Plasticity of Circuit Formation and Olfactory Perception in Mice

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Cargèse Workshop

Corsica, France

Olfactory Perception

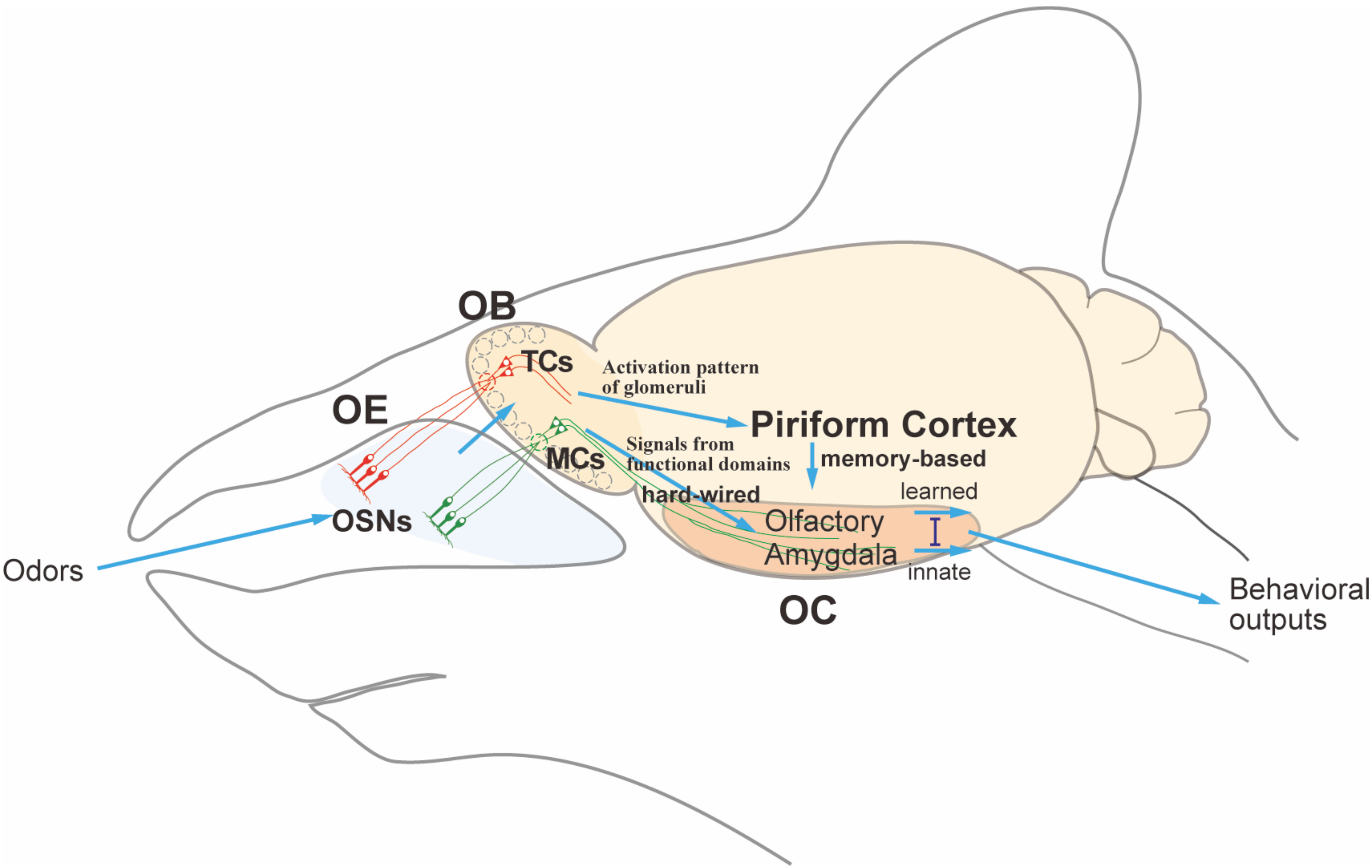
Attraction

like

Fear/Aversion

dislike

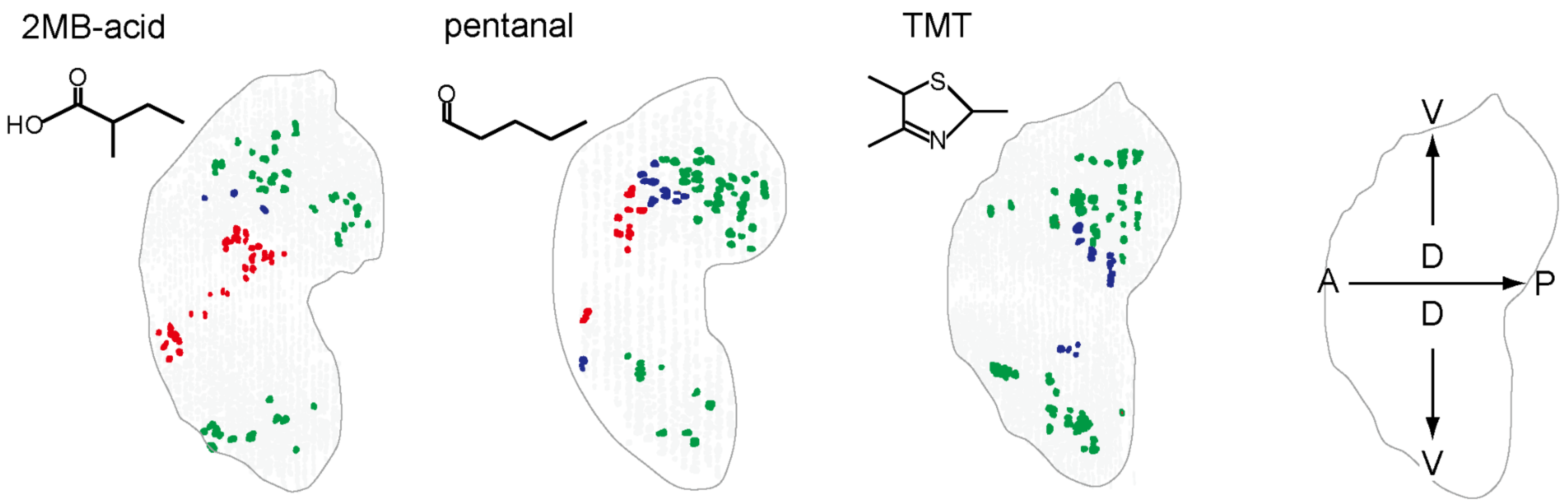
Mouse Olfactory System



Mori & Sakano, ***Annu. Rev. Physiol.*** (2021)

Combinatorial Patterns of Activated Glomeruli

(Odor map)



Olfactory Map Formation

One neuron – one receptor rule

One glomerulus – one receptor rule

Mori &Sakano, ***Annu. Rev. Neurosci.*** (2011)

Olfactory Map Formation

I. Single gene choice (One neuron – one receptor rule)

1. Stochastic gene activation by *cis*-acting enhancer elements

(Serizawa et al., *Nat. Neurosci.*, 2000; *Science*, 2003; Nishizumi et al., *PNAS*, 2008)

2. Negative-feedback regulation by functional ORs

(Serizawa et al., *Science*, 2003)

II. OR-instructed axonal projection (One glomerulus – one receptor rule)

1. A-P axis: Intrinsic receptor activity

(Imai et al., *Science*, 2006; 2009)

2. D-V axis: Positional information of OSNs

(Miyamichi et al., *J. Neurosci.*, 2005; Takeuchi et al., *Cell*, 2010)

3. Glomerular segregation: Spontaneous neuronal activity

(Serizawa et al., *Cell*, 2006; Nakashima et al., *Cell*, 2013)

Interpretation of Olfactory Maps

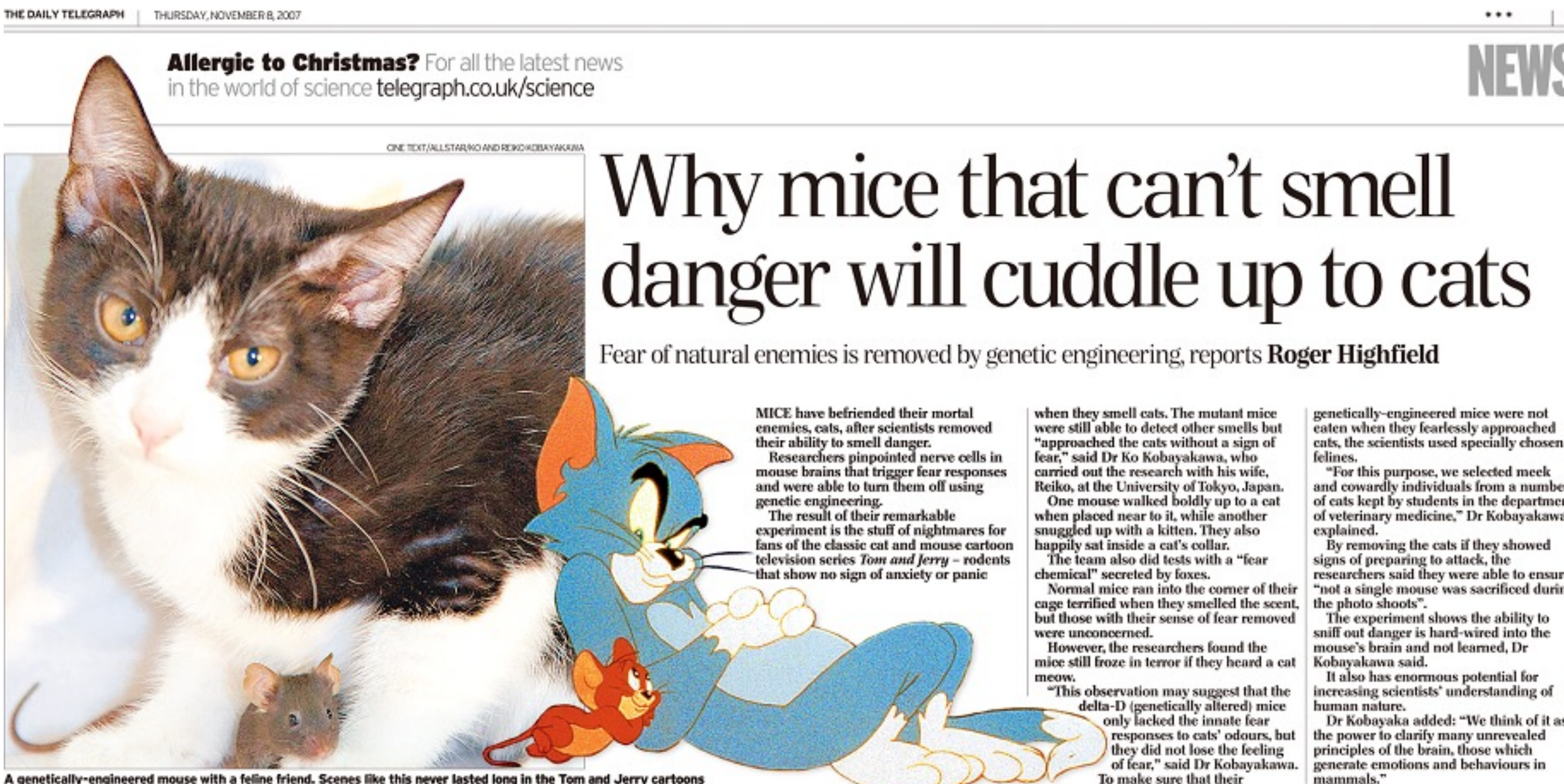
I. **Pattern recognition of activated glomeruli**

   (for learned decisions)

II. **Stimulation of functional domains**

   (for innate decisions)

Innate Decision is Independently Made from Learned Decision



THE DAILY TELEGRAPH | THURSDAY, NOVEMBER 8, 2007 | 5

NEWS

Why mice that can't smell danger will cuddle up to cats

Fear of natural enemies is removed by genetic engineering, reports **Roger Highfield**

MICE have befriended their mortal enemies, cats, after scientists removed their ability to smell danger.

Researchers pinpointed nerve cells in mouse brains that trigger fear responses and were able to turn them off using genetic engineering.

The result of their remarkable experiment is the stuff of nightmares for fans of the classic cat and mouse cartoon television series *Tom and Jerry* – rodents that show no sign of anxiety or panic when they smell cats. The mutant mice were still able to detect other smells but "approached the cats without a sign of fear," said Dr Ko Kobayakawa, who carried out the research with his wife, Reiko, at the University of Tokyo, Japan.

One mouse walked boldly up to a cat when placed near to it, while another snuggled up with a kitten. They also happily sat inside a cat's collar.

The team also did tests with a "fear chemical" secreted by foxes.

Normal mice ran into the corner of their cage terrified when they smelled the scent, but those with their sense of fear removed were unconcerned.

However, the researchers found the mice still froze in terror if they heard a cat meow.

"This observation may suggest that the delta-D (genetically altered) mice only lacked the innate fear responses to cats' odours, but they did not lose the feeling of fear," said Dr Kobayakawa.

To make sure that their genetically-engineered mice were not eaten when they fearlessly approached cats, the scientists used specially chosen felines.

"For this purpose, we selected meek and cowardly individuals from a number of cats kept by students in the department of veterinary medicine," Dr Kobayakawa explained.

By removing the cats if they showed signs of preparing to attack, the researchers said they were able to ensure "not a single mouse was sacrificed during the photo shoots".

The experiment shows the ability to sniff out danger is hard-wired into the mouse's brain and not learned, Dr Kobayakawa said.

It also has enormous potential for increasing scientists' understanding of human nature.

Dr Kobayaka added: "We think of it as the power to clarify many unrevealed principles of the brain, those which generate emotions and behaviours in mammals."

A genetically-engineered mouse with a feline friend. Scenes like this never lasted long in the Tom and Jerry cartoons

Kobayakawa et al., ***Daily Telegraph*** (2007)

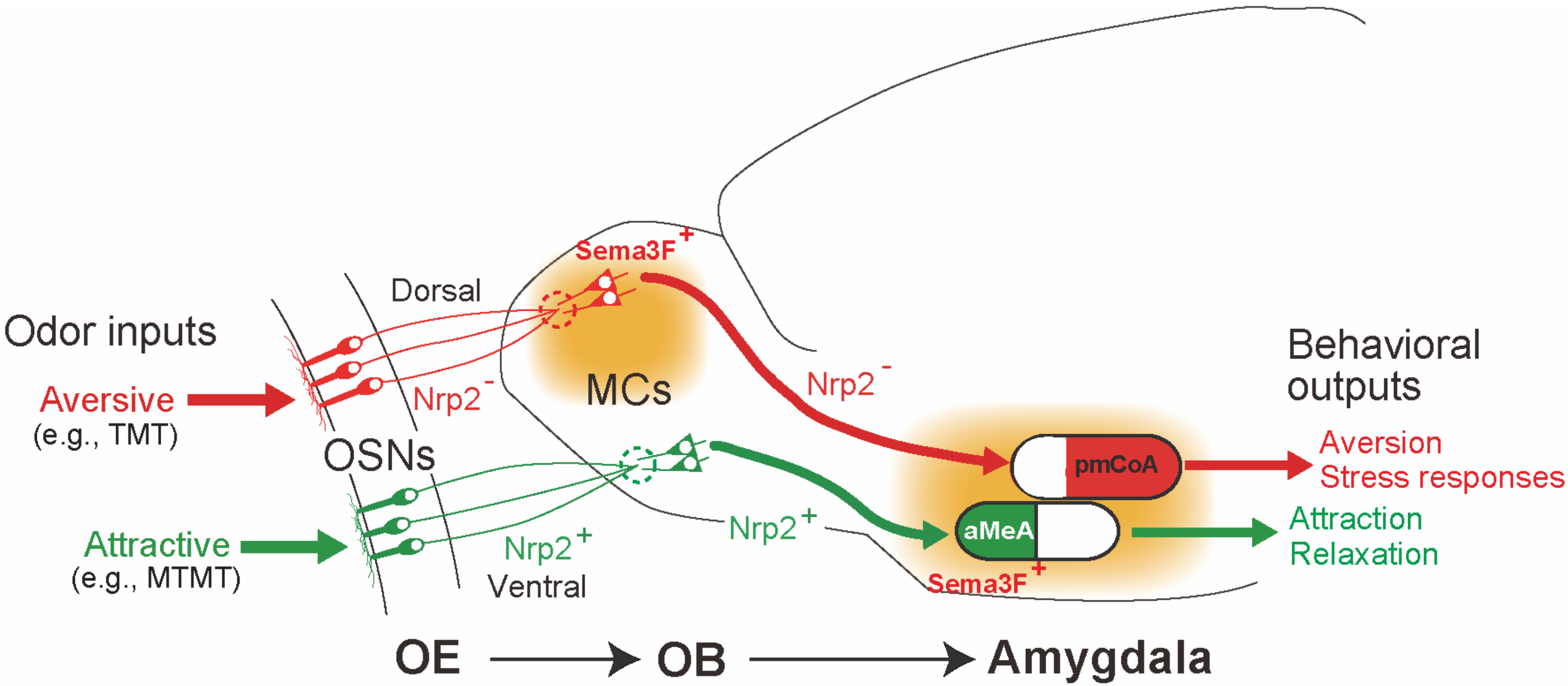
Kobayakawa et al., ***Nature*** (2007)

Two Types of Olfactory Decisions Made during Respiration

	Innate	Learned
Olfactory signals	Functional domains	Pattern of odor map
Projection neuron	MCs	TCs
Neural pathway	Direct (to Amygdala)	Multi-synaptic (via AON)
Respiratory phase	Exhalation	Inhalation

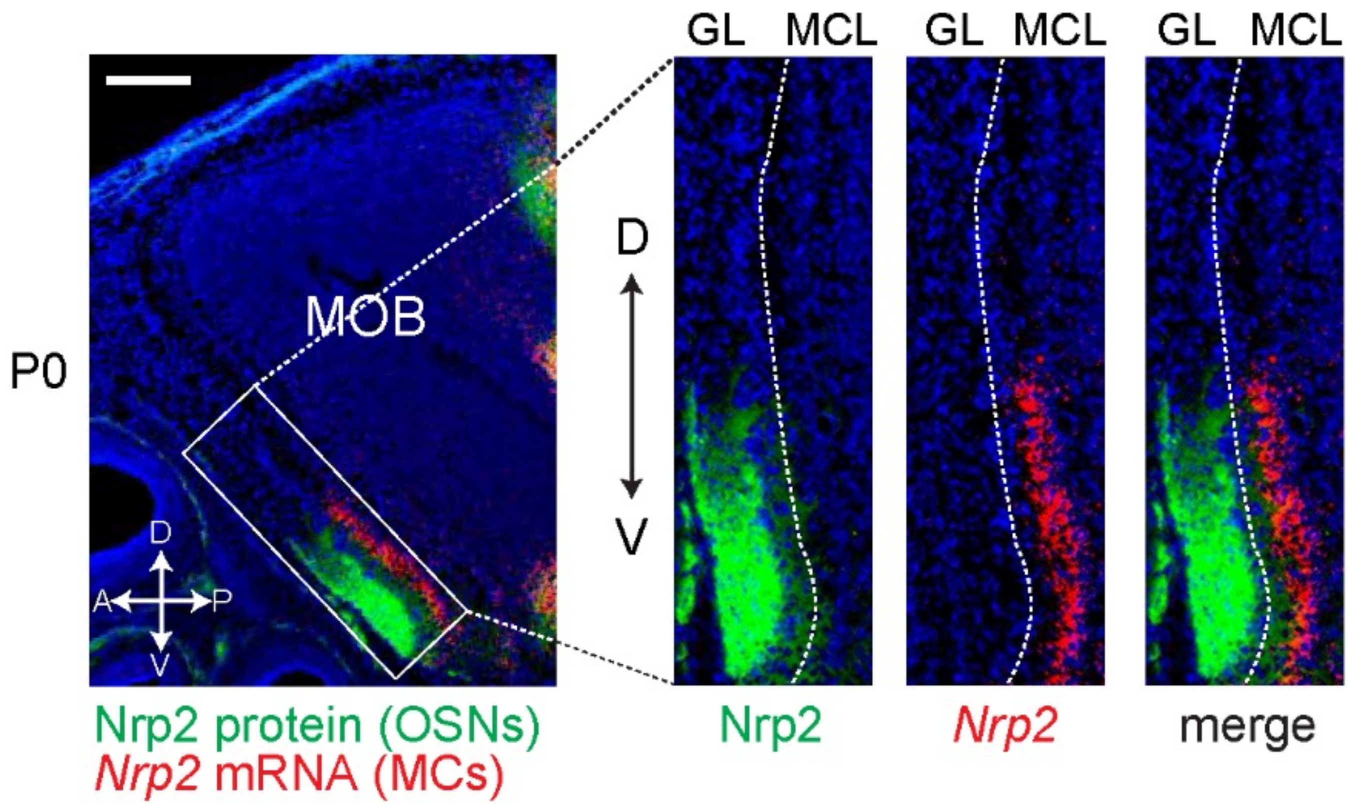
Mori ＆Sakano, ***Front. Neural Circuits*** (2022)

Innate Olfactory Circuits



Takeuchi et al., ***Cell*** (2016)
Inokuchi et al., ***Nat. Commun.*** (2017)
Nishizumi et al., ***Commun. Biol.*** (2019)

Coregulation of OSN Projection and Migration of Projection Neurons by Nrp2

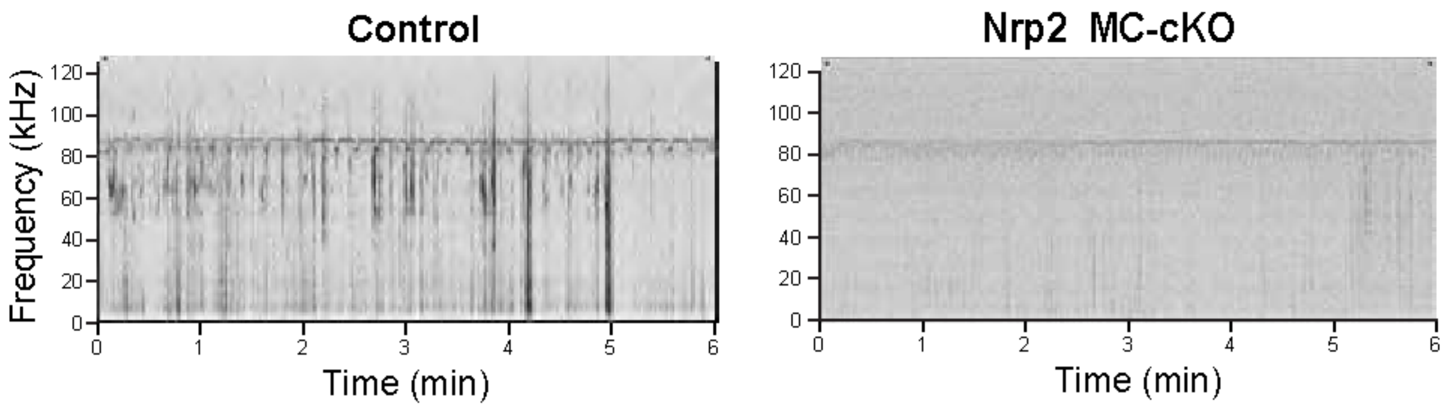


Both OSN axons and MCs are Nrp2^{+} in the ventral OB

Inokuchi et al., ***Nat. Commun.*** (2017)

MC-Specific Nrp2 cKO Affects Attractive Social Behaviors

Ultrasonic vocalization

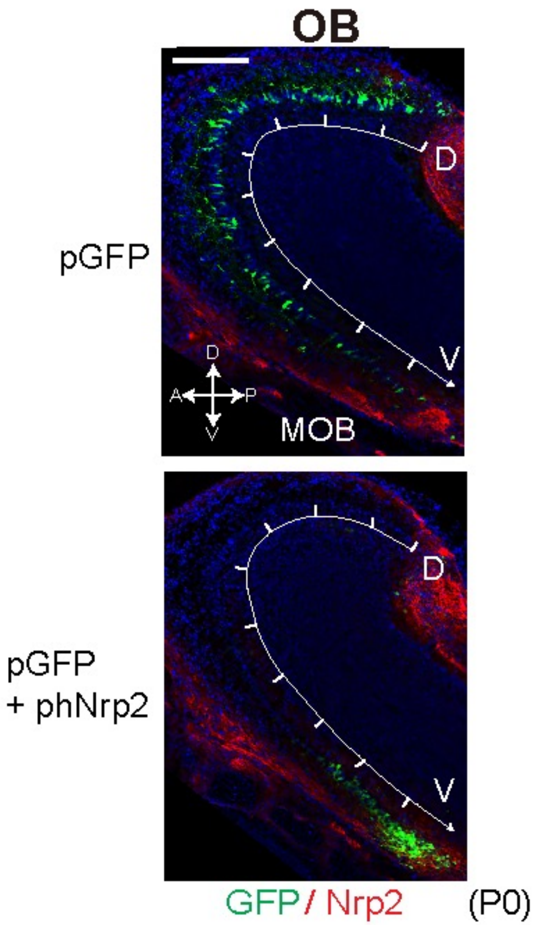


Affected	**Unaffected**
USV	Innate fear (TMT)
Pup suckling	Habituation/Dishabituation
♂/♀ attraction (MTMT)	

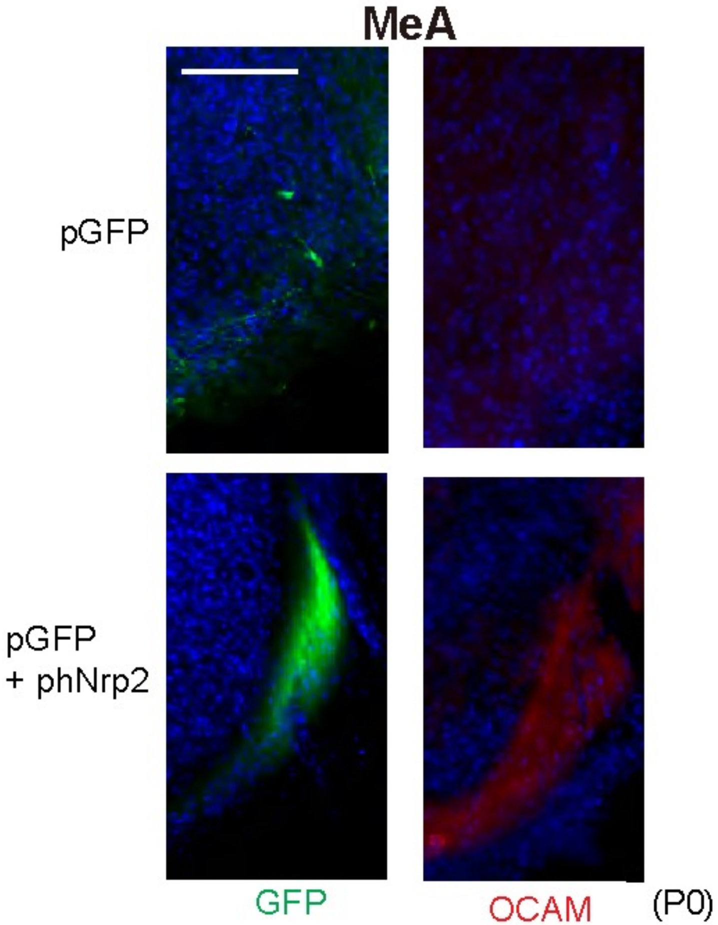
Inokuchi et al., ***Nat. Commun.*** (2017)

In Utero Electroporation of *hNrp2* into the Embryonic OB

(Nrp2 changes the fate of Nrp2$^-$ projection neurons)



Cell migration



Axonal projection

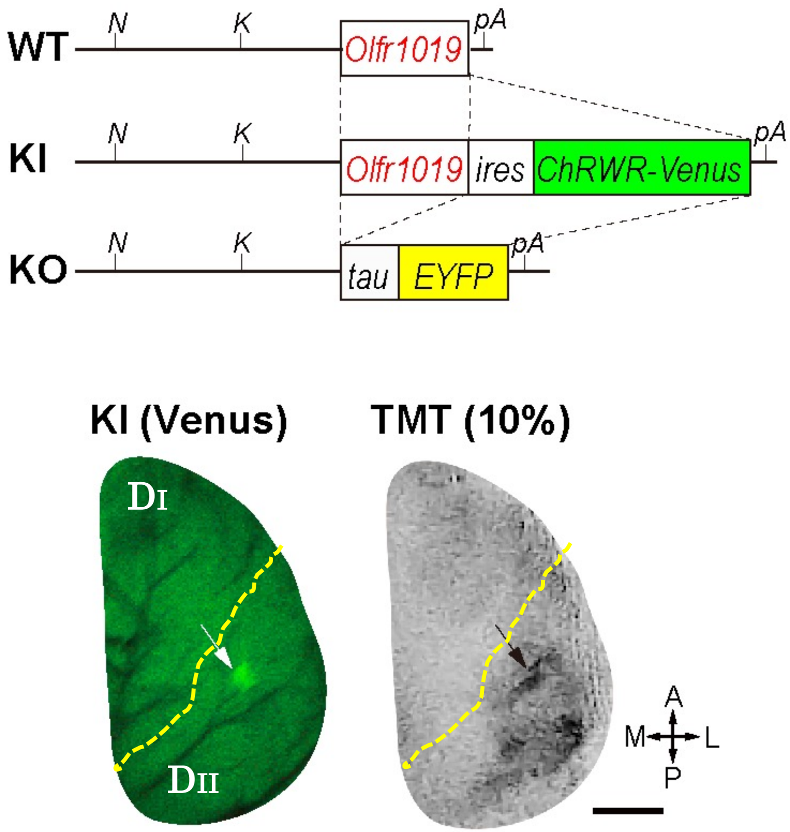
Inokuchi et al., ***Nat. Commun.*** (2017)

How is the Odor Map Interpreted for Innate Responses?

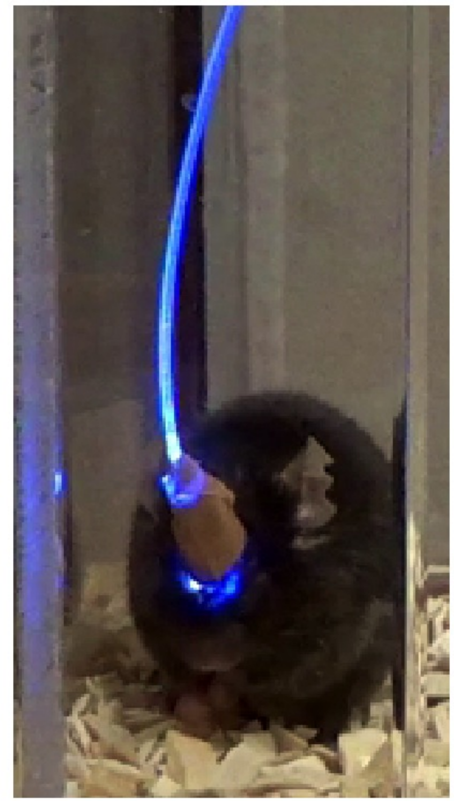
Is a pattern of activated glomeruli recognized as a whole?

Or, does a single glomerulus induce a specific odor response?

Channel-Rhodopsin KI Mouse of TMT-Responsive Olfr1019



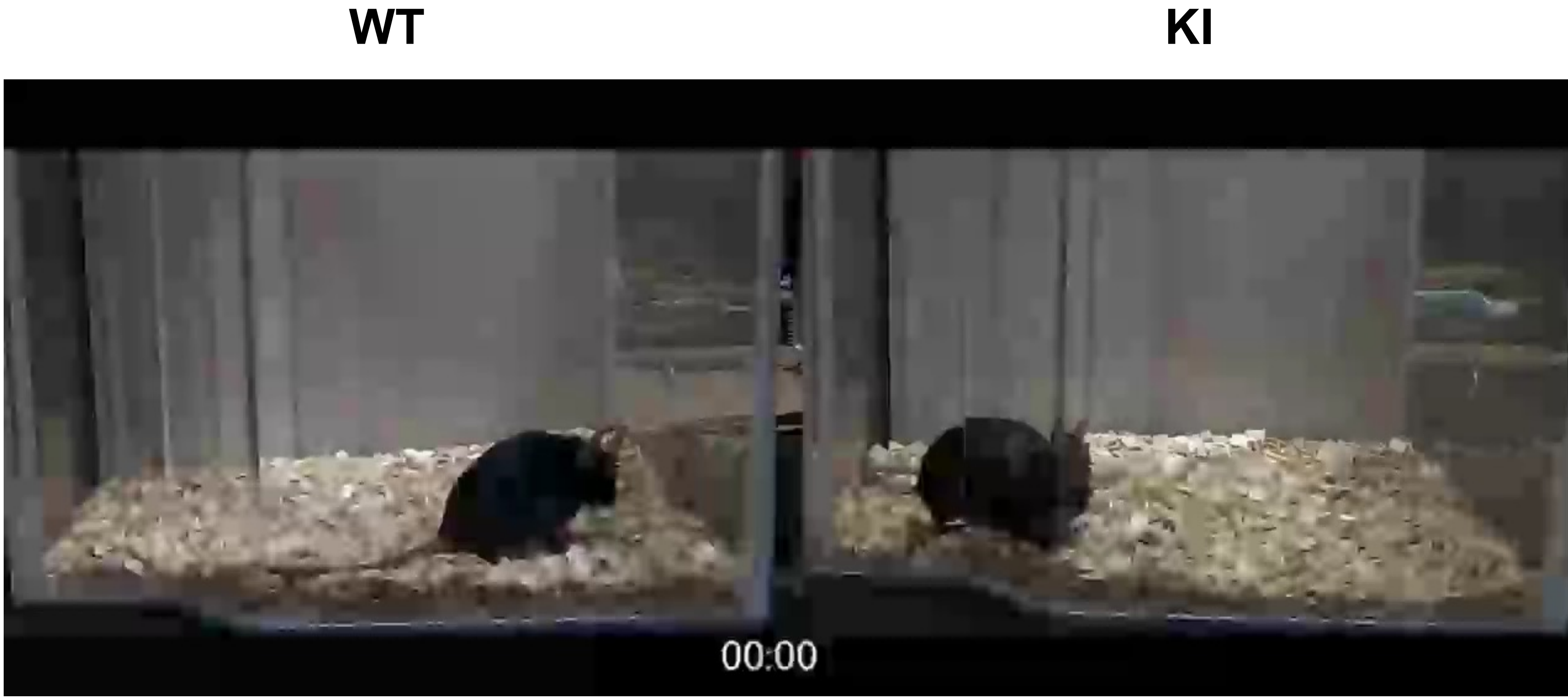
OB (dorsal view)



Phtoactivation of KI

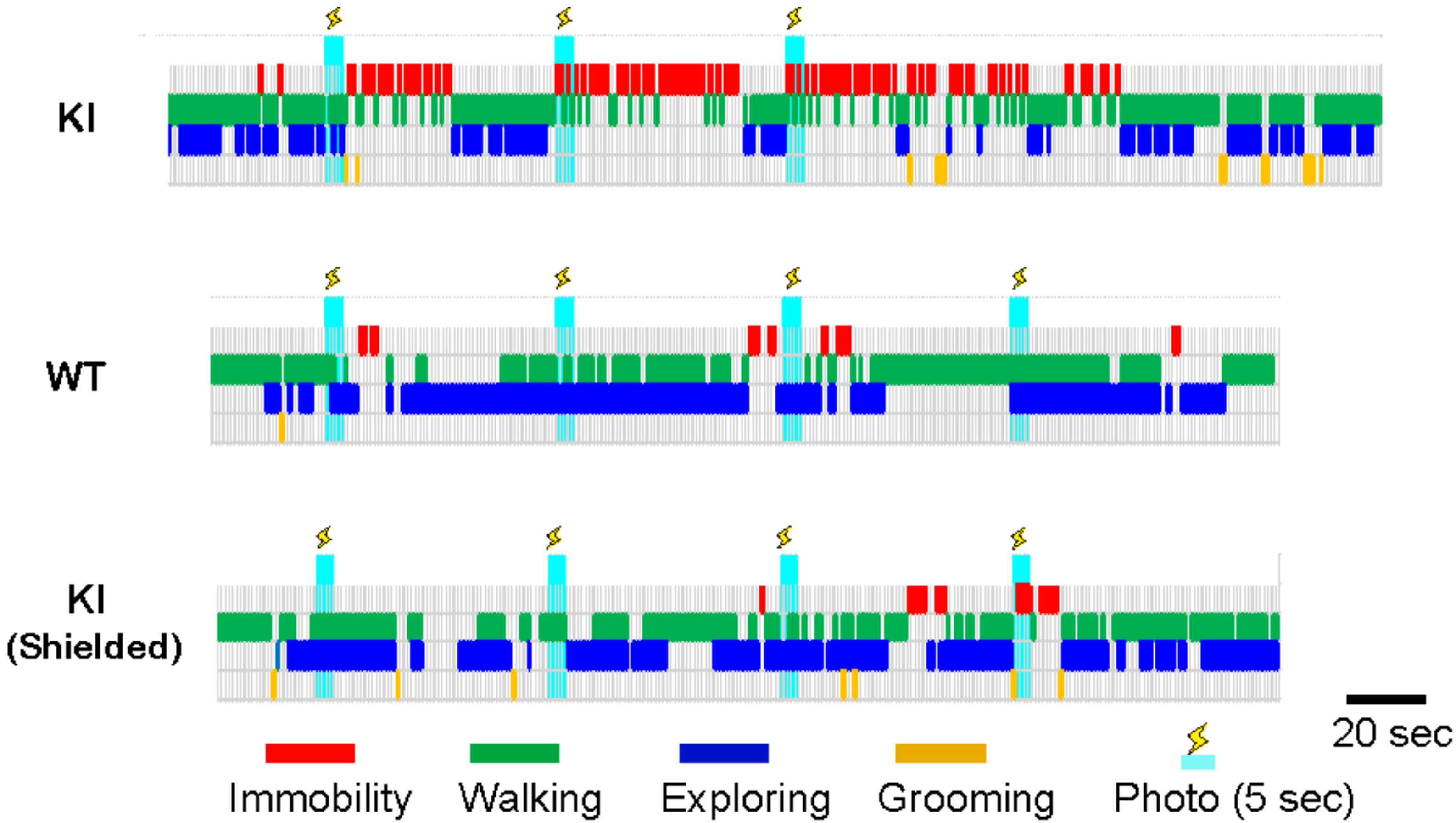
Saito et al., ***Nat. Commun.*** (2017)

Immobility but not Aversion is Induced by Photo-Activation of Olfr1019



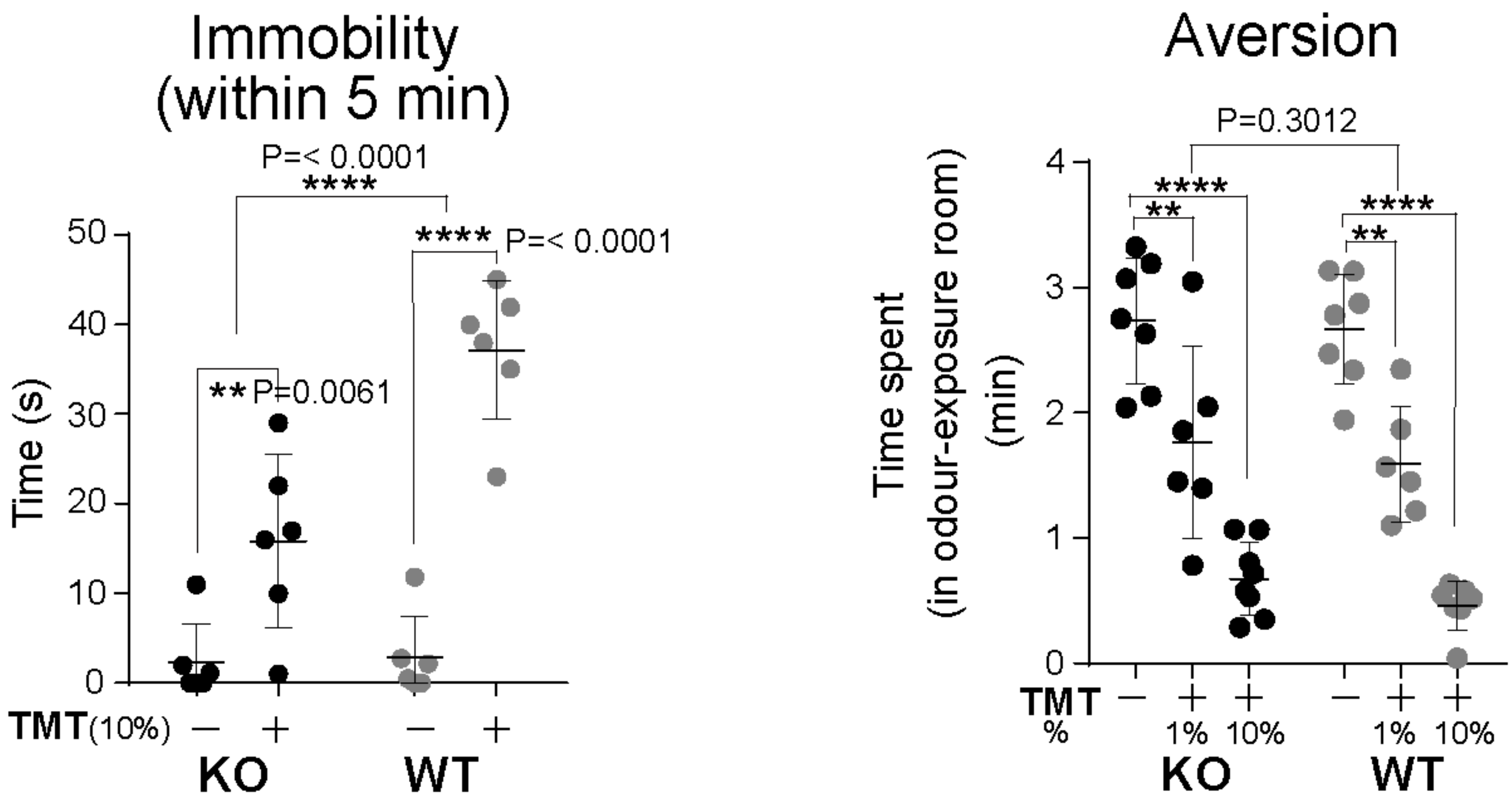
Saito et al., ***Nat. Commun.*** (2017)

Time Course Analysis of Various Behaviors



Saito et al., ***Nat. Commun.*** (2017)

Olfr1019 KO Affects Immobility, but not Aversion
(Responses to TMT)



Saito et al., ***Nat. Commun.*** (2017)

Innate Olfactory Behaviors can be Changed by Imprinting

1. Sema7A/PlxnC1 signaling triggers activity-dependent olfactory imprinting

2. Oxytocin is needed to impose the attractive quality on imprinted memory

Imprinting Discovered by Dr. Konrad Lorenz

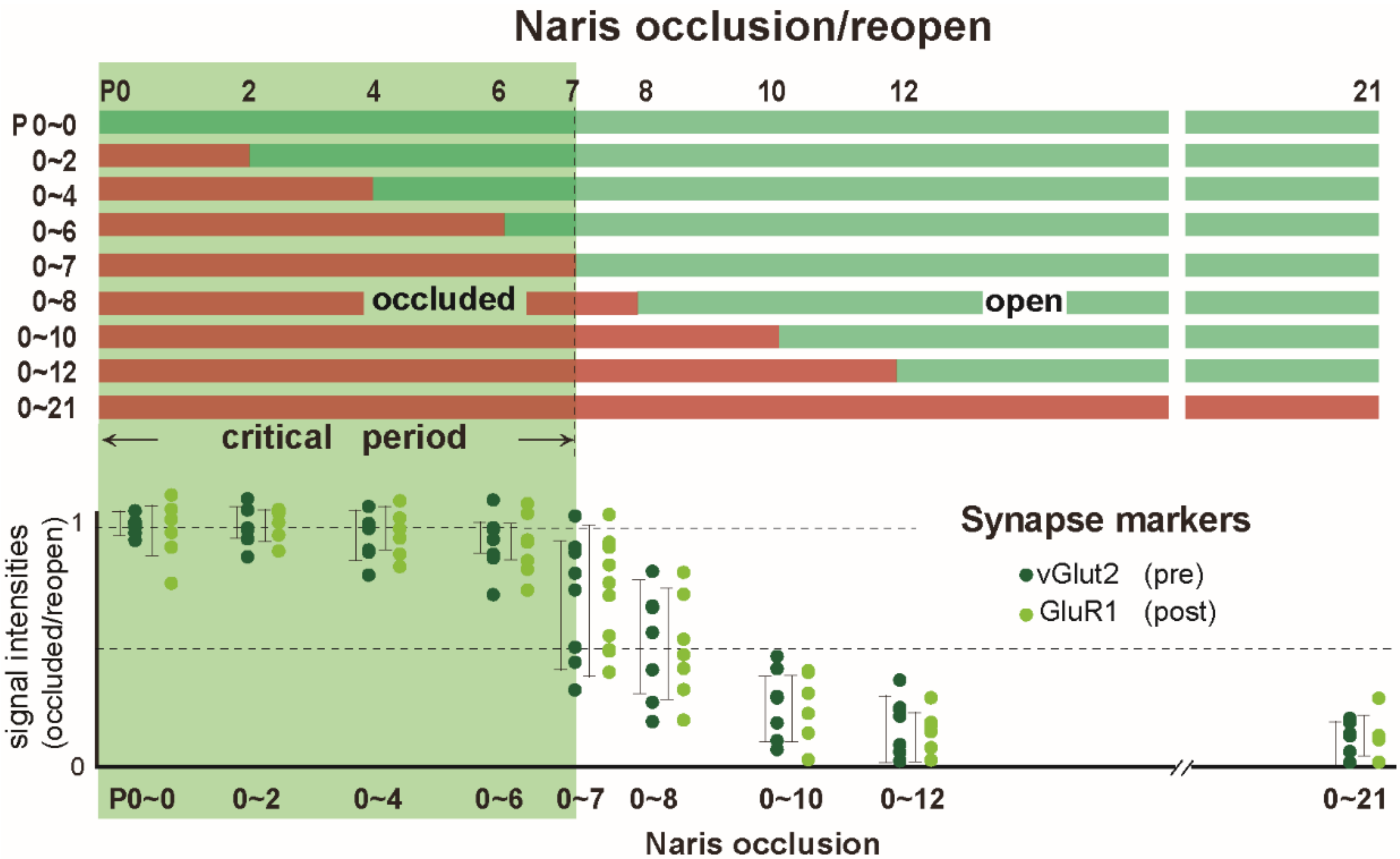
How is the Olfactory Imprinting Induced ?

Synaptic reinforcement ?

Re-wiring of axonal projection ?

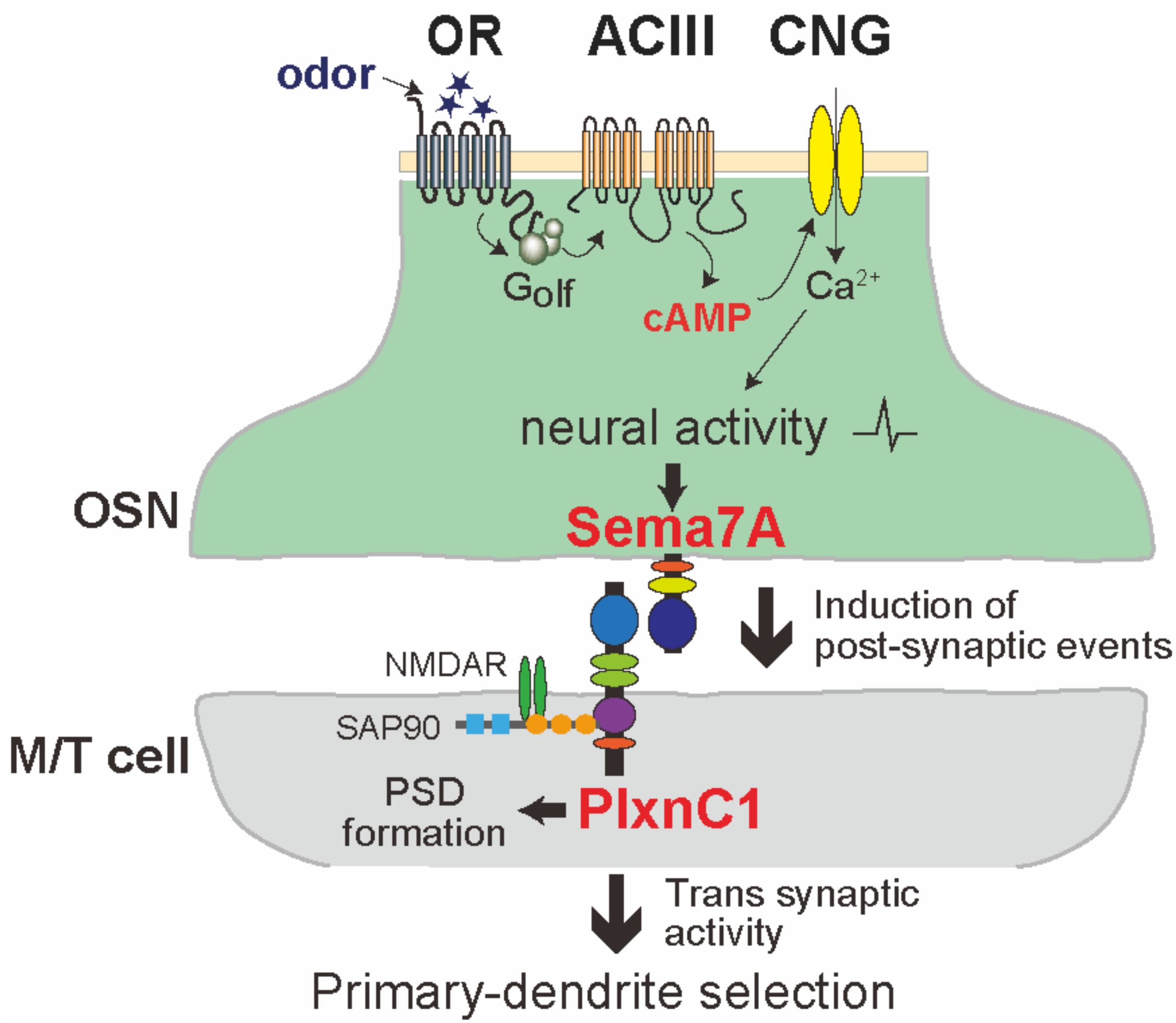
Learning during the critical period?

Olfactory Critical Period in Mice



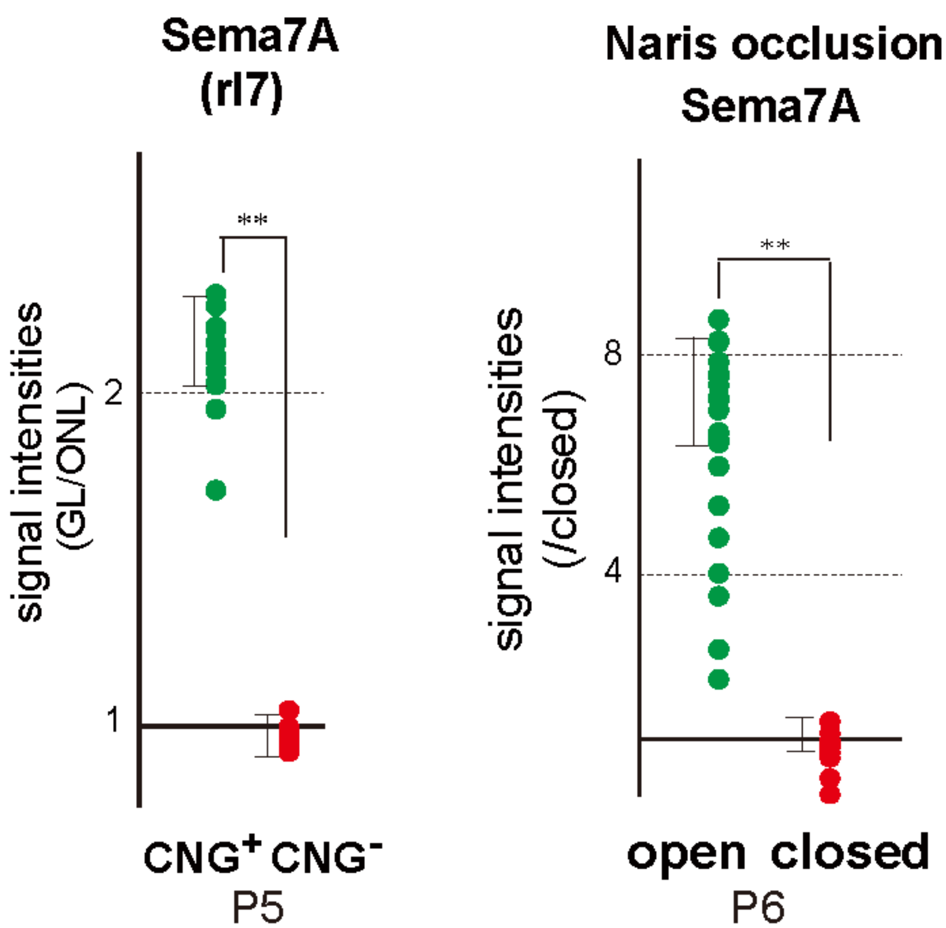
Inoue et al., ***eLife*** (2021)

Sema7A Signaling Promotes Synapse Formation within Glomeruli



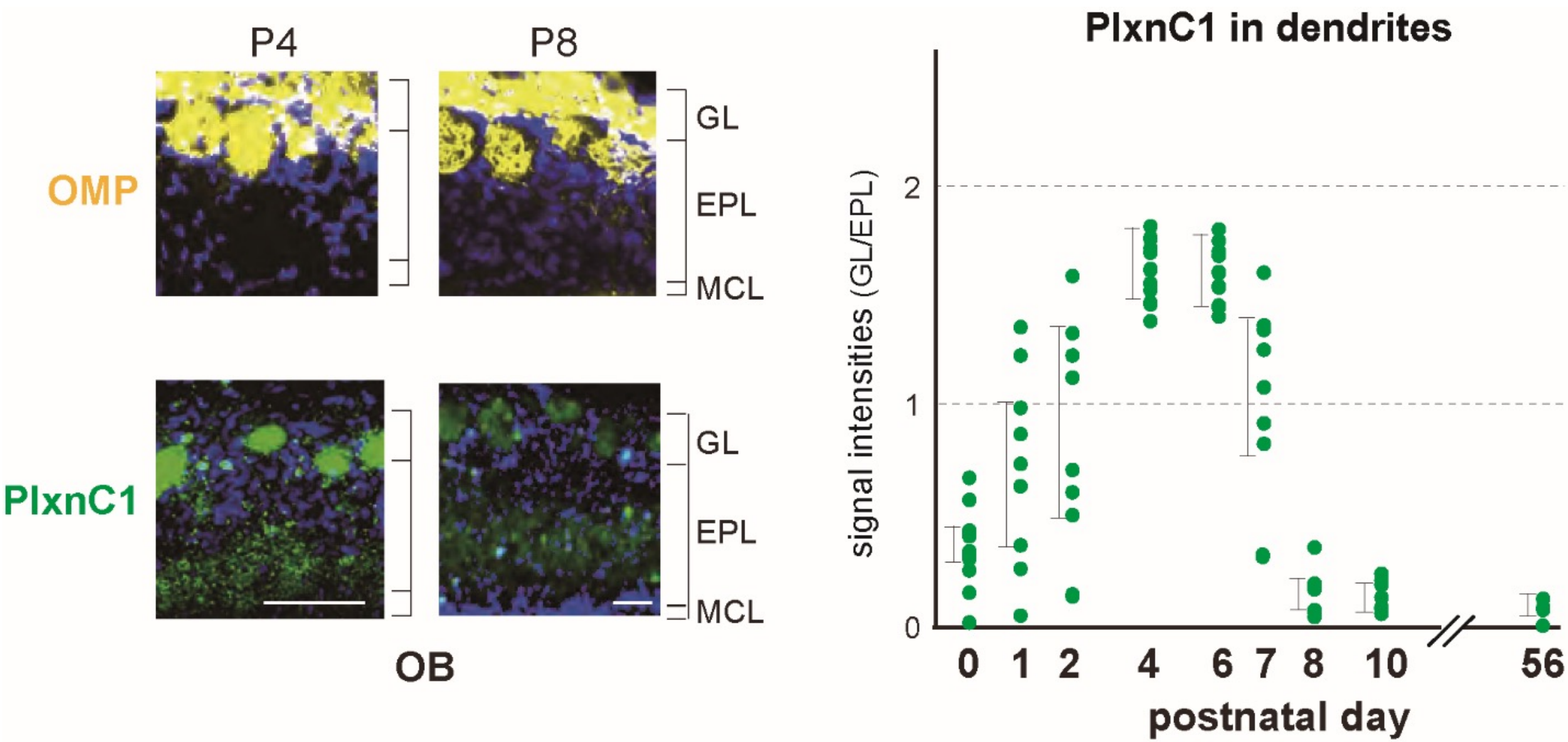
Inoue et al., ***Nat. Commun.*** (2018)

Imprinting is Activity-Dependent
(Sema7A expression is odor-evoked)



Inoue et al., ***Nat. Commun.*** (2018)

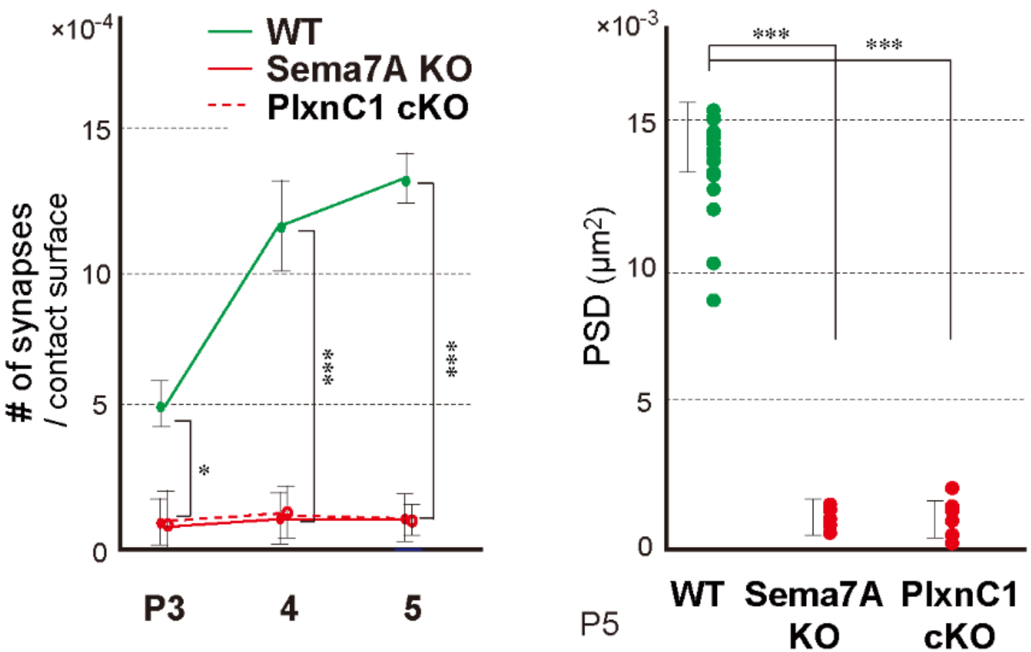
PlxnC1 Determines the Time Frame of Critical Period
(PlxnC1 is localized to M/T-cell dendrites
only during the first week after birth)



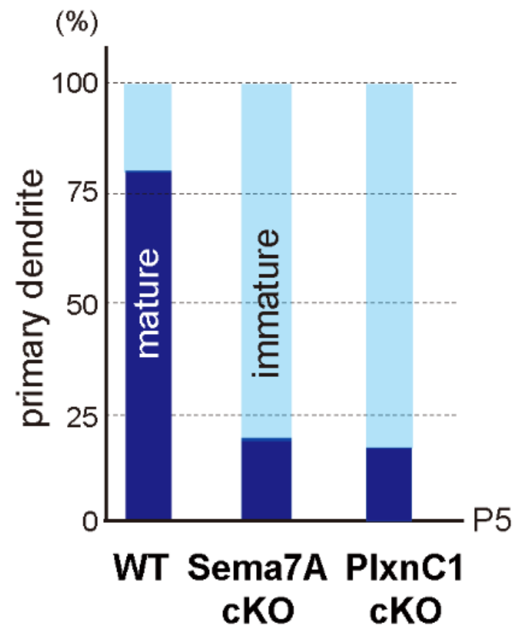
Inoue et al., ***Nat. Commun.*** (2018)

KO of Sema7A/PlxnC1 Affects Synapse Formation and Dendrite Selection

Synapse formation



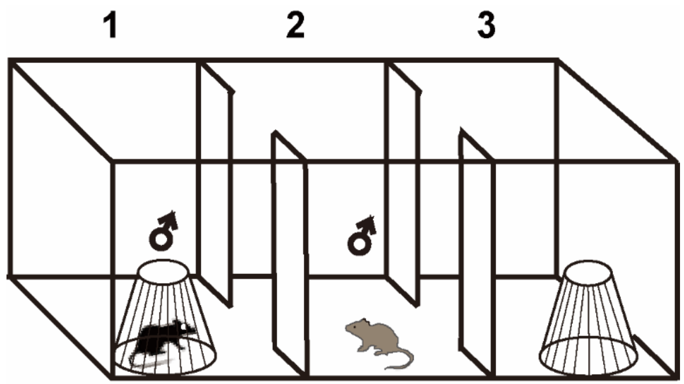
Dendrite maturation



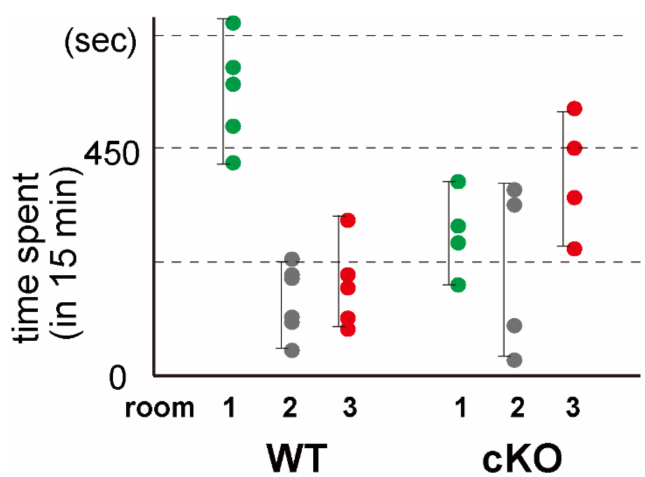
Inoue et al., ***Nat. Commun.*** (2018)

Three Chamber Test

(Olfactory inputs in neonates are essential for establishing sociality as adults)



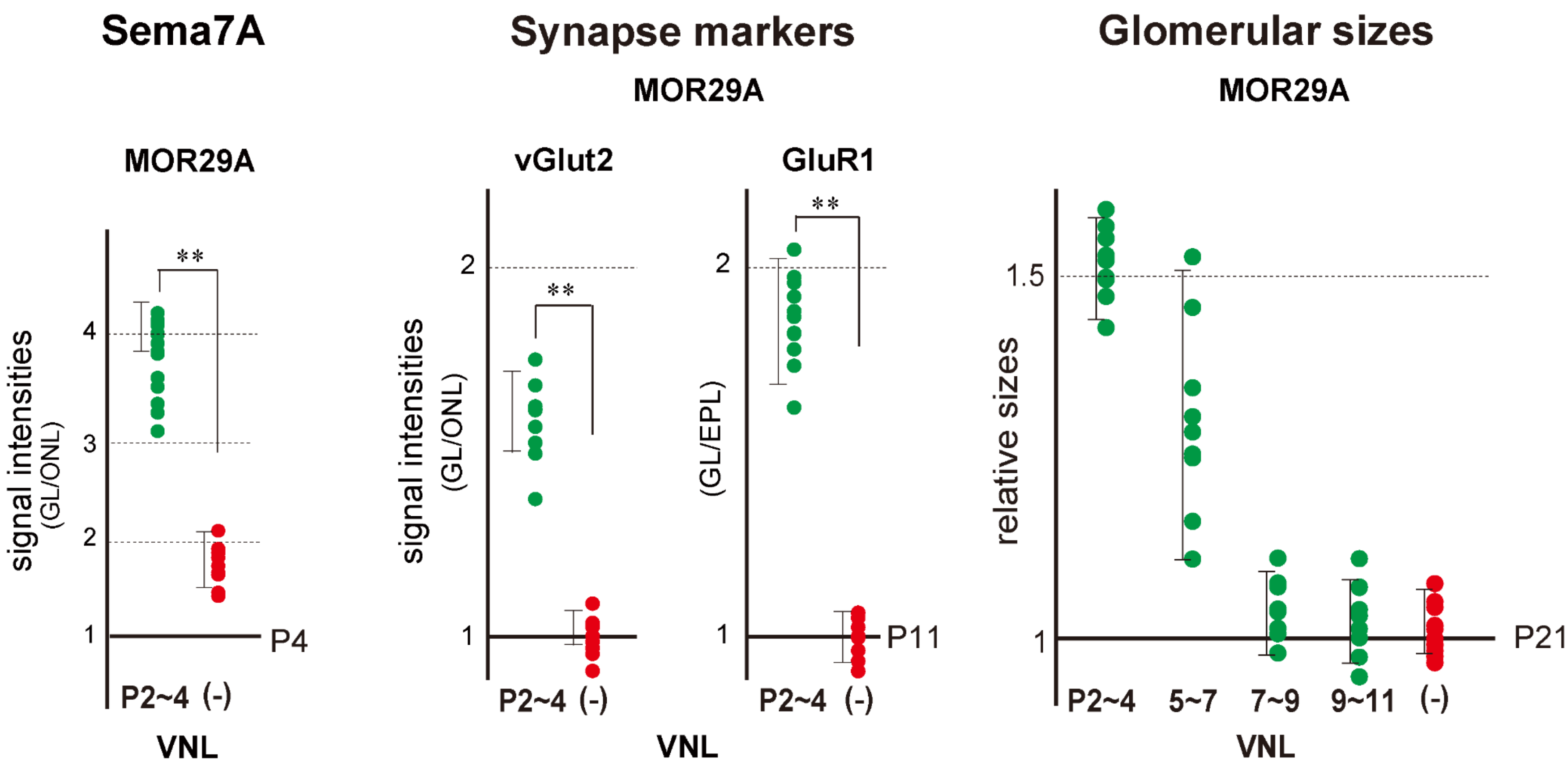
PlxnC1 cKO



Inoue et al., ***eLife*** (2021)

Synaptic Reinforcement in Olfactory Imprinting

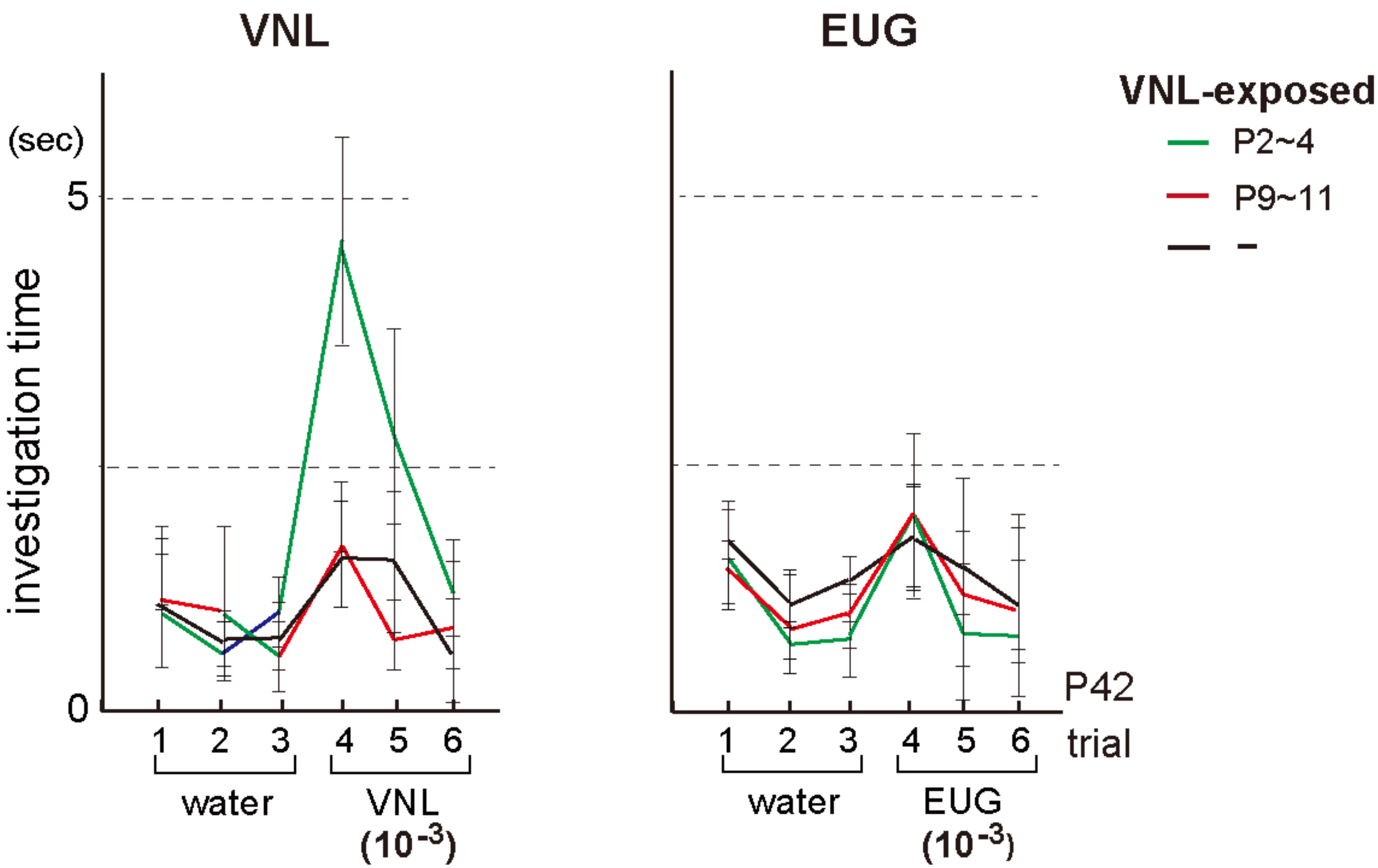
(VNL exposure)



Inoue et al., ***eLife*** (2021)

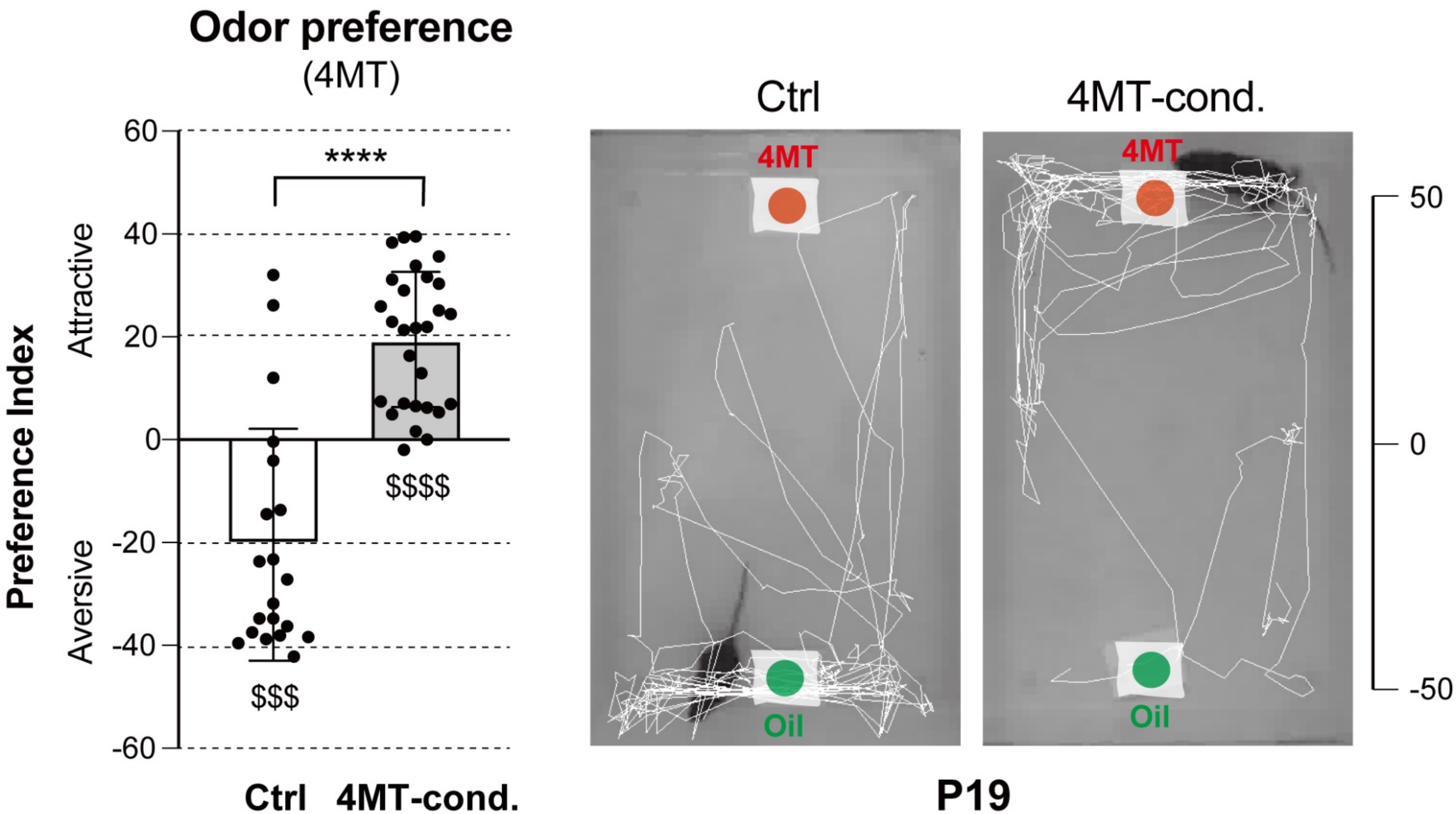
Olfactory Imprinting Increases Odor Responsiveness

Habituation/Dishabituation
(VNL-exposed)



Inoue et al., ***eLife*** (2021)

Odor Preference is Changed by Imprinting



Katori et al. (unpublished)

Imprinted Memory Changes Odor Responses

(Aversive odorant 4MT)

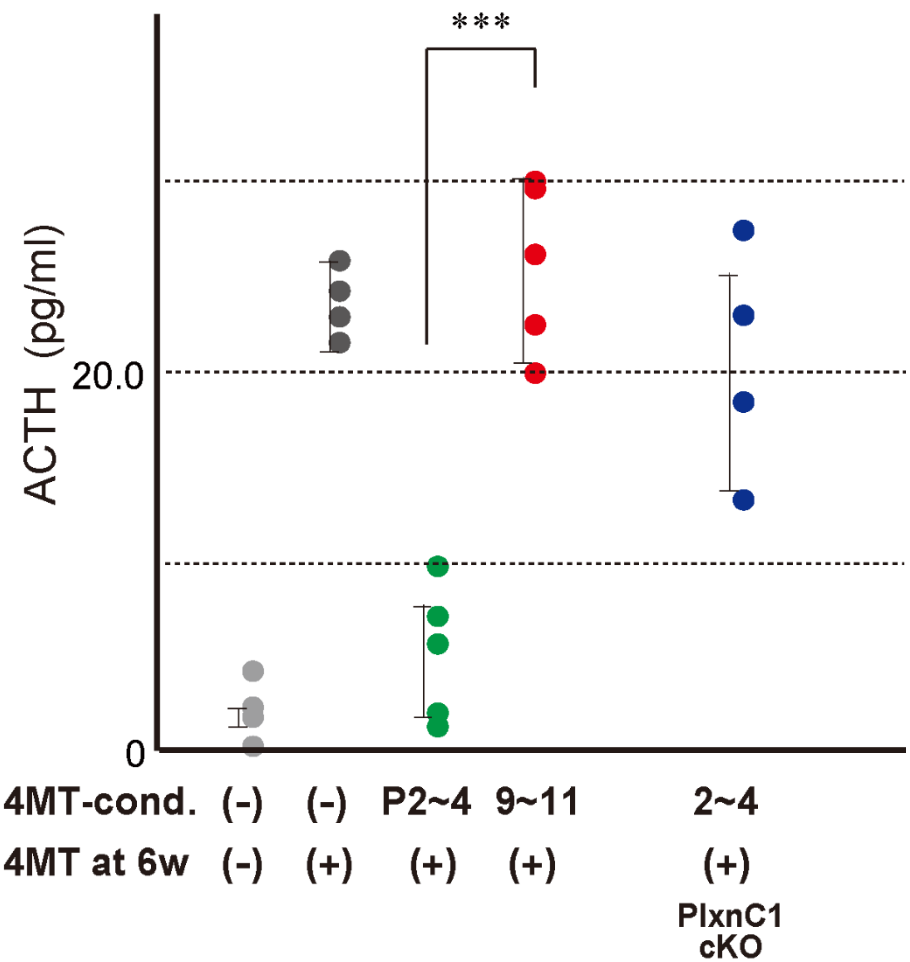
unconditioned

4MT-conditioned (P2～4)

Inoue et al., ***eLife*** (2021)

Imprinted Olfactory Memory Reduces Stress Reactions

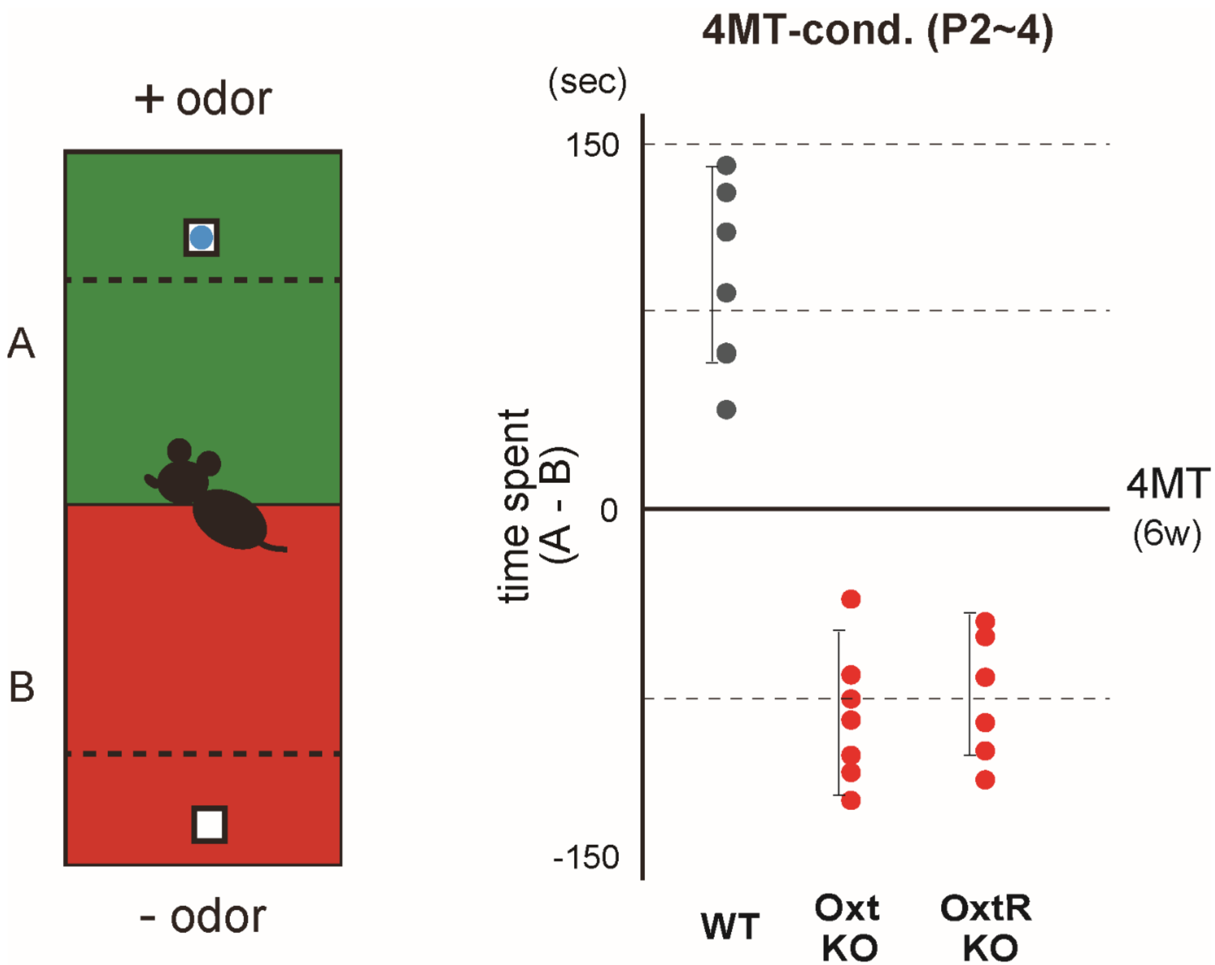
Suppression of ACTH rise



Inoue et al., ***eLife*** (2021)

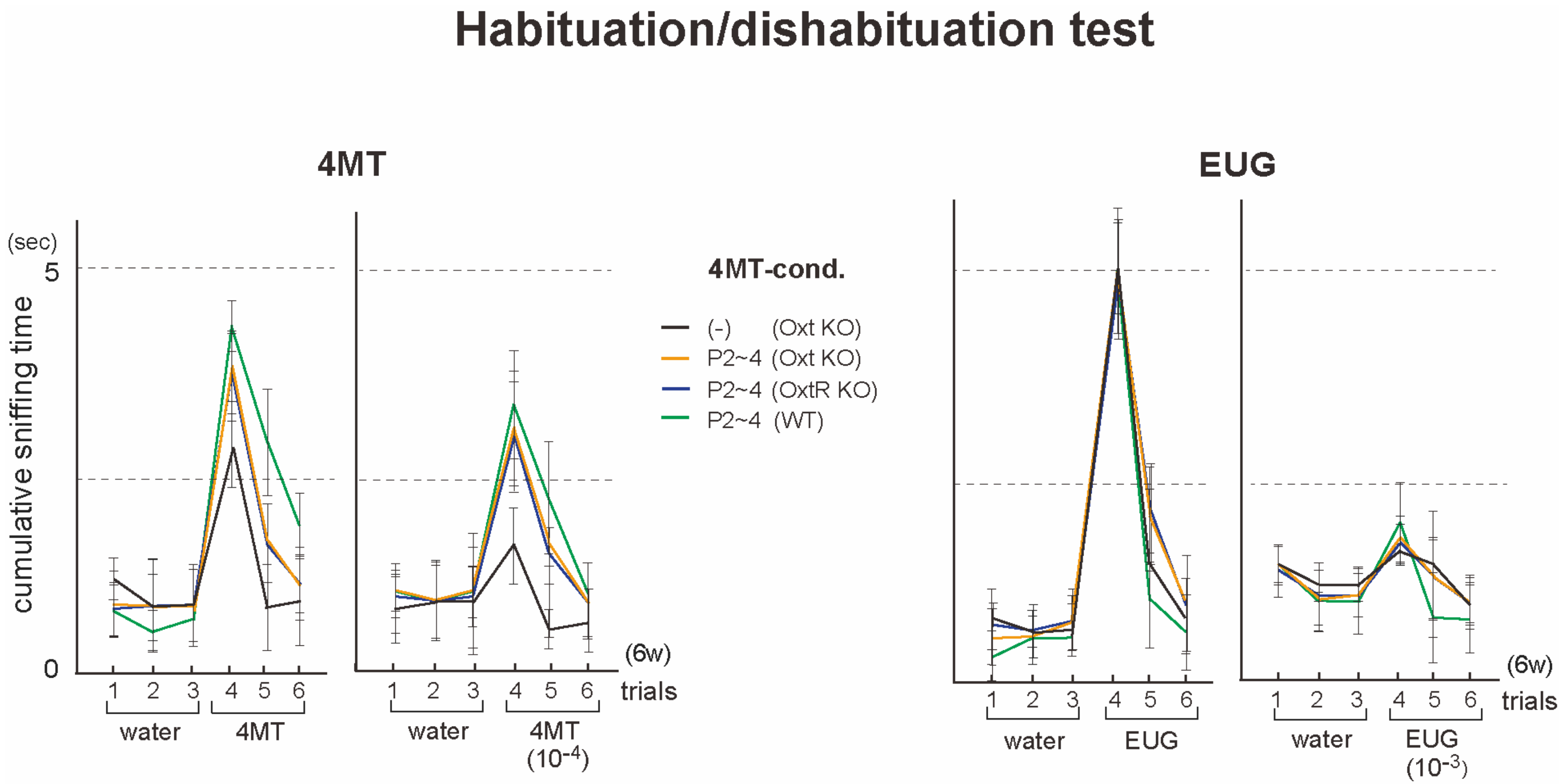
Odor Preference Test

(Oxytocin is needed to impose the positive quality on imprinted memory)



Inoue et al., ***eLife*** (2021)

Odor Responsiveness is Increased Even in the Oxt KO

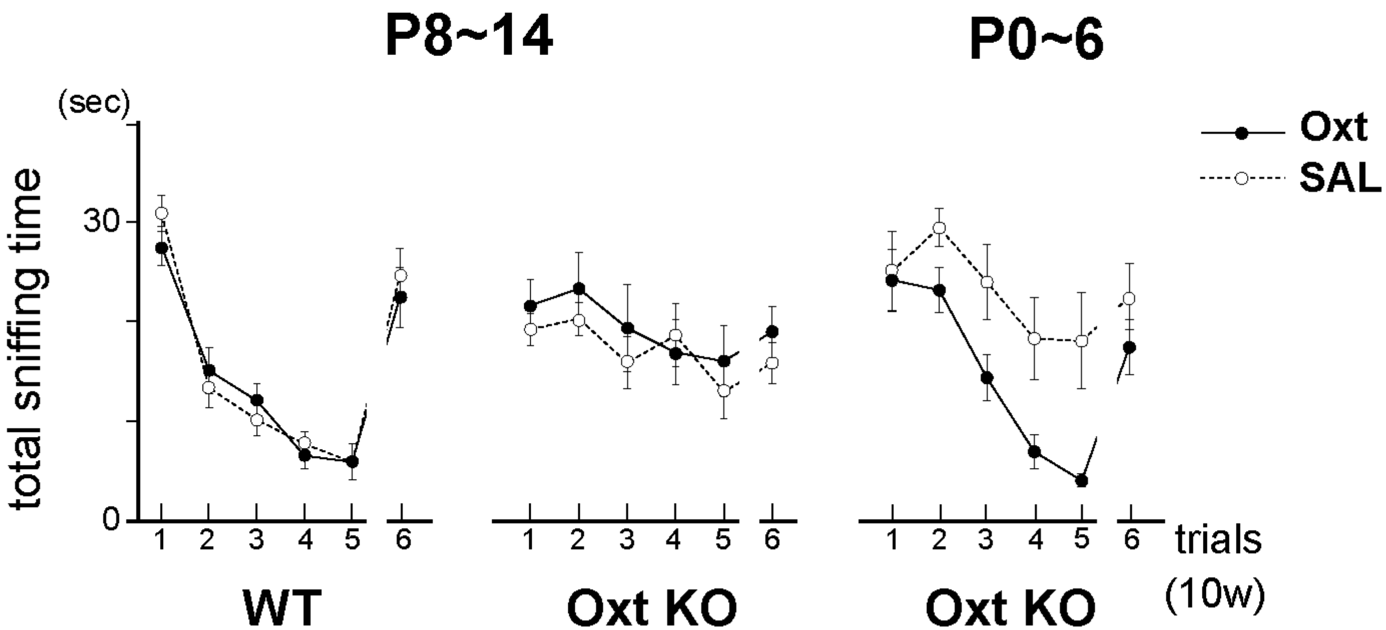


Inoue et al., ***eLife*** (2021)

Social Memory Test

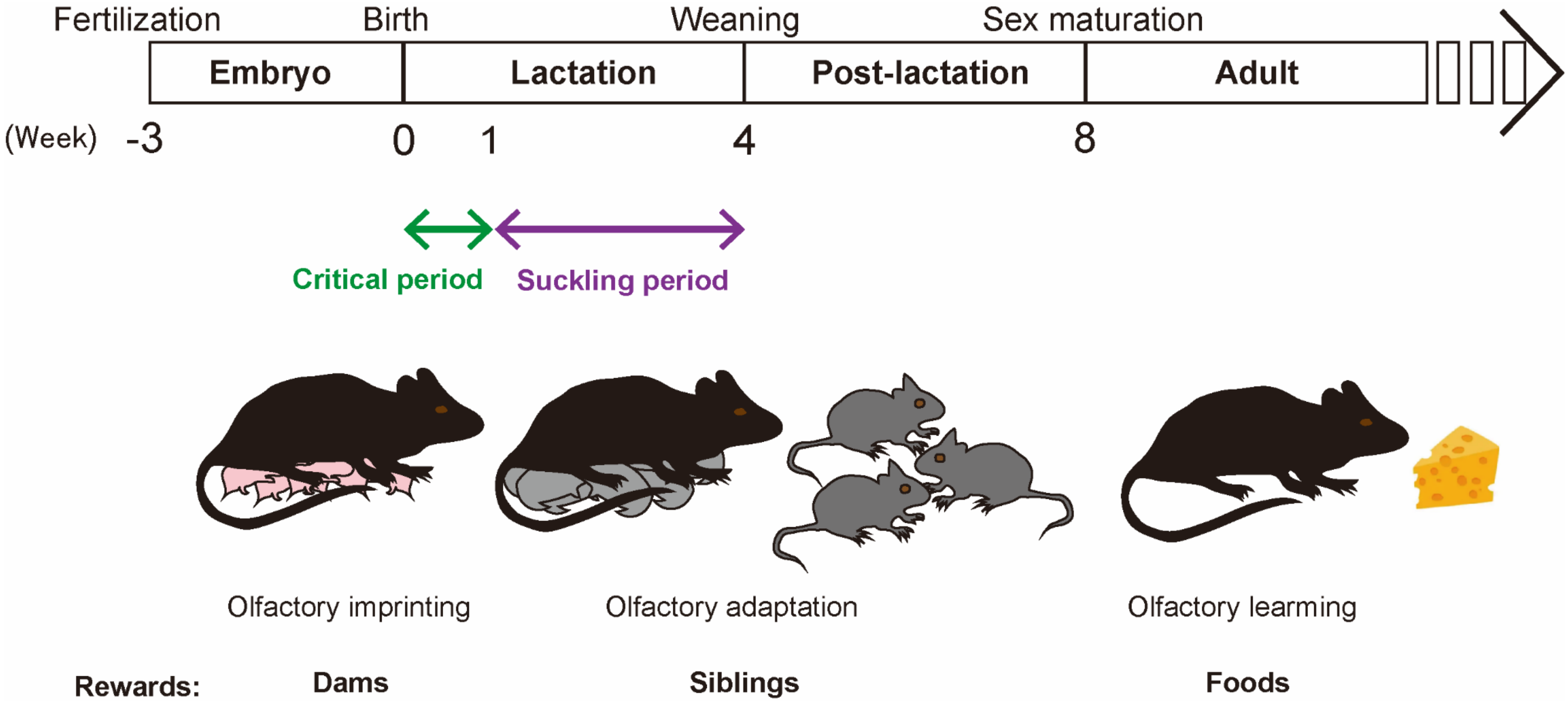
(Social-memory formation is restored in the Oxt KO by Oxt administration in neonates)

Intra-peritoneal injection

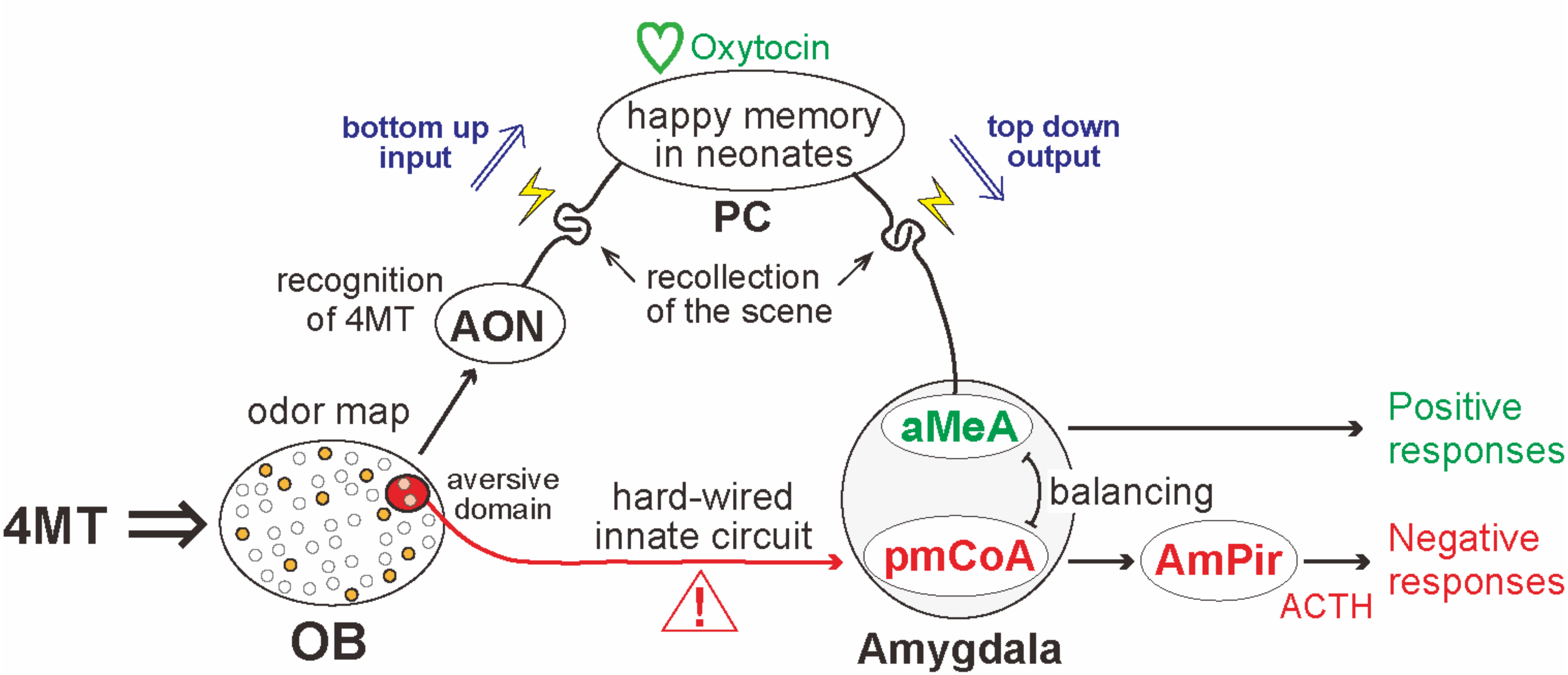


Inoue et al., ***eLife*** (2021)

Adaptive Changes in Odor Preference



Two Conflicting Decisions for 4MT
(innate vs. memory-based)



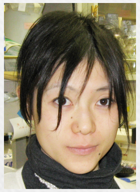
Mori & Sakano, ***Annu. Rev. Physiol.*** (2021)

Collaborators

(Univ. of Fukui)

Harumi Saito

Kasumi Inokuchi



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Lab Members

OR gene choice	:	Serizawa S, Miyamichi K, Nishizumi H, Ishii T
A-P positioning	:	Imai T, Yamazaki T
D-V positioning	:	Takeuchi H, Inokuchi K, Aoki M., Tsuboi A
Local segregation	:	Serizawa S, Miyamichi K, Takeuchi H
Stepwise regulation	:	Nakashima A, Takeuchi H, Imai T
Innate behaviours	:	Kobayakawa K, Koboyakawa R, Oka Y
Mitral/Tufted cells	:	Nagawa F, Miyashita A, Inoue N, Nishizumi H