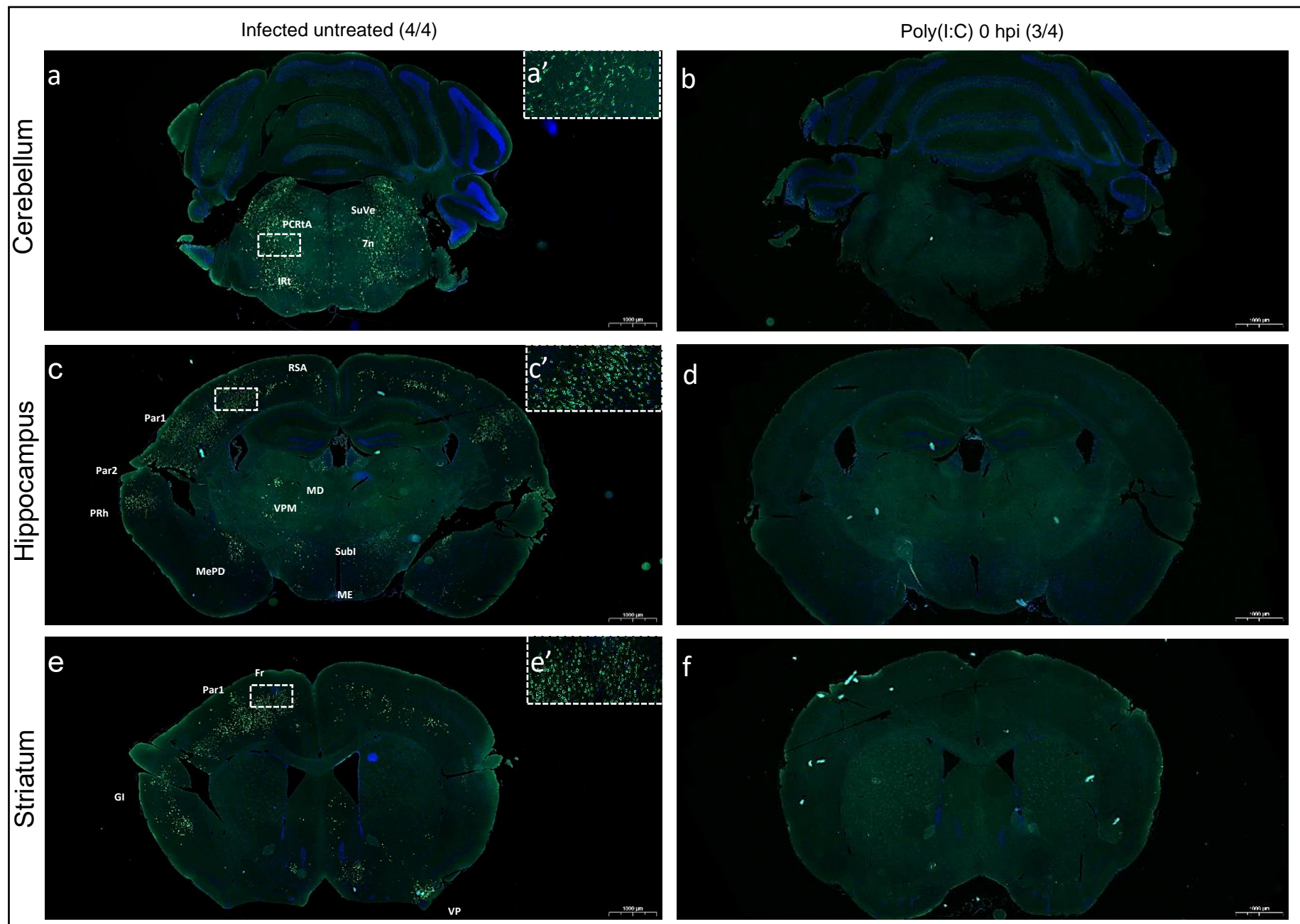


**Figure S1.** Prophylactic effect of Poly(I:C) following SARS-CoV-2 infection. Body weight changes (a) and mortality (b) of K18-hACE2 mice treated with 1.5mg/kg (i.n.) of Poly(I:C) 6 hours before infection with SARS-CoV-2 (500 PFU i.n.). Number of animals per group: naive n=3, Poly(I:C) 6 hbi n=9, Infected untreated n=9. Statistical significance was determined using the Holm-Sidak method as compared to infected untreated group \* $p < 0.005$  (a) or Mantel-Cox test \* $p < 0.05$ .



**Figure S2.** Histopathological brain analysis following Poly(I:C) treatment. SARS-CoV-2 immunolabeling of infected untreated and Poly(I:C) 0 hpi treated mice brains at 5 dpi. Brains were isolated and processed for paraffin embedding from infected untreated (**a, c, e**) and Poly(I:C) 0 hpi treated groups (**b, d, f**). Scale bar= 1000µm. n=4 per group. PCRtA - parvocellular reticular nucleus alpha; IRt – intermediate reticular nucleus; SuVe – superior vestibular nucleus; VPM – ventral posteromedial thalamic nucleus; MePD – Medial amygdala nucleus posterodorsal; MD – mediodorsal thalamic nucleus. ME – median eminence; SuBI – Subincertal nucleus; PRh – perirhinal cortex; RSA – Retrosplenial agranular cortex; Par1 – parietal cortex area 1; Par2 – parietal cortex area 2; FR – frontal cortex; GI – Granular insular cortex; VP – ventral pallidum. **a', c'** and **e'** are enlargements of the boxes in a, c and e, respectively.

**Table S1.** Synergistic effect of Poly(I:C) in SARS-CoV-2 infected mice. The synergistic values of 44 inflammatory related genes of Poly(I:C) treated and infected mice lungs were calculated. Genes are considered synergistically elevated when the value is  $\geq 1.2$ . Color scale bar indicating the fold change magnitude appears on the right.

Cytokines	
IFN $\alpha$	0.4
IFN $\beta$ 1	0.4
IFN $\gamma$	2.1
IL-1 $\alpha$	1.4
IL-1 $\beta$	4.6
IL-4	0.2
IL-6	1.3
TGF $\beta$ 1	1.6
TNF $\alpha$	3.7

Chemokines	
CCL12	1.0
CCL5	2.5
CCL8	0.8
CXCL10	1.8

Complement	
C1rb, C1ra	2.0
C1s1	1.5
C3	1.9

Metalloproteases	
MMP3	1.8
MMP8	4.5
MMP9	1.3
TIMP1	1.4

Antigen presentation	
H2-EB1	1.5
H2-K1	2.1

Interferon related	
Ifi27l2a	1.6
Ifi44	2.4
IFIT1	3.0
IFIT3	0.6
IRF7	1.7
Isg15	1.3
STAT1	2.0

Costimulatory receptors	
CD2	1.6
CD27	2.1
CD3e	2.3
CD3g	1.6
CD4	2.2
CD38	1.5
CD40	1.5
CD80	2.4
CD8a	2.1

Cell death	
FAS	0.9
<u>FASL</u>	1.5
Gzma	0.9
Gzmb	0.9
PRF1	0.8
Zbp1	3.9

