The Topography of dopamine dysfunction in schizophrenia

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OUTLINE

- **The Hypothesis**
- **The Evidence**
  - **Confirming the hypothesis**
  - **Refining the hypothesis**
  - **Expanding the hypothesis**
- **The Model(s)**
  - **Is dopamine dysregulation a downstream effect of other more upstream events?**
  - **Or could it be more proximal than generally thought?**

OUTLINE

- **The Hypothesis/ background**
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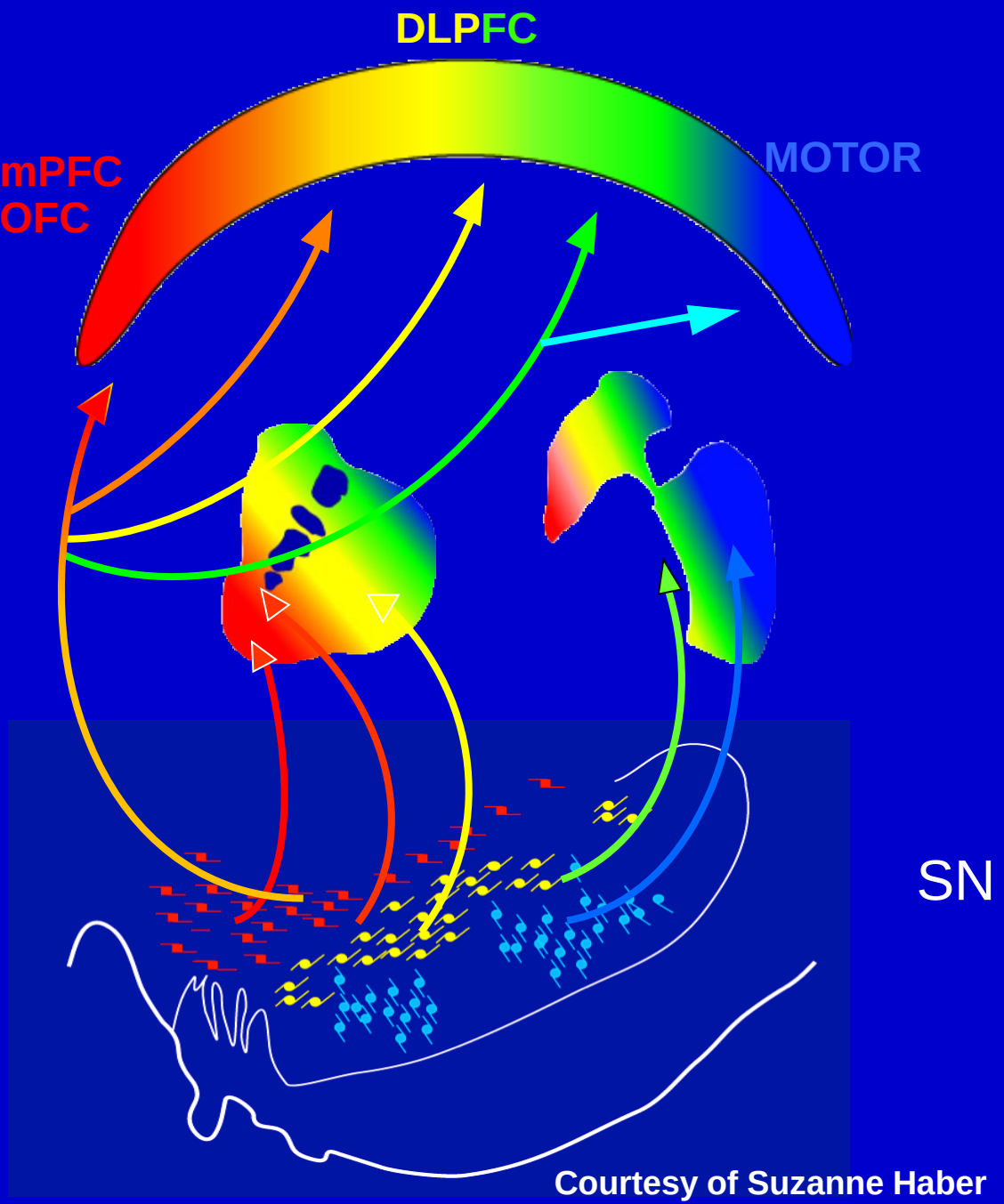
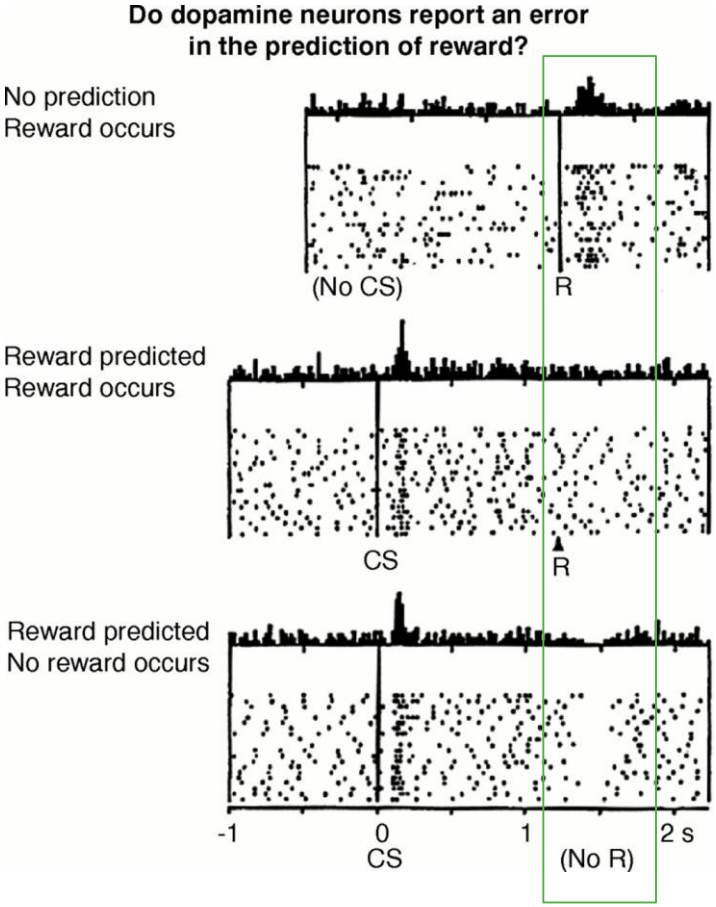
Dopaminergic Pathways



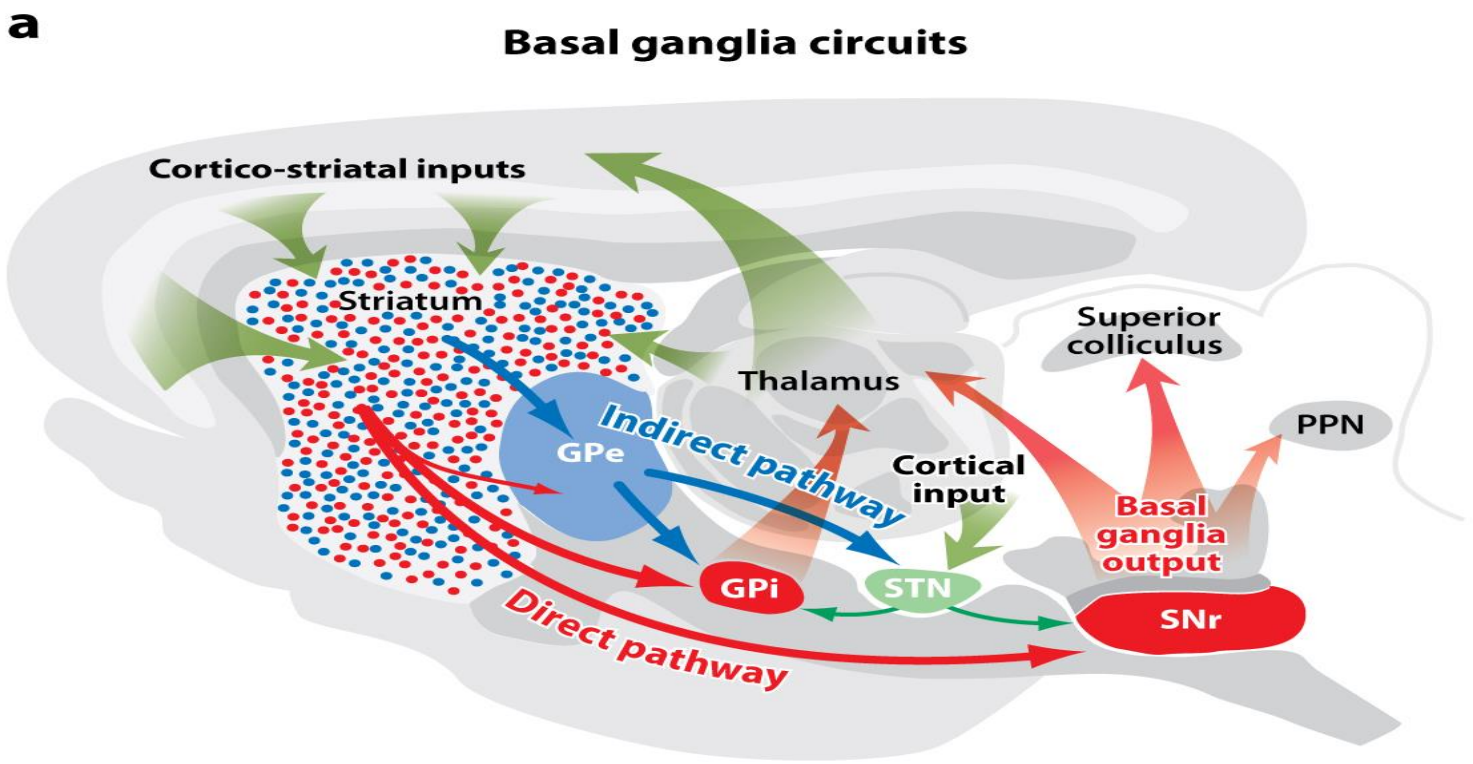
Midbrain Regulation of DA neuron firing

	Frequency	Basis	Regulation	Topography
Tonic	2-4 Hz	Pacemaker firing Tonic synaptic input	SK3, Ca^{2+} channels D2 autoreceptor	SN
Bursting	15-20 Hz 3-10 spikes	Excitatory input Inhibition of GABA input	NMDA receptor	VTA

Reward prediction-error (rPE) signals

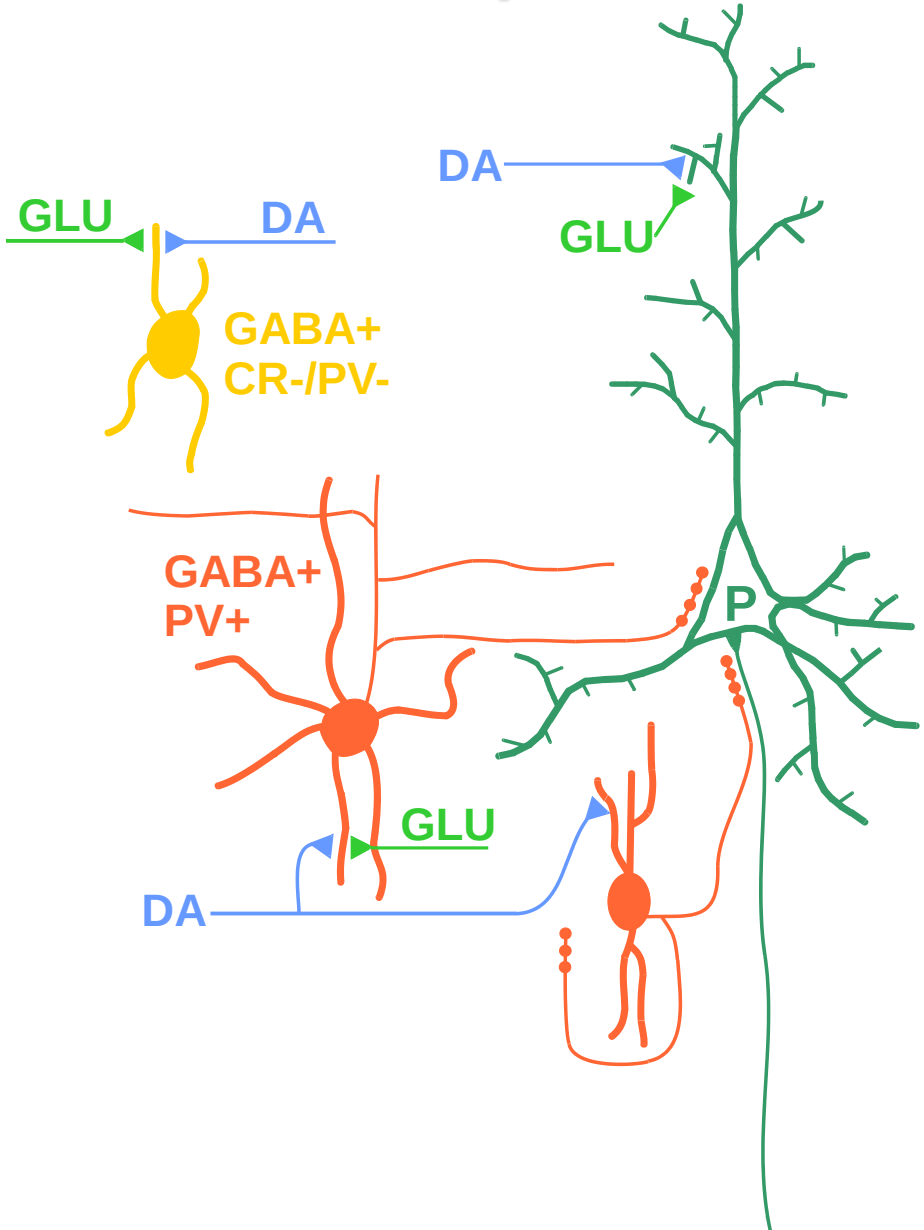


Schultz et al., O'Doherty et al., Daw et al., Glimcher et al.



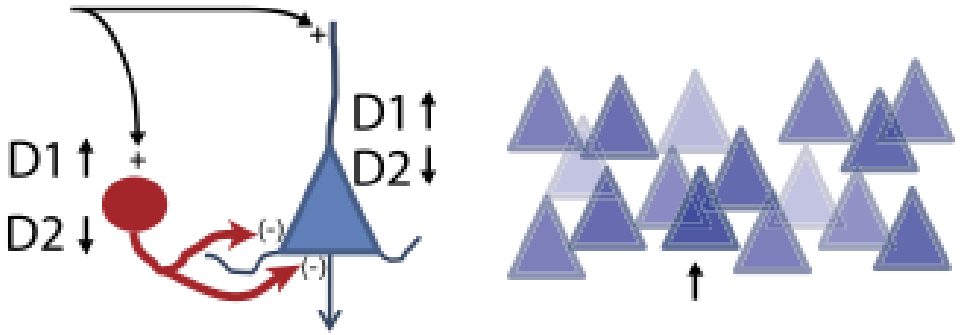
Gerfen CR, Surmeier DJ. 2011.
Annu. Rev. Neurosci. 34:441–66

Dopamine modulates the balance of Excitation/ inhibition in the prefrontal cortex

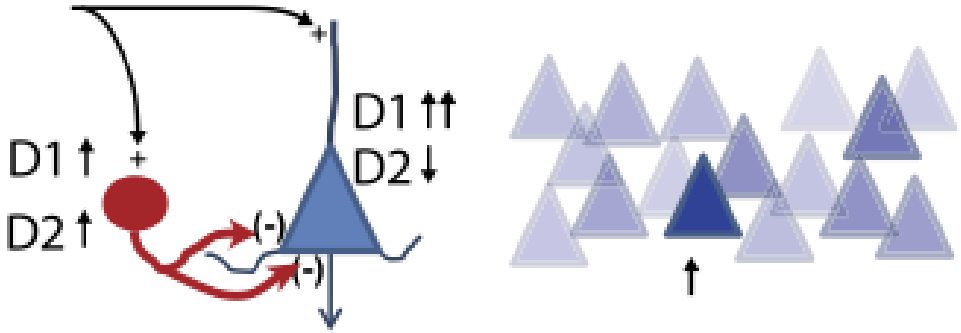


Adapted from D. Lewis

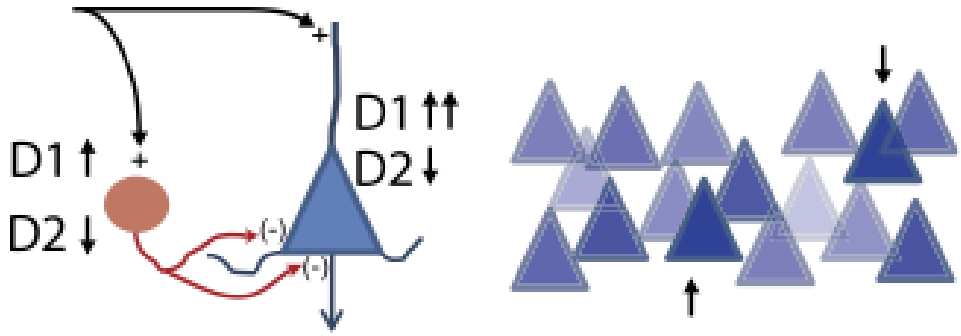
JUVENILE



ADULT



ADULT with LOSS of INTERNEURON FUNCTION



O'Donnnell, SCZ bull, 2011

THE HYPOTHESIS

- Antipsychotic properties of chlorpromazine (Delay & Denicker, 1952)
- Dopamine turnover increased by antipsychotics (Carlsson & Lindqvist, 1963)
- Overstimulation of DA receptors in SCZ (Van Rossum, 1966)
- Dopamine-sensitive adenylyl cyclase (Greengard et al., 1972)
- Antipsychotic binding sites (Snyder et al.; Seeman et al., 1976)
- D1 and D2 dopamine receptors (Spano, 1978; Kebabian & Calne, 1979)
- DA agonists produce psychosis (Angrist and Van kammen 1984, Lieberman 1987)
- First formulation: mesolimbic DA excess
- Re-formulation of DA in SCZ: subcortical excess and cortical deficit (Weinberger 1987, Davis,1990)

OUTLINE

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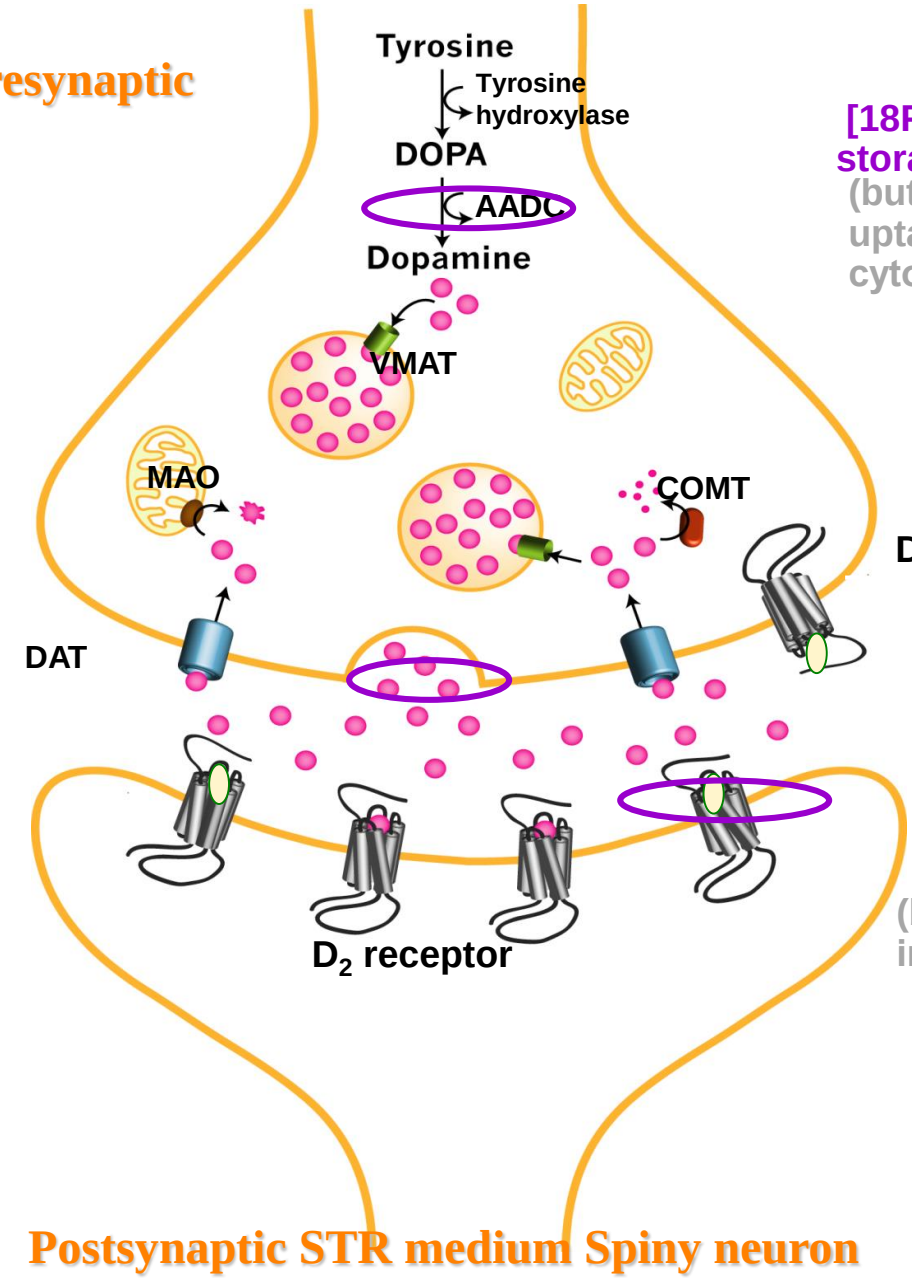
Imaging the striatal dopaminergic synapse



[18F]f-DOPA: synthesis and presynaptic storage (activity of AADC)

(but also uptake in DA neurons, VMAT activity and uptake in vesicles, pH in vesicles, metabolism in cytoplasm…)

Dopamine levels

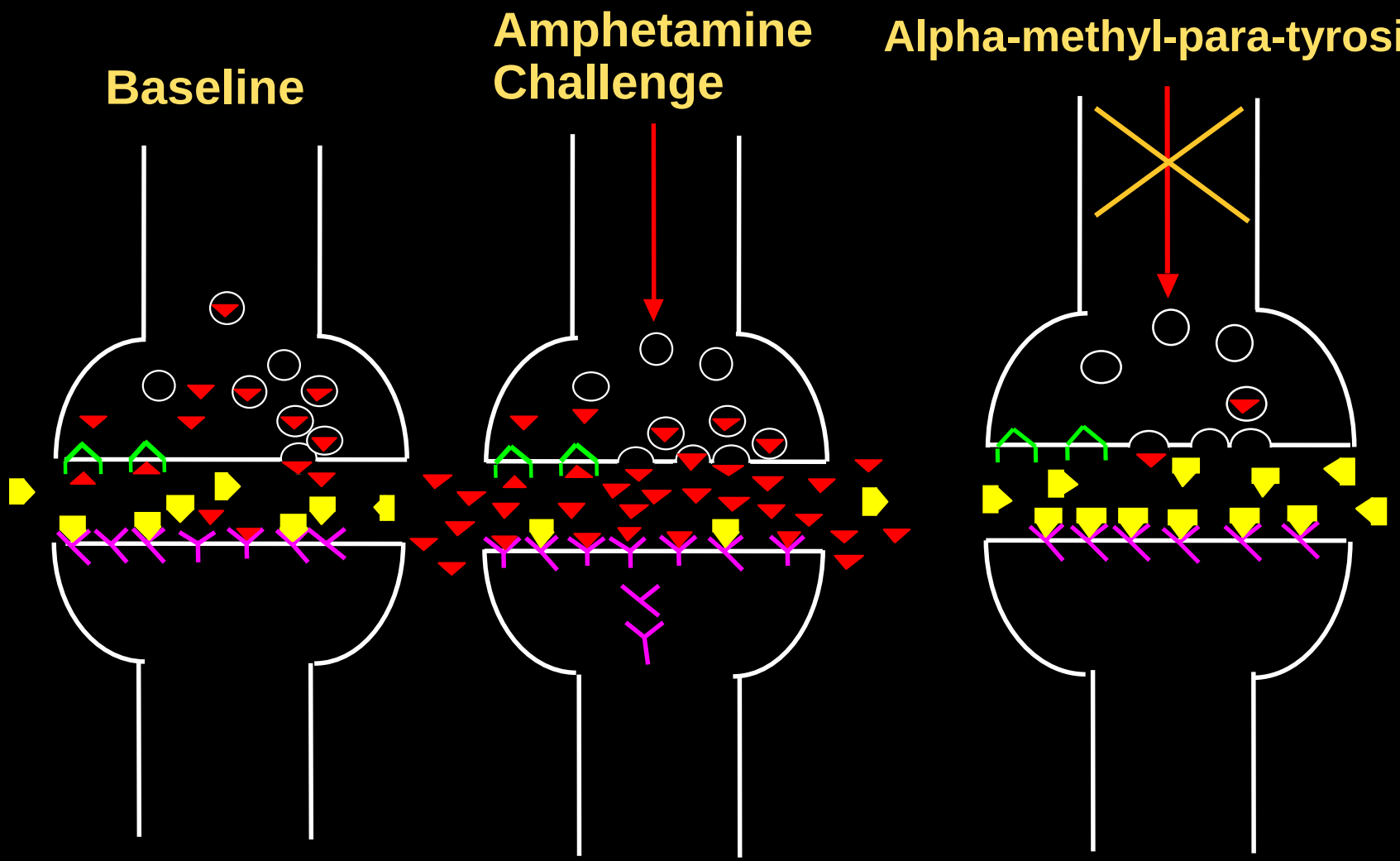
D2 receptor

(but also affected by dopamine occupancy, internalization, synaptic localization, affinity state…

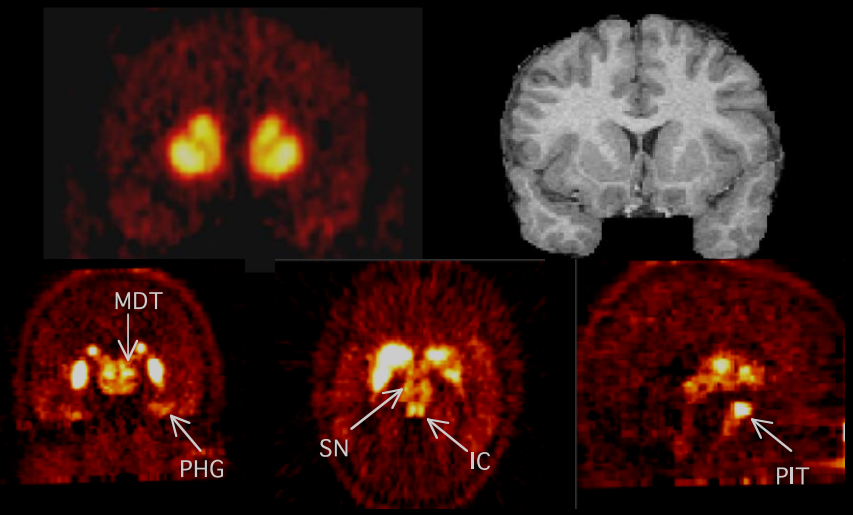
Imaging Dopamine

D2 radiotracer

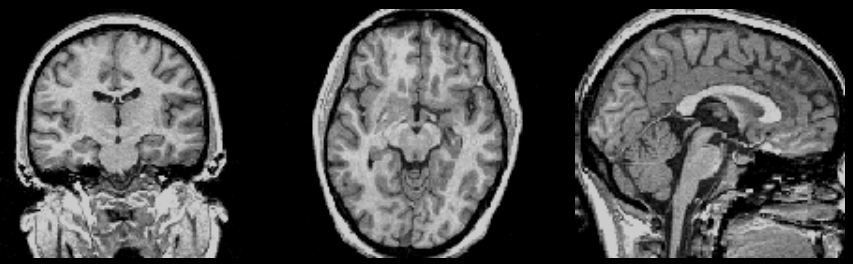
Dopamine



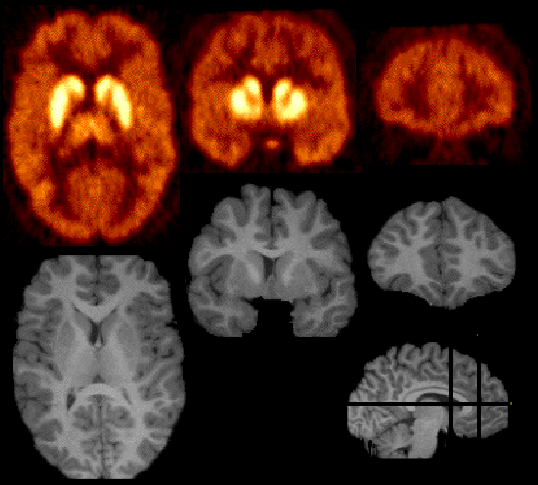
D2/3 PET imaging



[11C]raclopride

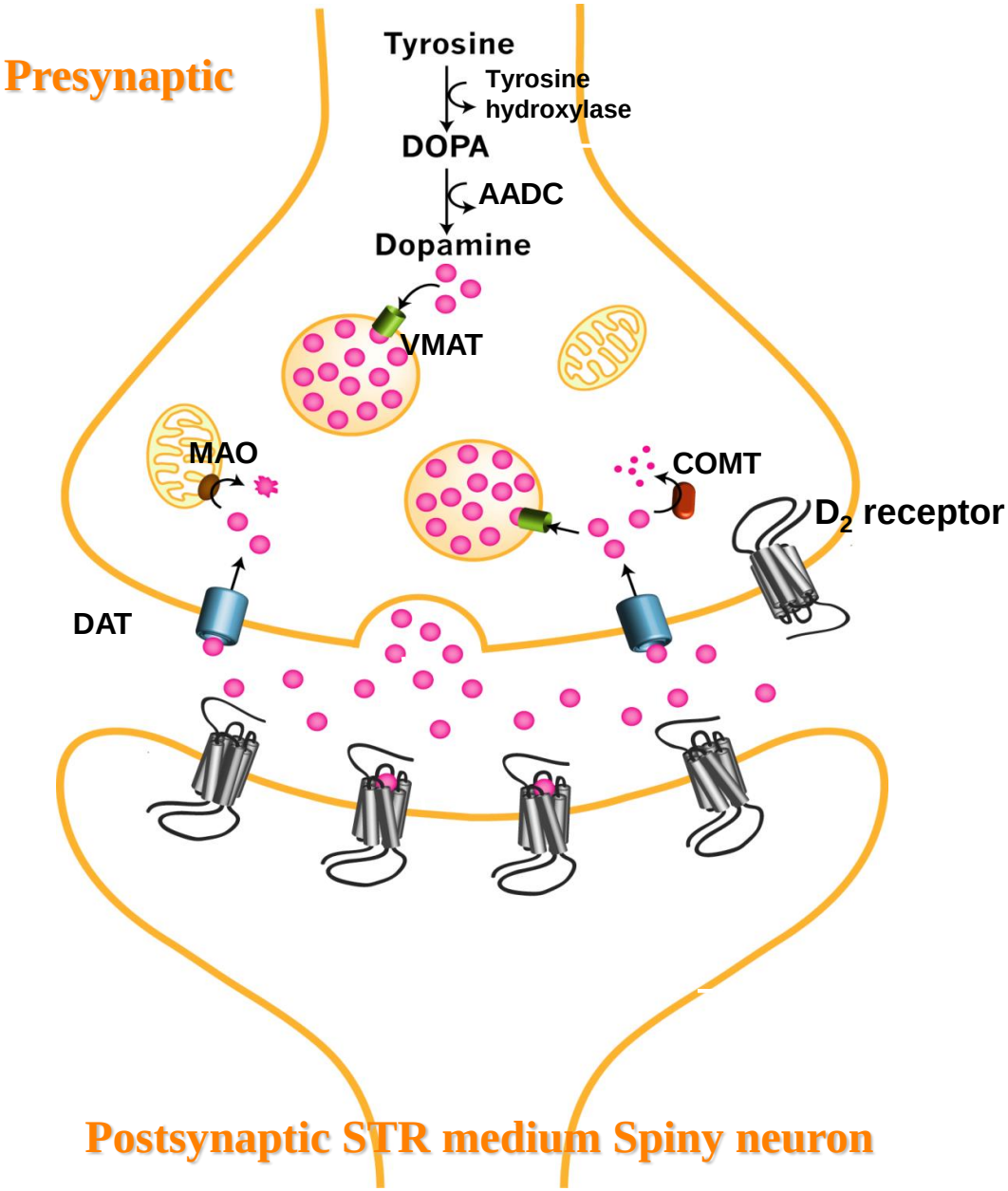


[11C]Fallypride



[11C]FLB457

STRIATAL dopamine alterations in schizophrenia



Dopamine "synthesis"

Reith et al., 1994
Hietala et al., 1995, 1999
Lindstorm et al., 1999
Meyer-Lindenberg et al., 2002
McGowan et al., 2004
Nozaki S et al., 2009
Howes et al., 2009

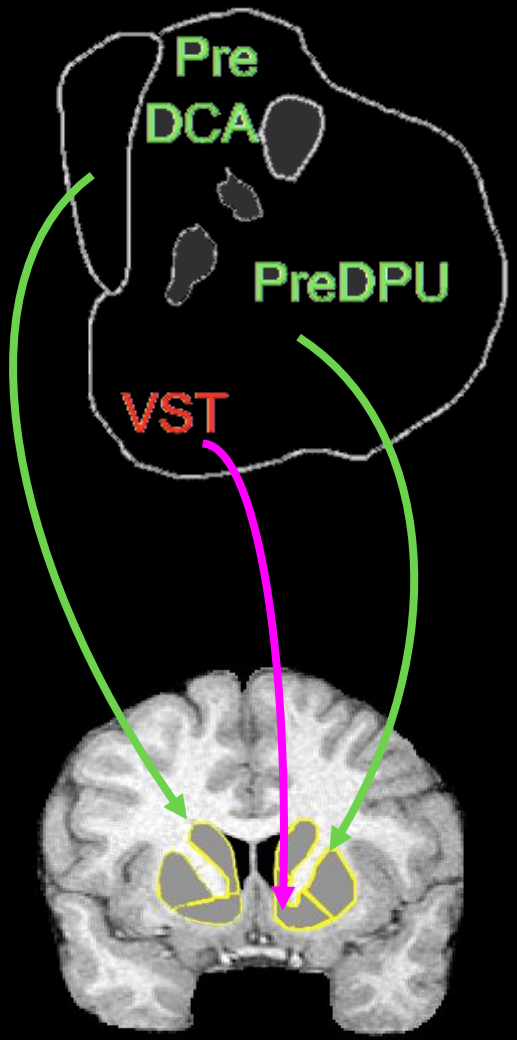
Dopamine "release"

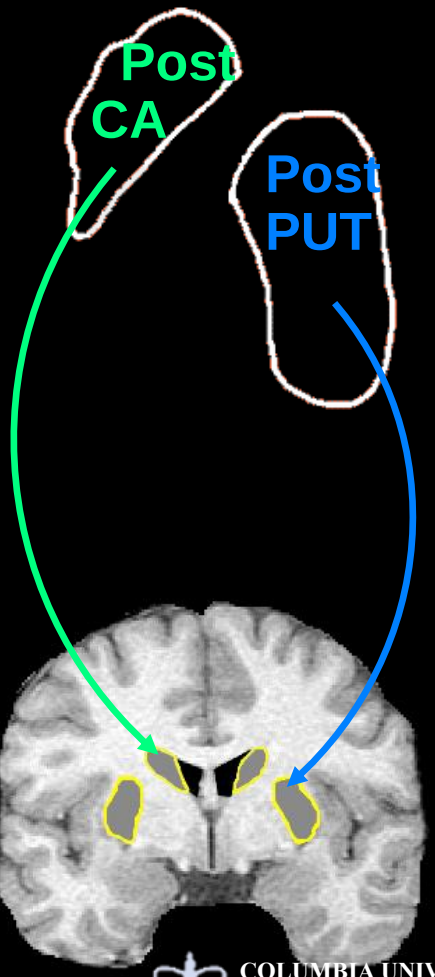
- Amphetamine challenge -
  Laruelle et al., 1996
  Breier et al., 1997
  Abi-Dargham et al., 1998
- AMPT -
  Abi-Dargham et al., 2000
  Kegeles et al., 2010

D_2 receptors

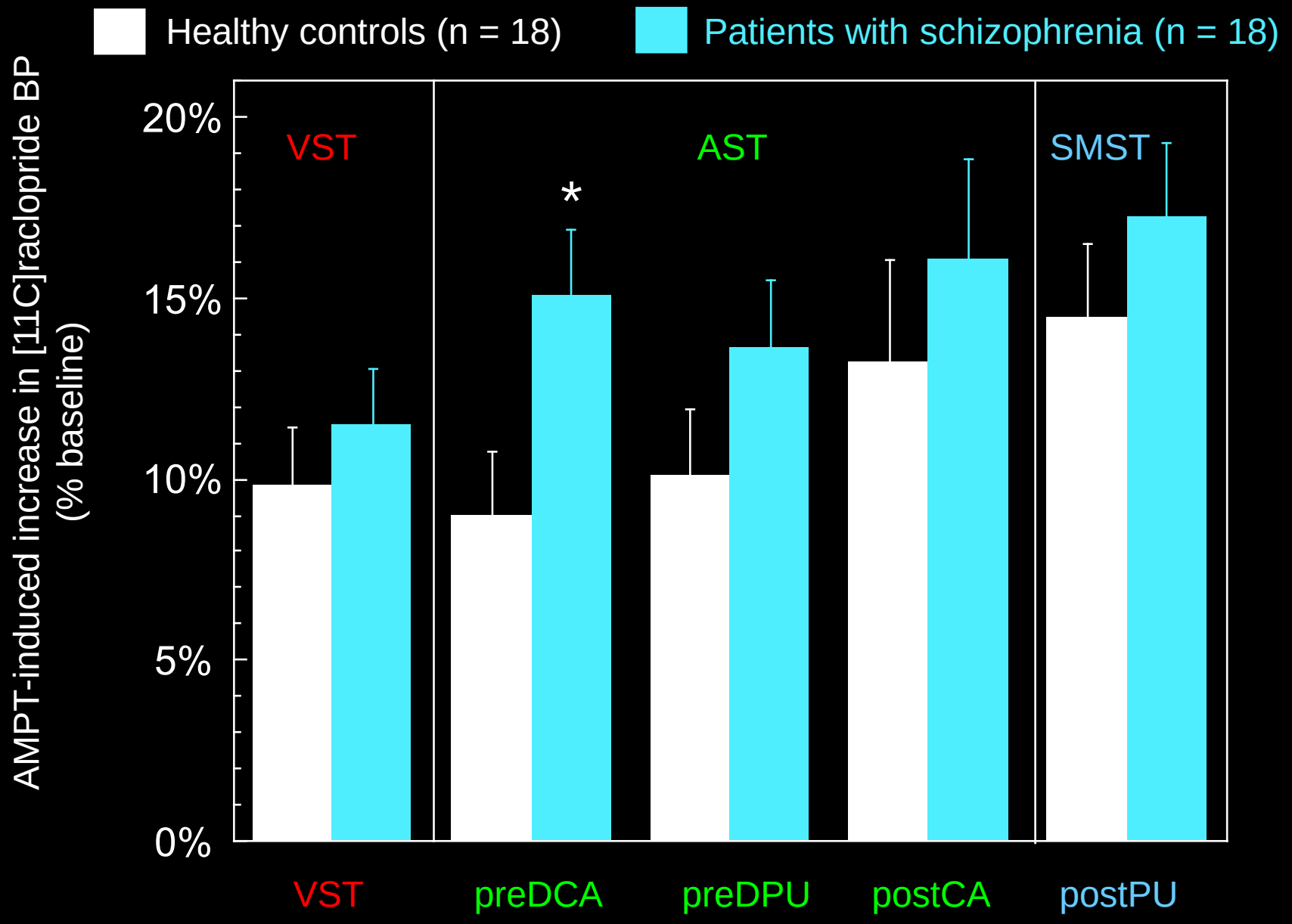
- Meta analyses -
  Weinberger & Laruelle, 2001
  Howes et al., 2012

Topography of STRIATAL DA alterations in striatal subdivisions:





Intrasynaptic dopamine in STR subdivisions in SCZ



** p < 0.05*

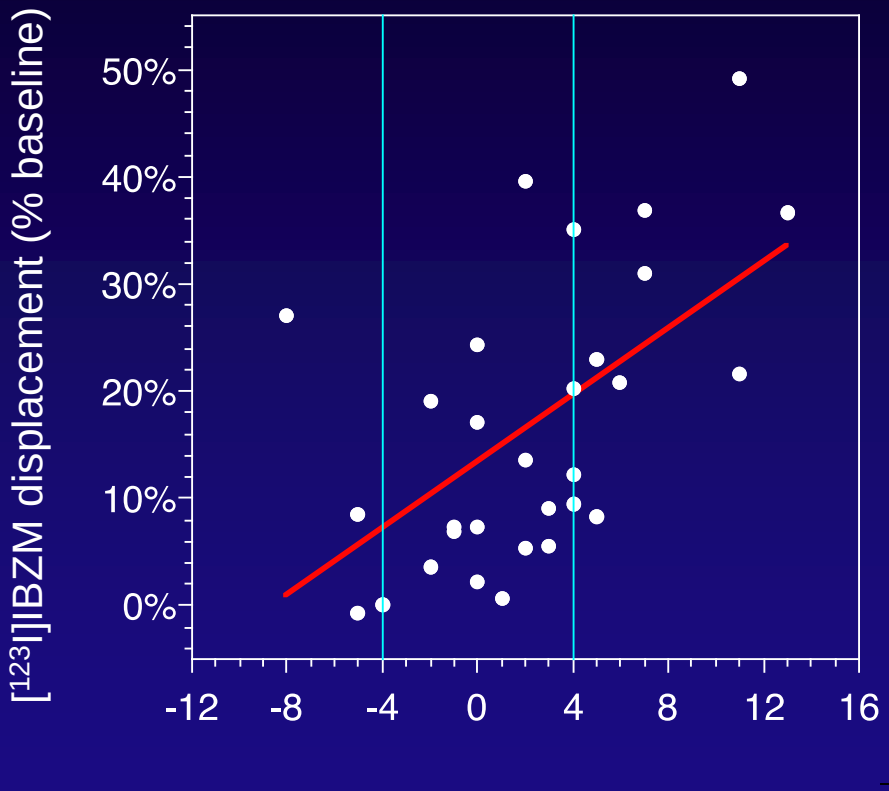
Kegeles et al, Archives of Gen Psychiatry, 2010

Striatal Dopamine Release and Psychotic Symptoms

Schizophrenia, n= 34

$r_P = 0.55$

STRIATUM

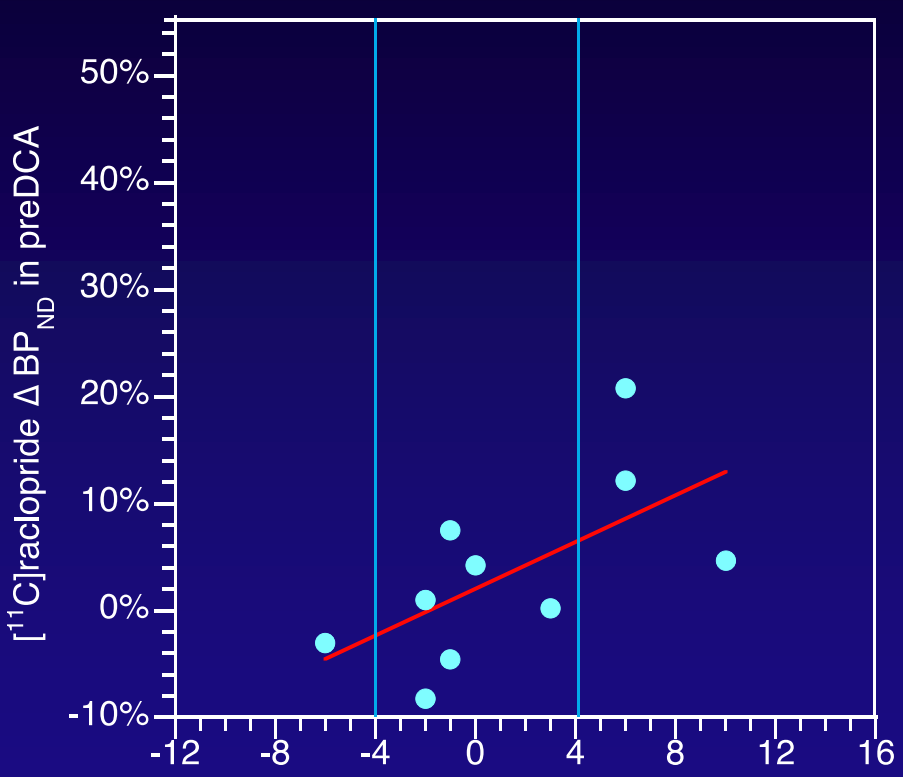


SCZ DD, n=10

$r_S = 0.69$

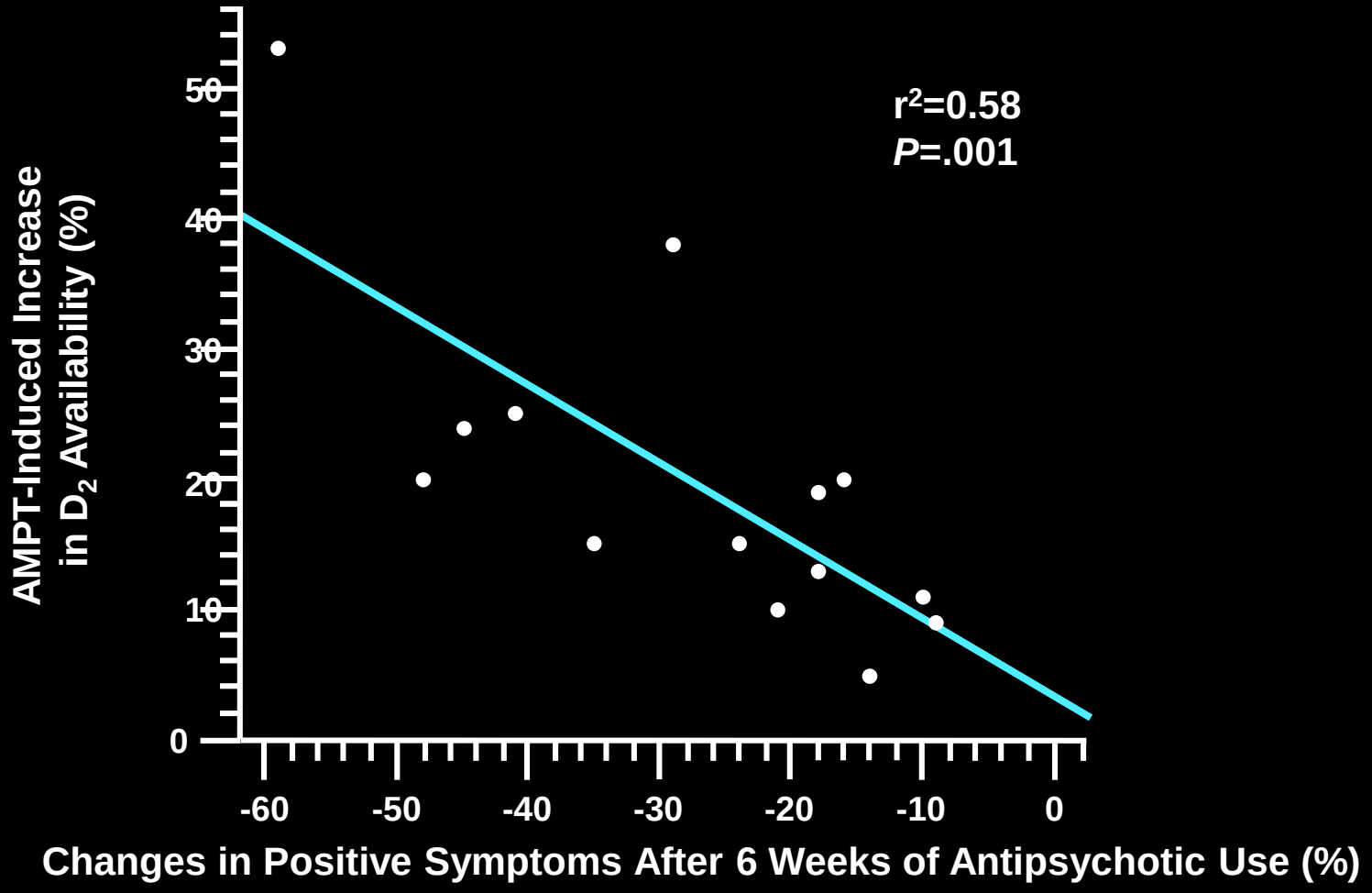
($r_P = 0.62$)

ROSTRAL caudate



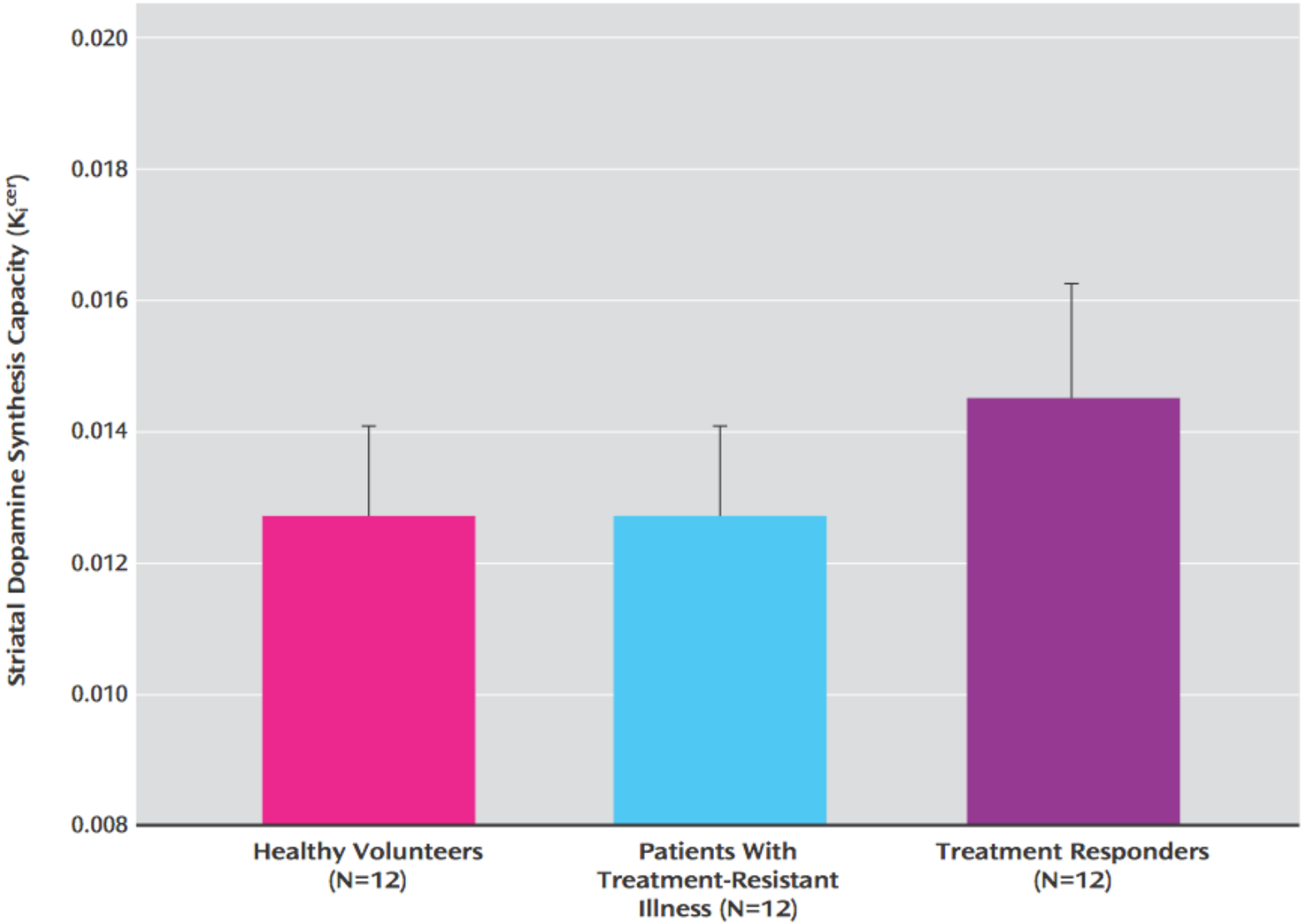
Change in Psychosis scores (PANSS)

High Synaptic Dopamine Predicts Treatment Response at 6 Weeks



Abi-Dargham A et al. *Proc Natl Acad Sci USA.* Vol. 97:8104-8109.

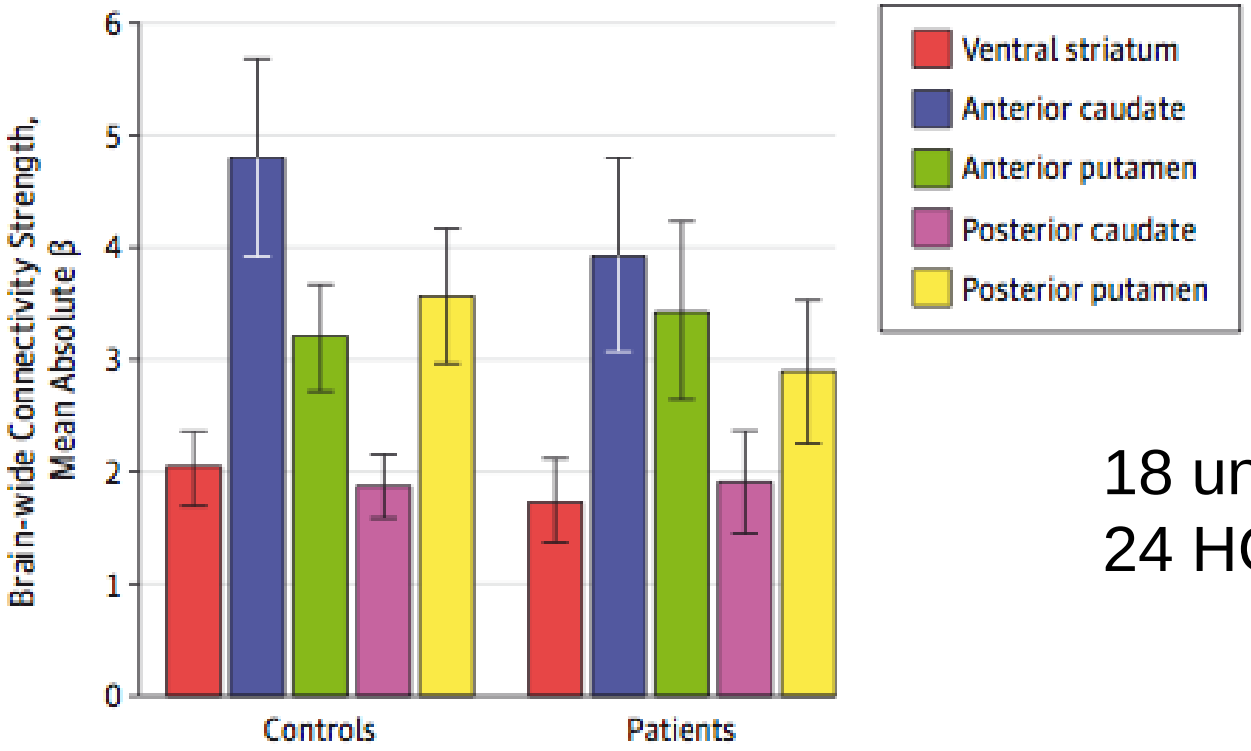
FIGURE 1. Mean Dopamine Synthesis Capacity for the Whole Striatum in Patients With Treatment-Resistant Schizophrenia, Treatment Responders, and Healthy Volunteers[a]



[a] The treatment-resistant group showed significantly lower dopamine synthesis capacity than the treatment responders (p=0.02, corrected for multiple comparisons). There were no significant differences between treatment-resistant patients and healthy volunteers. Error bars indicate standard deviation.

Demjaha et al, AJP, 2012

Figure 4. Global Brain Connectivity of Striatal Subregions in Patients and Healthy Controls

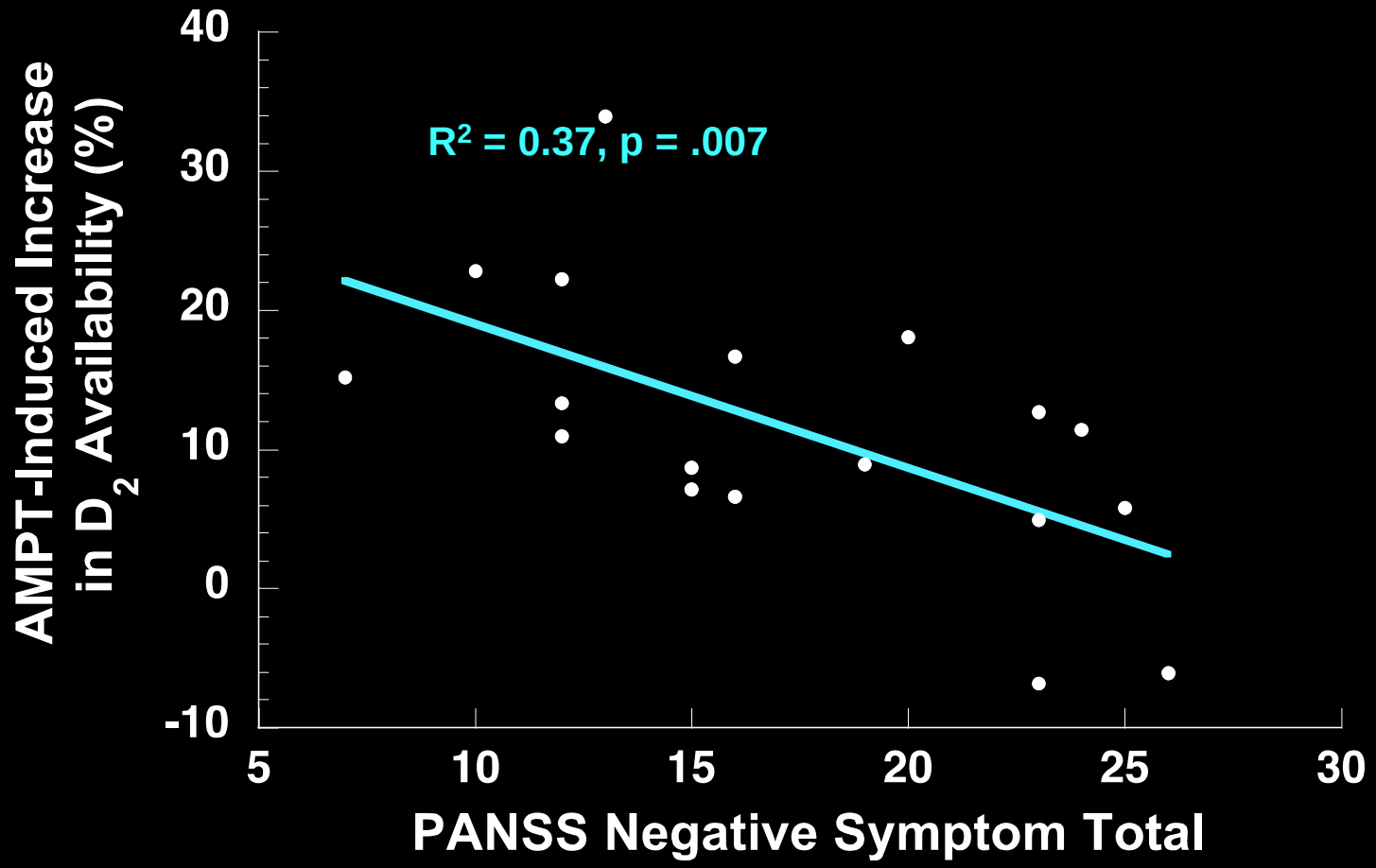


Mean (SEM) absolute β values across all extrastriatal brain voxels are plotted by striatal subregion and group.

18 unmed SCZ
24 HC

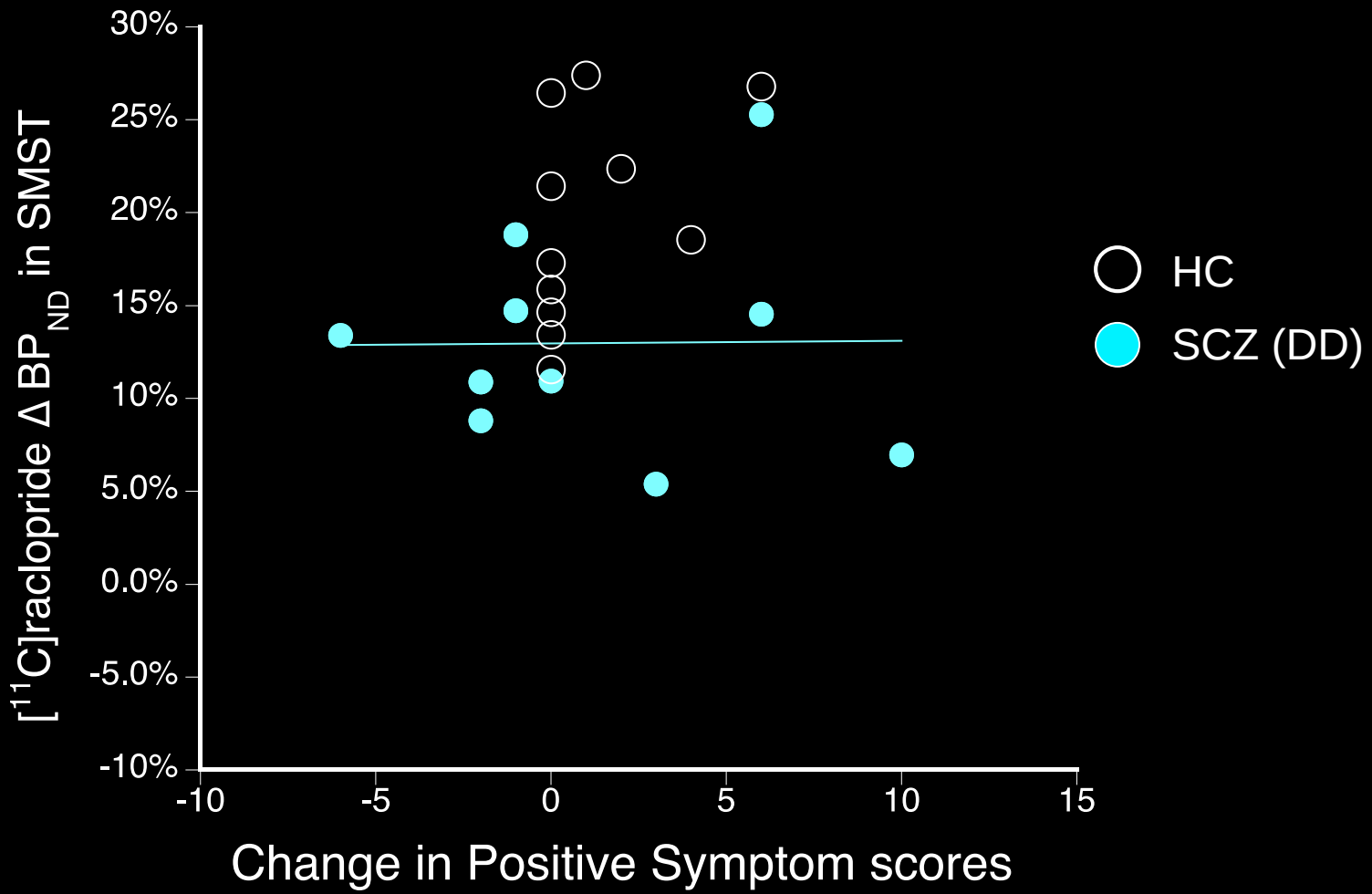
Horga, Cassidy, Xu, Moore, Slifstein, Van Snellenberg and Abi-Dargham, ***JAMA Psychiatry* 2016**

Negative Symptoms inversely related to Dopamine Levels in Ventral Striatum



Kegeles LS et al. *Arch Gen Psychiatry* 2010;67(3):231-239

But not in the sensorimotor striatum



Thompson et al, Mol Psychiatry 2012

Striatal Dopamine Release and Psychotic Symptoms

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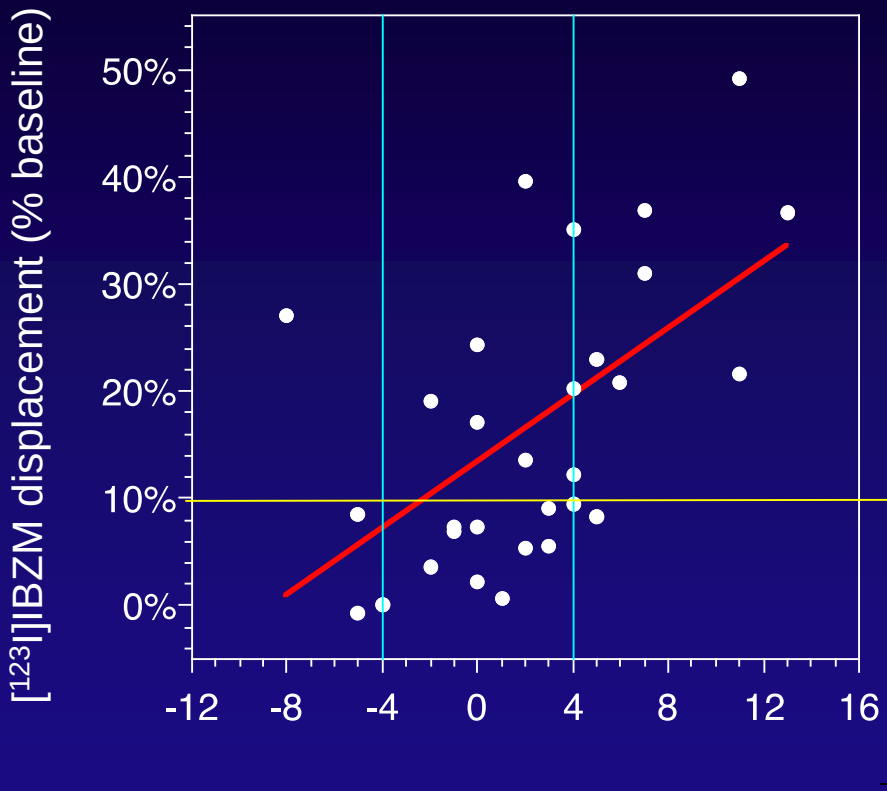
$r_P = 0.55$

STRIATUM

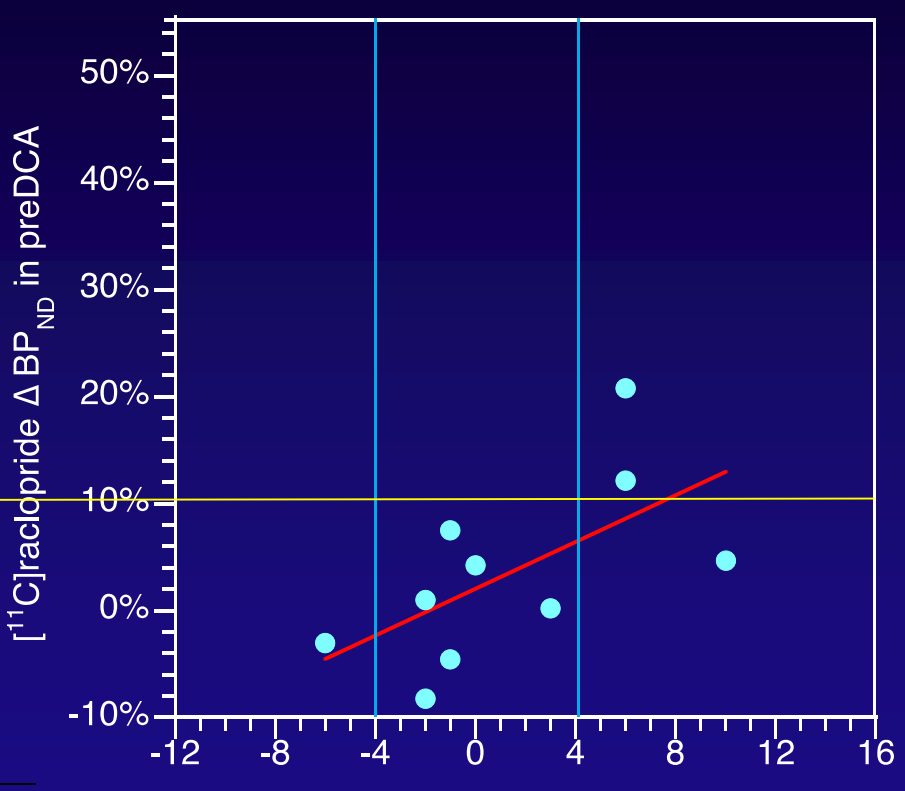


Dual Diagnosis, n=10

$r_S = 0.69$

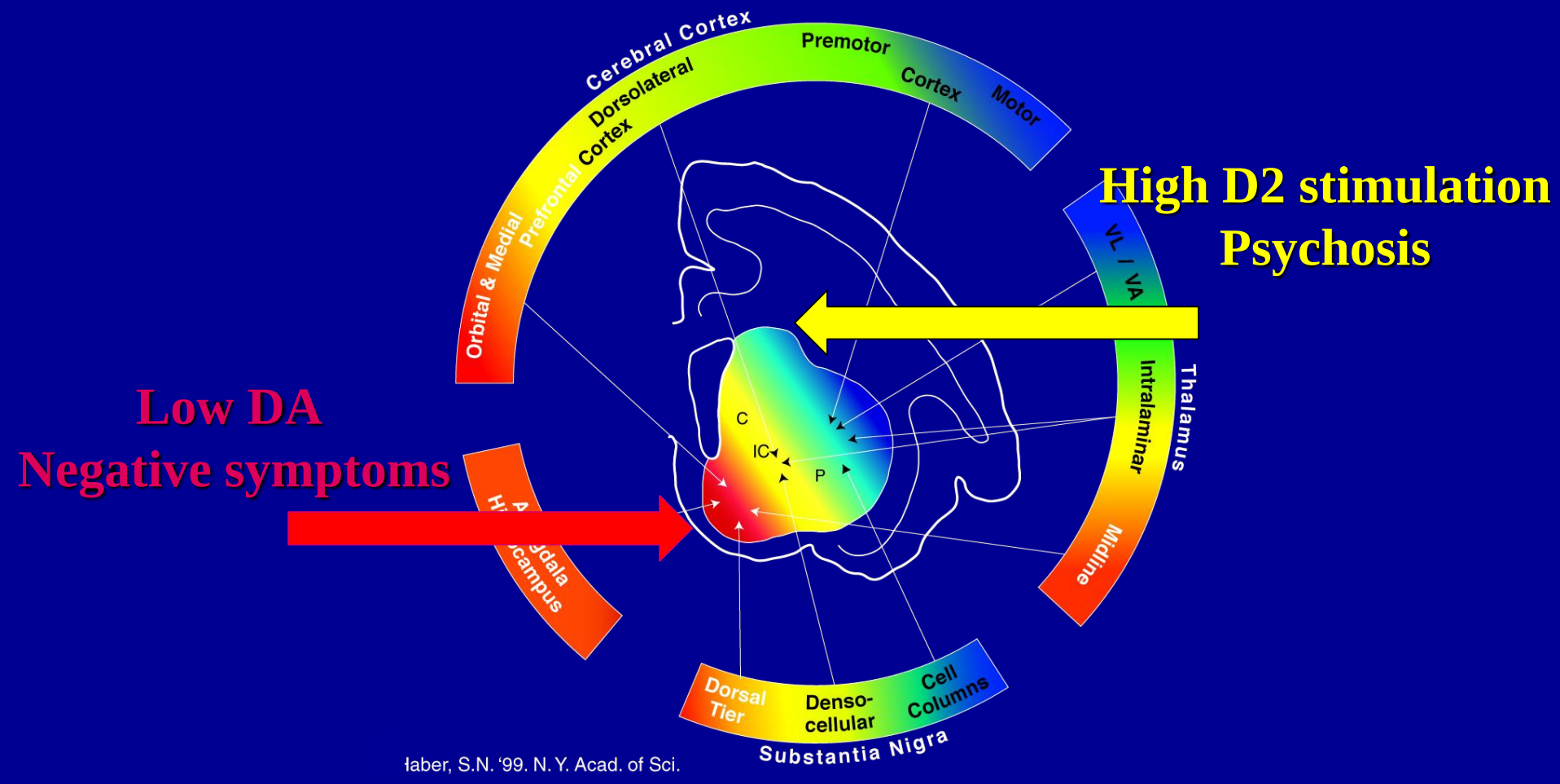
($r_P = 0.62$)

ROSTRAL caudate



Change in Psychosis scores (PANSS)

Thompson et al, Mol Psychiatry 2012

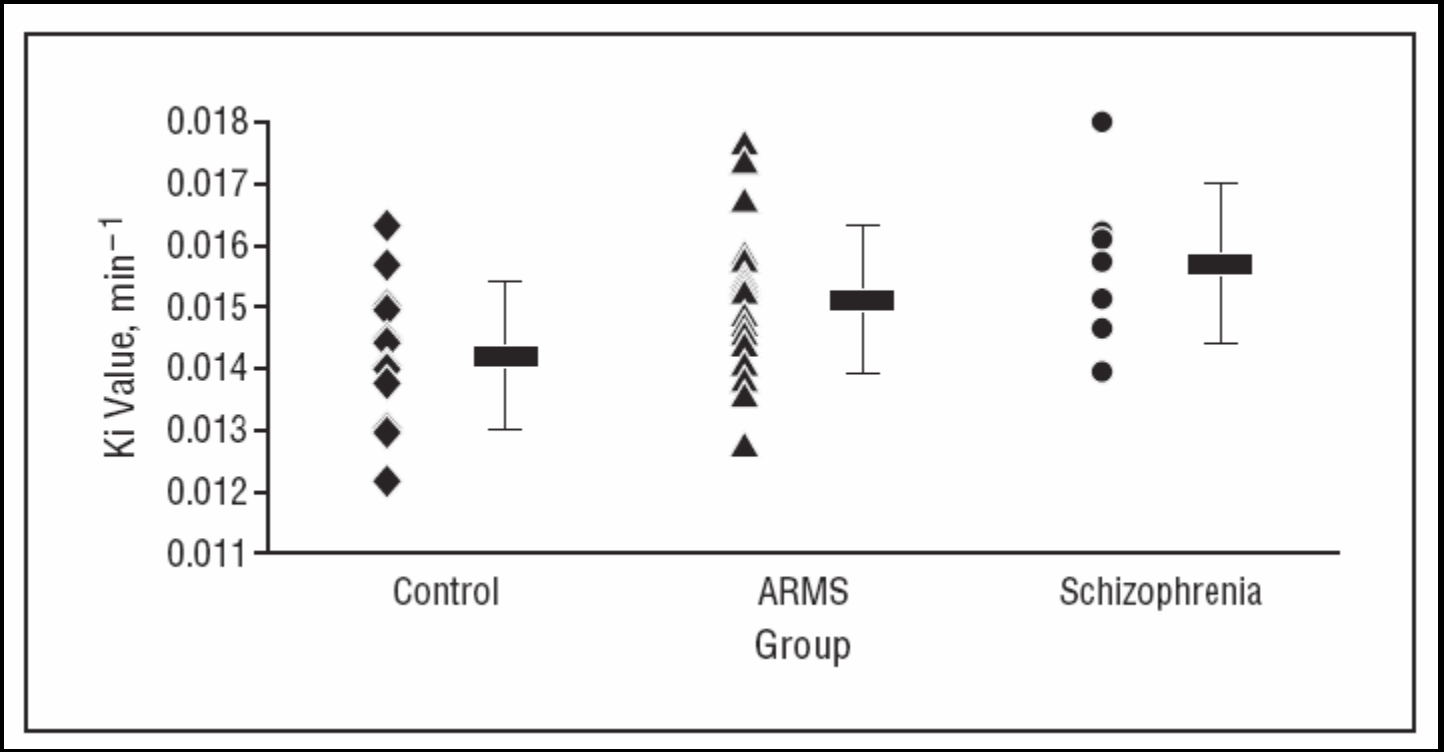


High D2 stimulation
Psychosis

Low DA
Negative symptoms

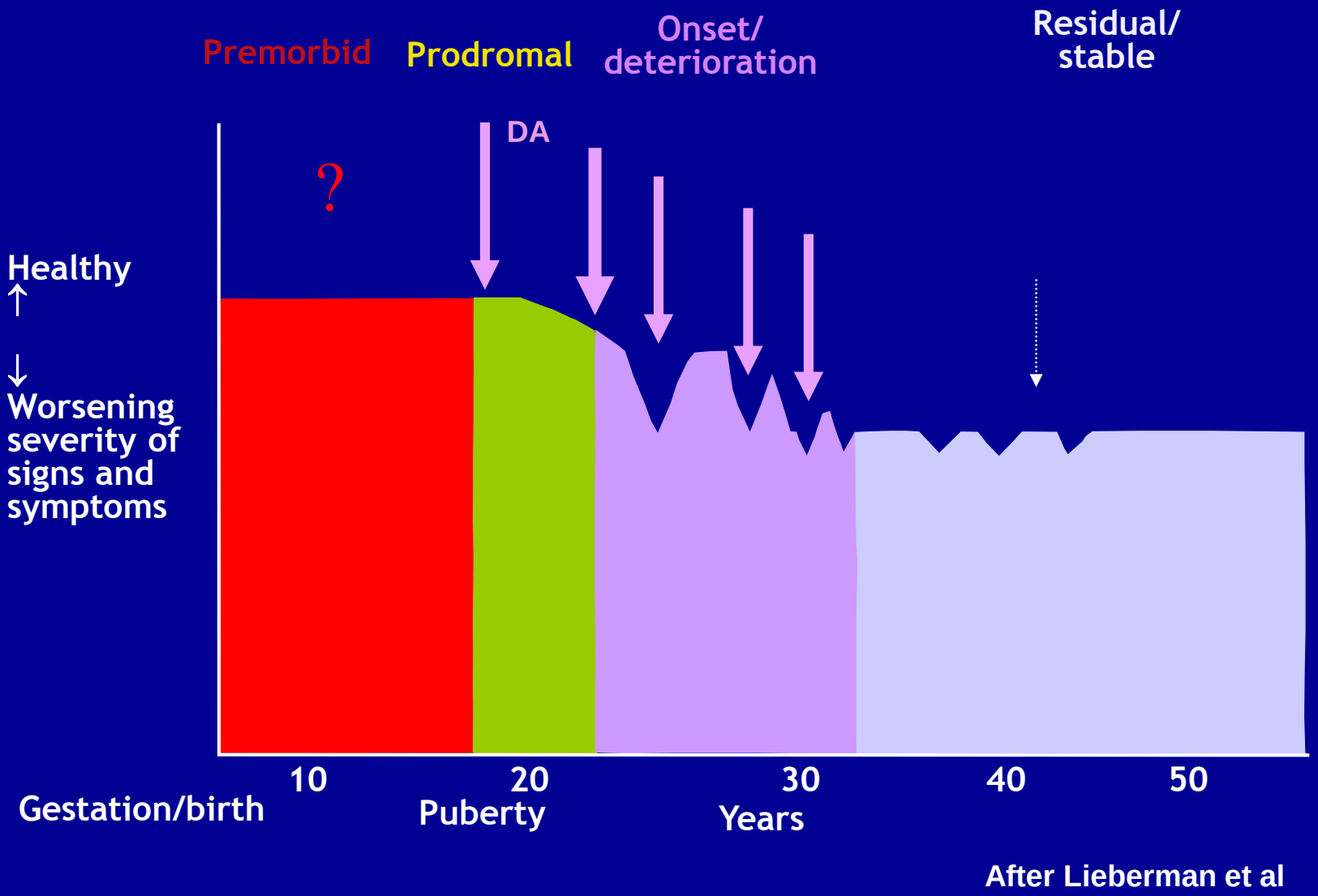
Haber and Mc Farland, Ann N Y Acad Sci.**1999, Kegeles et al, Archives of Gen Psychiatry, 2010**
Howes et al, Archives of Gen Psychiatry 2009

Dopamine synthesis in the prodrome: [18F]f-DOPA increased in striatum



Howes et al, Arch Gen Psych 2009
Howes et al, Molecular Psych 2011
Howes et al, Am J Psychiatry 2011

DA dysregulation is an early event, observed in the prodrome and predicts conversion



OUTLINE

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- The Evidence
  - Confirming the hypothesis
  - **Refining the hypothesis: Associative striatum is affected**
    - **» DA dysregulation precedes onset**
  - Expanding the hypothesis:
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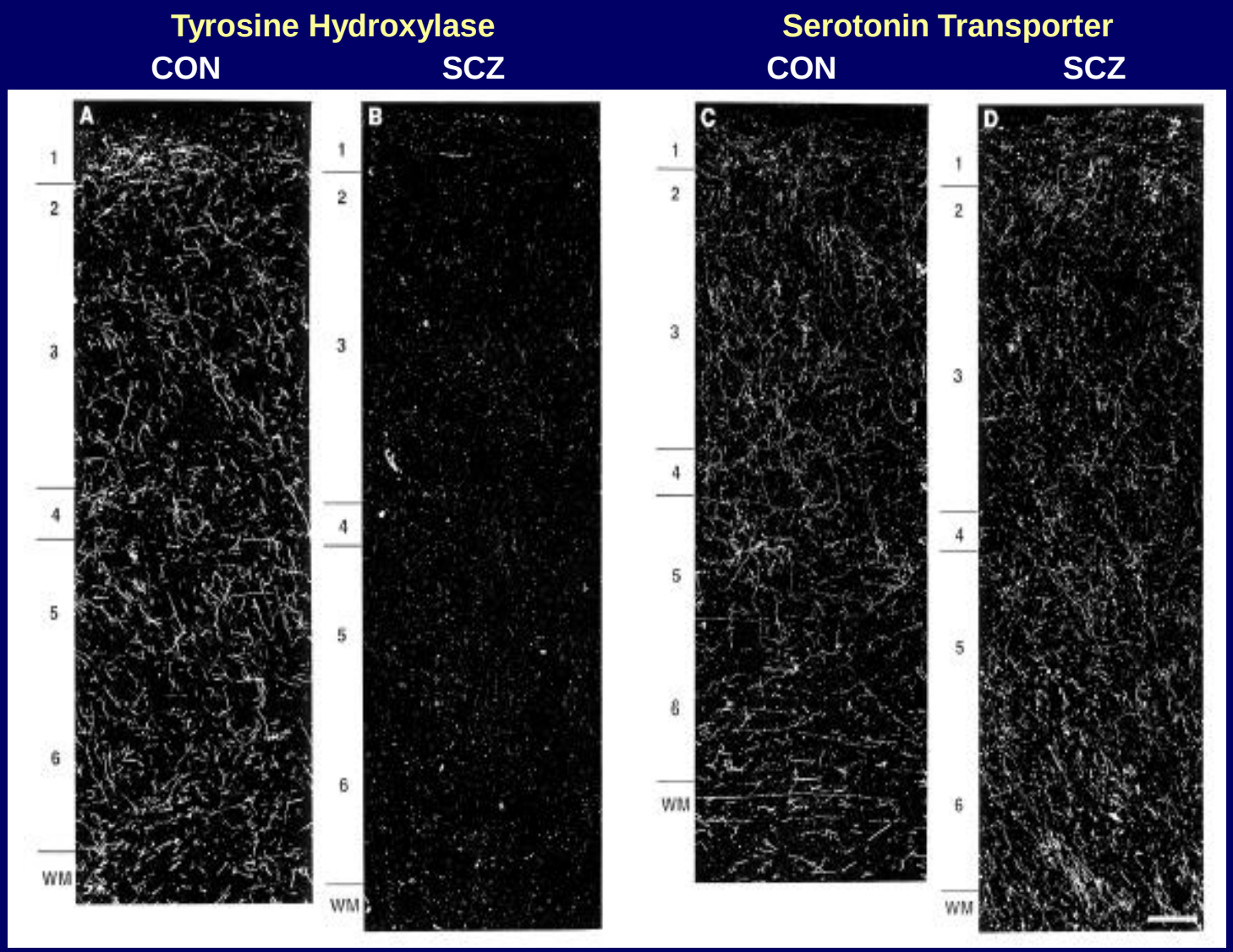
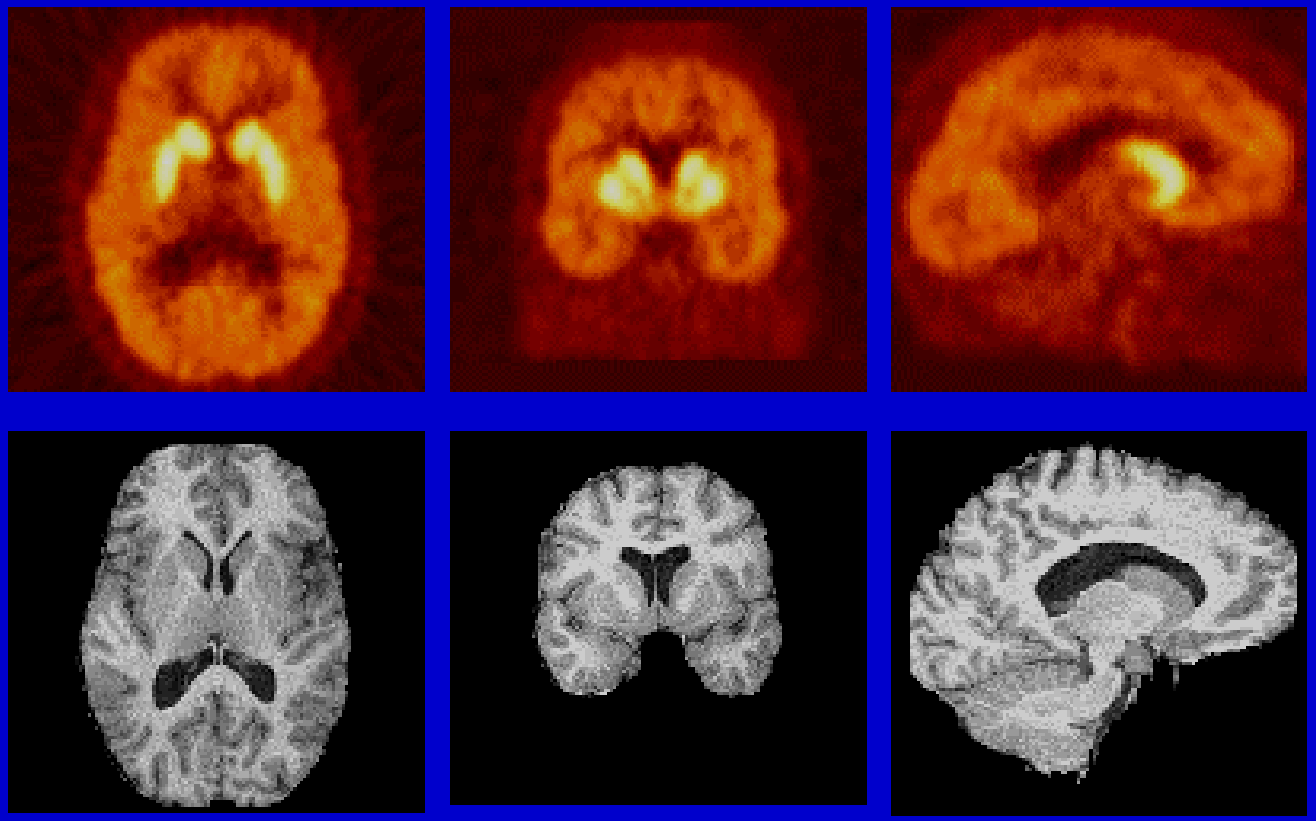
Cortical Dopamine in SCZ



Akil et al., Am J Psychiatry 1999;156:1580-1589

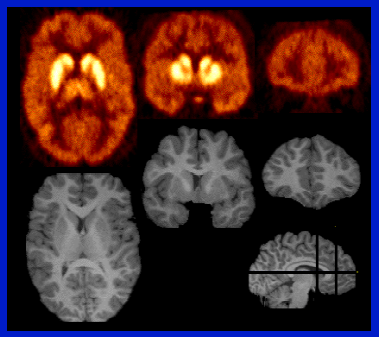
D1 PET imaging



PET studies of PFC D1 receptors in SCZ

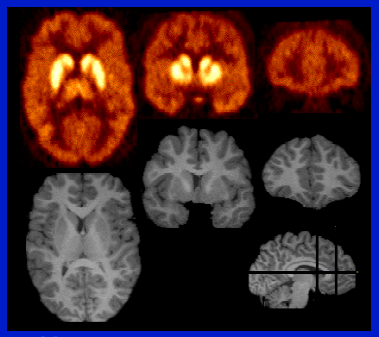
Study	Ligand	n patients (DN/DF)	n controls	Results
Okubo et al., 1997	[11C]SCH23390	17 (10/7)	18	↓
Karlsson et al., 2002	[11C]SCH23390	10 (10/0)	10	No change
Hirvonen et al., 2006	[11C]SCH23390	(0/9)	(11/13)	↑ Disc Twins ↓ MedicatedSCZ
Abi-Dargham et all, 2002	[11C]NNC112	16 (9/7)	16	↑
Abi-Dargham et all, 2009	[11C]NNC112	25 (12/13)	40	↑ In DN No change in DF

Imaging cortical DA release with [11C]FLB457/ amphetamine paradigm/ multimodal imaging



[11C]FLB457 scan 1

Oral Amph
0.5 mg/kg



[11C]FLB457 scan 2

Day-1

8:30 AM

10:00 AM

12:00 PM

3:00 PM

5:30 PM

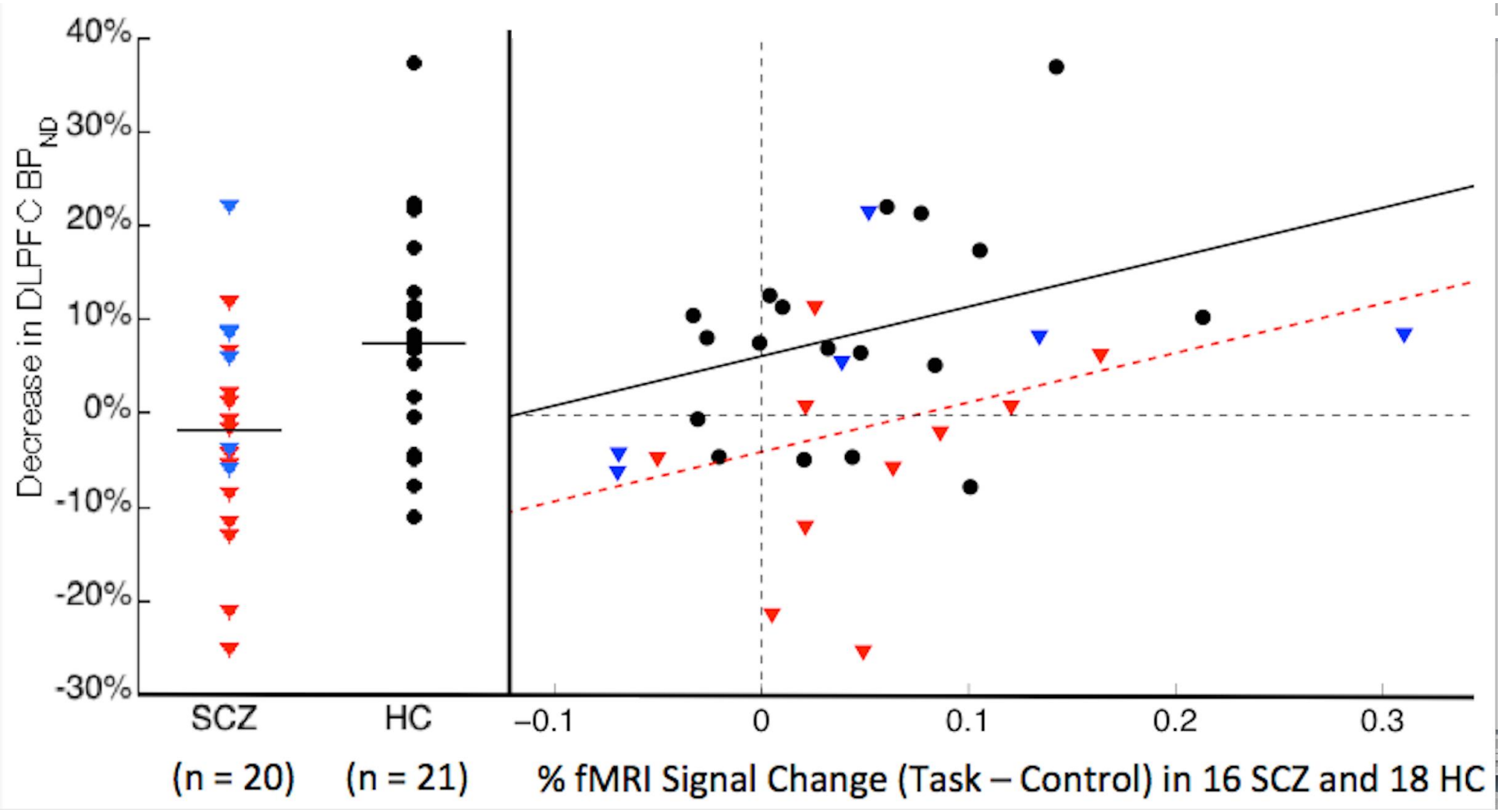
7:00 PM

PANSS

AIRS
PANSS

N-back
PANSS
Letter Number span

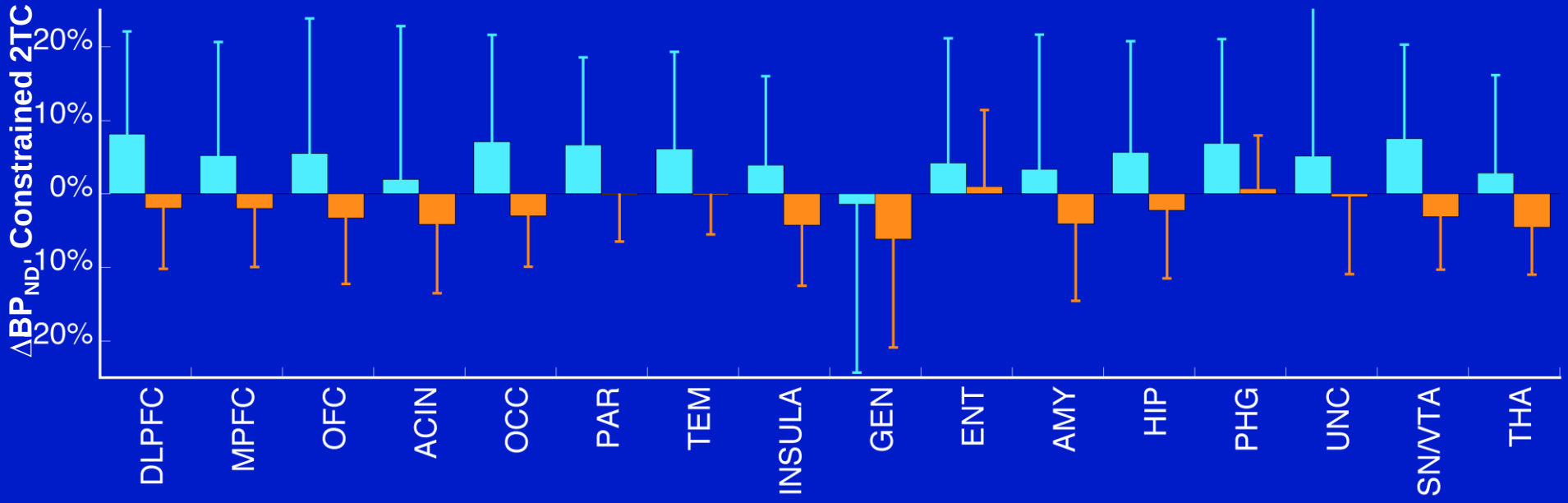
fMRI imaging session:
N back, SOT, resting state connectivity
Behavioral tests outside of the scanner



Slifstein et al, JAMA Psychiatry 2015

Generalized deficit in dopamine release capacity in SCZ

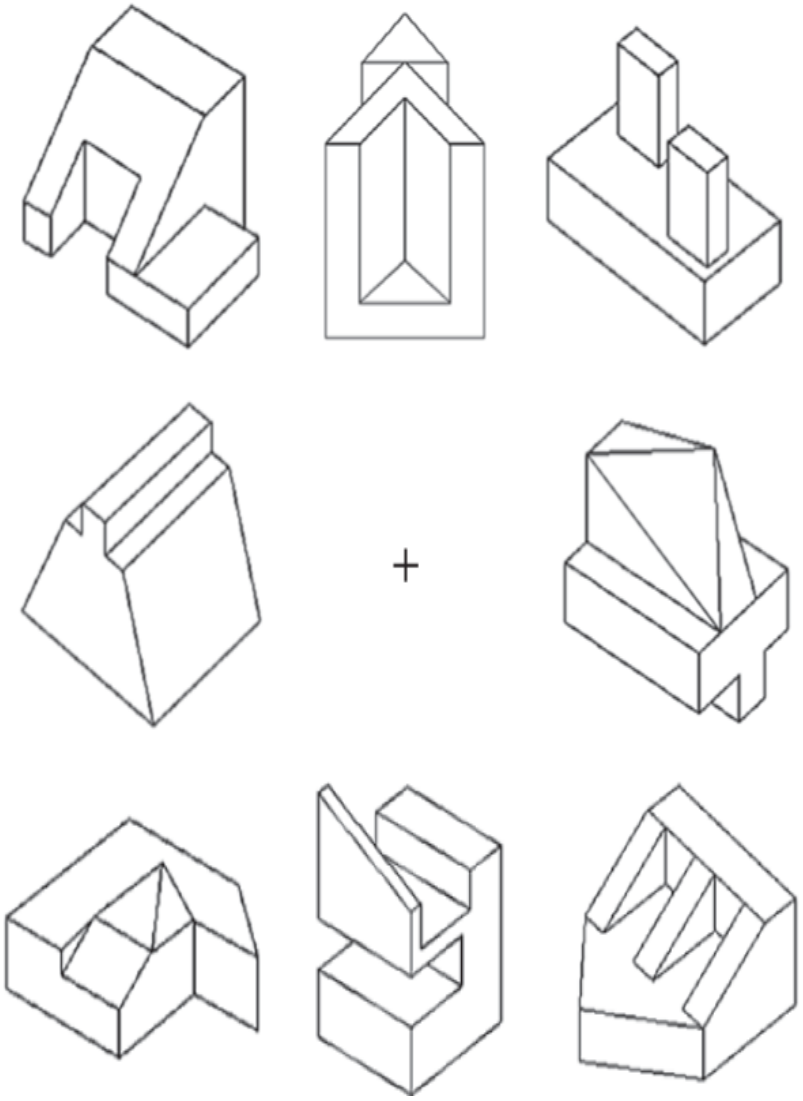
SCZ =20, HC = 21



Regional Averages in displacement of radiotracer ± SD

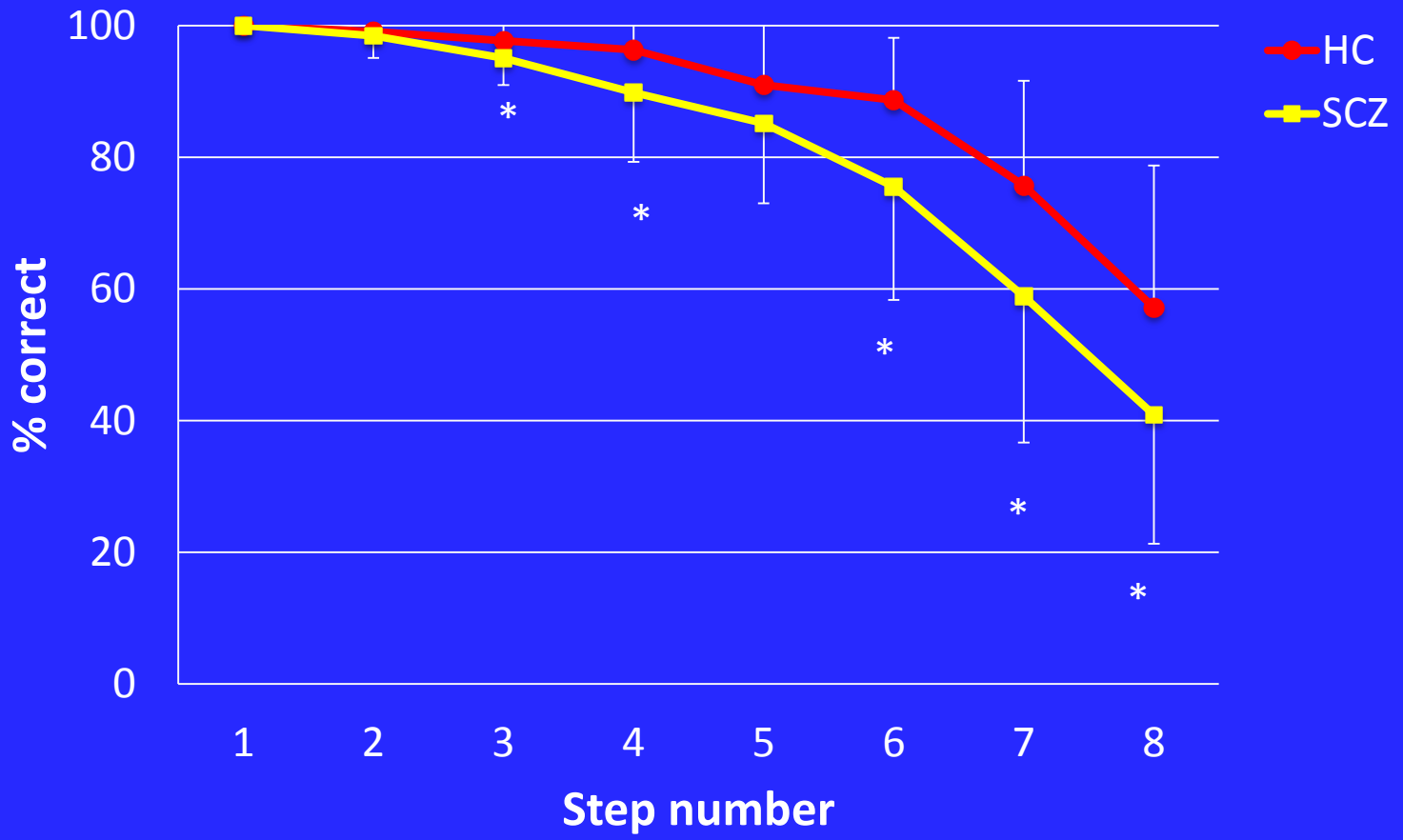
Slifstein et al, JAMA Psychiatry 2015

Self-Ordered Working Memory Task

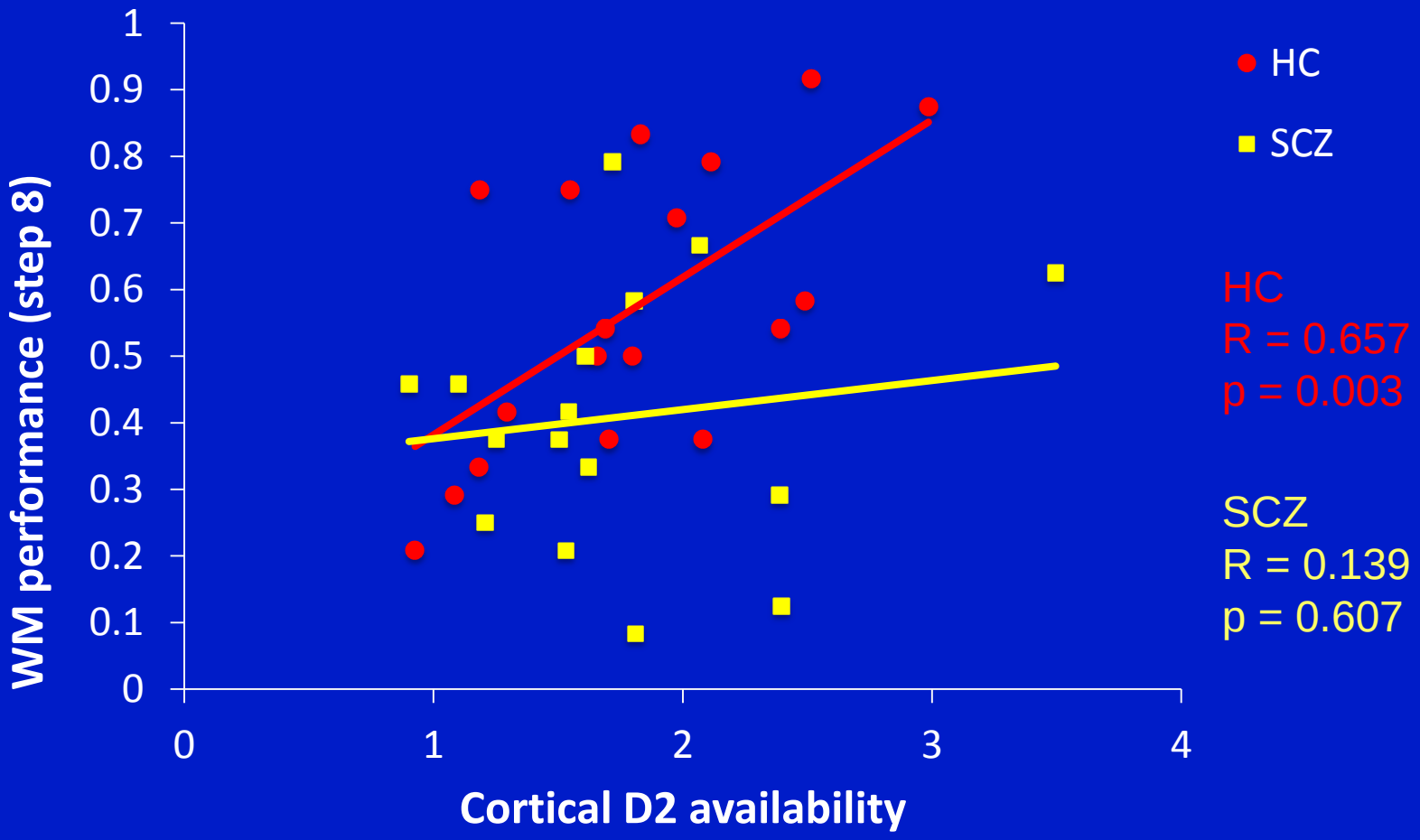


Jared Van Snellenberg

WM Performance



D2 levels in DLPFC predict Working Memory performance in HC



Slifstein et al, JAMA Psychiatry 2015

Neuroimaging of DLPFC Function in SCZ

ELSEVIER

Schizophrenia Research 60 (2003) 285–298

SCHIZOPHRENIA RESEARCH

www.elsevier.com/locate/schres

Prefrontal cortex dysfunction during working memory performance in schizophrenia: reconciling discrepant findings

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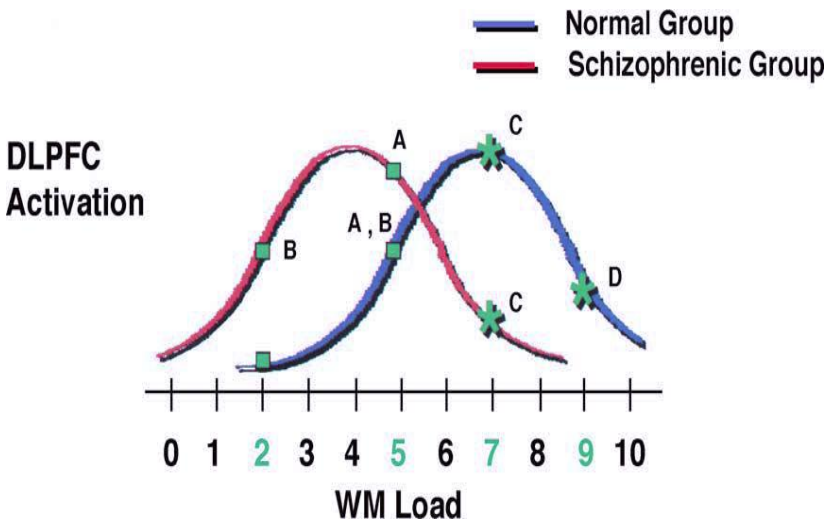
Received 23 December 2001; revised 25 March 2002; accepted 1 April 2002



Article

Complexity of Prefrontal Cortical Dysfunction in Schizophrenia: More Than Up or Down

Joseph H. Callicott, M.D.
Venkata S. Mattay, M.D.
Beth A. Verchinski, B.S.
Stefano Marenco, M.D.
Michael F. Egan, M.D.
Daniel R. Weinberger, M.D.

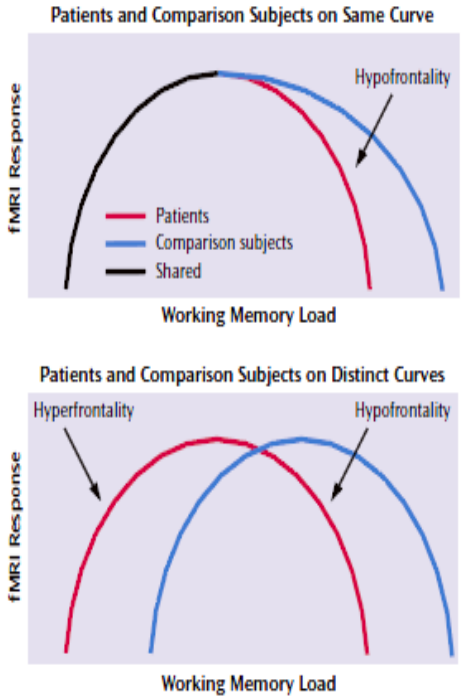
Objective: Numerous neuroimaging studies have examined the function of the dorsolateral prefrontal cortex in schizophrenia; although abnormalities usually are identified, it is unclear why some studies find too little activation and others too much. The authors' goal was to explore this phenomenon.

Method: They used the N-back working memory task and functional magnetic resonance imaging at 3 T to examine a group of 14 patients with schizophrenia and a matched comparison group of 14 healthy subjects.

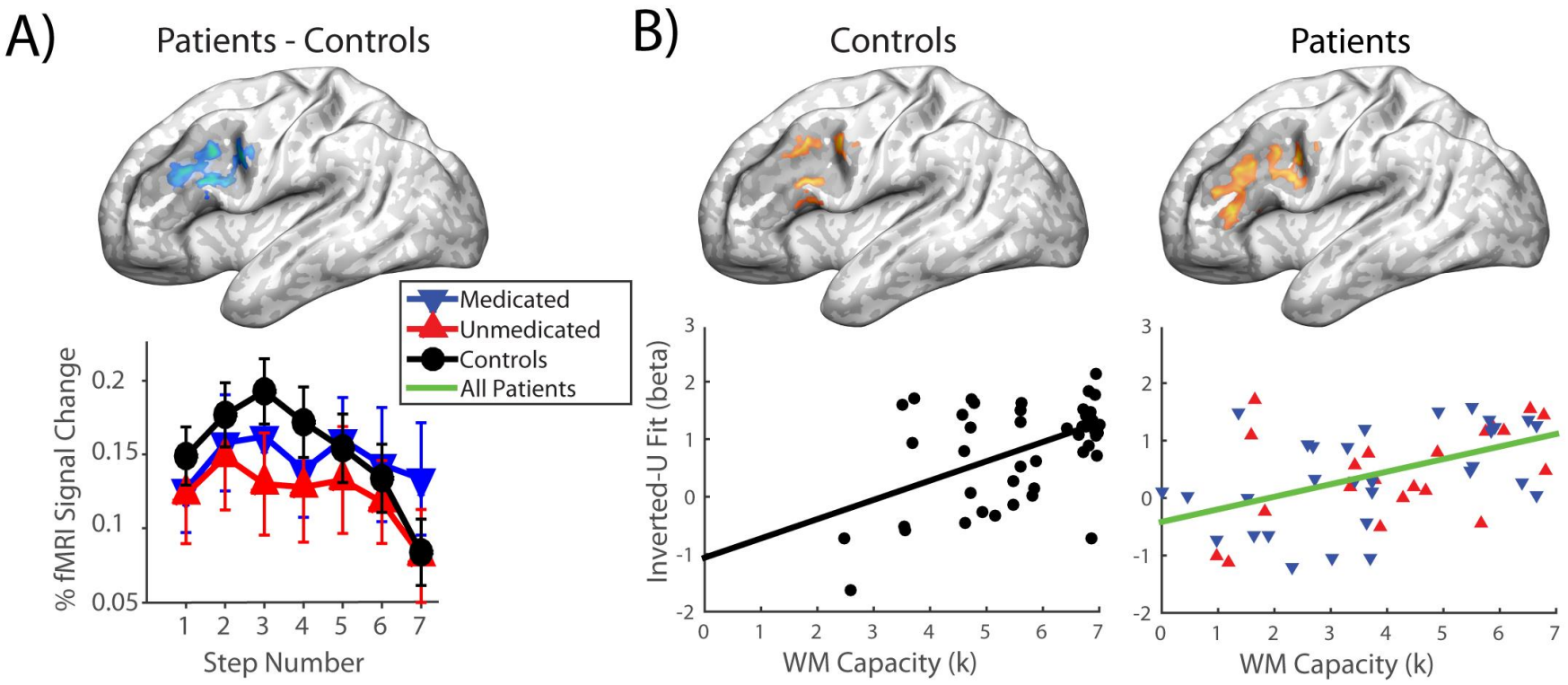
Results: Patients' performance was significantly worse on the two-back working memory task than that of healthy subjects. However, there were areas within the dorsolateral prefrontal cortex of the patients that were more active and areas that were less active than those of the healthy subjects. When the groups were subdivided on the basis of performance on the working memory task into healthy subjects and patients with high or low performance, locales of greater prefrontal activation and locales of less activation were found in the high-performing patients but only locales of underactivation were found in the low-performing patients.

Conclusions: These findings suggest that patients with schizophrenia whose performance on the N-back working memory task is similar to that of healthy comparison subjects use greater prefrontal resources but achieve lower accuracy (i.e., inefficiency) and that other patients with schizophrenia fail to sustain the prefrontal network that processes the information, achieving even lower accuracy as a result. These findings add to other evidence that abnormalities of prefrontal cortical function in schizophrenia are not reducible to simply too much or too little activity but, rather, reflect a compromised neural strategy for handling information mediated by the dorsolateral prefrontal cortex.

(Am J Psychiatry 2003; 160:2209–2215)



Mechanisms of WM Dysfunction in SCZ

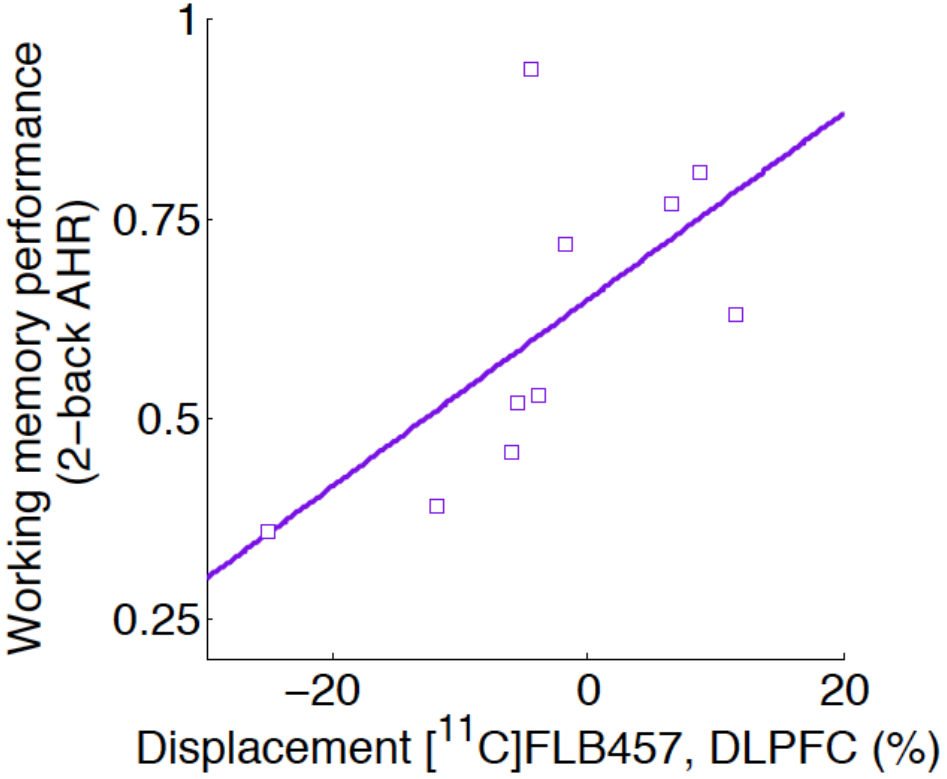


P < 0.05, Alphasim extent thresholded; DLPFC ROI in shaded region

Van Snellenberg et al., *Biol Psychiatry 2016*

Dopamine release predicts working-memory performance

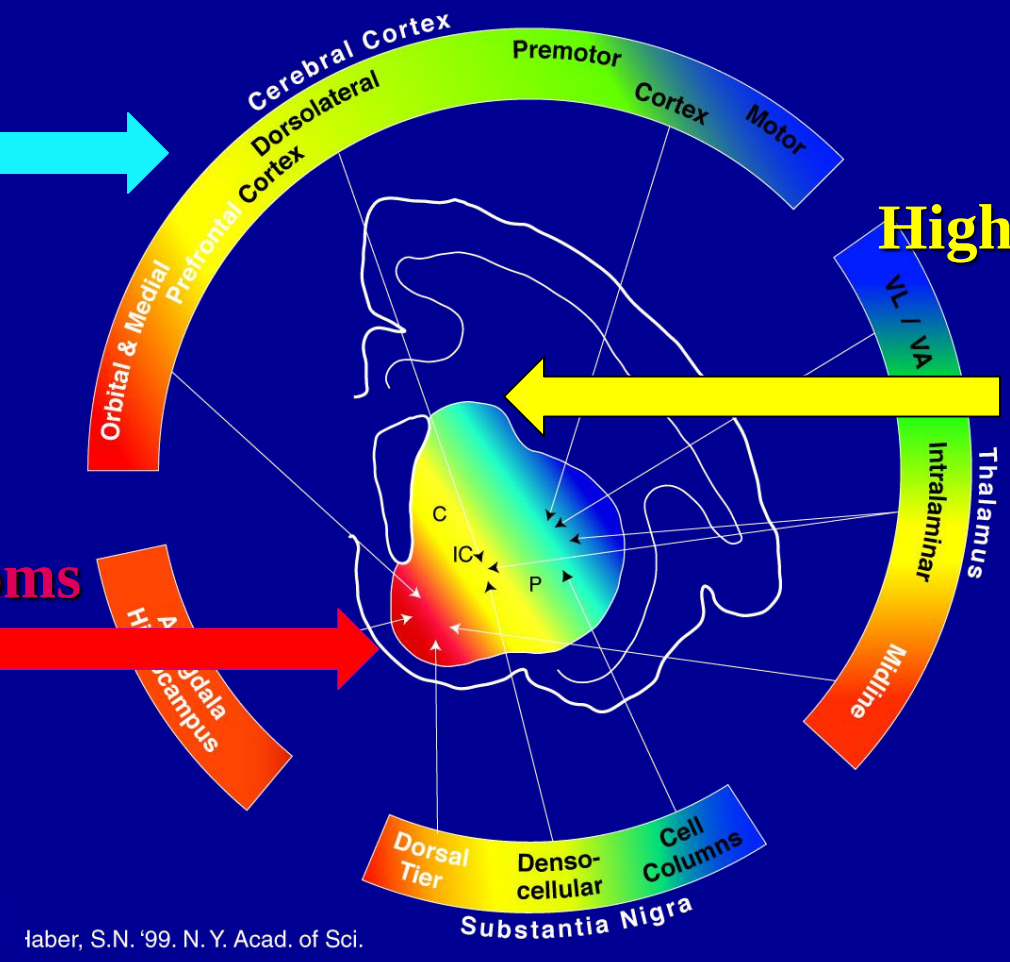
Schizophrenia



Schizophrenia (n=10)
β = 0.64
p = 0.046

Cassidy et al., *J Neurosci*, 2016

Low DA
Altered cortical function



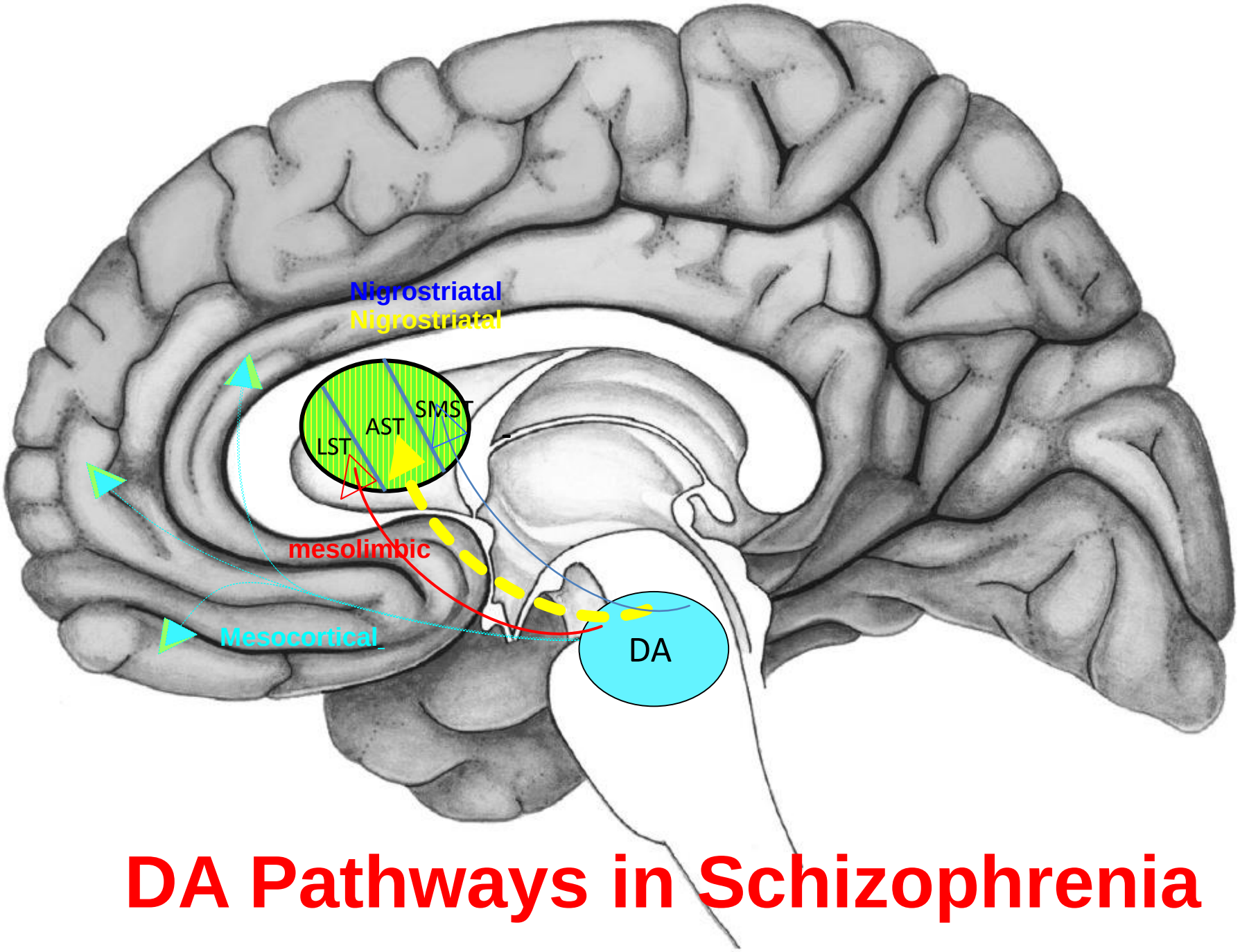
High D2 stimulation
Psychosis

Low DA
Negative symptoms

Haber and Mc Farland, Ann N Y Acad Sci.**1999, Kegeles et al, Archives of Gen Psychiatry, 2010**
Howes et al, Archives of Gen Psychiatry 2009, Slifstein et al, JAMA Psychiatry, 2015

OUTLINE

- The Hypothesis
- The Evidence
  - Confirming the hypothesis
  - Refining the hypothesis
  - **Expanding the hypothesis: extrastriatal deficit, midbrain deficit?**
- The Model(s)
  - Is dopamine dysregulation a downstream effect of other more upstream events?
  - Or could it be more proximal than generally thought?



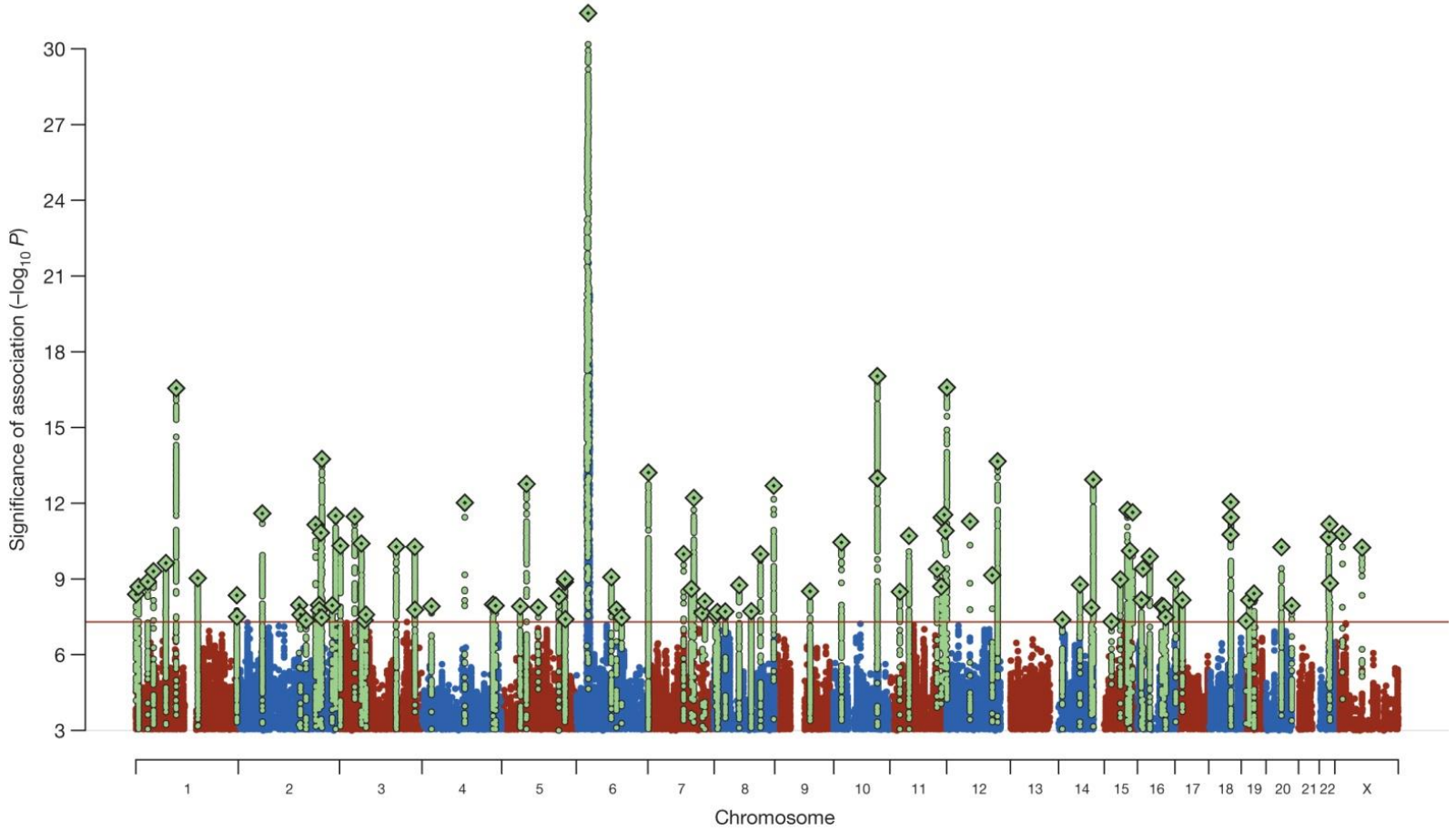
DA Pathways in Schizophrenia

OUTLINE

- The Hypothesis
- The Evidence
  - Confirming the hypothesis
  - Refining the hypothesis
  - Expanding the hypothesis
- **The Model(s)**
  - **Is dopamine dysregulation a downstream effect of other more upstream events?**
  - **Or could it be more proximal than generally thought?**

108 independent loci exceeding criteria for GWAS significance

These include D2 and other dopamine relevant genes



S Ripke *et al. Nature* **000**, 1-7 (2014) doi:10.1038/nature13595

nature

What are the consequences of increased D2 signaling during development?

Transgenic D2OE:
increase D2 by 15% in dorsal striatum to examine effects of increased D2 signaling on brain function and structure

Overexpression of D2Rs in the Striatum Leads to Deficits In Cognition And Motivation

1) **Non reversible** Deficit in **prefrontal dependent cognition**

(Kellendonk, Simpson et al. 2006 *Neuron* , Bach et al. 2008 *PNAS* , Ward et al. 2009 *Behavioral Neuroscience*

2) **Reversible** Deficit in **incentive motivation** (negative symptom)

(Drew et al. 2007 *J. Neuroscience*, Simpson et al. 2011 *Biological Psychiatry*, Ward et al. 2012 *Neuropsychopharmacology*)

How does the increased D2 signaling in striatum affect prefrontal dependent cognition?

Increased DA turnover CTX (Kellendonk, Simpson et al. 2006 *Neuron*)

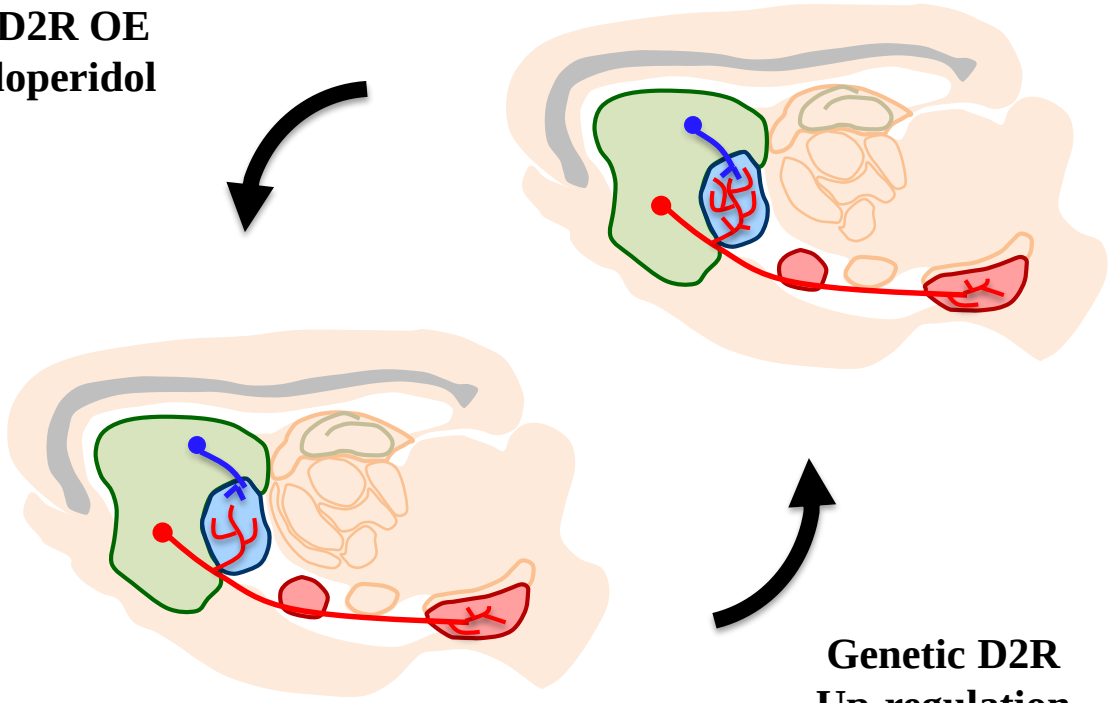
Decreased firing of VTA DA cells, due to decreased expression of NMDA receptors (Krabbe et al, *PNAS* 2015)

And even changes in anatomical collateral projections within basal ganglia:

C. Kellendonk

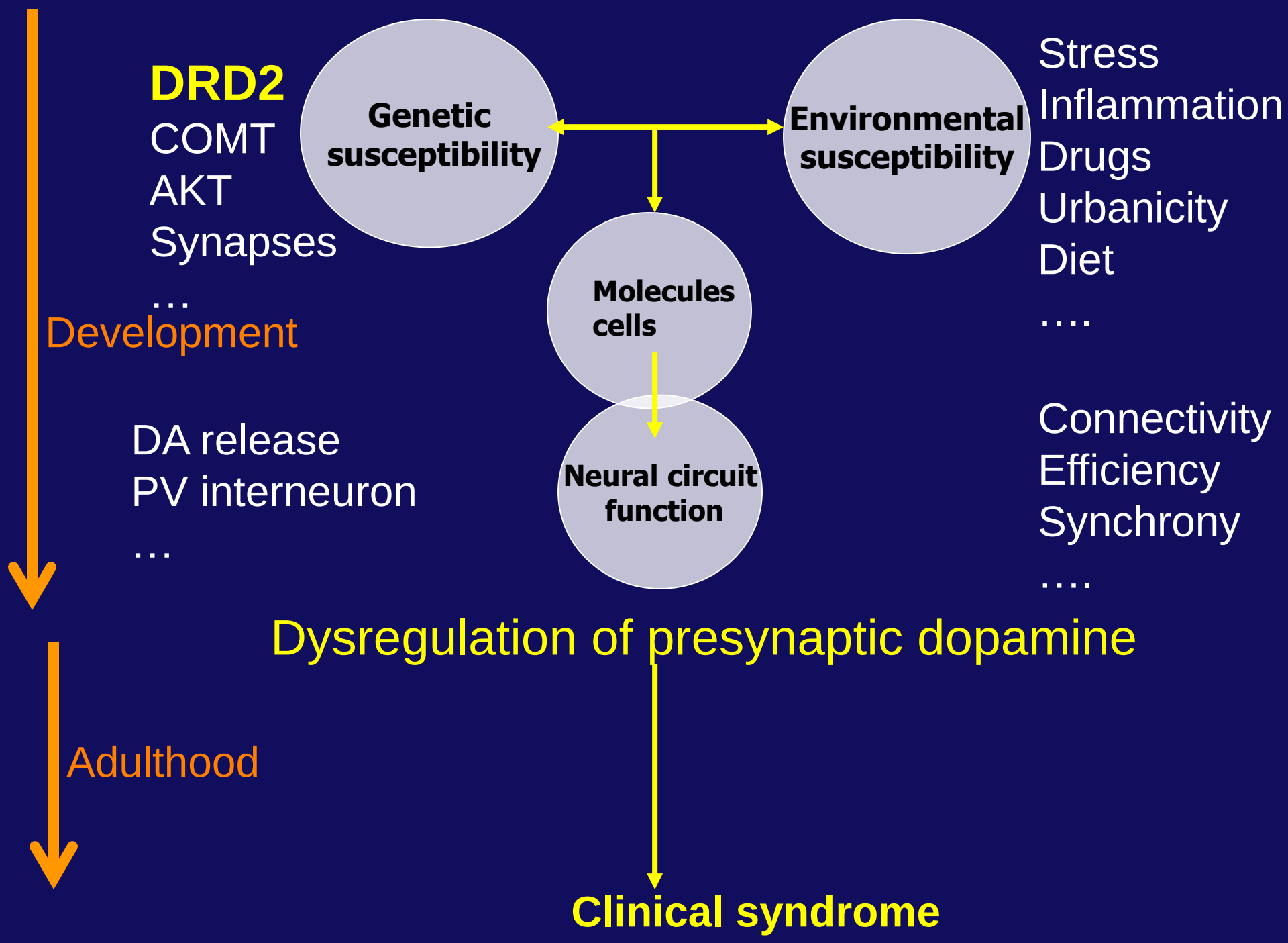
Bi-directional Modulation Of Bridging Collaterals By Dopamine D2 Receptors

Switching off D2R OE
Or chronic haloperidol



Genetic D2R
Up-regulation

Cazorla et al. 2012 *J. Neuroscience*
Cazorla et al. 2014 *Neuron*

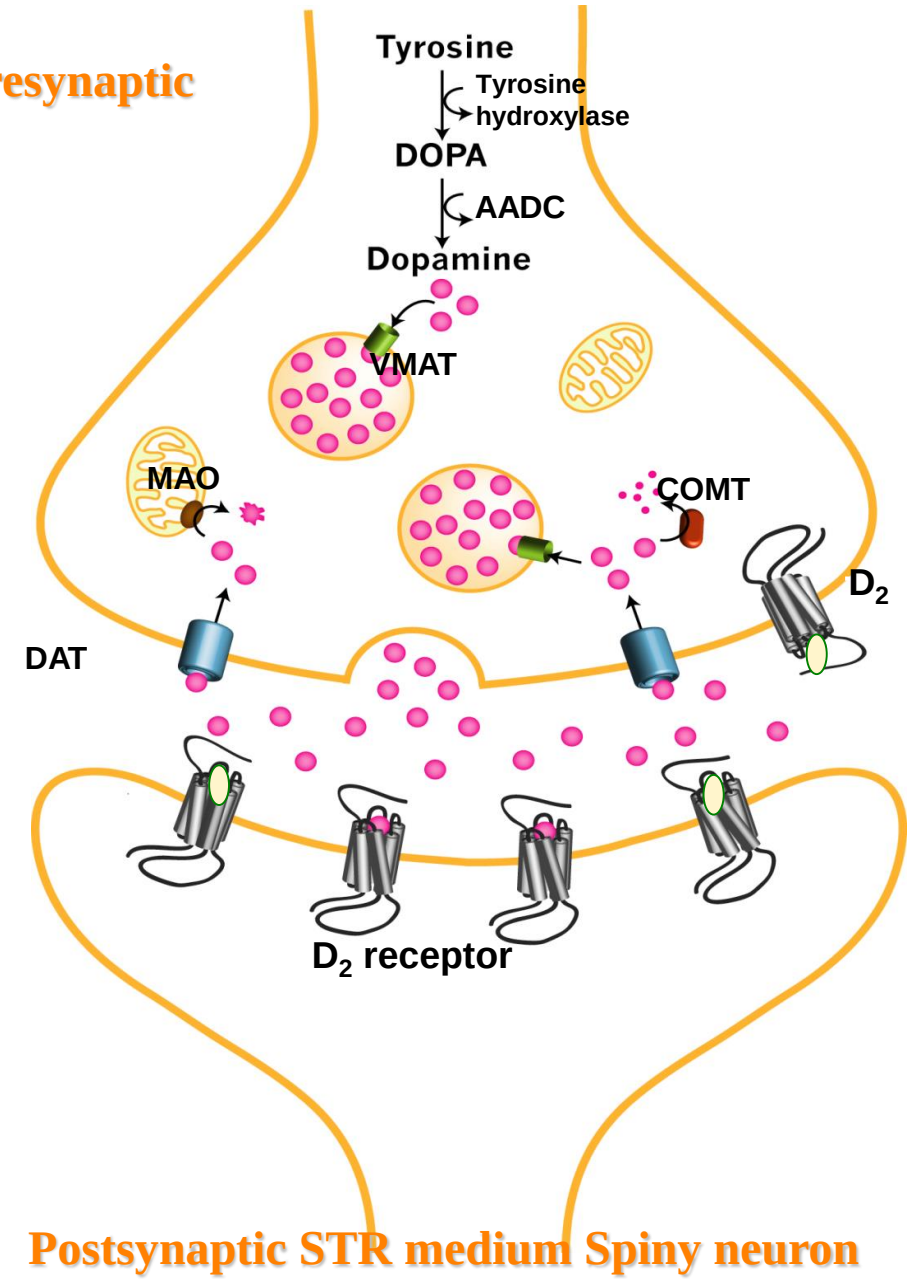

DRD2
COMT
AKT
Synapses
…
Development
Genetic susceptibility
Environmental susceptibility
Stress
Inflammation
Drugs
Urbanicity
Diet
….
Molecules cells
Neural circuit function
DA release
PV interneuron
…
Connectivity
Efficiency
Synchrony
….
Dysregulation of presynaptic dopamine
Adulthood
Clinical syndrome

Emerging questions and Future directions

- Does the dual phenotype (striatal excess , extrastriatal deficit) exist at a single patient level?
- Which is primary?: D2 vs presynaptic DA dysfunction, striatal vs extrastriatal?
- Can the global « deficit »: pancortical, amygdala, hippocampus, thalamus, midbrain, explain the different domains of pathology?
- How does this affect learning and translate into symptoms?
- Our treatments do not address this complexity!

- We need to understand the cellular mechanisms and consequences to develop better treatments

Potential cellular mechanisms for striatal DA dysregulation



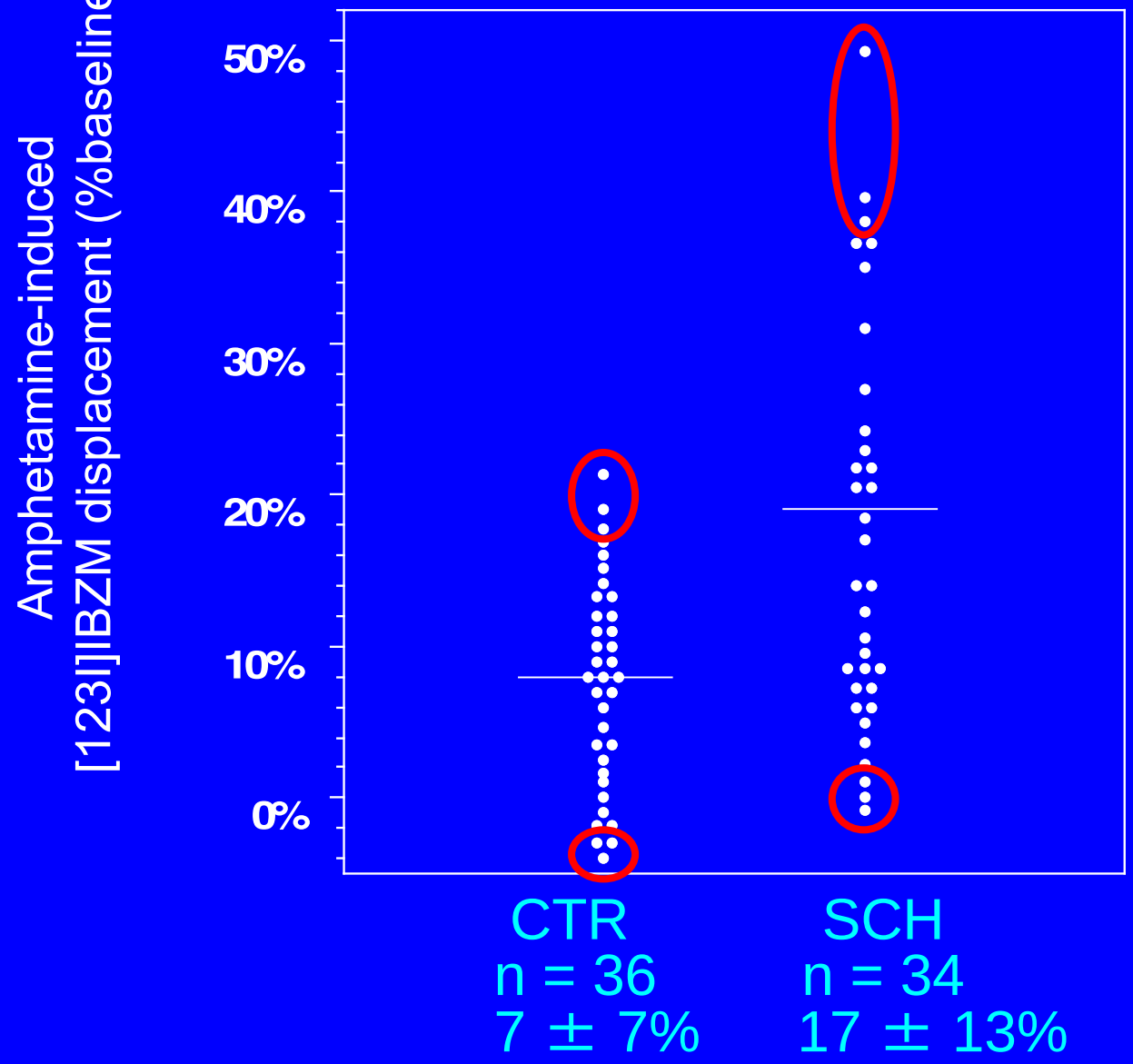
[18F]f-DOPA:

More transport of fdopa into cell: AAT
More synthesis: Tyr H or AADC activity
More storage: VMAT
Less metabolism: COMT or MAO
Specific problem with the D2 autoreceptors only in striatum: no feedback on the subset of cells that is overactive
Number of DA neurons
Excess firing activity of a subset of DA neurons

Amphetamine or AMPT:

More vesicles
Abnormal DAT function: “leaky” DAT and more synthesis to compensate?
D2 shifted intrasynaptically
D2 more sensitive to DA
ACH enhancement of DA release is abnormal
…..

Amphetamine-induced DA release in schizophrenia (striatum as a whole)



p = 0.001

Laruelle, PNAS, 1996
Abi-Dargham, AJP, 1998

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