Genetic control of motor axon circuitry: a noisy computation

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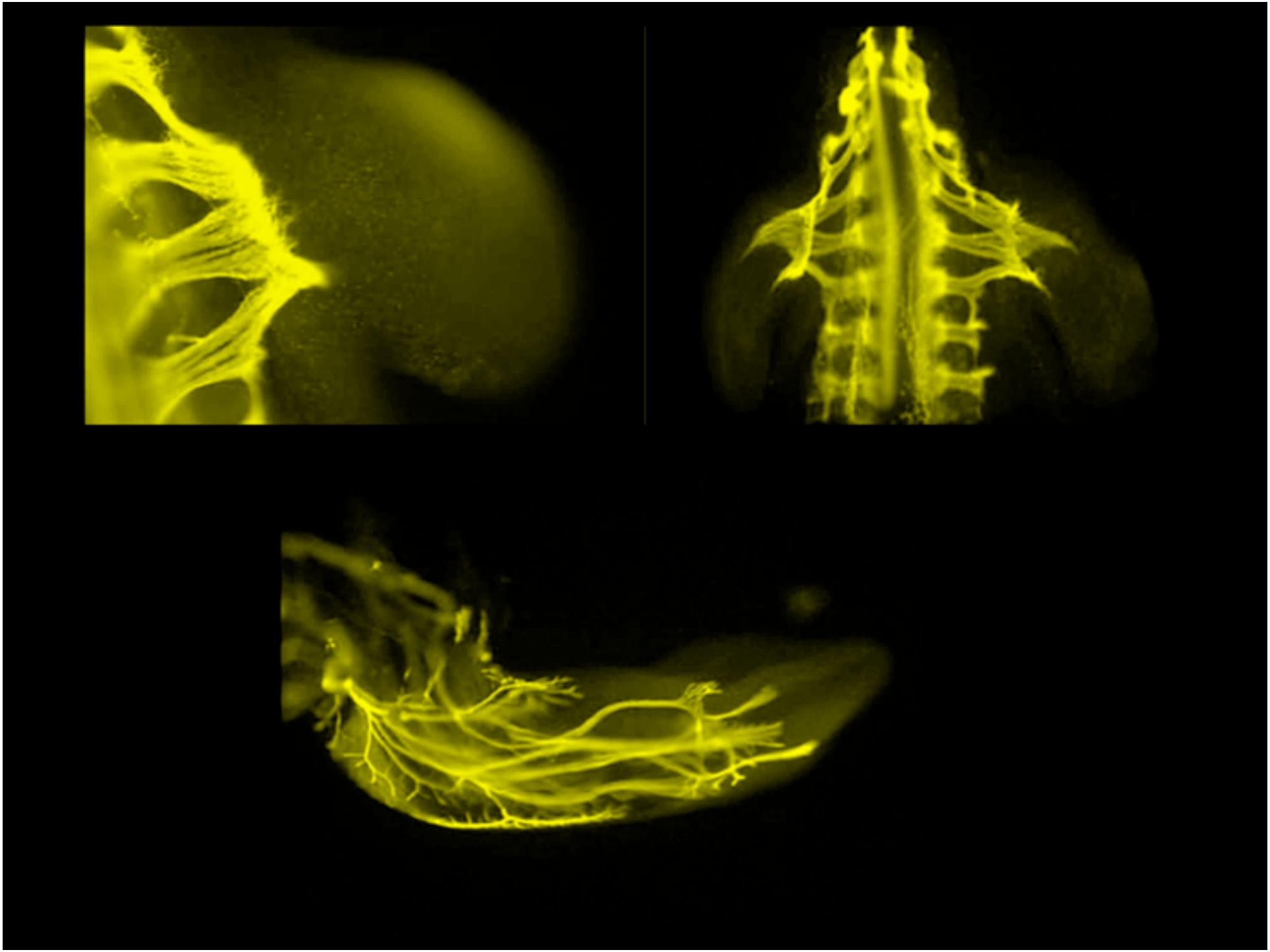
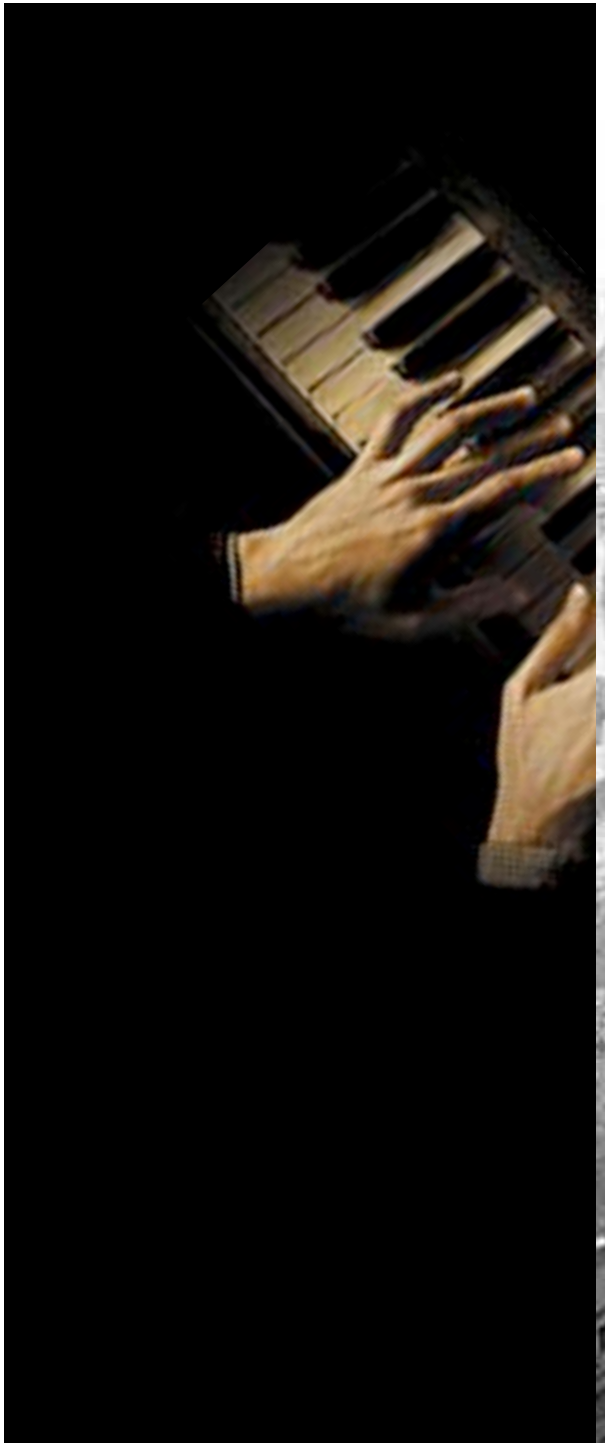
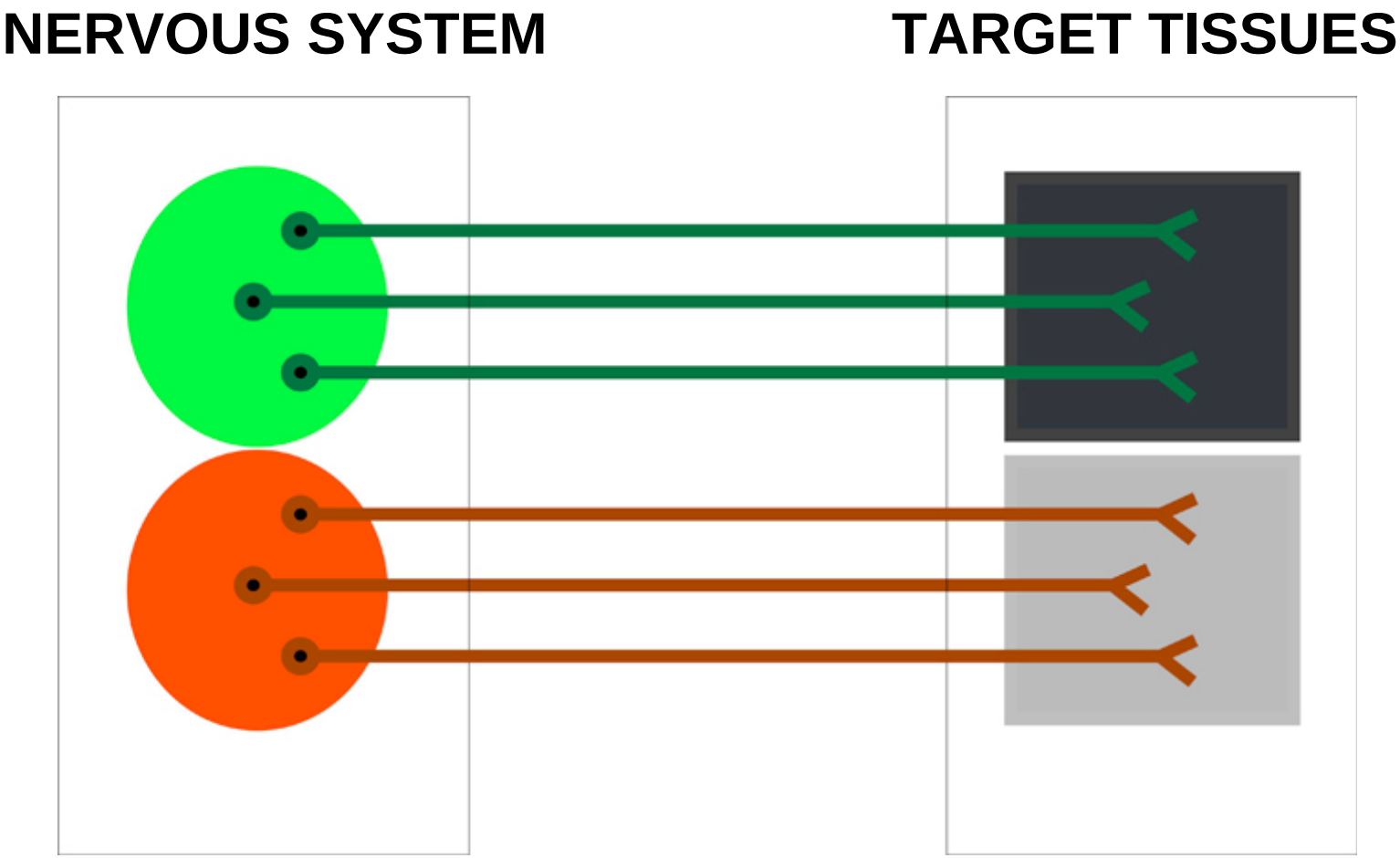
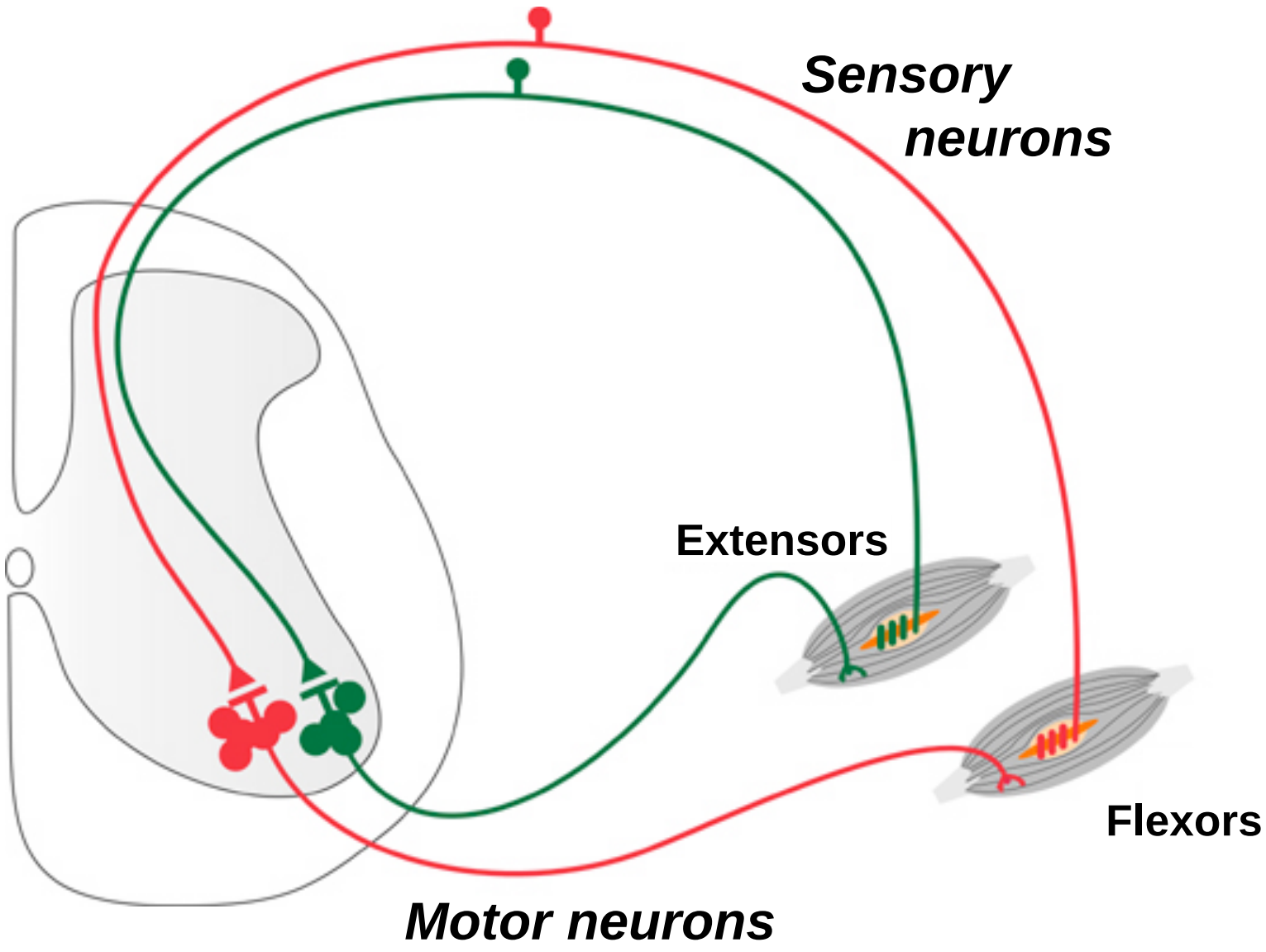


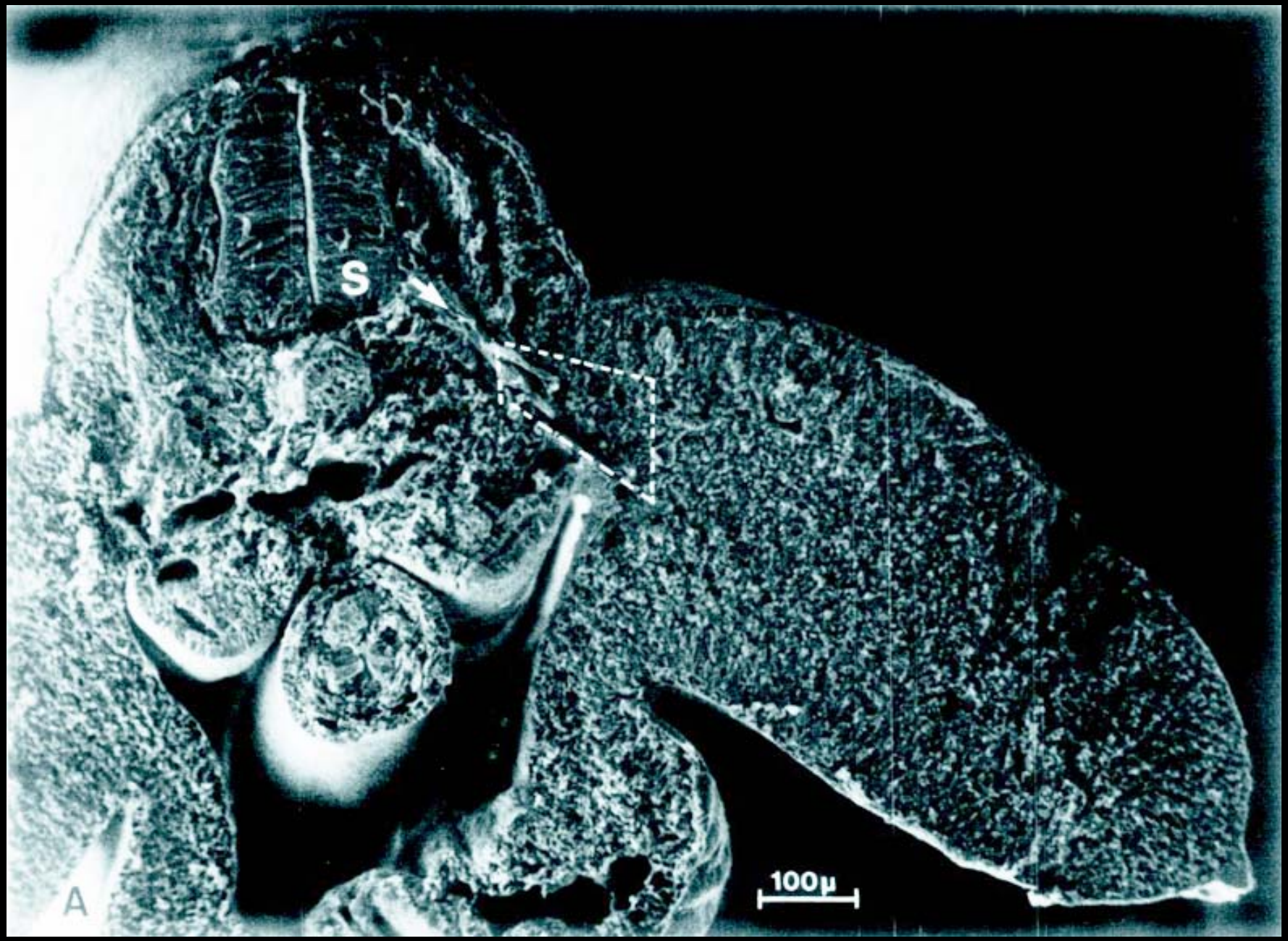


Topographic mapping



Motor neurons innervate target muscles





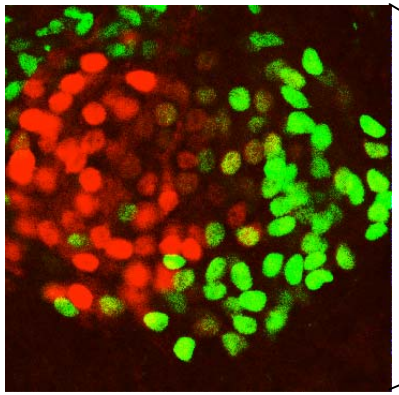
Tosney & Landmeser, 1985

Lateral Motor Column axonal projections

Motor column	LIM HD code
LMCl	: Lim1
LMCm	: Isl1

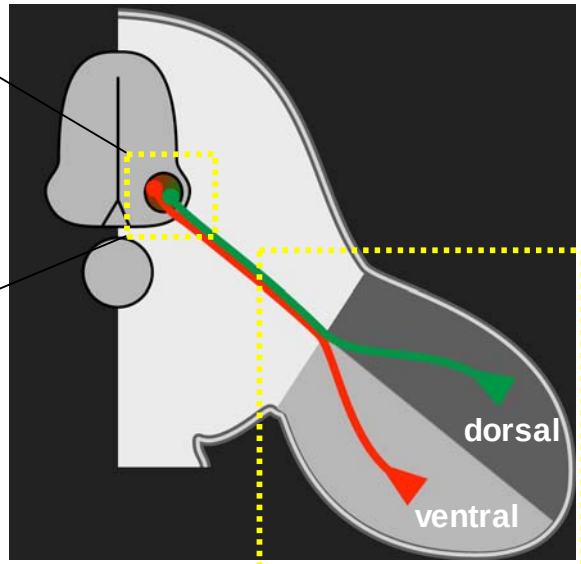
Limb mesenchyme	Lmx1b
dorsal	+
ventral	–

Isl1 Lim1

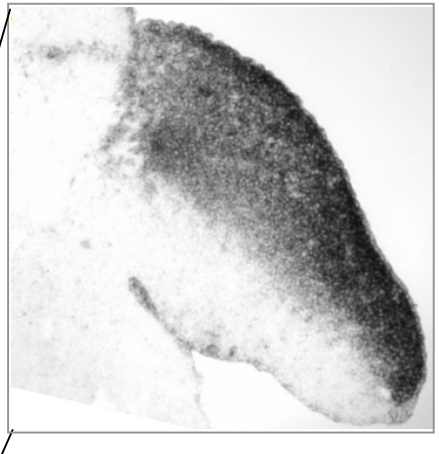


LMCm LMCl

Tsuchida et al., 1994

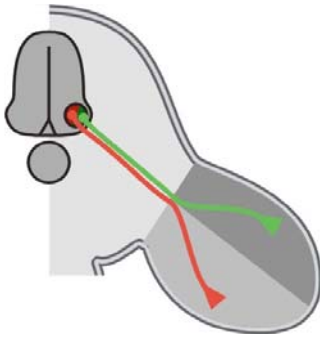


Lmx1b



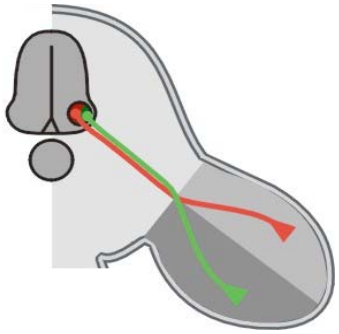
Riddle et al., 1995

Pathway selection is local and active



Wild type

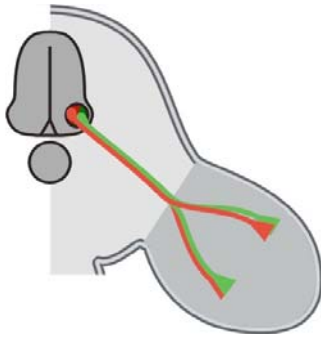
LMC(l)	Dorsal Limb
LMC(m)	Ventral Limb



Reversal

Whitelaw & Hollyday, 1983

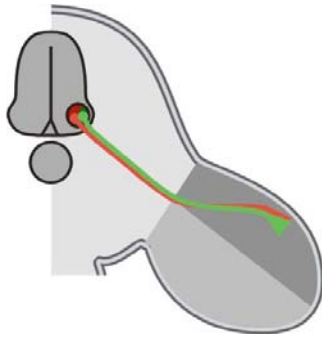
+	Ventral
+	Dorsal



Lmx1b-/-

Kania et al., 2000

+	–
+	+



EphA4 +++

Eberhart et al., 2002
Kania & Jessell, 2003

+	+
++	+

RESULT

Reversed trajectories

Apparently randomized trajectories

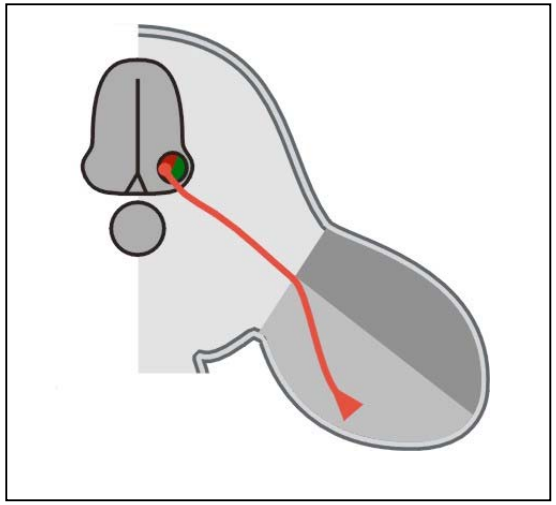
LMCm axons misrouted dorsally

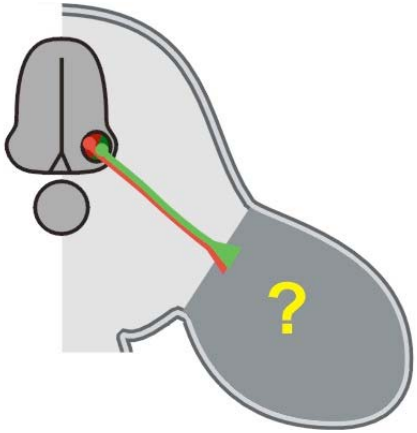
I. How are LMCm axons guided to the ventral limb?

II. What are the effector molecules that control LMCm trajectories?

III. Quantitative models, experimental predictions and tests

I. How are LMCm axons guided to the ventral limb?





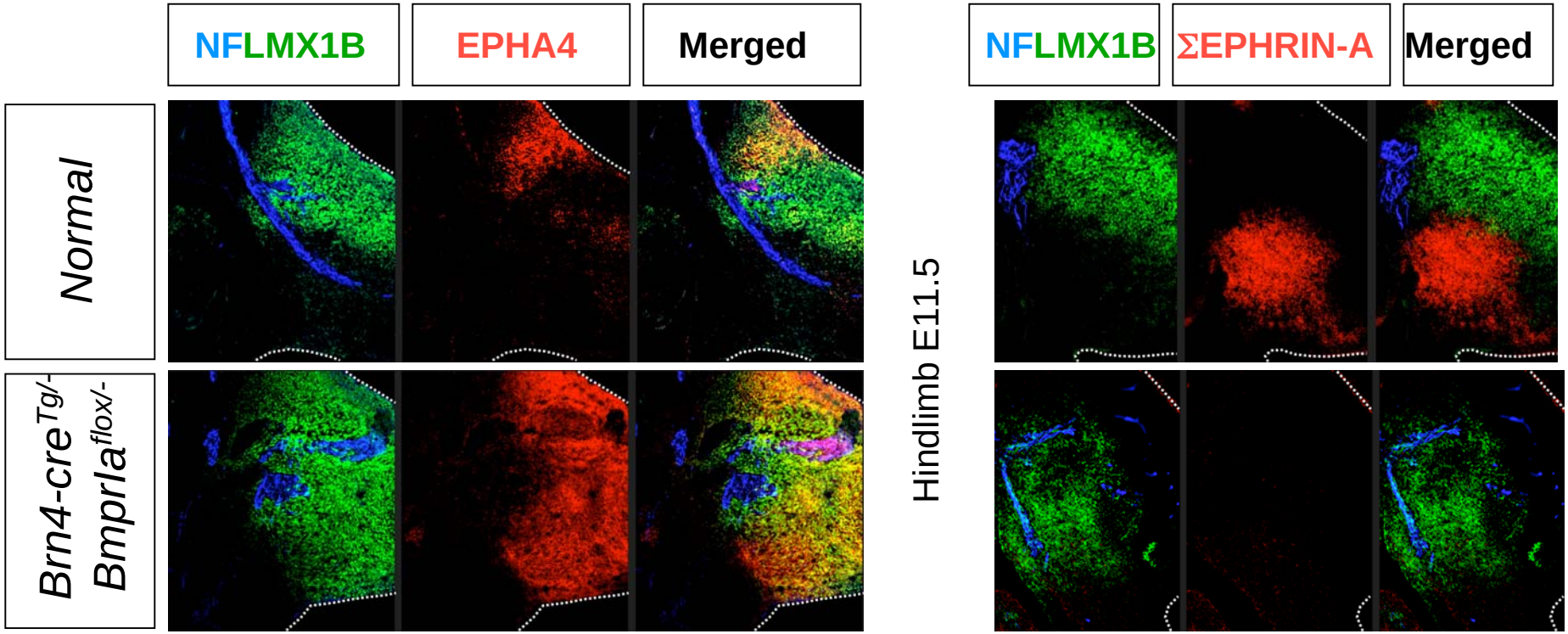
Bidorsal

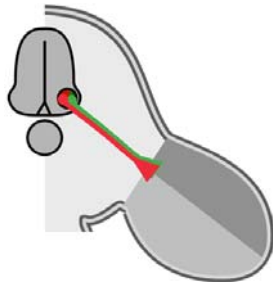
Bmp receptor Ia mouse conditional mutant
limbless chick mutant

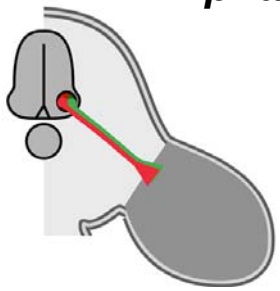
Bmprla$^{flox/-}$ hindlimbs are bidorsal

Dorsal markers are expanded

Ventral markers are absent

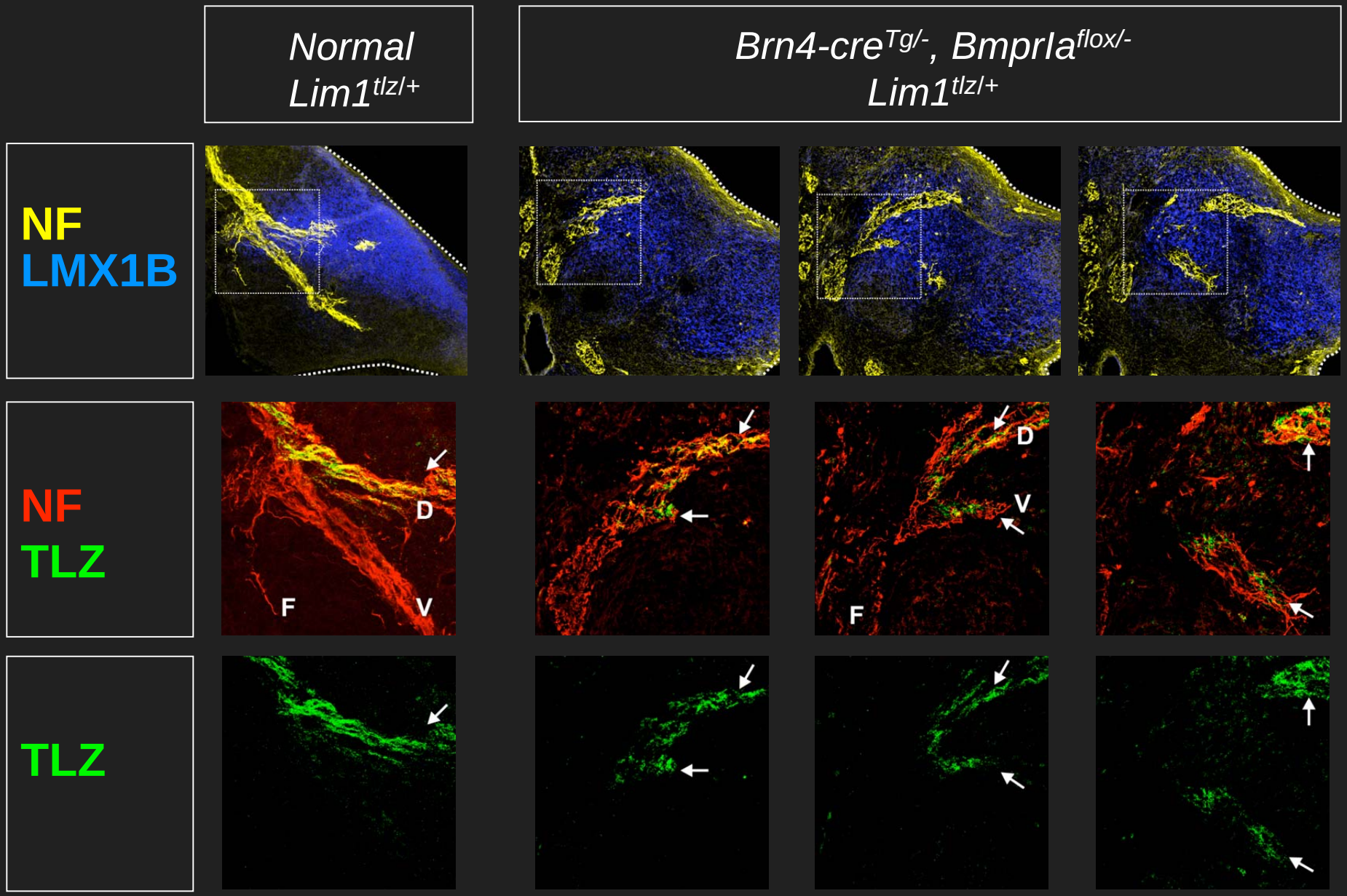




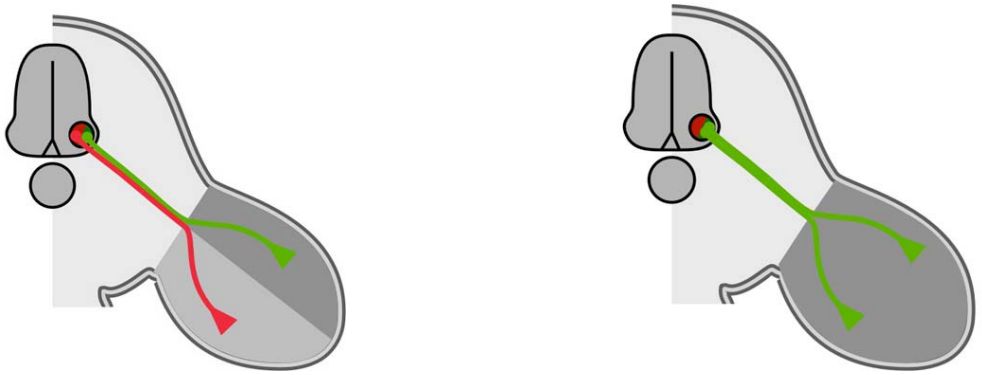


	Normal D	Normal V	*Bmprla*$^{flox/-}$ D	*Bmprla*$^{flox/-}$ V
Plzf	+	+	+	+
Lmx1b	+	–	+	+
EphA4	+	–	+	+
Σephrin-A	–	+	–	–

LMCl populates both limb nerve branches in mutants

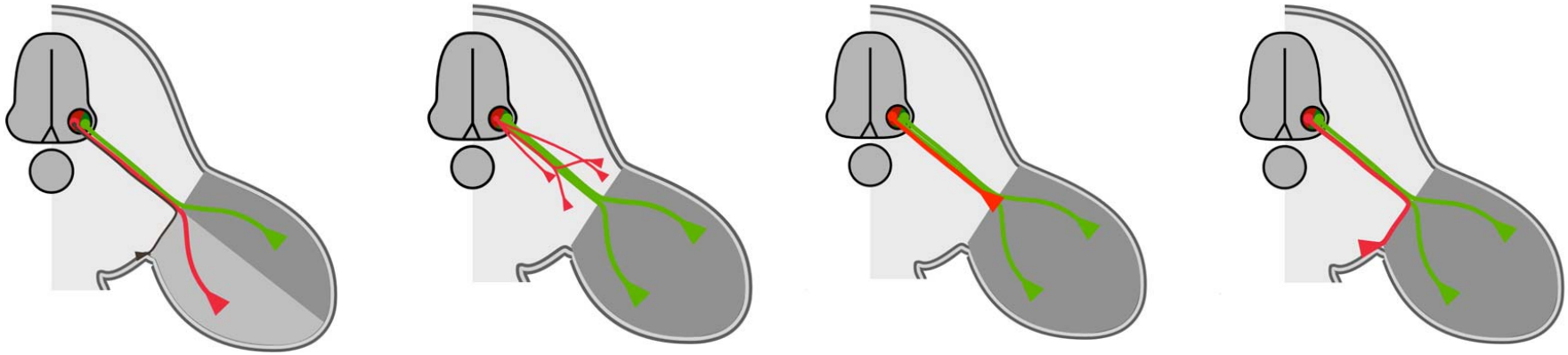


WT | *Brn4-cre$^{Tg/-}$, Bmprla$^{flox/-}$*



Where do the LMCm axons project?

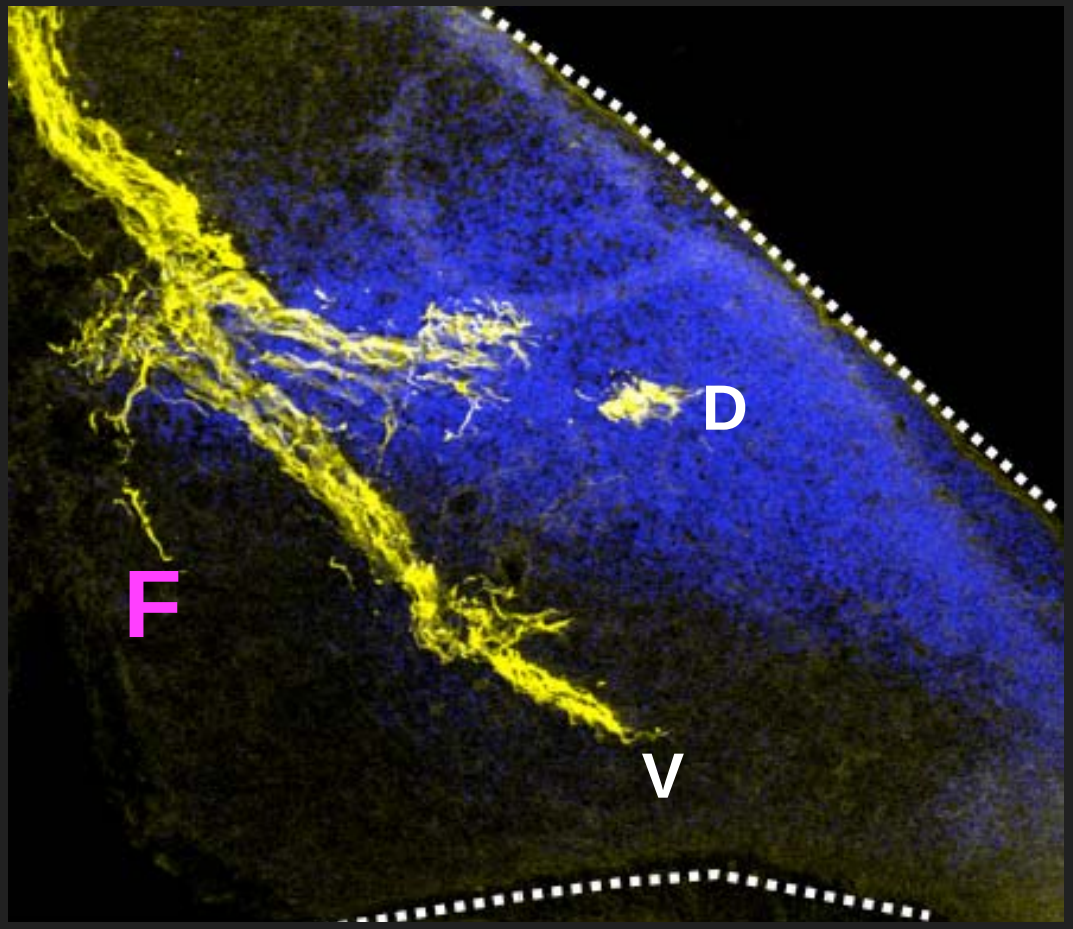
WT | *Brn4-cre$^{Tg/-}$, Bmprla$^{flox/-}$*



DISORGANIZED? STALLED? REDIRECTED?

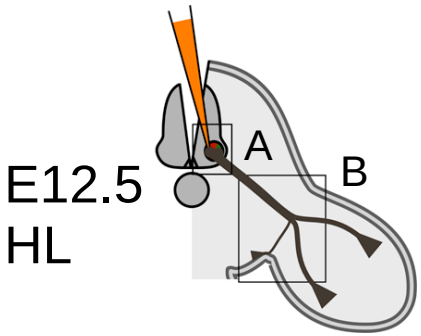
A third nerve branch innervates the flank

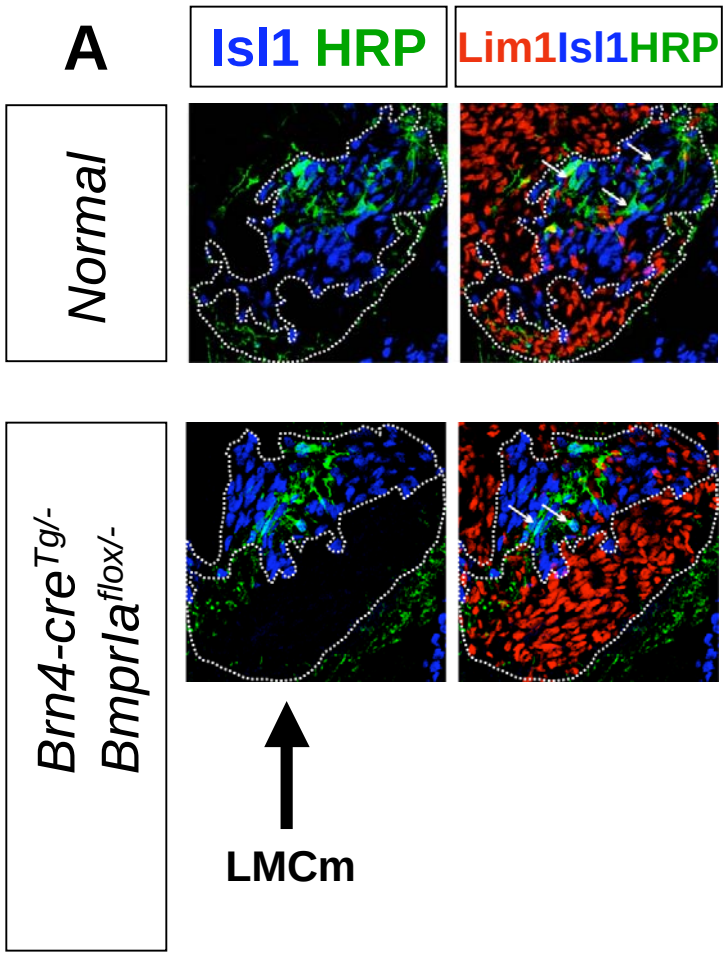
Nerves Dorsal limb

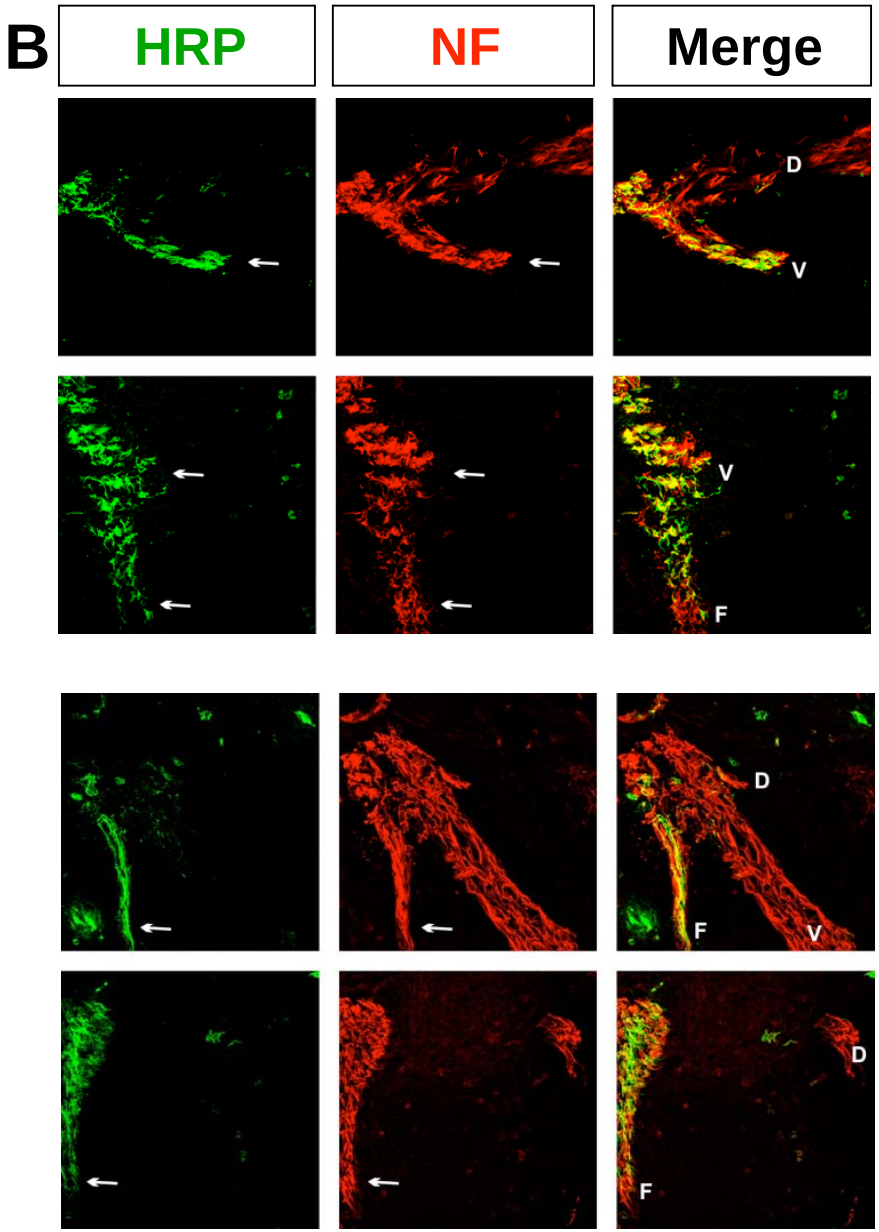


HL
E11.75

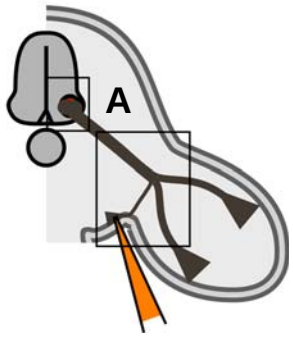
Mutant LMCm axons populate only the FLANK branch



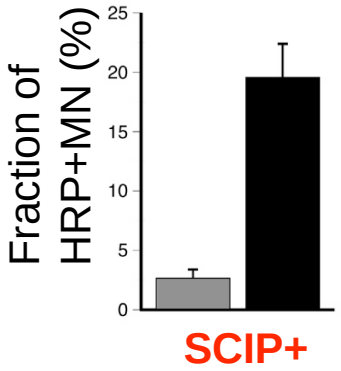




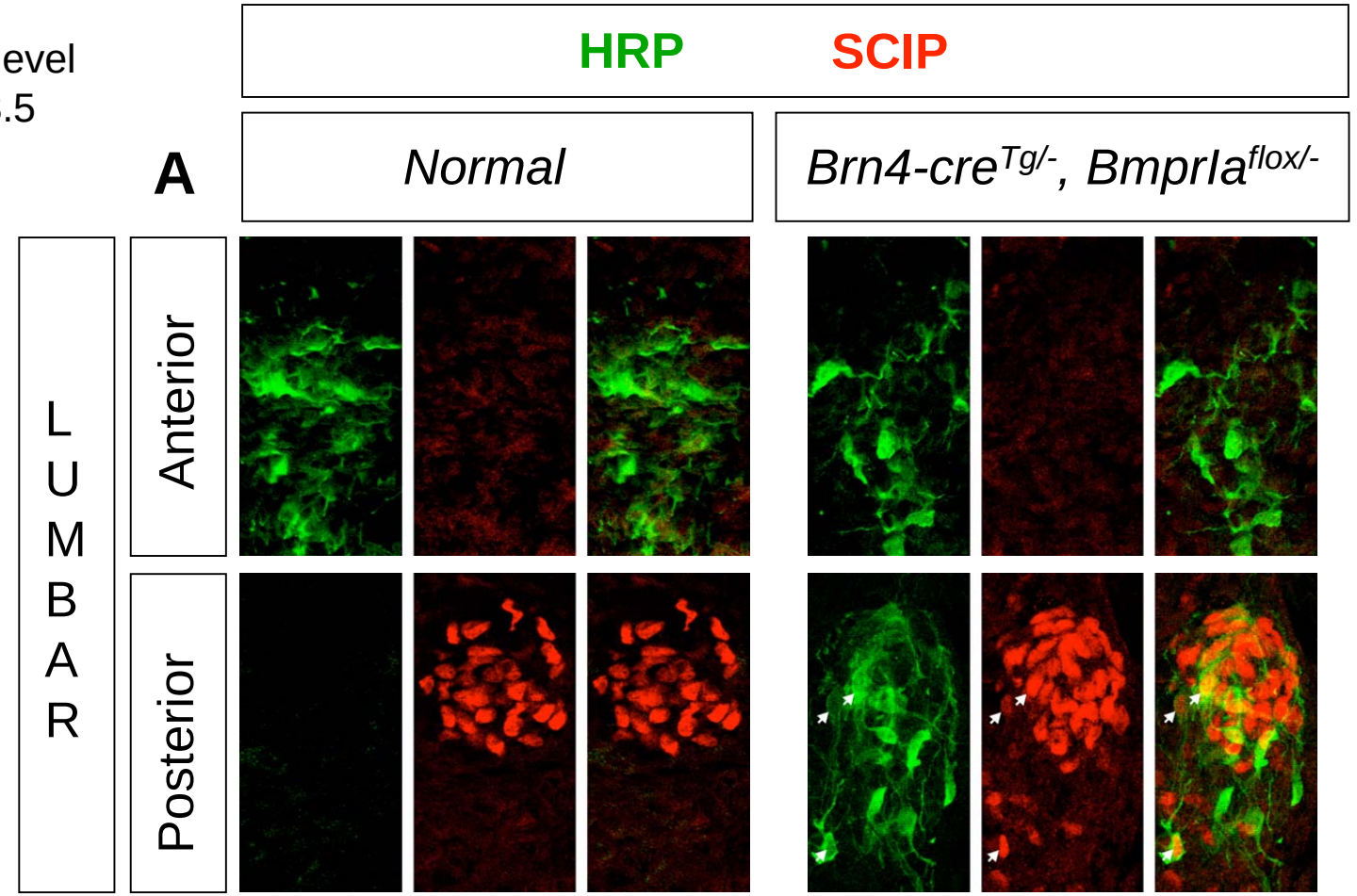
Limb-targeted LMCm axons are *redirected* to flank



HL level
E13.5



Normal
Brn4-cre$^{Tg/-}$
Bmprla$^{flox/-}$

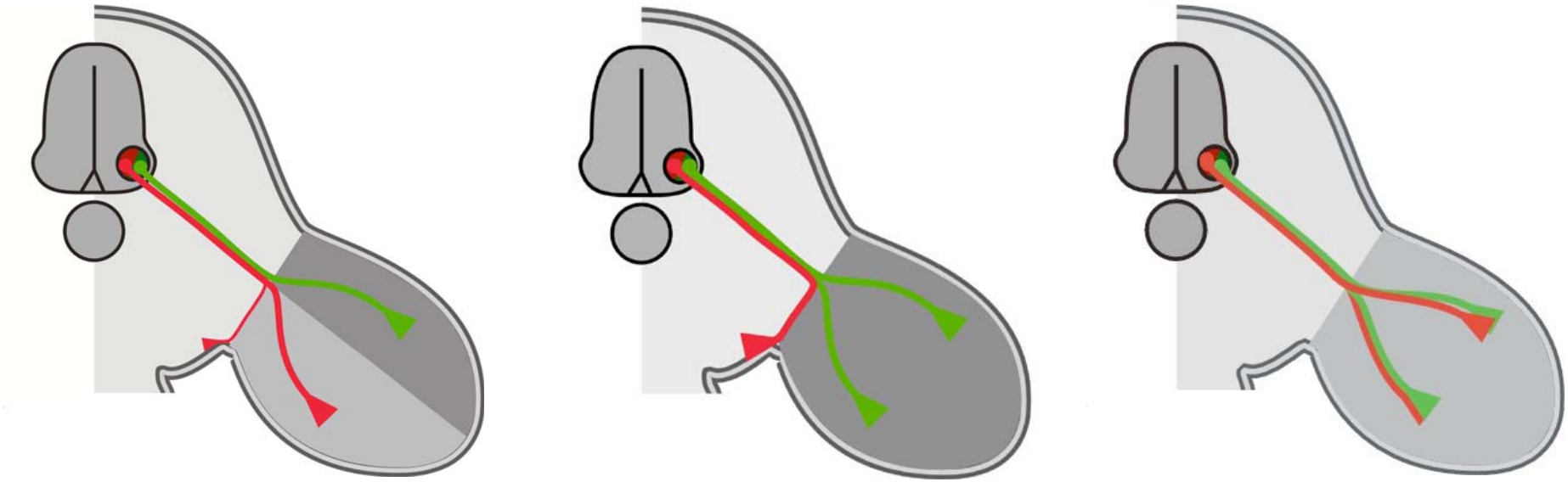


1. LMCm and LMCl have *non-symmetrical* preferences.

WT

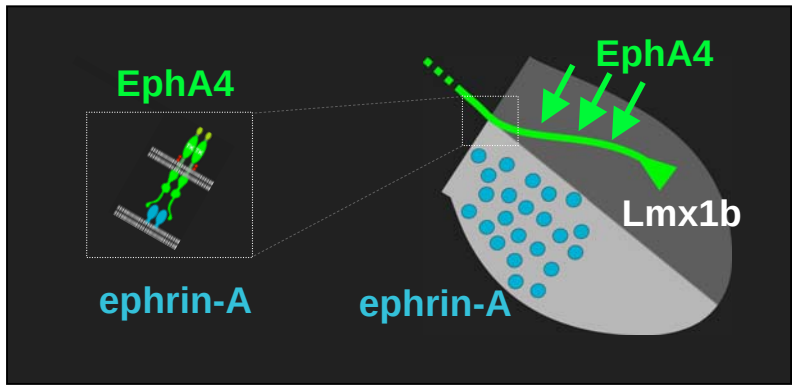
Bidorsal
***Bmprla*$^{flox/-}$**

Biventral
***Lmx1b*$^{-/-}$**



2. NEW TARGET: LMCm also innervate non-limb tissues.

II. What are the effector molecules that control LMCm trajectories?

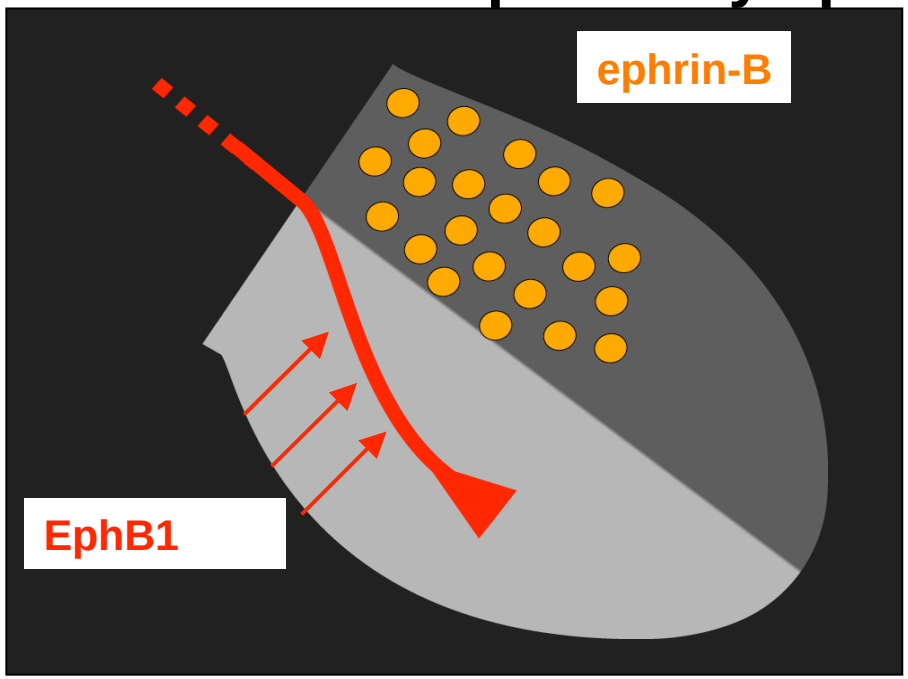


ephrin-A/EphA, GDNF/c-ret, Sema/Npn signaling influence LMCl trajectories

Kania et al., 2000
Helmbacher et al, 2000
Eberhart et al, 2002
Kania and Jessell, 2003
Huber et al., 2005
Kramer et al., 2006

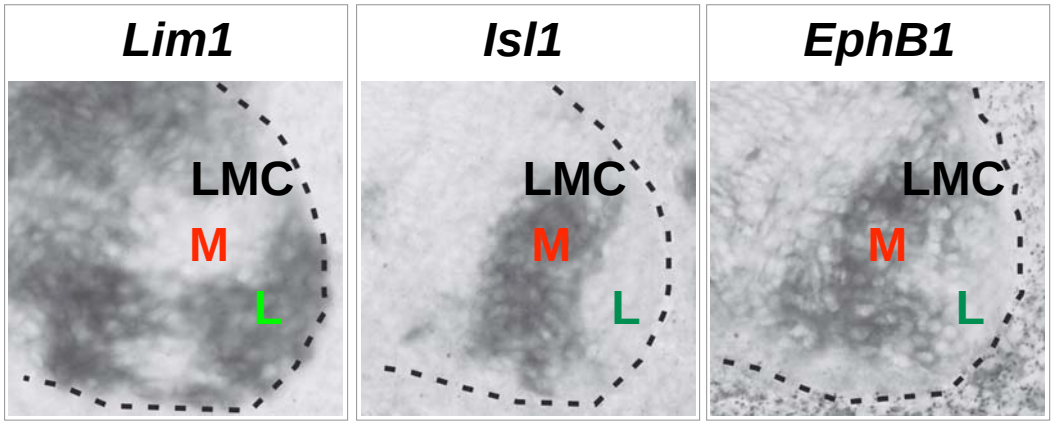
Hypothesis

EphB+ LMCm axons are repelled by ephrin-B+ dorsal limb



RECEPTORS

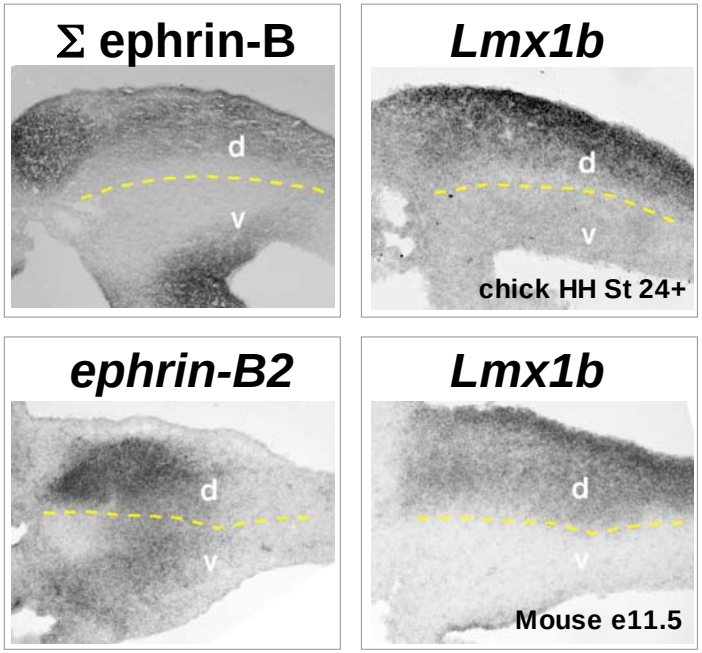
EphB1 in medial LMC neurons



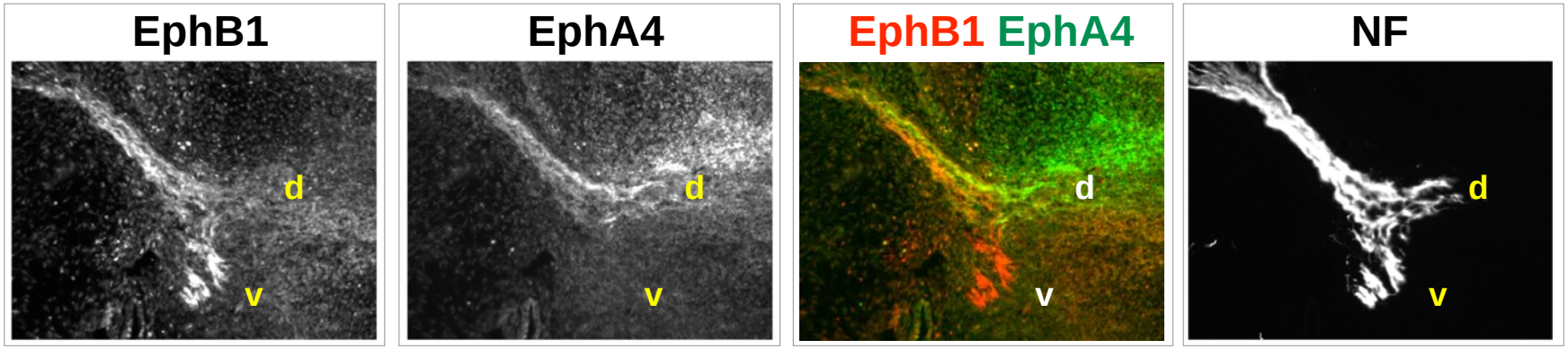
chick HH St 25+

LIGANDS

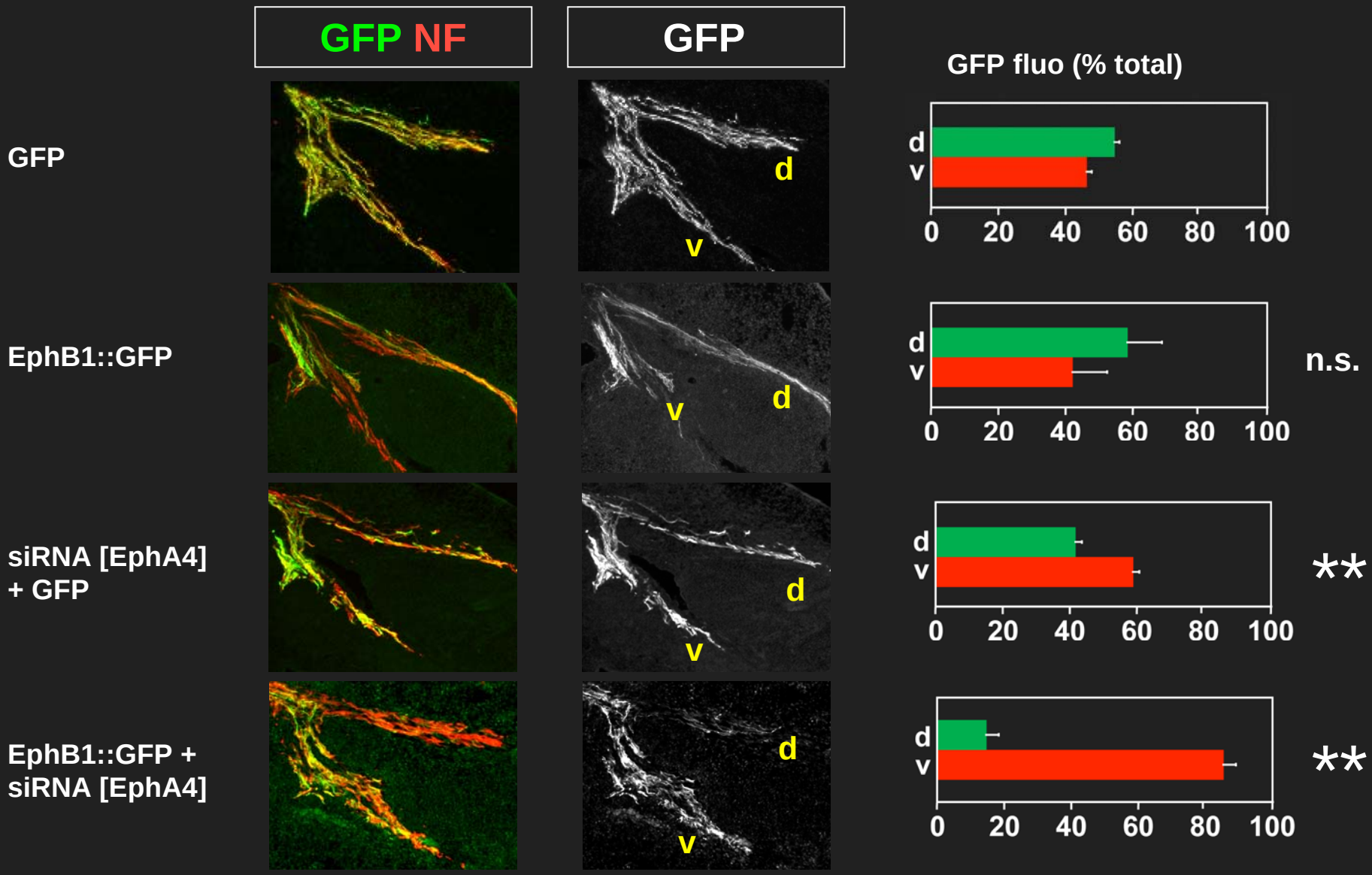
ephrin-B in dorsal limb



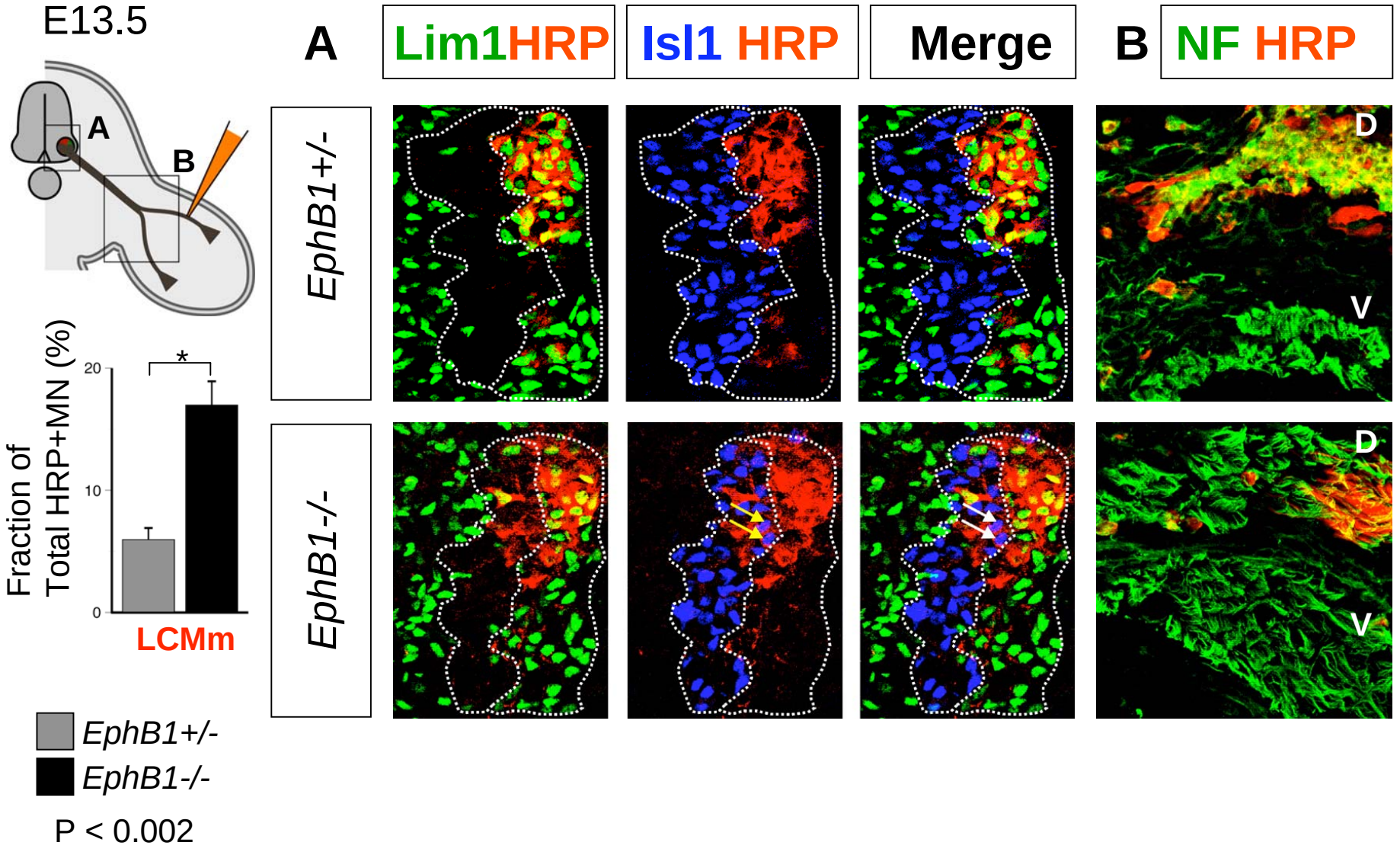
Limb nerve



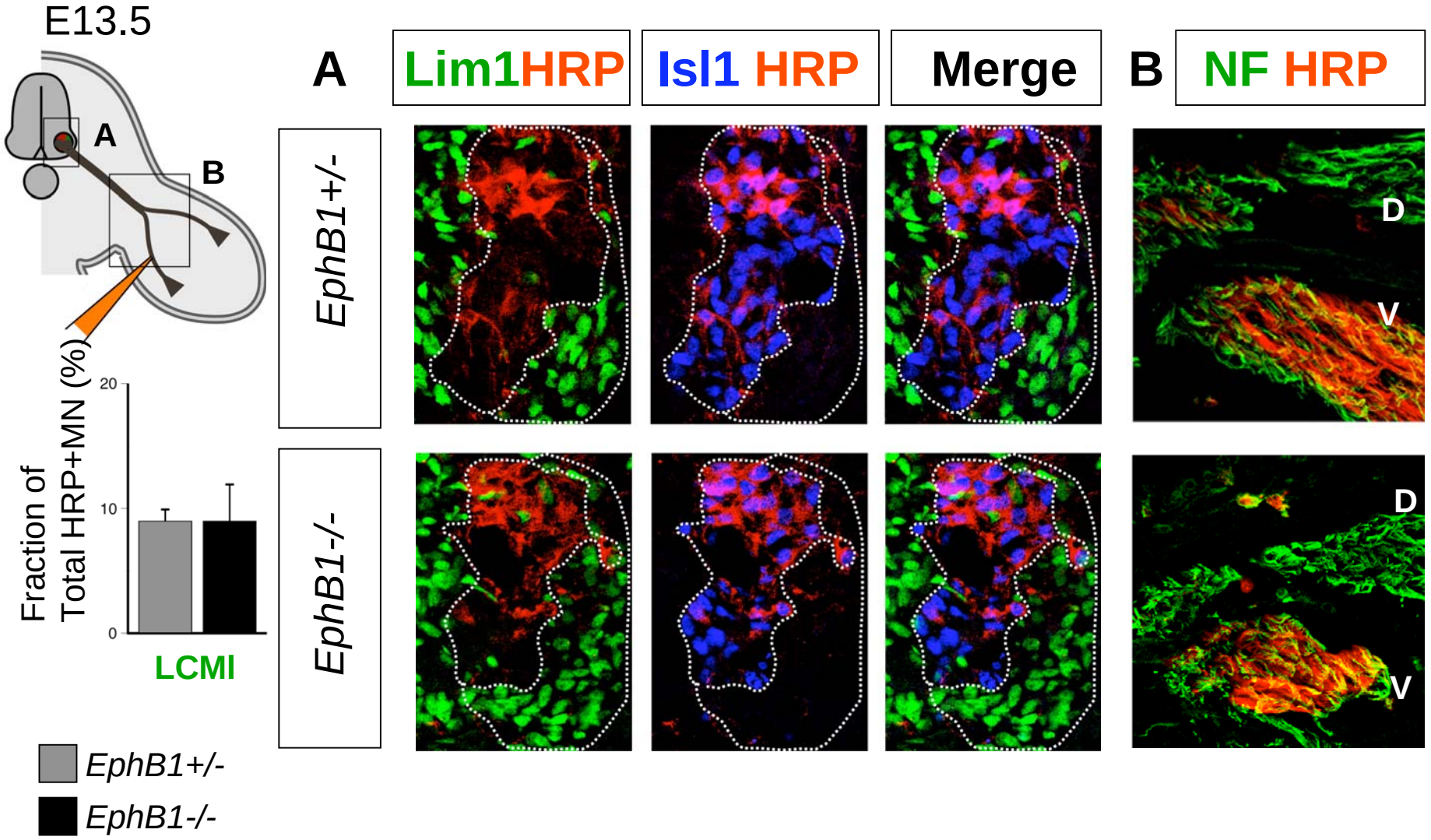
EphB1 expression can *redirect* LMC axons to the ventral limb



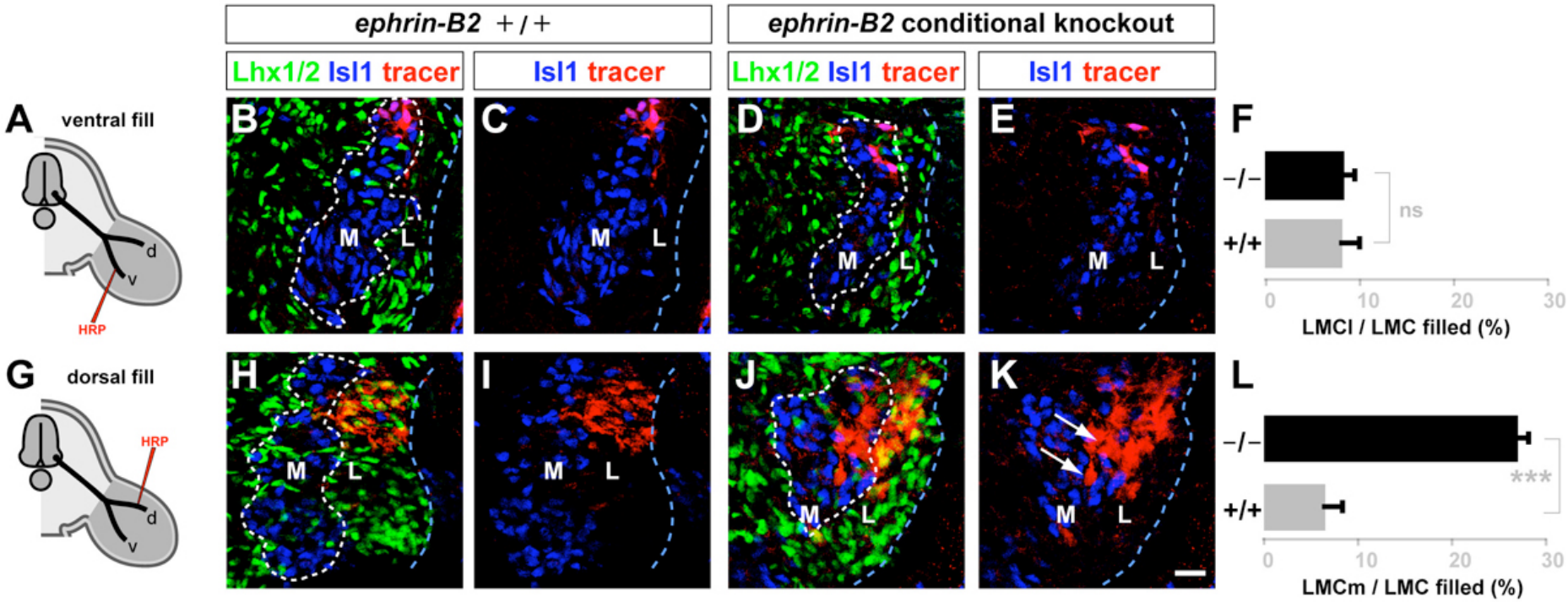
EphB1 is necessary for LMCm ventral targeting



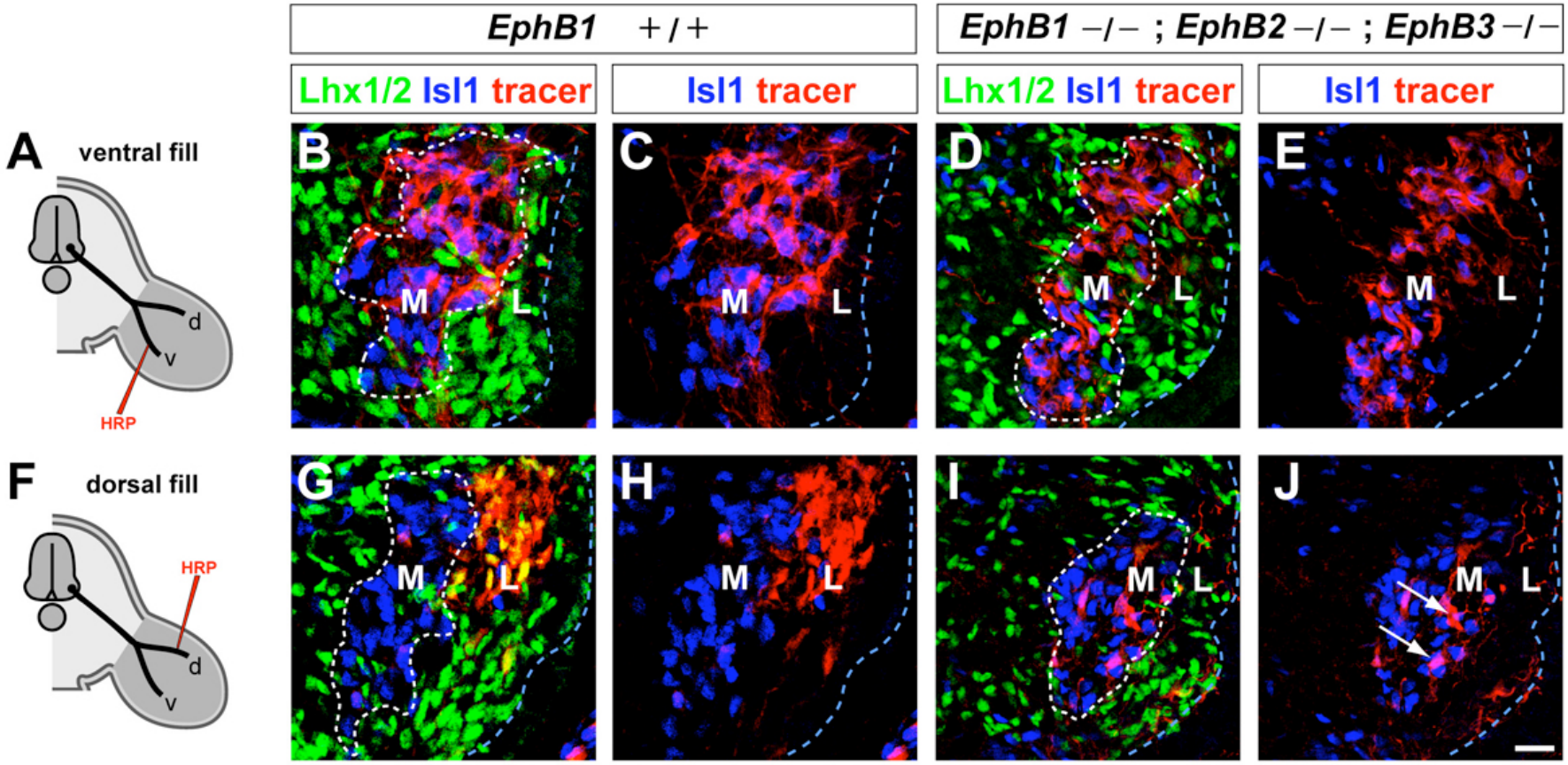
EphB1 does not influence LMCl projections

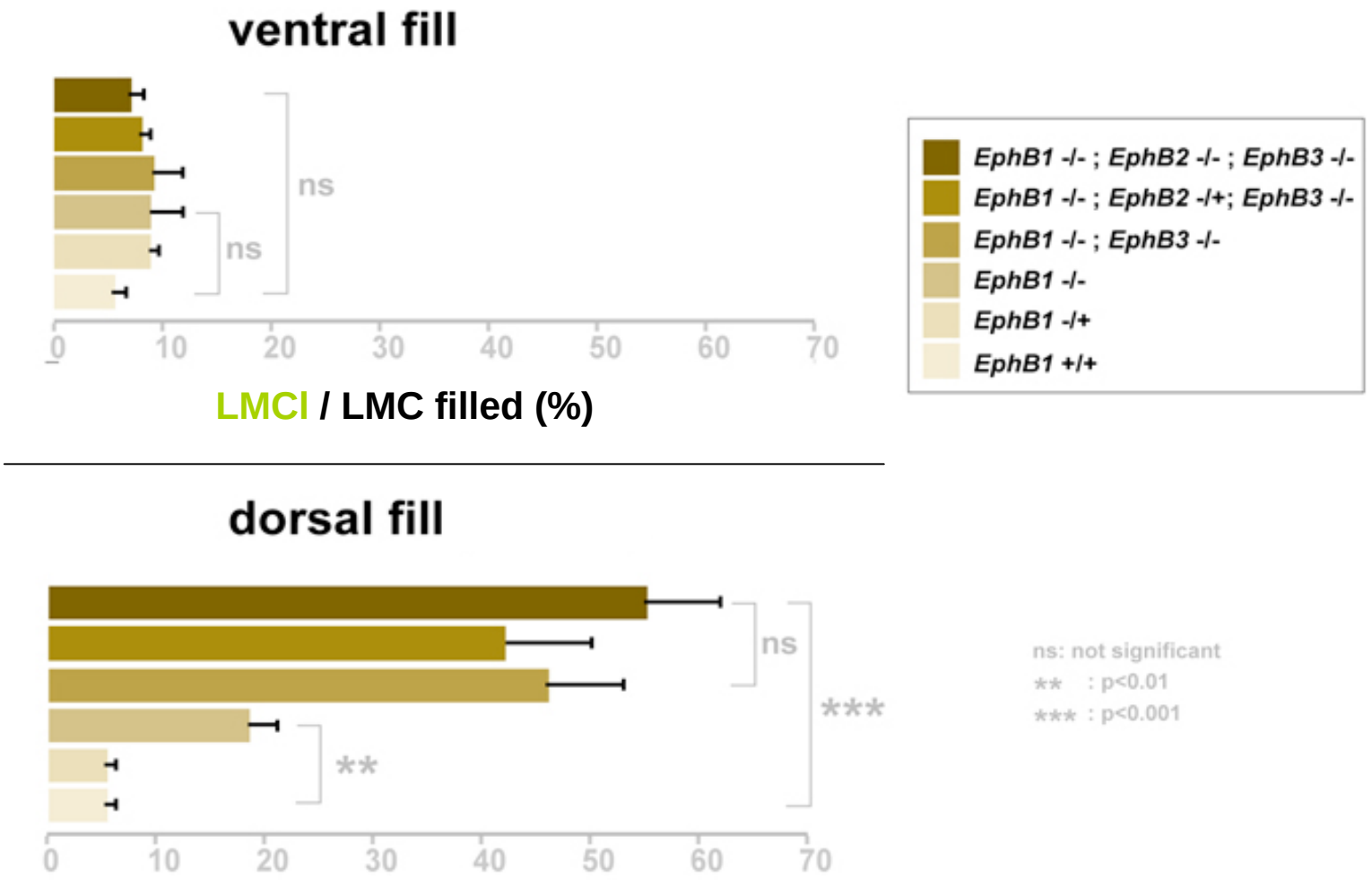


ephrin-B2 is necessary for LMCm ventral targeting



Three *EphB* receptors target LMCm axons ventrally



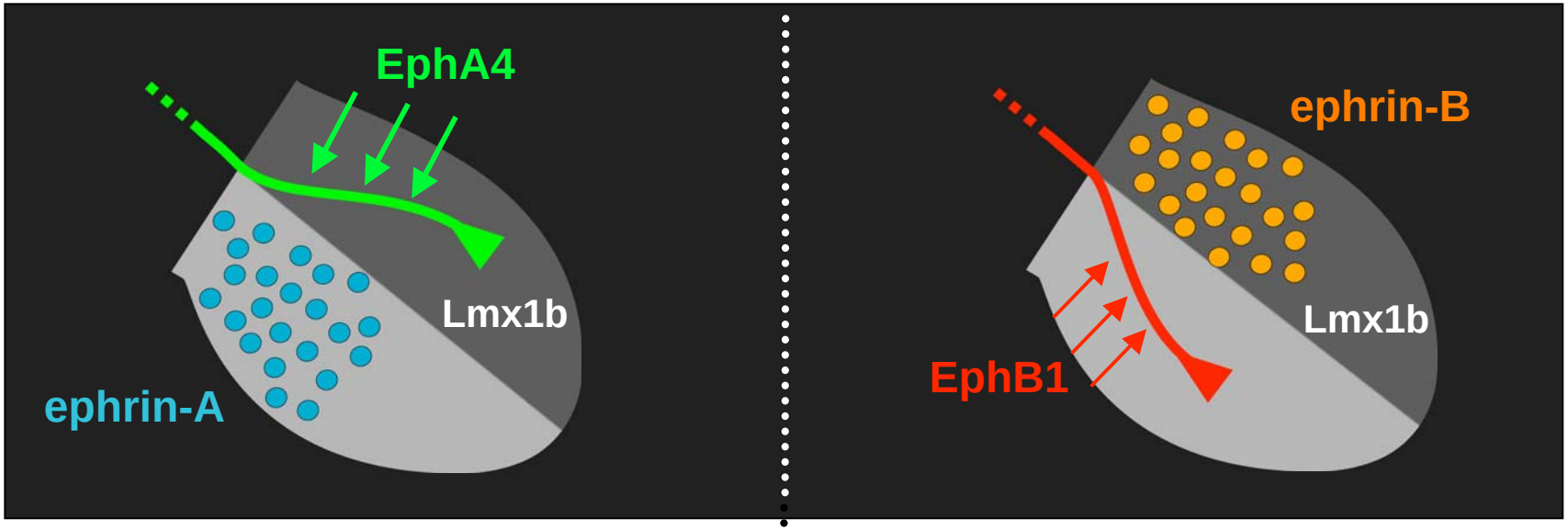

ventral fill
ns
ns
0
10
20
30
40
50
60
70
LMCl / LMC filled (%)
EphB1 -/- ; EphB2 -/- ; EphB3 -/-
EphB1 -/- ; EphB2 -/+; EphB3 -/-
EphB1 -/- ; EphB3 -/-
EphB1 -/-
EphB1 -/+
EphB1 +/+
dorsal fill
ns
***
**
0
10
20
30
40
50
60
70
LMCm / LMC filled (%)
ns: not significant
** : p<0.01
*** : p<0.001

Mirror symmetry ephrin-Eph signaling controls motor axon trajectories to the limb

EXPRESSION

Dorsal limb	b	A
Ventral limb	a	B

FUNCTIONAL

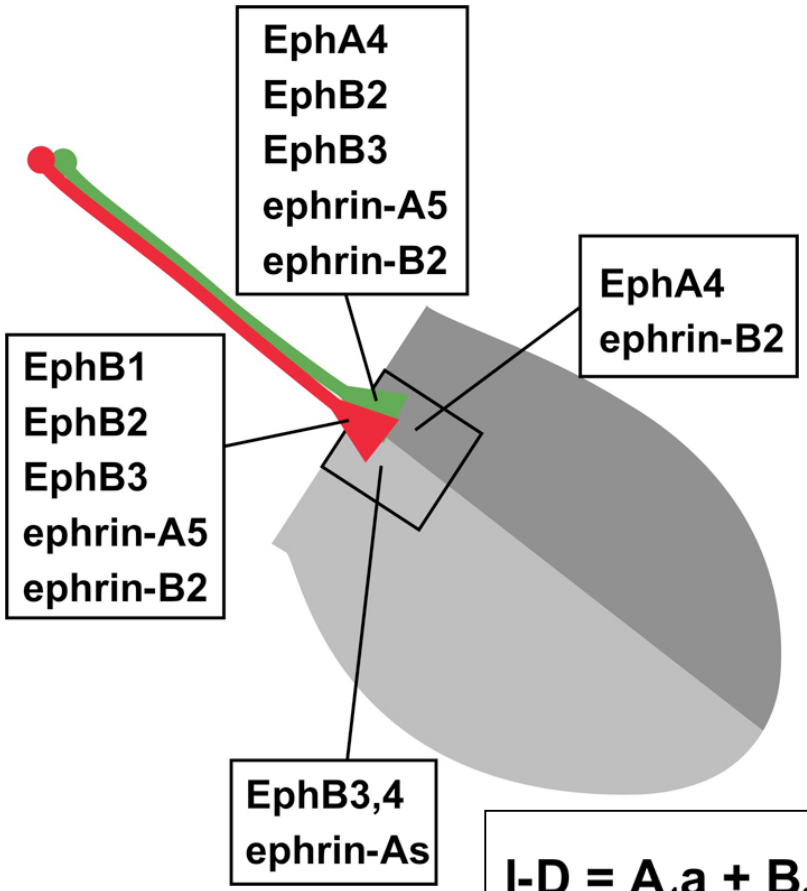


LMCl → EphA4 → Dorsal limb

LMCm → EphB1 → Ventral limb

III. Quantitative models, experimental predictions and tests

Axons integrate multiple cues at limb entry

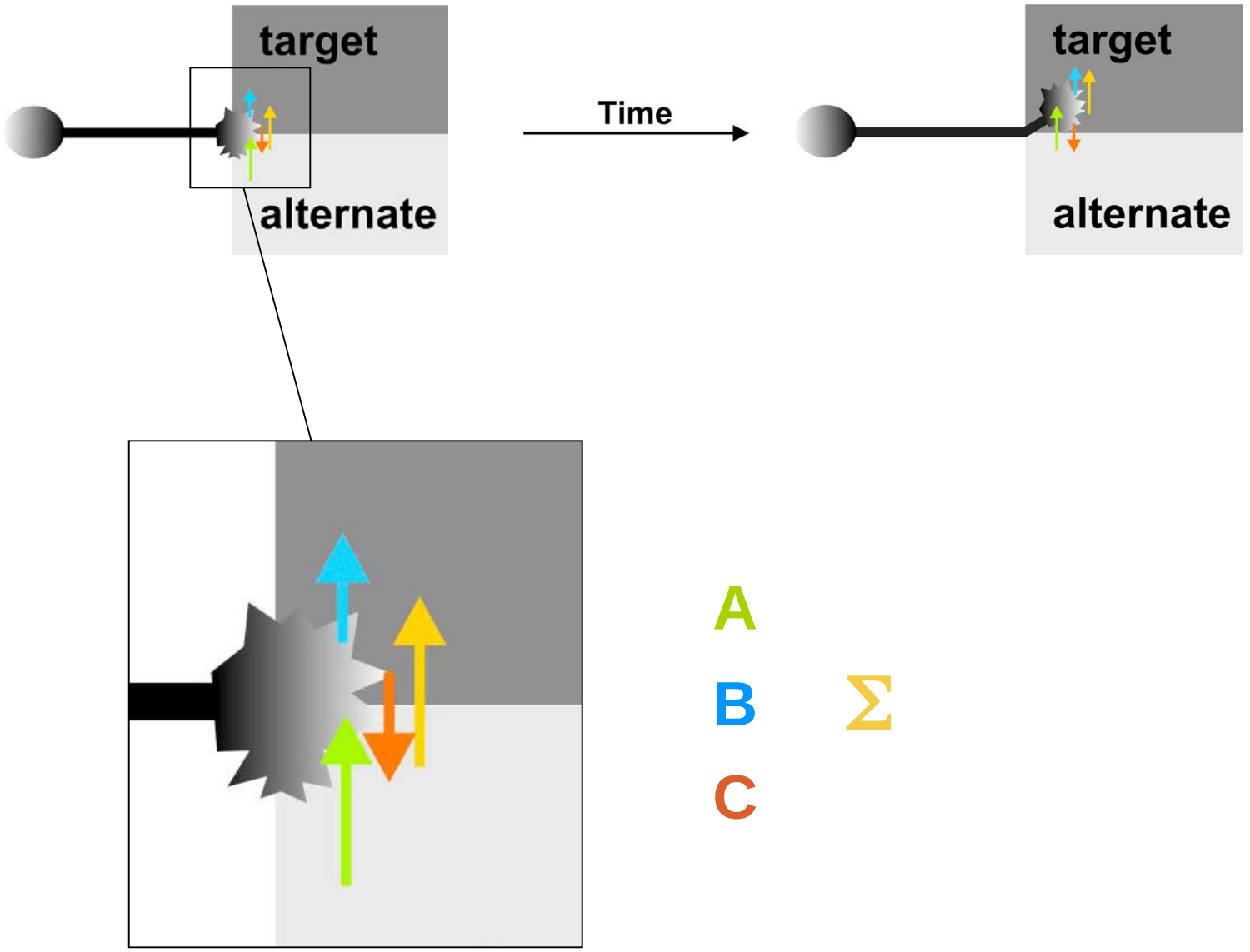


Axon	Interaction	Limb	Symbol
EphB1	>—<	ephrin-B2	B_1b_2
EphB2	>—<	ephrin-B2	B_2b_2
EphB3	>—<	ephrin-B2	B_3b_2
EphB2	>—<	ephrin-As	B_2a
EphA4	>—<	ephrin-As	A_4a
EphA4	>—<	ephrin-B2	A_4b_2
ephrin-B2	<—>	EphB3,4	b_2B_{34}
ephrin-A5	<—>	EphA4	a_5A_4
ephrin-B2	<—>	EphA4	b_2A_4

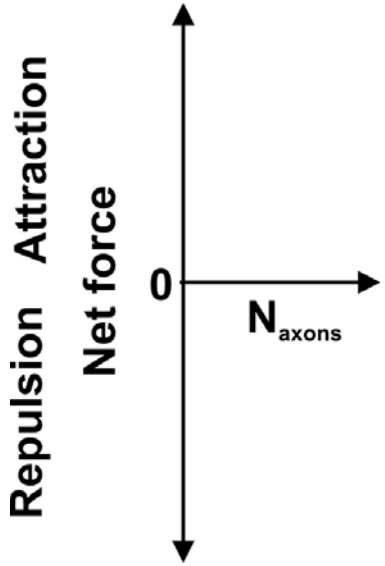
$$\text{I-D} = A_4a + B_2a + a_5A_4 + b_2A_4 - A_4b_2 - B_2b_2 - B_3b_2 - b_2B_{34} > 0$$

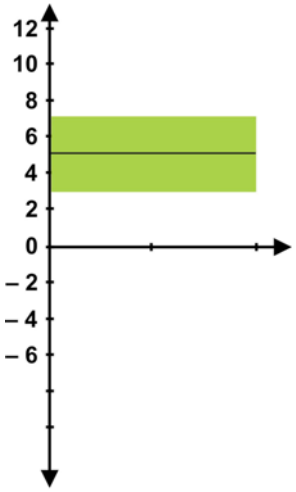
$$\text{m-V} = - B_1b_2 - B_2b_2 - B_3b_2 - b_2B_{34} + B_2a + a_5A_4 + b_2A_4 < 0$$

Axons integrate multiple cues at choice points



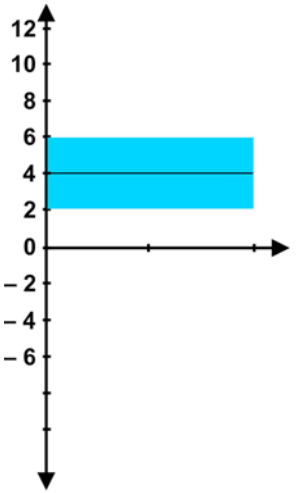
Cues are noisy





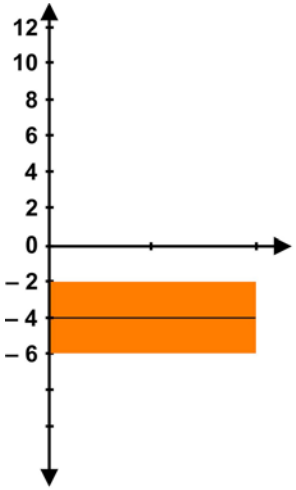
A

A = 5 ± 1



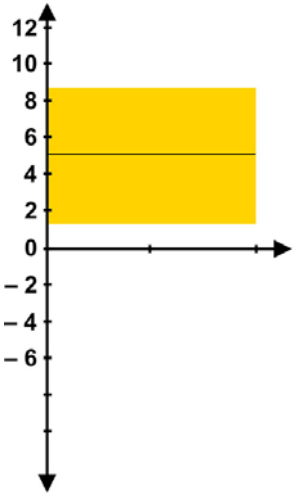
B

B = 4 ± 1



C

C = – 4 ± 1

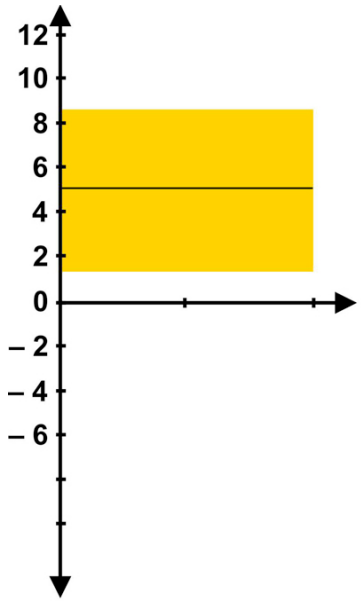


Σ_{wt} = A + B + C

Σ_{wt} = 5 ± √3

Cue noise can explain guidance defects of mutants

WILD TYPE



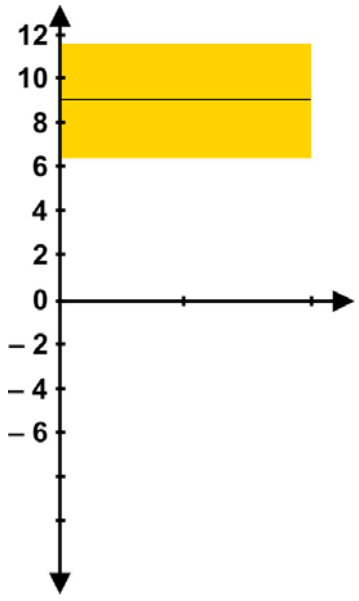
$\Sigma_{wt} = A + B + C$

$\Sigma_{wt} = 5 \pm \sqrt{3}$

100% to target

MUTANTS

Unaffected

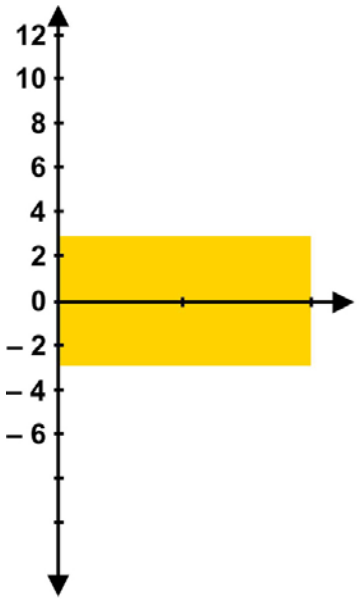


$\Sigma_{C=0} = A + B$

$\Sigma_{C=0} = 9 \pm \sqrt{2}$

100% to target

Randomized

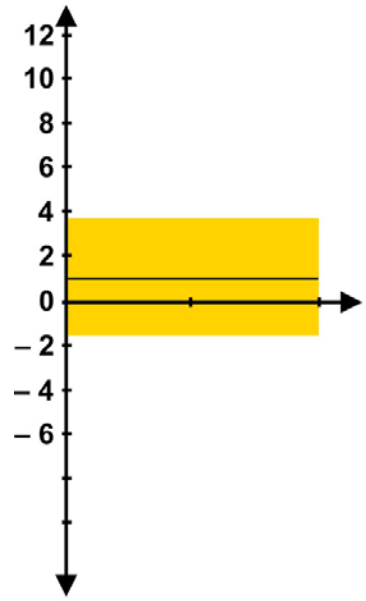


$\Sigma_{A=0} = B + C$

$\Sigma_{A=0} = 0 \pm \sqrt{2}$

50% to target
50% to alternate

Unequal



$\Sigma_{B=0} = A + C$

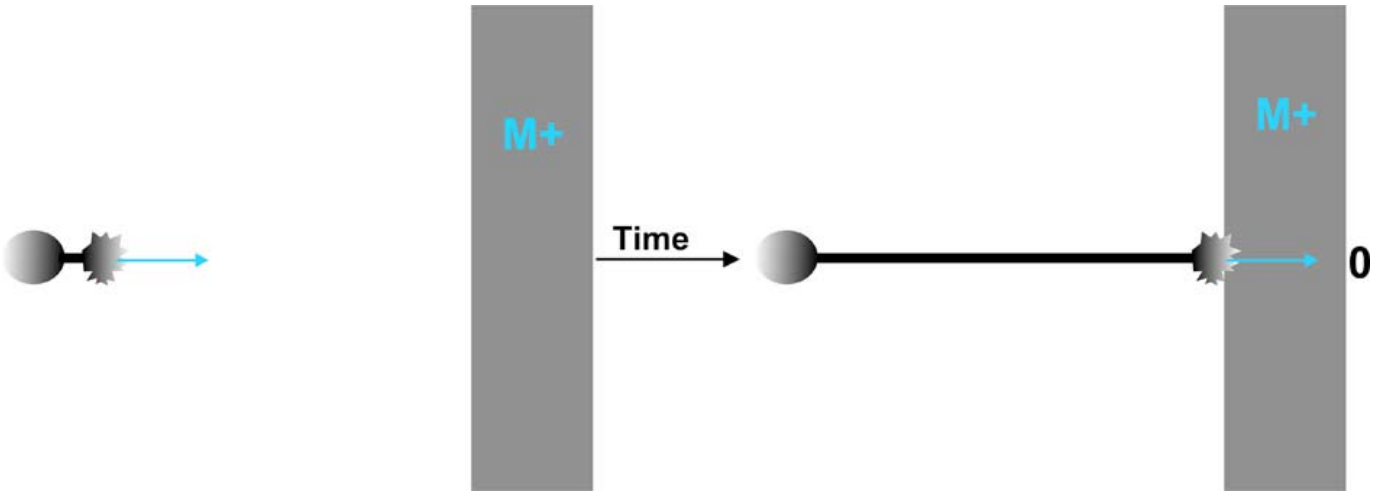
$\Sigma_{B=0} = 1 \pm \sqrt{2}$

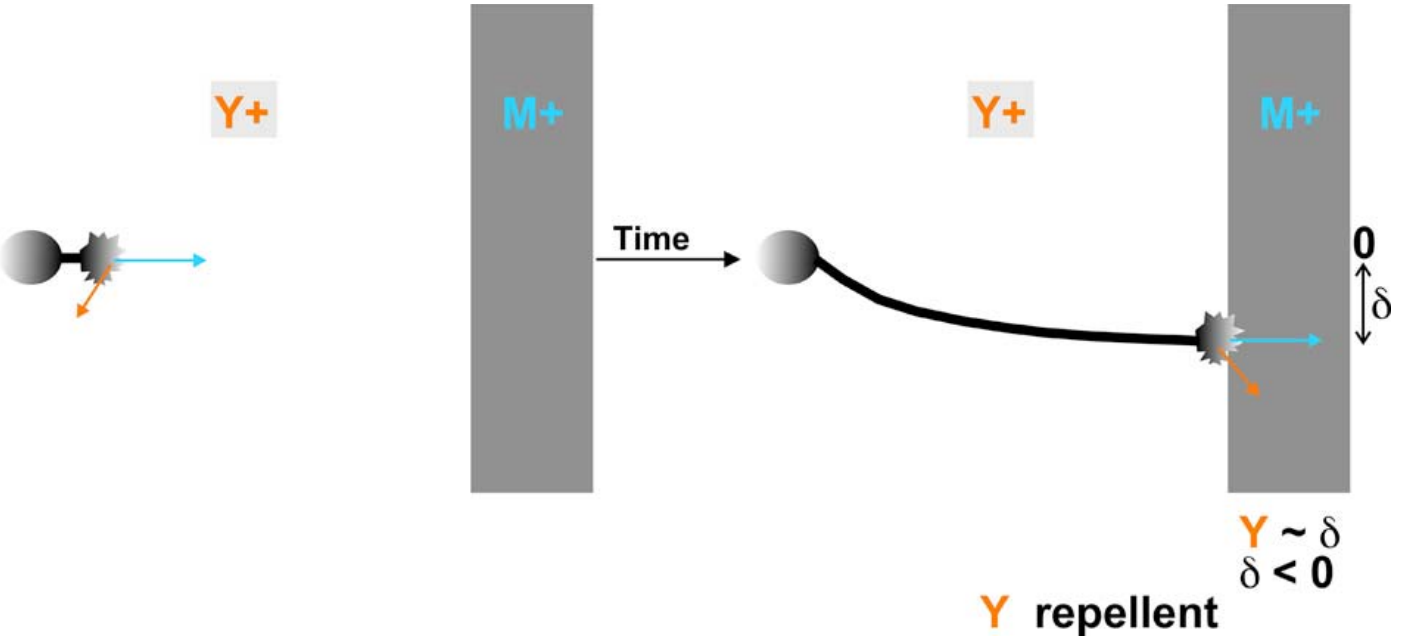
~75% to target
~25% to alternate

Model value

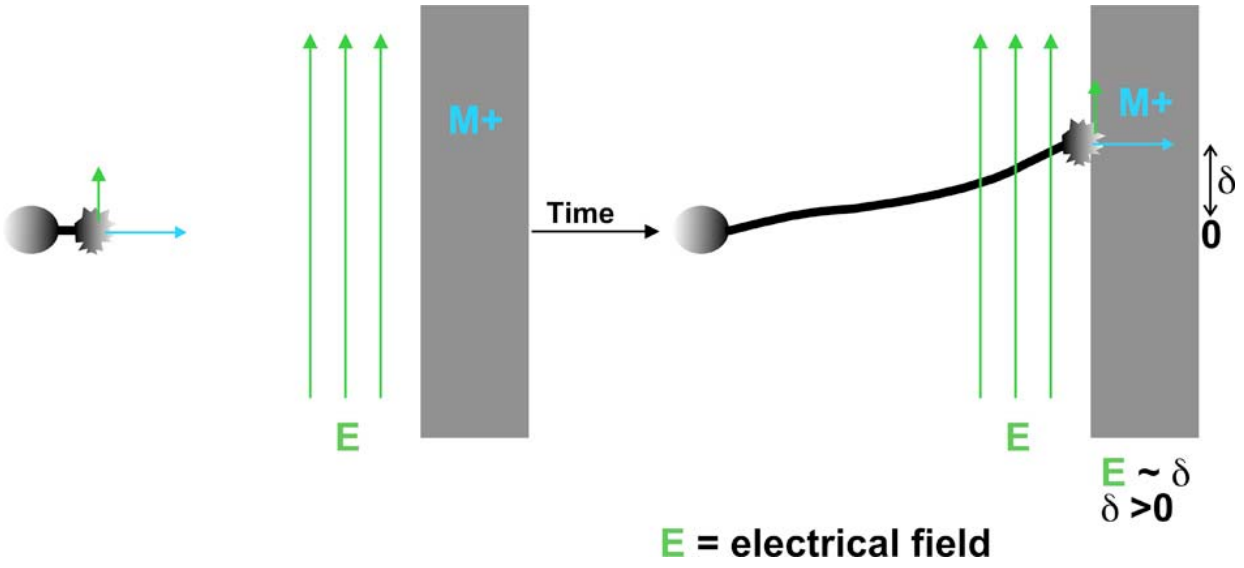
Explained	Predicted	Agnostic	New prediction
Lmx1b*$^{-/-}$** Kania et al., 2000 ***Bmprla*$^{flox/-}$** Luria et al., 2007 ***EphA4*$^{-/-}$** Helmbacher et al., 2000 ***Sema3F*$^{-/-}$** Huber et al., 2005 ***Npn2*$^{-/-}$** Huber et al., 2005 ***EphB1*$^{-/-}$** ***in optic chiasma Williams et al., 2005 ***EphB1*$^{-/-}$**	***EphB13*$^{-/-}$** ***EphB123*$^{-/-}$** ***ephrin-B2*$^{flox/-}$**	***GDNF*$^{-/-}$** Kramer et al., 2006 ***ret*$^{-/-}$** Kramer et al., 2006 ***Lhx3* Tg** Sharma et al., 2000	***EphA4 & B123*$^{-/-}$** **complete randomization of both LMCm and LMCl** ***ephrin-A235*$^{-/-}$** **> 2/3 LMCl mistargeted ventrally** **LMCm normal**

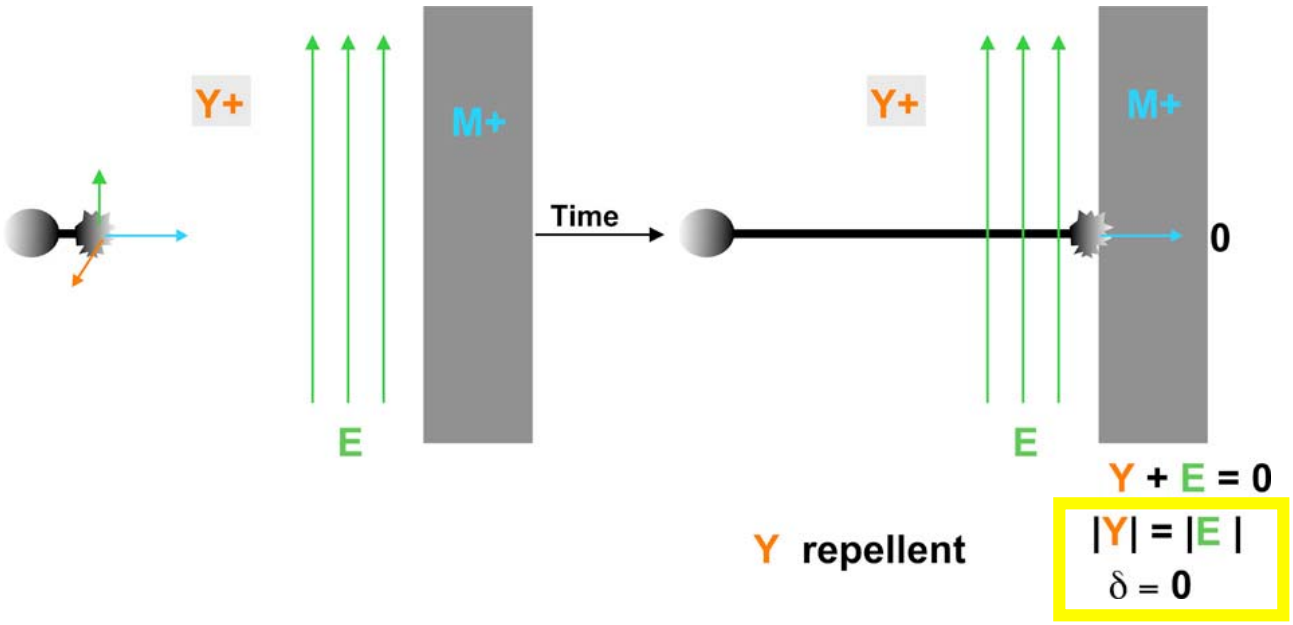
Trajectory changes reveal cue type





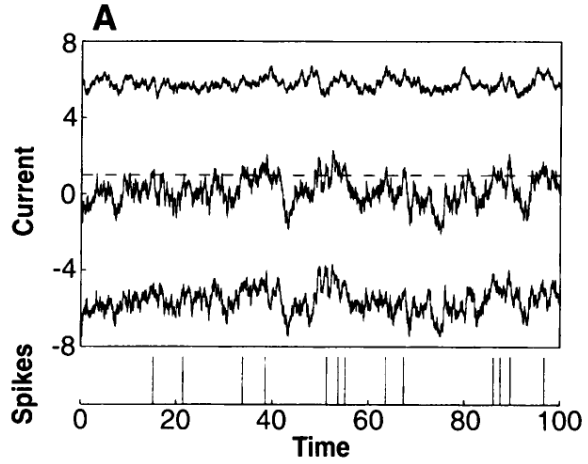
Cue strength: quantification using benchmarks





"Too much information" hypothesis:
Noise limits the information used for any decision controlled by competing cues

1. Construction of neural circuits



2. Neuronal firing rates

Van Vreeswisjk & Sompolinsky, 1996

3. Finance - the anti-portfolio effect

Vlad et al., 2007

4. Drosophila photoreceptor fields - 70% - 30% partitioning of the retina

Wernet et al., 2005

5. ES cells transient differentiation

Niiwa et al., 2008