



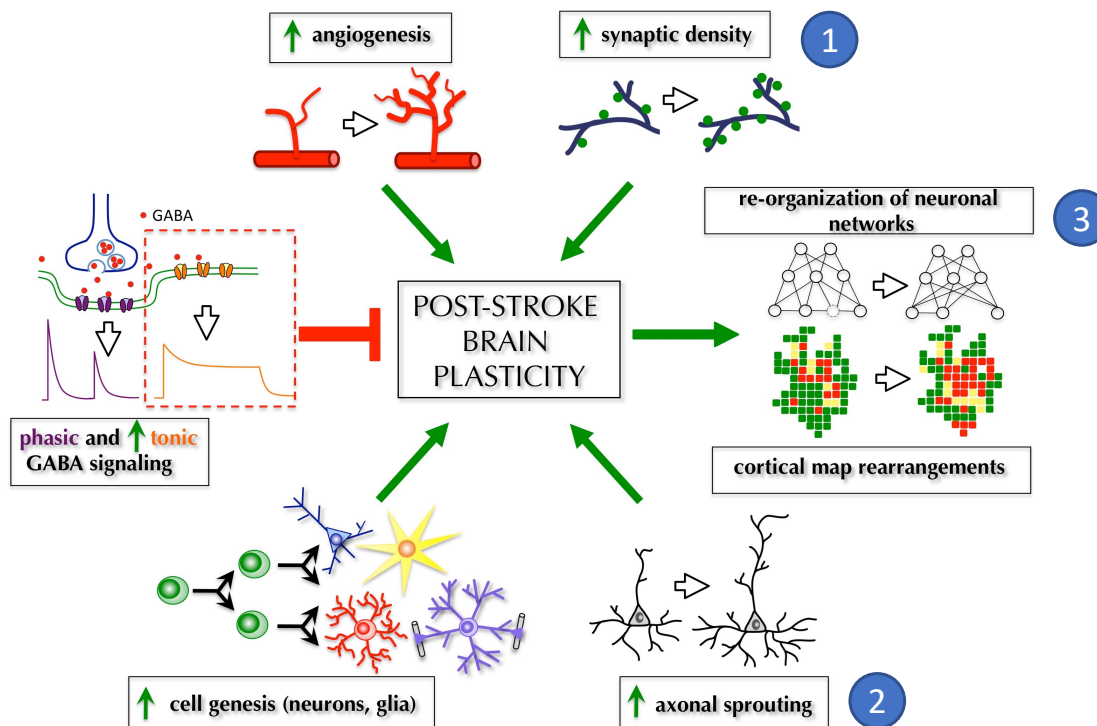
Novel therapeutic strategy to promote recovery after stroke

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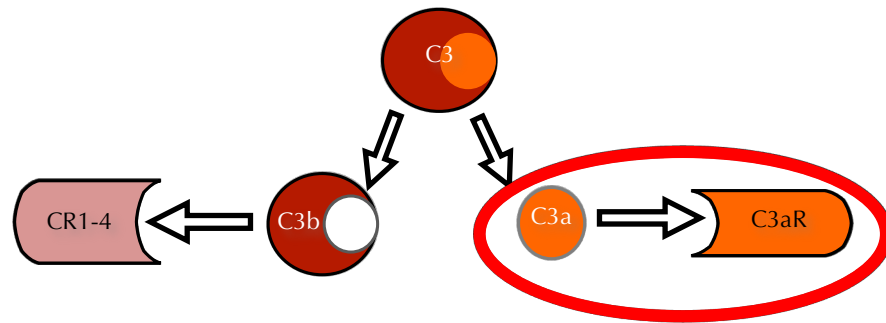
Neural plasticity in the peri-infarct region is the basis for functional recovery after stroke



Increased

- 1 density of excitatory synapses and
 - 2 axonal sprouting leading to the
 - 3 re-organization of neuronal networks
- form the structural basis of functional recovery after stroke

The complement C3a receptor (C3aR) is broadly expressed in the brain and C3aR expression is increased after injury

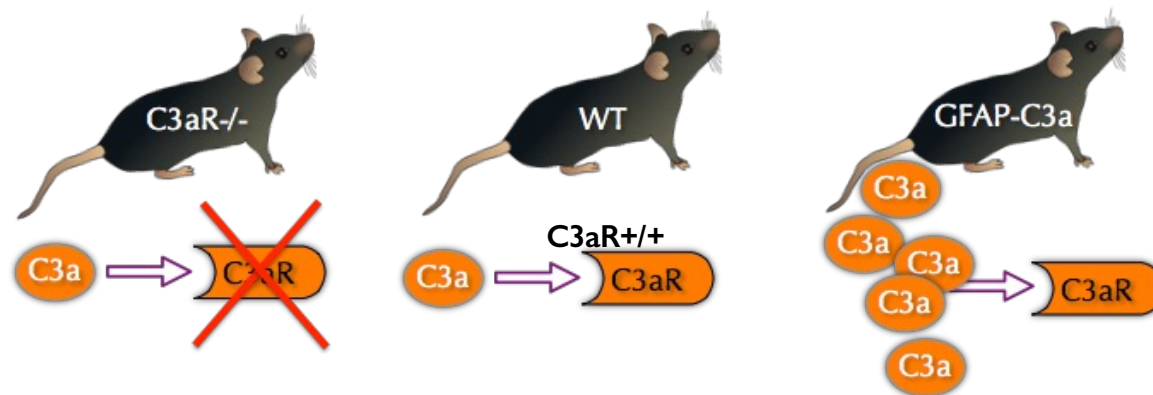


In the brain, **C3aR** is expressed by

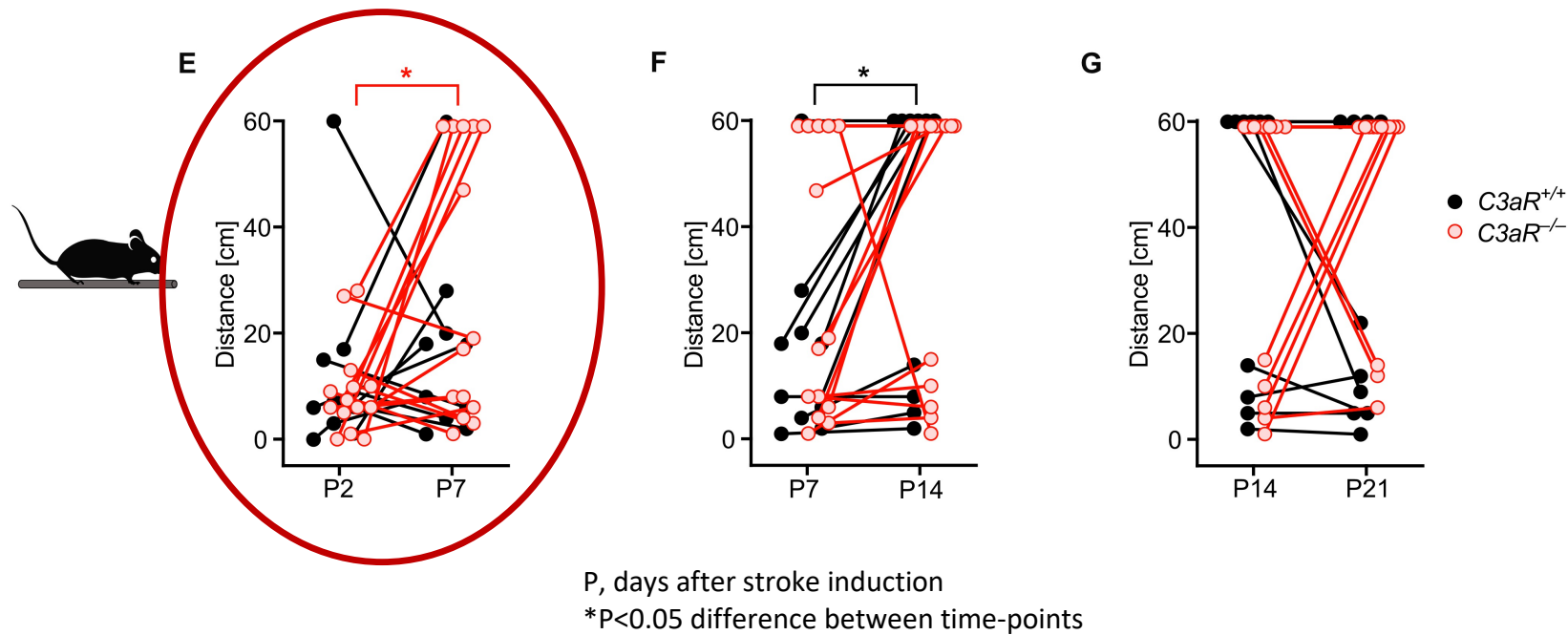
- neural progenitor cells
- neurons
- astrocytes
- microglia
- endothelial cells
- epithelial cells of the choroid plexus

C3a is generated by proteolytic cleavage of the third complement component (C3)

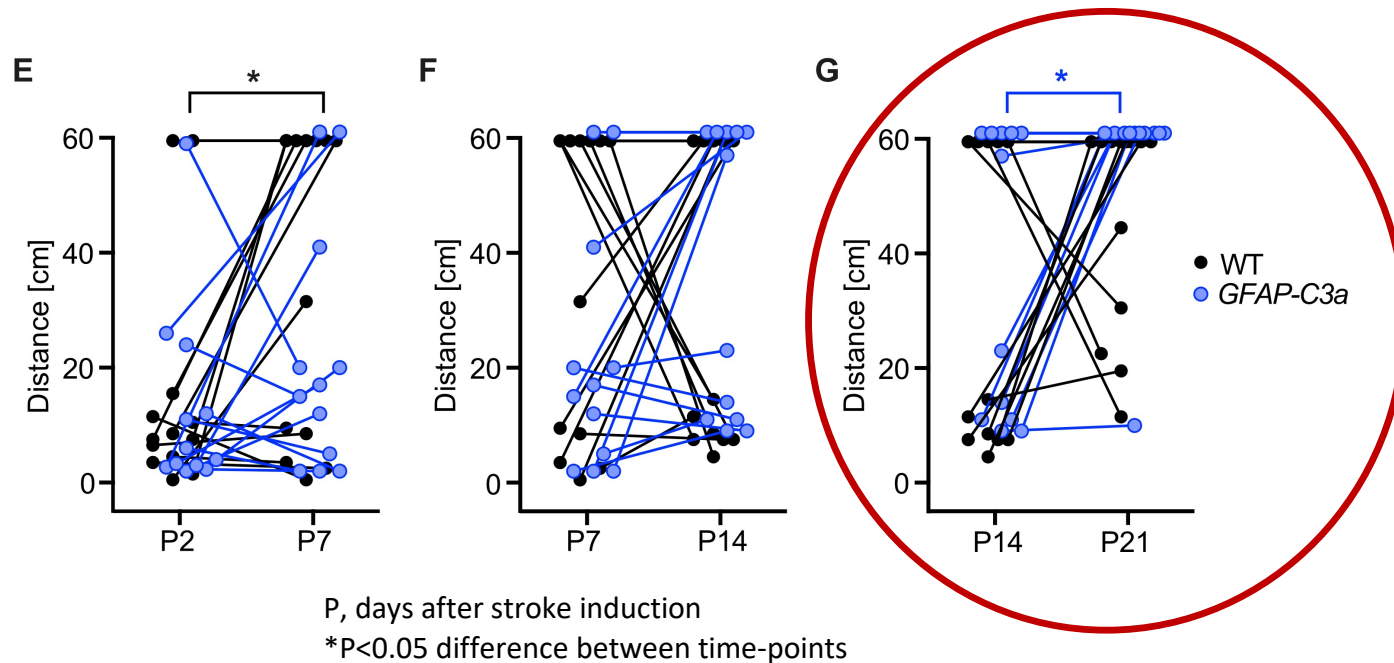
Studies in genetically modified mice identify C3aR as a neural plasticity modifier that promotes recovery after ischemic stroke



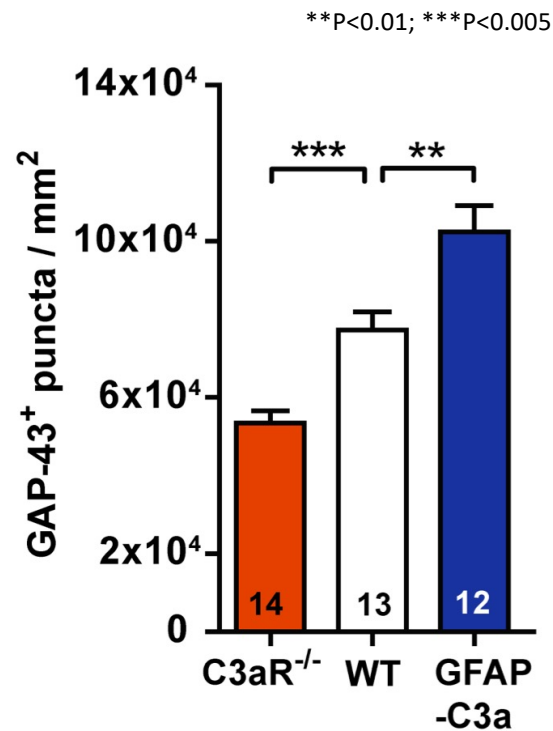
C3aR^{-/-} mice have better functional recovery in the acute phase after ischemic stroke



C3a over-expressing mice show better functional recovery in the post-acute phase after ischemic stroke



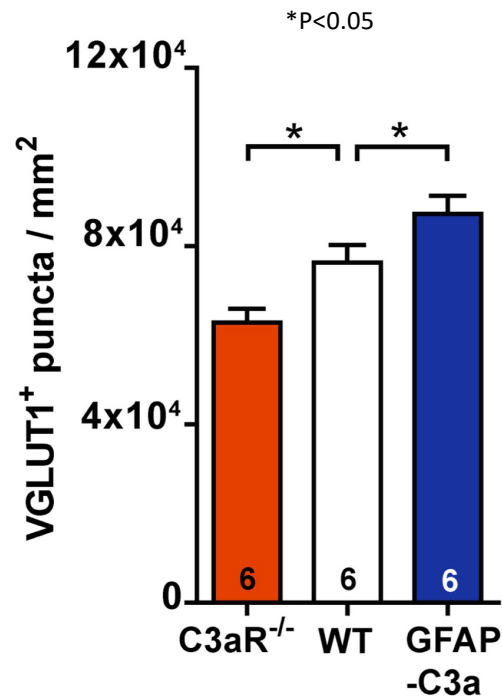
C3aR signaling stimulates axonal sprouting in the peri-infarct region



GAP-43 = growth associated protein 43

- expressed at high levels in neuronal growth cones during development and axonal sprouting or regeneration
- a crucial component of an effective regenerative response in the nervous system
- a marker of axonal sprouting

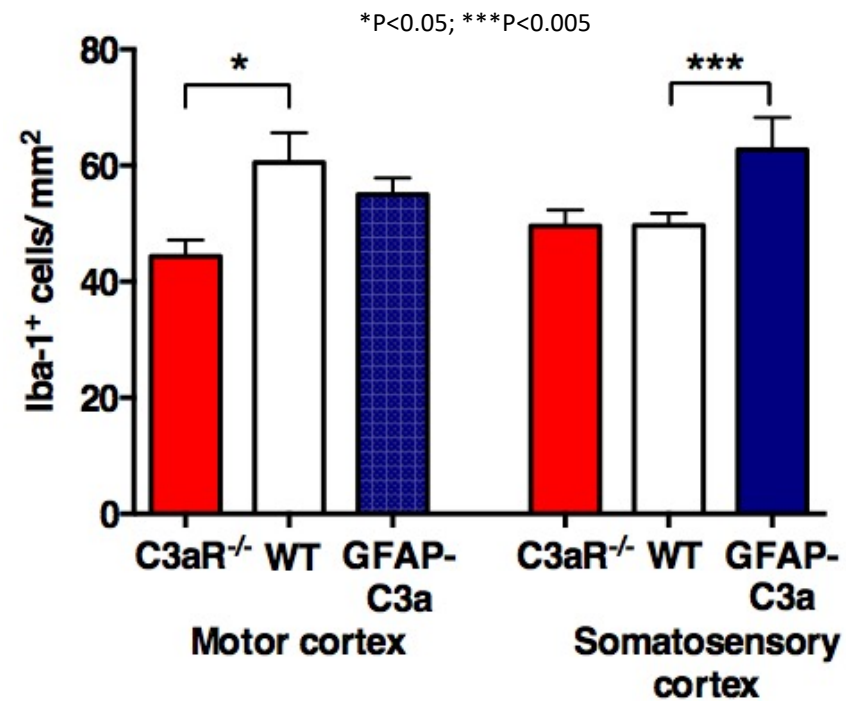
C3a-C3aR signaling increases the density of excitatory synapses in the peri-infarct region



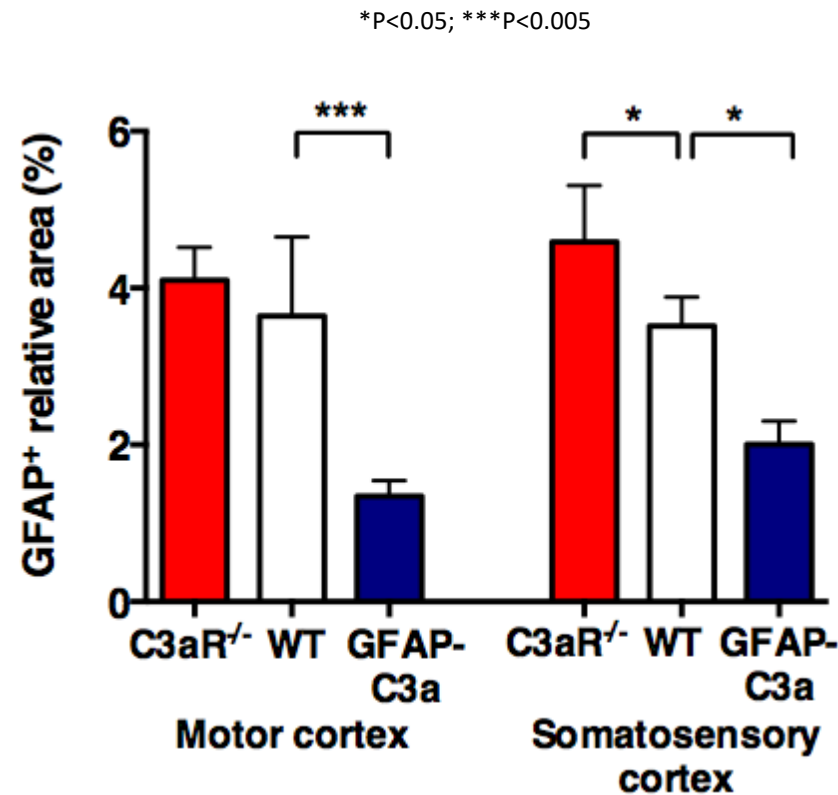
VGLUT1 = vesicular glutamate transporter 1

- Is expressed in excitatory presynaptic terminals
- Is a marker of excitatory synapses

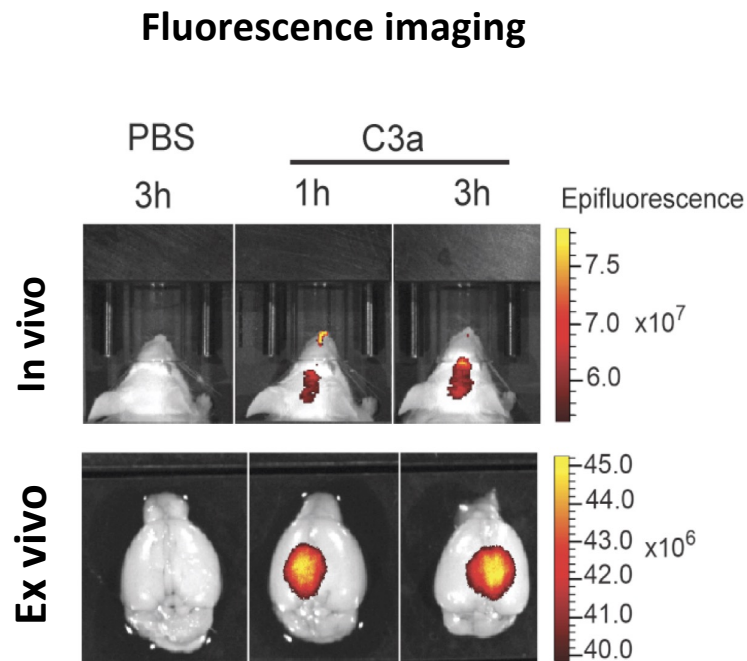
C3aR signaling contributes to peri-infarct microgliosis



C3aR signaling modulates reactive astrogliosis in the peri-infarct cortex

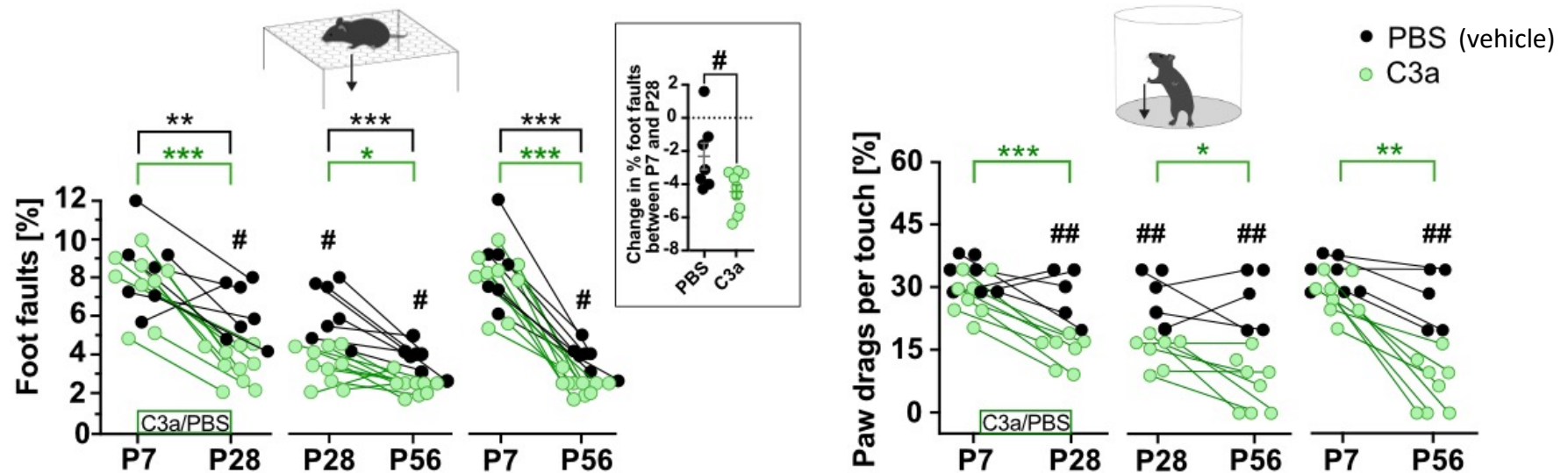


Intranasal administration is a feasible route for delivering C3a to the brain



In vivo and ex vivo imaging shows C3a in the brain 1h and 3h after intranasal administration

Intranasal treatment with C3a improves functional recovery after ischemic stroke



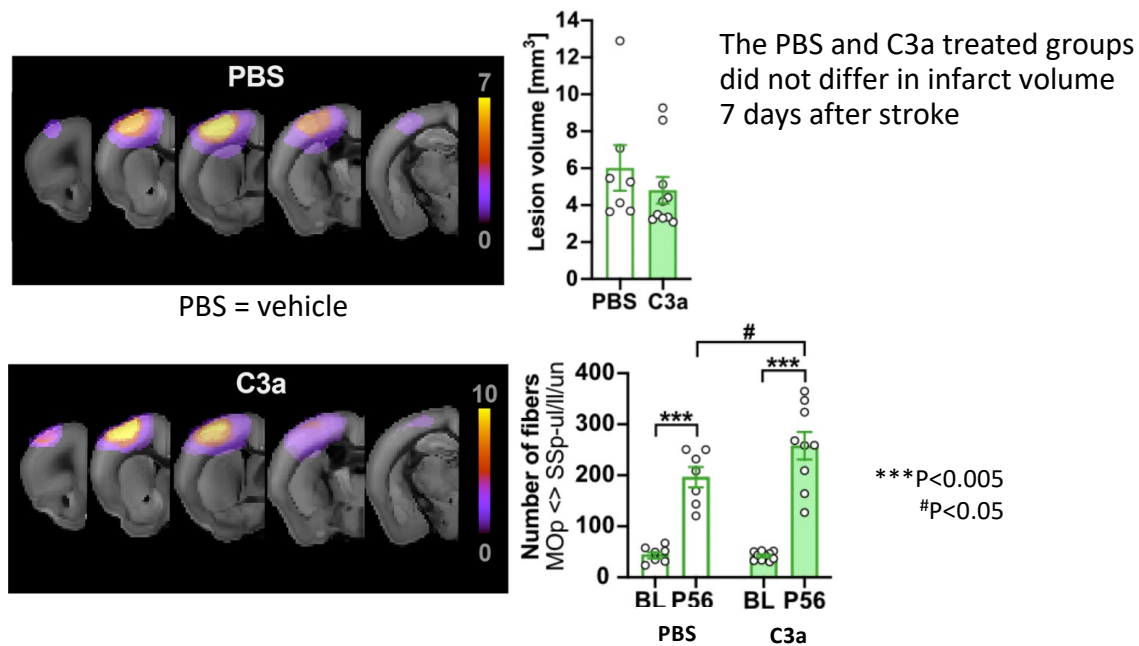
P, days after stroke induction

$P < 0.05$, ## $P < 0.01$, difference between groups

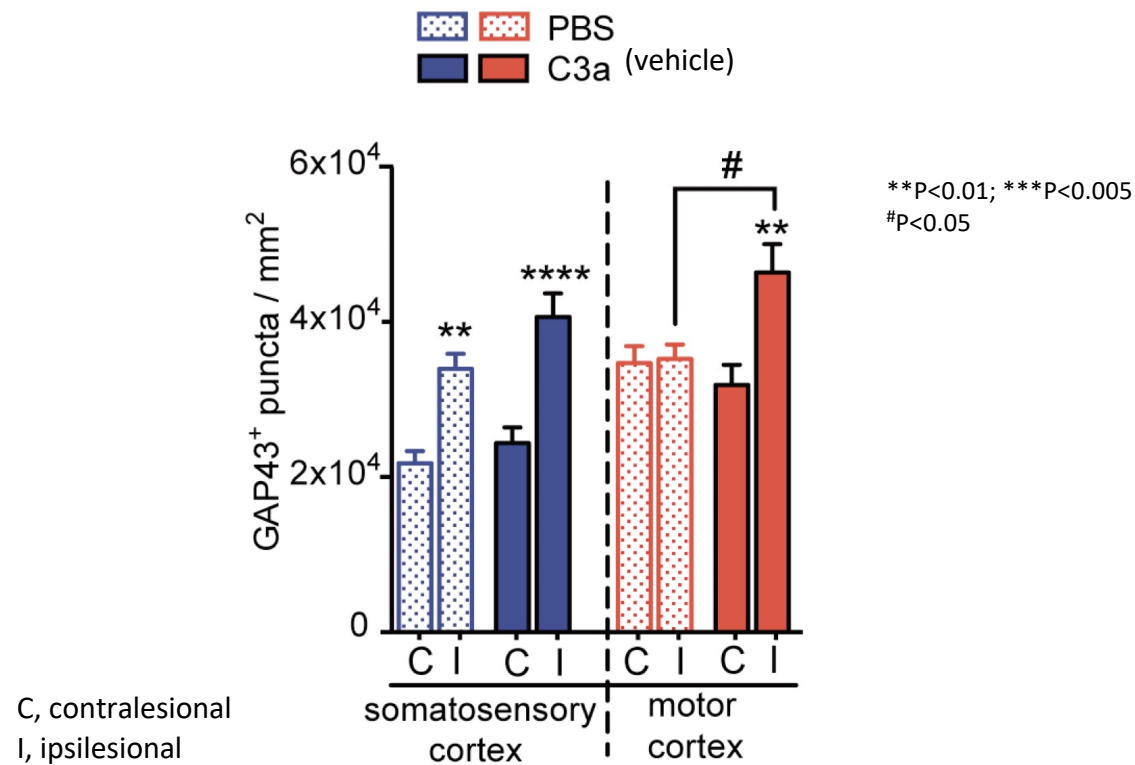
* $P < 0.05$, ** $P < 0.01$, *** $P < 0.005$, difference between time-points

Intranasal treatment with C3a increases neuronal connectivity in the peri-infarct motor cortex

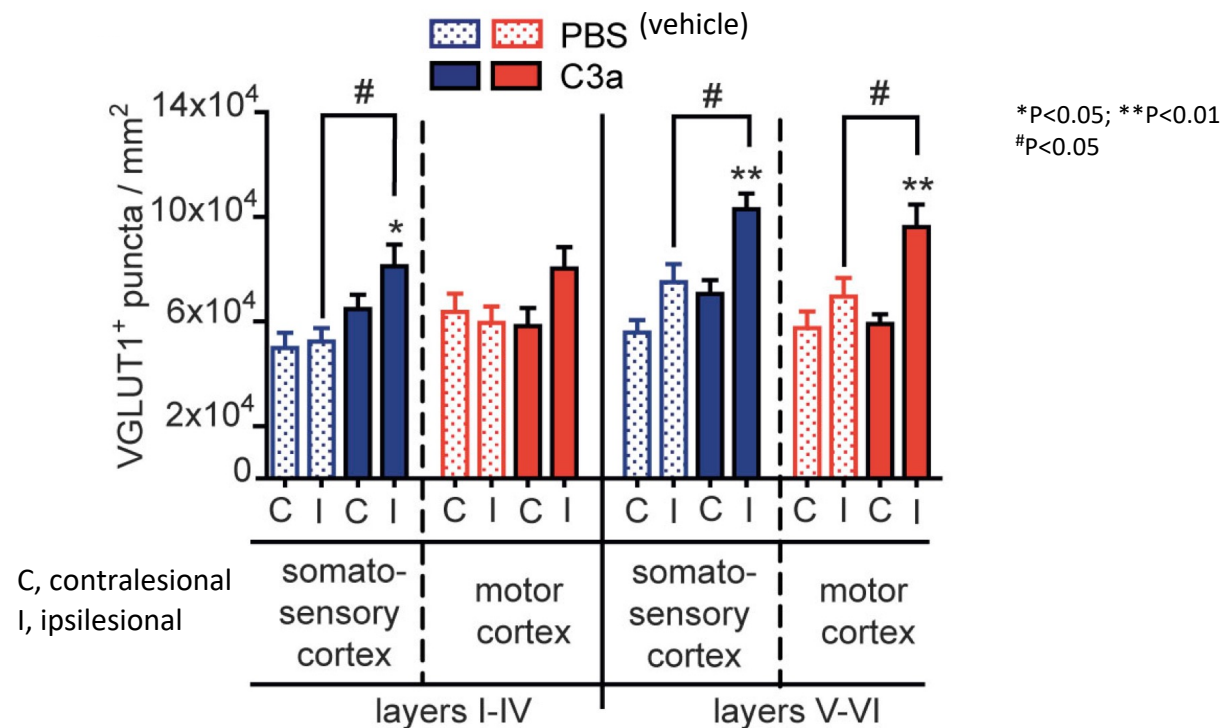
Magnetic resonance imaging



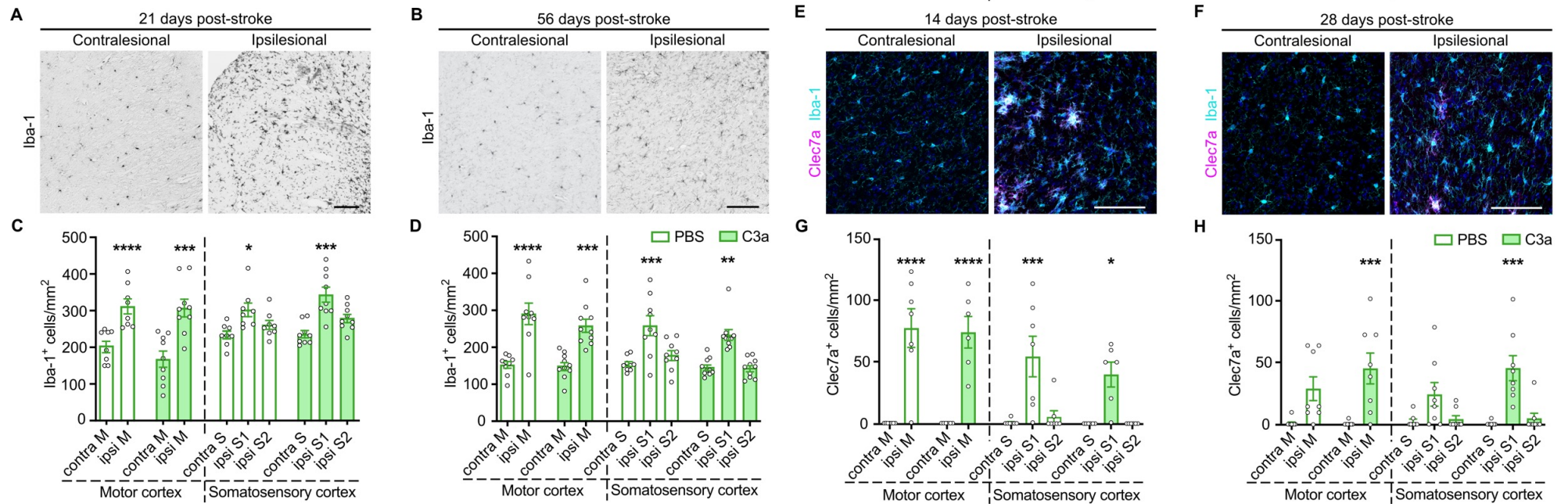
Intranasal treatment with C3a stimulates axonal sprouting in the peri-infarct cortex



Intranasal treatment with C3a increased the density of excitatory synapses in the peri-infarct cortex



Intranasal treatment with C3a does not affect reactive microgliosis



Clec7a – marker of disease-associated microglia
(Keren-Shaul et al, Cell, 2017)

*P<0.05, **P<0.01, ***P<0.005, ****P<0.001 difference between ipsi and contra

Summary

Intranasal treatment with C3a starting one week after experimental stroke

- stimulates adaptive neural plasticity and neuronal connectivity
- modulates astrocyte reactivity
- promotes functional recovery



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Avtal om läkarutbildning
och forskning mellan
Västra Götalandsregionen
och Göteborgs universitet