Supplementary Figure 1 (linked to Figure 1). LRRK2 mediates the effects of haloperidol on movement disruption

A. Western blot analysis of striatal extracts from mice across pharmacological treatments for 7 days, probed for pS106 Rab12 (LRRK2 kinase target), total Rab12, and β-actin.

B. Quantification of p-Rab12 band intensities normalized to total Rab12. n=6 mice

C. Quantification of total Rab12 band intensities normalized to total β-actin. n=6 mice

D. Distance traveled in the open field after 7 days of indicated pharmacological manipulations. N= 8, 8, 7, 8 mice, in order of groups presented.

E. Example of haloperidol and MLi-2 acute and chronic dosing schedule. Catalepsy was assessed 1 hour after the final haloperidol injection. Parts of the schematic were created with BioRender.com.
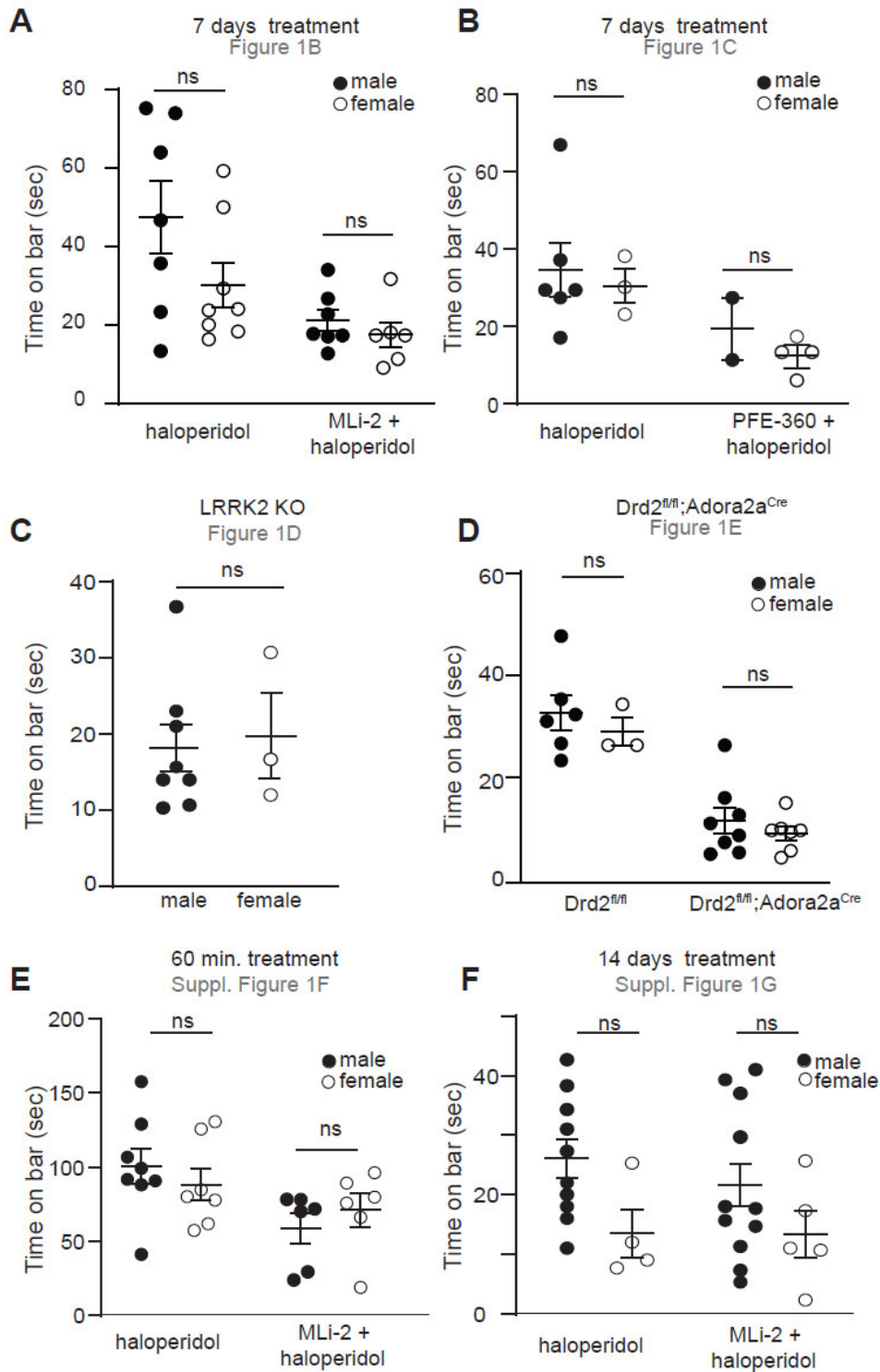
F. Catalepsy response of mice treated with haloperidol, MLI-2, or their combination. N=5, 13, 5, 12, in order of groups presented.

G. Cataleptic response after 14 days administration of haloperidol, MLi-2, or MLi-2 +haloperidol. N=9, 14, 10, 16.

H. Western blot analysis of striatal extracts from mice treated with MLI-2 or vehicle for 90 mins, as in F, probed for pS106 Rab12 (LRRK2 kinase target), total Rab12, and β-actin.
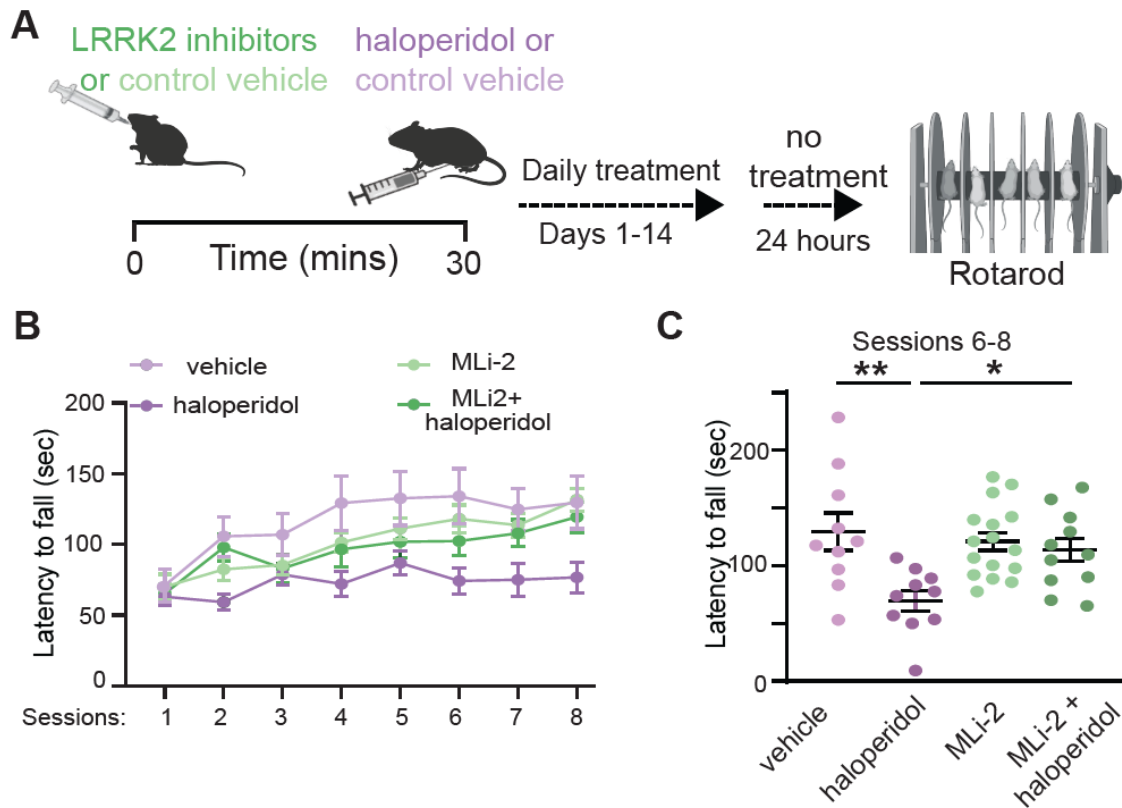
I. Table summarizing the magnitude of cataleptic response and the effects of LRRK2 inhibitor in cataleptic response across acute (1 hour), subchronic (7 days), and chronic (14 days) haloperidol treatment paradigms.

Data are represented as mean±SEM. Asterisks in B, C, D, F and G denote statistical significance for Tukey's multiple comparison tests after one-way ANOVA. *p<0.05, **p<0.01, ****p < 0.0001.

Supplementary Figure 2 (linked to Figure 1). Haloperidol induced cataleptic behaviors by sex

A-F. Summary graph showing the effect of sex across genotypes, pharmacological manipulations, and timepoints for data presented in Figure 1 and Supplementary Figure 1. Relevant figure panels are indicated. Data are represented as mean±SEM. ns, not significant for Tukey's multiple comparisons test, after two-way ANOVA, except for C (unpaired t-test).
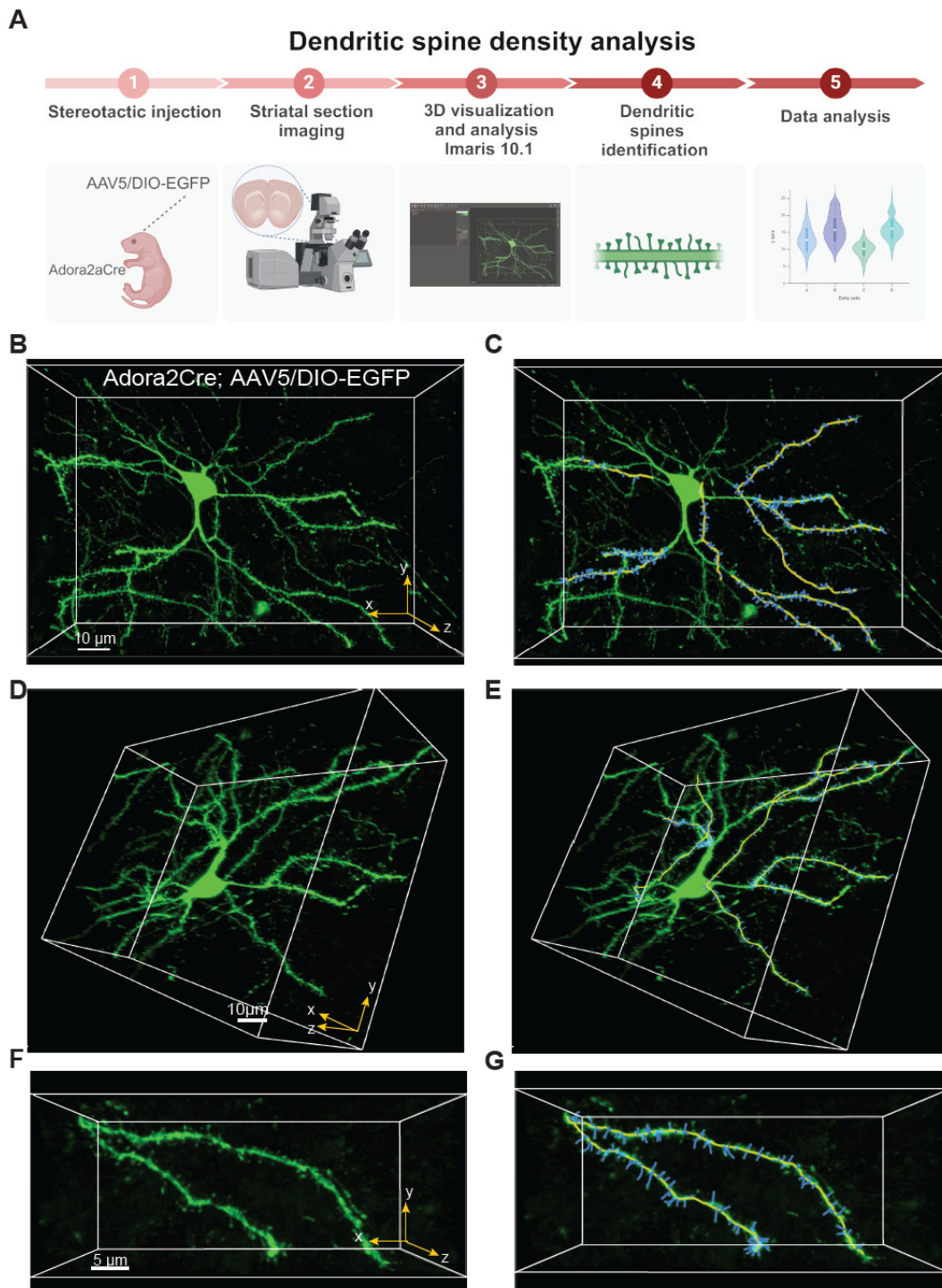
Supplementary Figure 3 (linked to Figure 1). LRRK2 kinase inhibitors restore haloperidol induced effects on striatal motor learning

A. Schematic of the experiment and treatment schedule; it contains schematics created with Biorender.com.
B. Accelerating rotarod performance (latency to fall) assessed over 8 daily sessions of 5 trials each. Mice received pharmacological compounds, as noted, and were assessed 24 hours after the final haloperidol injection. n=10, 10, 16, 11, in the order are presented.
C. The average latency to fall in the last 3 sessions of B (Session 6-8). Asterisks show statistical significance for Tukey's multiple comparison tests after one-way ANOVA; **p< 0.01, *p< 0.05.
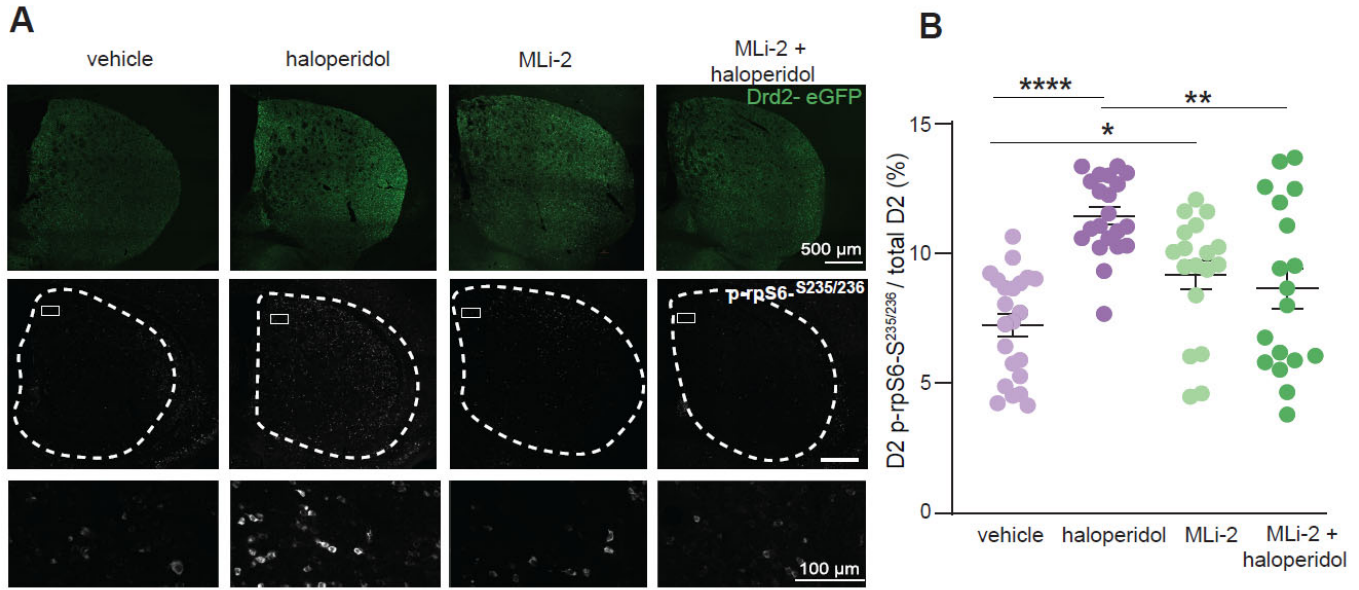
Supplementary Figure 4 (linked to Figure 2). Dendritic spines density measurement workflow

A. Workflow of experimental design for dendritic spine analysis using 3D visualization and analysis with Imaris 10.1. Created with BioRender.com.

B, C. Representative 3D volume rendering images of an *Adora2a^Cre* iSPN expressing AAV5/DIO-EGFP, and the corresponding 3D Imaris filament tracer. Scale bar=10 μm

D, E. A different perspective angle for each x-y-z image in B, C. Scale bar=10 μm

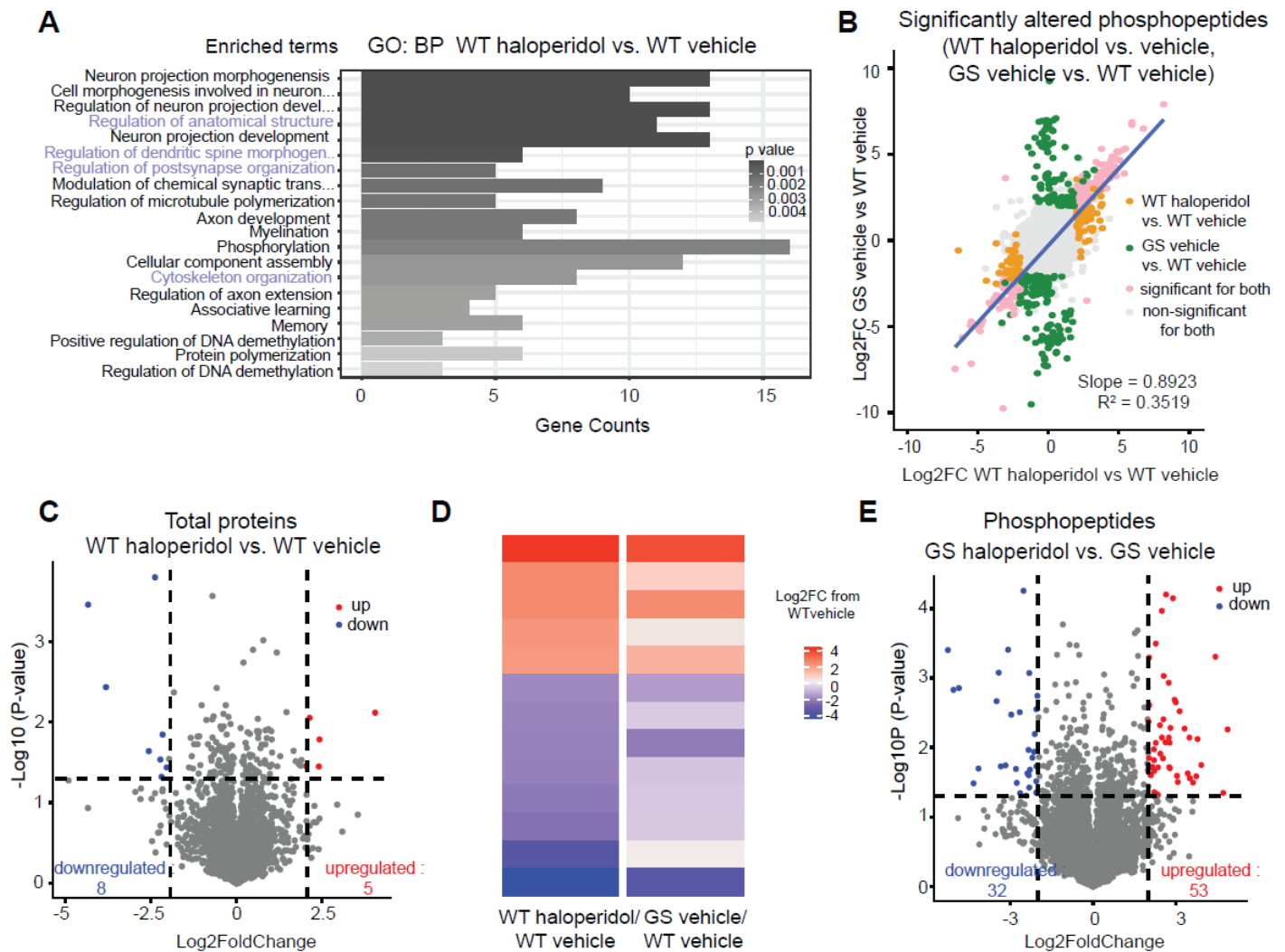**F, G.** Close-ups of dendritic segments from B, C. Scale bar=5 μm

Supplementary Figure 5 (linked to Figure 3). LRRK2 kinase inhibition restores haloperidol effects on rpS6 signaling in iSPNs

A. Representative images showing the distribution of eGFP (top) and p-rpS6 (middle) signal in striatal slices of *Drd2-eGFP* mice treated with vehicle, haloperidol, MLi2, or MLi2+ haloperidol for 7 days. The bottom row shows higher magnification images of p-rpS6 expression. First and second row : scale bar=500 μm; third row: scale bar=100 μm

B. Ratio of p-rpS6 positive Drd2-eGFP cells to total Drd2-eGFP cells. Data reflect mean±SEM. Asterisks show statistical significance for Tukey's multiple comparison tests after one-way ANOVA; **p< 0.01, ****p < 0.0001. N=18-22 sections/3-4 mice.

Supplementary Figure 6 (linked to Figure 3). Proteomic analysis of striatal extracts from haloperidol and vehicle-treated WT and GS mice
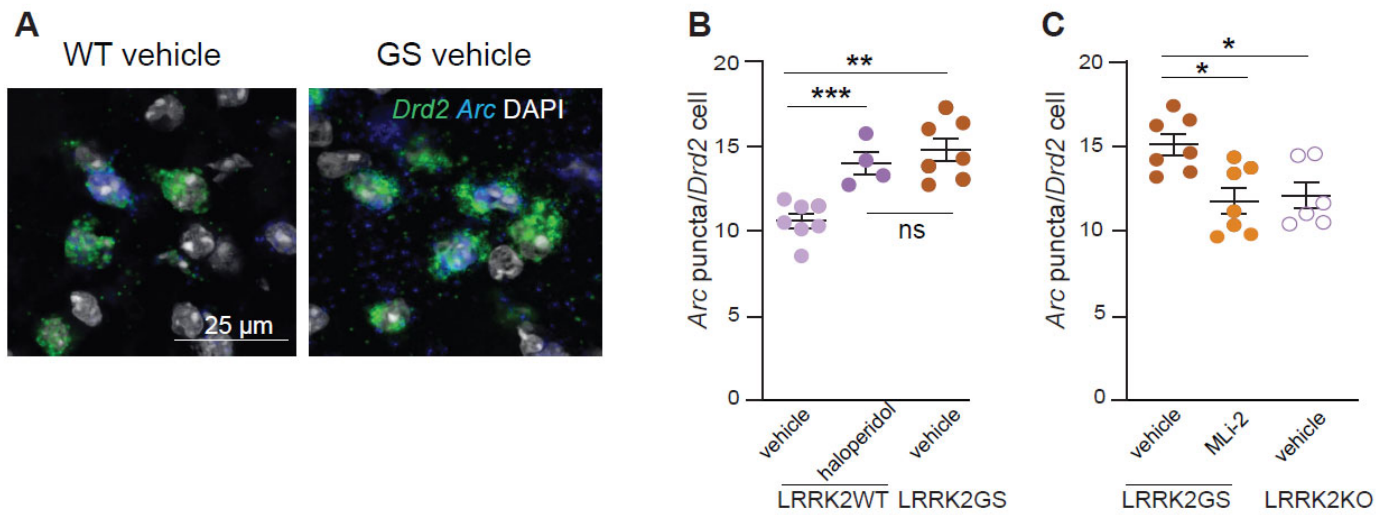
A. Results of GSEA for the Gene Ontology: Biological Processes gene set on genes with at least one significantly differentially regulated phosphopeptide for the WT haloperidol vs vehicle treated comparison. All pathways displayed are significantly differently regulated (adjusted p-value ≤ 0.05 by Fisher's test). Length of bars shows the number of genes in the pathway whose phosphostate is differentially regulated, and bars are shaded by adjusted p-value. Highlighted pathways are related to known LRRK2 functions.

B. Correlation plot for Fig 4E, comparing GS vehicle/WT vehicle to WT haloperidol-vehicle effect size. All points mapped, all significant phosphopeptides (|Log2FC| > 2 and p-value ≤ 0.05 by multiple unpaired t-tests) for either comparison are highlighted and used for correlation. Blue line represents the line of best fit.

C. Volcano plot of the striatal proteome comparing the haloperidol- vs. vehicle-treated WT mice. Differentially regulated proteins (|Log2FC| > 2 and p-value ≤ 0.05 by multiple unpaired t-tests) are colored in red and blue for up- and downregulated, respectively.

D. Heatmap of effect size (Log2FC) of either haloperidol treatment or LRRK2-GS for all proteins differentially expressed (|Log2FC| > 2 and p-value ≤ 0.05 multiple unpaired t-tests) compared to the vehicle-treated wild type condition in the wild type haloperidol- vs vehicle-treated comparison, mapped for both the wild type haloperidol- vs vehicle-treated comparison and the GS vs. wild type vehicle-treated comparison. Each bar represents a protein

E. Volcano plot of relative phosphopeptide for haloperidol- and vehicle-treated LRRK2-GS mutant mice. Phosphopeptides that are differentially regulated (|Log2FC| > 2 and p-value ≤ 0.05 by multiple unpaired t-tests) are colored in red and blue for up and downregulated, respectively.

Supplementary Figure 7 (linked to Figure 4). LRRK2 kinase activity underlies *Arc* increase in indirect pathway SPNs.

A. Example confocal images of *Arc* gene expression in iSPNs of LRRK2-WT and LRRK2-GS mice. Scale bar=25 μm

B. Quantification of the number of *Arc puncta* among *Drd2*-positive nuclei. LRRK2-WT mice treated with haloperidol, or vehicle and LRRK2-GS mice treated with vehicle. Each dot represents the average number of *Arc* puncta among *Drd2*-positive nuclei from one striatal section, n=4-7 sections/3-4 mice/group.

C. Quantification of *Arc* puncta among *Drd2*-positive nuclei in LRRK2-GS mice treated with vehicle, MLi2, and LRRK2- KO mice treated with vehicle for 2 hours. N=6-7 sections/3-4 mice.

Data reflect mean±SEM. Asterisks in B, C reflect statistical significance for Tukey post-hoc comparisons after one-way ANOVA. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.