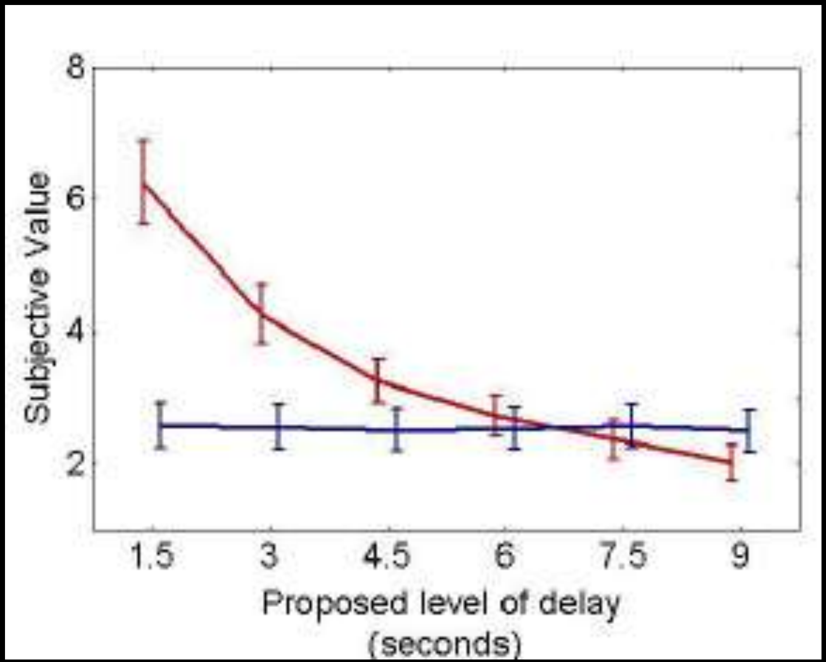
A: rAting of the cue
C: Proposed level of Cost
x: subject-specific constant corresponding to the ratio between viewing the large vs small reward
k*:* subject-specific constant corresponding to the discount factor

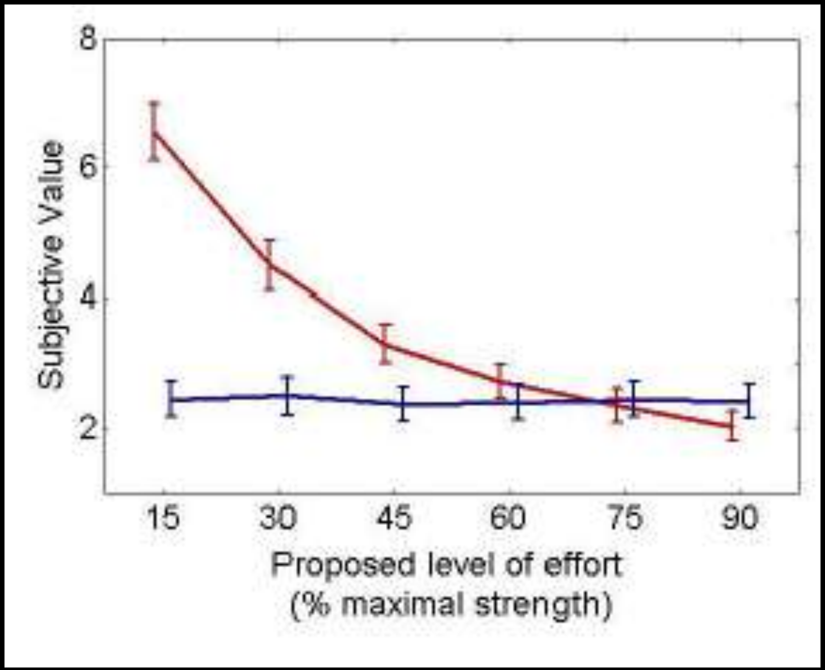
Softmax rule:
P(delayed option) = $1/(1/\exp(-SV_D/\beta_D))$

P(effortful option) = $1/(1/\exp(-SV_E/\beta_E))$

• Parameters *x, k, and* β adjusted using the least square method to minimize the distance between the behavioral choice and the probability of choice estimated by the model, across all sessions and subjects.

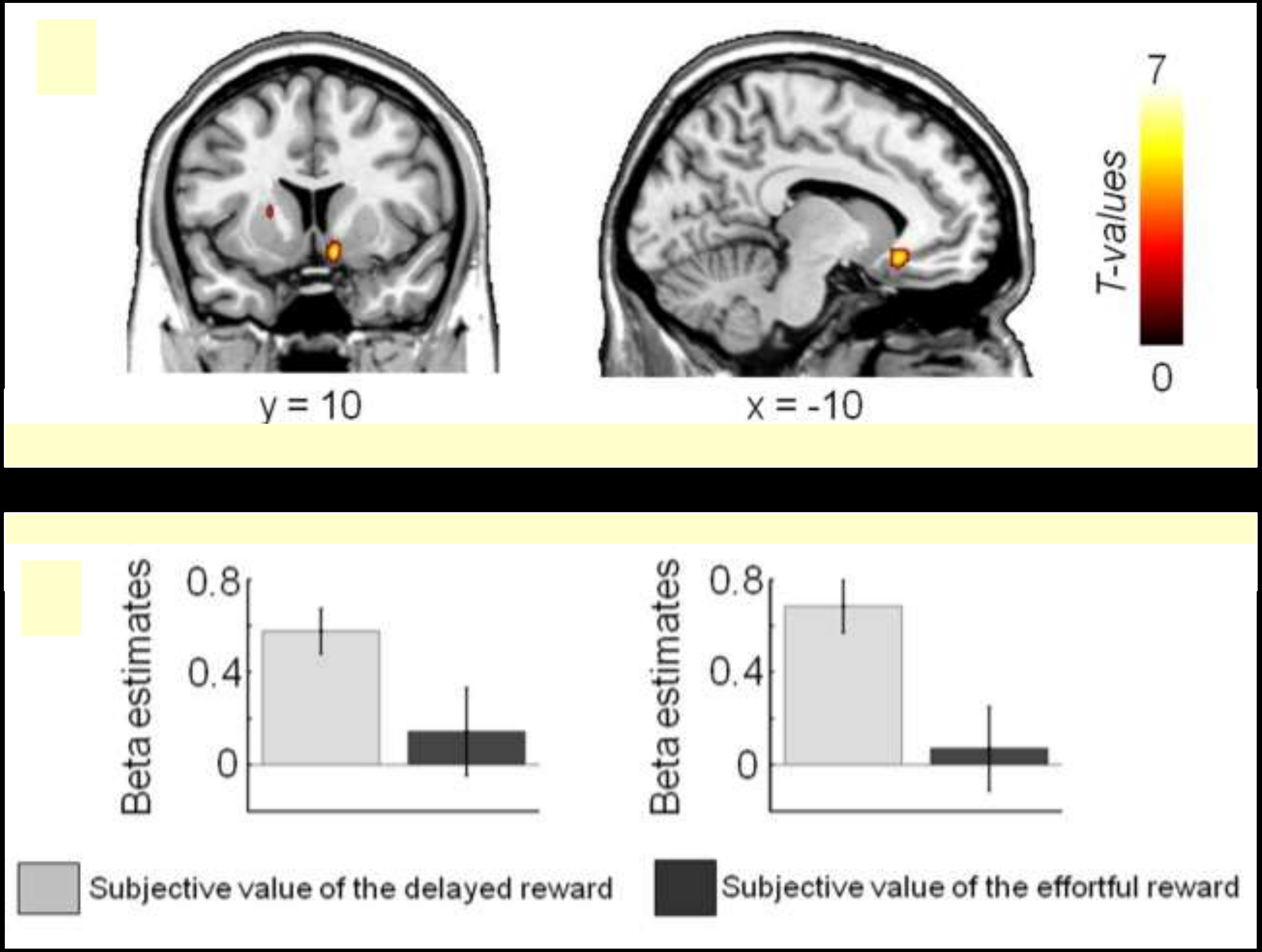
Subjective value of the reward associated with the costly option



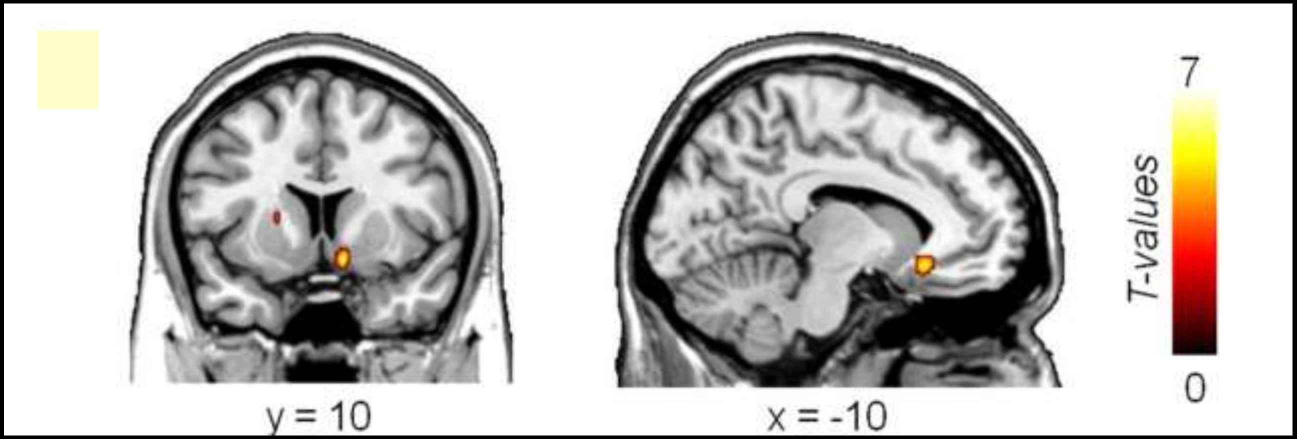


- Subjective value of the reward associated with the costly option decreased as the associated proposed level of delay or effort increased, demonstrating that delay and effort were effectively perceived as costs
- Subjective value of a high reward associated with a larger effort is discounted hyperbolically, as previously demonstrated for the subjective value of delayed reward
- Our design was effective to have subjects devalue primary rewards in a few seconds

Positive correlation with subjective value of the large reward associated with the delayed option

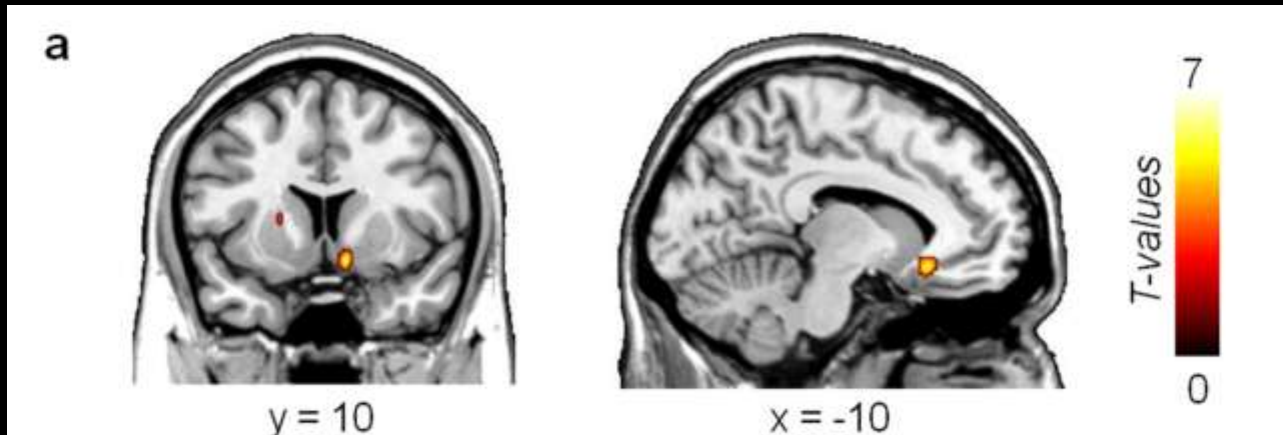


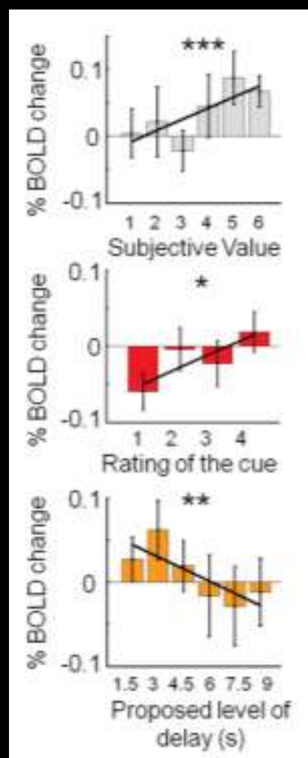
Positive correlation with subjective value of the large reward associated with the delayed option

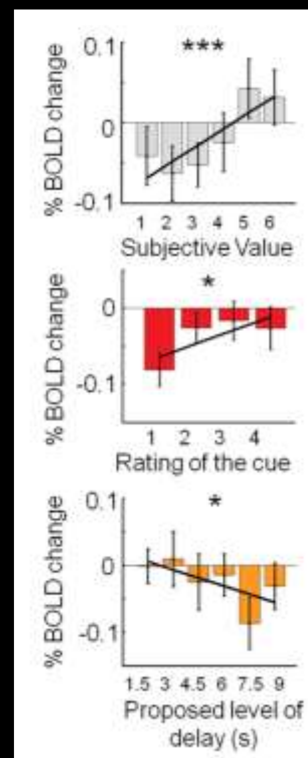


• Subjective valuation signals of erotic rewards really experienced inside the scanner are computed in similar limbic frontostriatal networks than non-experienced secondary (monetary) rewards, delayed from minutes to month/years.

Positive correlation with subjective value of the large reward associated with the delayed option





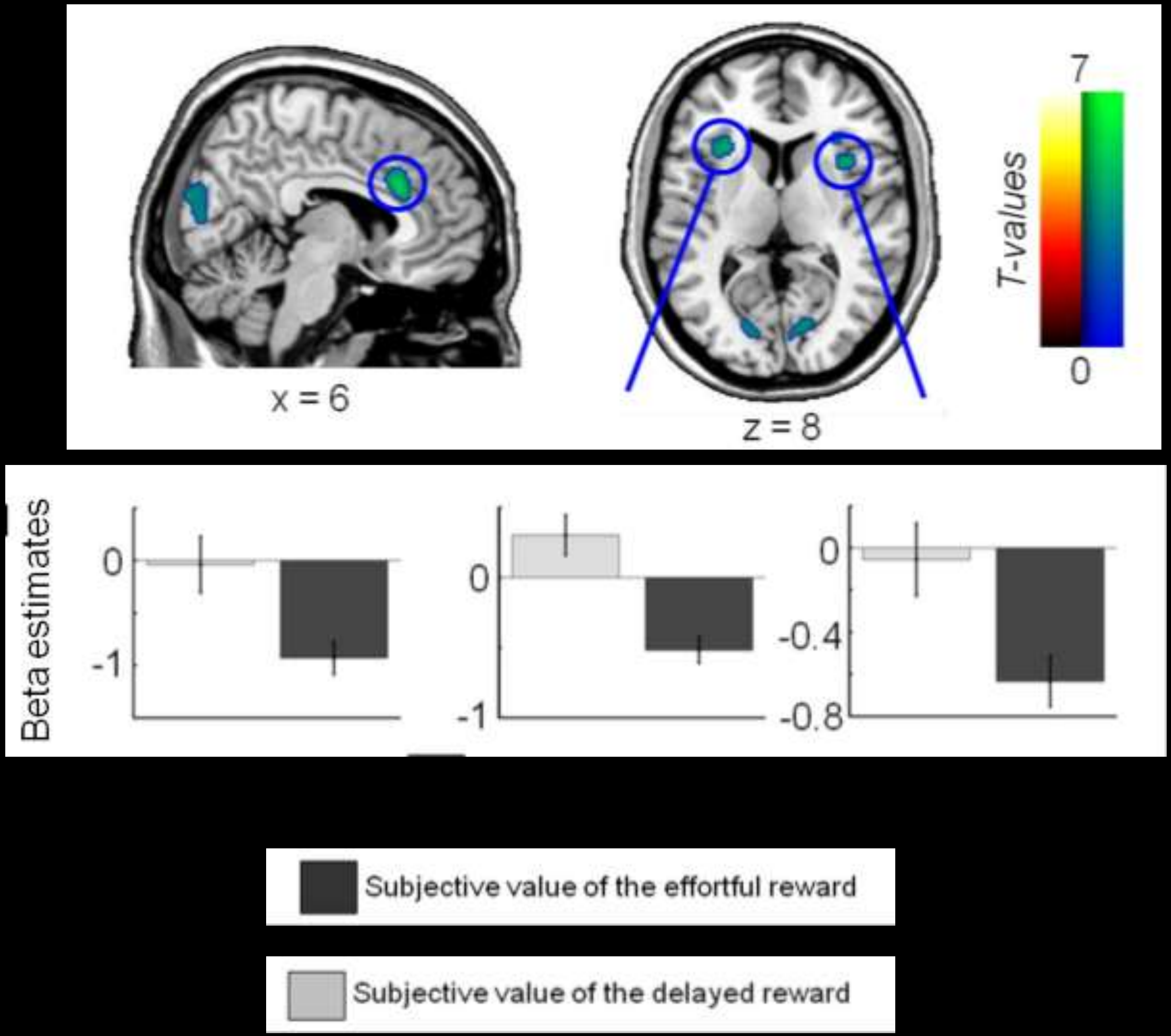


Subjective value of the delayed reward

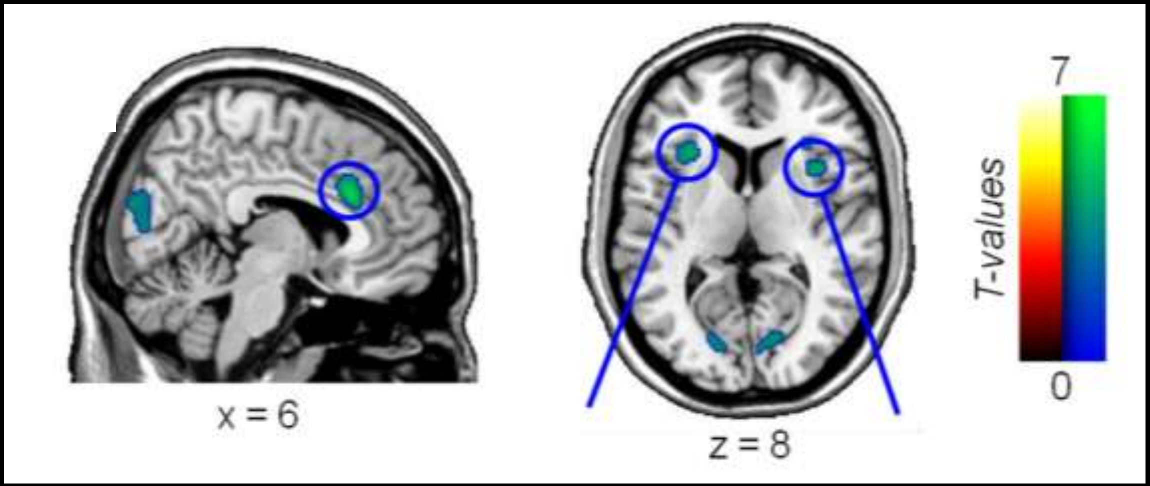
Incentive value of the cue

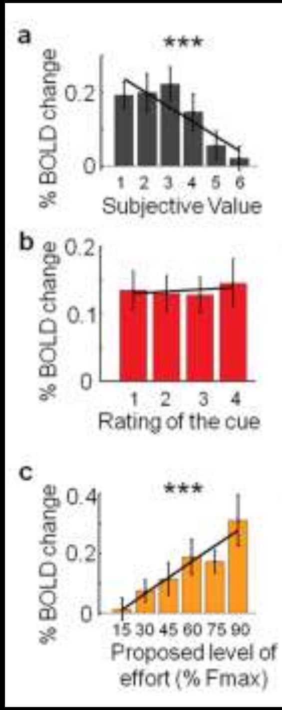
Proposed level of delay cost

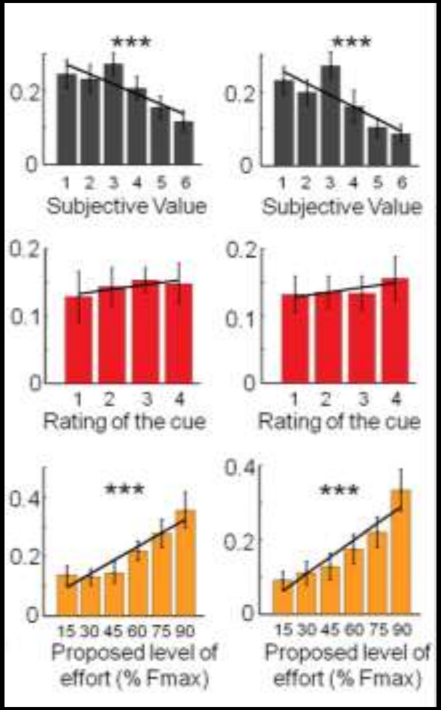
Negative correlation with subjective value of the large reward associated with the effortful option



Negative correlation with subjective value of the large reward associated with the effortful option







Subjective value of the effortful reward

Incentive value of the cue

Proposed level of effort

Conclusion

• A single computational model derived from economics theory, accounts for the behavior observed in both delay- and effort-discounting.

• Our neuroimaging data challenge the view of a unique neural system tracking the value of costly rewards regardless of the nature of the decision costs.

• They reveal distinct valuation subsystems in the human brain for different types of costs, reflecting in <u>opposite fashion</u> delayed reward and future energetic expenses.

• Although a separation of decision costs is not emphasized by standard accounts of economic decision making, it may prove a useful concept for understanding frontal contributions to decision making.

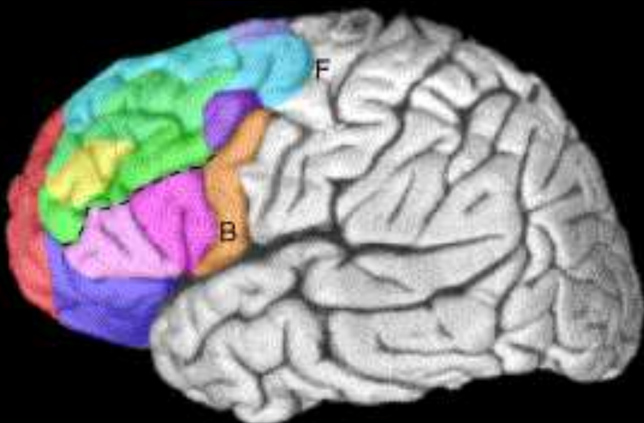
• Impaired decision making in neurological and psychiatric populations is characterized at different times by seemingly opposite patterns of both impulsiveness (delay aversion) and apathy (effort aversion).

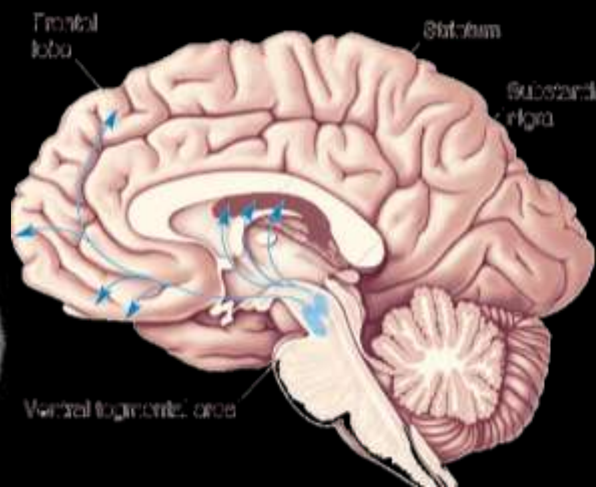
Three axes of research:

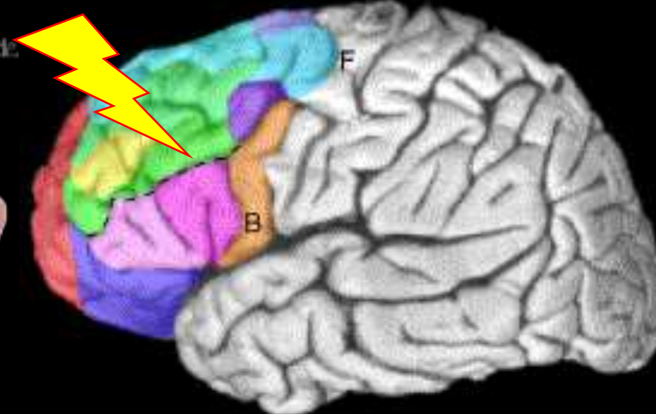
I.
Functional organization of the prefrontal cortex

II.
Study of the dopaminergic system

III.
Dysfunctions of the prefrontal cortex and the dopaminergic system







Decision making

Reward system

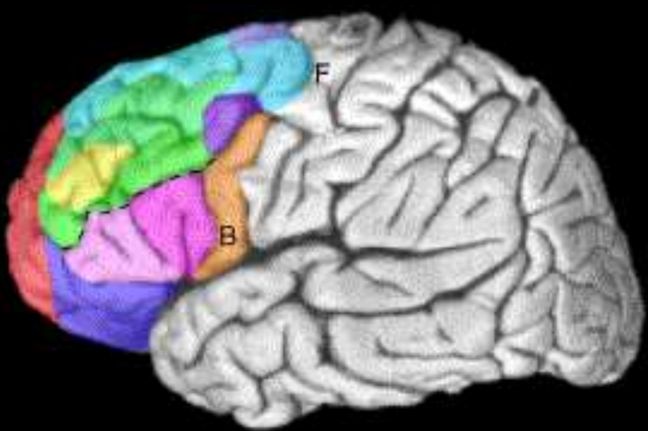
Schizophrenia,
Parkinson's disease,
Lesions of the PFC,
Pathologic gambling,
Anorexia,
Healthy aging

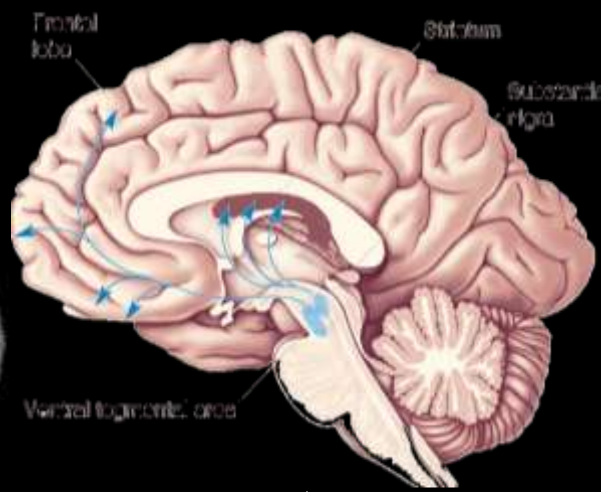
Fourth axis of research:

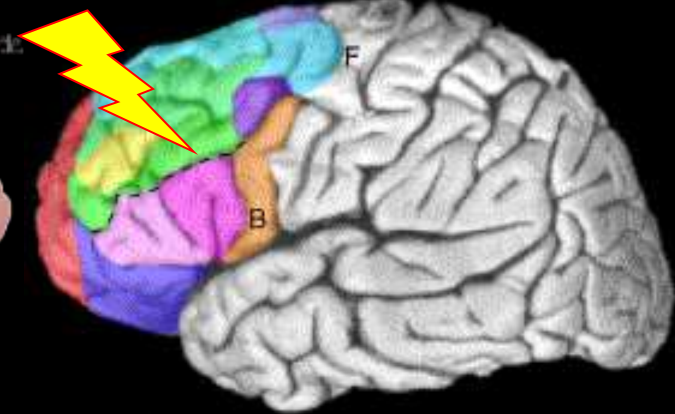
I.
Functional organization of the prefrontal cortex

II.
Study of the dopaminergic system

III.
Dysfunctions of the prefrontal cortex and the dopaminergic system

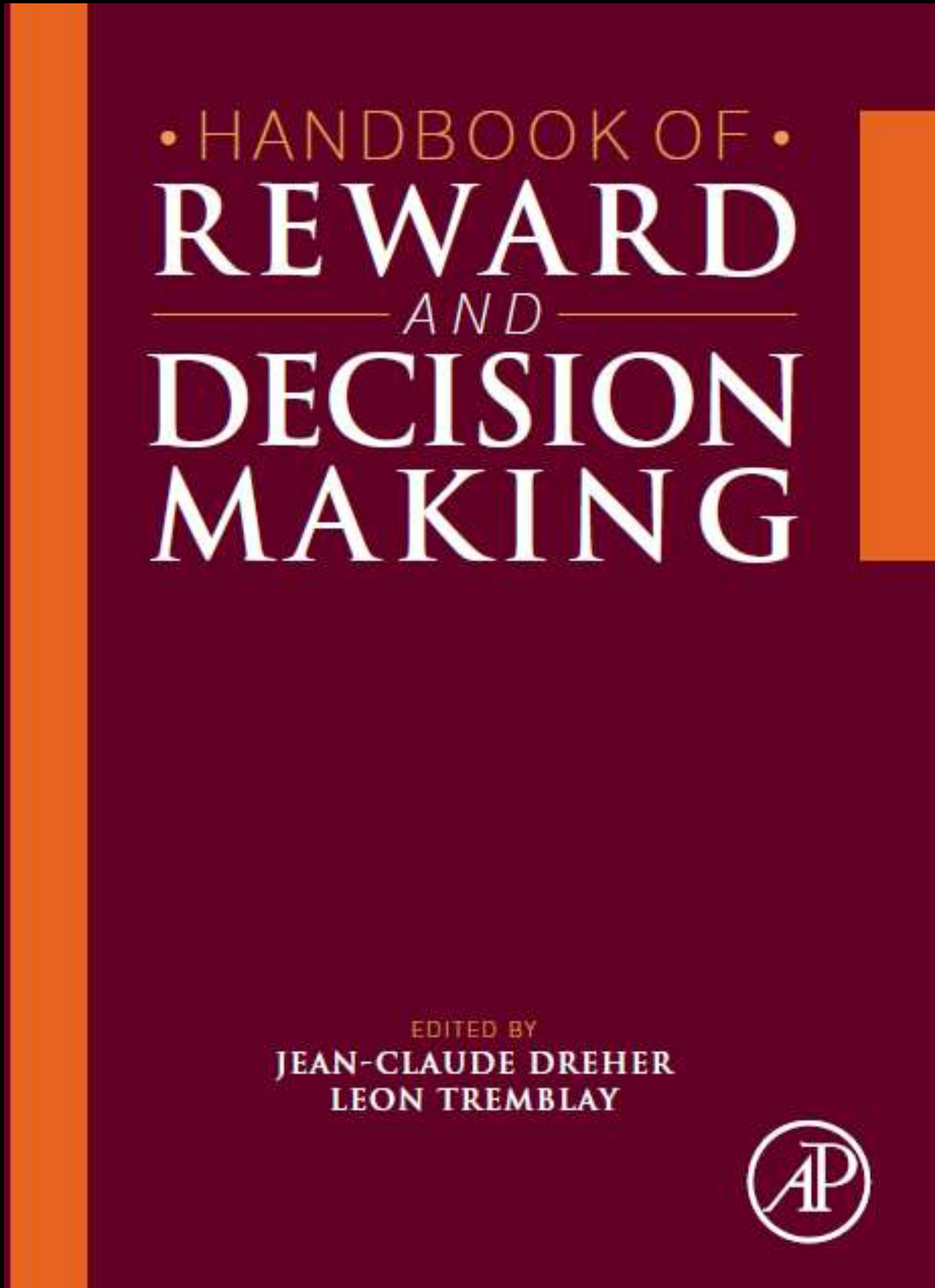






Decision making **Reward system** **Clinical Populations**

Genetic and gonadal steroid hormones influences ?



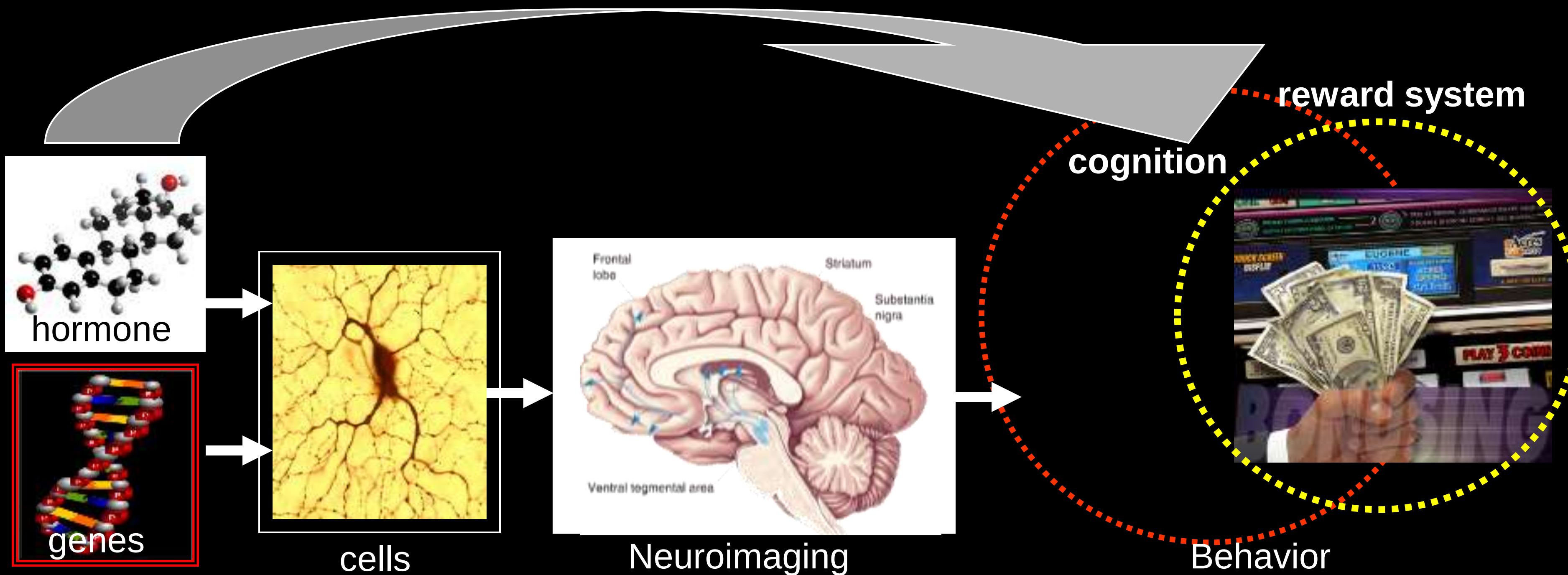
Handbook of Reward and Decision Making

Edited by: Jean-Claude Dreher and Leon Tremblay

Published by Academic Press (2009)

Effects of hormonal and genetic variations on the response of the human reward system

Linking hormones and genes to functional variation in brain systems related to cognition and motivation



• Inter-individual genetic differences may contribute to inheritable personality traits in the general population and to neuropsychiatric disorders.
• Hormonal variations can influence cognitive functions, affective state and vulnerability to drugs of abuse.

Menstrual cycle phase modulates reward-related neural function in women

Background

• Estrogen and progesterone not only influence ovulation and reproductive behavior but also affect cognitive functions, affective state and vulnerability to drugs of abuse.

• Animal studies show that the dopaminergic system is sensitive to circulating gonadal steroid hormones (e.g. female rats show the highest rates of cocaine self-admnistration shortly after estradiol peaks).

Goal of this study

• Investigate the influence of menstrual cycle phases on the human reward system using fMRI.

Dreher et al., *PNAS*, *2007*

Methods

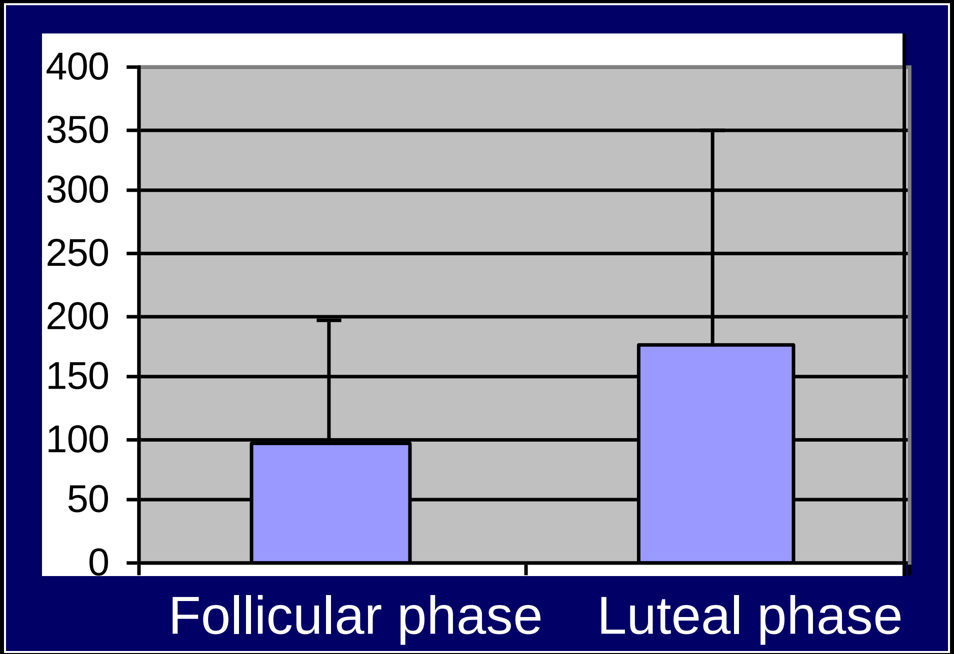
• 13 healthy young women (mean age= 27±5): no hormonal medication within the last 6 months, regular menstrual cycle duration, no CNS-active medication or illicit drugs and no regular consumption of nicotine or alcohol.

• Women studied with a repeated-measures, counterbalanced design across menstrual cycle phases (during the follicular phase: days 4-8 after menses and during the luteal phase: days 6-10 following Luteinizing Hormone surge).

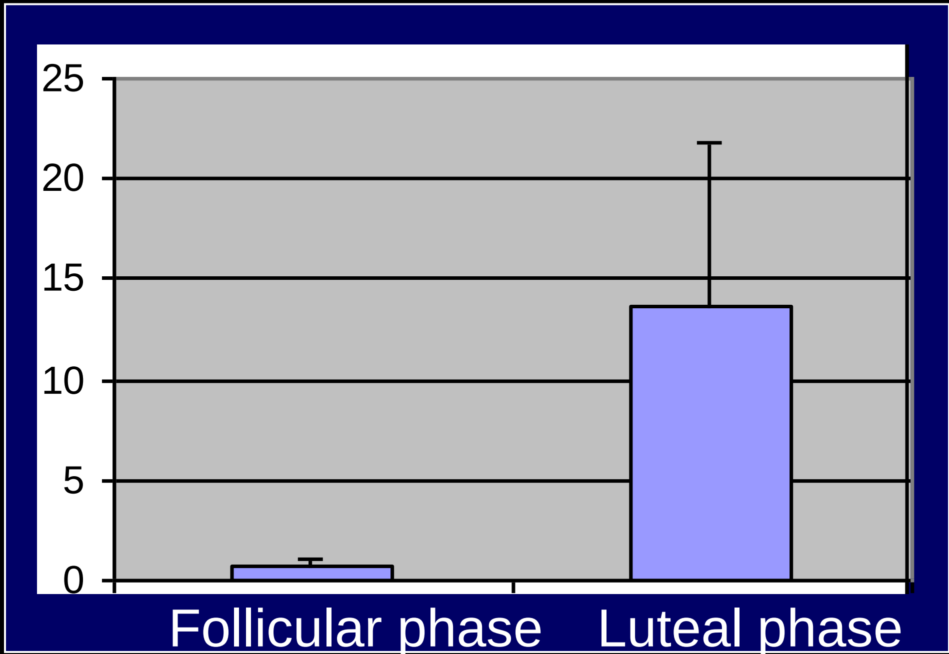
• Symptom rating scores (Beck Depression Inventory and Premenstrual Tension Syndrome rating scale) did not differ across menstrual cycle phases.

Serum steroid hormone levels

Estradiol level
(pg/mL)



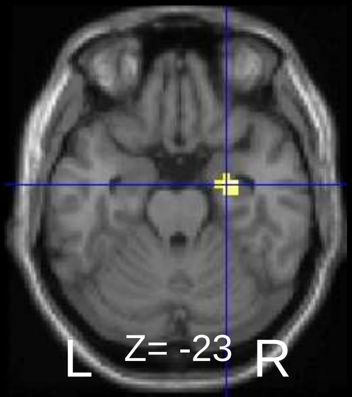
Progesterone level
(ng/mL)



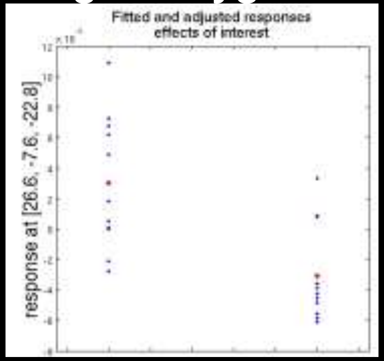
Menstrual cycle phase modulates reward-related neural function in women

FOLLICULAR phase > LUTEAL phase

REWARD ANTICIPATION

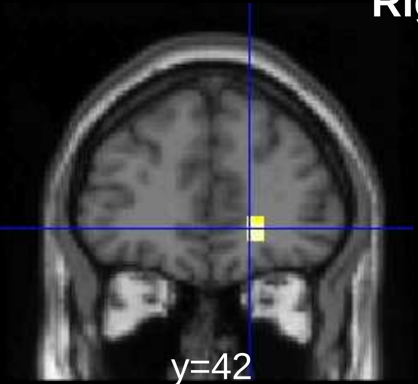


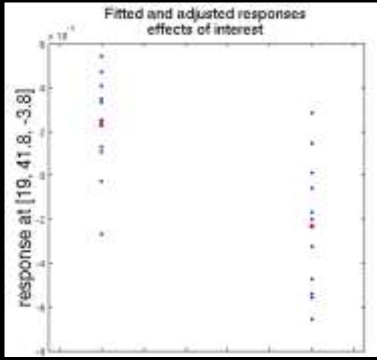
Right amygdala



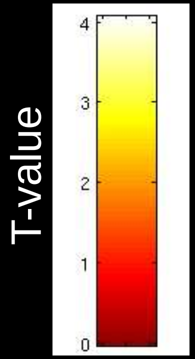
Follicular luteal

Right orbitofrontal cortex

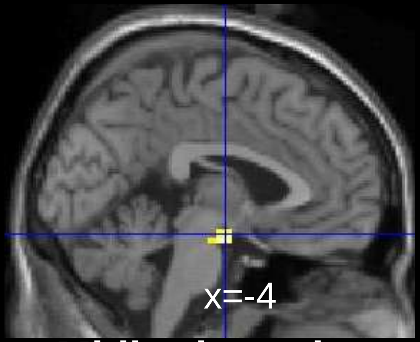




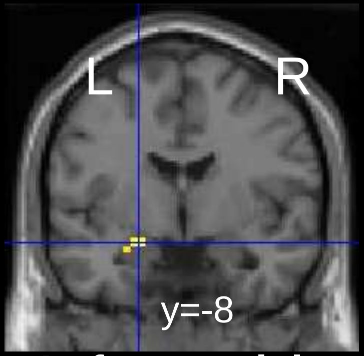
Follicular luteal



REWARDED vs NON-REWARDED OUTCOME



Midbrain region



Left amygdala

Dreher et al., *PNAS*, 2007

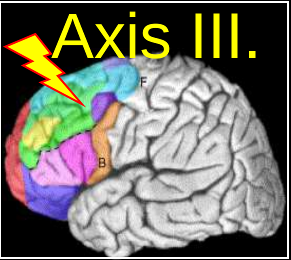
Conclusion

- These data demonstrate augmented reactivity of the reward system in women during the follicular phase.

- They provide the first evidence of a neurofunctional modulation of the reward system by gonadal steroid hormones in humans.

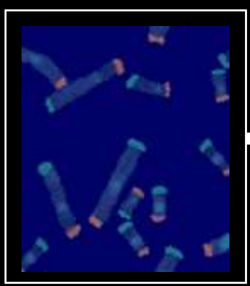
- Establish a foundation for understanding menstrual cycle effects on vulnerability to drugs of abuse, neuropsychiatric diseases with differential expression across males and females and hormonally-mediated mood disorders.

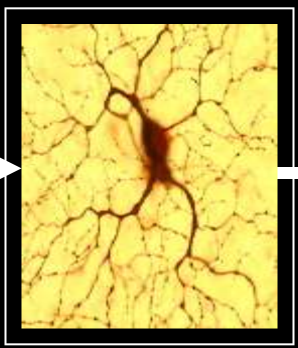
- The increased availability, receptivity, and desire that may occur during the ovulatory period has been thought to facilitate procreation. This may elucidate the neurobiological substrates of menstrual cycle influence on different types of motivated behavior (e.g., sexual preference and drug abuse).

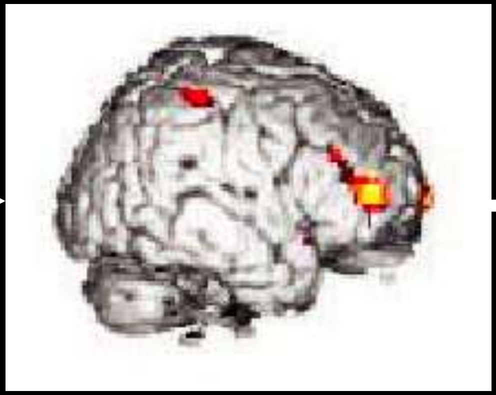


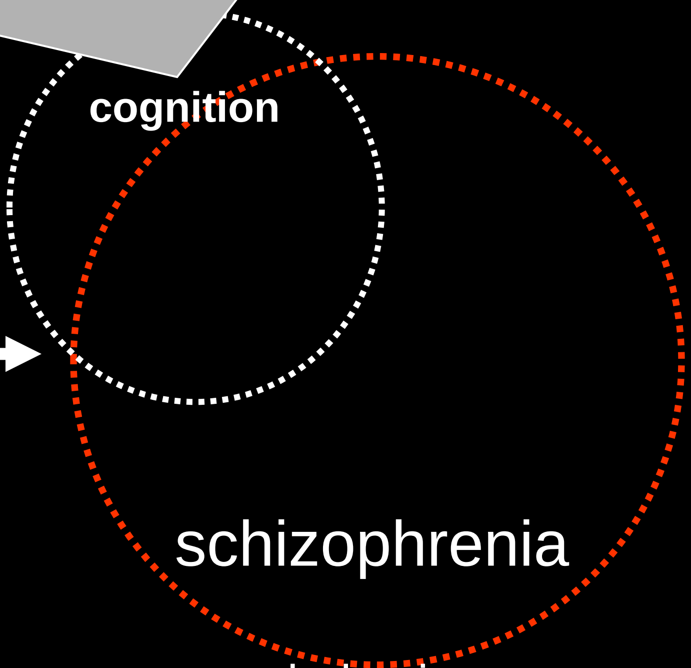
Genetical basis of vulnerability to neuropsychiatric disorders

Relationships between the effects of genetic variations and biological processes involved in schizophrenia







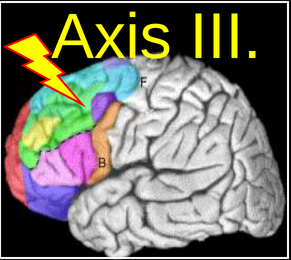


Genes:
- *Multiple susceptibility alleles, each of small effect*

Cellular level
- *Neuronal dysfunction*

System:
- *Prefrontal cortex dysfunction*

behavior:
- *Cognitive and motivational deficits*



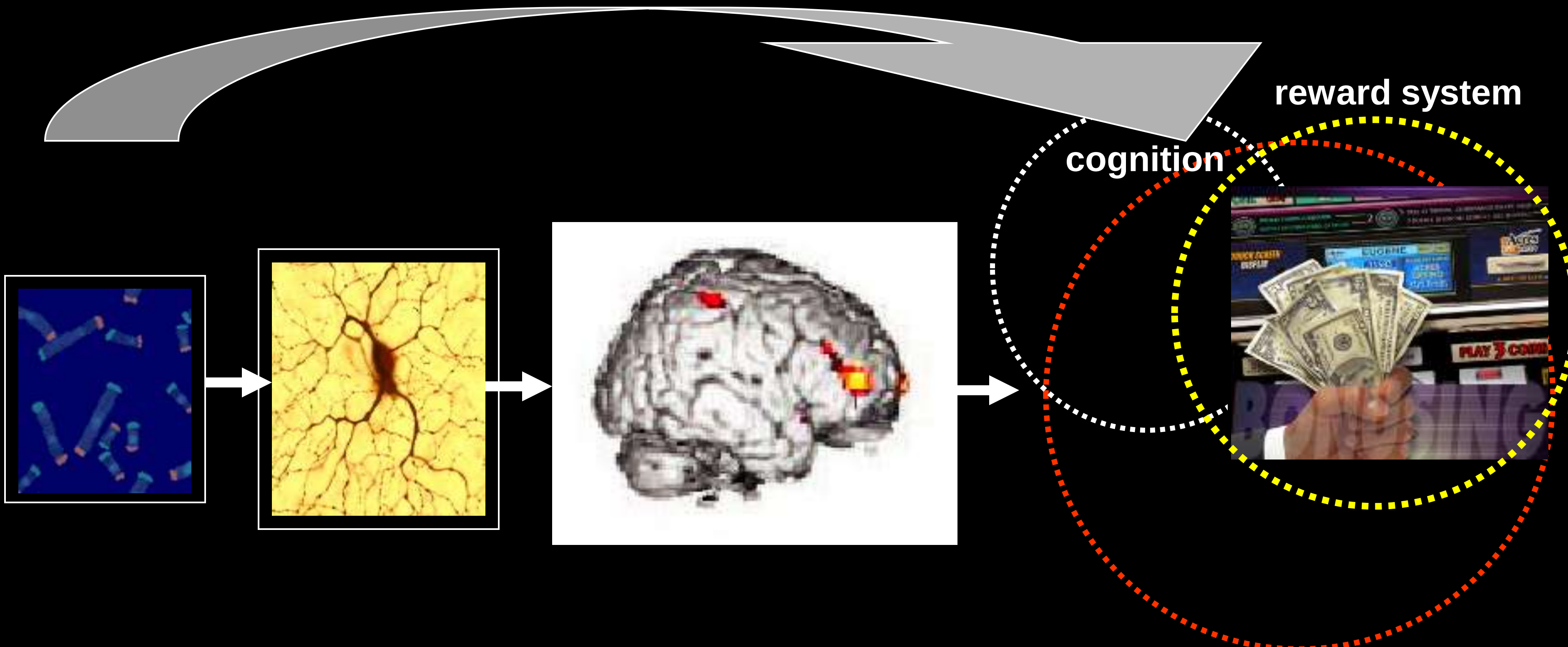
Genetical basis of vulnerability to neuropsychiatric disorders

• Although there are clear individual genetic differences regarding susceptibility to and manifestation of neuropsychopathologies (eg. schizophrenia, Parkinson's disease, pathological gambling, and drug addiction) the influence of genetic predispositions and variations on activation of the human reward system remains poorly understood.

• Investigating the effects of interindividual differences in dopamine signaling on the response of the reward system is an important research question because these differences may contribute to heritable personality traits in the general population and to neuropsychiatric conditions involving abnormalities in catecholamine neurotransmission

Effects of genetic variation in dopamine regulating genes on the response of the human reward system in healthy subjects

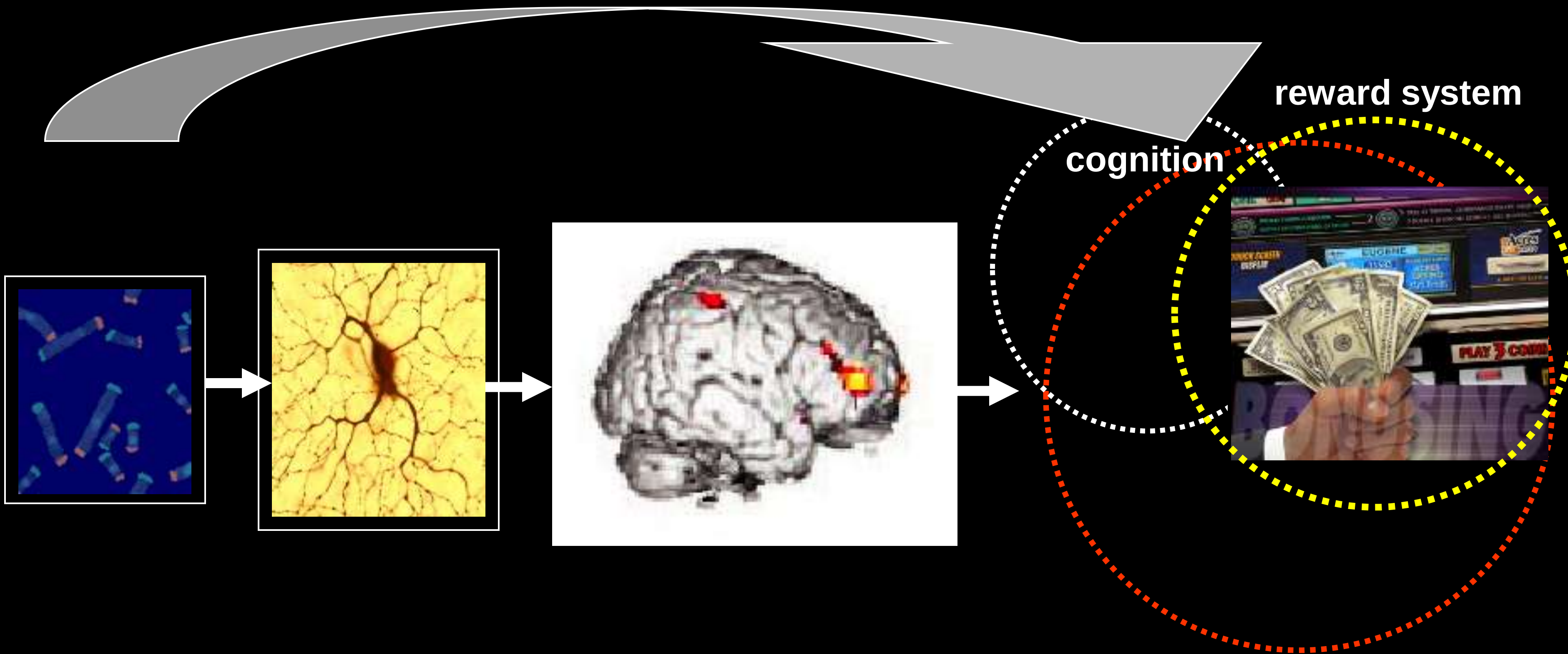
Linking genes to functional variation in brain systems related to cognition and motivation



- Influence of the polymorphisms of the catecholamine-O-methyltransferase (COMT) (methionine/methionine; valine/methionine; valine/valine) and the Dopamine Transporter (DAT) (9/9&9/10; 10/10) on the reward system.

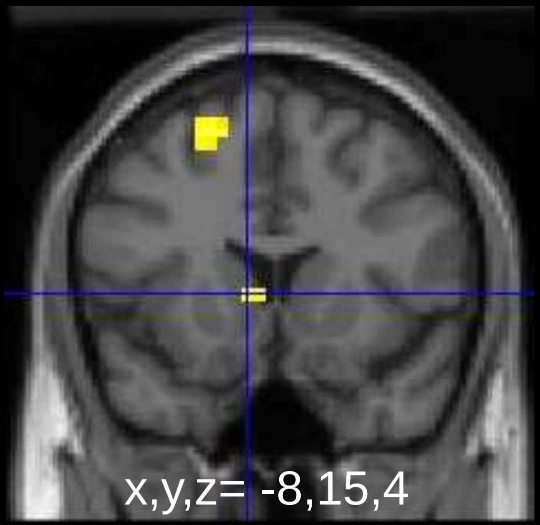
Effects of genetic variation in dopamine regulating genes on the response of the human reward system in healthy subjects

Linking genes to functional variation in brain systems related to cognition and motivation

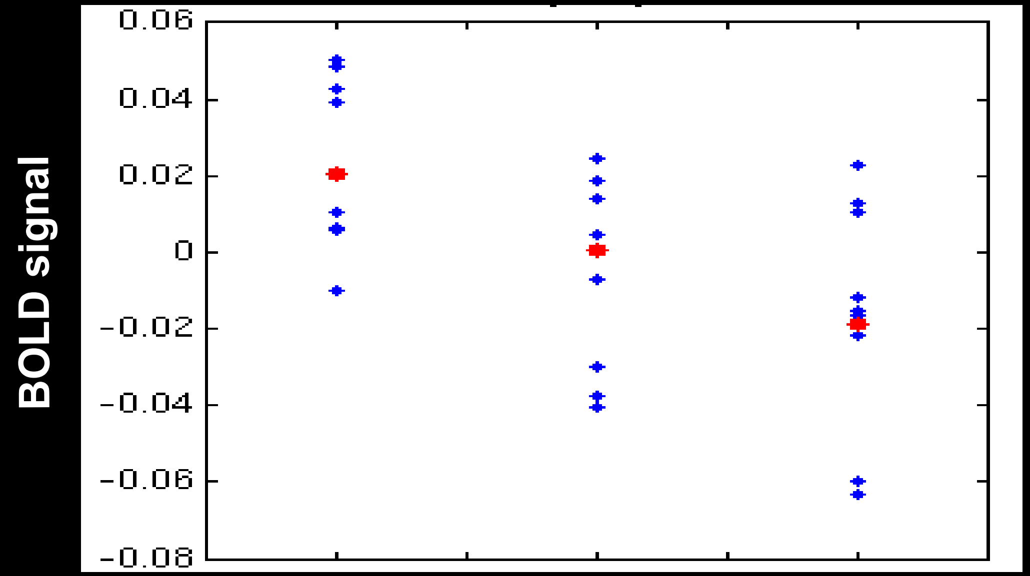


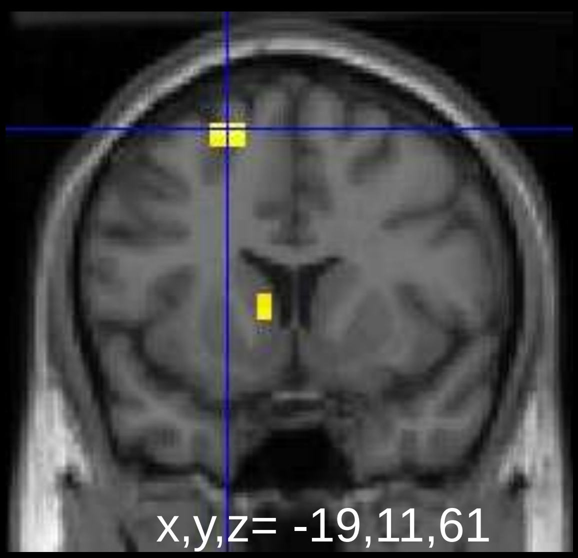
Dreher et al., *PNAS*, *2009*

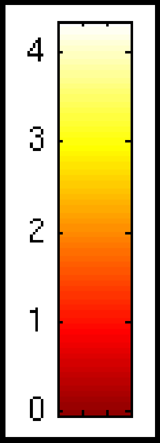
ANTICIPATION OF UNCERTAIN REWARDS: mm > vm > vv



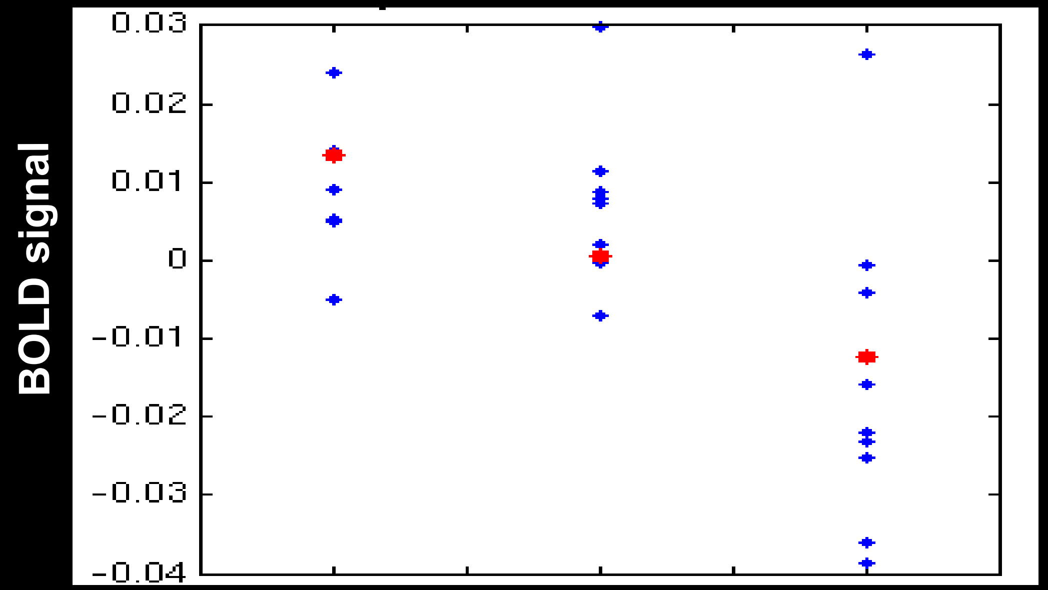
Left ventral striatum







Left superior frontal gyrus

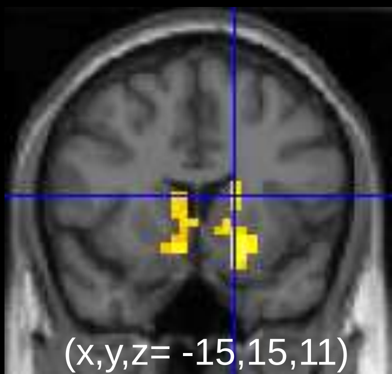


m/m v/m (intermediate) v/v

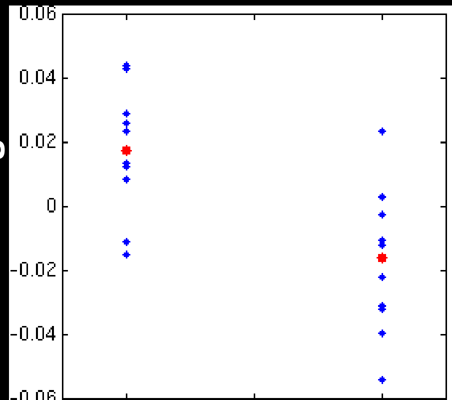
Low enzyme activity **High enzyme activity**

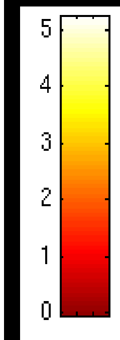
High synaptic DA **Low synaptic DA**

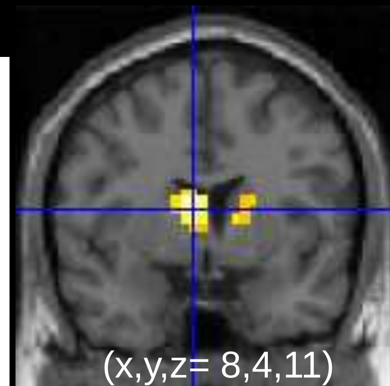
ANTICIPATION OF UNCERTAIN REWARDS: DAT 9/9 & 9/10 > 10/10



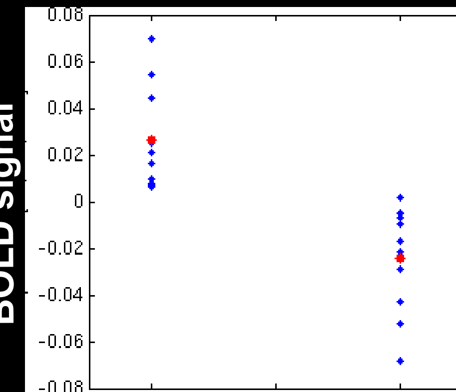
Left caudate nucleus





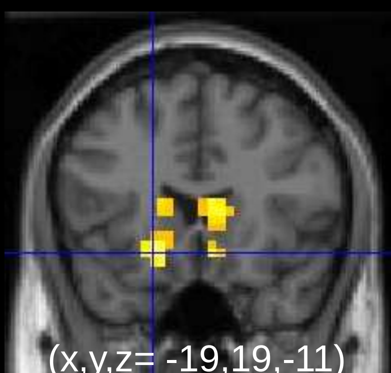


Right caudate nucleus

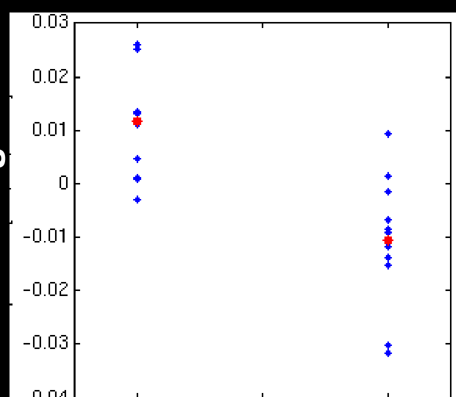


9R & 9/10R 10R 9R & 9/10R 10R

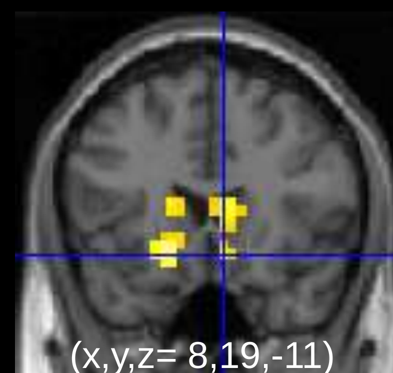
High synaptic DA **Low synaptic DA**



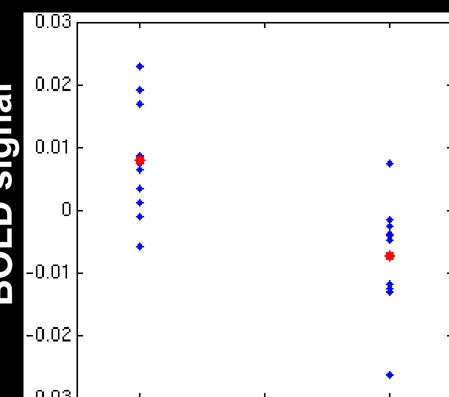
Left ventral striatum



9R & 9/10R 10R



Right ventral striatum



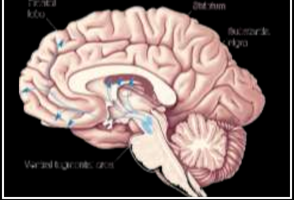
9R & 9/10R 10R

Dreher et al., *PNAS*, *2009*

Conclusion

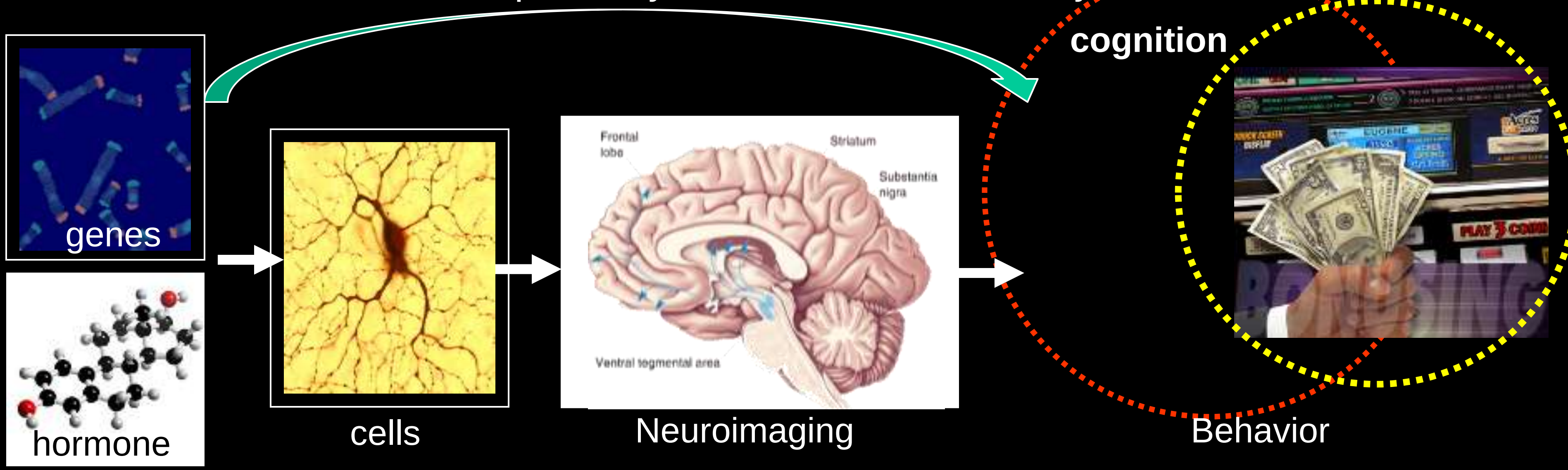
• Genetically-influenced variations in dopamine transmission modulate the response of a prefronto-striatal reward-related network involved in anticipation of rewards.

• These responses may contribute to individual differences in reward seeking behavior and in predisposition to neuropsychiatric disorders.



Axis II. Influences of genetic and hormonal variations on reward processing

Variation in dopamine genes and changes in gonadal steroid hormone levels influence responsivity of the human reward system



• First evidence of neurofunctional modulation of the reward system by gonadal steroid hormones in humans

• Neurobiological foundation for understanding their impact on vulnerability to drug abuse, neuropsychiatric diseases with differential expression across males and females and hormonally-mediated mood disorders.

Dreher et al., *PNAS*, 2007
Dreher et al., *PNAS*, 2008
Dreher et al., *PNAS*, 2009

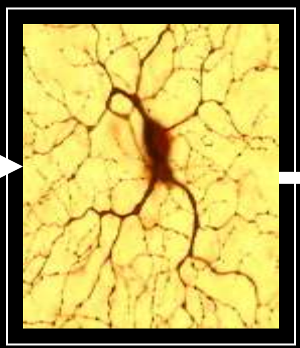
Axis II.

Influences of genetic and hormonal variations on reward processing

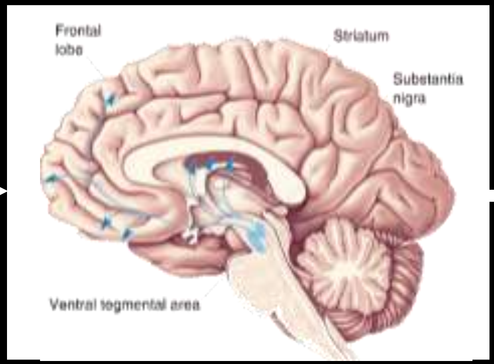
Variation in dopamine genes and changes in gonadal steroid hormone levels influence responsivity of the human reward system

genes

hormone



cells



Neuroimaging

reward system

cognition

Behavior

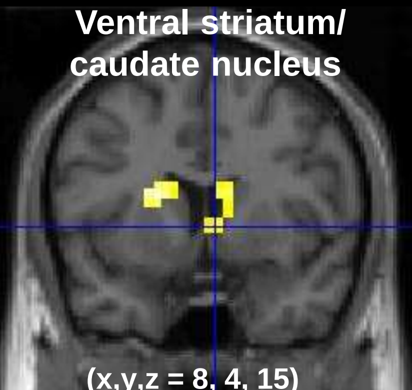
- Genetically-influenced variations in dopamine transmission modulate the response of brain regions involved in anticipation and reception of rewards.

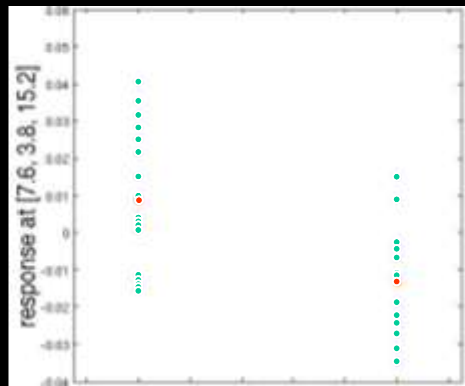
- These responses may contribute to individual differences in reward seeking behavior and in predisposition to neuropsychiatric disorders.

Dreher et al., *PNAS*, 2007
Dreher et al., *PNAS*, 2008
Dreher et al., *PNAS*, 2009

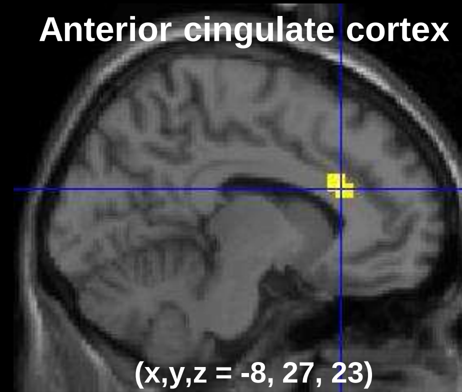
Age-related changes in midbrain dopaminergic regulation of the human reward system: a multimodal neuroimaging study (FDOPA PET and fMRI)

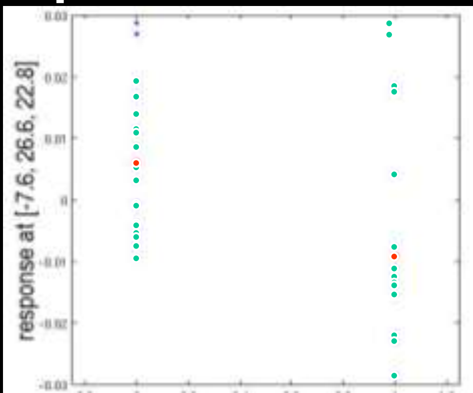
YOUNG > OLD   fMRI Results: Reward anticipation





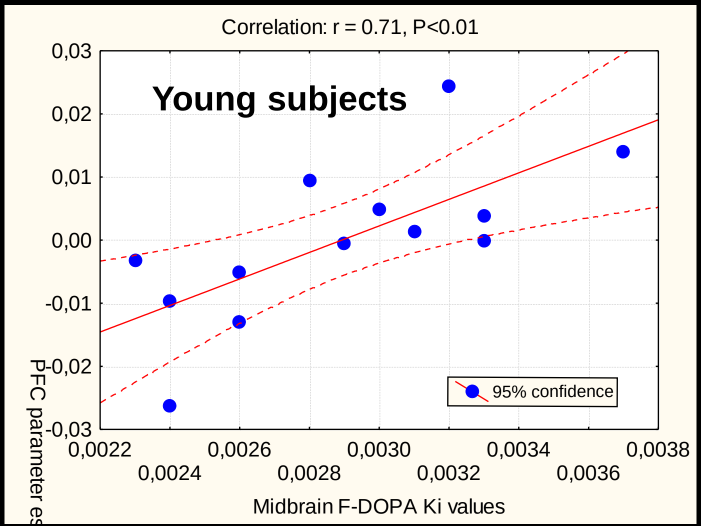
Young   Older

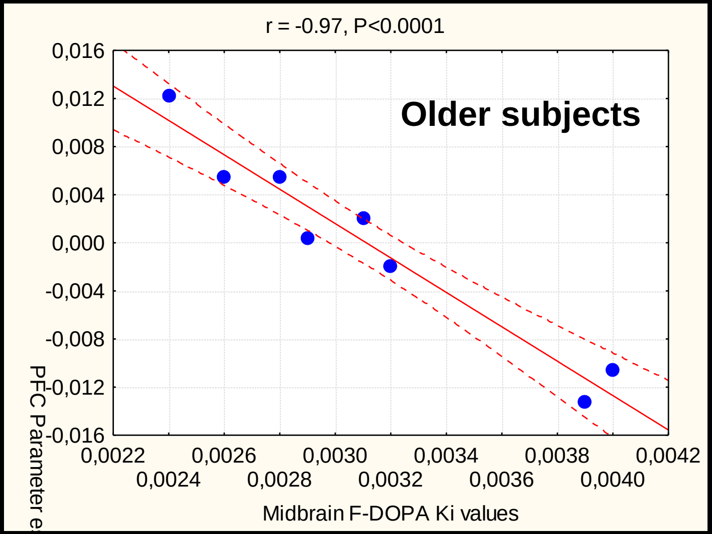




Young   Older

Correlation between lateral PFC activation and midbrain F-DOPA Ki





Dreher et al., *PNAS*, 2008

CONCLUSIONS: Reward-related fMRI studies

• Disentangle two brain systems involved in transient and sustained aspects of reward processing.

• Uncertainty coding at the time of the outcome in the hippocampus.

• Distinct orbitofrontal regions code primary and secondary rewards.

• Distinct valuation systems for delay and effort decision costs

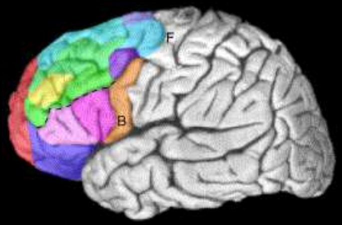
• Evidence of neurofunctional modulation of the reward system by gonadal steroid hormones in humans.

• Genetically-influenced variations in dopamine transmission modulate the response of a prefronto-striatal reward-related network involved in anticipation and reception of rewards.

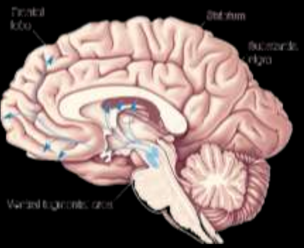
• Qualitative changes in the interaction between midbrain dopaminergic function and reward-related prefrontal activity during normal aging.

CONCLUSION

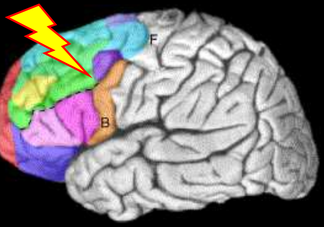
Understand the normal and pathological neural mechanisms of decision making and reward processing



• Functional organization of the prefrontal cortex

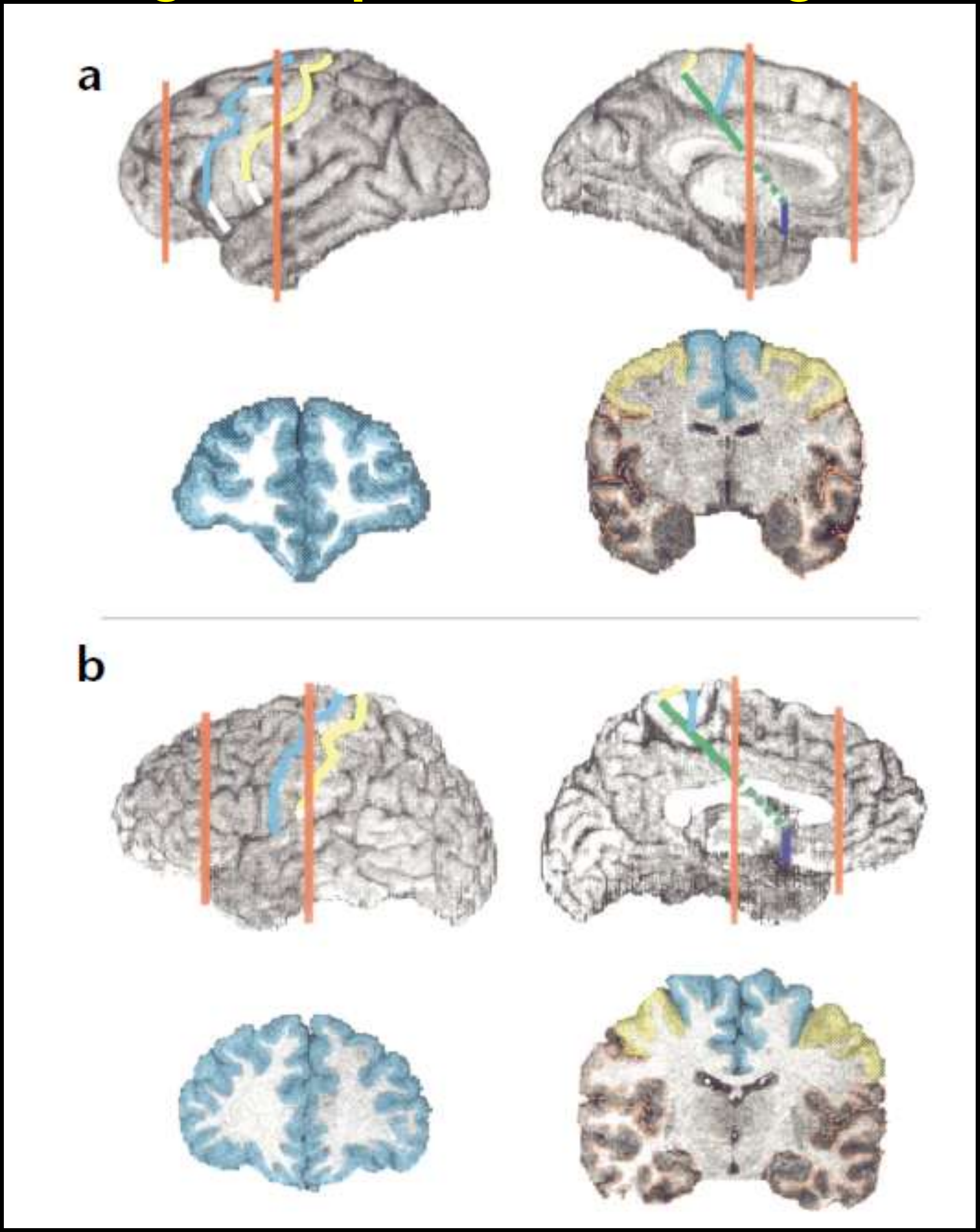


• Reward system in humans:
- Basic mechanisms
- Common and specific neural substrates for different types of rewards
- Genetic and hormonal influences
- Effects of aging



• Dysfunctions of cognitive and reward neural systems in patients with schizophrenia, Parkinson’s disease, patholgocial gambling, …

Humans and great apes share a large frontal cortex

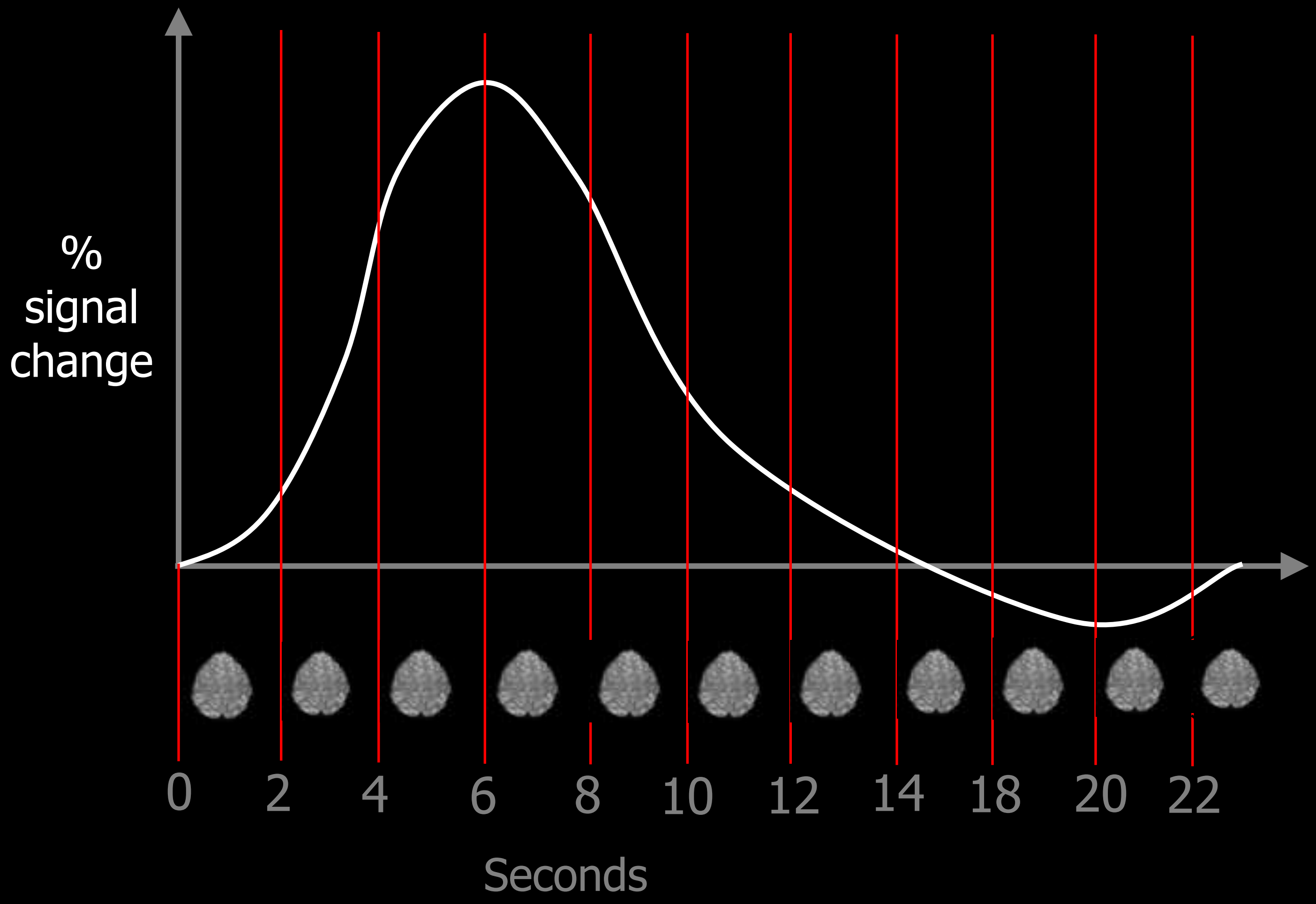


chimpanzee

Humans

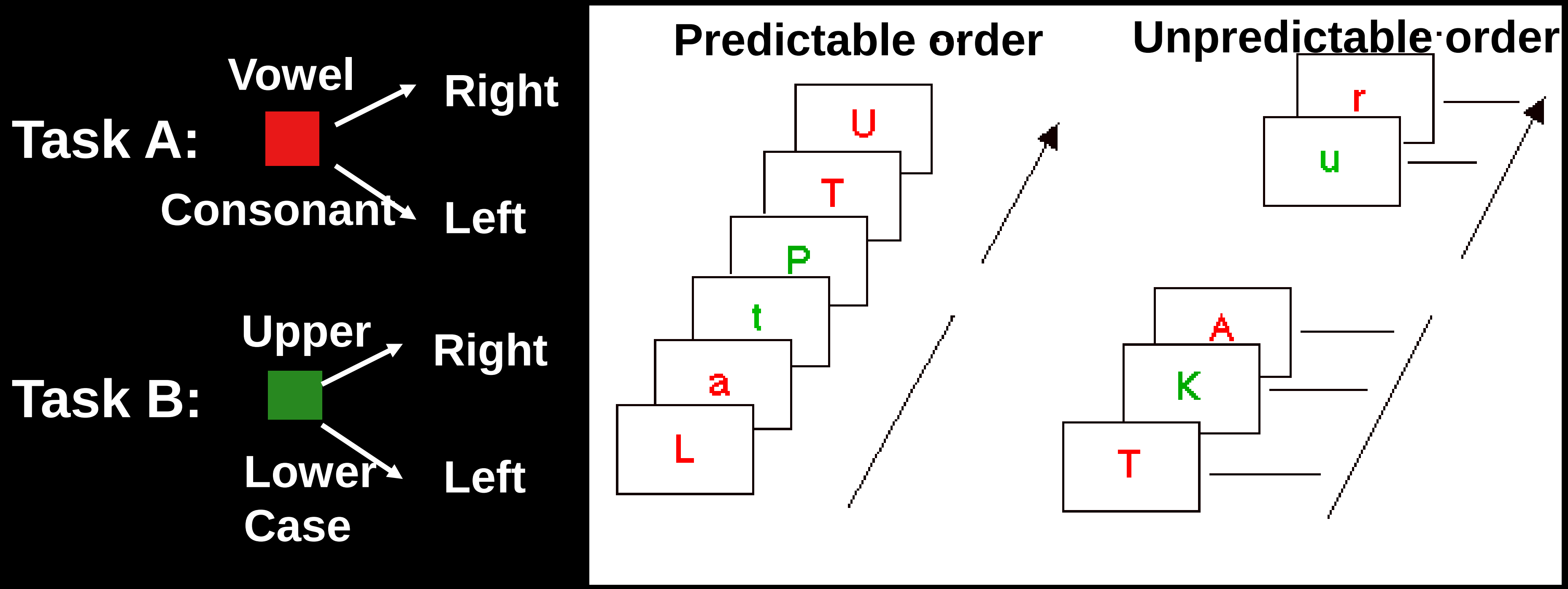
Semendeferi et al., *Nature Neuroscience*, 2002

Functional MRI: *BOLD response*



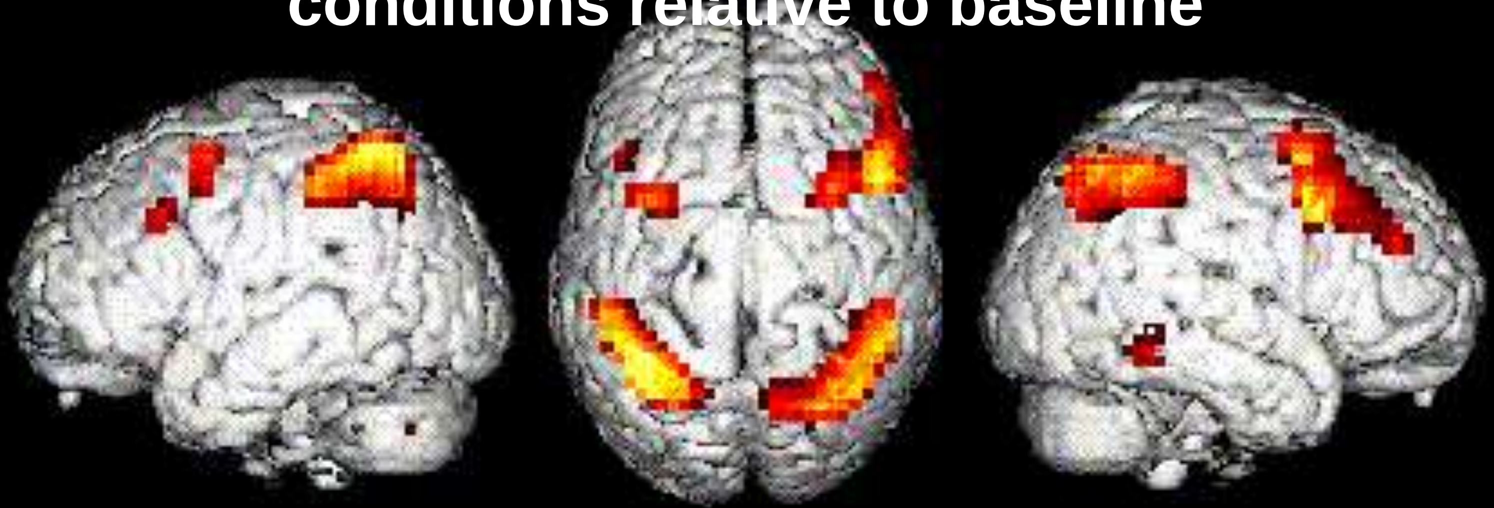
Decision flexibility

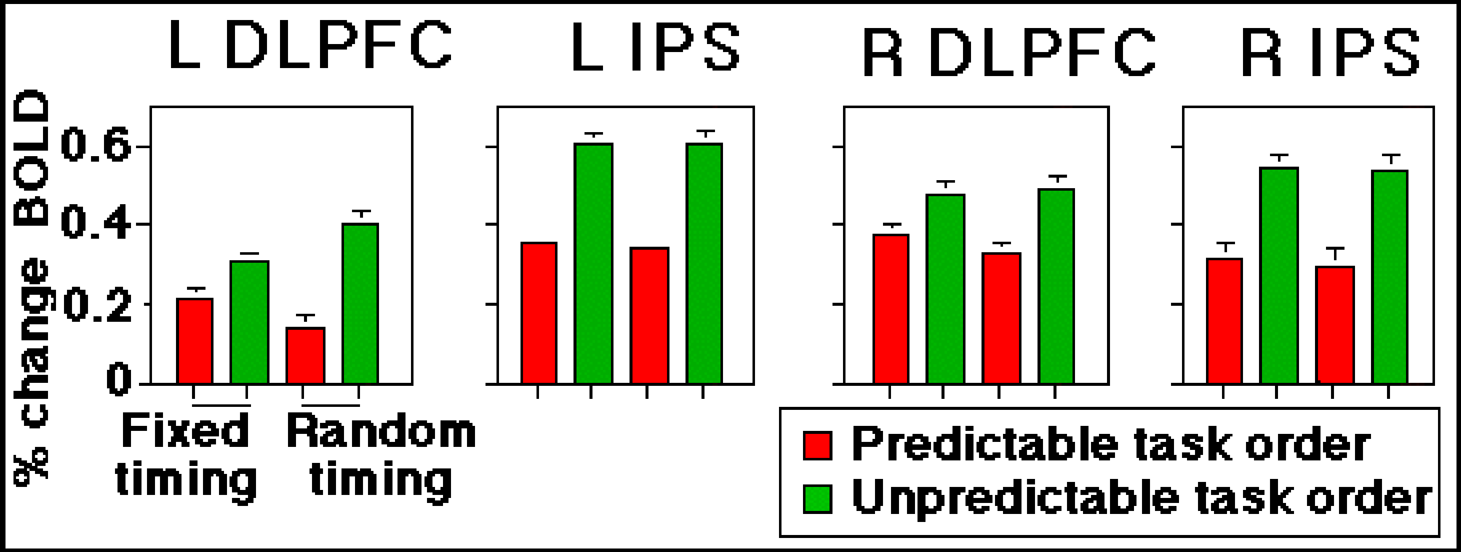
Task switching paradigm: Switch between tasks according to color cue (rule)



fMRI results

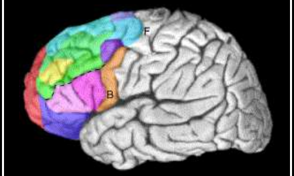
Common brain regions activated in all task switching conditions relative to baseline





Dreher et al., *Neuroimage*, 2002

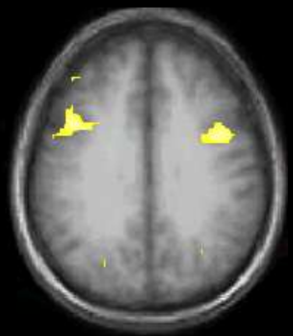
Axis I.



The roles of task sequence predictability and history during task switching

What are the roles of the statistical property of the task sequence and of the task sequence history on the way the prefrontal cortex is recruited?

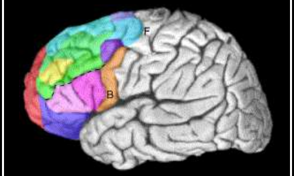
Task order predictability



Task order unpredictability

Dreher et al., *Neuroimage*, 2002

Axis I.



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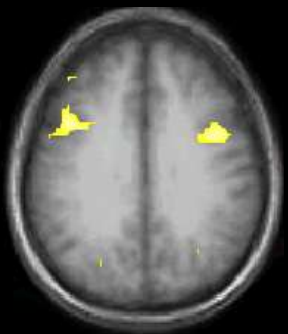


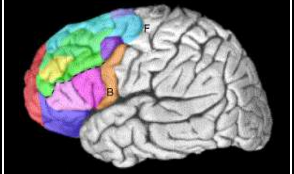
Task order unpredictability

Overcoming of residual inhibition during task switching

Dreher et al., *Neuroimage*, 2002

Dreher et al., *PNAS*, 2002

Axis I.

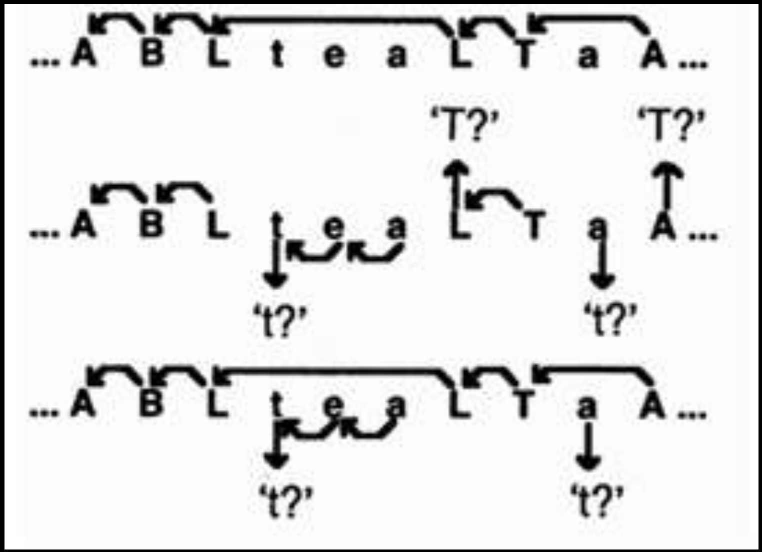


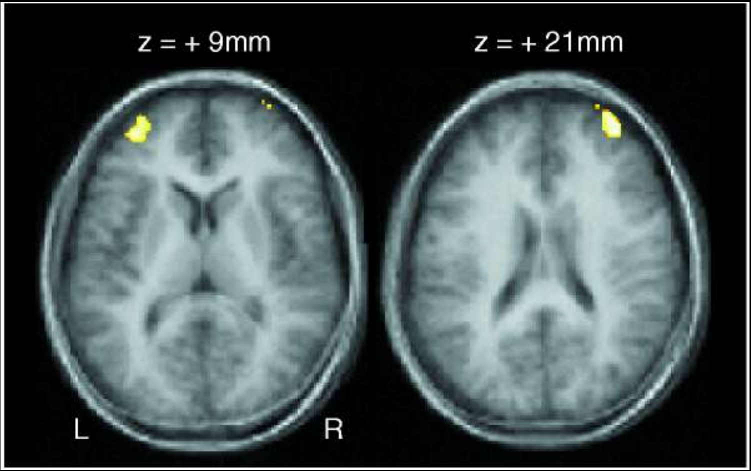
Role of the fronto-polar cortex in holding in mind goals while exploring and processing secondary goals

Delay

Task switching

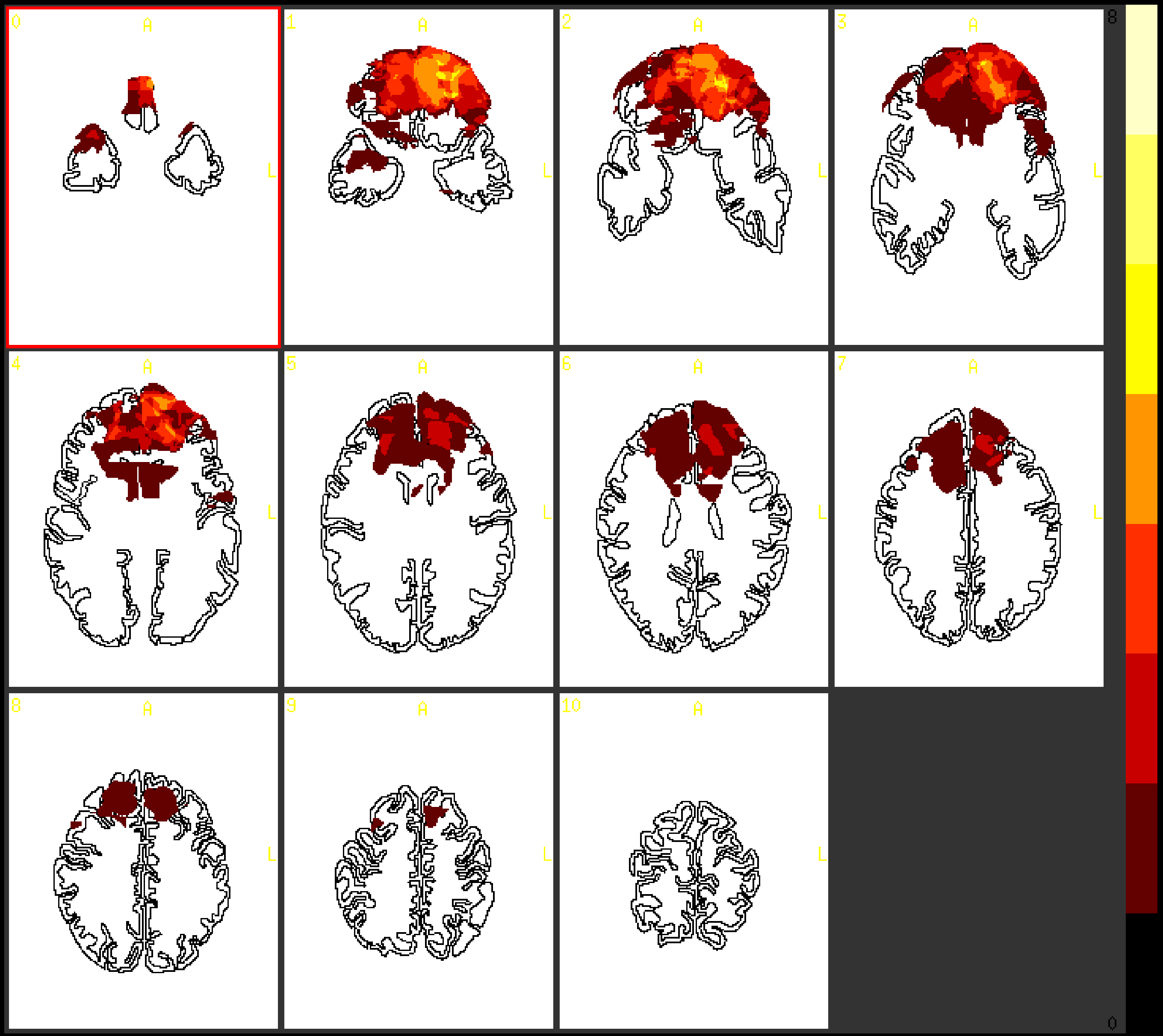
Branching





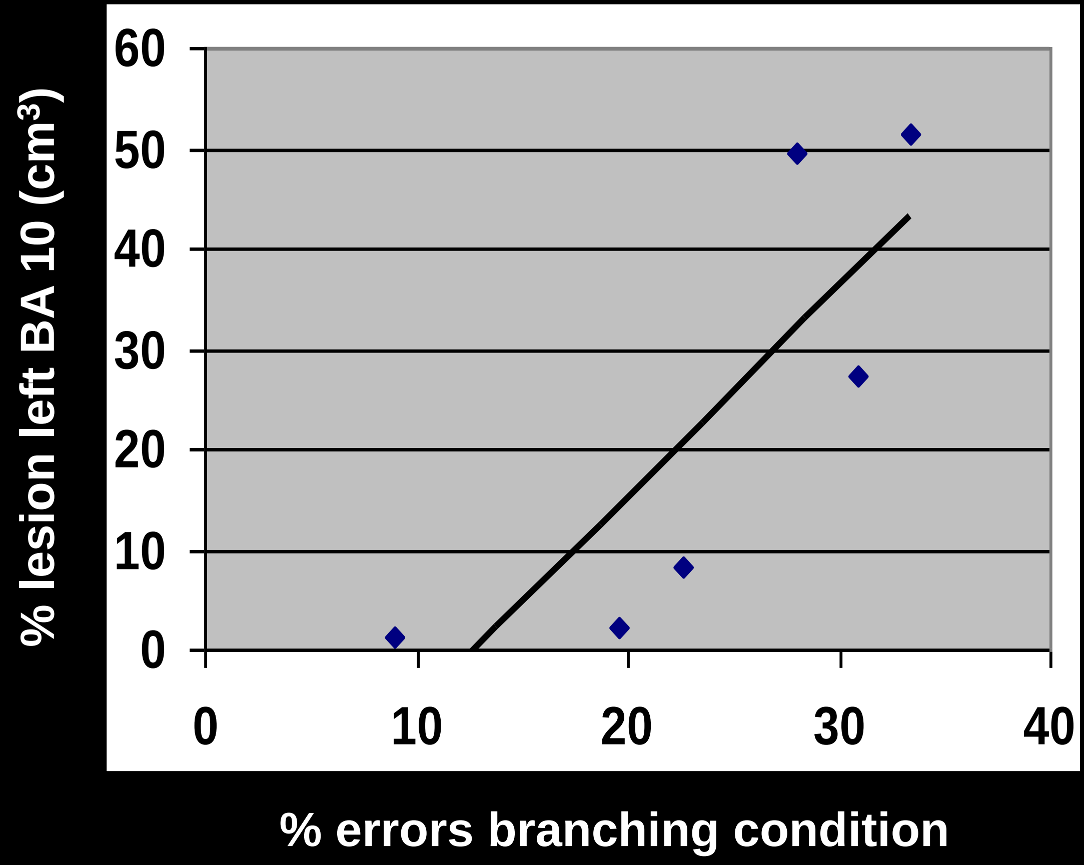
Koechlin et al., *Nature*, 1999

Patients with fronto-polar lesions (BA 10)



Dreher et al., *PLOS One*, 2009

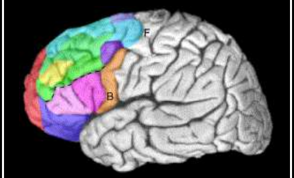
Correlation between the size of fronto-polar lesion and error rates in the branching condition



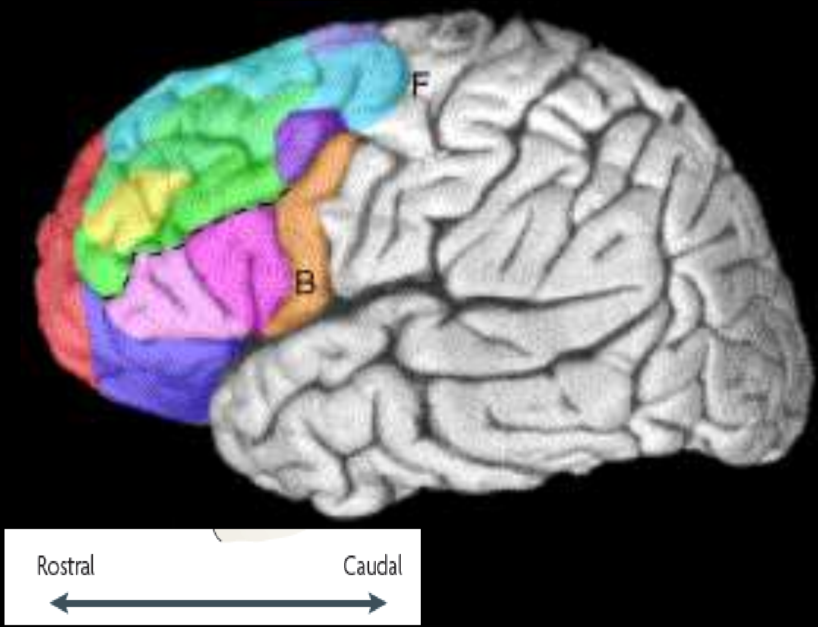
-> Fronto-polar cortex is necessary for holding in mind goals while exploring and processing secondary goals.

Dreher et al., *PLOS One,* 2009

Axis I.



Functional organization of the prefrontal cortex: Hierarchical organization of the frontal lobe



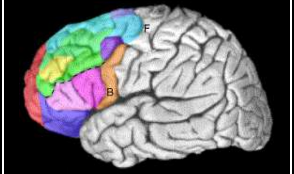
- Respective functions of the DLPFC, anterior medial PFC and fronto-polar cortex

- Roles of task order predictability and task sequence history on the way the PFC is recruited during task switching (DLPFC vs anterior medial PFC)

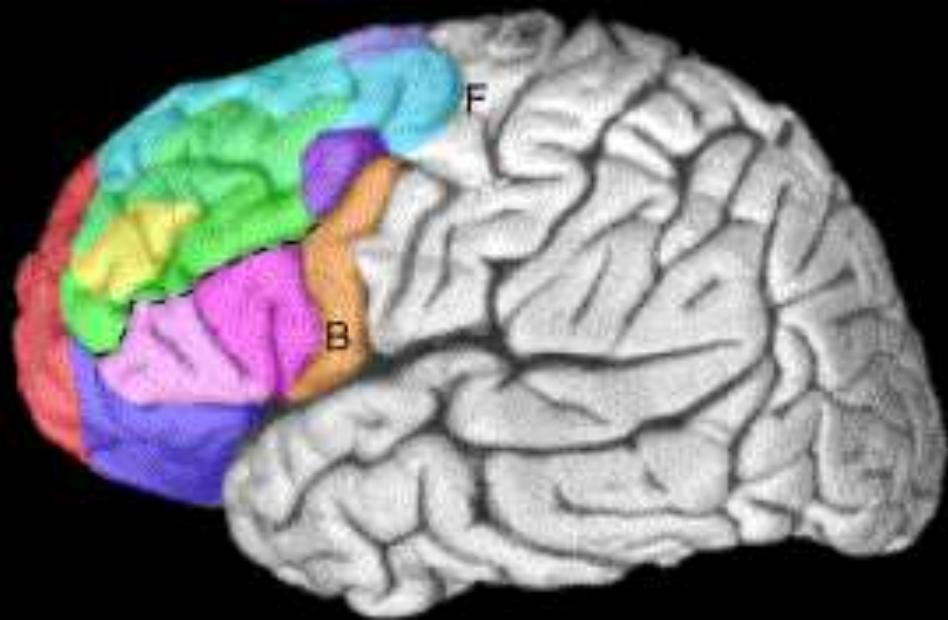
- Combination of working memory and task switching impaired with lesions of the fronto-polar cortex

- Further functional divisions within the orbitofrontal cortex?

Axis I.



Functional organization of the prefrontal cortex



Cognitive functions associated to the Dorsolateral Prefrontal Cortex (BA 9/46): Working memory, cognitive flexibility (task switching)

Cognitive function associated to the fronto-polar cortex (BA 10): Branching (combination of working memory and task switching)

Cognitive function associated to the orbitofrontal cortex: reward processing and motivation