Supplemental Figure Legends

Supplemental Figure 1: Sex does not impact B.1.351 infection Mice were intranasally infected with B.1.351 (5 x 10^5 pfu). A) Weight loss curves for mice infected at 8, 10, or 20 weeks of age (all male, n=5-6). B) Weight loss curves for 16-week-old male or female mice infected with B.1.351 (n=6-8). C) Viral titer in the Nasal turbinates and lung from 2, 4, 6, 8, 12 dpi measured via plaque assay (n=5-8). D) RNA transcript levels of *Ifnb, Ifng, Il1b, Tnf* at 4 and 6 dpi represented as fold change over mock (6 dpi) in the lung (n=4-6). E) Representative image of Spike RNA *in situ* hybridization for an entire sagittal section of the brain from 4 dpi counterstained with hematoxylin. F) Indicated Open field measurement for combined sexes at 30 dpi (n= 20). G) Representative image of Novel Object apparatus set-up. On the right the percentage of investigations of each object during a preference test (n=4). H) Selected open field measurements for male vs female mice at 30 dpi (n=8-10). I) The discrimination index for the NOR test for B.1.351 infected male vs female mice is displayed on the left at 30 dpi. On the right, the discrimination index plotted vs the maximum weight lost during infection. Linear regression was used to calculate the R-squared and p-value are displayed on chart (n=15-20). Data is represented as mean with SEM and was pooled or representative of 2-4 independent experiments. Statistical significance was determined using simple linear regression, one-way ANOVA, two-way ANOVA, student's t-test, or paired two-way ANOVA (for F). *=$p<0.05$, **=$p<0.01$.

Supplemental Figure 2: T cells are increased in the cortex after SARS-CoV-2 infection. Mice were intranasally infected with B.1.351 and euthanized at the indicated timepoint. A) Representative pseudocolor plots of the cortex at 30 dpi showing gating strategy for blood, cortex, and hippocampus. Cells are gated on total lymphocytes → singlets → Live cells → CD45+ cells. Cells are then gated on Ly6G. CD3+ cells are defined as CD45+ Ly6G-, CD3+. CD19+ Cells are defined as CD45+, Ly6G-, CD3-. Myeloid cells are defined as CD45+, Ly6G-,

CD3-, CD19- then analyzed via CD45 vs CD11b expression. B) Frequency of the indicated population as a percentage of the total CD45+ cells in the blood at 6 dpi (n=6-8) and C) 30 dpi (n=7-9) D) Frequency of Ly6C Low or High cells in the total $CD45^{high}$ CD11b+ (Monocyte) population at 6 and 30 dpi in the blood. E) The count per gram of tissue for the indicated cell population in the cortex (top row) or hippocampus (bottom row) at 6 dpi (n=6-8) or F) 30 dpi (n=7-9) Data is represented as mean with SEM and was pooled from 2 independent experiments. Statistical significance was determined two-way ANOVA, student's t-test, or *=p<0.05, **=p<0.01, ***=p<0.001.

Supplemental Figure 3: $CD45^{Mid}$CD11b+ cells are microglia after B.1.351 infection. A) Representative pseudocolor flow plots showing expression of P2RY12 or Ly6C on $CD45^{mid}$ Cd11b+ cells at 6 dpi from B.1.351 infected mice. B) Representative images of IBA-1 expression in the DG after B.1.351 infection or mock at 6 and 30 dpi. Below is the percentage of IBA-1+ area in the indicated hippocampal region at 6 and 30 dpi. All image analysis and acquisition were performed blinded and quantification was averaged from 2-4 slices for each mouse. Scale bar is 20 μM. Data is represented as mean with SEM and was pooled from 2 independent experiments. Statistical significance was determined two-way ANOVA, or *=p<0.05, **=p<0.01,

Supplemental Figure 4: PR8 infection does not induce hippocampal IL-1β. C57Bl/6J mice at 14 weeks of age were intranasally infected with B.1.351, PR8 (2000 $TCID_{50}$) or mock infected with PBS. A) The percent of original weight for mock and PR8 infected mice (n=8). B) qRT-PCR was performed for PR8 RNA in the indicated tissue. Values are represented as delta C_T normalized to GAPDH. Dotted line indicates the limit of detection. C) qRT-PCR was performed for the indicated gene on mock, 3, and 6 dpi samples from the lung, cortex, and hippocampus

(n=4). D) Representative images of Isotype control for IL-1β (Goat IgG) from 6 dpi B.1.351 mice on the left. On the right, mice were intracranially infected with WNV-E218A, harvested at 7 dpi and hippocampal slices were stained for IL-1β expression as a positive control. E) Representative images of IL-1β staining in the DG with quantification of the total percent IL-1β+ are on the right for the DG, CA3, and CA1 for mock and 6 dpi PR8 or B.1.351 (n=4). F) Representative images of IBA-1 staining in the DG with the total % IBA-1 area quantified on the right for mock and 6 dpi PR8 or B.1.351. All image analysis and acquisition were performed blinded and quantification was averaged from 2-4 slices for each mouse. Scale bar is 20 μM. Data is represented as mean with SEM and was pooled from 2 independent experiments. Statistical significance was determined two-way ANOVA, or *=p<0.05, **=p<0.01, ***=p<0.001, ****=p<0.0001.

Supplemental Figure 5: Decreased neurogenesis does not occur during PR8 infection. C57Bl/6J mice were intranasally infected with PR8. A) Representative images of Ki67 and DCX staining in the SGZ of the DG at 6 dpi from mock and PR8 infected animals. Quantified on the right is the number of DCX+, Ki67+, and Ki67+ DCX+ (n=7-8). Mice were intranasally infected with B.1.351 and harvested at the indicated timepoints. B) Number of synaptophysin+ puncta or homer1+ puncta represented as the % of the number of average mock puncta in the indicated sub-region of the hippocampus at 6dpi (n=5-8) or C) 30 dpi (n=6-9). D) Representative images of the DG showing staining for NeuN, TUNEL, and DAPI. Below, quantification of the total number of TUNEL+ NeuN+ cells per mm^2 for each subregion of the hippocampus (n=4-5). All image analysis and acquisition were performed blinded and quantification was averaged from 2-4 slices for each mouse. Scale bar is 20 μM. Data is represented as mean with SEM and was pooled from 2 independent experiments. Statistical significance was determined two-way ANOVA, or *=p<0.05.

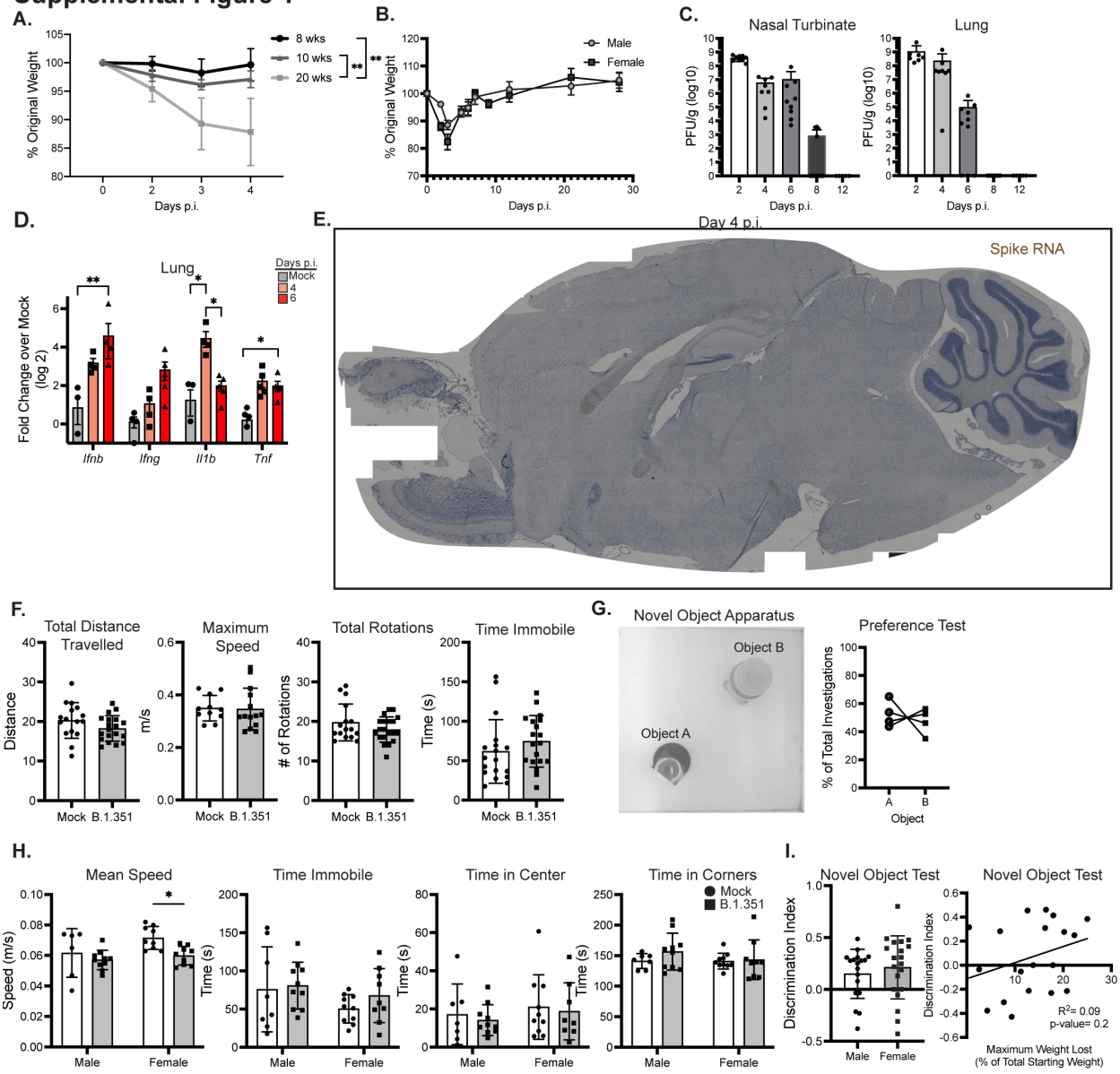
Supplemental Figure 6: IL-1R1 signaling on NSCs does not impact synapse formation. Nestin-Cre^{ERT2} x IL-1R1$^{fl/fl}$ littermates (Cre+ and Cre-) were intraperitoneally (I.P.) injected with Tamoxifen for 5 days. 10 days after the last tamoxifen injection, mice were intranasally infected with B.1.351. A) Weight loss curves for Mock and B.1.351 infected Nestin-Cre- and Nestin-Cre+ mice. B) Representative images of Ki67 and DCX staining in the DG at 30 dpi. C) Representative z-stacks of Synaptophysin and Homer in the DG at 30 dpi. D) Number of puncta for each marker and the number of overlapping (synapse) puncta was quantified as the total number of puncta per mm^2 and represented as a percentage of the number of puncta in mock samples for each region (n=4-8). E) Mice were trained for the NOR test and the percentage of total investigations of identical Object 1a and 1b is shown for Mock and B.1.351 Nestin-Cre- and Nestin-Cre+ mice at 31 dpi (n=4-8). F) Selected open field measurements at 30 dpi (n=4-8). G) Simple linear regressions between the discrimination index calculated from the Novel object test and the # of Ki67+DCX+ cells, the # of BrdU+ GFAP+ Cells, or the # of Synapse puncta for B.1.351 infected mice for Nestin-Cre- mice at 30 dpi. All image analysis and acquisition was performed blinded and quantification was averaged from 3-5 slices for each mouse. Scale bar is 20 μM. Data is represented as mean with SEM and was pooled from 2 independent experiments. Statistical significance was determined one-way or two-way ANOVA, student's t-test, or simple linear regression. *=p<0.05, **=p<0.01.

Supplemental Figure 7: Vaccination provides neutralizing antibodies in C57Bl/6 mice. A) Experimental schematic: Mice were intranasally vaccinated with 10^8 ChAd-Spike (S) or empty vector ChAD-Control (CTL) at day -30 p.i. At day -7, a cheek bleed was performed. At day 0, mice were intranasally infected with 5 x 10^5 pfu B.1.351. Mice were harvested at the indicated timepoint. B) FRNTs were performed to measure the % of B.1.351 neutralized by serum collected at - 21 days post vaccination from ChAd-CTL or ChAd-S inoculated animals (n=8). C).

The total number of CD3+ cells per gram of tissue was quantified for mock and 6 dpi ChAd-CTL or ChAd-S animals via flow cytometry. Data is represented as mean with standard error of the mean and either representative of or pooled from 2 independent experiments. Statistical significance was determined by -way ANOVA, *=$p<0.05$.

Supplemental Figure 8: Vaccination does not impact open field performance after breakthrough infection. Mice were intranasally vaccinated with 10^8 ChAd-S or ChAd-CTL, then challenged with B.1.351 30 days later. A) Selected open field test parameters measured at 30 dpi from ChAd-CTL or ChAd-S mice (n=5-10). B) At 31 dpi, mice underwent training for the Novel Object test. On the left, the % of total investigations (nose pokes) spent with identical Object 1A or 1B. On the right, the discrimination index for mock and 30 dpi ChAd-CTL and ChAd-S mice (n=5-20). Data is represented as mean with standard error of the mean and pooled from 2 independent experiments.

Supplemental Figure 1



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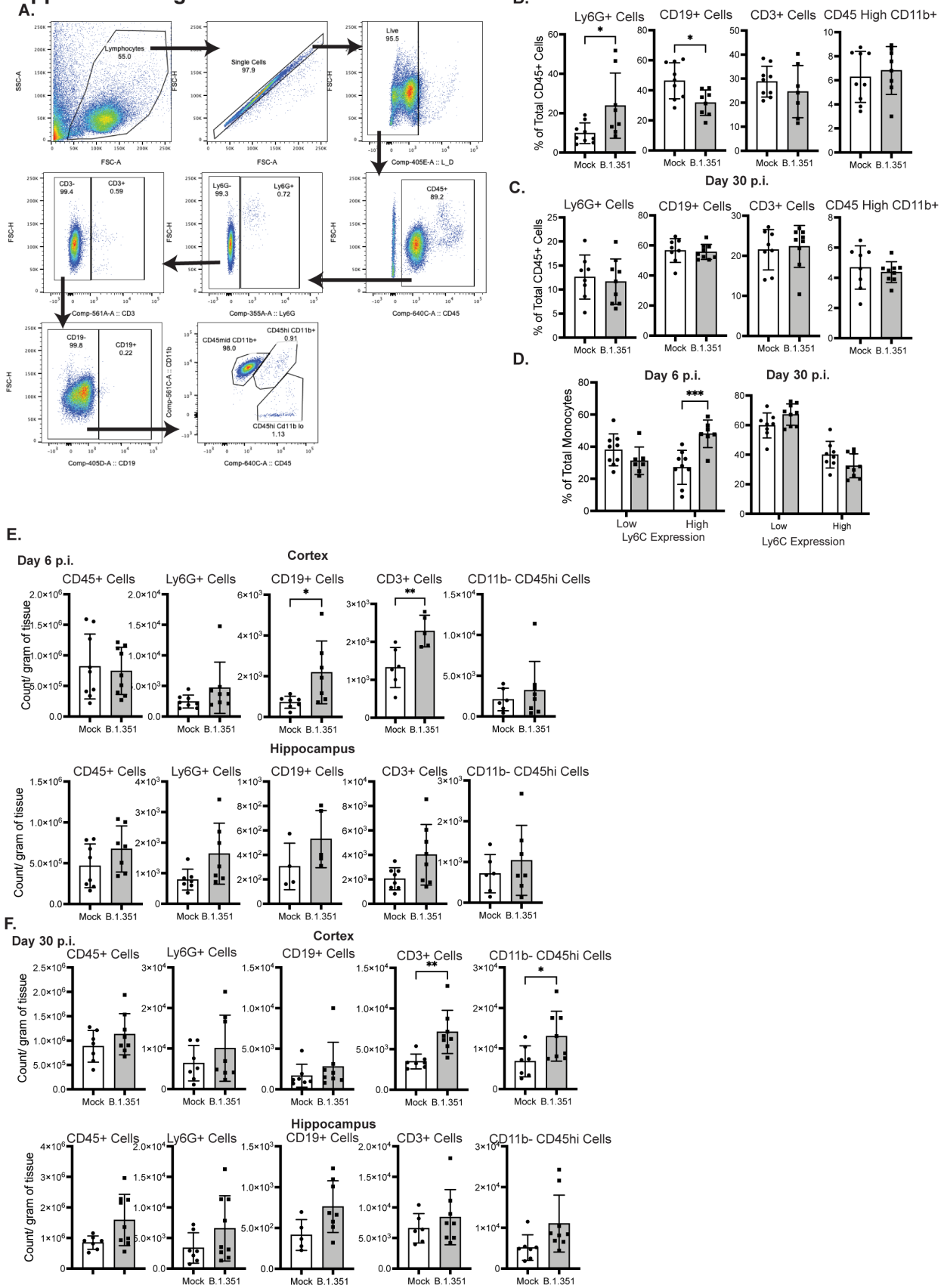

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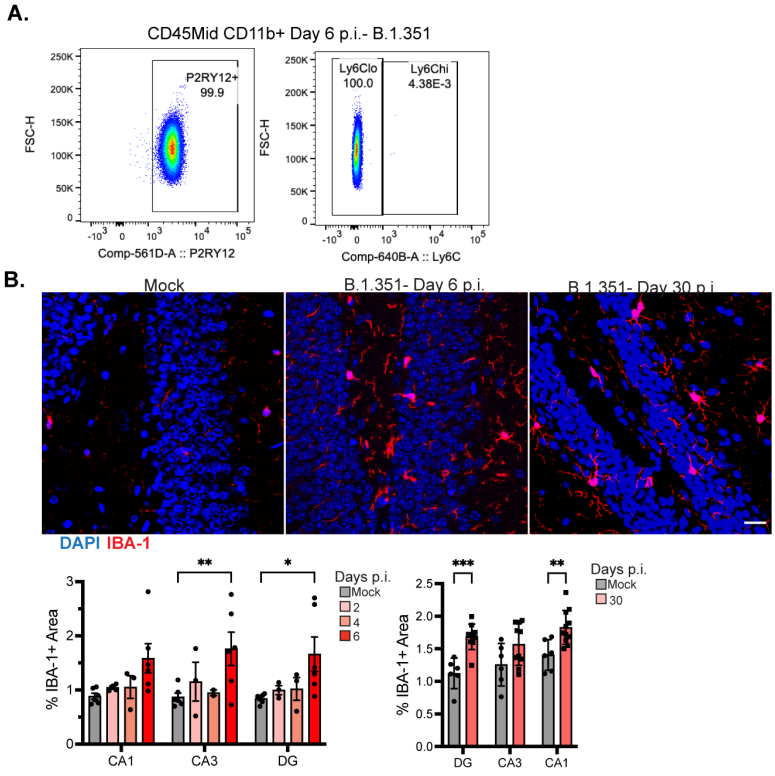

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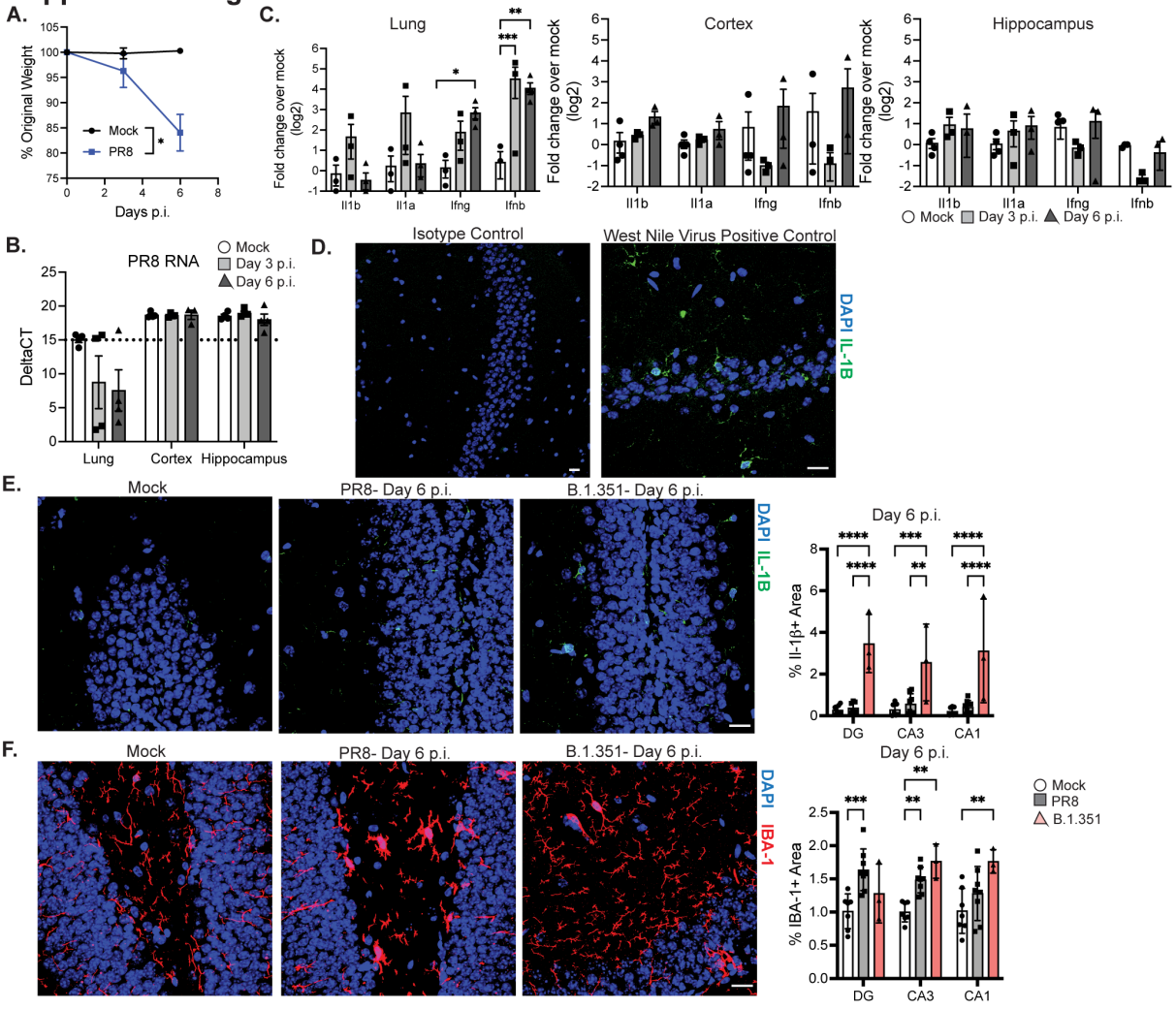

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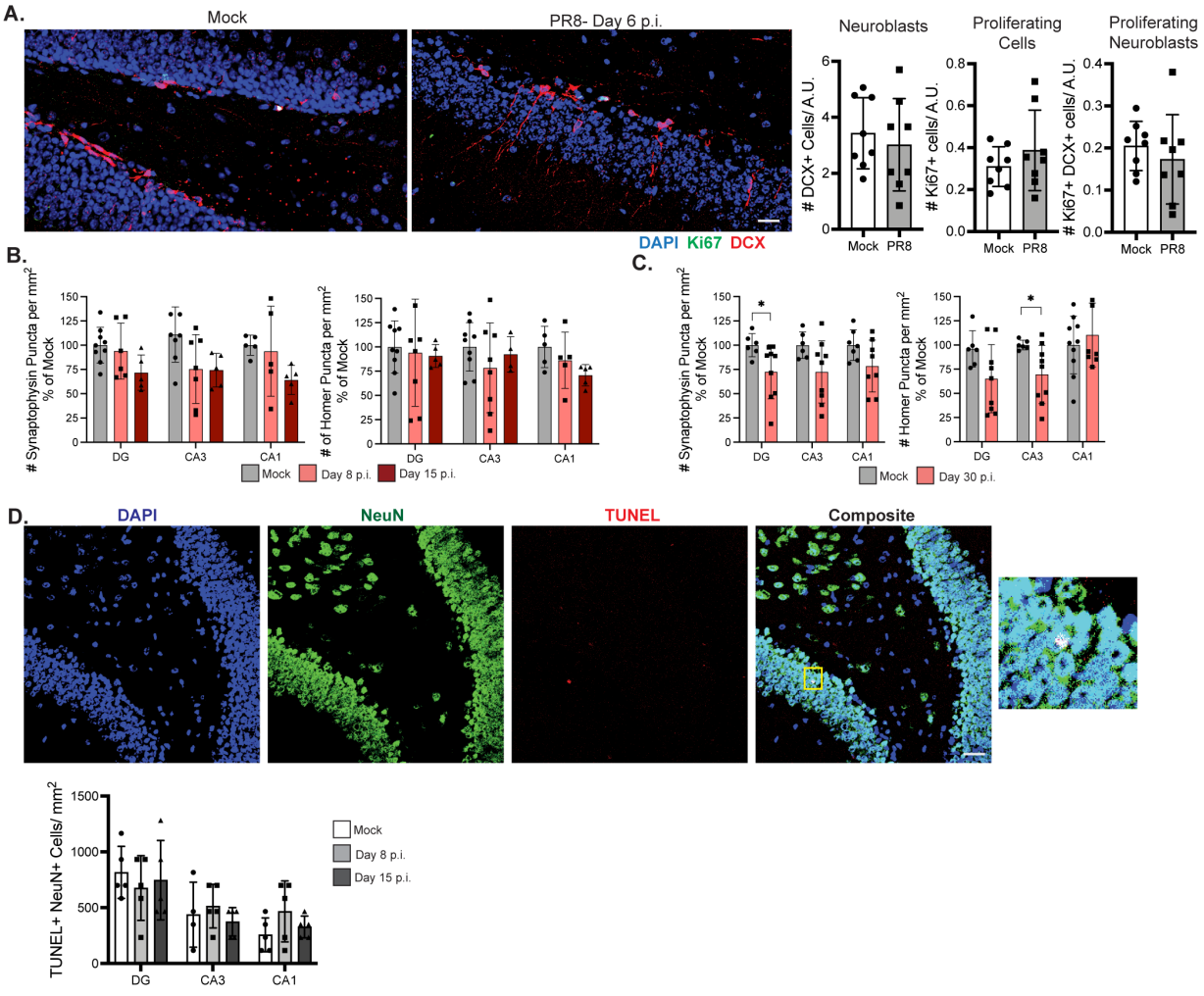

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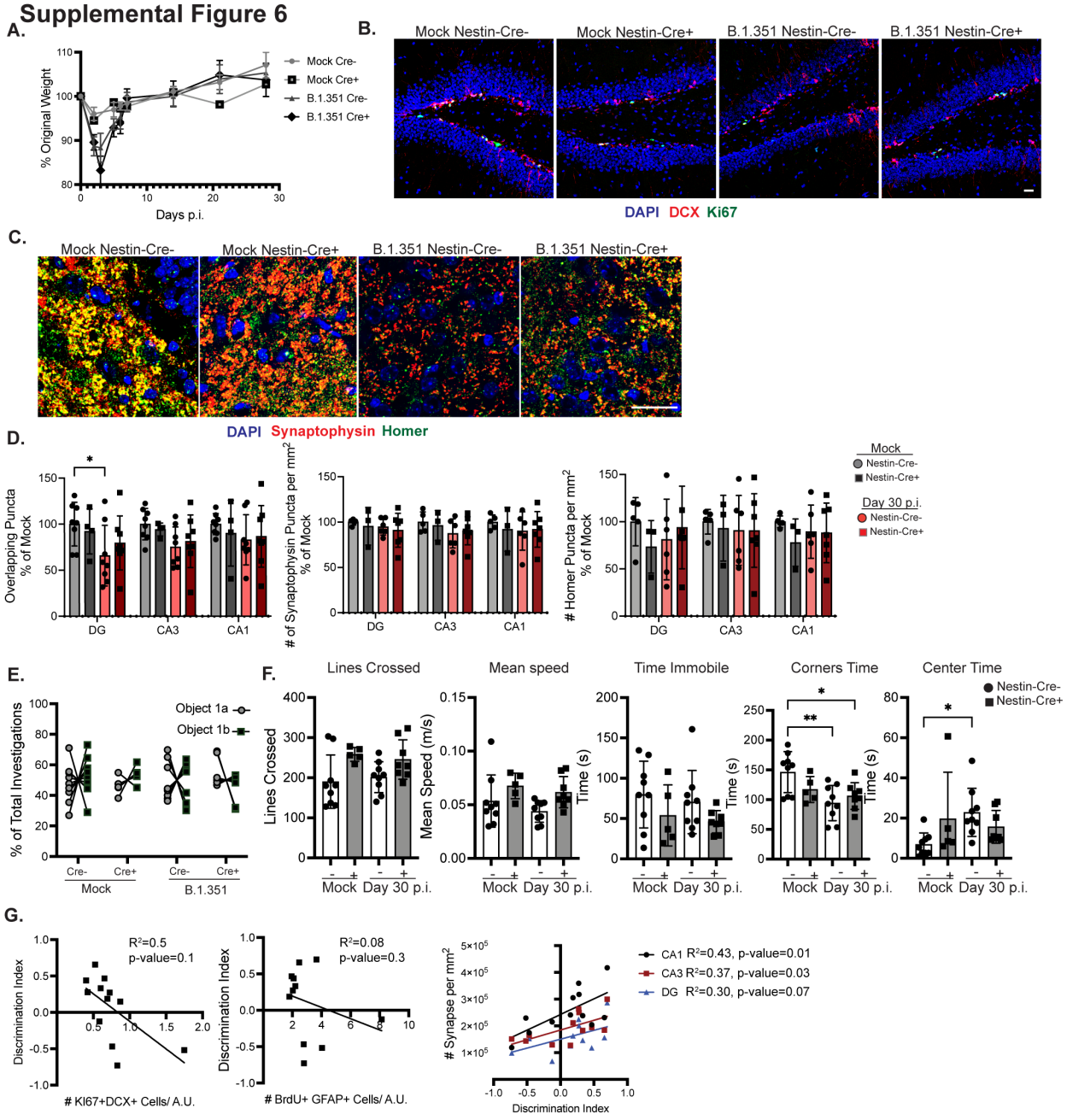
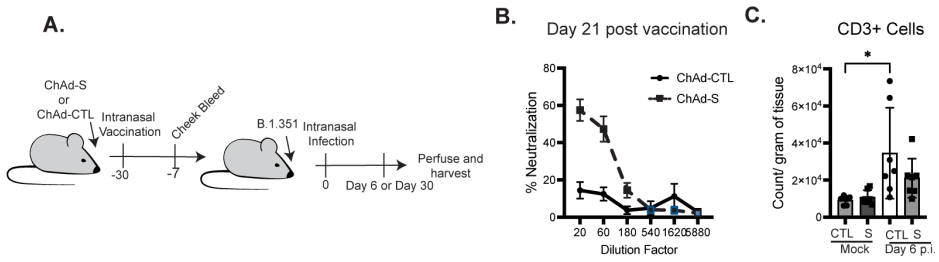


Supplemental Figure 7



Supplemental Figure 8: