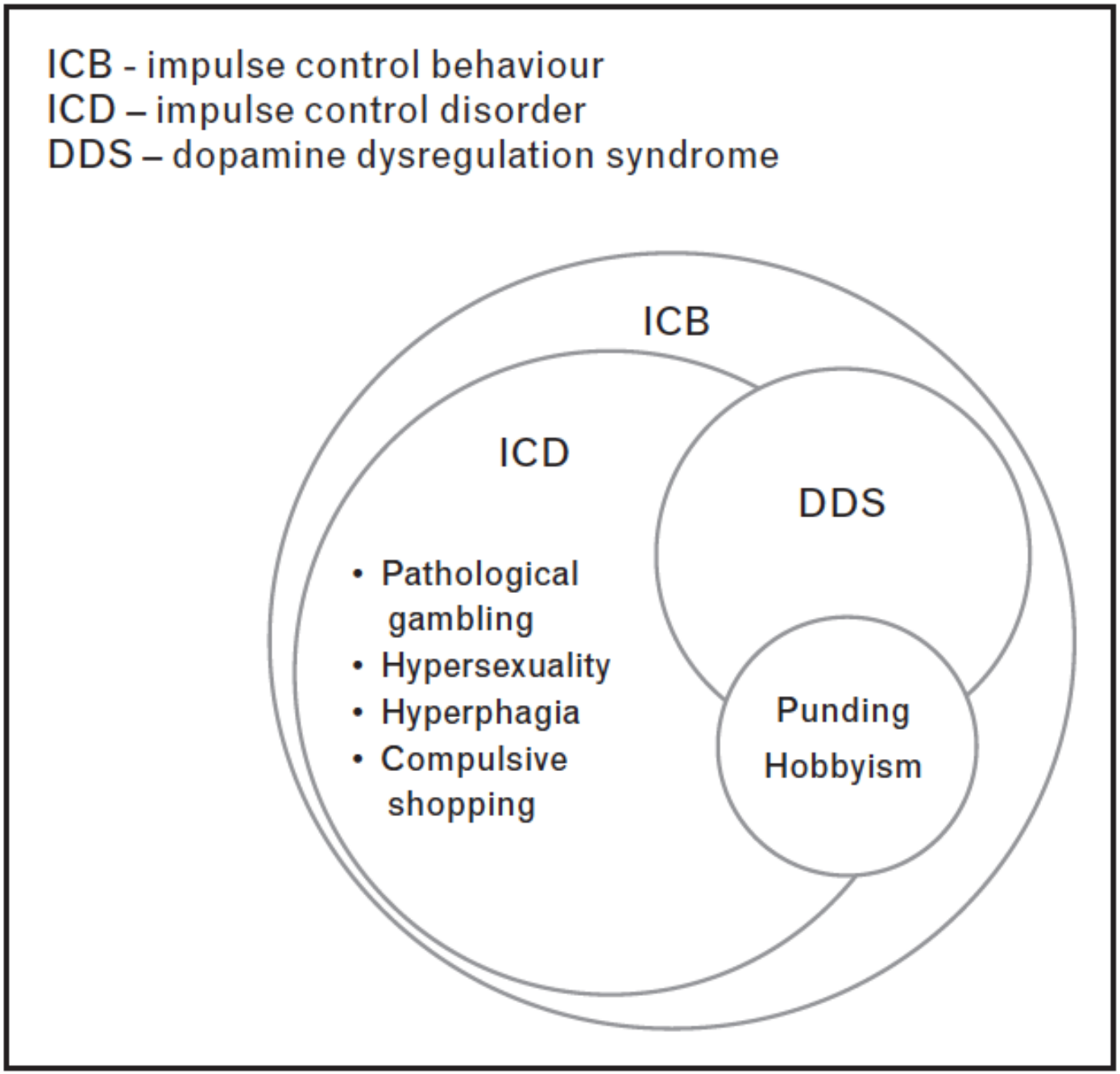
Le basi neurobiologiche del disturbo del controllo degli impulsi

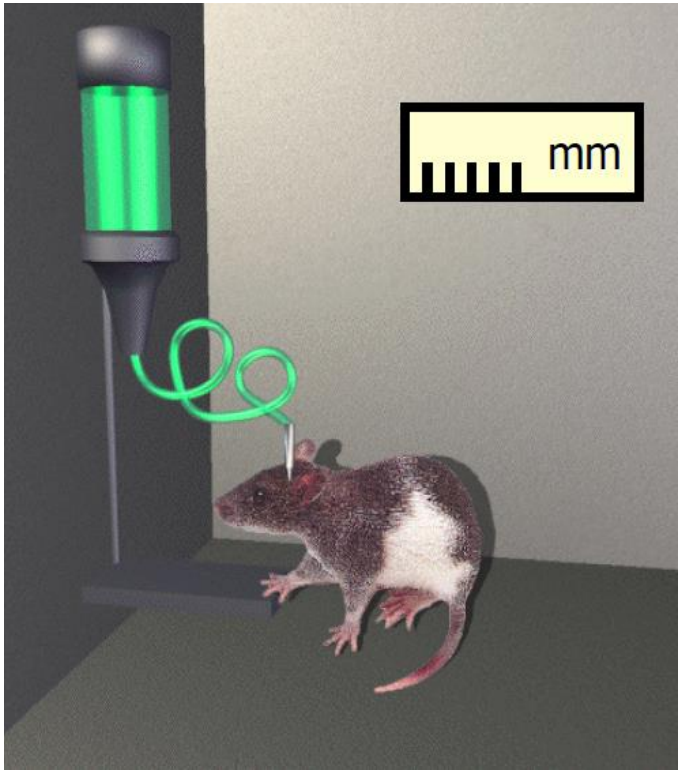
Enrico Grassi

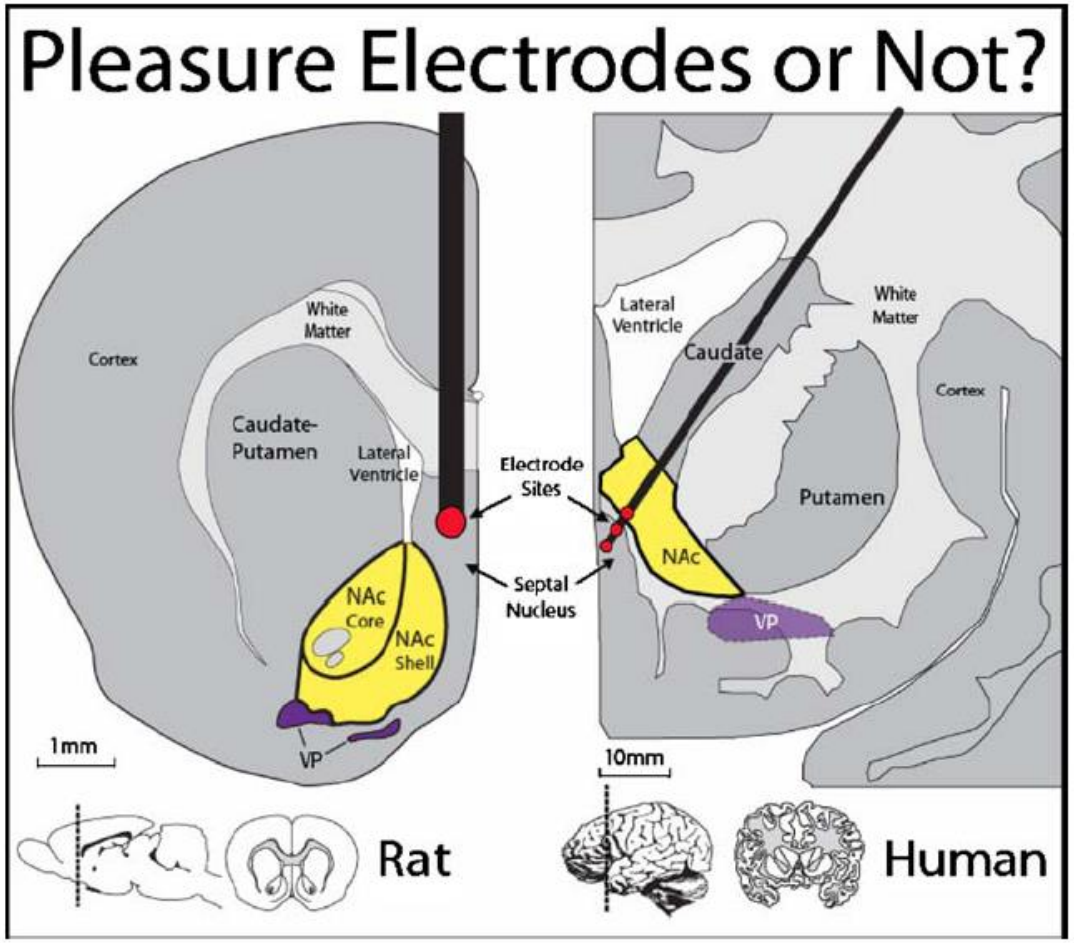
U.O. Neurologia
Ospedale di Prato

ICD occur in about 17% of individuals treated with dopamine agonist.



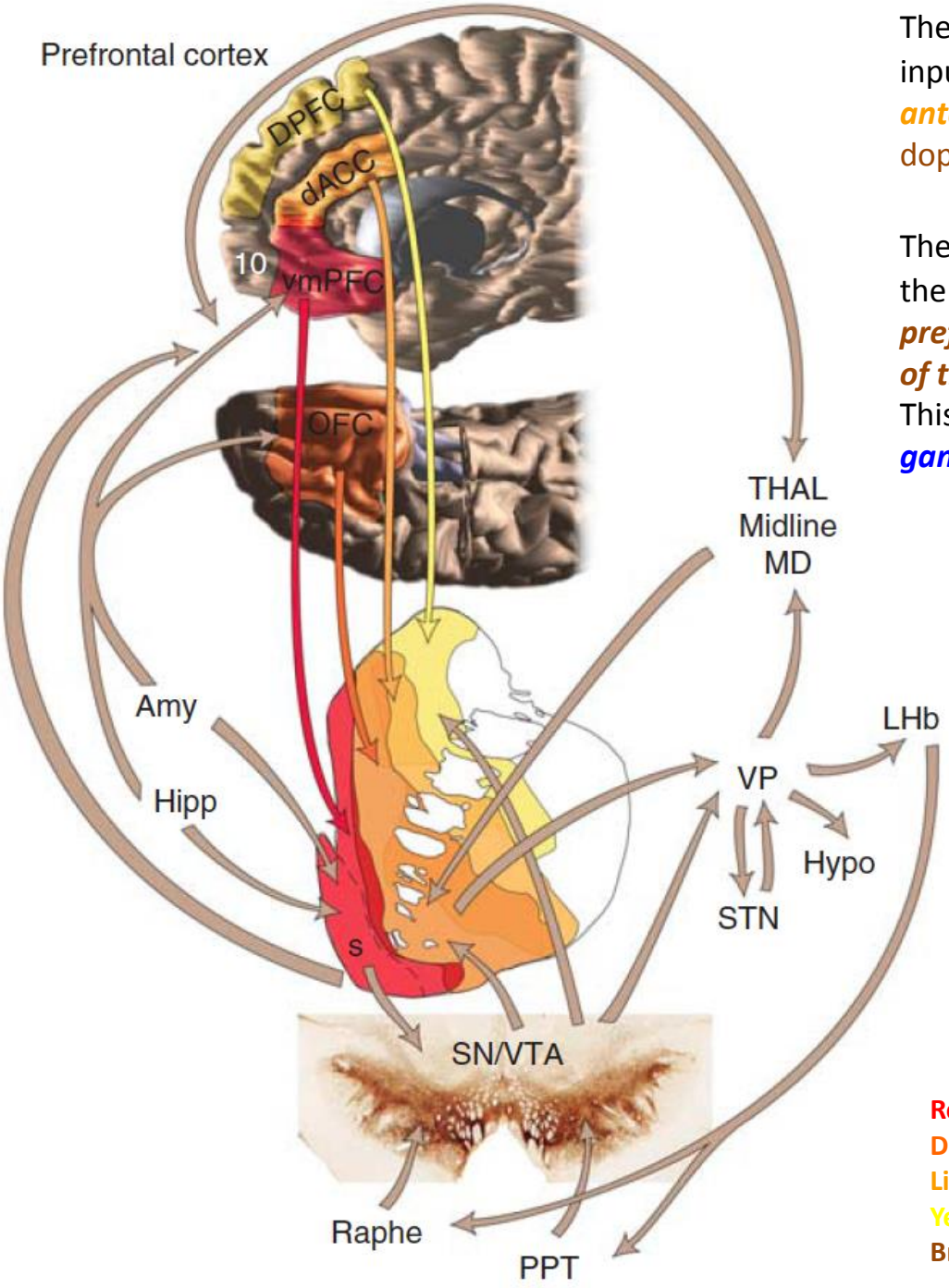
Just **over fifty years ago**, psychologists **James Olds and Peter Milner**, working at McGill University in Canada, carried out their pioneering experiments which discovered that rats would repeatedly -even up to **2000 times per hour** - press levers to receive tiny jolts of current injected through electrodes implanted in the region of the ***septum*** and ***Nucleus Accumbens***.
These powerful findings seemed to suggest that Olds and Milner had discovered the ***pleasure center in the brain***.





It was never clear from these patients' subjective reports that the electrodes did indeed cause real pleasure.

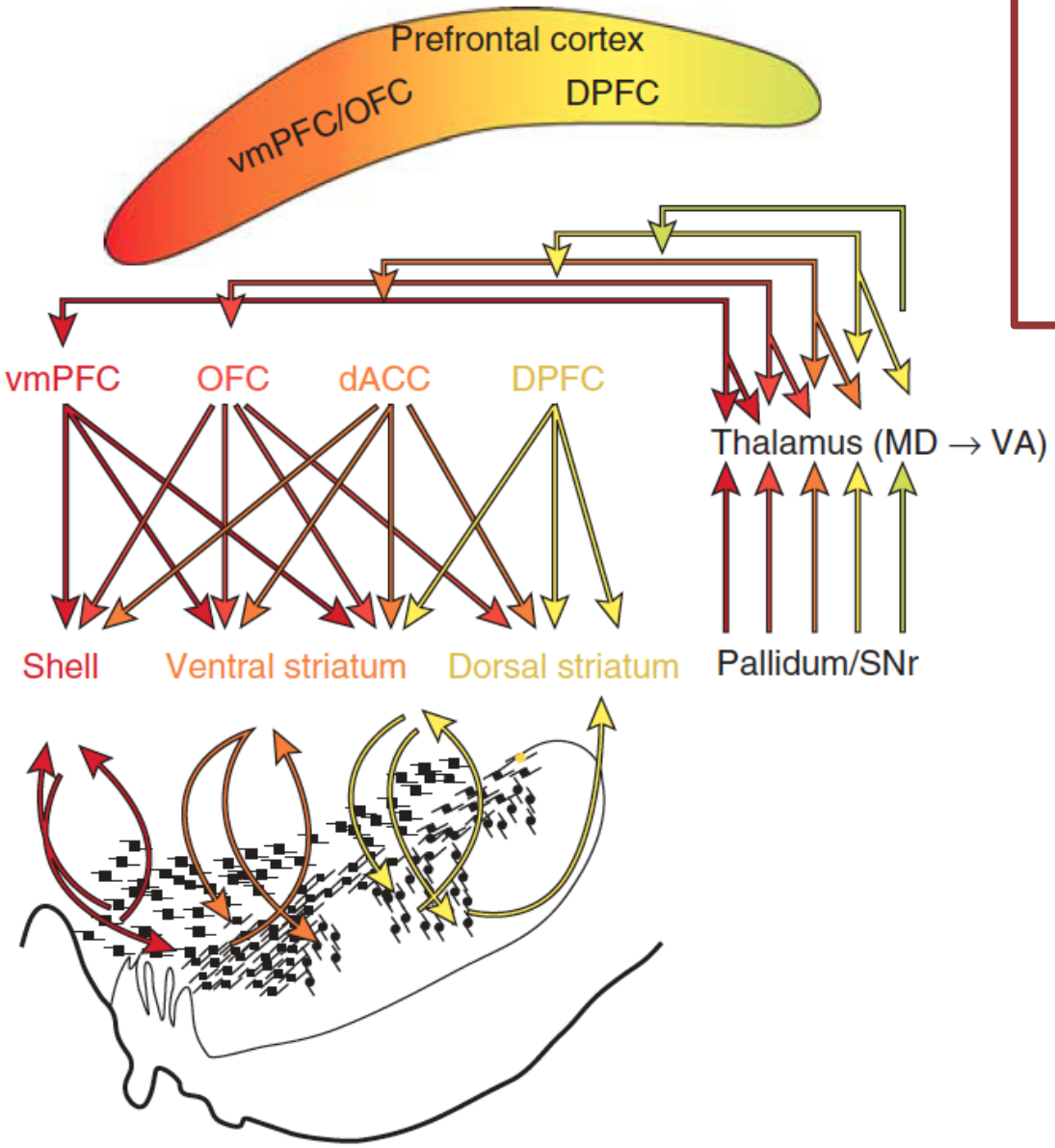
Some researchers today suggest that the electrodes never caused intense pleasure or ***'liking'*** after all, but only a form of ***'wanting'*** or motivation to obtain the stimulation



The ***VS receives*** its main cortical glutamatergic input from the ***orbital frontal cortex (OFC)*** and ***anterior cingulate cortex (ACC)*** and a massive dopaminergic input from the ***midbrain SN/VTA***.

The ***VS projects*** to the ***ventral pallidum (VP)*** and to the ***VTA/SN***, which, in turn, project back to the ***prefrontal cortex***, via the ***medial dorsal (MD) nucleus of the thalamus***.
This circuit is an integral part of the ***cortico-basal ganglia system***.

Red arrow: input from the **vmPFC**
Dark orange arrow: input from the **OFC**
Light orange arrow: input from the **dACC**
Yellow arrow: input form the **dPFC**
Brown arrows: other main connections of the reward circuit.



Reward *does not work in isolation, but its pathways interface with circuits that mediate* ***cognitive function*** *to affect* ***motor planning***.

To win at a ***card game***, desire is not sufficient. One has to understand the rules of the game, remember the cards played before executing the play. In addition, there is a complex interaction between the desire to put cards in play and the inhibition of impulse to play them too early.
Action plans developed toward obtaining a goal require a combination of ***reward processing***, ***cognitive planning***, and ***motor control***.

(1) Fibers from different prefrontal areas converge within subregions of the striatum.
(2) Through the organization of striato-nigrostriatal (SNS) projections, the VS can influence the dorsal striatum.
(3) The cortico-thalamic projection carries information from reward- related regions, through cognitive, and motor controls.

Review

Neuroscience & Biobehavioral Reviews

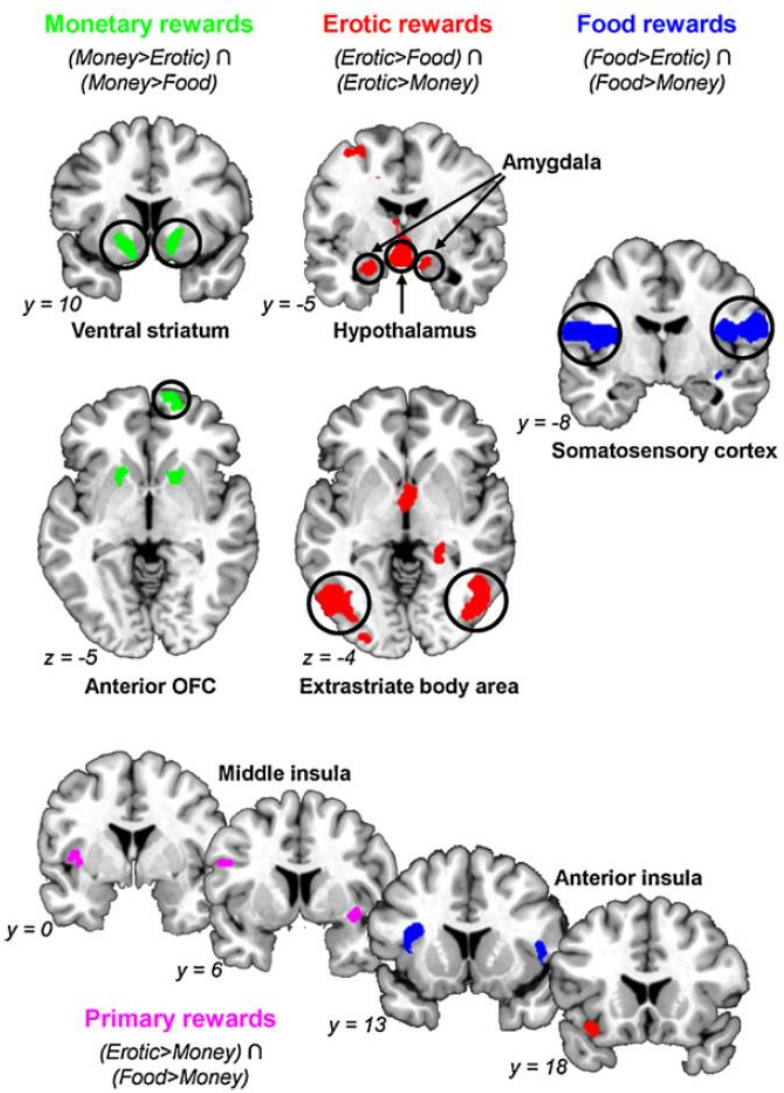
Volume 37, Issue 4, May 2013, Pages 681–696

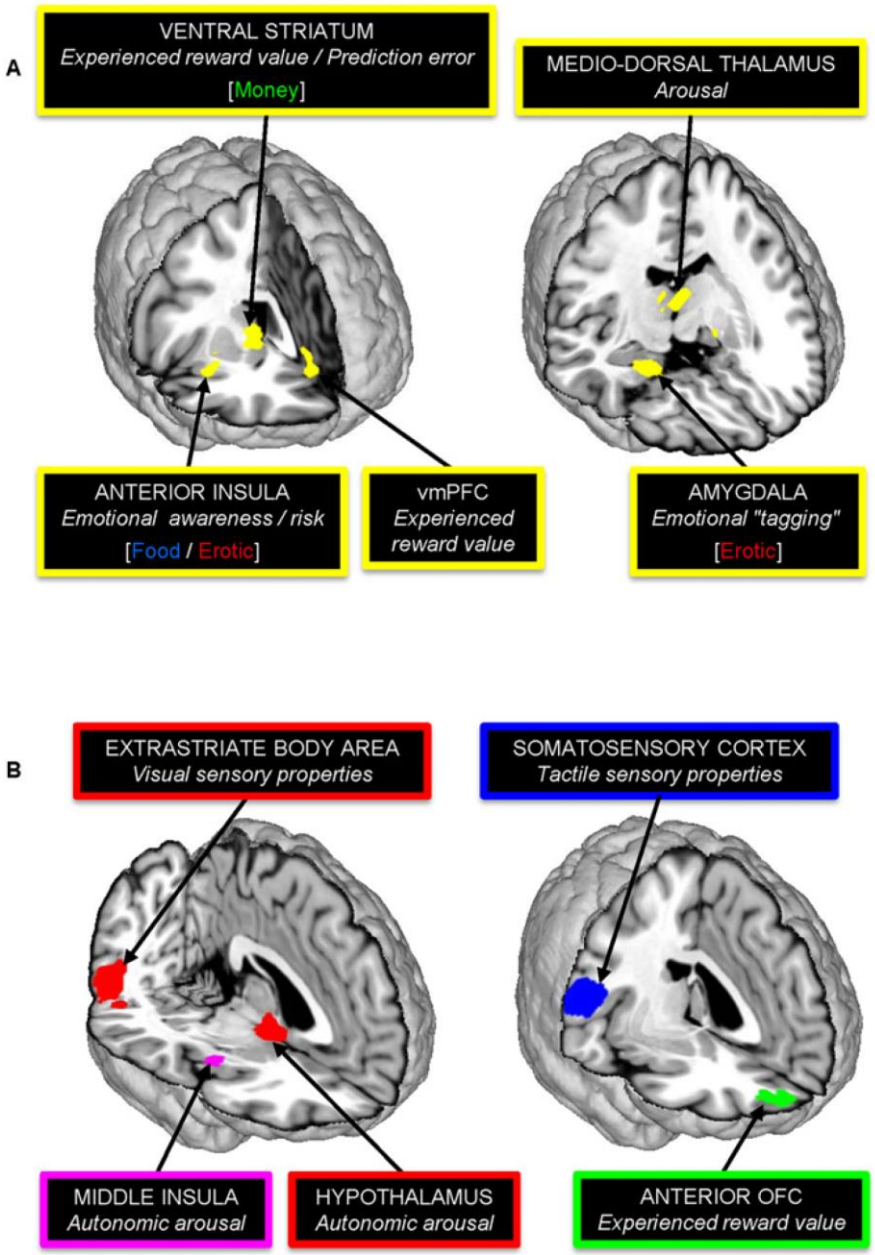
Processing of primary and secondary rewards: A quantitative meta-analysis and review of human functional neuroimaging studies

Guillaume Sescousse [1], Xavier Caldú [2], Bàrbara Segura [3], Jean-Claude Dreher*

Reward and Decision Making Team, Cognitive Neuroscience Centre, CNRS, 67 Bd Pinel, 69675 Bron, France

Meta-analysis using a **voxel-based approach**, of 87 studies (1452 subjects) comparing the brain responses to ***monetary***, ***erotic*** and ***food*** reward.





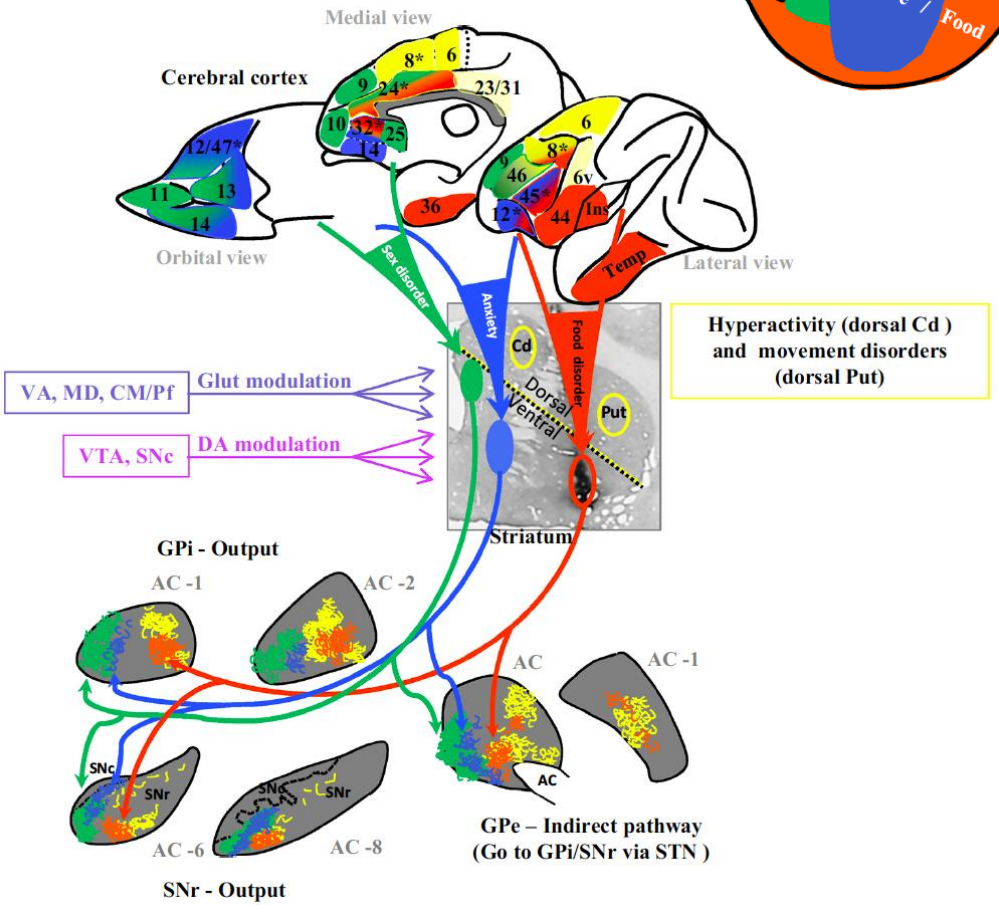
Brain Struct Funct
DOI 10.1007/s00429-014-0911-9

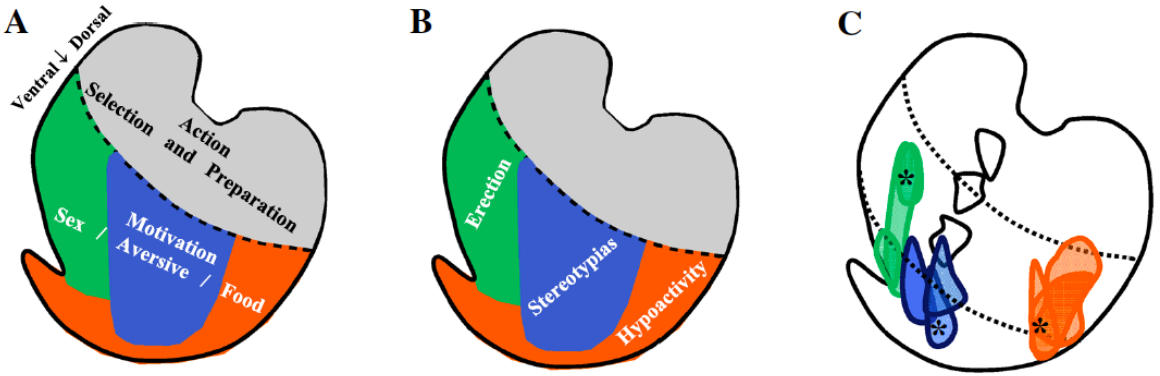
ORIGINAL ARTICLE

Cortico-basal ganglia circuits involved in different motivation disorders in non-human primates

Véronique Sgambato-Faure · Yulia Worbe · Justine Epinat · Jean Féger · Léon Tremblay

Received: 23 May 2014 / Accepted: 4 October 2014





Within the ventral striatum, three distinct topographically-organised circuits can be distinguished.

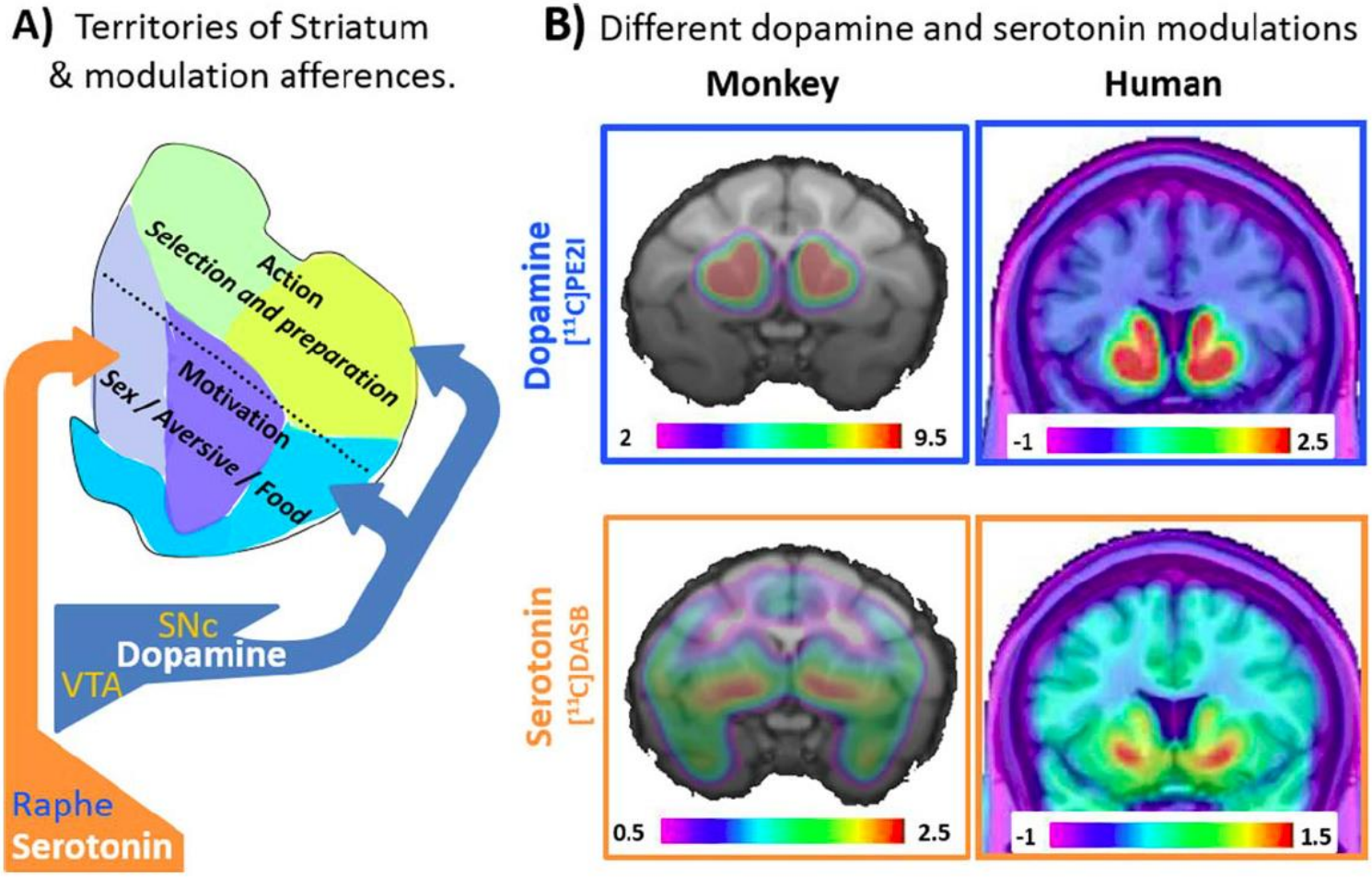
Pharmacological primate studies with local dysfunction induced by microinjections with **bicuculline**, a GABAa antagonist, show that different regions in the VS regulate different behaviours.

The medial region is associated with compulsive **sexual behaviours**,

the central region with **repetitive grooming** (eg, licking or biting fingers), and

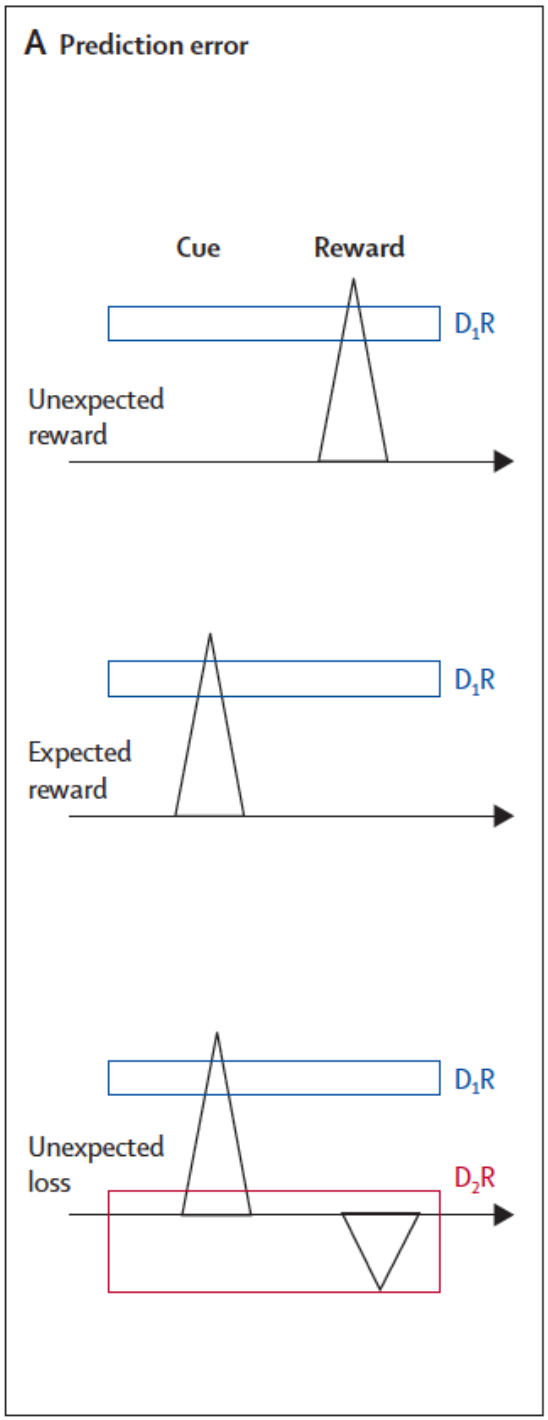
the lateral regions with hypoactivity linked to loss of **food motivation**.

Worbe Y, Baup N, Grabli D, et al. Behavioral and movement disorders induced by local inhibitory dysfunction in primate striatum. Cereb Cortex 2009;19: 1844-1856.



In monkeys and humans PET imaging obtained from reversible disturbances (by bicuculline injections) inside the anterior striatum strongly suggest a striatal partition into different areas involved in the ***selection and preparation of actions*** inside the **DORSAL PART**, whereas the **VENTRAL PART** involved in ***motivation***, divided into different domains, from the medial to the lateral striatum; (sexual, defensive, and food motivation).

Modulatory action, by ***serotonergic afferents*** from the raphe nucleus, could have a greater effect on motivational processes (ventral striatum), whereas ***dopaminergic afferents*** from the SNc and the VTA can have a greatest effect on all the functions owing to their wide distribution throughout the striatal territories (dorsal and ventral regions).



Novel rewards or unexpected rewards are associated with enhanced striatal phasic dopamine release, also known as **positive prediction error** (or the difference between what one receives and what one expects).

By contrast, losses or unexpected omissions of reward are associated with a phasic cessation of dopamine activity, also known as **negative prediction error**.

Phasic dopamine promotes ***learning from positive outcomes via D_1 receptors*** (so-called Go pathway) to facilitate movement and promotes ***learning from negative outcomes via D_2 receptors*** (so-called NoGo pathway) to inhibit movement.

Thus, **chronic stimulation of postsynaptic D_2Rs** might interfere with the detection of negative prediction errors or the representation of unfavourable outcomes, which could *decrease sensitivity to negative outcomes*.

Dopaminergic medications are hypothesised to ***enhance learning from positive feedback*** (ie, rewards) and ***impair learning from negative feedback*** (ie, losses); this relative imbalance presents as **IMPULSIVITY**.

Neuron
Article

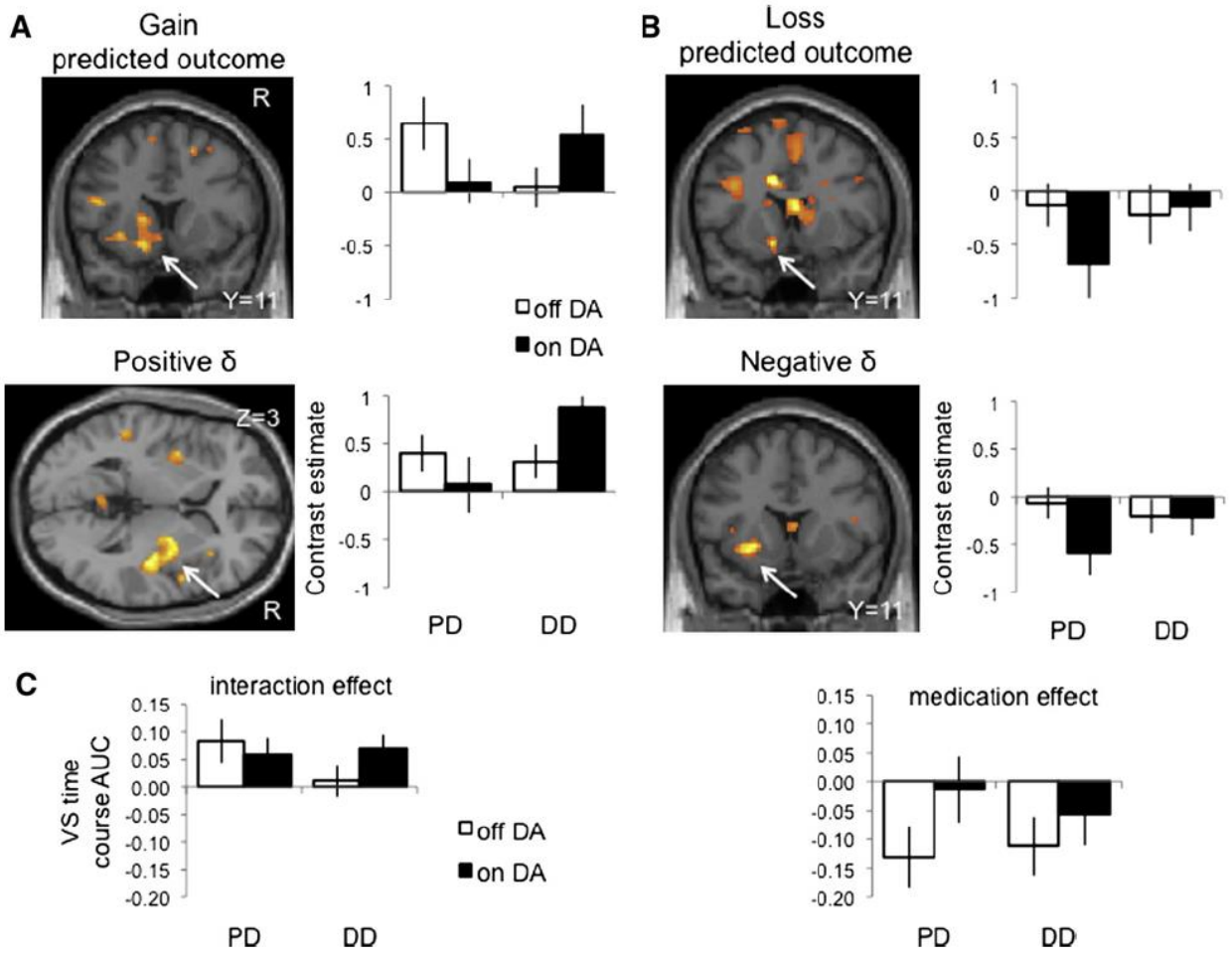
Neuron 65, 135–142, January 14, 2010

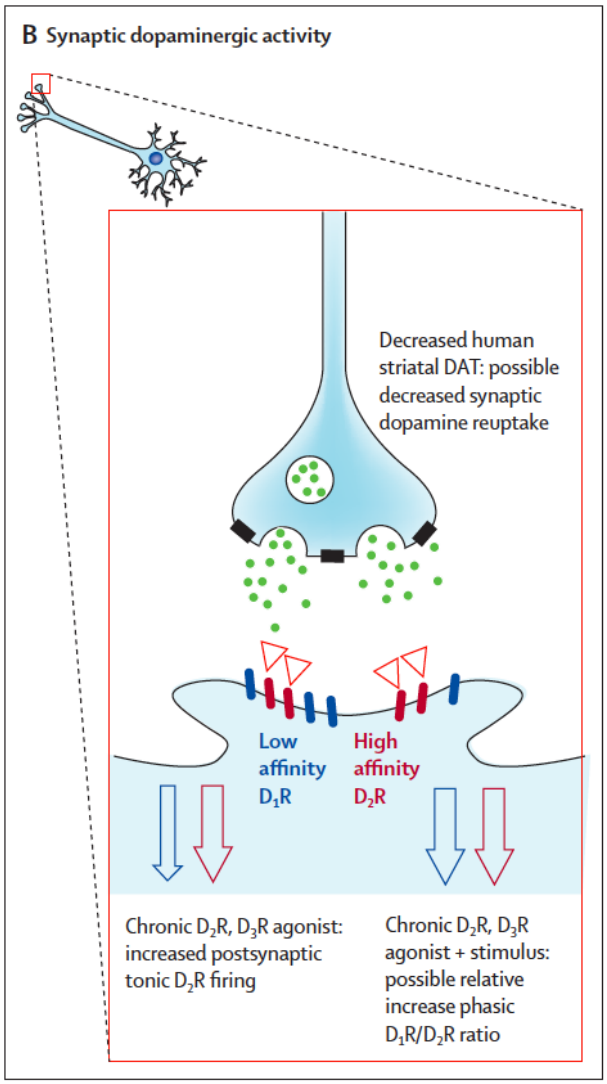
Mechanisms Underlying Dopamine-Mediated Reward Bias in Compulsive Behaviors

Valerie Voon,[1,*] Mathias Pessiglione,[2] Christina Brezing,[1] Cecile Gallea,[1] Hubert H. Fernandez,[3] Raymond J. Dolan,[4] and Mark Hallett[1]

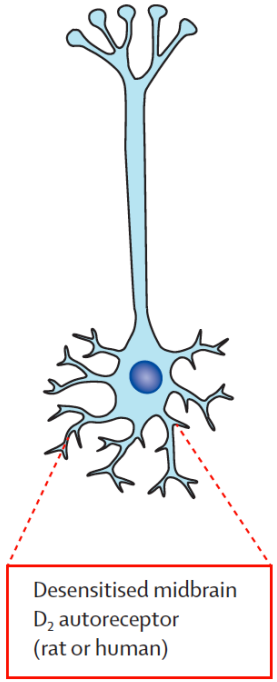
In this study patients with **PD and ICD on DA agonists** showed ***enhanced learning from rewards***, compared with patients without impulse control disorders only.

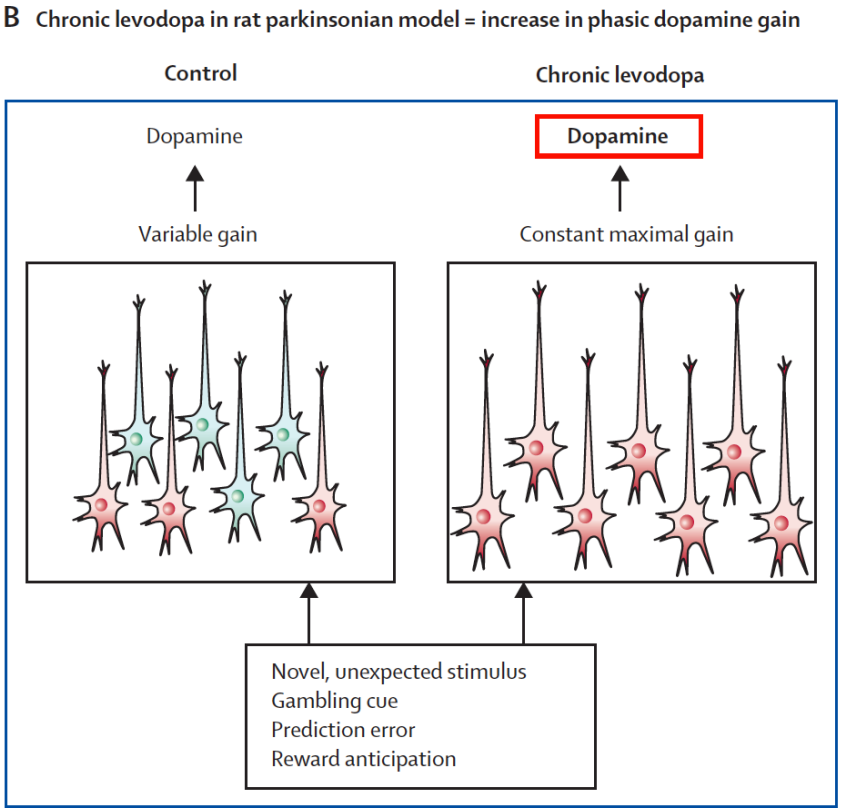
Patients with PD and ICD had ***higher ventral striatal activity*** to positive prediction error and expected reward when treated with DA agonists, compared with no dopamine agonist treatment.



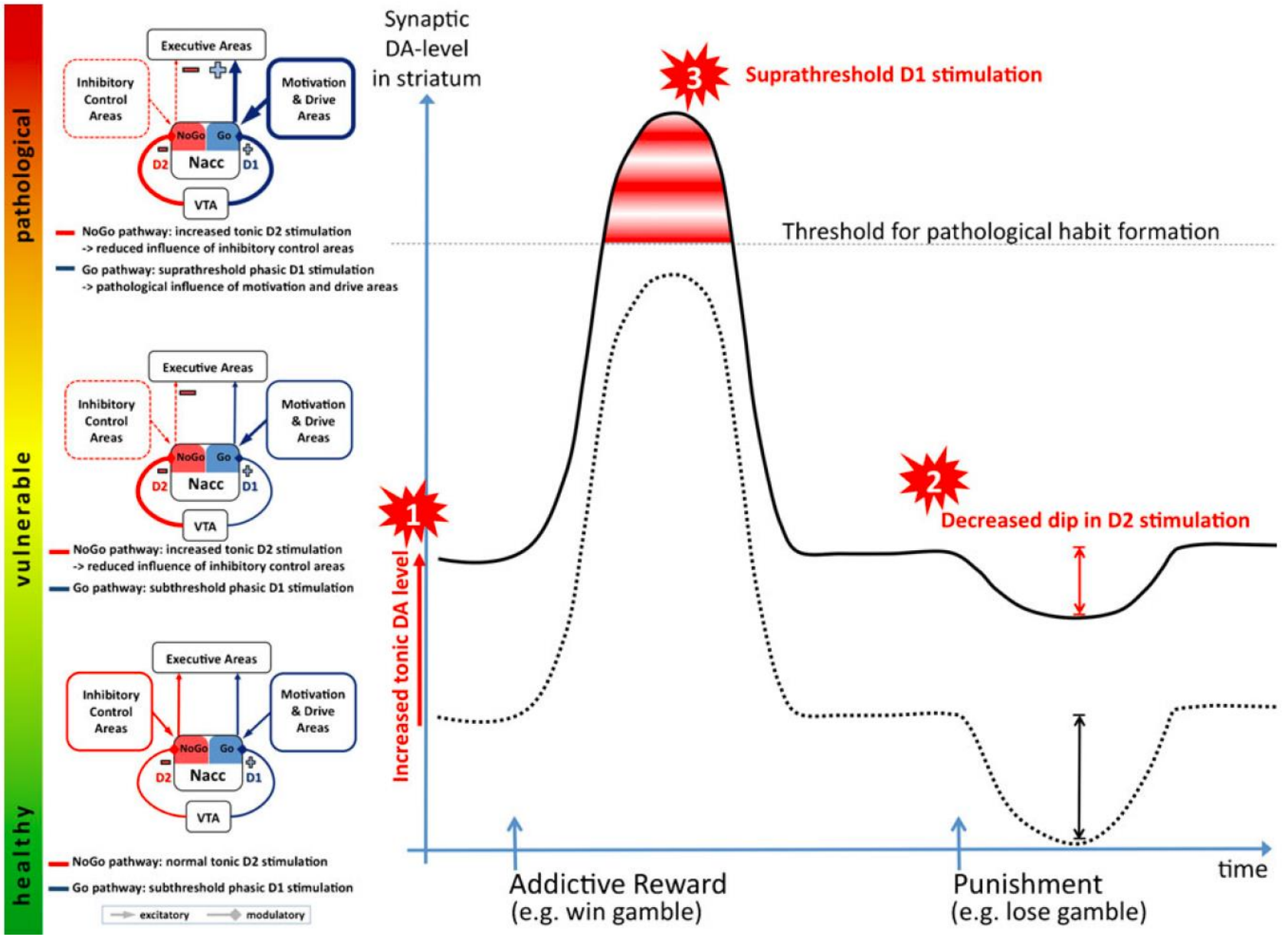


Chronic levodopa administration in a parkinsonian rodent model is associated with an increase in the proportion of spontaneously firing neurons (red neurons). This mechanism is mediated by ***desensitisation of D_2 autoreceptors***.



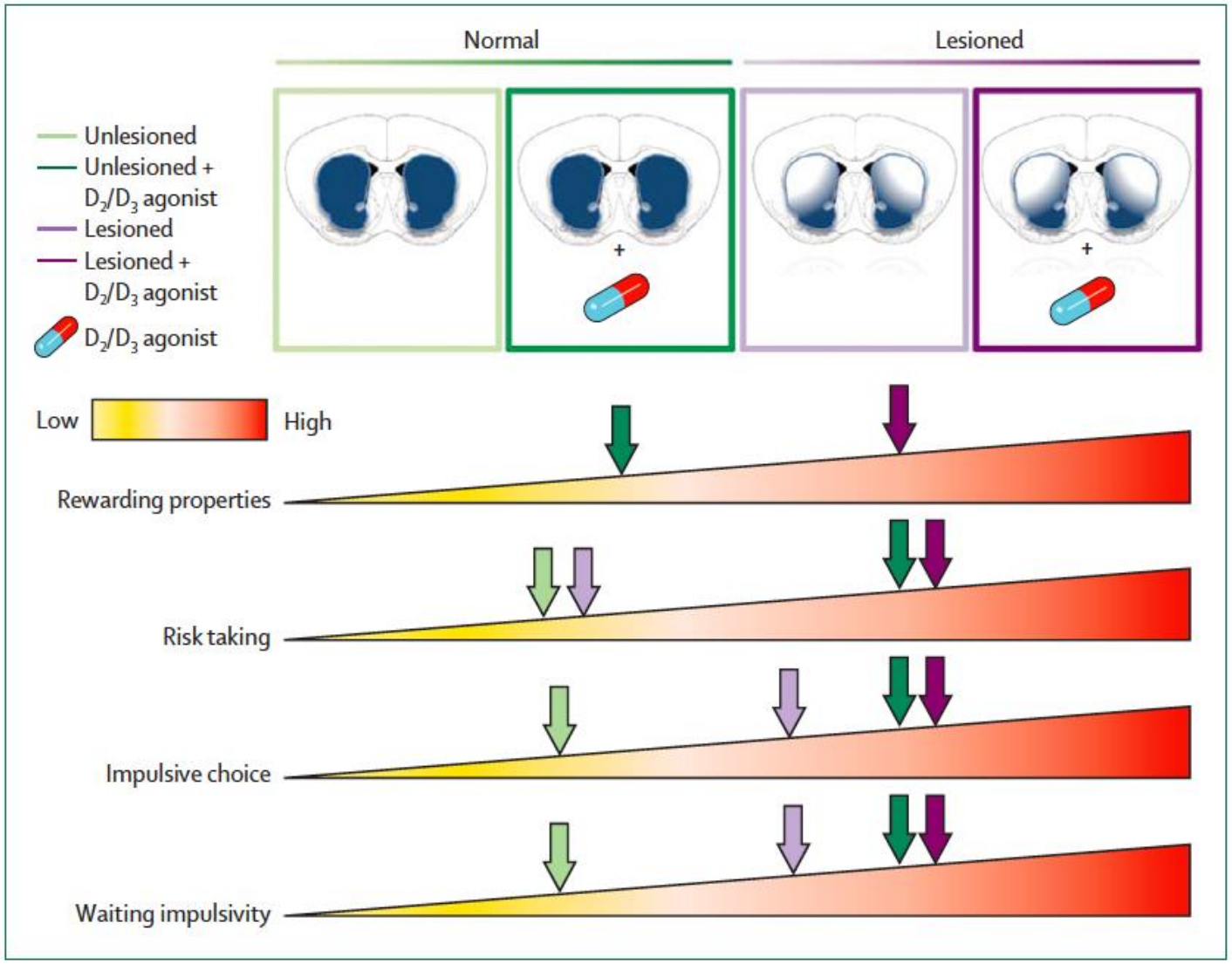


Changes in patients with PD and ICD on dopamine agonists with **decreased striatal dopamine transporter** (black square). **D_2R and D_3R agonists** (red triangle) **tonically bind to D_2R.**



1) Vulnerable individuals have increased tonic DA level, leading to reduced influence of inhibitory control areas via increased D2 receptor activation **2) increased D2 receptor activation interferes with the dip following punishments**; **3) adequate reinforcing stimuli** now lead to suprathreshold D1 receptor stimulation, which drives the formation of **pathological habits.**

Effect of parkinsonian nigrostriatal lesions and D_2or D_3 agonists on the rewarding properties of dopamine replacement therapy



Nigrostriatal degeneration results in an increase in the rewarding properties of D_2 and D_3 agonists. The nigrostriatal lesion might also contribute to the pathophysiology of impulse control disorders by increasing impulsivity. **Exposure to D_2 or D_3 agonists contributes to increased risk taking and impulsivity**.

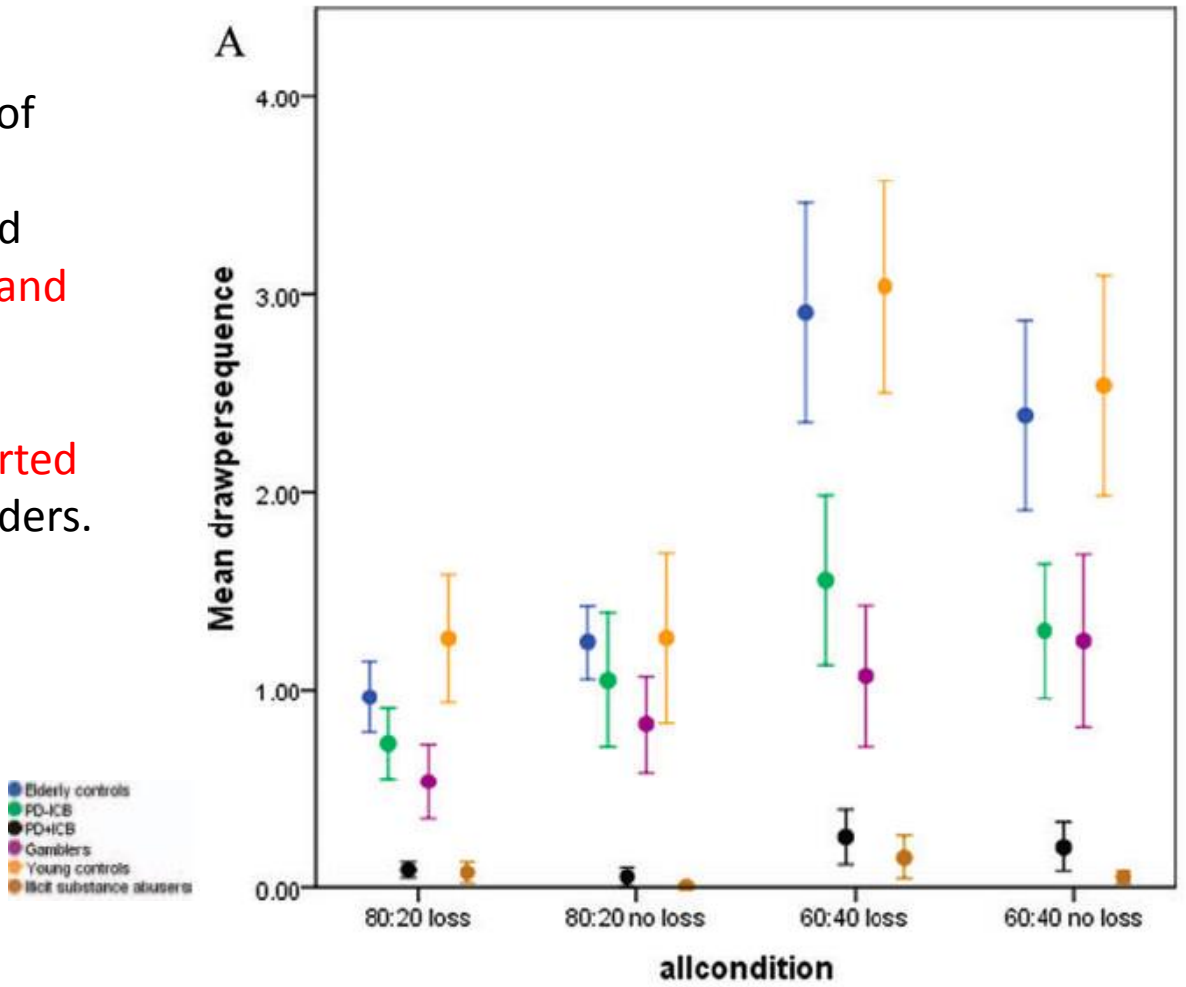
RESEARCH ARTICLE

Decision Making, Impulsivity, and Addictions: Do Parkinson's Disease Patients Jump to Conclusions?

Atbin Djamshidian, MD,[1] Sean S. O'Sullivan, MRCPI,[1] Yanosh Sanotsky, MD, PhD,[2] Stephen Sharman,[7] Yuriy Matviyenko, MD, PhD,[6] Thomas Foltynie, MD, PhD, MRCP,[3] Rosanna Michalczuk,[7] Iciar Aviles-Olmos, MD,[3] Ludmyla Fedoryshyn, MD, PhD,[2] Karen M. Doherty, MD, MRCP,[1] Yuriy Filts, MD,[5] Marianna Selikhova, MD, PhD,[1] Henrietta Bowden-Jones, MRCPsych,[8] Eileen Joyce, MD, PhD,[7] Andrew J. Lees, MD, FRCP,[1*] and Bruno B. Averbeck, PhD[3,4*†]

Movement Disorders, Vol. 27, No. 9, 2012

Reflection impulsivity—ie, rapid decision making or accumulation of little evidence before making a decision—was higher in medicated patients with Parkinson's disease and impulse control disorders than those without impulse control disorders, but similar to that reported for people with drug misuse disorders.



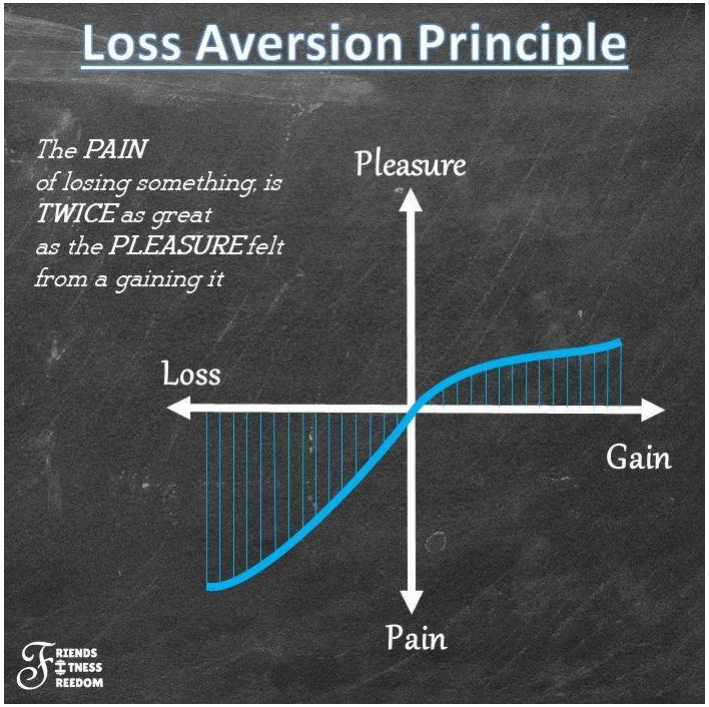
Risk-taking in PD patients with ICDs appears to be unrelated to LOSS AVERSION and may reflect underlying uncertainty about mapping future actions into rewards.

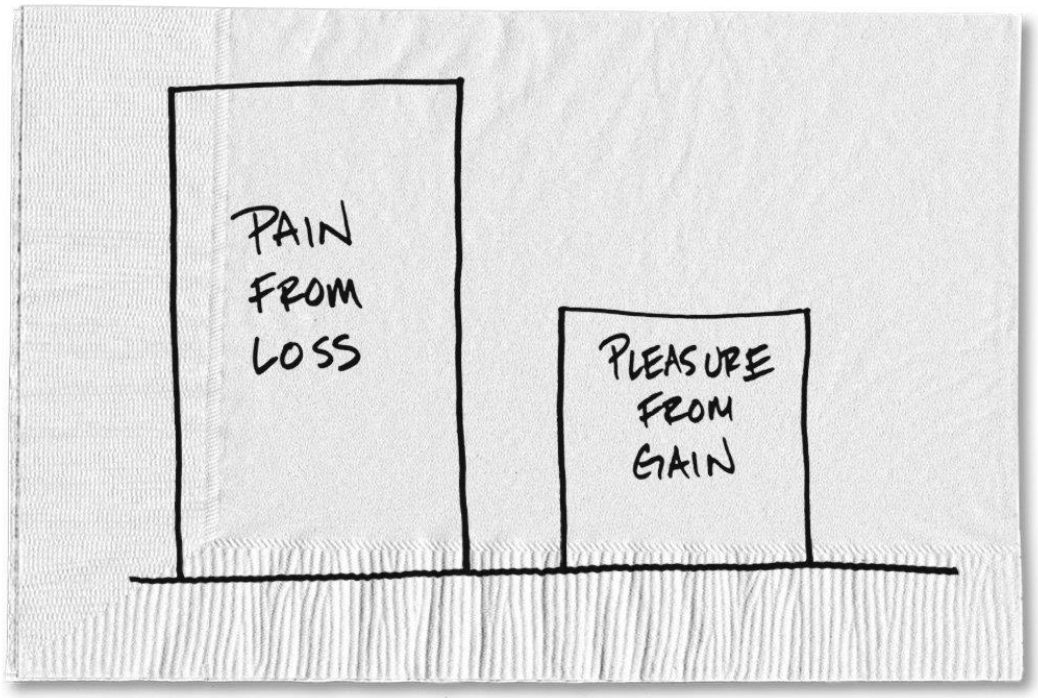
- **Greater reflection impulsivity** (or decisions under uncertainty without adequate information sampling),

- **Delay discounting** (preference of a small immediate over a larger delayed reward)

- **Reduced sensitivity to adverse outcomes** (negative prediction errors) during learning

- **Novelty seeking in the context of uncertainty**

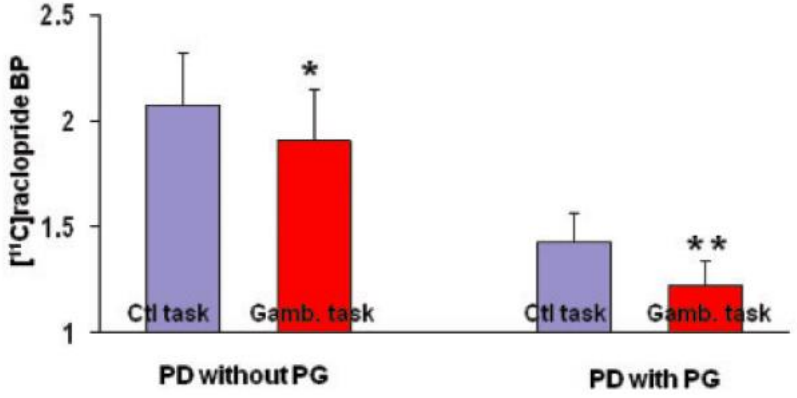




Increased striatal dopamine release in Parkinsonian patients with pathological gambling: a [^{11}C] raclopride PET study

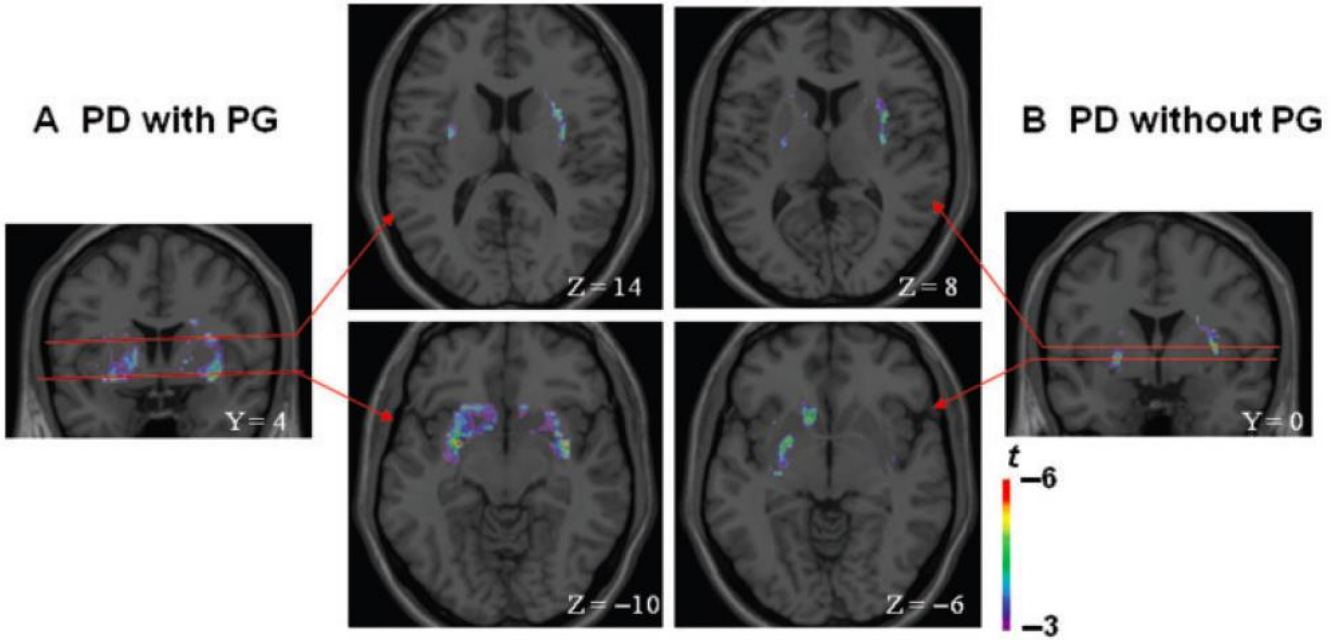
T. D. L. Steeves,[1,2] J. Miyasaki,[1] M. Zurowski,[3] A. E. Lang,[1] G. Pellecchia,[2] T. Van Eimeren,[2] P. Rusjan,[2] S. Houle[2] and A. P. Strafella[1,2,4]

After presentation of a reward, PET studies show **increased DA release** and **reduction in dopamine transporter in the ventral striatum** of PD patients with pathological gambling (PG) reflecting greater dopaminergic release.



11C] raclopride is sensitive to competition from endogenously released DA in response to drugs or tasks that induce dopamine release.

Thus, dopamine receptor abnormalities, including reduction in transporter proteins, support the hypothesis that PD itself may predispose patients to Impulsivity.



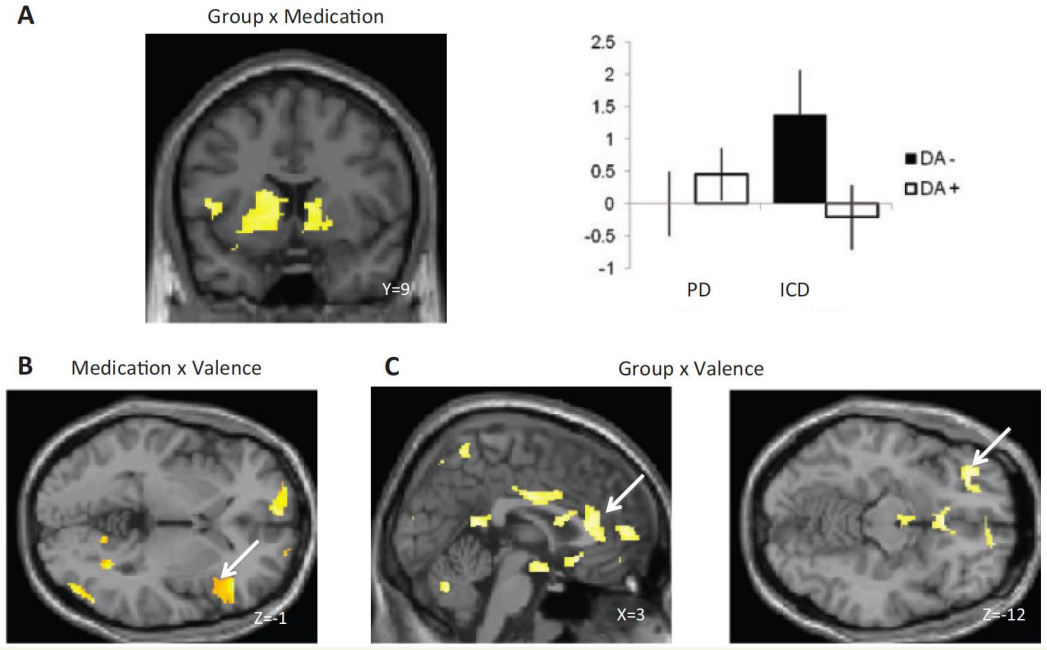
Dopamine agonists and risk: impulse control disorders in Parkinson's disease

Valerie Voon,[1,2] Jennifer Gao,[2] Christina Brezing,[2] Mkael Symmonds,[3] Vindhya Ekanayake,[2] Hubert Fernandez,[4] Raymond J. Dolan[3] and Mark Hallett[2]

Patients with impulse control disorder appear to have a bias towards risky choices independent of the effect of **loss aversion**.

Dopamine agonists increase risk taking in PD patients with ICDs, possibly by **impairing risk evaluation in the striatum**, that is accompanied by **lower ventral striatal, orbitofrontal, and anterior cingulate activity**

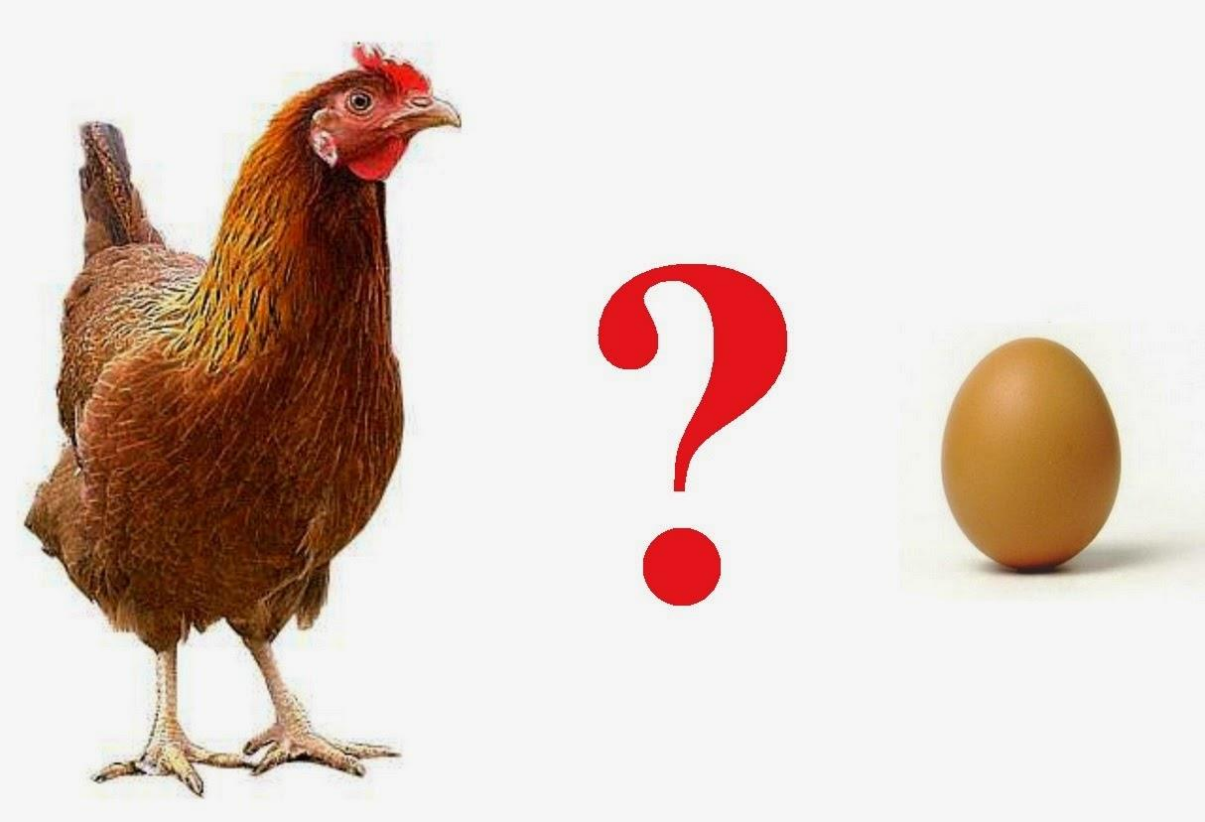
This could arise from a relative 'overdose' from exogenous dopaminergic agonists when **'on' medication**, and possibly even from endogenous dopamine (as compared with levels in the motor cortex to dorsal striatum) when **'off' medication**.



IMPULSIVITY is characterized by a ***preference for immediately available rewards*** (even if smaller), instead of delayed rewards (even if larger).

It has been postulated that impulsive-compulsive spectrum behaviors (ICBs) in Parkinson's disease (PD) reflect **overvaluation of rewards**, resulting from excessive dopaminergic transmission in the ventral striatum.

However, as the ventral striatum is also strongly implicated in **delay discounting**, an alternative explanation would be that, similar to stimulant-dependent individuals, PD patients with ICBs impulsively *discount future rewards*.



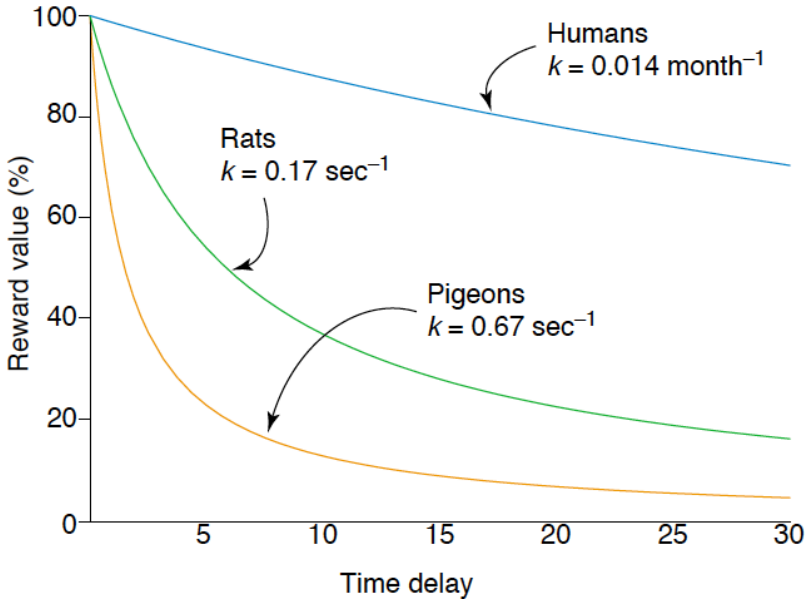
Separate Neural Systems Value Immediate and Delayed Monetary Rewards

Samuel M. McClure,[1]* David I. Laibson,[2] George Loewenstein,[3] Jonathan D. Cohen[1,4]

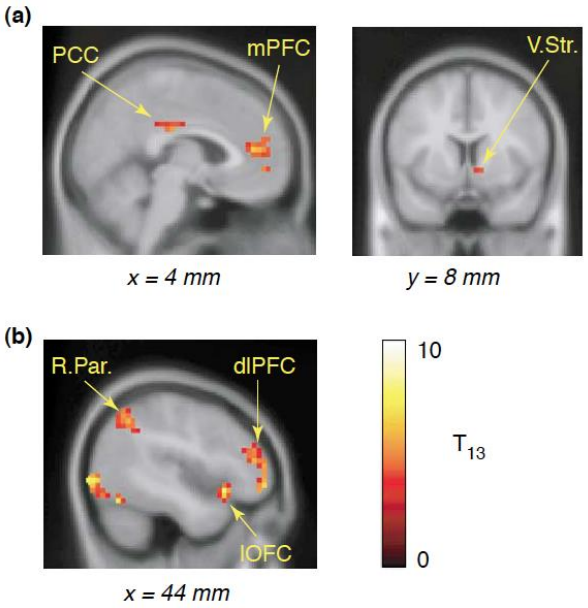
SCIENCE VOL 306 15 OCTOBER 2004

[1]Department of Psychology and Center for the Study of Brain, Mind, and Behavior, Princeton University, Princeton, NJ 08544, USA. [2]Department of Economics, Harvard University, and National Bureau of Economic Research, Cambridge, MA 02138, USA. [3]Department of Social and Decision Sciences, Carnegie Mellon University, Pittsburgh, PA 15213, USA. [4]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA 15260, USA.

Aesop's fable *"The Ant and the Grassohopper"*



The ***discounting rate*** describes how quickly the reward is devalued over time: for pigeons and rats, is a matter of seconds. For humans on the order of months rather than seconds



Immediate reward actively engage the ***ventral striatum***, as well as ***medial and orbitofrontal areas*** -areas rich in dopaminergic innervation- highly conserved across evolution, for the computation of utility that occurred in the absence of neural structures capable of sophisticated planning for the future. : **β System**

By contrast, the **δ System** areas of ***frontal and parietal cortex*** commonly associated with more abstract forms of reasoning and planning were consistently involved, independently of **when the reward became available**.

Neuropsychopharmacology (2010) 35, 2155–2164

www.neuropsychopharmacology.org

Intact Reward Learning but Elevated Delay Discounting in Parkinson's Disease Patients With Impulsive-Compulsive Spectrum Behaviors

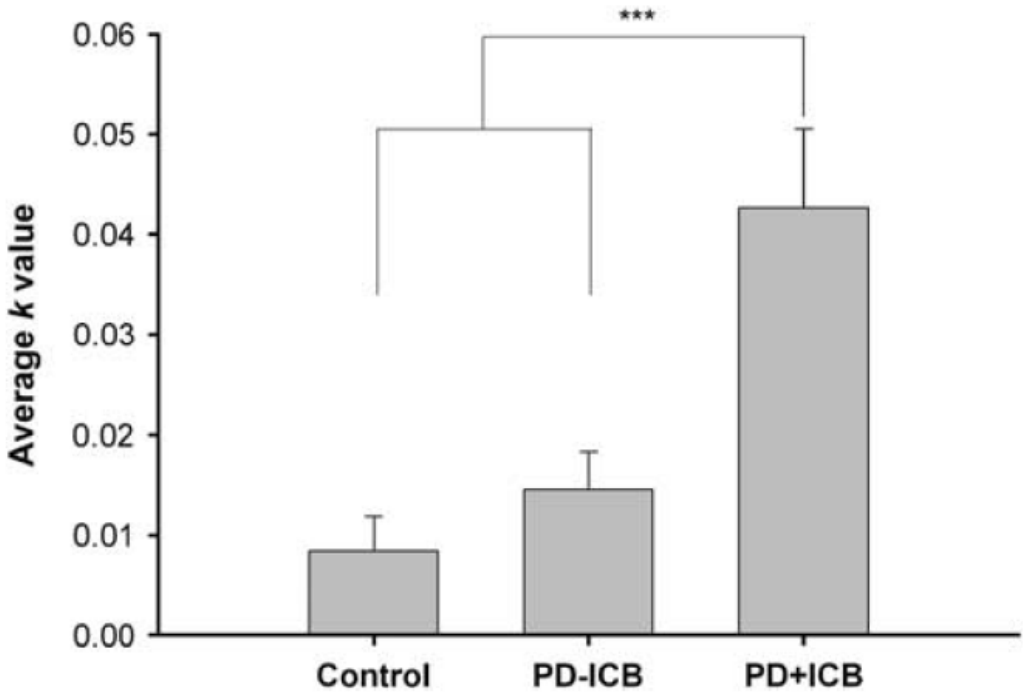
Charlotte R Housden[1], Sean S O'Sullivan[2], Eileen M Joyce[3], Andrew J Lees[2] and Jonathan P Roiser*[,4]

[1]Department of Psychiatry, University of Cambridge, Cambridge, UK; [2]Reta Lila Weston Institute of Neurological Studies, Institute of Neurology, University College London, Queen Square, London, UK; [3]Institute of Neurology, University College London, Queen Square, London, UK; [4]Institute of Cognitive Neuroscience, University College London, Queen Square, London, UK

PD patients with ICDs consistently demonstrate a strong preference for the small immediate rewards.

Disrupted delay discounting with intact reward incentive performance in PD patients presenting ICDs likely reflects *impairment in waiting for the delayed reward, rather than an enhanced incentive toward the small immediate reward*.

Suggesting that **dopamine agonists** may be associated with greater subjective devaluation of the delayed, higher reward magnitude.



NATURE NEUROSCIENCE VOLUME 8 | NUMBER 6 | JUNE 2005

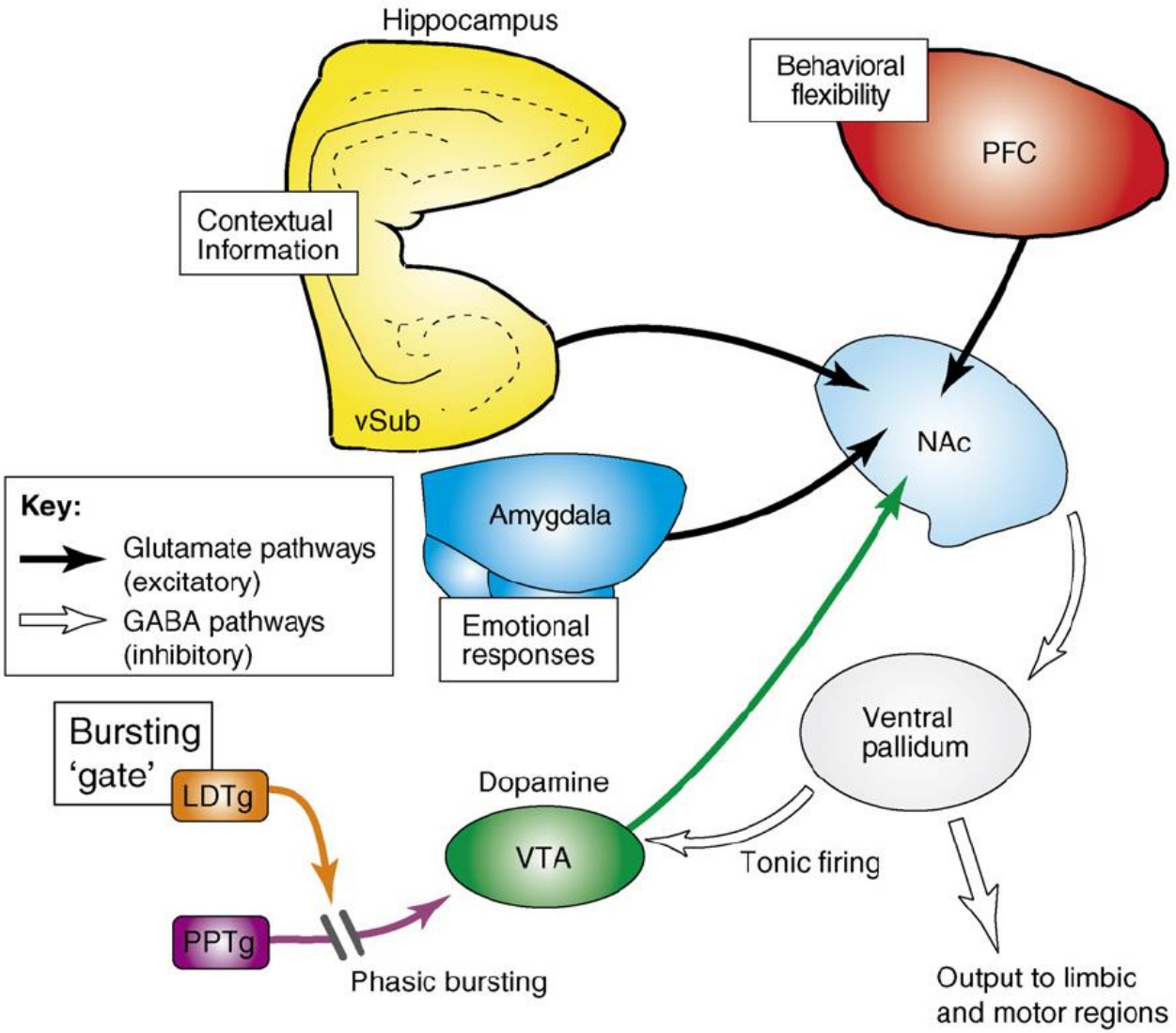
Dopaminergic modulation of limbic and cortical drive of nucleus accumbens in goal-directed behavior

Yukiori Goto & Anthony A Grace

The ventral striatum including the **nucleus accumbens** receives two prominent excitatory glutamatergic inputs: the **prefrontal cortex** and the ventral **hippocampus subiculum**.

The **prefrontal cortex** input enables *behavioral flexibility*, or the ability to shift behavioral focus as task contingencies change.

The **subiculum** is a context-dependent structure that is believed to keep an organism *focused on a task*.



REVIEW
Neuropsychopharmacology REVIEWS (2010) 35, 27–47

www.neuropsychopharmacology.org

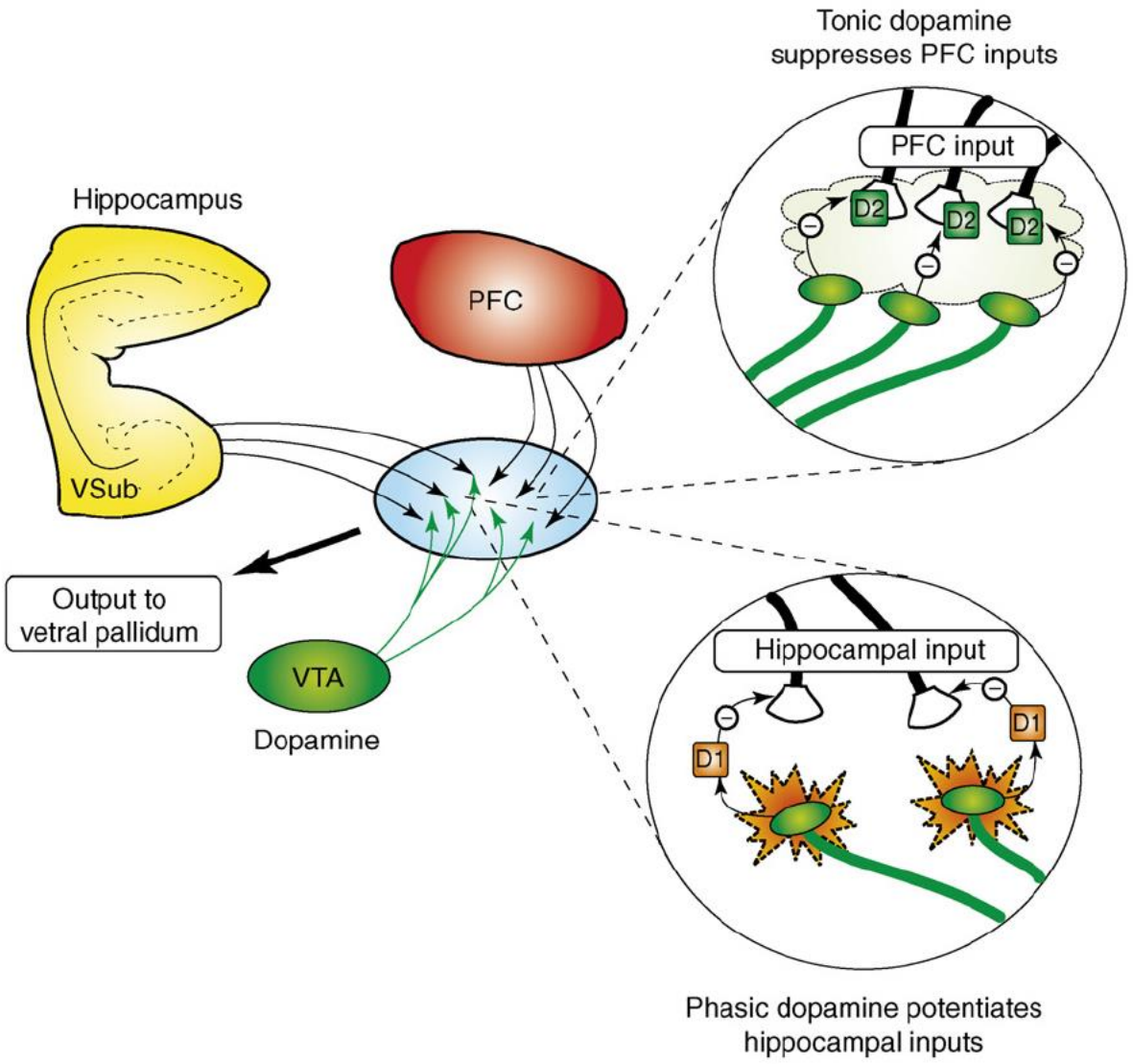
Cortico-Basal Ganglia Reward Network: Microcircuitry

Susan R Sesack*,[1,2] and Anthony A Grace*,[1,2]

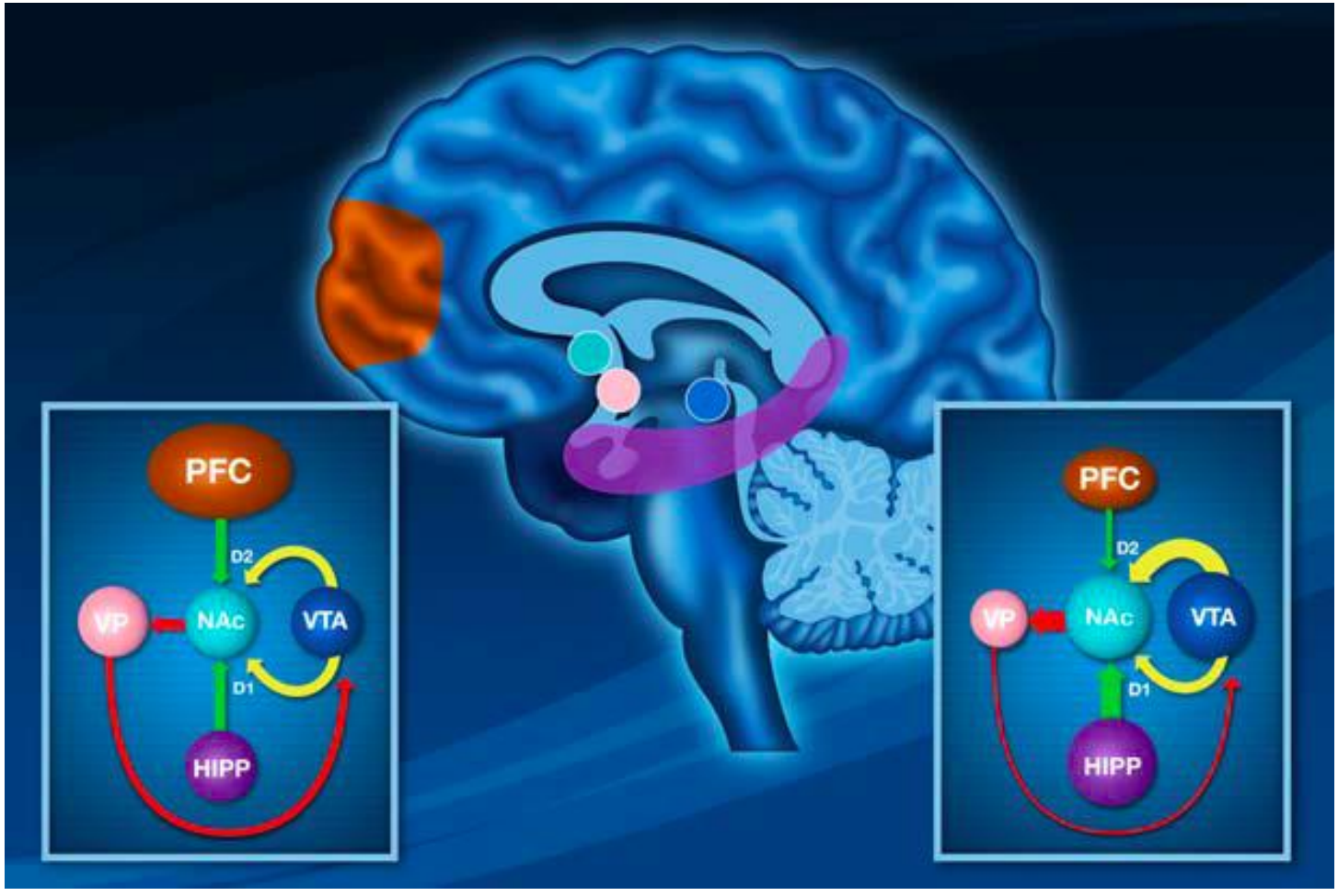
[1]Department of Neuroscience, University of Pittsburgh, Pittsburgh, PA, USA; [2]Department of Psychiatry, University of Pittsburgh, Pittsburgh, PA, USA

Increased dopamine input **facilitating the hippocampal input via a D1**- dependent process, whereas **D2 stimulation attenuates prefrontal cortical drive**.

A model of functioning of this system suggests that when a task is rewarding, there is an increase in dopamine input, *facilitating the hippocampal drive to maintain focus* on the currently rewarded task while *preventing the prefrontal cortex from deviating from this task*.



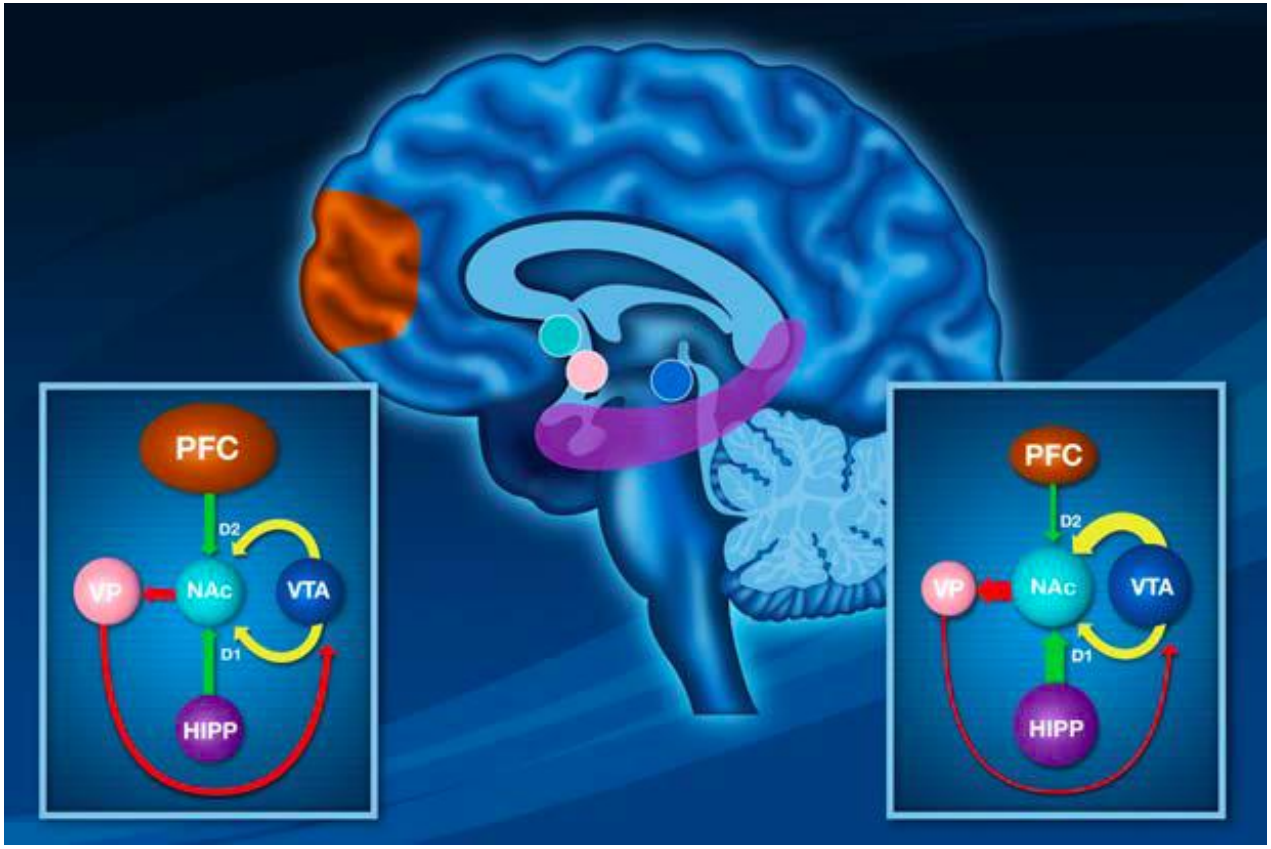
If a behavior fails to produce a reward, as in LOWER LEFT , there would be an attenuation of dopamine neuron activity (negative reward prediction error), with *decreasing hippocampal drive, and disinhibiting the prefrontal cortex*.
This would enable the prefrontal cortex to shift focus to a different response.



If the system is disrupted, as in LOWER RIGHT, such as after repeated dopamine agonist administration, then *overstimulation of the dopamine system* would occur and a *persistent focus on a single task to the exclusion of prefrontal cortex-drive goal-directed behavior*.

In such conditions, there would be a continued *potentiation of hippocampal focus independent of the rewarding nature of the stimuli*, causing the organism to perseverate an impulsive task.

Because of the *high levels of D2 receptor activation*, the *prefrontal cortex* would not be capable of shifting behaviors toward a more goal-oriented condition, thereby locking the system in this behaviorally ineffective state.



REVIEW

Clinical Spectrum of Impulse Control Disorders in Parkinson's Disease

Daniel Weintraub, MD,[1,2*] Anthony S. David, FRCP, FRCPsych, MD, MSc,[3] Andrew H. Evans, FRACP,[4] Jon E. Grant, MD, MPH,[5] and Mark Stacy, MD[6]

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