

Article

Prenatal interleukin 6 elevation increases glutamatergic synapse density and disrupts hippocampal connectivity in offspring

Filippo Mirabella,^{1,2} Genni Desiato,^{2,9,11} Sara Mancinelli,^{2,11} Giuliana Fossati,² Marco Rasile,¹ Raffaella Morini,² Marija Markicevic,³ Christina Grimm,³ Clara Amegandjin,^{4,5} Alberto Termanini,⁶ Clelia Peano,^{7,8} Paolo Kunderfranco,⁶ Graziella di Cristo,^{4,5} Valerio Zerbi,^{3,10} Elisabetta Menna,^{2,9} Simona Lodato,^{1,2} Michela Matteoli,^{2,9,*} and Davide Pozzi^{1,2,12,*}

Table of Contents

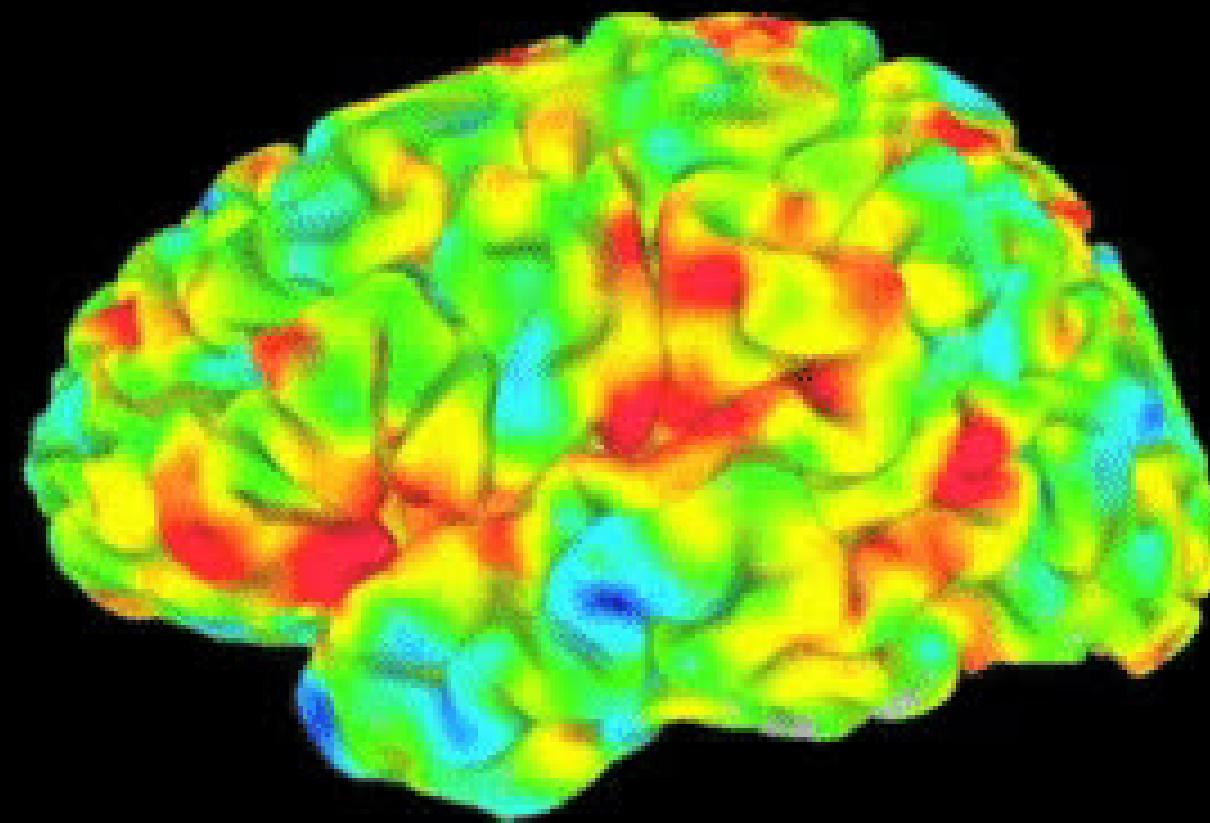
- **Background Knowledge**
- **Figure Analysis**
- **Conclusion**
- **Q&A**

Prenatal interleukin 6 elevation
increases glutamatergic synapse density
and disrupts hippocampal connectivity in offspring

태아기에 IL-6가 올라가면
아이의 글루타메이트성(흥분성) 시냅스 밀도가 증가되고
해마 정상적인 연결이 방해받는다.

Key concepts

- IL-6
- Glutamate
- GABA
- Hippocampus



- Functional Connectivity

Key vocabulary

VGLUT

VGAT

PSD-95

Synaptogenesis

i.p

i.c.v

GD15: Gestational Day 15

E15: Embryonic Day 15

P15: Post-natal Day 15

DIV: Days *in vitro*

1. Transient prenatal IL-6 elevation enhances hippocampal glutamatergic synapses and functional connectivity in adulthood

Figure 1

1. Transient prenatal IL-6 elevation enhances hippocampal glutamatergic synapses and functional connectivity in adulthood

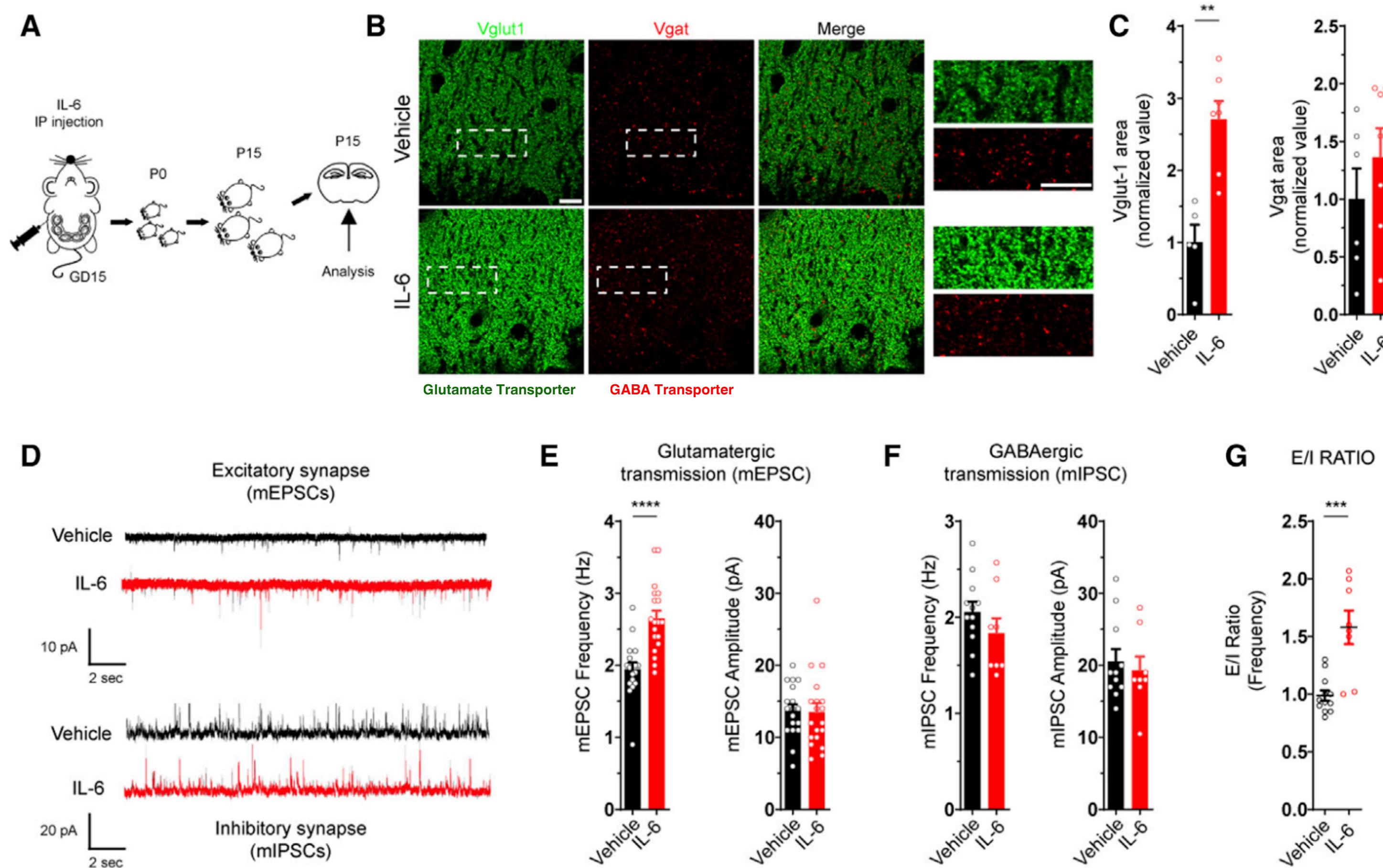


Figure 1

1. Transient prenatal IL-6 elevation enhances hippocampal glutamatergic synapses and functional connectivity in adulthood

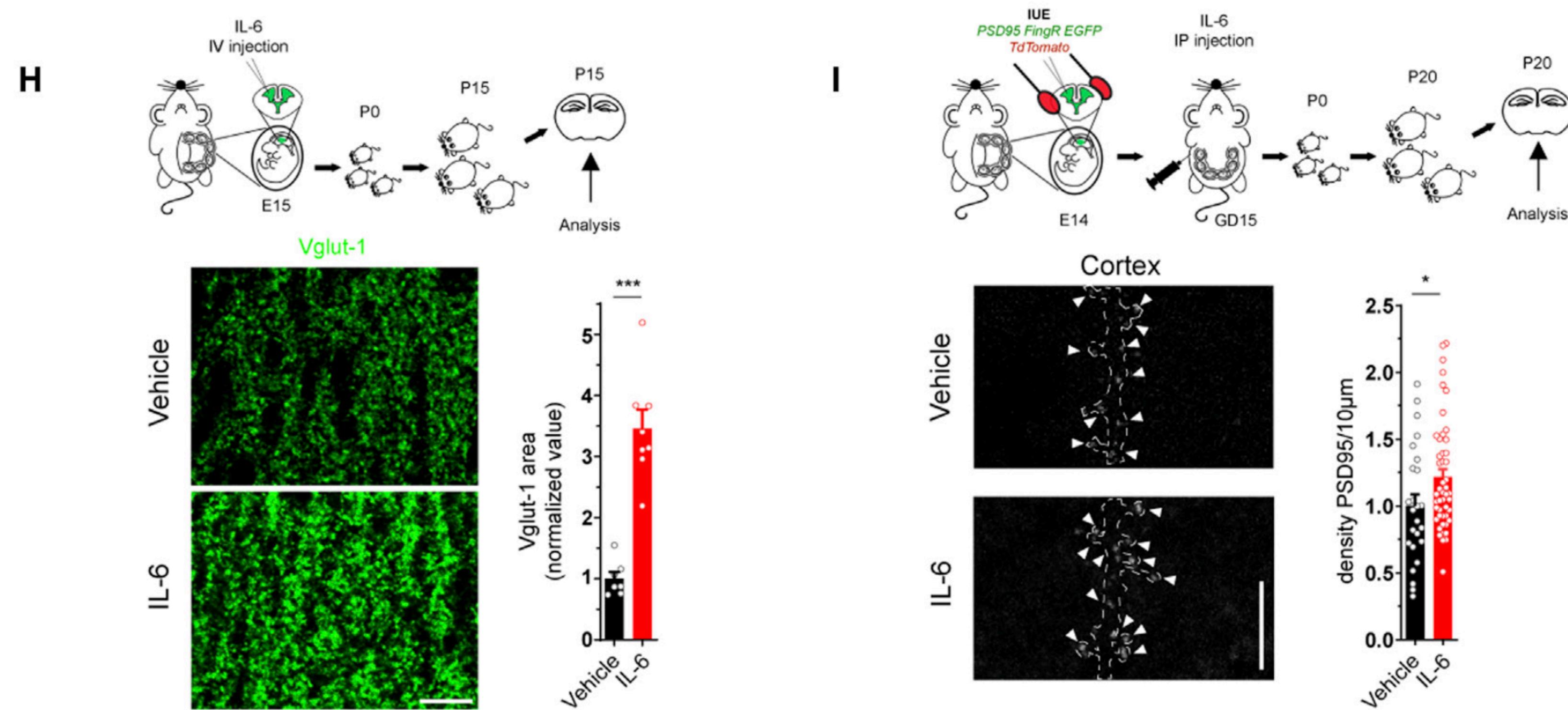
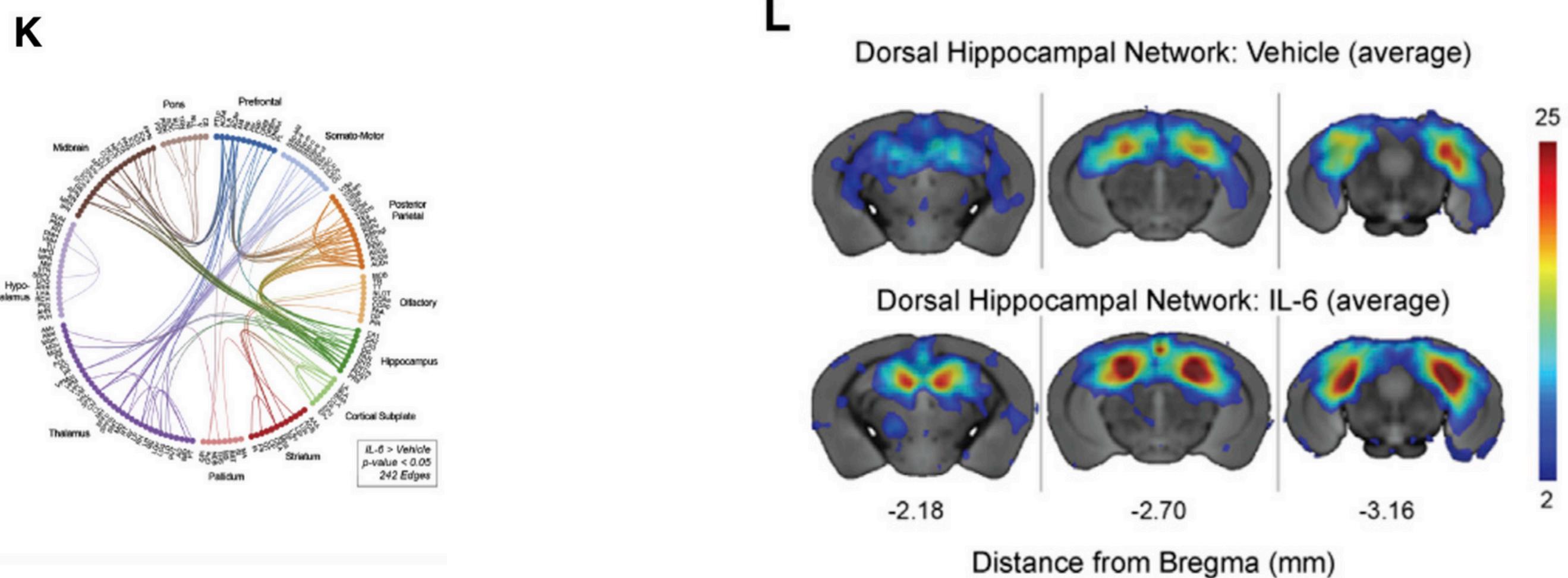


Figure 1

1. Transient prenatal IL-6 elevation enhances hippocampal glutamatergic synapses and functional connectivity in adulthood



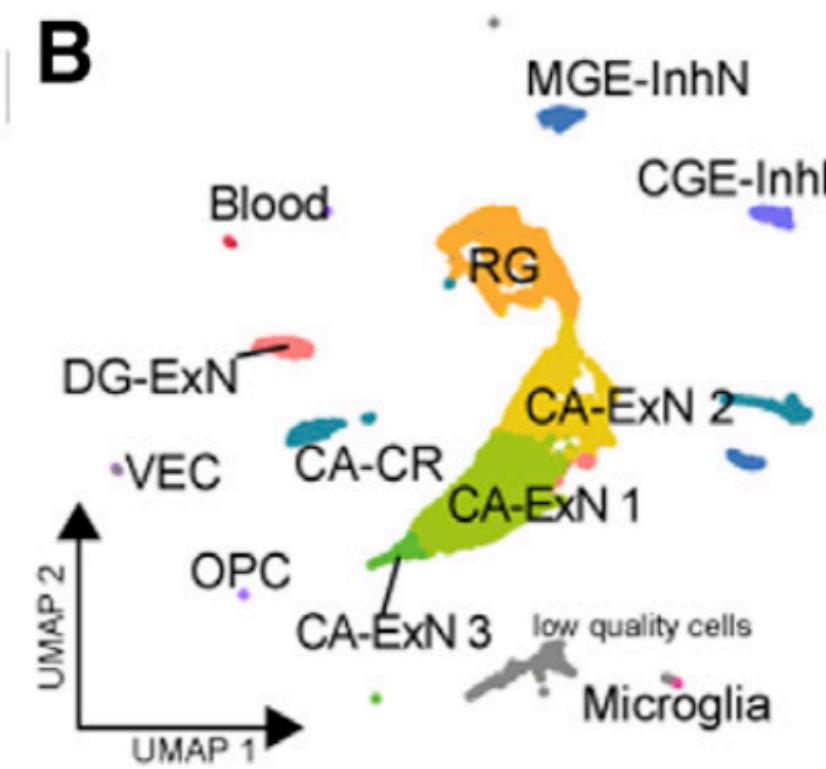
**# hippocampal glutamatergic synapses
functional connectivity in adulthood**



**2. Prenatal IL-6 engages molecular programs of
synaptogenesis in developing hippocampal neurons**

Figure 2

2. Prenatal IL-6 engages molecular programs of synaptogenesis in developing hippocampal neurons



CA-ExN 1
RG
CA-ExN 2(early postmitotic)
low quality cells
CA-CR
DG-ExN
MGE-InhN
CGE-InhN
CA-ExN 3
VC
OPC
Blood
Microglia

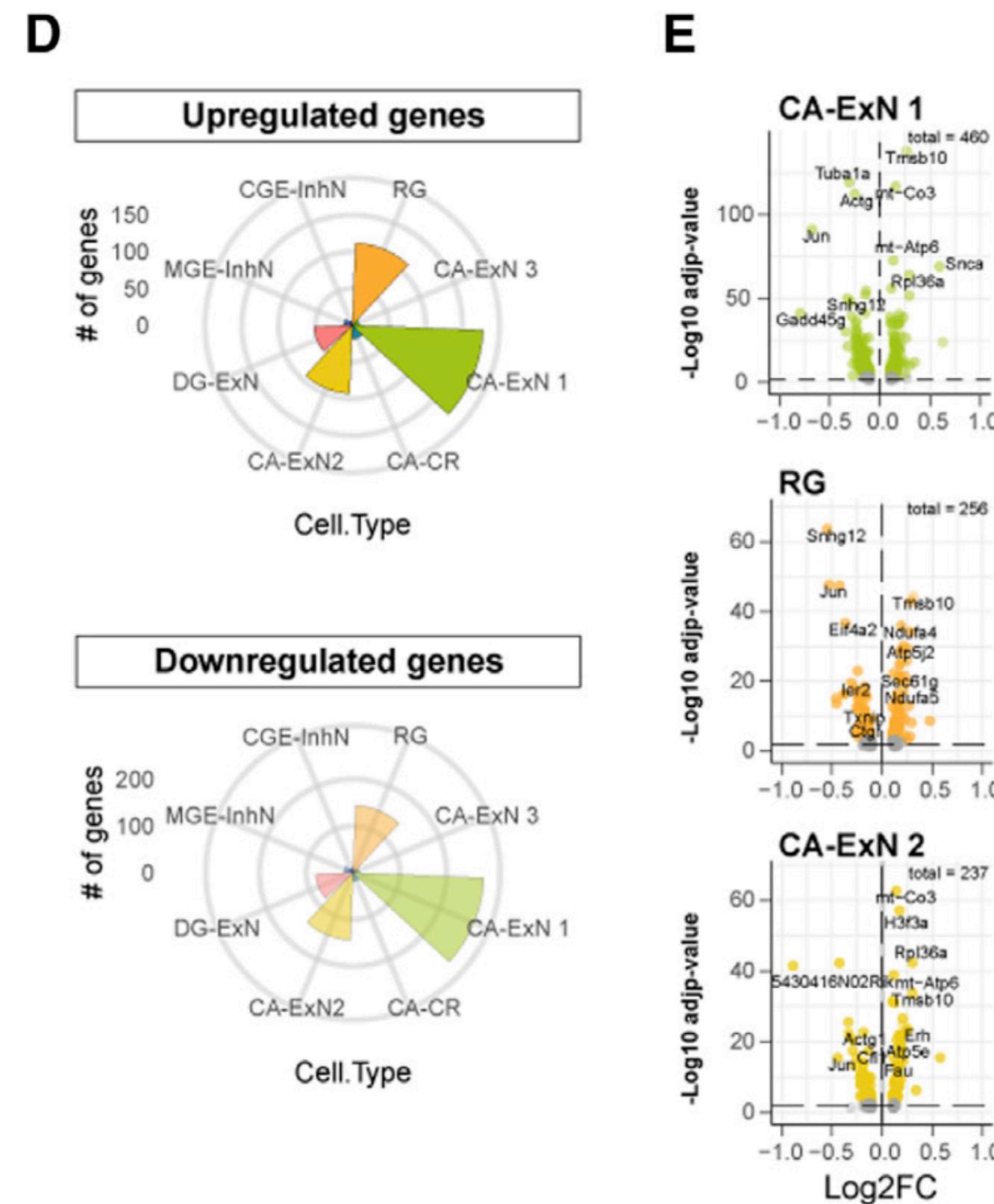
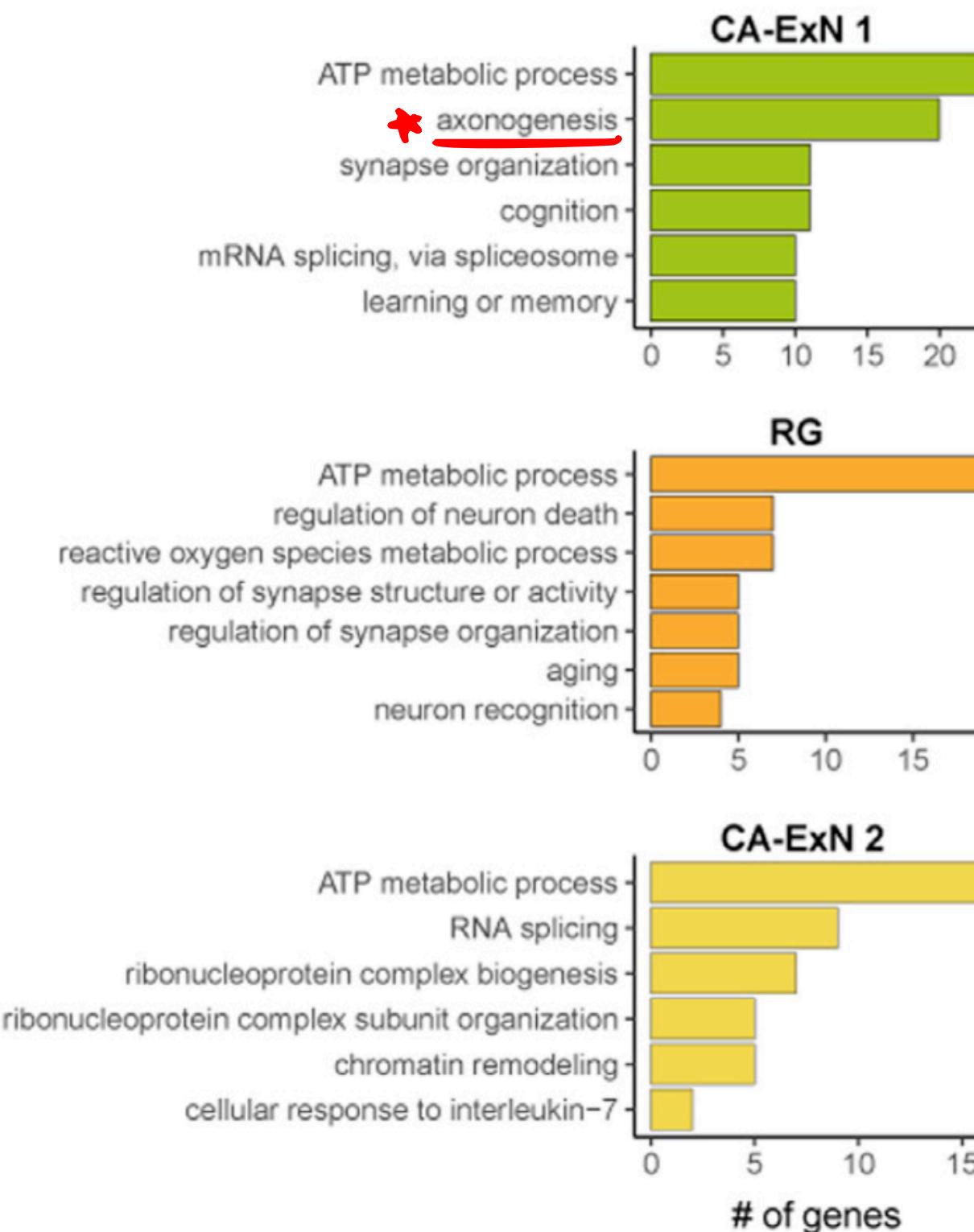


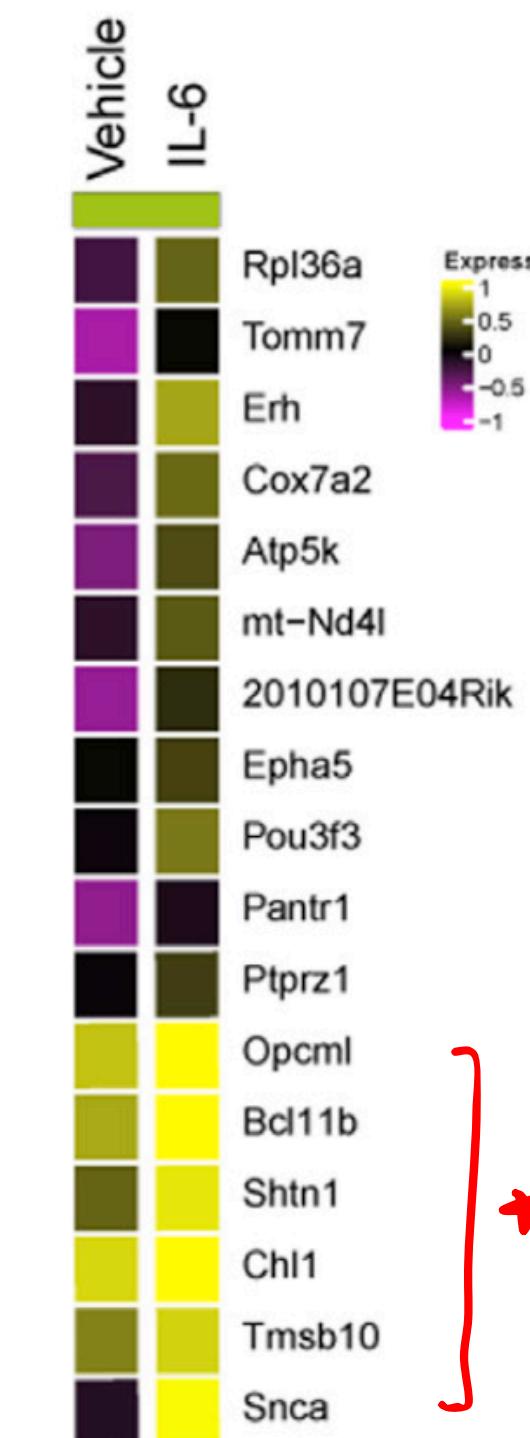
Figure 2

2. Prenatal IL-6 engages molecular programs of synaptogenesis in developing hippocampal neurons

F



G



Opcml: cortical spine maturation

Bcl11b: regulation of the apoptotic process and cell proliferation

Shtn1: axon formation

Chl1: codes cell adhesion molecule

Tmsb10: tissue regeneration and inflammatory regulation

Snca: providing instructions for making a small protein called alpha-synuclein

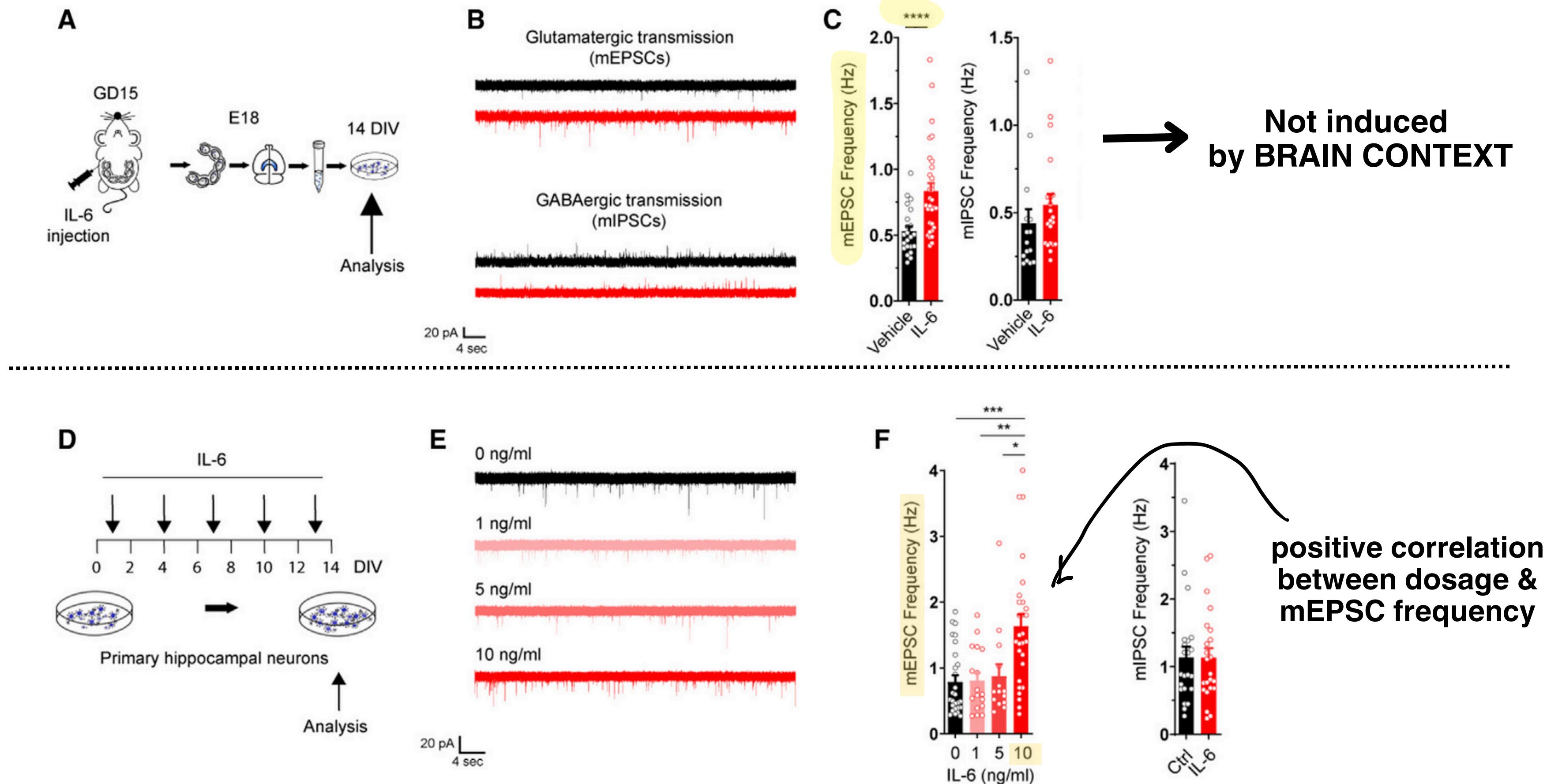
**# synaptogenic
genetically programmed**



**3. IL-6 selectively enhances glutamatergic synaptogenesis
through direct action on neurons**

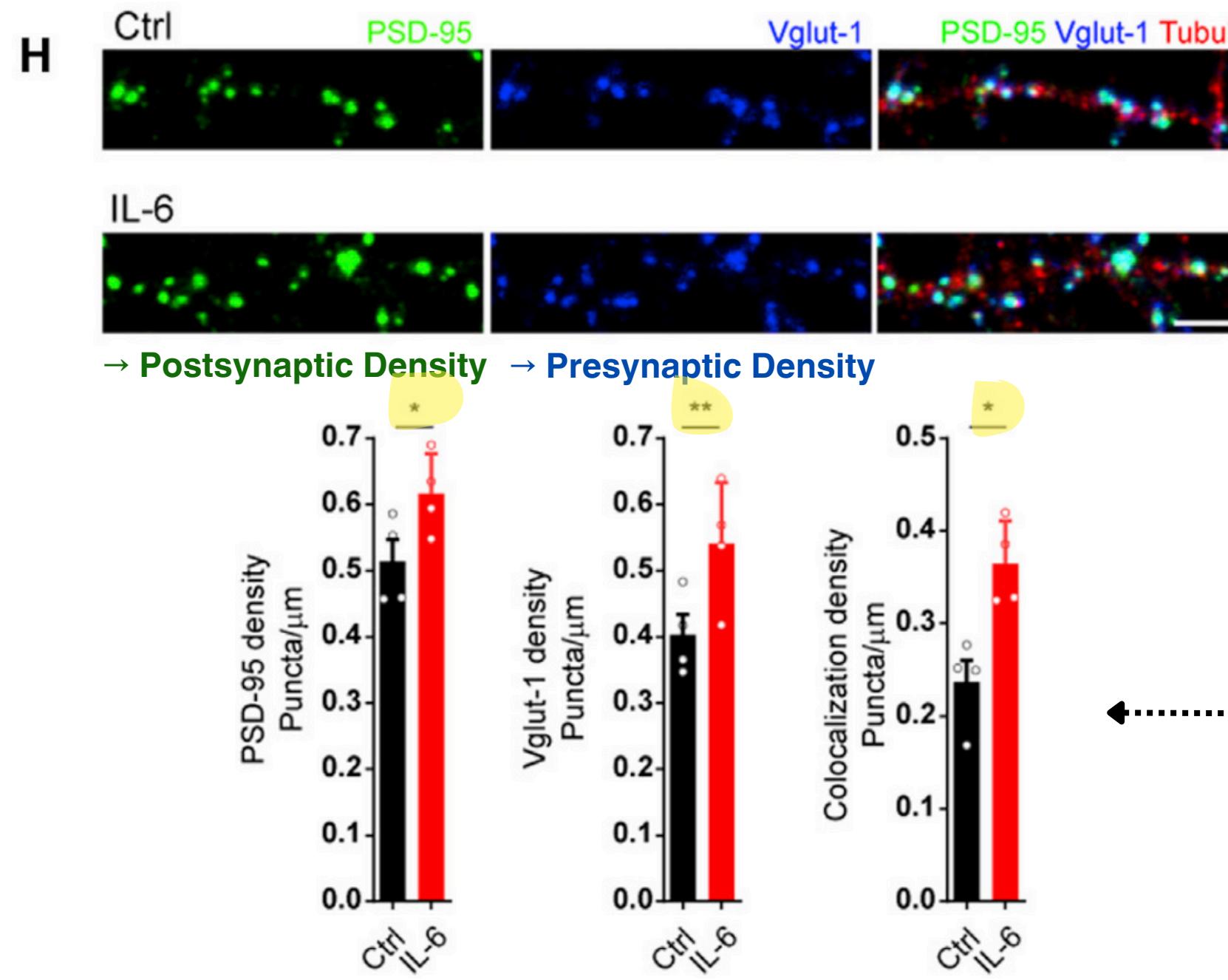
Figure 3

3. IL-6 selectively enhances glutamatergic synaptogenesis through direct action on neurons

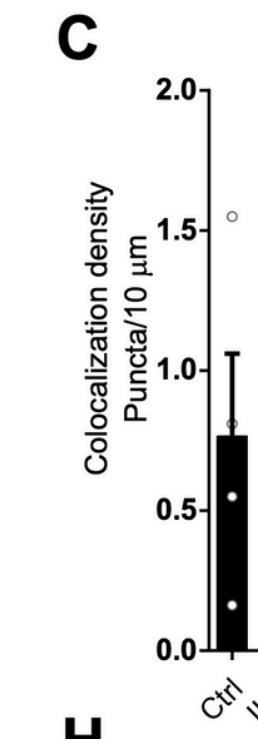
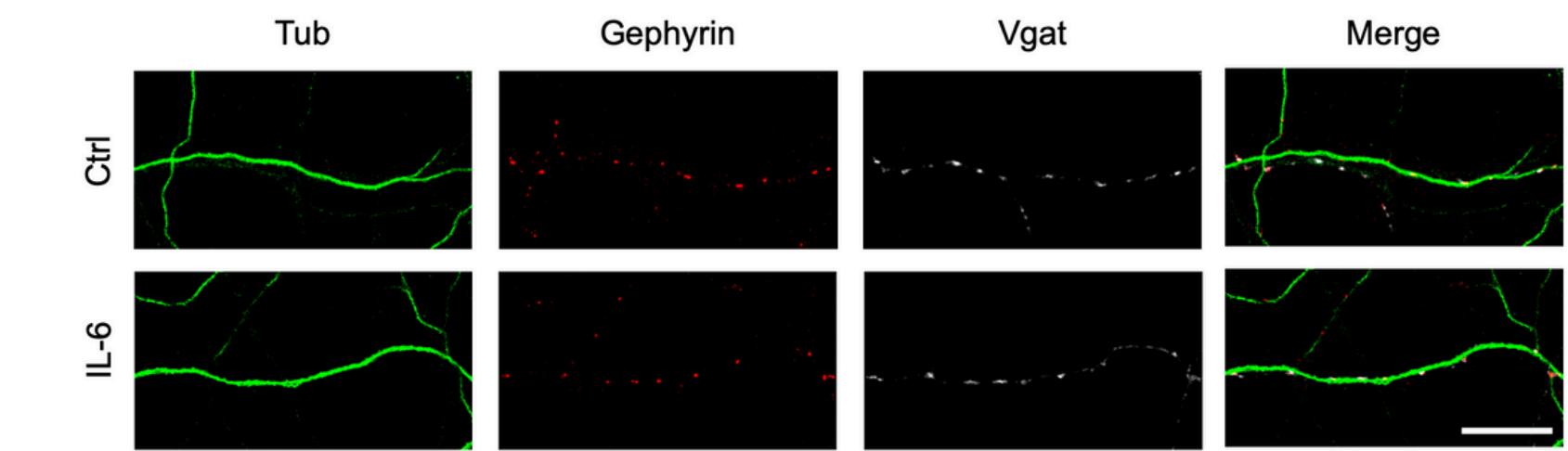


3. IL-6 selectively enhances glutamatergic synaptogenesis through direct action on neurons

Figure 3



Supplementary Figure 4



E/I imbalance @*in vitro*

@Supplemental Figure 4

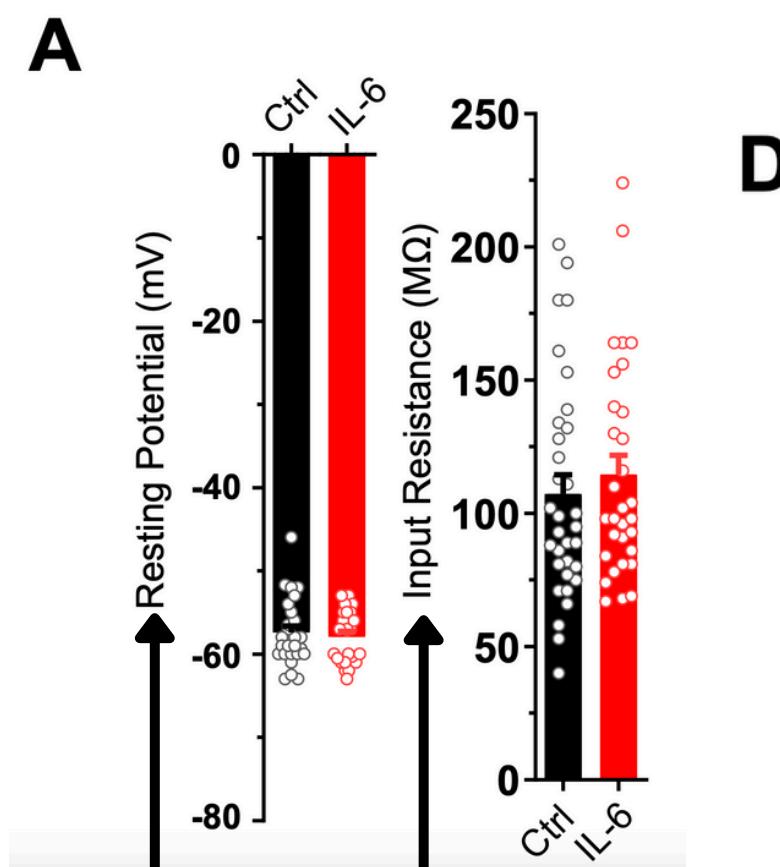
3. IL-6 selectively enhances glutamatergic synaptogenesis through direct action on neurons

Resting Potential:

- Intrinsic electrical properties of the neuron.
- Excitability of neurons.

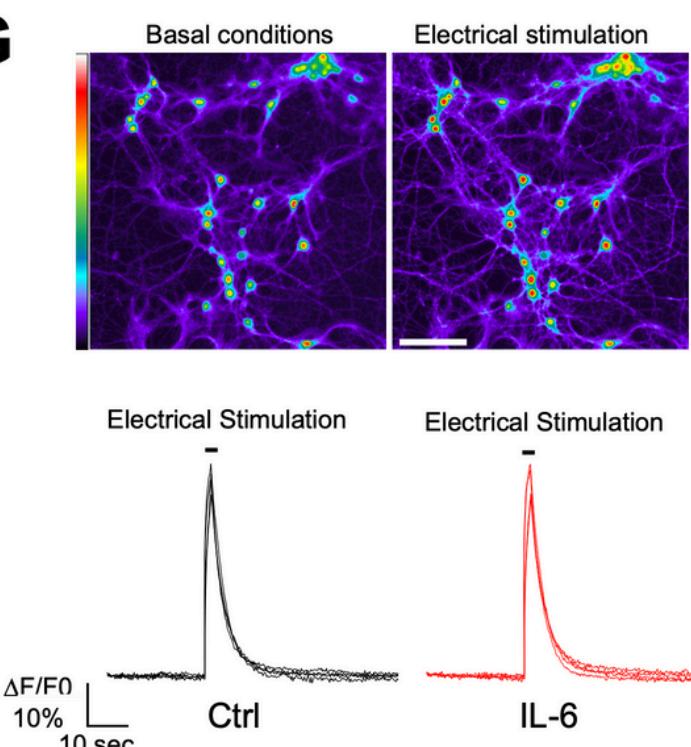
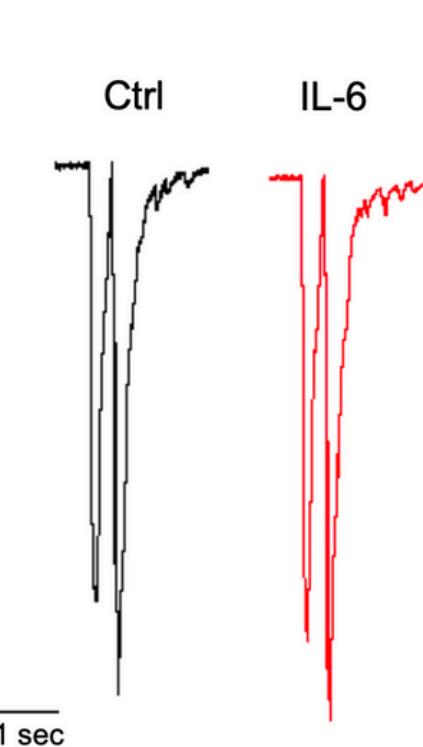
Membrane Resistance:

- Ion permeability
- Density or function of ion channels.

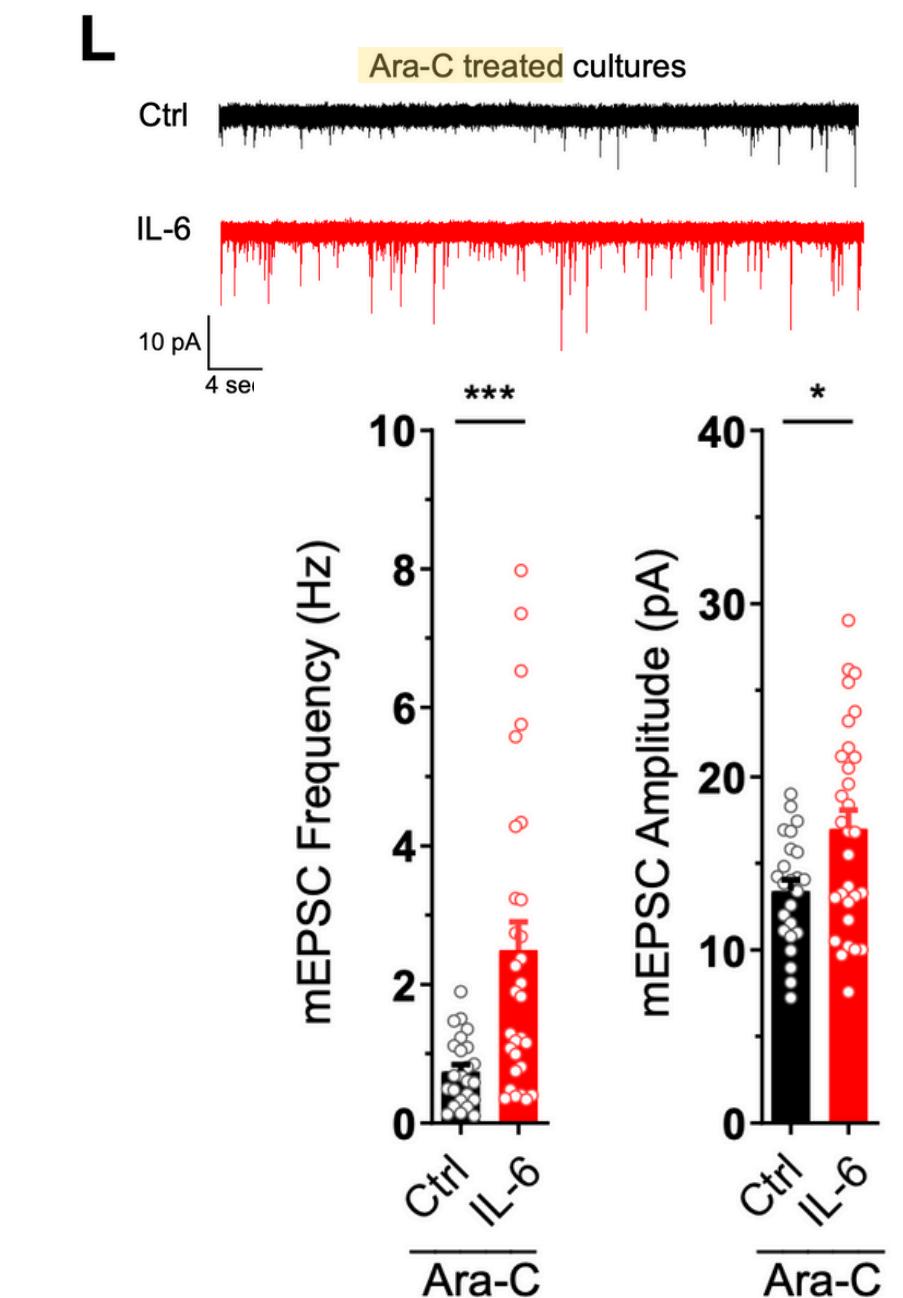
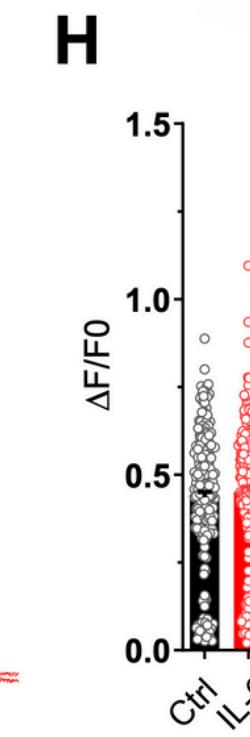


indicators of passive membrane properties in neurons:

Short Term-plasticity



Neuronal Excitability



Ara-C: ↓ astrocytic component

NOT homeostatic compensatory mechanism

ST-plasticity & neuronal excitability => no difference in trmt&ctrl

NOT astrocytes

in enhancement of excitatory neurotransmission

IL-6 selectively enhance EPSC synapses
Direct Action of IL-6 on Neurons



4. A single pulse of IL-6 at stages preceding synaptogenesis is sufficient to promote a long-lasting increase in glutamatergic synaptic transmission

Figure 4

4. A single pulse of IL-6 at stages preceding synaptogenesis is sufficient to promote a long-lasting increase in glutamatergic synaptic transmission

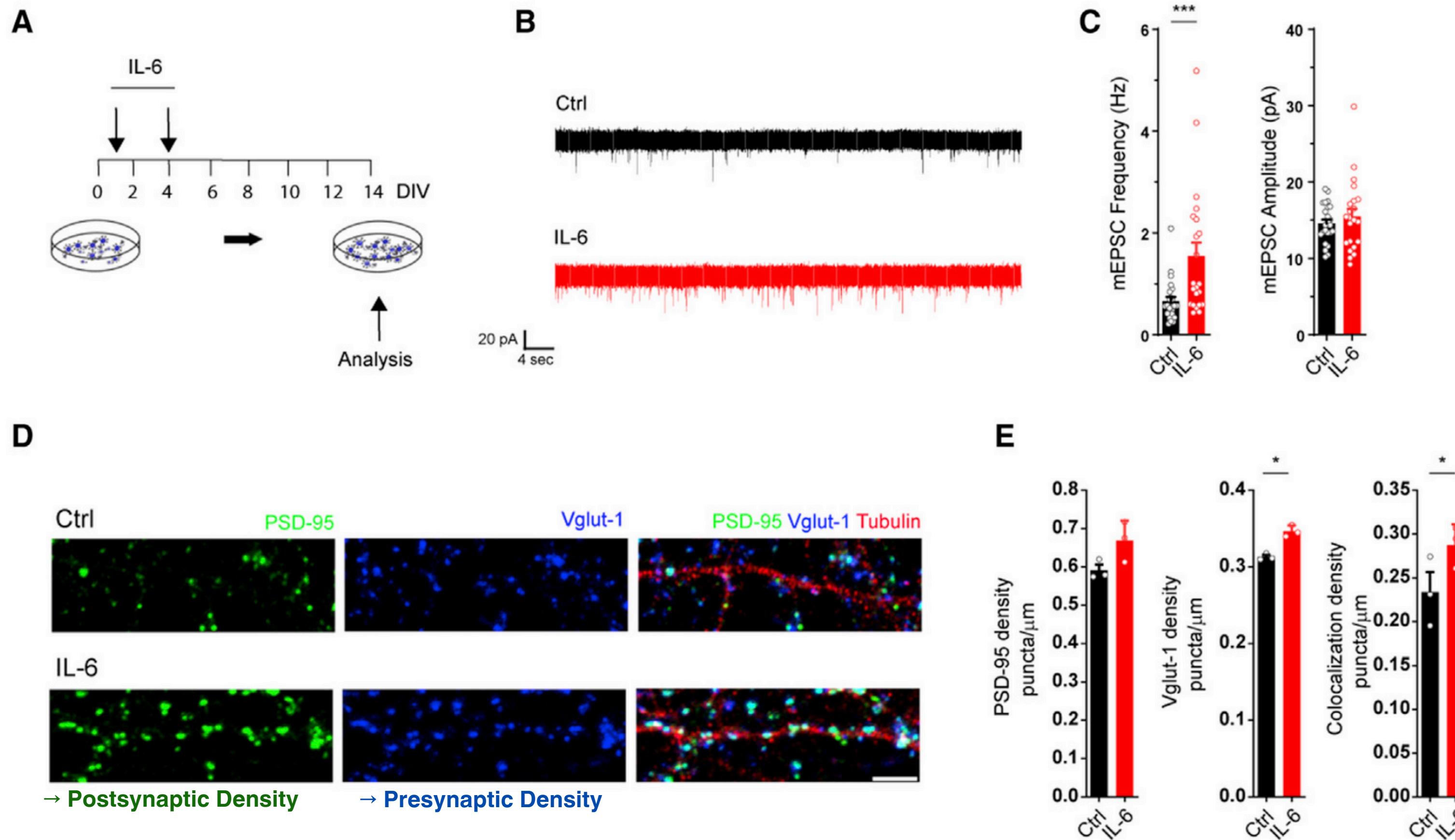
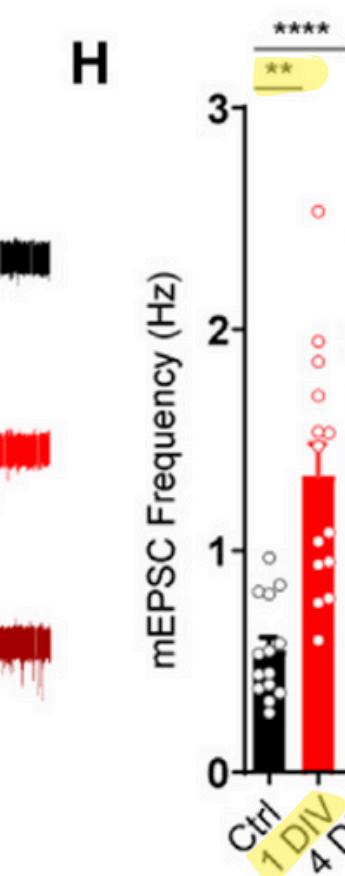
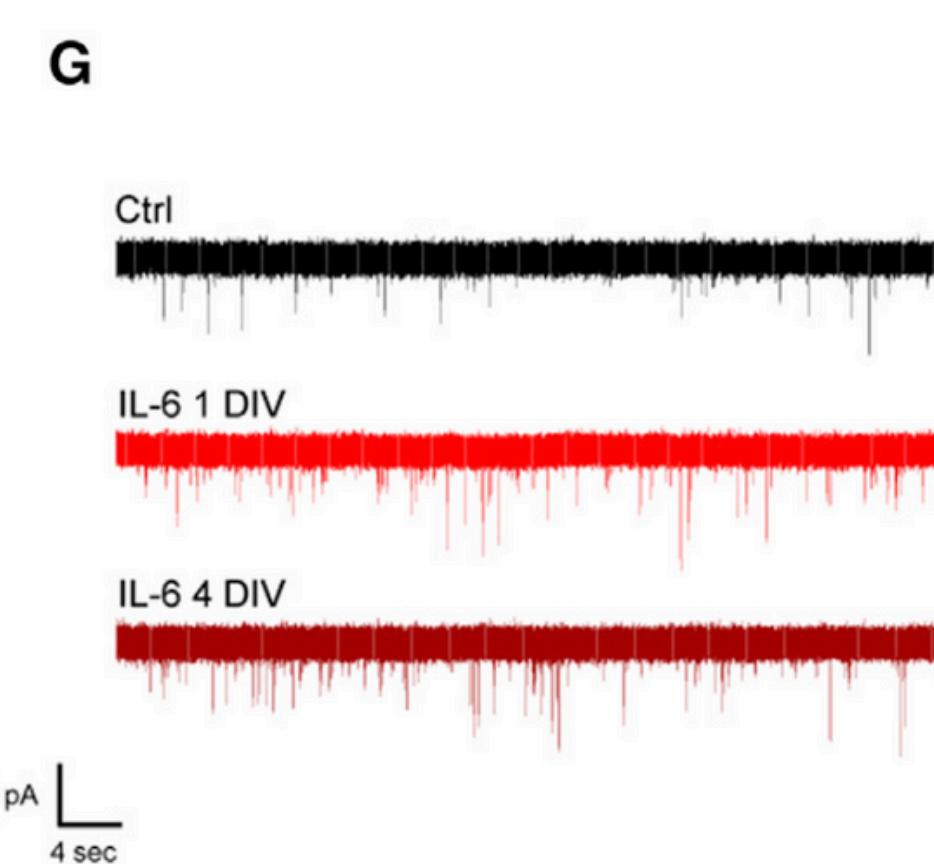
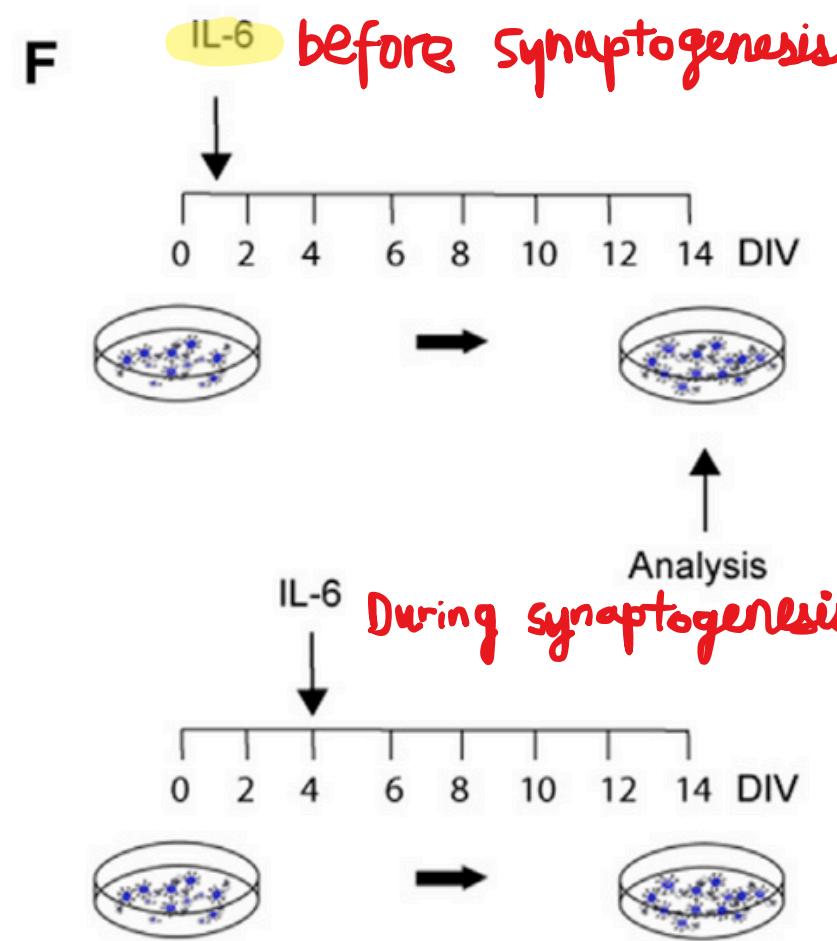
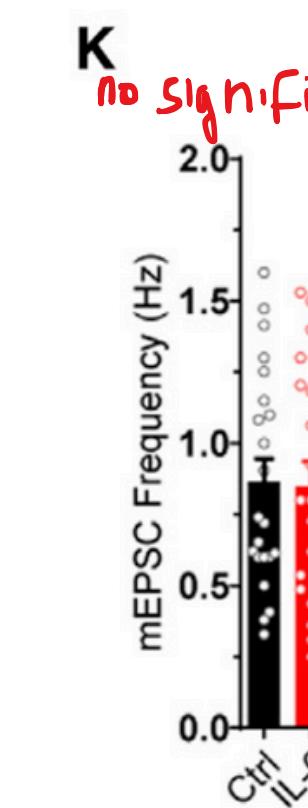
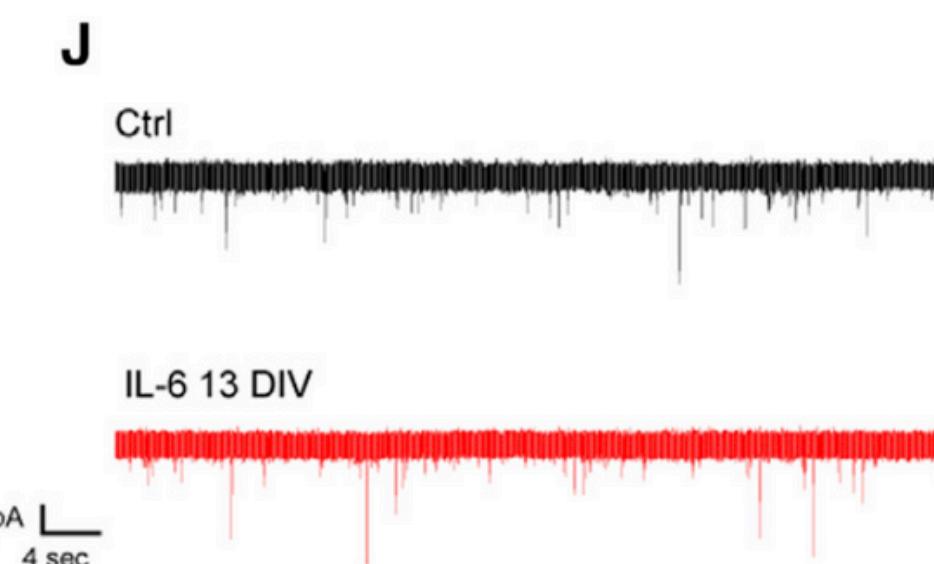
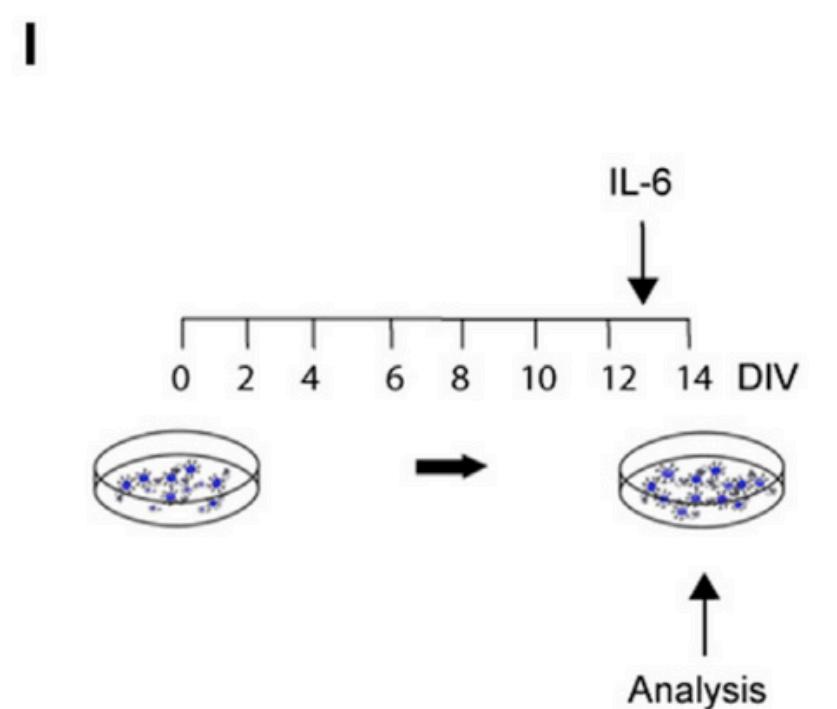


Figure 4

4. A single pulse of IL-6 at stages preceding synaptogenesis is sufficient to promote a long-lasting increase in glutamatergic synaptic transmission



Early Stages
Single Pulse



No significance

SHOULD BE
Early Stages

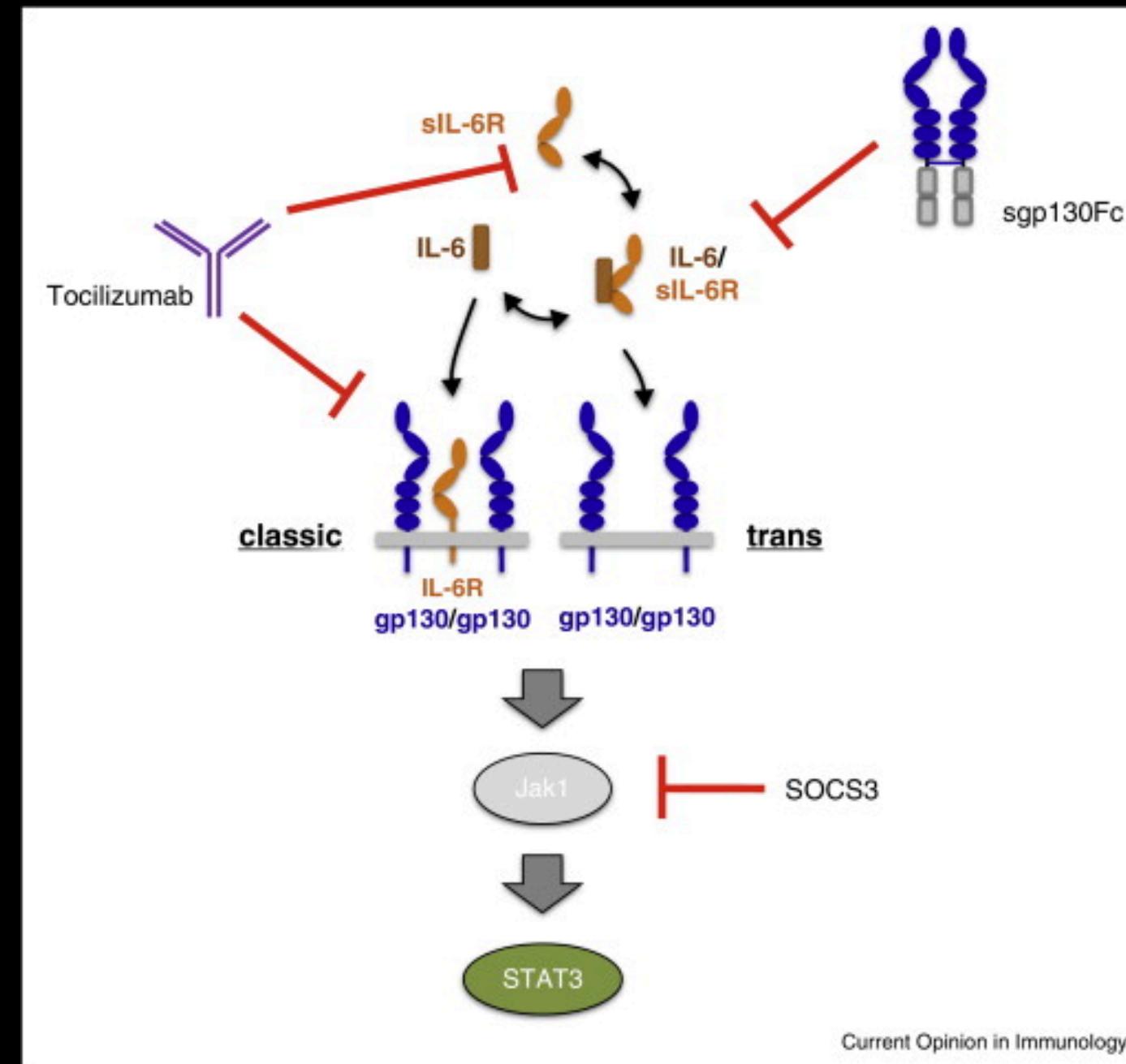
What we have learned so far = PHENOMENA

Impact of transient prenatal IL-6 elevation

-  **hippocampal glutamatergic synapses #E/I imbalance**
- **hyperconnectivity in adulthood**

How it influences synaptogenesis

- **Genetic programs in developing hippocampal neurons**
- **Direct action on neurons**
- **Only a single pulse of IL-6 at stages preceding synaptogenesis** 



What we now look for =

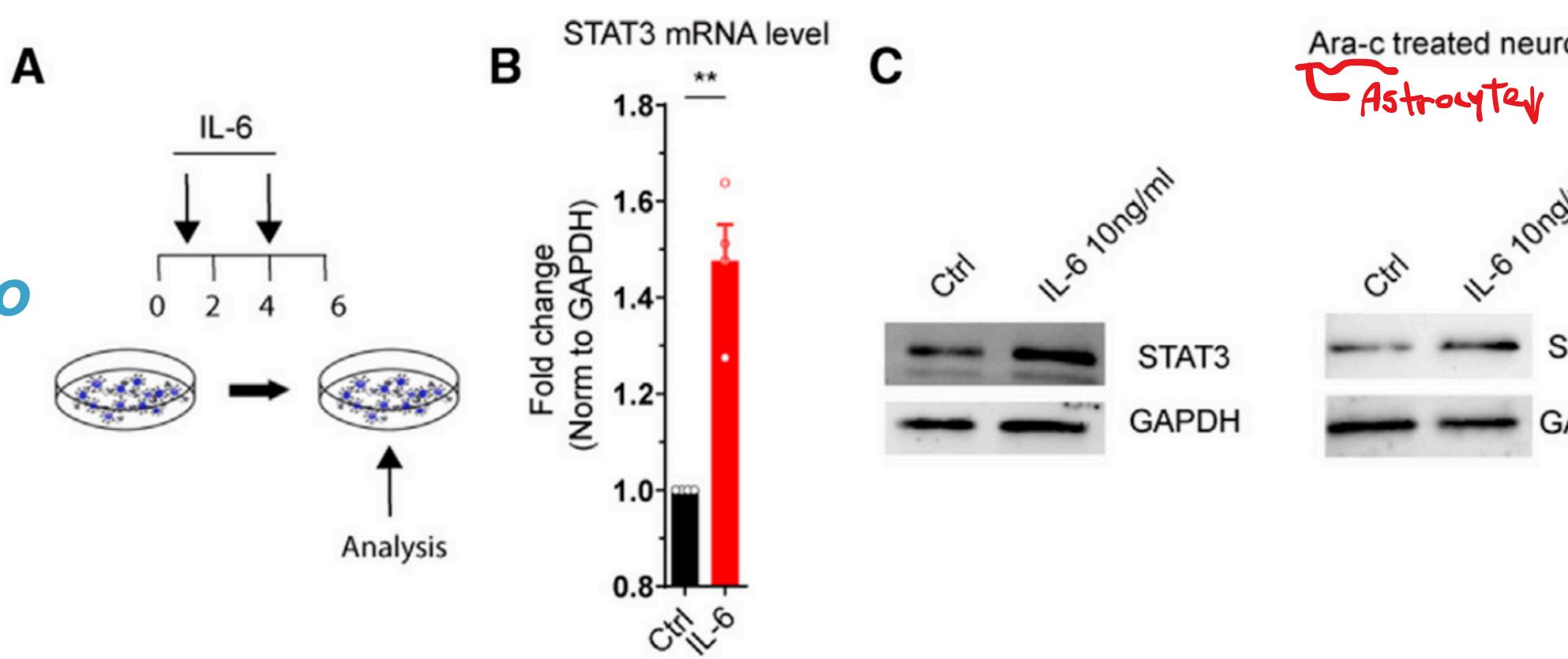
**INTRACELLULAR
INTERACTION**

5. STAT3 activity is required for the IL-6-dependent increase glutamatergic synapses

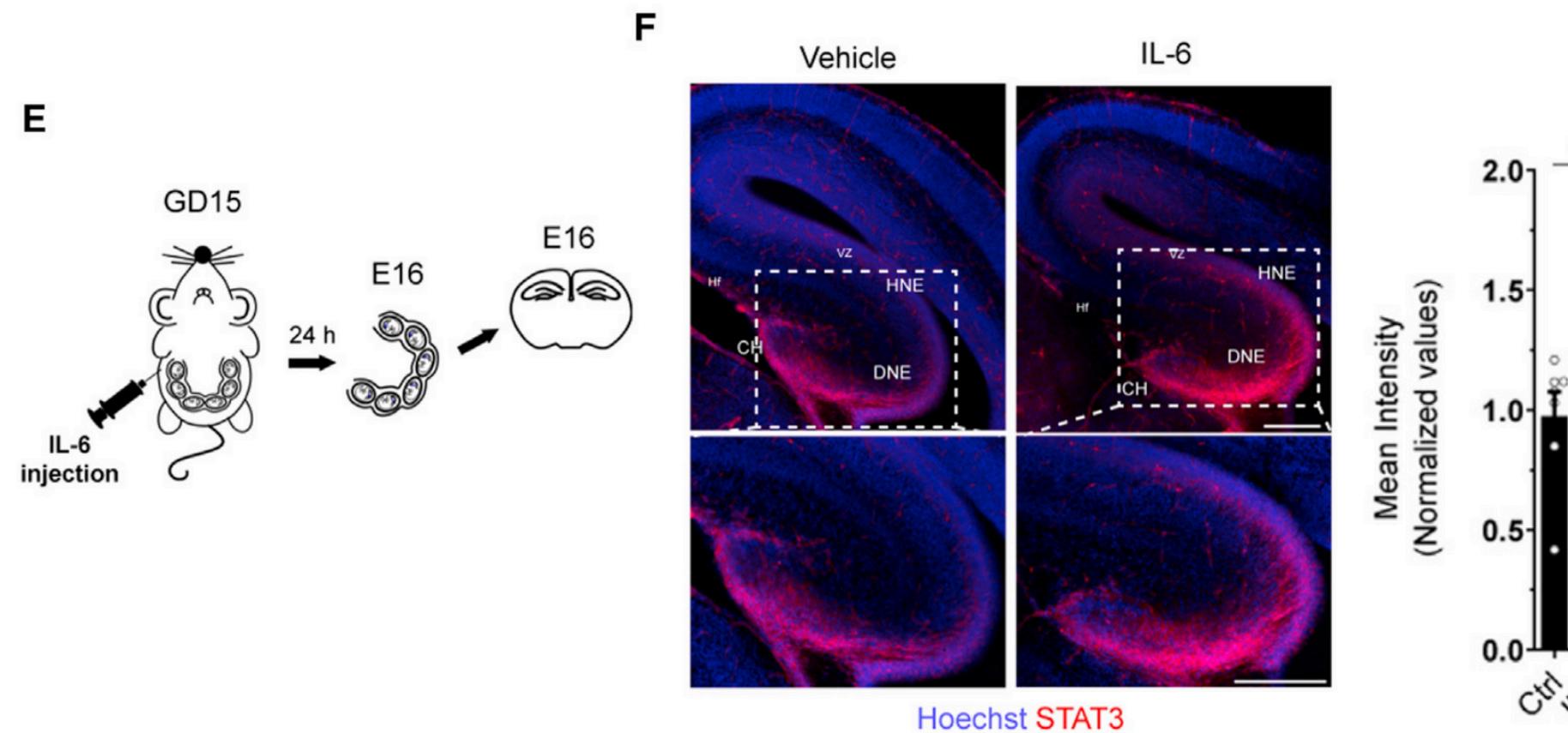
Figure 5

5. STAT3 activity is required for the IL-6-dependent increase glutamatergic synapses

in vitro



in vivo

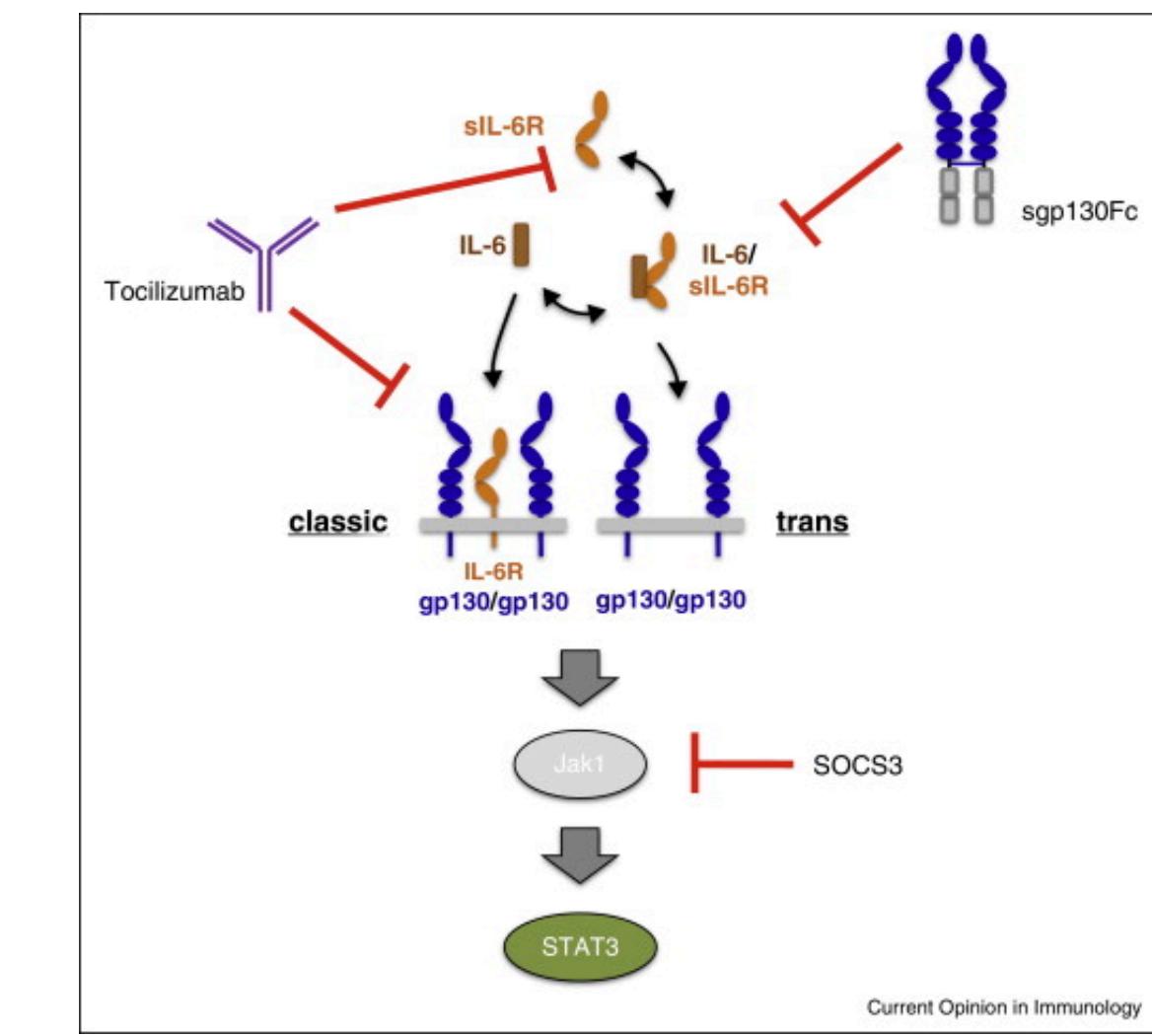
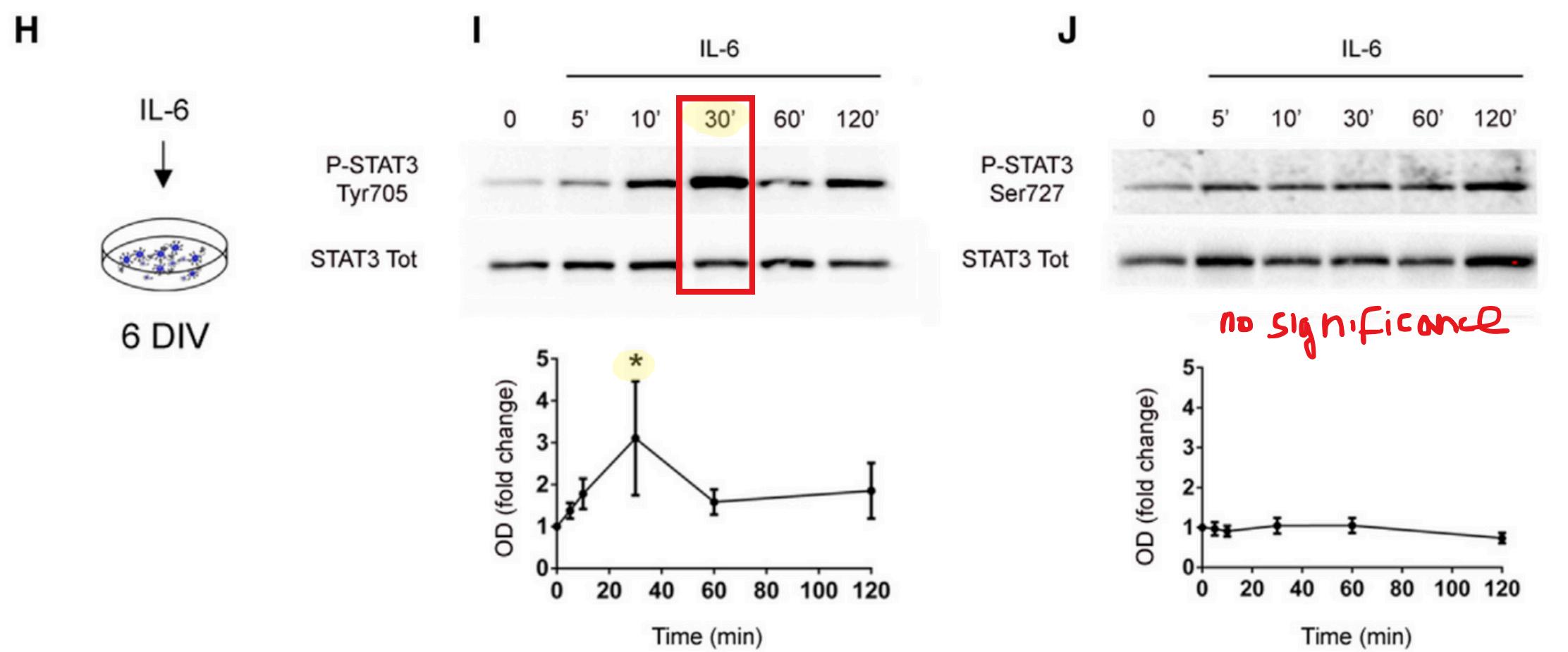


-> No OD decrement in IL-6 & Ara-c treated neurons

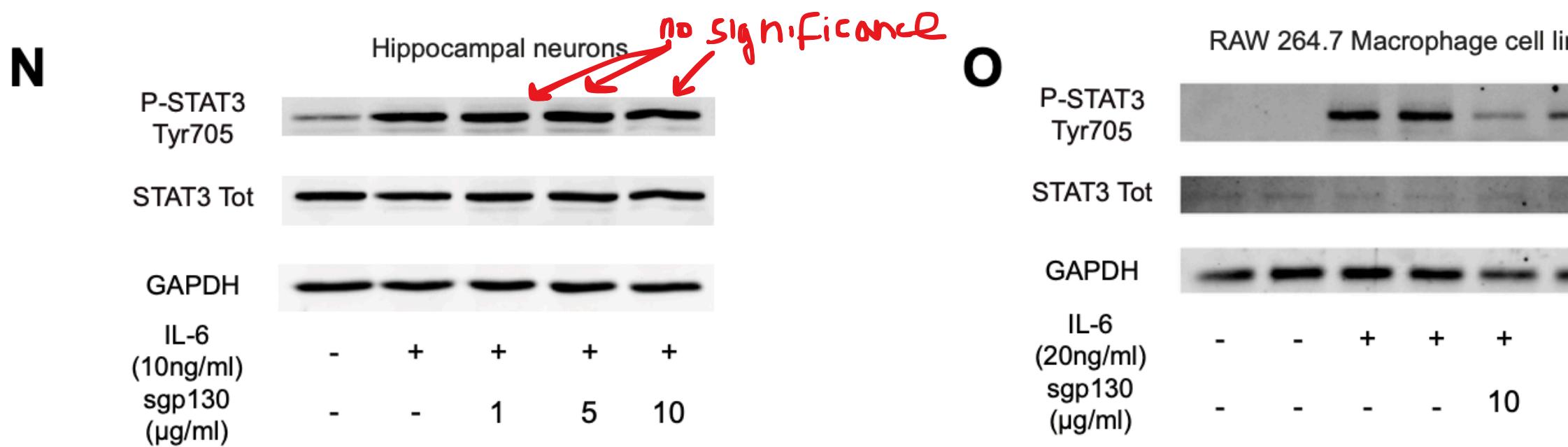
Neuron-specific STAT3 activation
upon IL-6 treatment
at early stages of development

Figure 5

5. STAT3 activity is required for the IL-6-dependent increase glutamatergic synapses



Supplemental Figure 5



classical signaling

sgp130: soluble gp130 receptor
binds to the [IL-6+sIL-6R]
-> inhibit the activation of STAT3

Figure 6

5. STAT3 activity is required for the IL-6-dependent increase glutamatergic synapses

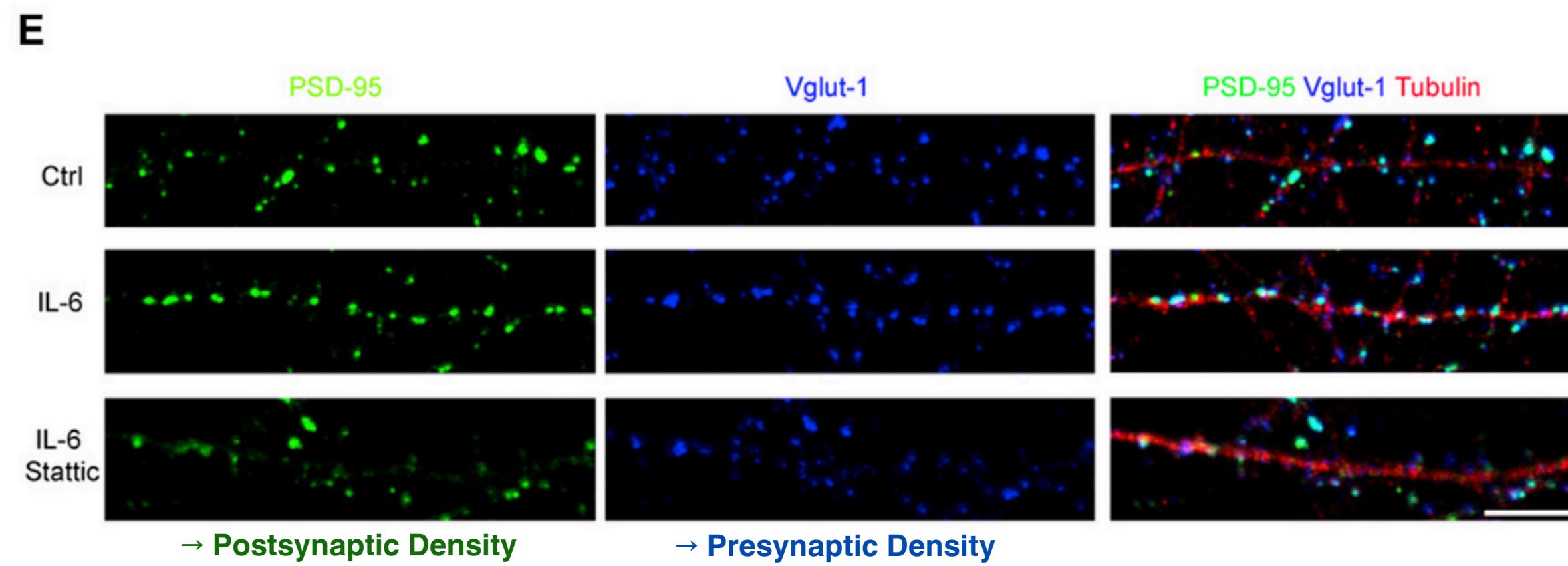
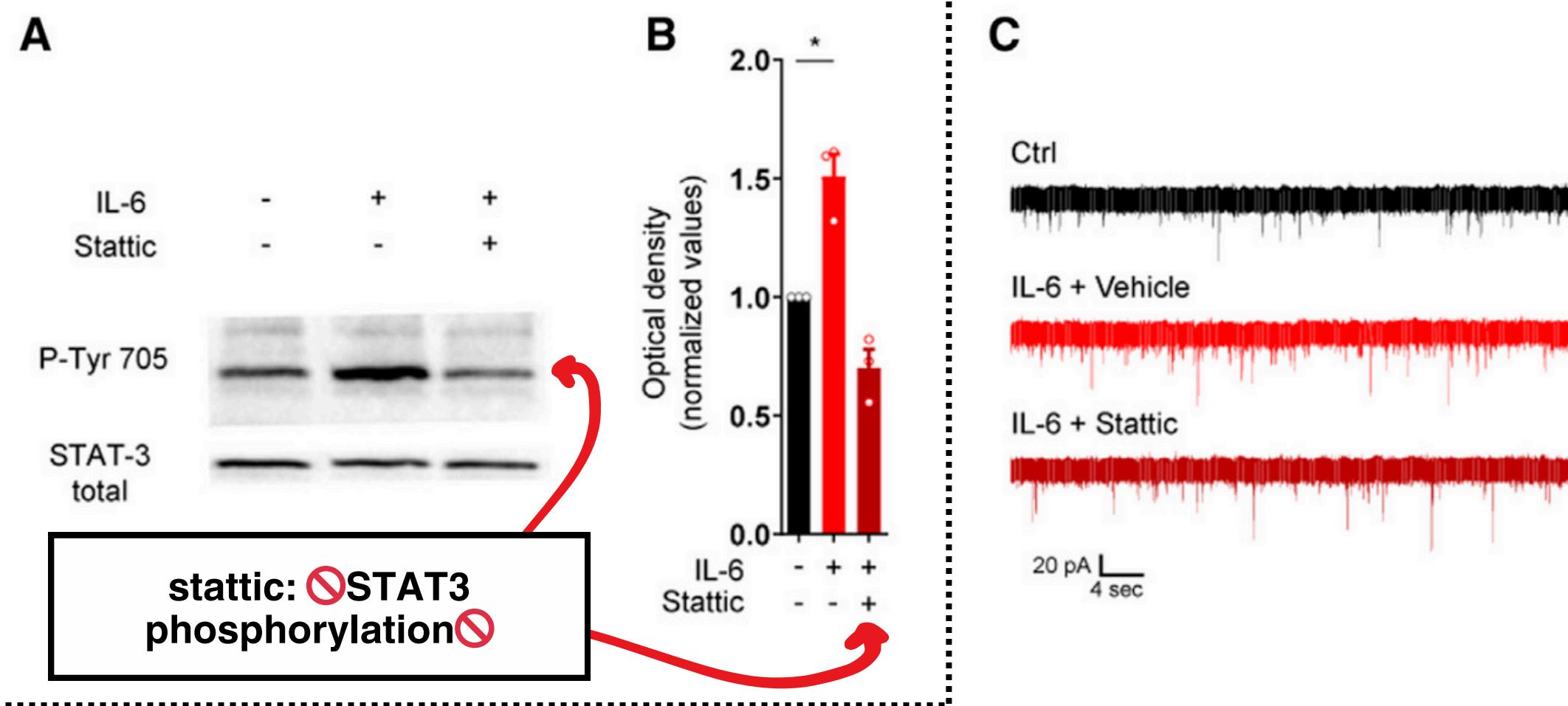
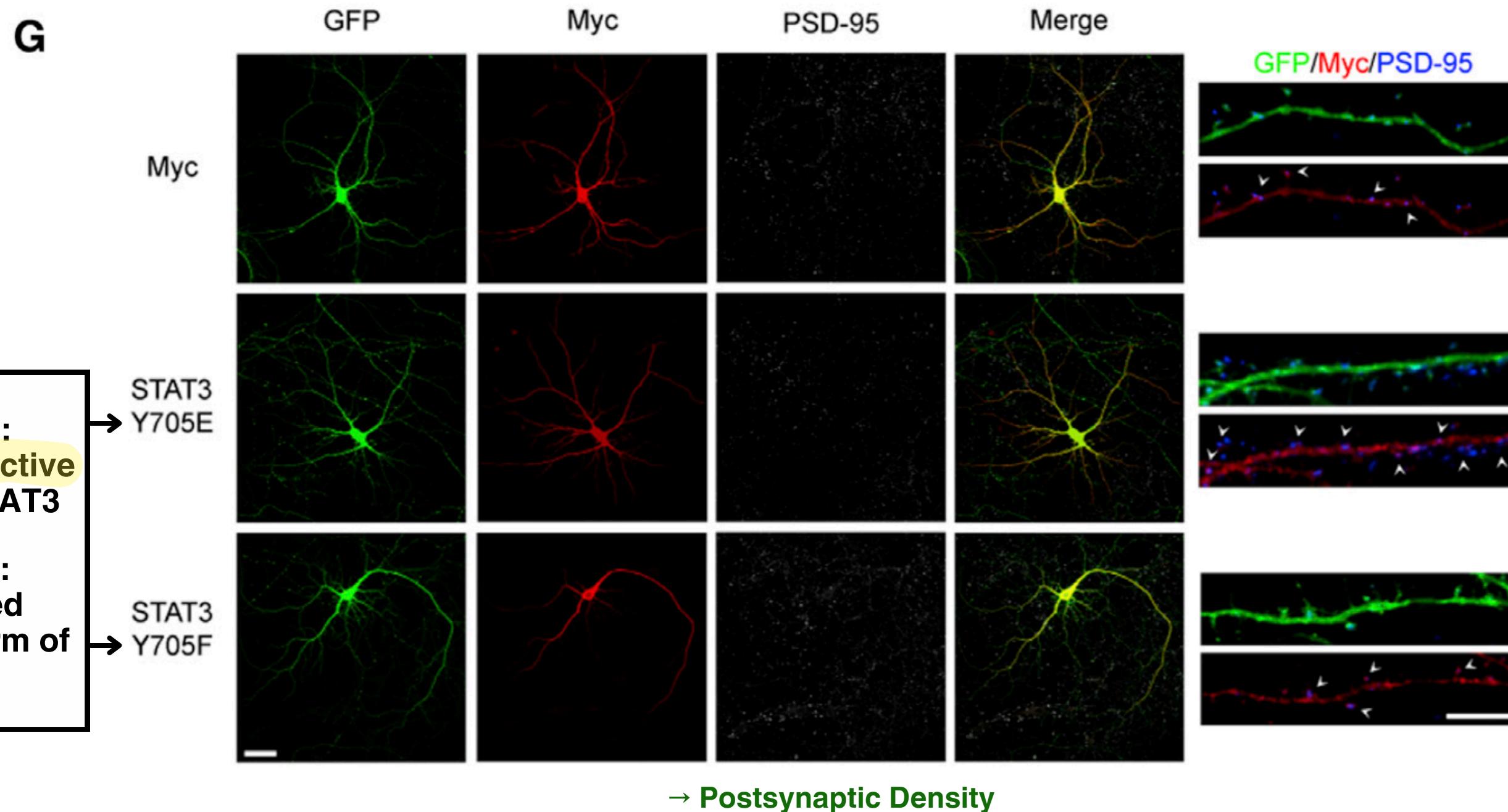


Figure 6

5. STAT3 activity is required for the IL-6-dependent increase glutamatergic synapses



6. IL-6 promotes glutamatergic synaptogenesis through a STAT3-dependent genomic effect involving RGS4-activity

Figure 6

6. IL-6 promotes glutamatergic synaptogenesis through a STAT3-dependent genomic effect involving RGS4-activity

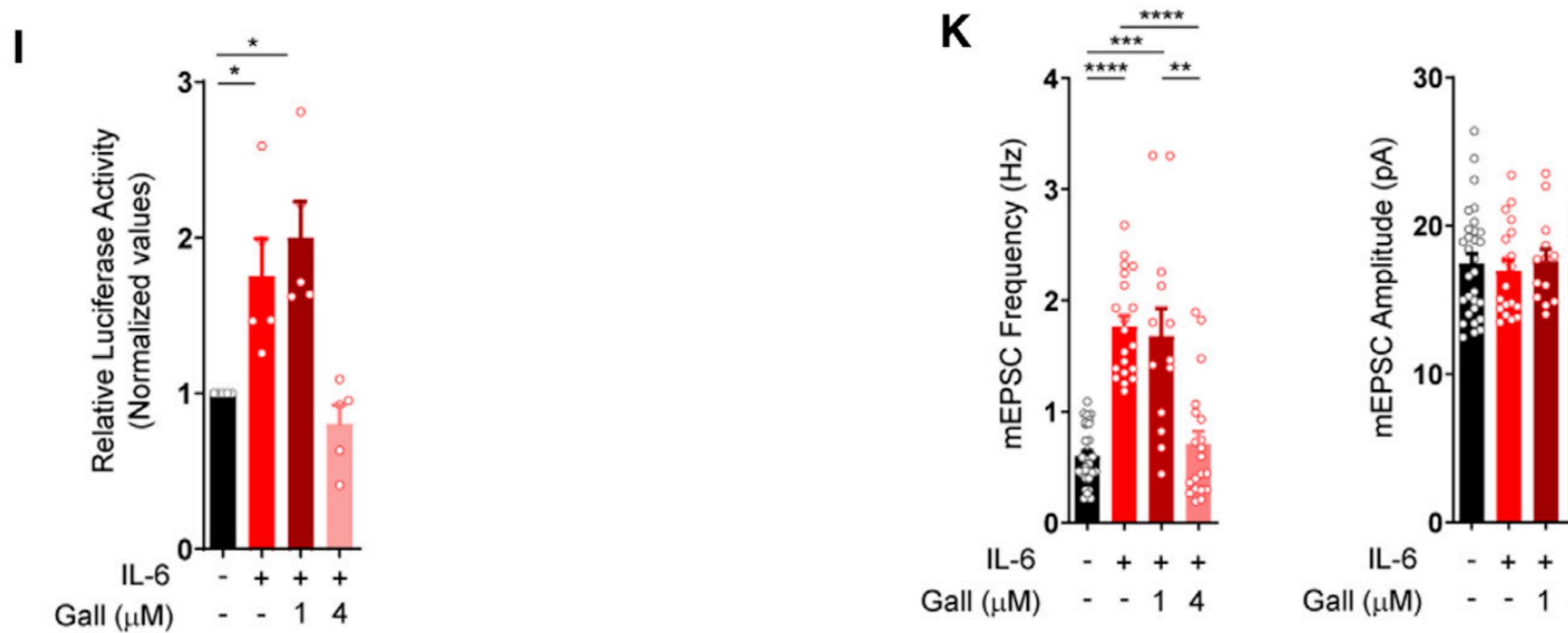


Figure 7

6. IL-6 promotes glutamatergic synaptogenesis through a STAT3-dependent genomic effect involving RGS4-activity

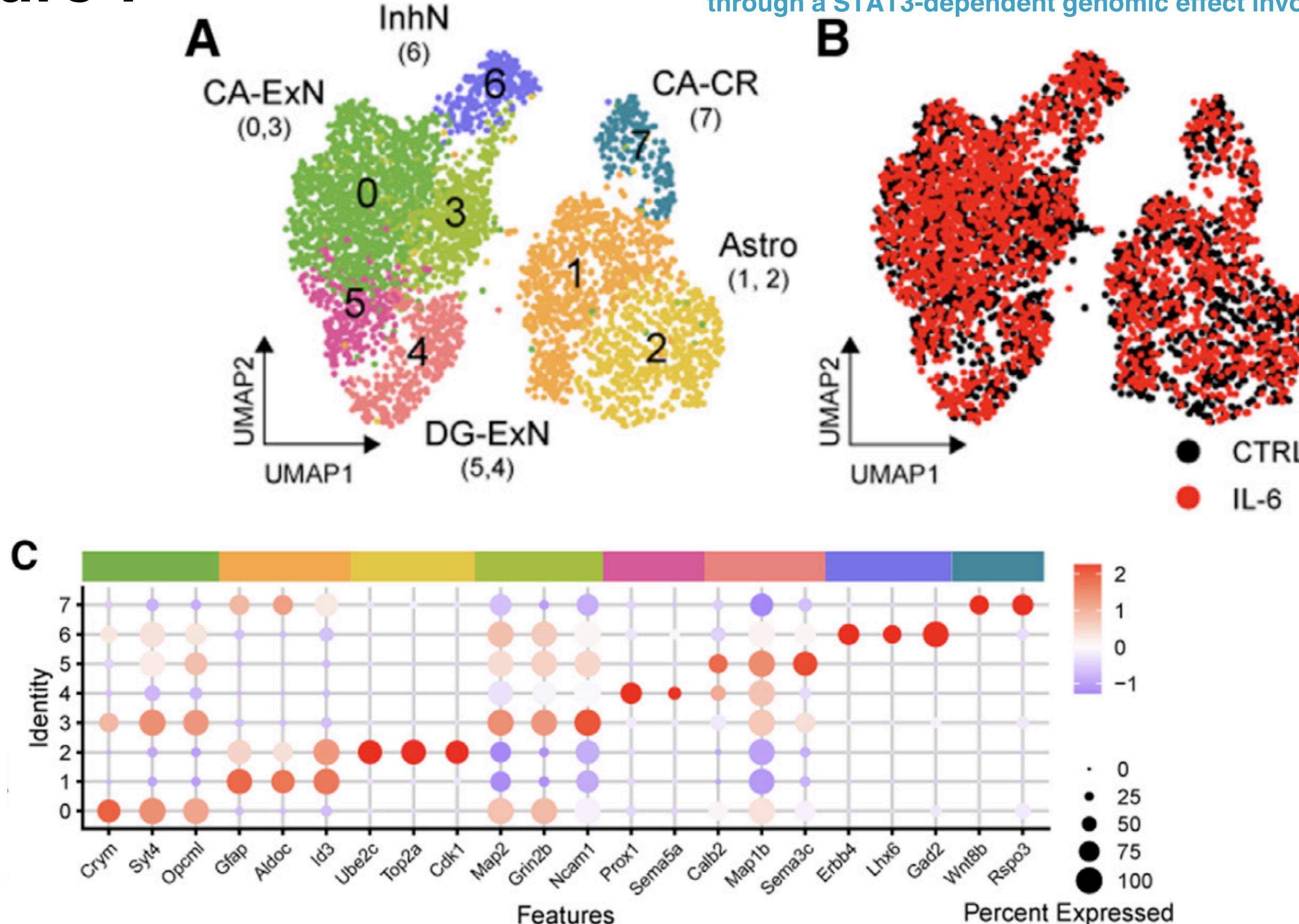


Figure 7

6. IL-6 promotes glutamatergic synaptogenesis through a STAT3-dependent genomic effect involving RGS4-activity

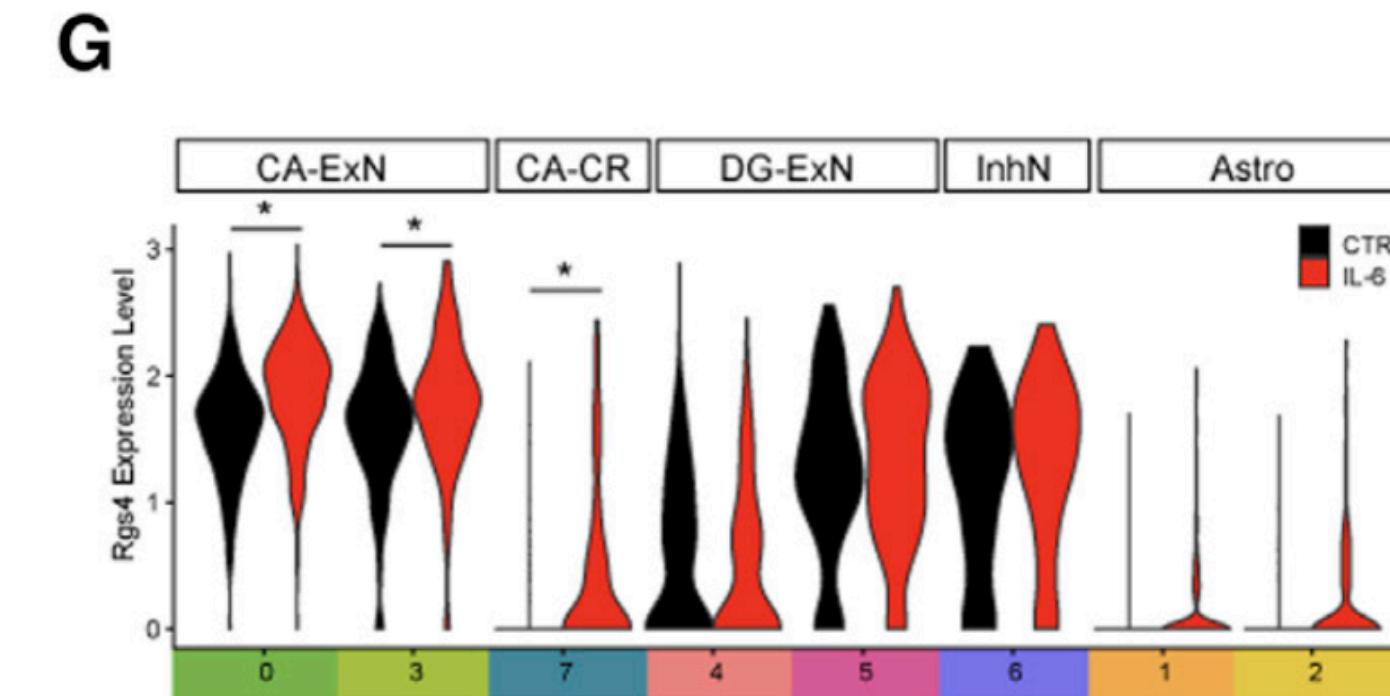
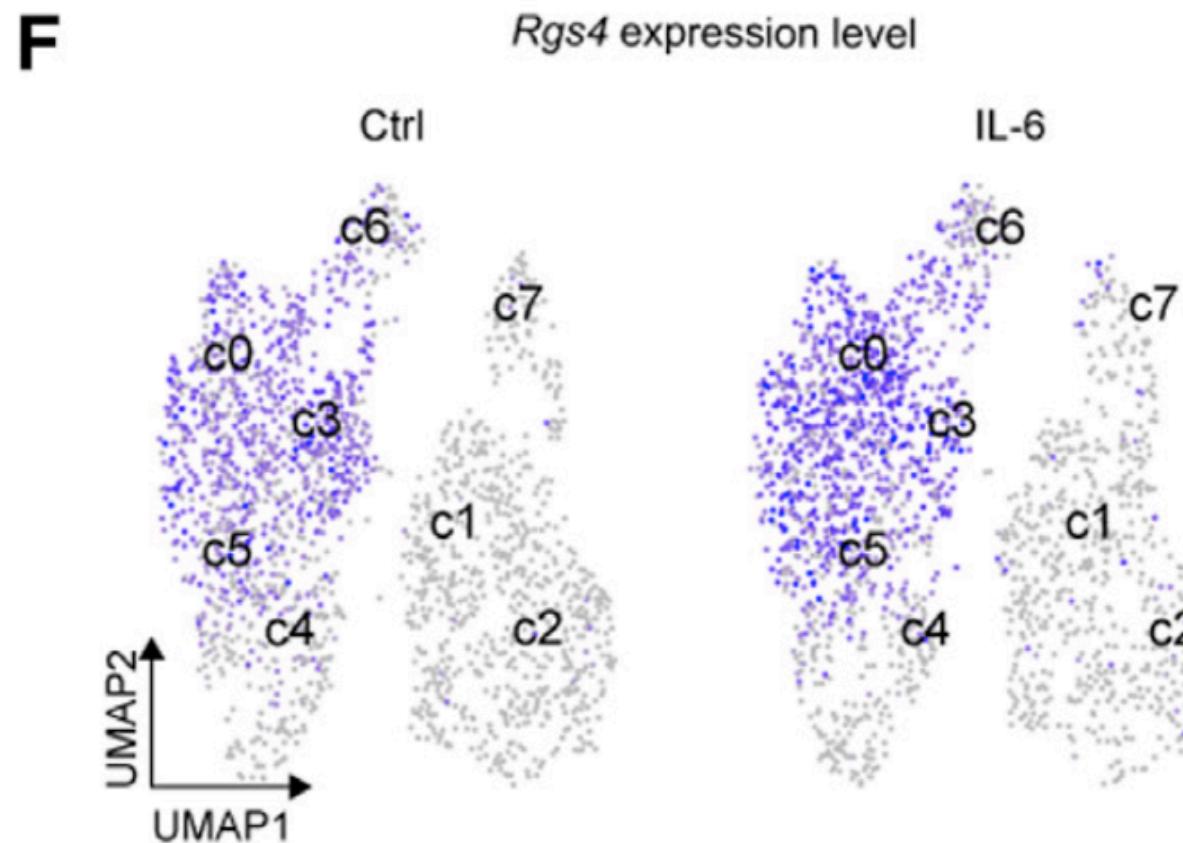
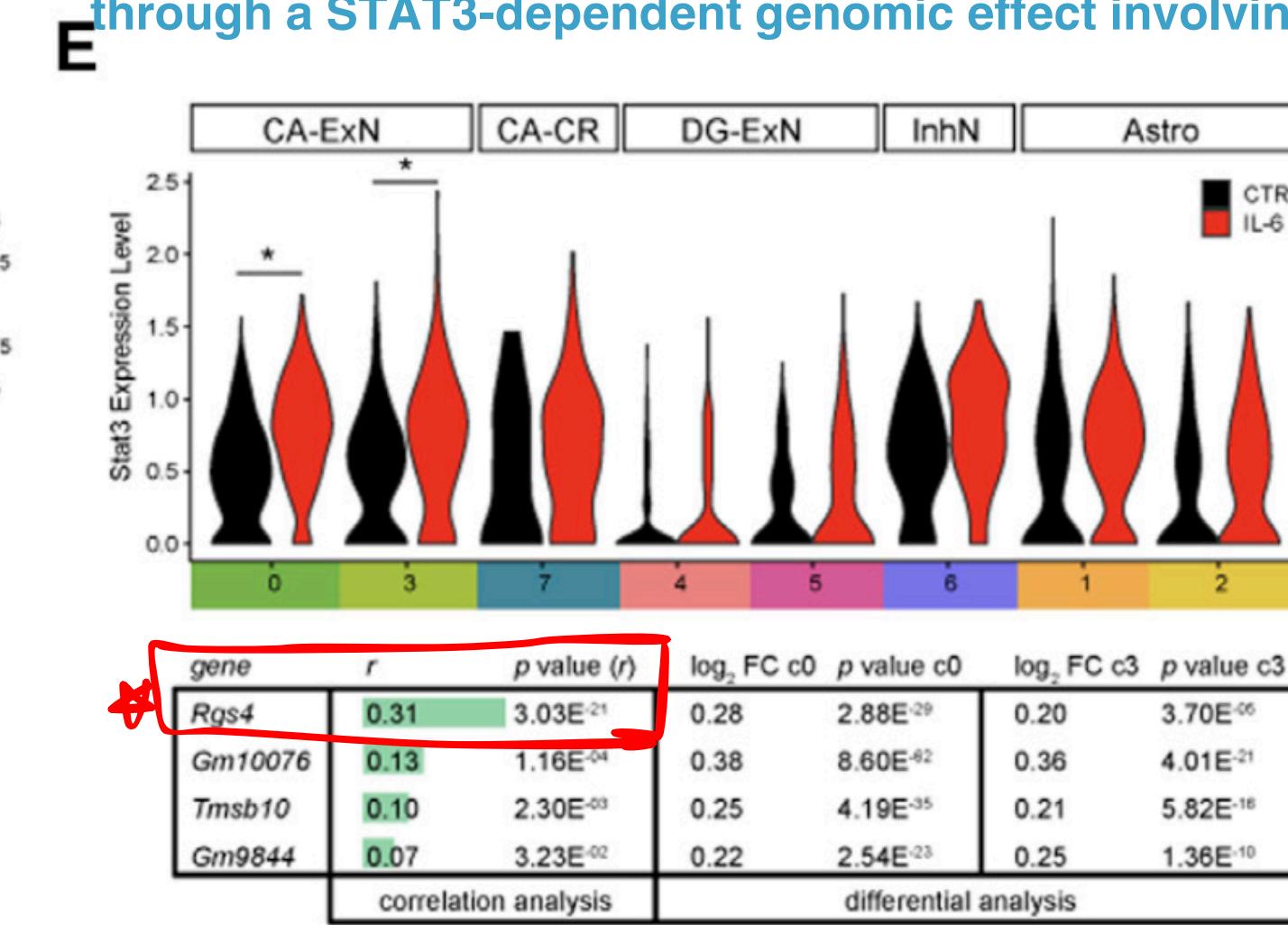
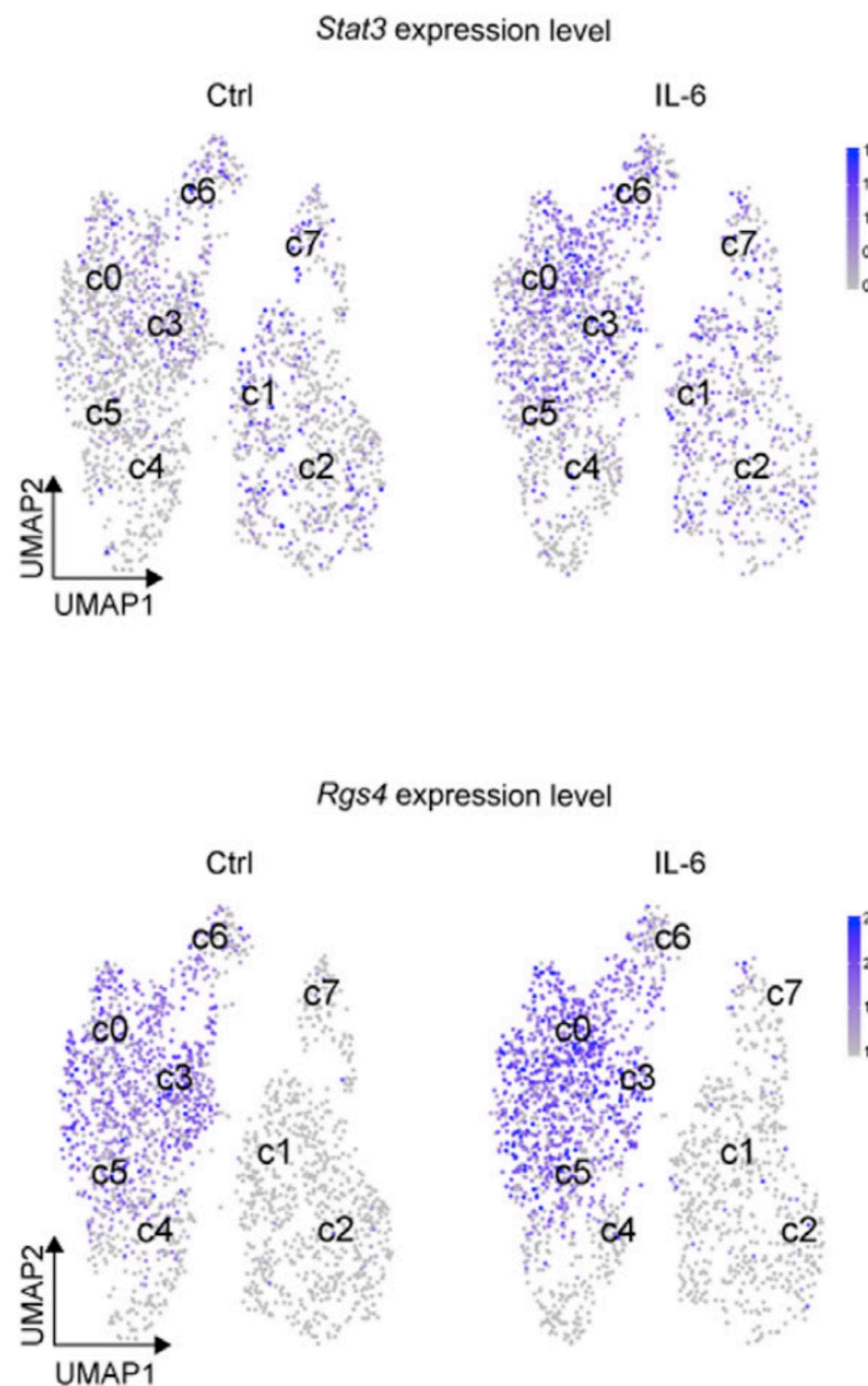
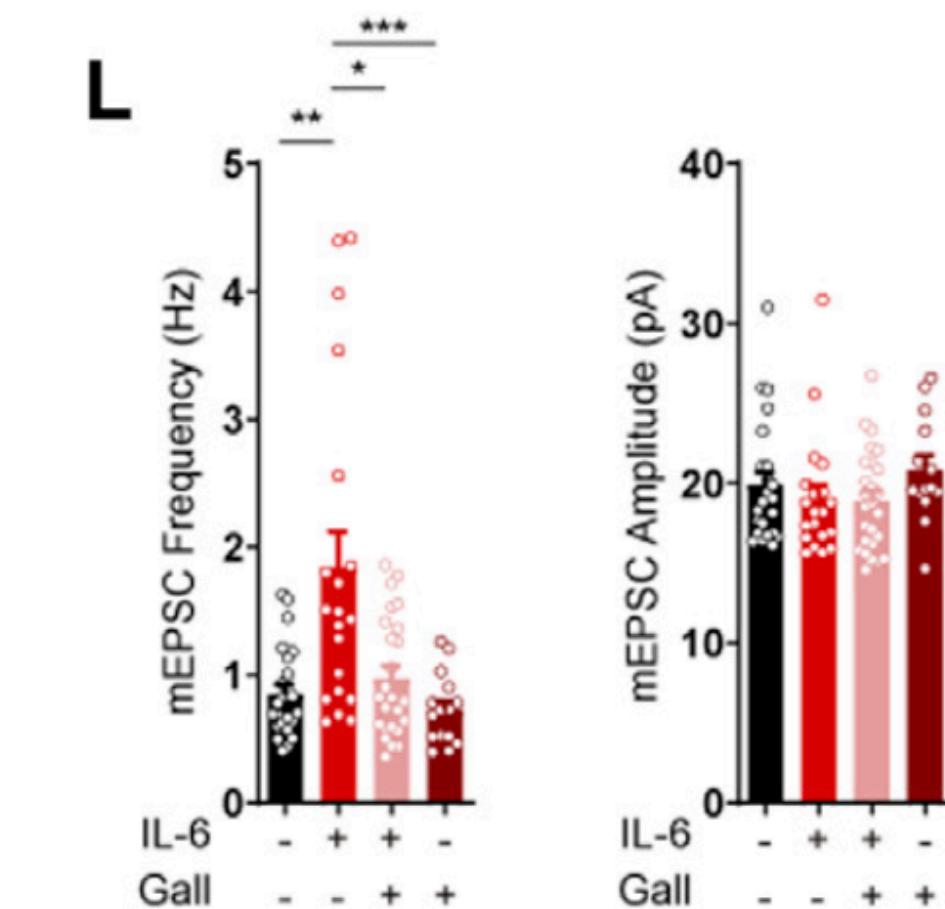
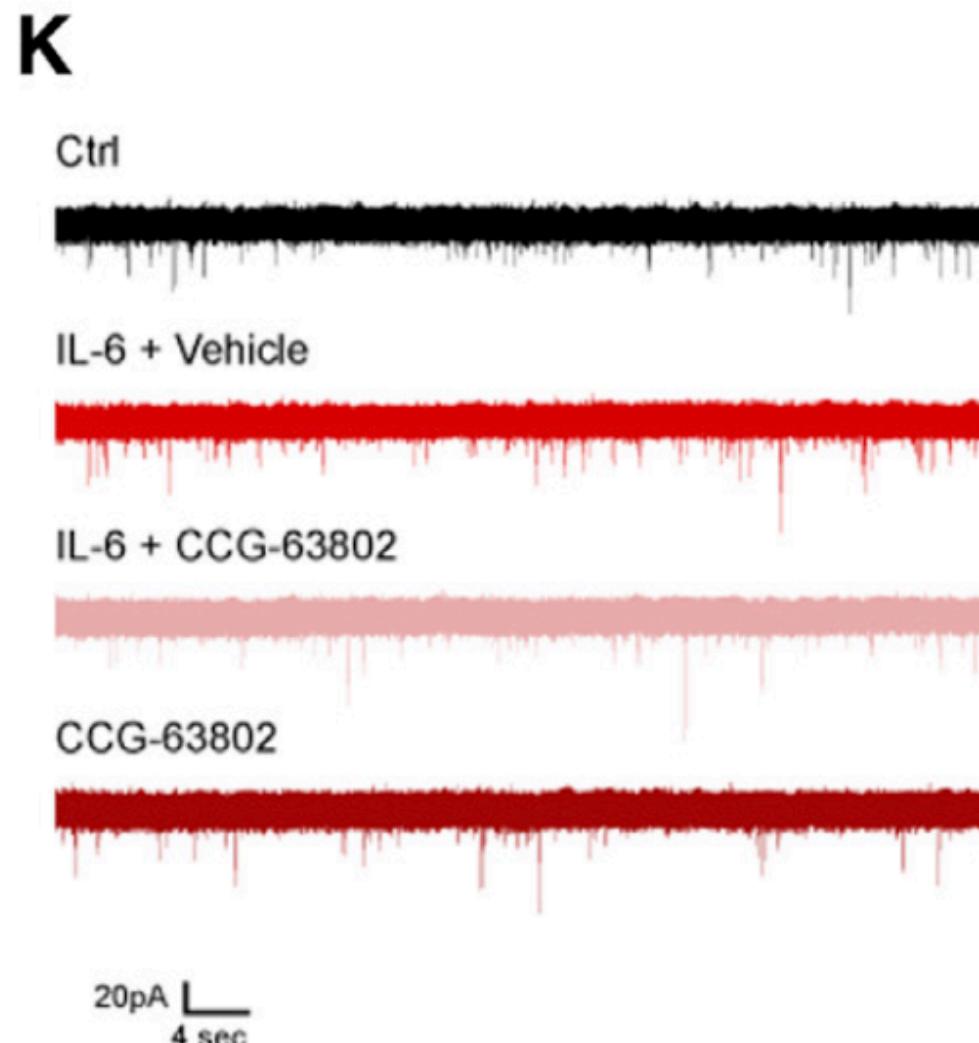
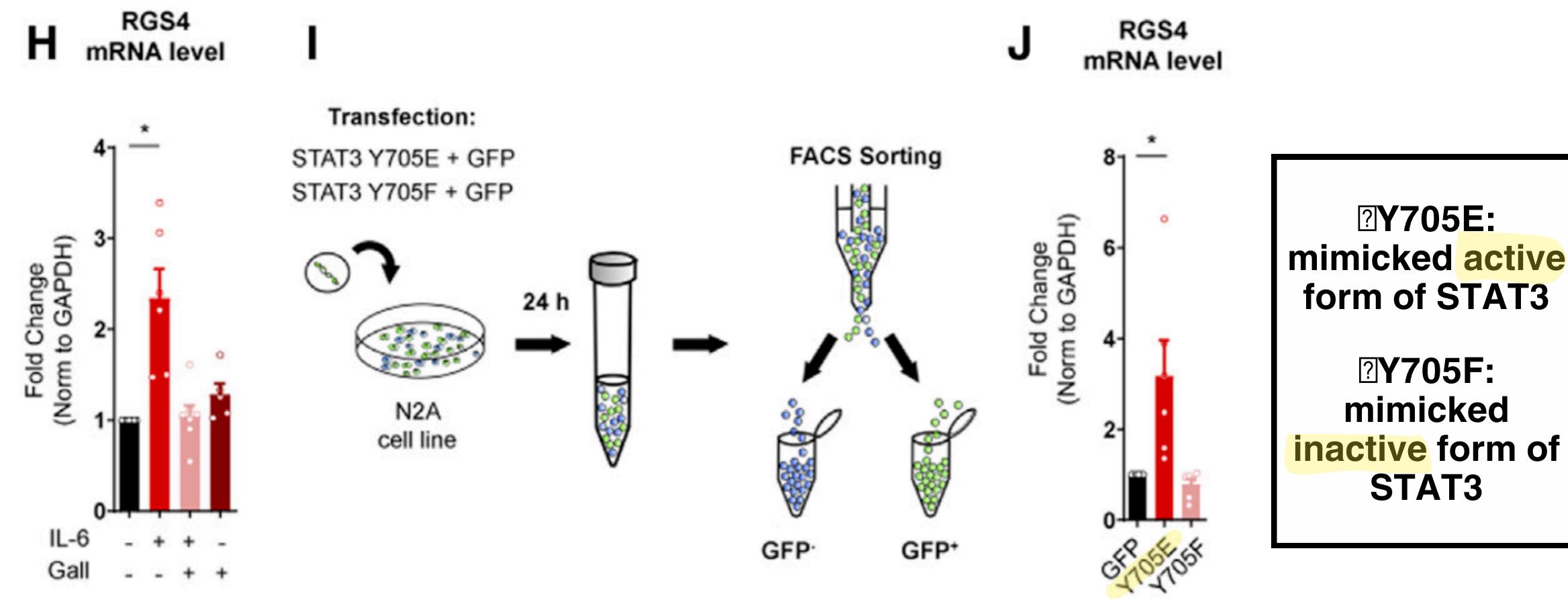


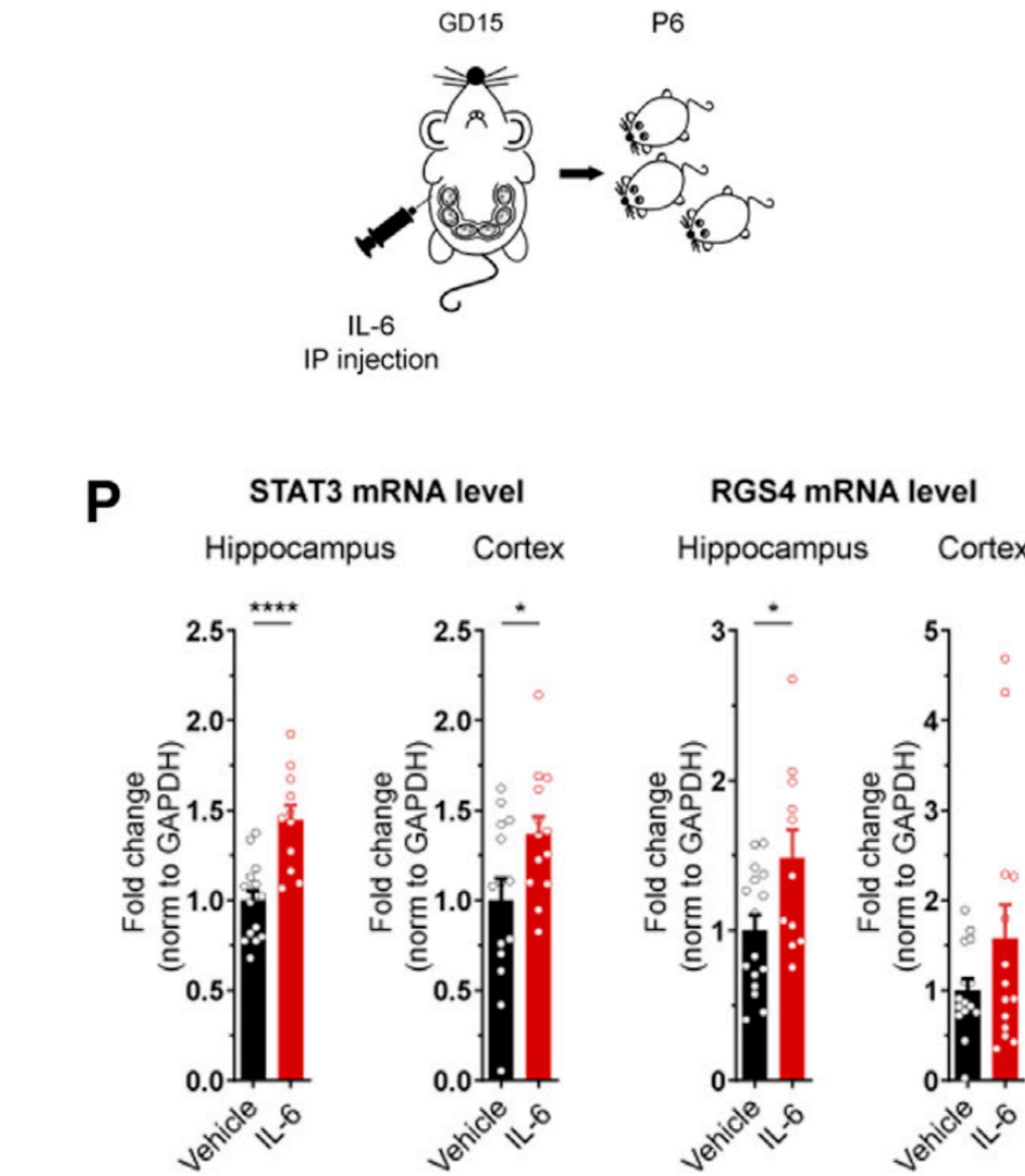
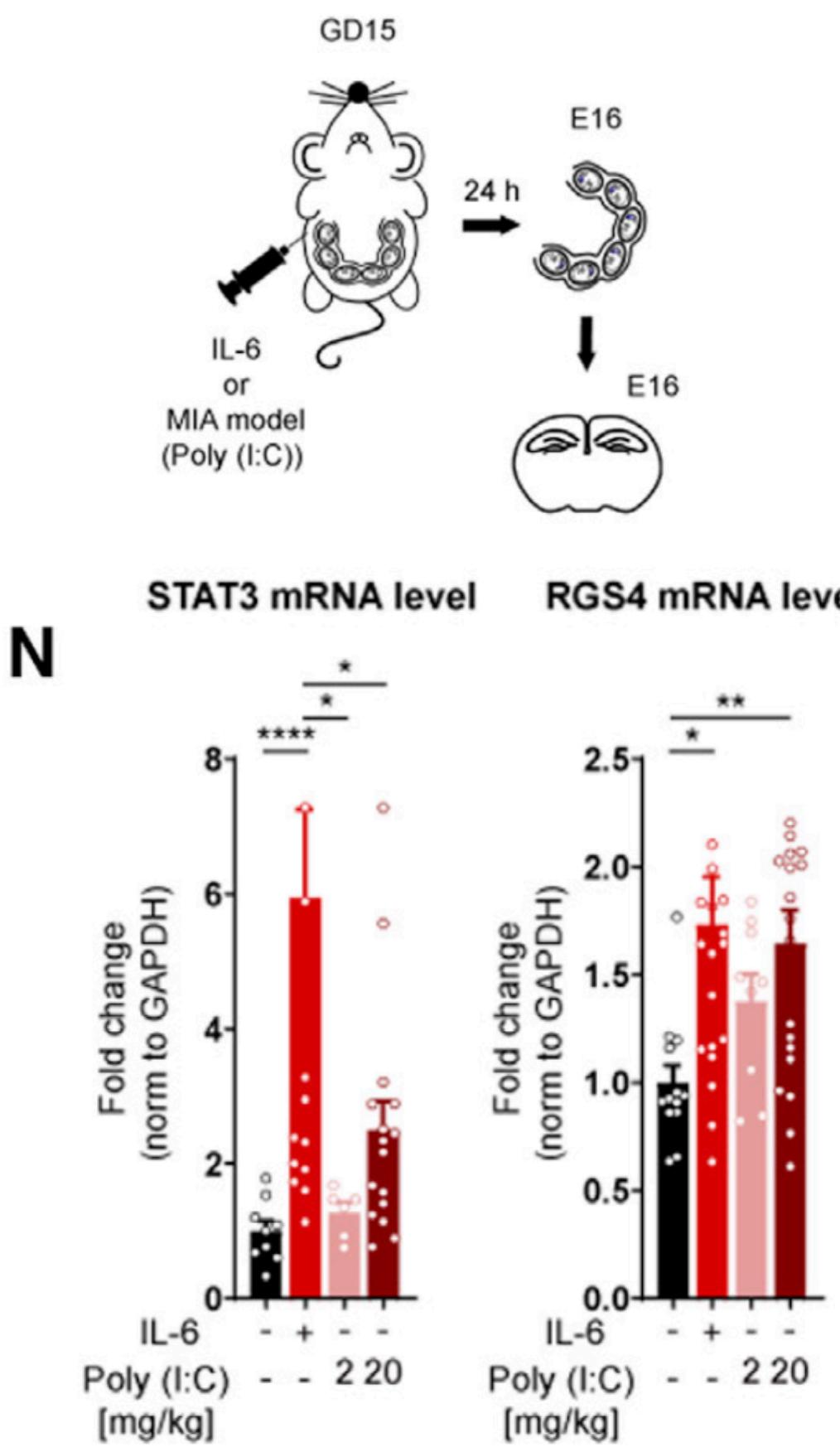
Figure 7



6. IL-6 promotes glutamatergic synaptogenesis through a STAT3-dependent genomic effect involving RGS4-activity

Figure 7 M

O₆. IL-6 promotes glutamatergic synaptogenesis through a STAT3-dependent genomic effect involving RGS4-activity



**Where the observed phenomena come from
& how they work**

SARS-CoV-2

Autism & Schizophrenia

Q&A

Thanks for Listening