



@University of Electro-Communications

September 9, 2016

Bridge Over Troubled Synapses —シナプスに架ける橋

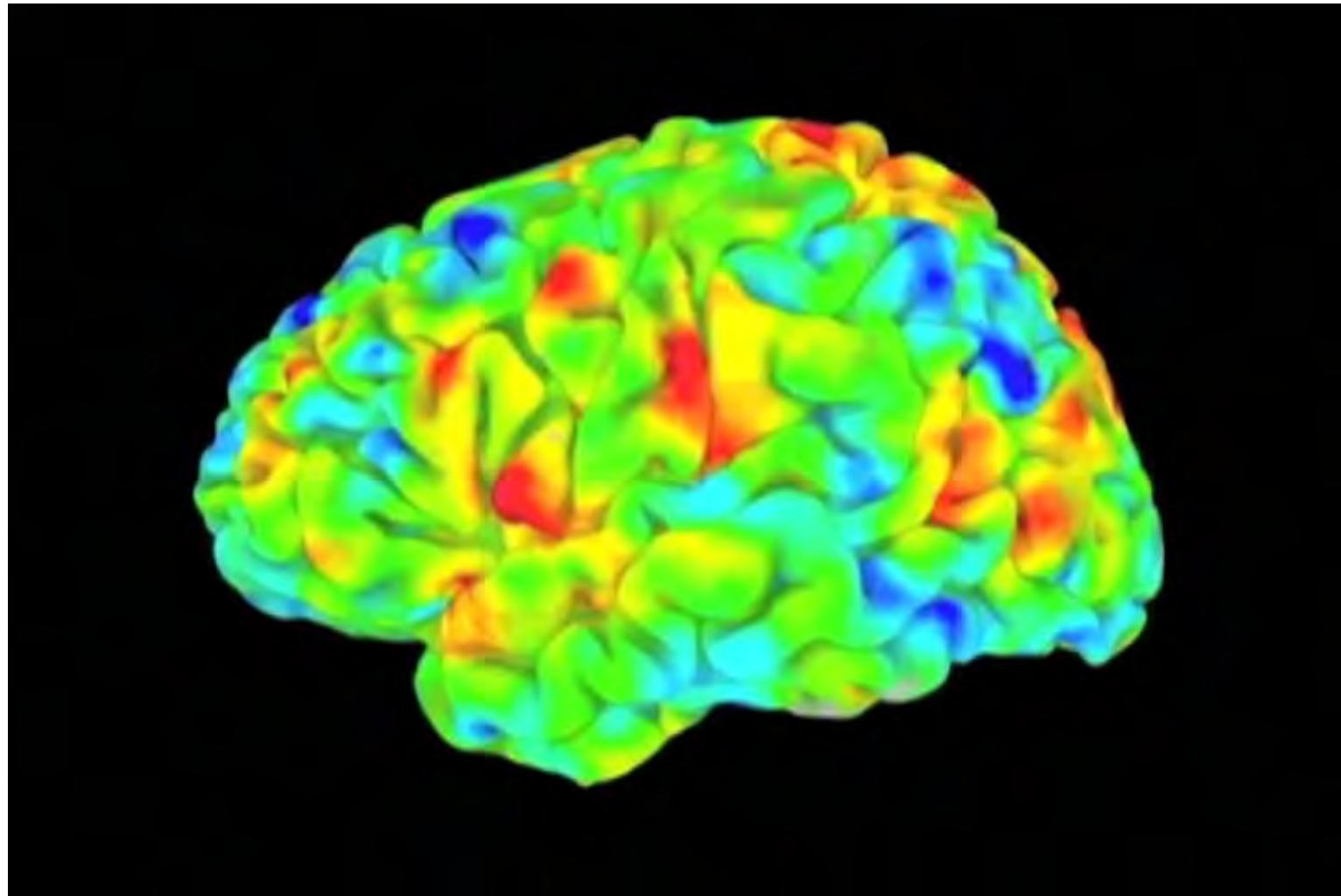
Michisuke Yuzaki



School of Medicine
Keio University
1858
CALAMVS
GLADIO
FORTIOR

Department of Physiology

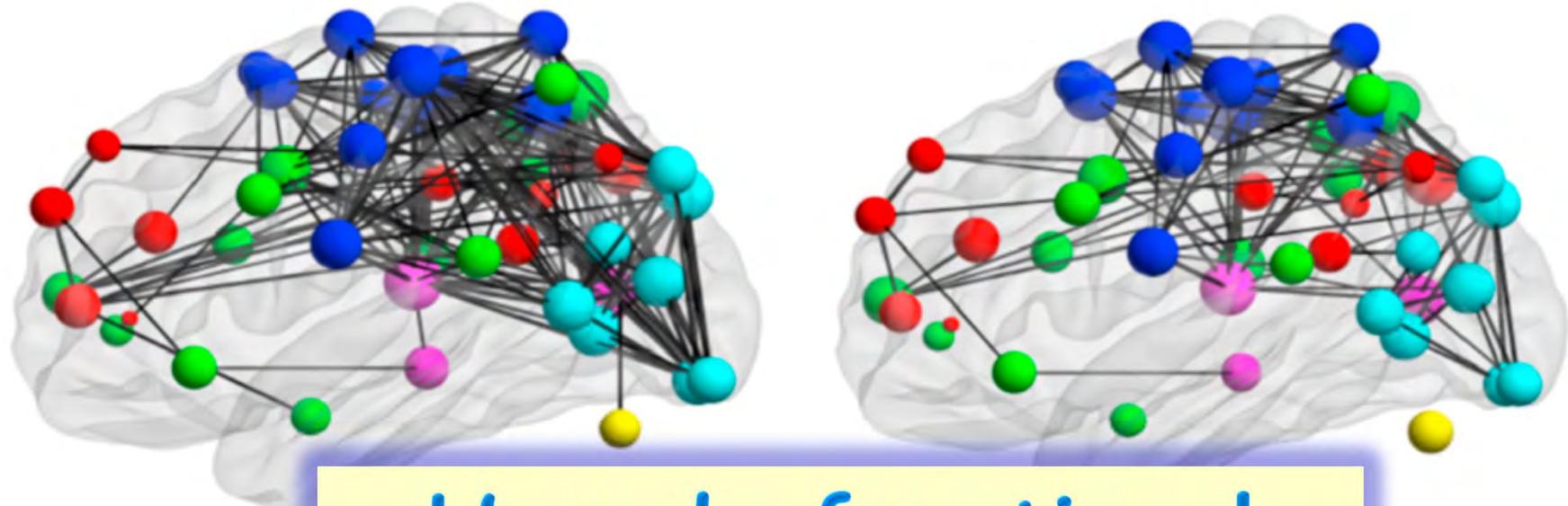
Visualization of active circuits by f-MRI



Hersher, Nature Med, Mar 13, 2012

“Functional networks” visualized by rs-fMRI

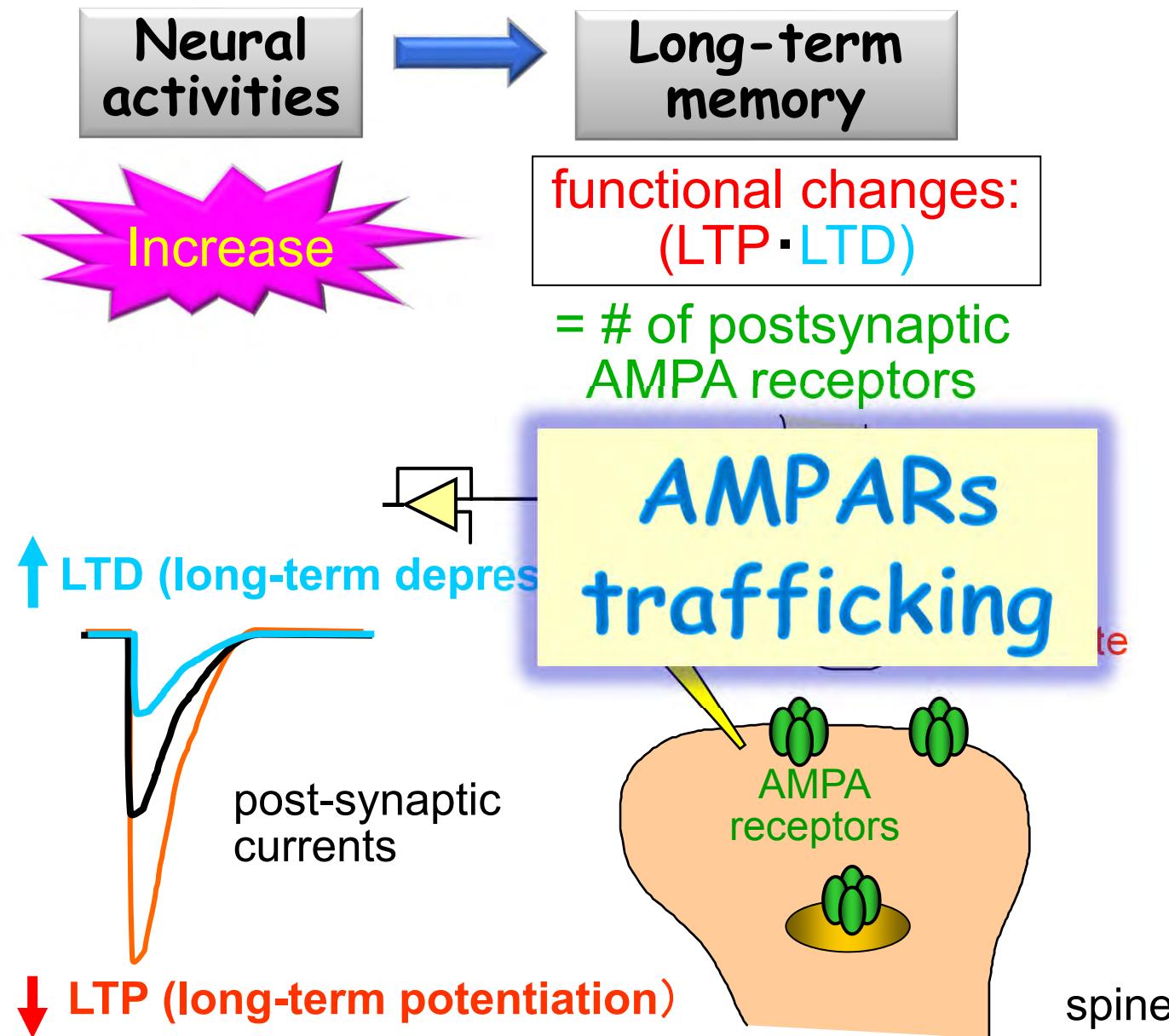
Yu et al, Schizophrenic Res, 2013



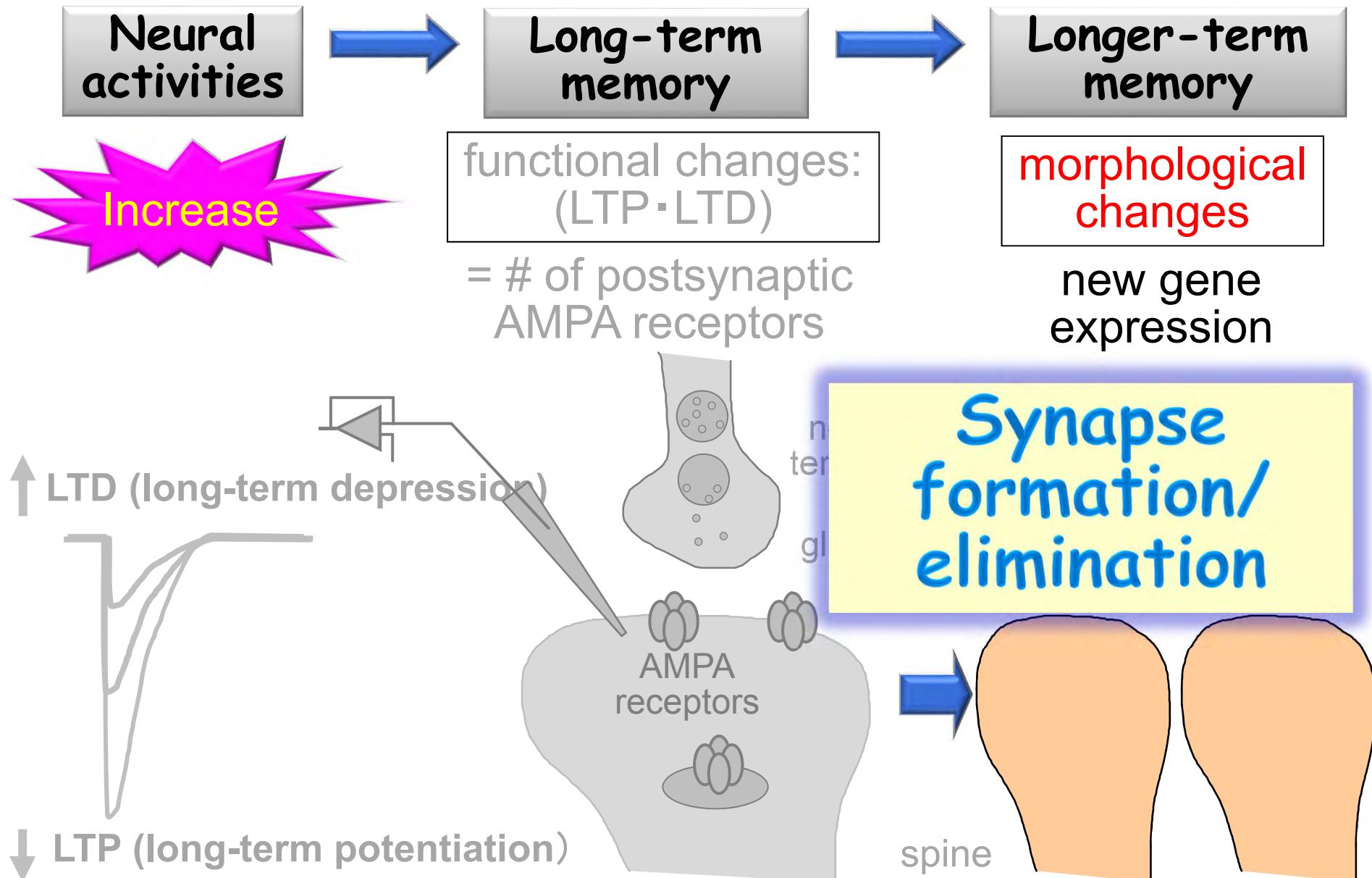
How do functional
networks change?

= *Synaptic plasticity*

Functional/morphological changes @ synapses



Functional/morphological changes @ synapses



Menu

Bridge Over Troubled Synapses —シナプスに架ける橋

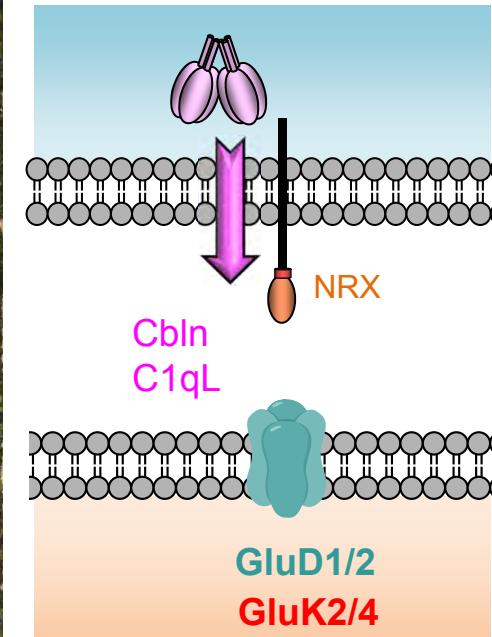
- Cbln1 as a prototype of C1q family
- C1q-like 1 (C1qL1)—Yet another synapse organizer
- C1q family in the hippocampus

Synapse organizers—key molecules in neuropsychiatric disorders

Ménage à Trois



Sandwich-type



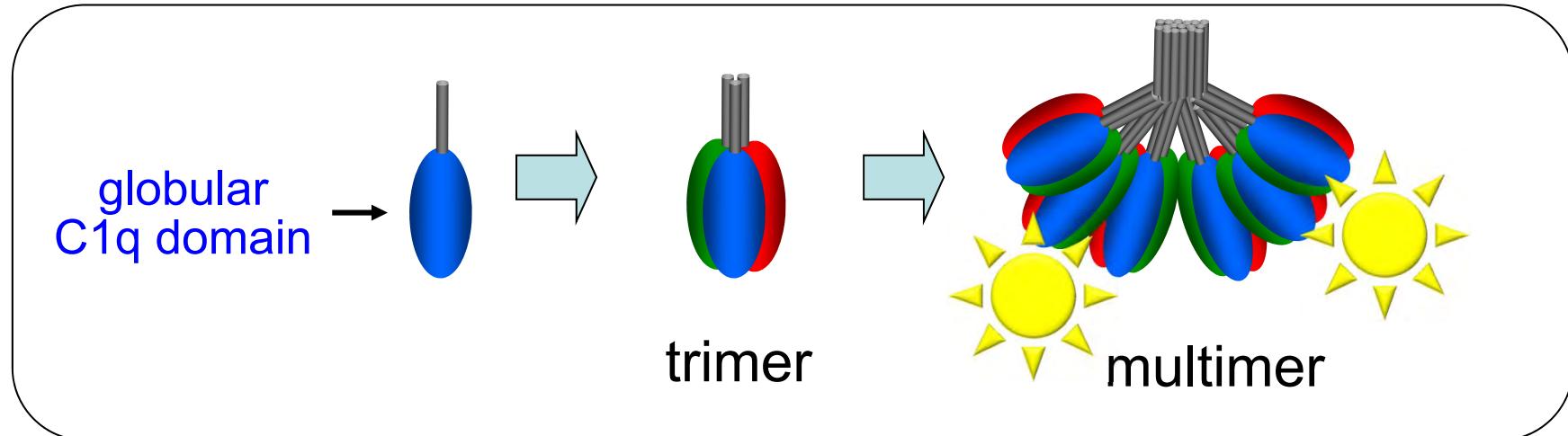
C1q family

Synaptic Ménage à Trois

Elisabetta Furlanis¹ and Peter Scheiffele^{1,*}
Neuron

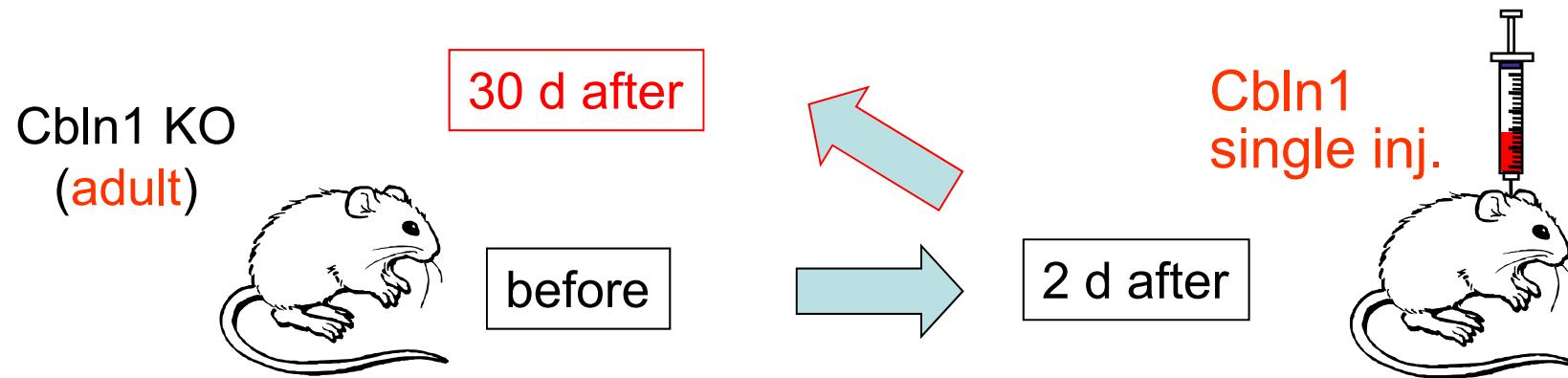
Previews

C1q proteins: secreted signaling molecules



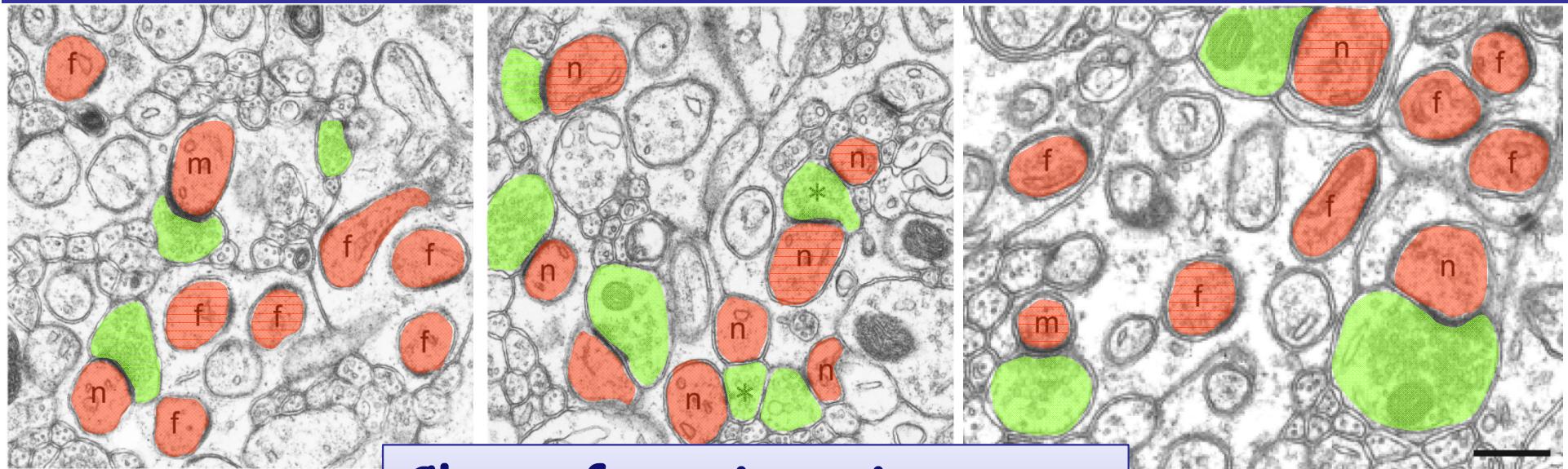
- Complement C1q → recognize **foreign objects** → removal
- 32 members → Some C1q proteins regulate CNS synapses!
 - **Cbln1-4** ··· *Nat Neurosci* '05; *Science* '10, '16
 - **C1qL1-4** ··· *Neuron* '15, '16
 - **C1q** (complement) ··· Stevens et al, *Cell* '07

Cbln1 rescues ataxia in Cbln1 KO *in vivo*



Ito-Ishida et al, *J Neurosci*, 2008

Cbln1 induces rapid & transient synaptogenesis *in vivo*

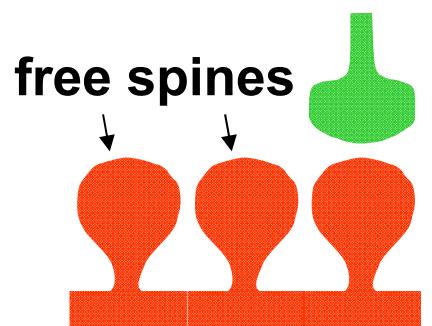


control (KO)

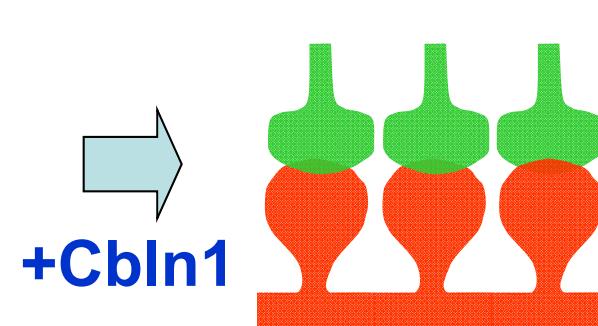
granule cell axons

Clear functions in
mature brains *in vivo* !!

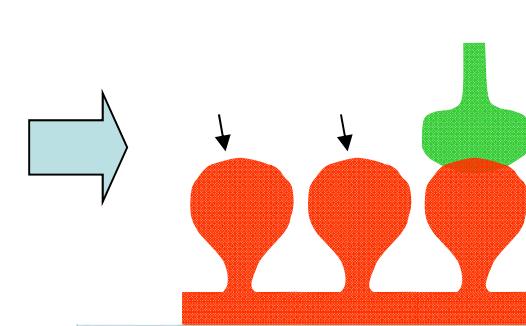
35 d later



dendritic spines
(Purkinje cells)

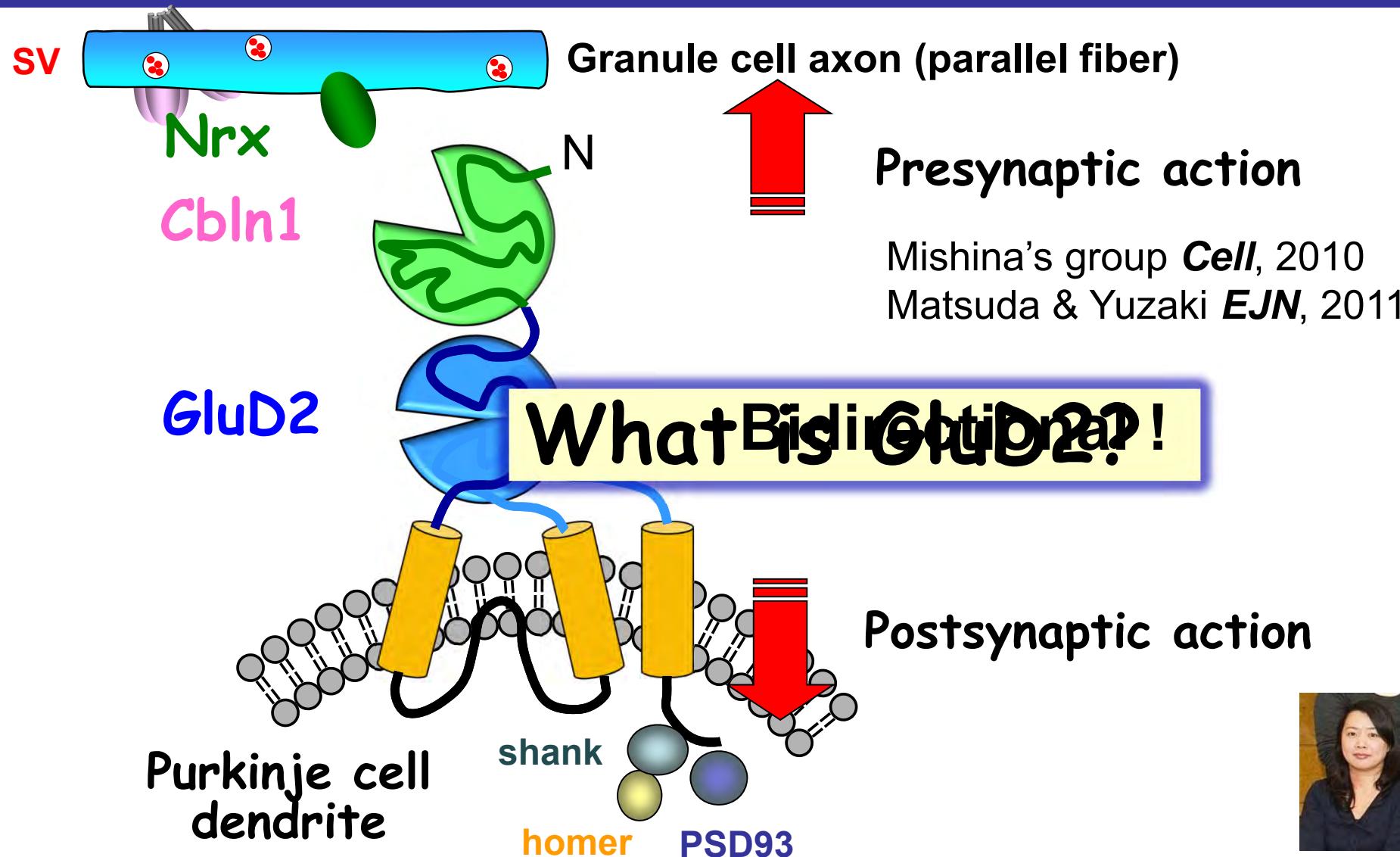


+Cbln1



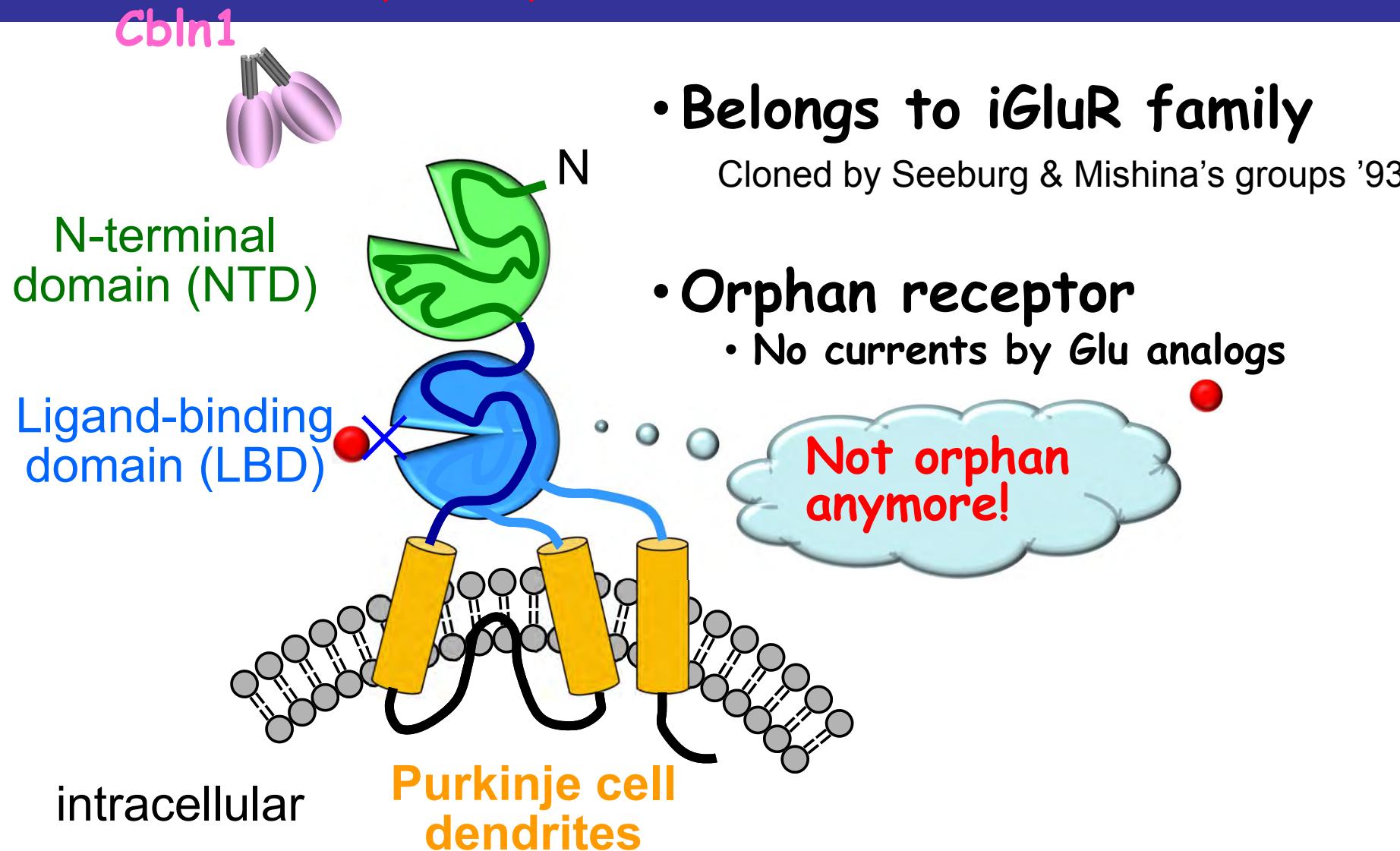
Cbln1 is necessary for
synapse maintenance!!

Nrx-Cbln1-GluD2: a sandwich-type synapse organizer

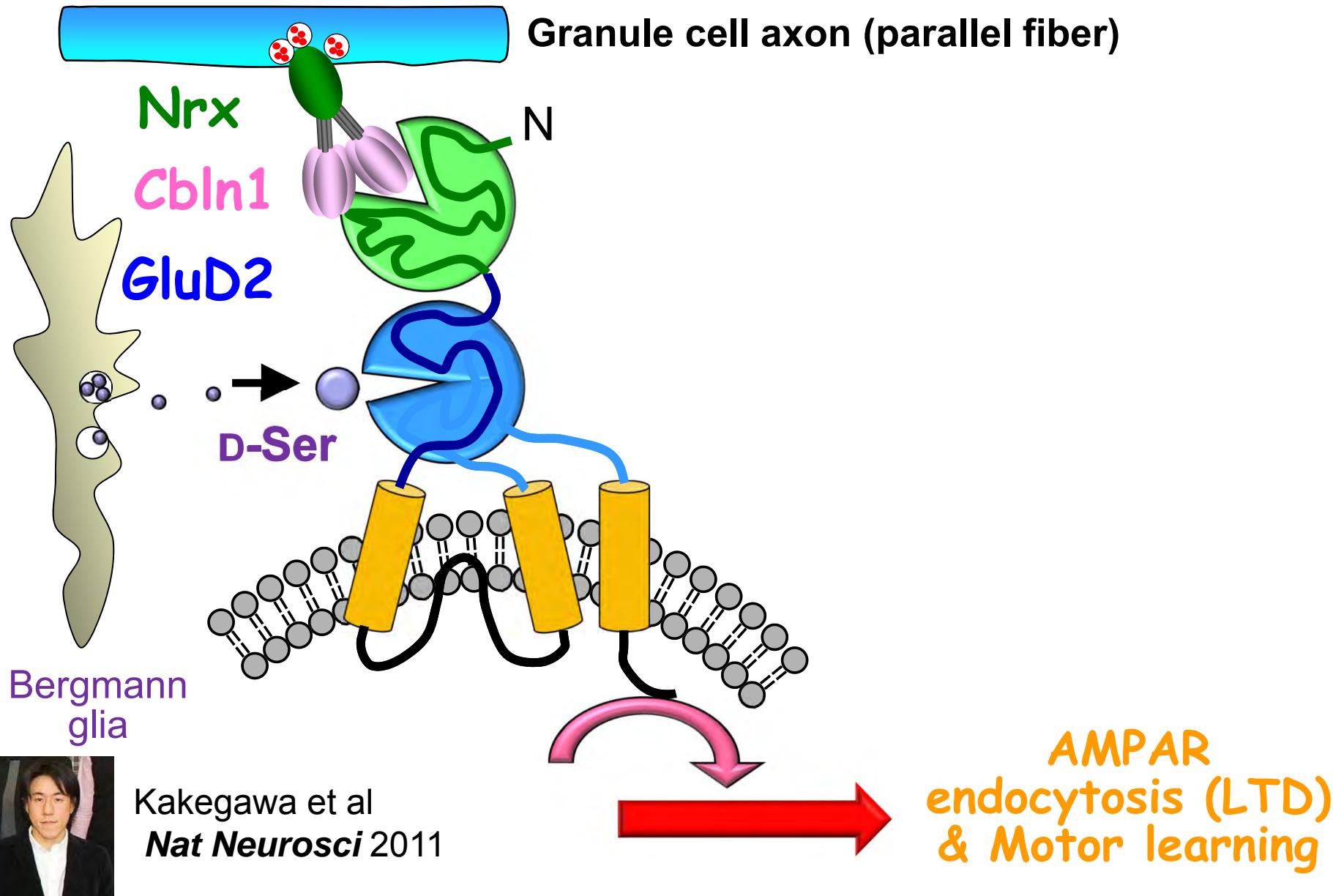


Matsuda et al *Science* 2010
Yuzaki *Curr Opin Neurobiol*, 2010

~~Orphan receptor GluD2~~



D-Ser: yet another GluD2 ligand to regulate LTD



Kakegawa et al
Nat Neurosci 2011

Cbln1: a new synaptic organizer

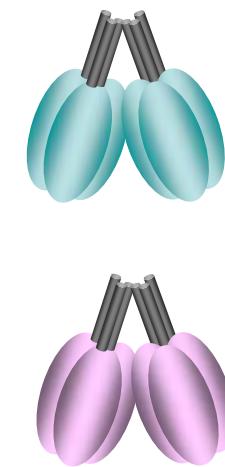
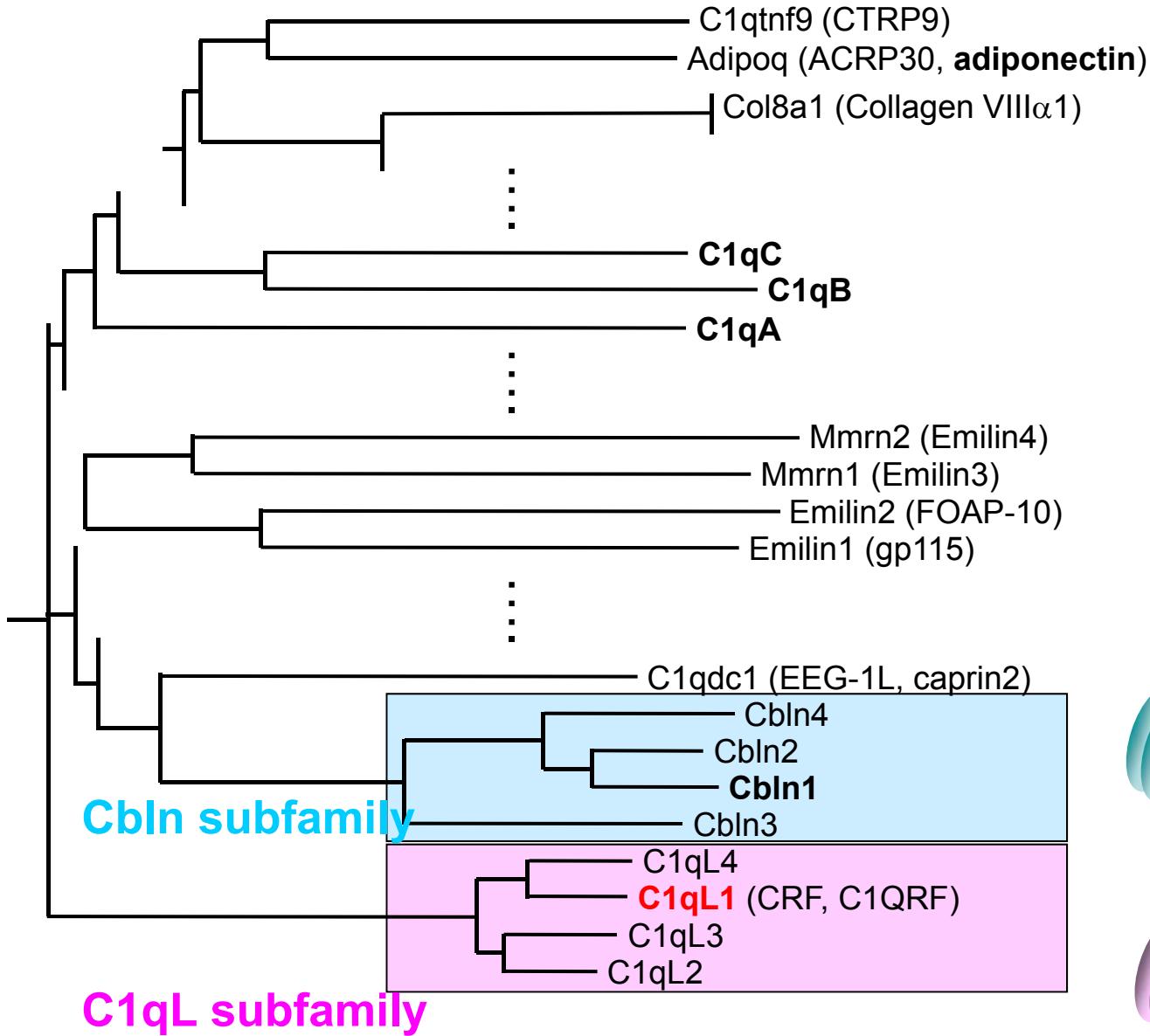
- Released from cerebellar granule cells
→ binds to Nrx(PF) & GluD2(PCs)
- Necessary for development throughout adulthood
- At PF-PC synapses
 - Forms and maintains presynaptic boutons
 - Regulates LTD via D-Ser from glia
- Activity-dep. release via TeNT-insensitive vesicles

Menu

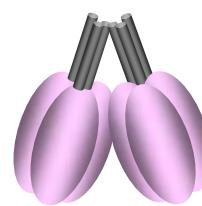
Bridge Over Troubled Synapses —シナプスに架ける橋

- Cbln1 as a prototype of C1q family
- C1q-like 1 (C1qL1)—Yet another synapse organizer
- C1q family in the hippocampus

The C1q family (32 members)



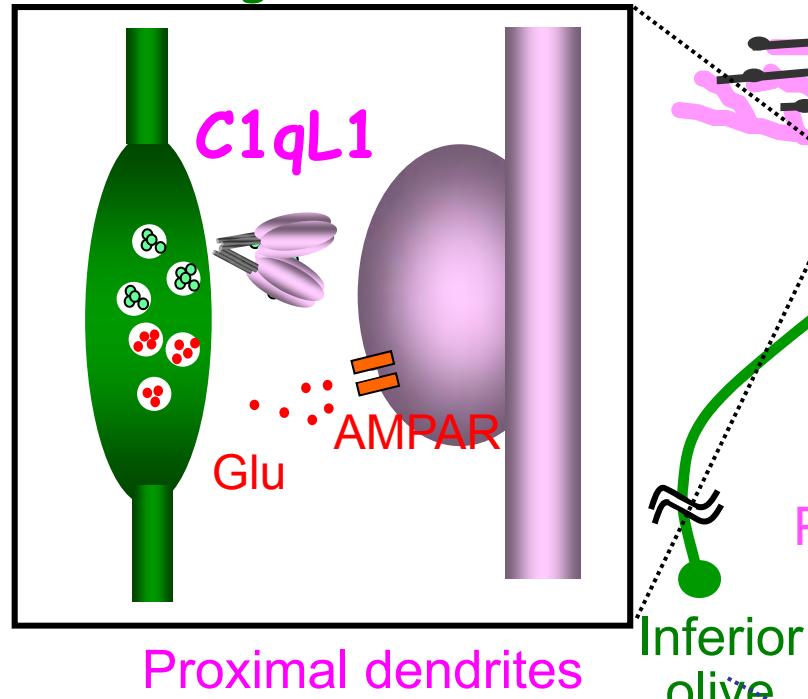
Synapse formation



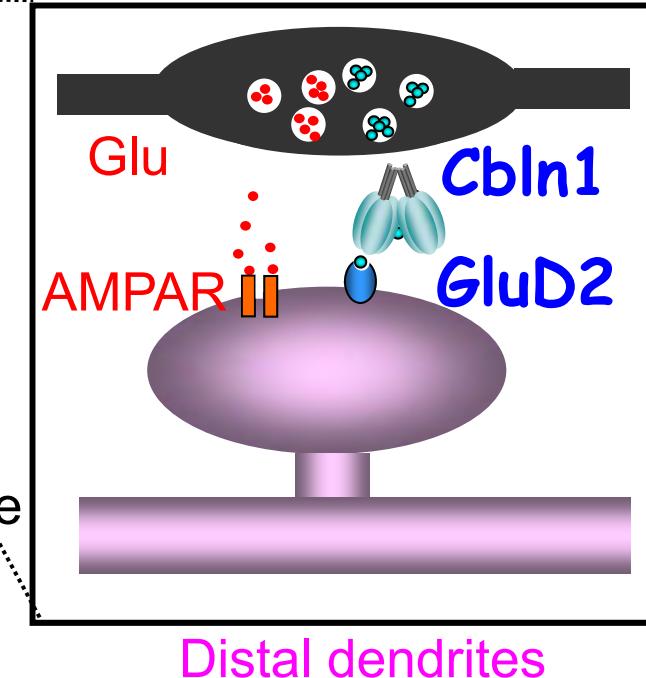
??

Cbln1 and C1qL1 in two different inputs to PC

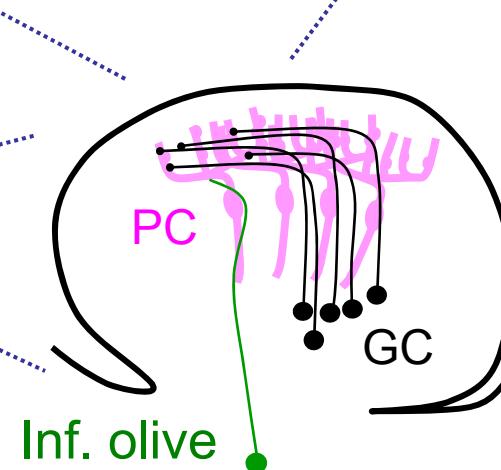
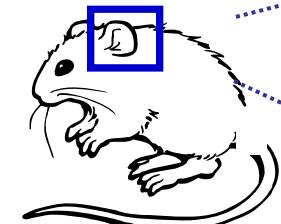
Climbing fiber (CF)



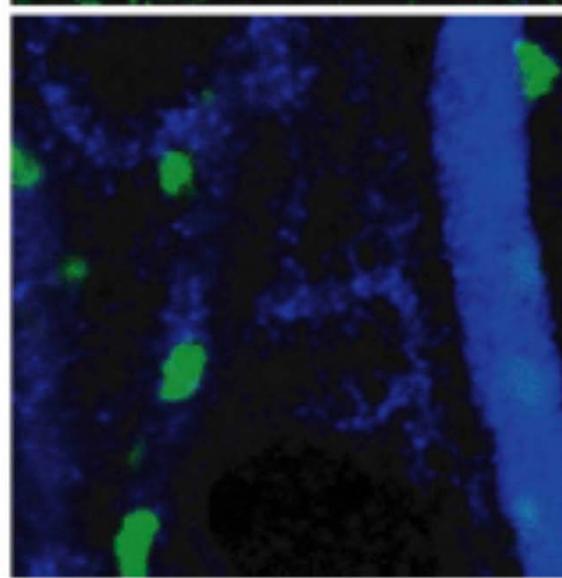
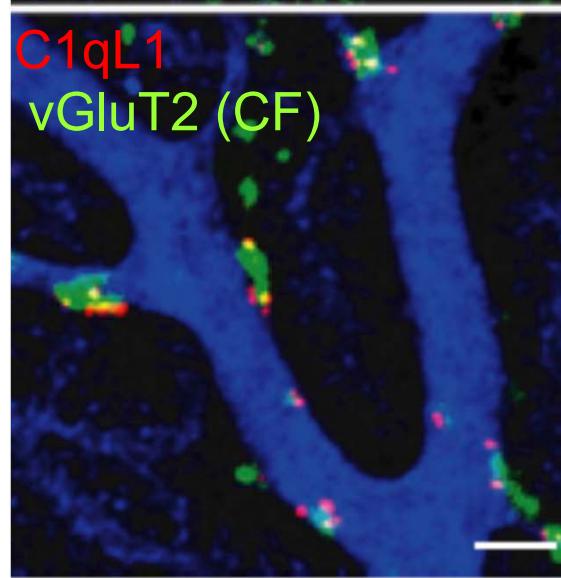
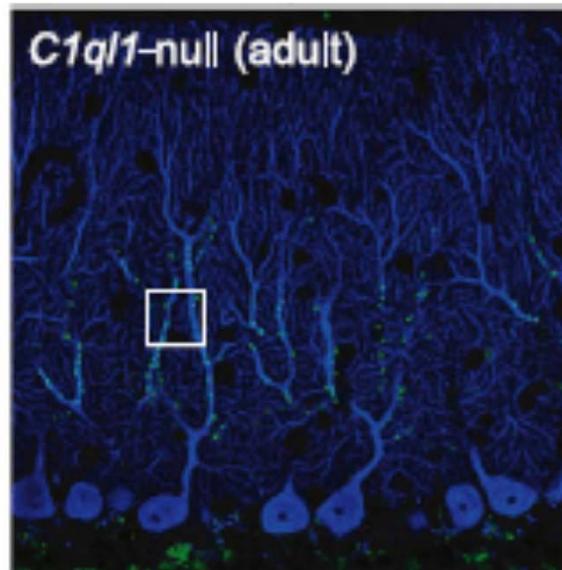
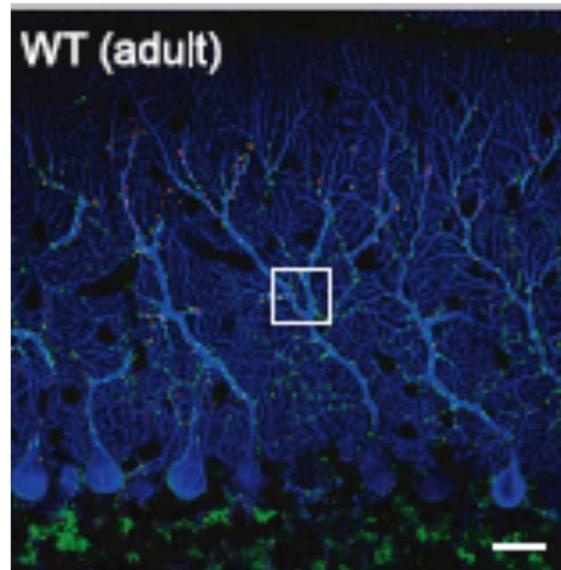
Parallel fiber (PF)



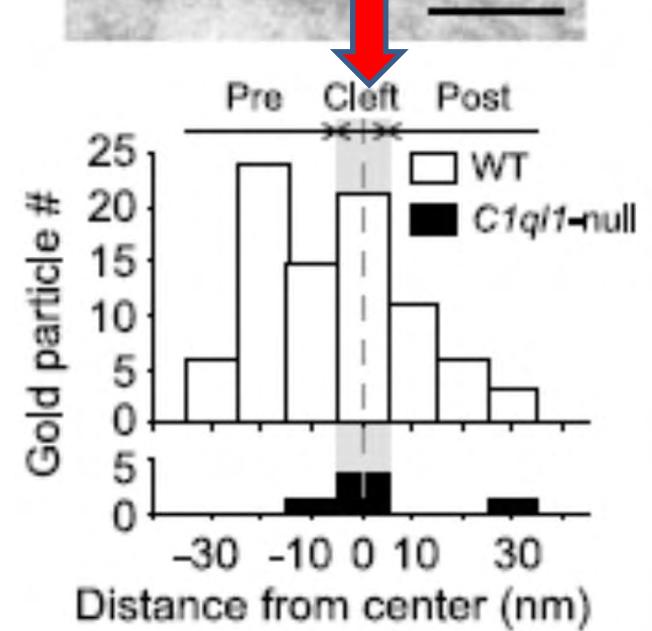
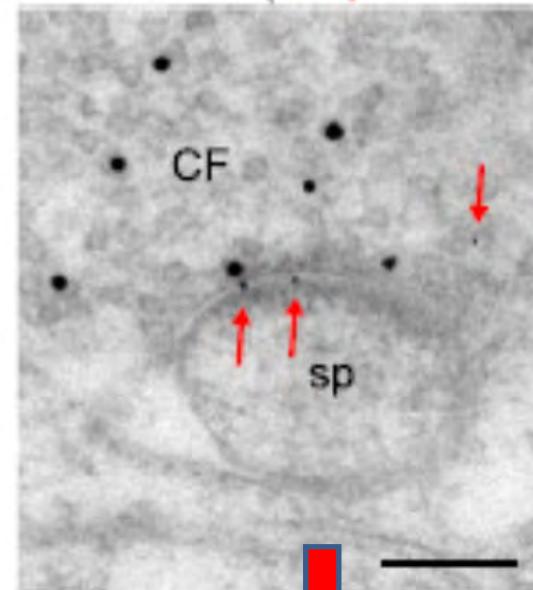
cerebellum



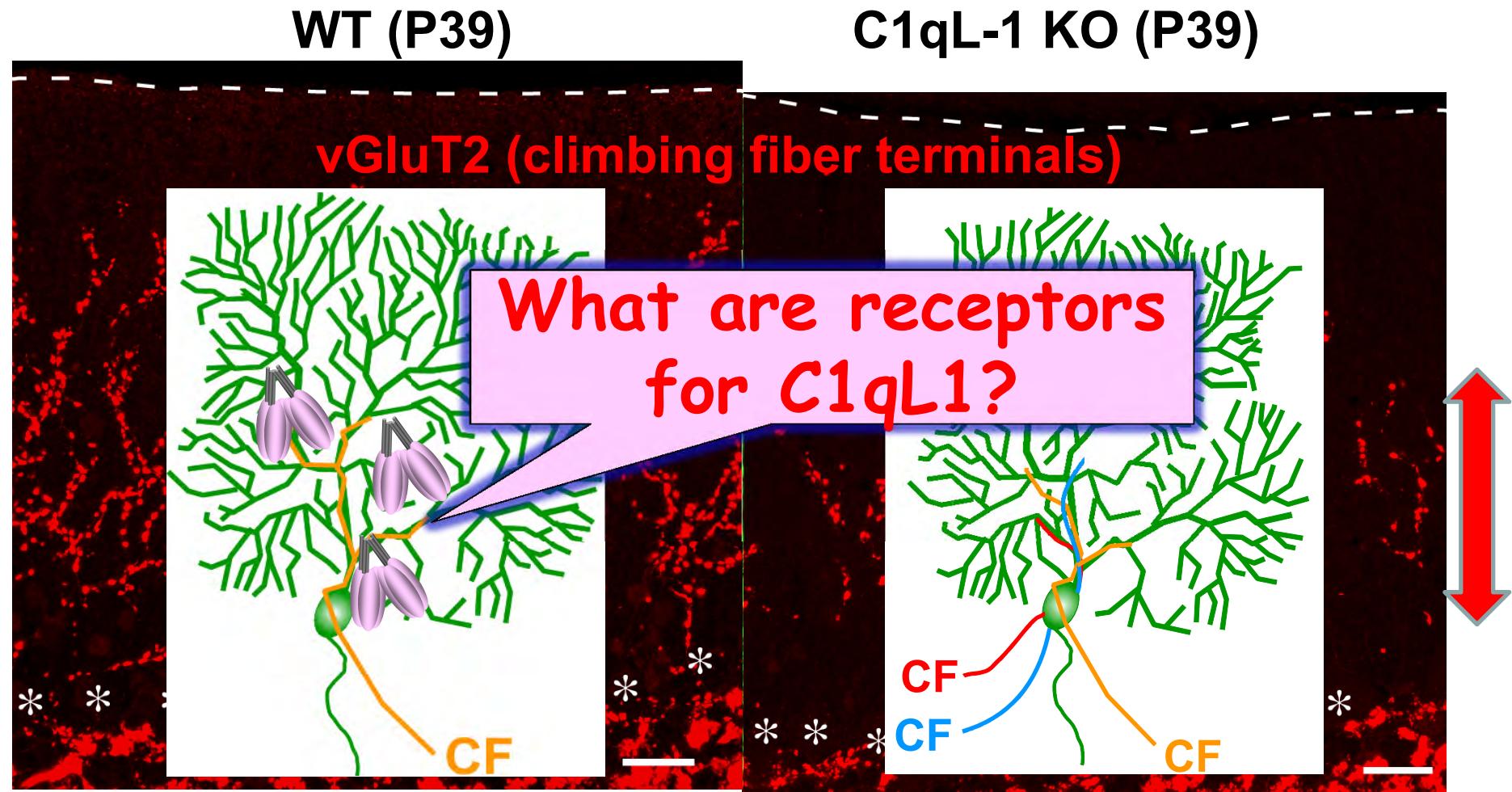
C1qL1 localizes at CF synaptic clefts (vGluT2+)



Immuno-EM (*C1qL1*/vGluT2)



Severe reduction of CF synapses in C1qL1 KO



- decreased # of CF synapses
- retracted CF territory
- multiple CFs innervate single PC



Kakegawa et al
Neuron 2015

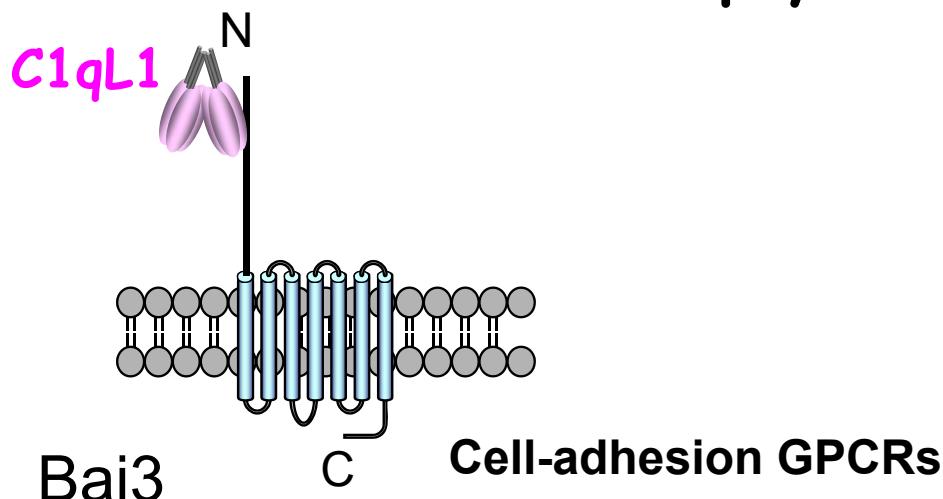
Brain Angiogenesis Inhibitor (Bai) 3: adhesion GPCRs

- Highly expressed in brain
- Pull-down assay identified **C1ql1-3 as ligands**

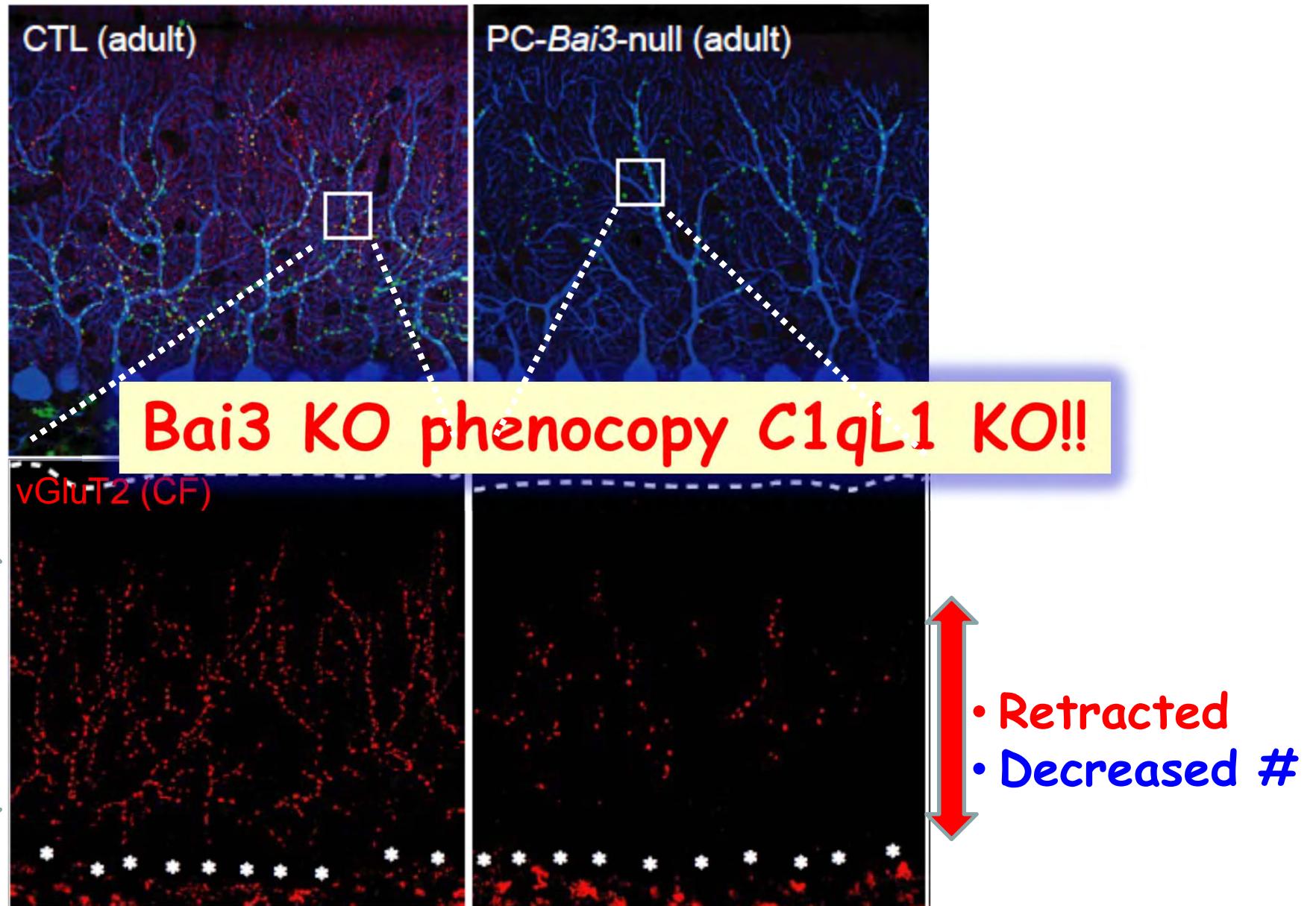
Bolliger et al, PNAS 2010

- Linked to psychiatric disorders

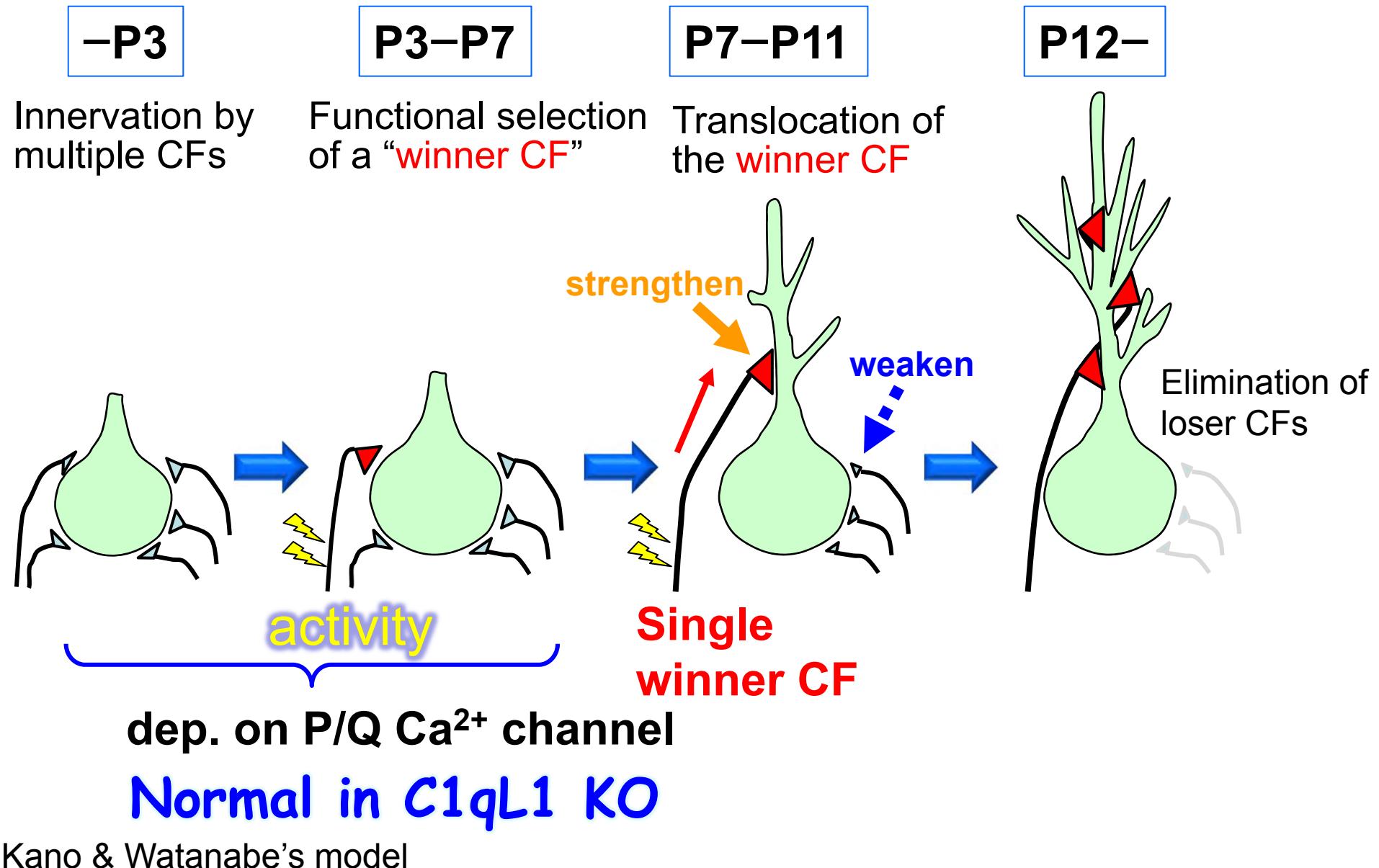
Lanoue et al, Mol. Psychiat 2013



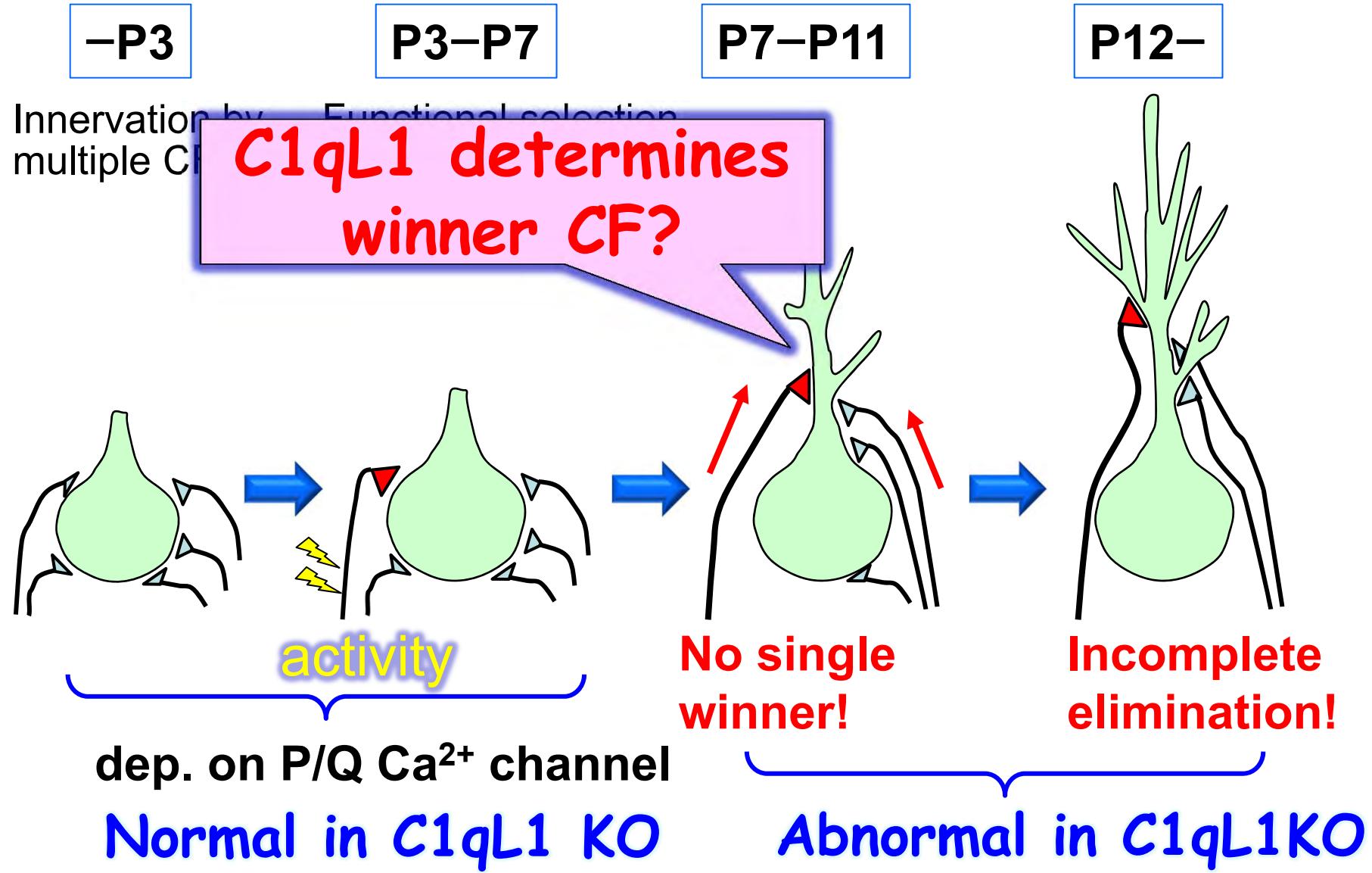
Bai3 is located at CF synapses



Formation of CF synapses during development

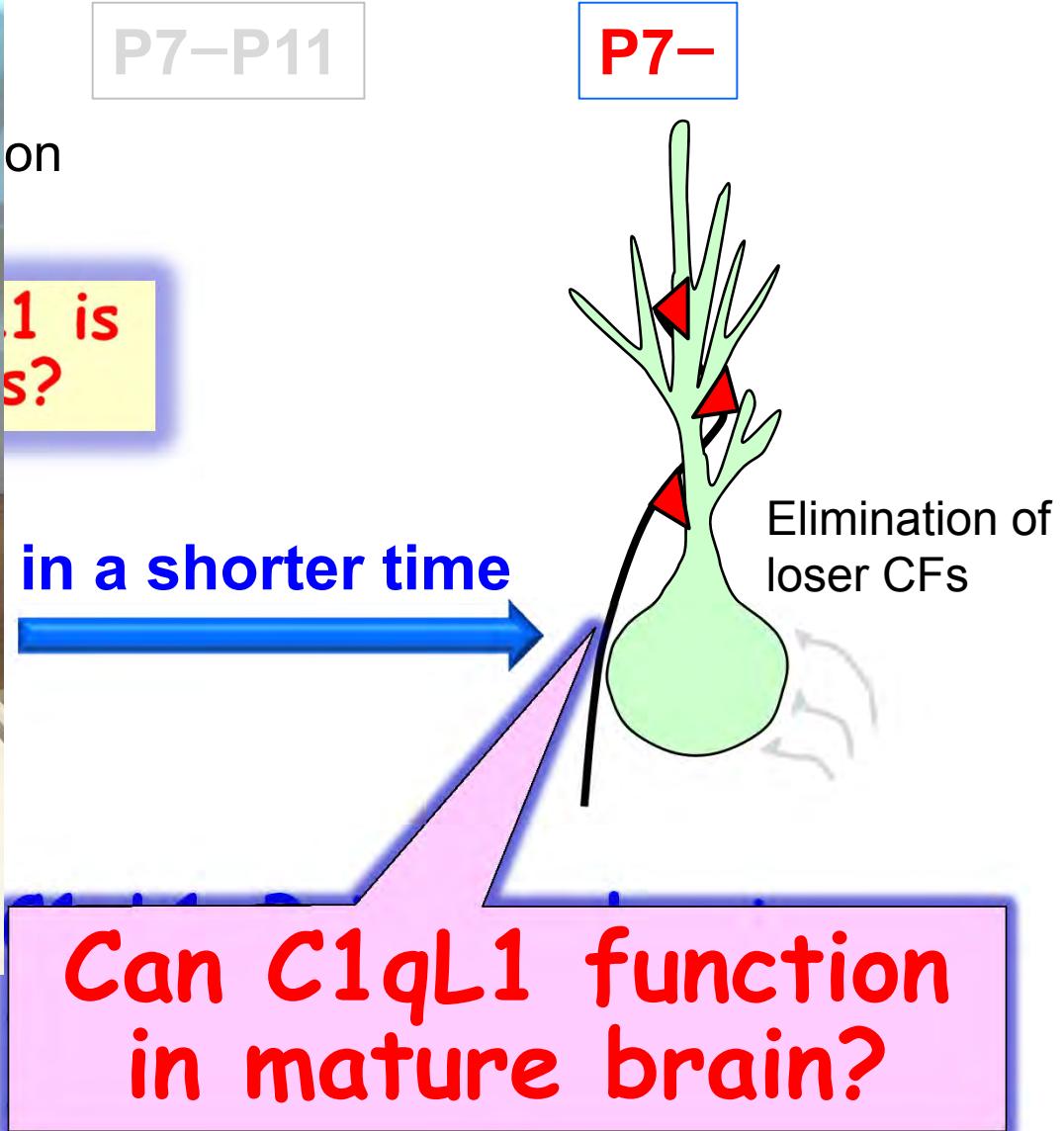


Abnormal CF synapse formation in C1qL1 KO

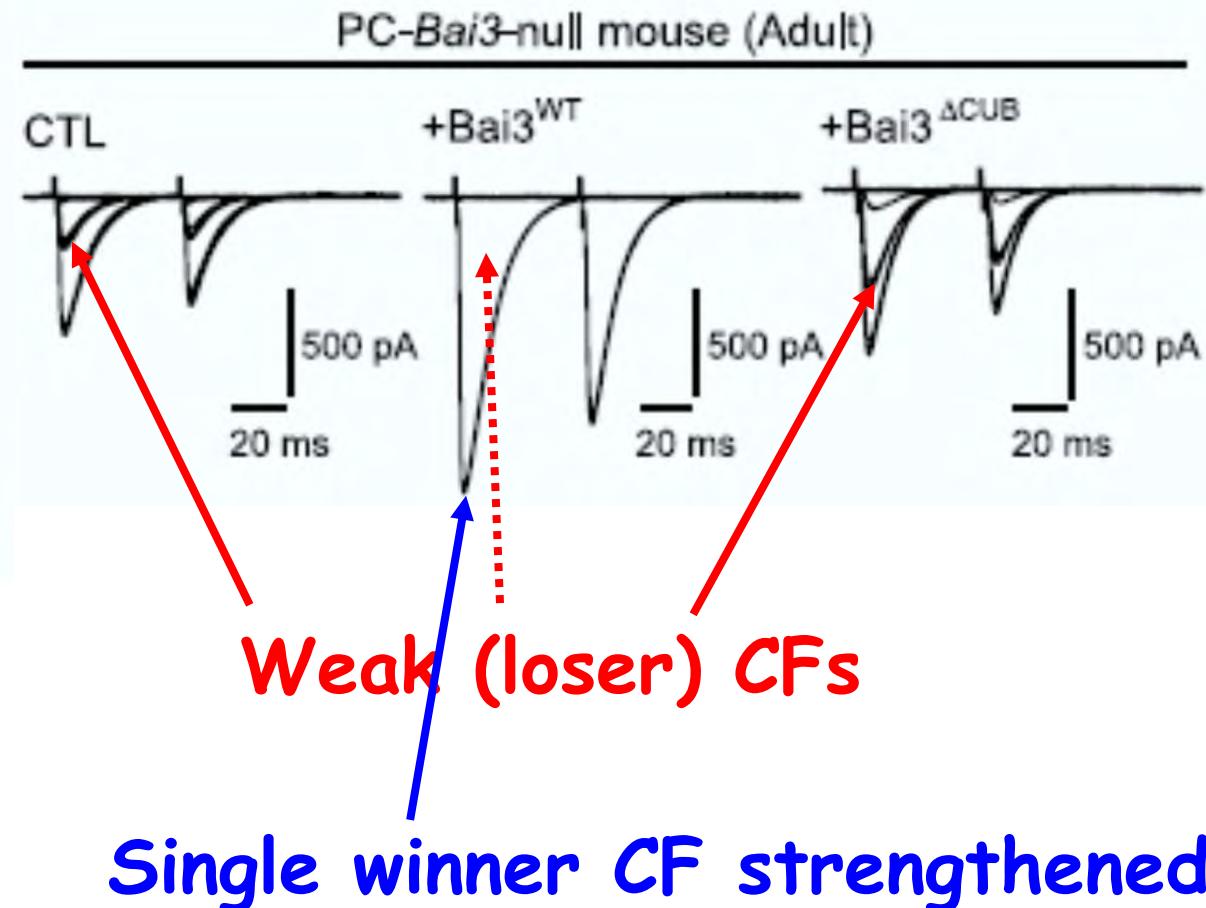
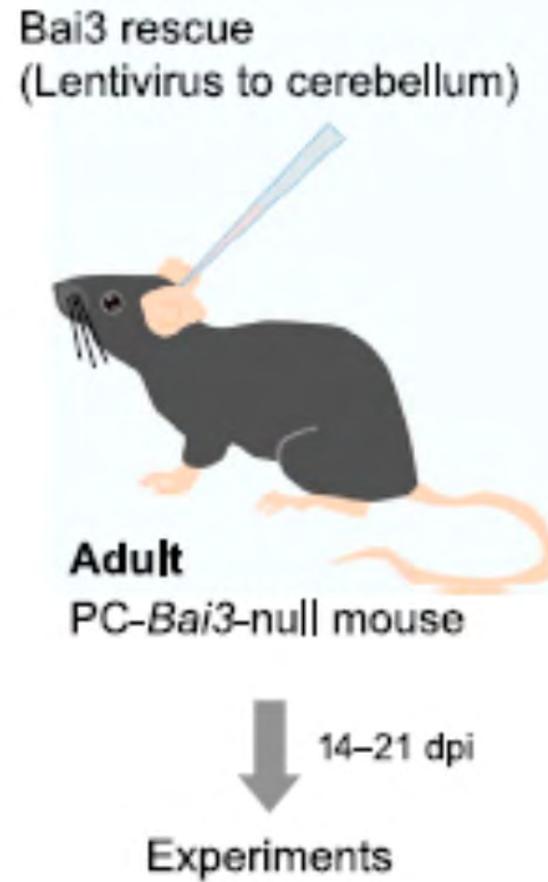


Kano & Watanabe's model

Like Shiva – "the Destroyer" and "the Creator"



C1qL1-Bai3 restores normal CF synapses in adult



"the Destroyer" and "the Creator"

Dual roles of C1qL1 in synapse maturation

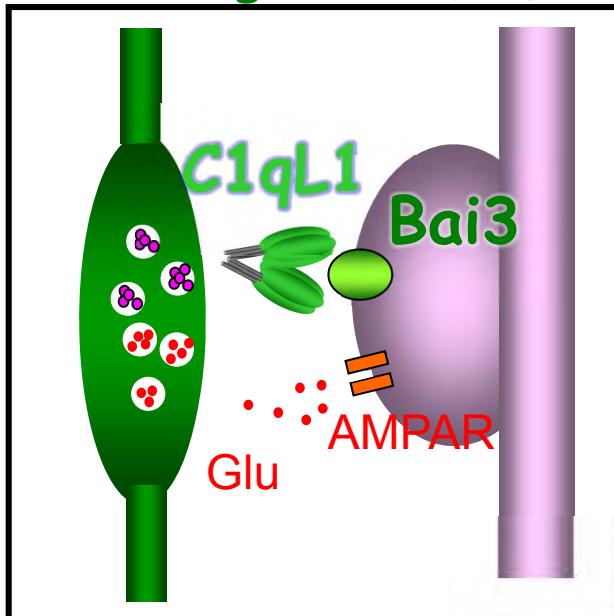
- During development
 - Strengthening of a single winner CF
 - Weakening of a looser CFs
- Even after maturation
 - Strengthening of strong CF
 - Elimination of weak CF
- Bai3 serves as a receptor



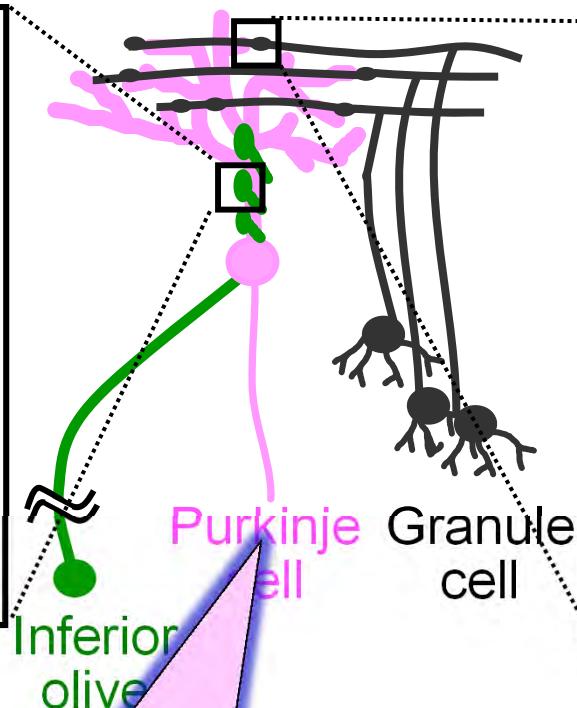
Summary

Cbln1 & C1ql1: new synaptic organizers

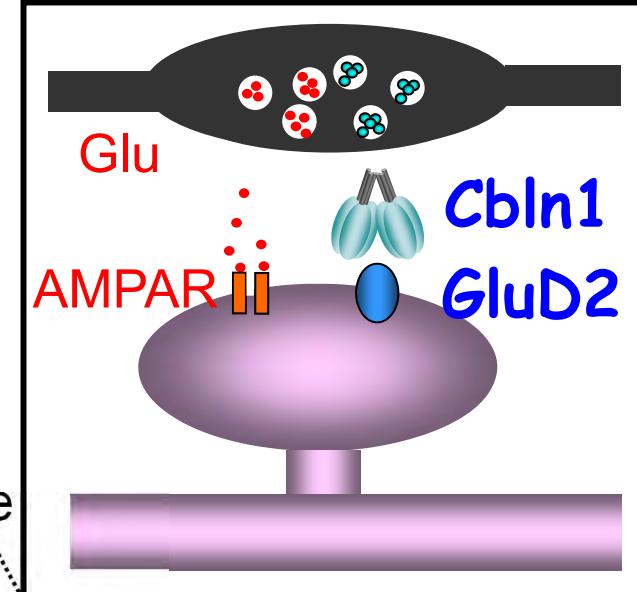
Climbing fiber (CF)



Proximal dendrites



Parallel fiber (PF)



Distal dendrites

@CF synapses

- Strengthens
- Eliminates

@PF synapses

and maintains PF

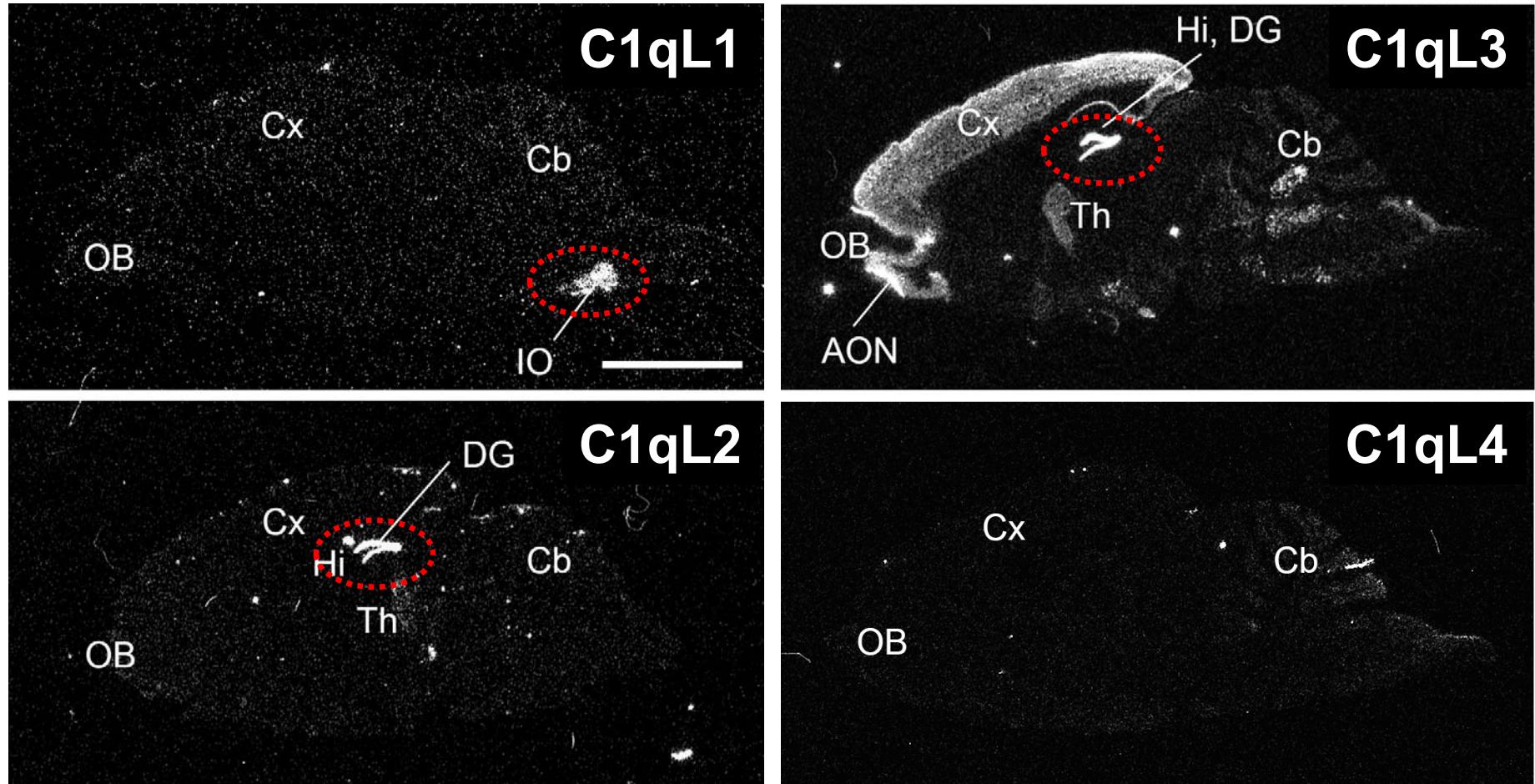
How about outside
cerebellum?

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Expression of C1qL subfamily in adult brain (ISH)

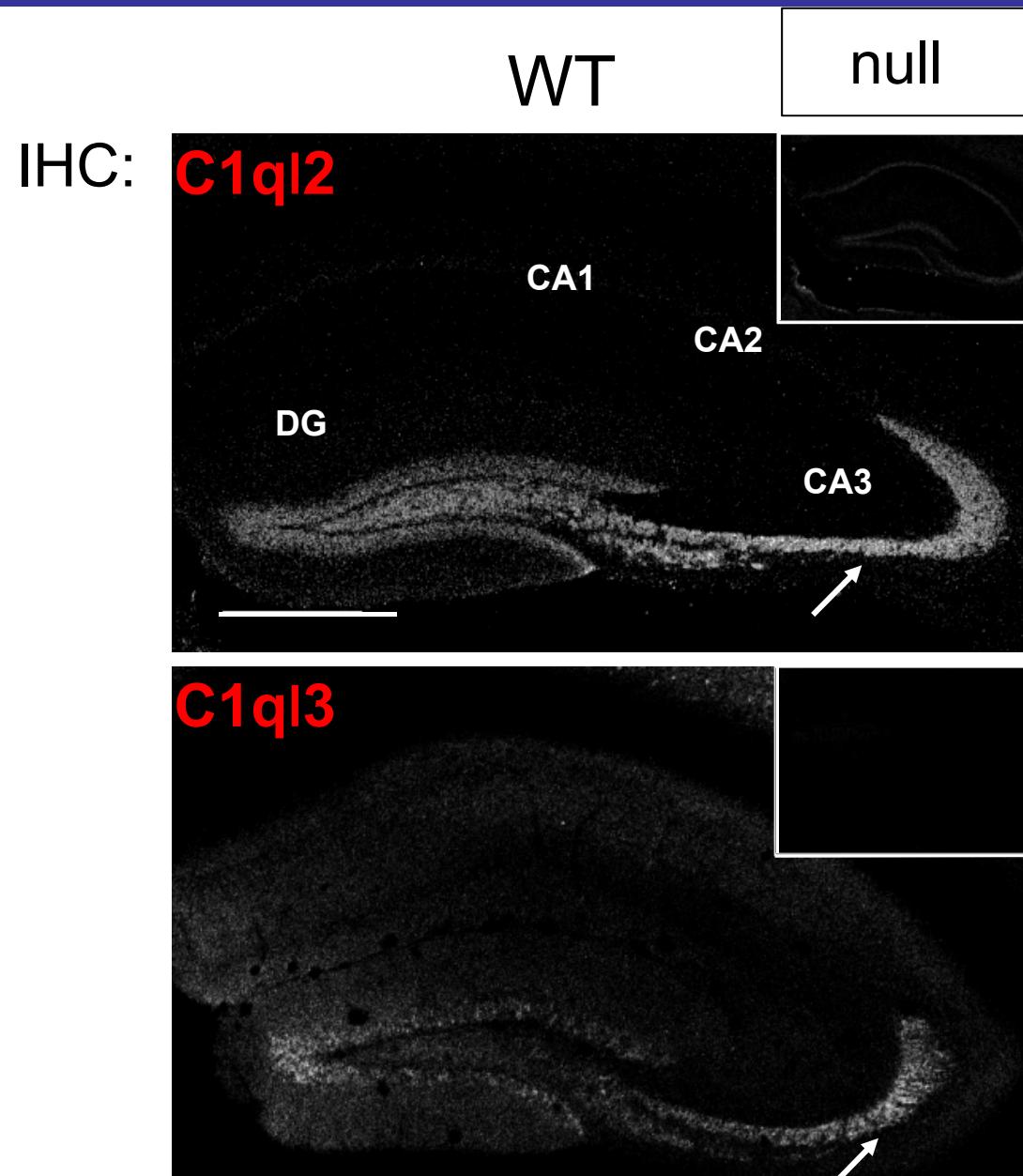


C1qL1 in inf. olive

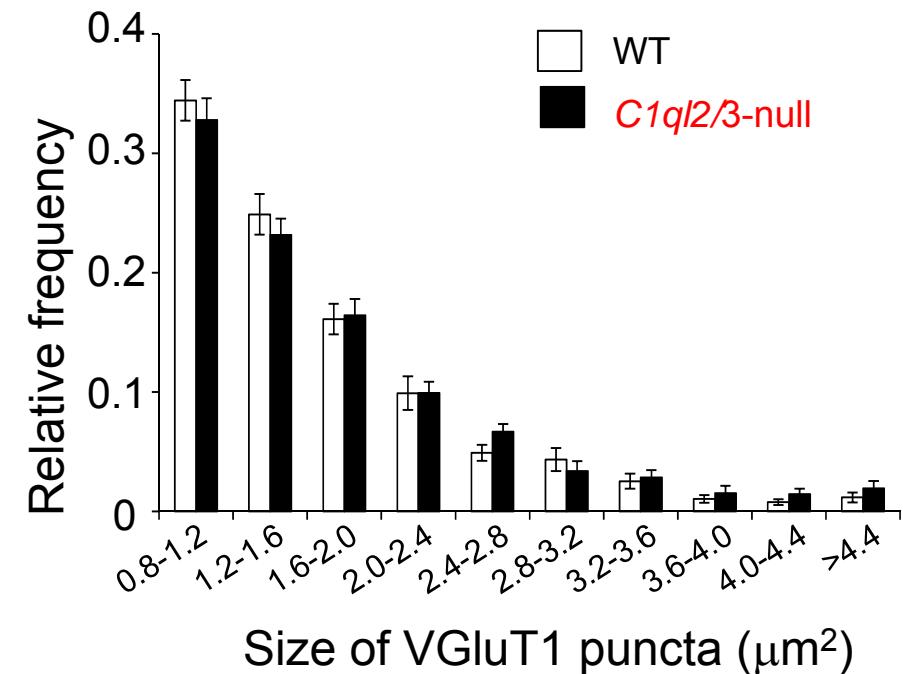
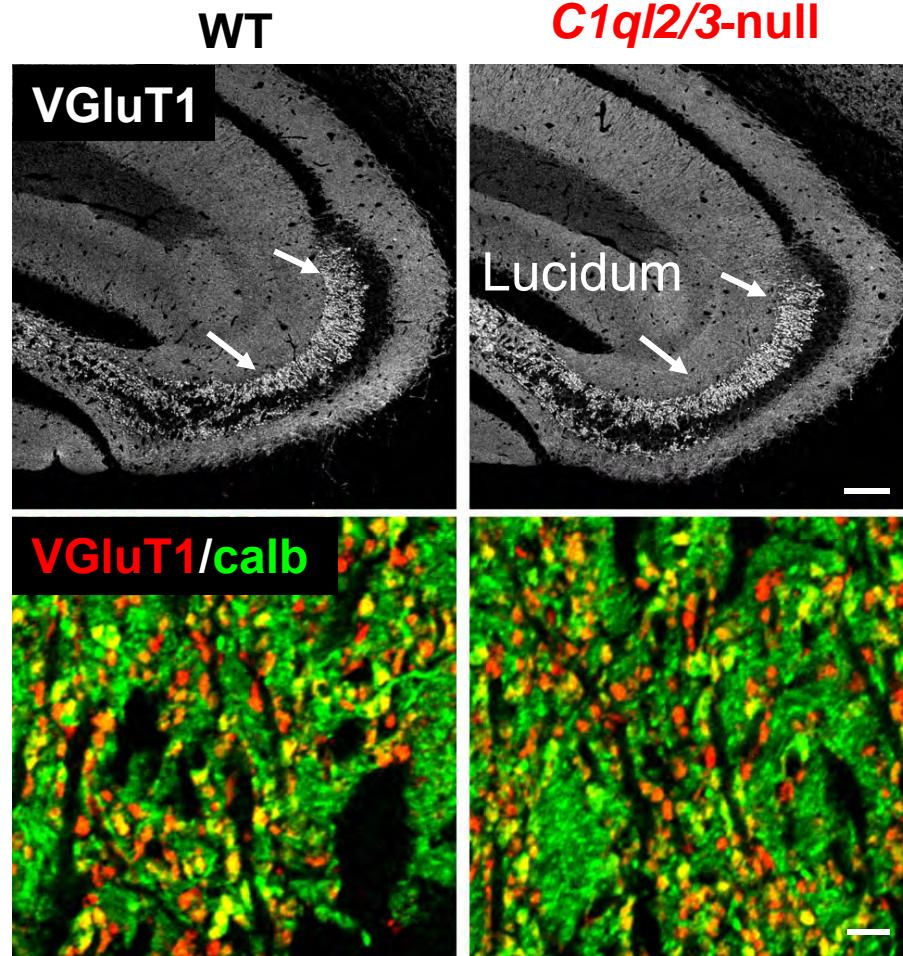
C1qL2 & 3 in the dentate gyrus

Iijima et al, *Eur J Neurosci* 2010

C1qL2 and C1qL3 localize at MF-CA3 synapses

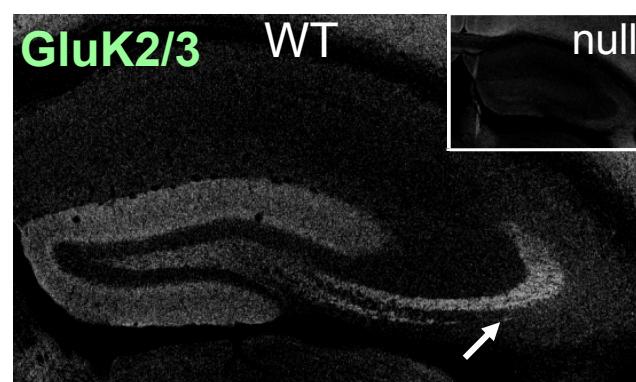
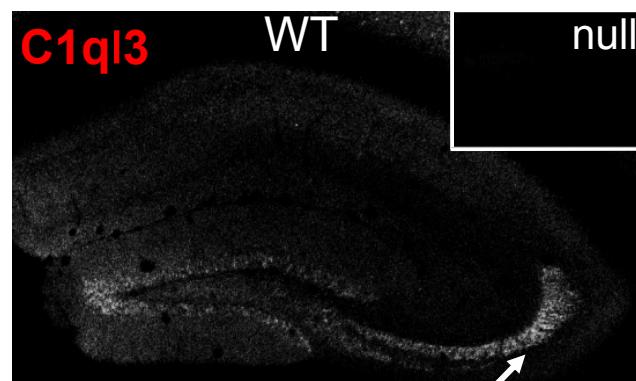
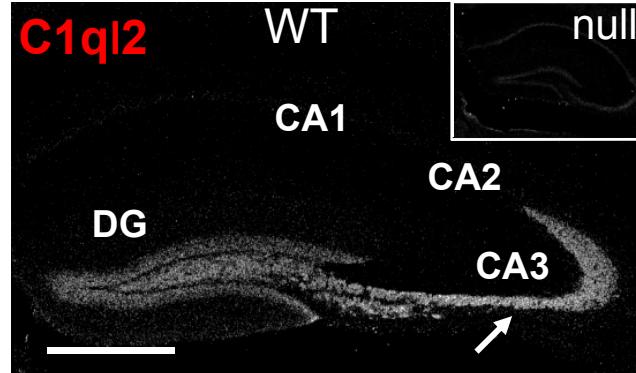


C1qL2/3 do not regulate MF–CA3 synapse formation

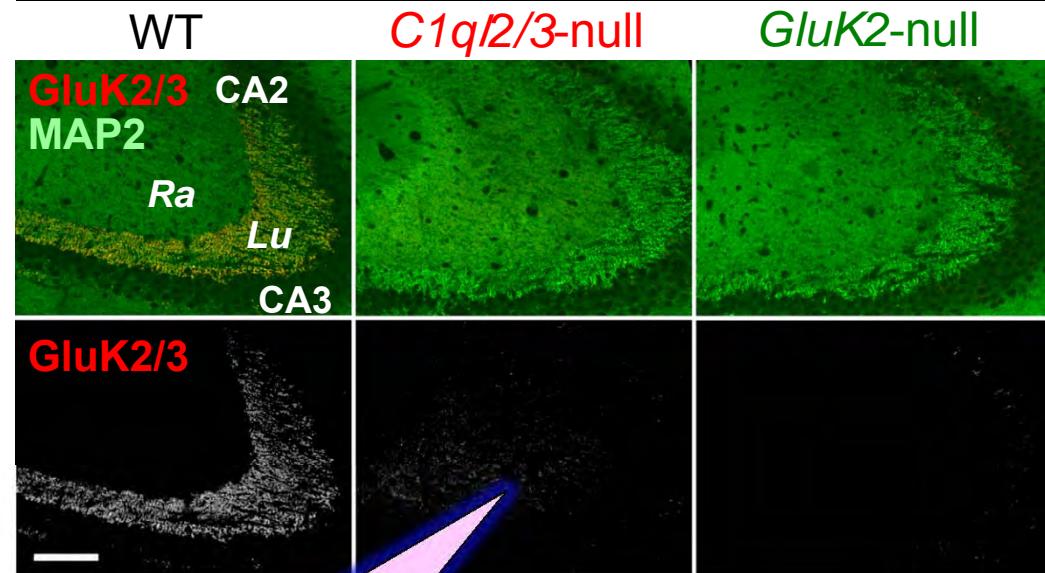


C1qL2/3 determine synaptic localization of GluK2/3

IHC:



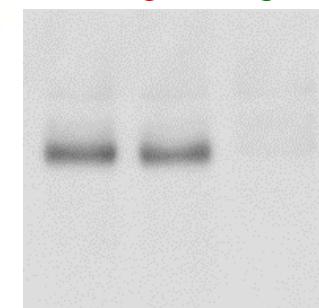
IHC: GluK2/3



No synaptic
GluK2/3!

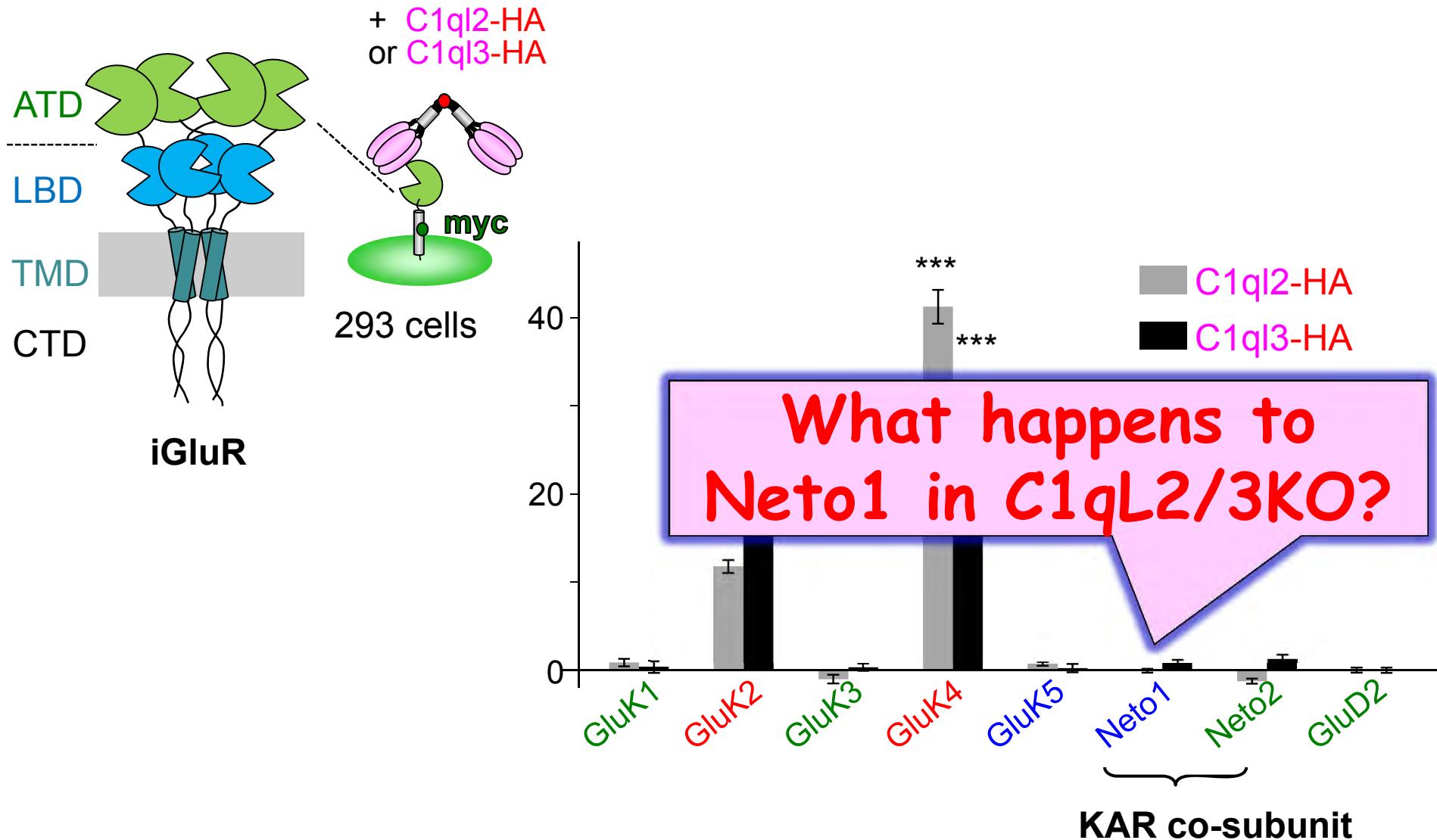
WT
C1q2/3-null
GluK2-null

CA3

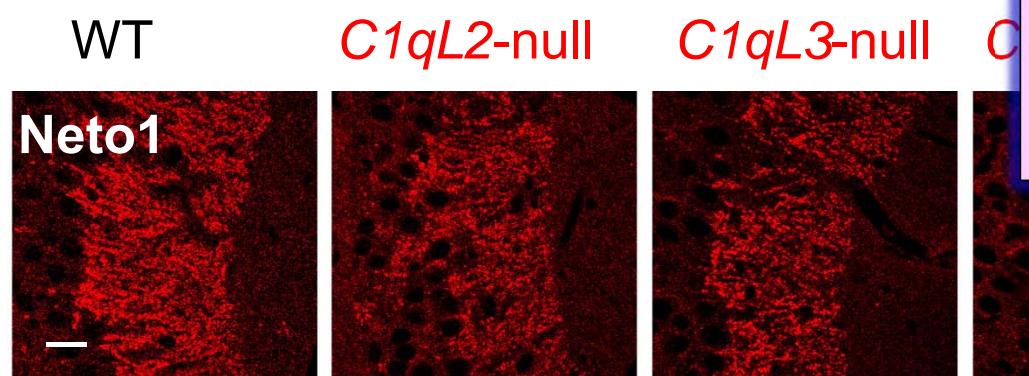


IB: GluK2/3

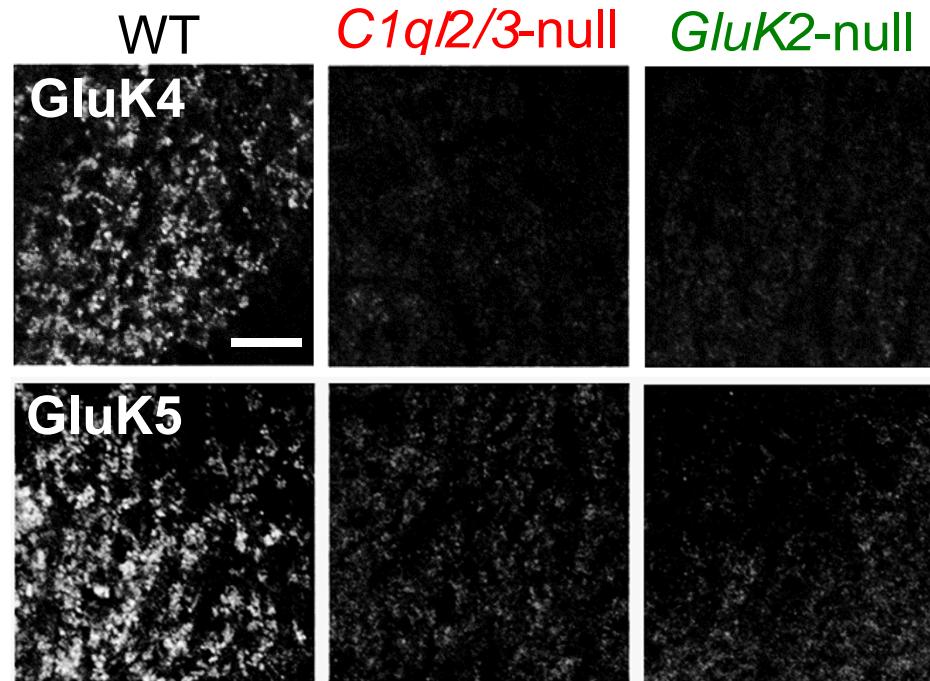
C1qL2/3 specifically bind to GluK2 and GluK4



C1qL2/3 as a master regulator of KARs



Functions of
KARs in KO?

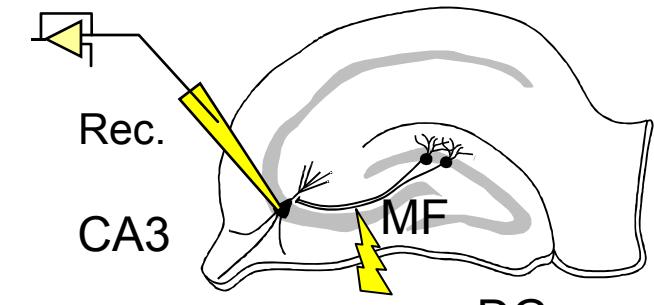


C1qL2 & C1qL3

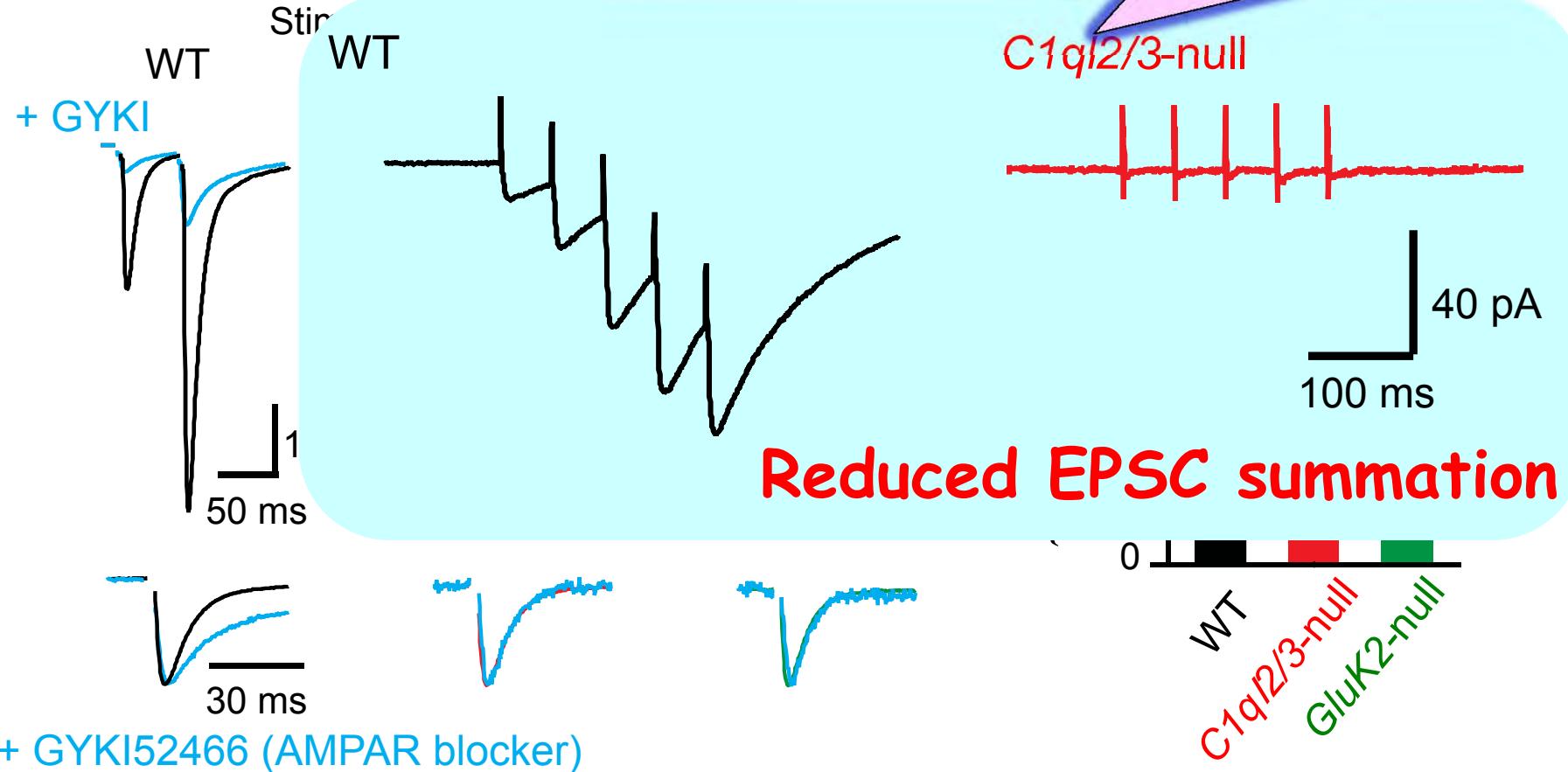
GluK2, GluK4

KARs
(Neto1, GluK5...)

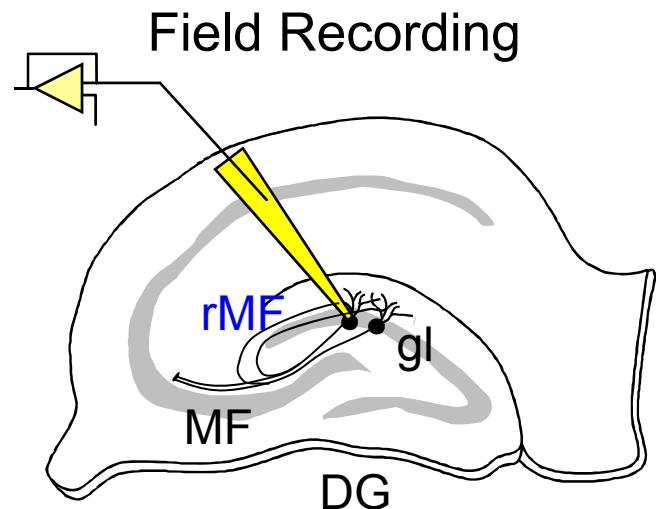
Slow KAR-dep. EPSC is missing in C1qL2/3 KO



Pathological significance
in epilepsy?

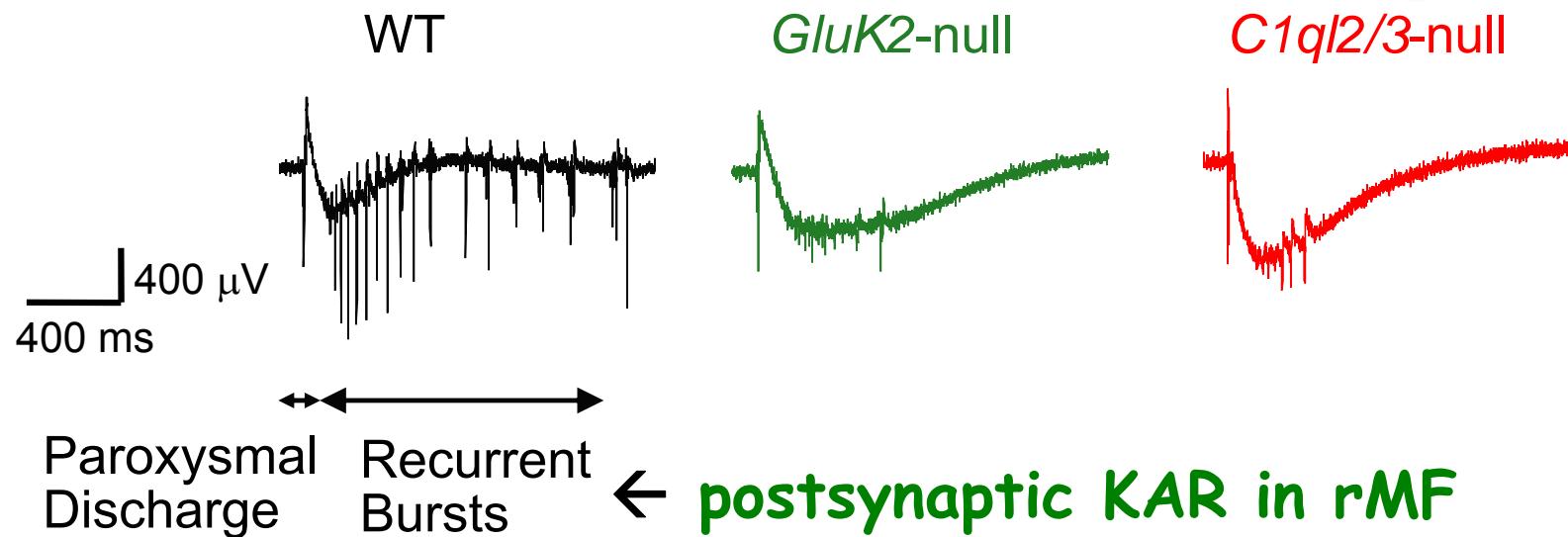


Less seizure-like activities in C1ql2/3 KO



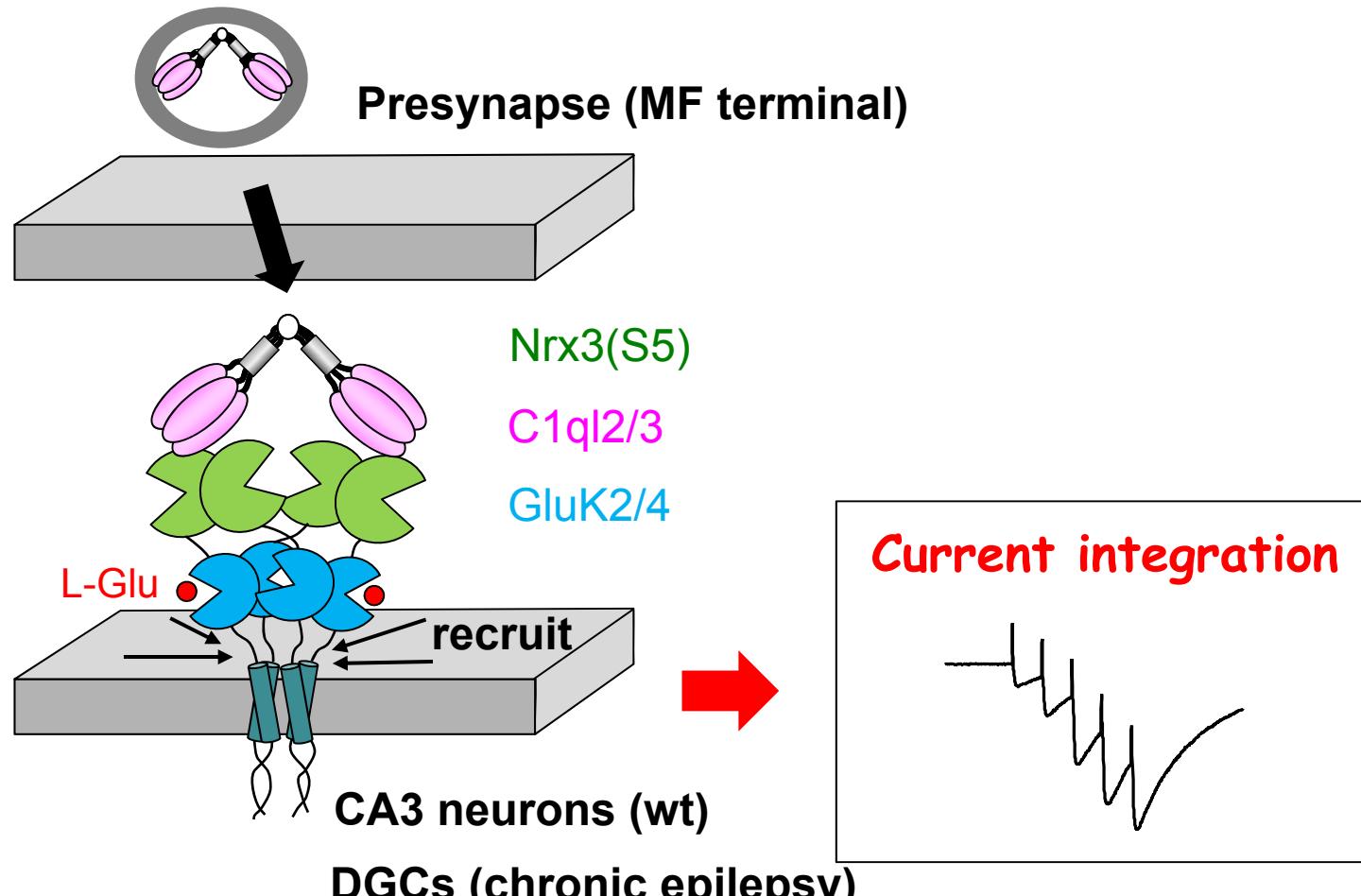
P9 Slice culture
→ + Pilocarpine 5 div for 2 d
→ Record at 9-12 div

MF sprouting w/o postsynaptic KARs!!



Summary

C1ql2/3 recruits KARs at MF–CA3 synapses



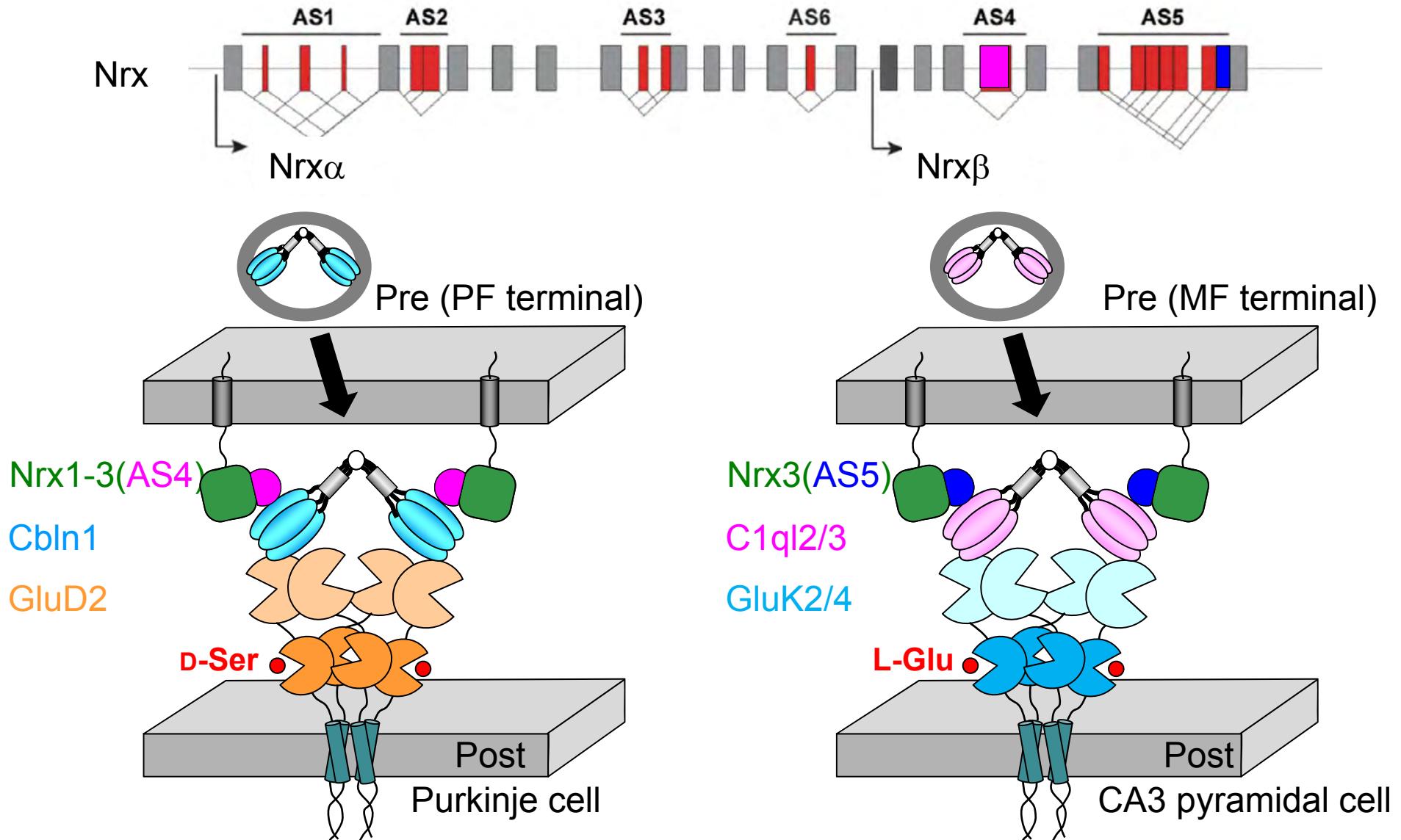
Matsuda et al *Neuron*, 2016

Menu

Bridge Over Troubled Synapses —シナプスに架ける橋

- Cbln1 as a prototype of C1q family
- C1q-like 1 (C1qL1)—Yet another synapse organizer
- C1q family in the hippocampus
- How is C1q family regulated trans-synaptically?

Cbln1 and C1qL2/3 bind to specific Nrx isoforms

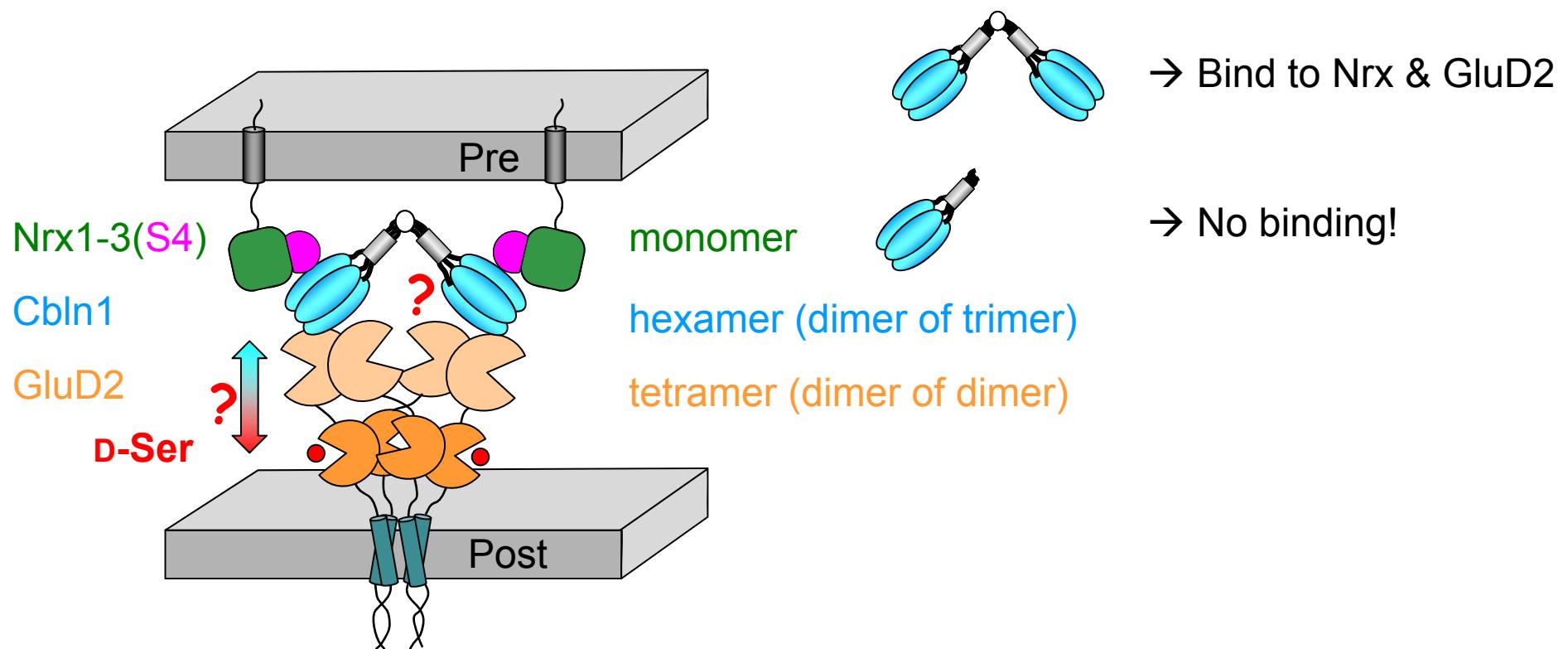


Matsuda et al, *Eur J Neurosci* 2011

Matsuda et al, *Neuron* 2016

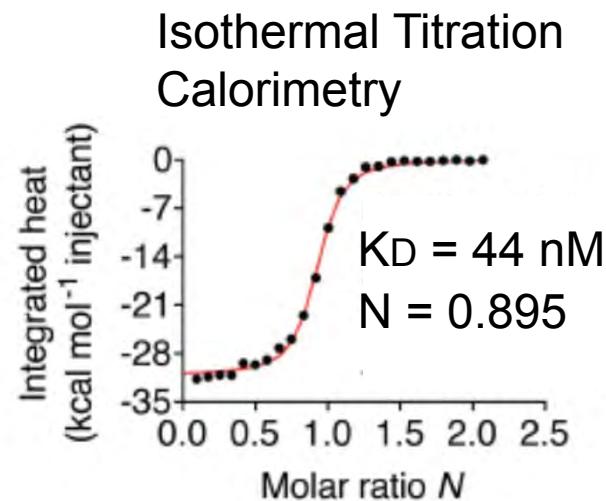
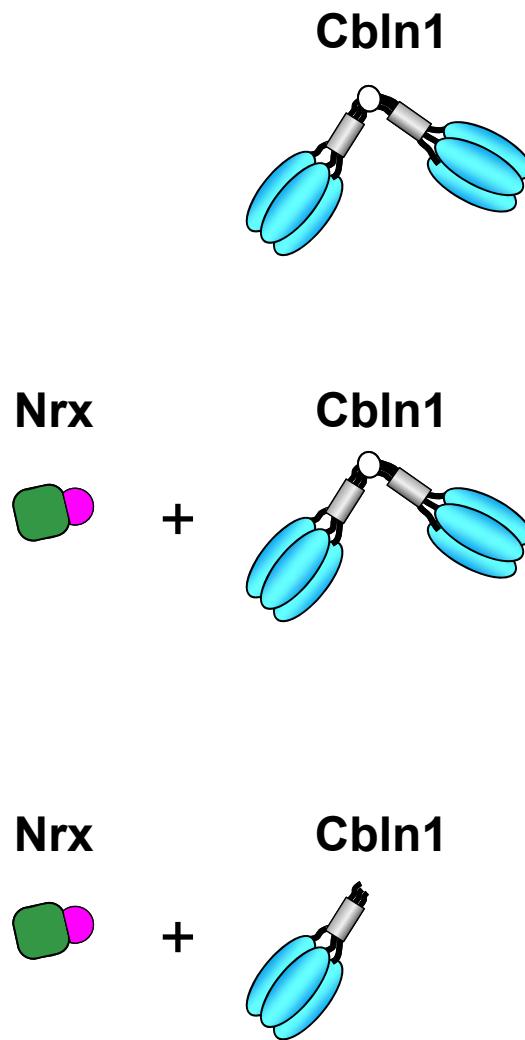
Cbln1 and C1qL2/3 bind to specific Nrx isoforms

- Symmetry mismatch: how is hexameic Cbln1 recognized?

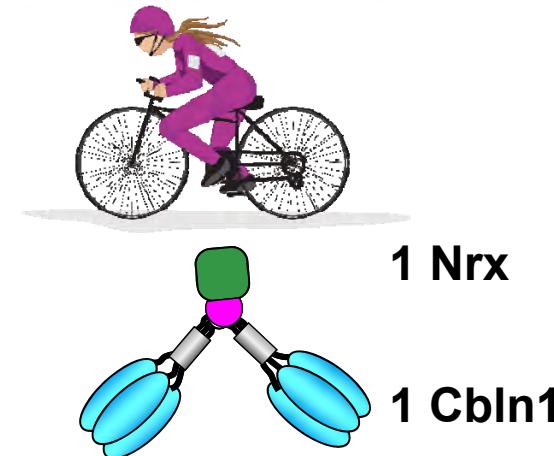
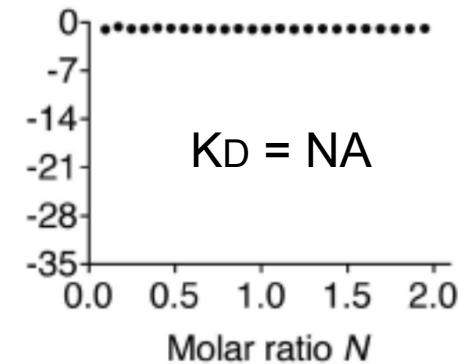
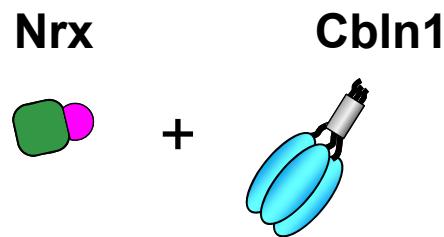
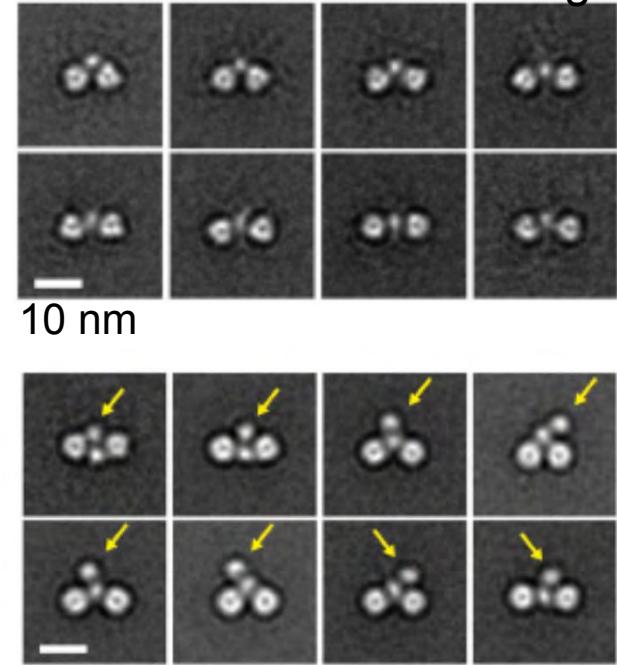


- Allosteric interaction? Cbln1 binding vs. D-Ser binding?

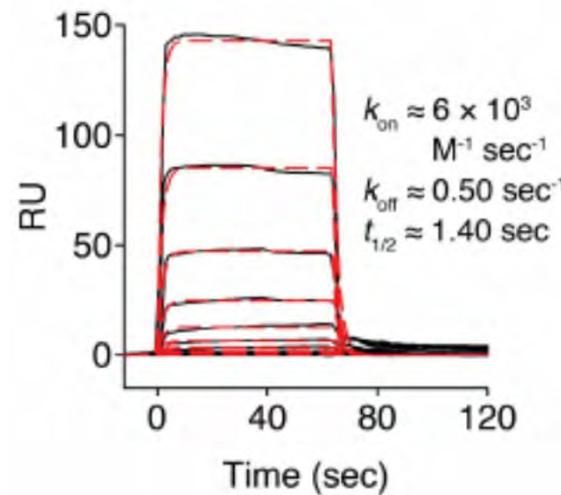
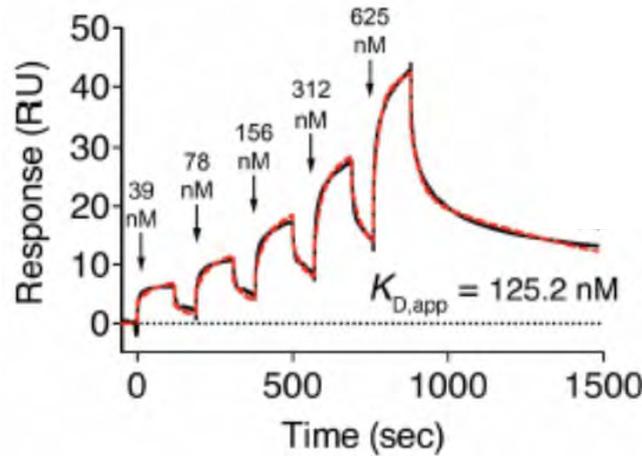
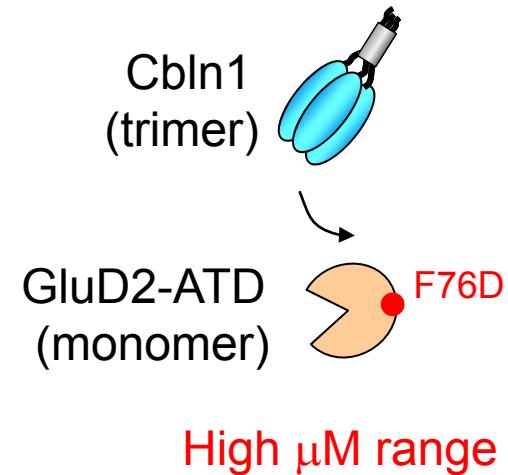
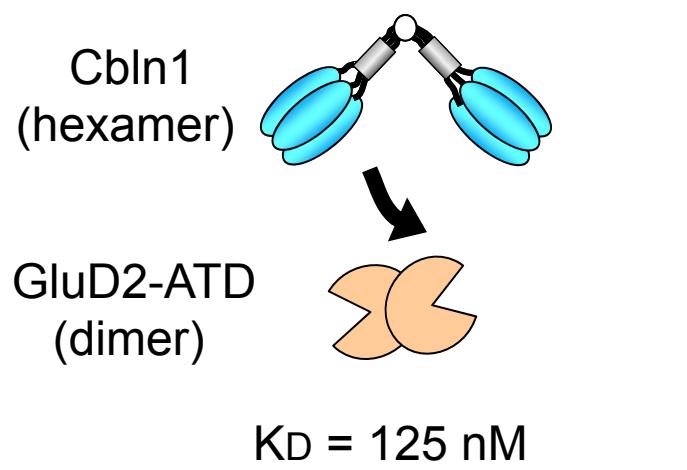
1 Nrx binds to 1 Cbln1 hexamer



Negative –stain EM class average

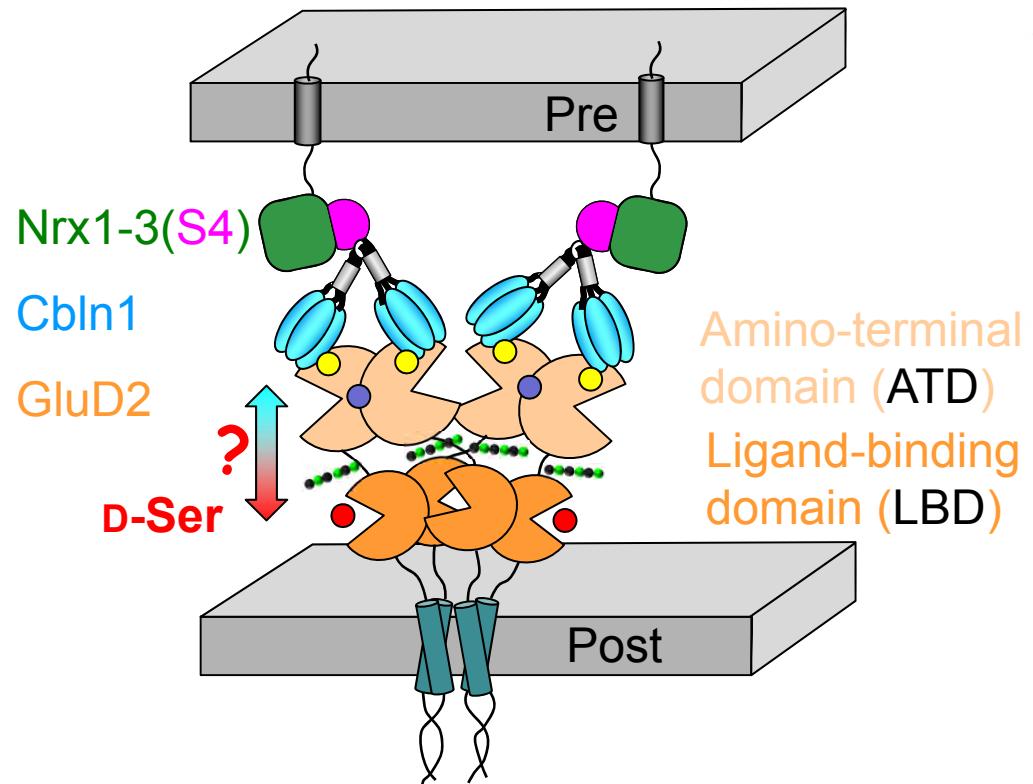


Cbln1 trimer binds to GluD2 ATD monomer



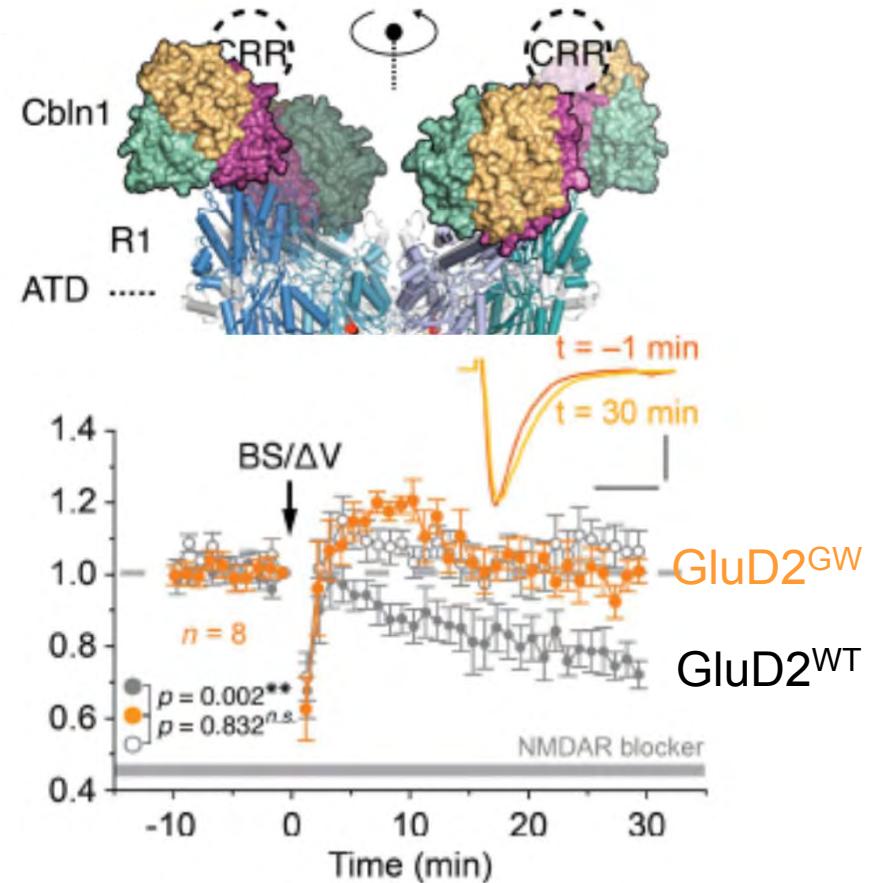
“Avidity” enhances Cbln1 - GluD2 binding

D-Ser signaling requires Cbln1 binding to GluD2



- **Allosteric interaction?**

- ATD-LBD glycan wedge (GluD2^{GW})
- No Cbln1 binding (GluD2^{ΔCbln1})
- Monomeric ATD (GluD2^{mono})



D-Ser-dependent LTD was impaired!

Elegheert et al *Science* 2016

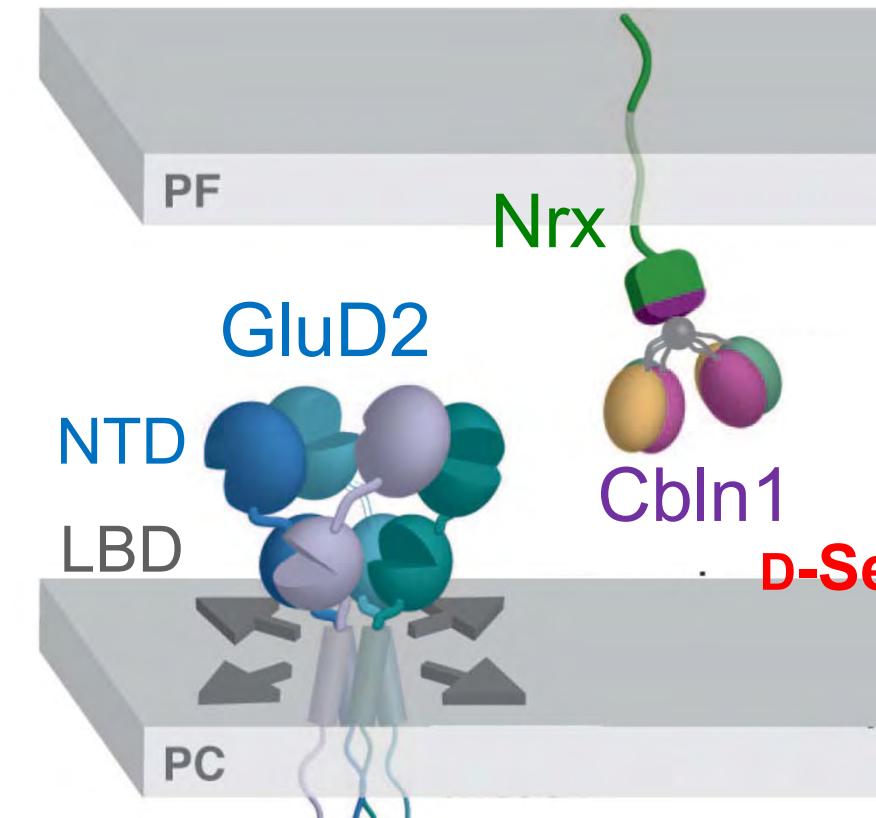
Summary

Structural paradigm for transsynaptic Nrx-Cbln1-GluD2 signaling

Parallel fiber
(Granule cell axons)

Avidity-
enhanced binding

Ito-Ishida,
Neuron, 2012



Parallel fiber

Purkinje cell

Allosteric
interaction

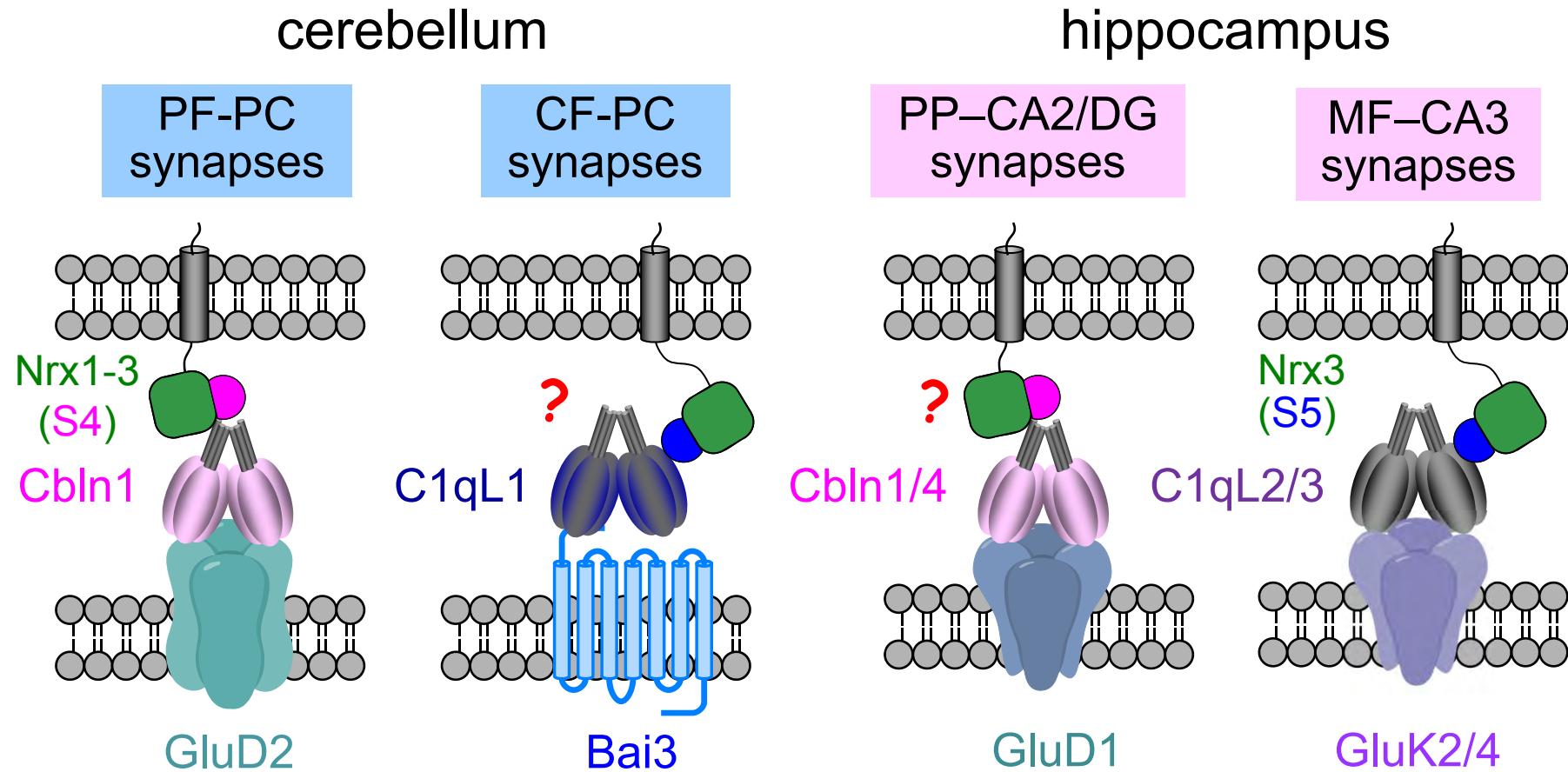
Purkinje cell
dendrite

Elegheert, *Science*, 2016

LTD
regulation

Summary

C1q family: Synaptic Ménage à Trois



Cblns
C1qls

- **Synapse formation/maturation**
- **Synapse elimination**
- **Regulation of postsynaptic iGluRs**

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Dr. Masahiko Watanabe
Hokkaido Univ.



Dr. Kenji Sakimura
Niigata Univ.



Dr. Radu Aricescu
Univ Oxford, UK

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