High D2 stimulation
Psychosis

Relates to psychosis
And its treatment response

Low DA
Negative symptoms

Howes et al, Archives of Gen Psychiatry 2009
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.

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

18 unmed SCZ
24 HC
Disrupted Functional Connectivity in Schizophrenia

Horga et al, JAMA Psychiatry, 2016
How does DA dysregulation lead to symptoms
Variable context tone reproduction task

Consistent context = strong expectation of short tone

Test: long tone is perceived as shorter than it is

Variable context = weak expectation of short tone

Test: long tone is perceived unbiased

Teufel, Current Biology 28, R148–R169, February 19, 2018
Expectations due to prior sensory input

Prediction

Certainty of context

Perception

Sensory input

Dopamine
OUTLINE

1- Schizophrenia as a global brain disease
2- The role of dopamine within this global pathology
3- Imaging dopamine
4- Findings in striatum
5- Findings in extrastriatal brain areas
6- Modeling dopamine dysfunction in mice
7- Synthesis and future directions
Imaging cortical DA release with $[11\text{C}]$FLB457/ amphetamine paradigm/ multimodal imaging

Oral Amph 0.5 mg/kg

$[11\text{C}]$FLB457 scan 1

$[11\text{C}]$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

% fMRI Signal Change (Task – Control) in 16 SCZ and 18 HC

Decrement in DLPFC BP

SCZ (n = 20)  HC (n = 21)
Slifstein et al, JAMA Psychiatry 2015

Decrease in DLPFC BPND

(n = 20)  (n = 21) % fMRI Signal Change (Task - Control) in 16 SCZ and 18 HC
Dopamine release in DLPFC correlates to working-memory performance (n back)

Schizophrenia (n=10)
β = 0.64
p = 0.046
Self-Ordered Working Memory Task
WM Performance

[Graph showing WM performance over steps for HC and SCZ groups. HC group shows a generally higher performance than SCZ group at each step.]
Mechanisms of WM Dysfunction in SCZ

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

Van Snellenberg et al., Biol Psychiatry 2016
Low DA
Altered cortical function

Low DA
Negative symptoms

High D2 stimulation
Psychosis

Generalized deficit in dopamine release capacity in SCZ

Slifstein et al, JAMA Psychiatry 2015
Nigrostriatal
DA
LST
AST
SMST

Mesocortical
Mesolimbic
Nigrostriatal
Nigrostriatal
Kegeles et al, Archives of Gen Psychiatry, 2010

Abi-Dargham et al, Biol Psychiatry cover, Jan 2017
[18F]VAT in one human volunteer
[\textsuperscript{18}F]VAT in one human subject

Coronal view at level of striatum. PET fused to coregistered MRI. Summed over 150 min scan
Interim summary

Confirmation of striatal DA excess, present even in prodrome, and predicts conversion
Topography: Nigrostriatal/ associative rather than mesolimbic
Evidence of DA cortical deficit
DA deficit may be global
Functional significance: multilevel impact; includes abnormal connectivity, abnormal prediction error or predictive learning, abnormal cognition
OUTLINE

1- Schizophrenia as a global brain disease
2- The role of dopamine within this global pathology
3- Imaging dopamine
4- Findings in striatum
5- Findings in extrastriatal brain areas
6- Modeling dopamine dysfunction in mice
7- Synthesis and future directions
Fifteen percent increase in D2 expression **during development** in dorsal striatum

Dopamine D2 receptor over-expressing mouse (D2OE)
# D2OE Behavioral Deficits

## Cognitive Deficits

<table>
<thead>
<tr>
<th></th>
<th>PTs w SCZ</th>
<th>D2OE Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conditional Associative Learning</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Inhibitory Control</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Reversal Learning</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Time Perception</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Time Production</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Working Memory</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Maintenance of Info. in WM</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Problem Solving</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

Simpson & Kellendonk, Biol. Psy., 2017
### D2OE Behavioral Deficits

#### Motivational Deficits

<table>
<thead>
<tr>
<th></th>
<th>PTs w SCZ</th>
<th>D2OE Mice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent Effort Expenditure</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Allocation of Effort for Rewards</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Reward Value-Based Decisions</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Hedonic Reaction</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

Simpson & Kellendonk, Biol. Psy., 2017
Effects of D2 OE in the mouse

Wild Type Mouse

D2OE Mouse

Altered 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

Simpson & Kellendonk, Biol. Psy., 2017
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
Back translation: connectivity of rostral caudate to GPe

$\text{d} = 0.87$
$P = 0.017$

Van Snellenberg et al., *Preliminary Data*
OUTLINE

1- Schizophrenia as a global brain disease
2- The role of dopamine within this global pathology
3- Imaging dopamine
4- Findings in striatum
5- Findings in extrastriatal brain areas
6- Modeling dopamine dysfunction in mice
7- Synthesis and future directions
Genetic susceptibility

Environmental susceptibility

Molecules
cells

Neural circuit function

Development

DRD2
COMT
AKT
Synapses

DA release
PV interneuron

Dysregulation of presynaptic dopamine

Adulthood

Inflammation
Drugs
Urbanicity
Diet

Connectivity
Efficiency
Synchrony

Clinical syndrome
Natural course of schizophrenia

Premorbid  Prodromal  Onset/ deterioration  Residual/ stable
Genes/environment  Migration defects  Apoptosis

Dysconnectivity

Striatal Dopamine increase
Hippocampal GABA deficit/ Glutamate excess/ NMDA

Neurodegeneration: oxidative

Healthy  Symptomatic

Cell differentiation
Synaptogenesis
Pruning

Myelination/ circuit formation

10  20  30  40  50

After Lieberman et al Mol Psych. 2018
Where are we in the big scheme of things…..

• Does the dual phenotype (striatal excess, extrastriatal deficit) exist at a single patient level?
• which is primary?
• What are the precise cellular mechanisms of dopamine dysregulation?
• Can local regulation of DA in the associative striatum be altered? What are the factors at play?
• The link to symptoms:
• The functional properties of small and large circuits within the brain is affected by dopamine, and by dopaminergic dysregulation
• What are the precise mechanisms leading from abnormal dopamine kinetics to symptoms?
My team at Columbia University
My team at Stony Brook University
Columbia University / NYSPI

Division of Translational Imaging

Mark Slifstein PhD
Roberto Gil, MD
Larry Kegeles, MD, PhD
Ragy Girgis, MD
Guillermo Horga, MD
Jared Van Snellenberg, PhD
Cliff Cassidy, PhD
Jodi Weinstein, MD
Xiaoyan Xu PhD

Funding: NIMH, NIDA, NARSAD

Conte Center

Eric Kandel, MD, PhD
Jonathan Javitch MD, PhD
Jeff Lieberman MD
Holly Moore, PhD
Steve Rayport, MD, PhD
Daphna Shohamy, PhD
Eleanor Simpson, PhD
Christoph Kellendonk, PhD
Rochester U:
Suzanne Haber, PhD
U Pittsburgh
Raj Narendran MD
Yale collaborators:
Cyril D’ Souza, Robert Malison,
 Richard Carson, Henry Huang,
Nabeel Nabulsi
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
- Dysfunction of D2 autoreceptors
- 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
  …..
Future direction: DAergic cells from hiPSCs from subjects with extreme levels of DA release to examine mechanisms of DA dysfunction in collaboration with J Javitch.

\[ n = 36 \quad CTR \quad 7 \pm 7\% \]

\[ n = 34 \quad SCH \quad 17 \pm 13\% \]

\[ p = 0.001 \]

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