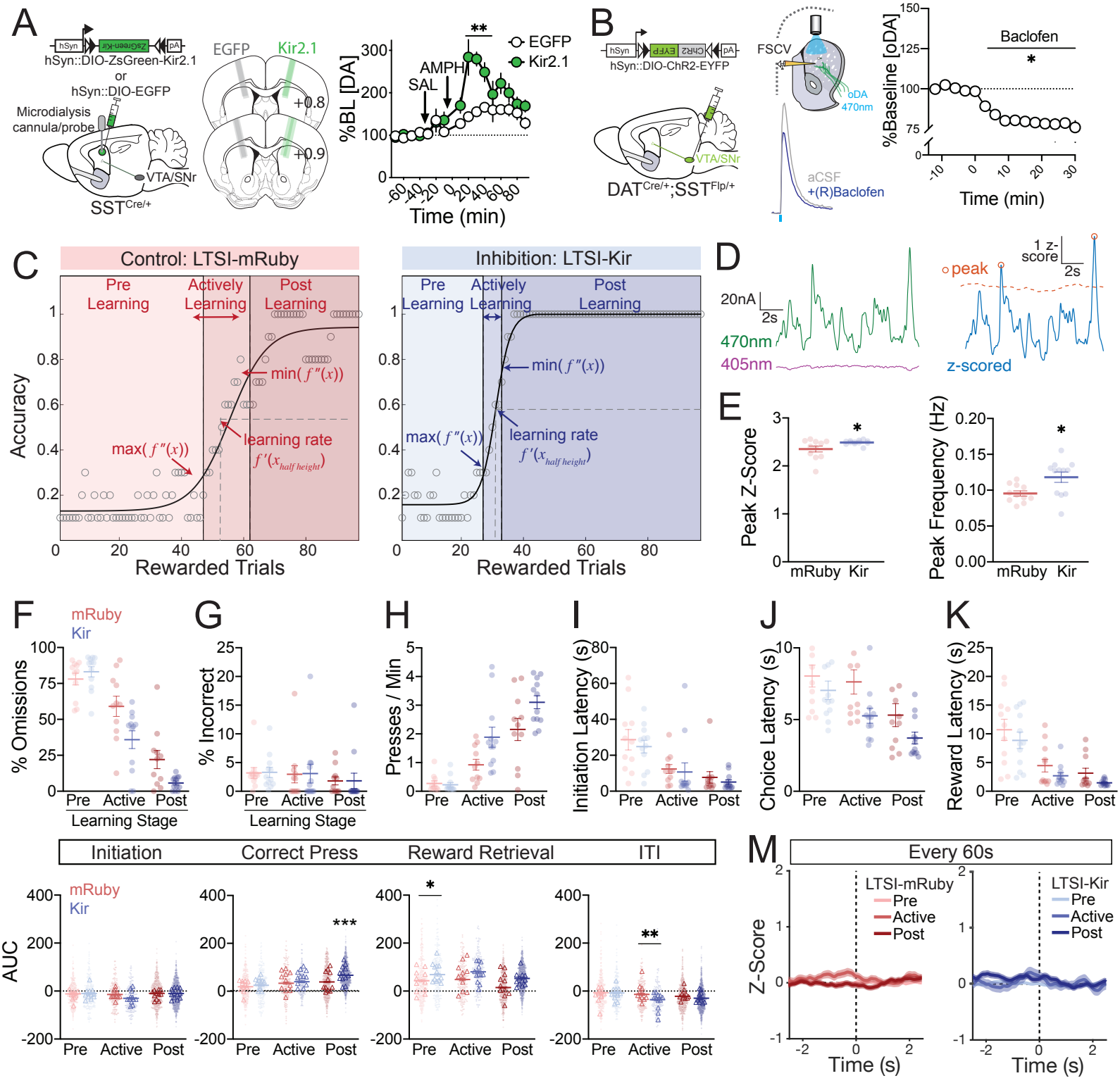
A
hSyn
ZsGreen-Kir
pA
hSyn::DIO-ZsGreen-Kir2.1
or
hSyn::DIO-EGFP
Microdialysis cannula/probe
VTA/SNr
SST^Cre/+
EGFP
Kir2.1
+0.8
+0.9
%BL [DA]
AMPH
SAL
**
EGFP
Kir2.1
Time (min)
B
hSyn
ChR2
EYFP
pA
hSyn::DIO-ChR2-EYFP
VTA/SNr
DAT^Cre/+;SST^Flp/+
FSCV
oDA
470nm
aCSF
+(R)Baclofen
%Baseline [oDA]
Baclofen
*
Time (min)
C
Control: LTSI-mRuby
Inhibition: LTSI-Kir
Pre Learning
Actively Learning
Post Learning
Accuracy
min(f″(x))
max(f″(x))
learning rate
f′(x_half height)
Rewarded Trials
D
20nA
2s
470nm
405nm
peak
1 z-score
2s
z-scored
E
Peak Z-Score
Peak Frequency (Hz)
mRuby
Kir
*
F
mRuby
Kir
% Omissions
Pre
Active
Post
Learning Stage
G
% Incorrect
H
Presses / Min
I
Initiation Latency (s)
J
Choice Latency (s)
K
Reward Latency (s)
Initiation
Correct Press
Reward Retrieval
ITI
AUC
*
***
**
M
Every 60s
LTSI-mRuby
LTSI-Kir
Pre
Active
Post
Z-Score
Time (s)

Figure S1. LTSI inhibition amplifies dopamine and accelerates operant learning; related to Figures 1 and 2. (A) Experimental design for *in vivo* microdialysis experiment (left), and probe placements (right) for 4 mice expressing EGFP in the LTSIs of one hemisphere (gray) and Kir2.1 in LTSIs of the other hemisphere (green). LTSI inhibition significantly augments the extracellular dopamine response to d-amphetamine (AMPH, 1.0 mg/kg, i.p) (right). **p<0.01 vs baseline. (B) Experimental design for *in vitro* fast scan cyclic voltammetry experiment (left). Application of 100μM +(R)Bacolofen significantly suppresses optogenetically-evoked dopamine (right). *p<0.05 vs baseline. (C) Sample sigmoidal models of learning for a mouse expressing LTSI-mRuby (left) and LTSI-Kir (right). (D) Example traces of raw (left) and transformed (z-scored ΔF/F, see methods; right). Peaks above a moving threshold (orange dotted line, see methods) are indicated by orange dots. (E) Peak z-score (left) and frequency (right) in the 10min baseline period prior to the operant task of mice expressing LTSI-mRuby (control, n=11) or LTSI-Kir (inhibition, n=12). **p<0.01, ***p<0.001 vs LTSI-mRuby. (F-G) Proportion of (F) omissions (initiations without lever press), and (G) incorrect lever presses in pre-learning, active learning, and post-learning periods. (H) Rate of lever presses across learning stages. (I-K) Latencies to (I) initiate, (J) press a lever, and (K) retrieve reward across learning stages. (L) Total area under the curve (AUC) of the PETH for the 1s before and after behavioral events. (M) PETHs aligned to timestamps every 60s as opposed to behavioral events. **p<0.01, ***p<0.001 vs mRuby control at the same learning stage. Lines in dot plots represent mean and dots represent individual data points. All other data represented as mean ± SEM. See Data S1 for detailed statistics.

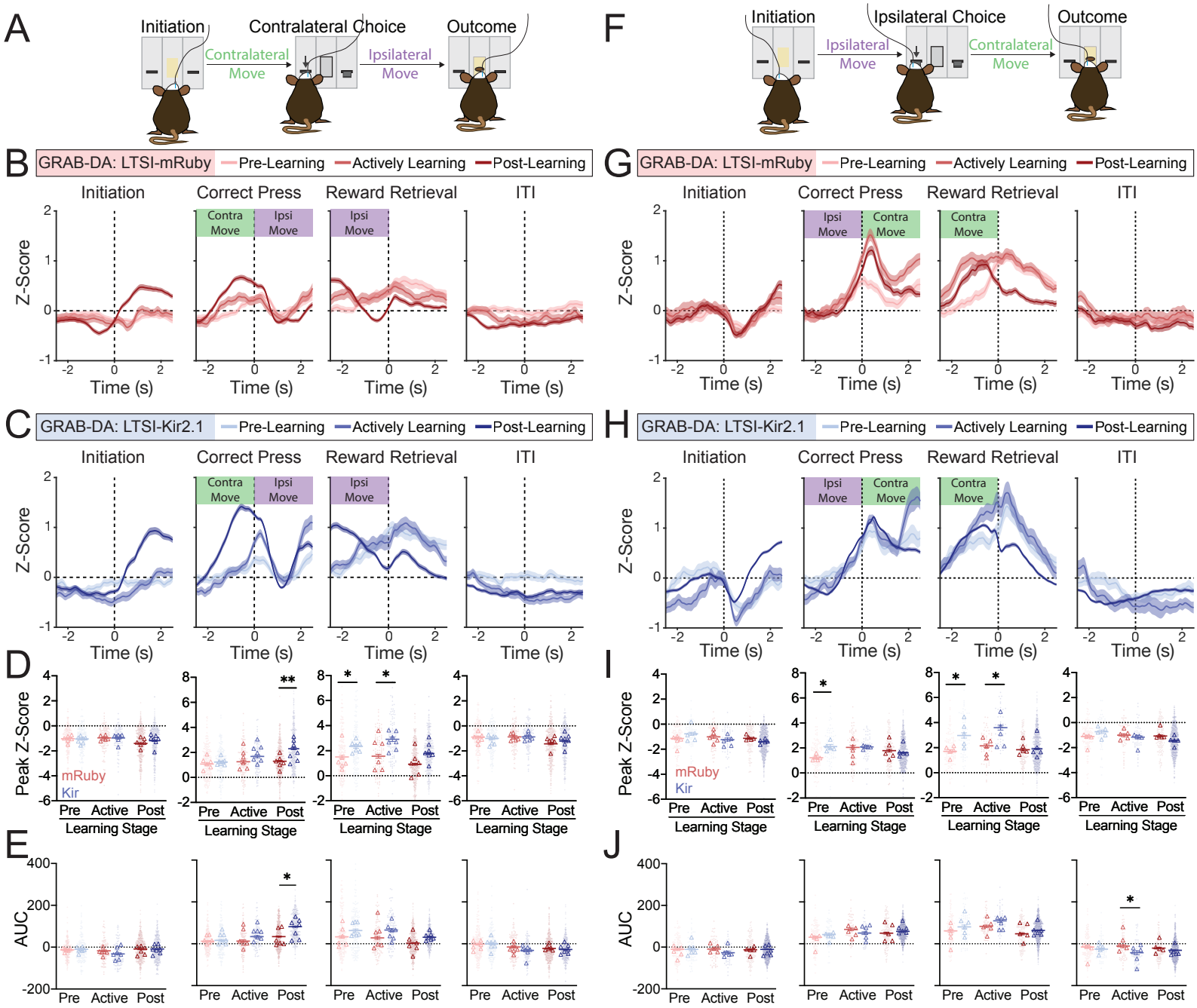
A
Initiation
Contralateral Choice
Outcome
Contralateral Move
Ipsilateral Move
F
Initiation
Ipsilateral Choice
Outcome
Ipsilateral Move
Contralateral Move
B
GRAB-DA: LTSI-mRuby
Pre-Learning
Actively Learning
Post-Learning
Initiation
Correct Press
Reward Retrieval
ITI
Contra Move
Ipsi Move
Z-Score
Time (s)
G
GRAB-DA: LTSI-mRuby
Pre-Learning
Actively Learning
Post-Learning
C
GRAB-DA: LTSI-Kir2.1
Pre-Learning
Actively Learning
Post-Learning
H
GRAB-DA: LTSI-Kir2.1
Pre-Learning
Actively Learning
Post-Learning
D
Peak Z-Score
mRuby
Kir
Pre Active Post
Learning Stage
I
E
AUC
J

Figure S2. LTSI inhibition amplifies dopamine signals as mice make contralateral movements; related to Figure 2. (A) As mice press a lever contralateral to the striatal implant, they make a contralateral movement towards the lever followed by an ipsilateral movement towards the reward magazine. (B) Peri-event temporal histograms (PETHs) for initiations, correct presses, reward retrievals, and ITIs of pre-learning, actively learning, and post-learning trials for LTSI-mRuby control mice training to press the lever contralateral to the striatal implant (n=6). (C) PETHs for the same behavioral events for LTSI-Kir2.1 inhibited mice training to press the lever contralateral to the implant (n=7). (D) Peak (minima for initiation and ITI, maxima for correct press and reward retrieval) Z-scores relative to the signal at the end of the ITI. (E) Total areas under the curve (AUC) in the window of 1s before and after the behavioral event. (F) As mice press a lever ipsilateral to the striatal implant, they make an ipsilateral movement towards the lever followed by a contralateral movement towards the reward magazine. (G) Peri-event temporal histograms (PETHs) for initiations, correct presses, reward retrievals, and ITIs of pre-learning, actively learning, and post-learning trials for LTSI-mRuby control mice training to press the lever ipsilateral to the striatal implant (n=5). (H) PETHs for the same behavioral events for LTSI-Kir2.1 inhibited mice training to press the lever ipsilateral to the implant (n=5). (I) Peak (minima for initiation and ITI, maxima for correct press and reward retrieval) Z-scores relative to the signal at the end of the ITI. (J) Total areas under the curve (AUC) in the window of 1s before and after the behavioral event.*$p<0.05$, **$p<0.01$, ***$p<0.001$ vs mRuby control for same learning stage. Lines in dot plots represent means; dots represent individual trials and open triangles represent animal means. All PETH data represented as mean ± SEM. See Data S1 for detailed statistics.

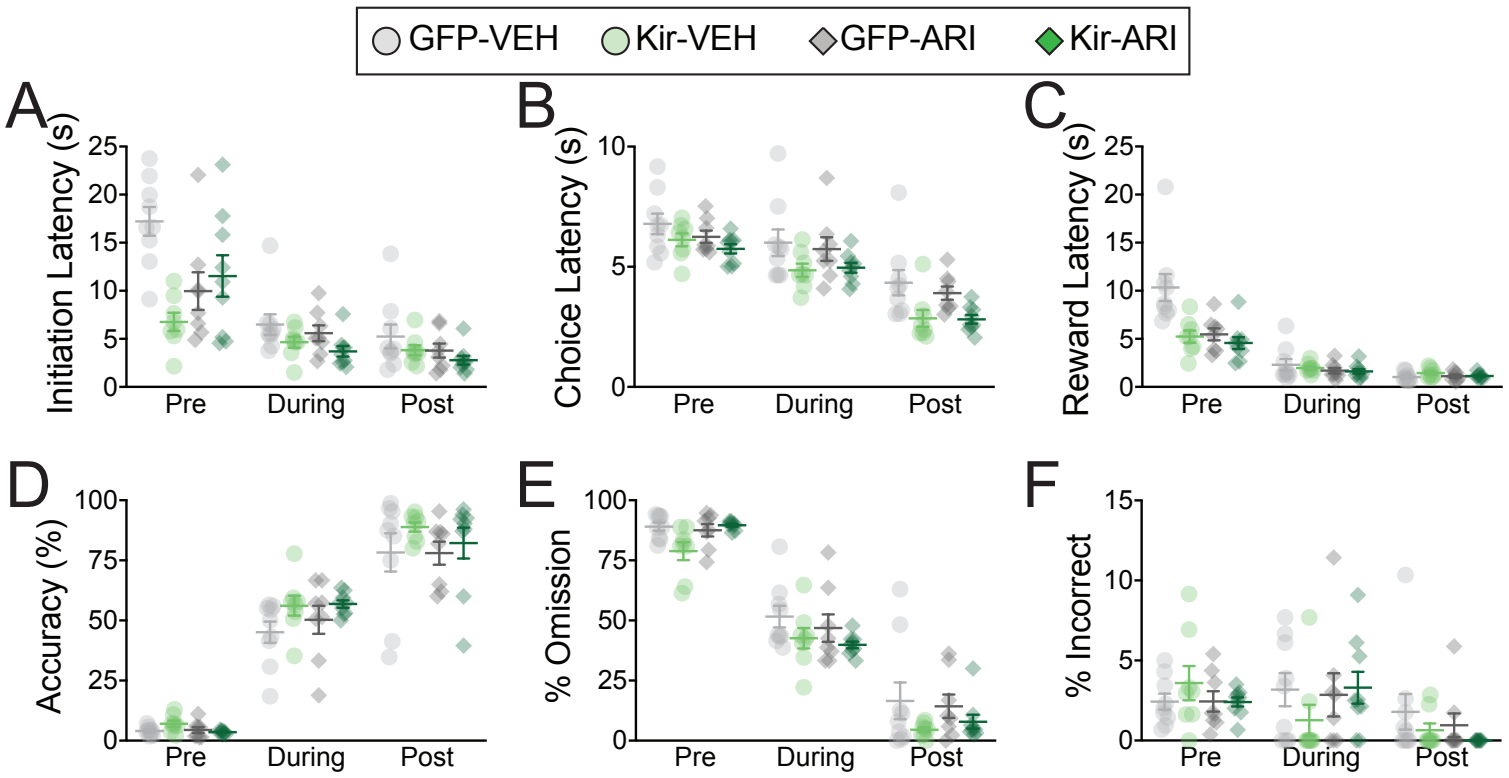
GFP-VEH
Kir-VEH
GFP-ARI
Kir-ARI
A
Initiation Latency (s)
25
20
15
10
5
0
Pre
During
Post
B
Choice Latency (s)
10
5
0
Pre
During
Post
C
Reward Latency (s)
25
20
15
10
5
0
Pre
During
Post
D
Accuracy (%)
100
75
50
25
0
Pre
During
Post
E
% Omission
100
75
50
25
0
Pre
During
Post
F
% Incorrect
15
10
5
0
Pre
During
Post

Figure S3. Intra-striatal dopamine D2 partial agonism prevents effects of LTSI inhibition on learning; related to Figure 3. (A-C) Latencies to (A) initiate, (B) lever press, and (C) retrieve reward across learning stages. (D-F) Proportions of (D) correct presses, (E) omitted responses, and (F) incorrect lever presses across learning stages. All box and whiskers data represented as median ± interquartile range, with whiskers showing entire spread. See Data S1 for detailed statistics.