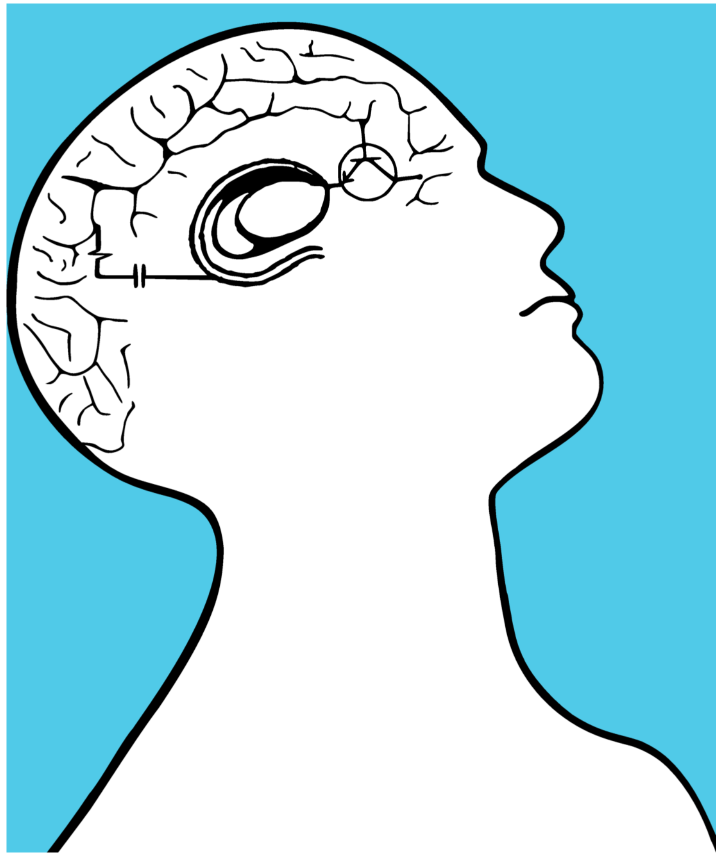
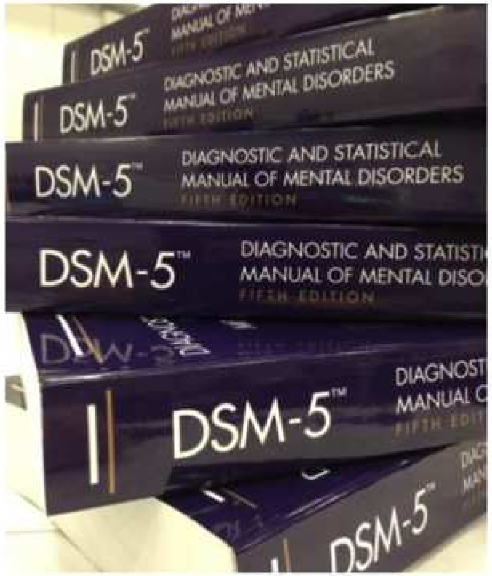
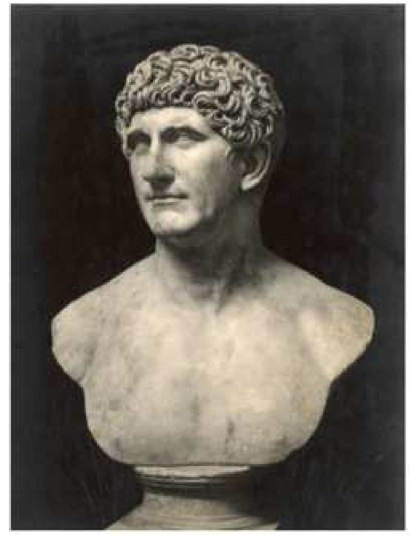
Computational Psychiatry and Neurology



Michael J. Frank
Laboratory for Neural Computation and Cognition
Brown University


DSM-5™
DIAGNOSTIC AND STATISTICAL
MANUAL OF MENTAL DISORDERS
FIFTH EDITION

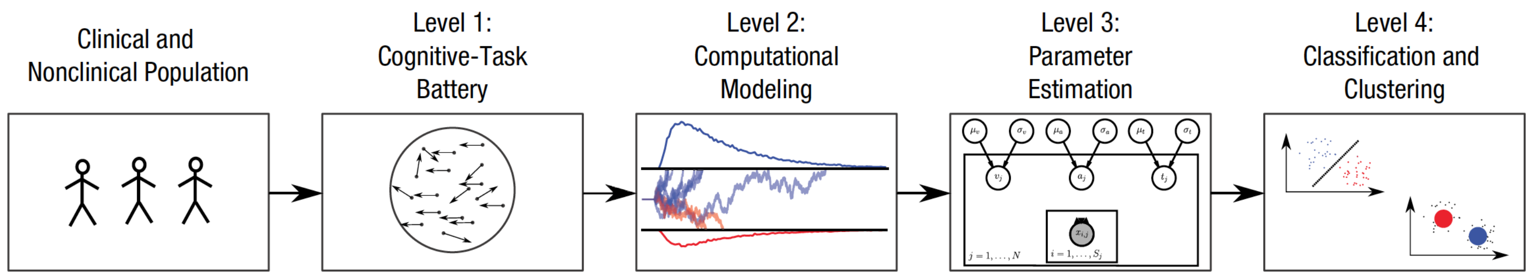


Symptom lists can describe a ‘disease’ state but don’t point to mechanism

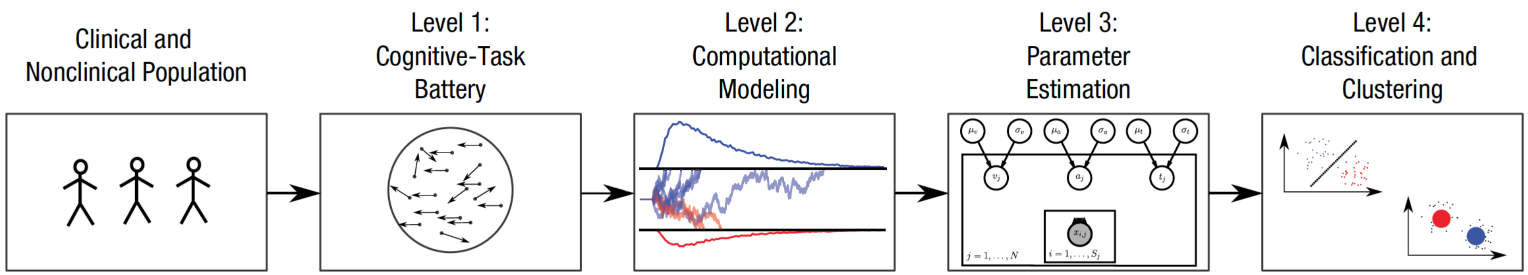
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication; to abnormalities in eye contact and body language or deficits in understanding and use of gestures, to total lack of facial expressions or nonverbal communication.
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts; to difficulties in sharing imaginative play or in making friends; to an absence of interest in peers.
Specify current severity:
Severity is based on social communication impairments and restricted, repetitive patterns of behavior (see Table 2).

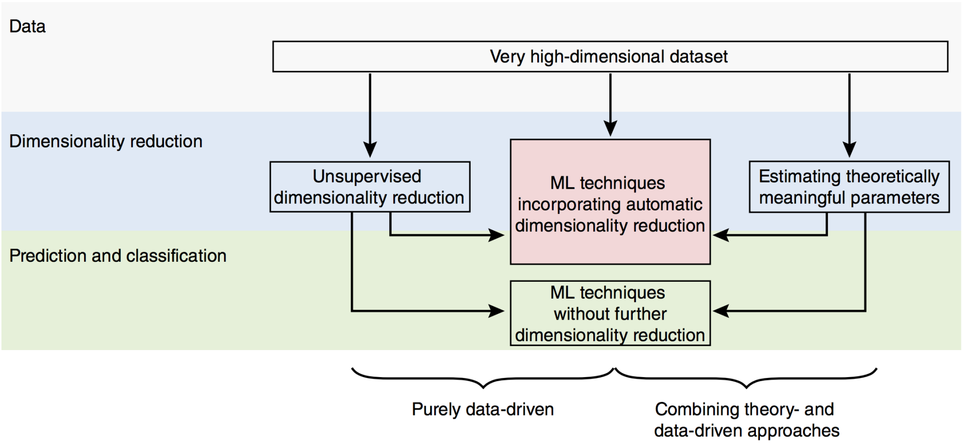
B. Restricted, repetitive patterns of behavior, interests, or activities as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive):
1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g. simple motor stereotypies, lining up toys or flipping objects, echolalia, idiosyncratic phrases).
2. Insistence on sameness, excessive adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat food every day).
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g. strong attachment to or preoccupation with unusual objects, excessively circumscribed or perseverative interests).
4. Hyper-or hyporeactivity to sensory input or unusual interest in sensory aspects of the environment (e.g. apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement).
Specify current severity:
Severity is based on social communication impairments and restricted, repetitive patterns of behavior (see Table 2)

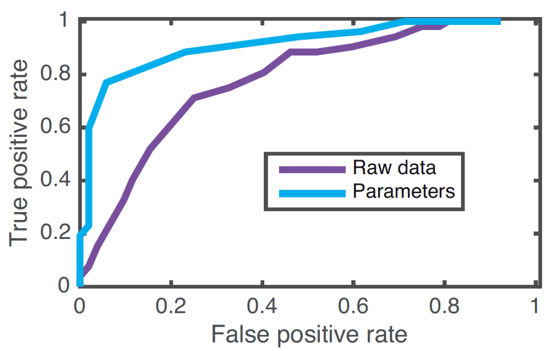
Computation as a link between brain, mind, and pathology



Computation as a link between brain, mind, and pathology







Maia & Frank, 2011; Wiecki, Poland & Frank, 2015; Huys, Maia & Frank 2016

Decision making and impulse control is multi-faceted

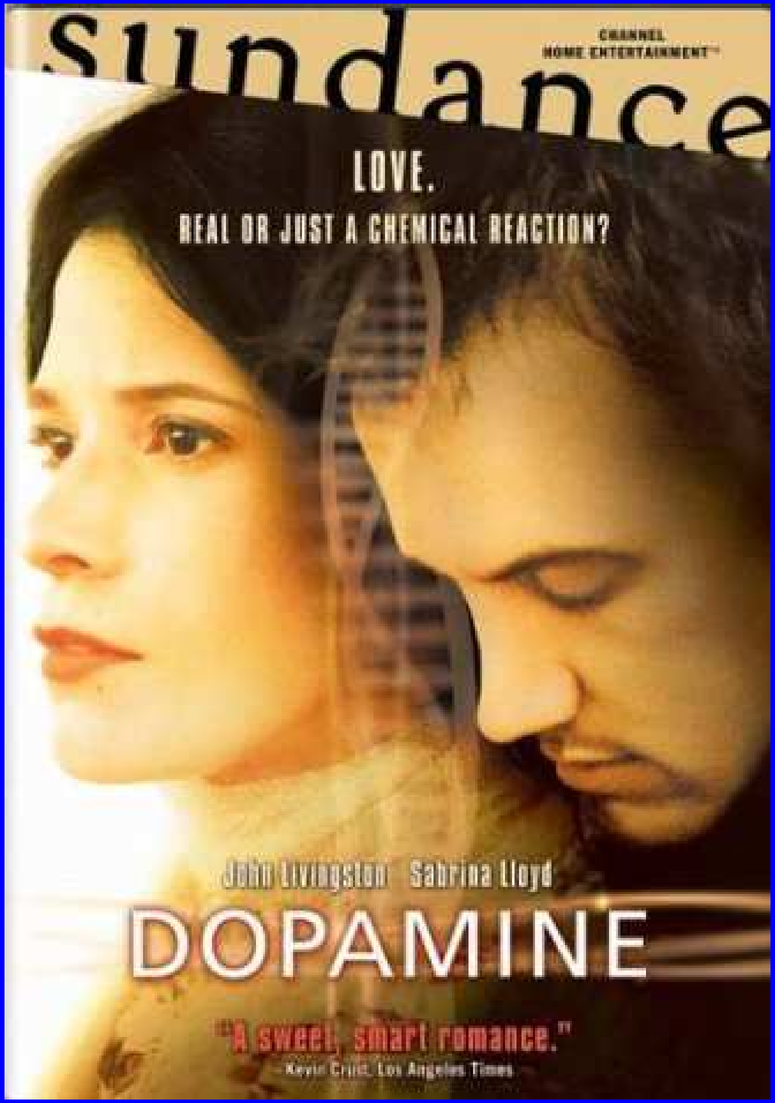
- Reward/Utility function
- Decision weights on costs vs. benefits; risk
- Learning from gains vs. losses
- Immediate vs delayed rewards

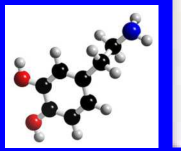
Decision making and impulse control is multi-faceted

- Reward/Utility function
- Decision weights on costs vs. benefits; risk
- Learning from gains vs. losses
- Immediate vs delayed rewards

"Impulsivity": alterations of separable neural mechanisms

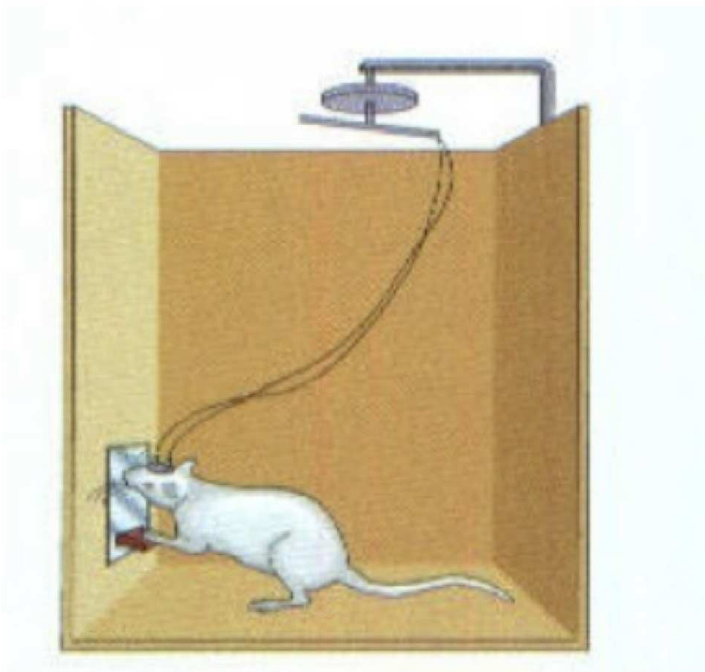
- Strong impulses; failure to control impulses; failure to signal costs, etc.
- Drug abuse; gambling; excacerbated by stress, etc


sundance
CHANNEL
HOME ENTERTAINMENT
LOVE.
REAL OR JUST A CHEMICAL REACTION?
John Livingston Sabrina Lloyd
DOPAMINE
"A sweet, smart romance."
- Kevin Crust, Los Angeles Times

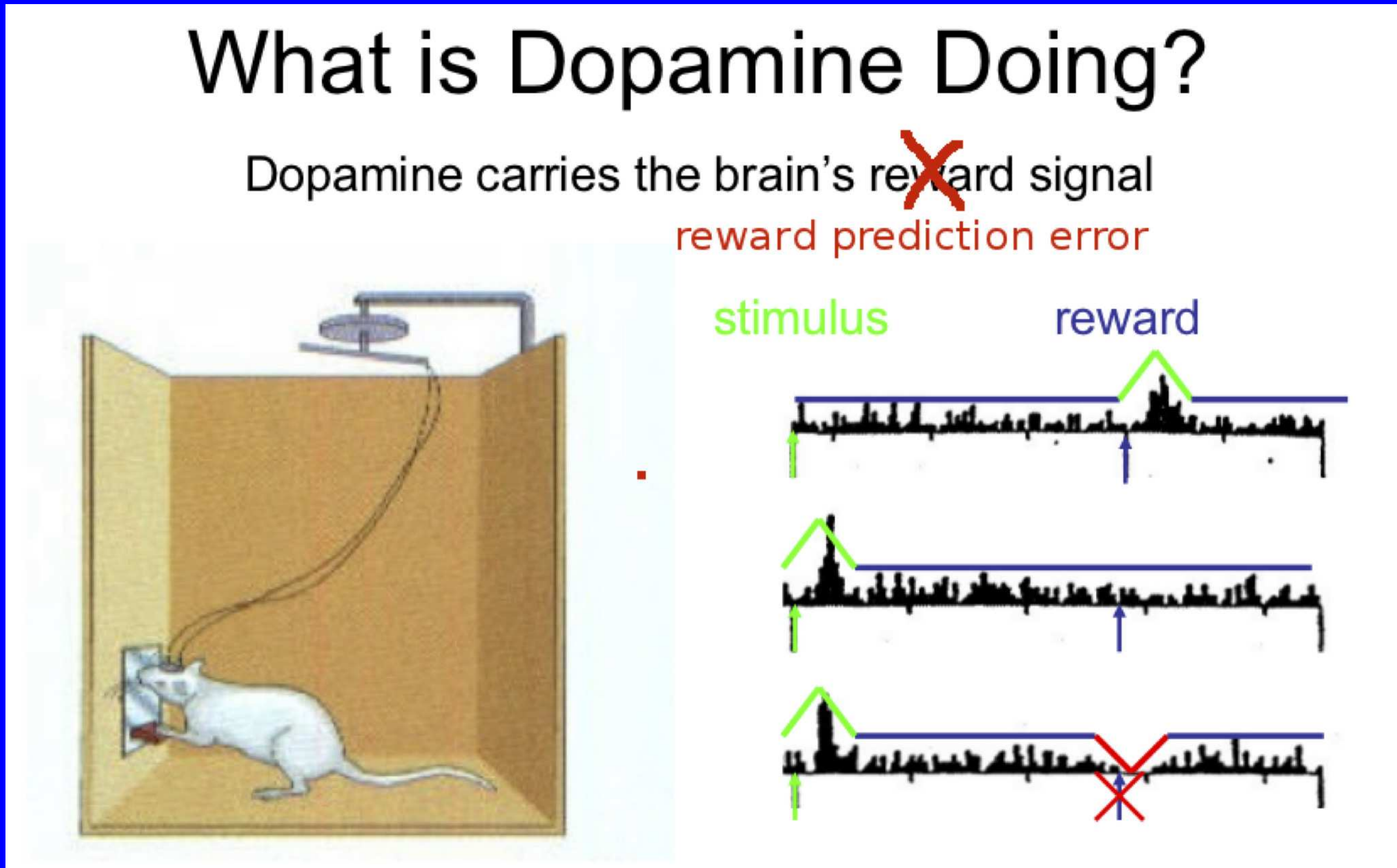


What is Dopamine Doing?

Dopamine carries the brain's reward signal

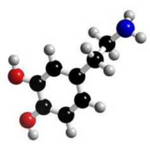


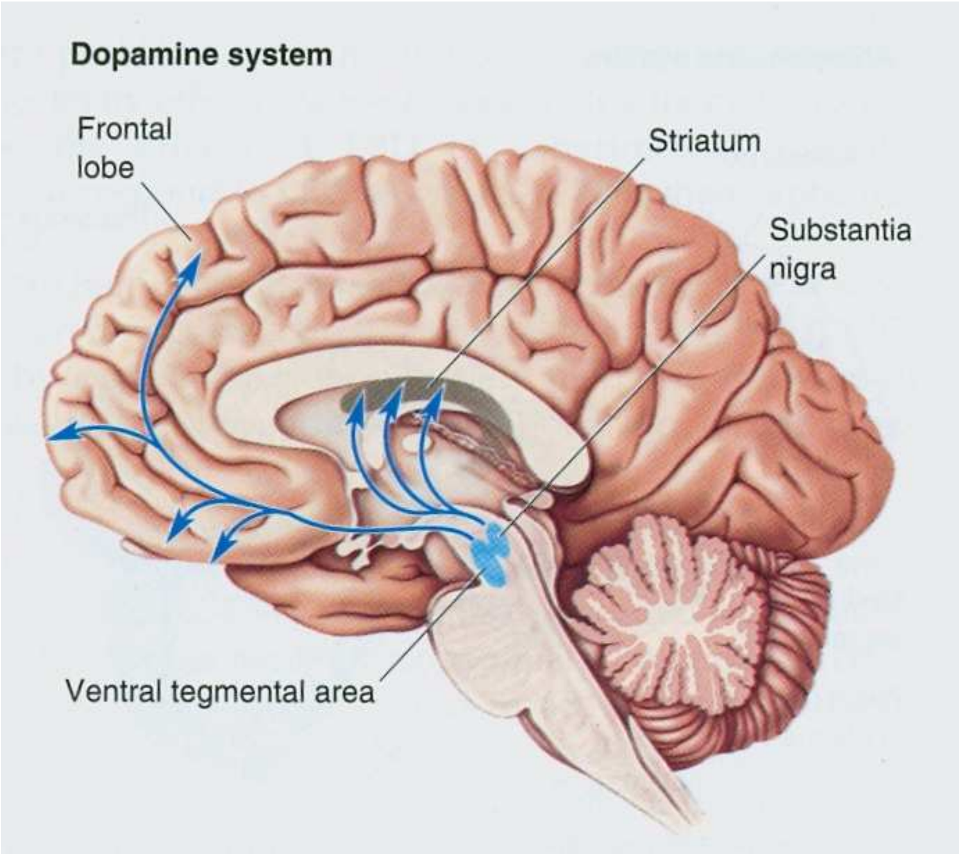
Wise & Romper 89



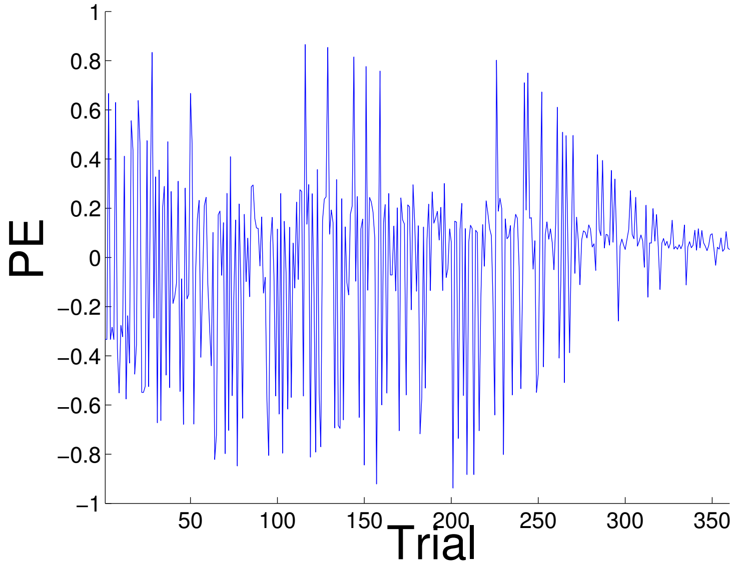
Montague et all 96; Schultz et al 97...

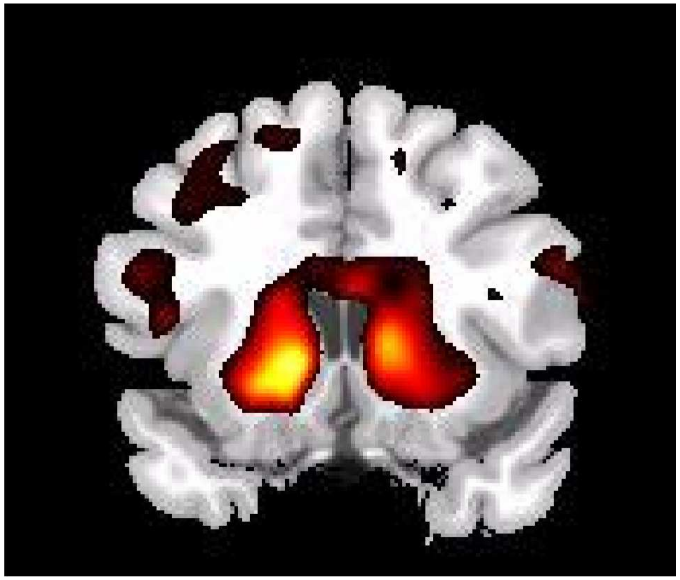
How are dopamine RPE signals used to learn *what to do*?





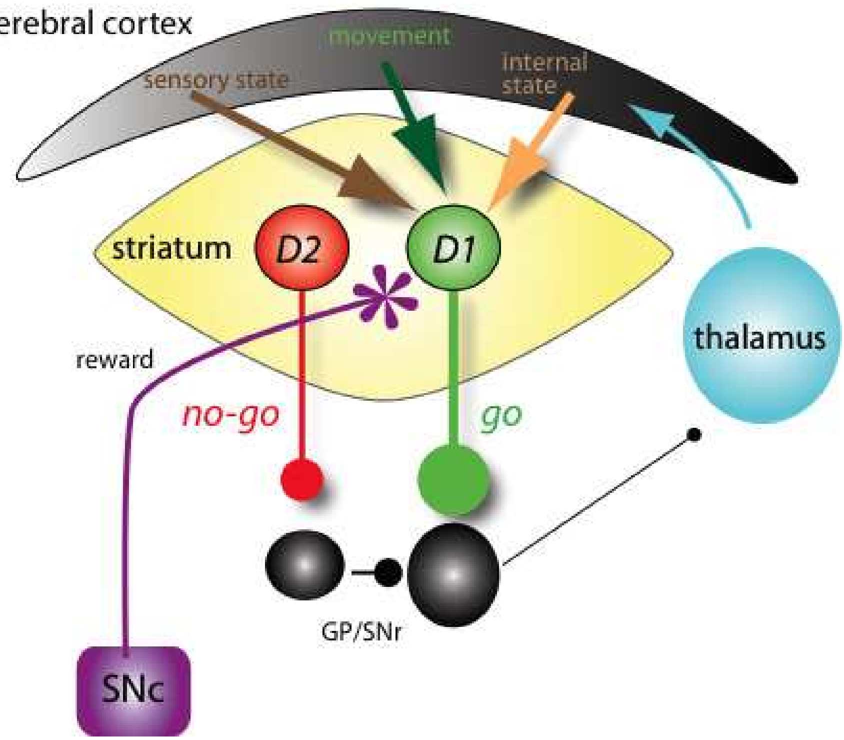
Reward prediction error and human functional imaging





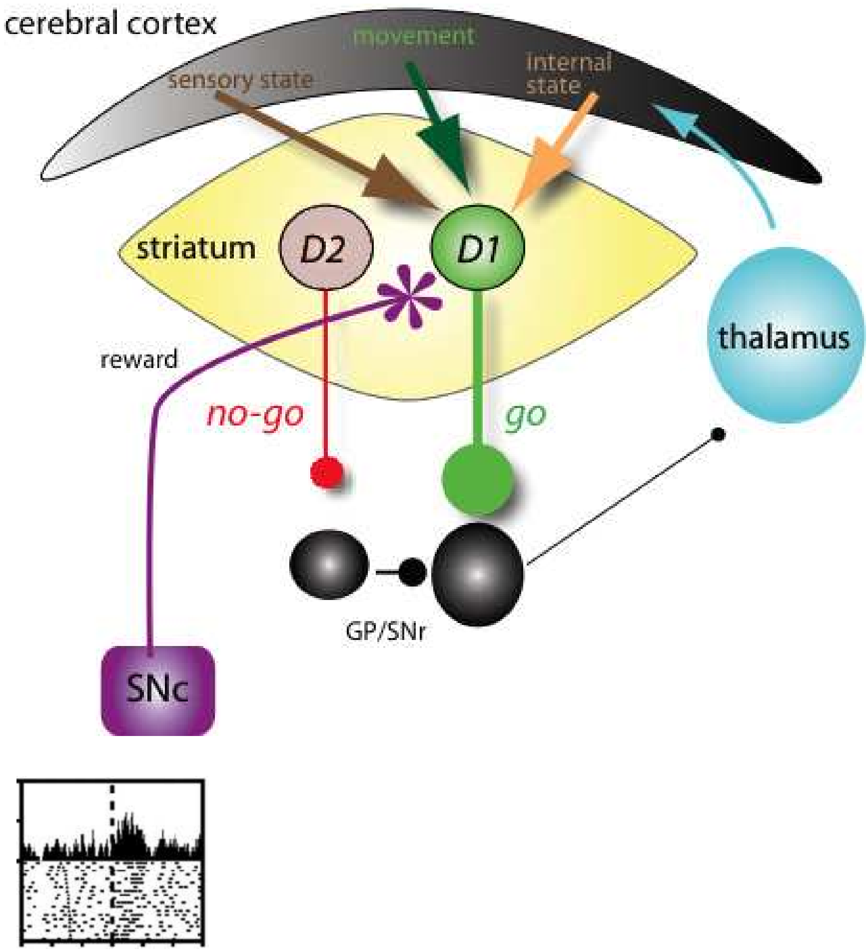
McClure et al, 2003; O'Doherty et al, 2004; Daw et al, 2006; Caplin et al, 2010; Badre & Frank, 2011 etc

Dual pathways in the Basal Ganglia: Cartoon version



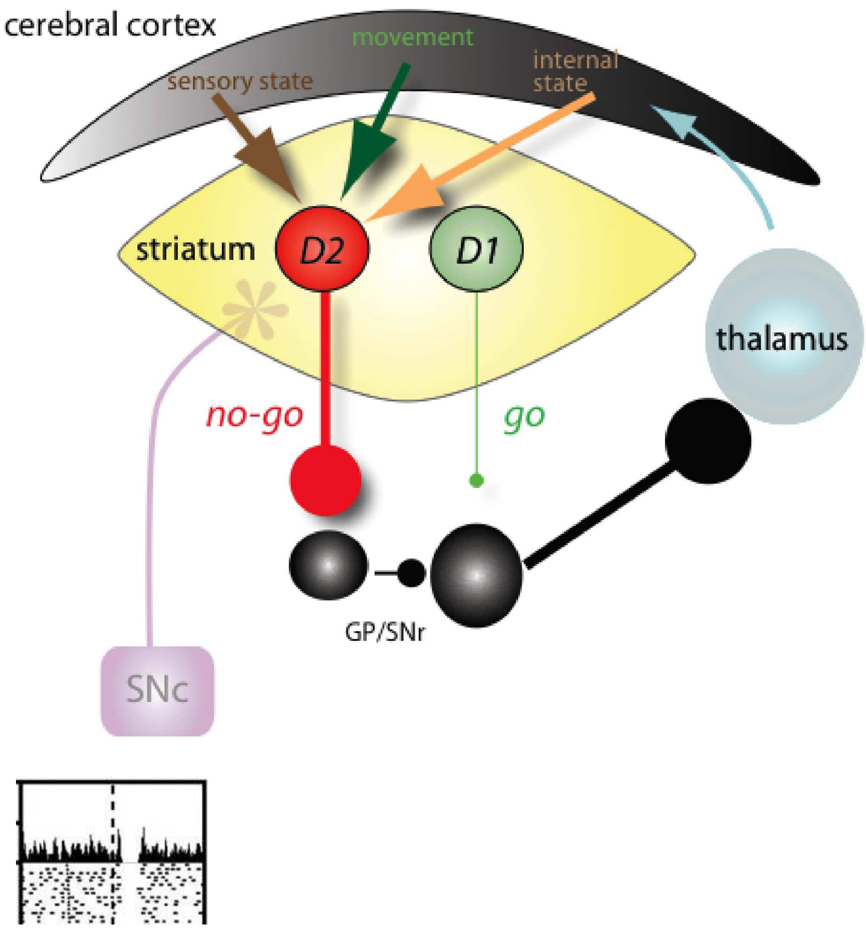
- Go/NoGo terminology is misleading (implies “act” vs. “not act”)
- Benefit vs. cost of alternative actions (both at the same time!)
- Phasic DA signals drive learning via modulation of activation dynamics

D1 effects on BG learning: Positive RPE



pos RPE promotes synaptic plasticity in Go neurons

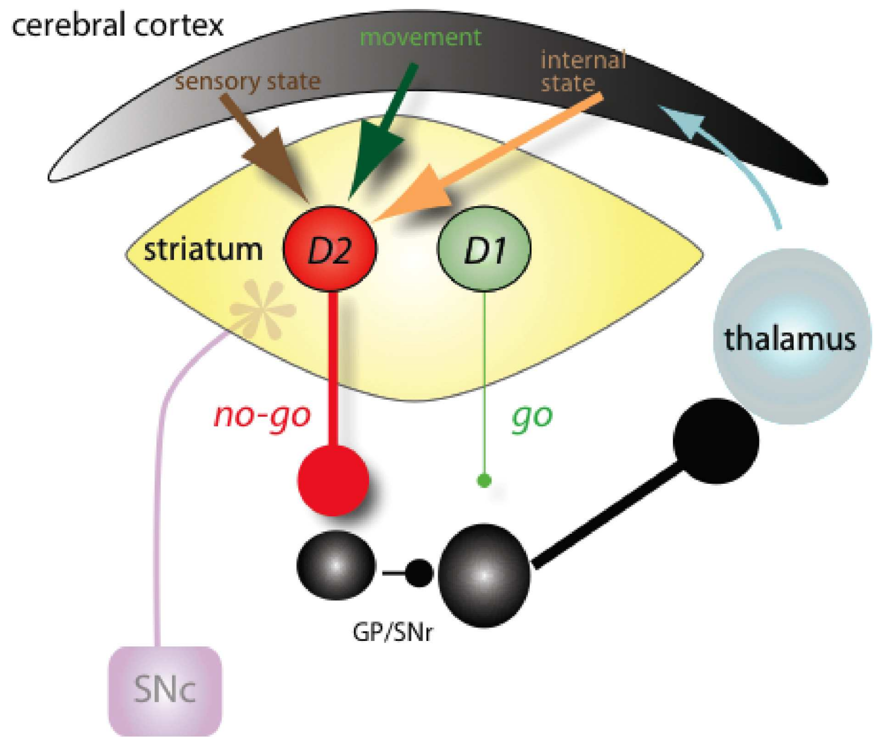
D2 effects on BG learning: Negative PE

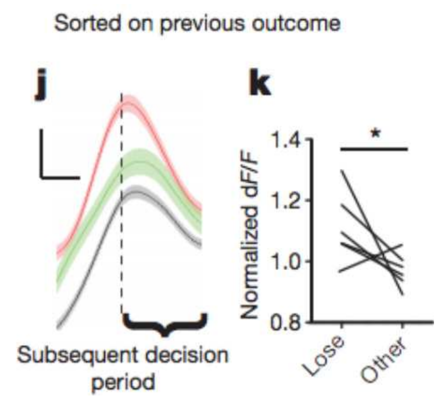


- originally: prediction based on computation (function) and circumstantial data
- D2 weights accumulate with experience - learned Parkinsonism

Frank et al, 2004; 2005

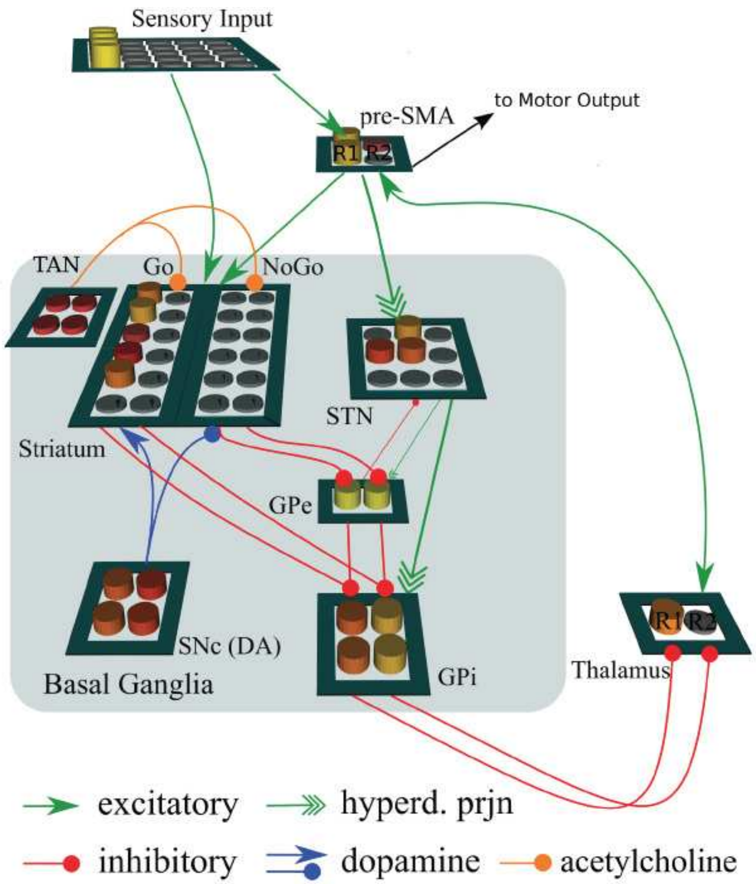
D2 effects on BG learning: Negative PE



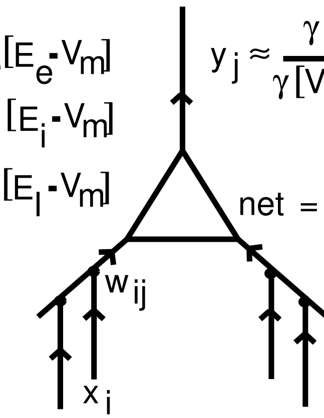


Zalocusky et al, 2016

Neural circuit model of BG in learning / decision making



$$c\dot{V}_m = g_e \bar{g}_e [E_e - V_m] + g_i \bar{g}_i [E_i - V_m] + g_l \bar{g}_l [E_l - V_m] + \ldots$$

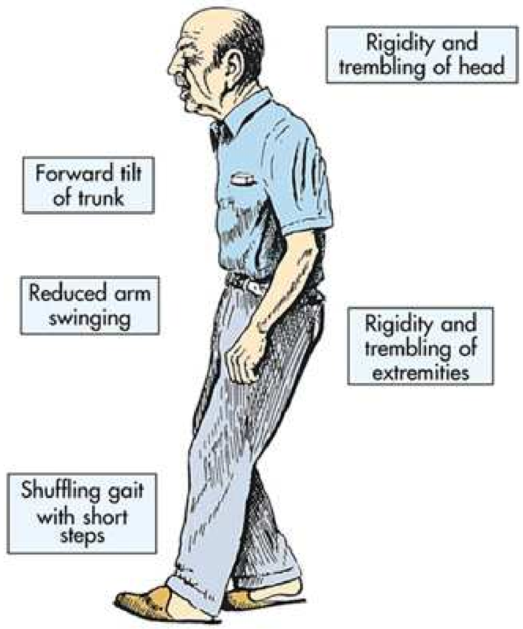


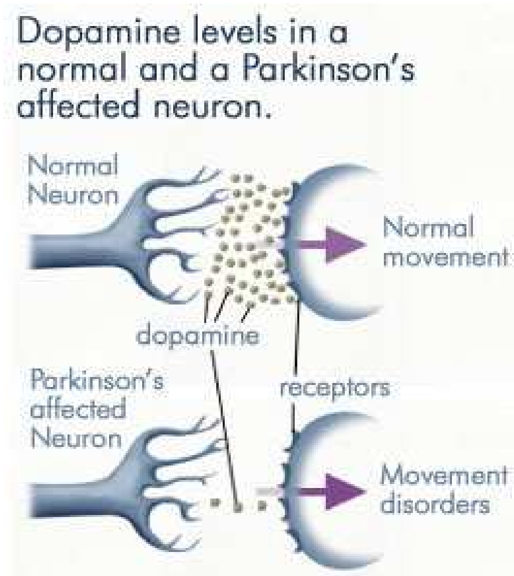
$$y_j \approx \frac{\gamma[V_m - \Theta]_+}{\gamma[V_m - \Theta]_+ + 1}$$

$$net = g_e \approx \langle x_i w_{ij} \rangle + \frac{\beta}{N}$$

Frank, 2005, 2006; Franklin & Frank, 2016

Parkinson's disease and dopamine: motivated action

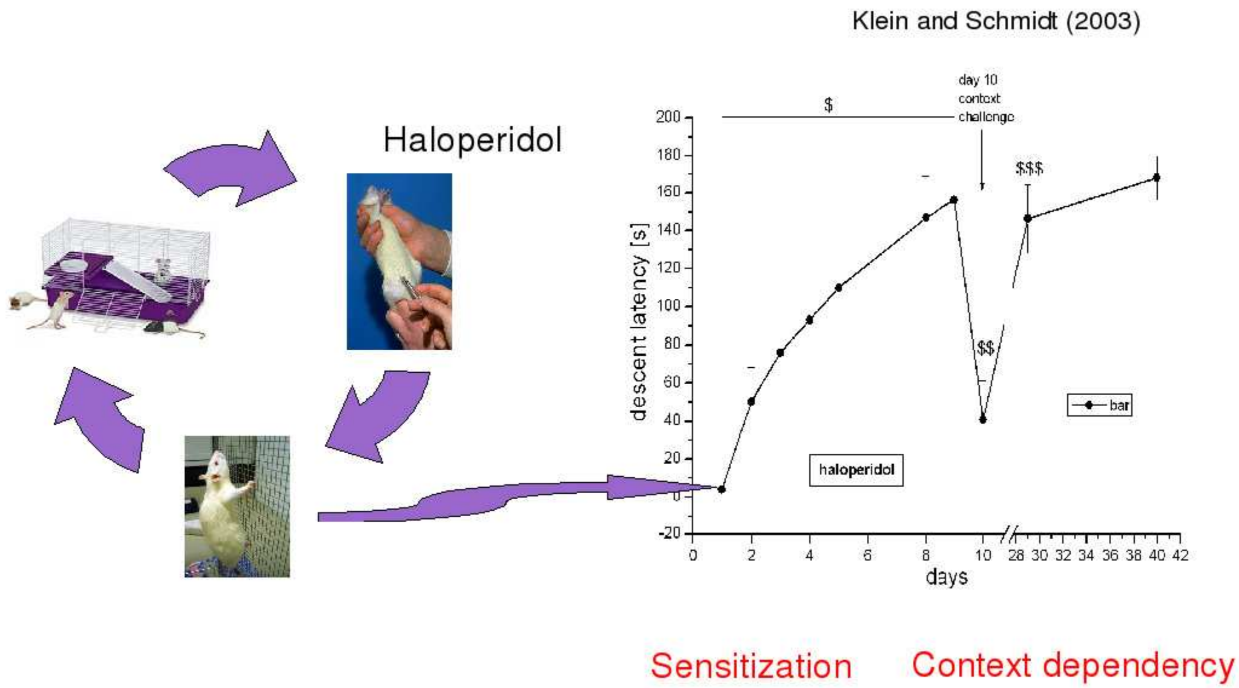




- Models suggest that DA modulates motivational *incentive* and *learning*, too

- *Also: excess BG DA can induce impulsivity, e.g. pathological gambling, compulsive shopping* (*for review Dagher & Robbins, 2009)*

Model implications: PD symptoms can be learned



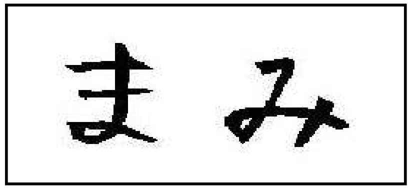
A case of exaggerated NoGo learning??

- suggests novel drug targets for motor symptoms: GPR6 effects
- predicts PD patients are biased to learn from negative RPEs

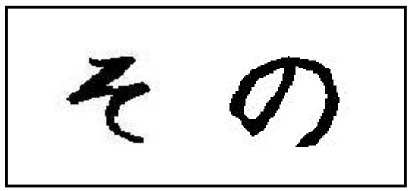
see also Beeler, Frank et al 2012 - aberrant learning in D2 cells

Human probabilistic reinforcement learning

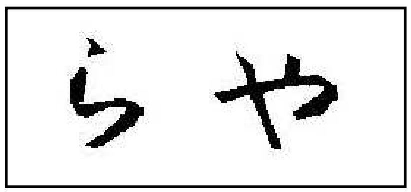
Train



A (80/20) B (20/80)



C (70/30) D (30/70)



E (60/40) F (40/60)

Test

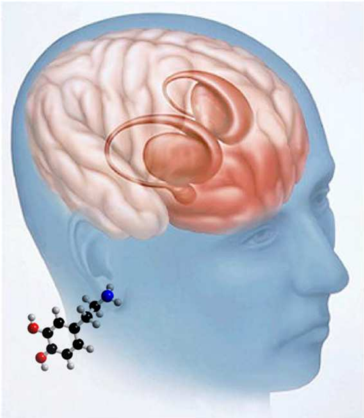
A > CDEF **Choose A?**

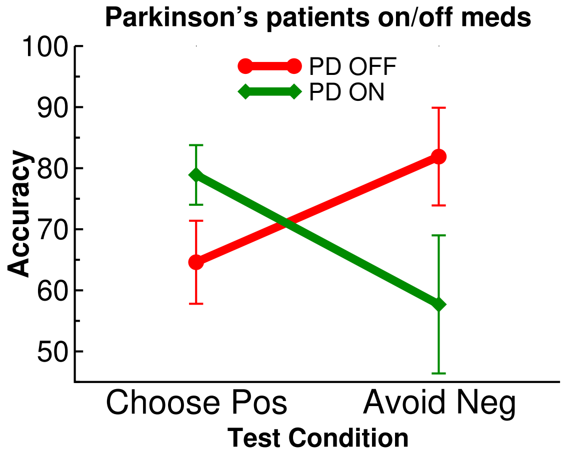
B < CDEF **Avoid B?**

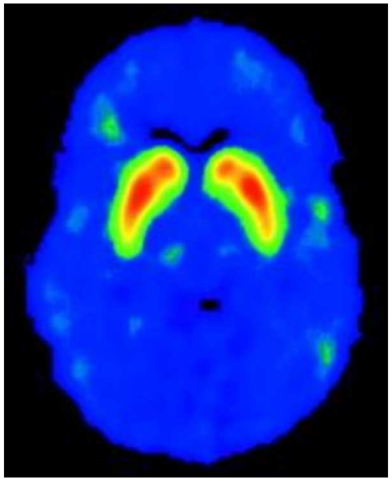
AC, AD, AE, AF “Go-A”

BC, BD, BE, BF “NoGo-B”

Converging evidence: probabilistic RL in lab and in life



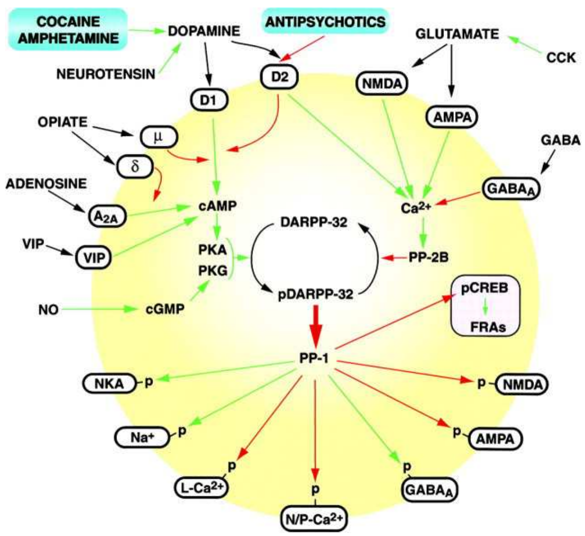


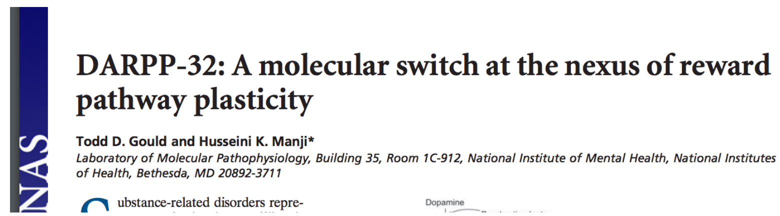


Frank et al (04, 06 , 07), Cockburn et al 14, Cox et al 2015…

Genetics of striatal dopamine function

- *DARPP-32*: intracellular protein concentrated in striatum, differential effects on *D1* vs *D2*-dependent plasticity (*Greengard Nobel Prize 2000*)





DARPP-32: A molecular switch at the nexus of reward pathway plasticity

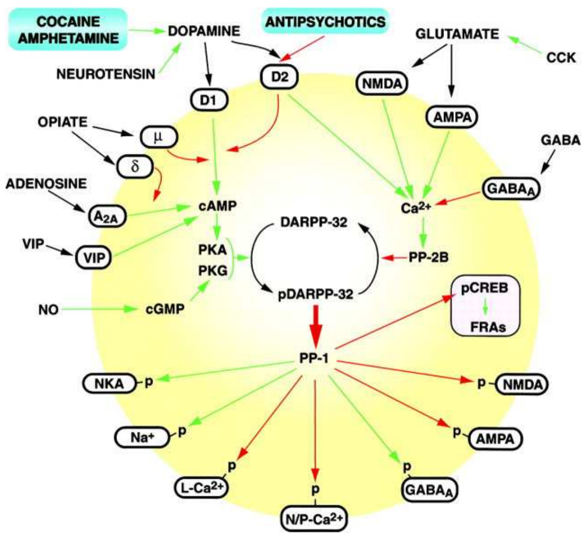
Todd D. Gould and Husseini K. Manji*

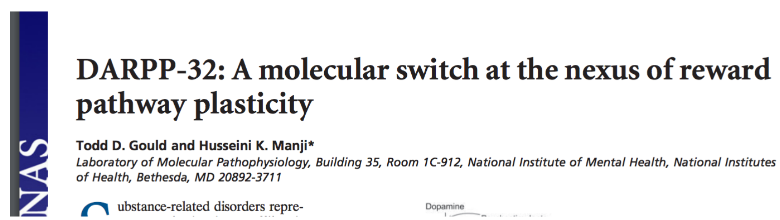
Laboratory of Molecular Pathophysiology, Building 35, Room 1C-912, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892-3711

ubstance-related disorders repre-

Genetics of striatal dopamine function

- *DARPP-32*: intracellular protein concentrated in striatum, differential effects on *D1* vs *D2*-dependent plasticity (*Greengard Nobel Prize 2000*)





PNAS

DARPP-32: A molecular switch at the nexus of reward pathway plasticity

Todd D. Gould and Husseini K. Manji*

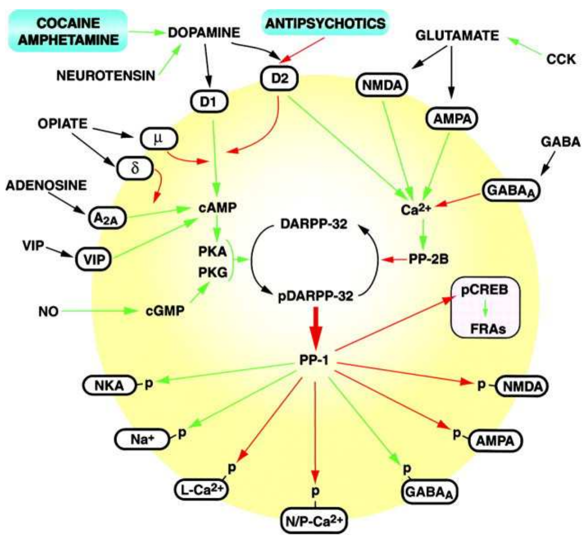
Laboratory of Molecular Pathophysiology, Building 35, Room 1C-912, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892-3711

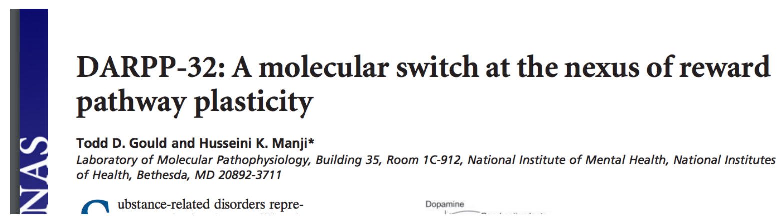
Substance-related disorders repre-

What about Nobel Laureate Bob Dylan's thoughts on DARPP-32?!

Genetics of striatal dopamine function

- *DARPP-32*: intracellular protein concentrated in striatum, differential effects on *D1* vs *D2*-dependent plasticity (*Greengard Nobel Prize 2000*)




PNAS

DARPP-32: A molecular switch at the nexus of reward pathway plasticity

Todd D. Gould and Husseini K. Manji*

Laboratory of Molecular Pathophysiology, Building 35, Room 1C-912, National Institute of Mental Health, National Institutes of Health, Bethesda, MD 20892-3711

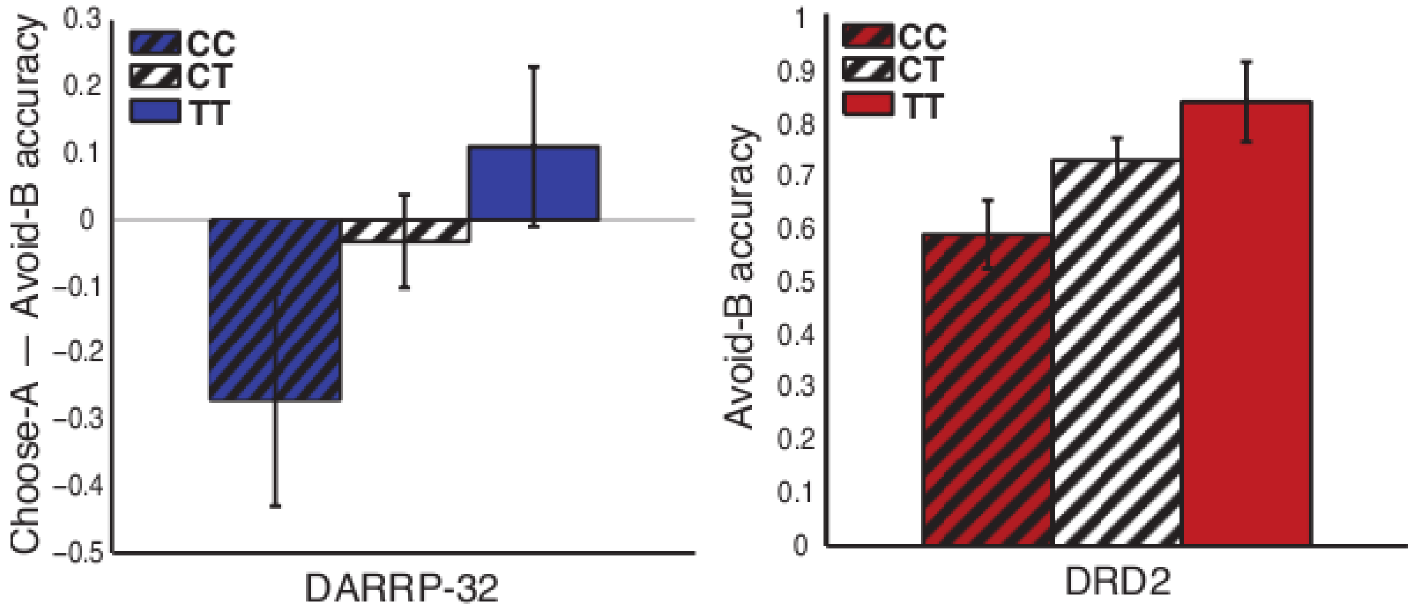
Substance-related disorders repre-

What about Nobel Laureate Bob Dylan's thoughts on DARPP-32?!

⇒ *Model: D1>D2= probabilistic Go>NoGo learning*

Human DARPP-32 effects on gain vs loss learning

N = 80



Doll et al, 2011, 2016; Frank et al., 2007; Cockburn et al 2014

Deep Brain Stimulation of the Subthalamic Nucleus (STN)

But not all is grand in the world of DBS...

But not all is grand in the world of DBS...

hi, i found your email address in an article i was reading about dbs surgery for parkinsons. my dad had the surgery last may and we have a mess on our hands. two months following the surgery we began to notice some personality changes. he became impulsive, cocky, oblivious to his surroundings, forgetful, has lied, he has no empathy, he uses foul language ... canceled his 2 follow up dr appointments, he was always very detailed oriented and now he is sloppy, and he is spending a lot of money. he has NOT gone one day without buying something. he can't sit still, he's always on the move. going somewhere and buying something...

But not all is grand in the world of DBS...

hi, i found your email address in an article i was reading about dbs surgery for parkinsons. my dad had the surgery last may and we have a mess on our hands. two months following the surgery we began to notice some personality changes. he became impulsive, cocky, oblivious to his surroundings, forgetful, has lied, he has no empathy, he uses foul language ... canceled his 2 follow up dr appointments, he was always very detailed oriented and now he is sloppy, and he is spending a lot of money. he has NOT gone one day without buying something. he can't sit still, he's always on the move. going somewhere and buying something...

STN-DBS dramatically improves PD motor symptoms, but can induce impulsivity

(Saint-Cyr et al 06, Frank et al, 07; Wylie et al 10; Hälbig et al 09; Green et al 13)

But not all is grand in the world of DBS...

hi, i found your email address in an article i was reading about dbs surgery for parkinsons. my dad had the surgery last may and we have a mess on our hands. two months following the surgery we began to notice some personality changes. he became impulsive, cocky, oblivious to his surroundings, forgetful, has lied, he has no empathy, he uses foul language ... canceled his 2 follow up dr appointments, he was always very detailed oriented and now he is sloppy, and he is spending a lot of money. he has NOT gone one day without buying something. he can't sit still, he's always on the move. going somewhere and buying something...

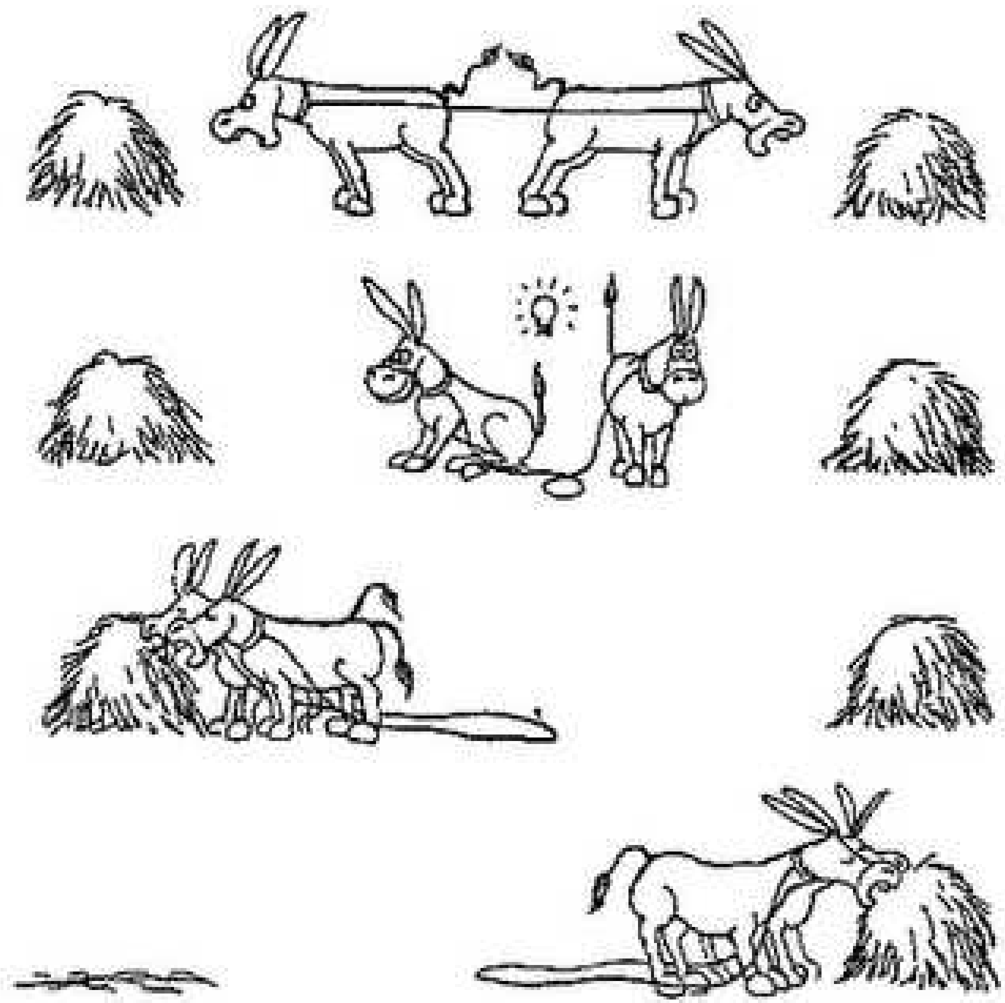
STN-DBS dramatically improves PD motor symptoms, but can induce impulsivity

(Saint-Cyr et al 06, Frank et al, 07; Wylie et al 10; Hälbig et al 09; Green et al 13)

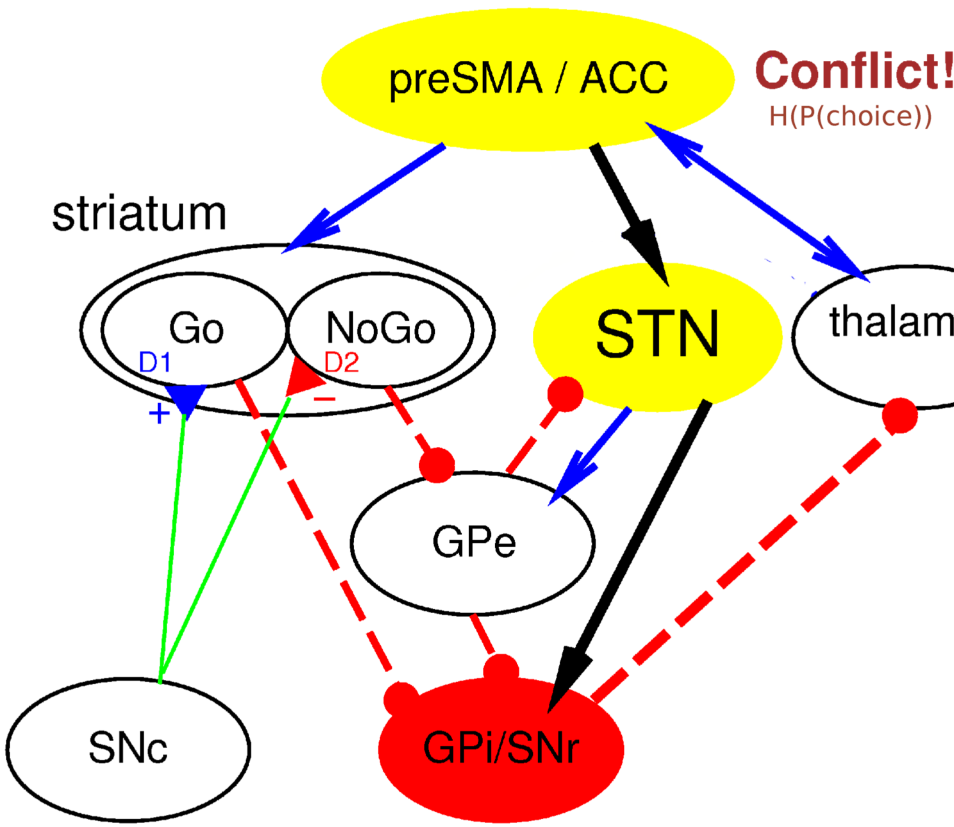
Mechanism? What sort of models can be useful?

From reinforcement learning...

...to reward conflict-based decision making



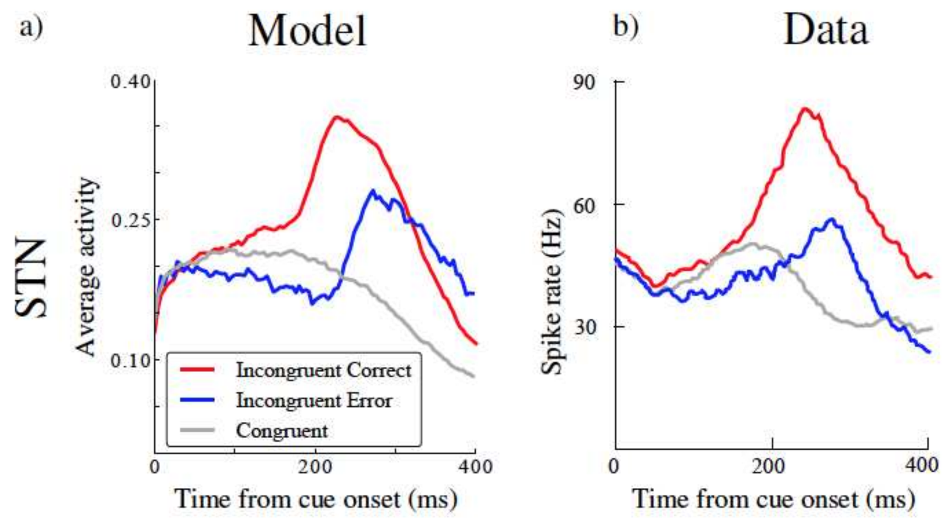
Subthalamic Nucleus:
Dynamic modulation of decision threshold



- Conflict (uncertainty) in choice prob: $\Rightarrow$ *Hold Your Horses!*

STN electrophysiology: decision conflict

spike rate:



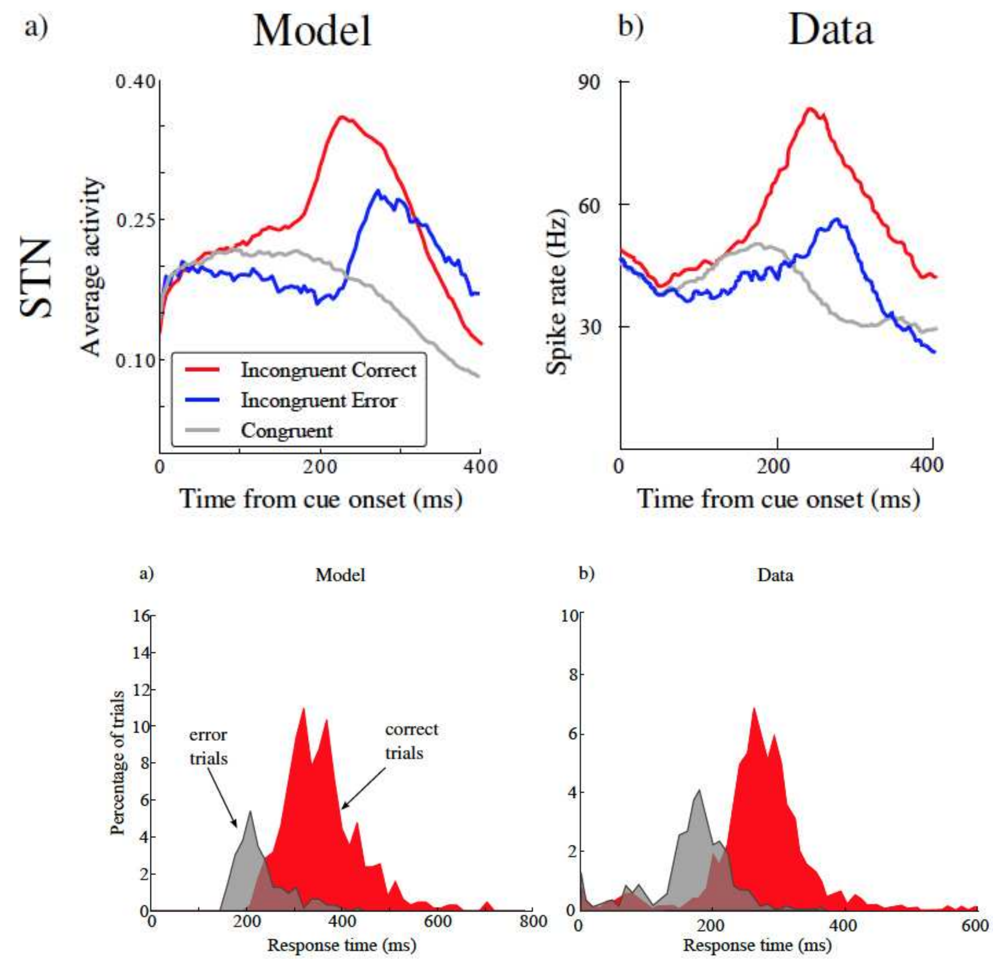
data from Isoda & Hikosaka 2008

Wiecki & Frank, 2013 *Psych Review*

STN electrophysiology: decision conflict

spike rate:

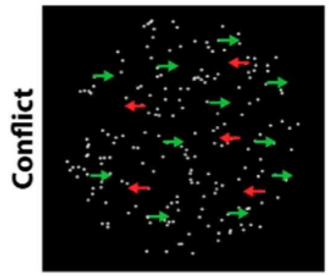
behavior:

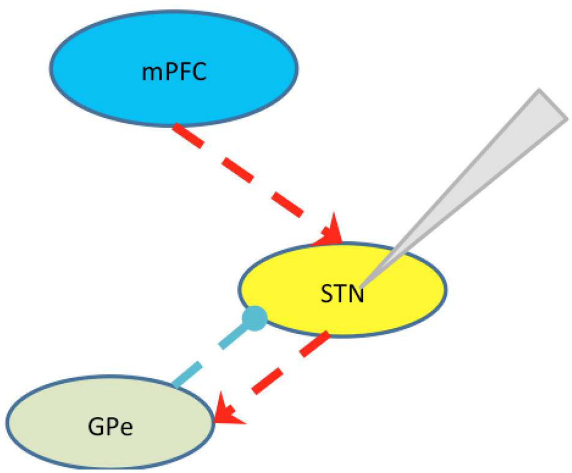


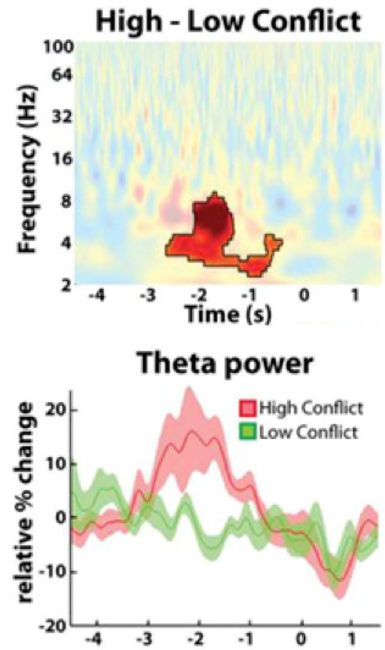
data from Isoda & Hikosaka 2008

Wiecki & Frank, 2013 *Psych Review*

STN theta power encodes conflict

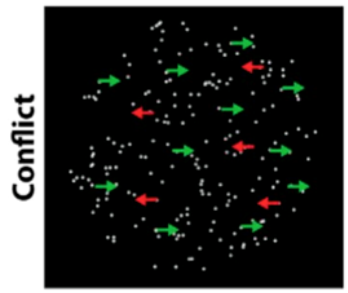


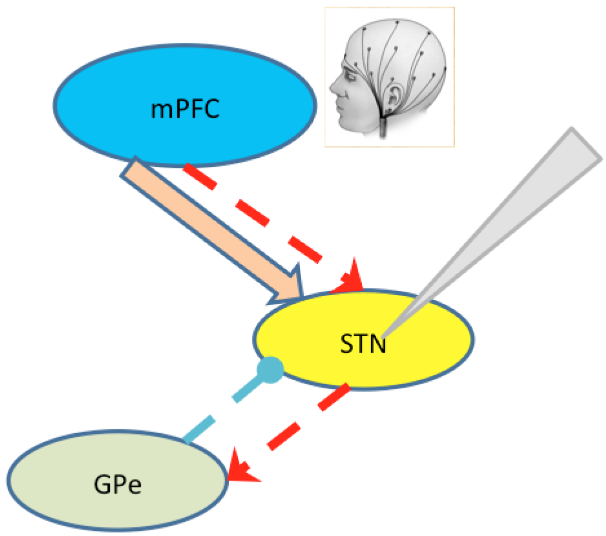


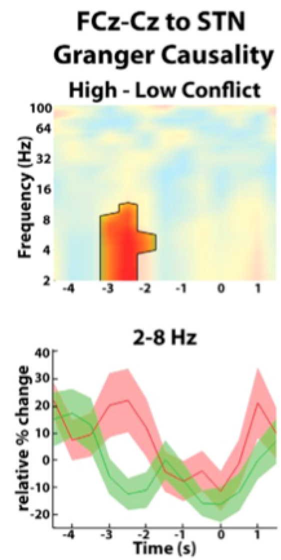


Zavala, B. et al, J Neurosci. 2014;33:14758-14766

mPFC theta influences STN theta







Zavala, B. et al, J Neurosci. 2014;33:14758-14766

Human probabilistic reward/choice conflict

A (80%) B (20%) C (70%) D (30%) E (60%) F (40%)

Low Conflict: e.g., 80 vs 30% $H(P_{softmax}) = .06$

High Conflict: e.g., 80 vs 70% $H(P_{softmax}) = .84$

Human probabilistic reward/choice conflict

A (80%) B (20%) C (70%) D (30%) E (60%) F (40%)

Low Conflict: e.g., 80 vs 30% $H(P_{softmax}) = .06$

High Conflict: e.g., 80 vs 70% $H(P_{softmax}) = .84$

$\rightarrow$ Need STN to prevent impulsive responses

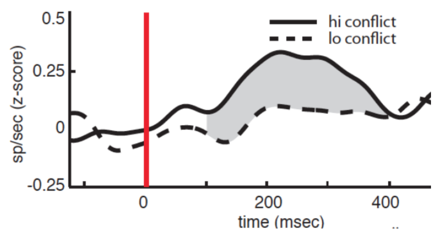
Human probabilistic reward/choice conflict

A (80%) B (20%) C (70%) D (30%) E (60%) F (40%)

Low Conflict: e.g., 80 vs 30% $H(P_{softmax}) = .06$

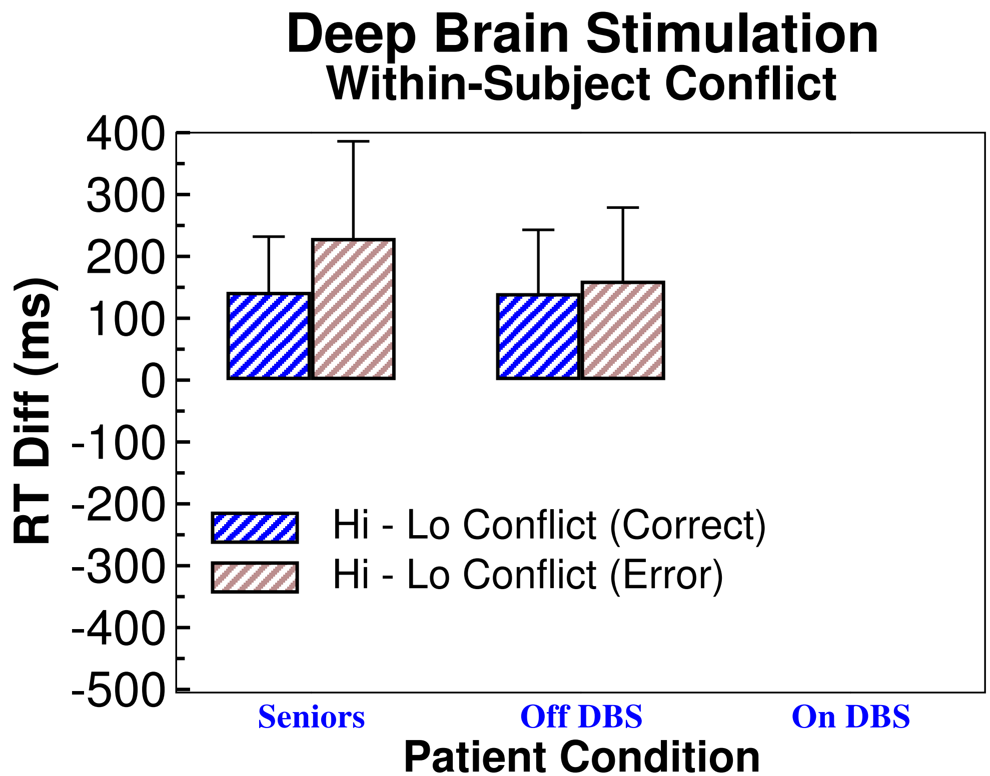
High Conflict: e.g., 80 vs 70% $H(P_{softmax}) = .84$

$\rightarrow$ Need STN to prevent impulsive responses



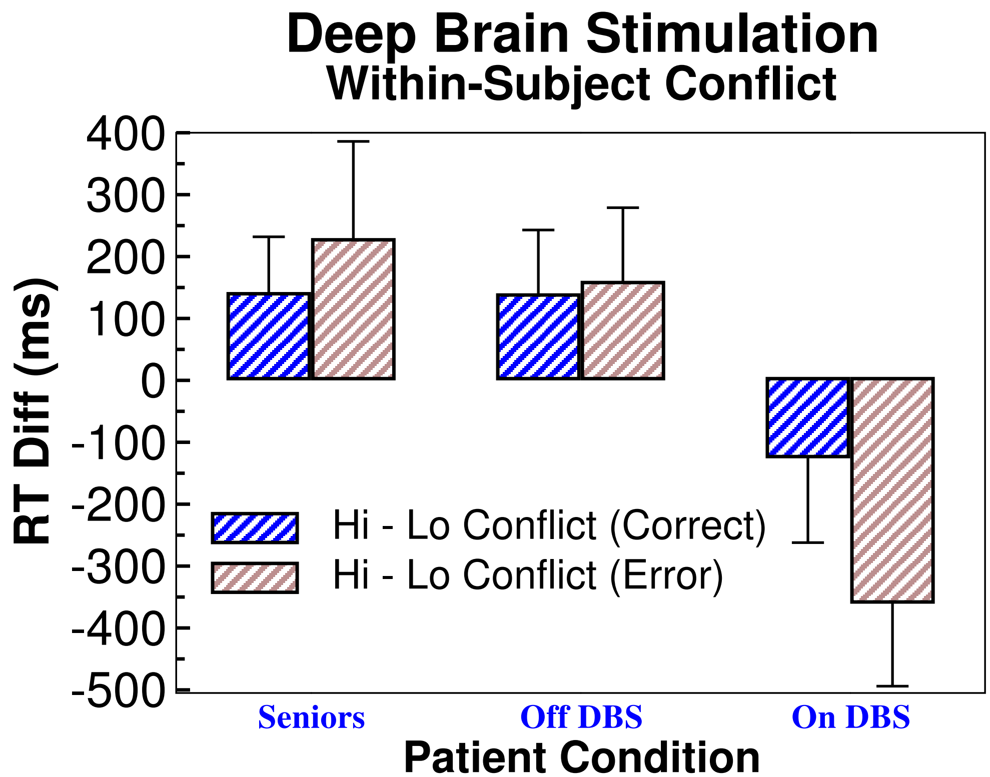
human STN spiking, Zaghloul et al., 2012

STN-DBS reverses conflict RT adjustments



Frank, Samanta, Moustafa & Sherman (2007)

STN-DBS reverses conflict RT adjustments



- these effects are not seen with DA medications

Frank, Samanta, Moustafa & Sherman (2007)

see also Wylie et al 10; Hälbig et al 09; Cavanagh et al 11; Coulthard et al 12; Green et al 13

Linking across levels of computation in model-based cognitive neuroscience

Reinforcement-Based Decision Making in Corticostriatal Circuits: Mutual Constraints by Neurocomputational and Diffusion Models

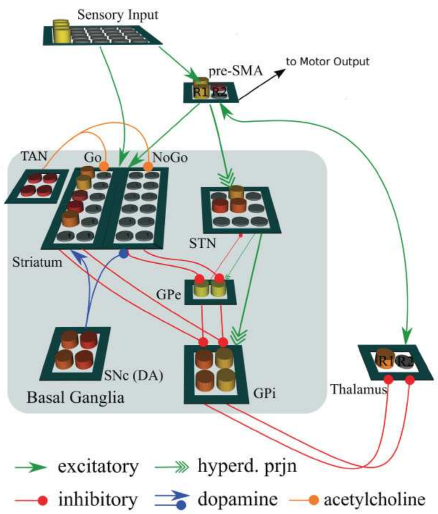
- Strategy to interpret and link across levels of description
- Mutually informative: algorithm informs biological interpretation and vice-versa

Frank, 2015; Collins & Frank, 2013; Ratcliff & Frank, 2012; Franklin & Frank, 2016

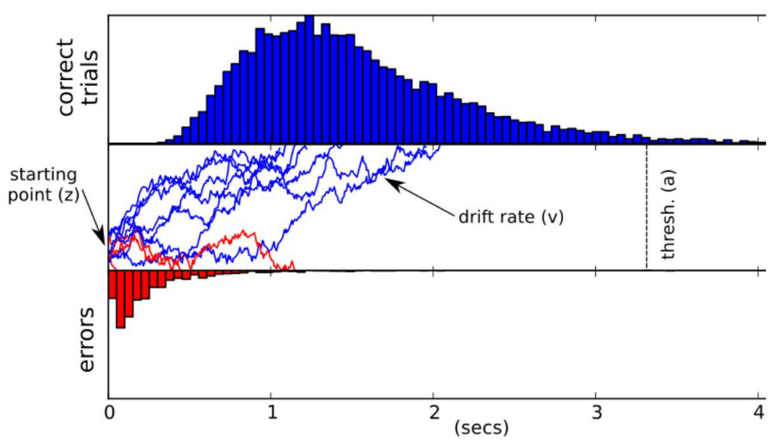
Linking across levels of computation in model-based cognitive neuroscience

Reinforcement-Based Decision Making in Corticostriatal Circuits: Mutual Constraints by Neurocomputational and Diffusion Models

- Strategy to interpret and link across levels of description
- Mutually informative: algorithm informs biological interpretation and vice-versa

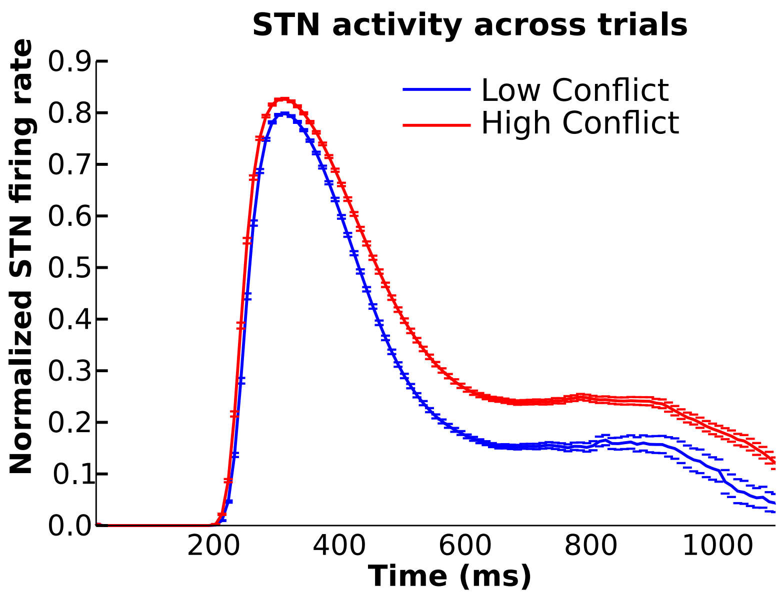


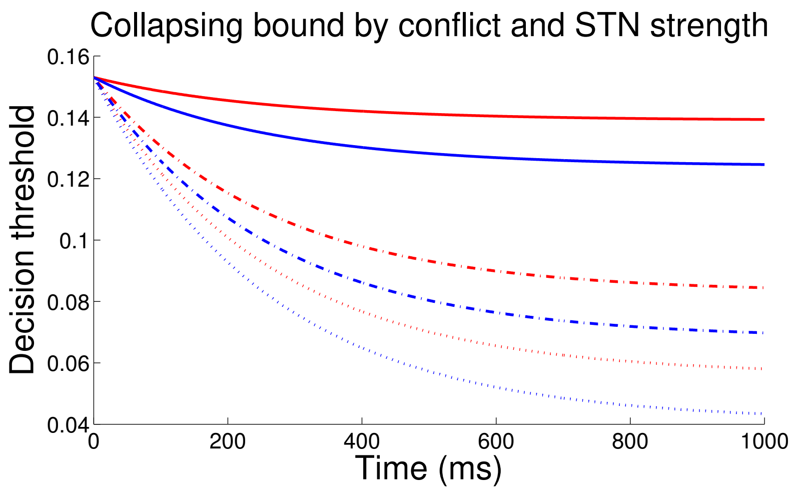
$\Longleftarrow\Longrightarrow$



Frank, 2015; Collins & Frank, 2013; Ratcliff & Frank, 2012; Franklin & Frank, 2016

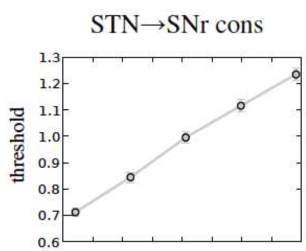
Diffusion model fits to BG neural model





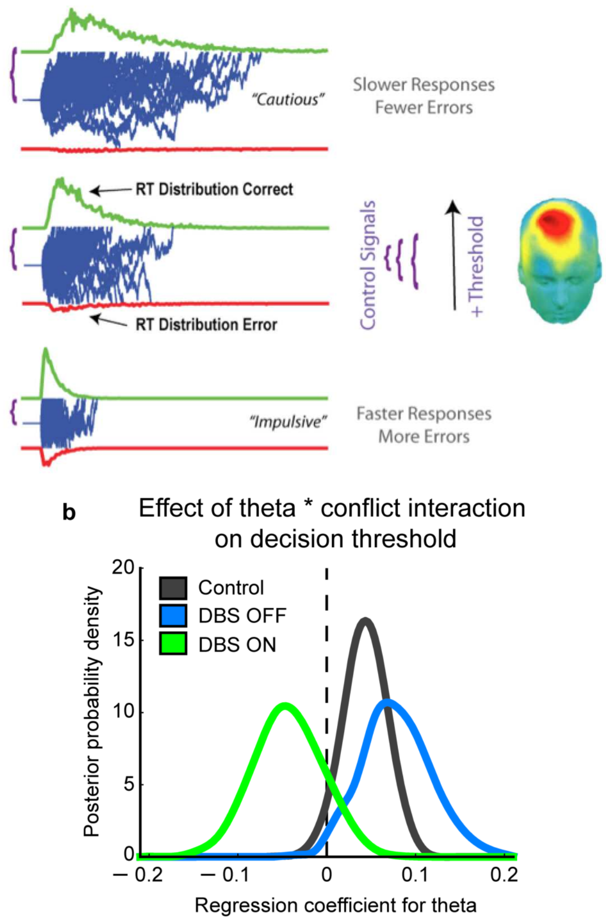
Simulated STN activity

Best fit threshold trajectories



Ratcliff & Frank, 2012; Wiecki & Frank 2013

STN-DBS reverses mPFC influence over decision threshold



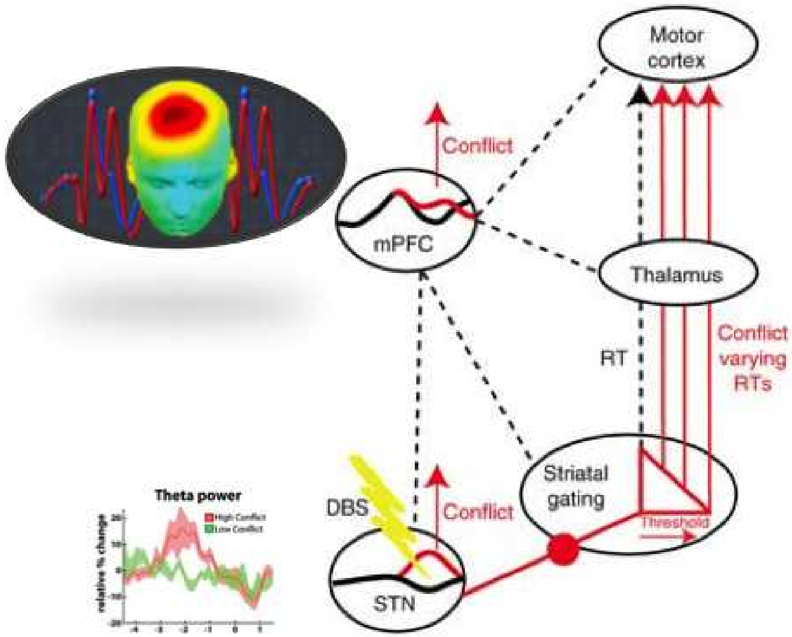
hierarchical-Bayes param estimation tool for DDM: `http://ski.clps.brown.edu/hddm_docs`

Mechanism

nature neuroscience

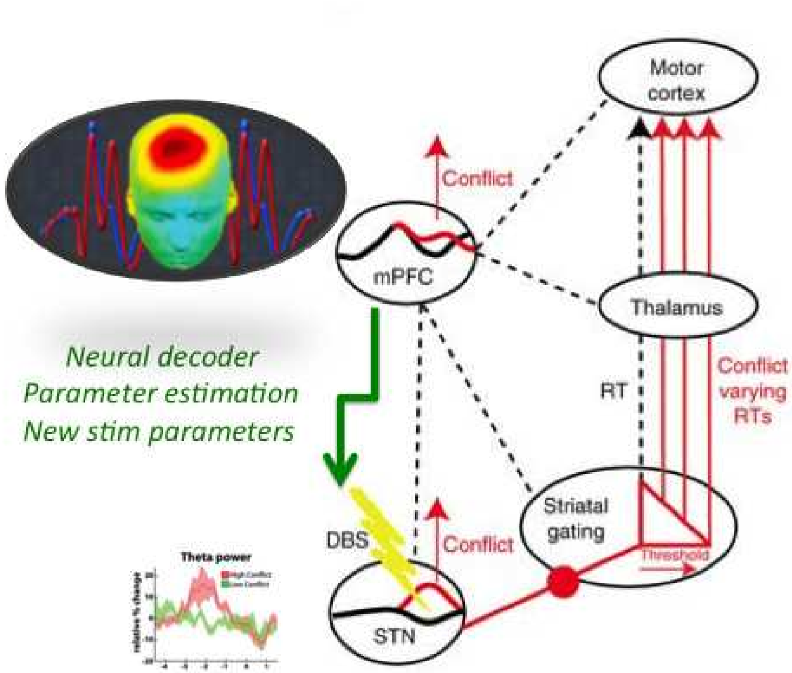
Subthalamic nucleus stimulation reverses mediofrontal influence over decision threshold

James F Cavanagh[1], Thomas V Wiecki[1], Michael X Cohen[2,3], Christina M Figueroa[1], Johan Samanta[4,5], Scott J Sherman[4] & Michael J Frank[1,6,7]



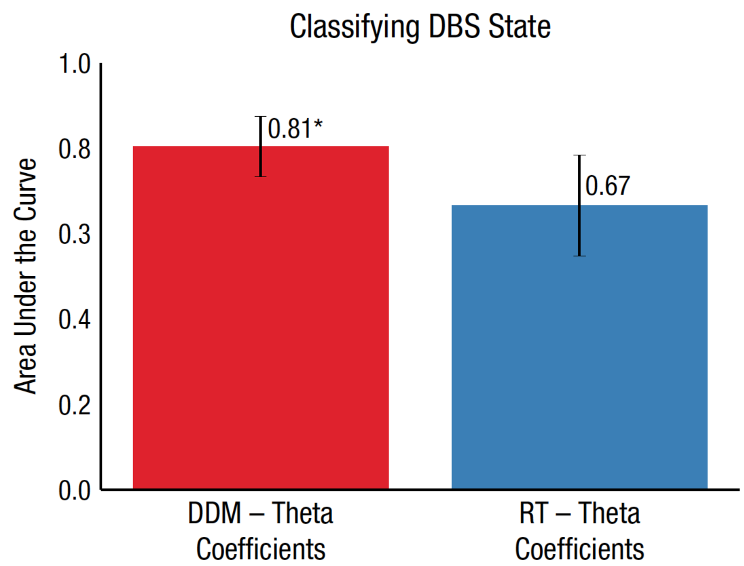
Cavanagh et al 2011; see also Frank et al 2015, *JNeuro* in fMRI

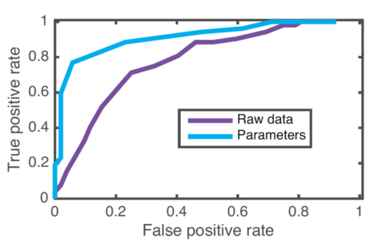
Opportunity for real-time neuromodulation



see also Frank et al 2015, *JNeuro* in fMRI

Computational psychiatry: classification of DBS state





Wiecki, Poland & Frank 2013

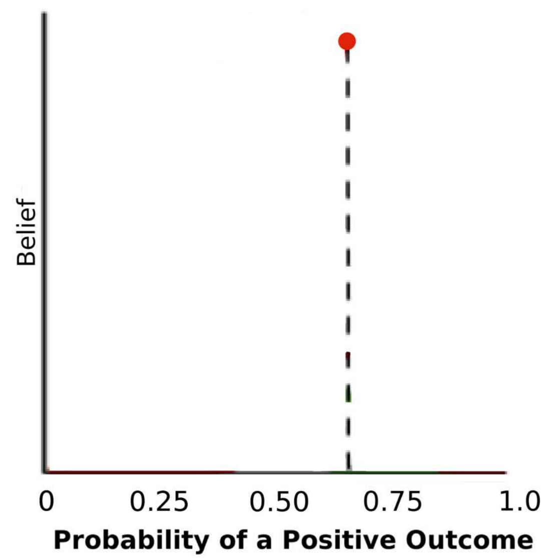
Also classifies Huntington's disease before symptom onset! Wiecki et al., 2016 etc.

Exploration vs Exploitation and Schizophrenia

- By exploiting learned strategies, we can get a certain amount of reward
- But when to explore?
- Theory: Explore based on relative *uncertainty* about whether other actions might yield better outcomes than status quo (Dayan & Sejnowksi 96)

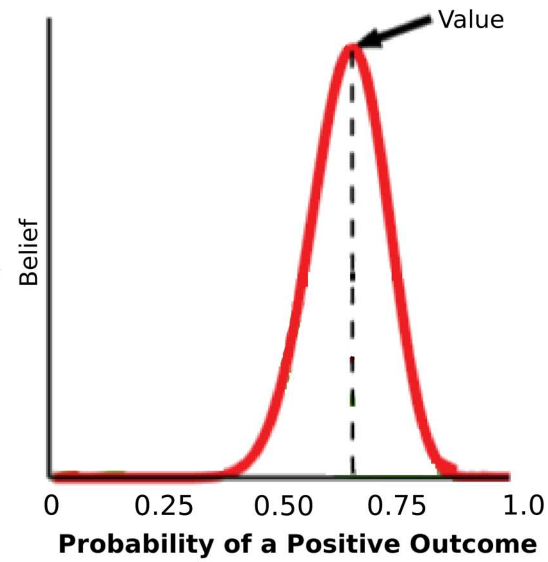
Exploration vs Exploitation and Schizophrenia

- By exploiting learned strategies, we can get a certain amount of reward
- But when to explore?
- Theory: Explore based on relative *uncertainty* about whether other actions might yield better outcomes than status quo (Dayan & Sejnowksi 96)



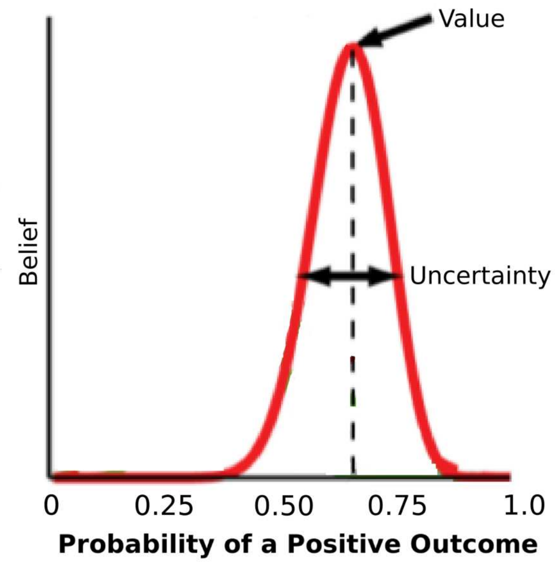
Exploration

- By exploiting learned strategies, we can get a certain amount of reward
- But when to explore?
- Theory: Explore based on relative *uncertainty* about whether other actions might yield better outcomes than status quo



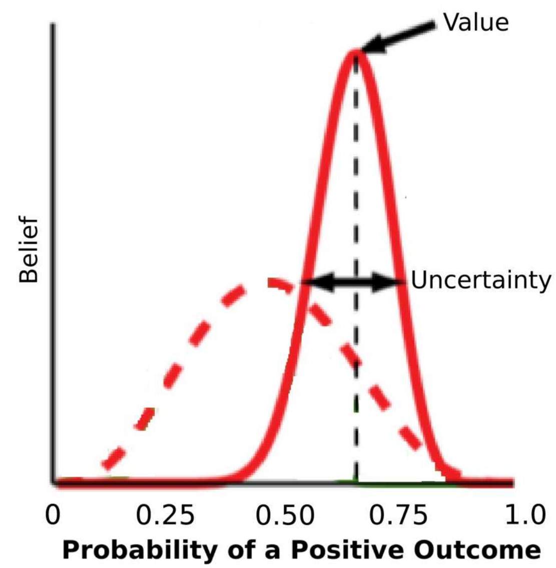
Exploration

- By exploiting learned strategies, we can get a certain amount of reward
- But when to explore?
- Theory: Explore based on relative *uncertainty* about whether other actions might yield better outcomes than status quo



Exploration

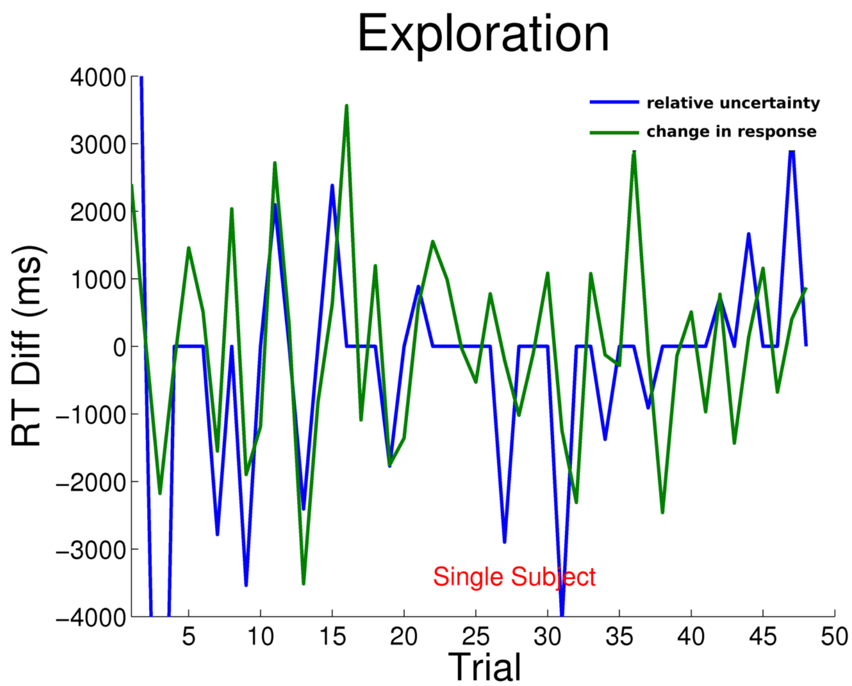
- By exploiting learned strategies, we can get a certain amount of reward
- But when to explore?
- Theory: Explore based on relative *uncertainty* about whether other actions might yield better outcomes than status quo

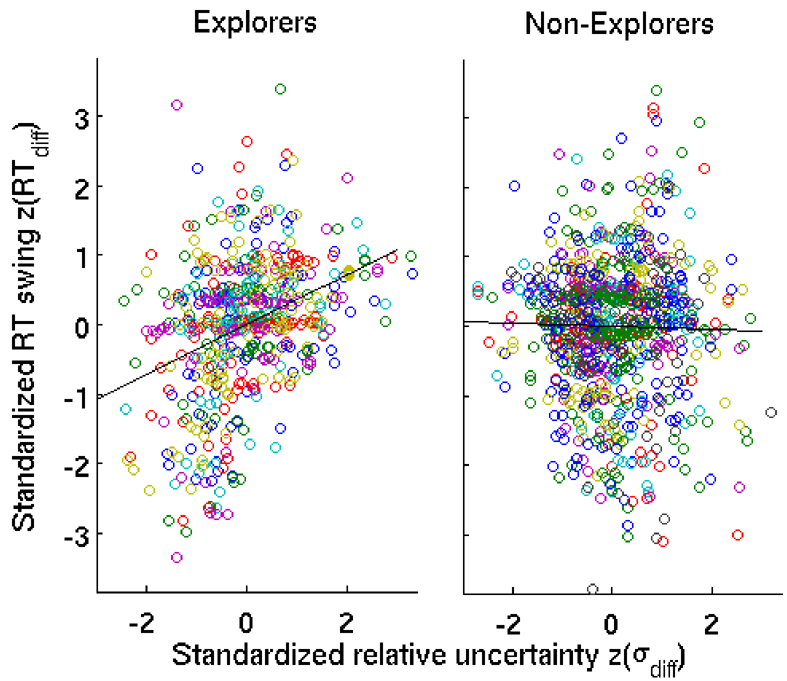


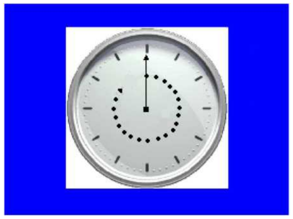
*

$$\mathbf{Explore(s,t)} = \epsilon\left[\sigma_{\delta|s,a=slow} - \sigma_{\delta|s,a=fast}\right]$$

Uncertainty-driven exploration

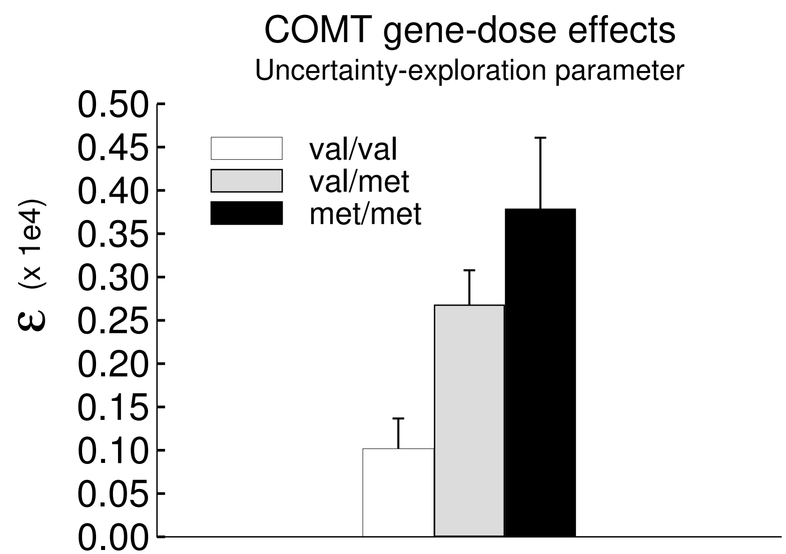






Frank et al '09, Badre et al 2012

Prefrontal gene effect on uncertainty-driven exploration

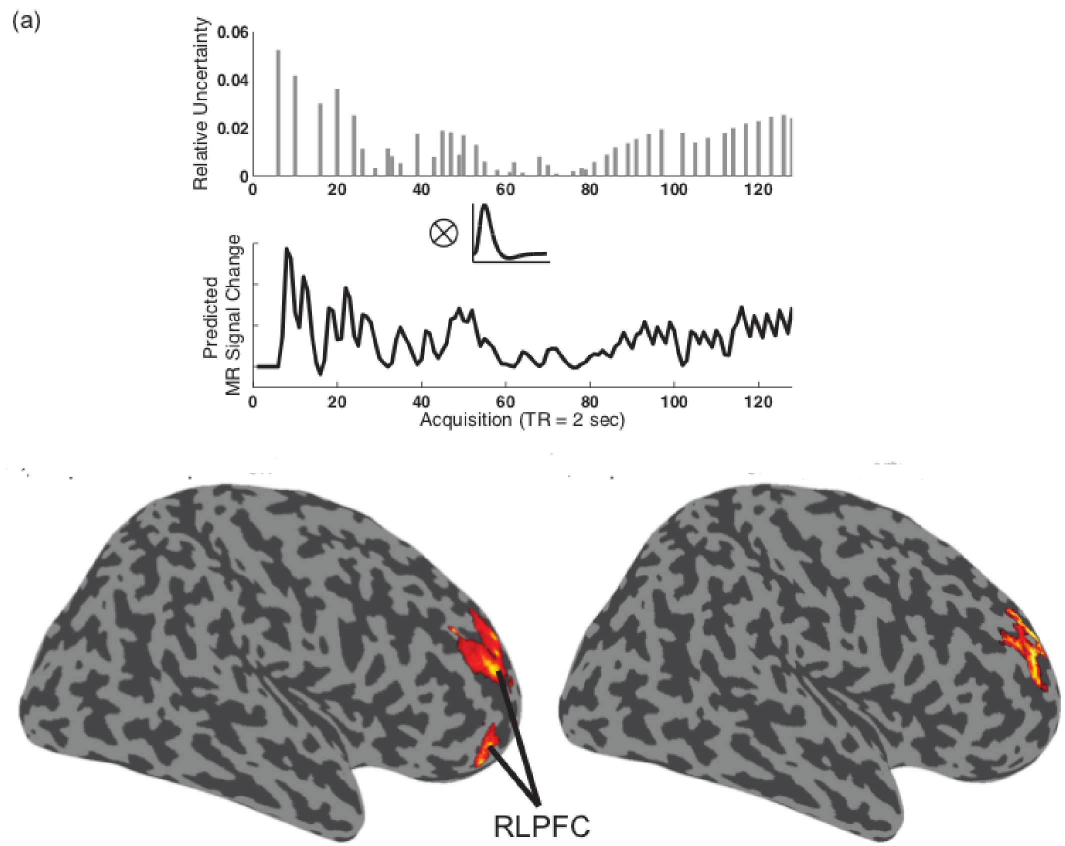


Frank, Doll, Oas-Terpstra & Moreno (2009, *Nature Neuroscience*)

and pharmacologically via tolcapone: Kayser et al 2015, *NPP*

Does the brain track relative uncertainty for exploration?

Does the brain track relative uncertainty for exploration?

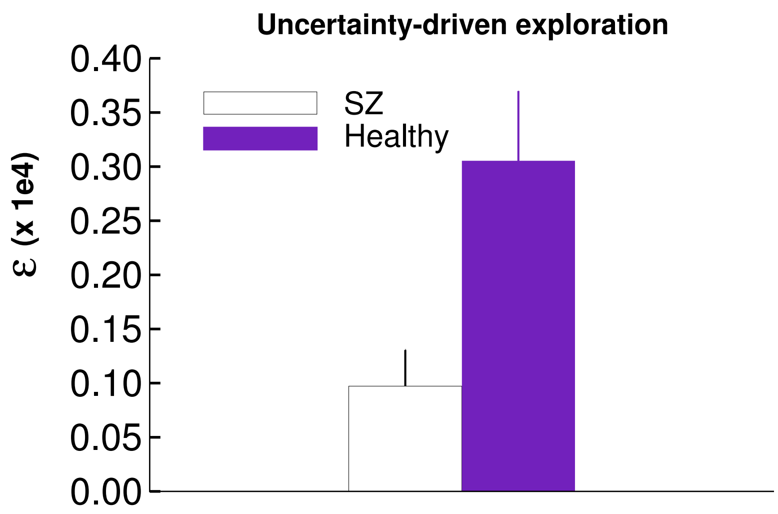


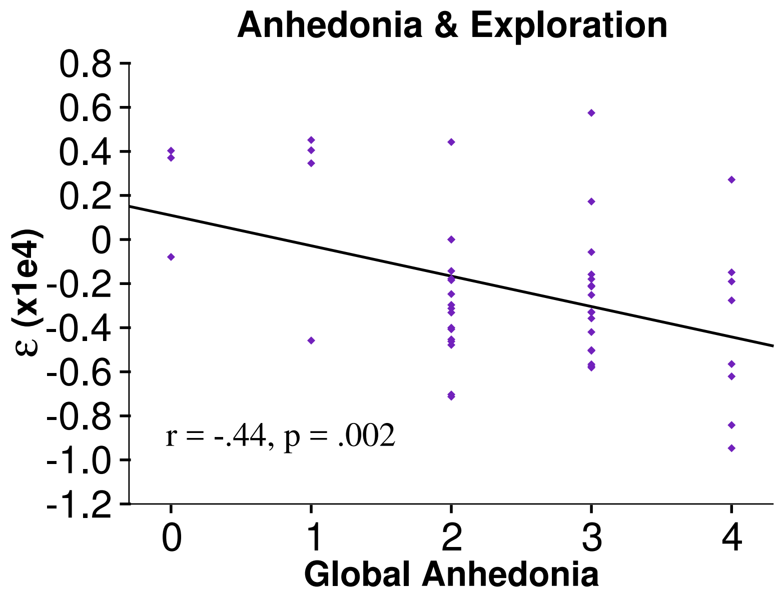
$\epsilon > 0$ ('explorers') *explorers > non-explorers*

Badre et al 2012, Neuron

Also with EEG: Cavanagh et al 2012 Cerebral Cortex

Anhedonia in schizophrenia is related to reduced uncertainty-driven exploration



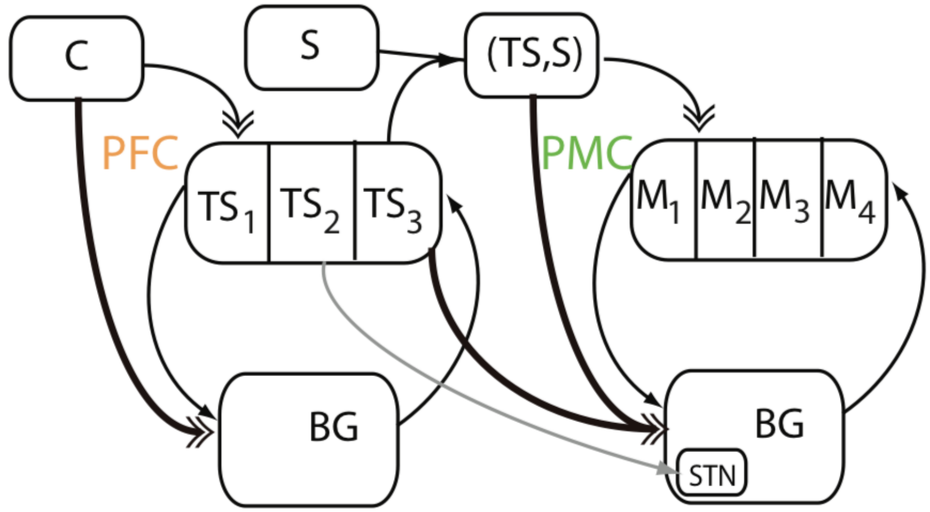


- Anhedonia: reward seeking, e.g. initiating social/recreational activitiesexperience pleasure

r = -.45, p = .002

Strauss et al 2011

Hierarchical interactions in BG-FC circuits: PFC & cognitive control influences on learning



Collins & Frank 2013; 2016; Frank & Badre 2012

Summary

- Dopamine modulates motivated learning and choice: costs vs. benefits
- Frontal Cortex⇒Subthalamic nucleus controls impulsive urges by dynamically adjusting *decision thresholds*, allowing more time to make high conflict decisions
- anterior prefrontal cortex needed for directed exploration to reduce uncertainty
- These mechanisms are dissociable and their disruption may lead to distinct types of impulsivity
- Hierarchical PFC-BG interactions support structured, generalizable task-set learning

Thanks To…

Anne Collins
Thomas Wiecki
Jim Cavanagh
Nick Franklin
Jeff Cockburn
Jeff Beeler
Jim Gold
Bradley Doll
Kevin Bath
Sean Masters
Julie Helmers
Alain Dagher
David Badre
Andrea Mueller

Lab for Neural Computation and Cognition

THE MICHAEL J. FOX FOUNDATION FOR PARKINSON'S RESEARCH

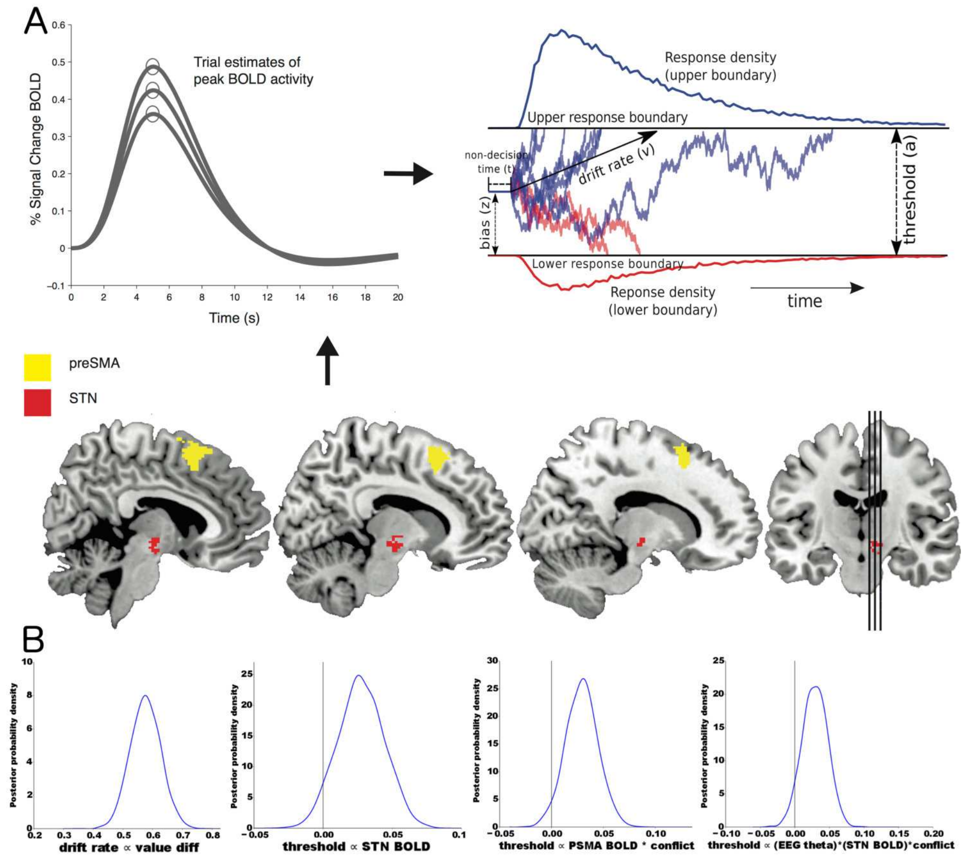
NIMH

NATIONAL SCIENCE FOUNDATION

cognitive, linguistic & psychological sciences

BROWN INSTITUTE FOR BRAIN SCIENCE

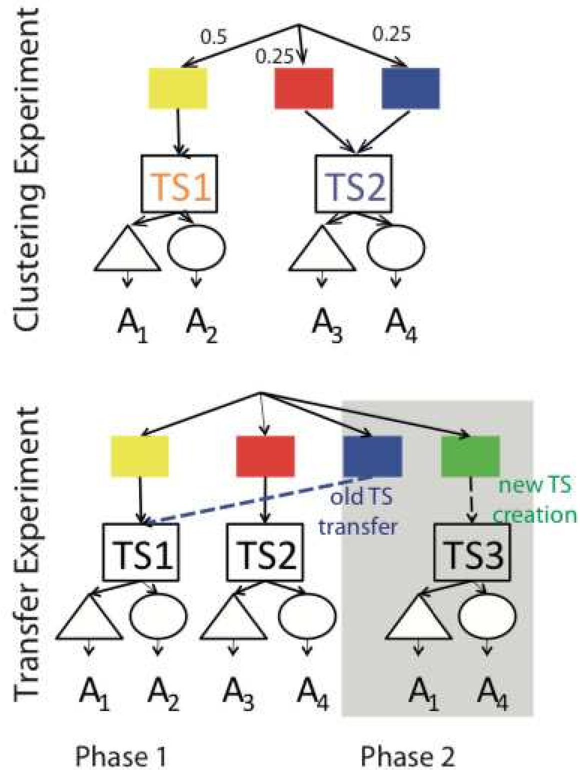
fMRI and EEG experiment



Frank et al 2015

also: STN spikes directly linked to threshold during conflict task, Herz et al 2016

Re-using and creating task-sets



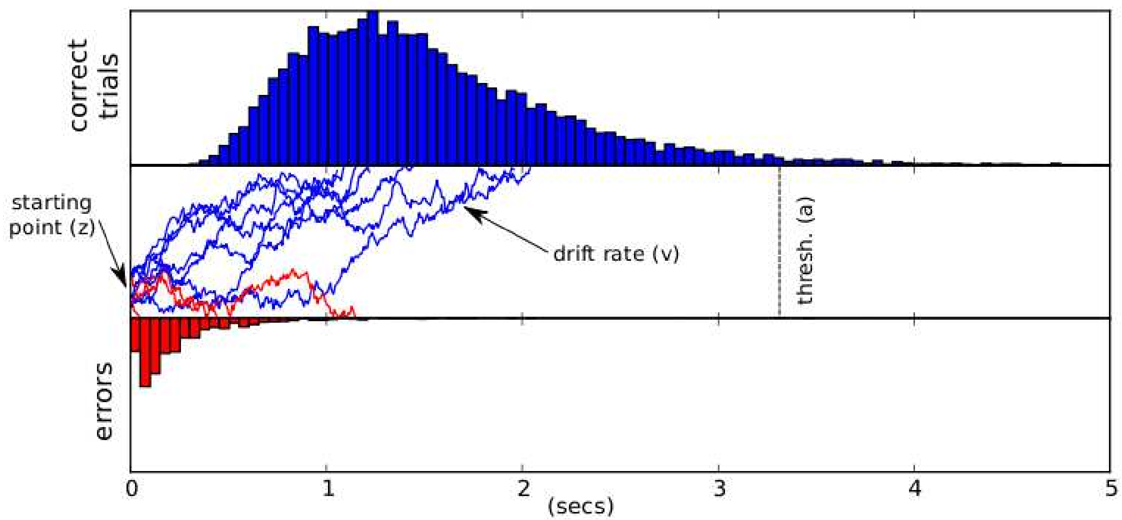
Collins & Frank 2013, *Psych Rev*; Collins et al, 2014 *J Neurosci*; Collins & Frank, in review

fMRI evidence: Badre & Frank 2012

Abstraction: the drift diffusion model

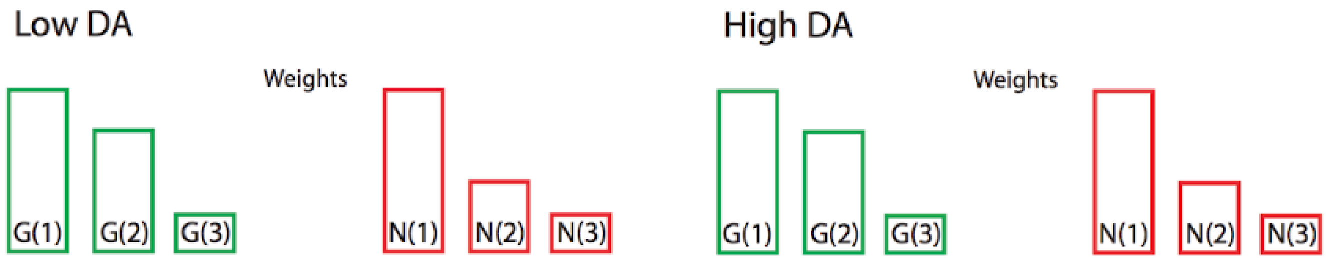
Drift-Diffusion-Model (DDM)

Models decision making as a noisy accumulation of evidence; once the diffusion process crosses one of two thresholds, a response is made.



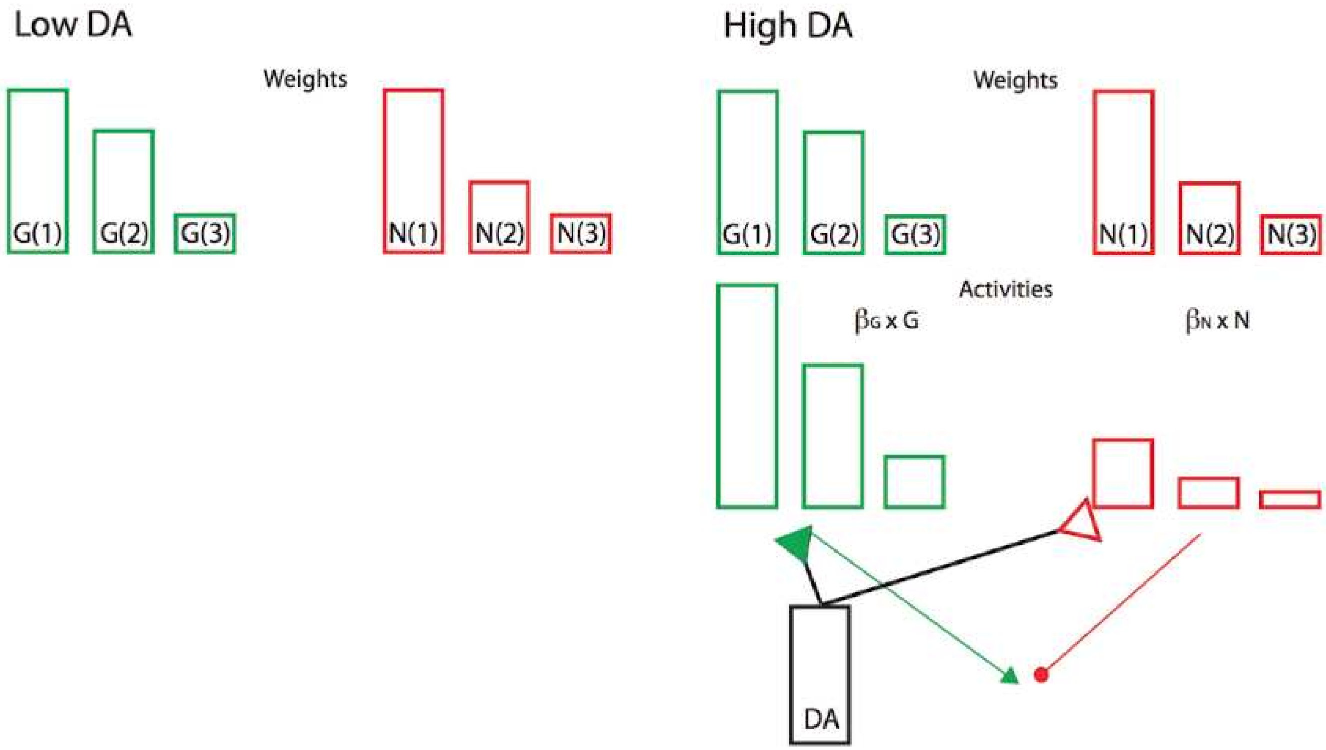
- Provides quantitative fits to decision choice proportions and RT distributions
- Allows estimation of decision threshold (a), separately from other factors (v, z, Ter)

Not just learning: dopamine and “choice incentive”



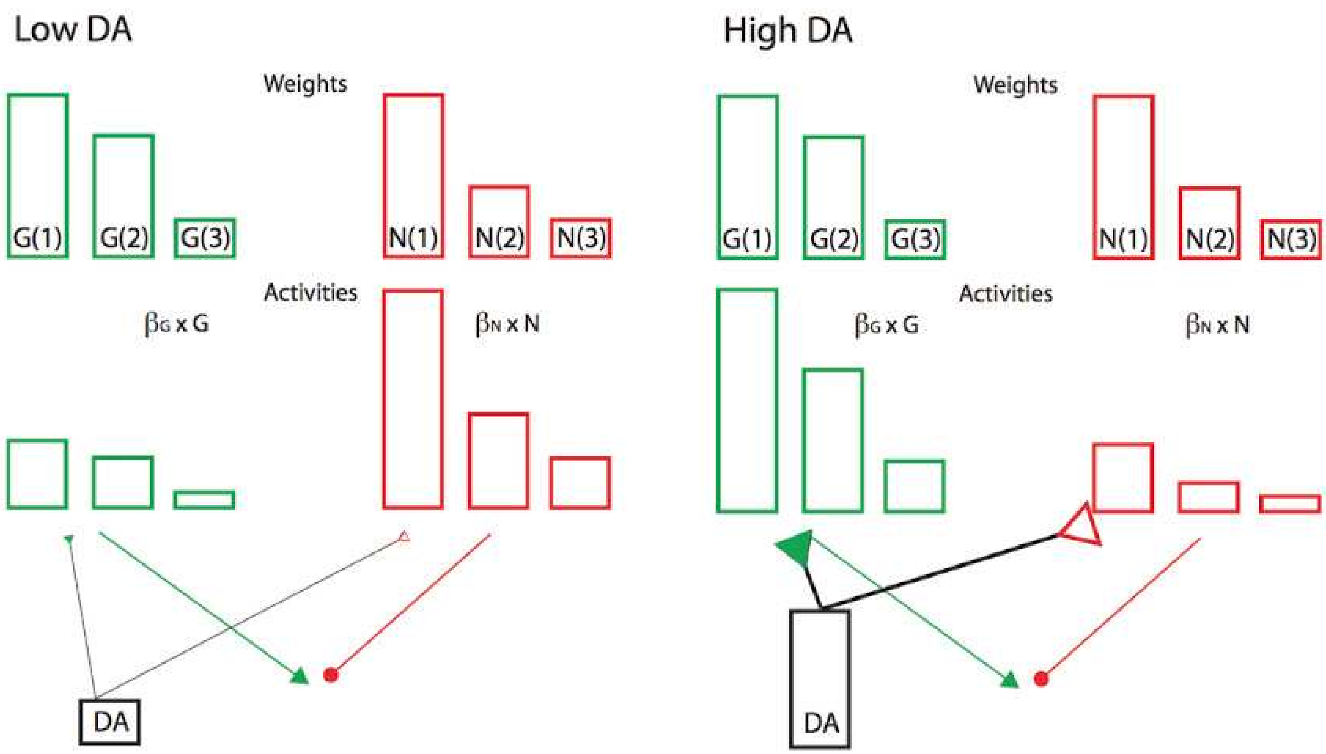
Collins & Frank, *Psych Rev*, 2014

Not just learning: dopamine and "choice incentive"



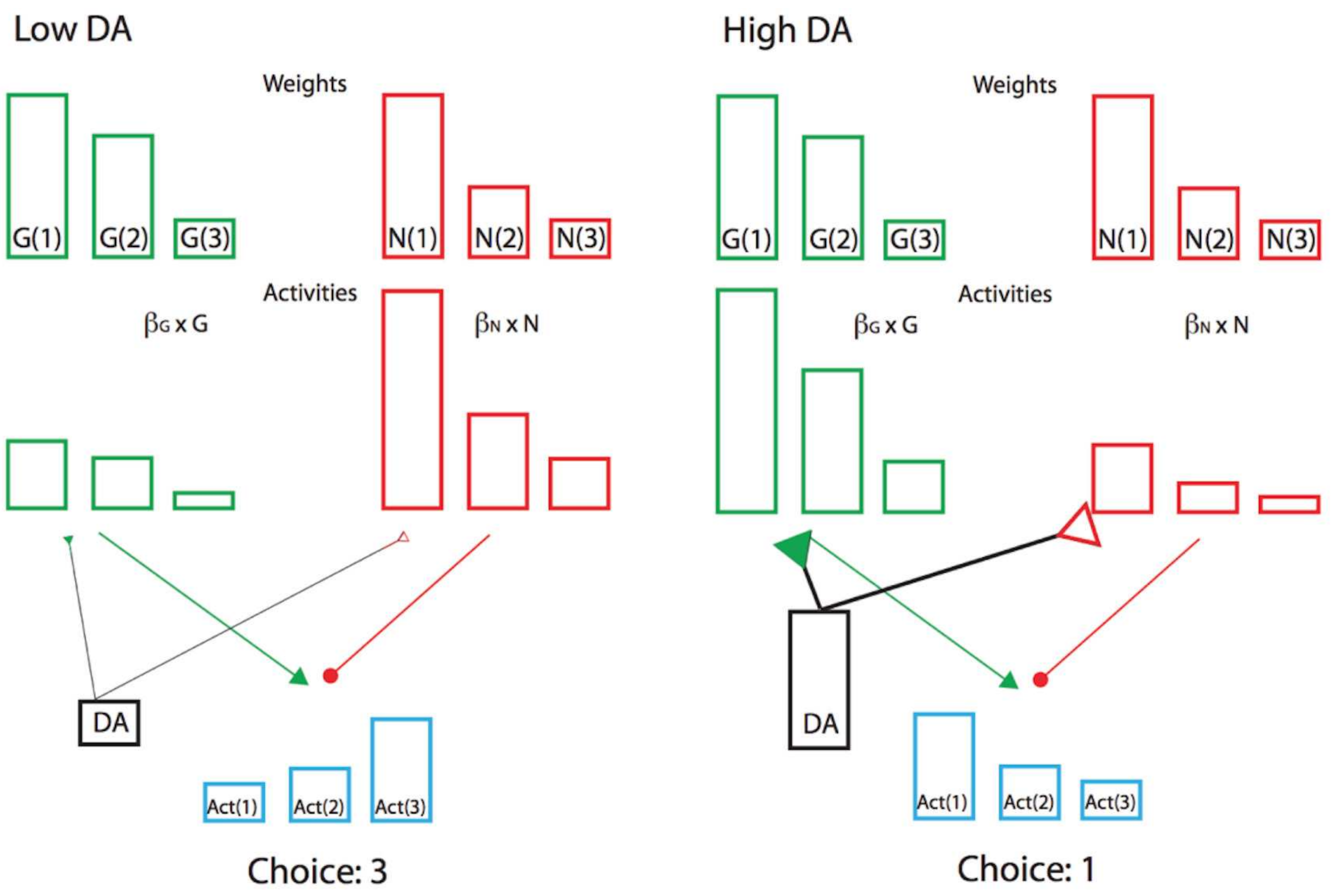
Collins & Frank, *Psych Rev*, 2014

Not just learning: dopamine and "choice incentive"



Collins & Frank, *Psych Rev*, 2014

Not just learning: dopamine and "choice incentive"



Collins & Frank, *Psych Rev*, 2014

DA affects risky choice, cost vs benefits in effort: Floresco, Rutledge, Salamone, etc.