Striosomes selectively mediate value-based learning possibly through FSIs

Sabrina Drammis & Jiajia Zhao

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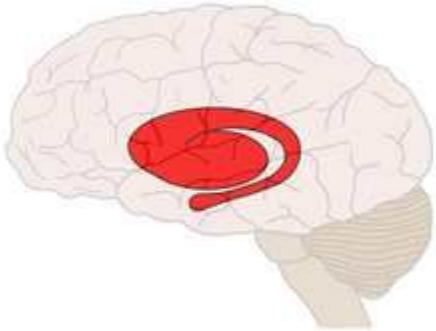
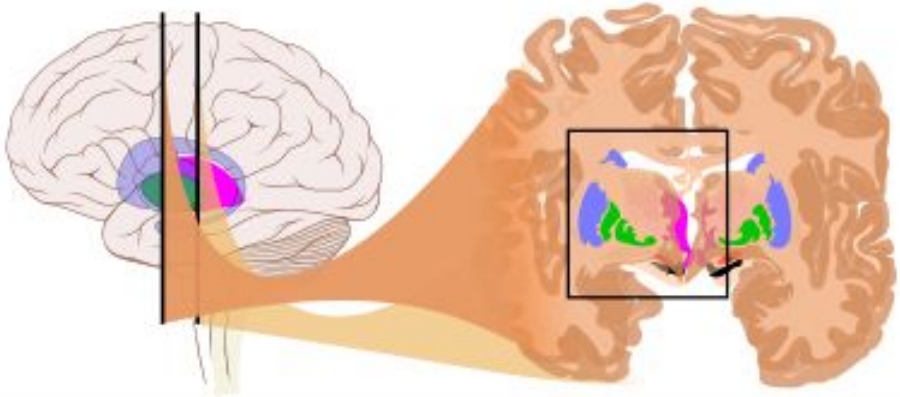
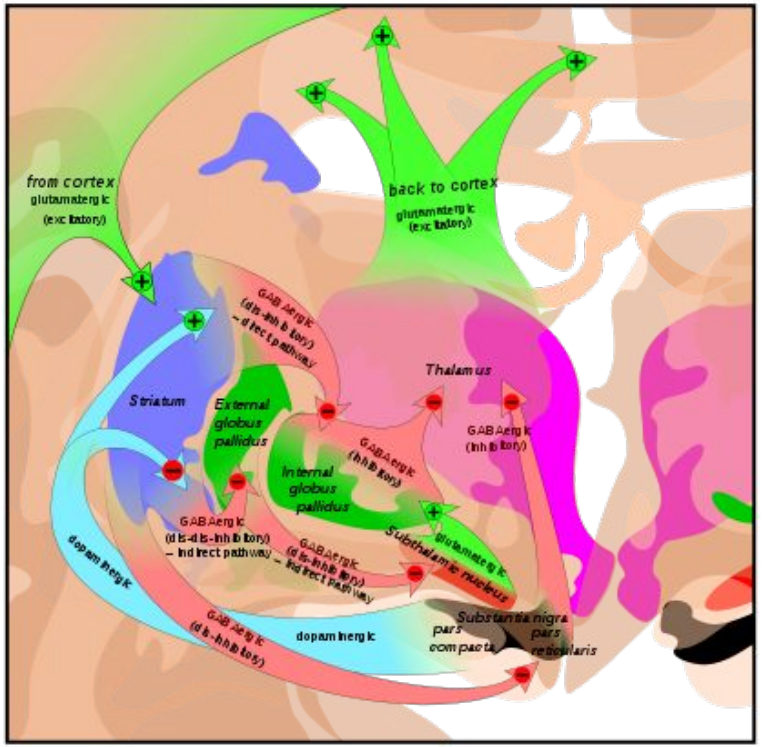





from cortex
glutamatergic
(excitatory)
back to cortex
glutamatergic
(excitatory)
GABAergic
(dis-inhibitory)
– direct pathway
Striatum
External
globus
pallidus
Thalamus
GABAergic
(inhibitory)
GABAergic
(inhibitory)
Internal
globus
pallidus
GABAergic
(dis-dis-inhibitory)
– indirect pathway
GABAergic
(dis-inhibitory)
– indirect pathway
glutamatergic
Subthalamic nucleus
dopaminergic
GABAergic
(dis-inhibitory)
dopaminergic
Substantia nigra
pars
compacta
pars
reticularis

Associated disorders

Parkinson’s disease

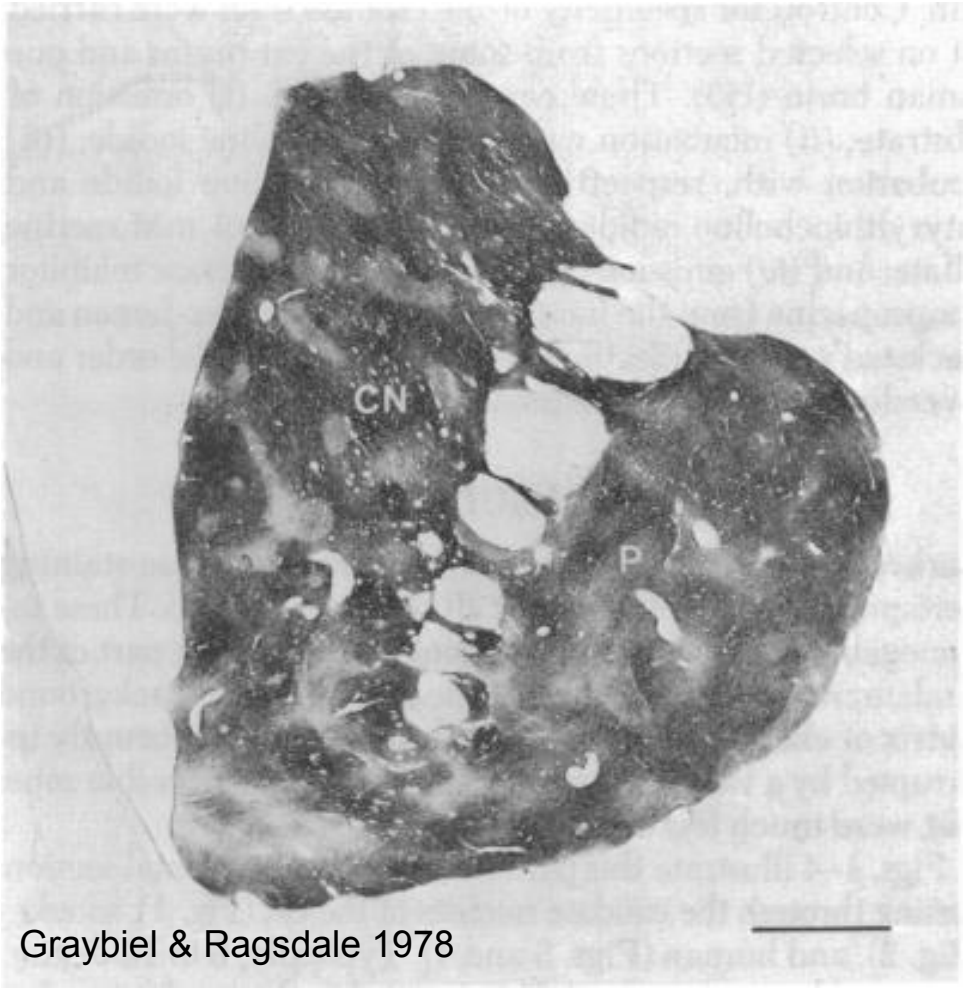
Huntington’s disease

Autism spectrum disorder

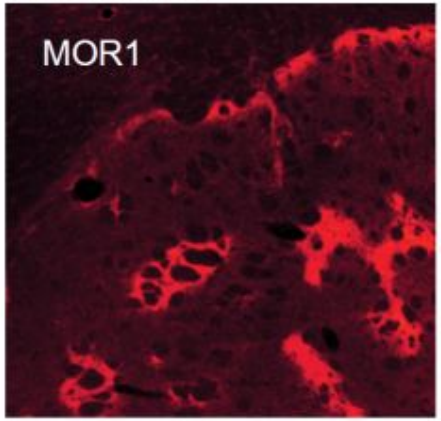
Addiction

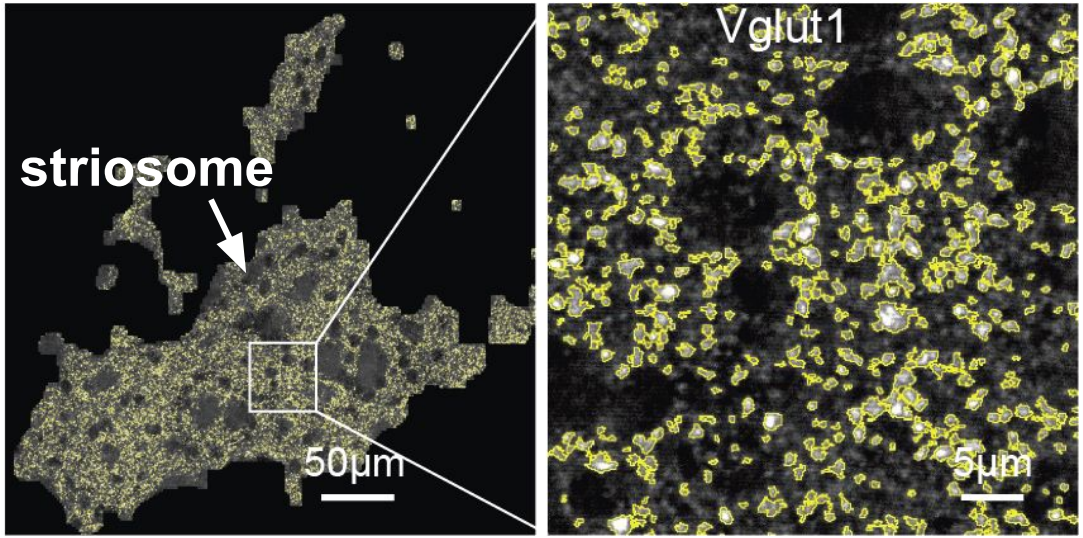
Mood

Bipolar disorder

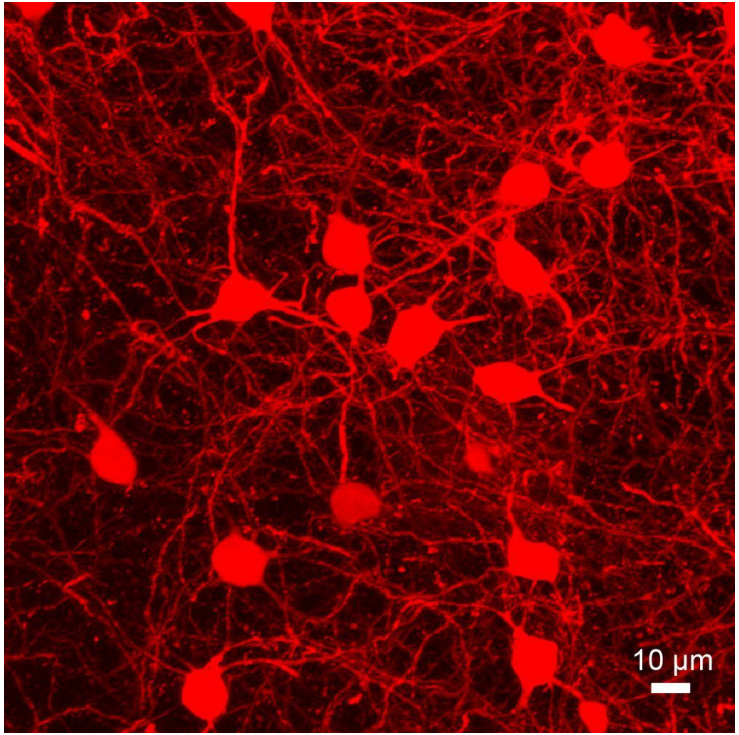


Graybiel & Ragsdale 1978




striosome
50μm
Vglut1
5μm

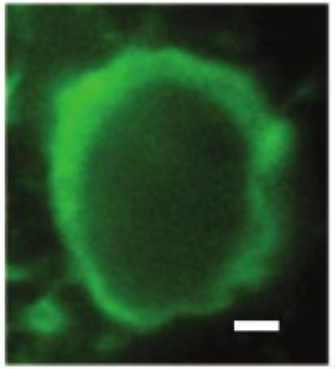
medium spiny neurons (MSNs) / spiny projection neurons (SPNs)



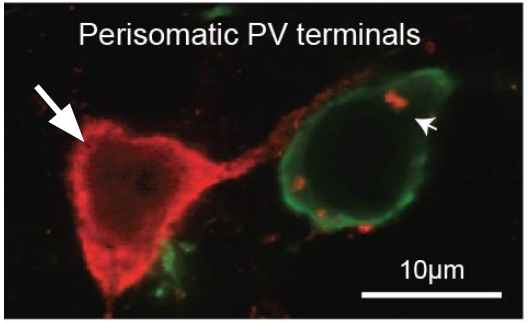
95% of neurons in the striatum

D1/D2 dopamine receptors

GABAergic inhibitory

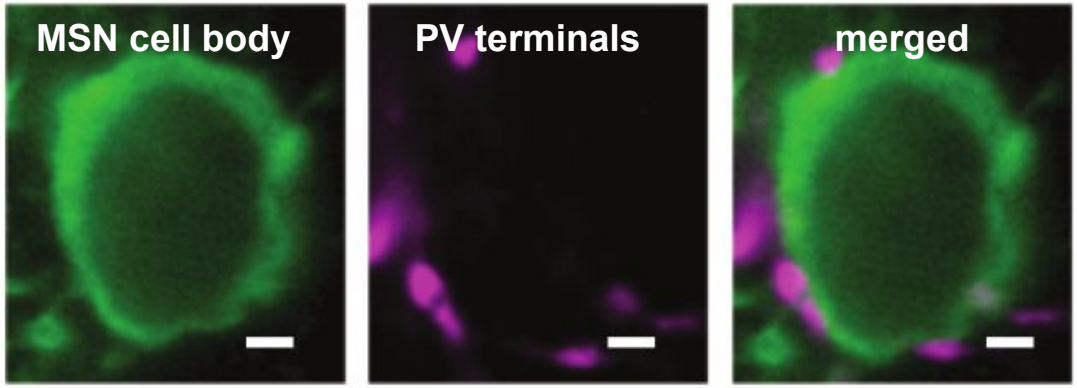


Paravalbumin (PV) inhibitory interneurons

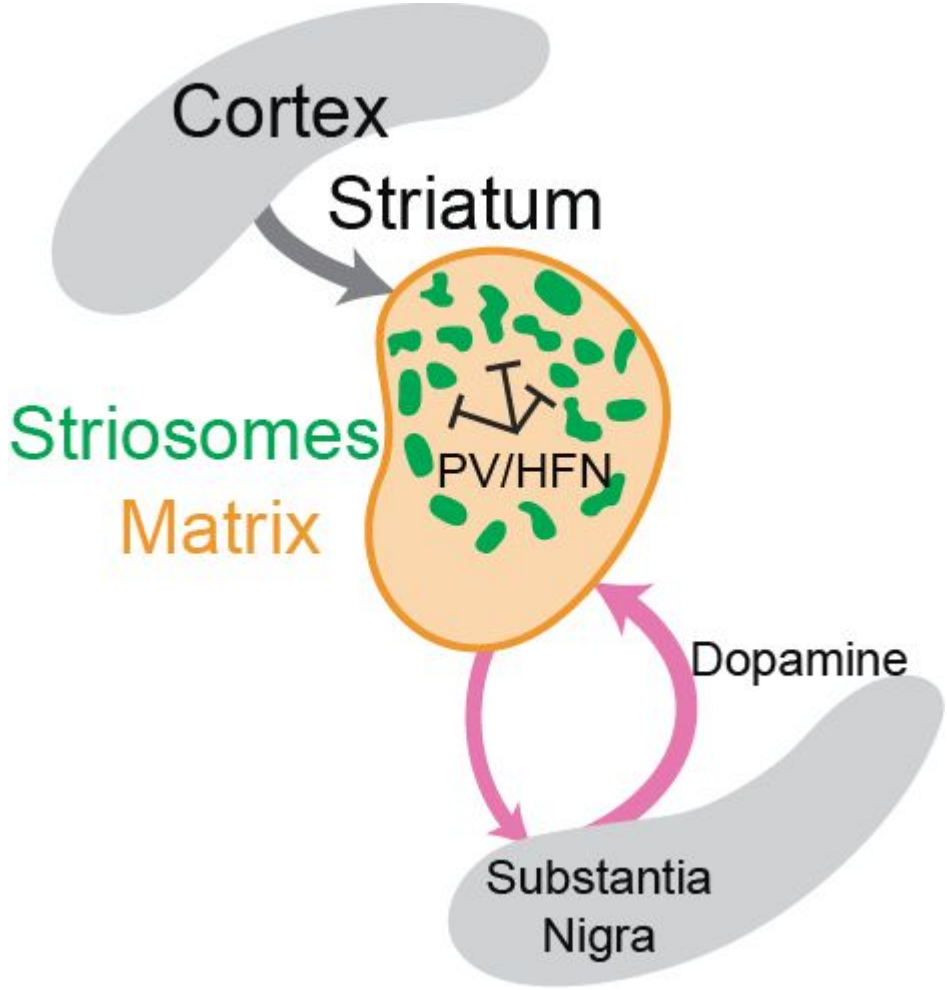


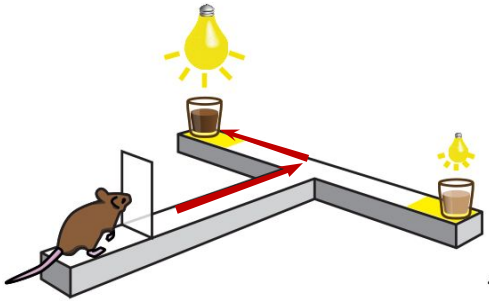
common inhibitory interneuron in striatum

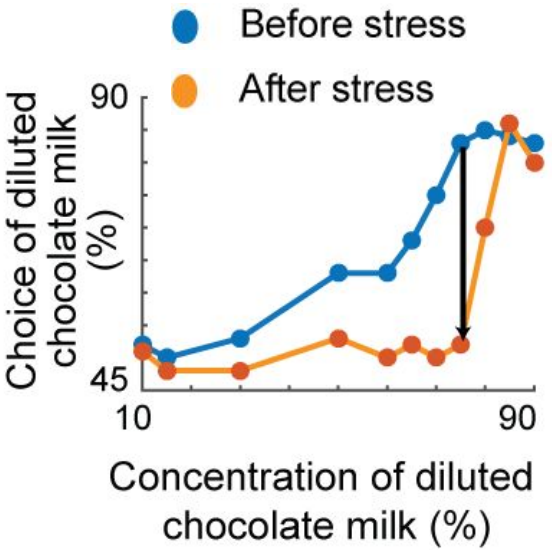
majority synapse on the soma (or close)

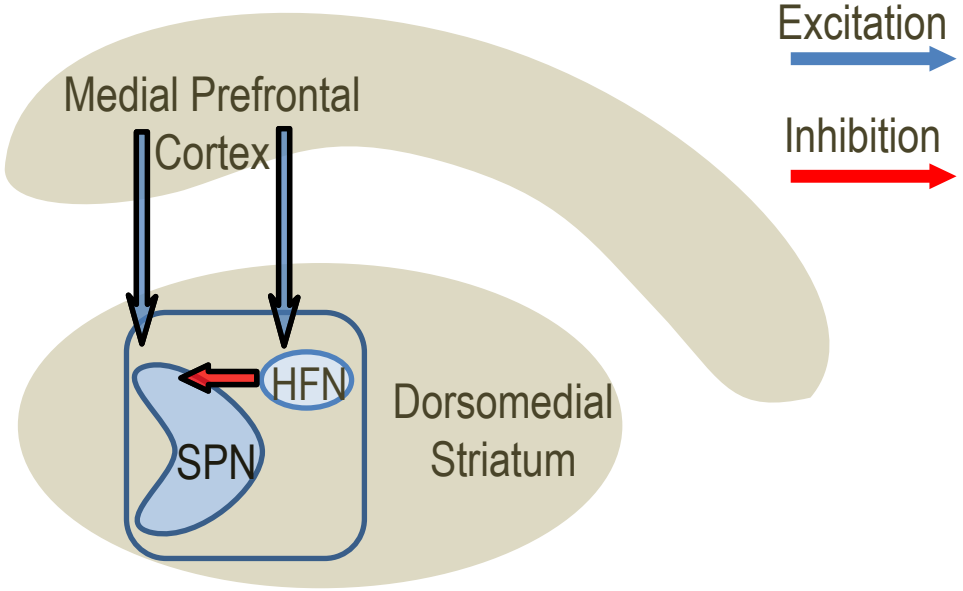


also called…
FSI and HFN

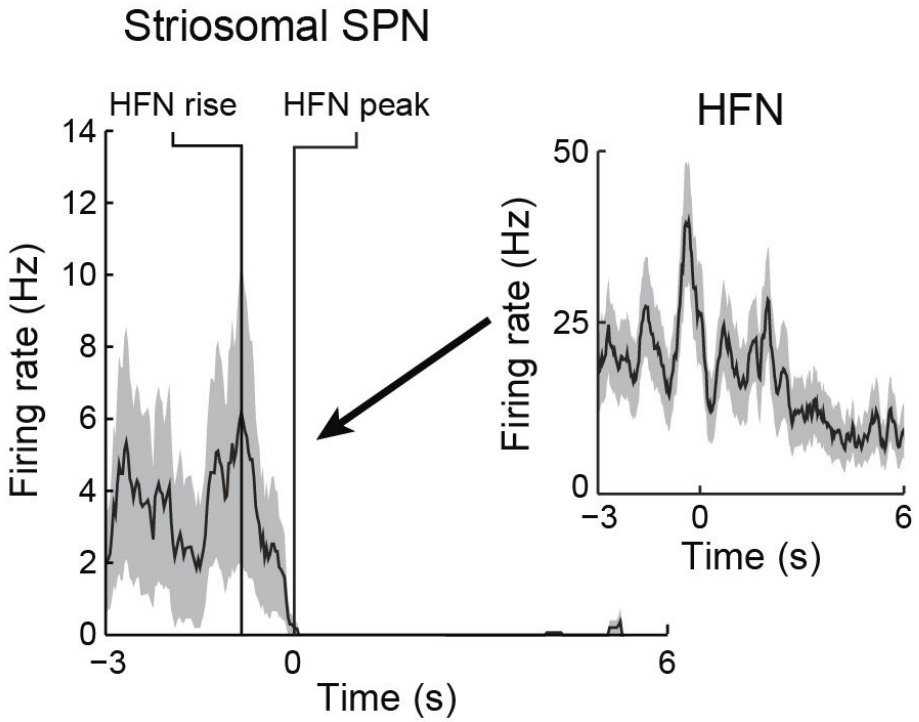

Cortex
Striatum
Striosomes
Matrix
PV/HFN
Dopamine
Substantia
Nigra





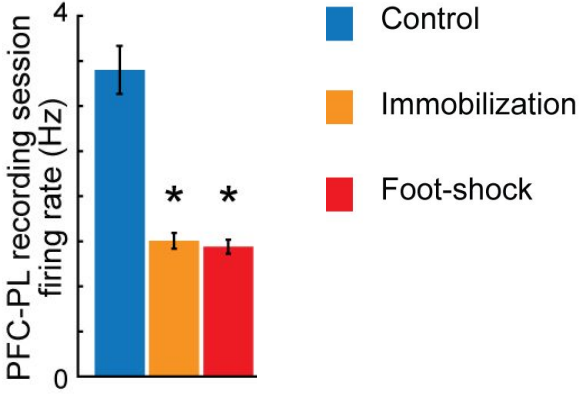


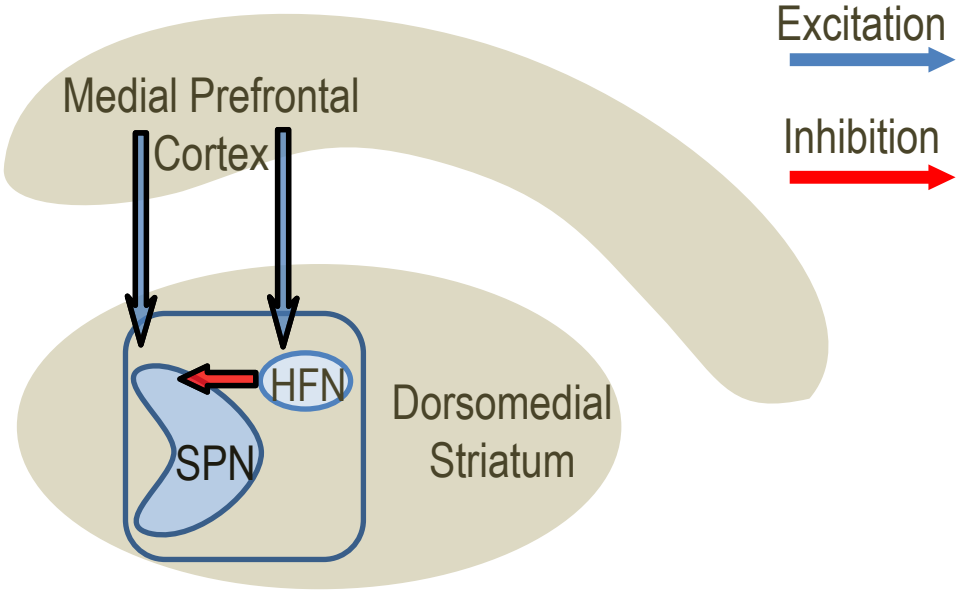
Friedman et al. 2017



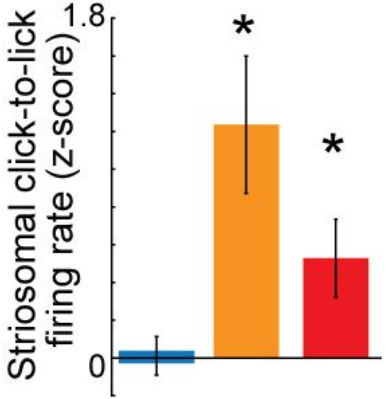
Friedman et al. 2015

PFC

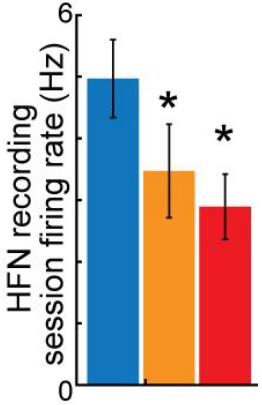




striosomal SPN



HFN

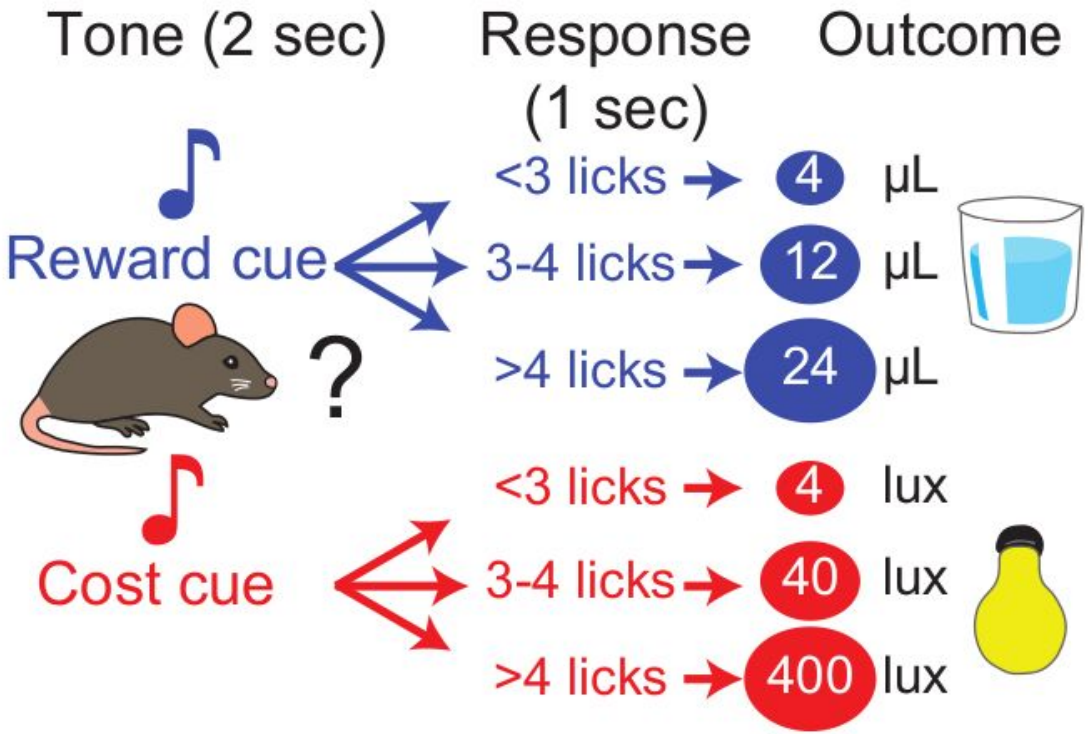


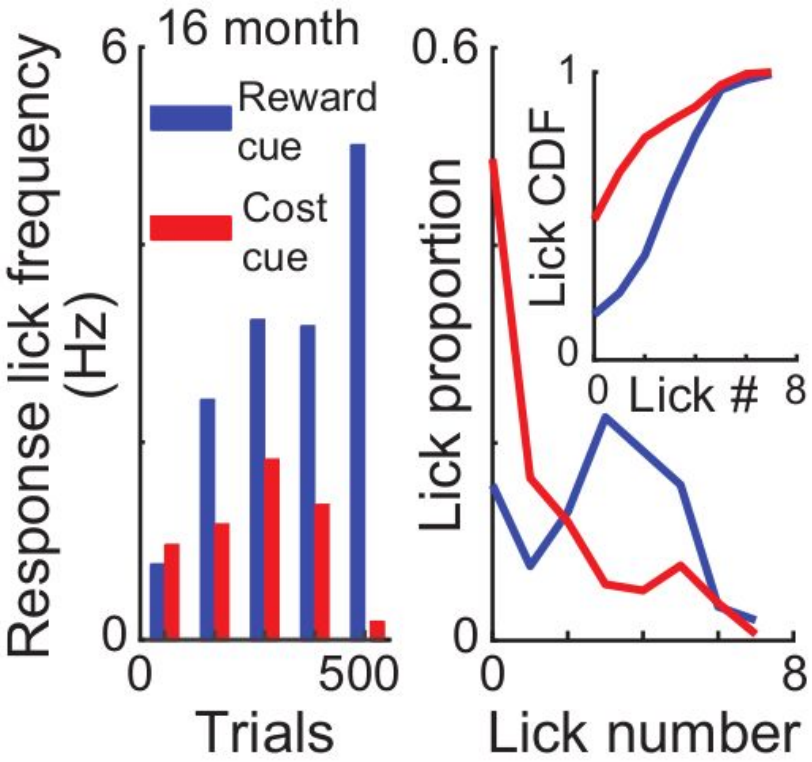
Friedman et al. 2017

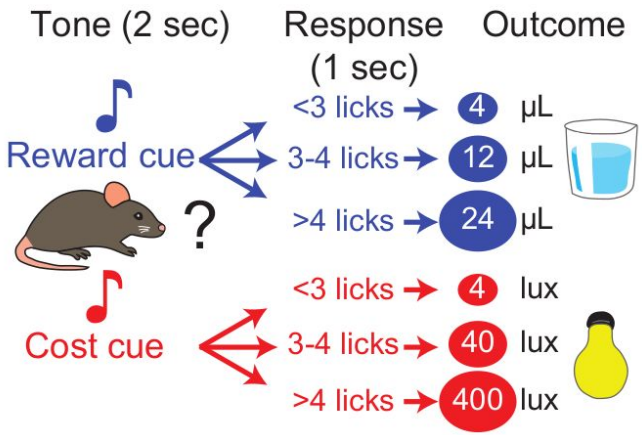
What is the function of the striosomal compartments in learning a decision-making task?

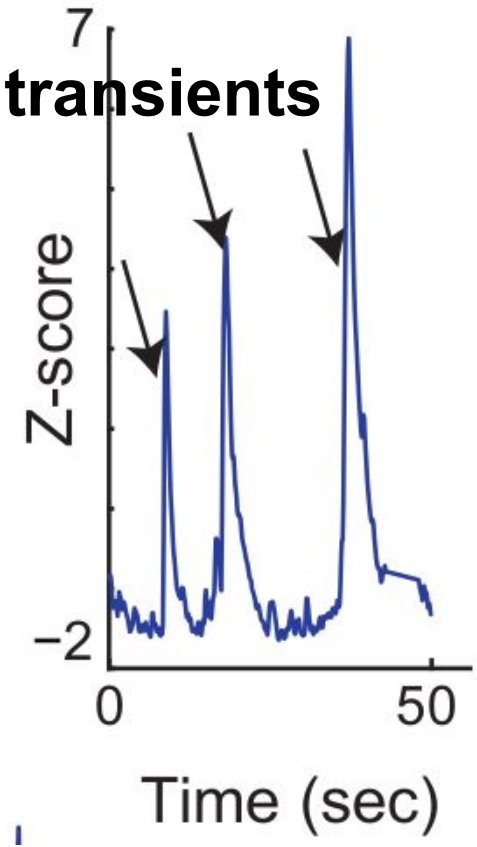
(How does aging and disorder, HD, affect learning)

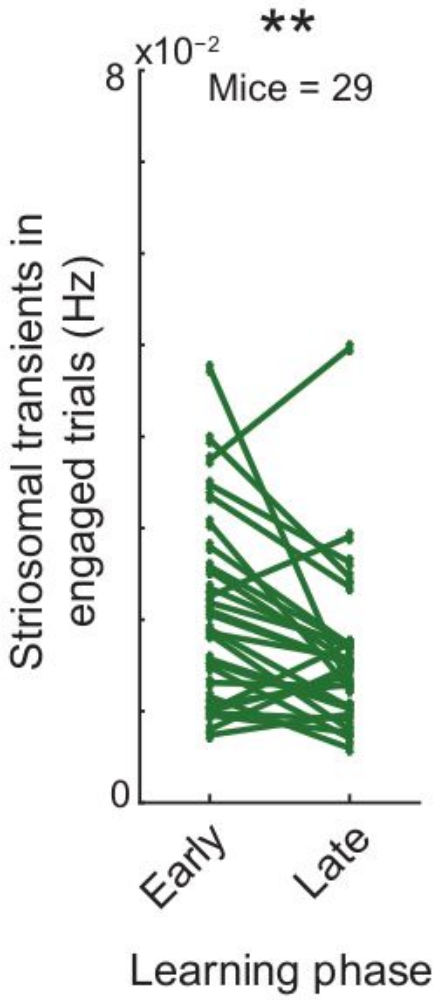
(Are PV neurons selectively critical for control of learning-related activity?)

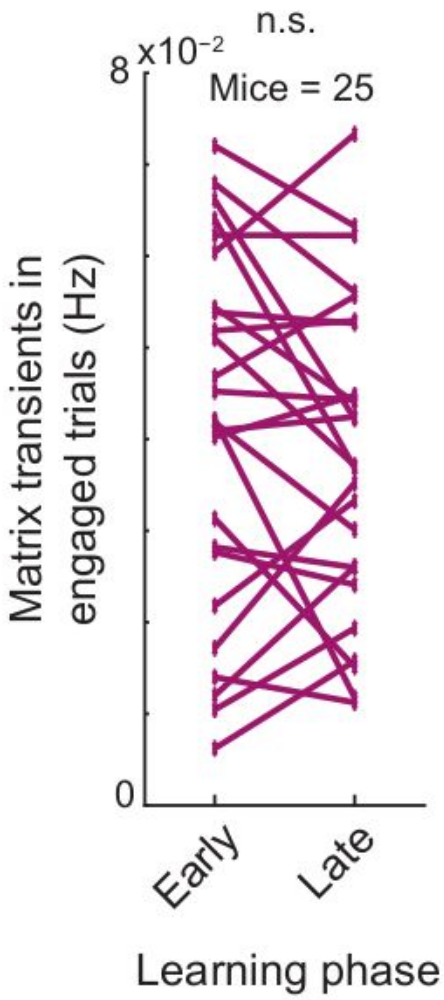

Tone (2 sec)
Response (1 sec)
Outcome
Reward cue
?
<3 licks → 4 µL
3-4 licks → 12 µL
>4 licks → 24 µL
Cost cue
<3 licks → 4 lux
3-4 licks → 40 lux
>4 licks → 400 lux


16 month
Response lick frequency (Hz)
6
0
0
500
Trials
Reward cue
Cost cue
Lick proportion
0.6
0
0
8
Lick number
Lick CDF
1
0
0
Lick #
8

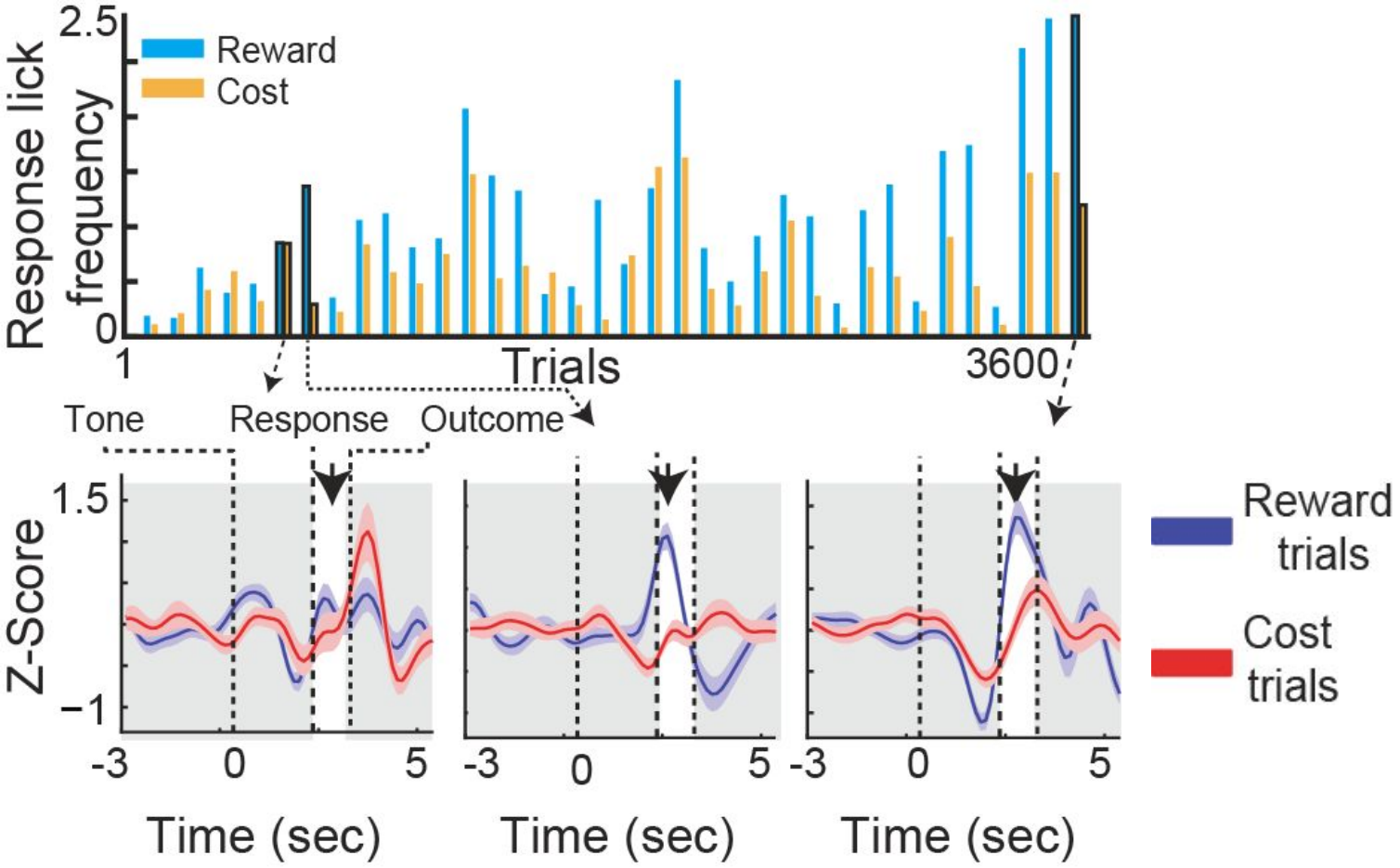

Tone (2 sec)
Response (1 sec)
Outcome
Reward cue
<3 licks → 4 µL
3-4 licks → 12 µL
>4 licks → 24 µL
?
Cost cue
<3 licks → 4 lux
3-4 licks → 40 lux
>4 licks → 400 lux

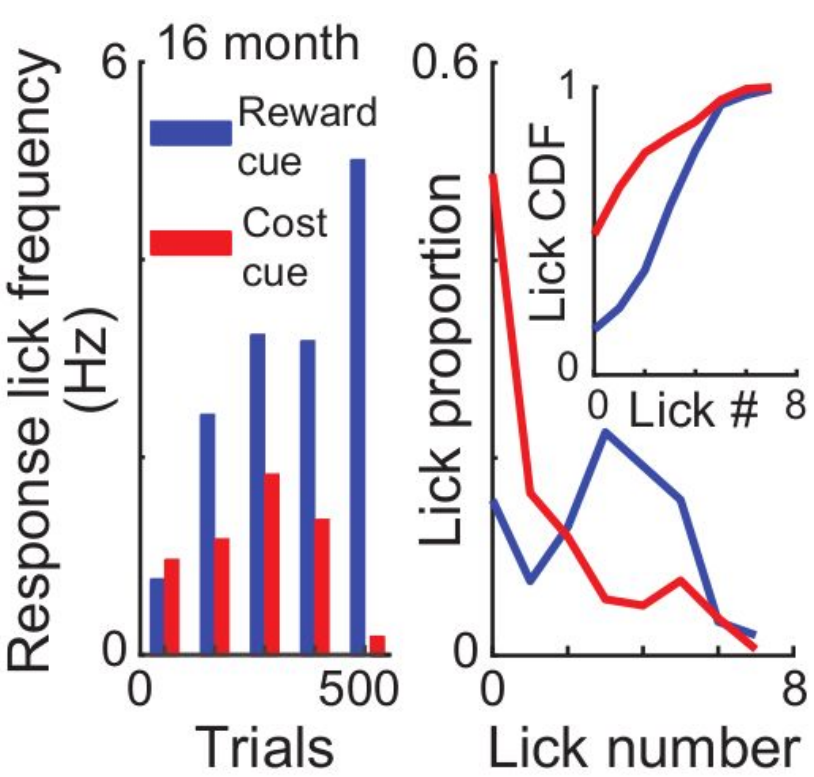

transients
7
Z-score
−2
0
50
Time (sec)

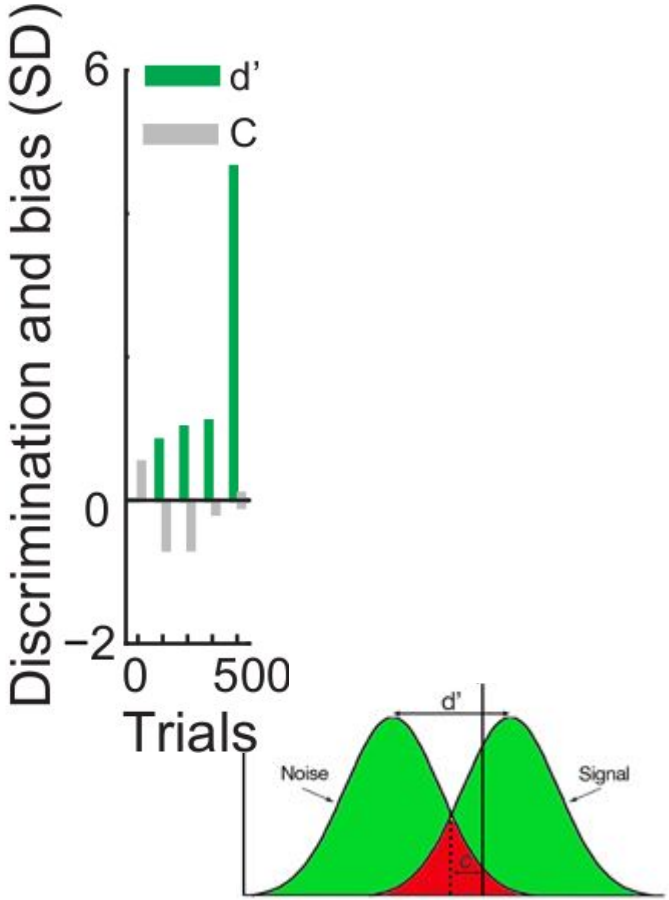

**
x10⁻²
8
Mice = 29
Striosomal transients in engaged trials (Hz)
0
Early
Late
Learning phase


n.s.
x10⁻²
8
Mice = 25
Matrix transients in engaged trials (Hz)
0
Early
Late
Learning phase

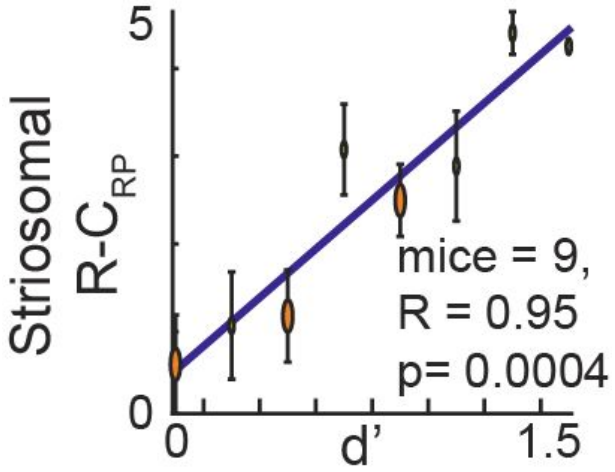
***striosomal activity, but not matrix activity, is shaped by discrimination learning**


Response lick frequency
2.5
0
Reward
Cost
1
Trials
3600
Tone
Response
Outcome
Z-Score
1.5
−1
-3
0
5
Time (sec)
Reward trials
Cost trials

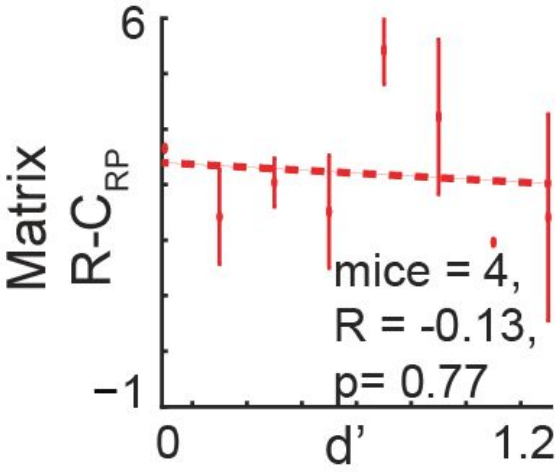

16 month
Reward cue
Cost cue
Response lick frequency (Hz)
6
0
0
500
Trials
Lick proportion
0.6
0
0
8
Lick number
Lick CDF
1
0
0
Lick #
8


Discrimination and bias (SD)
6
0
−2
d'
C
0
500
Trials
d'
Noise
Signal
c

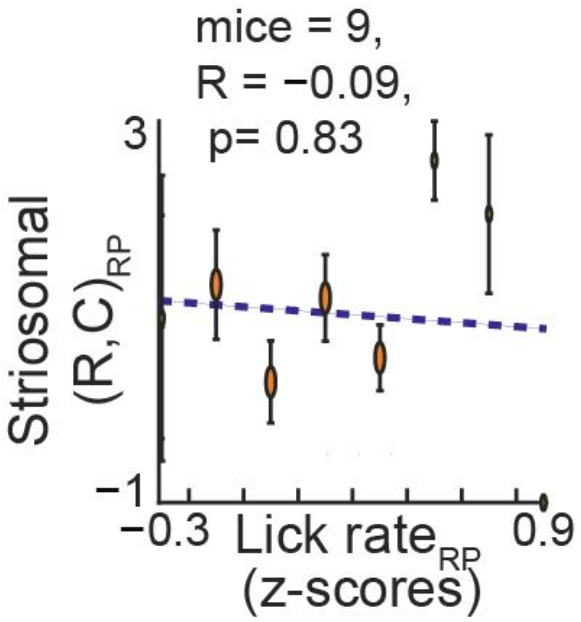
striosomes



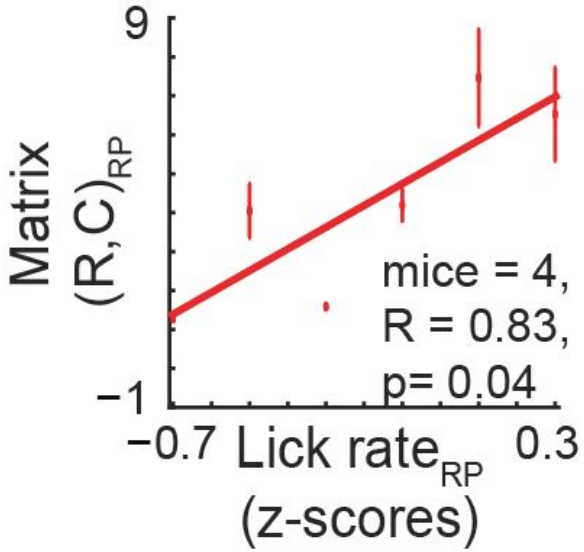
matrix



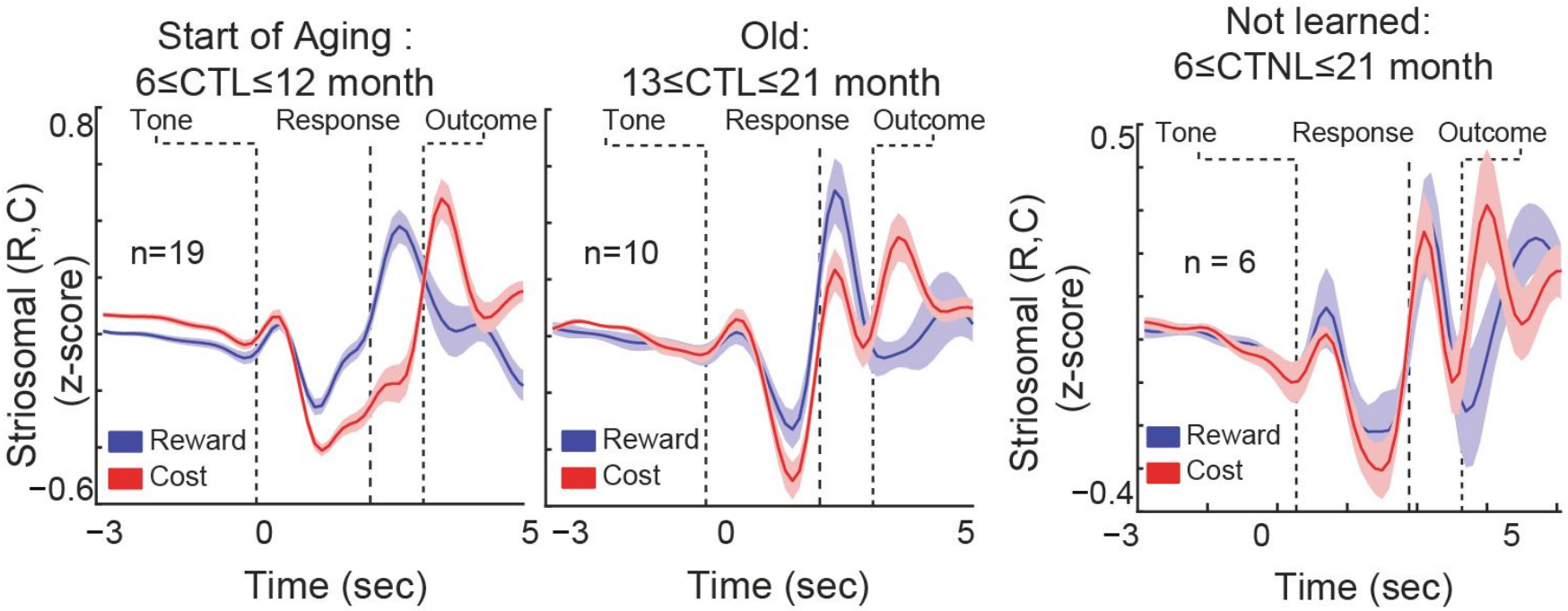
striosomes

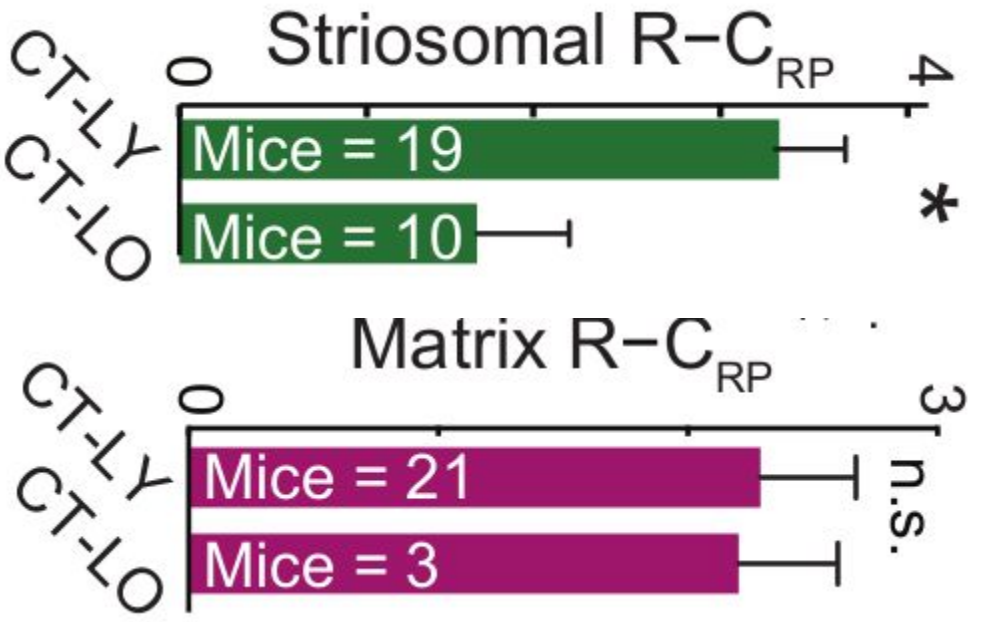


matrix

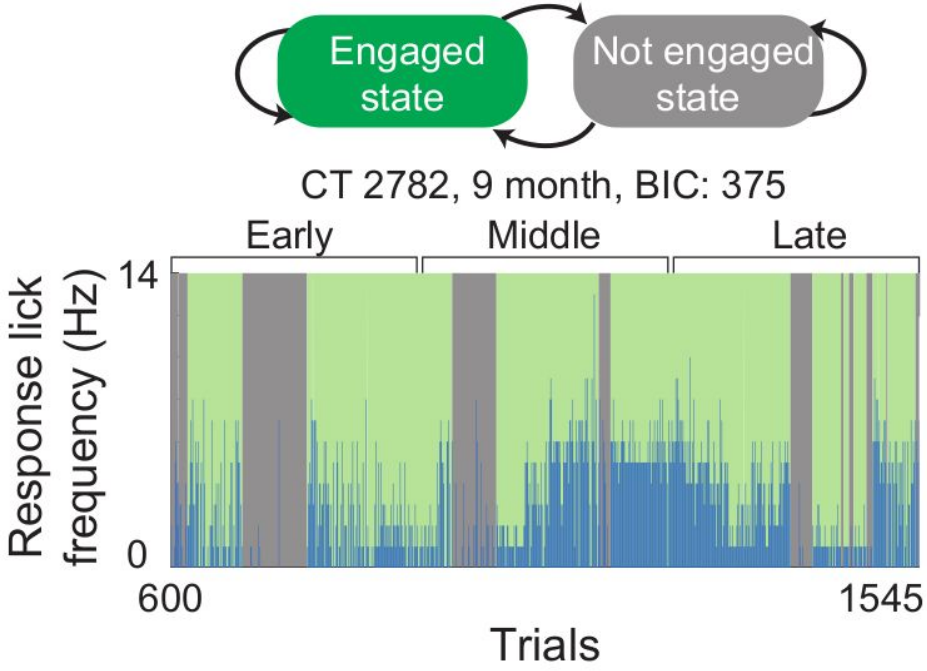


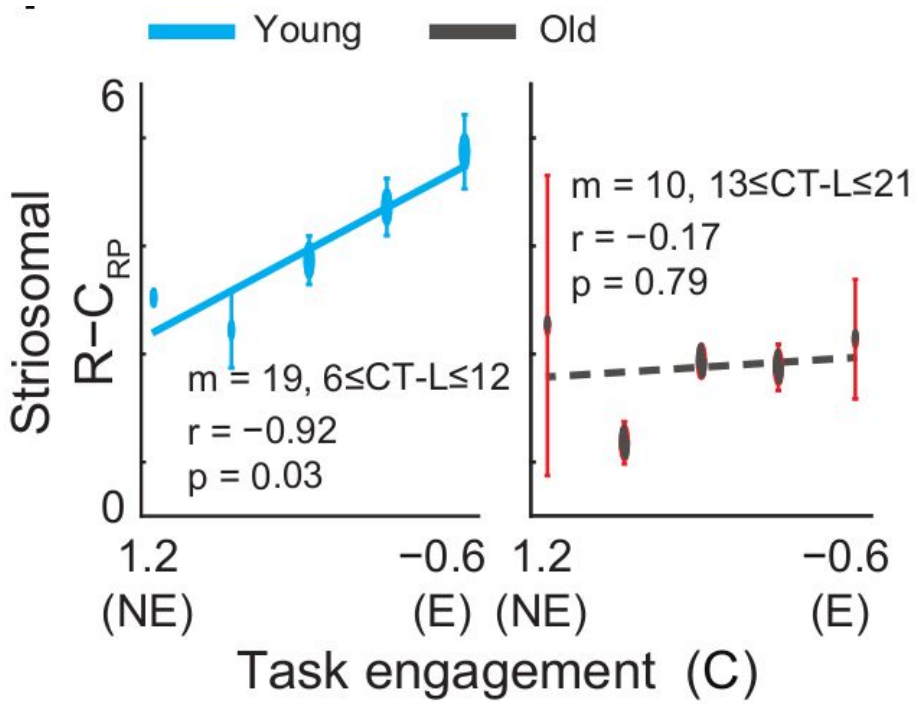
***striosomal activity, but not matrix activity, encodes discrimination levels during learning**


Start of Aging :
6≤CTL≤12 month
Old:
13≤CTL≤21 month
Not learned:
6≤CTNL≤21 month
Tone
Response
Outcome
n=19
n=10
n = 6
Reward
Cost
Striosomal (R,C)
(z-score)
0.8
−0.6
0.5
−0.4
−3
0
5
Time (sec)

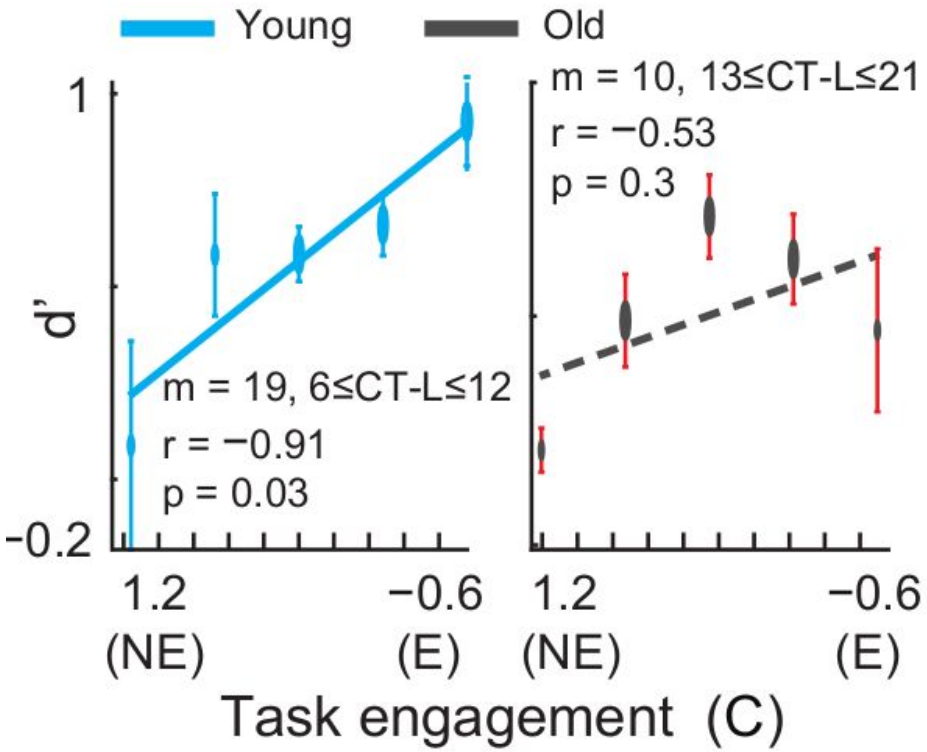

Striosomal R−C RP
0
4
CT-LY
CT-LO
Mice = 19
Mice = 10
*
Matrix R−C RP
0
3
CT-LY
CT-LO
Mice = 21
Mice = 3
n.s.

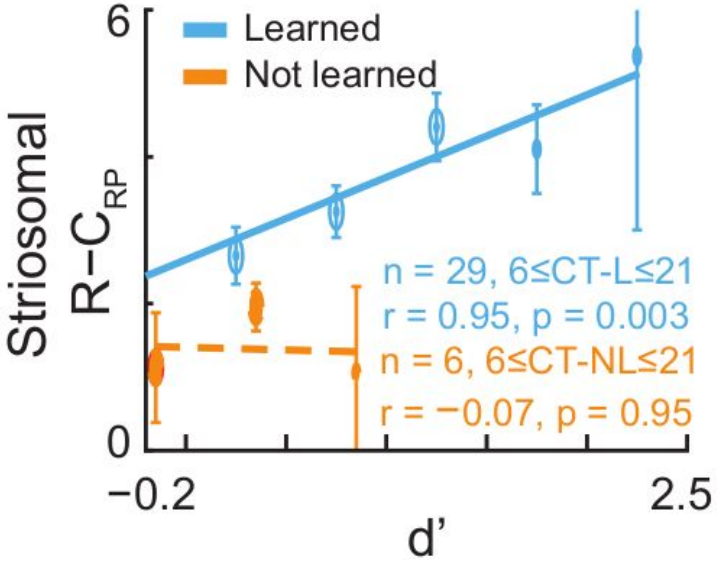
*aging results in less negative C_{RP} striosomal activity


Engaged state
Not engaged state
CT 2782, 9 month, BIC: 375
Early
Middle
Late
Response lick frequency (Hz)
14
0
600
1545
Trials

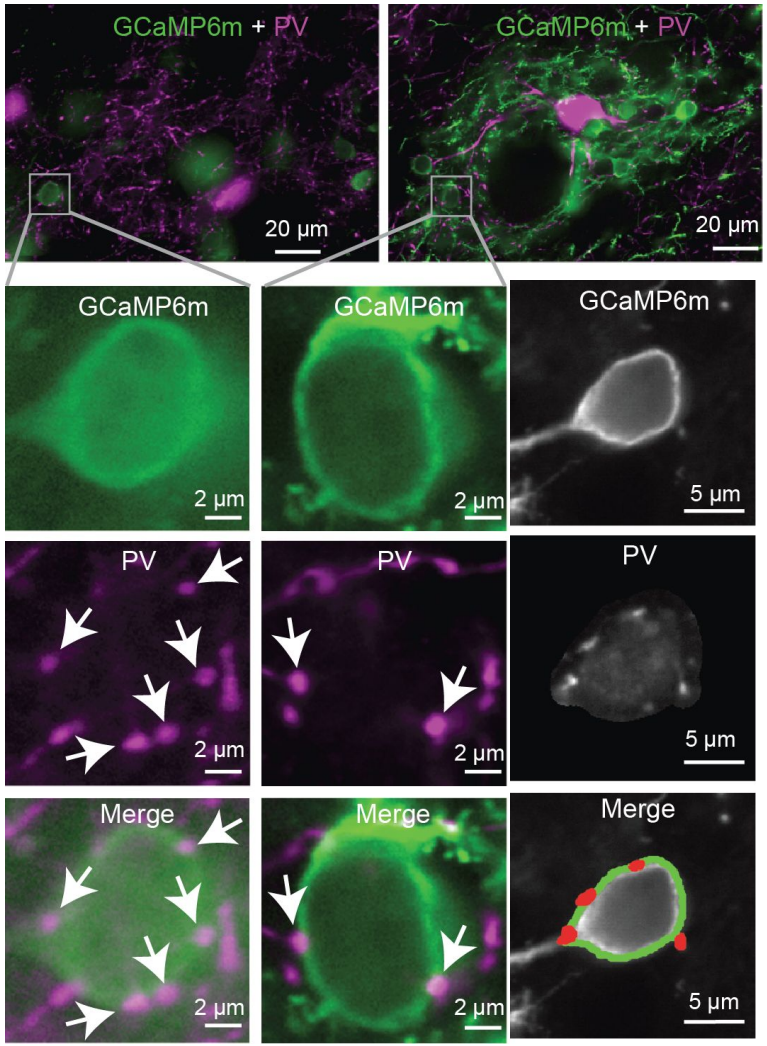

Young
Old
Striosomal
R−C_RP
6
0
m = 19, 6≤CT-L≤12
r = −0.92
p = 0.03
m = 10, 13≤CT-L≤21
r = −0.17
p = 0.79
1.2
(NE)
−0.6
(E)
1.2
(NE)
−0.6
(E)
Task engagement (C)

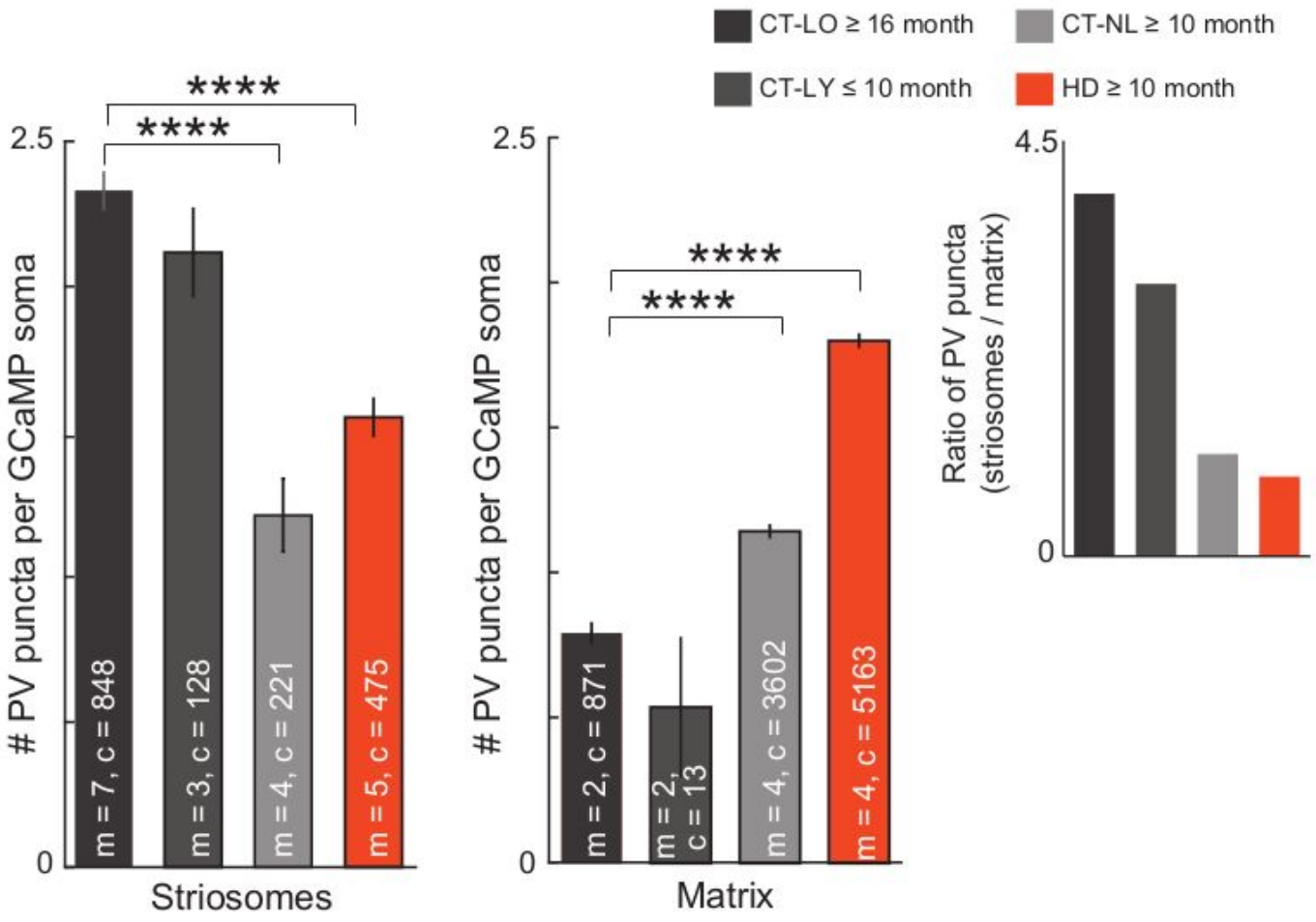
*aging results in reduced correlation between striosomal activity and task engagement

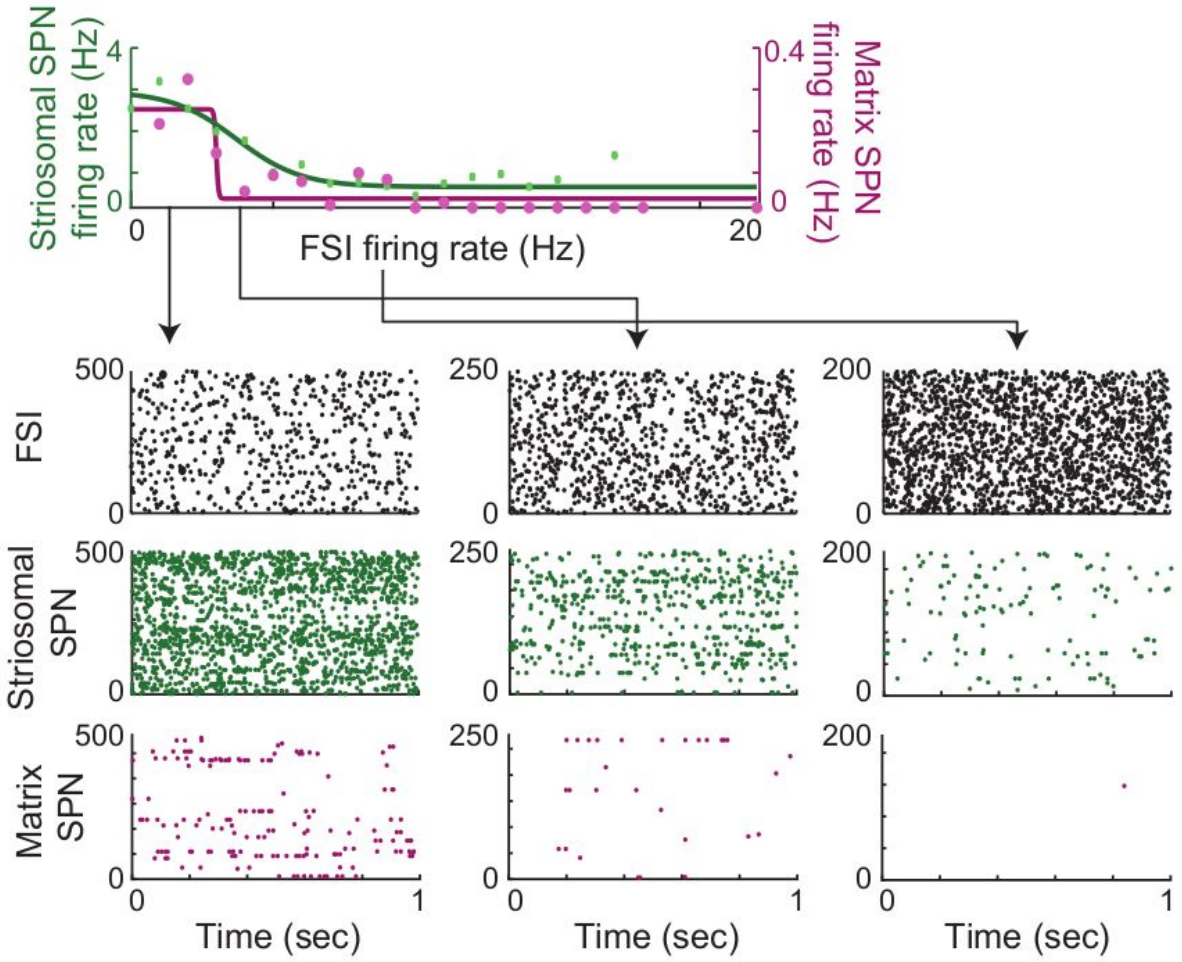

Young
Old
1
d'
−0.2
m = 19, 6≤CT-L≤12
r = −0.91
p = 0.03
m = 10, 13≤CT-L≤21
r = −0.53
p = 0.3
1.2
(NE)
−0.6
(E)
1.2
(NE)
−0.6
(E)
Task engagement (C)

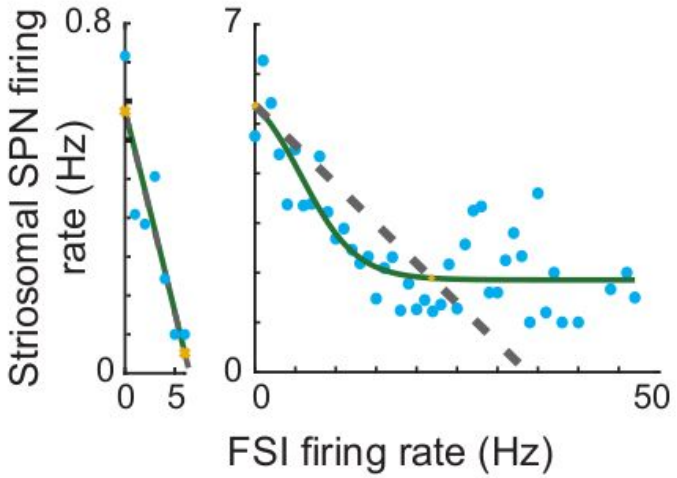

6
Learned
Not learned
Striosomal
R−C_RP
n = 29, 6≤CT-L≤21
r = 0.95, p = 0.003
n = 6, 6≤CT-NL≤21
r = −0.07, p = 0.95
0
−0.2
2.5
d'

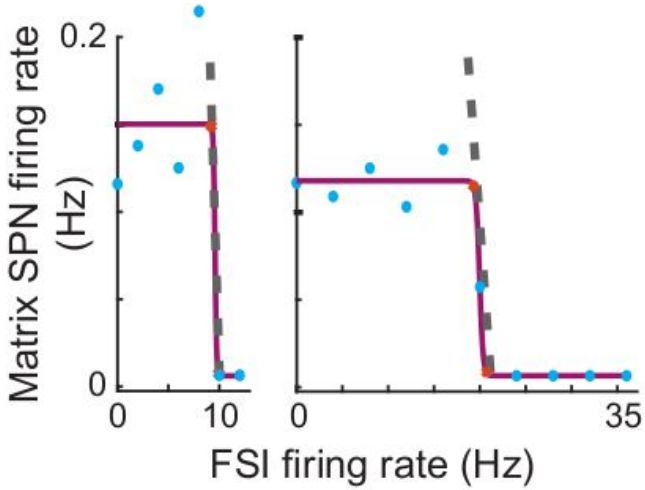
*aging results in a reduction between task engagement and learning

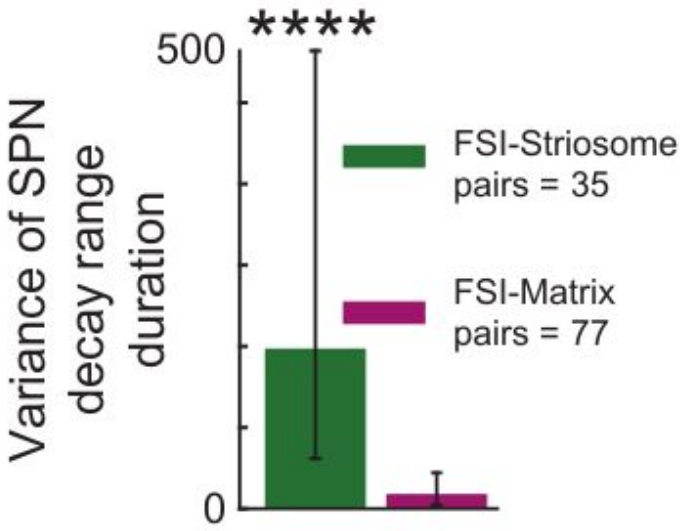

GCaMP6m + PV
20 μm
GCaMP6m + PV
20 μm
GCaMP6m
2 μm
GCaMP6m
2 μm
GCaMP6m
5 μm
PV
2 μm
PV
2 μm
PV
5 μm
Merge
2 μm
Merge
2 μm
Merge
5 μm


CT-LO ≥ 16 month
CT-NL ≥ 10 month
CT-LY ≤ 10 month
HD ≥ 10 month
****
****
2.5
PV puncta per GCaMP soma
0
m = 7, c = 848
m = 3, c = 128
m = 4, c = 221
m = 5, c = 475
Striosomes
****
****
2.5
PV puncta per GCaMP soma
0
m = 2, c = 871
m = 2, c = 13
m = 4, c = 3602
m = 4, c = 5163
Matrix
4.5
Ratio of PV puncta (striosomes / matrix)
0

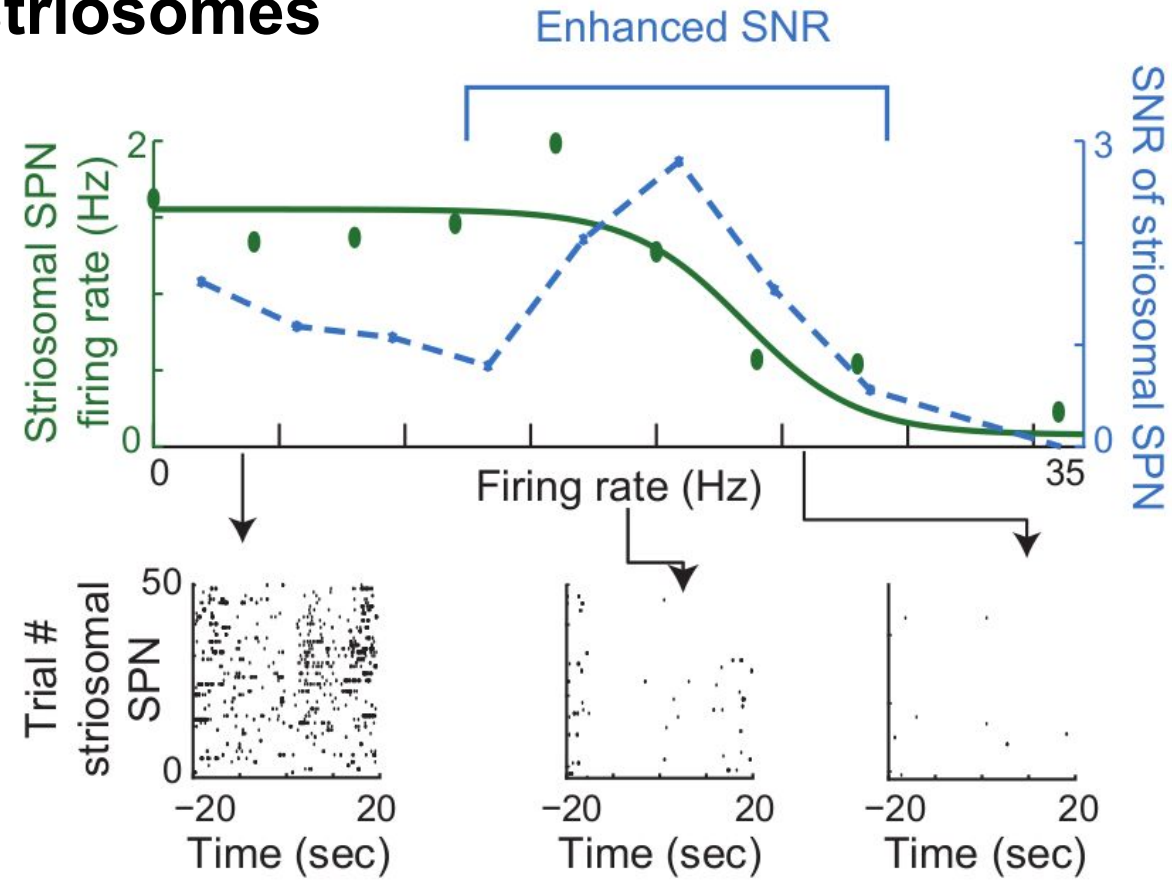

Striosomal SPN firing rate (Hz)
4
0
0
20
FSI firing rate (Hz)
0.4
0
Matrix SPN firing rate (Hz)
FSI
Striosomal SPN
Matrix SPN
500
250
200
0
1
Time (sec)


Striosomal SPN firing rate (Hz)
0.8
0
0 5
7
0
0 50
FSI firing rate (Hz)

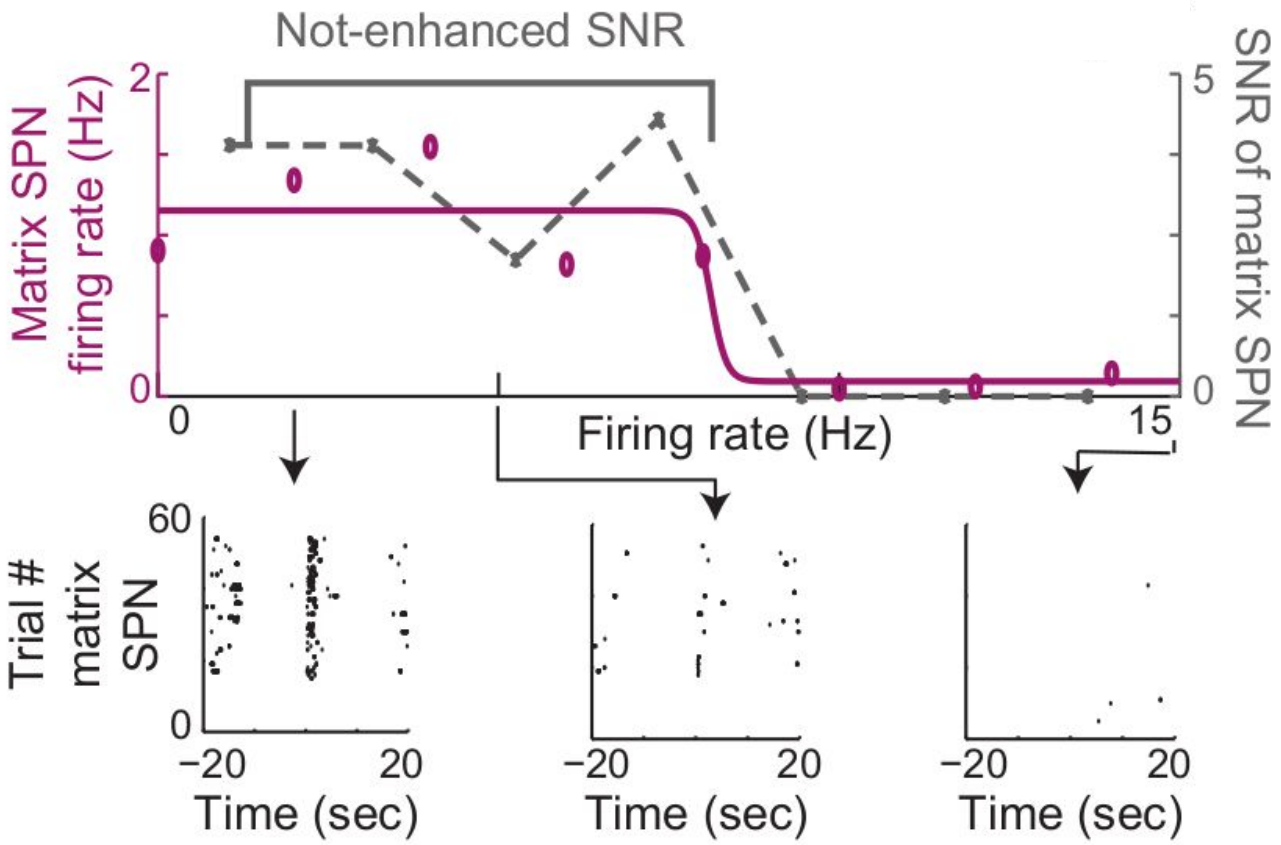

Matrix SPN firing rate (Hz)
0.2
0
0 10
0 35
FSI firing rate (Hz)


****
500
0
Variance of SPN decay range duration
FSI-Striosome pairs = 35
FSI-Matrix pairs = 77

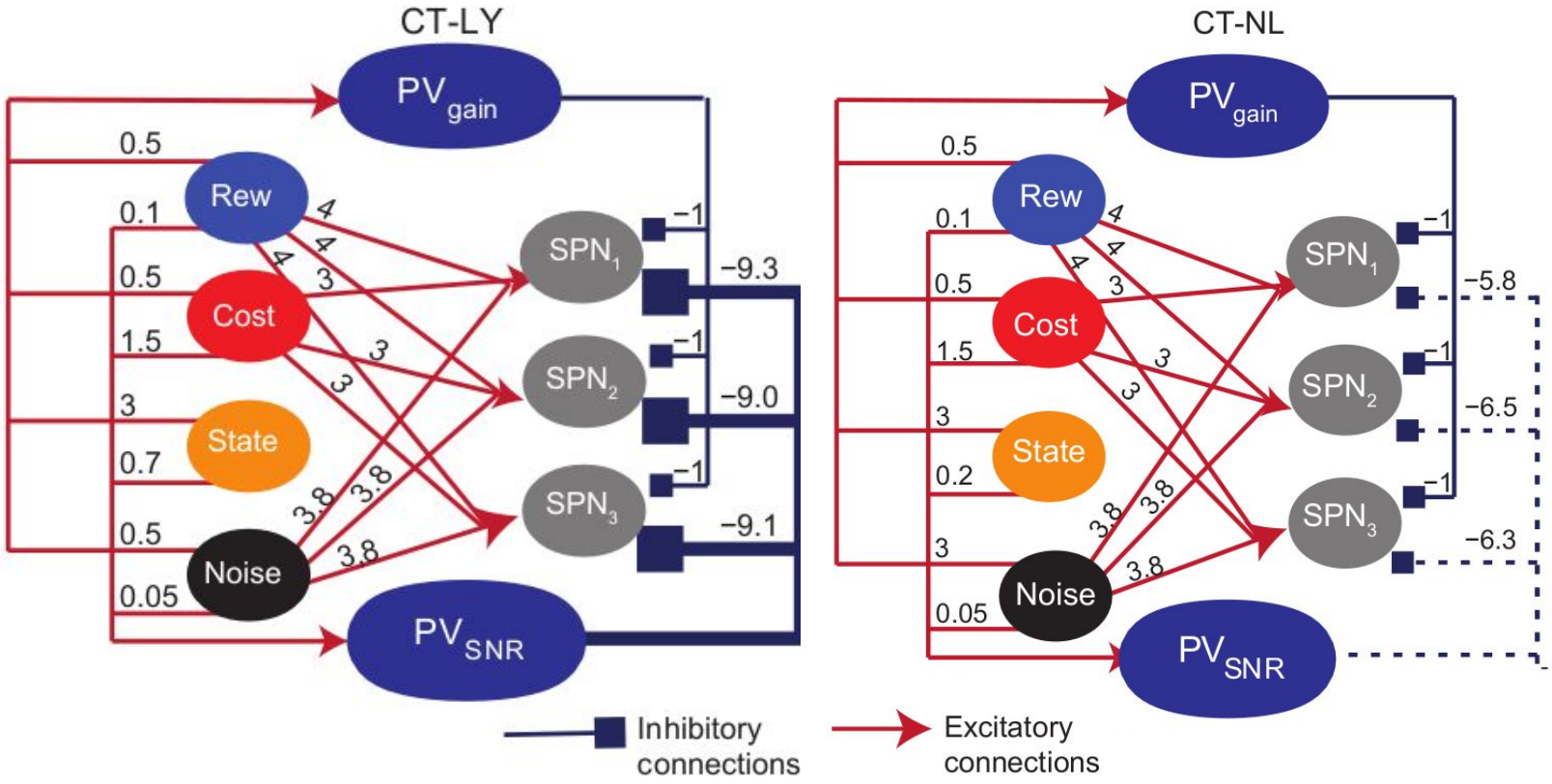
striosomes

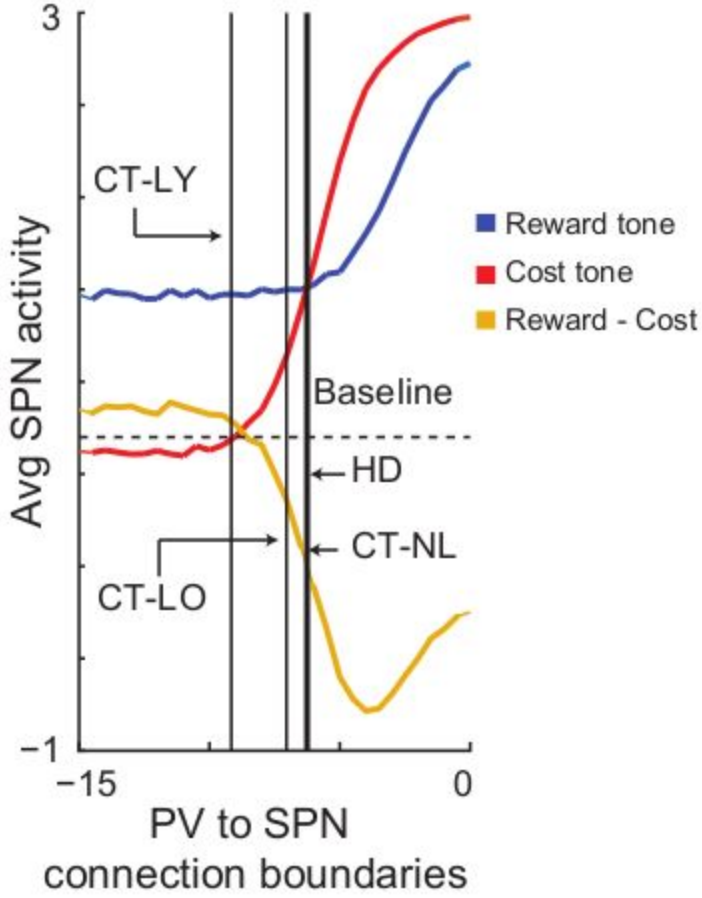

Enhanced SNR
Striosomal SPN firing rate (Hz)
2
0
3
0
SNR of striosomal SPN
0
35
Firing rate (Hz)
Trial # striosomal SPN
50
0
−20
20
Time (sec)
−20
20
Time (sec)
−20
20
Time (sec)

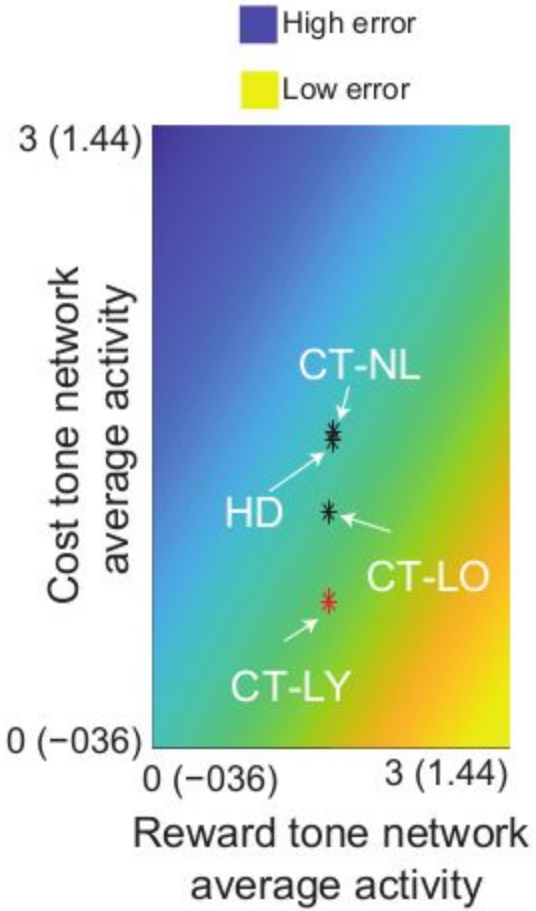
matrix

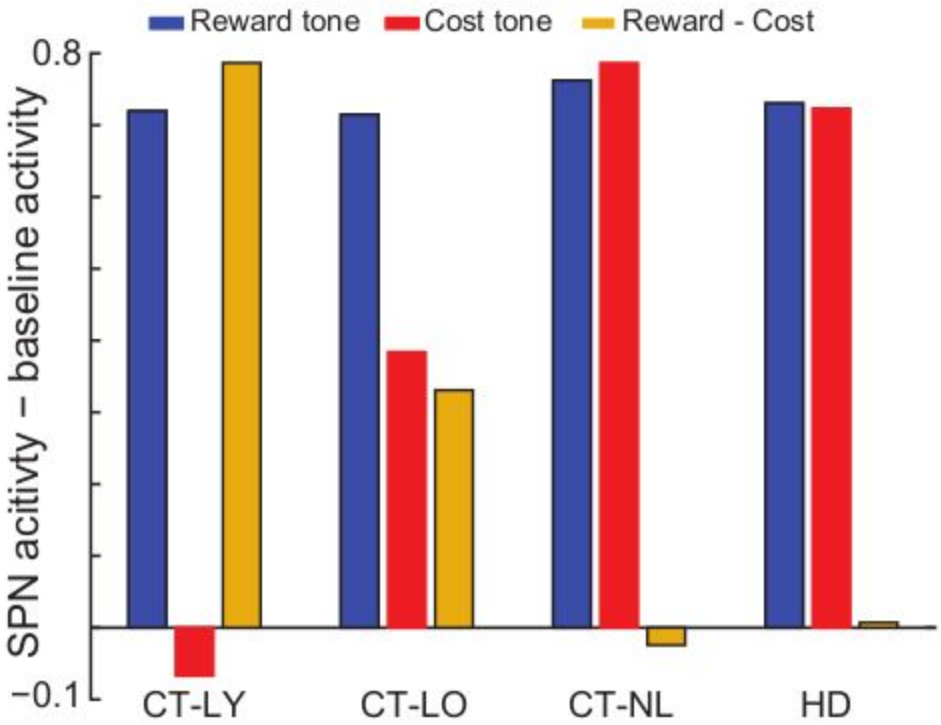

Not-enhanced SNR
Matrix SPN firing rate (Hz)
2
0
5
0
SNR of matrix SPN
0
Firing rate (Hz)
15
Trial # matrix SPN
60
0
−20
20
Time (sec)
−20
20
Time (sec)
−20
20
Time (sec)

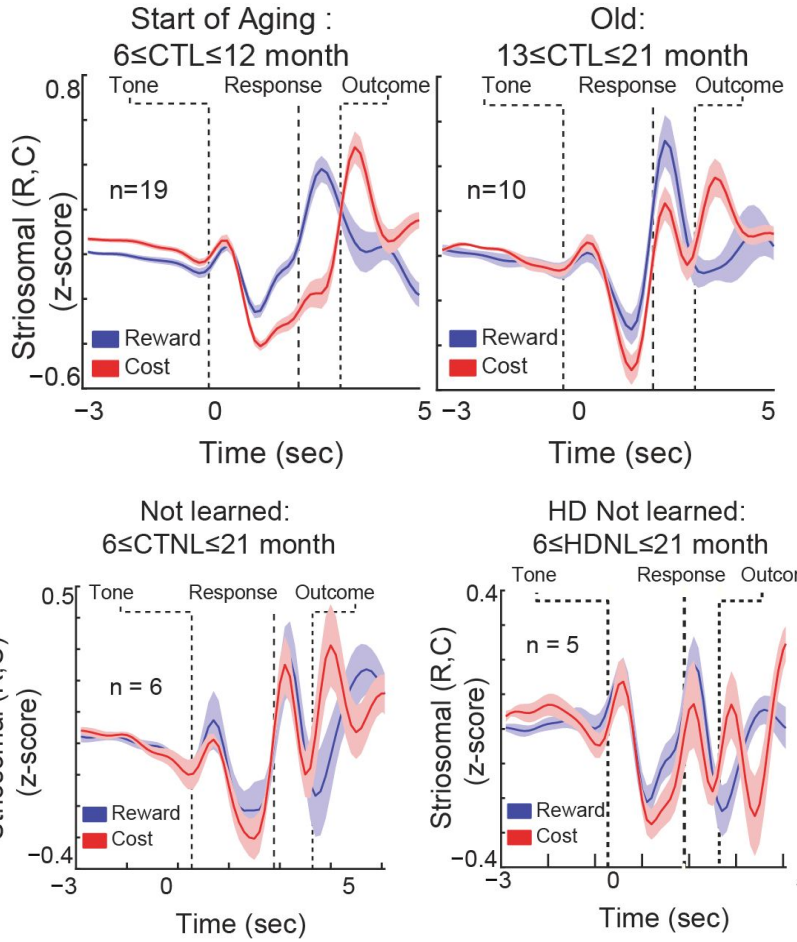
*fewer matrix PV-MSN contact points (than striosomes) may underlie the PV responses activity differences across compartments

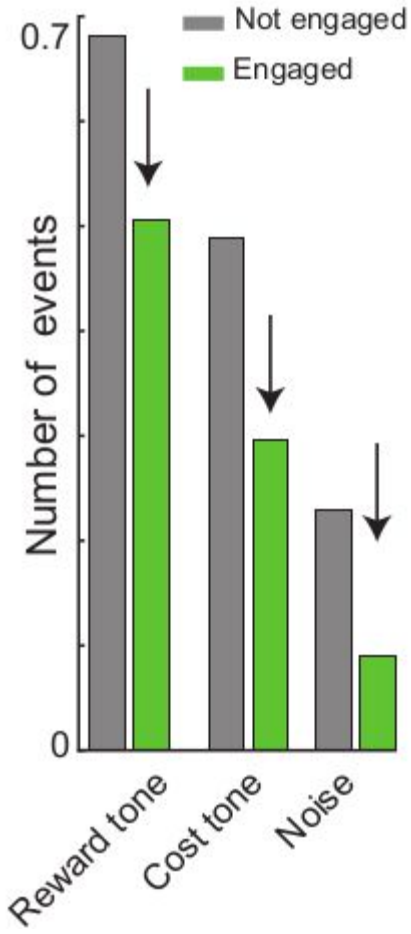

CT-LY
PV gain
Rew
Cost
State
Noise
PV SNR
SPN1
SPN2
SPN3
0.5
0.1
0.5
1.5
3
0.7
0.5
0.05
4
4
4
3
3
3
3.8
3.8
3.8
−1
−1
−1
−9.3
−9.0
−9.1
CT-NL
PV gain
Rew
Cost
State
Noise
PV SNR
SPN1
SPN2
SPN3
0.5
0.1
0.5
1.5
3
0.2
3
0.05
4
4
4
3
3
3
3.8
3.8
3.8
−1
−1
−1
−5.8
−6.5
−6.3
Inhibitory connections
Excitatory connections

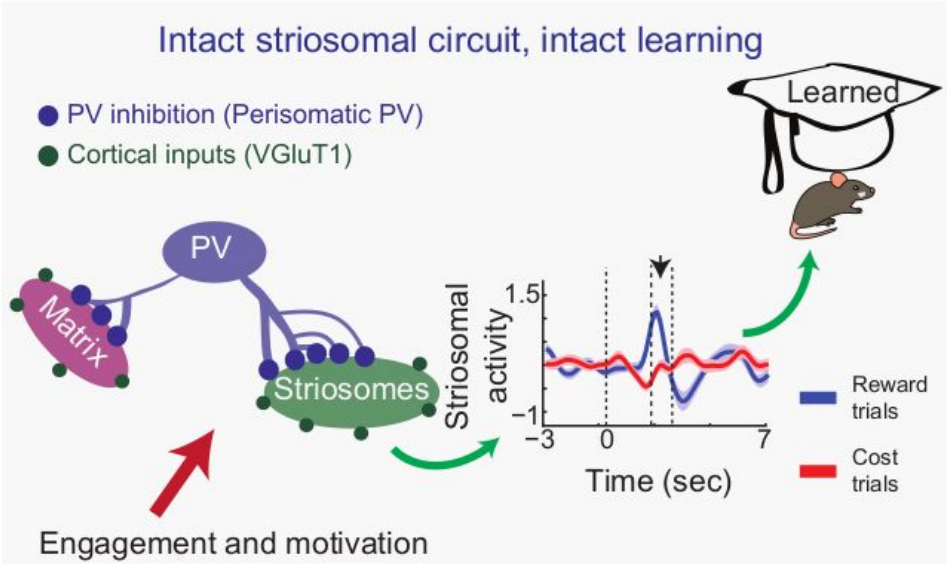

3
−1
−15
0
Avg SPN activity
PV to SPN
connection boundaries
CT-LY
CT-LO
Baseline
HD
CT-NL
Reward tone
Cost tone
Reward - Cost

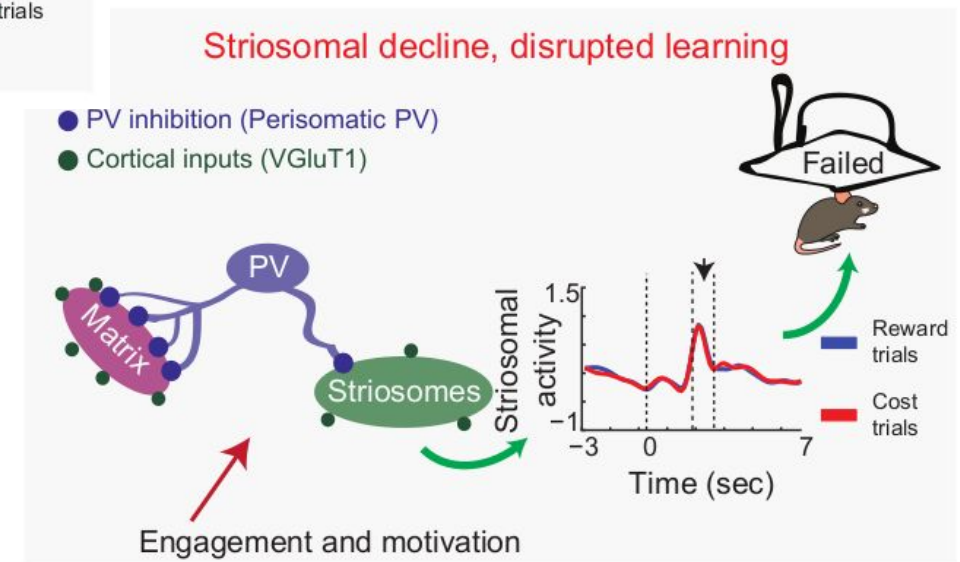

High error
Low error
3 (1.44)
0 (−036)
Cost tone network
average activity
CT-NL
HD
CT-LO
CT-LY
0 (−036)
3 (1.44)
Reward tone network
average activity


Reward tone
Cost tone
Reward - Cost
SPN acitivty – baseline activity
0.8
−0.1
CT-LY
CT-LO
CT-NL
HD


Start of Aging :
6≤CTL≤12 month
Old:
13≤CTL≤21 month
Not learned:
6≤CTNL≤21 month
HD Not learned:
6≤HDNL≤21 month
Tone
Response
Outcome
Striosomal (R,C)
(z-score)
n=19
n=10
n = 6
n = 5
Reward
Cost
Time (sec)
0.8
−0.6
0.5
−0.4
0.4
−3
0
5


Not engaged
Engaged
0.7
0
Number of events
Reward tone
Cost tone
Noise


Intact striosomal circuit, intact learning
PV inhibition (Perisomatic PV)
Cortical inputs (VGluT1)
Learned
PV
Matrix
Striosomes
Striosomal activity
1.5
−1
−3
0
7
Time (sec)
Reward trials
Cost trials
Engagement and motivation


Striosomal decline, disrupted learning
PV inhibition (Perisomatic PV)
Cortical inputs (VGluT1)
Failed
PV
Matrix
Striosomes
Striosomal activity
1.5
−1
−3
0
7
Time (sec)
Reward trials
Cost trials
Engagement and motivation

Further ideas

Old mice have a disconnect b/w engagement and discrimination. This could be introduced into the model.

HD neural activity is cost-driven - can we design learning-from-cost vs learning-from-reward versions of our model?

How does cortical input and spine reduction in HD animals incorporate into our model?

What are the interesting pieces/levels to focus on?

Model the learning process.

Circuit modeling in a more fine-tuned way, so that the model behavior (SPN activity - baseline pattern) is more tightly replicating empirical data.

What is the emergent behavior when we have a network of these neurons (neural population)?

SNR differences - how could this impact general network learning ability?

Aging affect speed of learning? Perhaps can prove that the relatationship of discrimination level and time taken to learn (maybe some definition of convergence)

Contributions

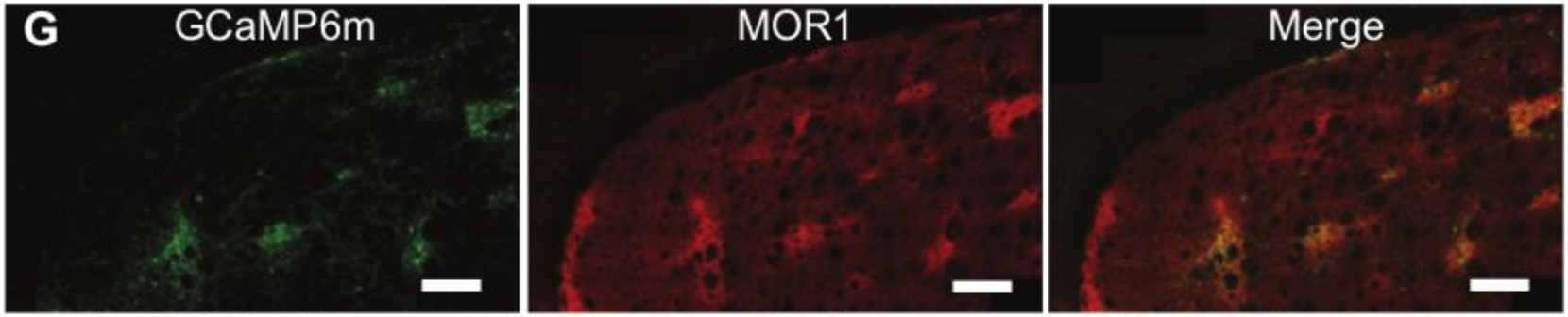
Striosomes are critical for valance-based learning, driven by engagement

Selective dysfunction in striosomes prevents learning in aging and HD

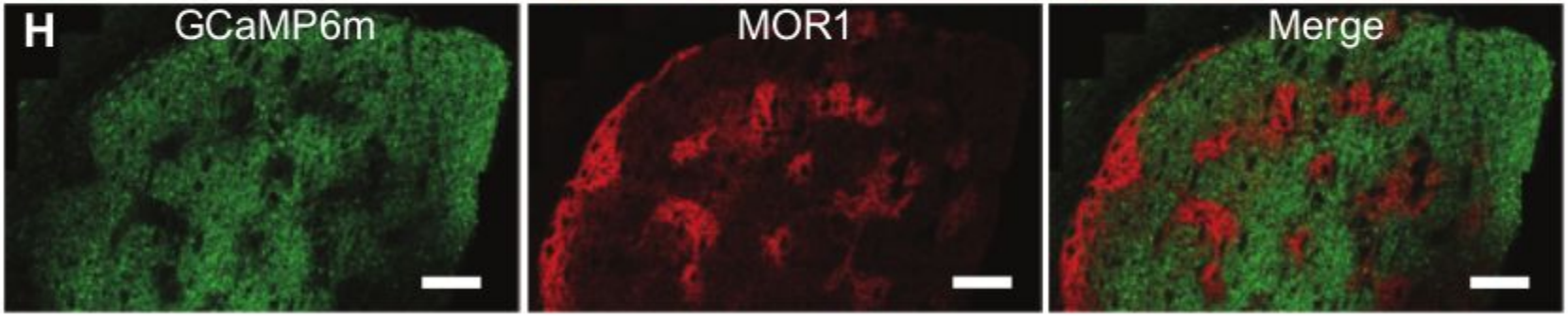
Matrix and striosomal compartments have striking anatomical and functional differences

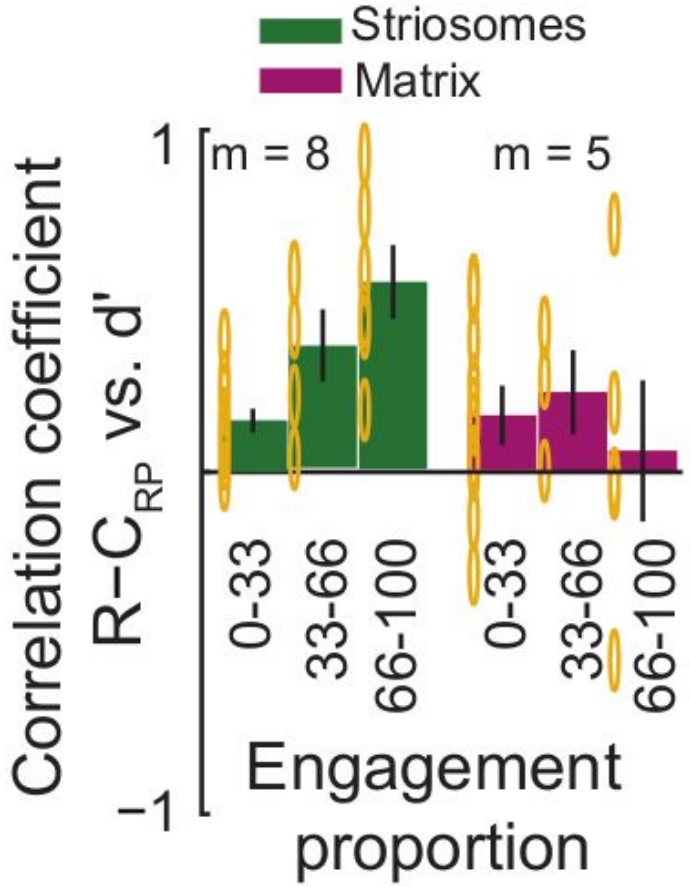
Through a SNN model we demonstrate a hypotheses that the PV-striosomal microcircuit is central to controlling striosomal response activity and learning

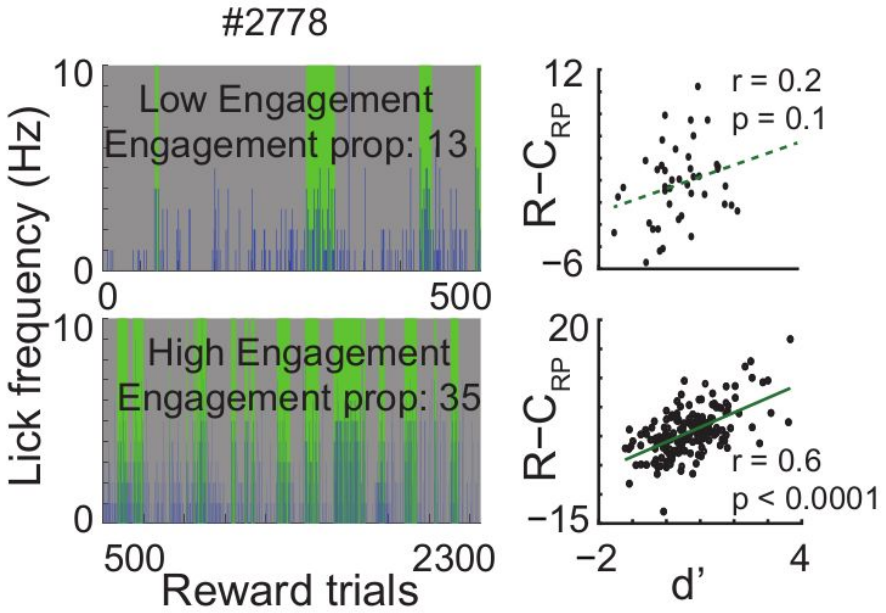
striosomes



matrix




Striosomes
Matrix
m = 8
m = 5
1
−1
Correlation coefficient
R−C_RP vs. d'
0-33
33-66
66-100
0-33
33-66
66-100
Engagement proportion


#2778
Low Engagement
Engagement prop: 13
High Engagement
Engagement prop: 35
Lick frequency (Hz)
10
0
0
500
500
2300
Reward trials
R−C_RP
12
−6
r = 0.2
p = 0.1
20
−15
r = 0.6
p < 0.0001
−2
4
d'