Part 1: The eyes have it (neurodev)

Part 2: Something fishy about balance (neuroloco)

KITP, July 28 2022

David Schoppik
@schoppik, NYU Grossman School of Medicine

The eyes have it!

or

Neuronal birthdate organizes the vestibulo-ocular reflex circuit

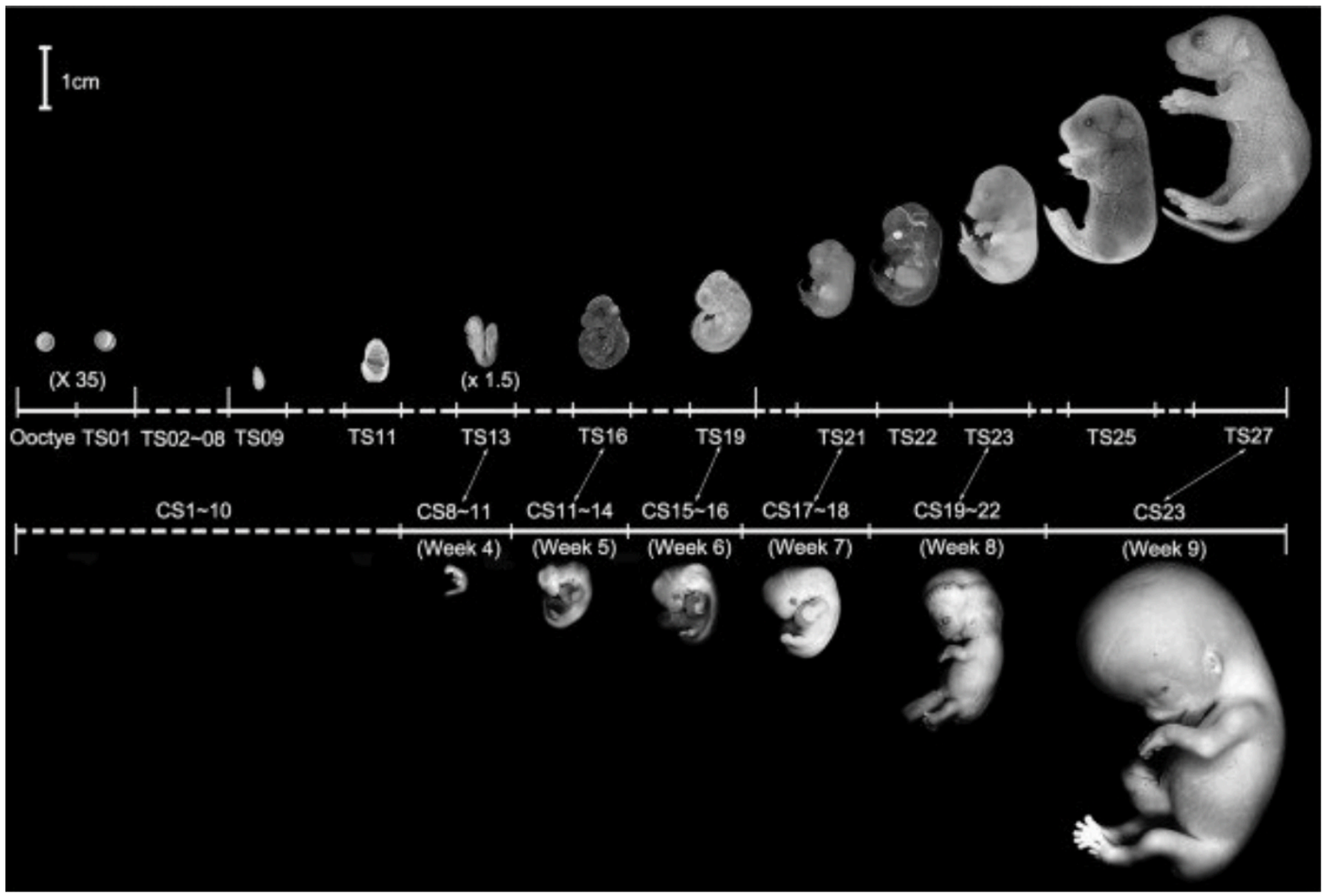
KITP, July 28 2022 pt 1

David Schoppik
NYU Grossman School of Medicine

1. Simple principles can have exceptional explanatory power (thanks, Physics!)
2. The neuroscience of behavior has precious few examples of simple principles.
3. But developmental neuroscience does.

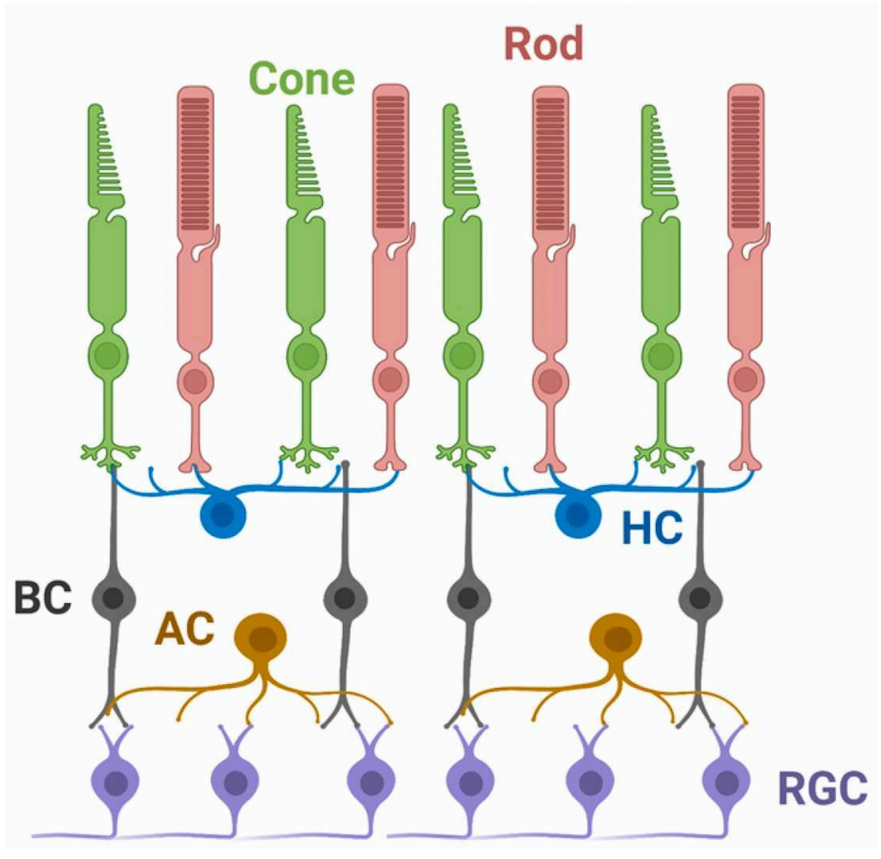
Can we link the principles that underlie development to the neural circuits responsible for behavior?

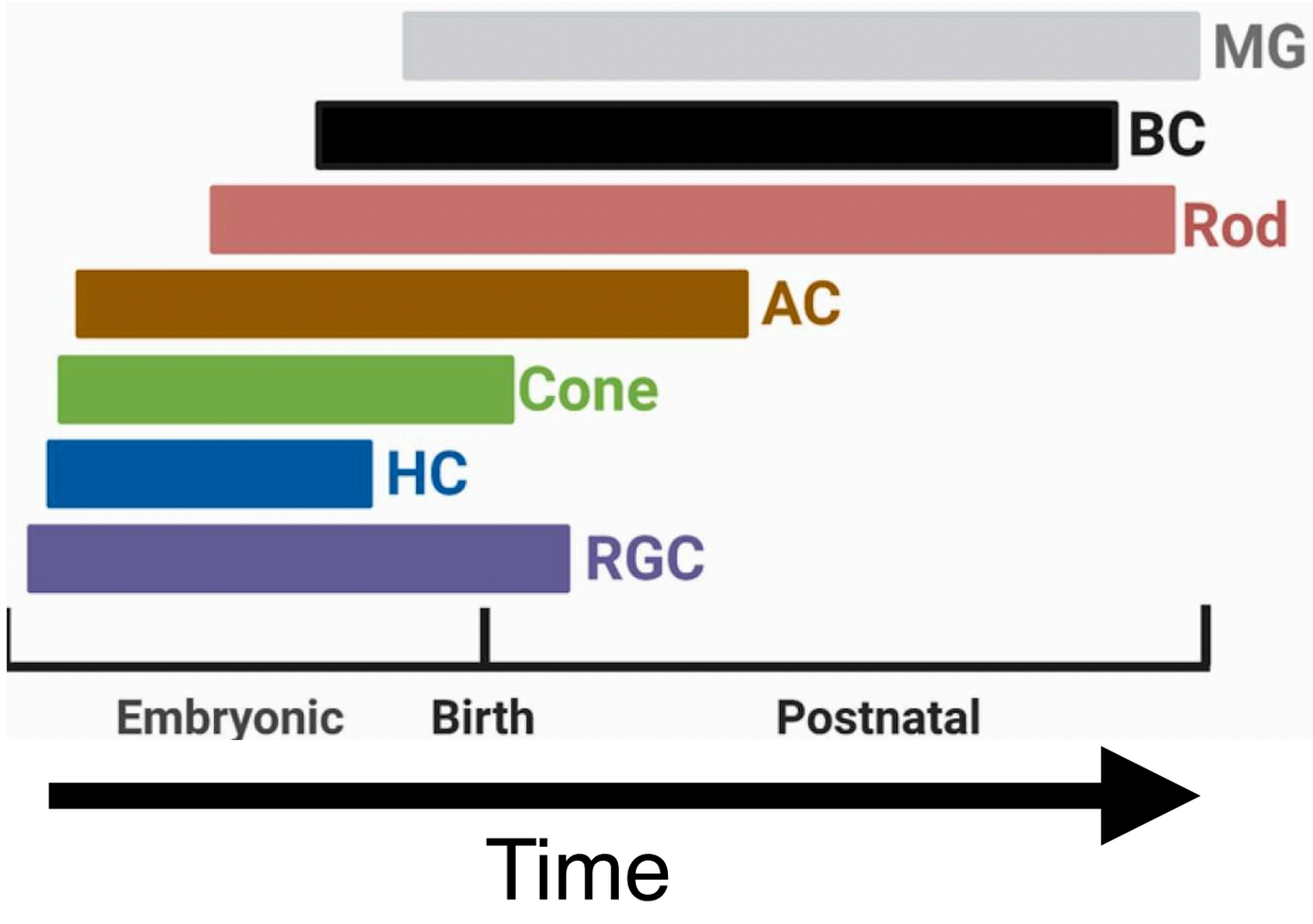
Development happens over time (duh)



Xue et al 2013

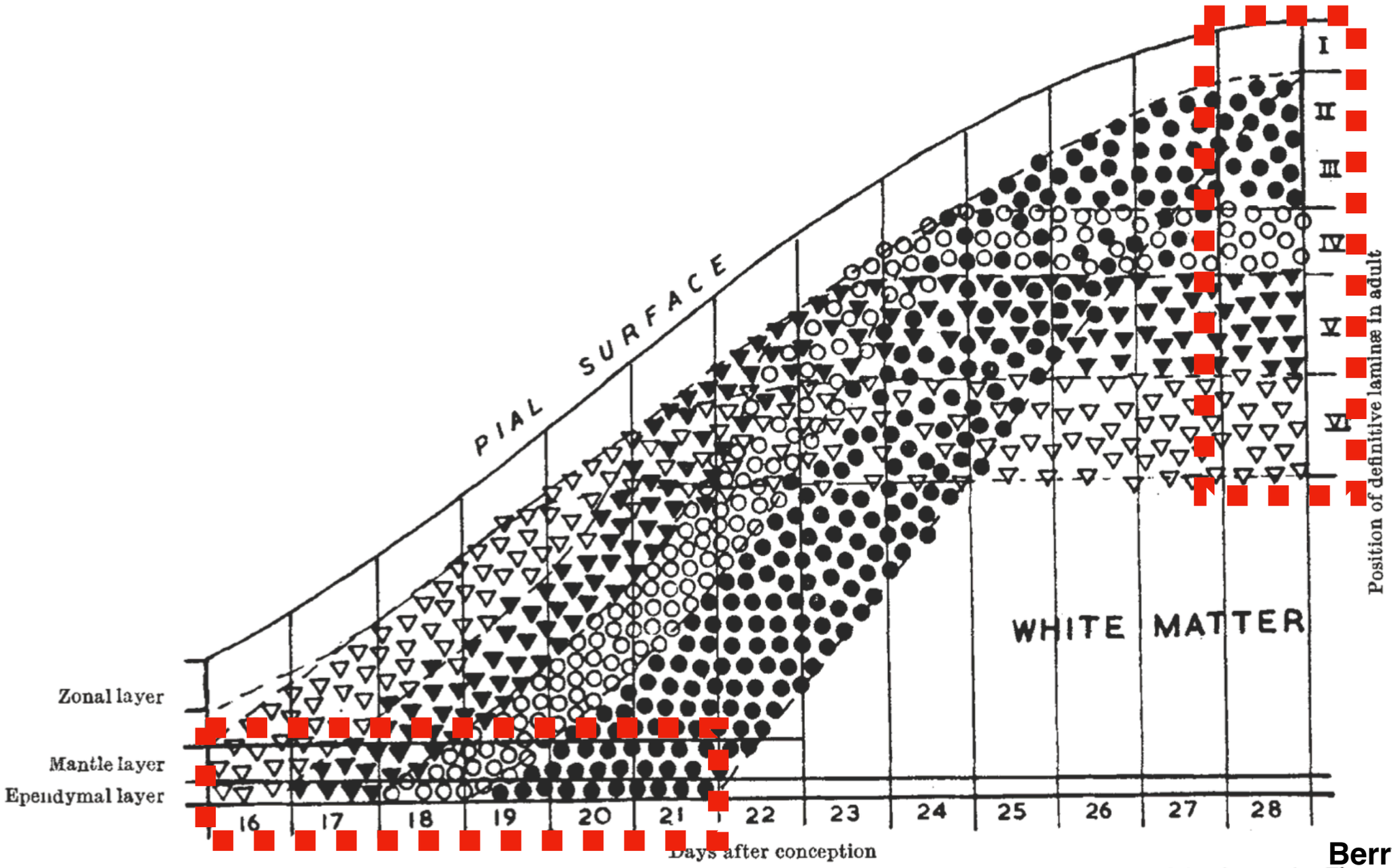
Neuronal diversity emerges in time





El-Danaf et al 2022

Birthdate can give rise to spatial organization

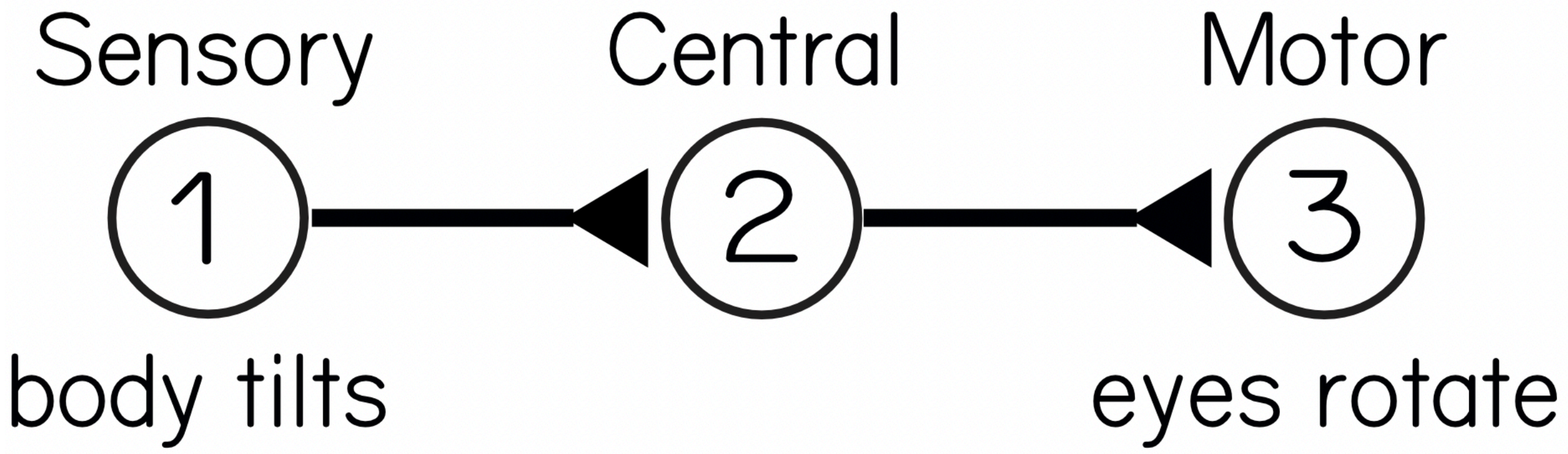


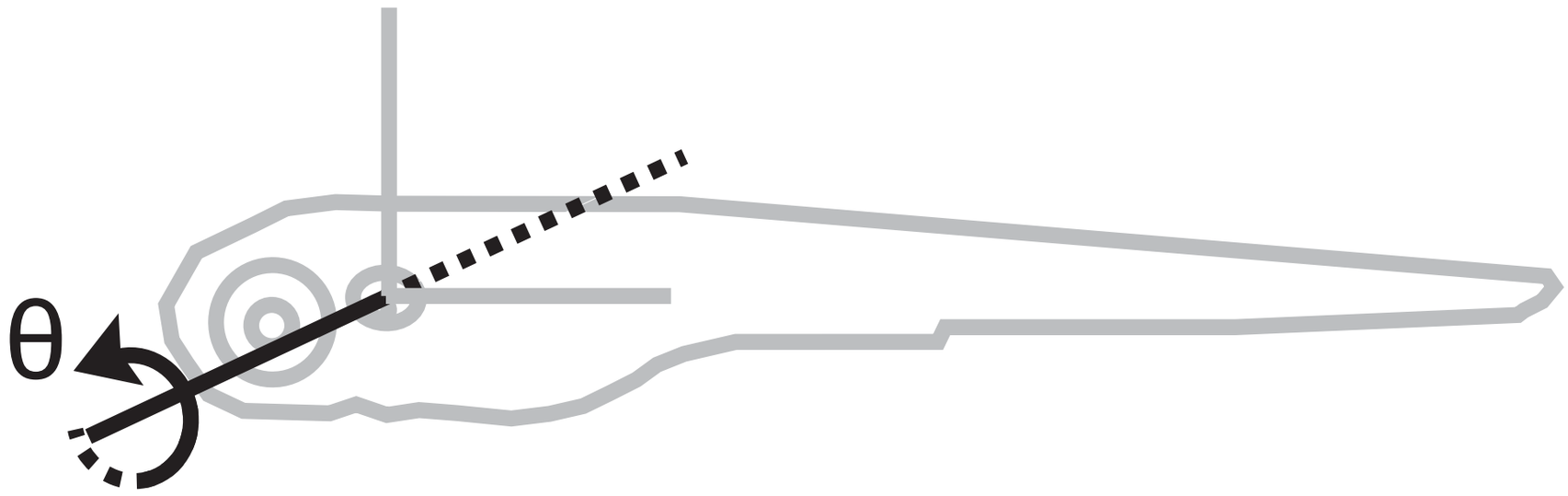
Berry et al 1964

Can birthdate organize a sensorimotor circuit?

How vertebrate brains stabilize gaze:

the vestibulo-ocular reflex circuit


Sensory
Central
Motor
1
2
3
body tilts
eyes rotate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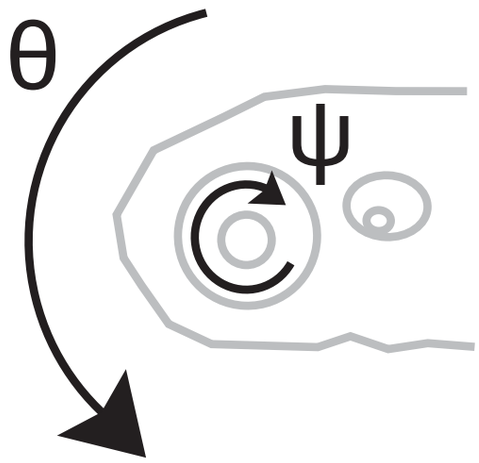
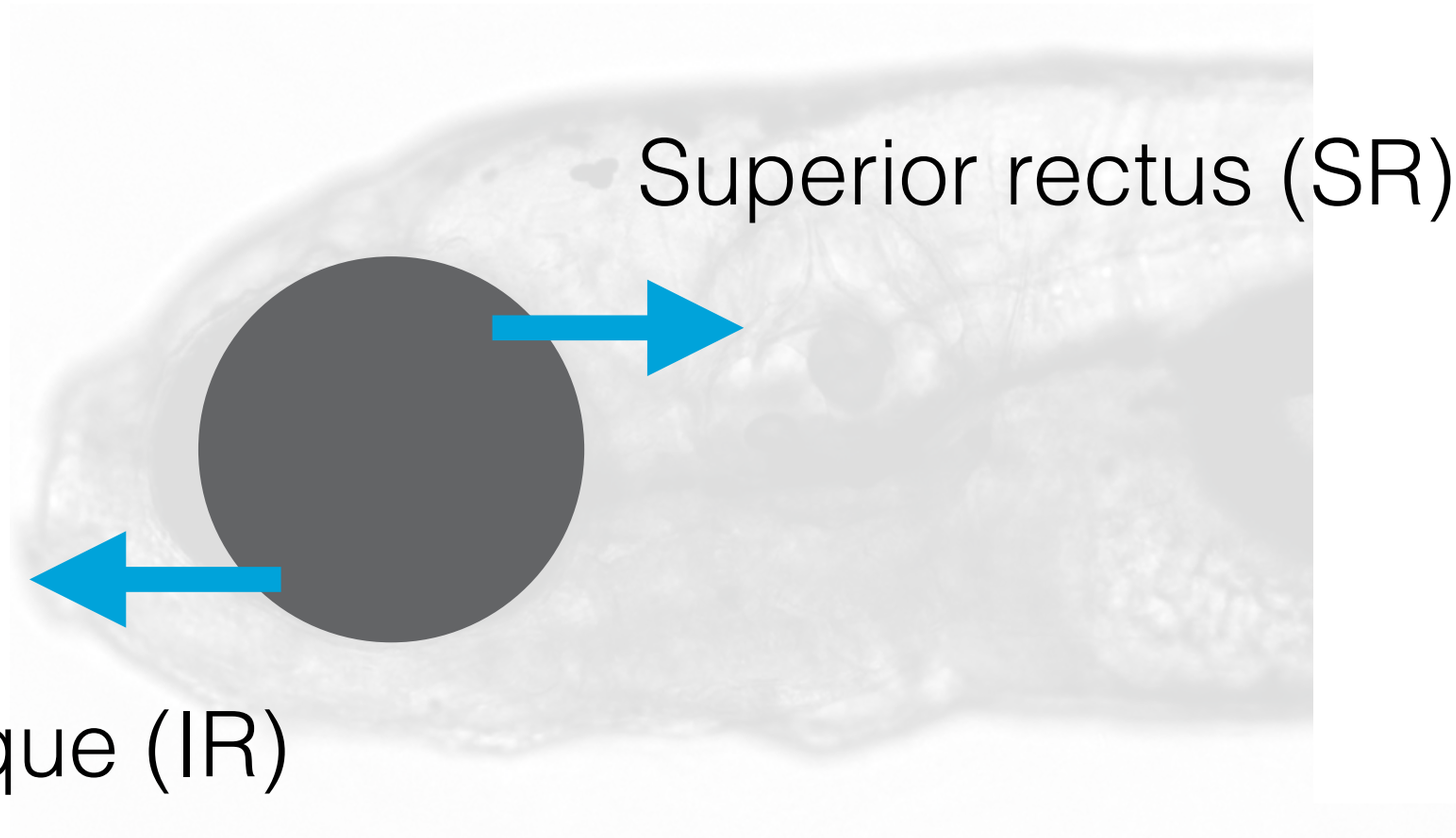
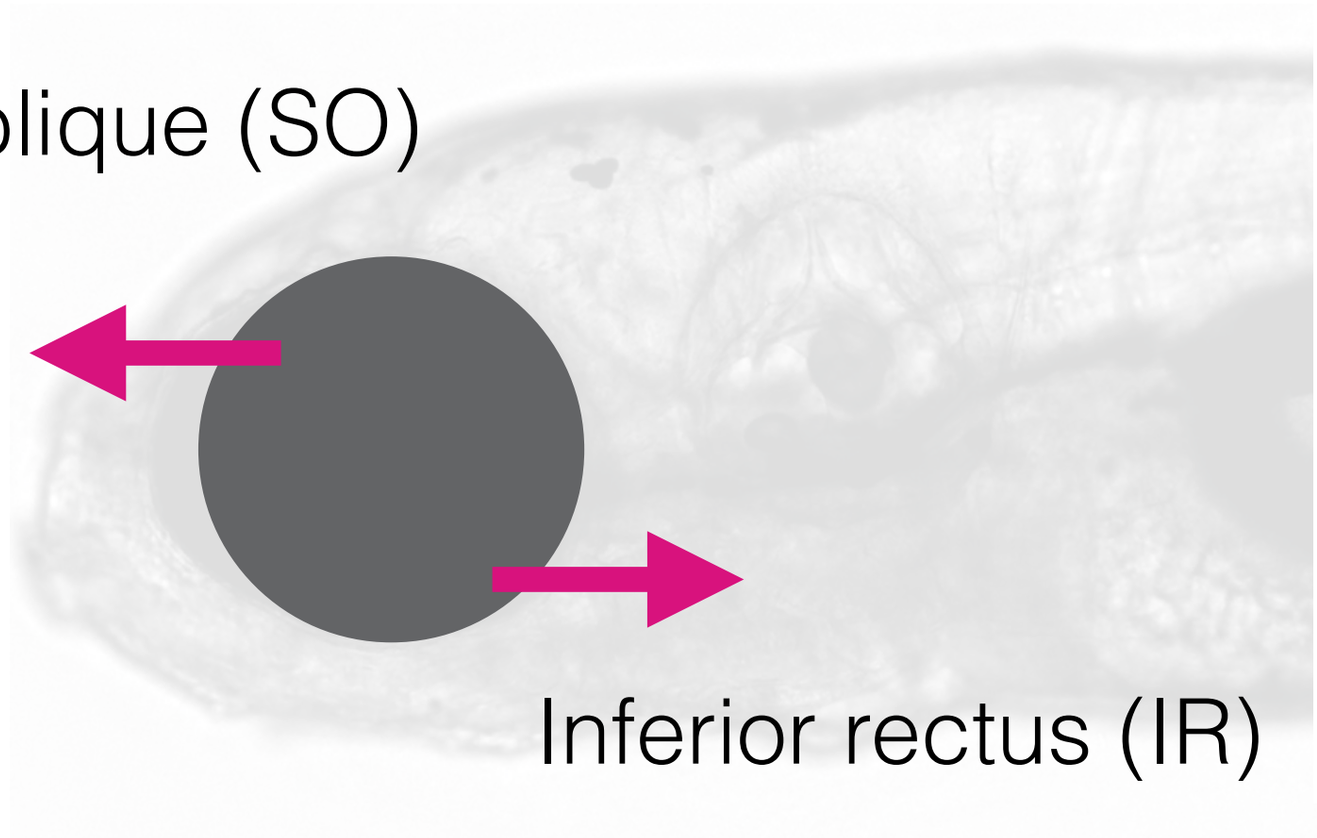


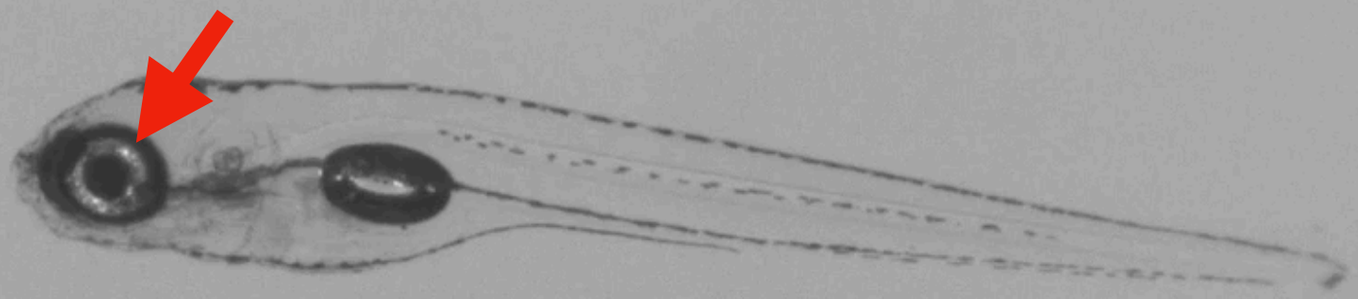


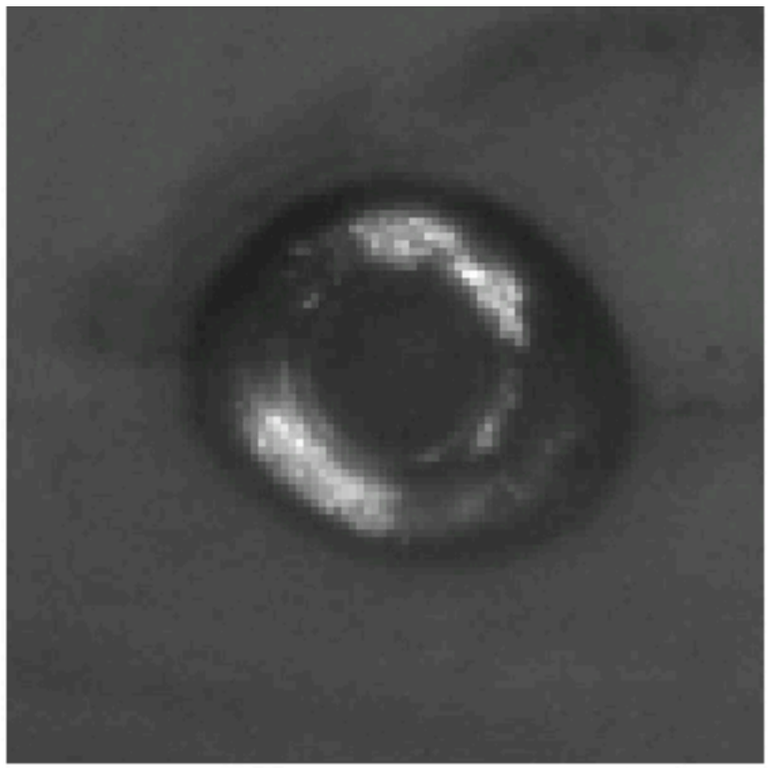
“Eyes-up” torsional movement

Superior oblique (SO)

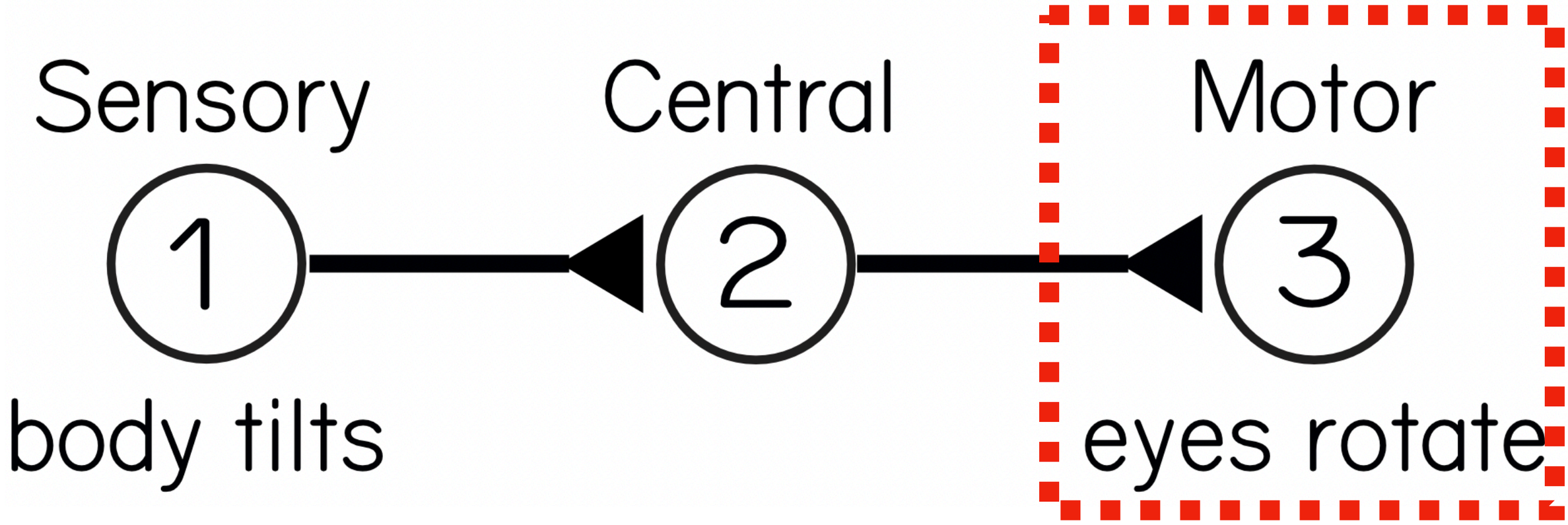


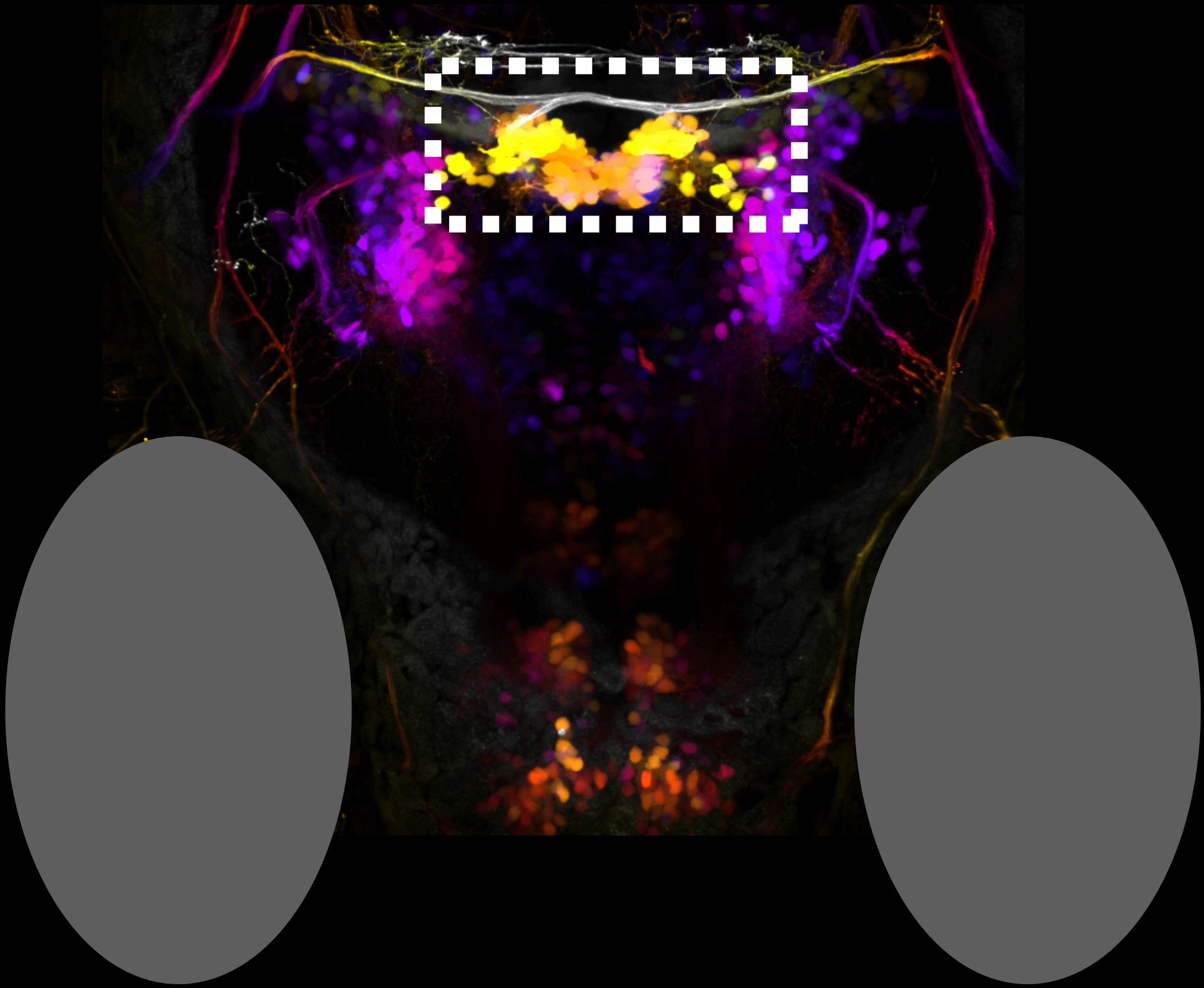
“Eyes-down” torsional movement



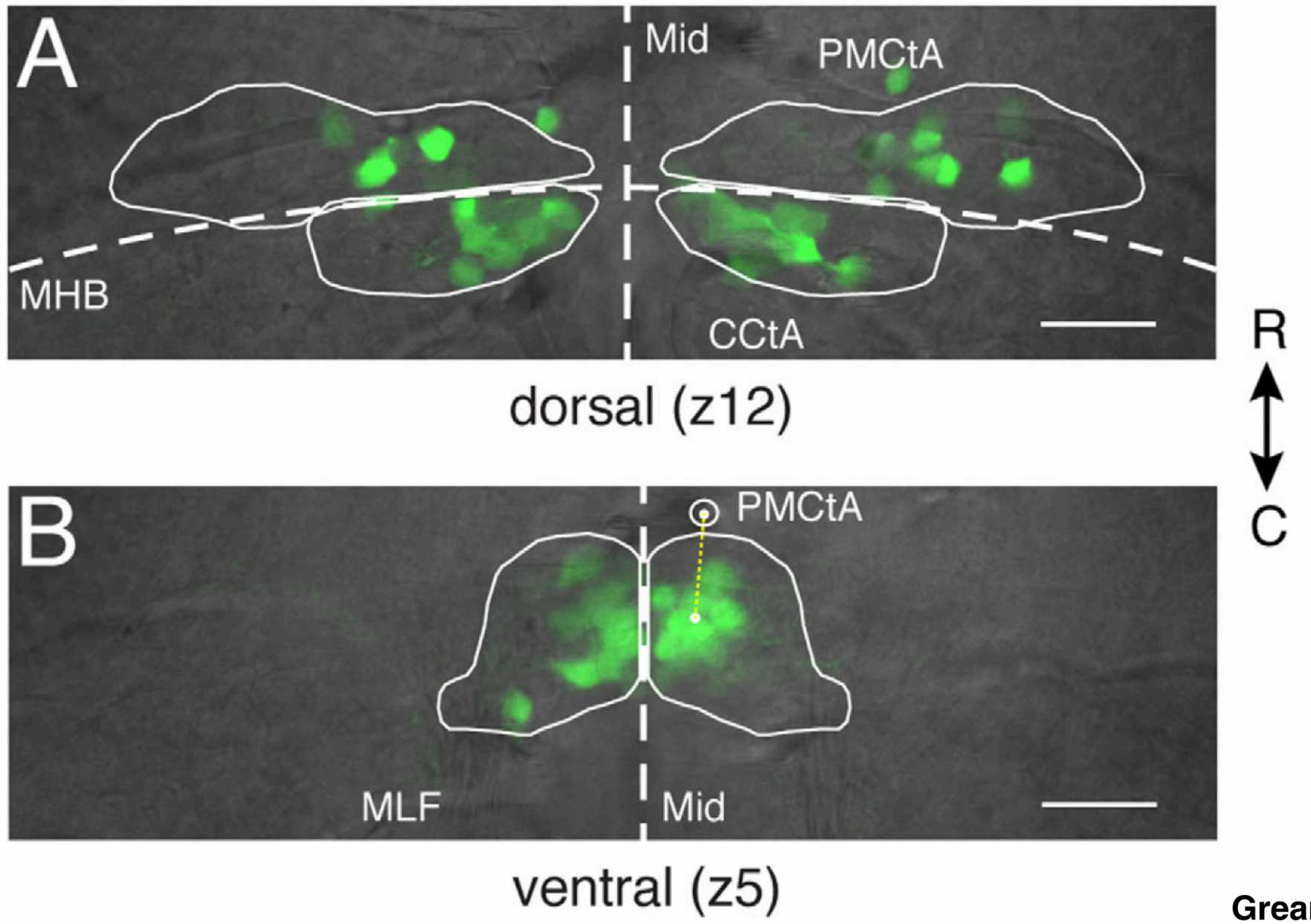


Marie Greaney


Sensory
Central
Motor
1
2
3
body tilts
eyes rotate

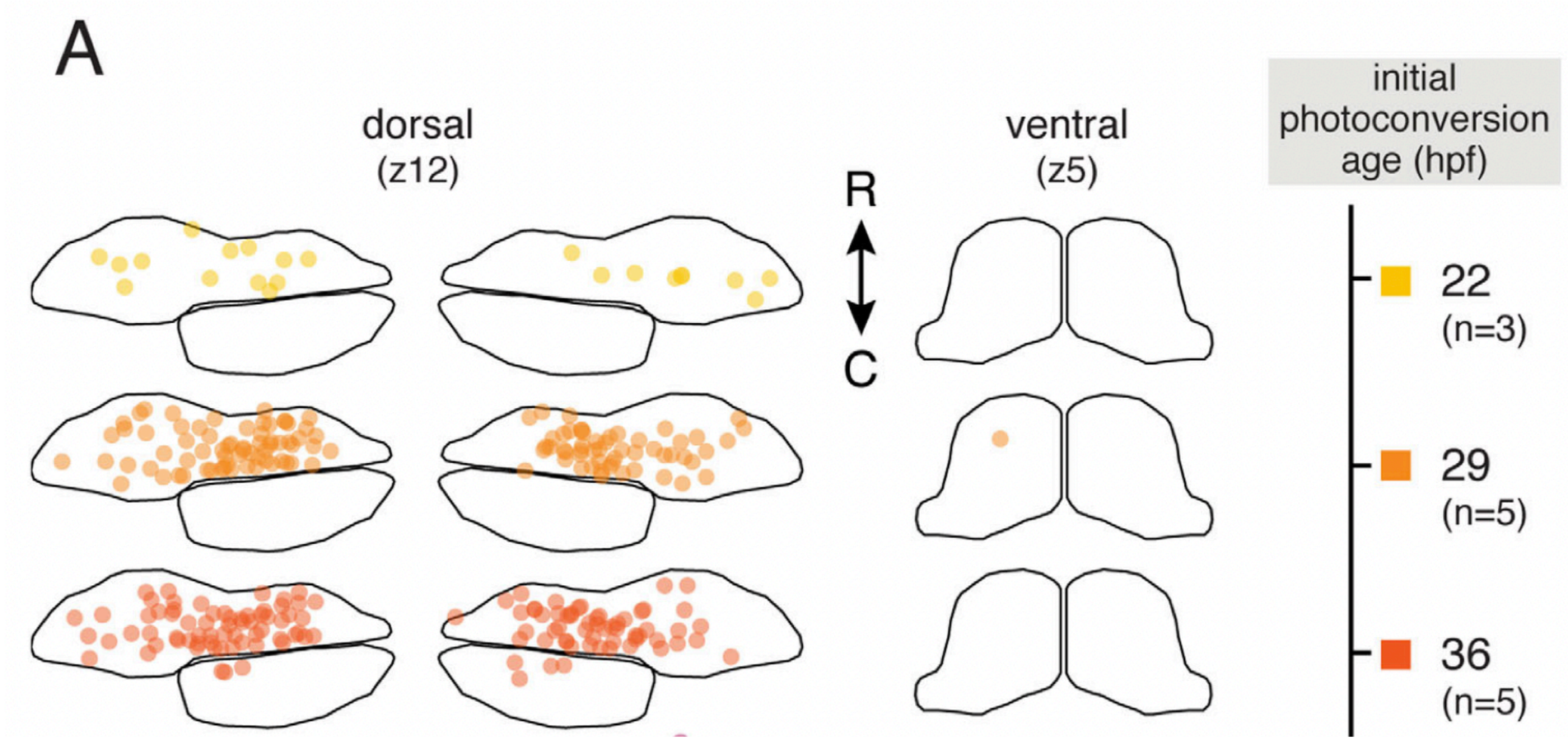


Anatomical organization of extraocular motor neurons



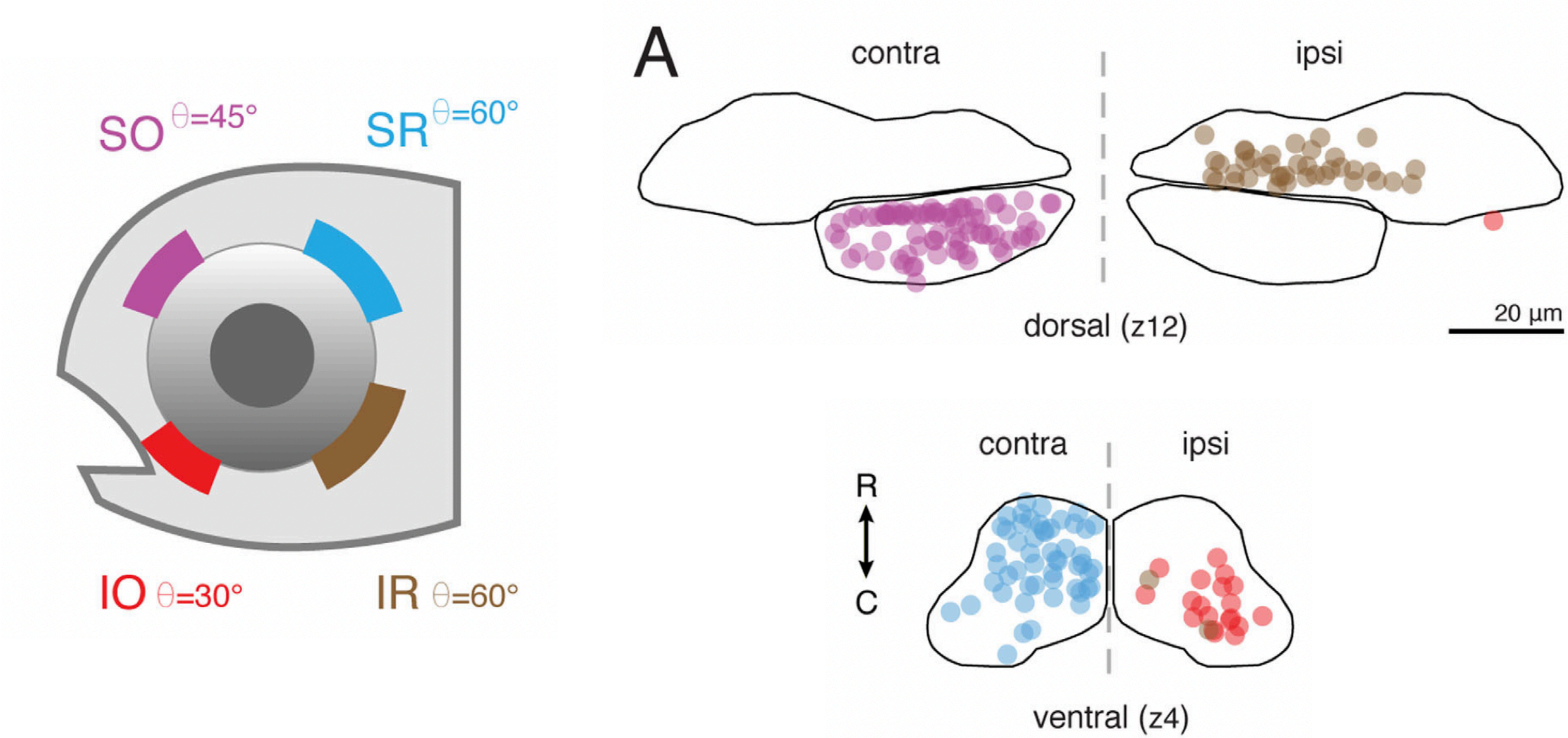
Greaney et al 2017

Motor neurons develop temporally

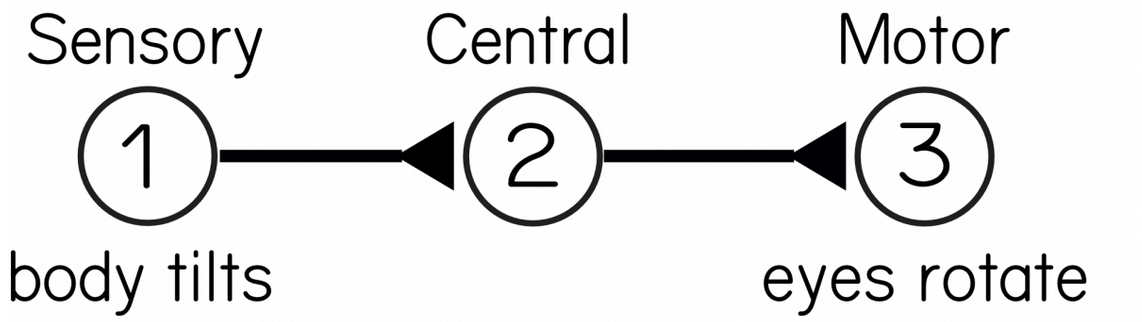


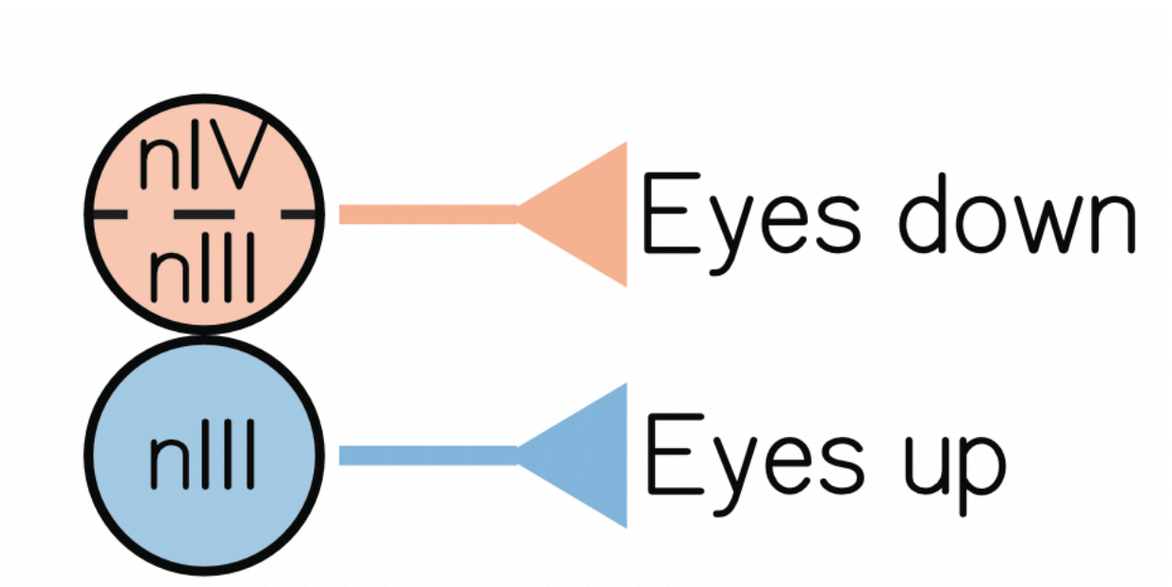
Greaney et al 2017

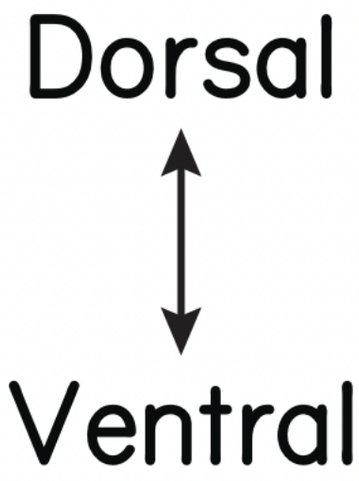
Motor neuron pools are spatially localized



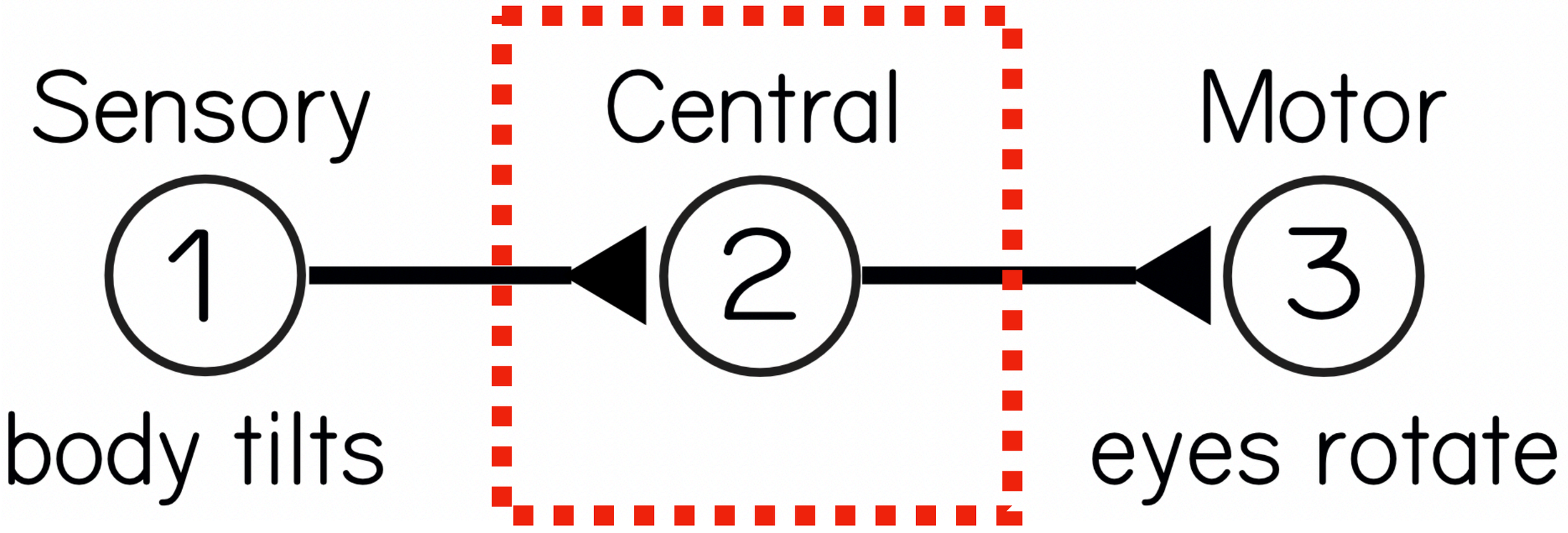
Greaney et al 2017


Sensory
Central
Motor
1
2
3
body tilts
eyes rotate


nIV
nIII
Eyes down
nIII
Eyes up


Dorsal
Ventral

Dena Goldblatt


Sensory
Central
Motor
1
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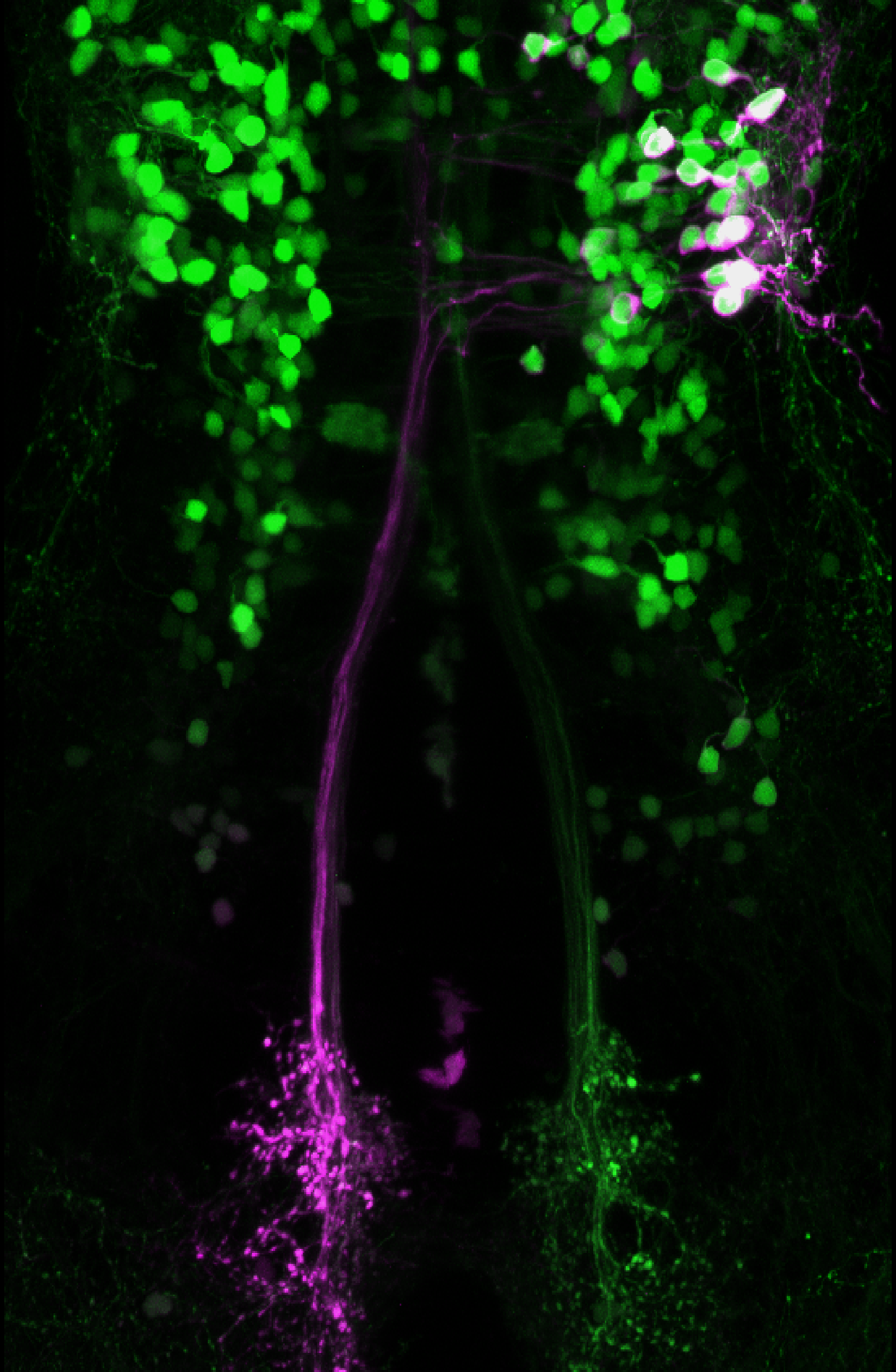
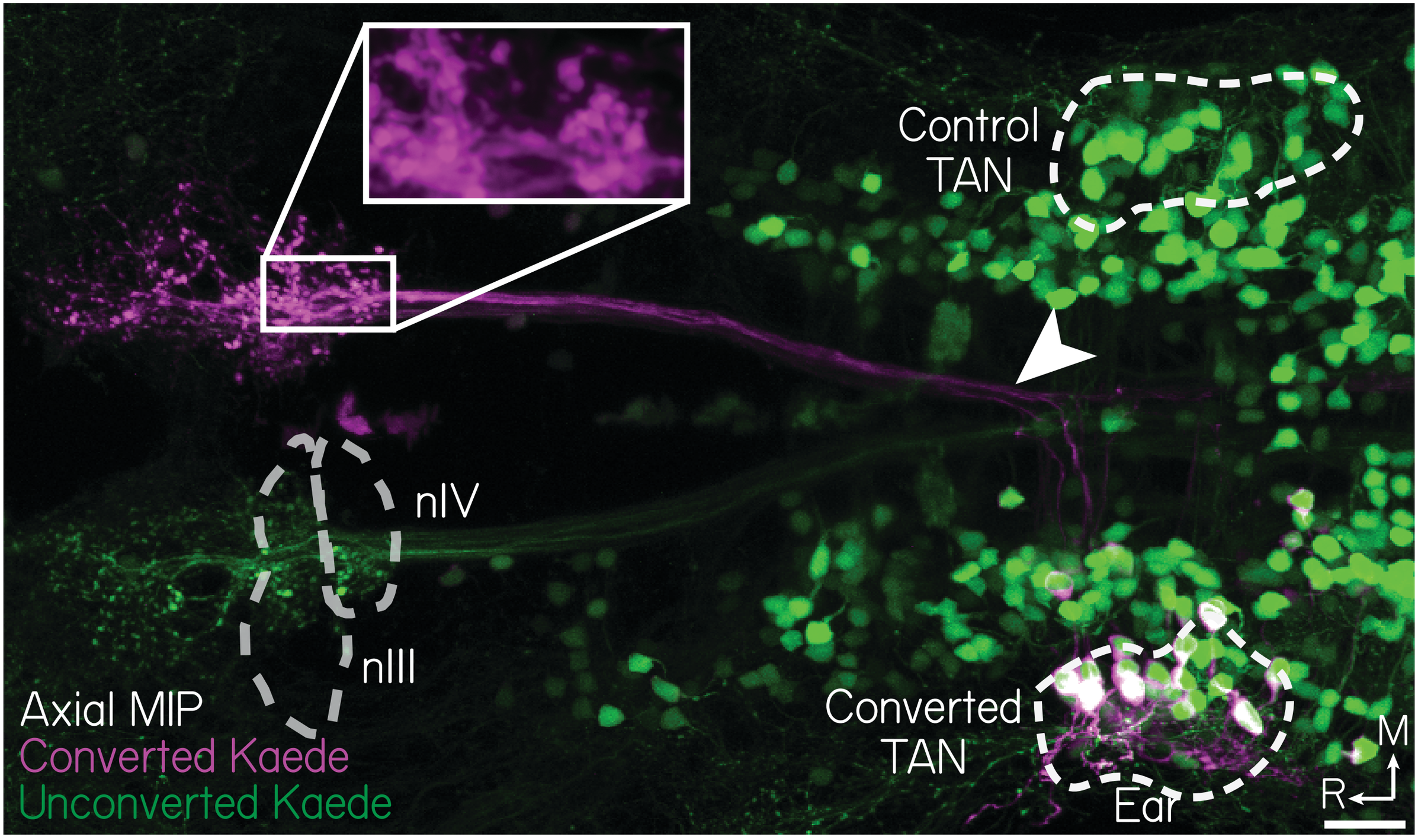
3
body tilts
eyes rotate



Localizing gaze-stabilizing central vestibular projection neurons

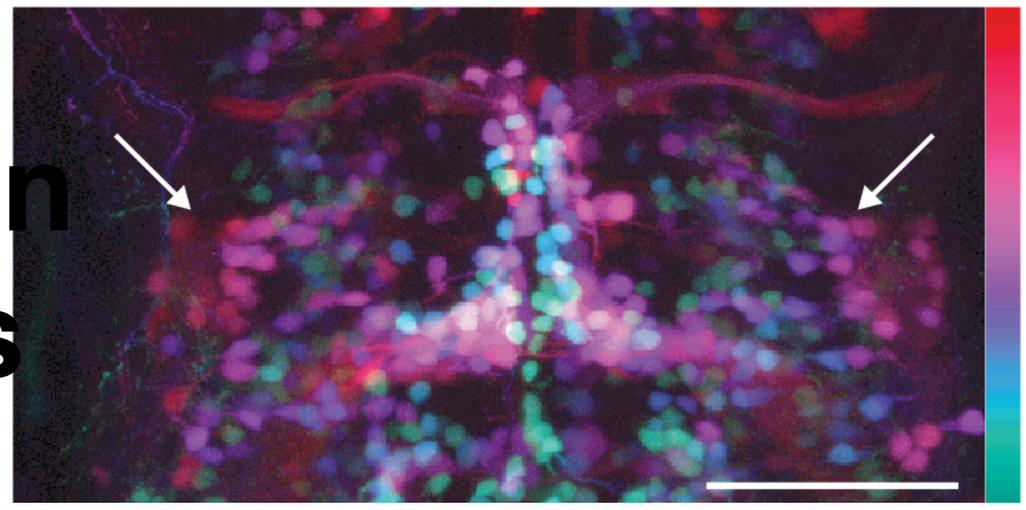


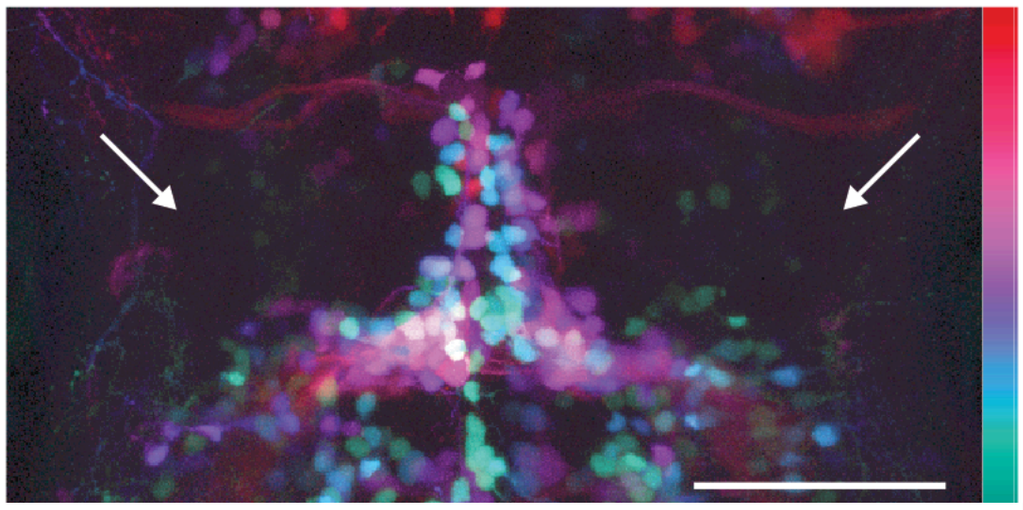
Marie Greaney

Projection neurons are indispensable for gaze stabilization

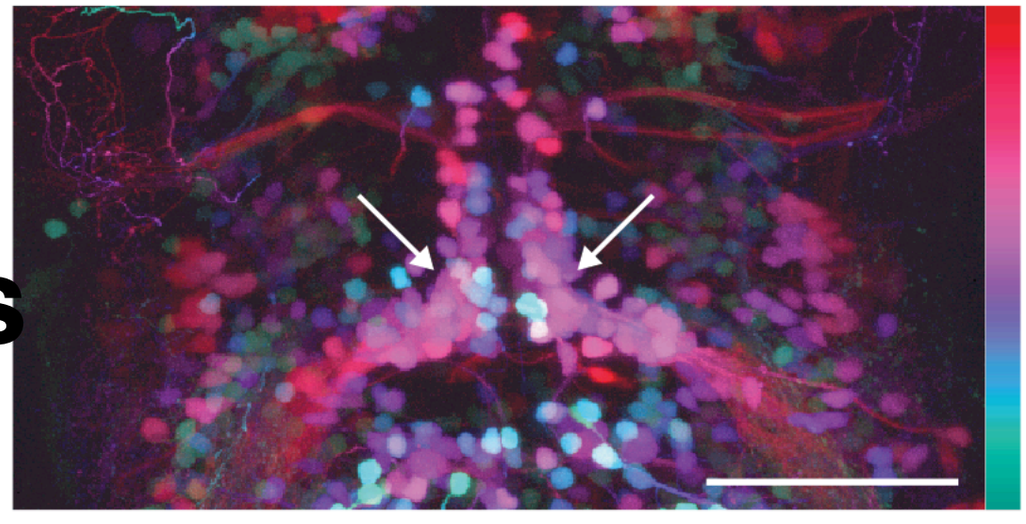
Before (Pre) **After (Post)**

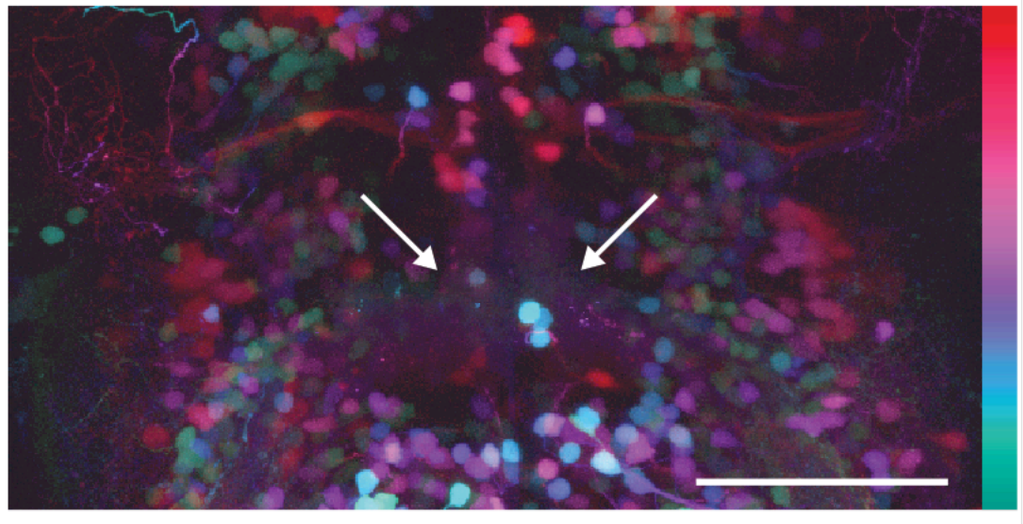
Projection Neurons





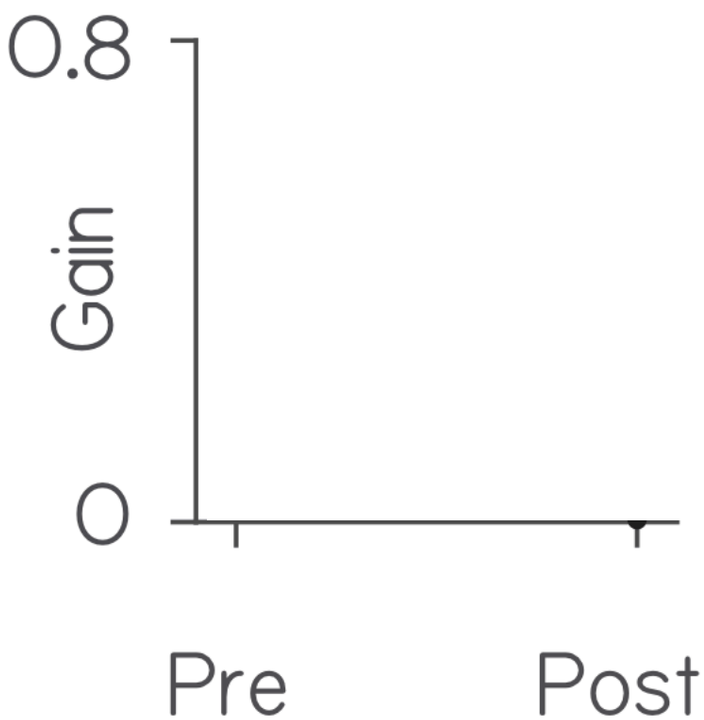
Other Neurons



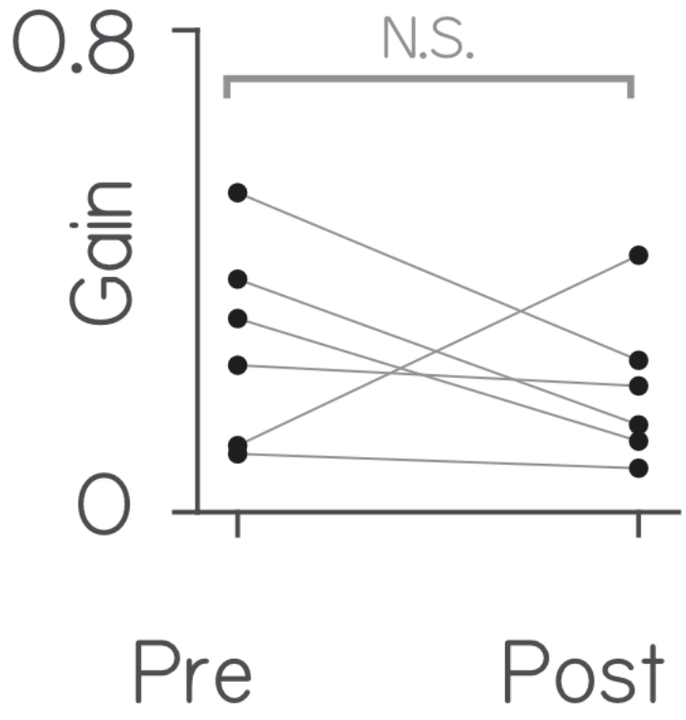


Schoppik et al 2018

Projection neurons are indispensable for gaze stabilization



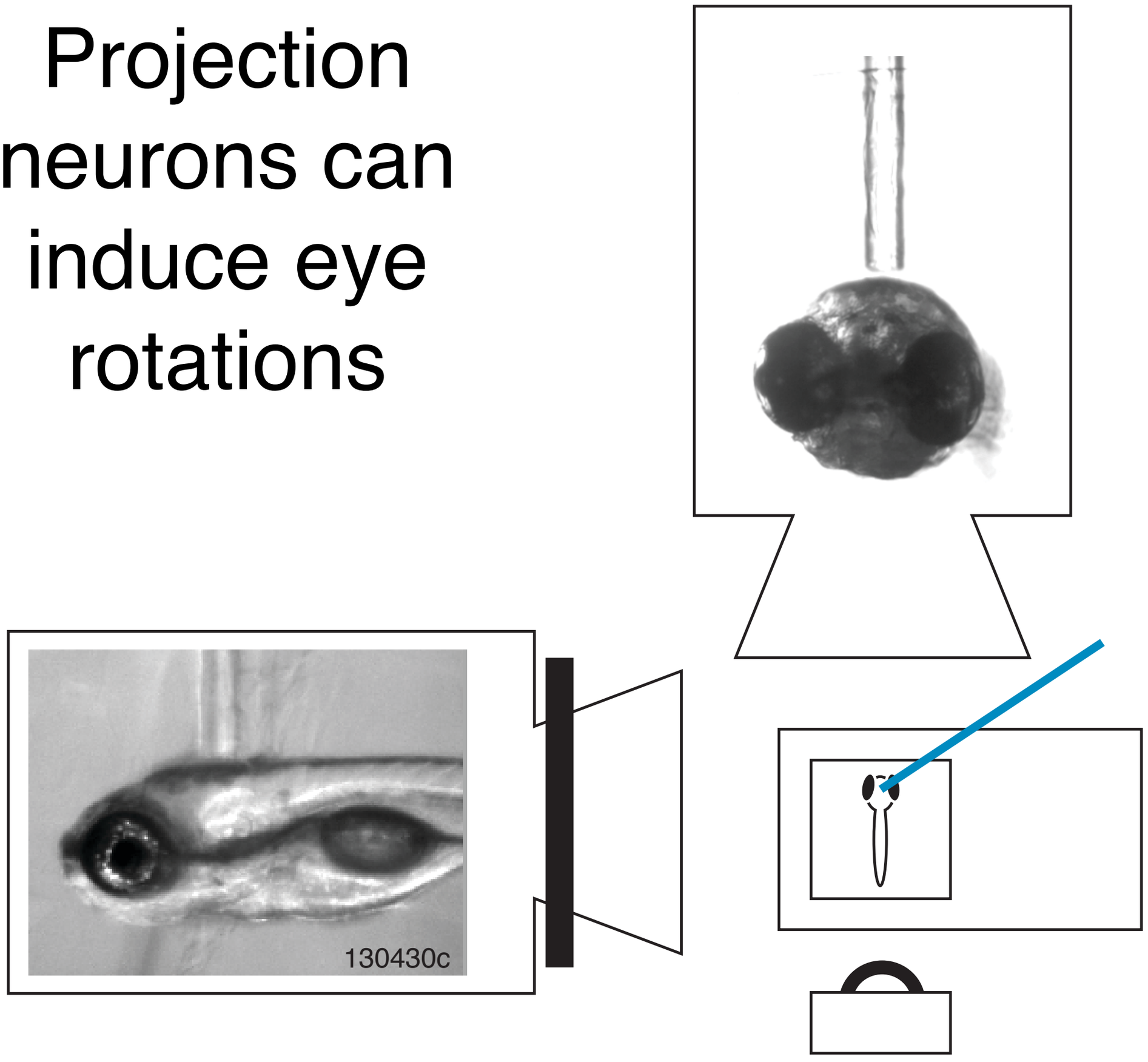
Projection Neurons



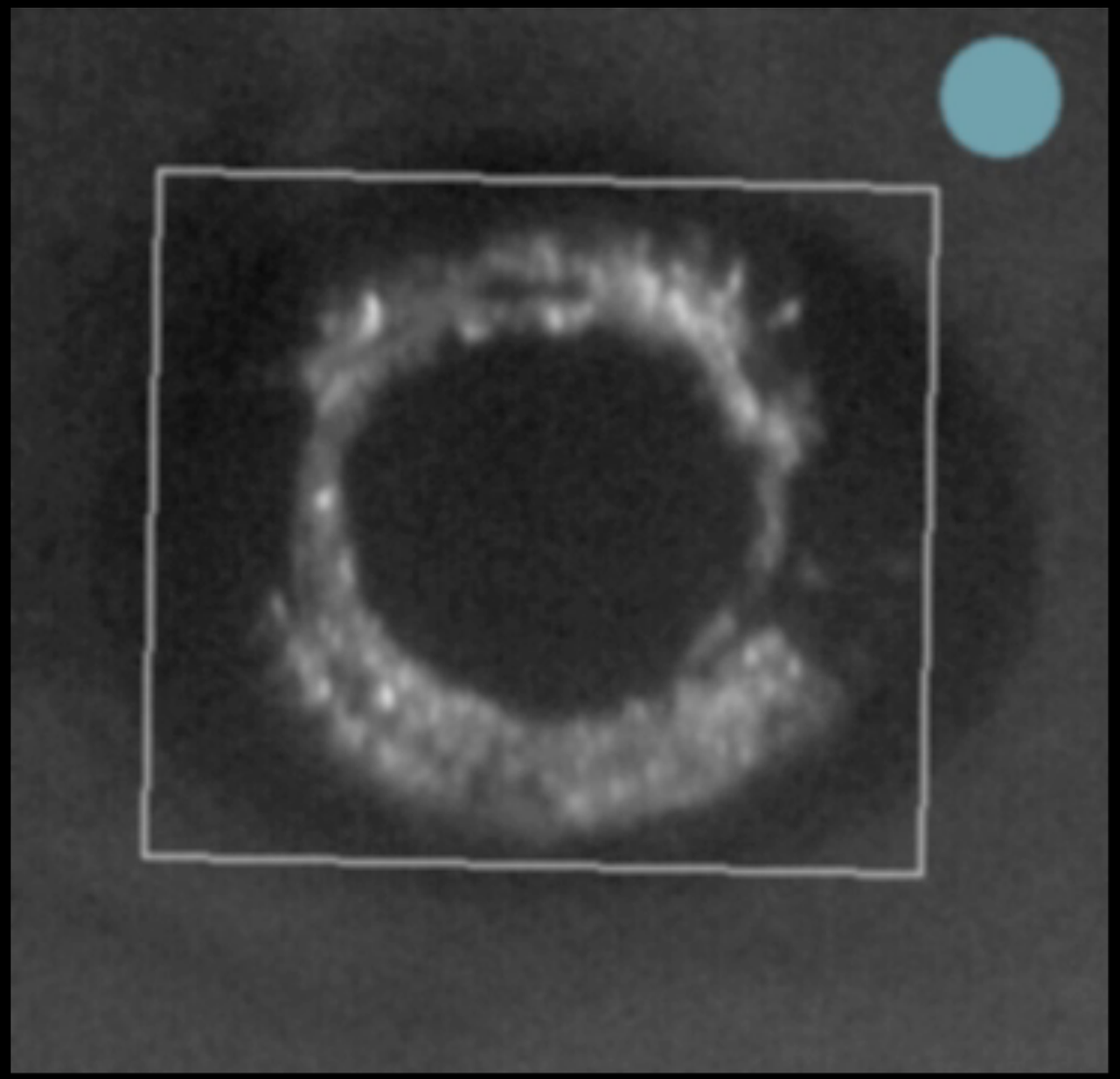
Other Neurons

Schoppik et al 2018

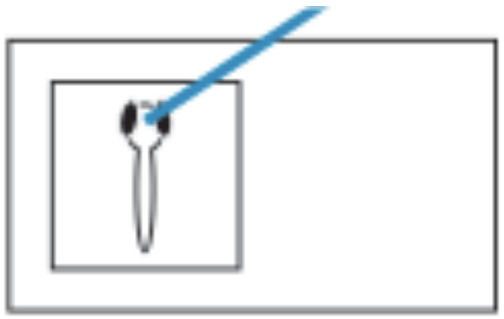
Projection neurons can induce eye rotations

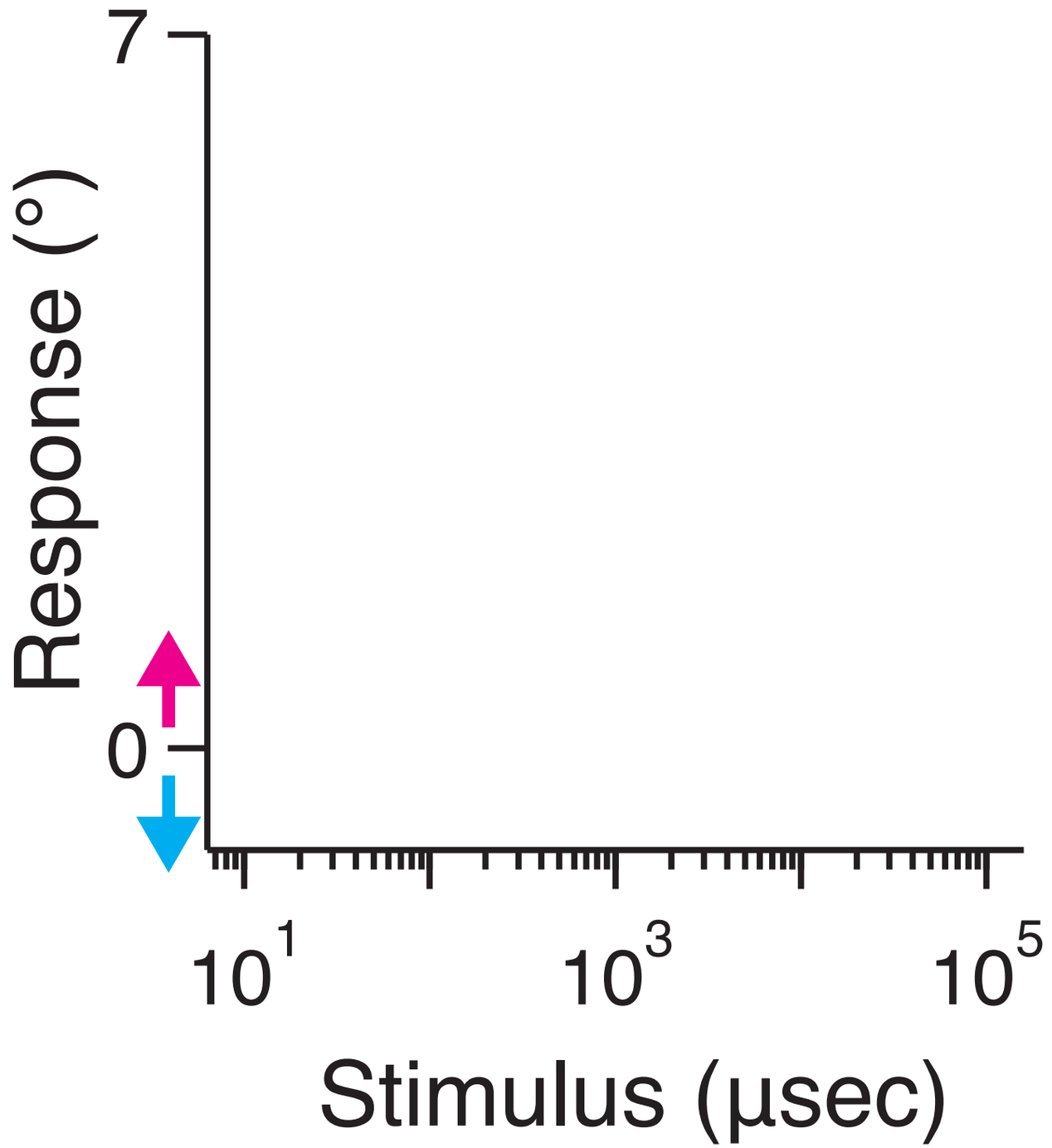


Schoppik et al 2018



Projection neurons can induce eye rotations





Schoppik et al 2018

Birthdating projection neurons

Born

Not born

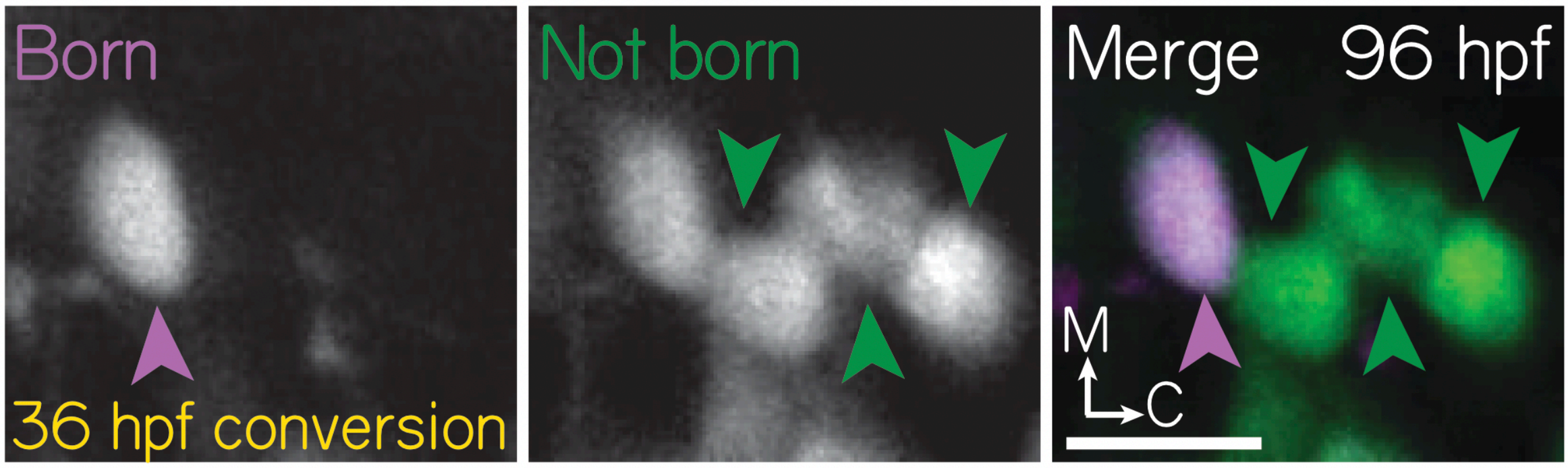
Photoconversion

Imaging

22 30 36 42 48 96-120

Hours post-fertilization (hpf)

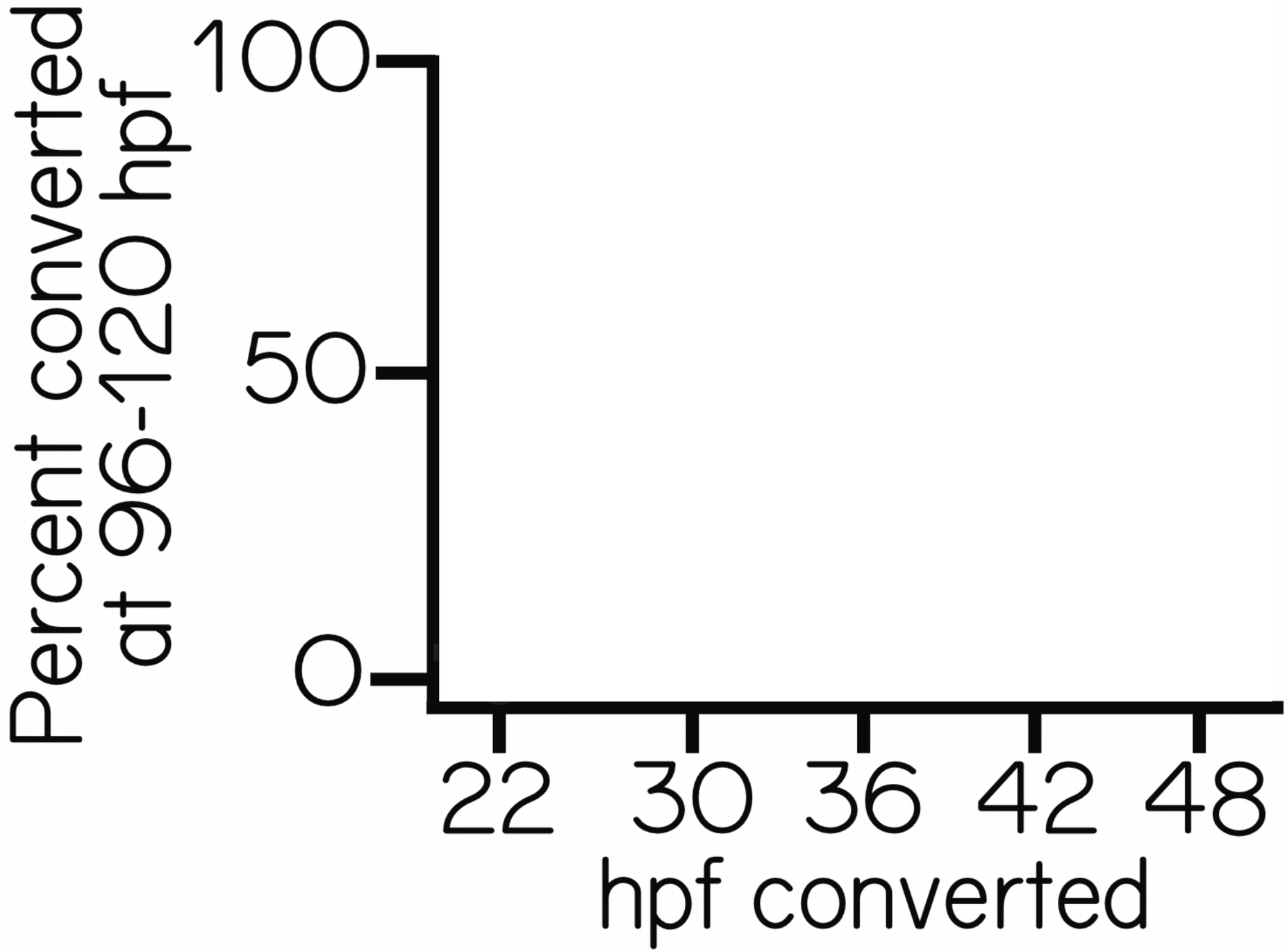
Birthdating projection neurons



Born

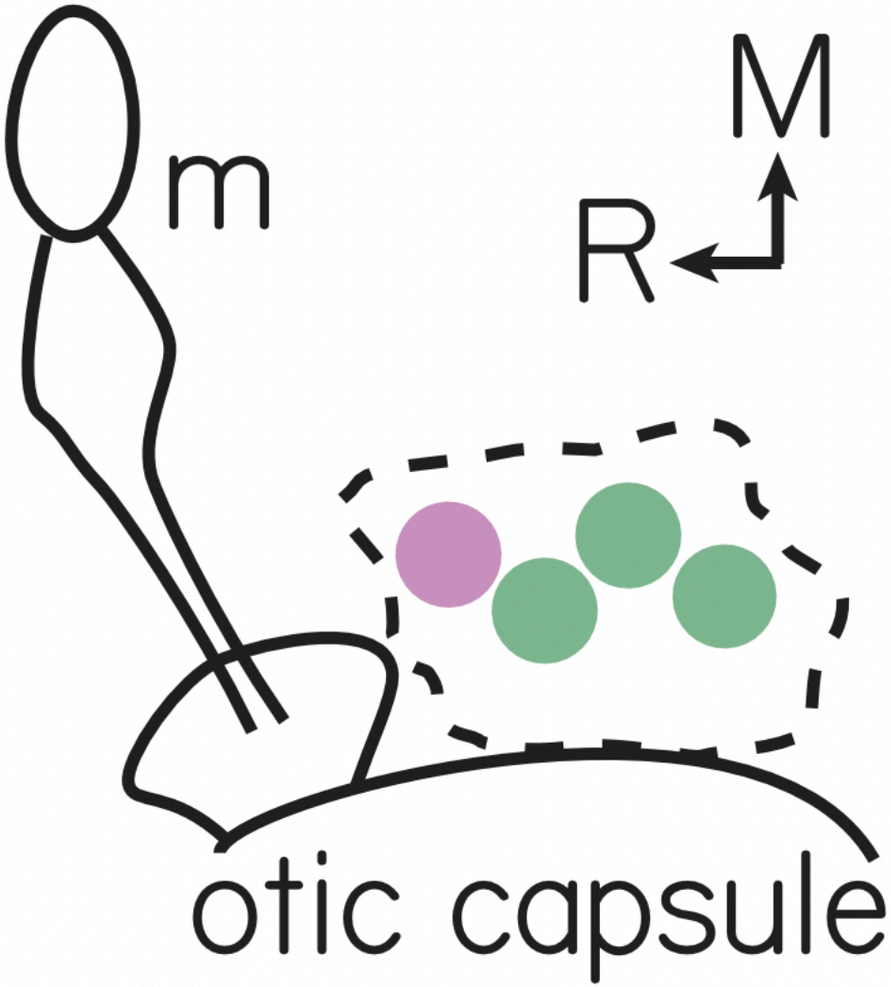
Not born

Birthdating projection neurons

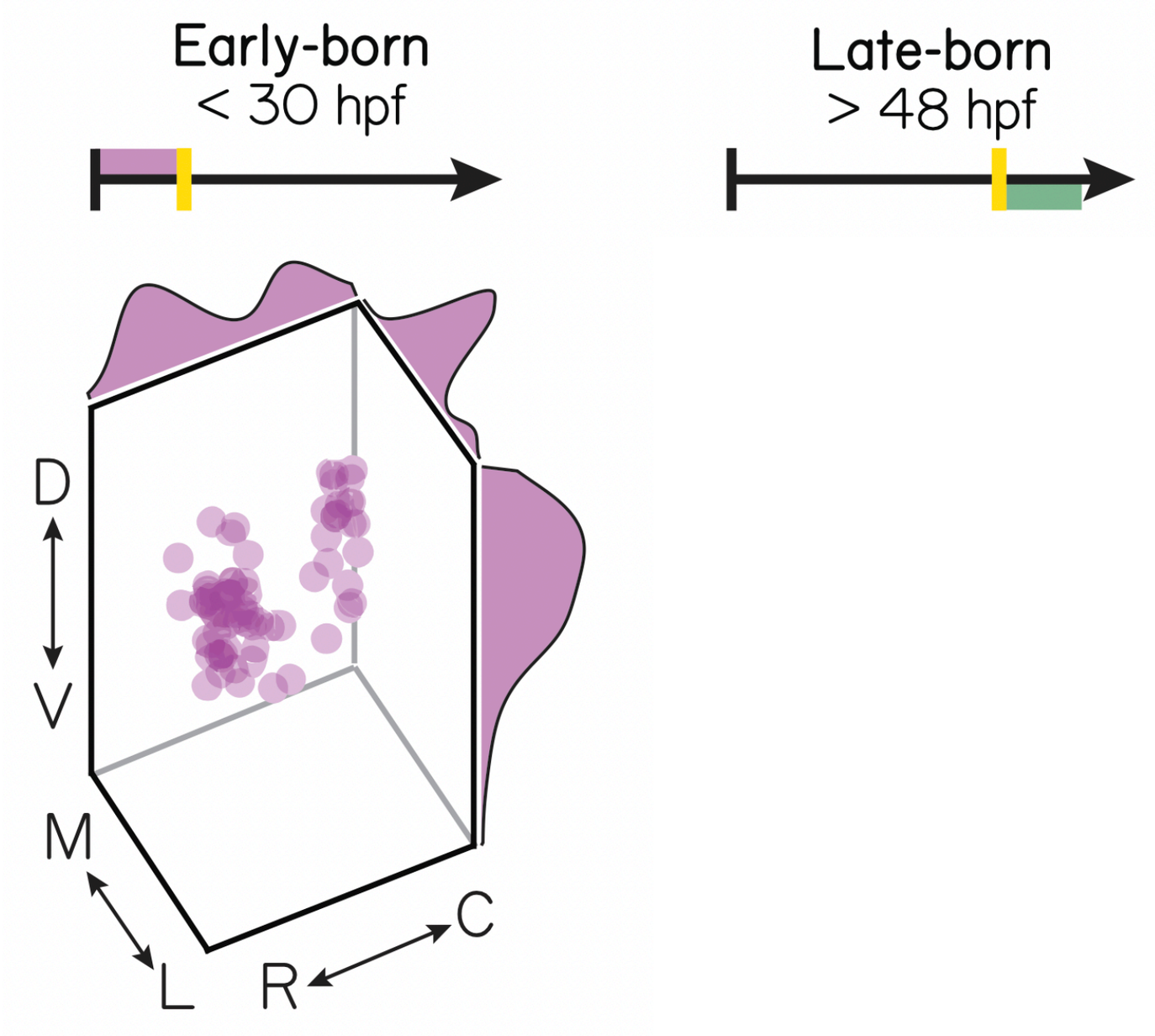


Localizing birthdated projection neurons in space

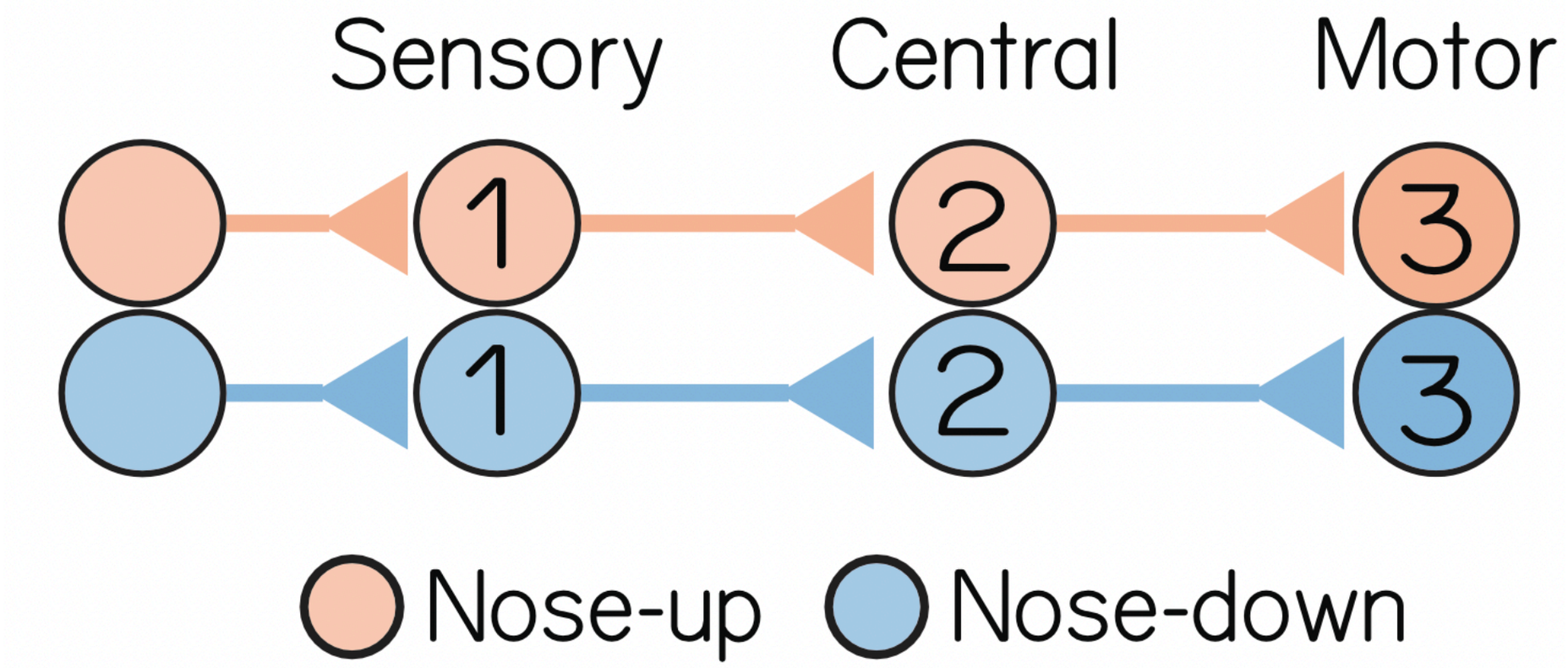
Landmarks for
brain registration



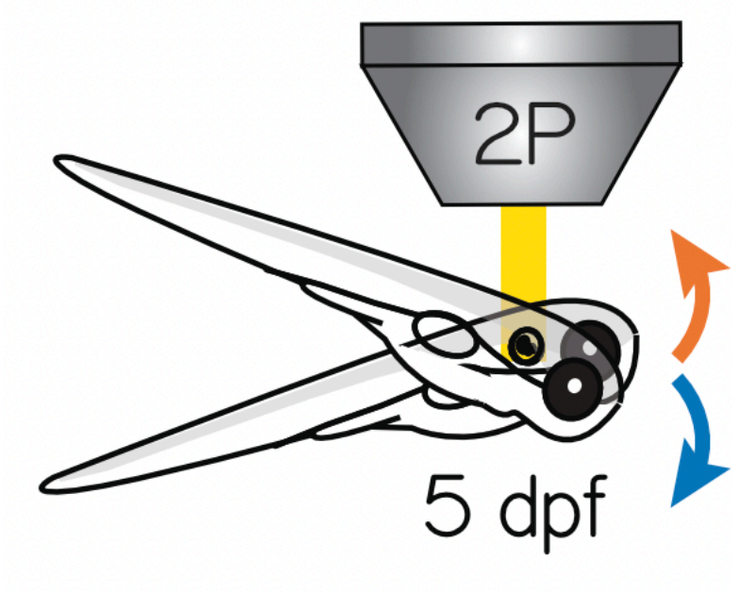
Early and late-born projection neurons are differentially organized in space

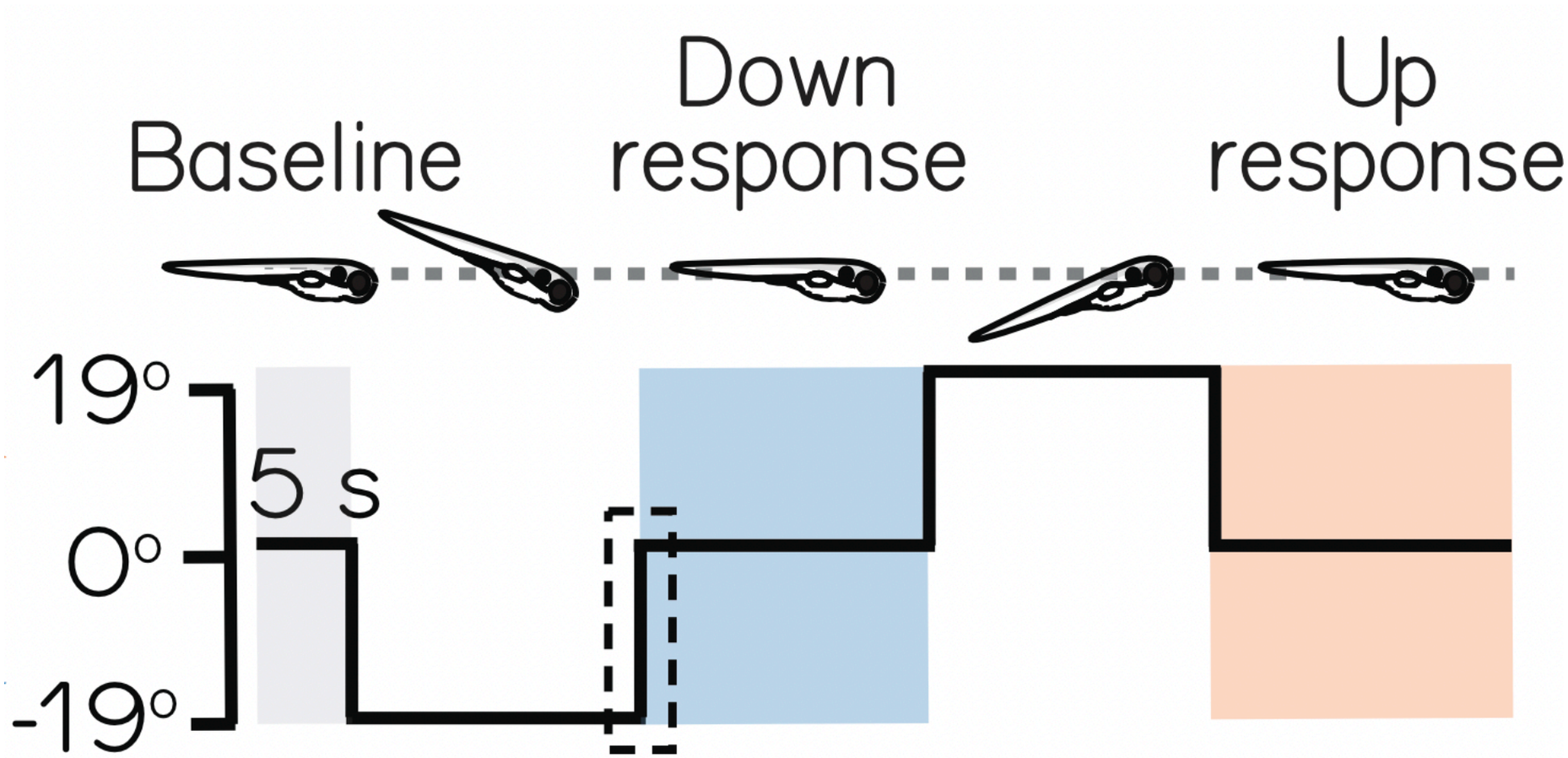


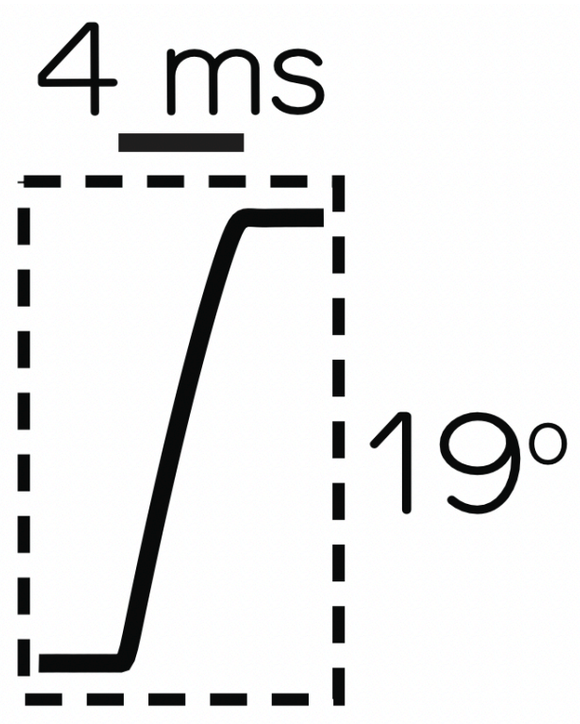
The vertical vestibulo-ocular reflex is organized into channels



Functional classification of projection neurons



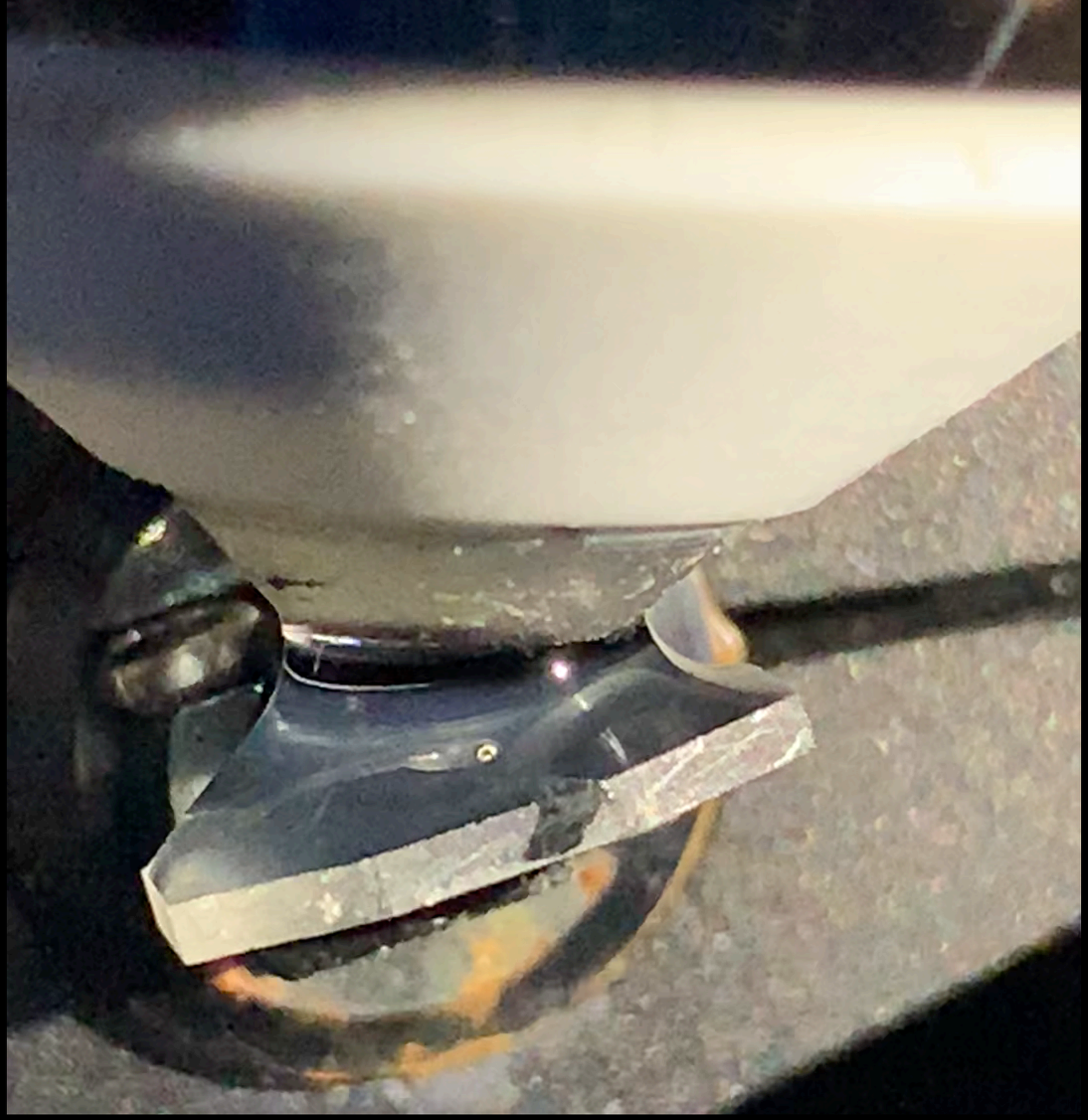

Baseline
Down response
Up response
19°
0°
-19°
5 s


4 ms
19°

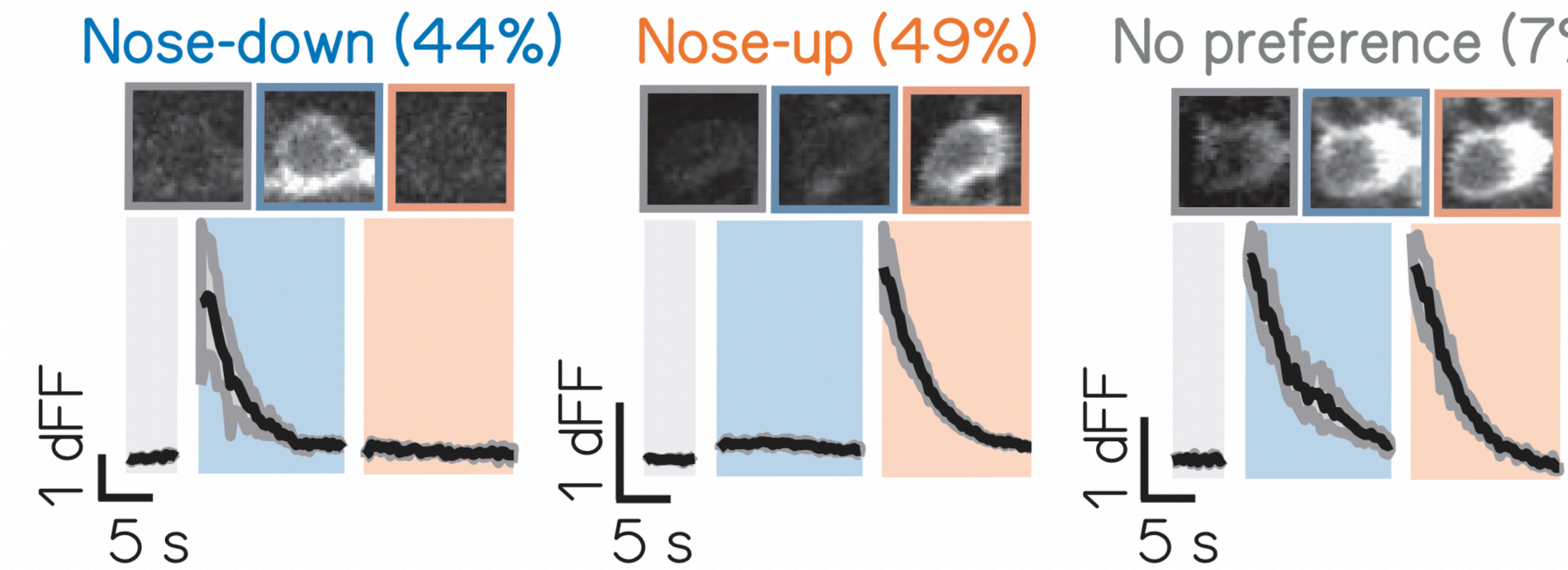
Objective

Fish

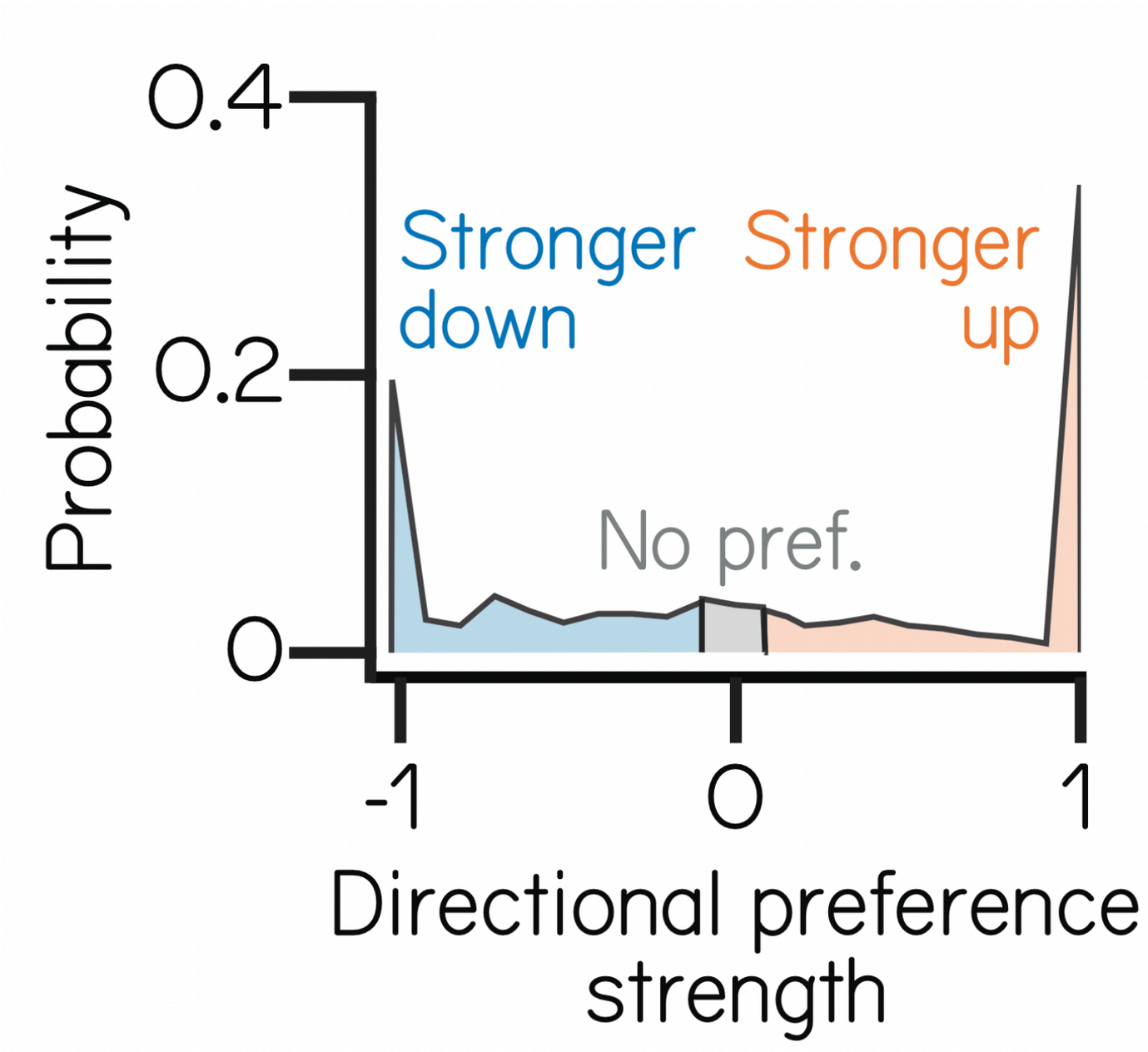
Galvo



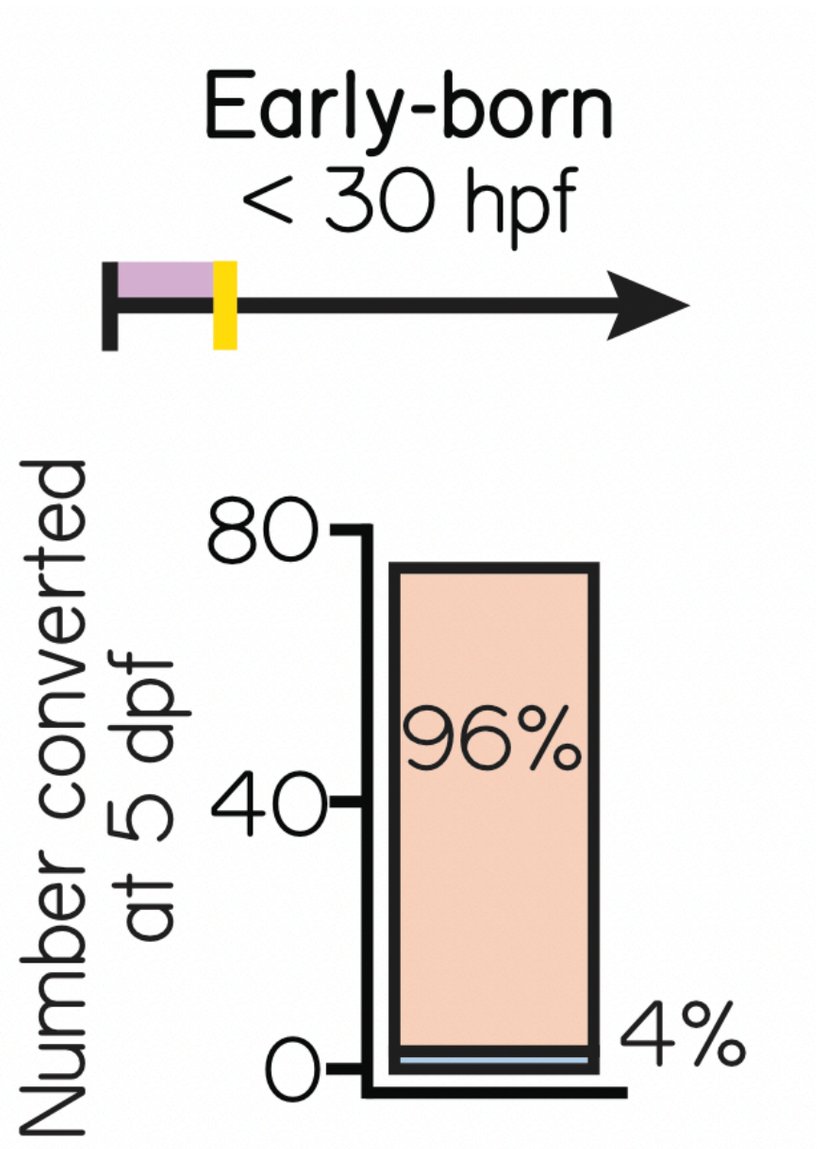
Projection neurons can be classified by their response to tilts



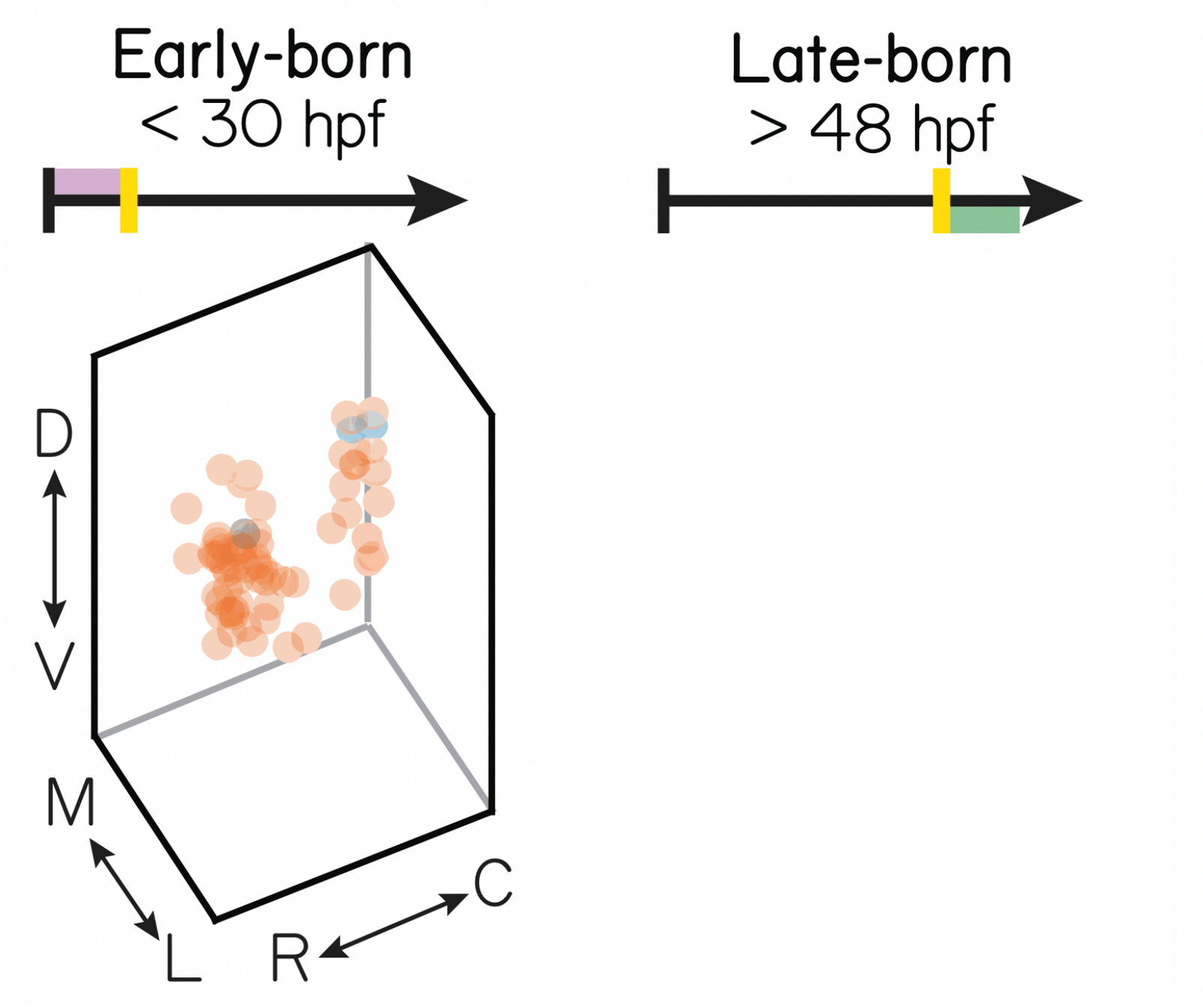
Projection neurons can be classified by their response to tilts



Birthdate predicts the response to tilts…

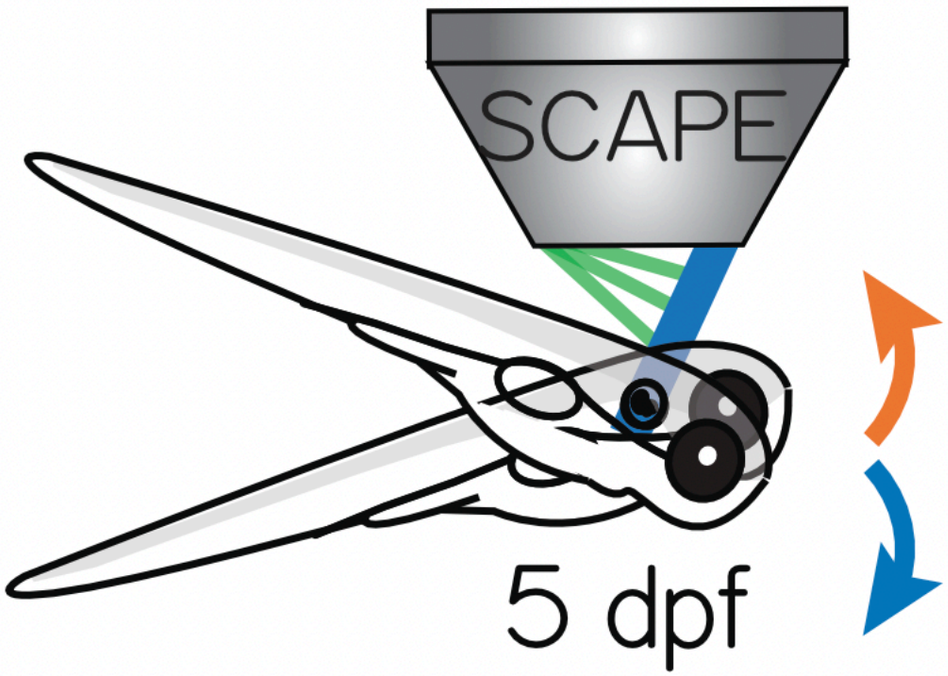


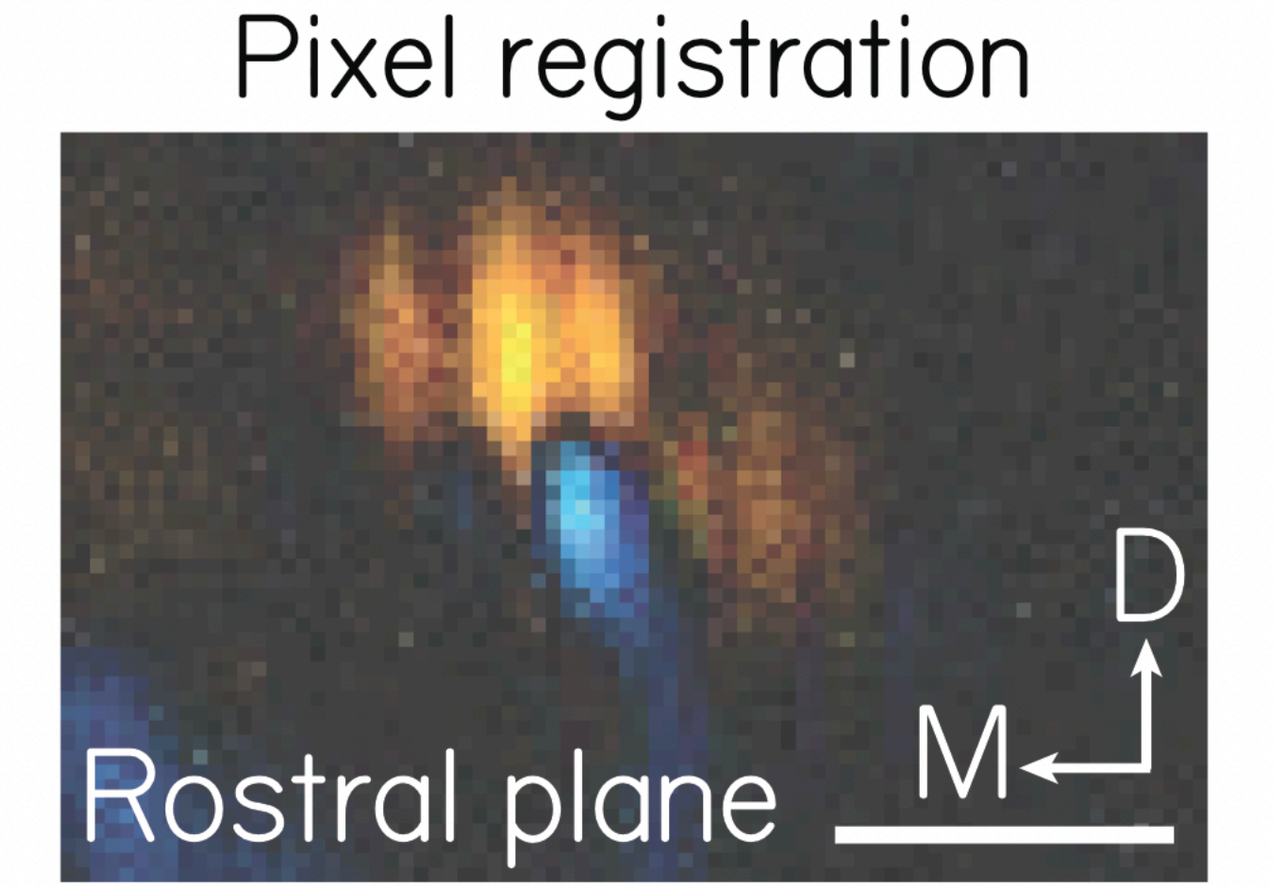
…and organizes projection neurons in space.



Prof. Elizabeth MC Hillman,

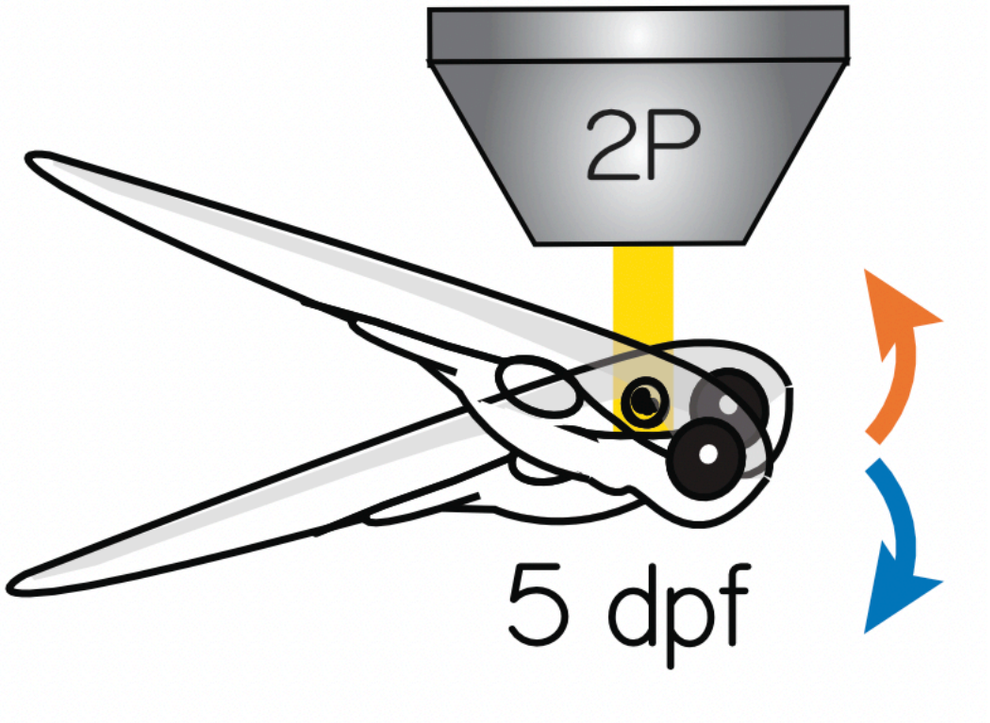
Wenze Li
Venkata Voleti
Citlali Perez Campos
Kripa Patel

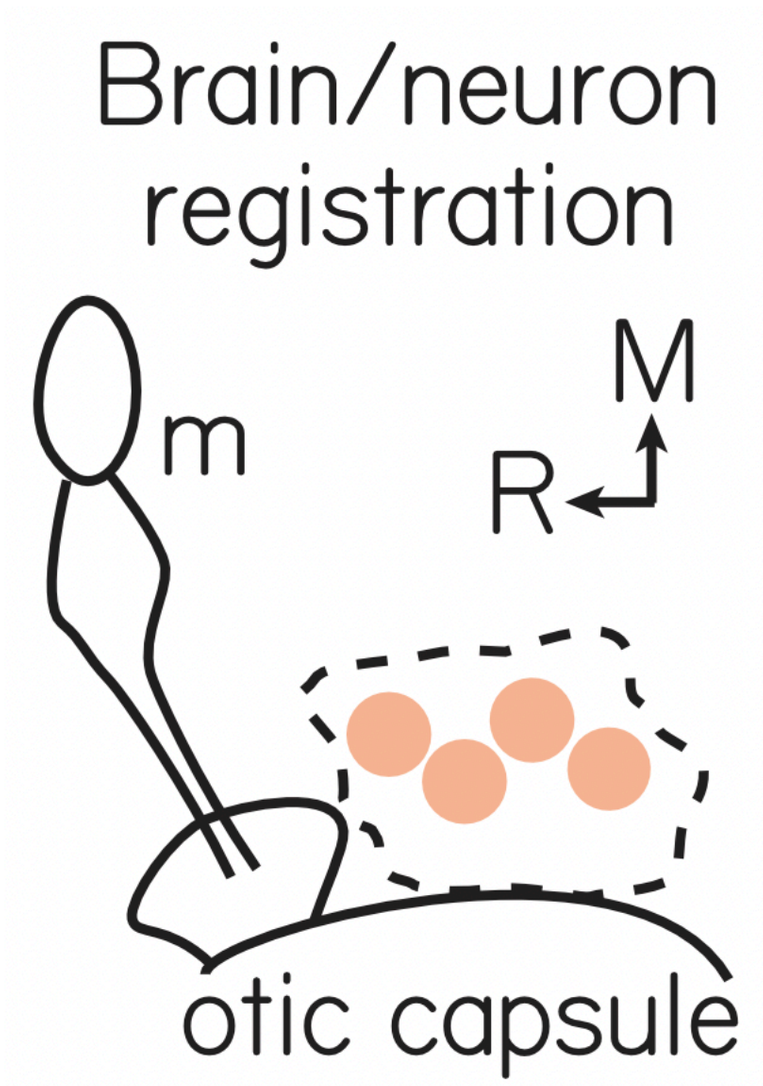




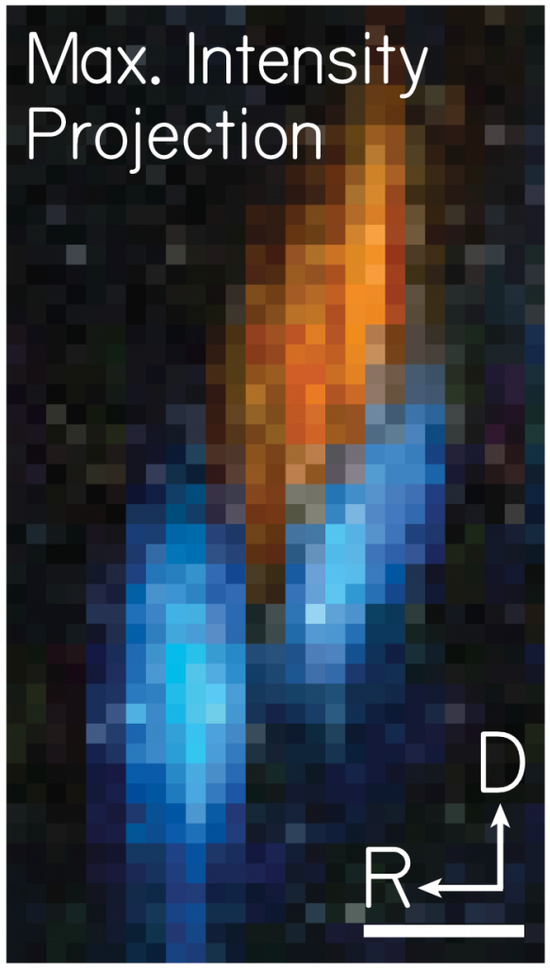
Stronger nose-up

Stronger nose-down

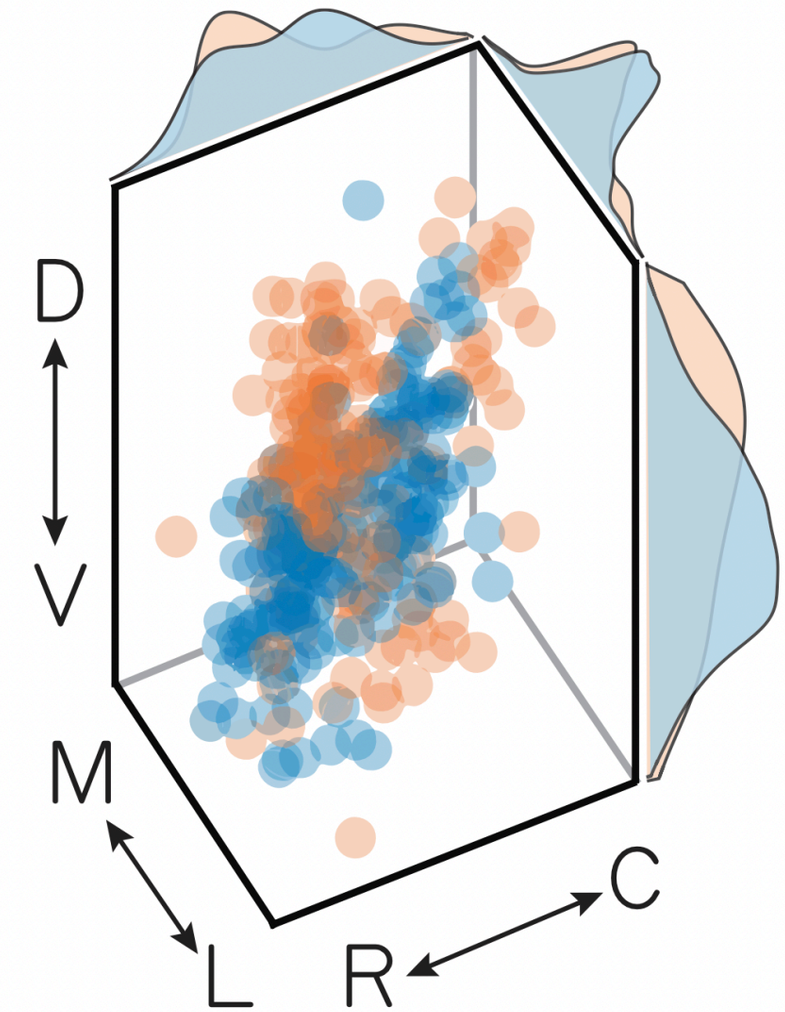

2P
5 dpf

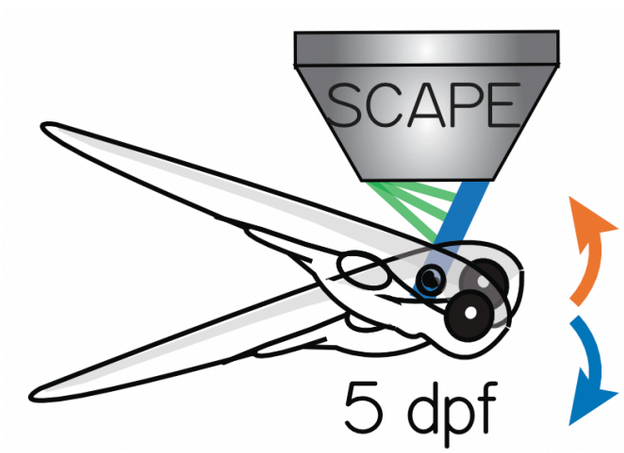

Brain/neuron registration
m
M
R
otic capsule

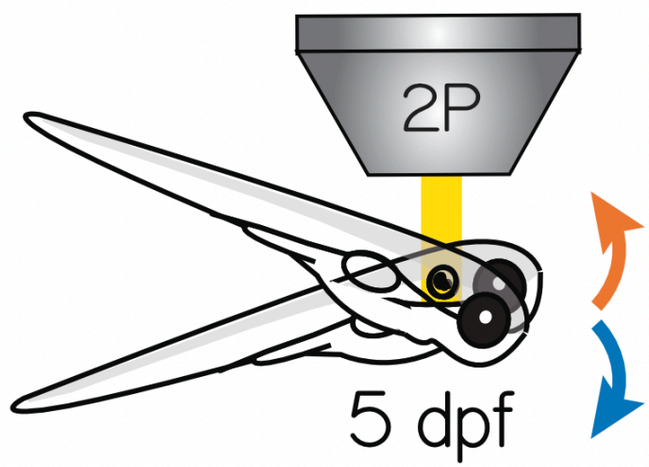
Volumetric map

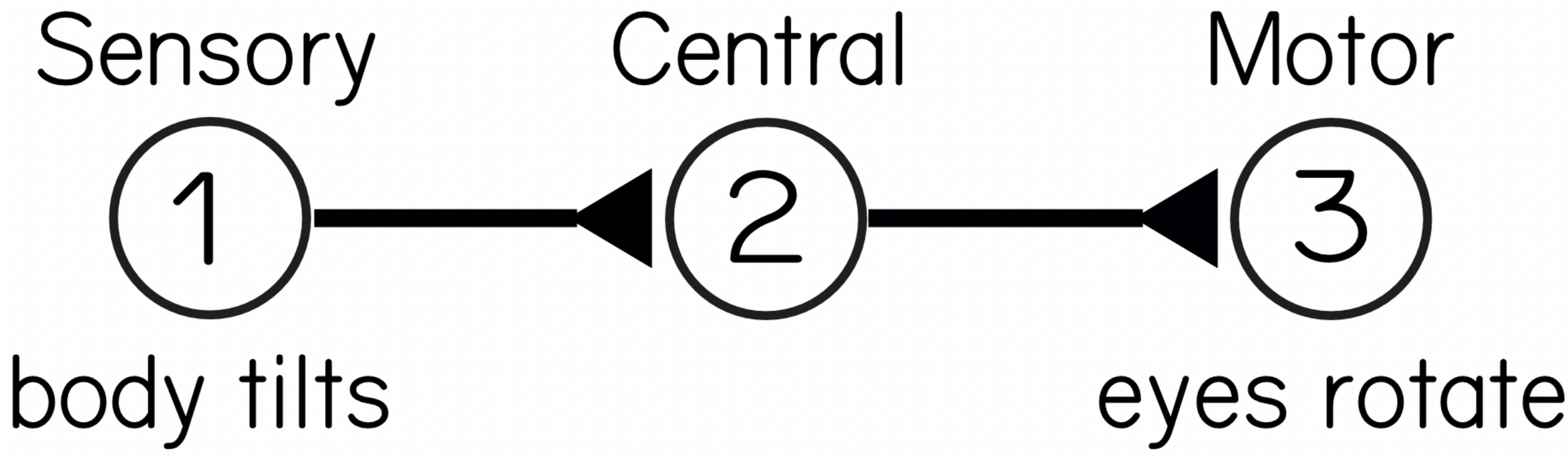


Two-photon map

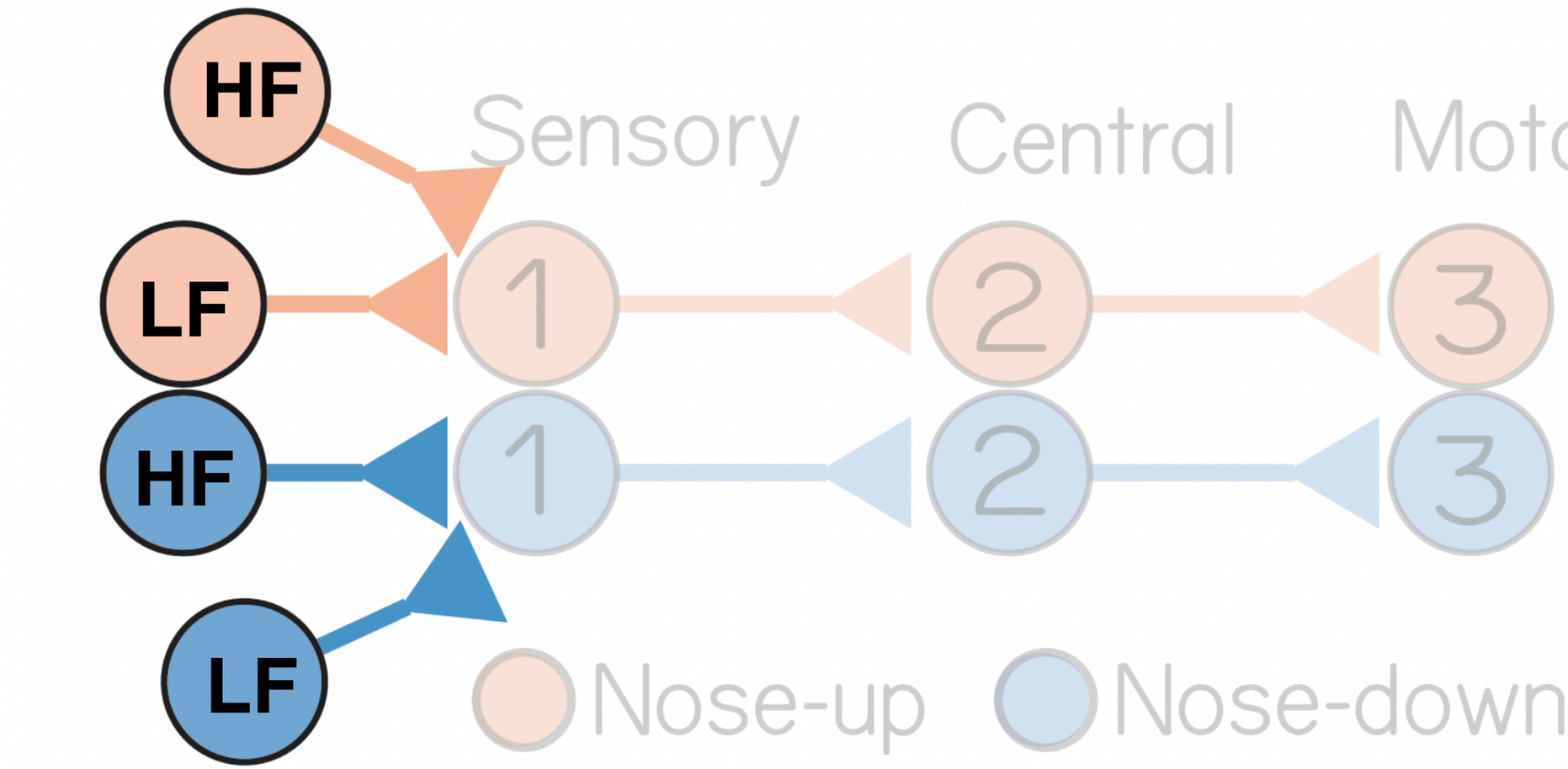






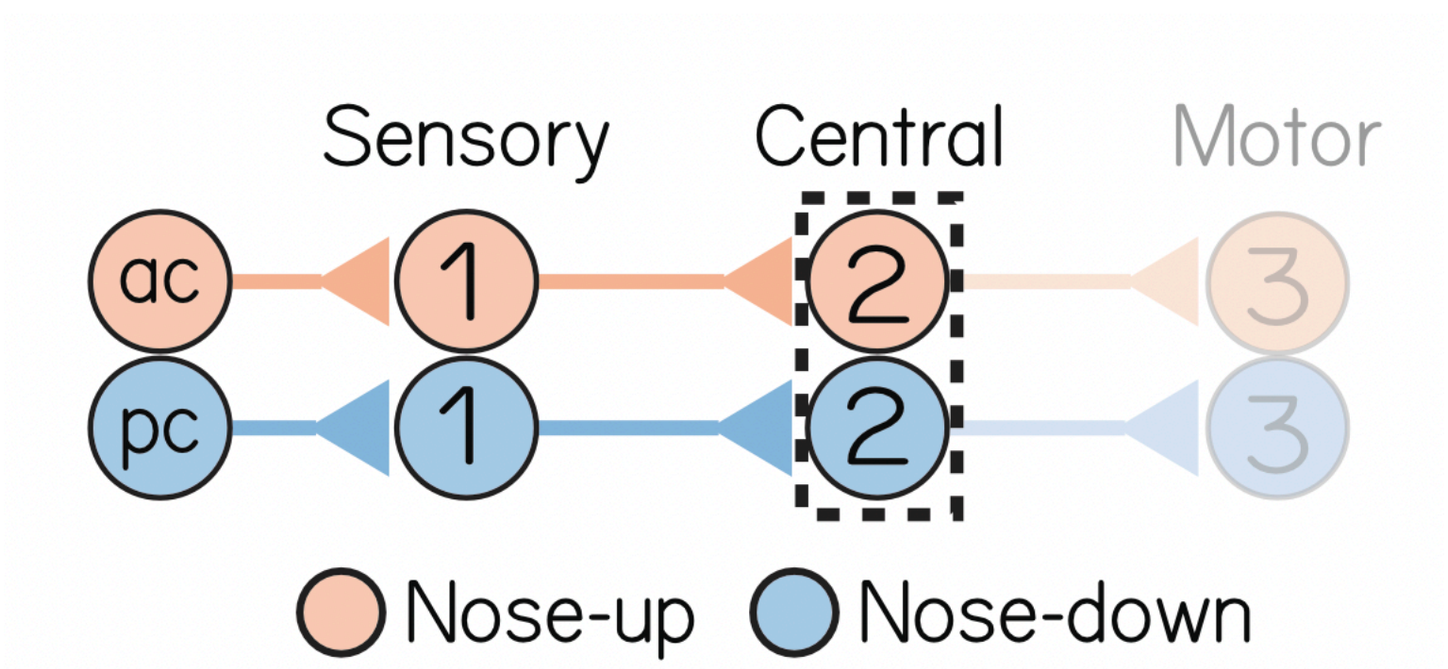

Sensory
Central
Motor
1
2
3
body tilts
eyes rotate

There are two transducers for tilt: otoliths and canals

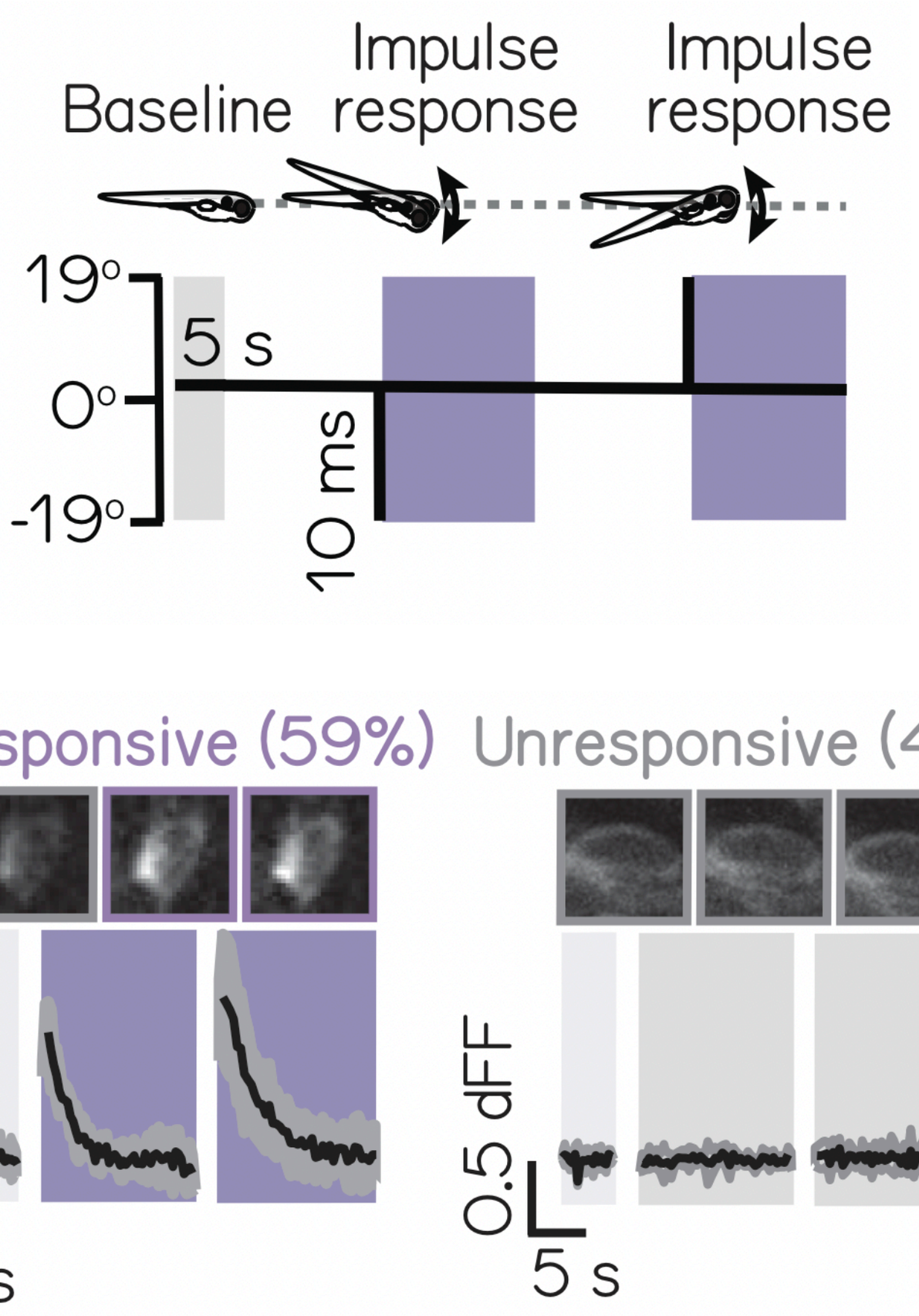


F = high pass (canals), LF = low pass (otoliths)

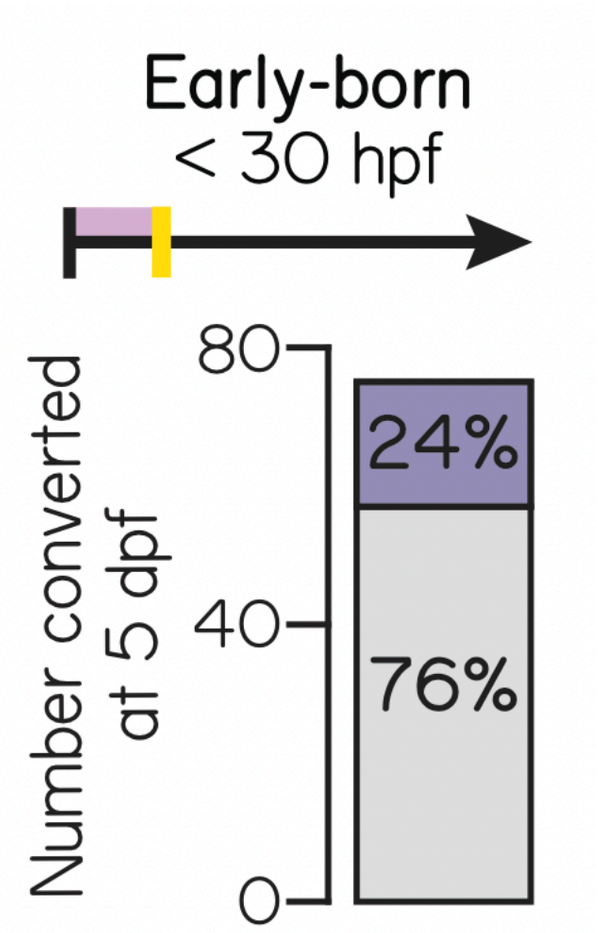
Birthdate organizes projection neurons that receive input from the canals

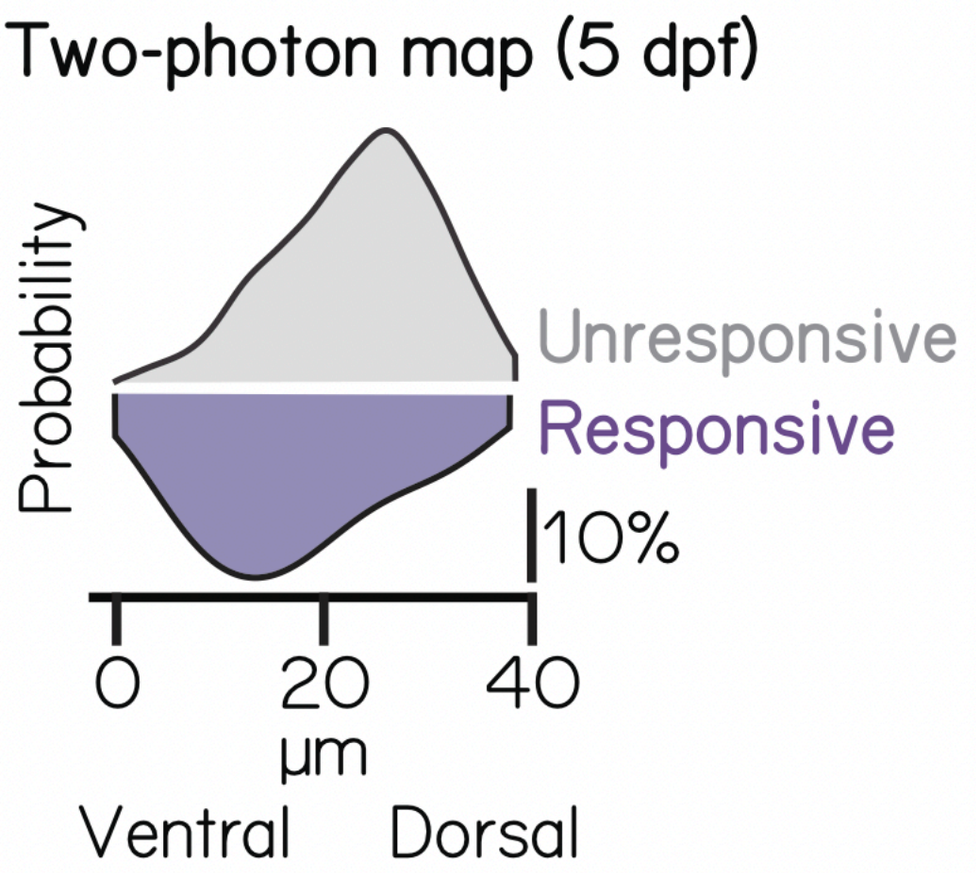


ac/pc = high pass (anterior canal / posterior canal)

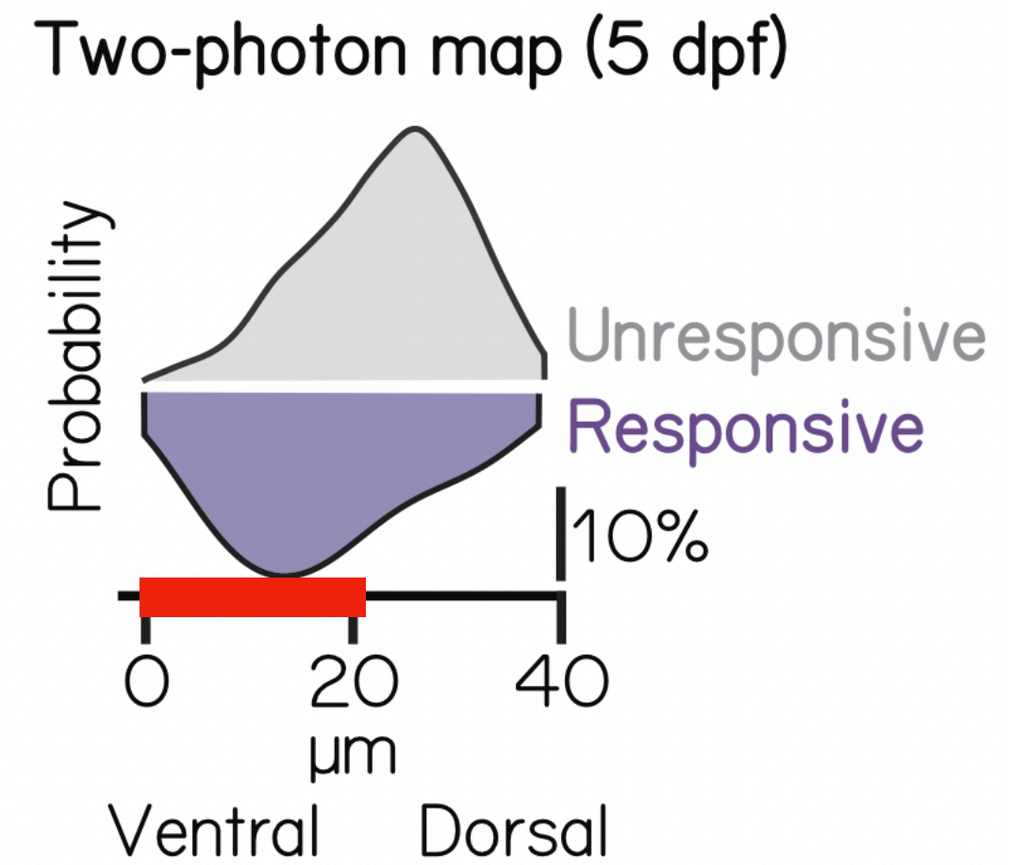

Baseline
Impulse response
Impulse response
19°
0°
-19°
5 s
10 ms
Responsive (59%)
Unresponsive (41%)
0.5 dFF
5 s
0.5 dFF
5 s

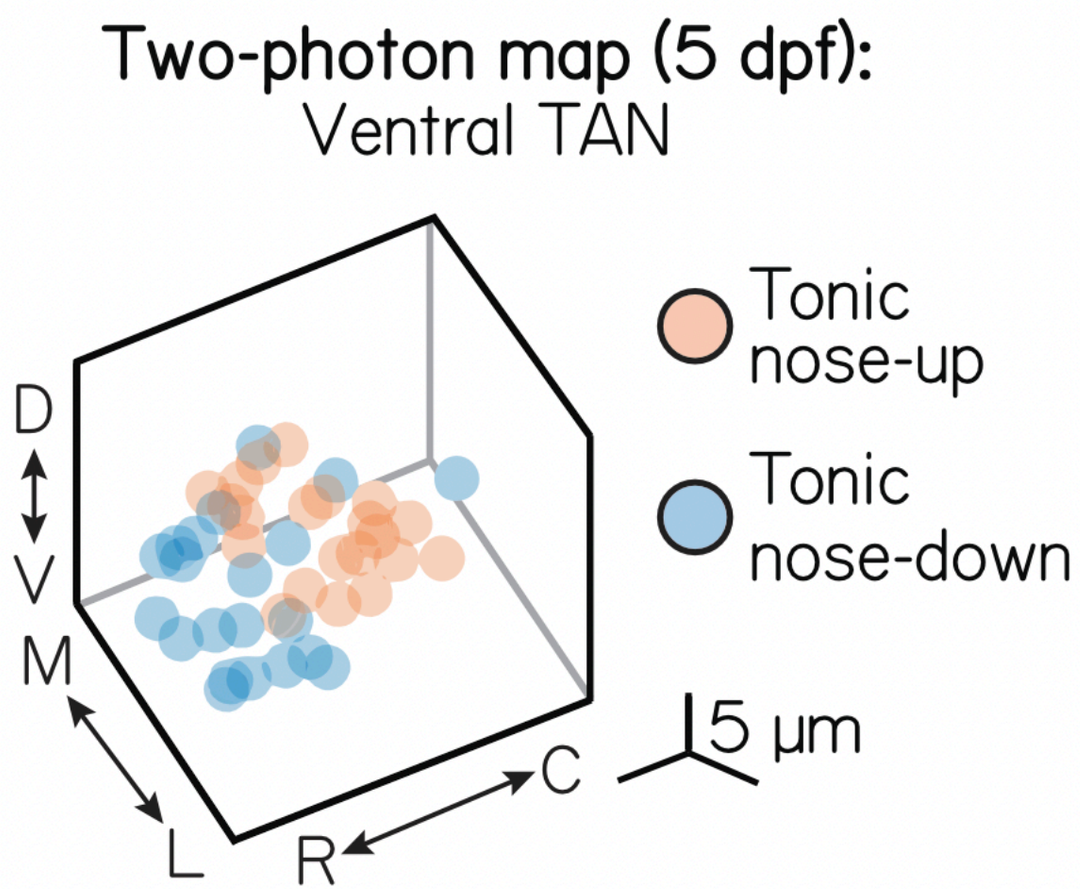
Birthdate organizes impulse-sensitive projection neurons





Late-born (ventral) projection neurons show topography for tilt direction

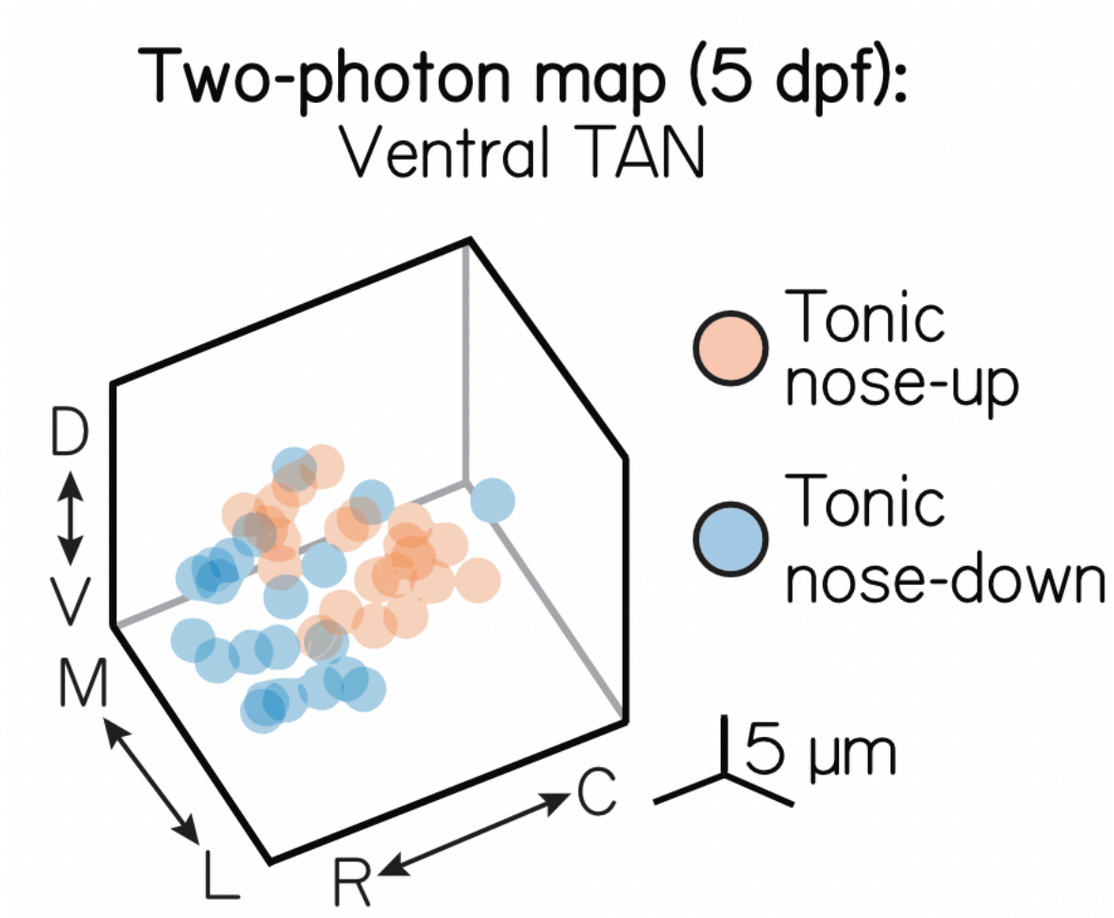




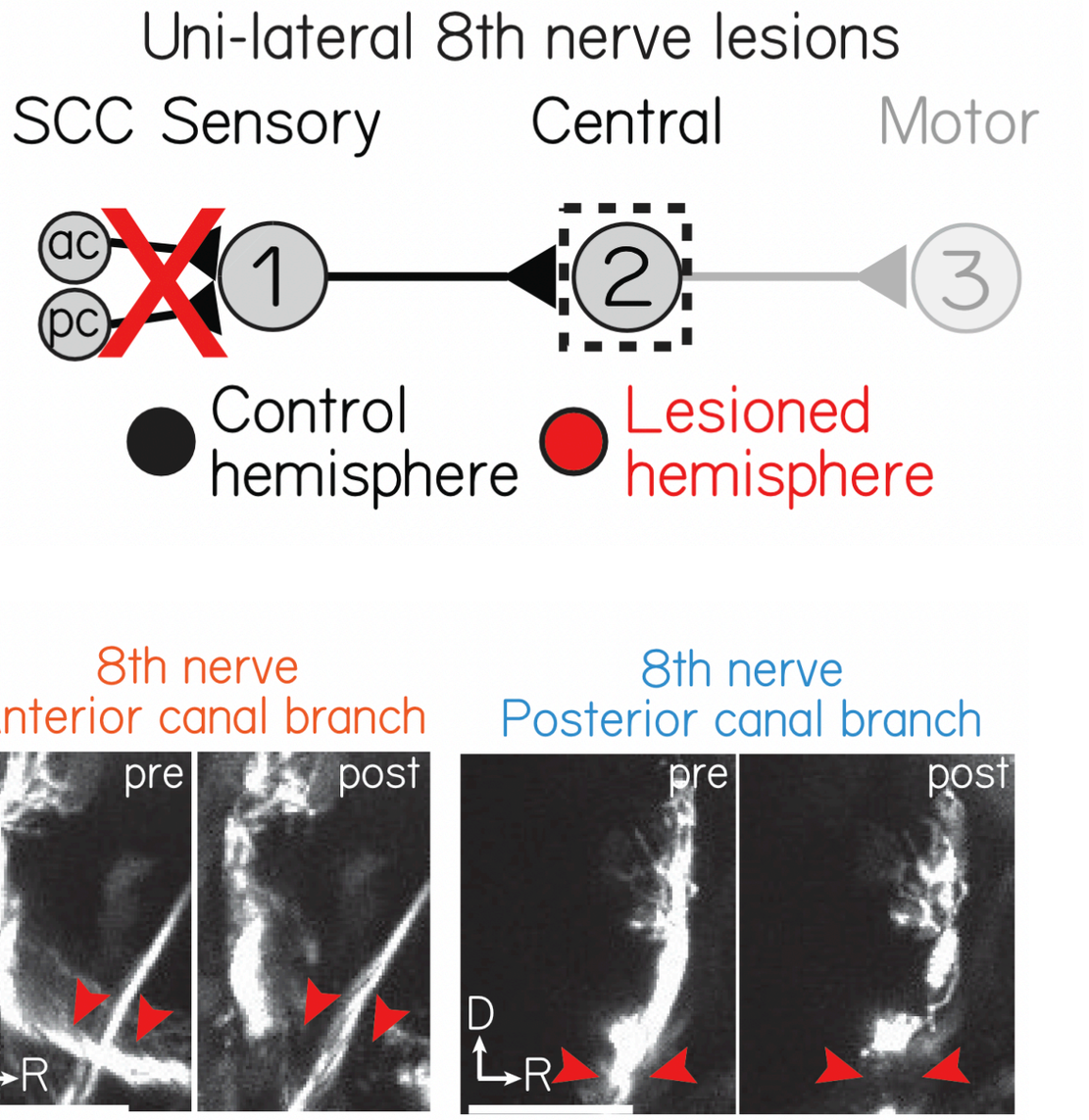
Prof. Martha Bagnall, Ph.

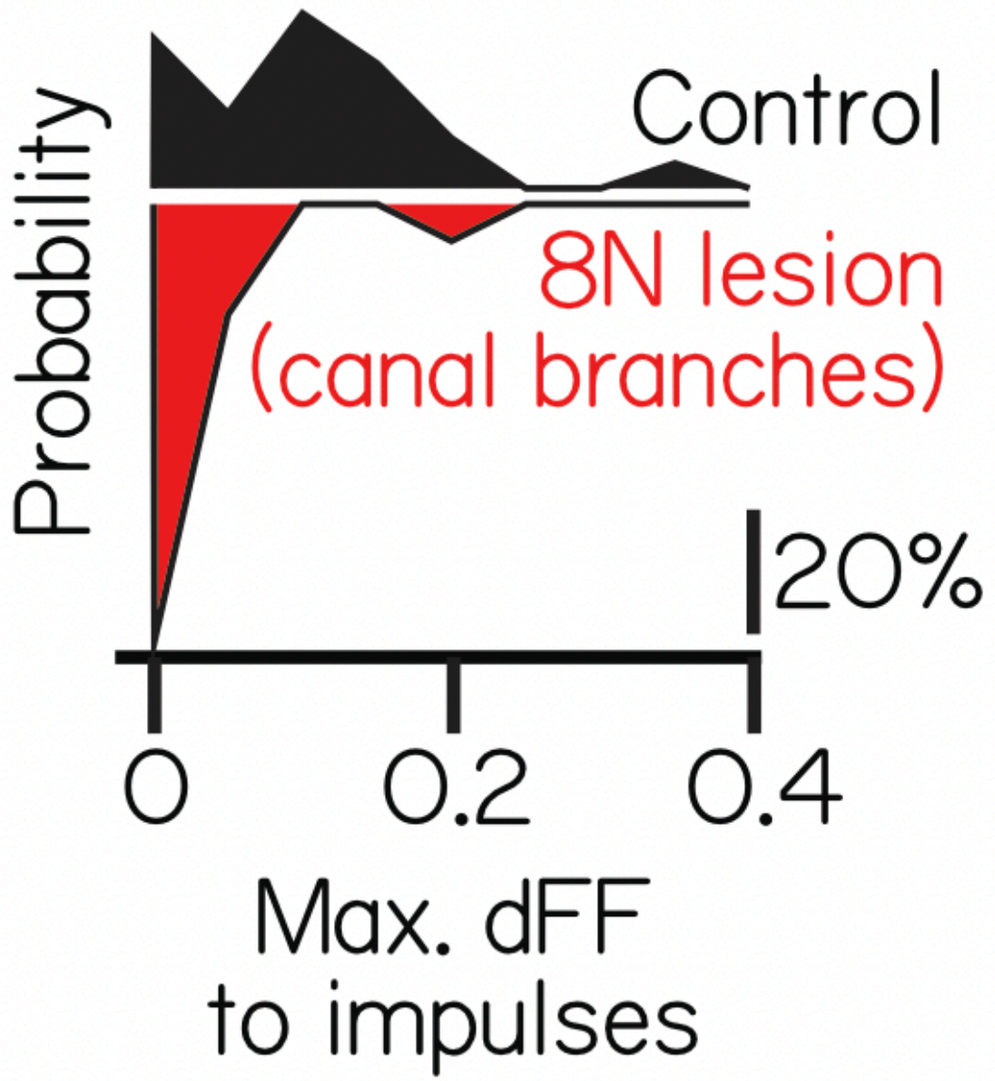
Washington University, St. Louis

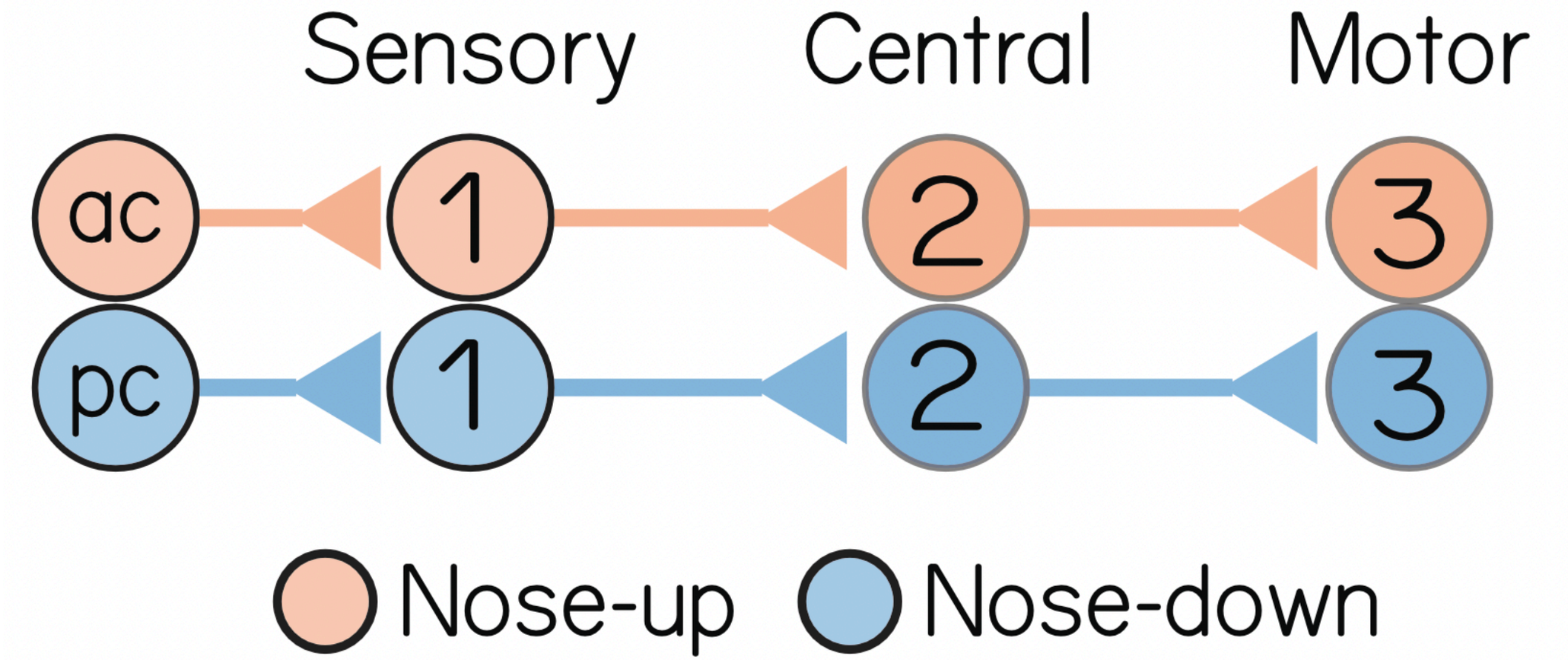
Impulse-sensitive projection neurons receive canal input

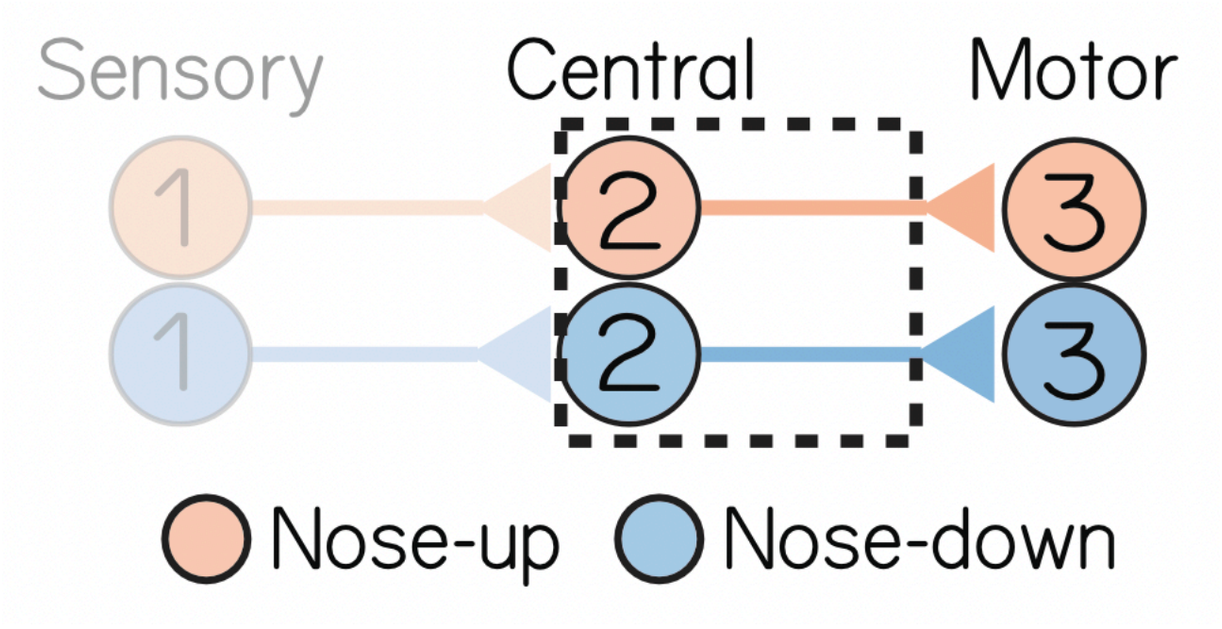


Loss of canal input reduces the impulse response

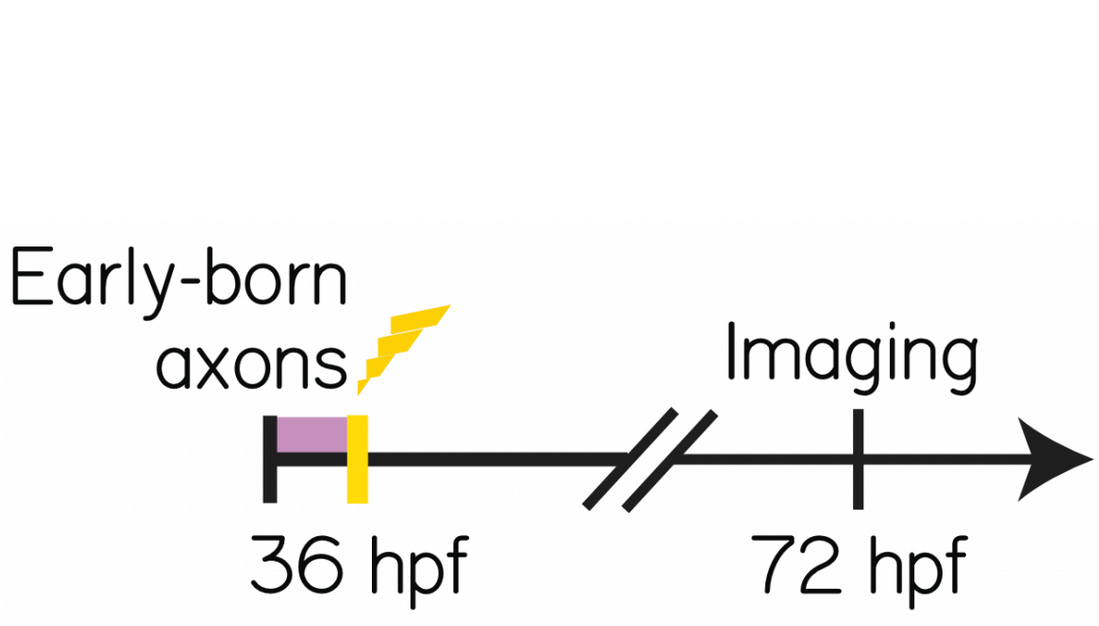


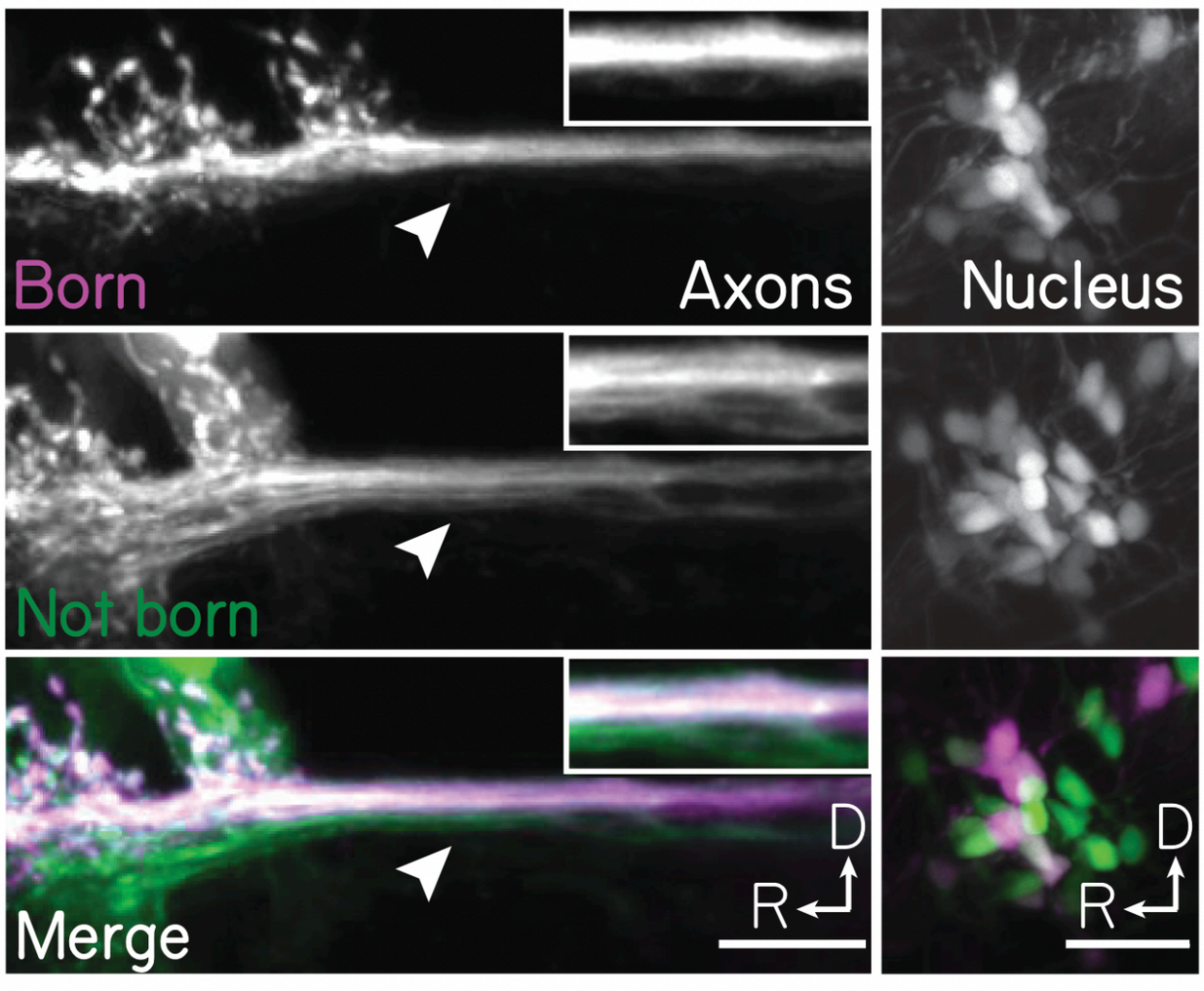


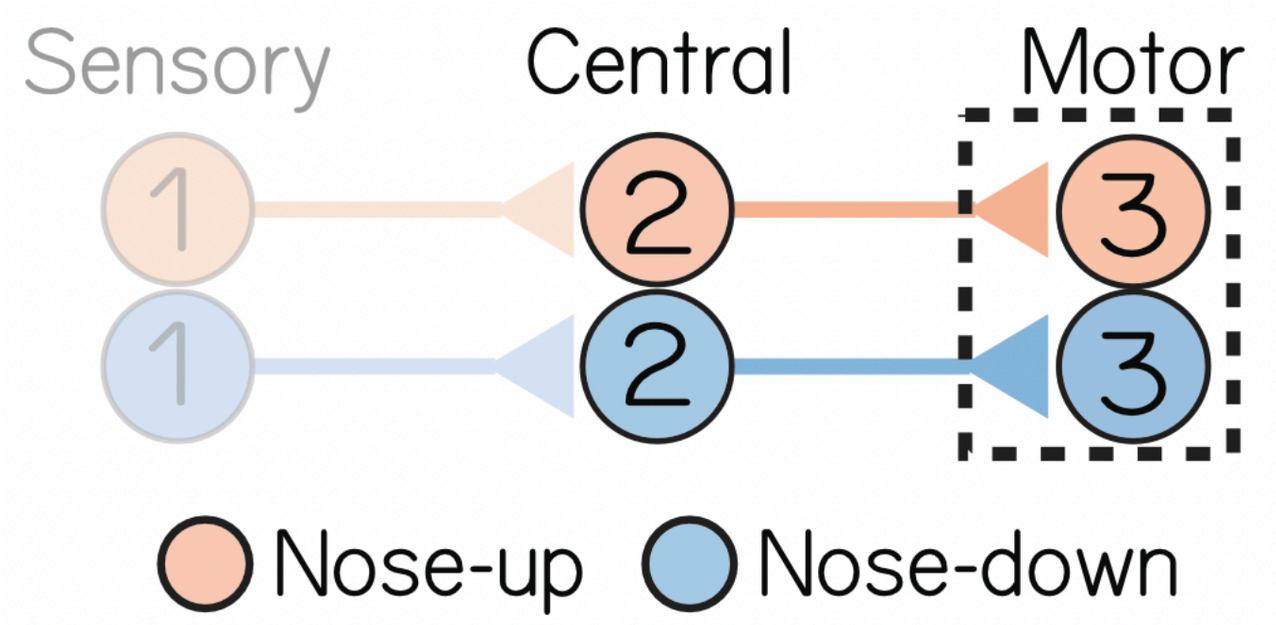

Sensory
Central
Motor
ac
1
2
3
pc
1
2
3
Nose-up
Nose-down


Sensory
Central
Motor
1
2
3
1
2
3
Nose-up
Nose-down

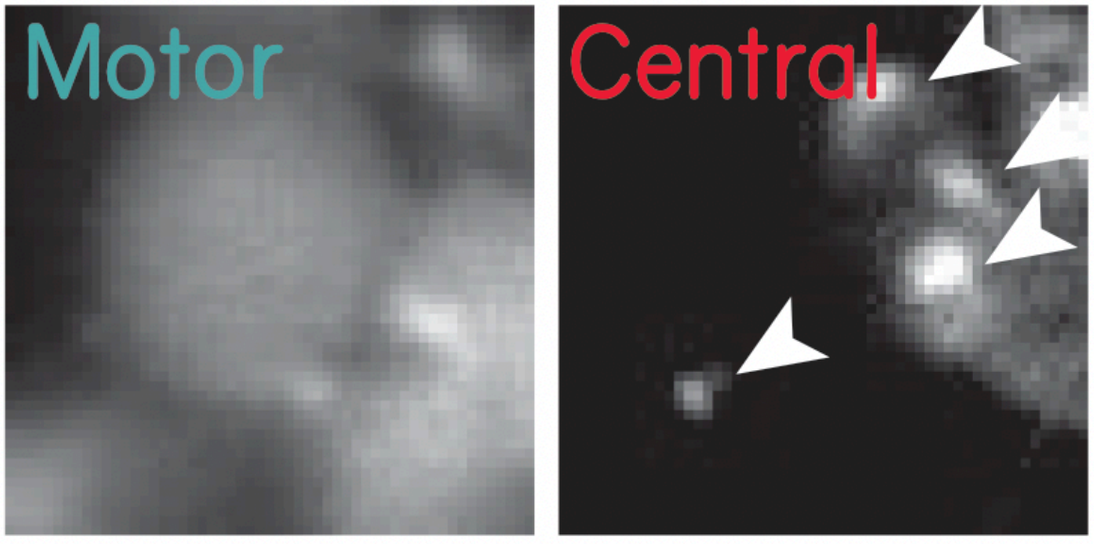
Birthdate organizes projection neuron axons in space

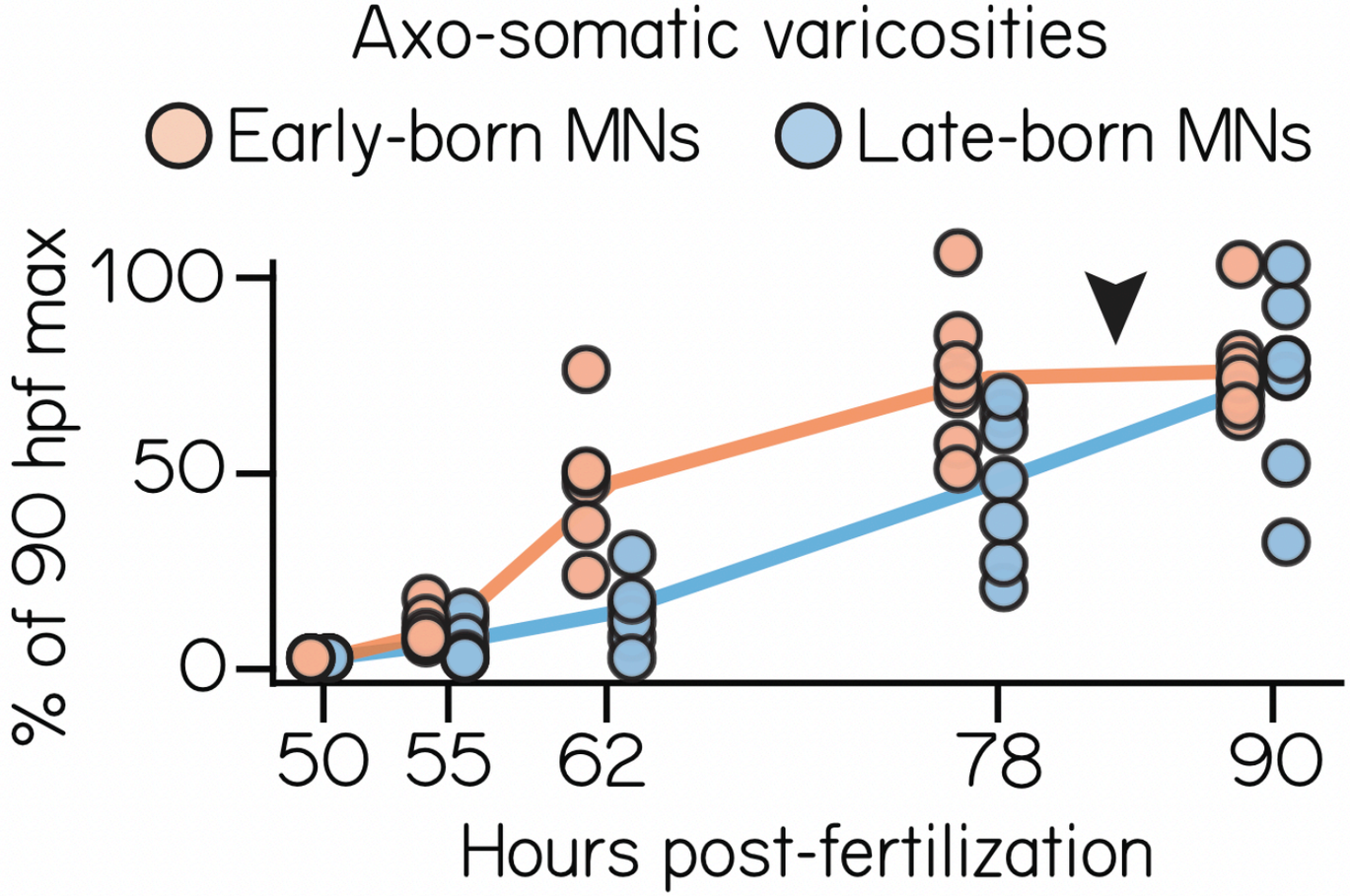


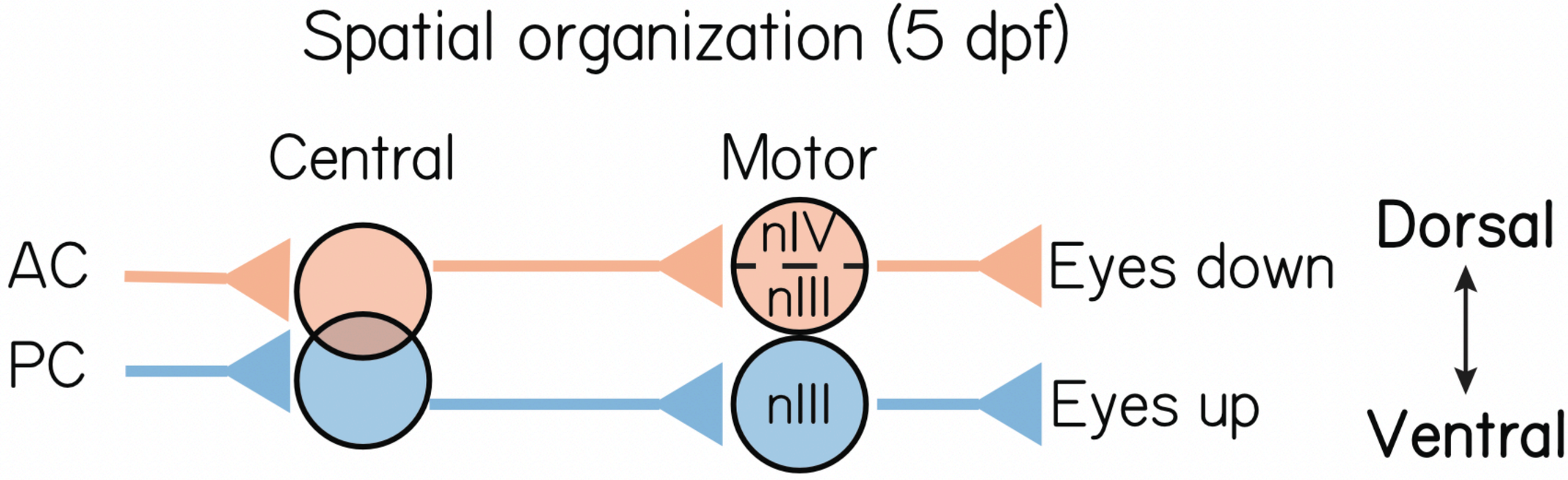



Sensory
Central
Motor
1
2
3
1
2
3
Nose-up
Nose-down

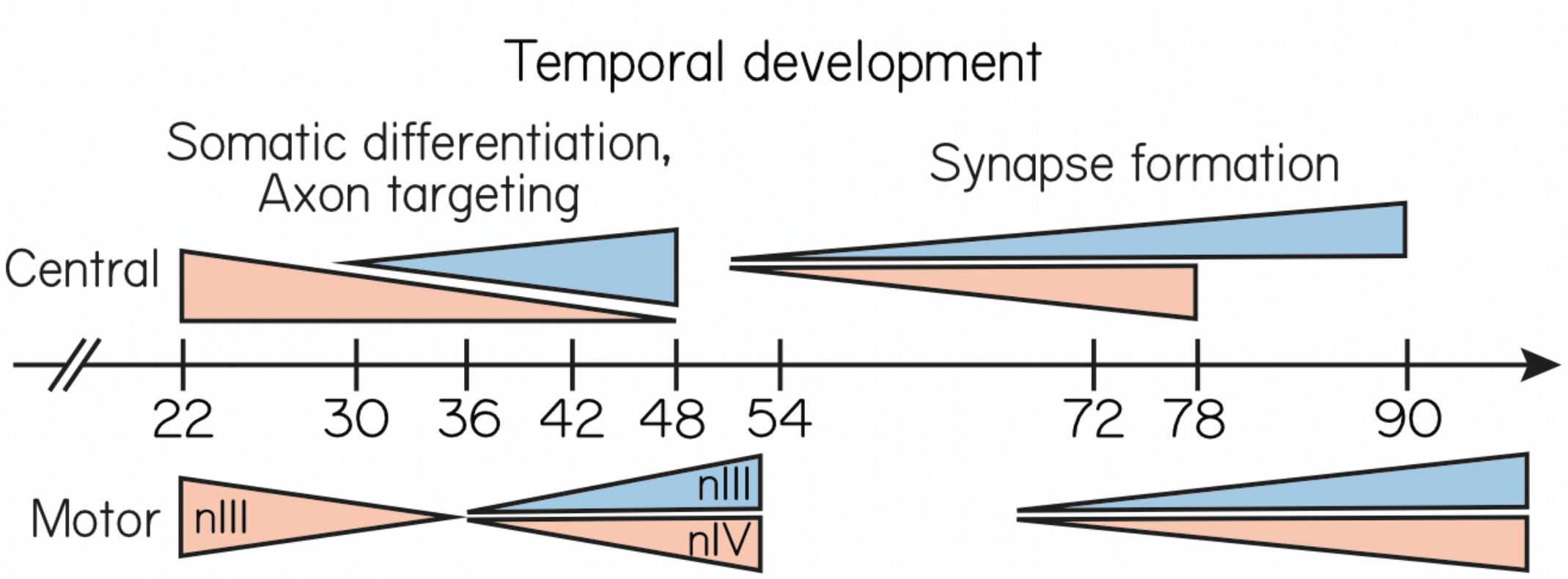
Birthdate anticipates the rate of synaptogenesis between projection neurons and motor neurons







See also
Liu…Bagnall bioRxiv 2022!



Can general developmental principles organize a functional sensorimotor circuit for behavior?

Yes! Birthdate organizes the vestibulo-ocular reflex circuit

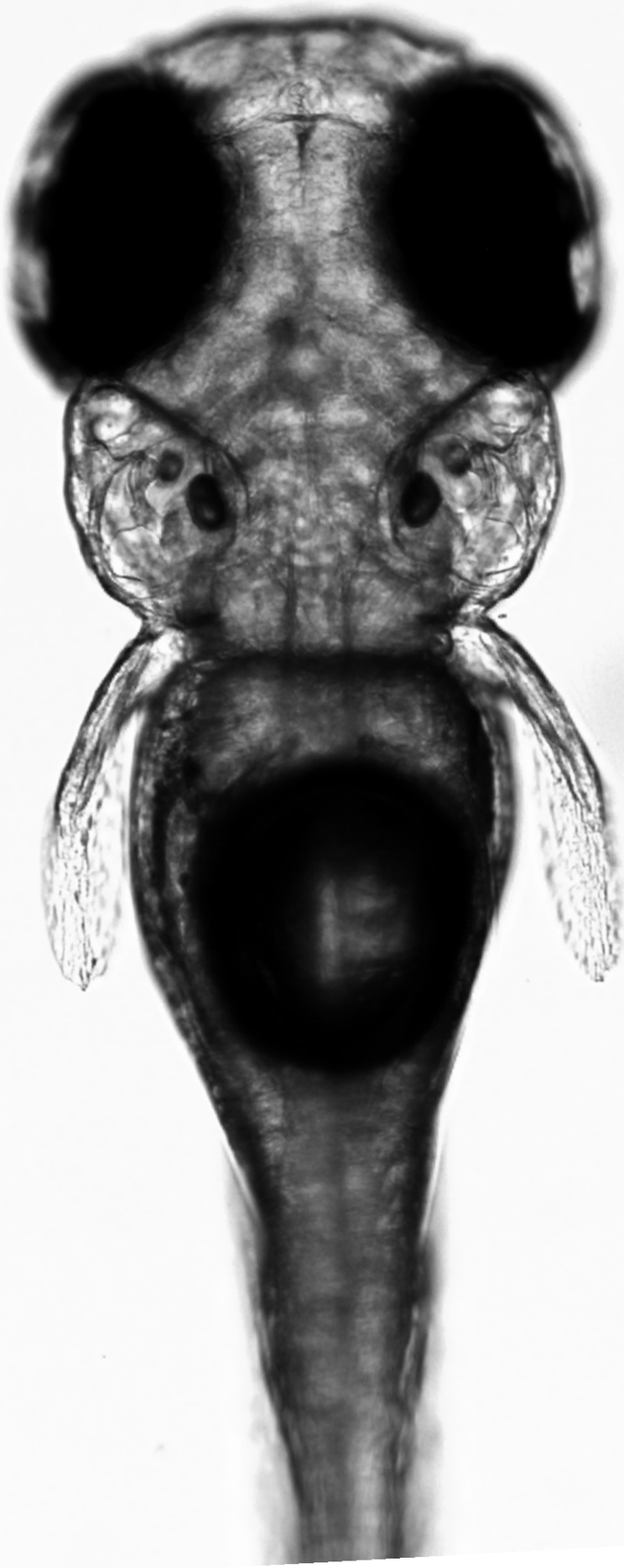
Something fishy about balance

or

Identifying populations of neurons responsible for postural reflexes

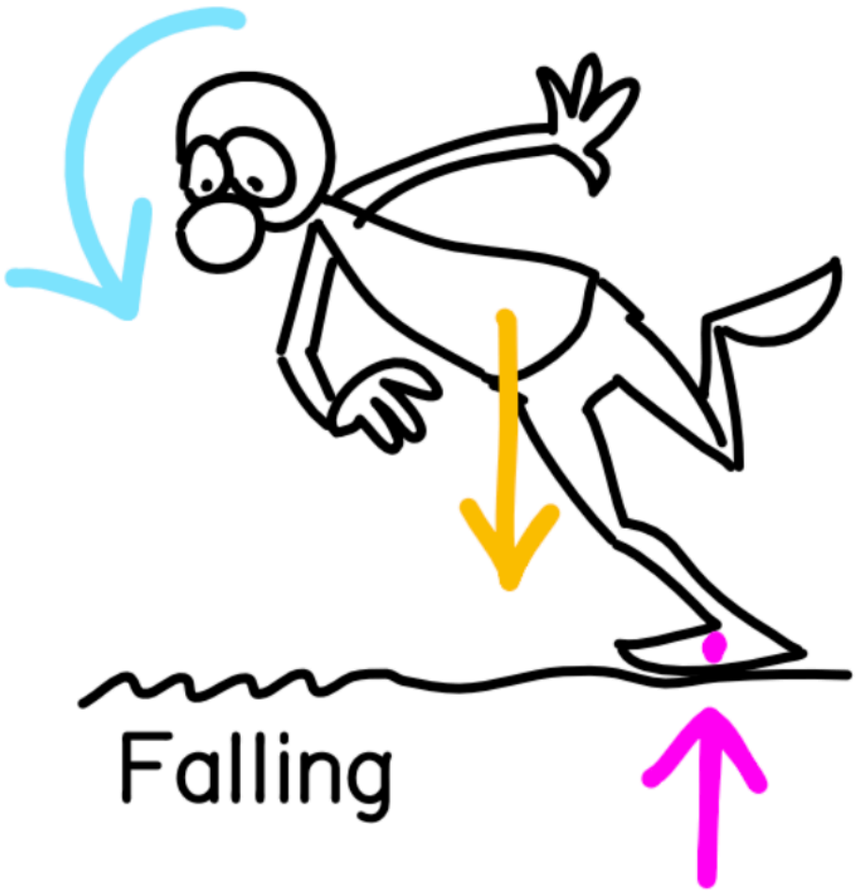
KITP, July 28 2022 pt 2

David Schoppik
NYU Grossman School of Medicine



Key facts about larval zebrafish for busy physicists

- Small (3-4mm, *Re* 10-100)
- Same ancient balance / gaze-stabilizing neural circuits as other vertebrates
- ~175K neurons total
- Transparent
- Genetically accessible
- Develop quickly (4 days to swim, 3 months to maturity)



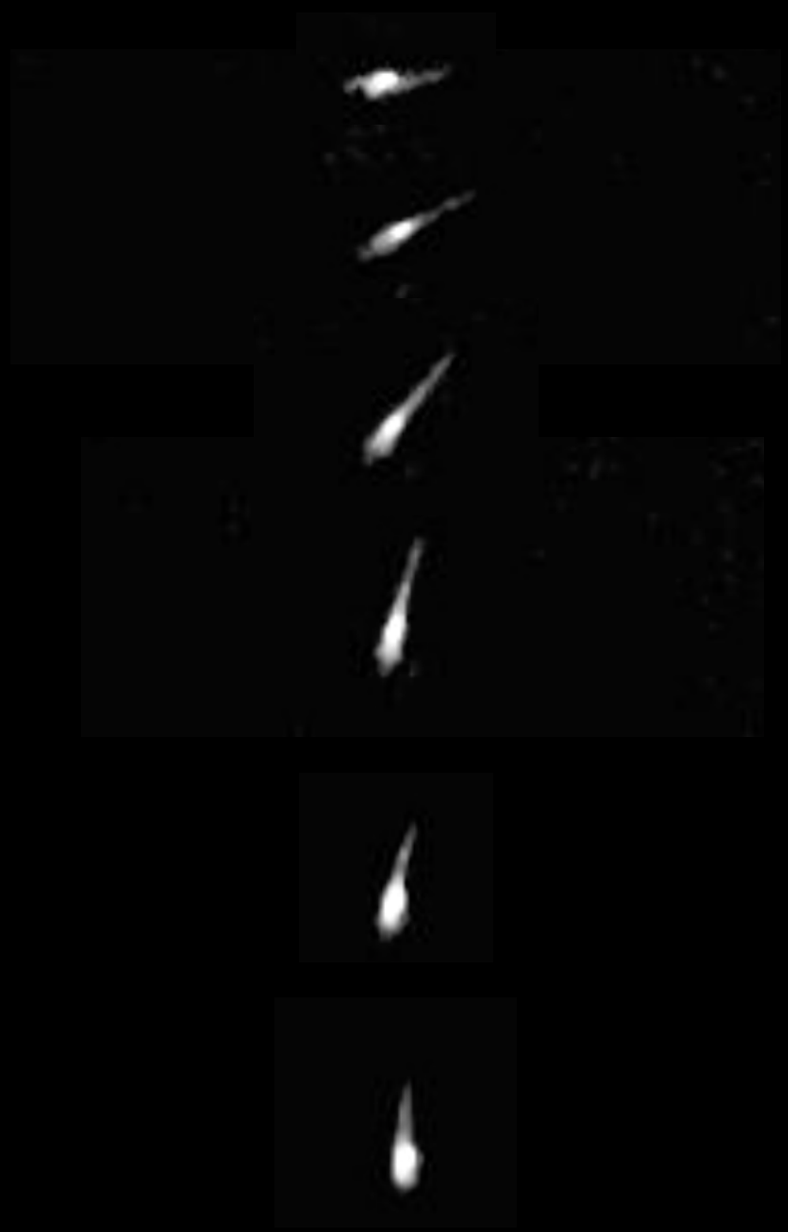
After Ferdinand Englände

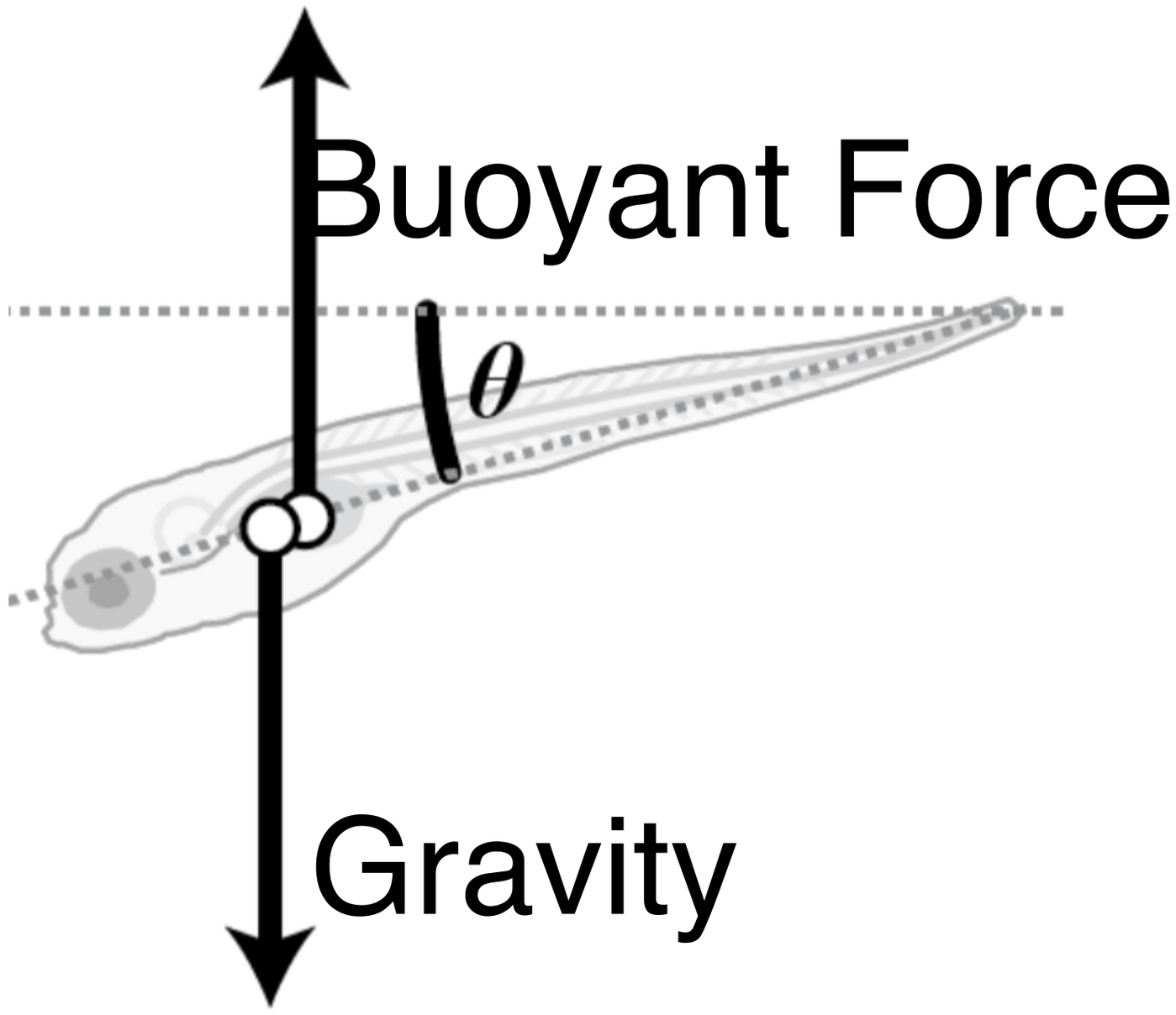
David Ehrlich, Ph.D.

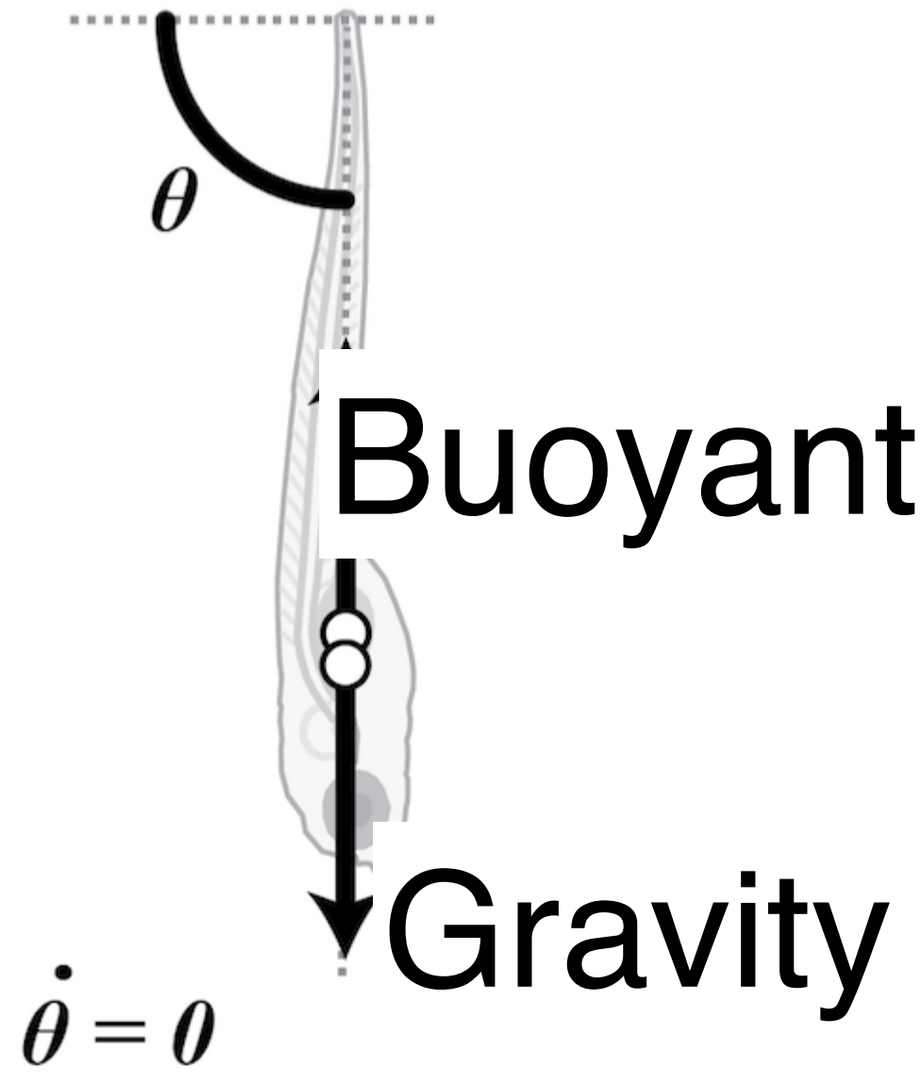
Ehrlich & Schoppik 2017a
Ehrlich & Schoppik 2017b bioRxiv
Ehrlich & Schoppik 2019

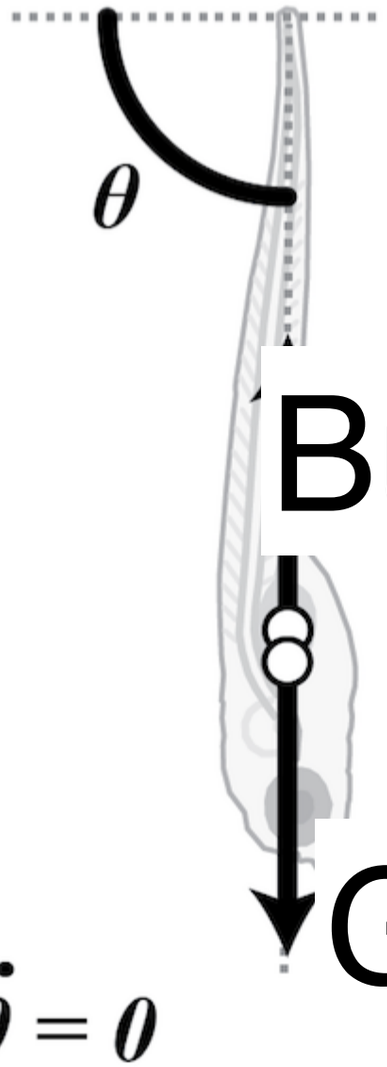
Now running his own lab at UW Madison

Anesthetized zebrafish rotate & fall!




Buoyant Force
θ
Gravity


θ
Buoyant Force
Gravity
$\dot{\theta} = 0$



Buoyant Force

$\dot{\theta} = 0$

Active equilibrium

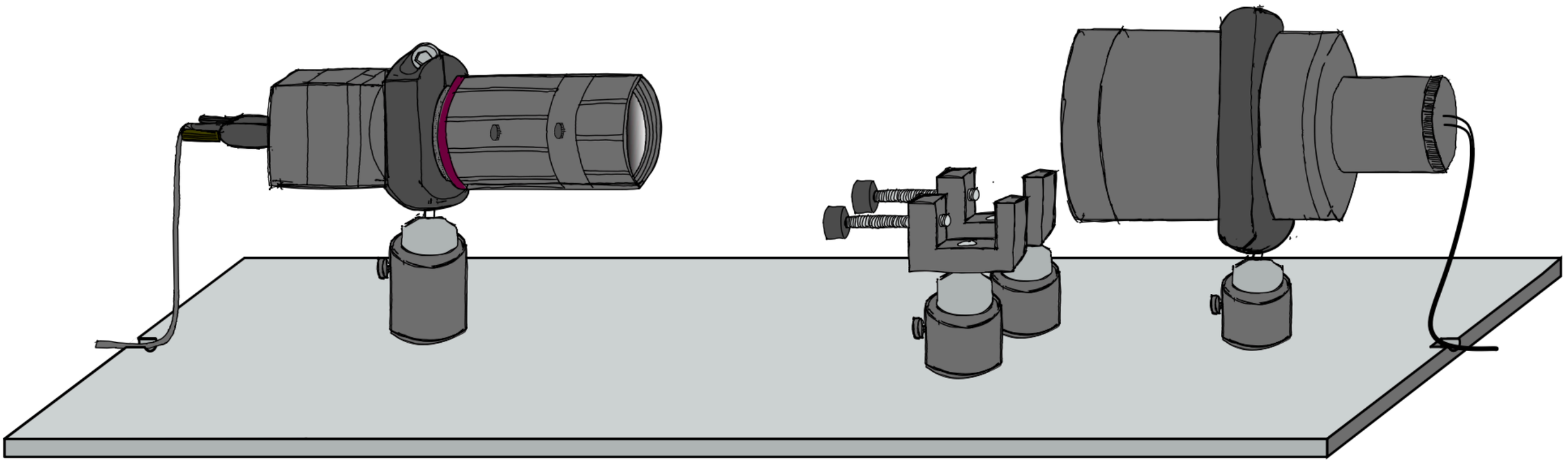
Bout timing

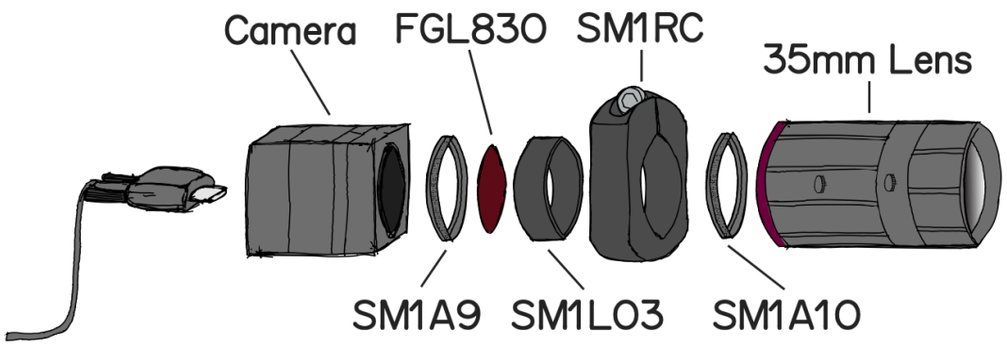
or

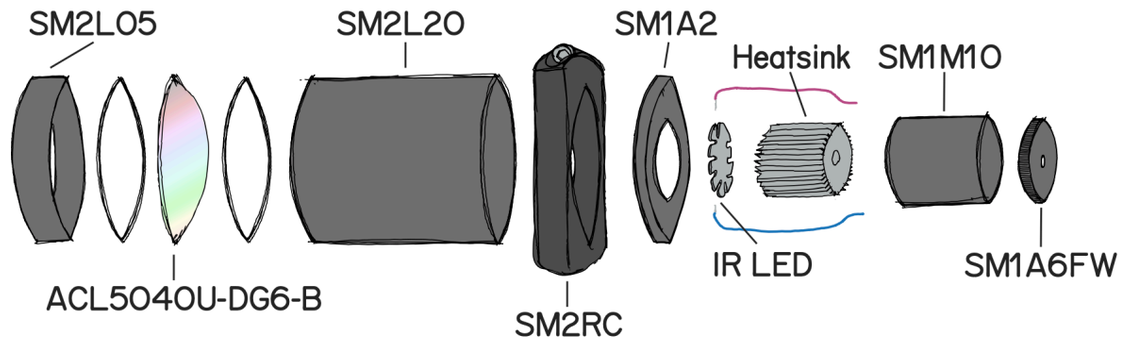
Why do fish move when they do?

Ehrlich & Schoppik 2017a

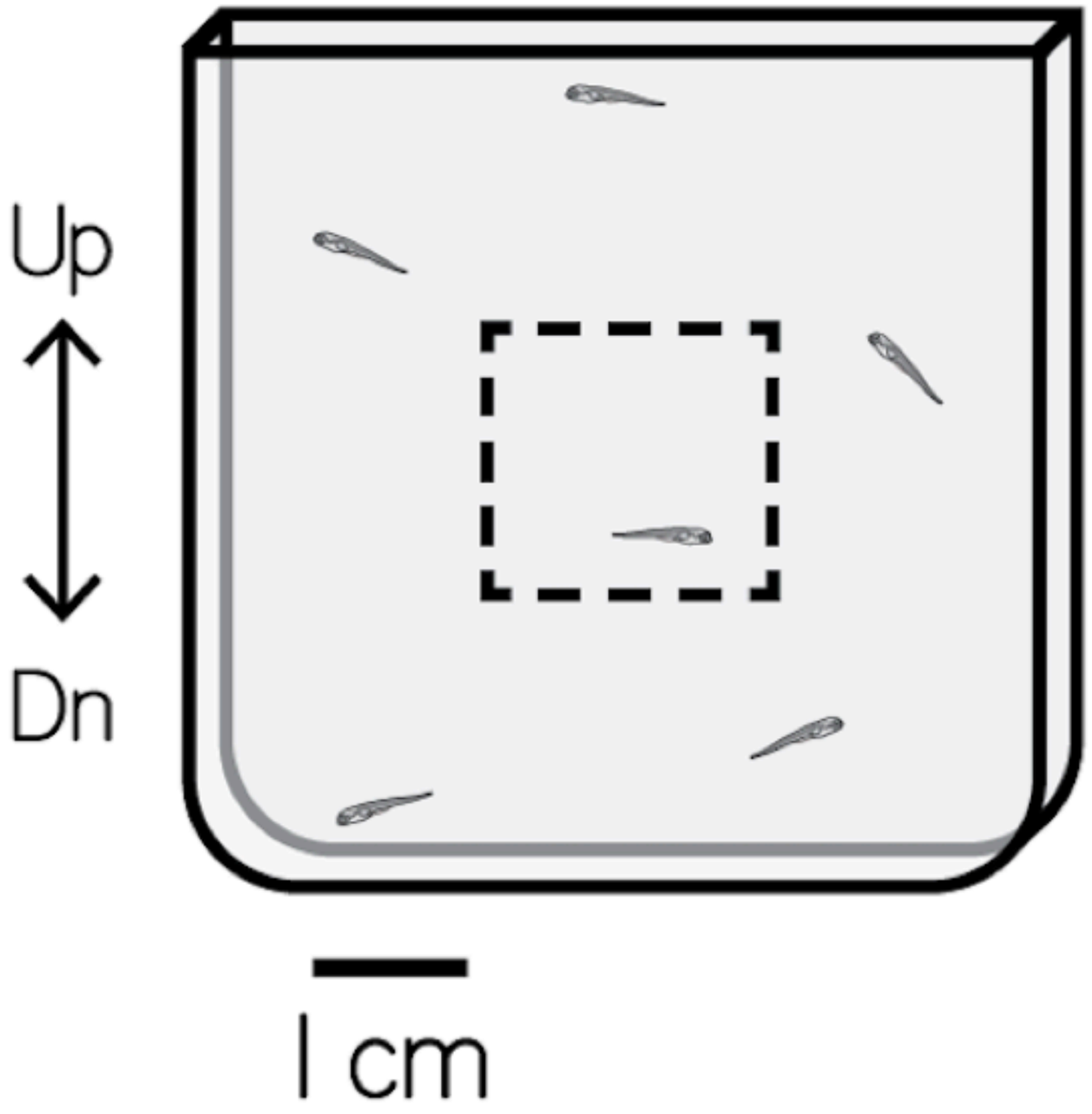
Measuring posture



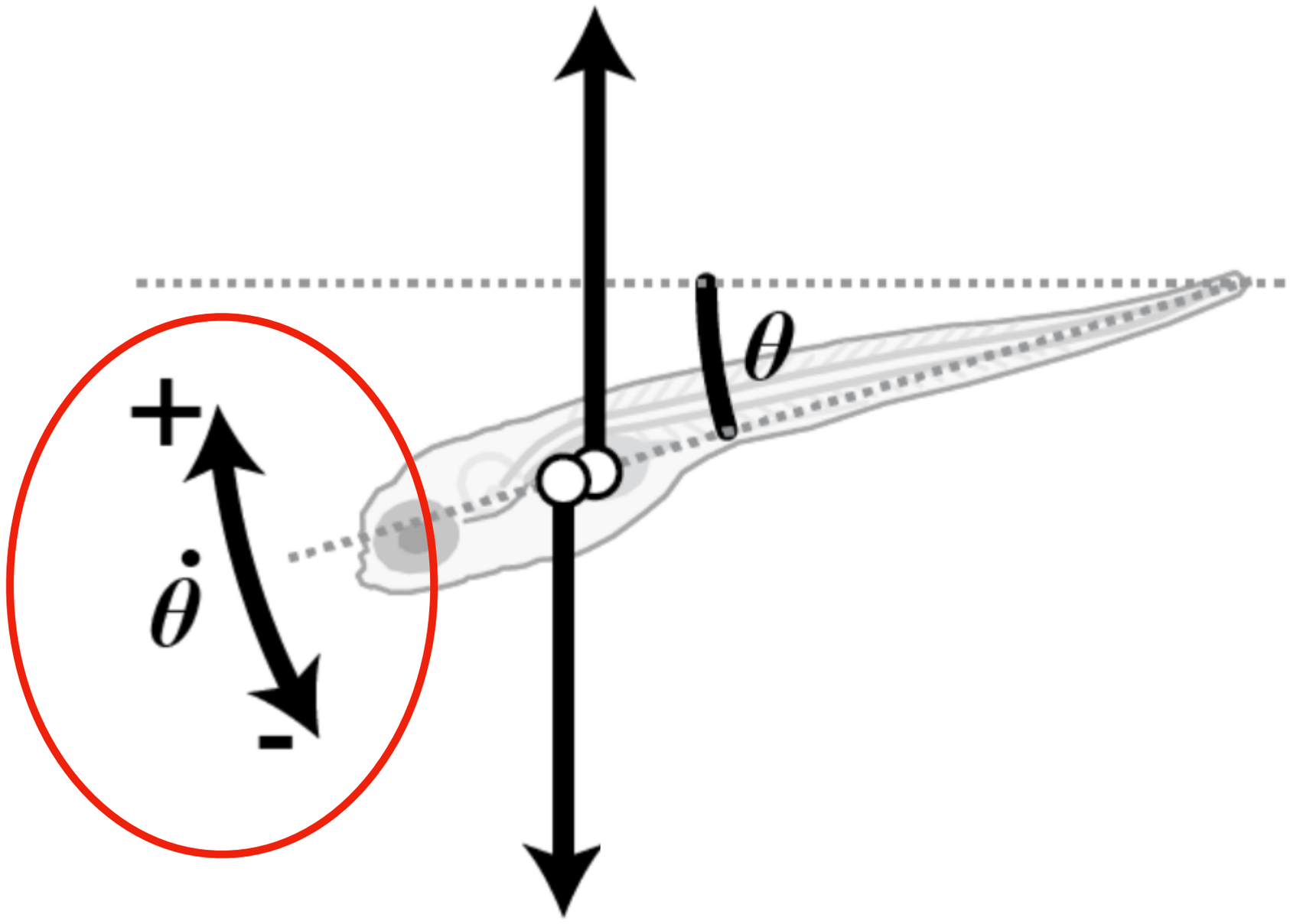




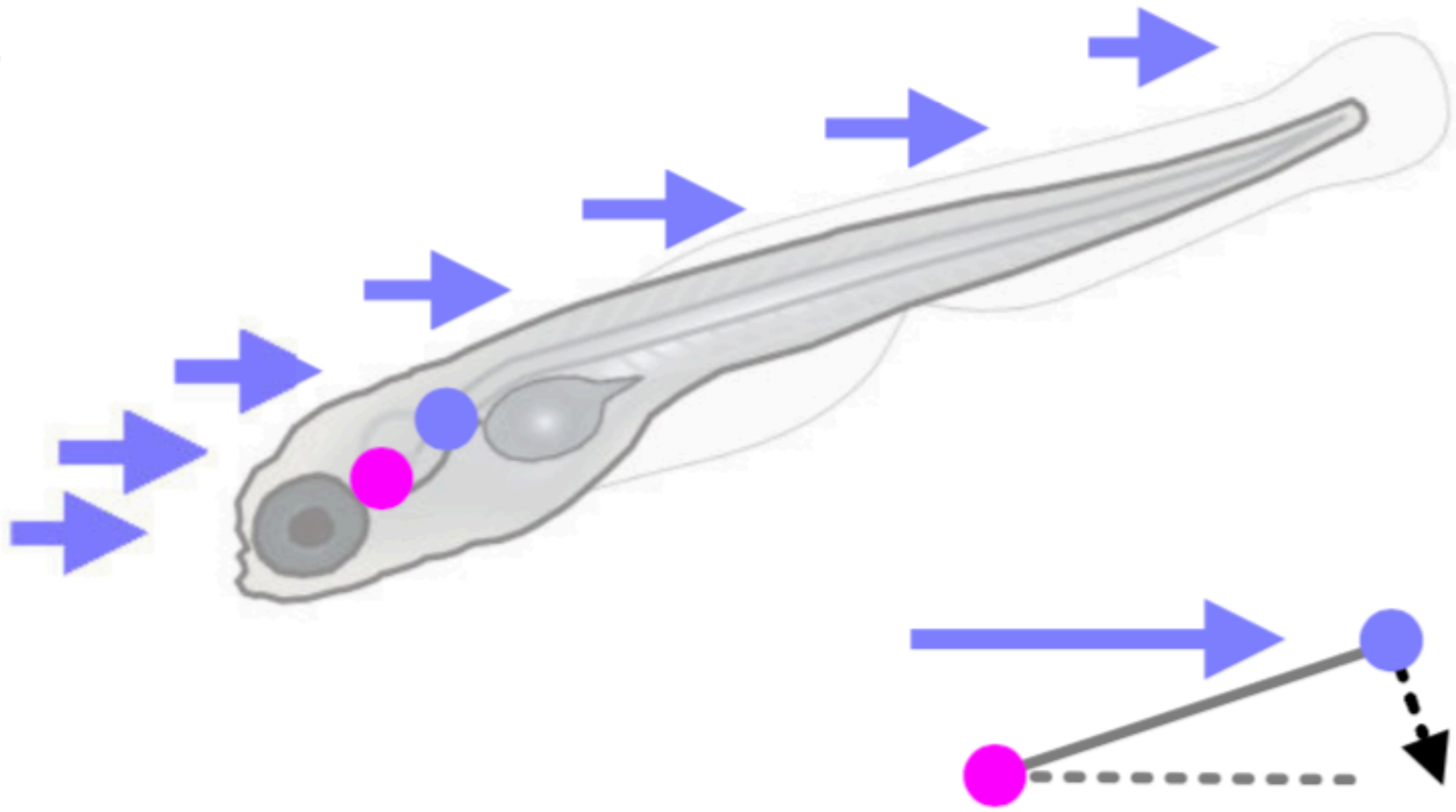
Franzi Auer, Ph.D.


Up
Dn
1 cm

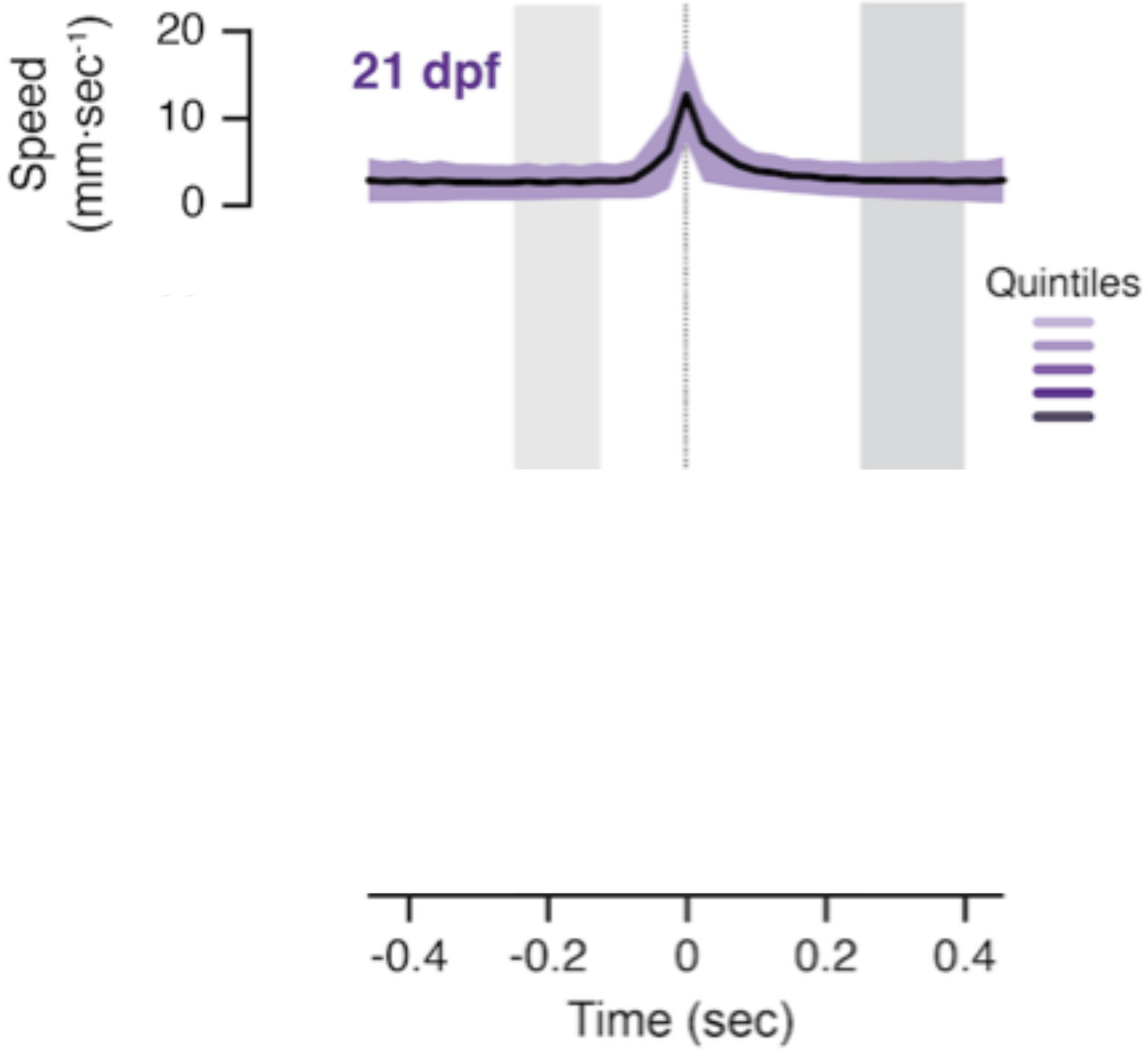
Fish swim to cancel destabilizing torques

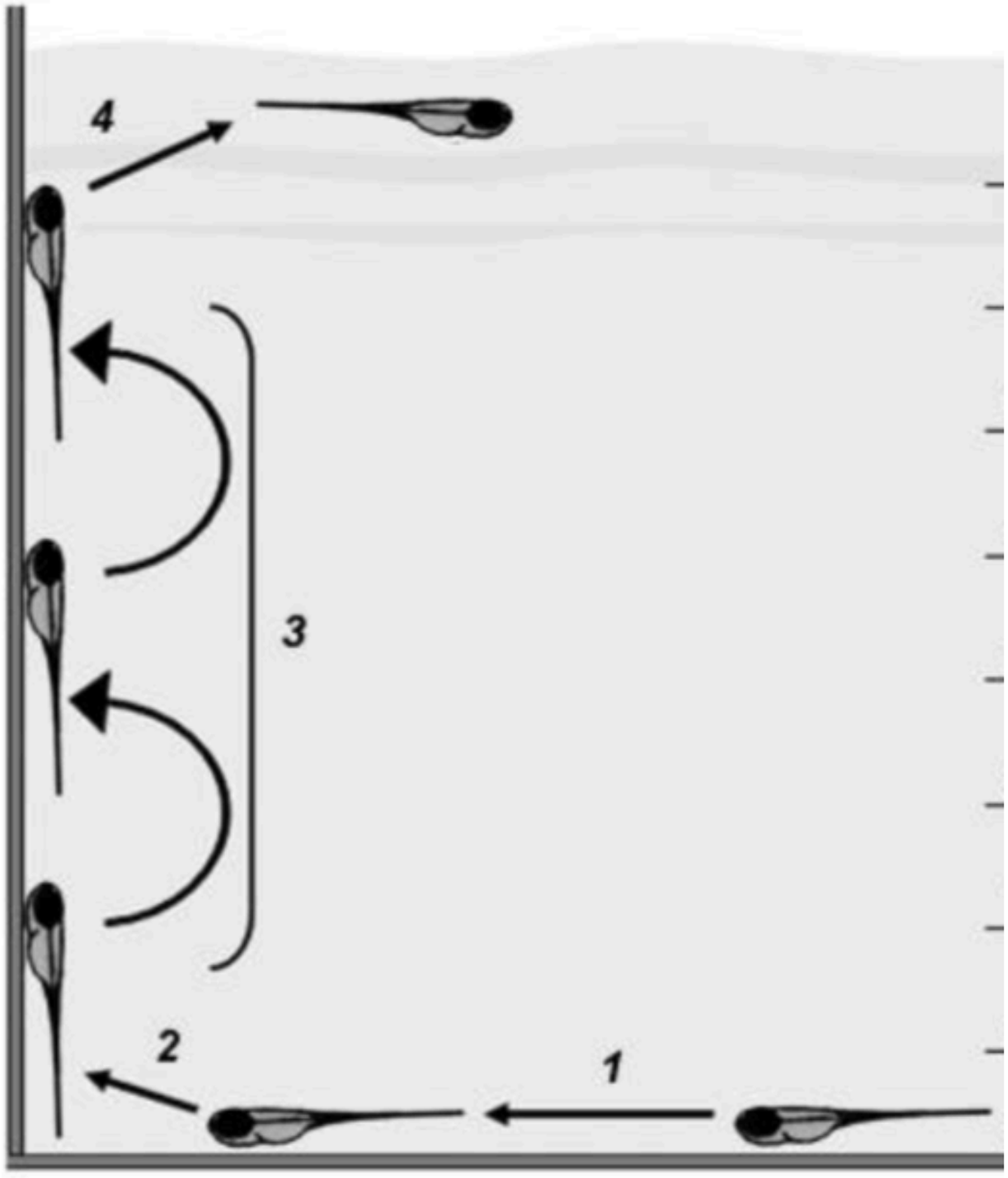



N
E
S



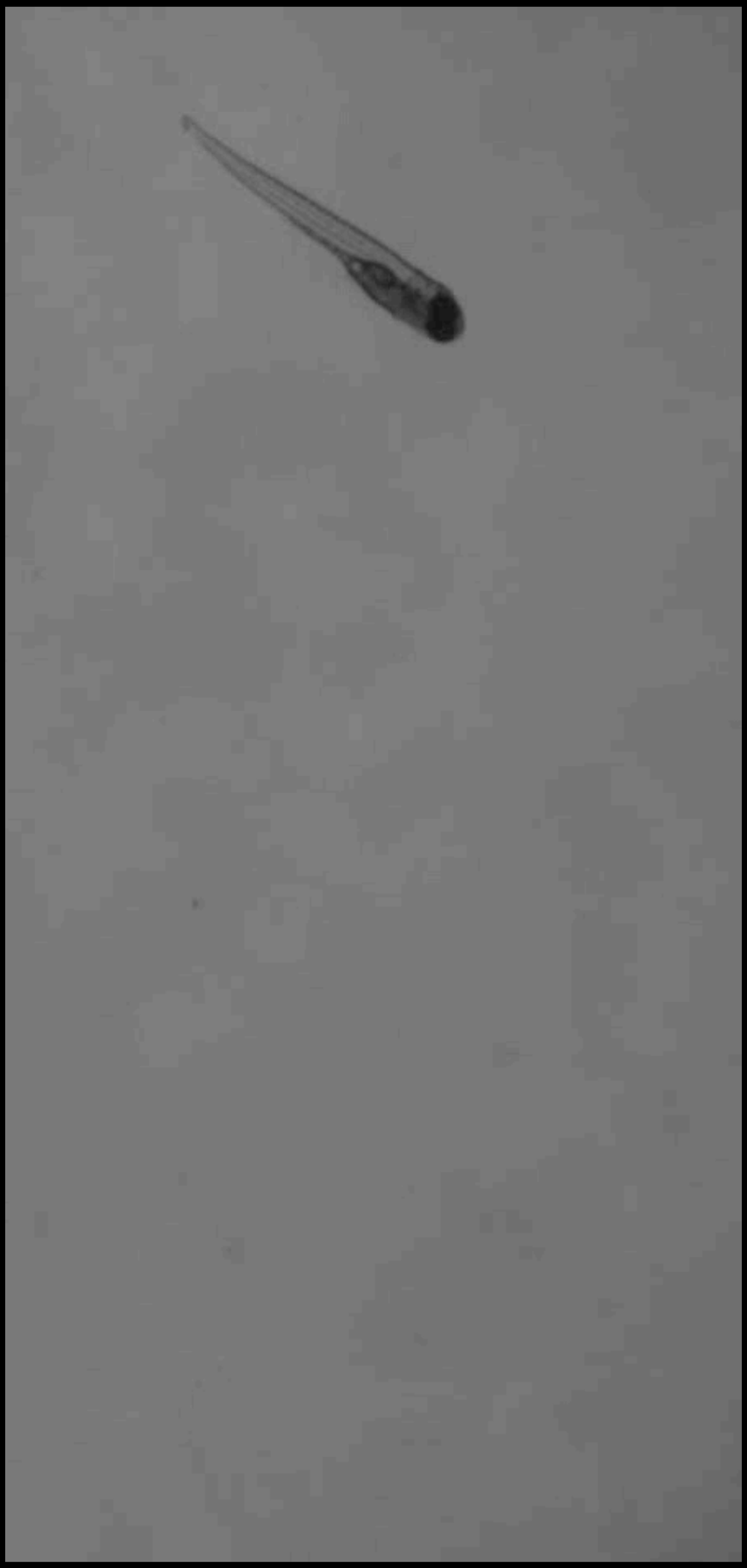
Bagnall & Schoppik 20

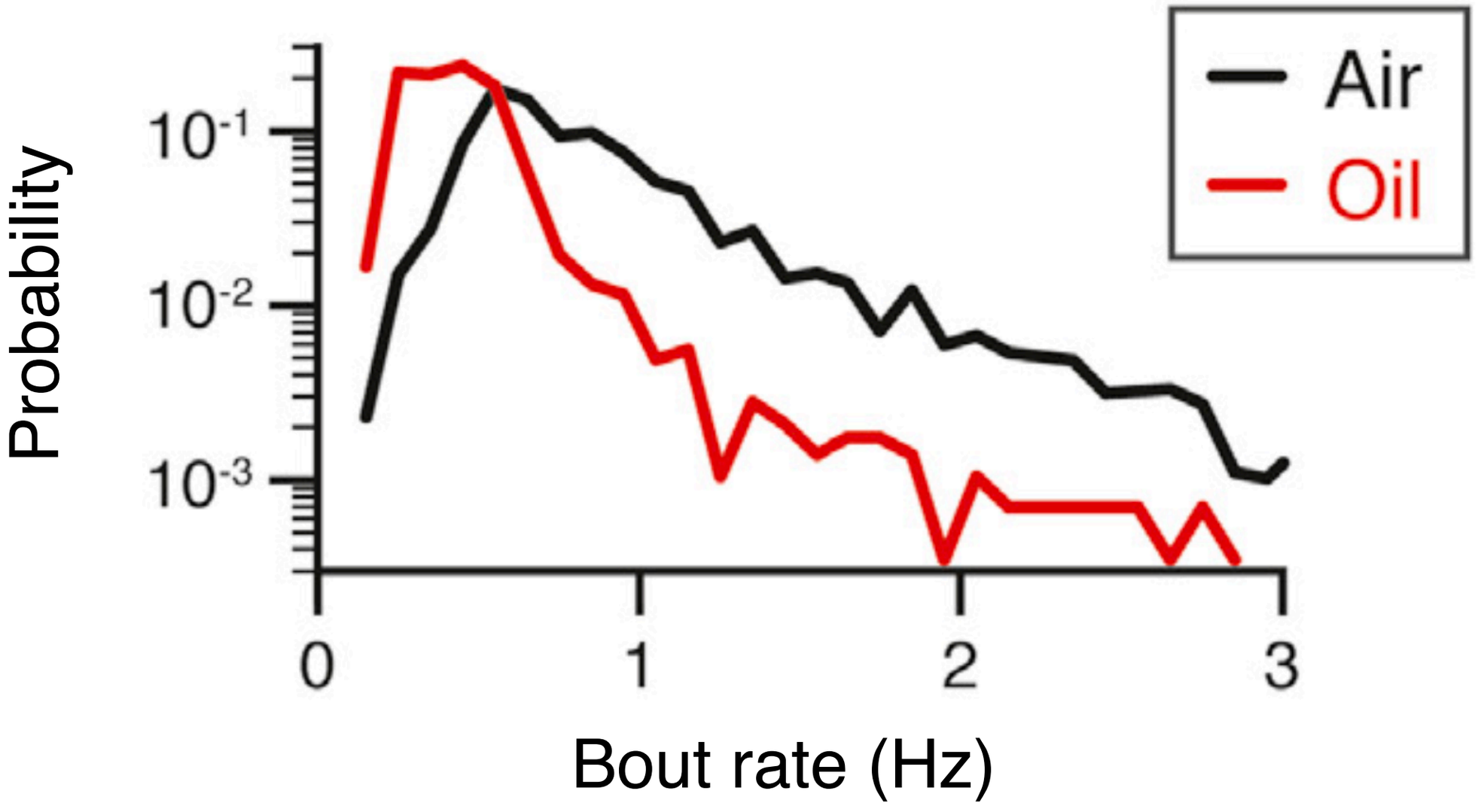

Speed (mm·sec⁻¹)
20
10
0
21 dpf
Quintiles
-0.4
-0.2
0
0.2
0.4
Time (sec)



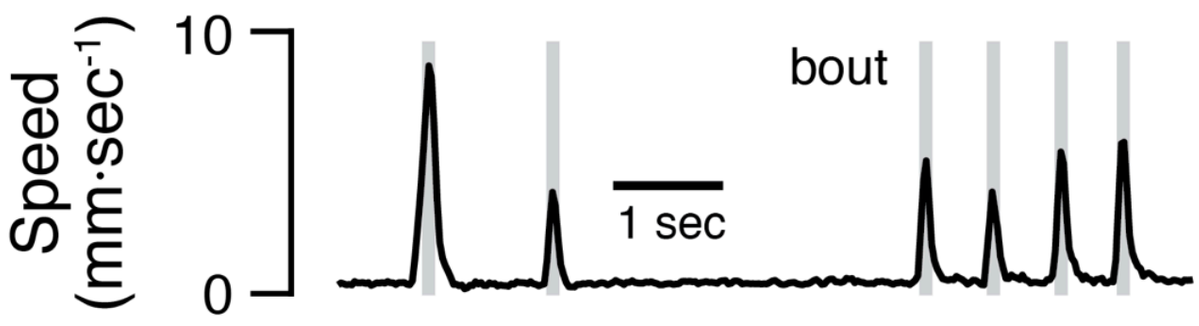
Lindsey et. al. 2010

Ehrlich & Schoppik, 2017




Air
Oil
Probability
10^{-1}
10^{-2}
10^{-3}
0
1
2
3
Bout rate (Hz)

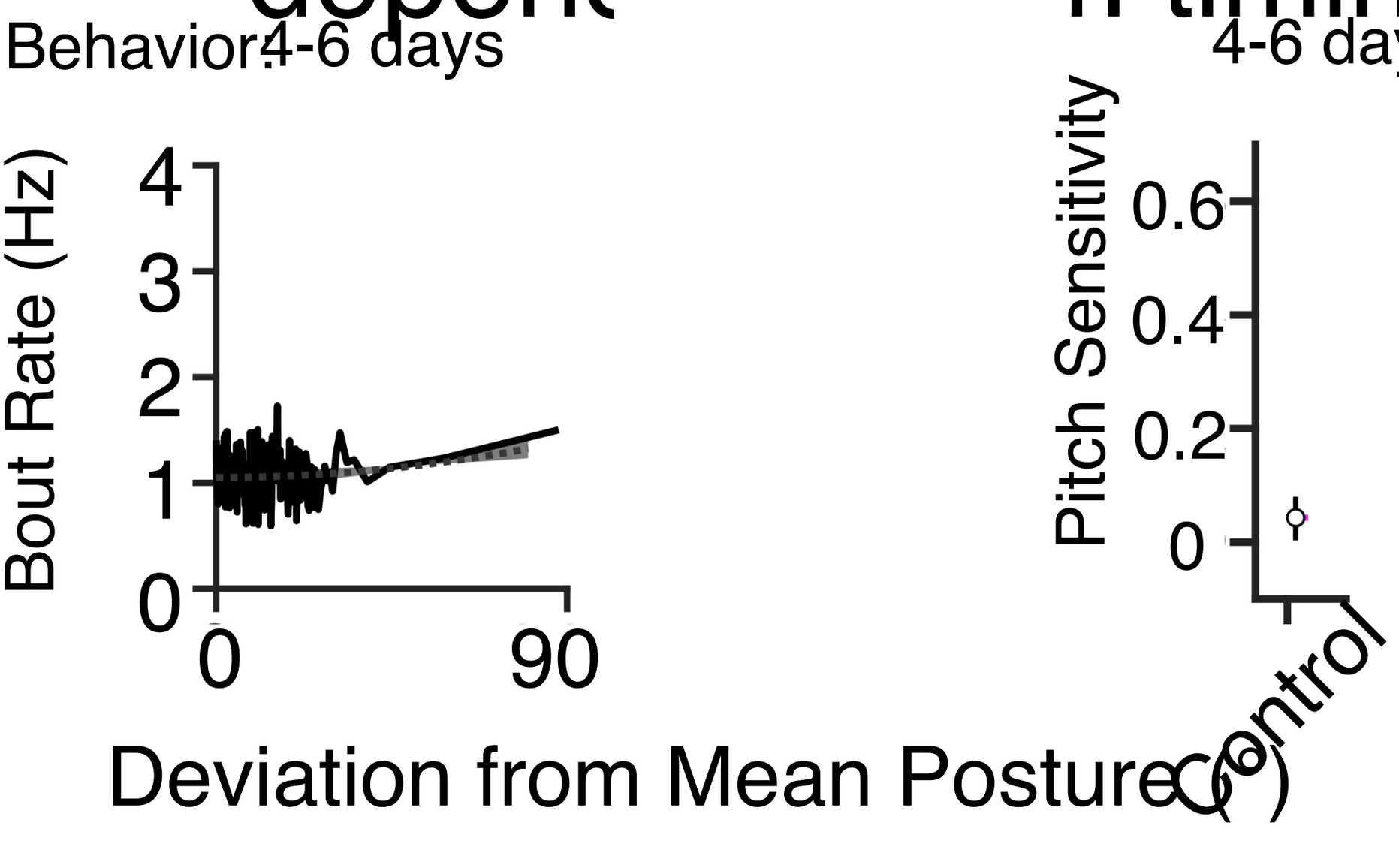
Swim timing corrects for instability in larval fish



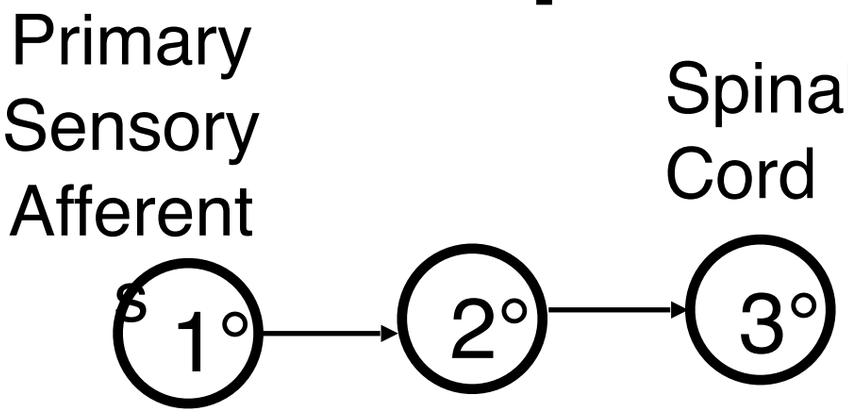
Ehrlich and Schoppik, 2017

Kyla Hamling

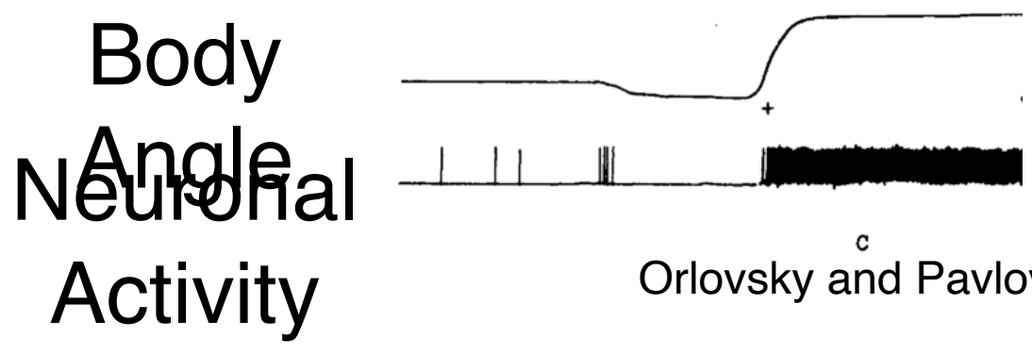
As larval zebrafish develop, postural control transitions from random timing to posture-dependent swim timing



Central vestibulospinal neurons are well-poised for a role in postural control

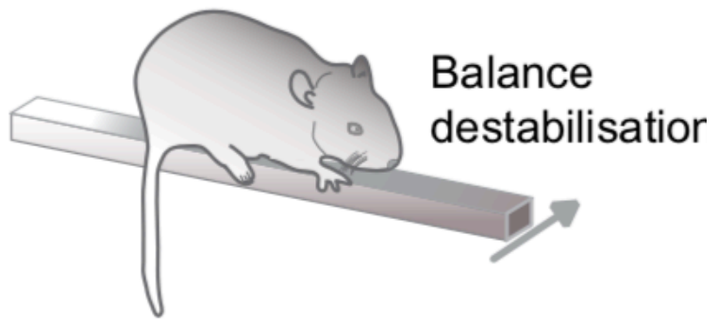


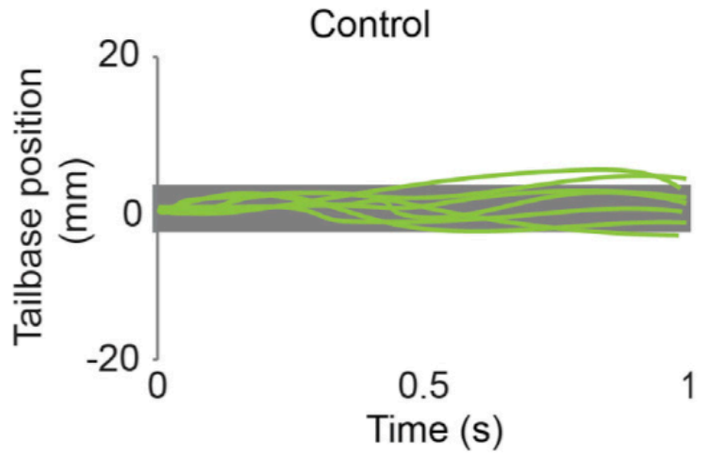
- Receive direct excitatory inputs from vestibular afferents (Walberg, Bowsher, and Brodal 1958; Peterson 1970; Liu et al., 2020)
- Synapse onto motor neurons and interneurons in spinal cord (Grillner, Hongo, Lund 1970; Wilson & Yoshida 1969; Murray et al., 2018; Basaldella et al., 2015)
- Encode changes in posture (Orlovsky and Pavlova 1972; Liu et al., 2020; Hamling et al., Biorxiv)
- Born well before posture control comes online (Kasumacic, Glover, Perreault 2010; Hamling et al., Biorxiv)

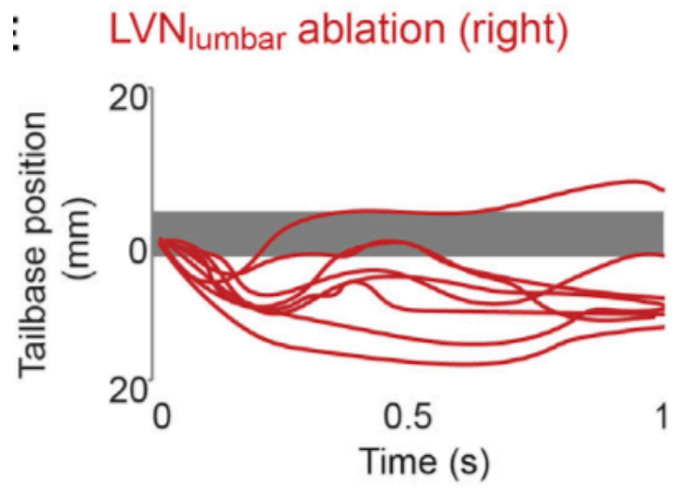


Orlovsky and Pavlova, 1972

Vestibulospinal neurons are necessary for posture-correcting behaviors

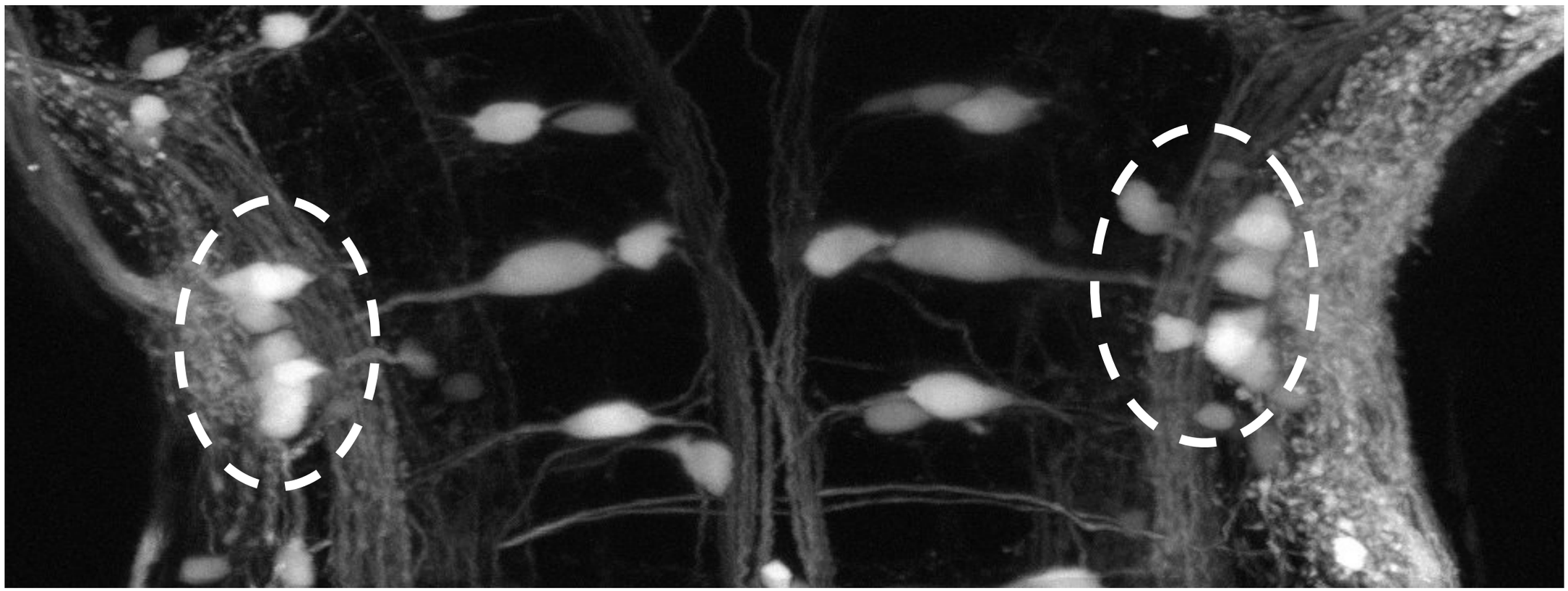






Murray et al., 2018

Genetic tools grant access to vestibulospinal cells in fish

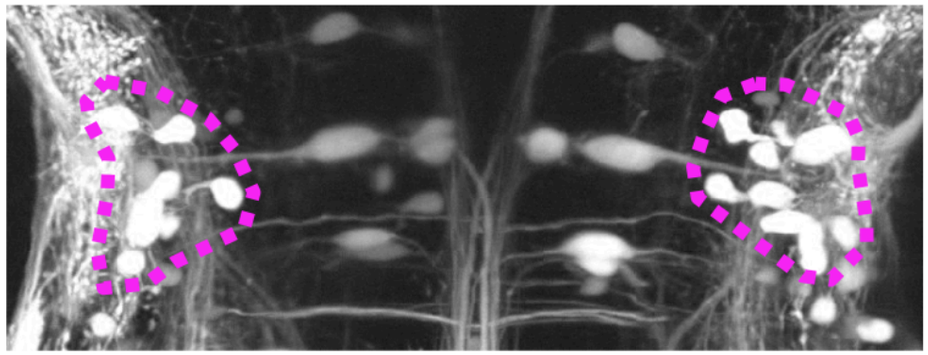


Nefma:Gal4/
UAS:GFP

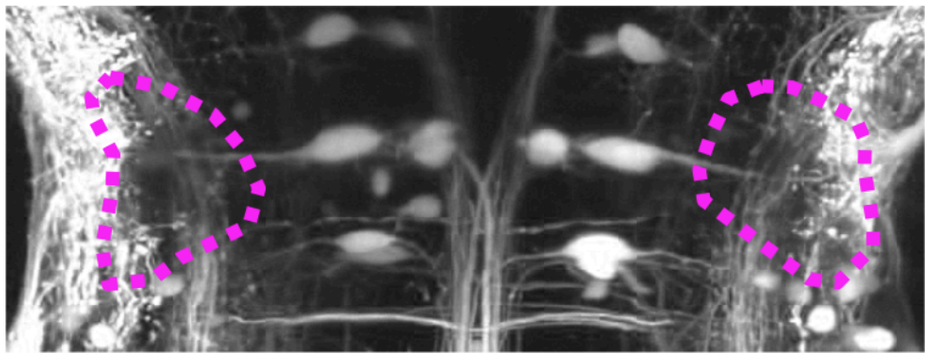
Labels ~30 cells (~60% of total VS cell

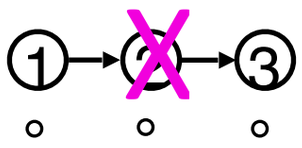
What role do VS neurons play in postural development?

Pre-Lesion



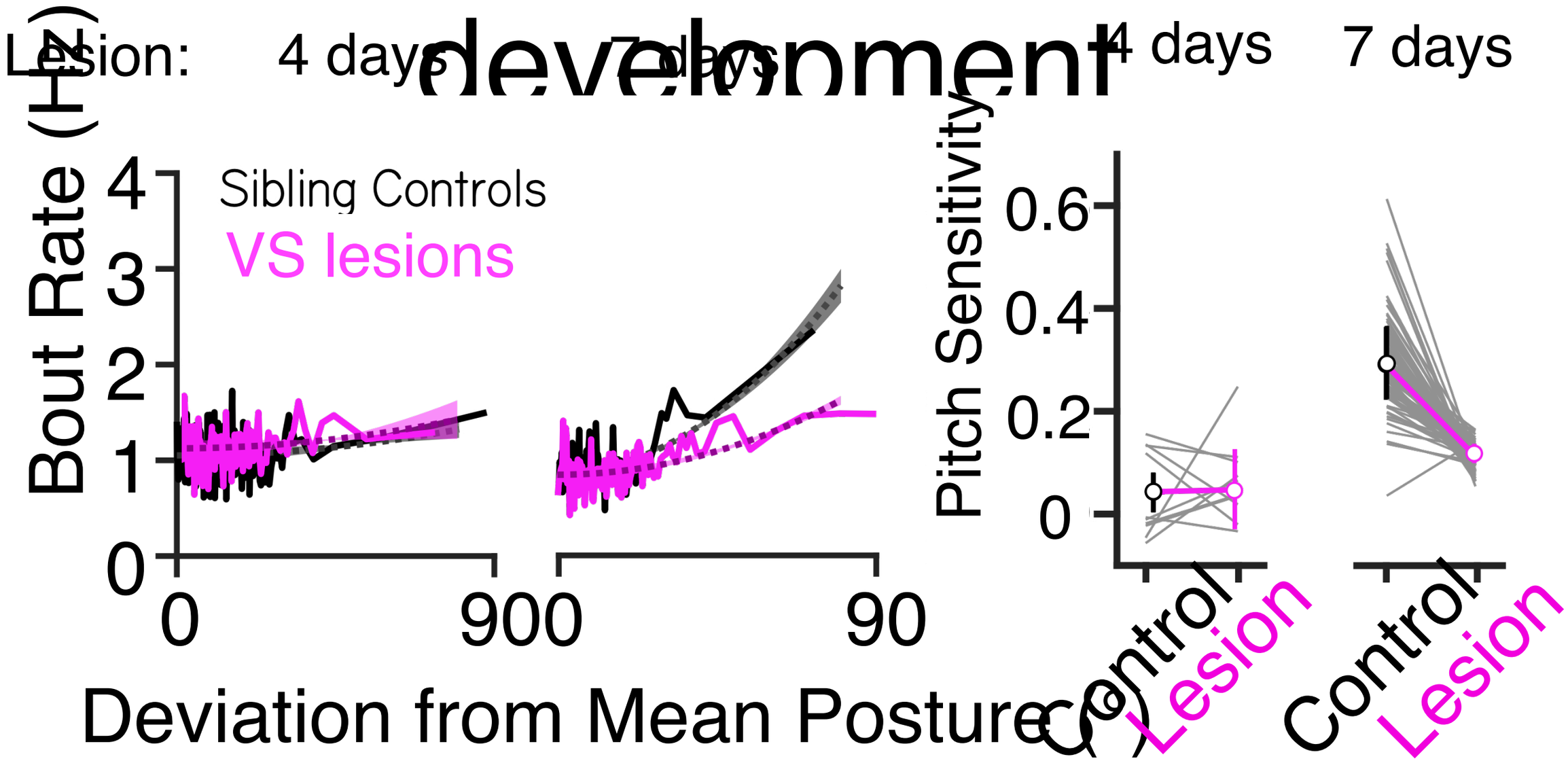
Post-Lesion

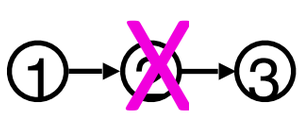




Lesion	Behavior
4 dpf	4-6 dpf
7 dpf	7-9 dpf

Vestibulospinal lesions compromise postural maintenance later in development





1. Bouts correct destabilization.
2. As they develop, larvae come to bout preferentially when unstable.
3. Vestibulospinal neurons are indispensable for proper timing of corrective bouts.

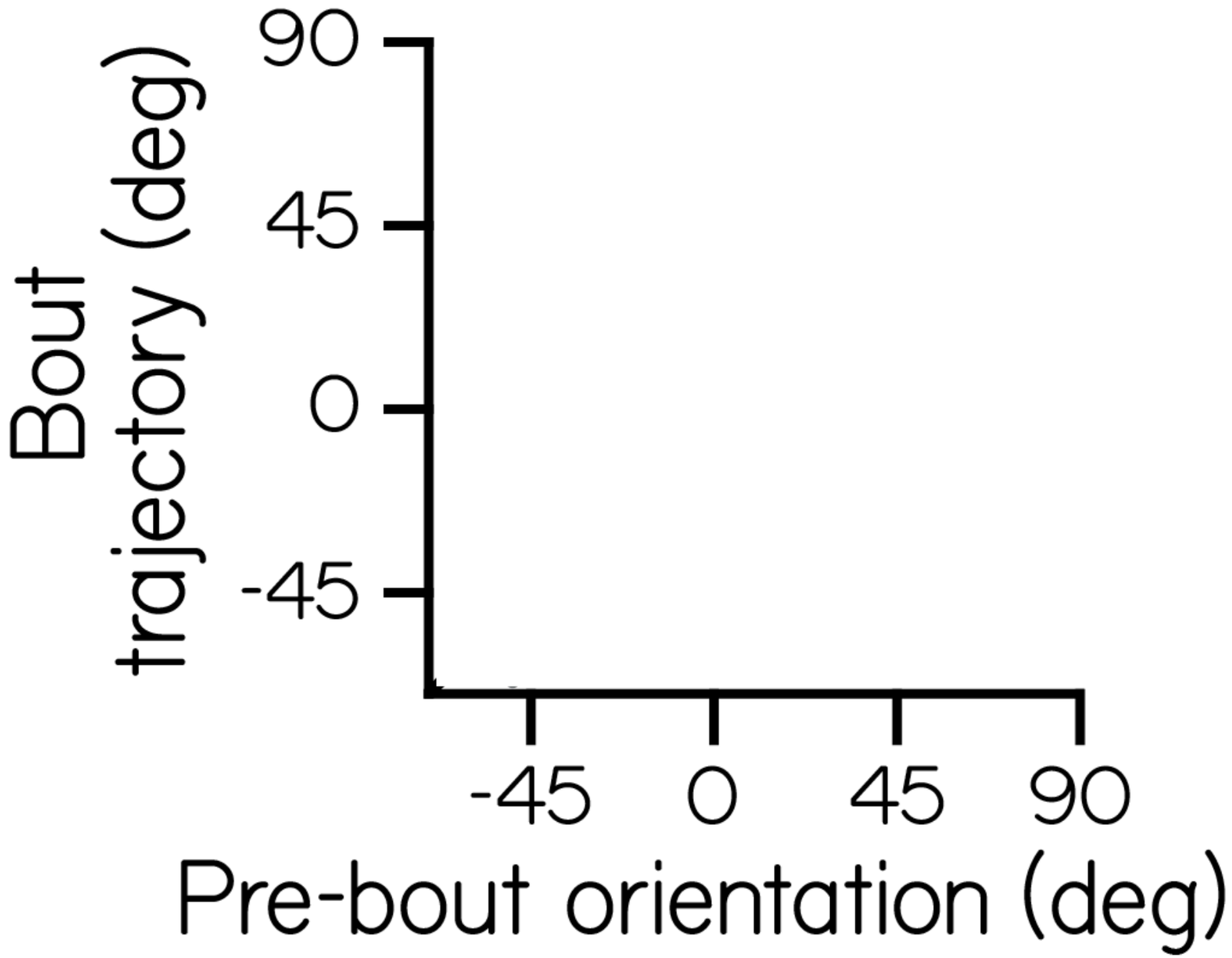
Ehrlich & Schoppik 201
Hamling et. al. 2021 bioR

Bout kinematics

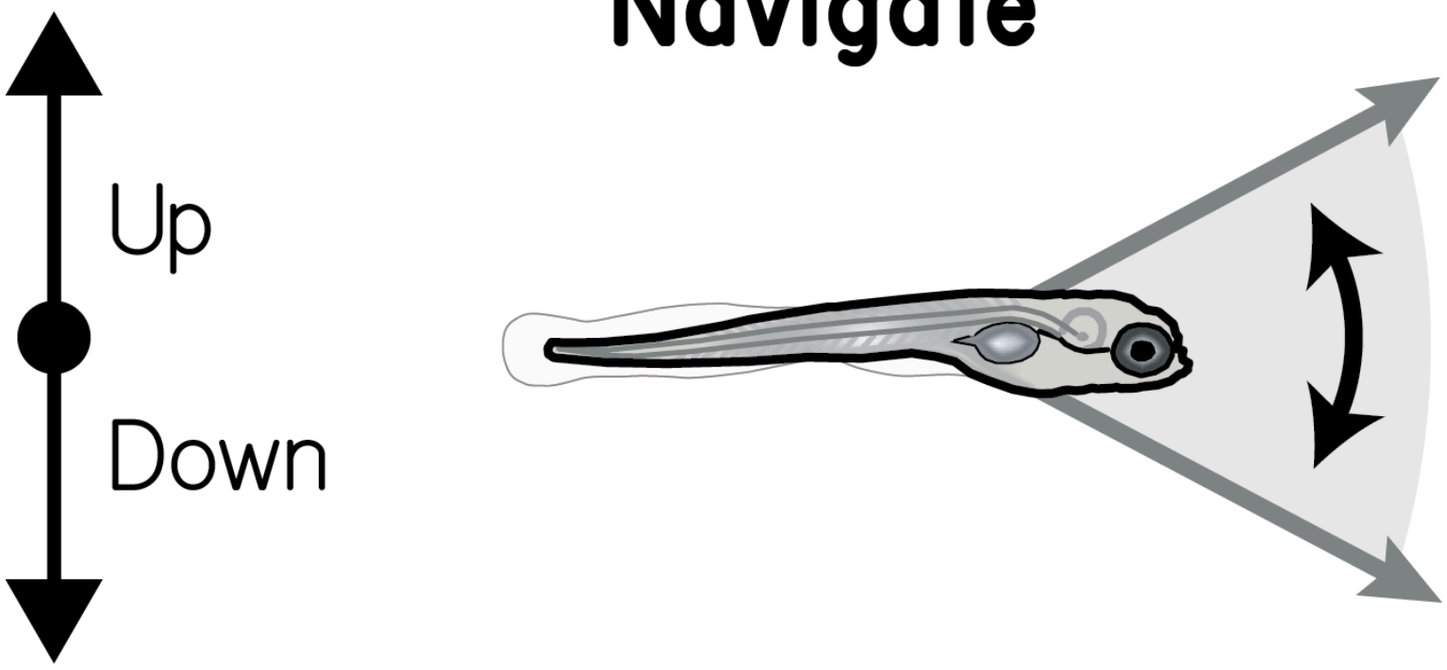
or

How do fish navigate in depth?

***Ehrlich & Schoppik 2017b**

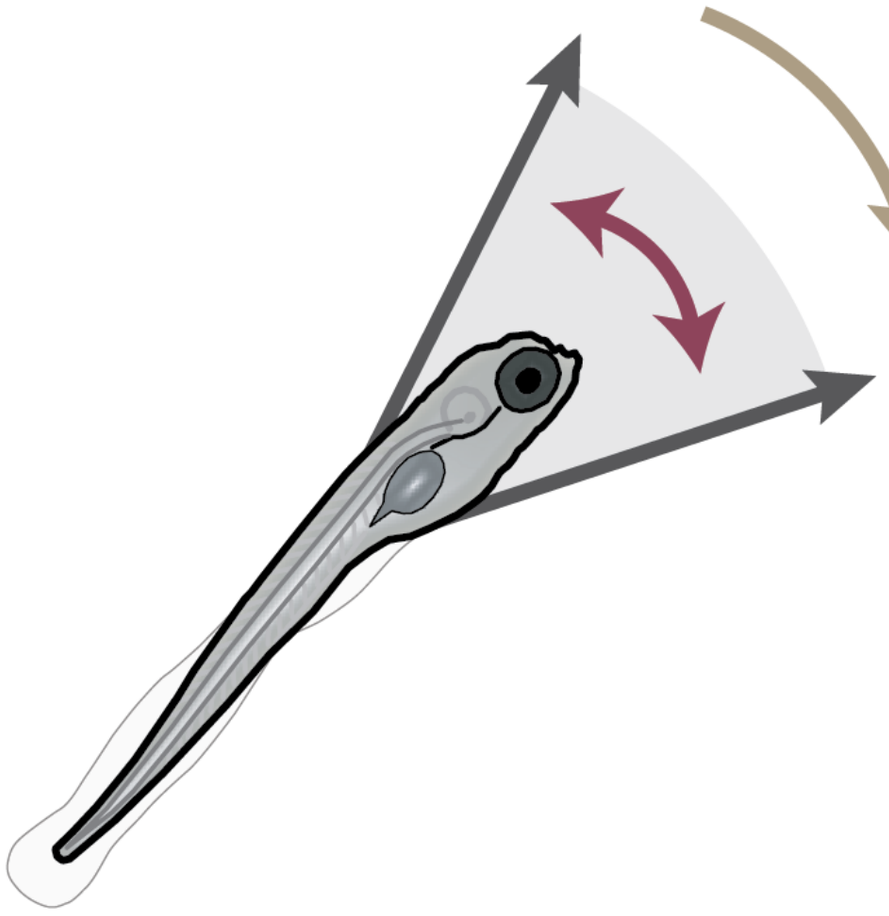

Bout trajectory (deg)
90
45
0
-45
-45
0
45
90
Pre-bout orientation (deg)

Navigate



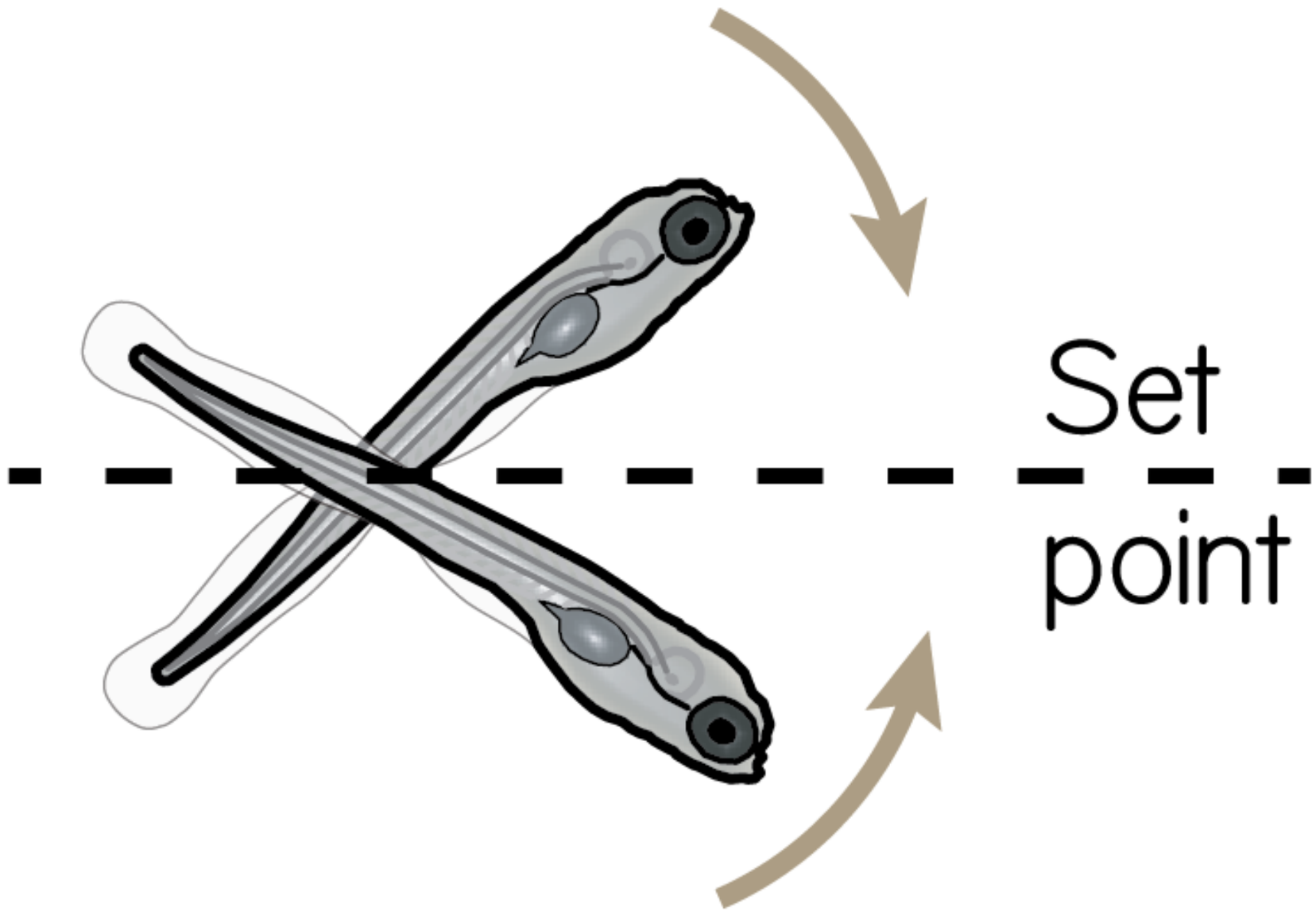
1. Navigate

2. Balance



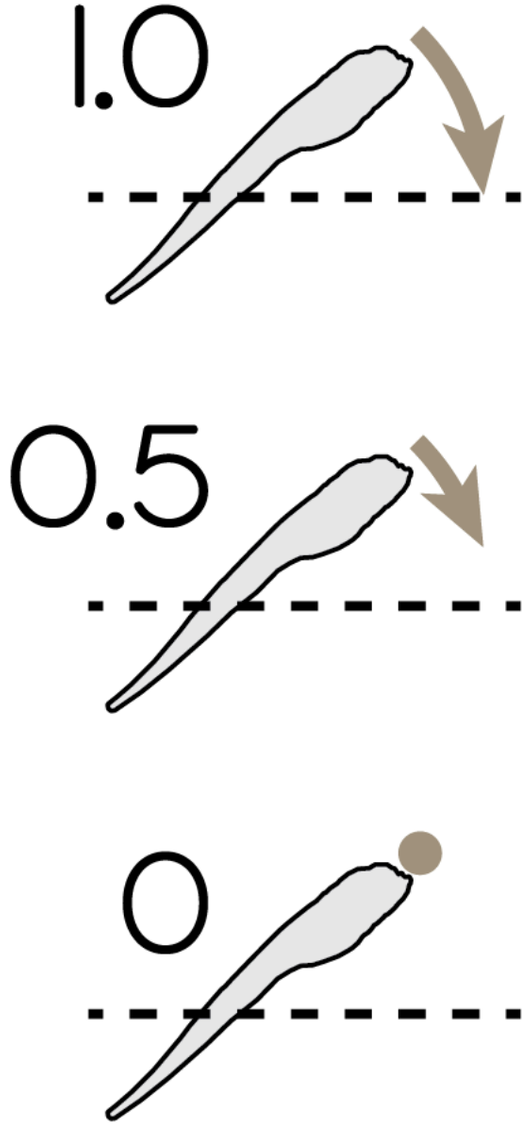
*Ehrlich & Schoppik 2017b

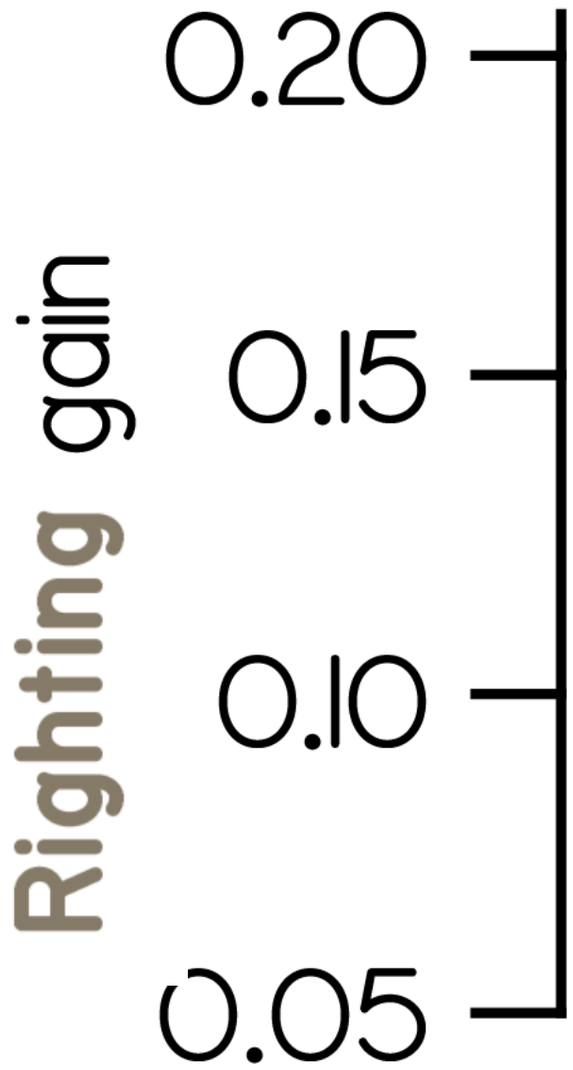
Righting



Righting

gain

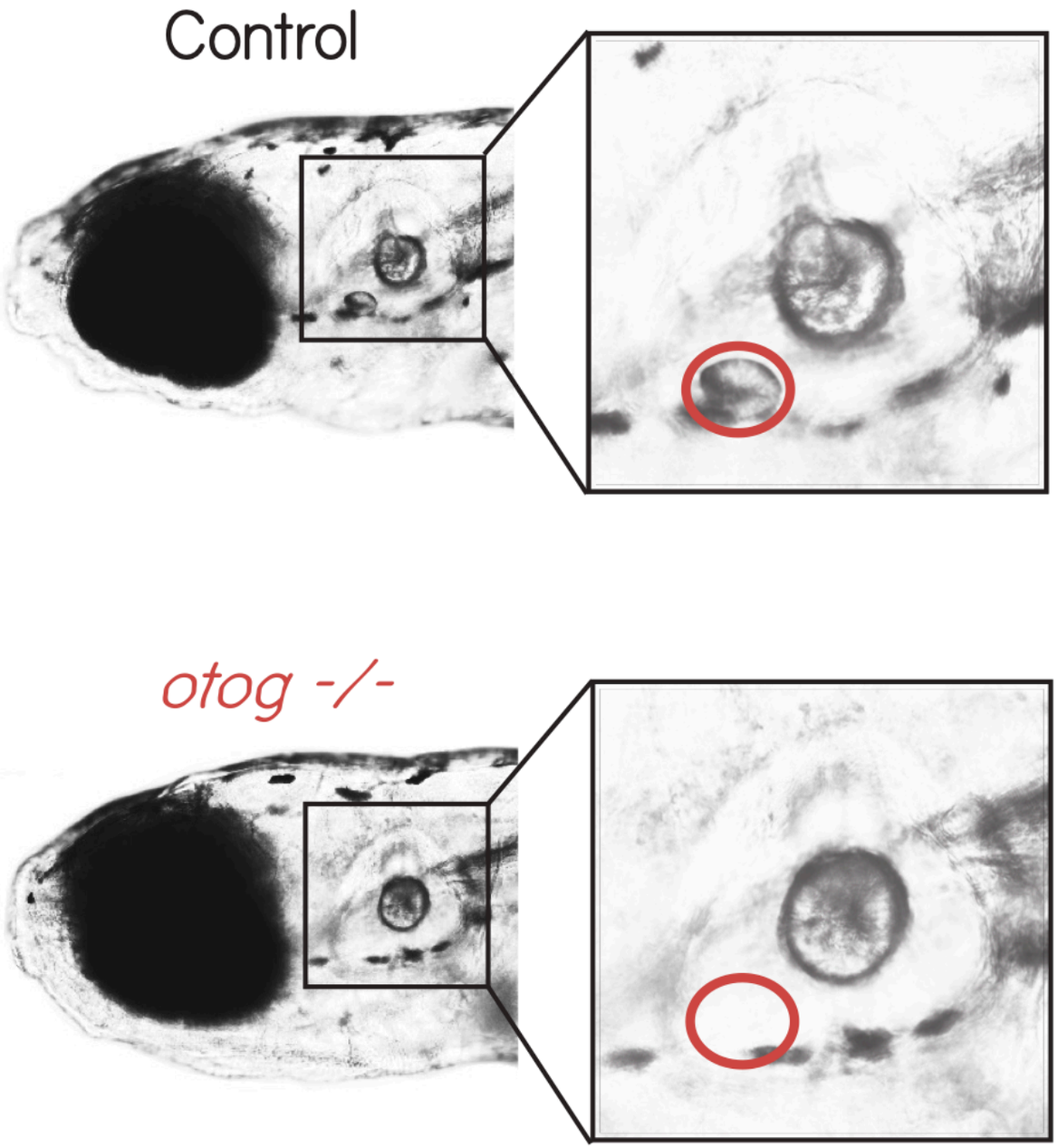


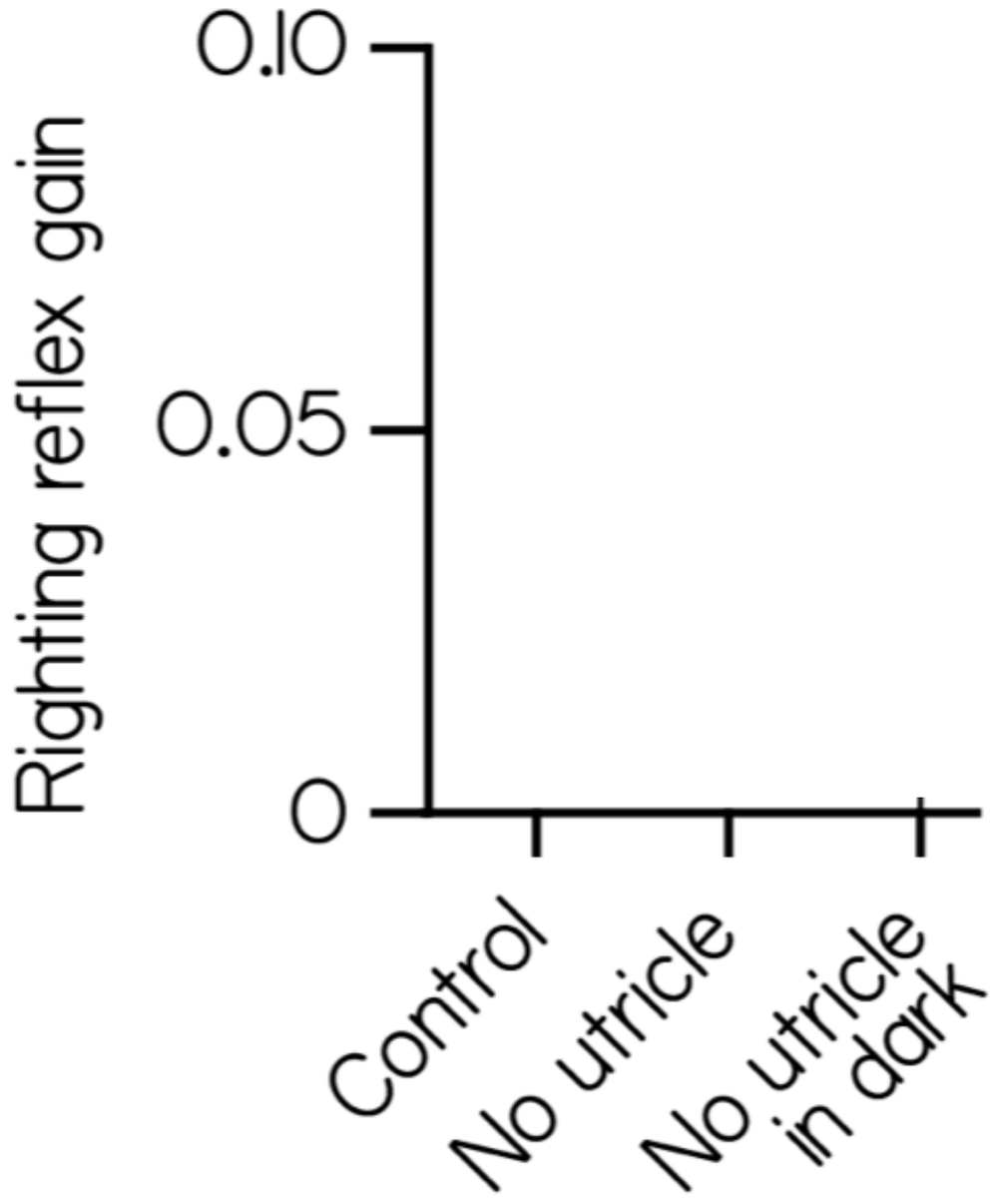


1 2 3

Age (wpf)

The righting reflex can use visual and vestibular input





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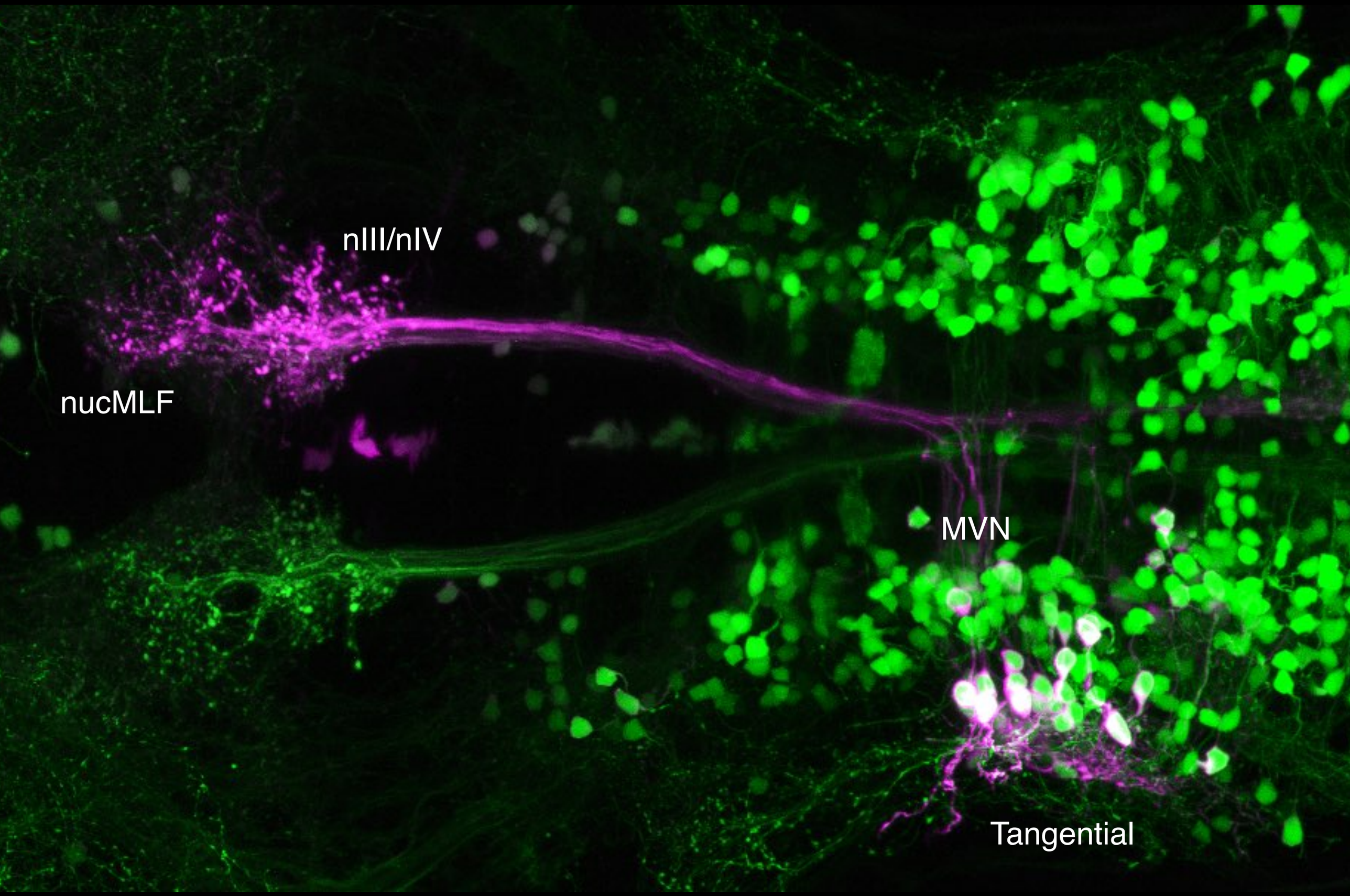
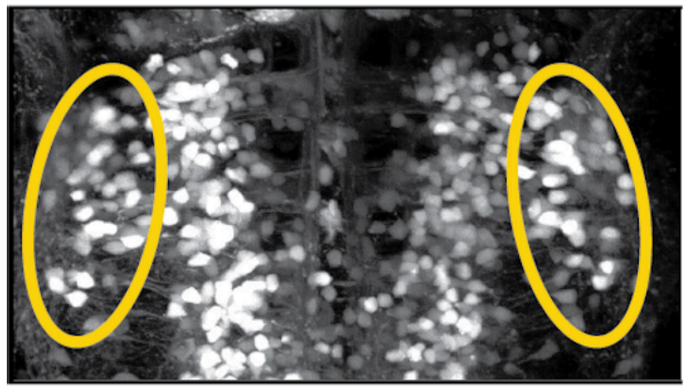

nIII/nIV
nucMLF
MVN
Tangential

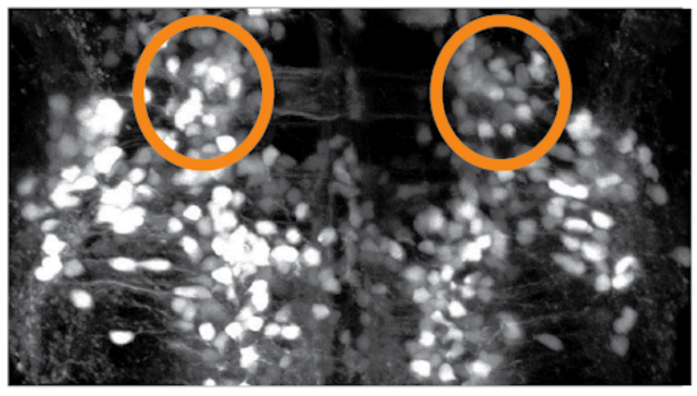
Tangential vestibular nucleus

pre post



Medial vestibular nucleus

pre post



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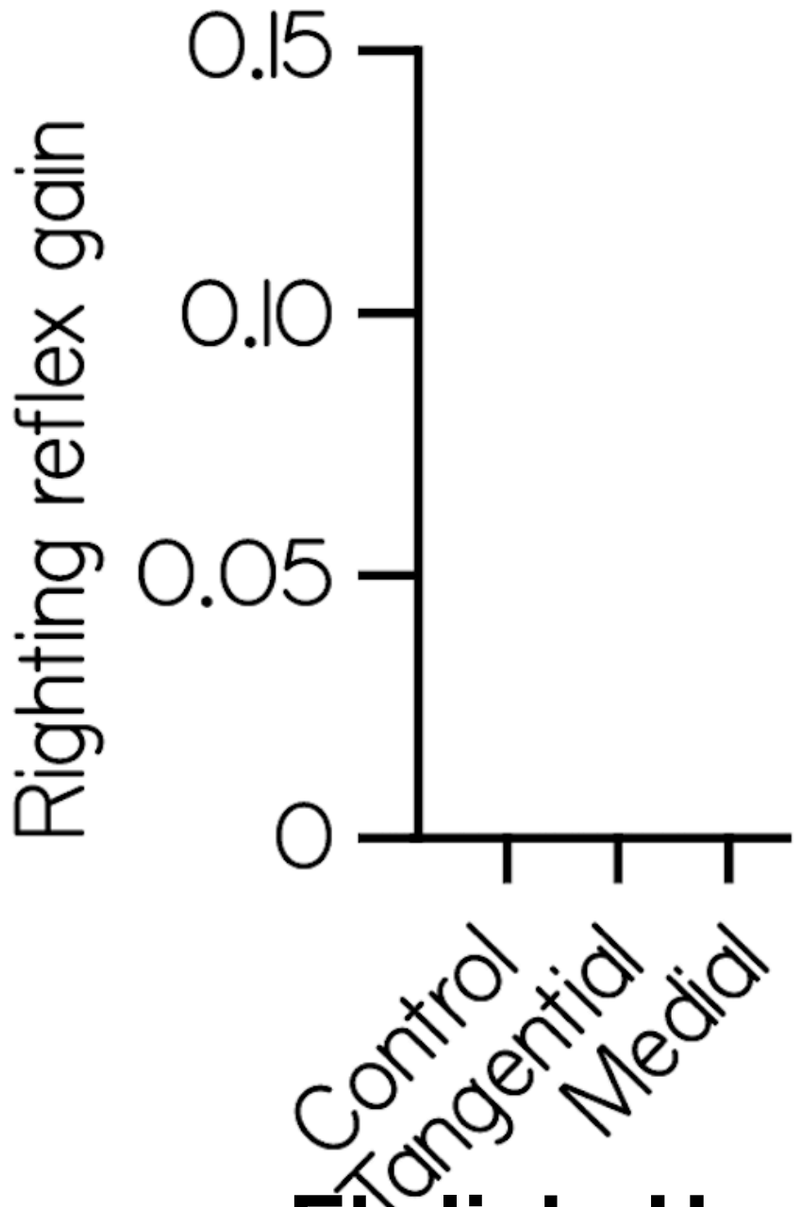
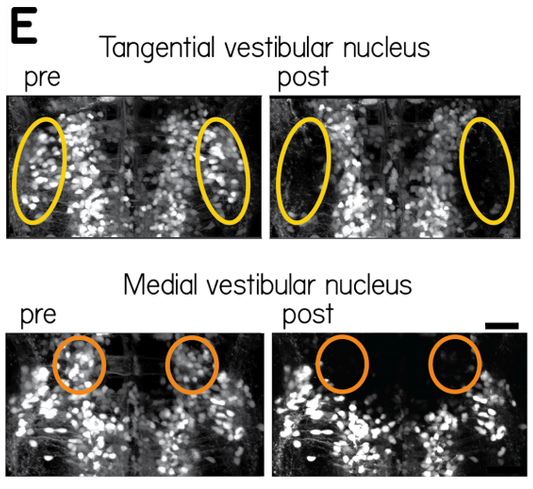
Loss of neurons in the tangential vestibular nucleus compromises the ability to correct posture.





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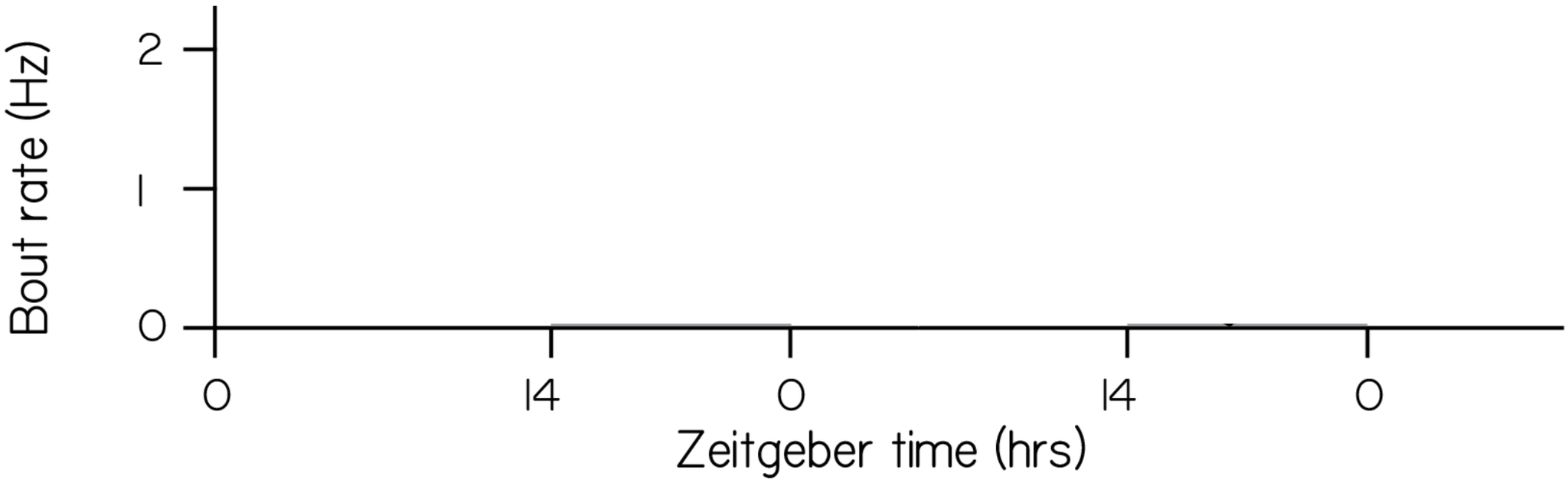
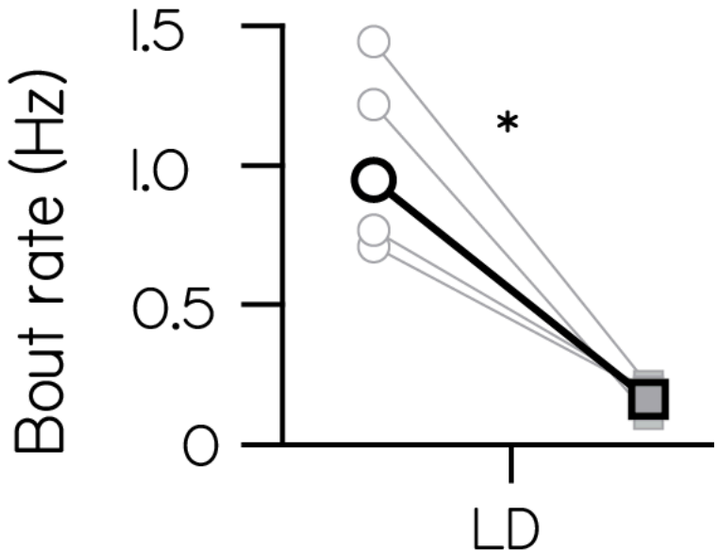
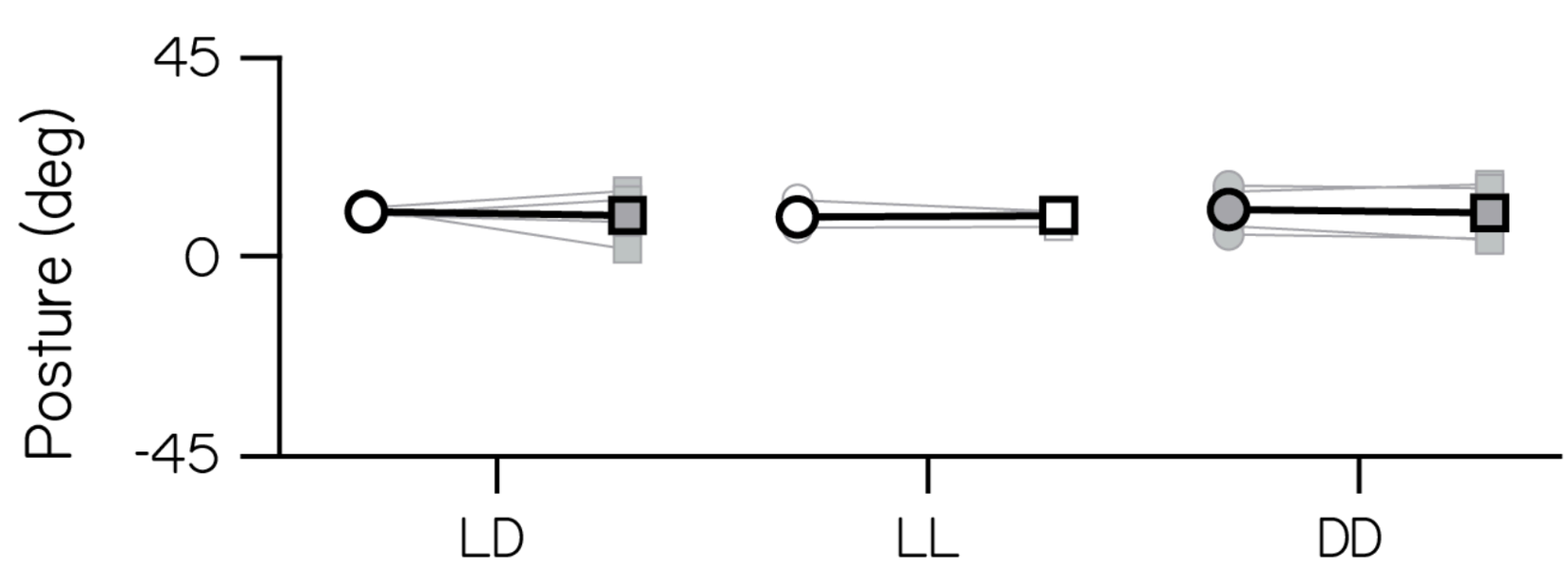
What happens at night?

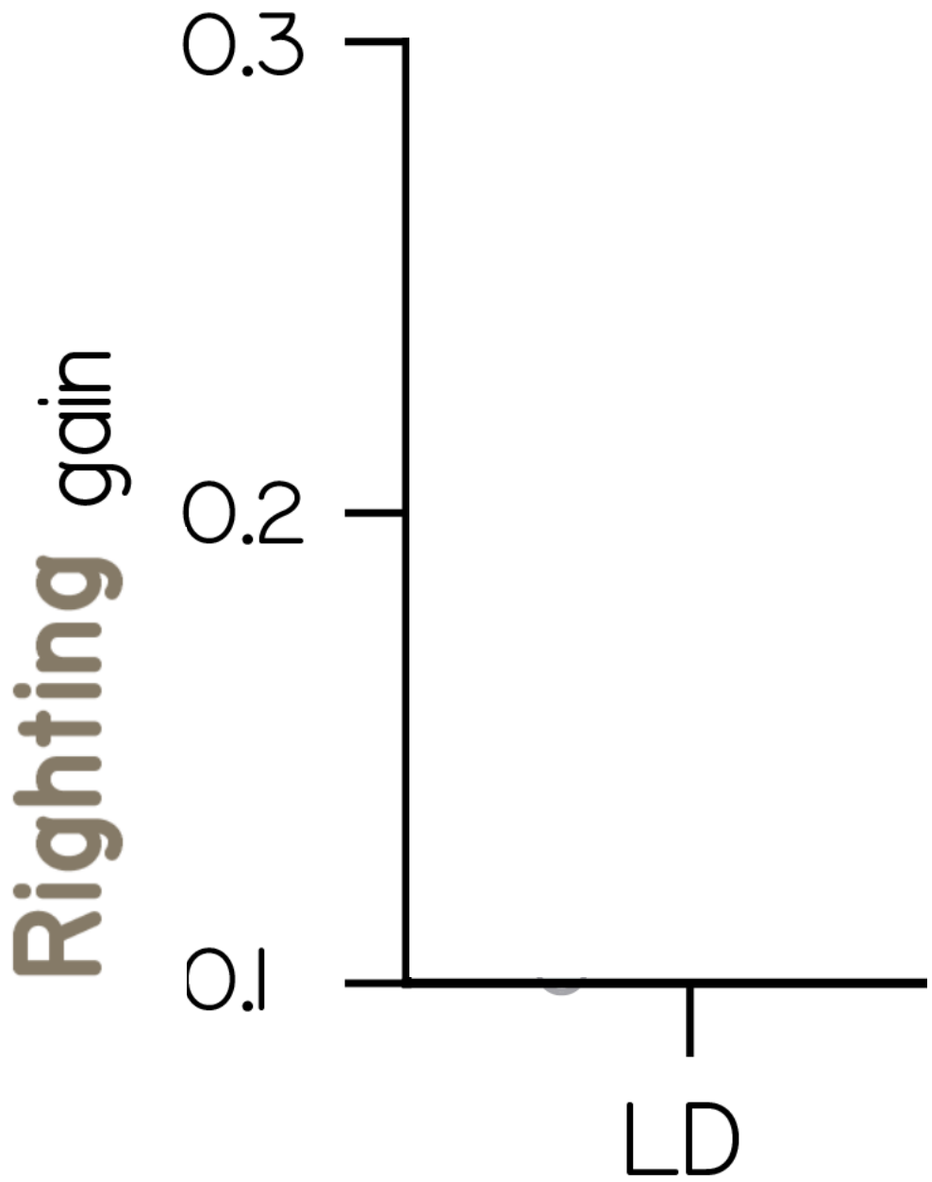

Light
Dark
Light
Dark
Light
Bout rate (Hz)
2
1
0
0
14
0
14
0
Zeitgeber time (hrs)


Bout rate (Hz)
1.5
1.0
0.5
0
*
LD


Posture (deg)
45
0
-45
LD
LL
DD


Day
Night

How can fish maintain posture given that they make fewer bouts at night?

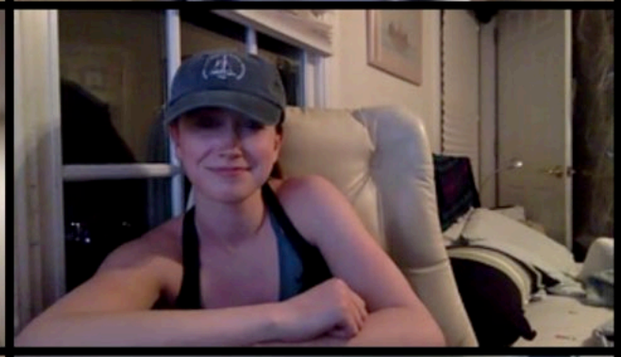


Day

Night

Summary:

1. Fish make bouts when unstable
2. Each bout partially returns the fish to its preferred posture
3. Amazingly, fish are better able to return to their preferred posture at night.



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