The role of activity in the generation of cortical interneuron diversity

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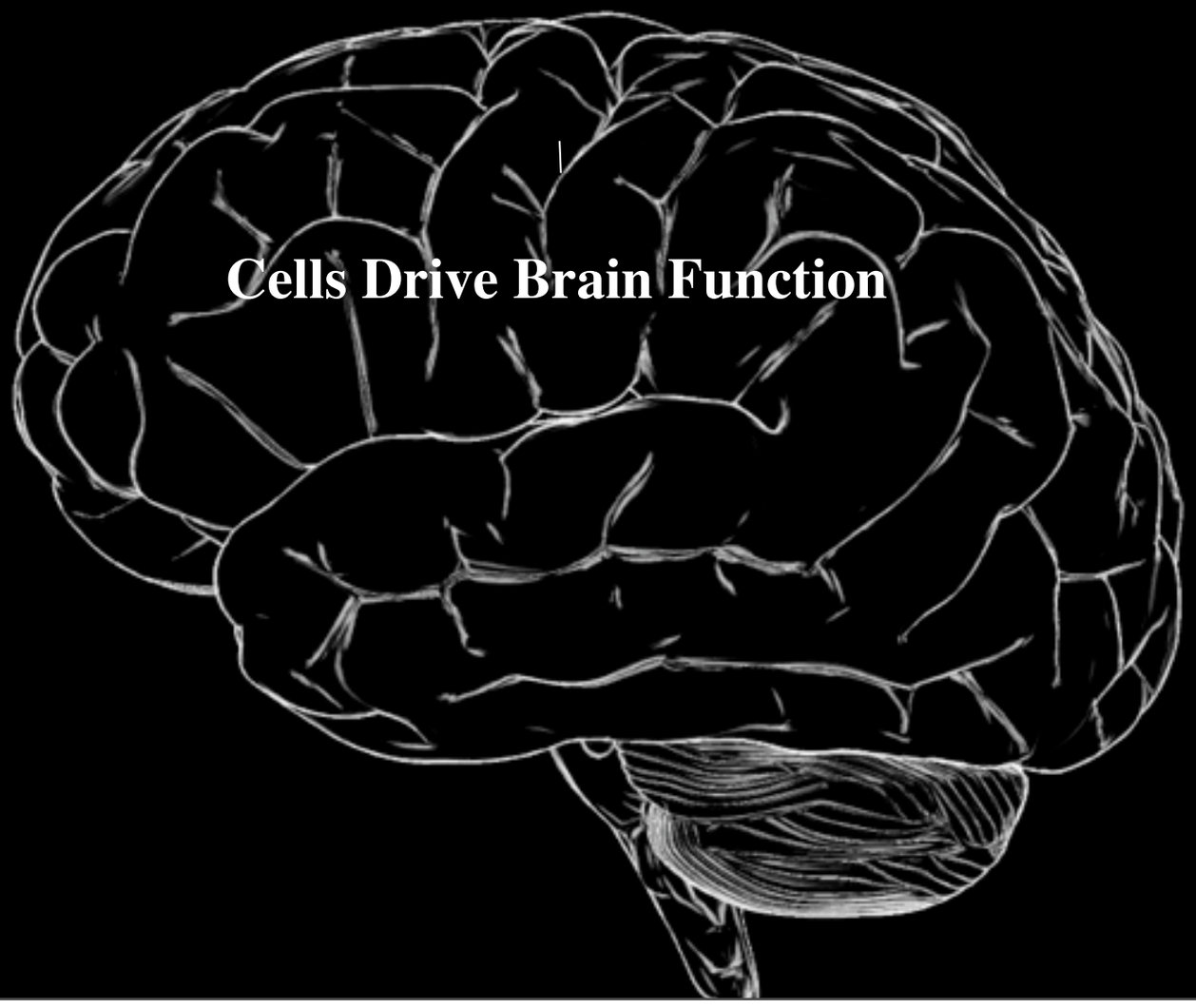
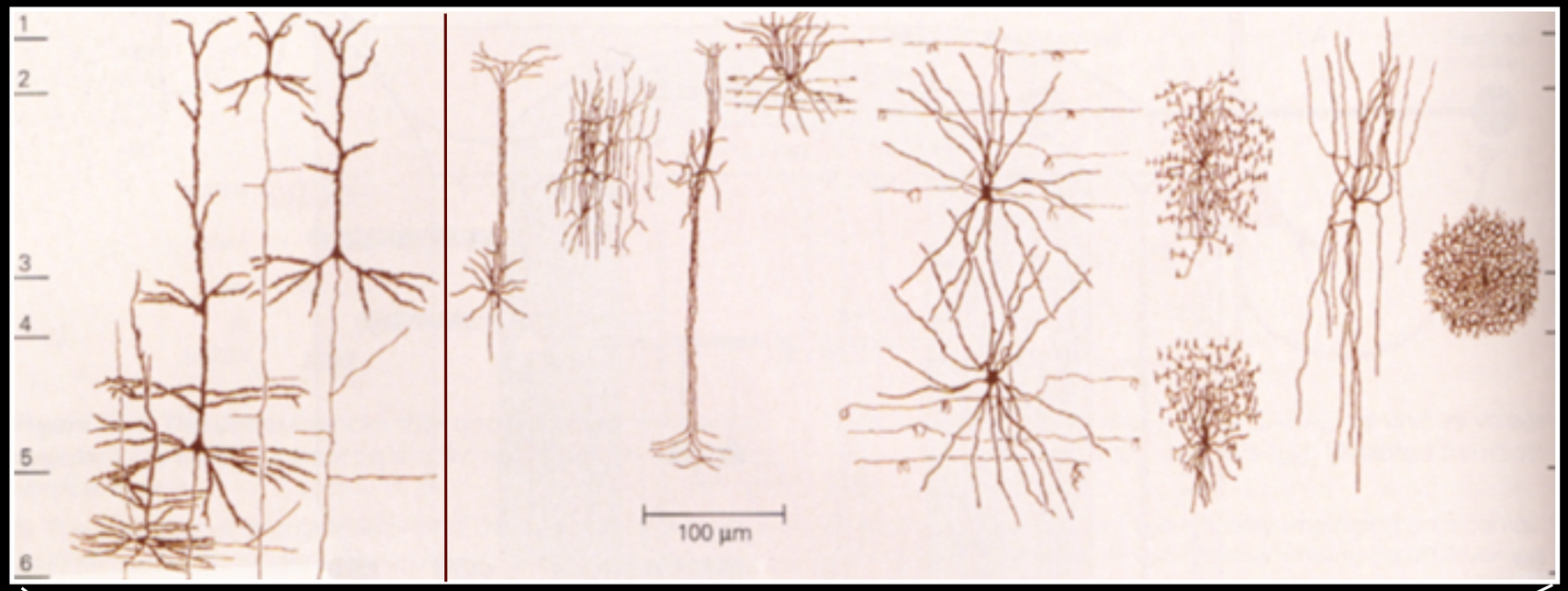
Gord Fishell
Smilow Neuroscience program
NYU Medical Center



Cells Drive Brain Function



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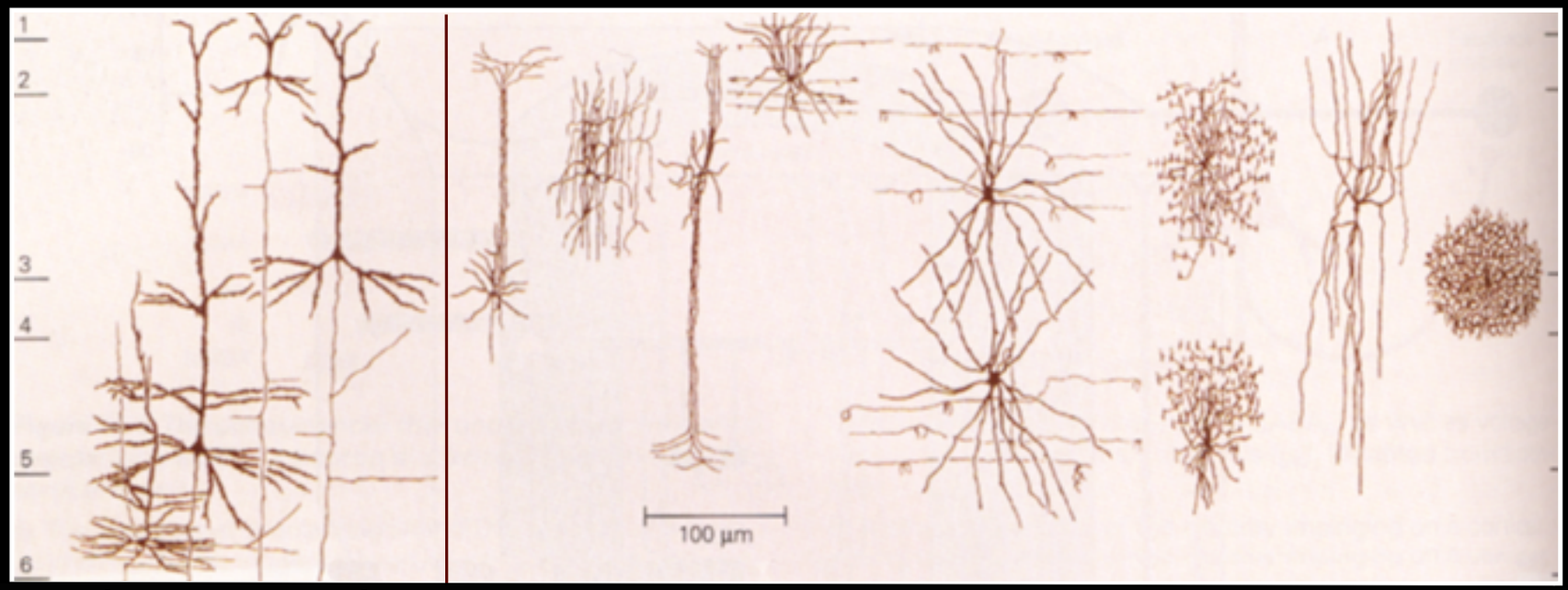
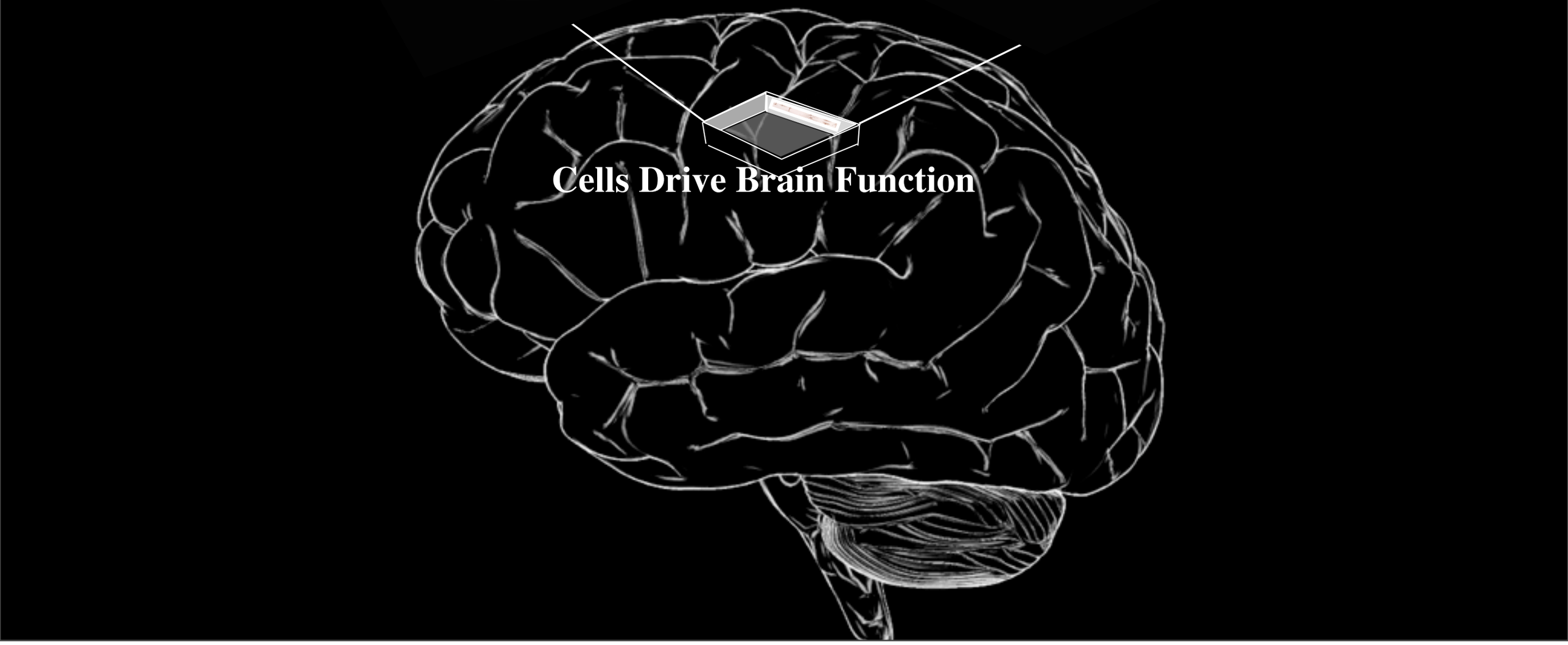


Glutamateric principal cells



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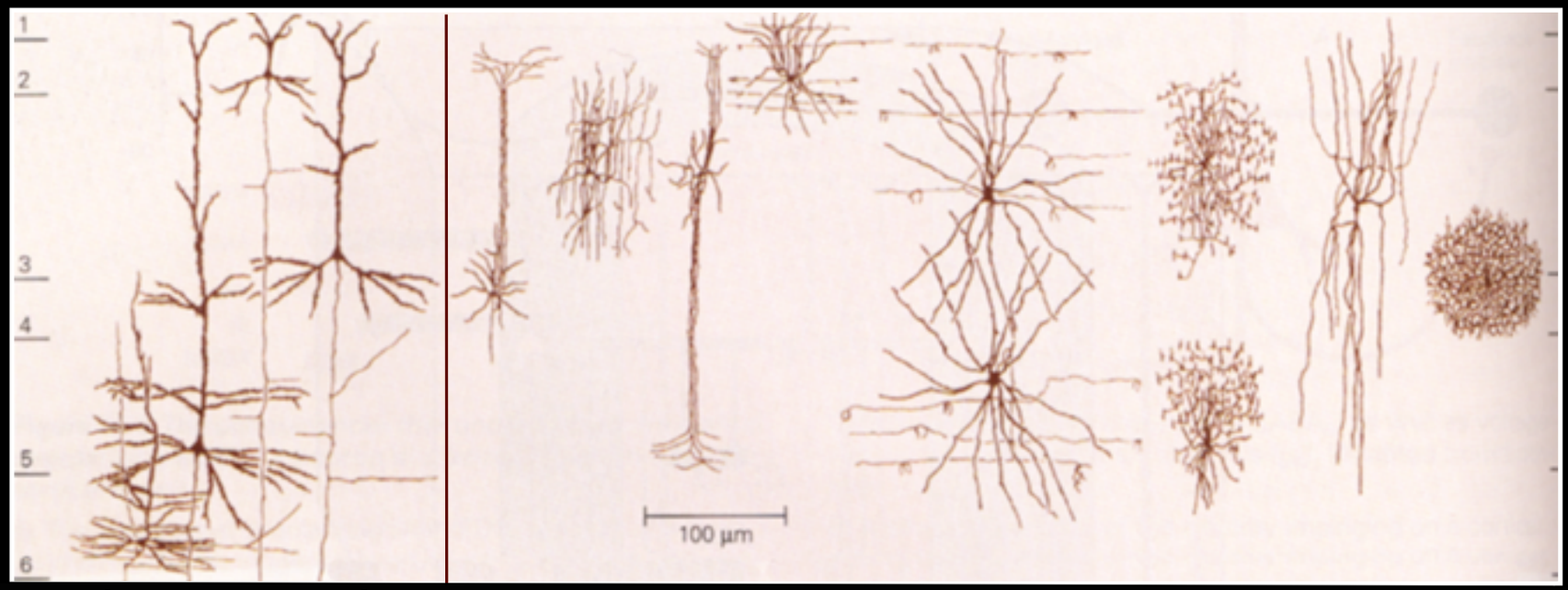
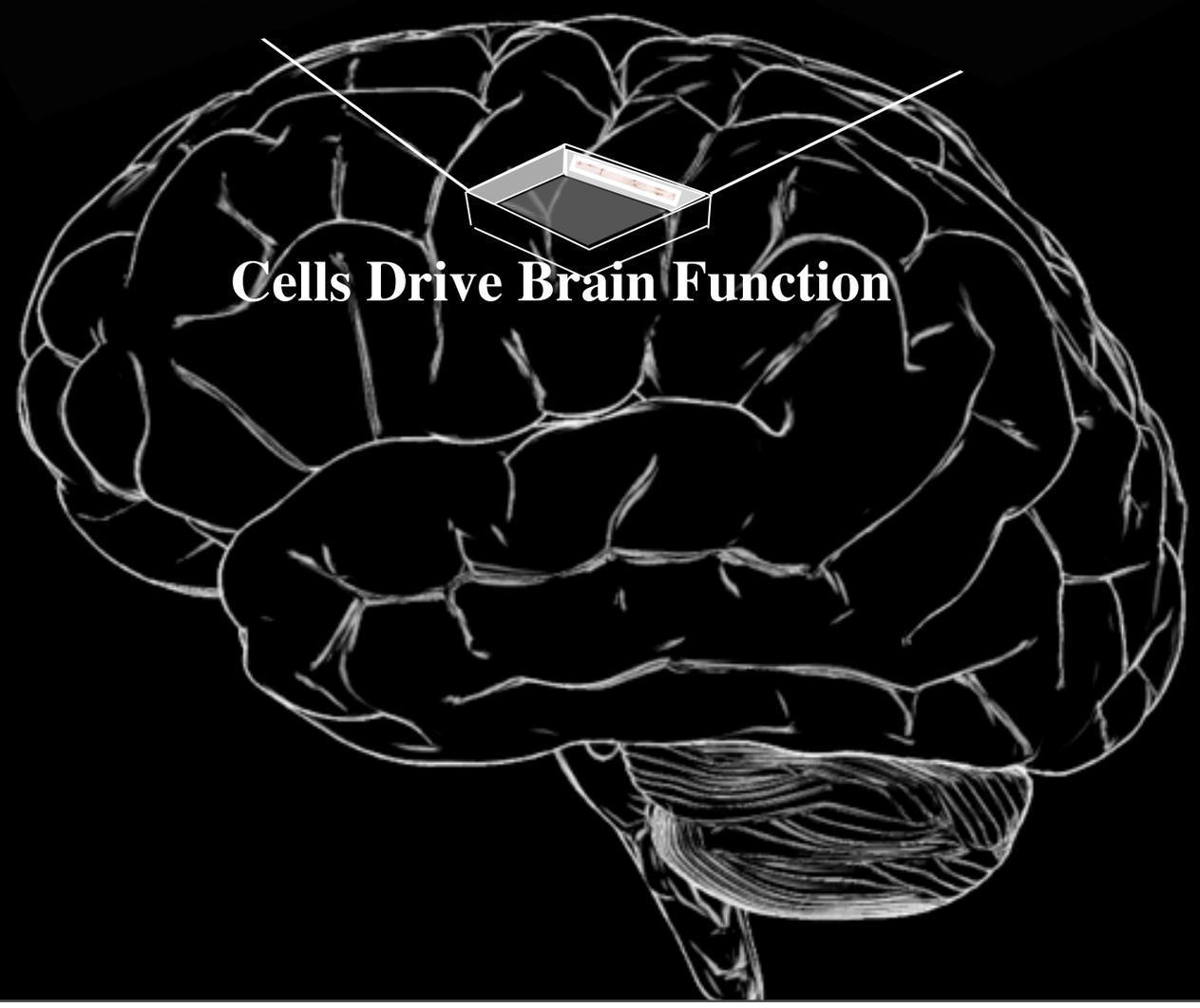


Glutamateric principal cells

Pyramidal neurons

80% of brain cells.



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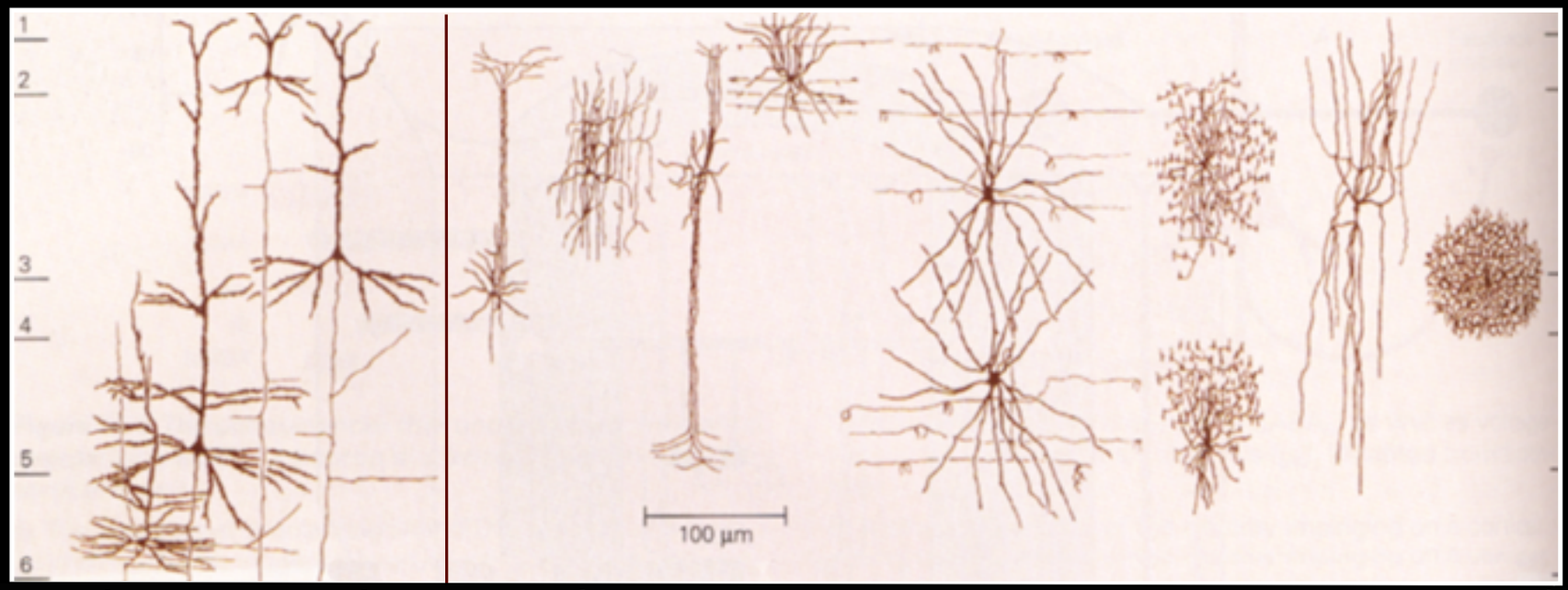

Glutamateric principal cells

GABAergic interneurons

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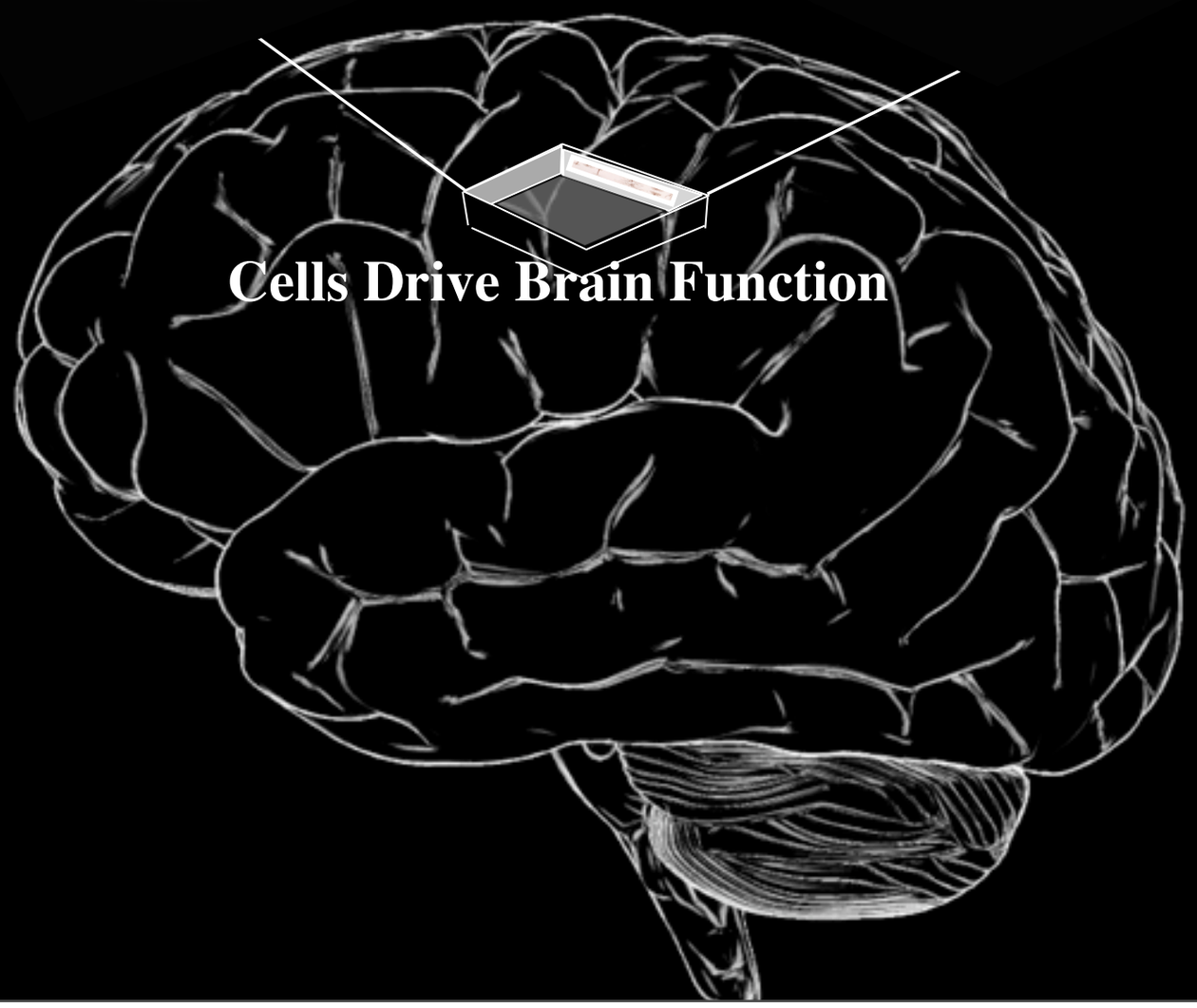

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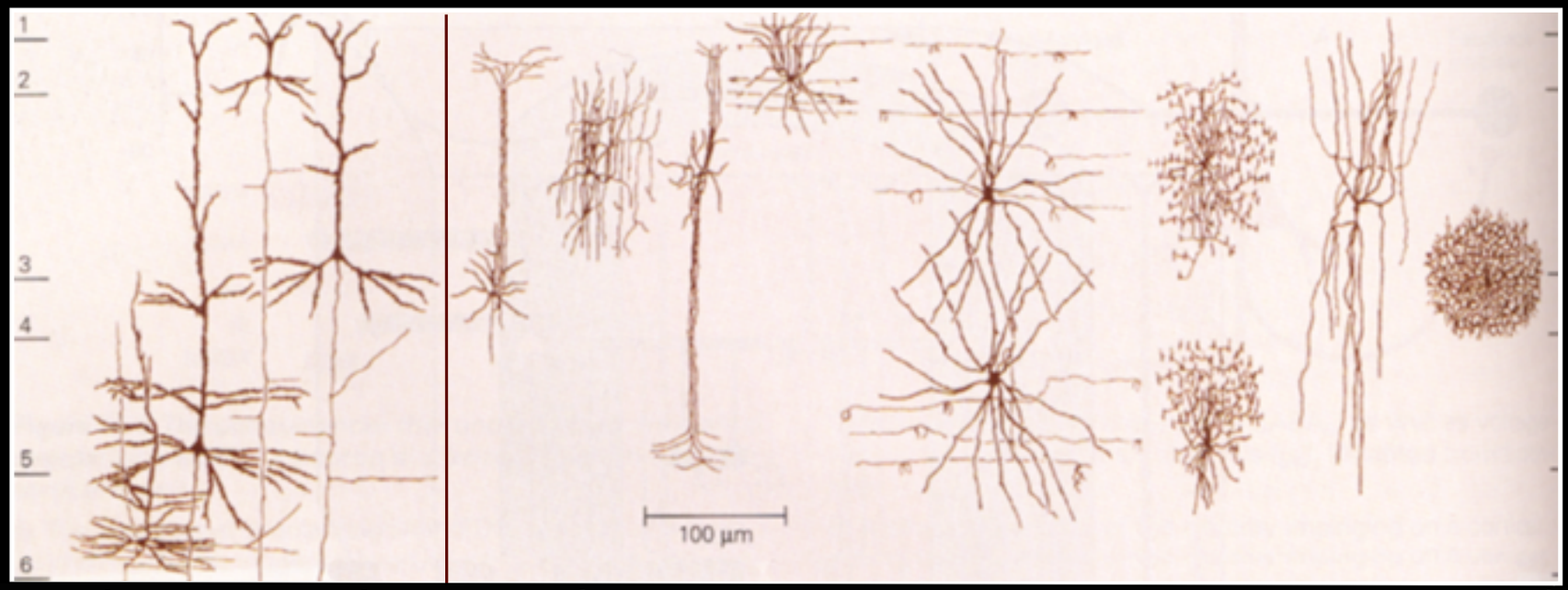
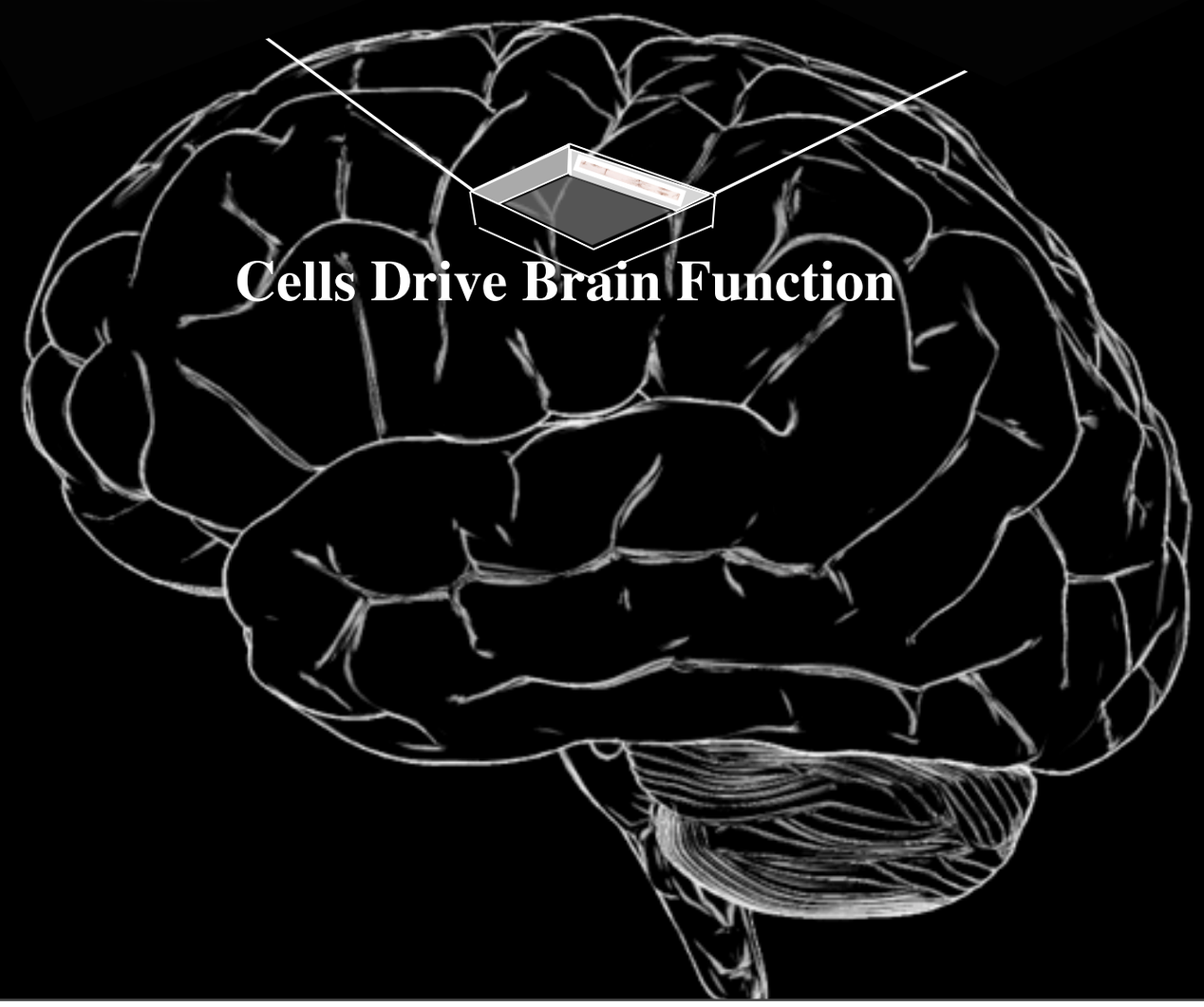


Glutamateric principal cells

GABAergic interneurons



Cells Drive Brain Function

Pyramidal neurons

80% of brain cells.

Gabaergic interneurons

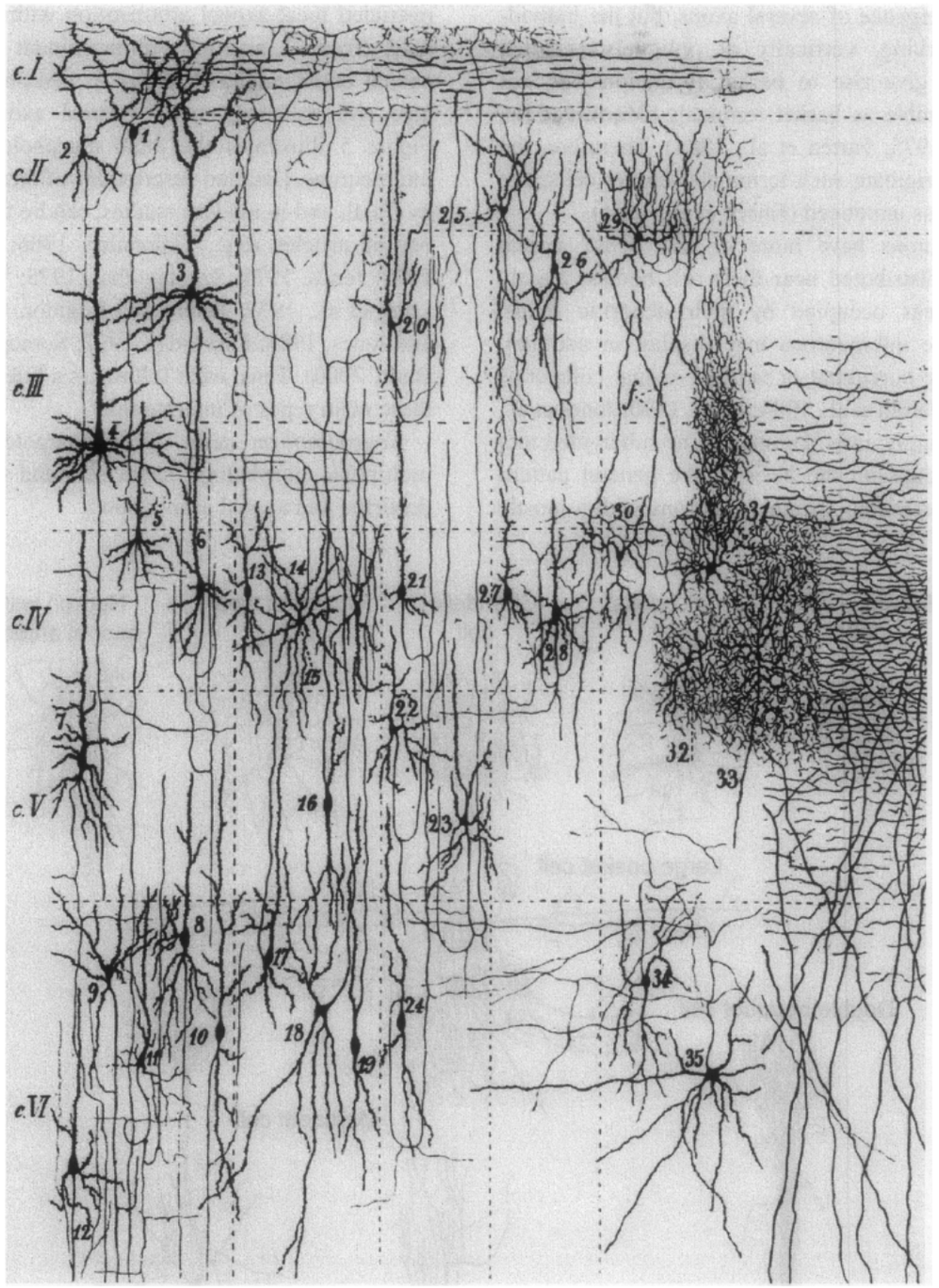
20% of brain cells

…and 20 different kinds!!

GABAergic cortical interneurons

Cortical interneurons (in rodents)

- **20-30% of cortical neurons**
- **mostly inhibitory and GABAergic**
- **do not typically project to distant brain regions, 'local circuit neurons'**



Cajal, 1906

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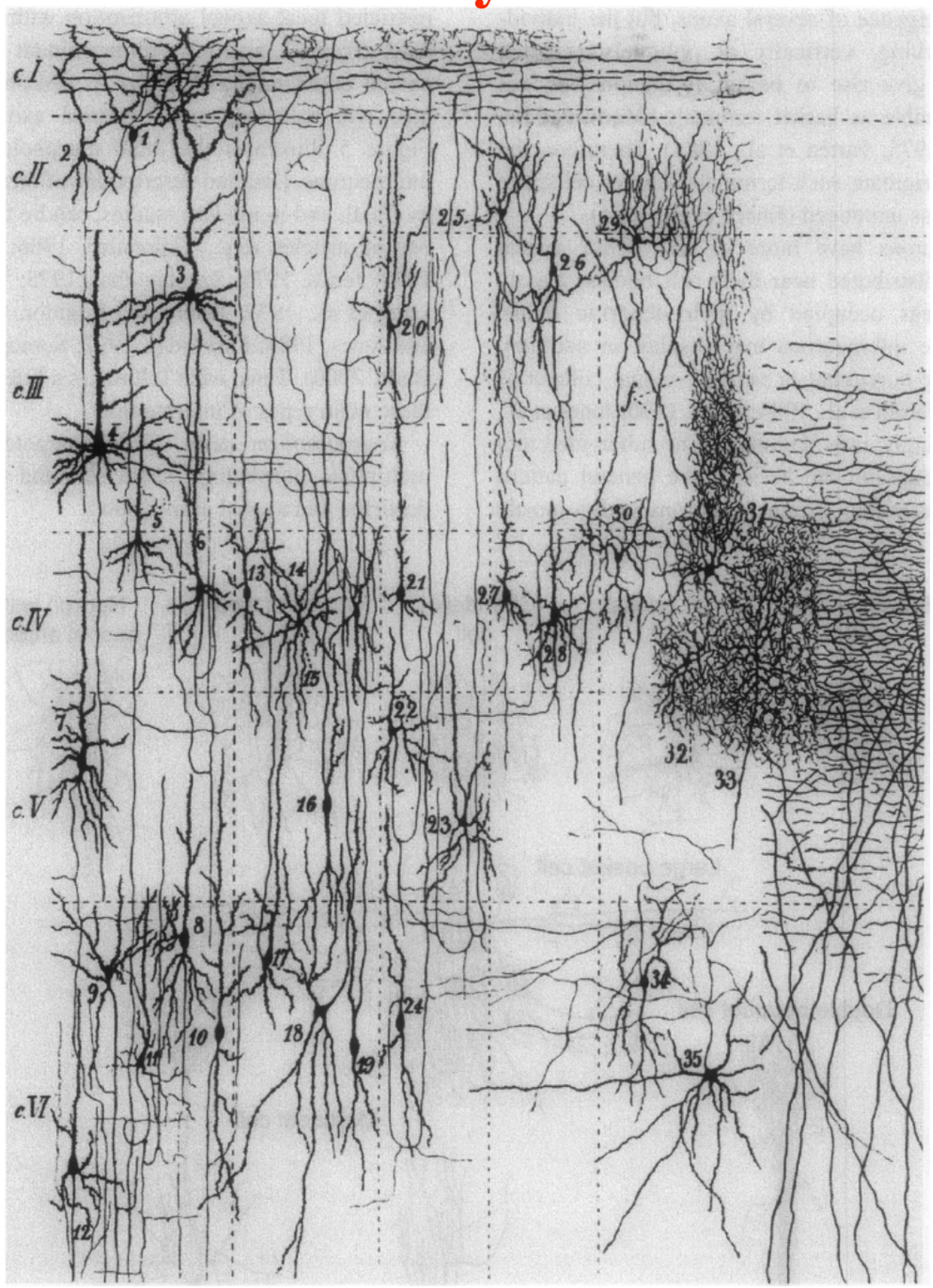
Excitatory network



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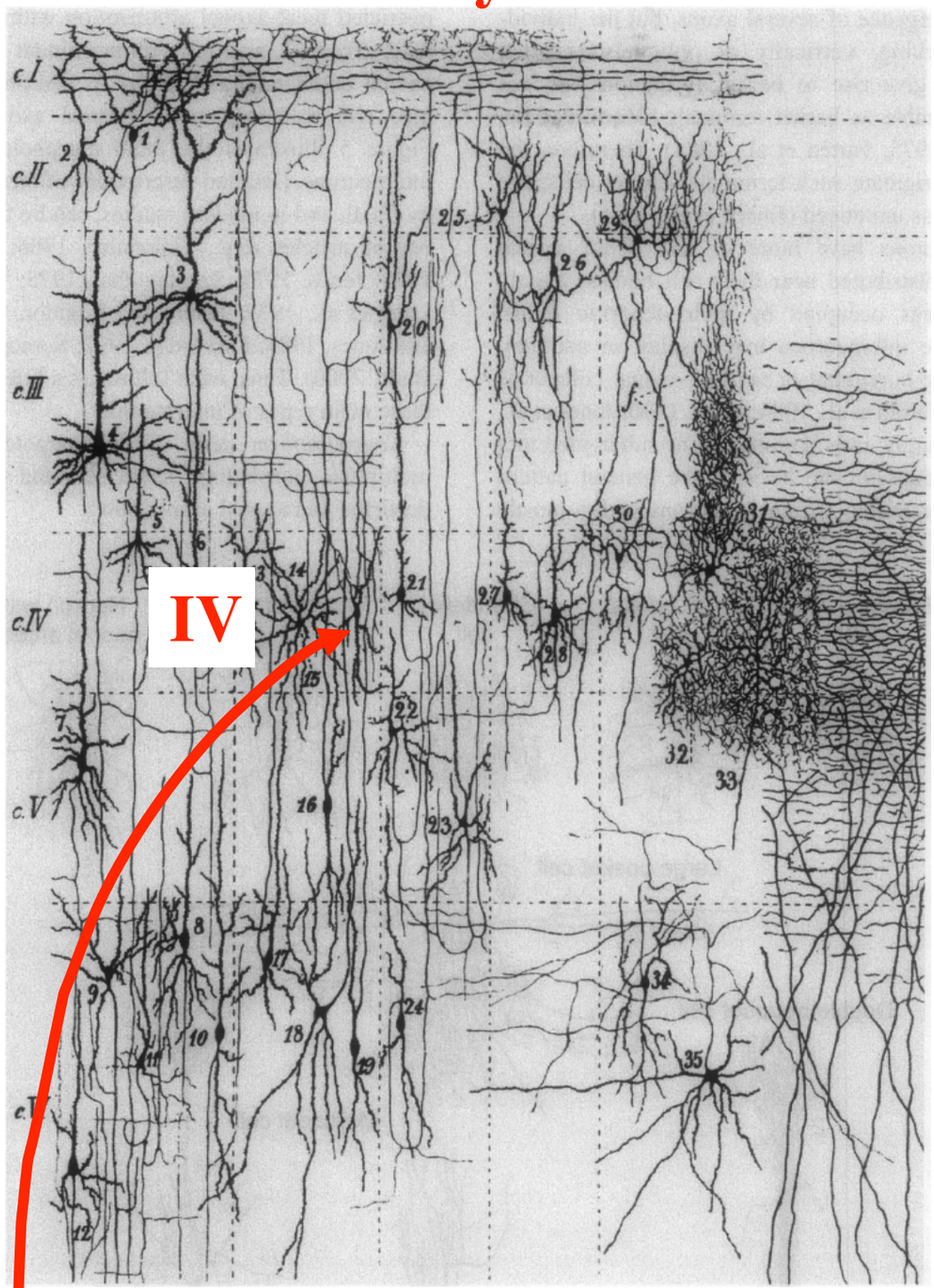

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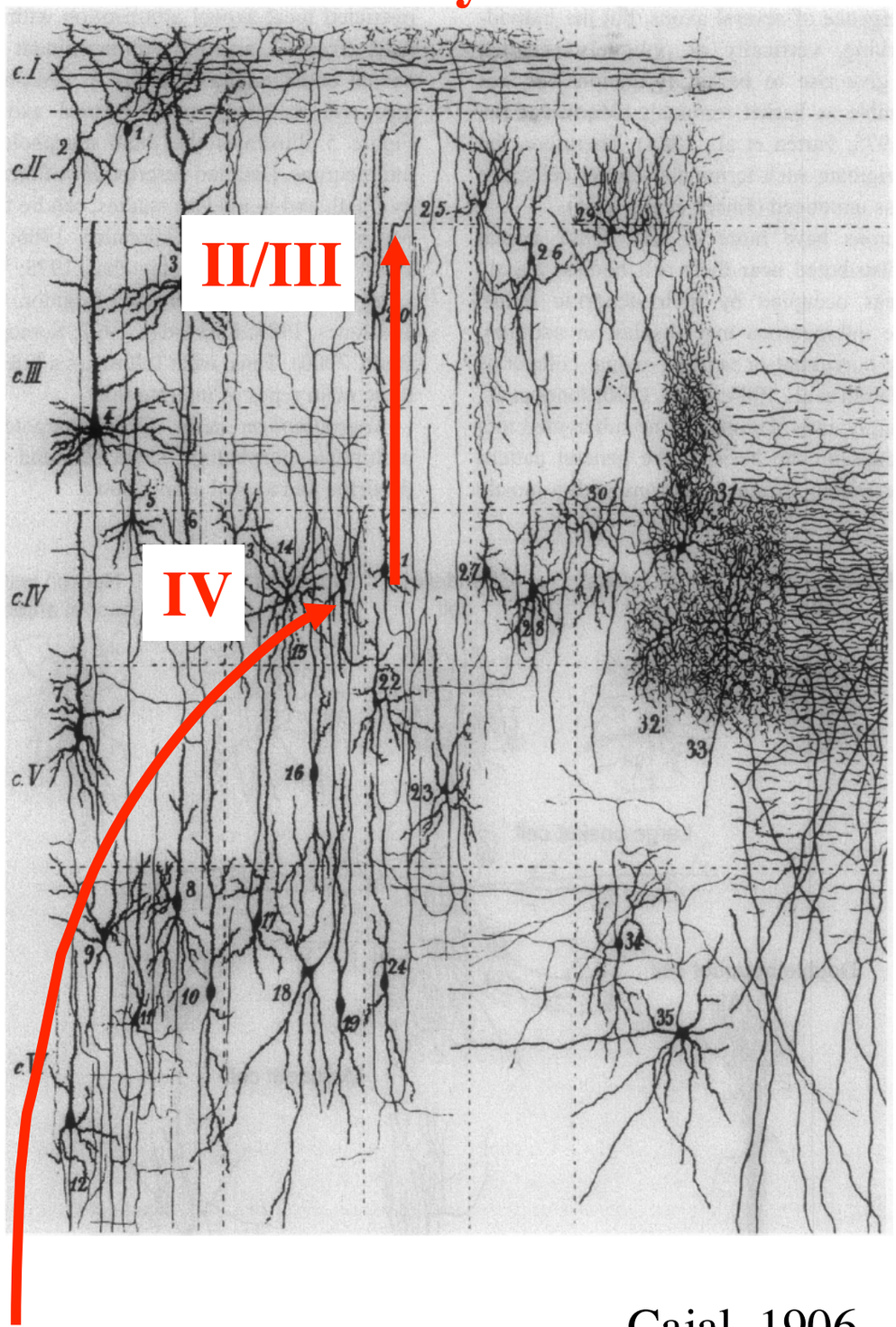

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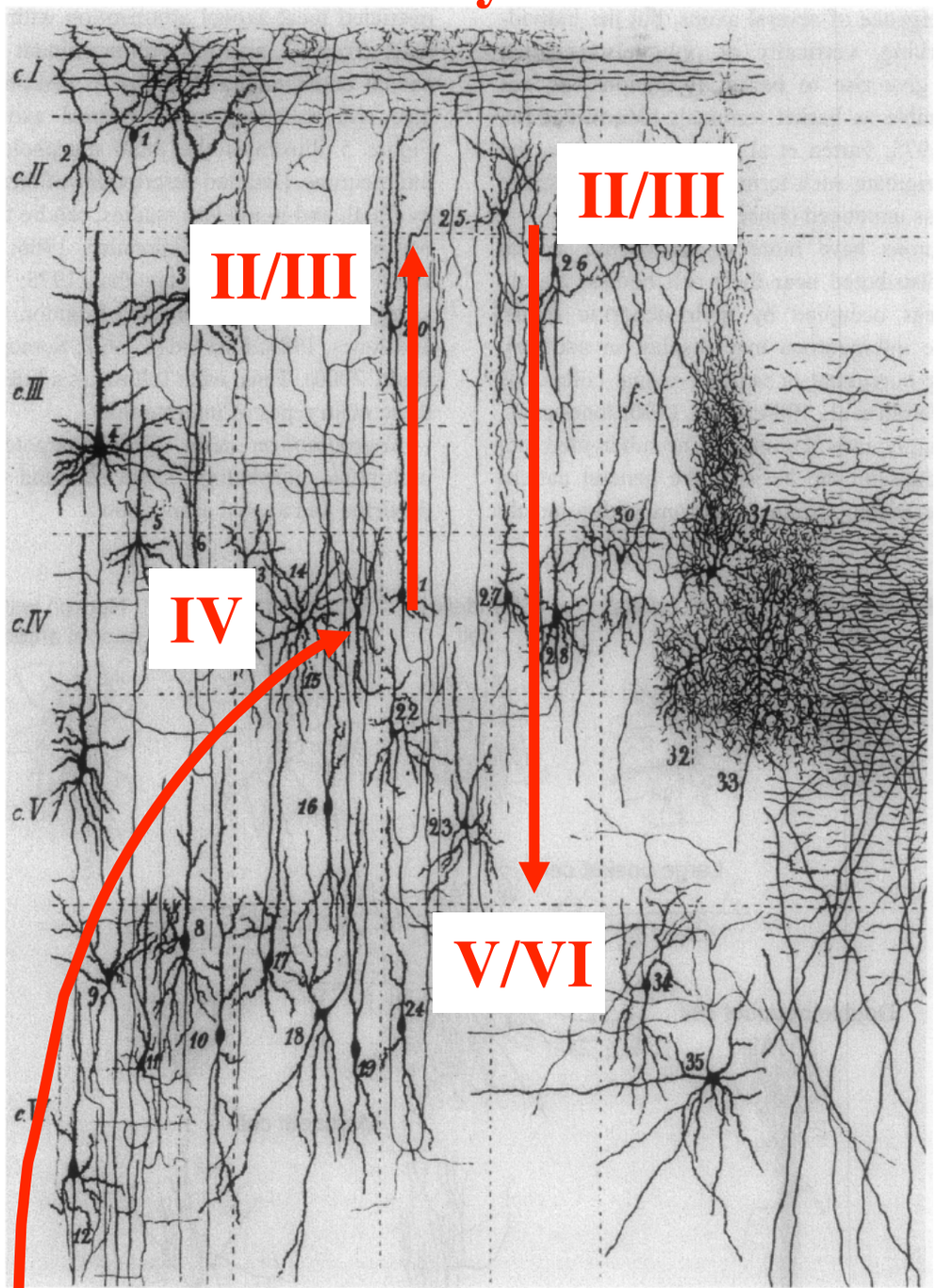

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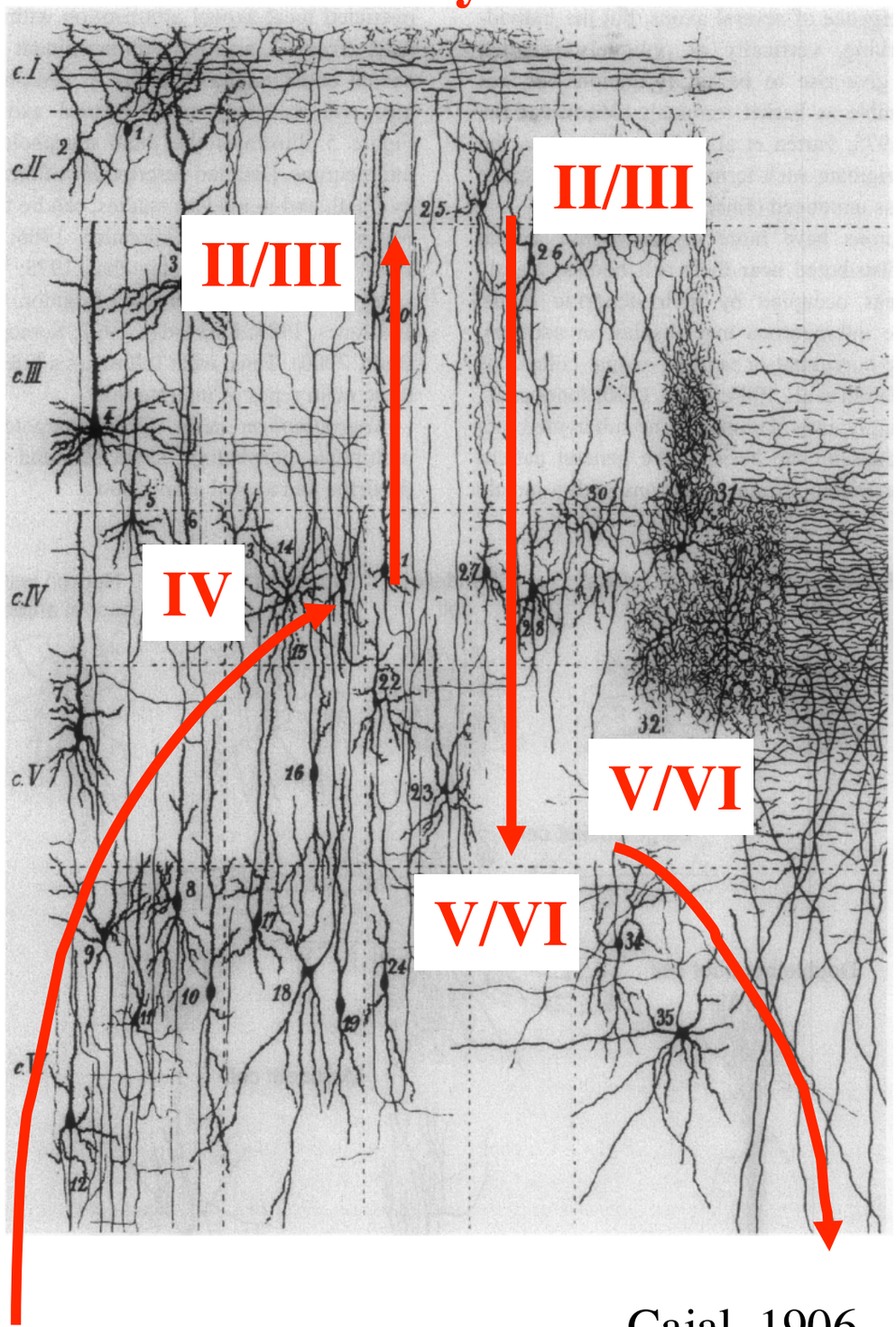

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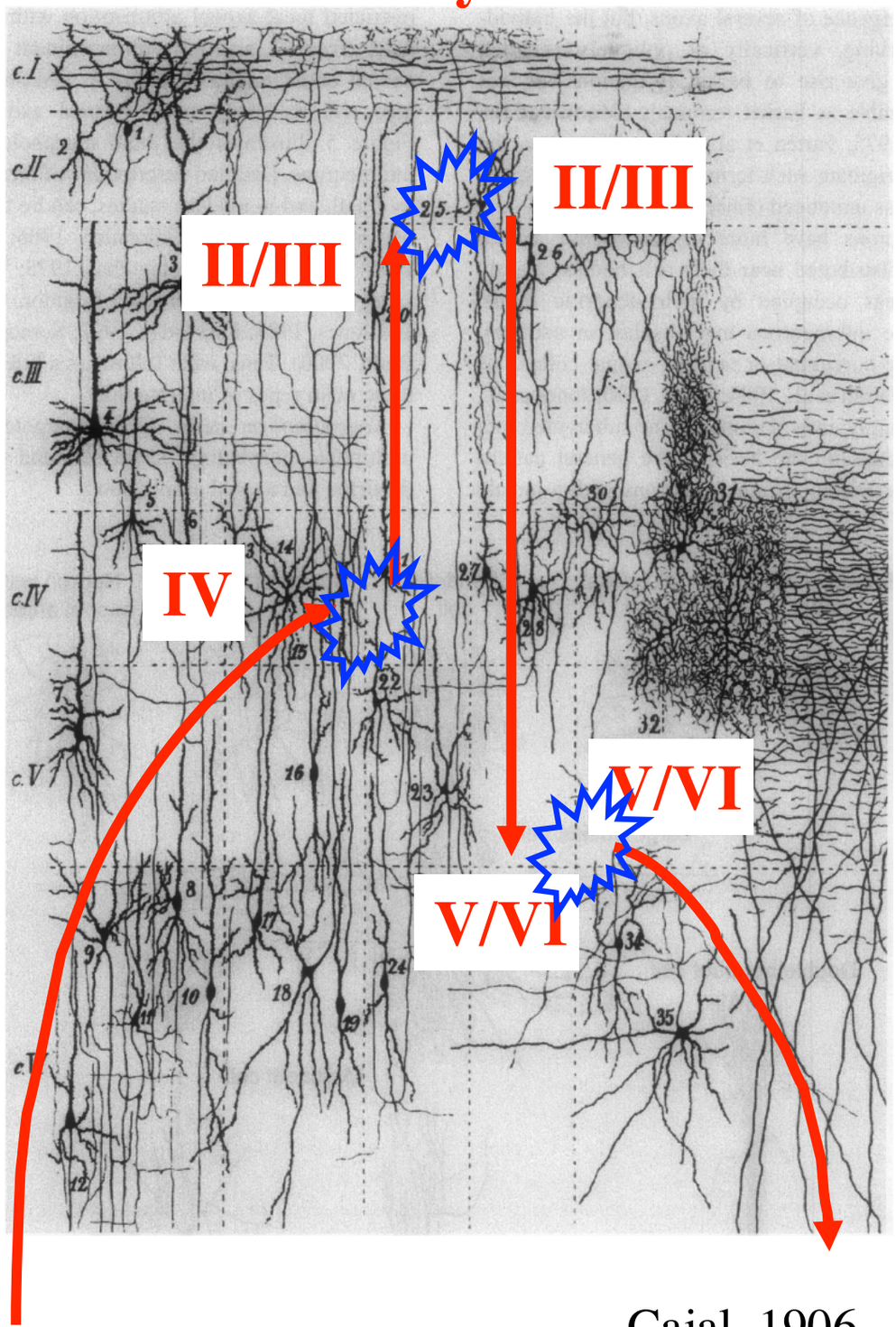
Gating

Feedforward inhibition

Feedback inhibition

Rhythm generation

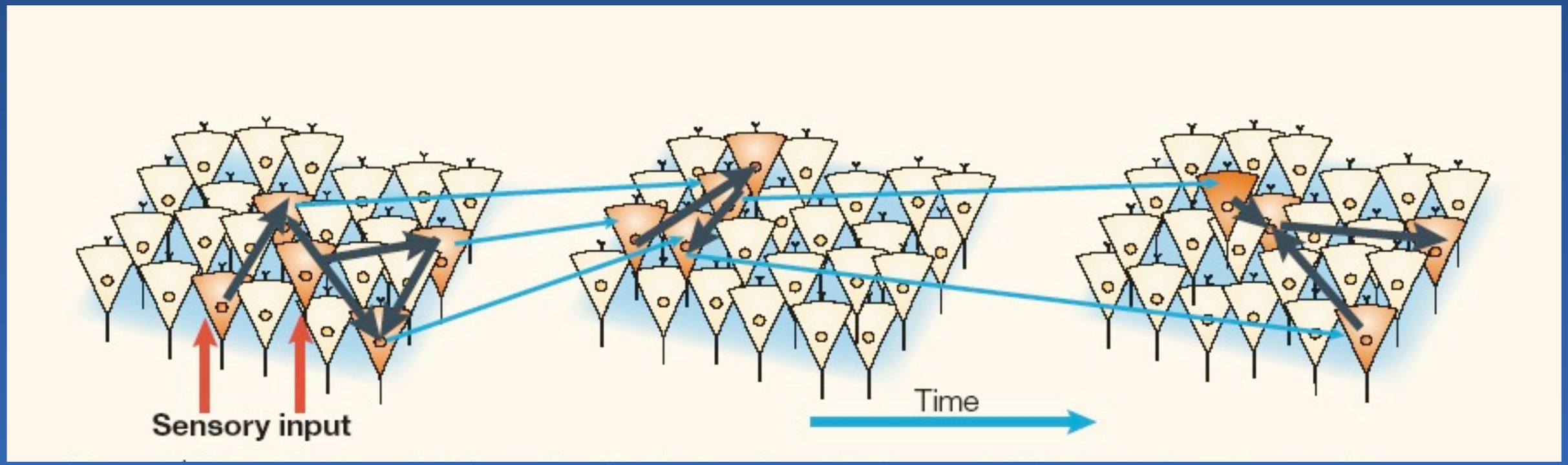
Excitatory network



Cajal, 1906

The Cell Assembly Hypothesis

"The Organization of Behavior" Donald Hebb 1949



Donald Hebb
1904-1985

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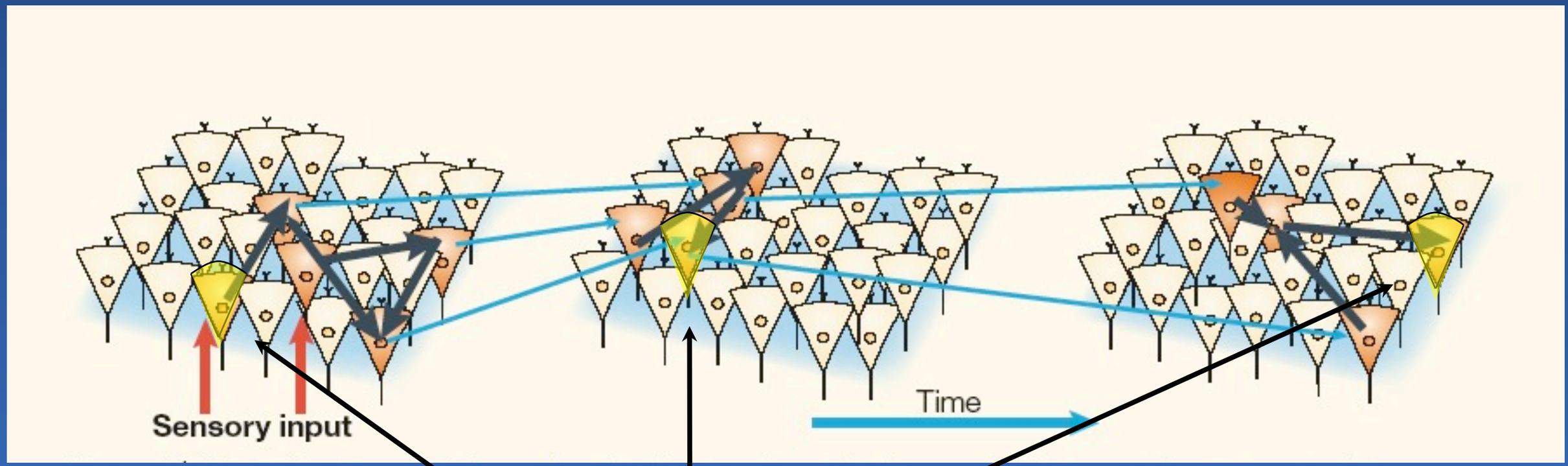
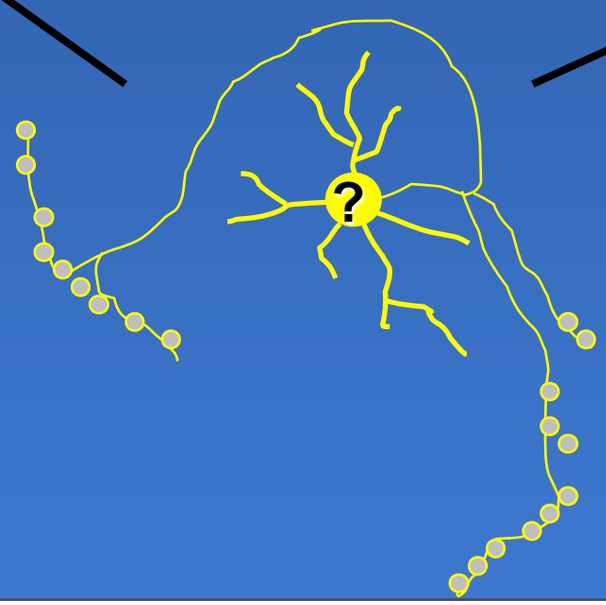
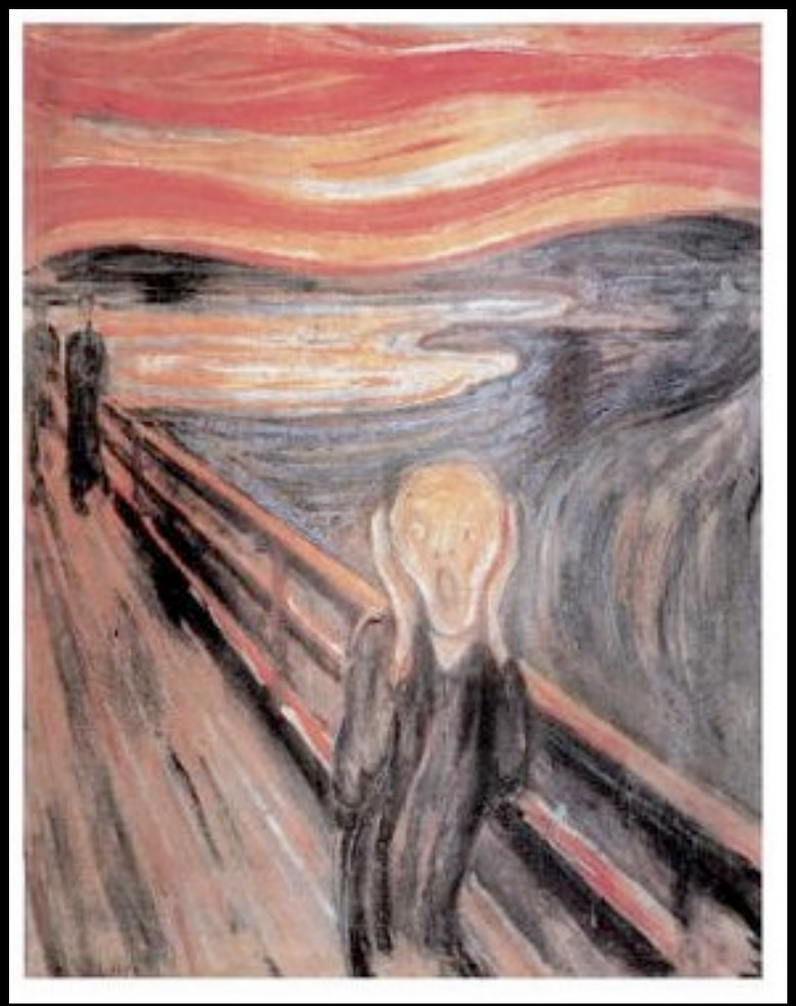




Donald Hebb
1904-1985

Linking affective brain disorders to their biological cause



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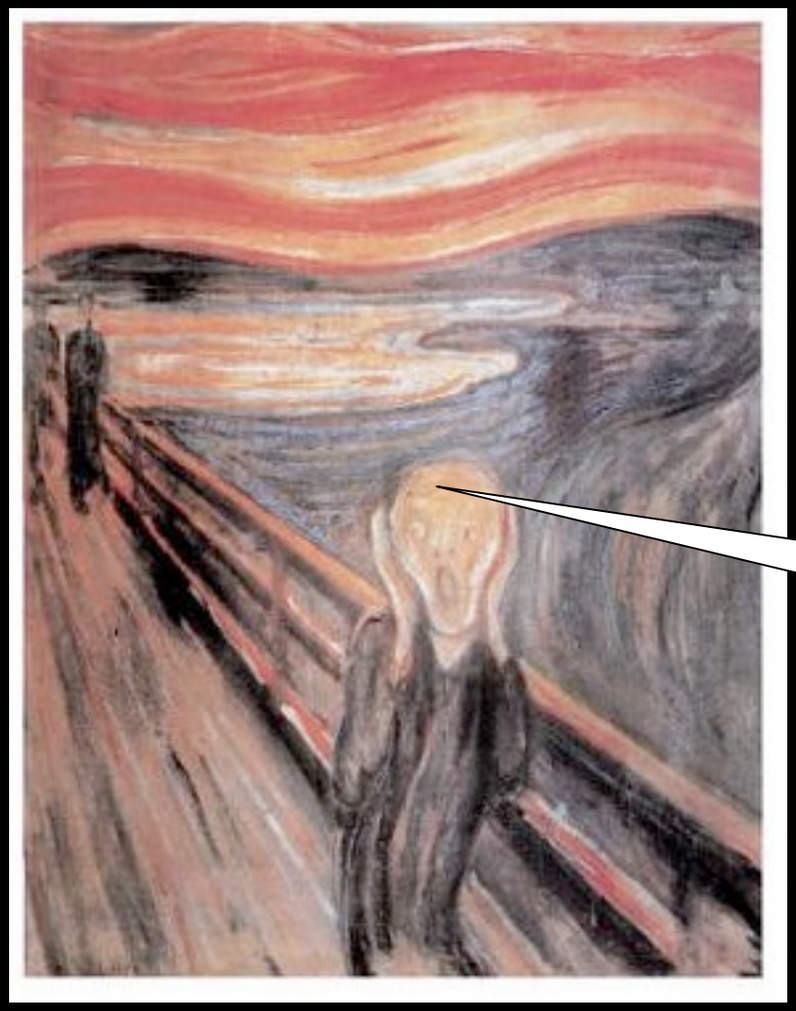

End (hg18)	Size (bp)	Type	Duplicated or deleted genes	Genes disrupted at SV breakpoints
	Cases (n = 150)			
146,292,286	1,349,136	del	11	*NBPF10*
232,673,340	209,095	dup	3	*SLC35F3, TARBP1*
49,319,683	670,929	dup	3	*STON1-GTF2A1L*
212,191,651	399,157	del	1	*ERBB4*
7,314,117	136,520	del	1	*GRM7*
53,191,698	135,181	dup	2	*PRKCD*
198,573,215	1,348,553	del	20	-
36,693,387	502,683	del	4	*SKP2, SLC1A3*
77,857,149	498,447	dup	2	*MAGI2, PHTF2*
115,966,446	15,668,290	dup	82	*SLC12A9, CAV1*
151,531,755	461,992	dup	4	*PRKAG2, MLL3*
142,393,948	368,516	dup	3	*PTK2*
3,118,374	1,105,058	dup	4	*SMARCA2*
3,544,339	440,089	del	1	-
25,852,420	526,889	dup	1	-
33,540,102	279,213	dup	2	*HIPK3, C11orf41*
83,943,977	263,008	del	1	*DLG2*
53,768,132	282,769	dup	1	-
7,565,943	495,017	dup	2	*LAMA1, PTPRM*
59,363,706	317,744	dup	13	*TMC4*
32,715,286	666,705	dup	1	*LARGE*
57,772,954	57,772,954	dup	entire Y	-
57,723,933	152,391	dup	1	-
	Controls (n = 268)			
100,204,503	219,761	del	2	*FRRS1*
8,581,679	410,026	del	1	-
81,408,551	1,740,703	del	1	*ROBO1*
96,143,673	413,043	del	1	*MANEA*
84,699,929	363,921	del	1	-
112,334,786	1,300,896	dup	6	*FLJ31818*
127,422,401	338,843	del	1	*SND1*
11,755,764	3,611,148	del	20	*CTSB*
13,216,945	575,532	dup	3	*MPDZ*
25,248,947	665,297	dup	7	*SOX5, LYRM5*
29,990,037	196,994	del	1	*TMTC1*
69,748,827	352,892	del	2	*HYDIN*
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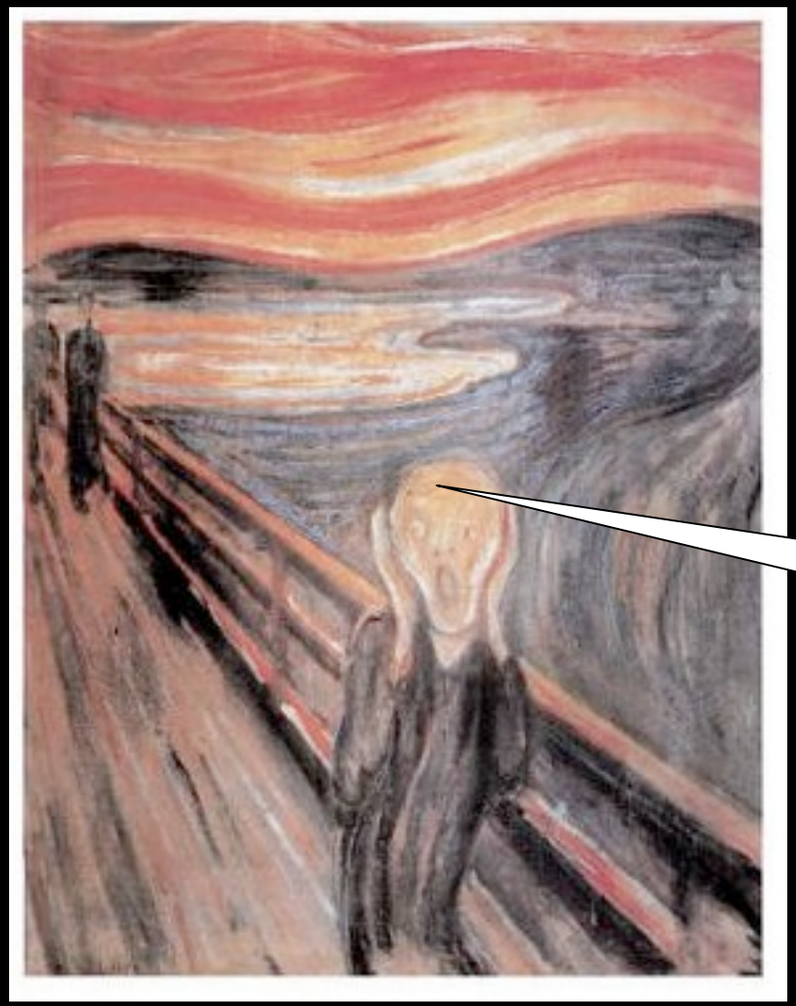
Linking affective brain disorders to their biological cause



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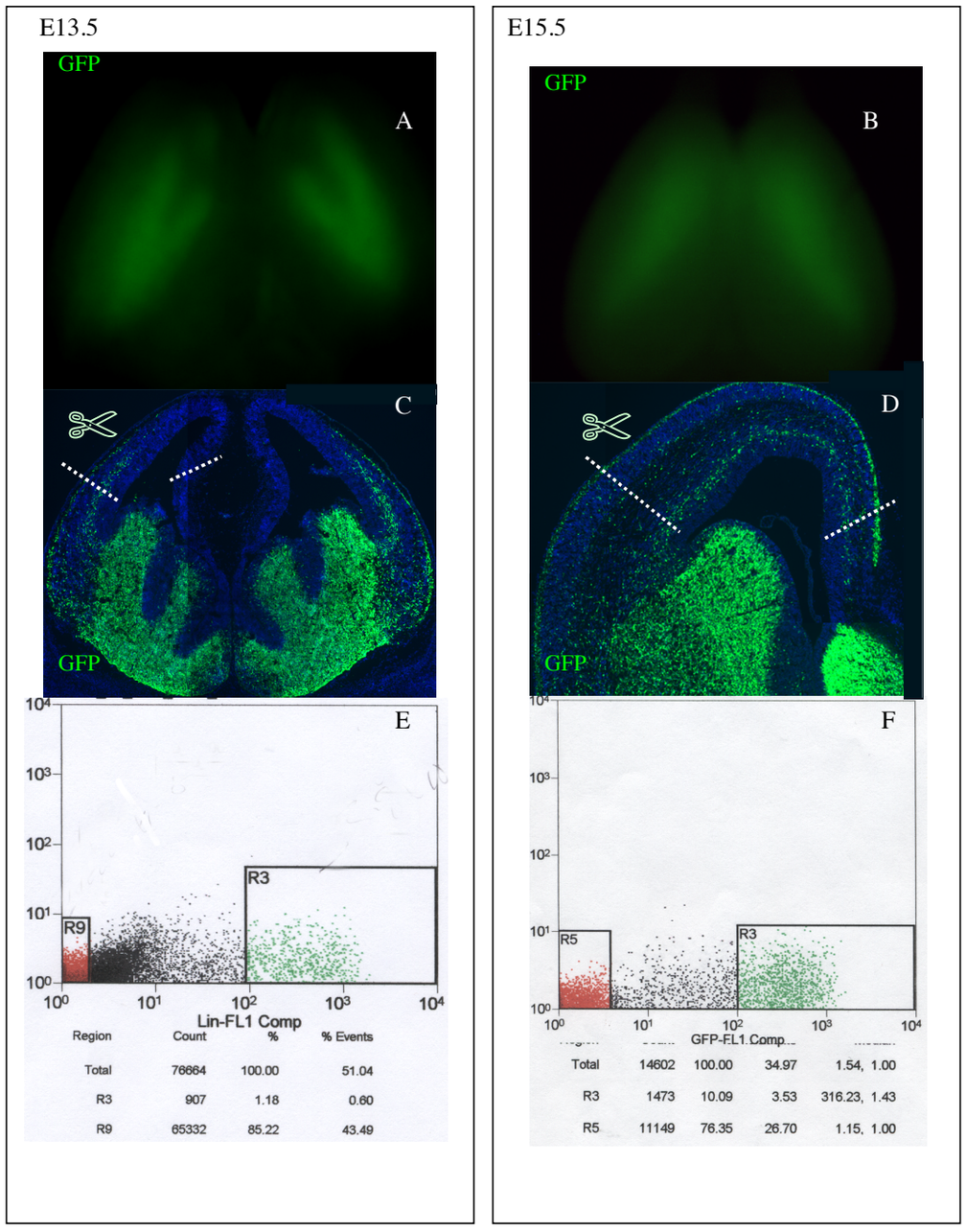
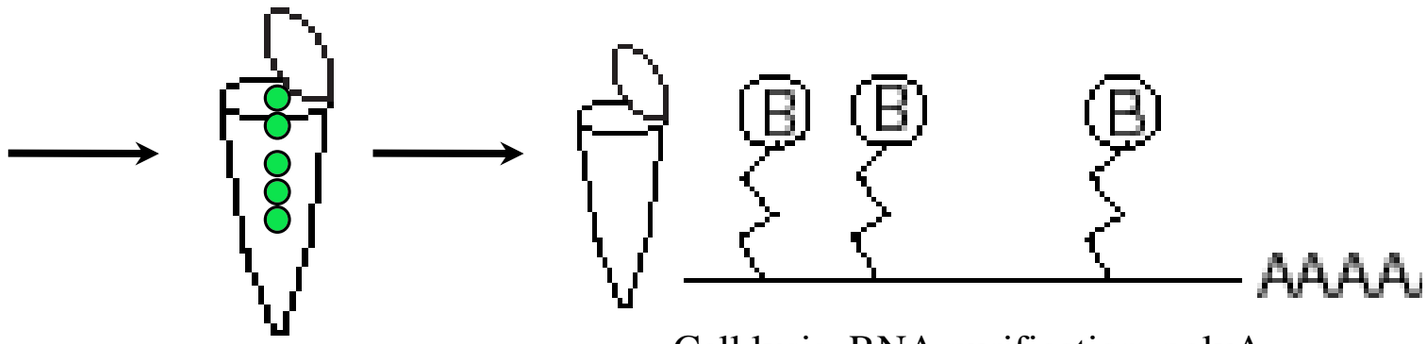
Microarray analysis of Cortical Interneurons

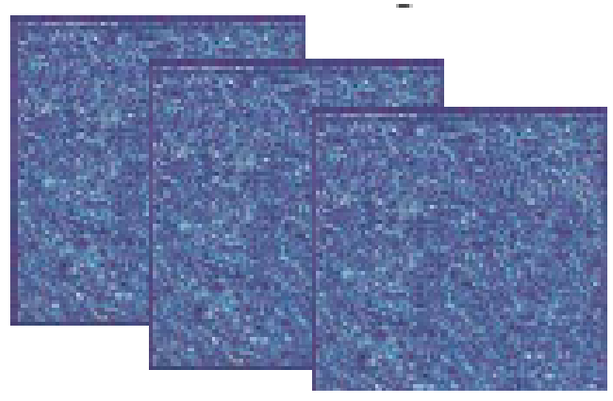
cortex. We dissected the cortex of this m
E13.5 and E15.5





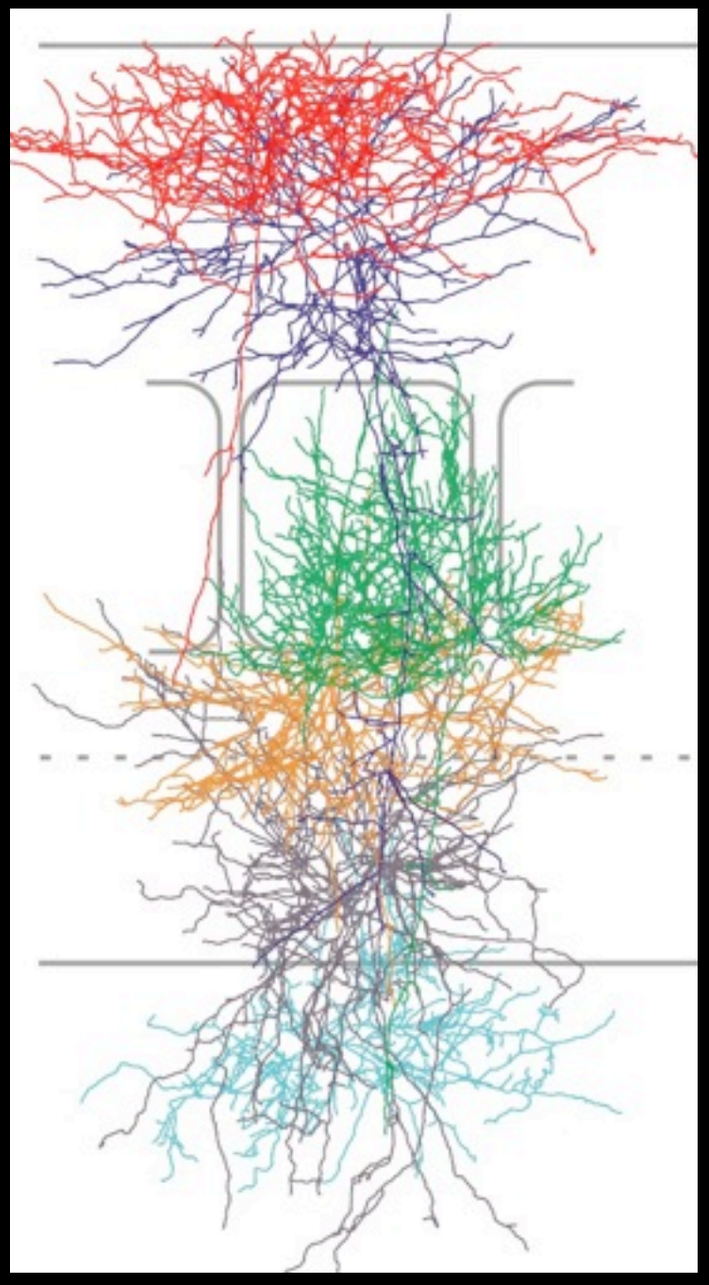
FACS sorting

Cell lysis, RNA purification, polyA RNA amplification, and labeling with biotin (B)



Microarray hybridization and scanning

Genes expressed in local projection neurons linked to psychiatric disorders



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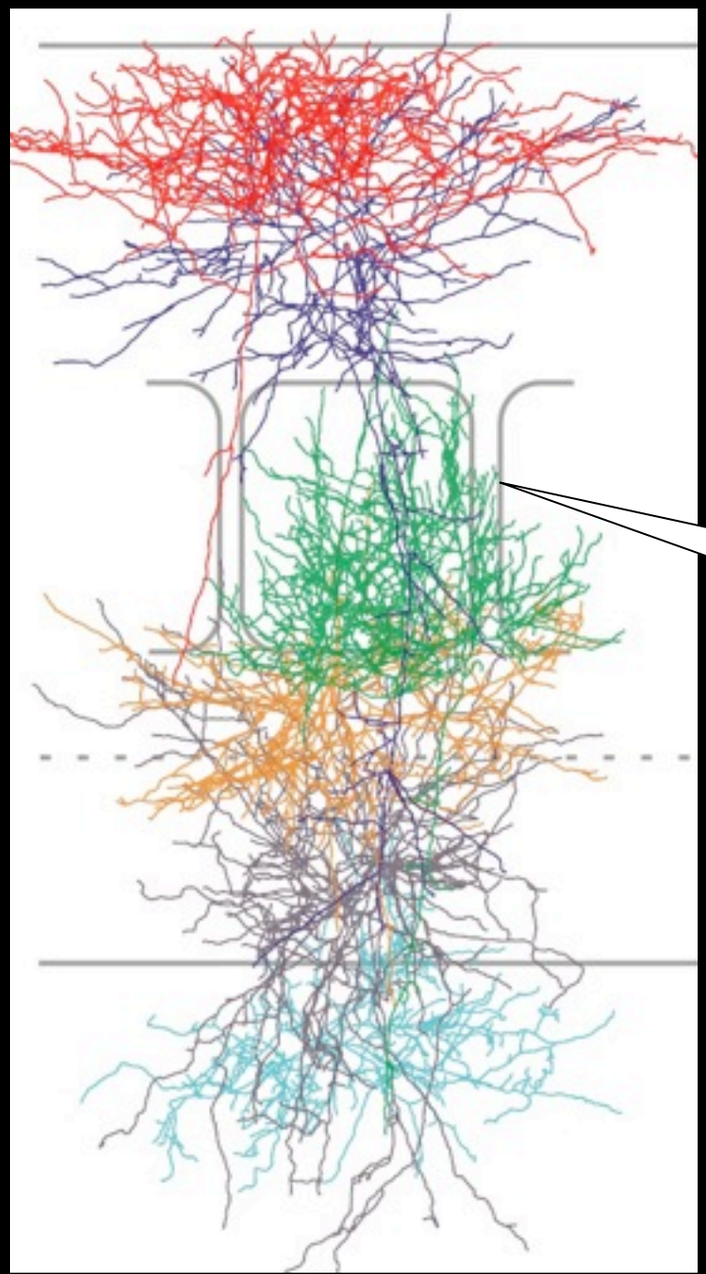
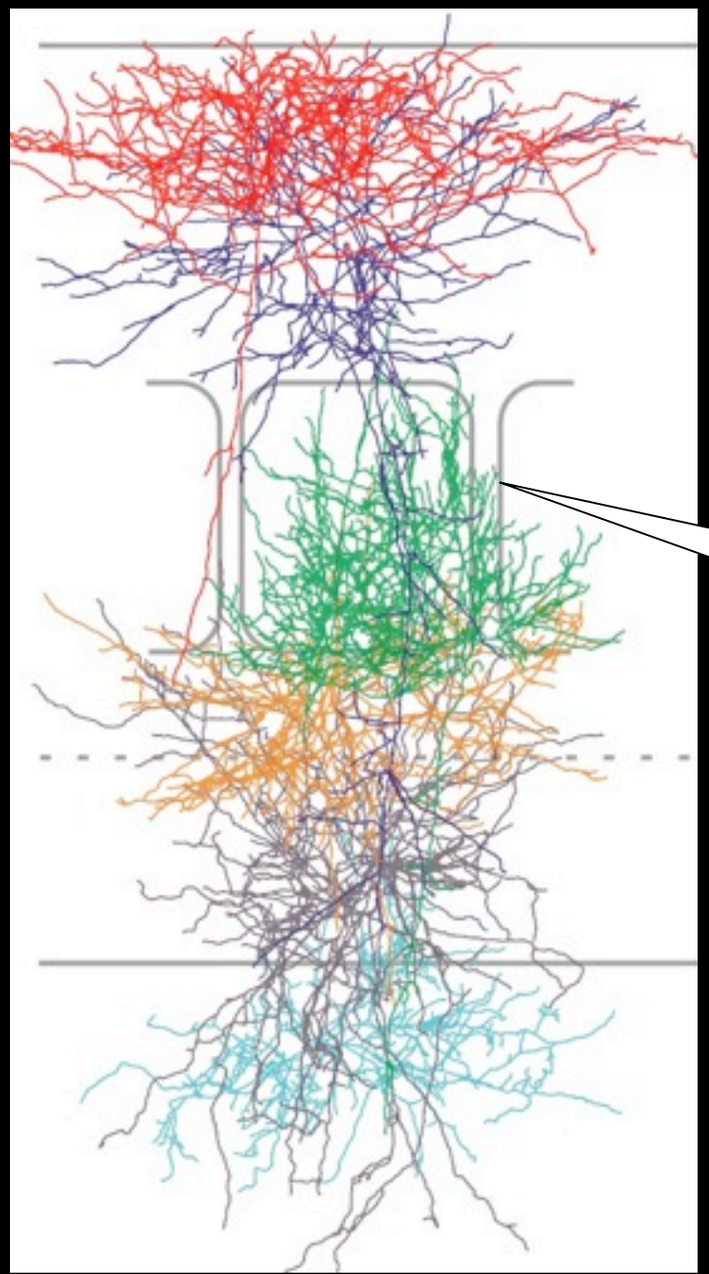


Genes expressed in developing interneurons linked to neurological disorders

Gene function	Gene	Human		Mouse	
		Disease	Ref.	Endophenotype	Ref.
Transcription factors/ regulators	*Npas3*	Schizophrenia	(Pickard et al. 2005; Pickard et al. 2006)	Impaired prepulse inhibition; Impaired social recognition.	(Erbel-Sieler et al. 2004)
	Hdac11	Autism	(Szatmari et al. 2007)	NA	
	Cited2	Autism	(Szatmari et al. 2007)	NA	
	Meis1	Autism	(Szatmari et al. 2007)	NA	
	Zfhx1b	Autism; Mental retardation; Epilepsy	(Inlow and Restifo 2004; Dastot-Le Moal et al. 2007; Hoffer et al. 2007)	NA	
	Arx	Epilepsy; mental retardation; lissencephaly	(Inlow and Restifo 2004; Kato et al. 2007)	Deficit in interneuron migration.	(Colombo et al. 2007)
Cell surface	*Ncam1*	Schizophrenia; Bipolar disorder	(Atz et al. 2007)	Abnormal interneurons; Impaired sensory gating and fear conditioning; Deficient prepulse inhibition; Impaired startle response.	(Pillai-Nair et al. 2005) (Plappert et al. 2005, 2006)
	Chl1	Mental retardation	(Frints et al. 2003)	Impaired prepulse inhibition; Impaired acoustic startle response	(Irintchev et al. 2004)
	Cntnap4	Autism	(Sebat et al. 2007)	NA	
	Sema3a	Autism	(Szatmari et al. 2007)	NA	
Channels/ neurotransmission	*Cacnb4*	Autism; epilepsy	(Escayg, De Waard, et al. 2000; Szatmari et al. 2007)	Ataxia; lethargy; seizures.	(Fletcher and Frankel 1999) (Burgess and Noebels 1999a, 1999b)
	Cacng2	Schizophrenia; epilepsy	(Sutrala et al. 2007)	Epileptic seizures	(Letts et al. 1998)
	Scn1a	Mental retardation; epilepsy	(Escayg, MacDonald, et al. 2000; Escayg et al. 2001; Inlow and Restifo 2004)	Epileptic seizures	(Ogiwara et al. 2007)
	Abat	Mental retardation; Autism; Schizophrenia	(Inlow and Restifo 2004; Barnby et al. 2005; Zhang et al. 2005)	NA	
	Kcnk2	Autism	(Szatmari et al. 2007)	*Kcnk2* deletion as an antidepression behavioral phenotype	(Heurteaux et al. 2006)
Others	*Dcx*	Epilepsy; Mental retardation	(Reiner et al. 2006)	Deficient interneuron migration.	(Friocourt et al. 2007)
	Man2a1	Autism	(Szatmari et al. 2007)	NA	
	Nr2f2	Autism	(Szatmari et al. 2007)	Defective tangential cell migration	(Tripodi et al. 2004)
	Shank3	Autism	(Durand et al. 2007; Szatmari et al. 2007)	NA	
	Sez6l2	Autism	(Szatmari et al. 2007)	NA	
	Dpp6	Autism	(Szatmari et al. 2007)	NA	
	Centg2	Autism	(Szatmari et al. 2007) (Wassink et al. 2005)	NA	
	Dtna	Autism	(Szatmari et al. 2007)	NA	

15% of local projection neuron genes are linked to psychiatric disorders



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	Cacng2	Schizophrenia; epilepsy	(Sutrala et al. 2007)	Epileptic seizures	(Letts et al. 1998)
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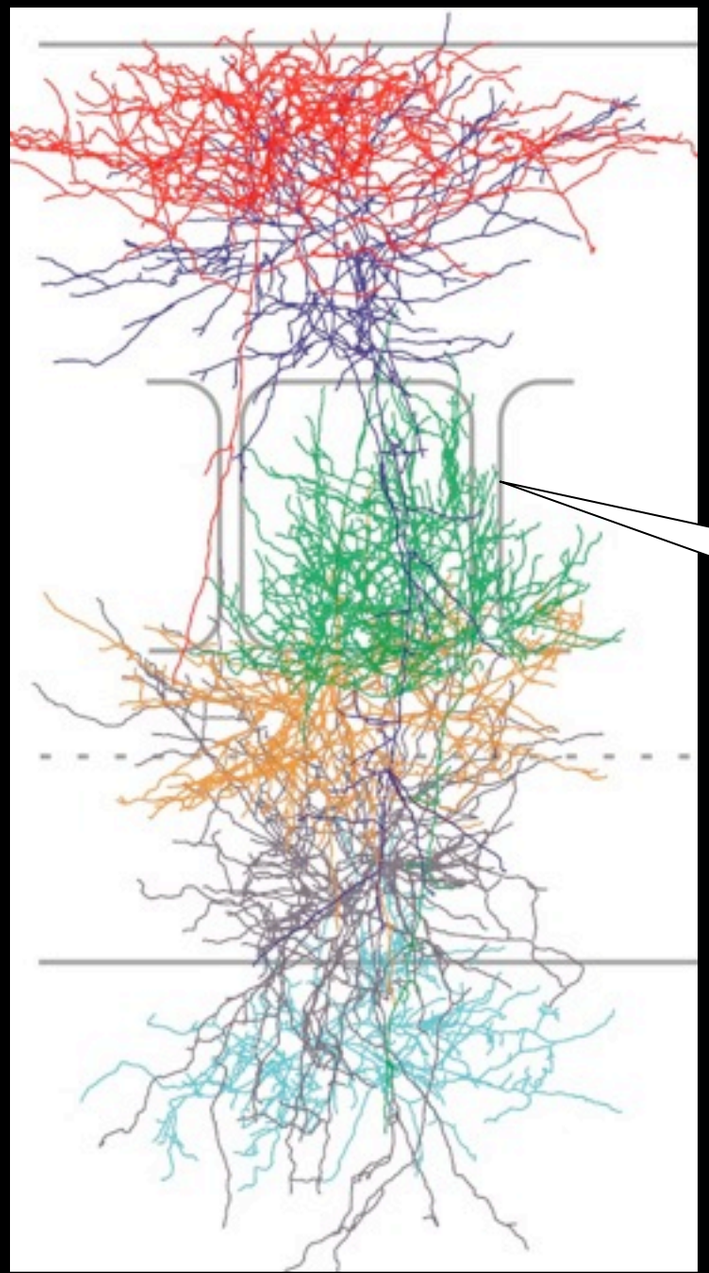
	Man2a1	Autism	(Szatmari et al. 2007)	NA	
	Nr2f2	Autism	(Szatmari et al. 2007)	Defective tangential cell migration	(Tripodi et al. 2004)
	Shank3	Autism	(Durand et al. 2007; Szatmari et al. 2007)	NA	
	Sez6l2	Autism	(Szatmari et al. 2007)	NA	
	Dpp6	Autism	(Szatmari et al. 2007)	NA	
	Centg2	Autism	(Szatmari et al. 2007) (Wassink et al. 2005)	NA	
	Dtna	Autism	(Szatmari et al. 2007)	NA	

...Versus 1% of genes expressed in long distance projection neurons.



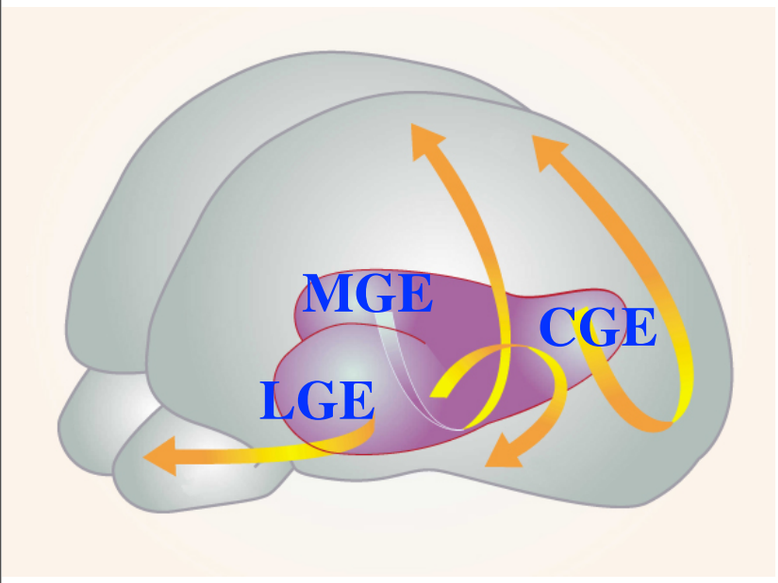
Genes expressed in developing interneurons linked to neurological disorders

Gene function	Gene	Human		Mouse	
		Disease	Ref.	Endophenotype	Ref.
Transcription factors/ regulators	*Npas3*	Schizophrenia	(Pickard et al. 2005; Pickard et al. 2006)	Impaired prepulse inhibition; Impaired social recognition.	(Erbel-Sieler et al. 2004)
	Hdac11	Autism	(Szatmari et al. 2007)	NA	
	Cited2	Autism	(Szatmari et al. 2007)	NA	
	Meis1	Autism	(Szatmari et al. 2007)	NA	
	Zfhx1b	Autism; Mental retardation; Epilepsy	(Inlow and Restifo 2004; Dastot-Le Moal et al. 2007; Hoffer et al. 2007)	NA	
	Arx	Epilepsy; mental retardation; lissencephaly	(Inlow and Restifo 2004; Kato et al. 2007)	Deficit in interneuron migration.	(Colombo et al. 2007)
Cell surface	*Ncam1*	Schizophrenia; Bipolar disorder	(Atz et al. 2007)	Abnormal interneurons; Impaired sensory gating and fear conditioning; Deficient prepulse inhibition; Impaired startle response.	(Pillai-Nair et al. 2005) (Plappert et al. 2005, 2006)
	Chl1	Mental retardation	(Frints et al. 2003)	Impaired prepulse inhibition; Impaired acoustic startle response	(Irintchev et al. 2004)
	Cntnap4	Autism	(Sebat et al. 2007)	NA	
	Sema3a	Autism	(Szatmari et al. 2007)	NA	
Channels/ neurotransmission	*Cacnb4*	Autism; epilepsy	(Escayg, De Waard, et al. 2000; Szatmari et al. 2007)	Ataxia; lethargy; seizures.	(Fletcher and Frankel 1999) (Burgess and Noebels 1999a, 1999b)
	Cacng2	Schizophrenia; epilepsy	(Sutrala et al. 2007)	Epileptic seizures	(Letts et al. 1998)
	Scn1a	Mental retardation; epilepsy	(Escayg, MacDonald, et al. 2000; Escayg et al. 2001; Inlow and Restifo 2004)	Epileptic seizures	(Ogiwara et al. 2007)
	Abat	Mental retardation; Autism; Schizophrenia	(Inlow and Restifo 2004; Barnby et al. 2005; Zhang et al. 2005)	NA	
	Kcnk2	Autism	(Szatmari et al. 2007)	*Kcnk2* deletion as an antidepression behavioral phenotype	(Heurteaux et al. 2006)
Others	*Dcx*	Epilepsy; Mental retardation	(Reiner et al. 2006)	Deficient interneuron migration.	(Friocourt et al. 2007)
	Man2a1	Autism	(Szatmari et al. 2007)	NA	
	Nr2f2	Autism	(Szatmari et al. 2007)	Defective tangential cell migration	(Tripodi et al. 2004)
	Shank3	Autism	(Durand et al. 2007; Szatmari et al. 2007)	NA	
	Sez6l2	Autism	(Szatmari et al. 2007)	NA	
	Dpp6	Autism	(Szatmari et al. 2007)	NA	
	Centg2	Autism	(Szatmari et al. 2007) (Wassink et al. 2005)	NA	
	Dtna	Autism	(Szatmari et al. 2007)	NA	

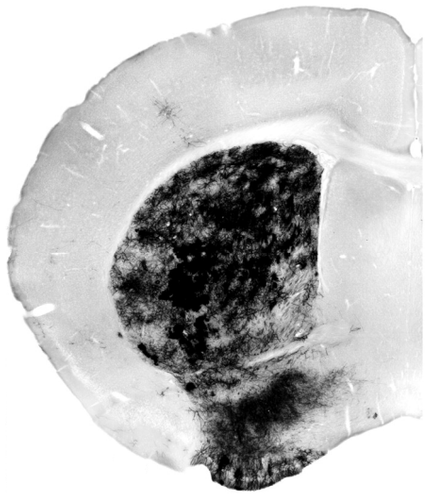
In vivo transplantation study

The MGE and CGE give rise to cortical interneurons

UBM guided *in vivo* transplantation

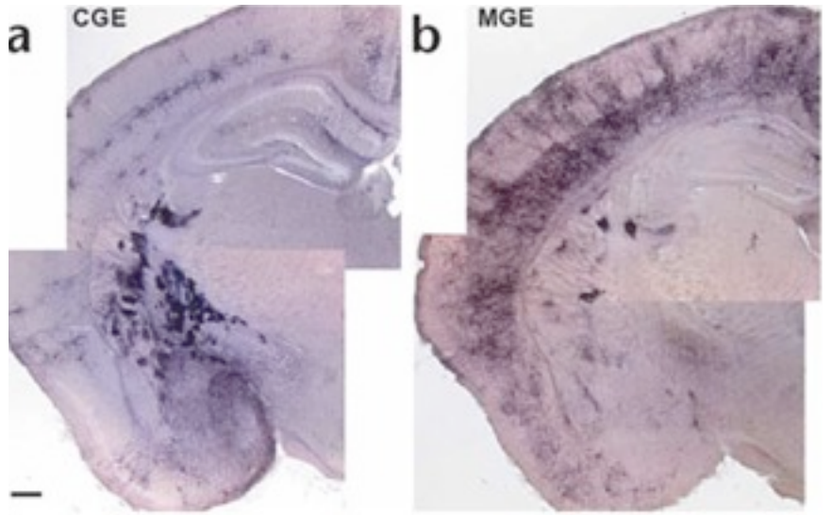


LGE



Wichterle et al., 2001

CGE MGE



Nery et al., 2002

- **The majority of cortical interneurons are generated in the MGE and CGE**
- **Interneuron subtypes seems regionally specified**

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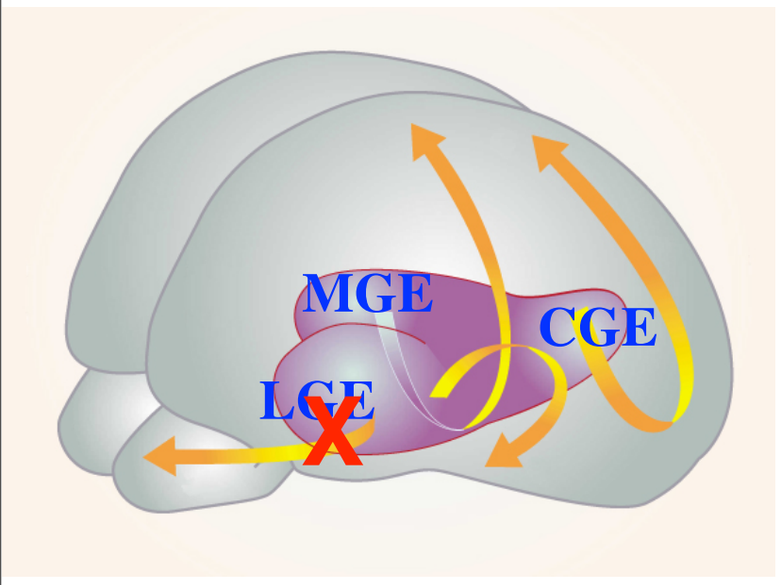
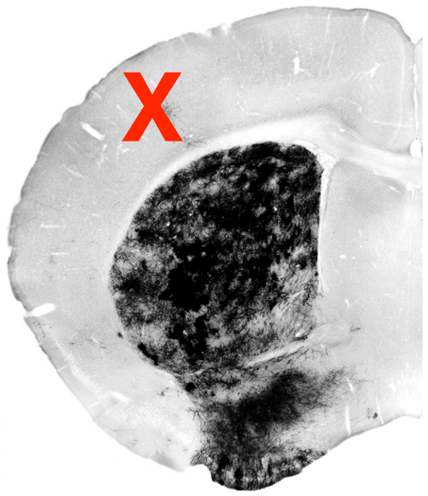
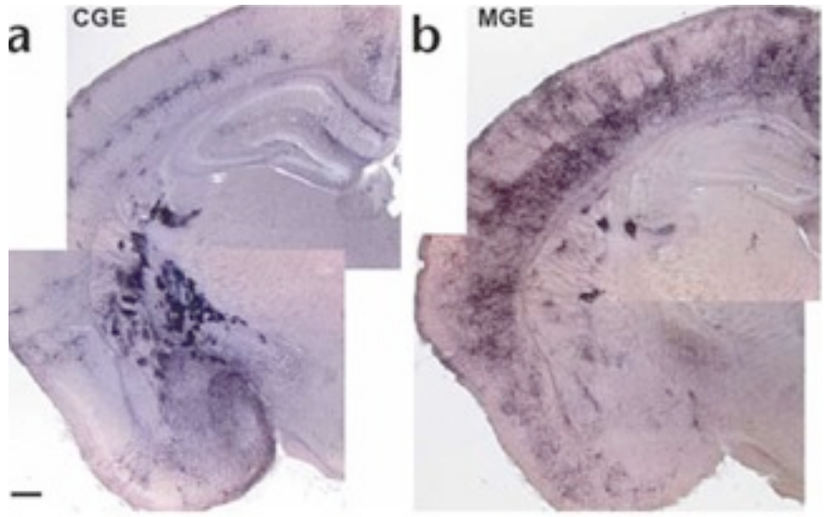


LGE



Wichterle et al., 2001

CGE MGE



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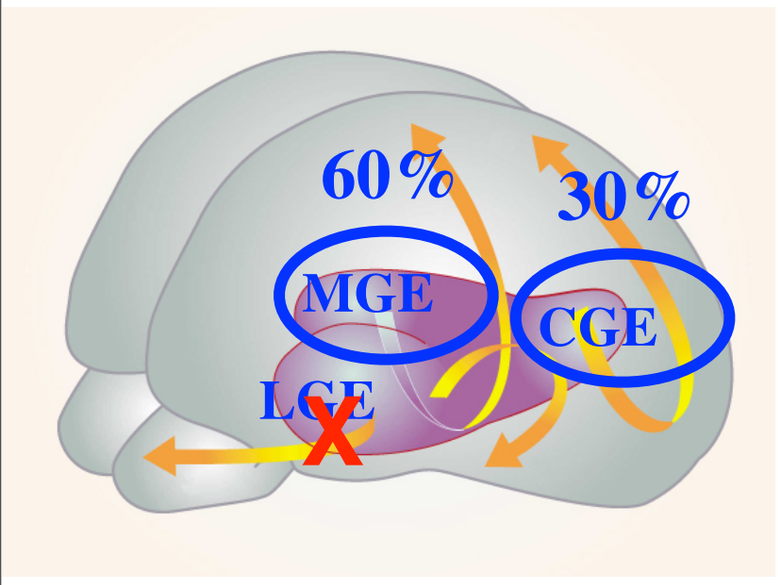
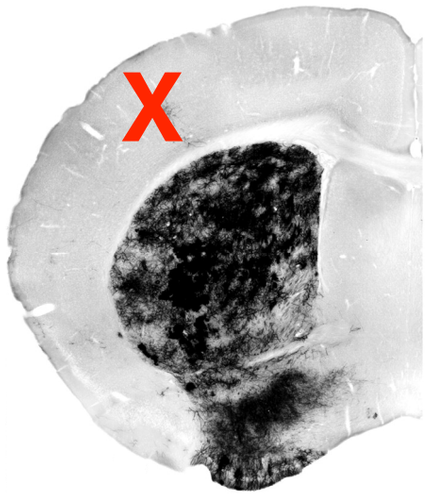
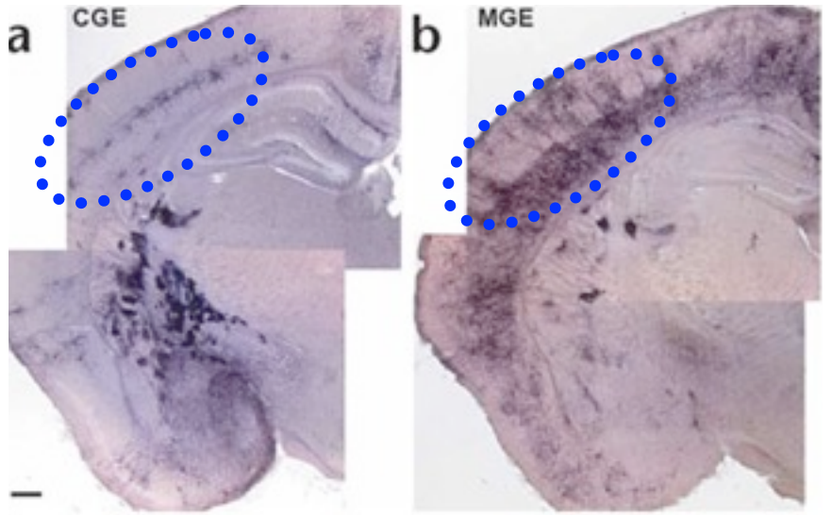


LGE



Wichterle et al., 2001

CGE MGE



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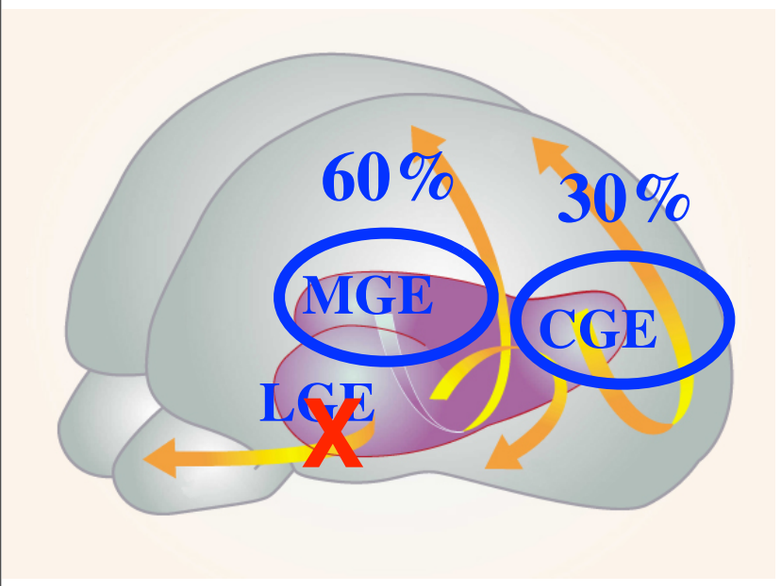
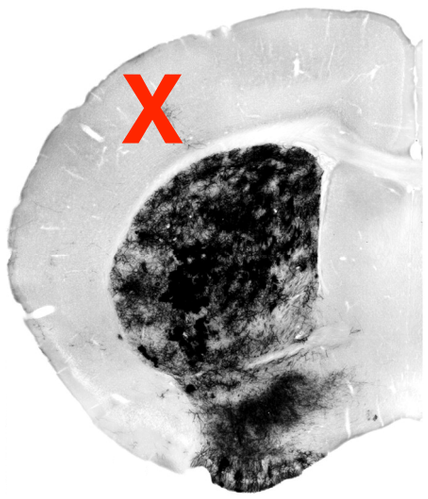
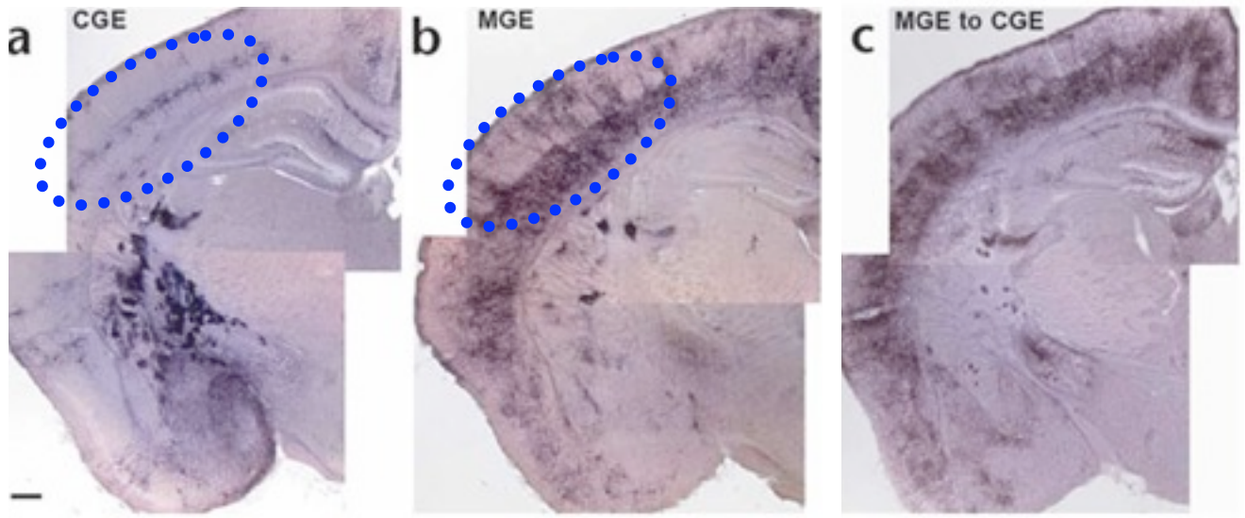


LGE



Wichterle et al., 2001

CGE MGE MGE→ CGE



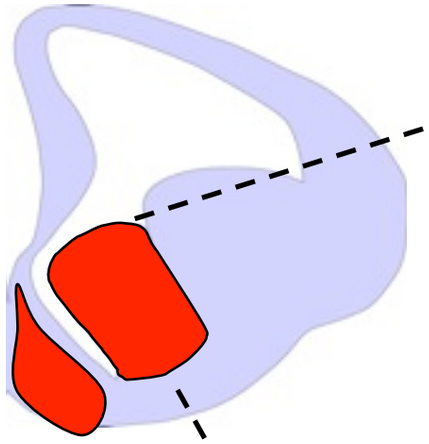
Nery et al., 2002

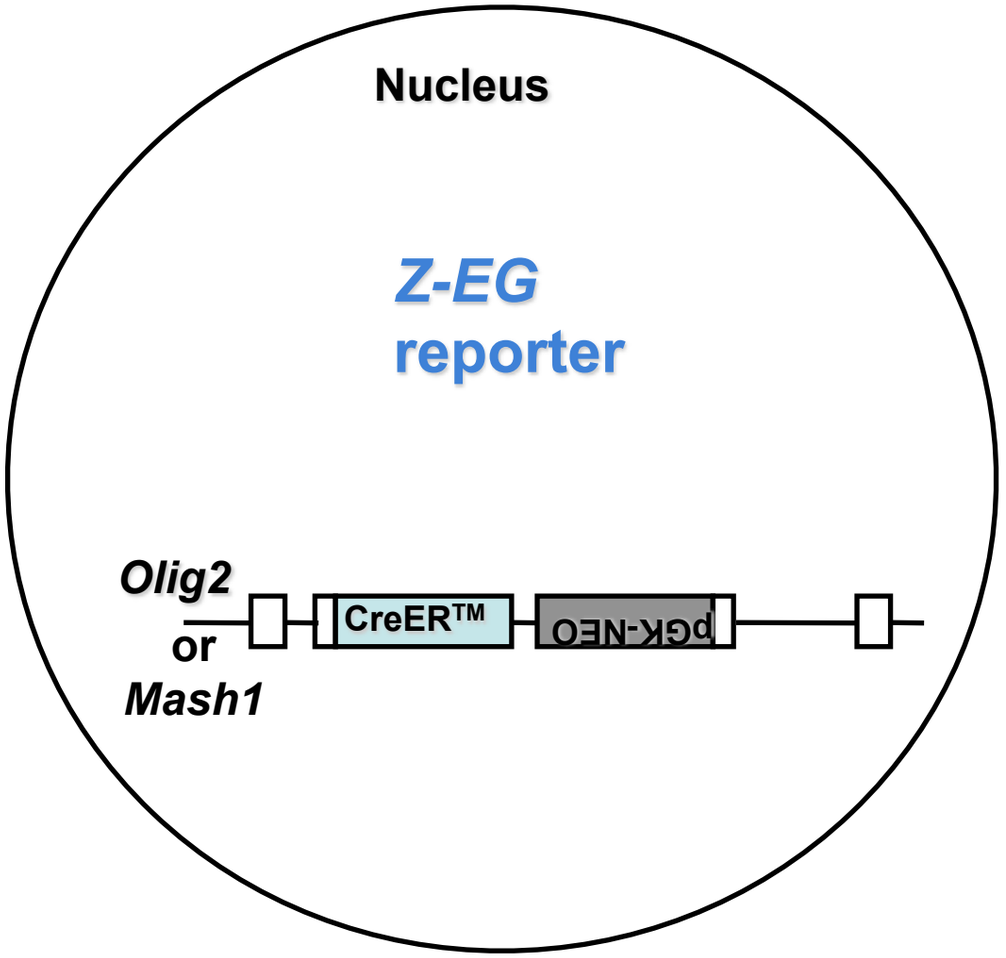
- **The majority of cortical interneurons are generated in the MGE and CGE**
- **Interneuron subtypes seems regionally specified**
- **Heterotopic transplantation study suggests that interneuron subtypes are intrinsically determined**

Genetically Birthdating of the MGE or CGE

Olig2^{CreER}: Temporal MGE fate mapping

Mash1^{CreER}: Temporal CGE fate mapping





Butt et al. Neuron 05; Miyoshi et al. JN 07,09; Sousa et al., CC09

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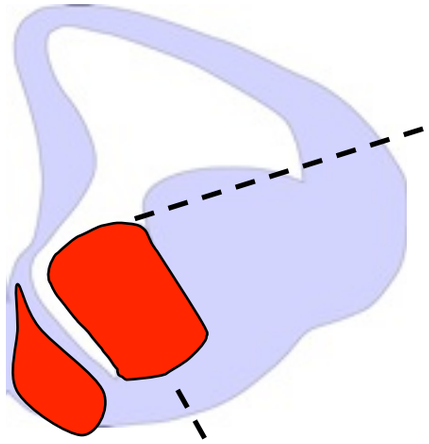

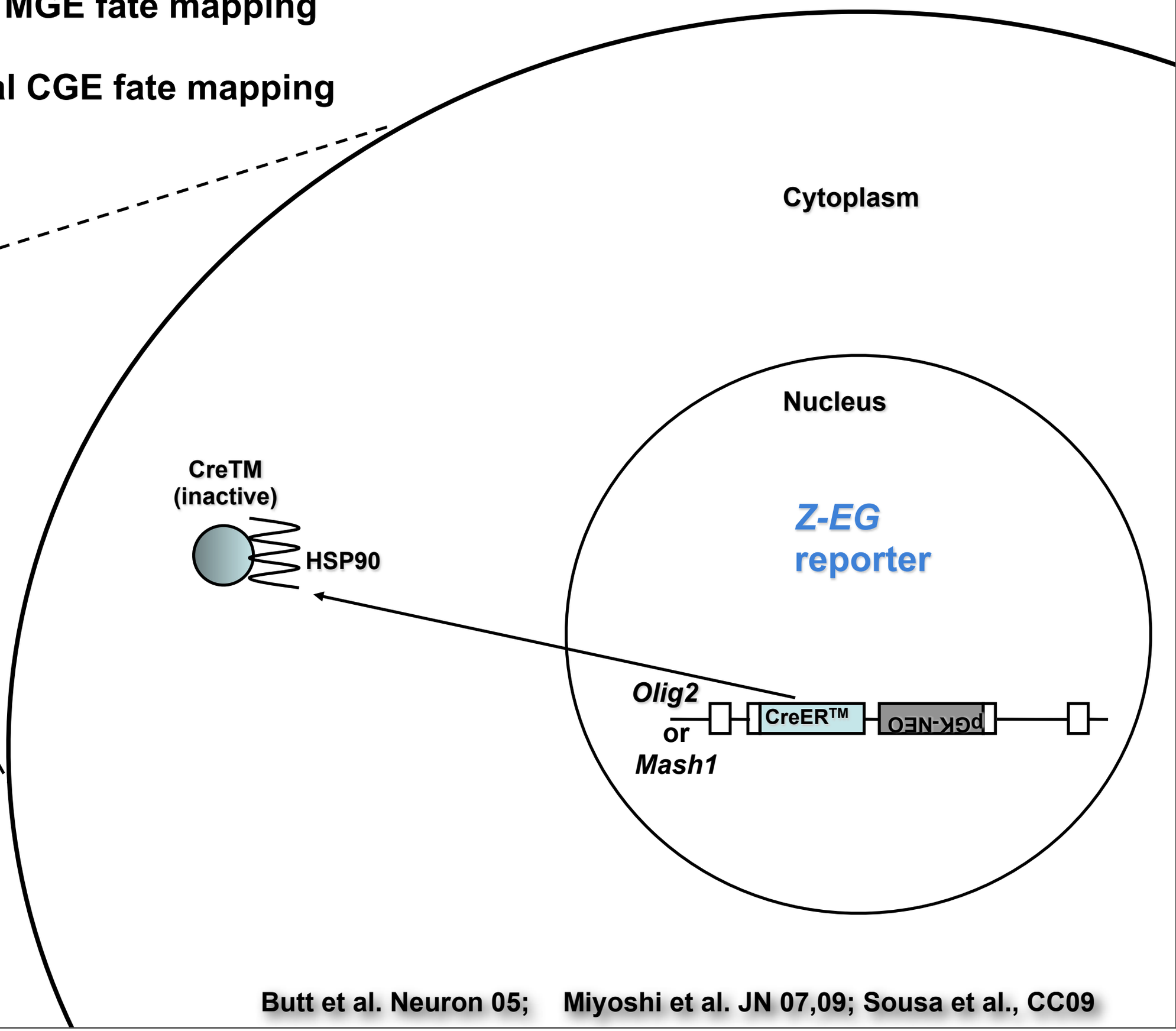

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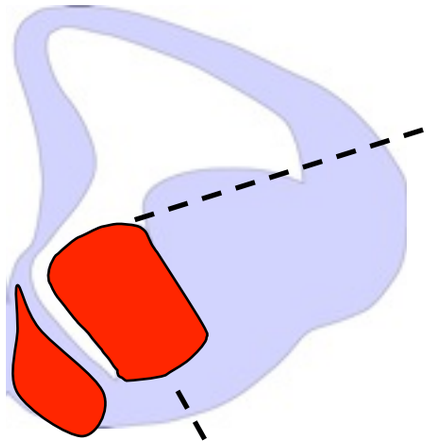

Cytoplasm

Nucleus

CreTM (inactive)

Tamoxifen

HSP90

Z-EG reporter

Olig2 or *Mash1*

Butt et al. Neuron 05; Miyoshi et al. JN 07,09; Sousa et al., CC09

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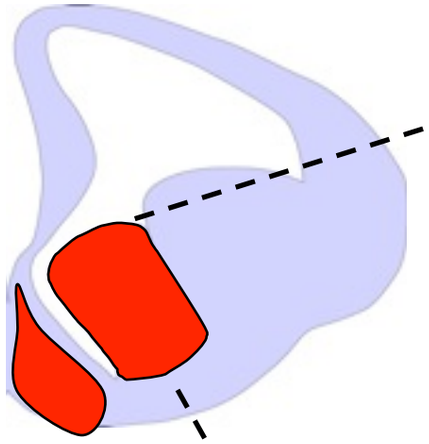

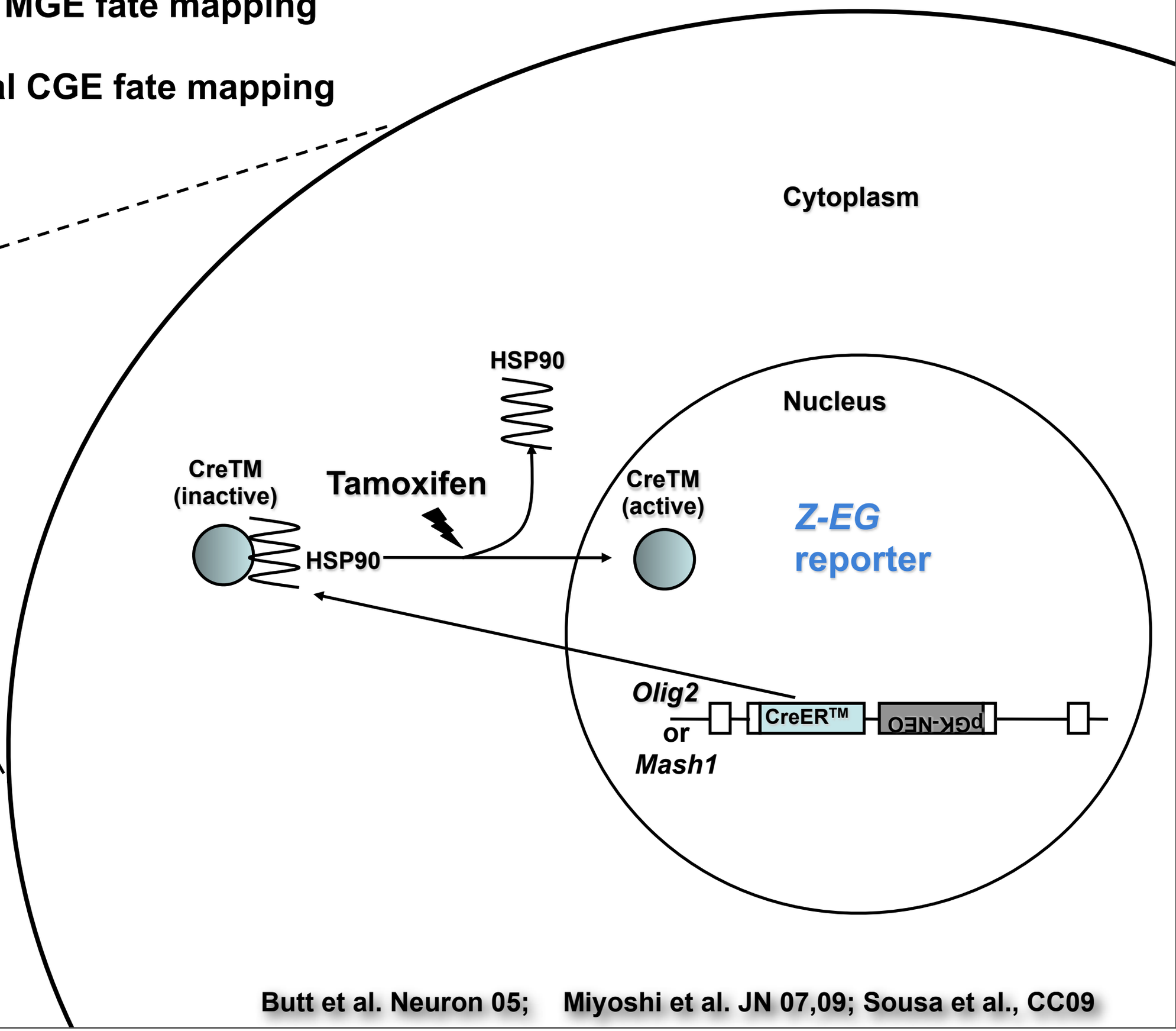

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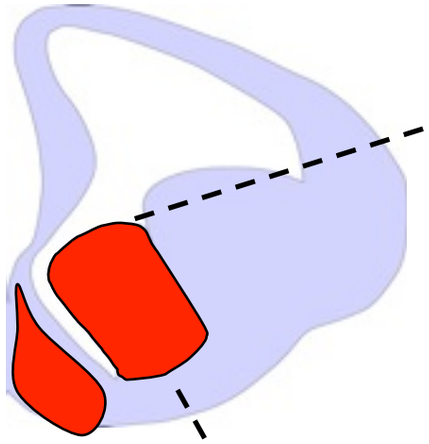

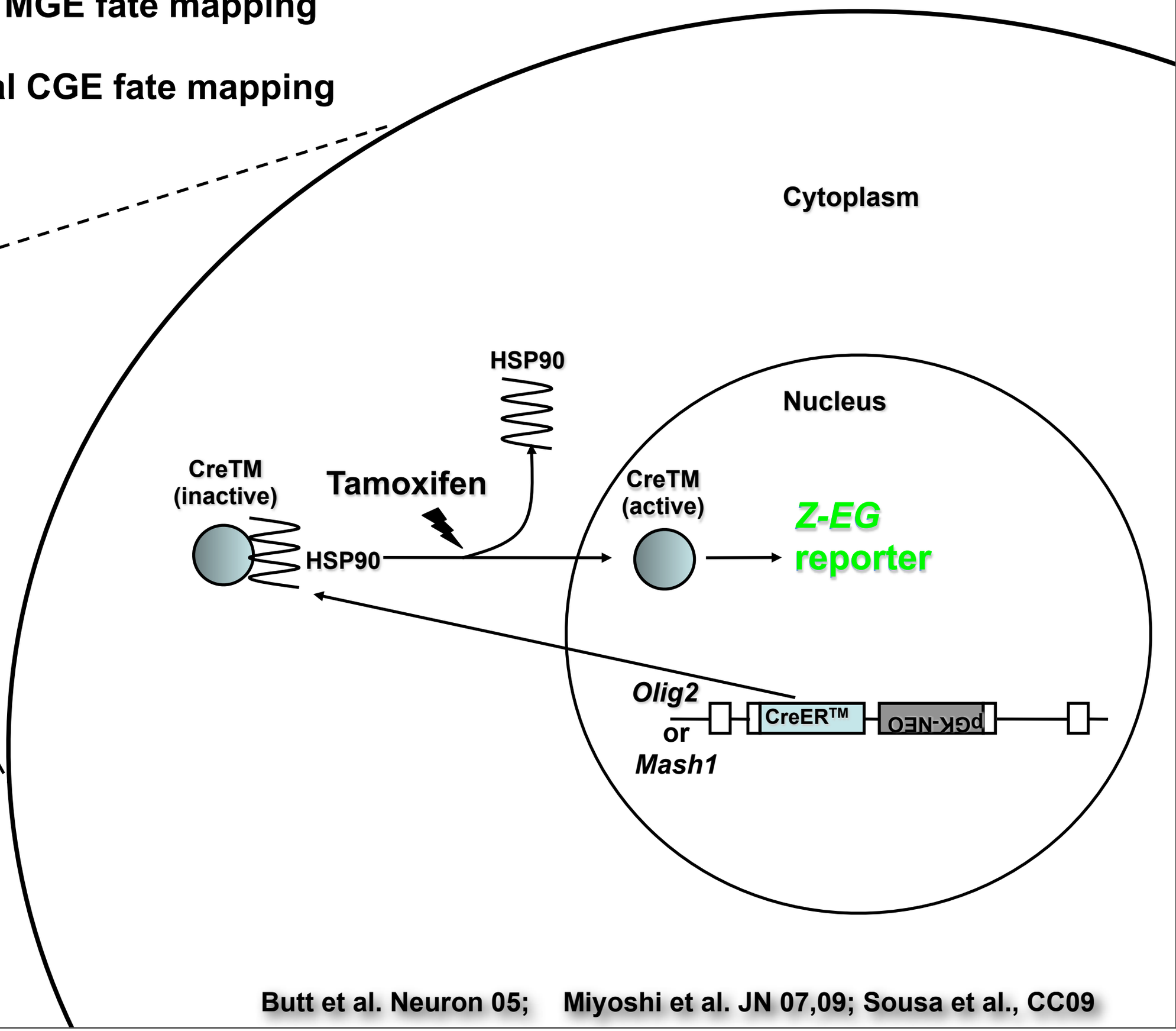

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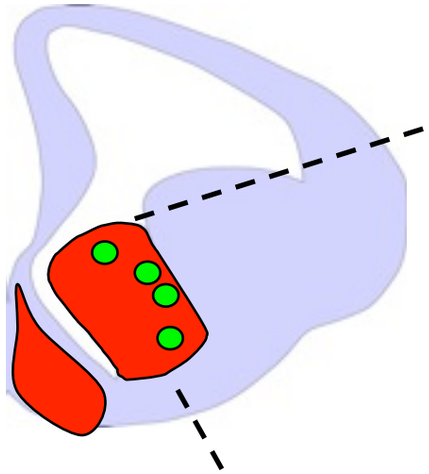

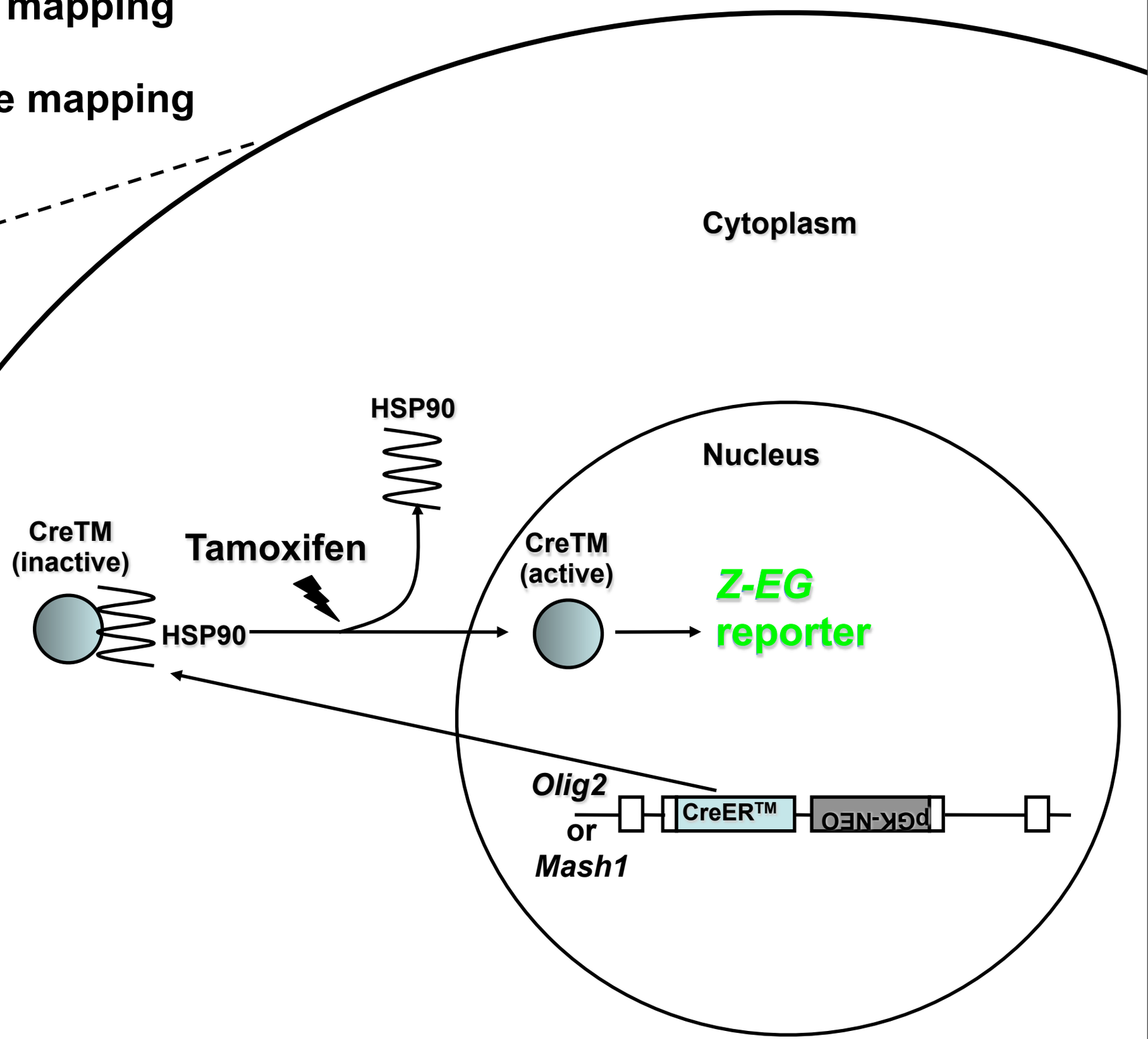

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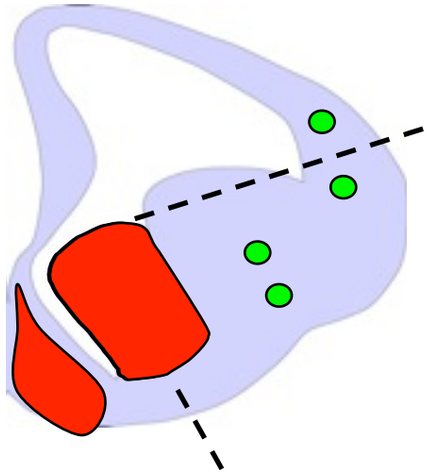

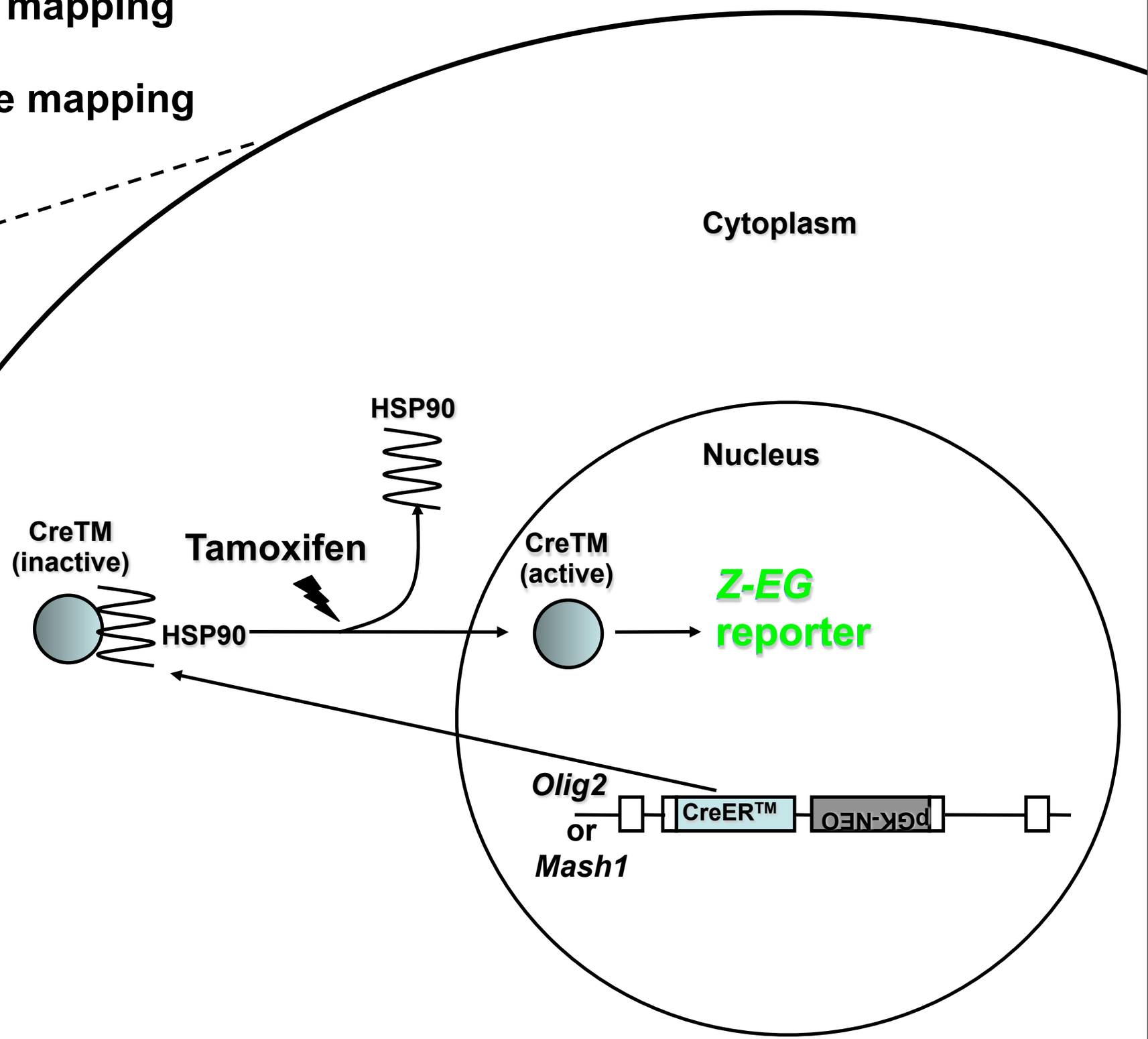

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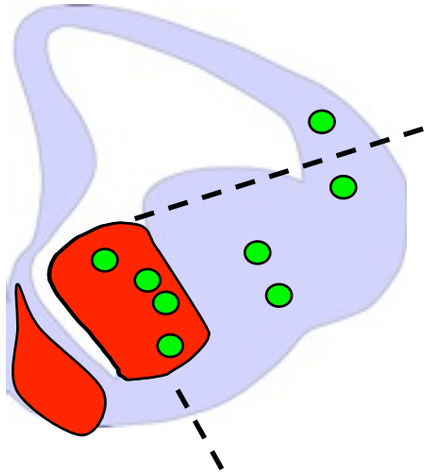

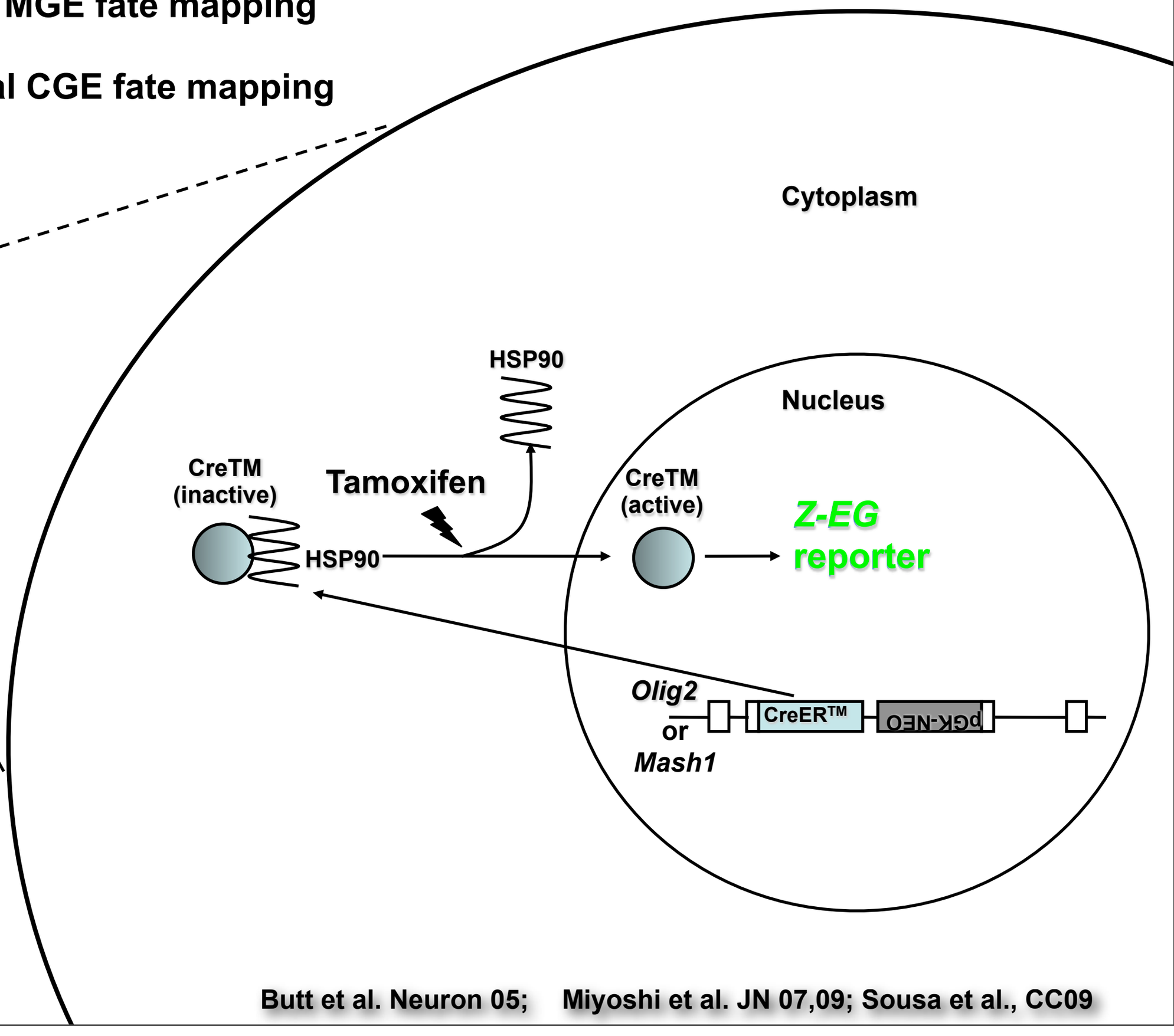

Butt et al. Neuron 05; Miyoshi et al. JN 07,09; Sousa et al., CC09

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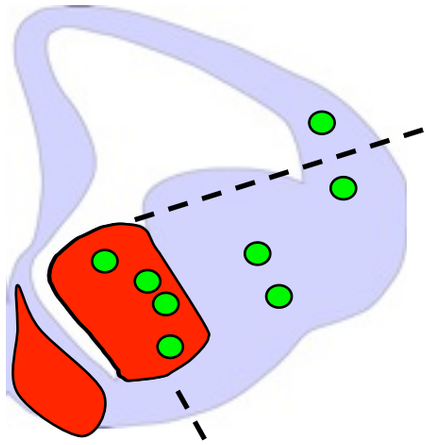
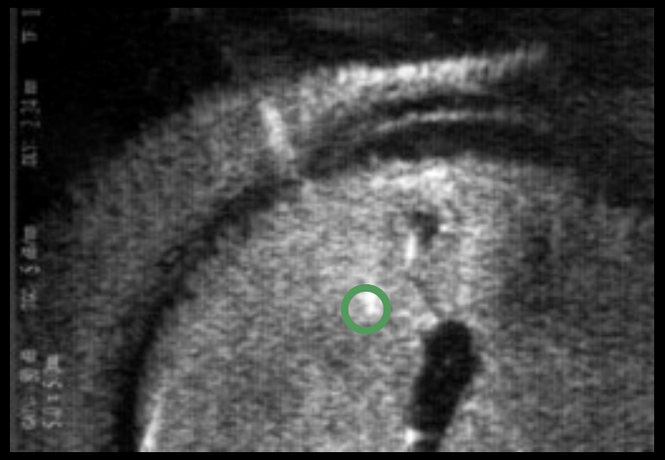


Butt et al. Neuron 05; Miyoshi et al. JN 07,09; Sousa et al., CC09

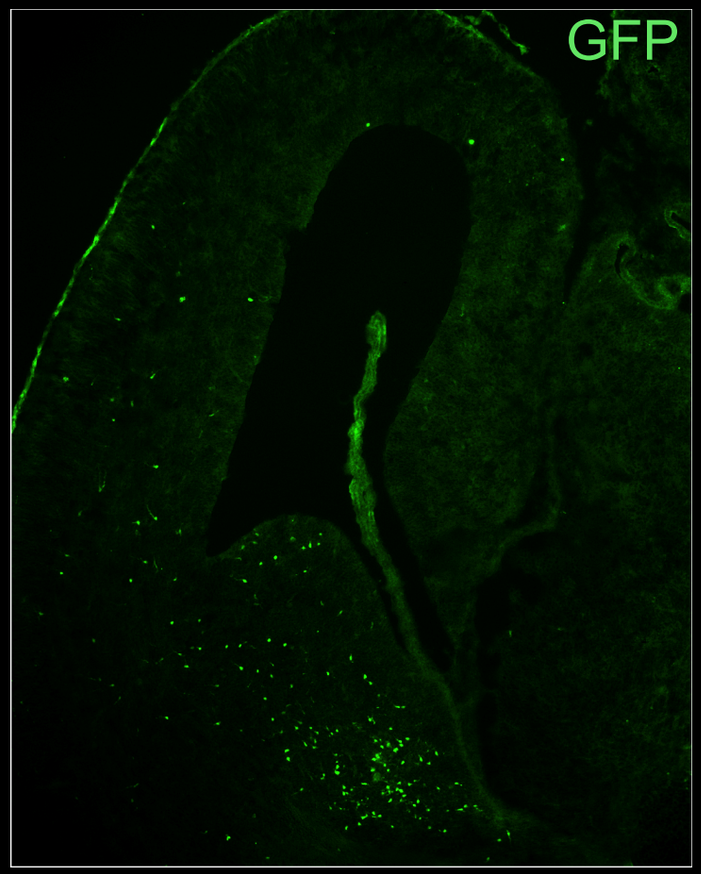
Short and long term MGE fate-mapping

E13.5

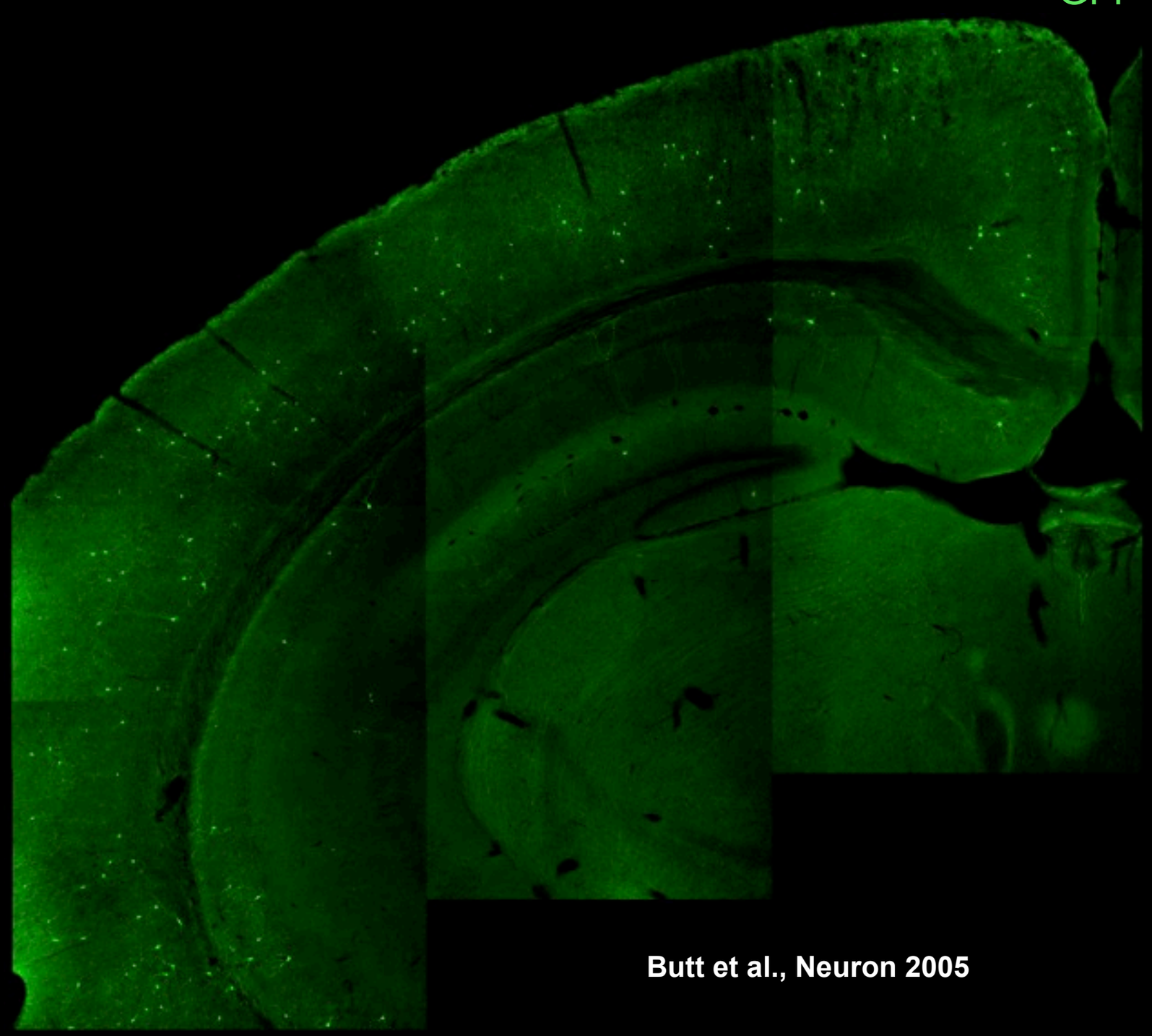
UBM



E14.5

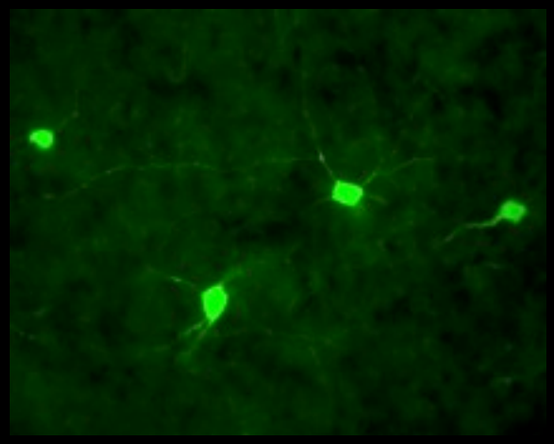


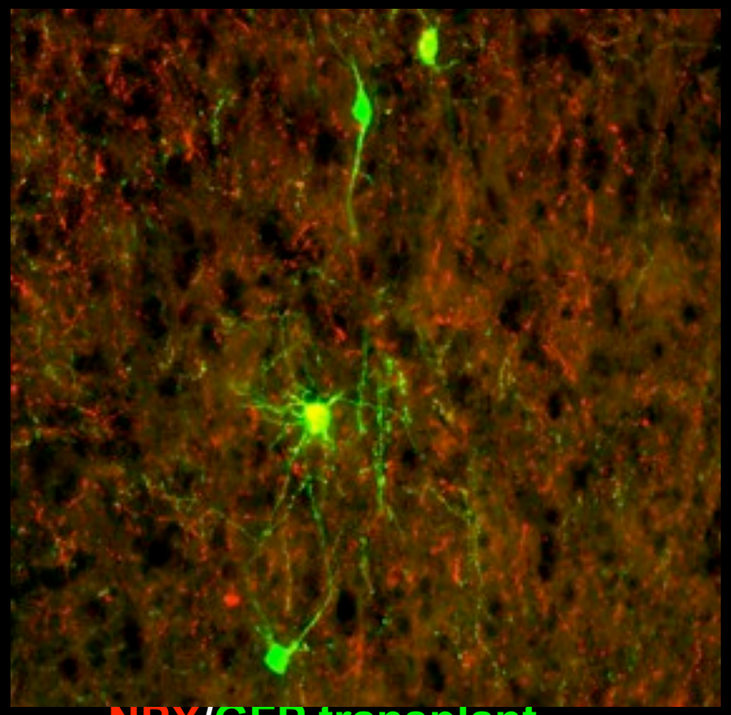
P21



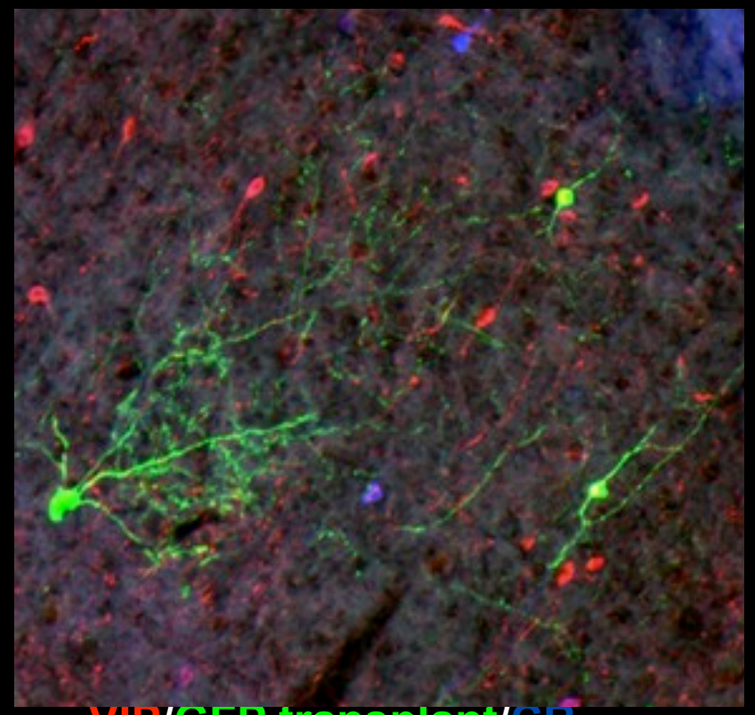
Butt et al., Neuron 2005

Complementary assays for interneuron subtype

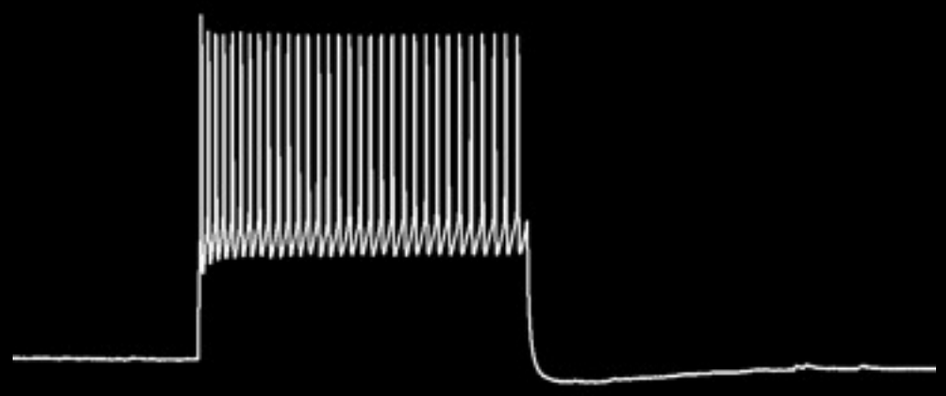




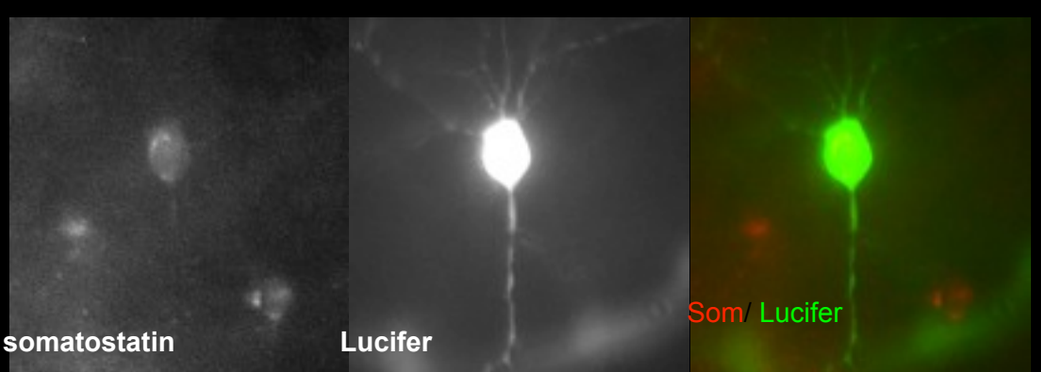
NPY/GFP transplant

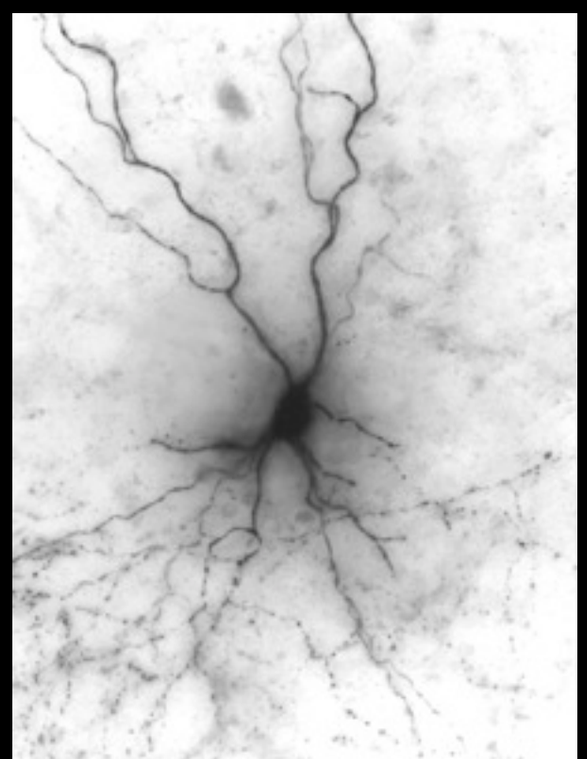


VIP/GFP transplant/CR



Fast-spiking electrophysiological profile



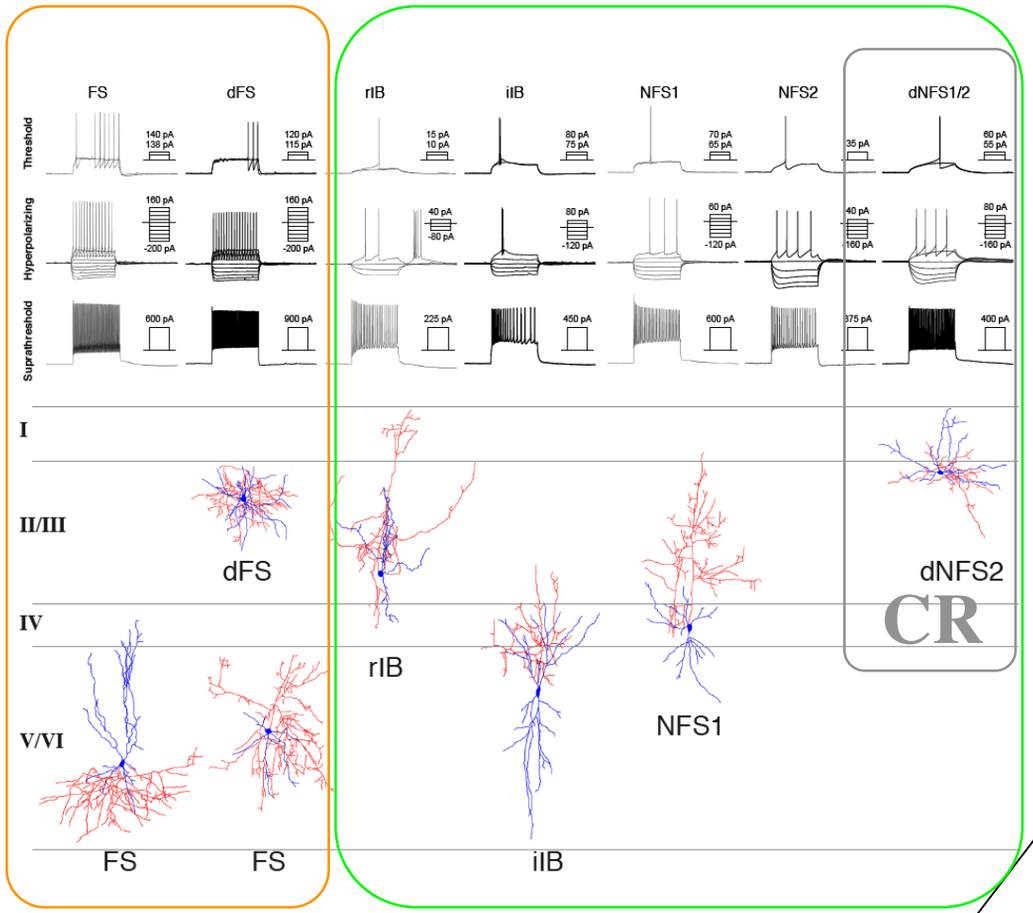


Basket cell morphology

Cortical interneuron subtypes derived from the MGE and CGE

PV

SST



MGE-derived

Butt et al. Neuron 05

Miyoshi et al. JN 07

Sousa et al., CC 09

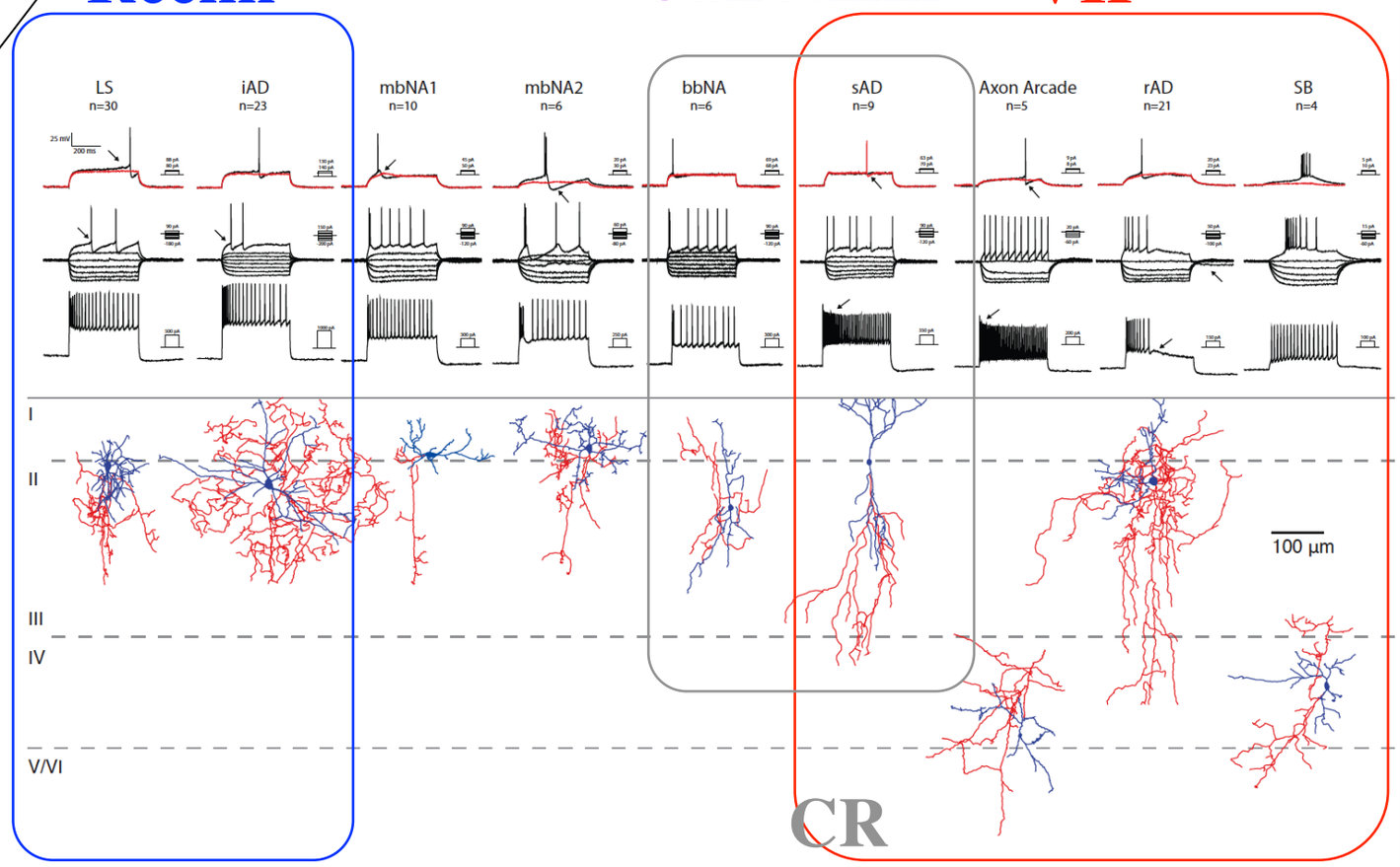
Miyoshi et al. JN 10

CGE-derived

Reelin

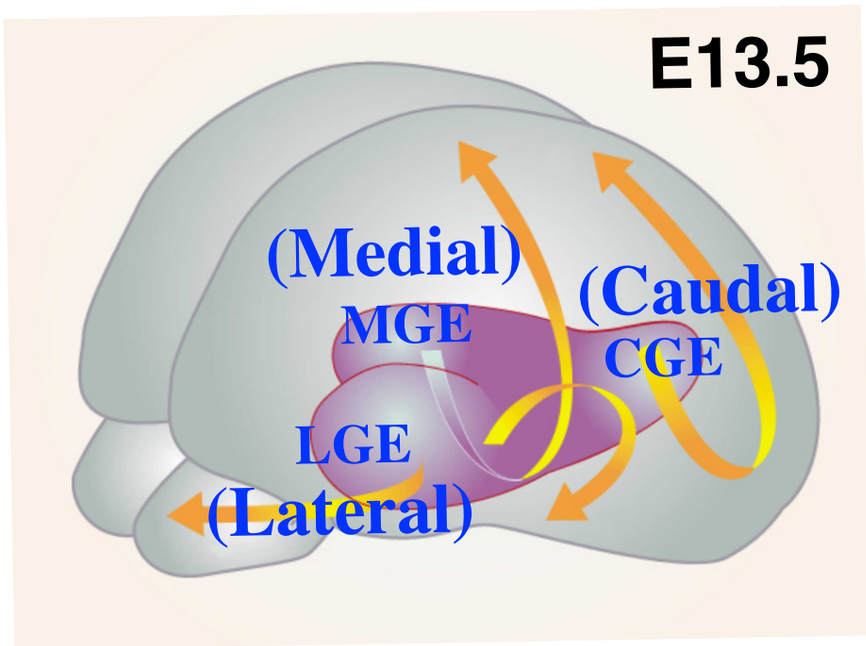
Calretinin

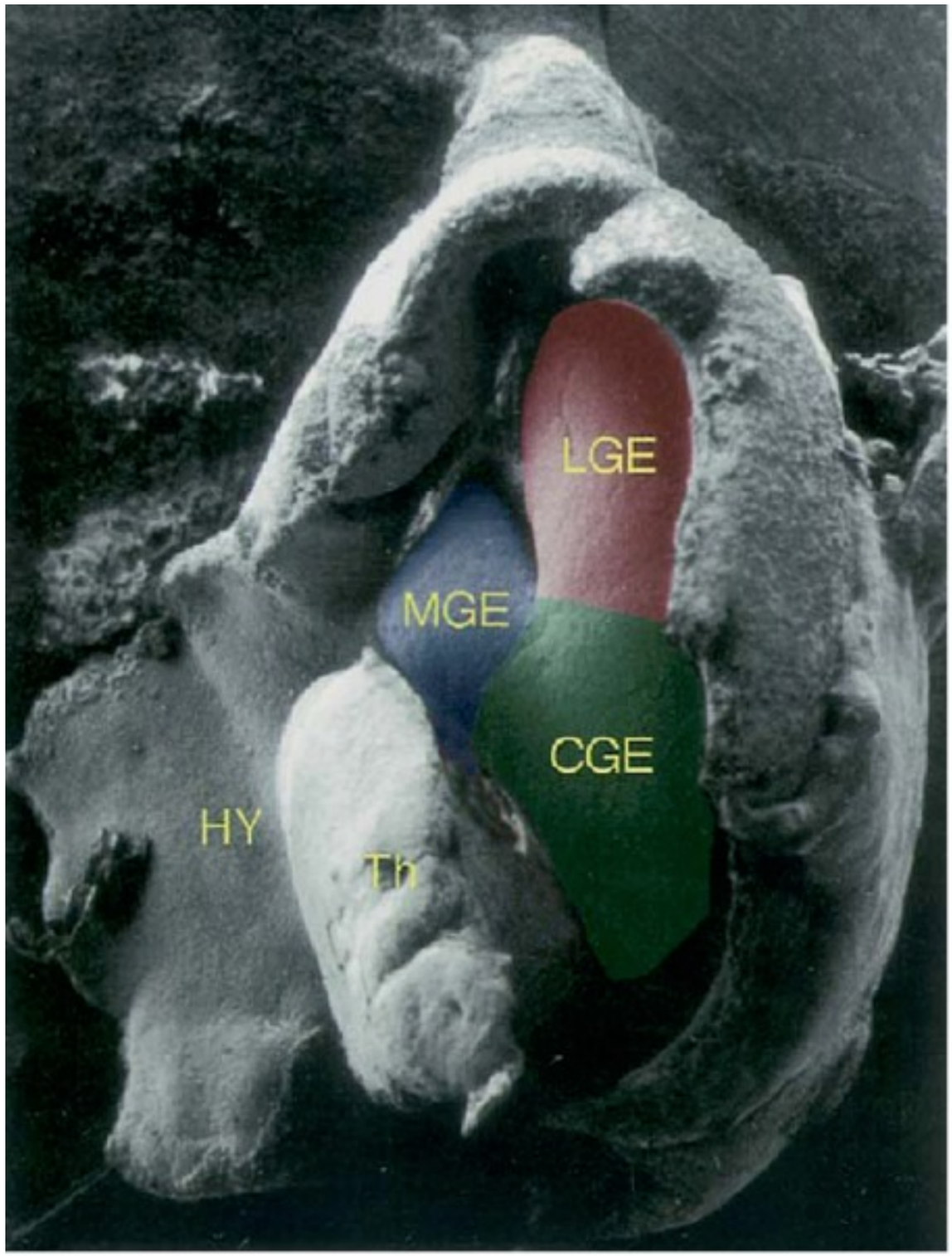
VIP



Neocortical GABAergic interneurons are ventrally derived

Interneurons are ventrally derived





(Aizawa et al., 2004)

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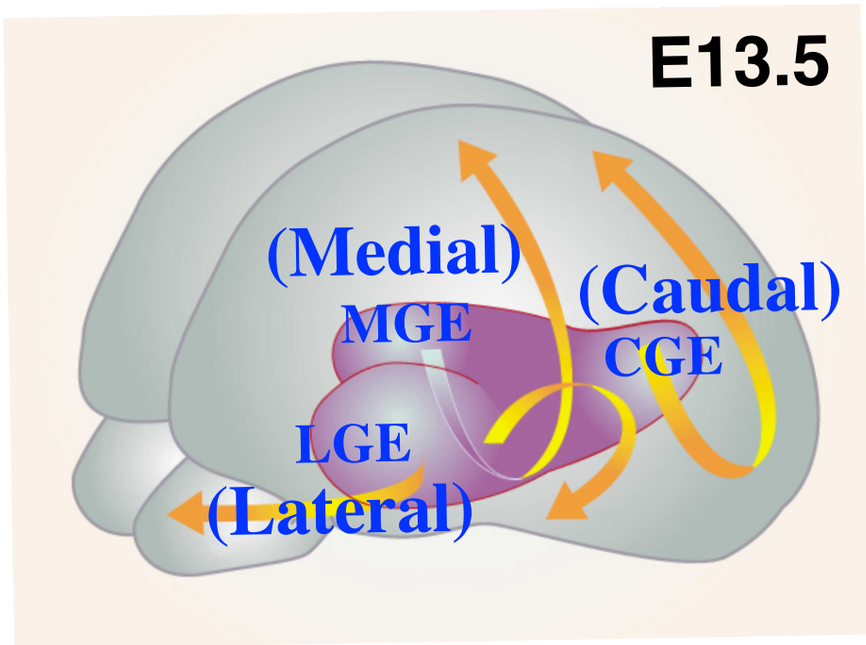
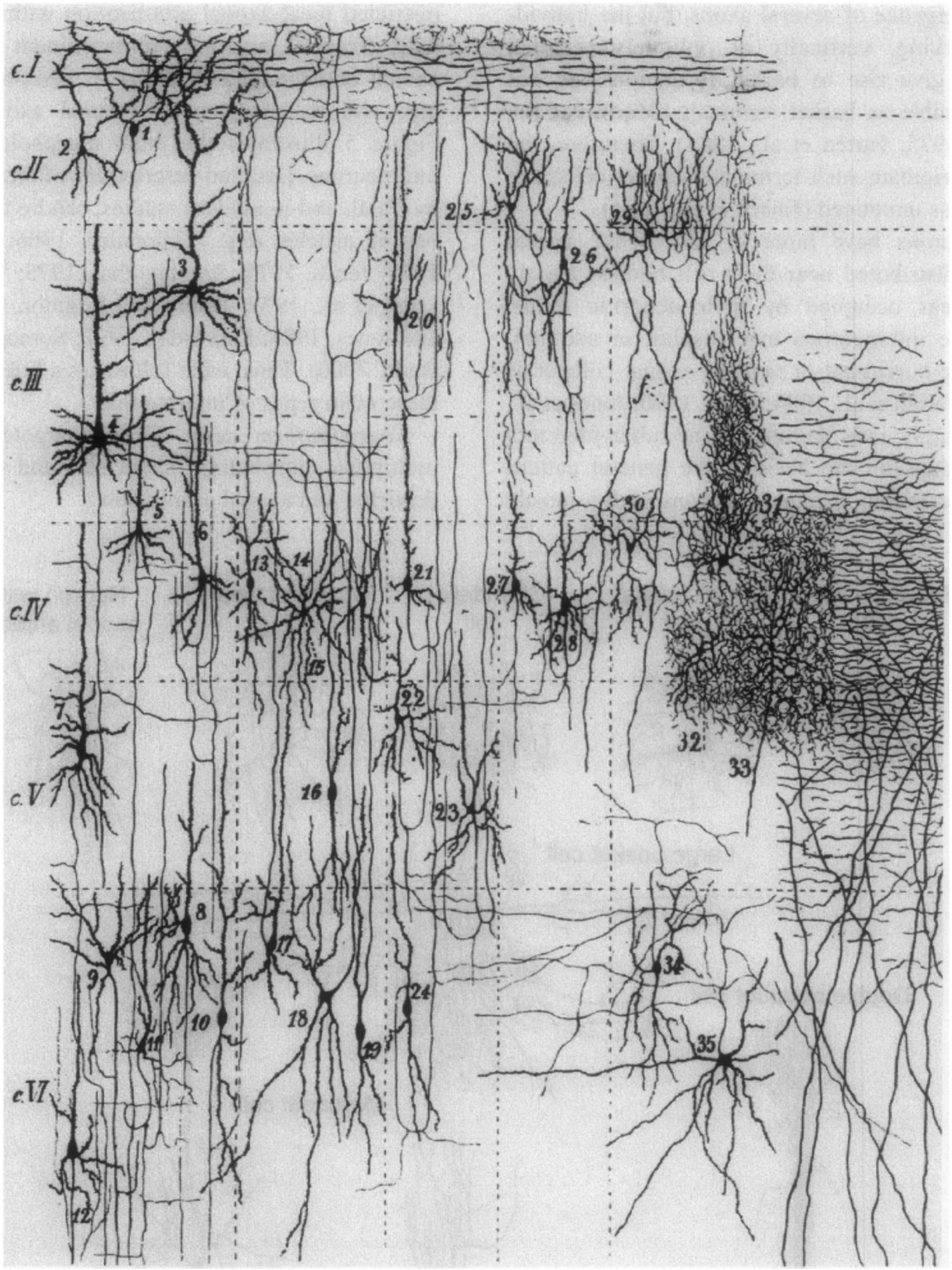
Interneurons are ventrally derived





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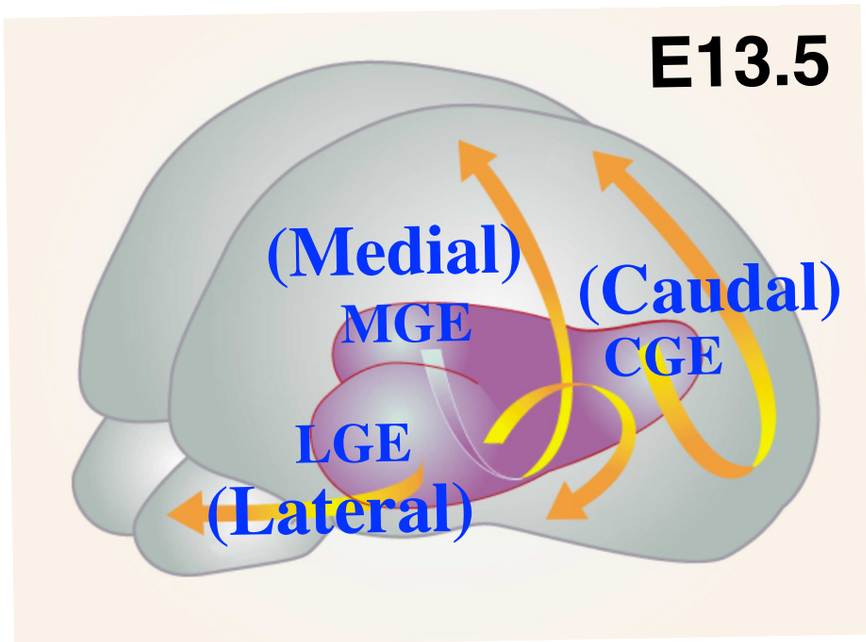
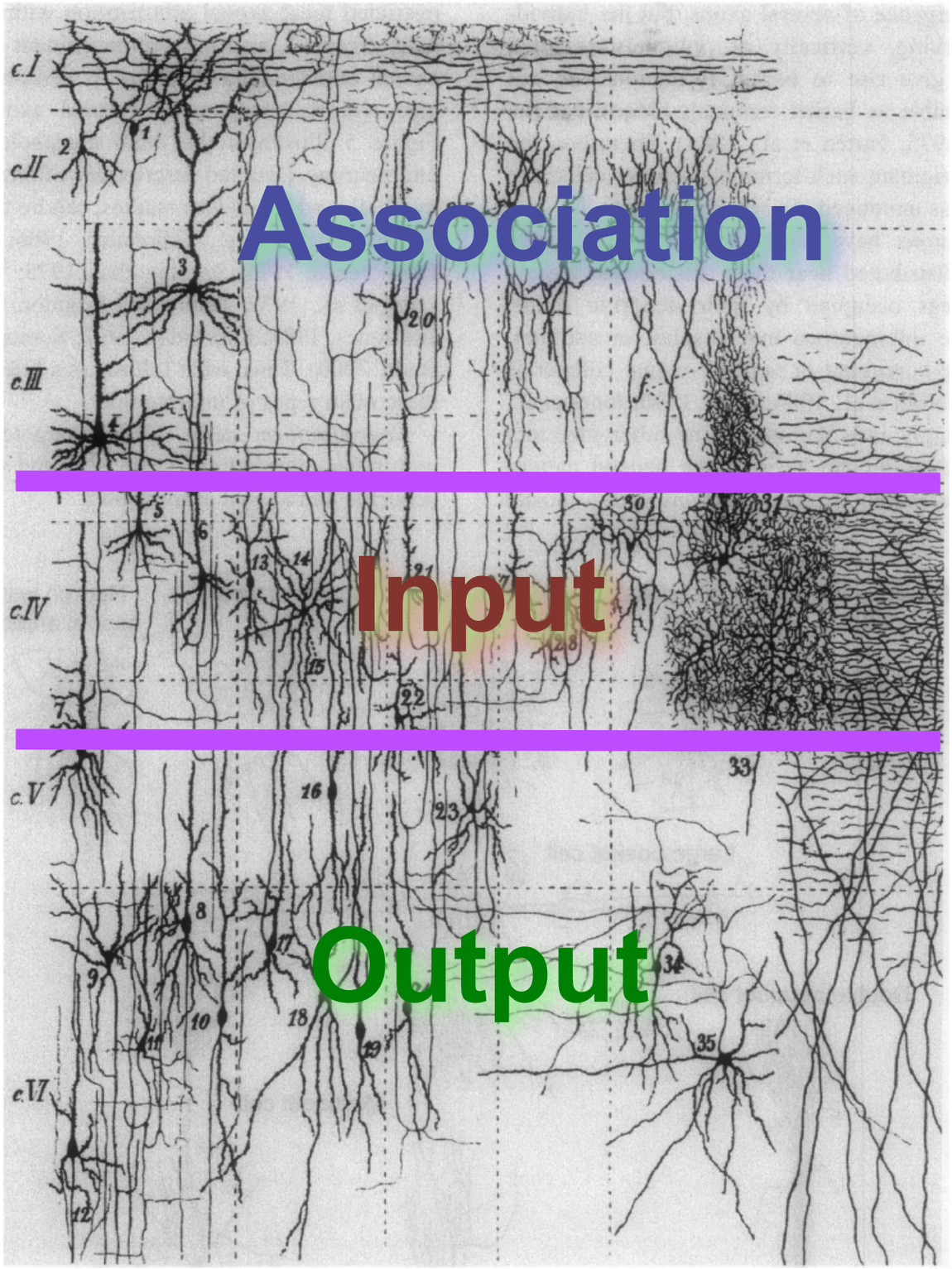
Interneurons are ventrally derived





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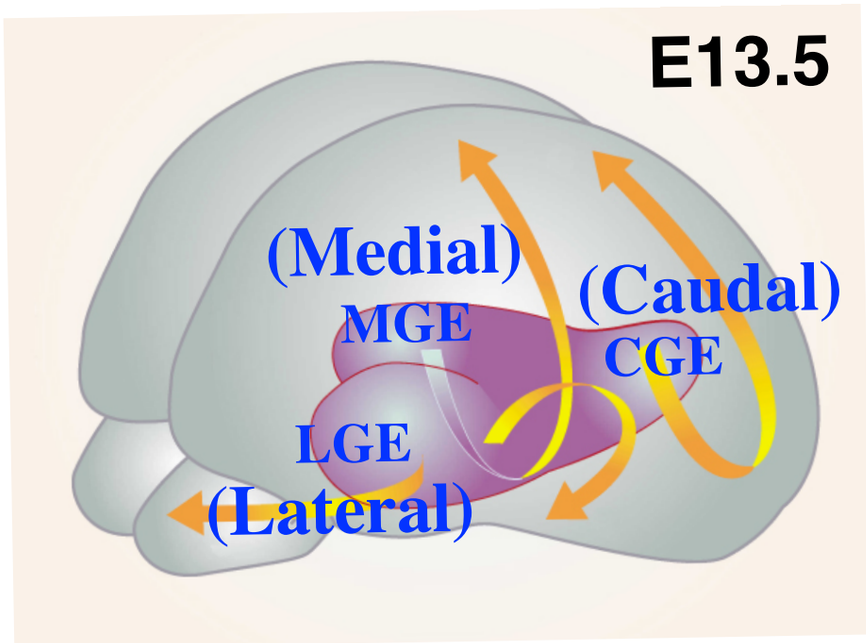

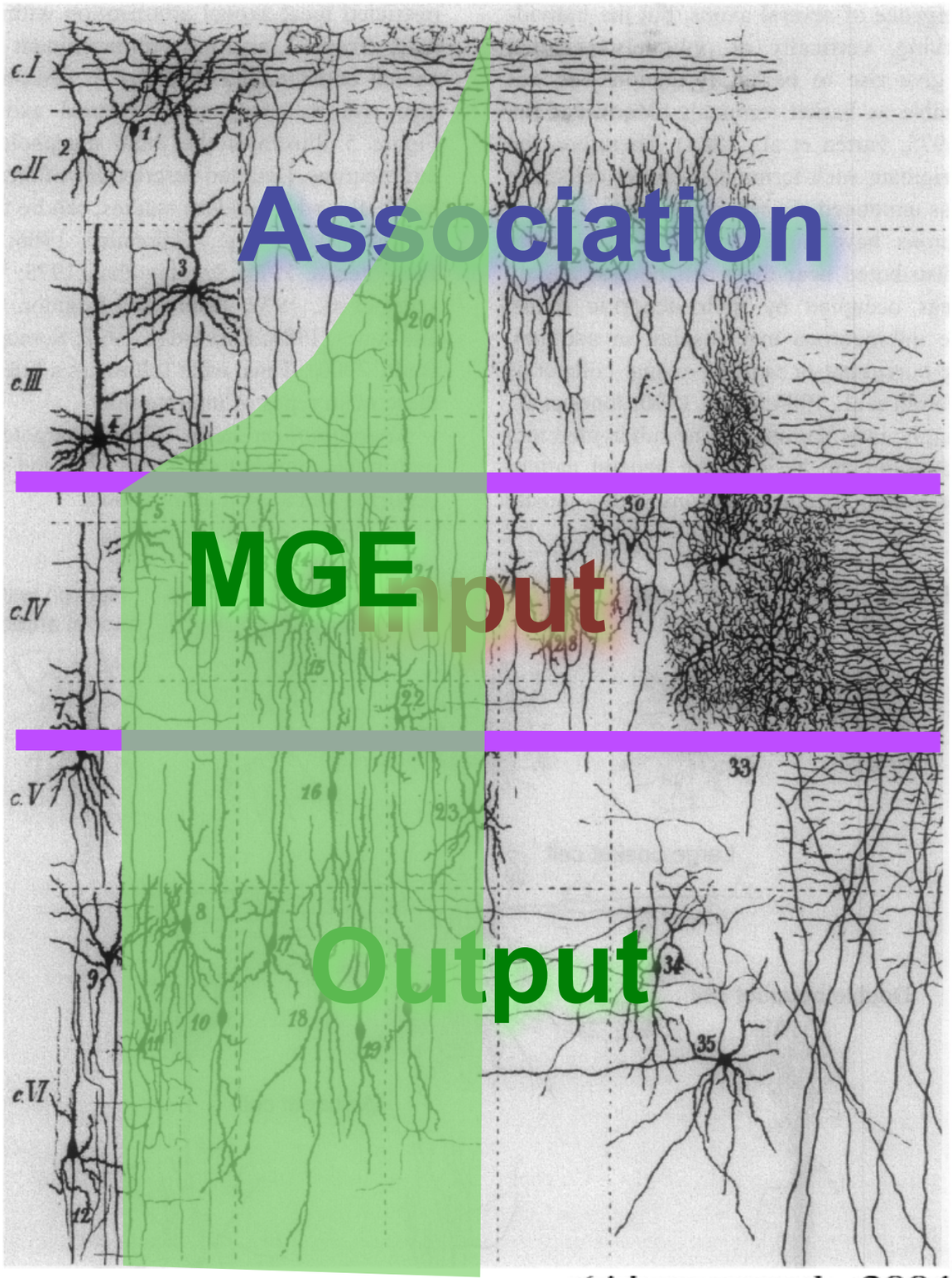

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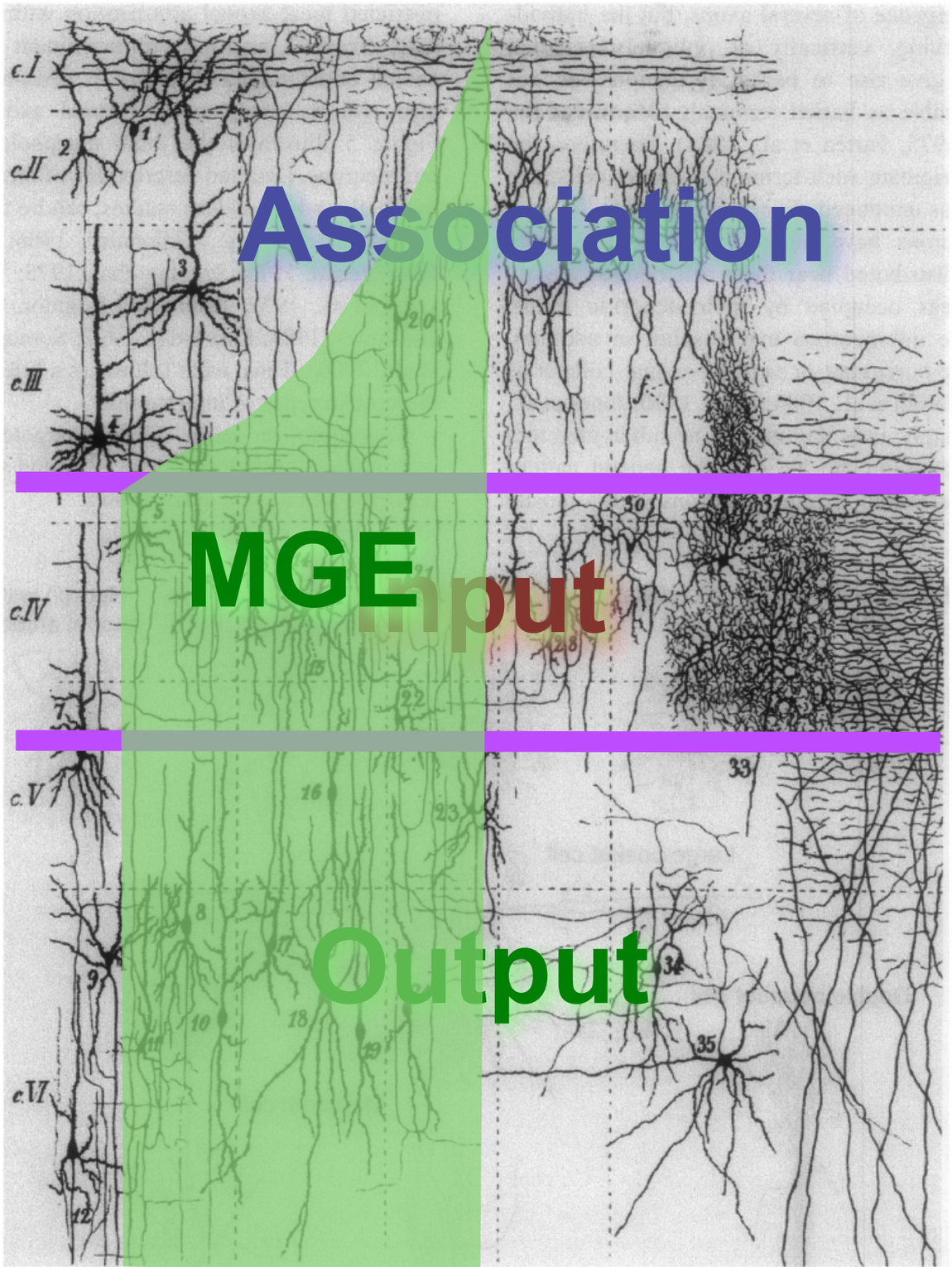

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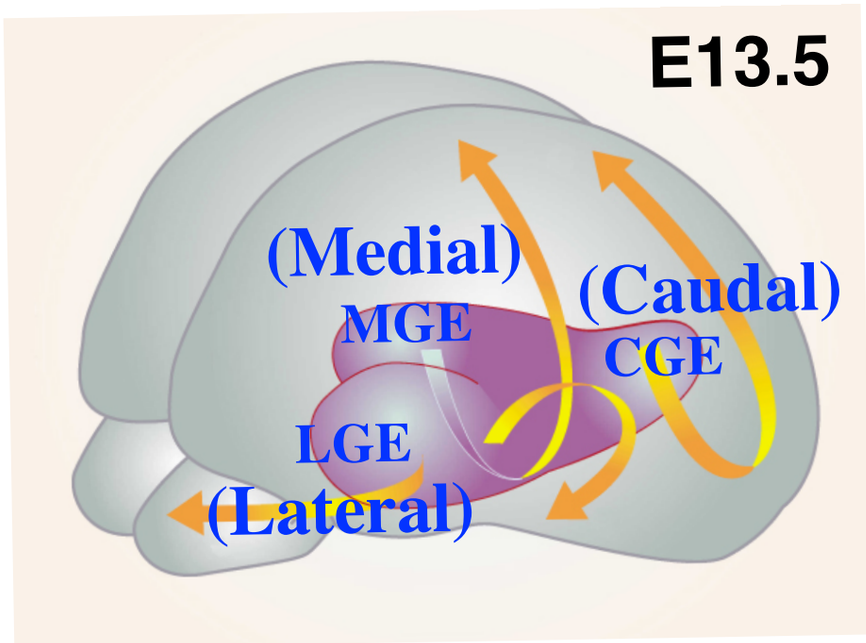

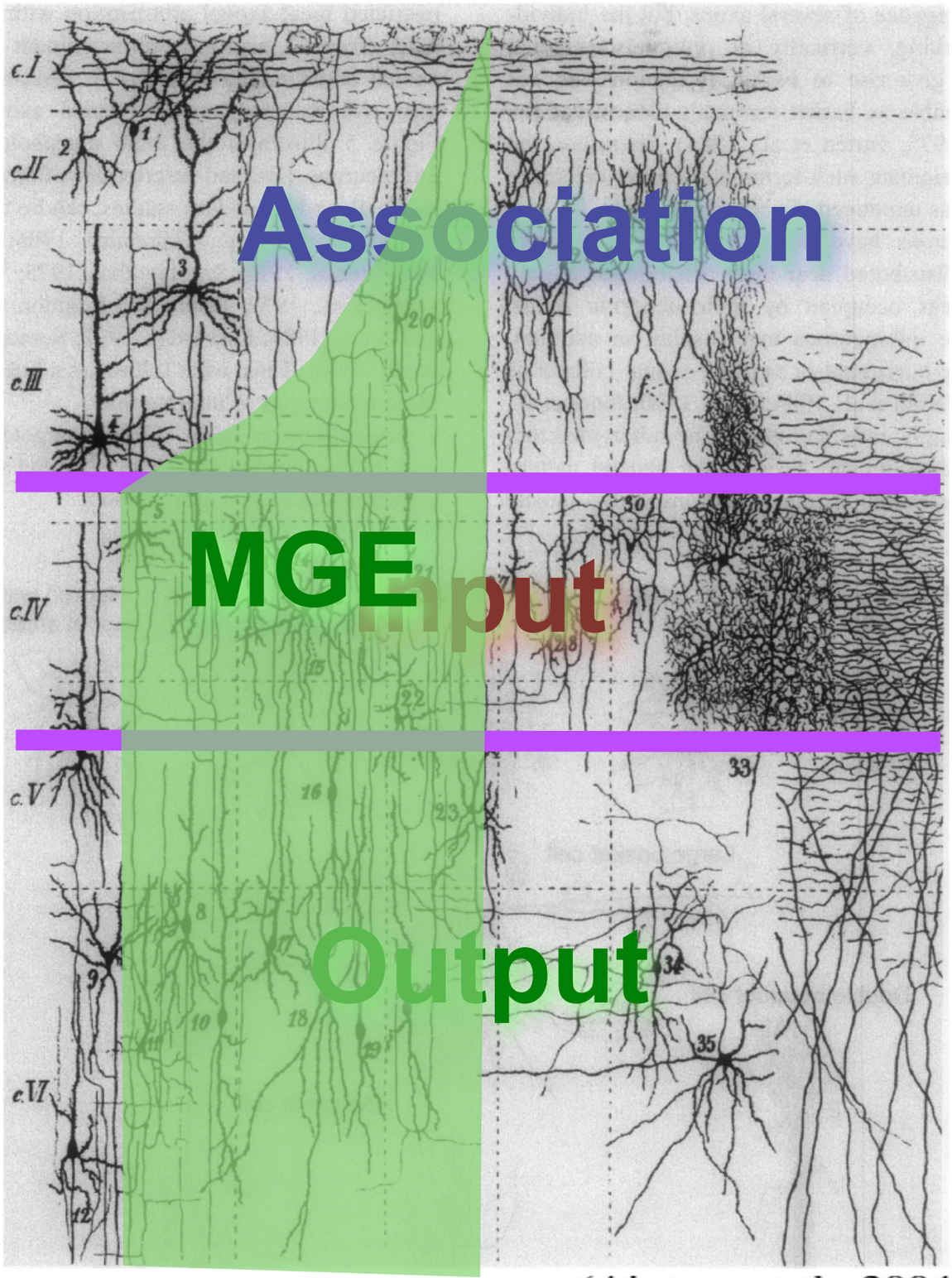

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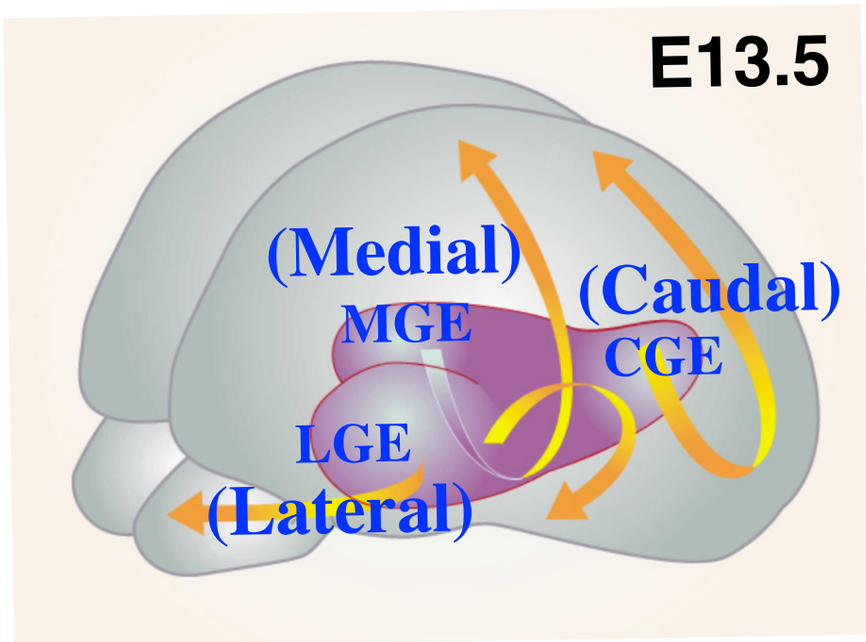

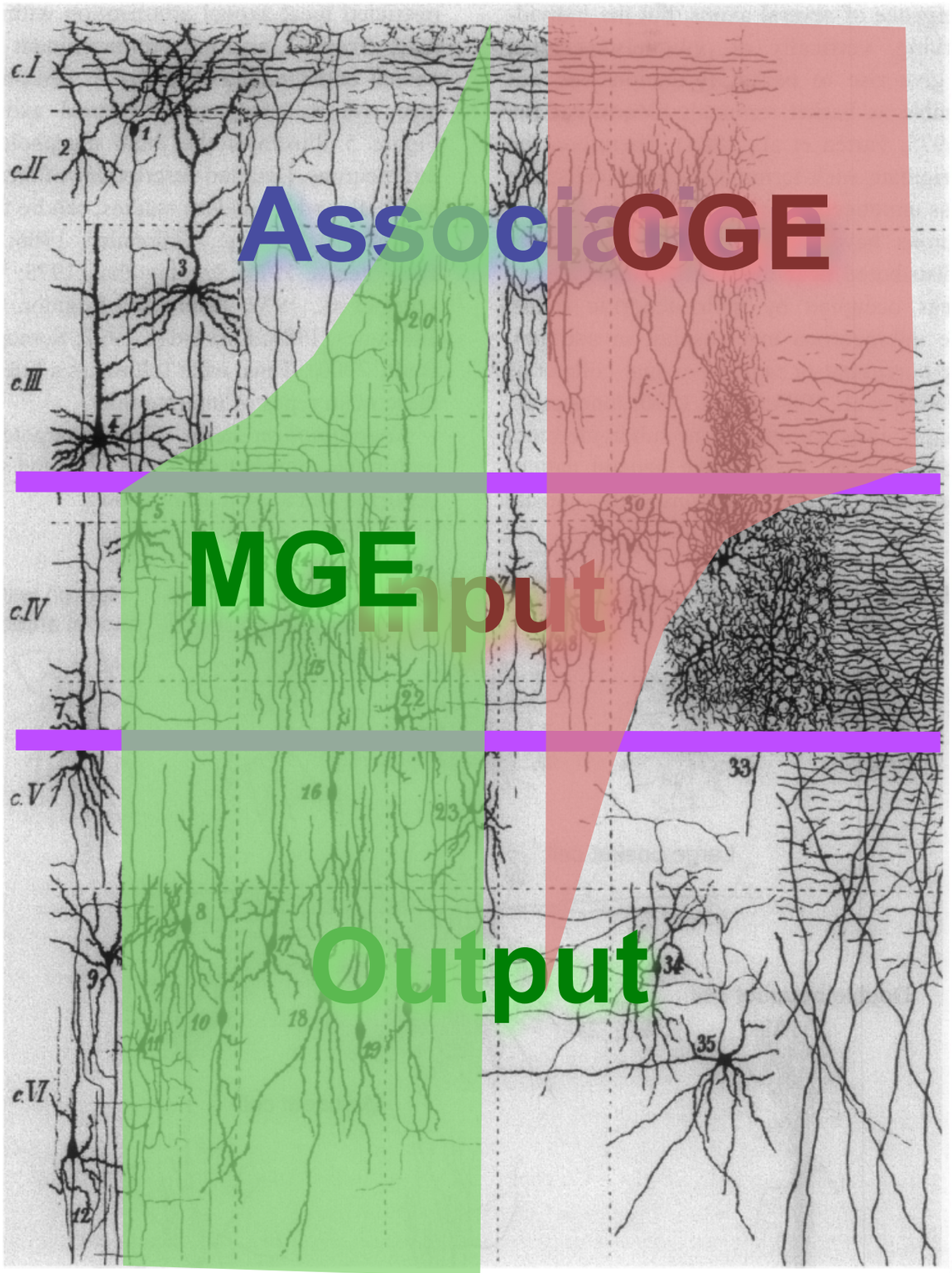

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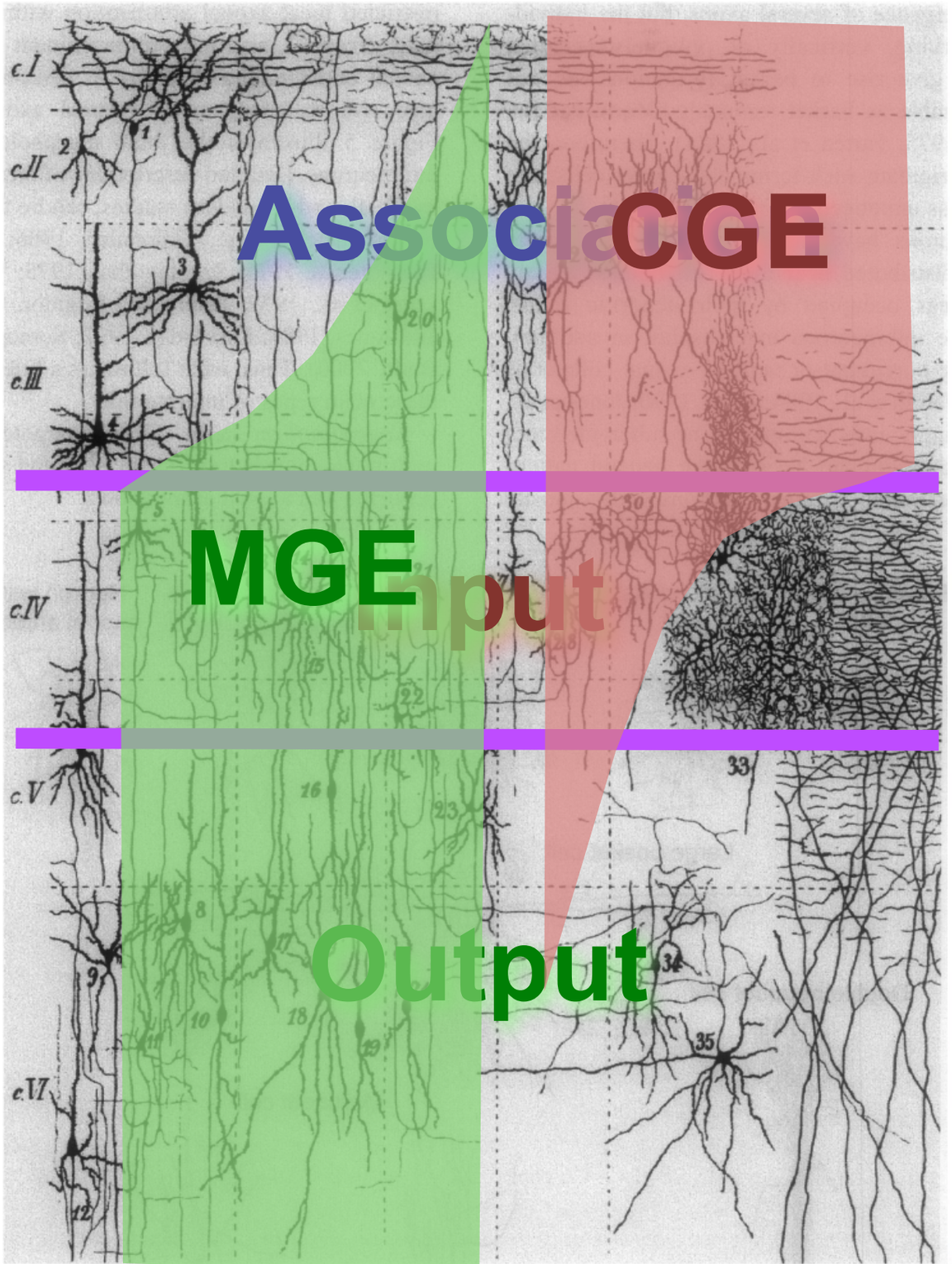

(Aizawa et al., 2004)

A cladistic approach to classifying cortical interneurons

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GABAergic Neurons

A cladistic approach to classifying cortical interneurons

- GABAergic Neurons
  - Projection
  - Interneuron

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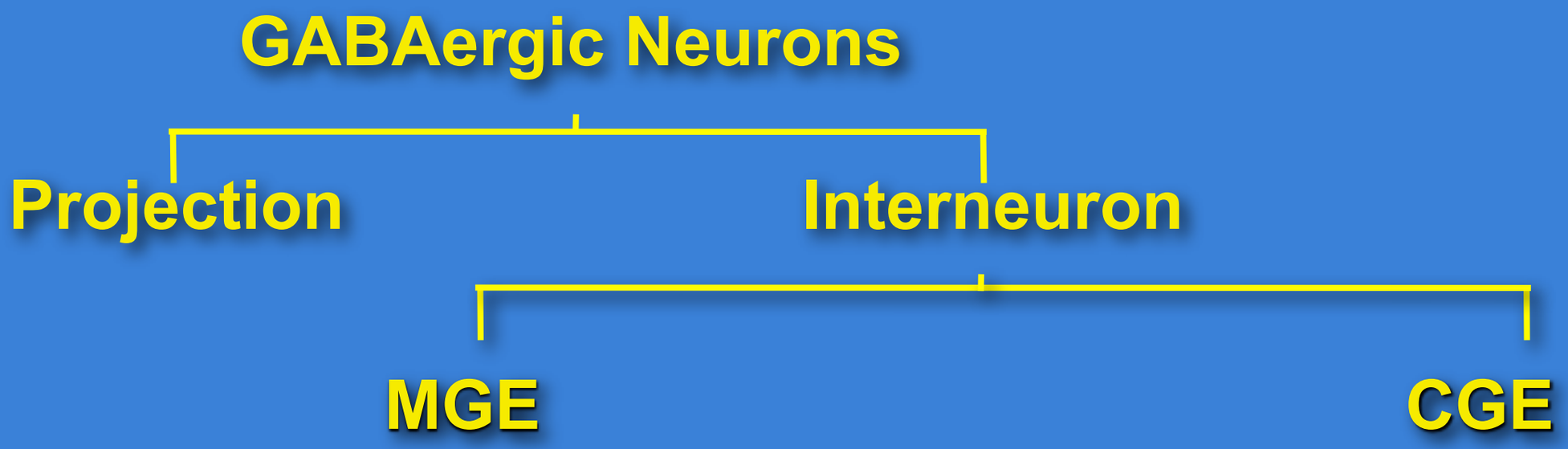

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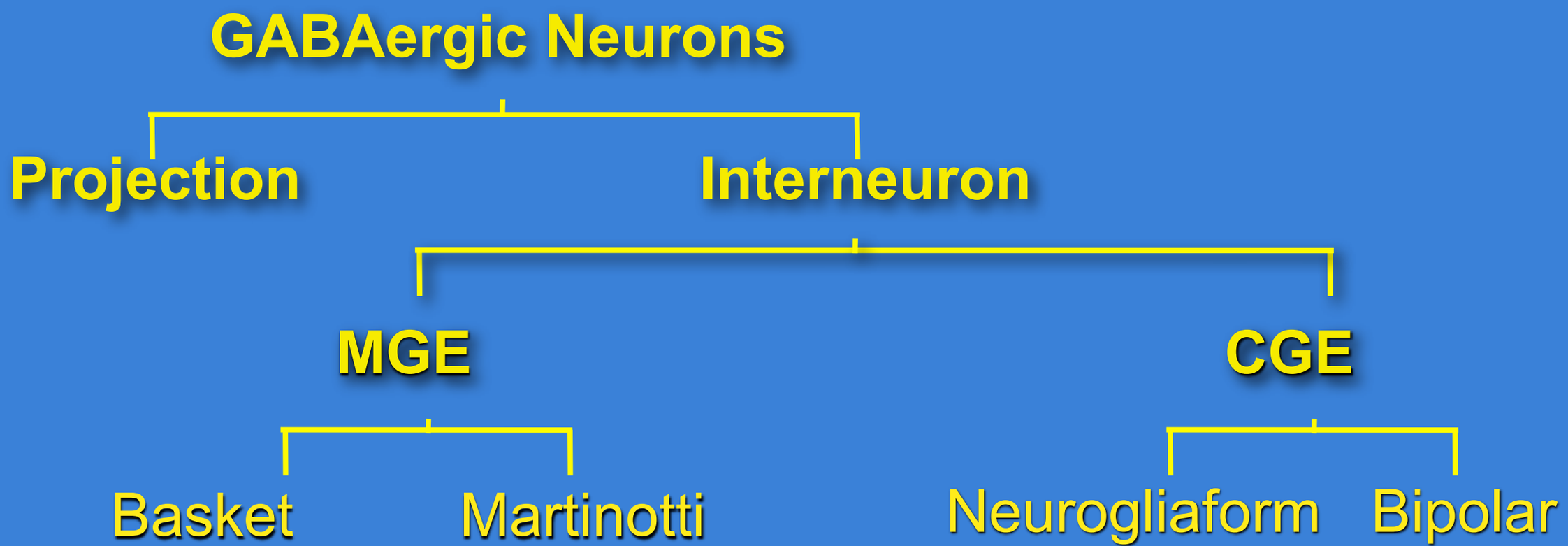

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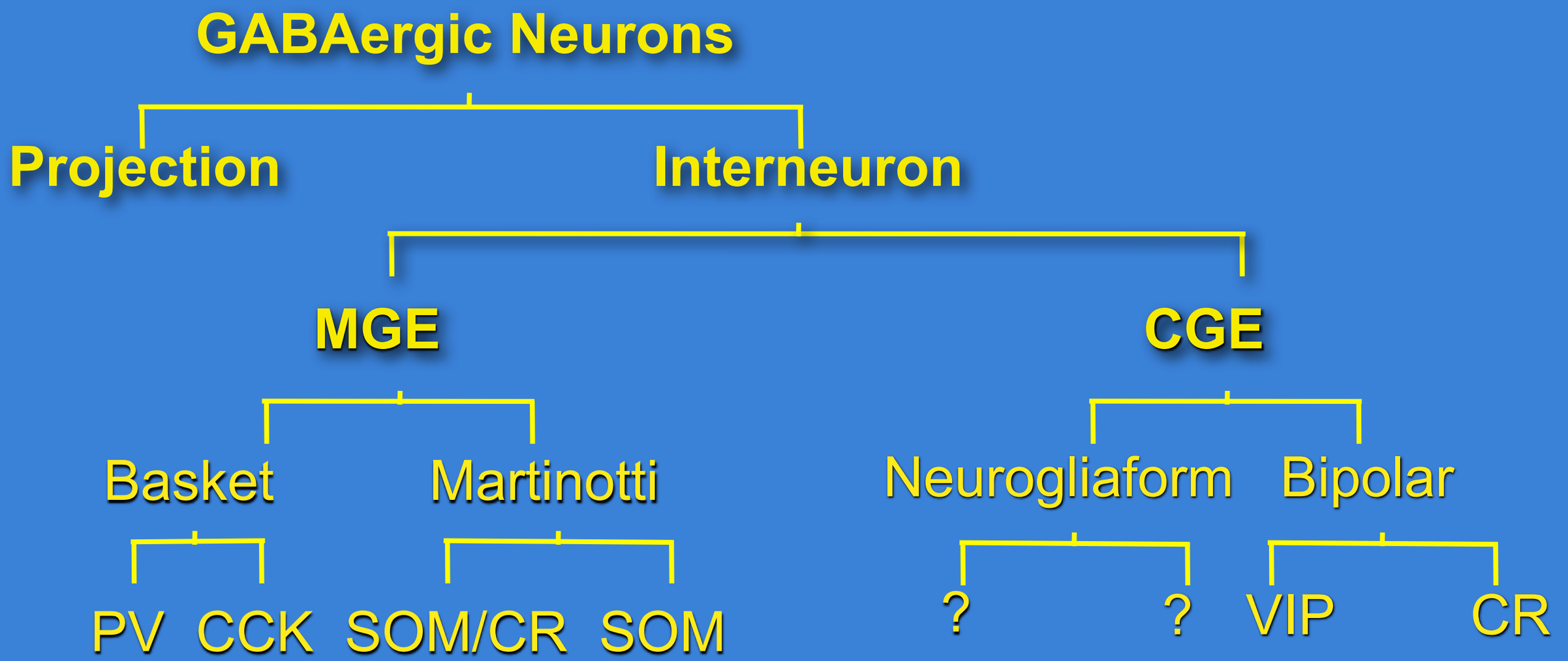

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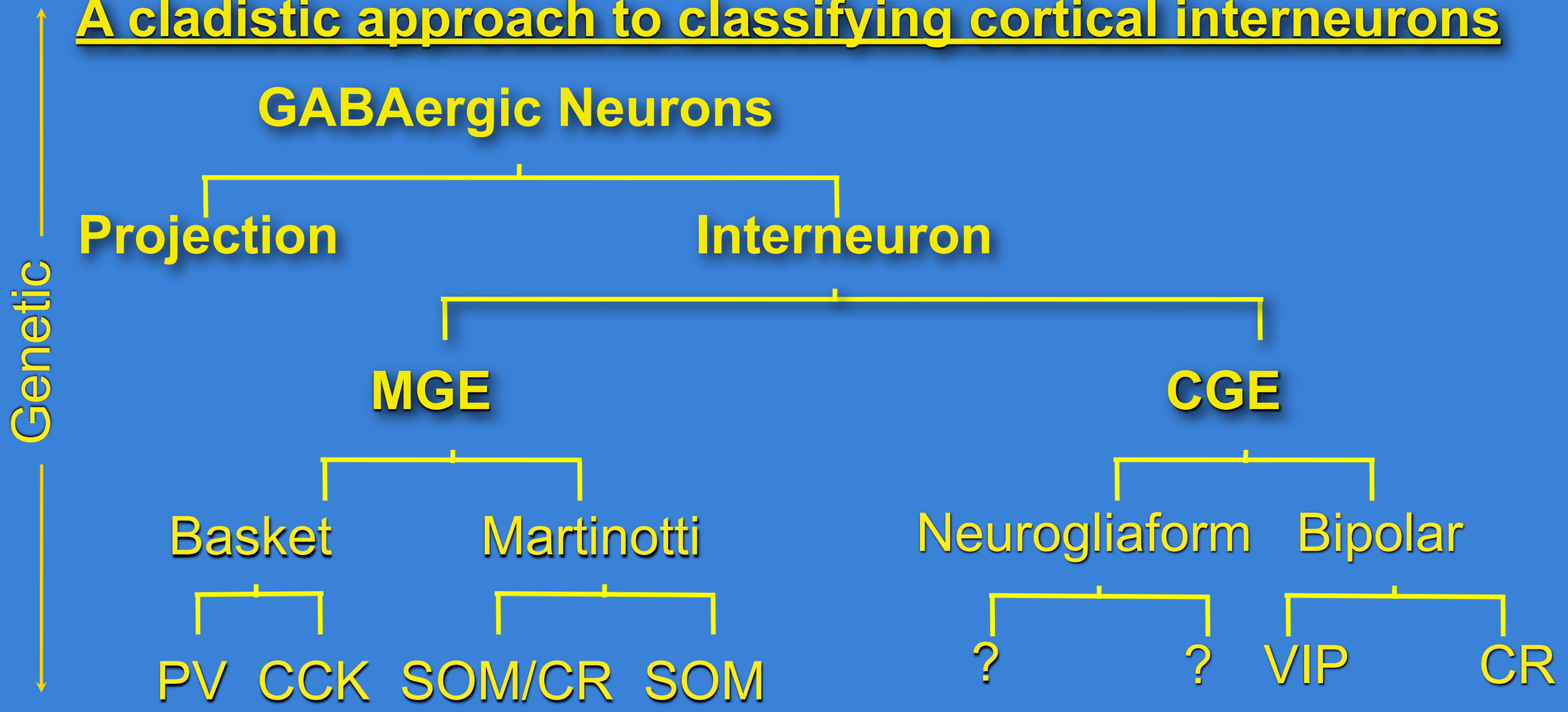

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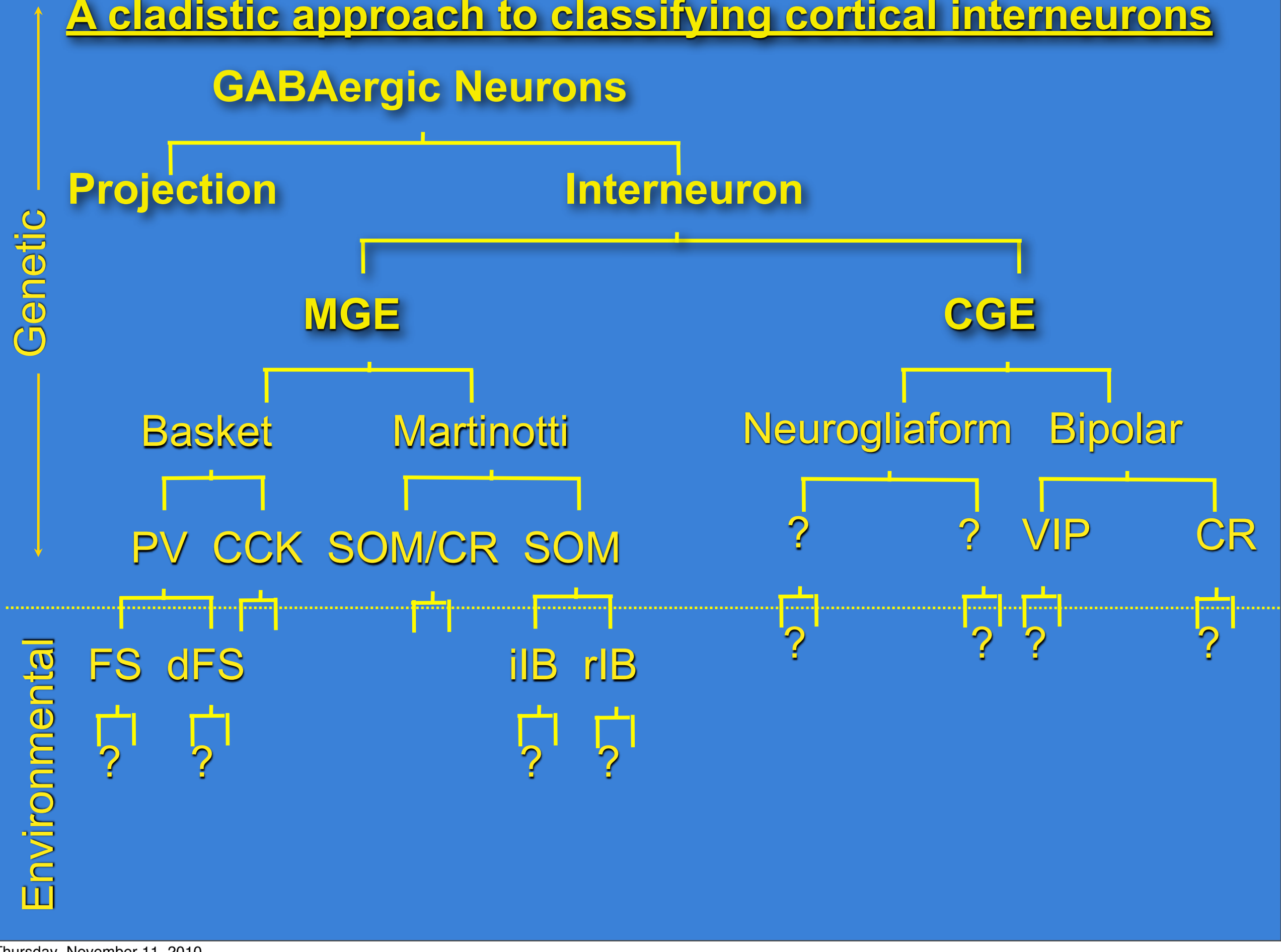

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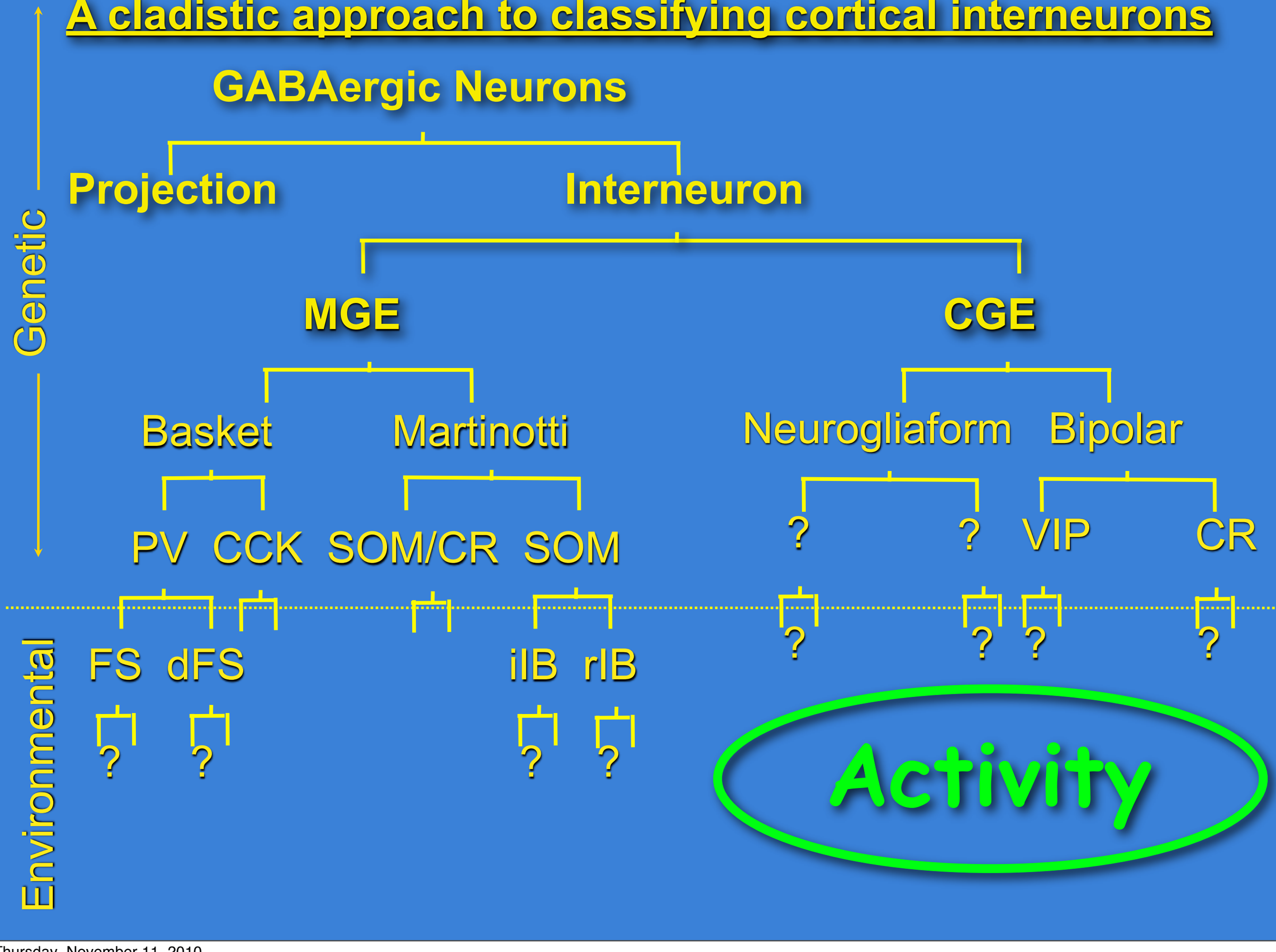

MGE

CGE

MGE

CGE

Nkx2.1

John Rubenstein, Butt et al., Neuron 2008

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↓

Lhx6

Vassilis Pachnis, Stewart Anderson

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Azid et al. (Macklis Lab) Nature Neuroscience 2009

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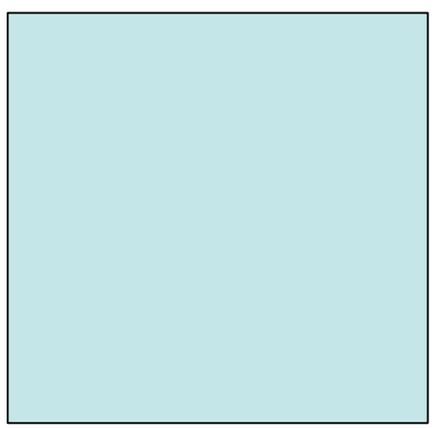
All Interneurons



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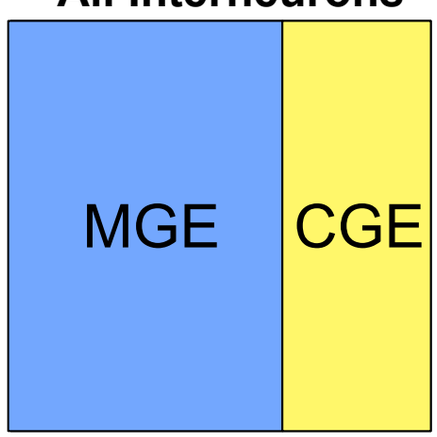

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All Interneurons

Basket Cells	NGF Cells
	bipolar Cells
Martinotti Cells	multi-polar Cells

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???

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Contextual Iterative Analysis

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As applied to cortical interneurons:

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- Genes expressed in adult cortical interneurons (AIBS)

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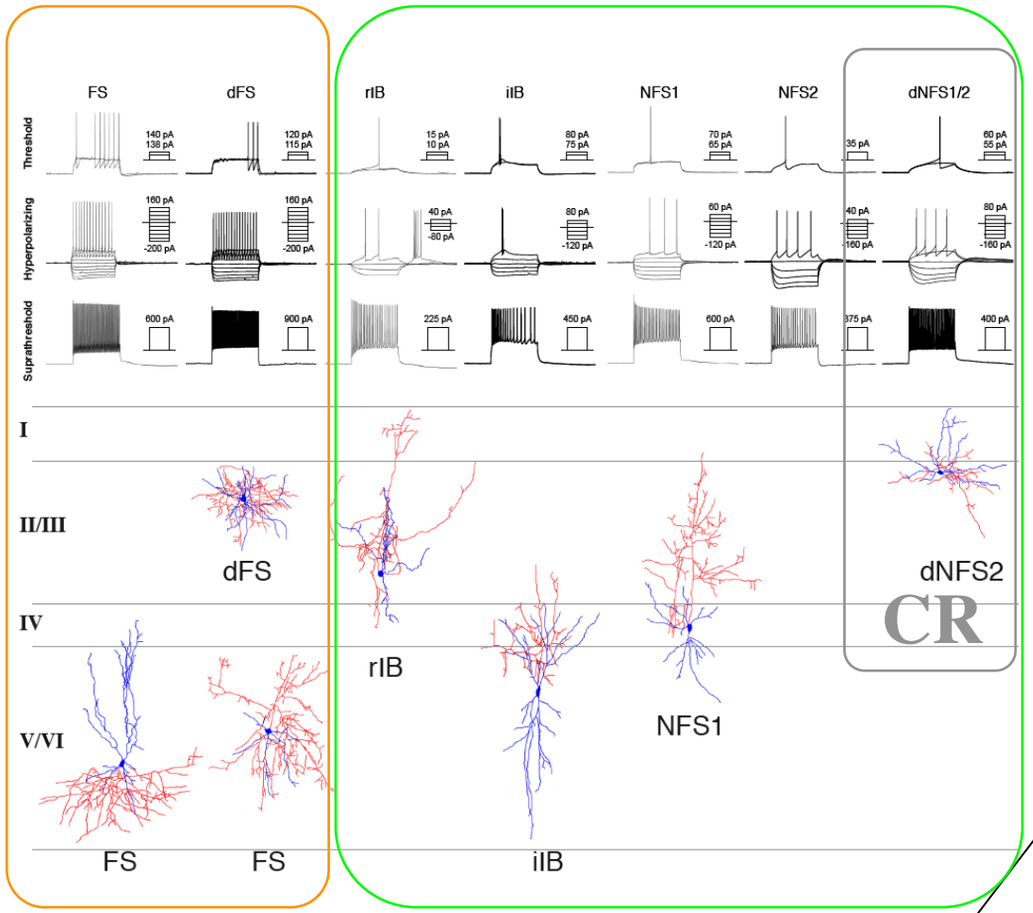
- Genes expressed in CGE-derived cortical interneurons.
- Genes initiated in interneurons upon integrating into the cortical plate

Cortical interneuron subtypes derived from the MGE and CGE

PV

SST



MGE-derived

Nery et al. NN 02

Butt et al. Neuron 05

Miyoshi et al. JN 07

Sousa et al., CC 09

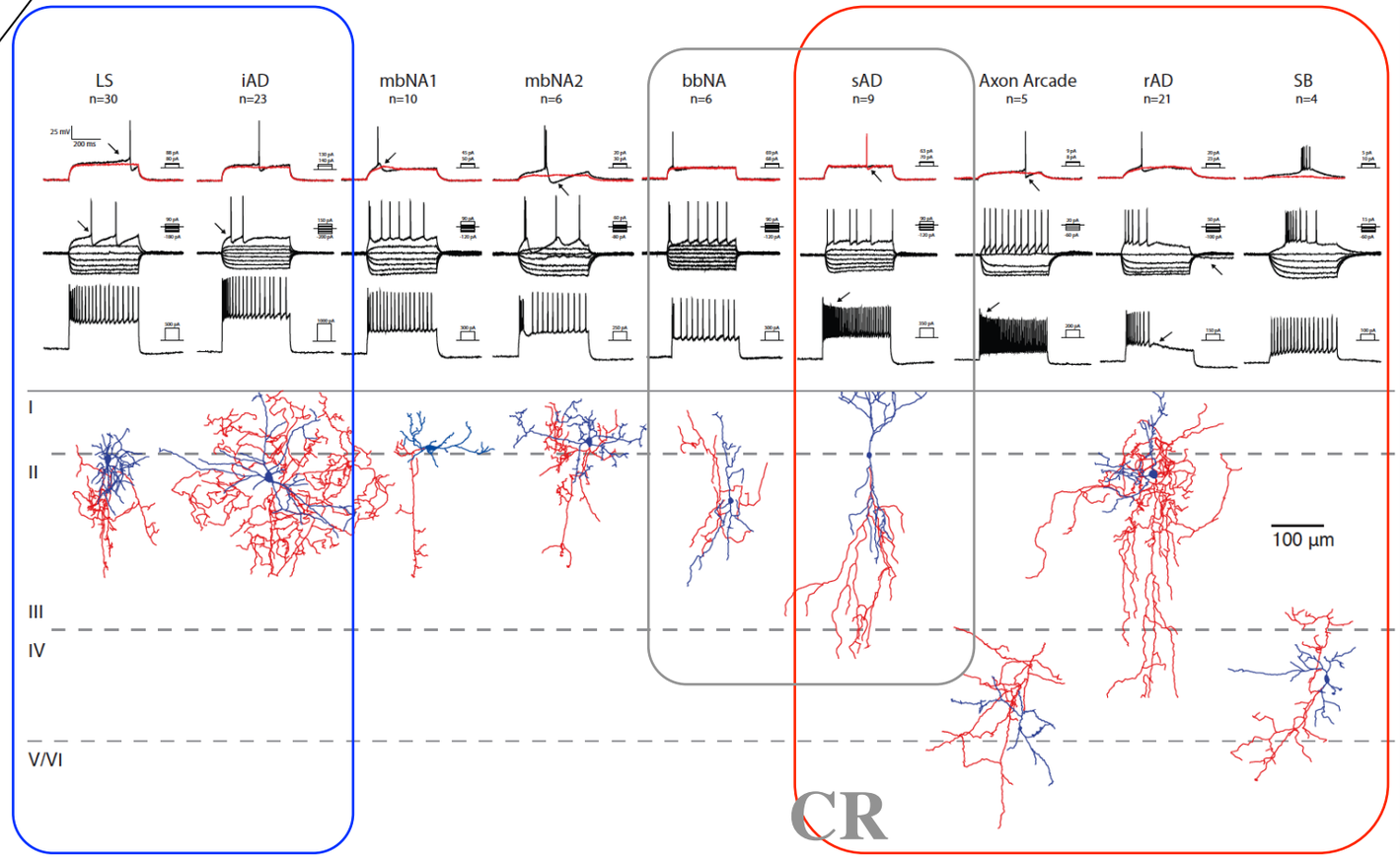
Miyoshi et al. JN 10

CGE-derived

Reelin

Calretinin

VIP



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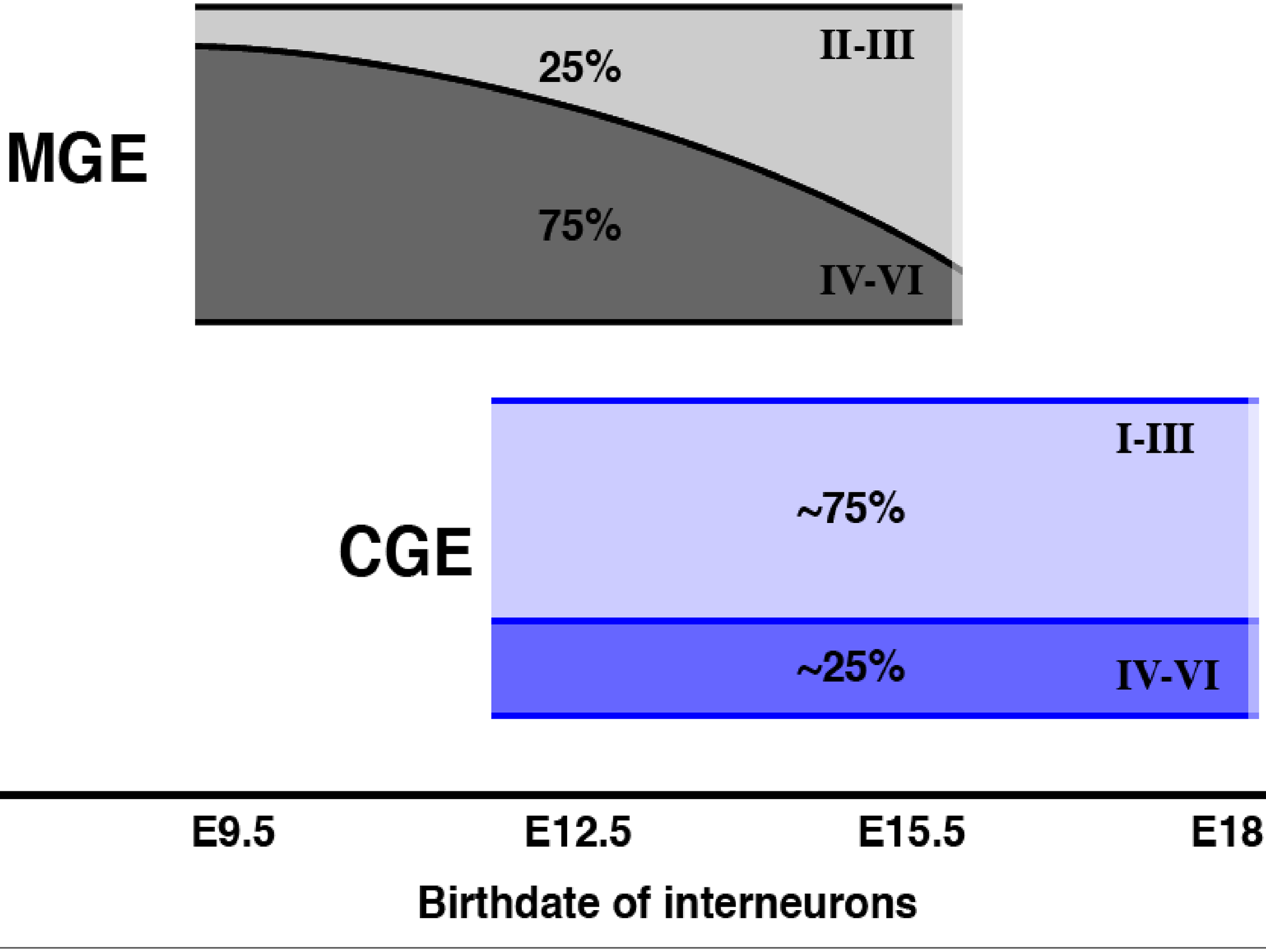


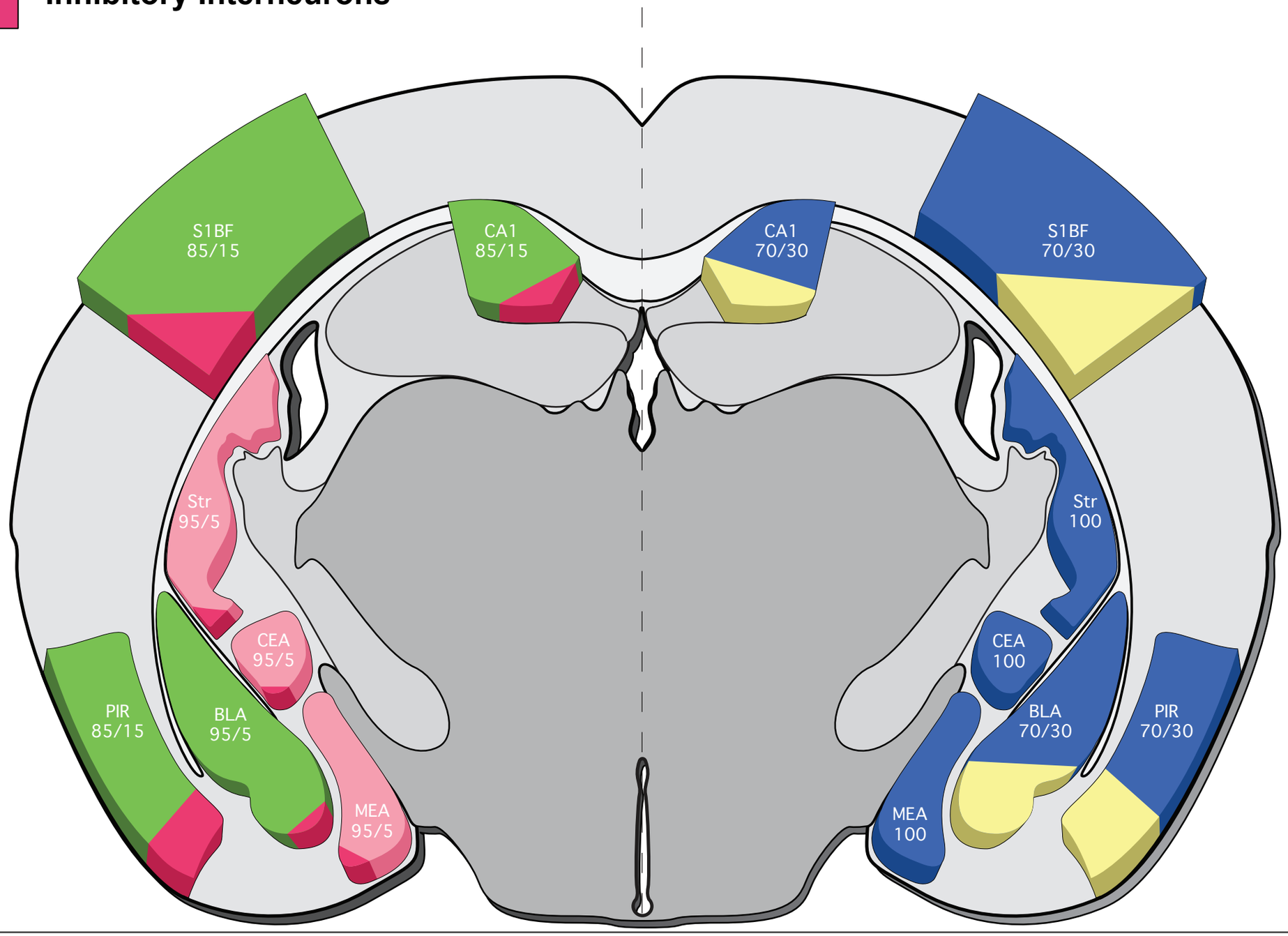
Excitatory Principal Cell

Inhibitory Principal Cell

Inhibitory Interneurons

MGE-Derived

CGE-Derived



MGE-derived

	Origin	Molecular marker	Functional properties	Laminar distribution	Morphology	Diversity
Fast-spiking basket cells	MGE	PV	Fast spiking firing pattern. Low input resistance and fast membrane time constant. Mediate fast, powerful and precise IPSPs.	Layers II-VI; highest proportion in layer IV.	Mostly multipolar, occasionally bitufted dendrites; dense local axon often extending to nearby columns, targeting the perisomatic domain (forming "basket" terminals) of principal cells and interneurons, including other FS cells.	1. Variations in expression of channels and receptors; e.g. Erg1 K+ channels in cingulate CX & hippocampus. 2. Layer-specific differences in threshold firing: delayed or onset spike and in degree of adaptation during large depolarizations. 3. Variations in axonal transcolumnar and translaminar extent and somato-dendritic size. 4. Facilitating inputs from corticothalamic axons, other excitatory inputs are depressing. 5. Fire early or late
Chandelier cells (axo-axonic cells).	MGE	PV	Firing pattern resembles FS basket cells, with higher input resistance & slower membrane time constant.	Layers II-VI. In rodents observed most often in layers II/III.	Multipolar or bitufted dendrites. Pre-terminal axon branches form short vertical rows of boutons resembling candlesticks, making synapses on the axonal initial segment of pyramidal cells.	
Martinotti cells	MGE	SST	Often called LTS cells (low threshold spiking). Some fire 2 or more spikes on slow depolarizing humps from hyperpolarized potentials, while others have an adapting regular spiking firing pattern. Often show rebound spike(s) on repolarization. Strongly facilitating excitatory inputs. Strong excitation by muscarinic agonists.	Layers III-VI;	Multipolar, bitufted or bipolar dendrites; ascending axon that typically leads to a dense axonal arborization in layer I. Target distal and tuft dendrites.	1. Calretinin positive and negative. 2. Variations in expression of other markers: reelin, NPY? 3. Variations in location and extent of distal axonal tuft.

CGE-derived

X-94 like SST neurons	MGE	SST	Lower input resistance and spikes of shorter duration than MCs, approaching those of FS cells. Often have a stuttering firing pattern during intermediate current injections. They were capable of firing at higher frequencies than MCs but in contrast to FS neurons exhibited spike frequency adaptation. Strongly facilitating excitatory inputs like MCs.	Layers IV and V	Multipolar dendrites. Axon ramifies extensively in layer IV.	
Neurogliaform cells	CGE	5HT3aR, reelin	Late spiking firing pattern: Delayed firing preceded by a slow depolarizing ramp at threshold and low current injections. Regular adapting firing during large current injections. Mediate combined slow GABAA and GABAB synaptic responses. Target dendritic spines but also produce non-synaptic "volume" GABA release.	Layers I-VI	Multipolar, short highly branched dendritic and axonal arbors around cell body.	
LS2	CGE	5HT3aR, reelin	Late spiking less robust than neurogliaform cells		Multipolar. Wider and less branched dendritic and axonal arborization than neurogliaform cells	
CCK-expressing interneurons	CGE (at least for VIP+)	CCK. Two populations VIP+ and VIP-. CB1 receptors.	BSNP or RSNP	Layers I-VI; predominantly in upper layers	At least some of these populations are basket cells. Large CCK cells are VIP-; small CCK cells are VIP+.	Two populations VIP+ and VIP-.
Bitufted Irregular Spiking	CGE	5HT3aR, VIP, CR+	Irregular spiking at low current injections and adapting regular spiking with amplitude accommodation during larger depolarizations. High membrane resistance.	Layers I-VI, mainly layers II/III	Bipolar/bitufted dendrites, descending intralaminar axon. May preferentially target other INs.	

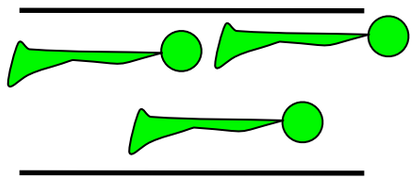
Neocortex	Hippocampus	Paleocortex/Piriform Cortex	Striatum	Basolateral Amygdala
Fast-spiking basket cells	Basket PV cells	Fast-spiking multipolar cells	Fast-spiking cells	Fast spiking cells with diverse firing patterns resembling the diversity observed in neocortex
Chandelier cells (axo-axonic cells).	Chandelier or axo-axonic cells	Chandelier cells PMID: 15679039		Chandelier cells (PMID: 6185547)
Martinotti cells	O-LM cells	Regular-spiking multipolar cells (somatostatin-expressing neurons)	Low threshold spiking (LTS or pLTS: persistent low threshold spiking) SST-expressing interneurons	SST-expressing BLA interneurons
X-94 like SST neurons				
Neurogliaform cells	Neurogliaform and Ivy cells. Most express NOS and are MGE derived.	Neurogliaform cells		Neurogliaform cells. PMID: 6199387
CCK-expressing interneurons	CCK basket cells (+VIP and VIP-/VGLUT3+)			
LS2		Horizontal cells which resemble the interneurons described in somatosensory cortex as LS2		
Bitufted Irregular Spiking	CR+ VIP interneuron targeting INs ? (2)			CGE derived VIP neurons are known to be present in BLA but have not been much characterized?
Bursting bipolar cells (bNA2)				
Projecting GABAergic neurons	Projecting GABAergic neurons: Back projection cells; hippocampus to septum projecting cells; double projection; oriens-retrohippocampal projection;			
	Bistratified cells			
	Other CCK INs: Schaffer collateral associated cells and Lacunosum-moleculare/ Perforant- Pathway (LM-PP) associated cells and the Lacunosum-moleculare/ Radiatum/Perforant- Pathway (LM-R-PP) associated cells			
	Trilaminar cells			
	CR (VIP-) IN targeting cells			
	Large calbindin			

HYPOTHETICAL MODEL

E10-18 P0 P0-7 P7-14 P21+

HYPOTHETICAL MODEL

E10-18 | P0 | P0-7 | P7-14 | P21+

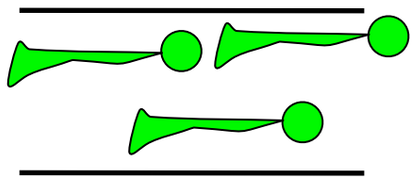
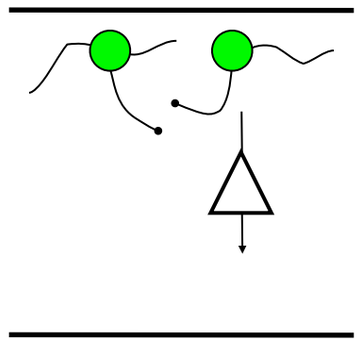


Immature INs arrive in dev-eloping cortex

Migration

In vitro slice preparation

HYPOTHETICAL MODEL

E10-18	P0	P0-7	P7-14	P21+
				
Immature INs arrive in dev-eloping cortex	Neurons start to extend processes			
Migration	Axon/dendrite pathfinding			
In vitro slice preparation	*In vitro* slice preparation tau-GFP			

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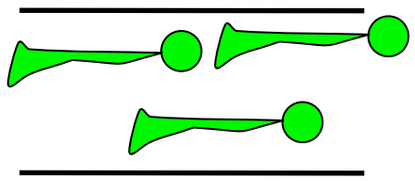	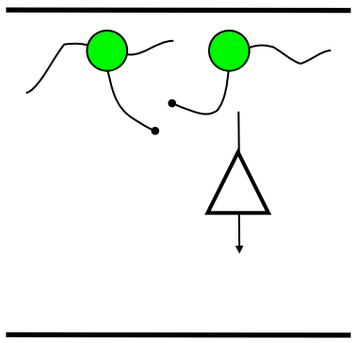	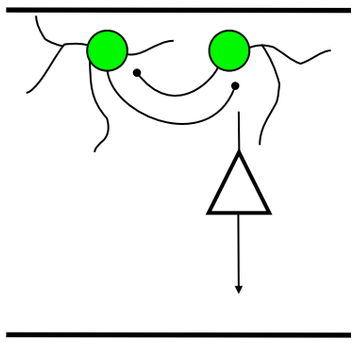		
Immature INs arrive in dev-eloping cortex	Neurons start to extend processes	Early develop-ment of inhib-tory network?		
Migration	Axon/dendrite pathfinding	Synapse refinement		
In vitro slice preparation	*In vitro* slice preparation tau-GFP	Dual recording - GABA dynamics and modulation. Test PYR-IN connectivity		

HYPOTHETICAL MODEL

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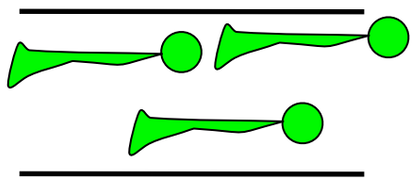
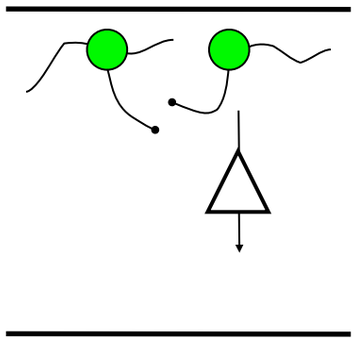
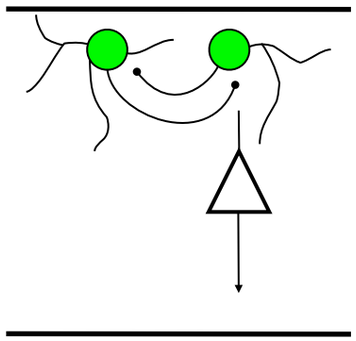
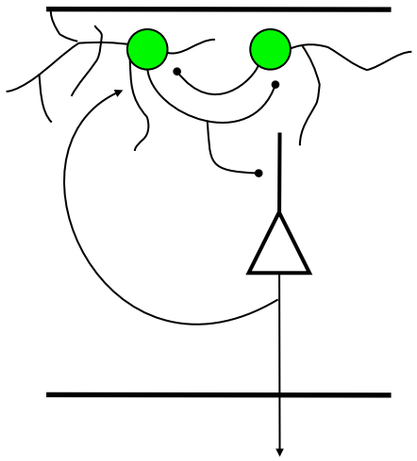
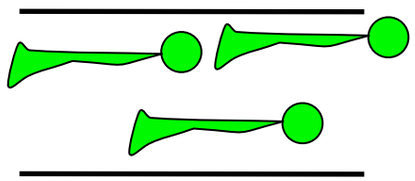
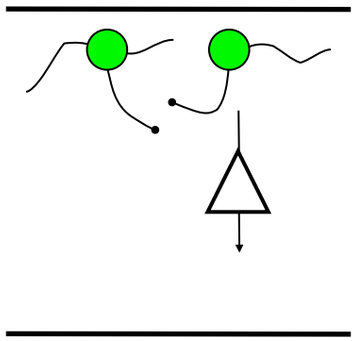
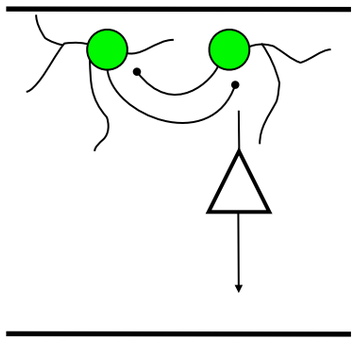
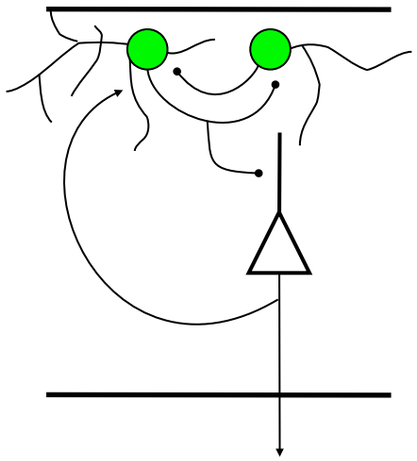
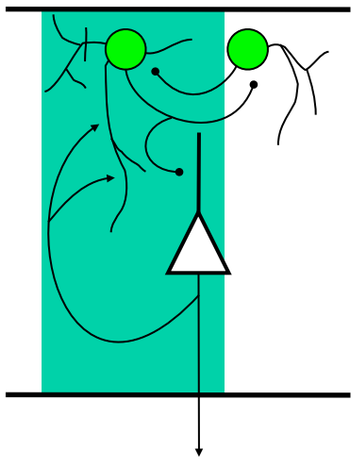
				
Immature INs arrive in developing cortex	Neurons start to extend processes	Early development of inhibtory network?	Network formation	
Migration	Axon/dendrite pathfinding	Synapse refinement	Cortical microcircuit	
In vitro slice preparation	*In vitro* slice preparation tau-GFP	Dual recording - GABA dynamics and modulation. Test PYR-IN connectivity	PYR>IN and IN>PYR connectivity, network activity	

HYPOTHETICAL MODEL

E10-18	P0	P0-7	P7-14	P21+
				
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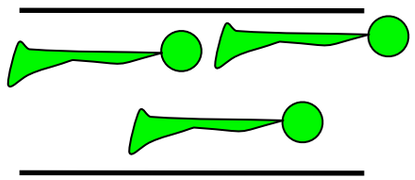
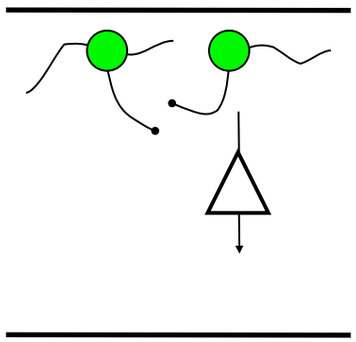
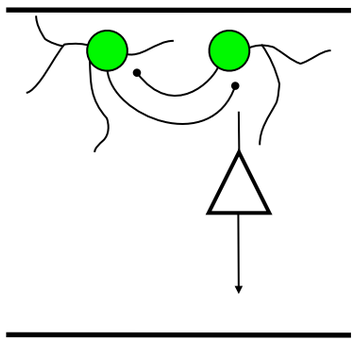
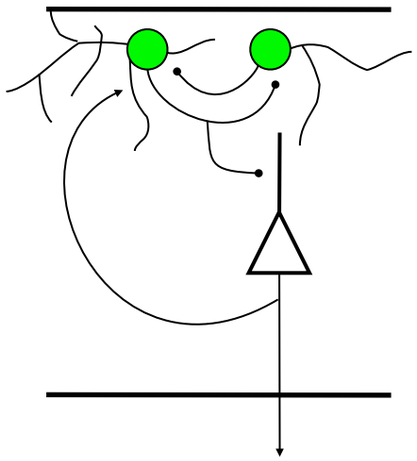
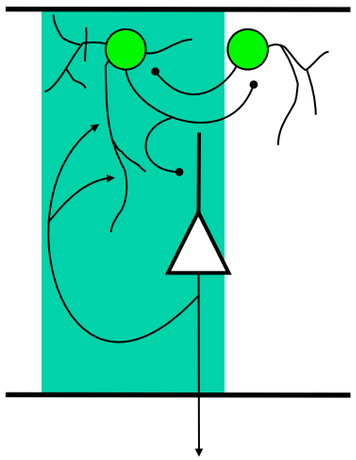
HYPOTHETICAL MODEL

E10-18	P0	P0-7	P7-14	P21+
	Slow Ca++ Oscilations			
				
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HYPOTHETICAL MODEL

E10-18	P0	P0-7	P7-14	P21+
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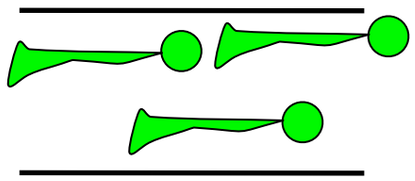	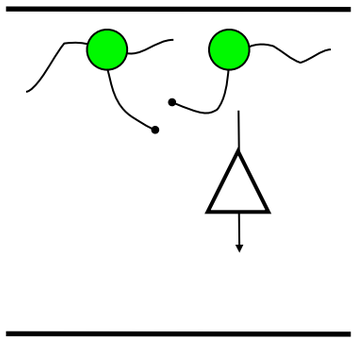	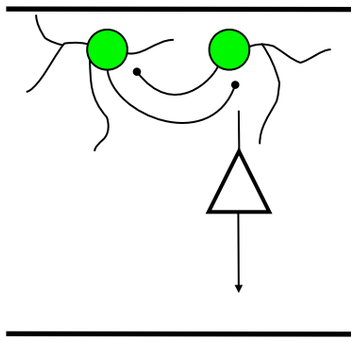	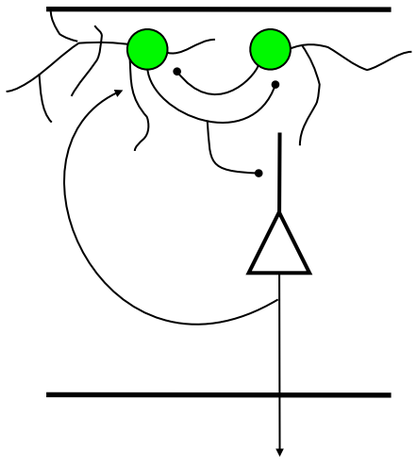	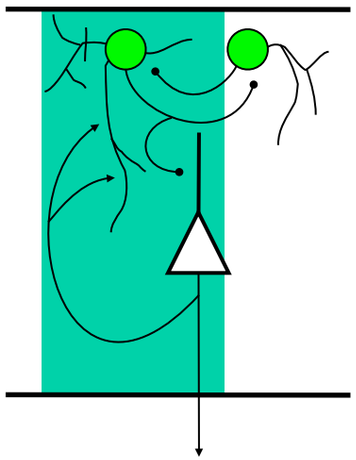
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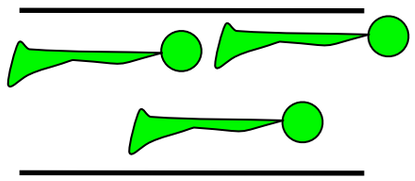	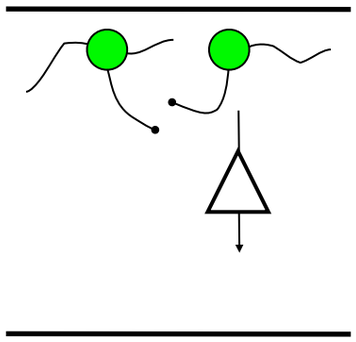	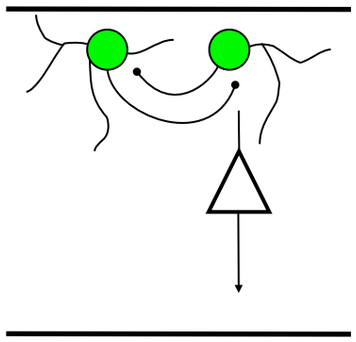	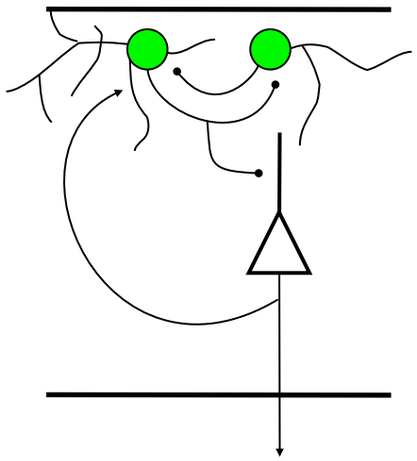	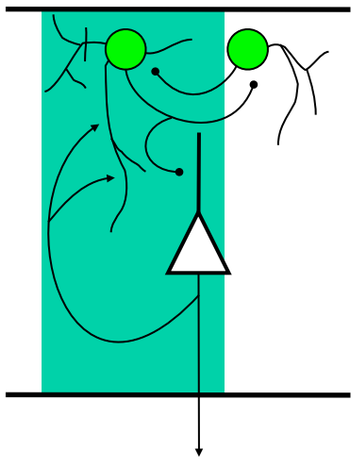
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HYPOTHETICAL MODEL

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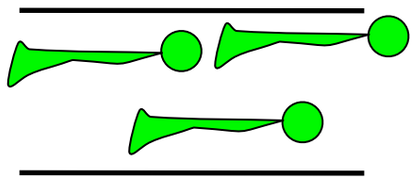	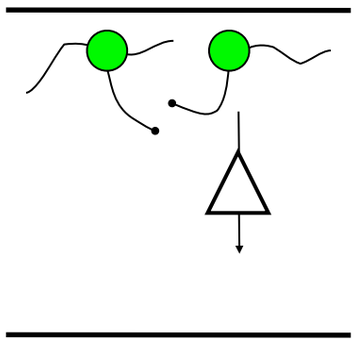	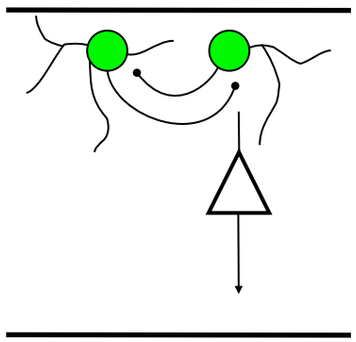	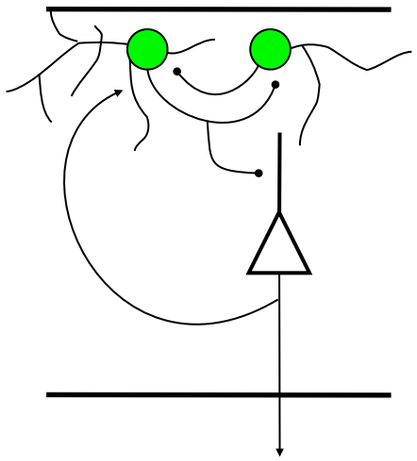	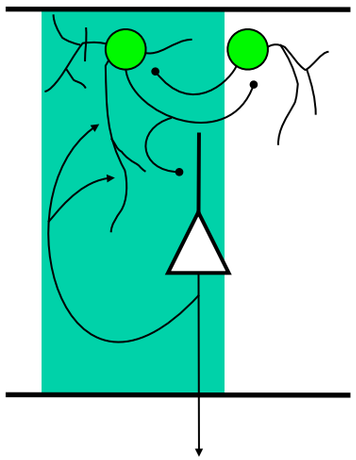
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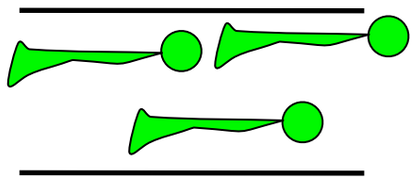	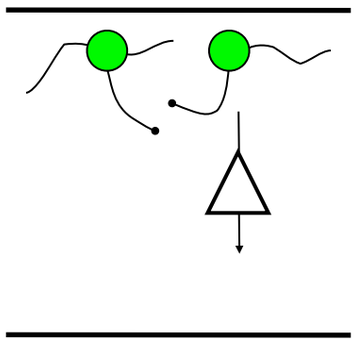	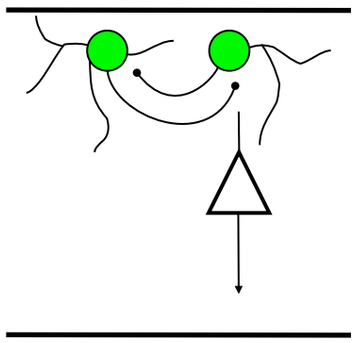	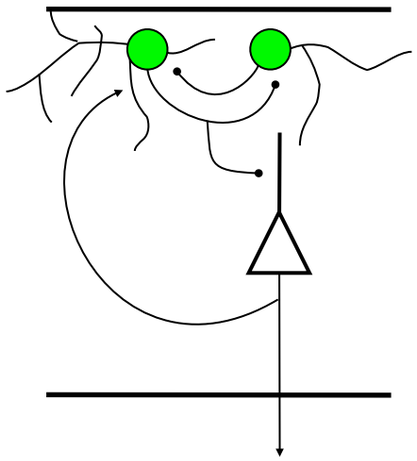	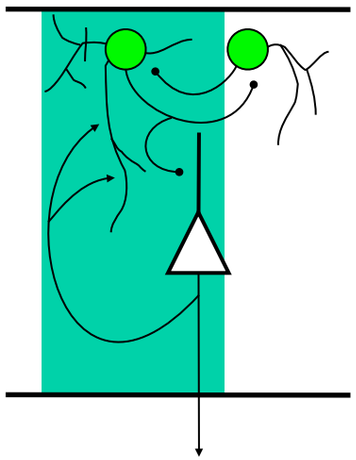
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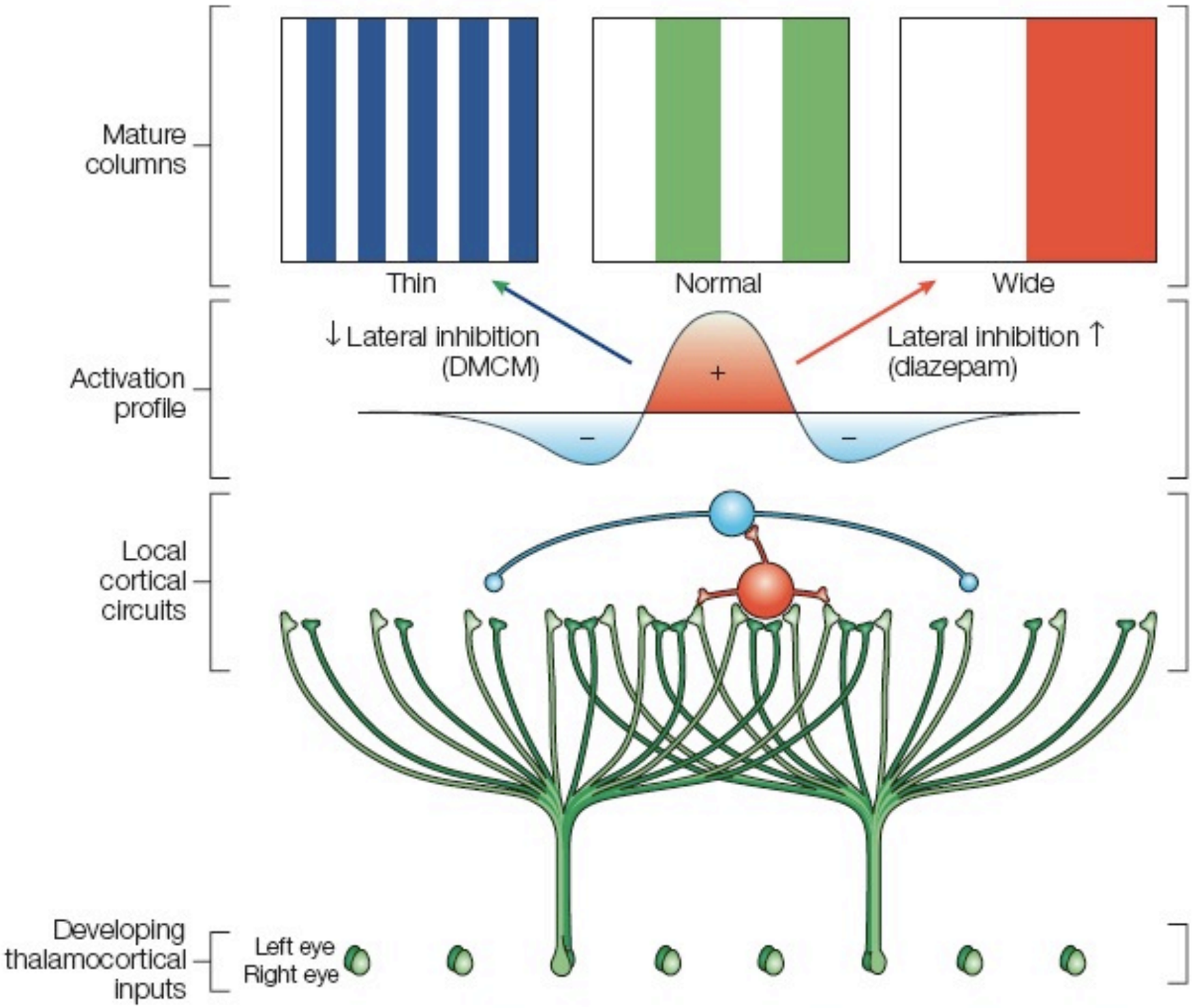
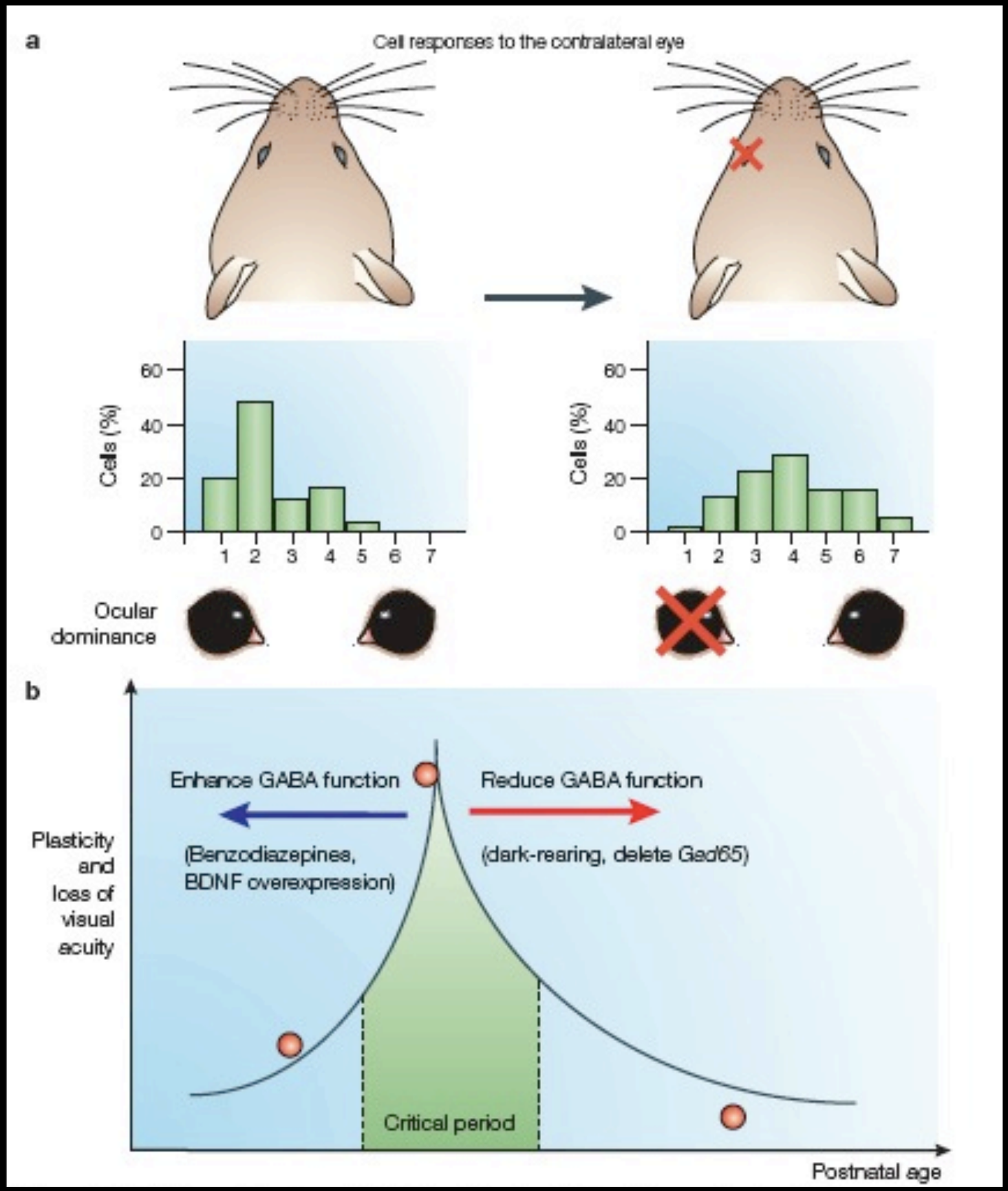


Figure 1 | **Local circuit control of developing columnar architecture in the neocortex.**


a
Cell responses to the contralateral eye
Cells (%)
60
40
20
0
1 2 3 4 5 6 7
Ocular dominance
b
Enhance GABA function
(Benzodiazepines, BDNF overexpression)
Reduce GABA function
(dark-rearing, delete Gad65)
Plasticity and loss of visual acuity
Critical period
Postnatal age

Manipulate the activity of developing interneurons

Natalia DeMarco

Theo Karayannis

Manipulate the activity of developing interneurons

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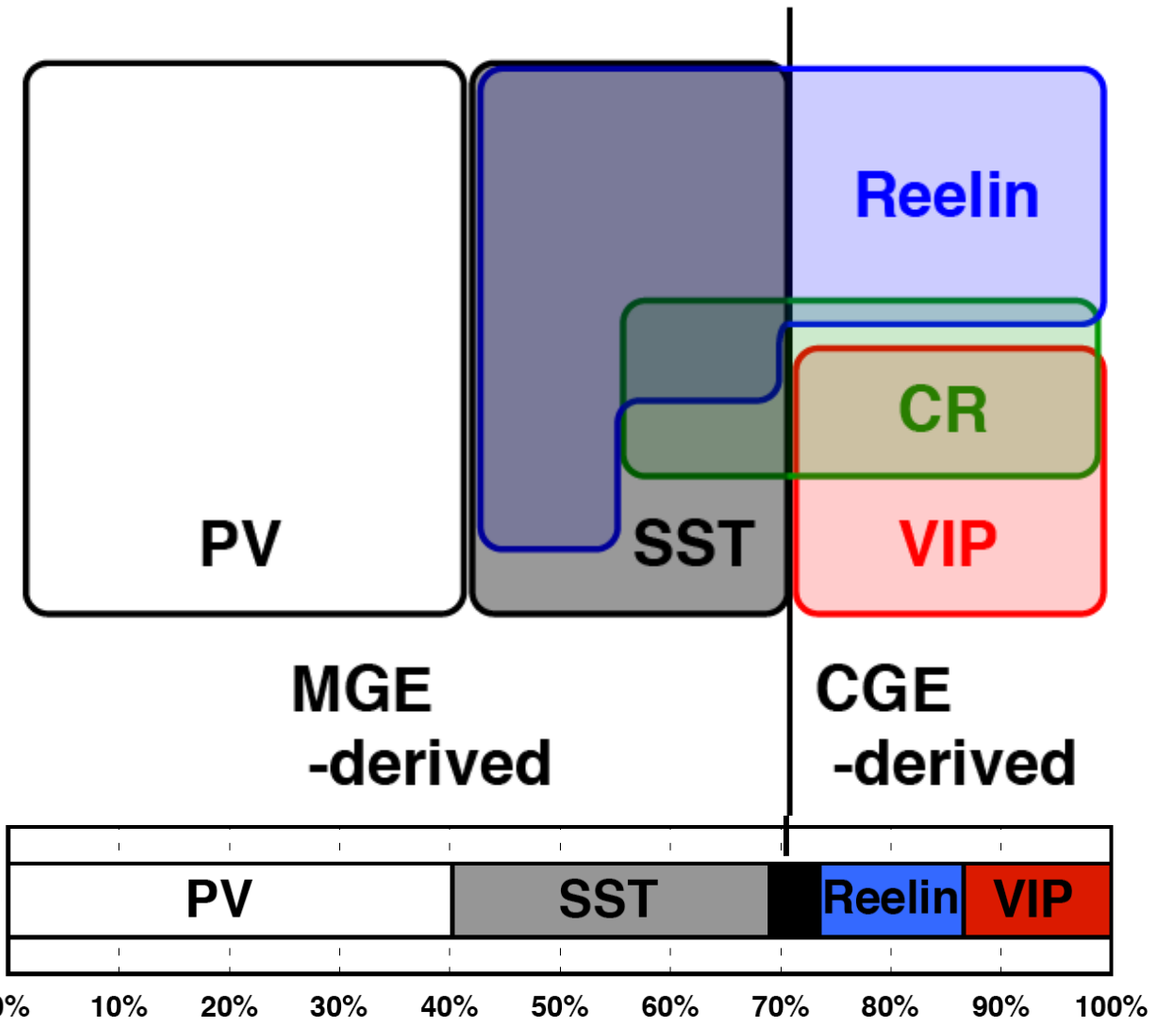
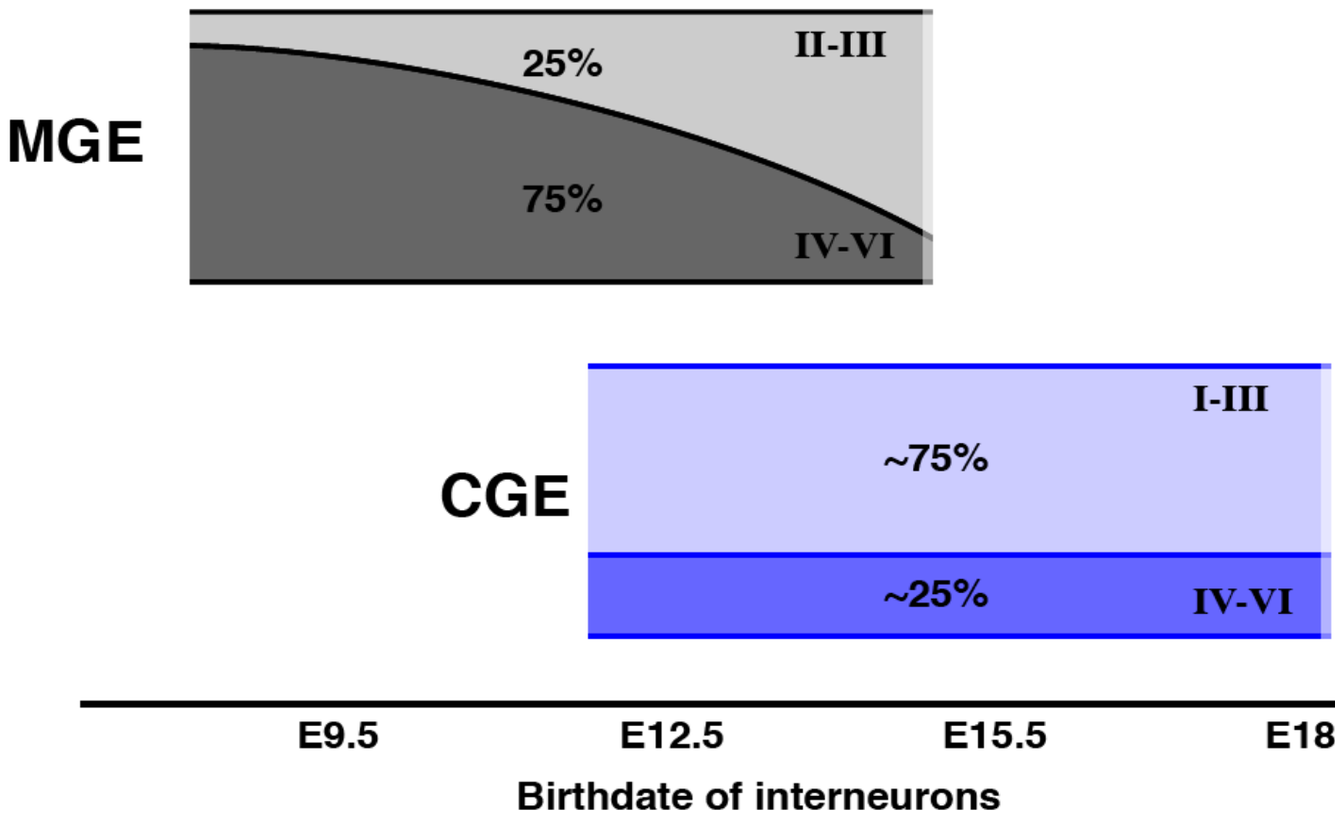
Theo Karayannis

Introduction of *Kir2.1* into CGE-derived interneurons

CGE-derived interneurons express Reelin or VIP

Mouse somatosensory cortex at P21





~70% ~30%

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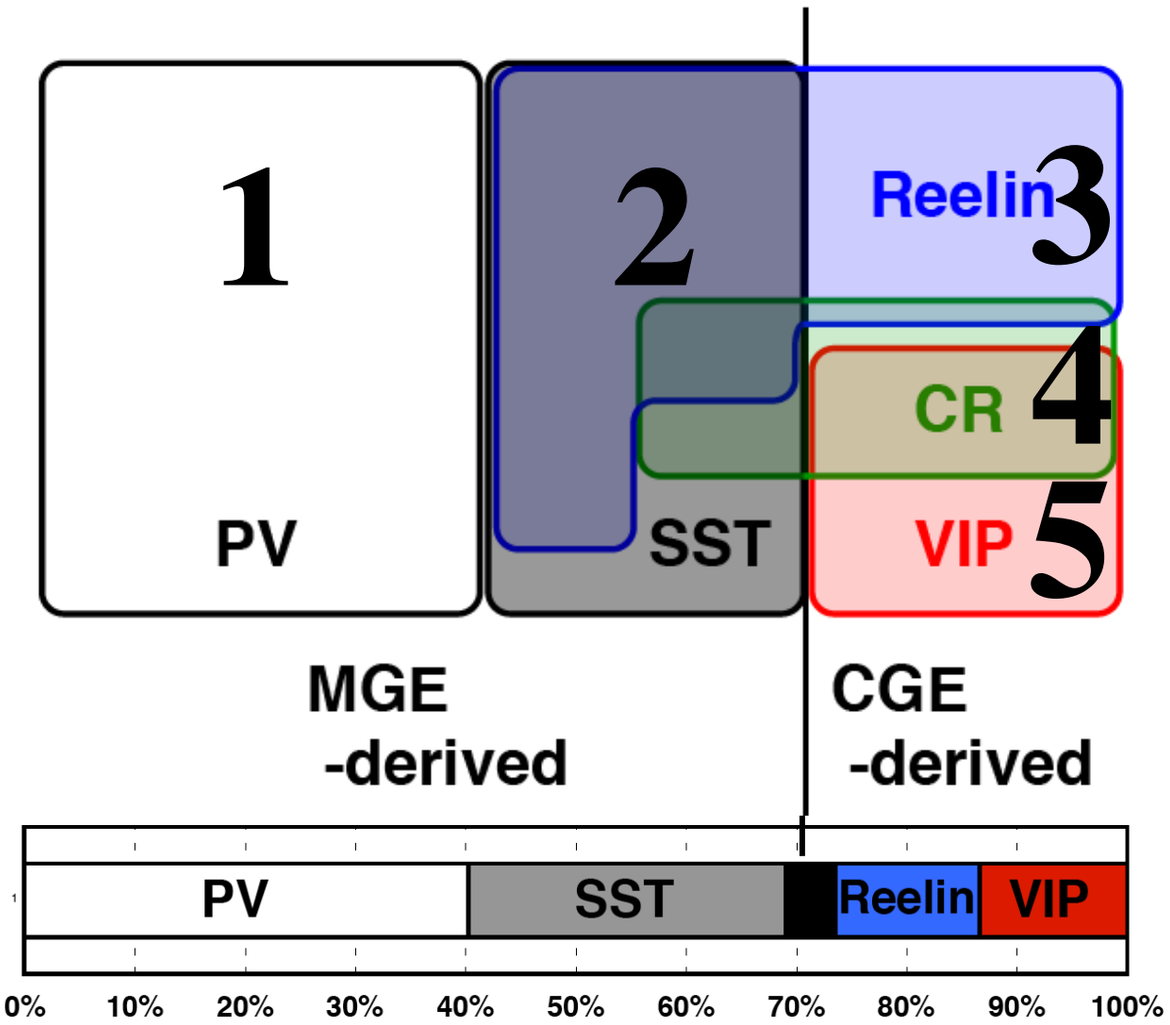

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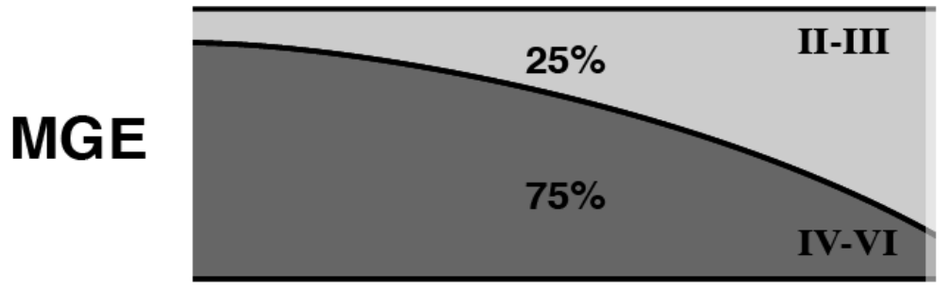

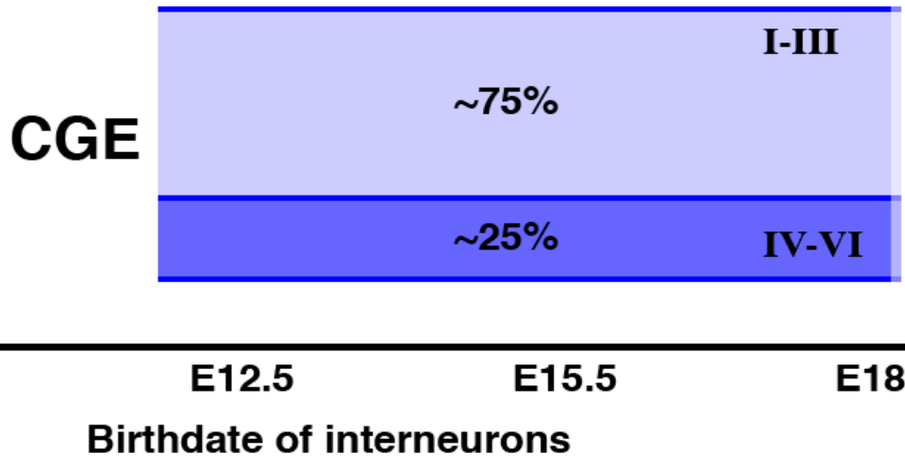

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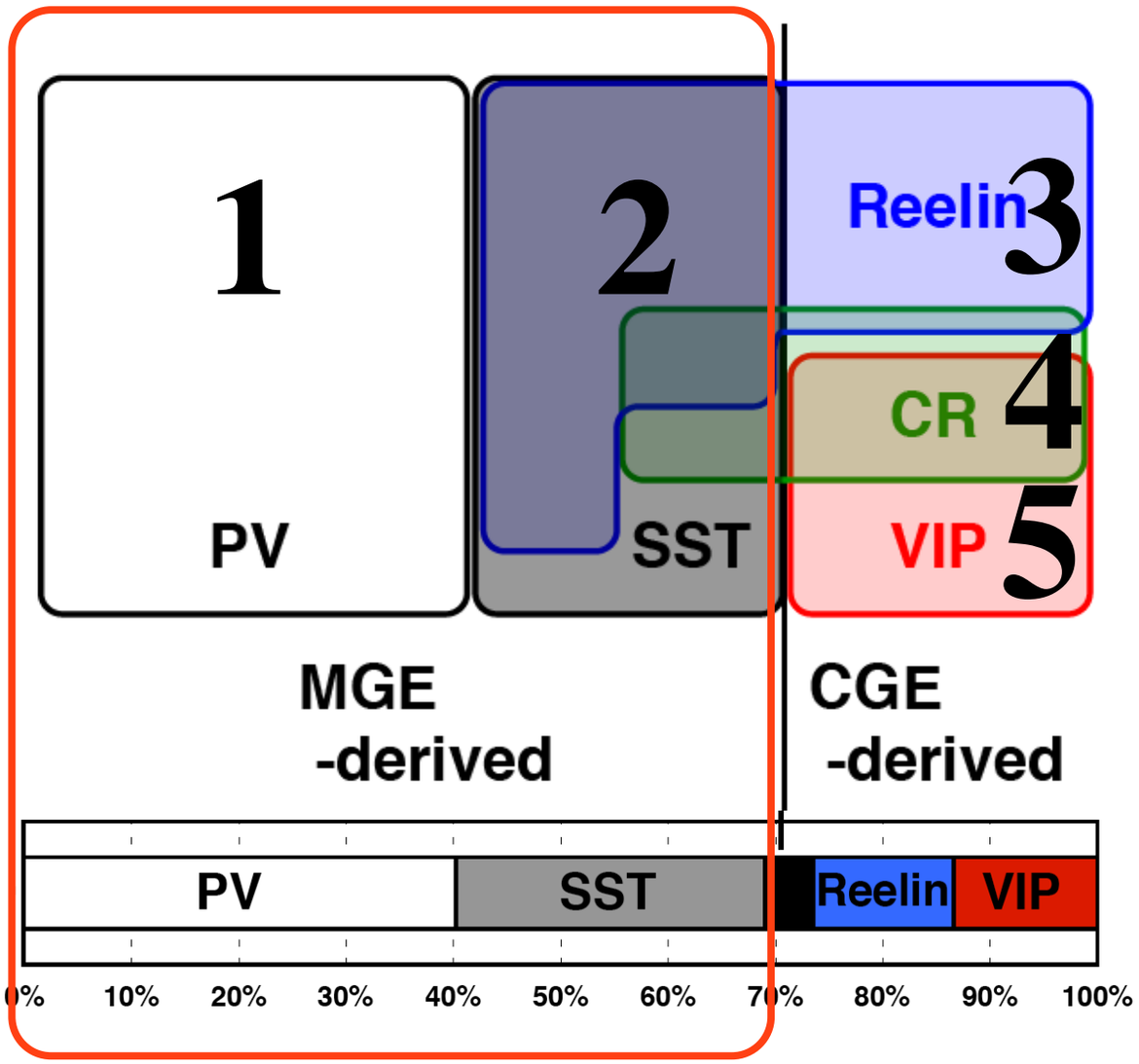

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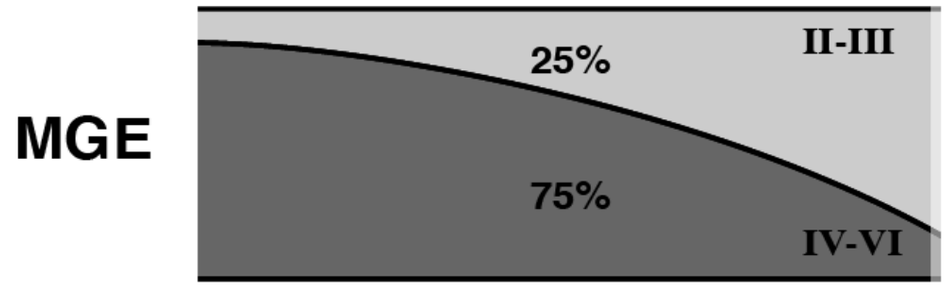

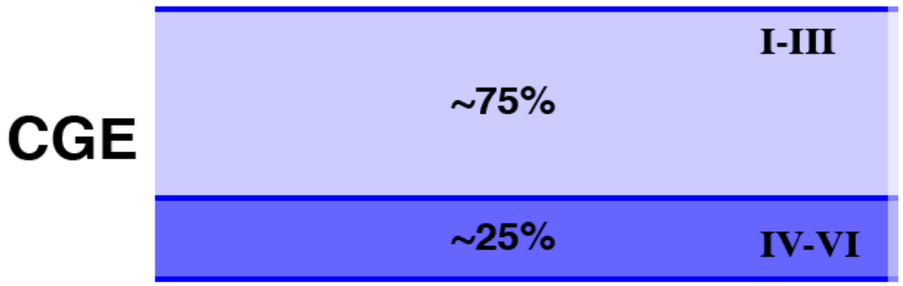

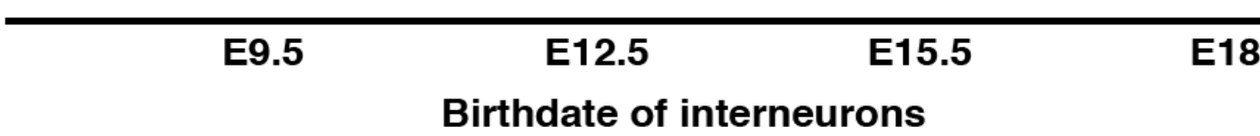

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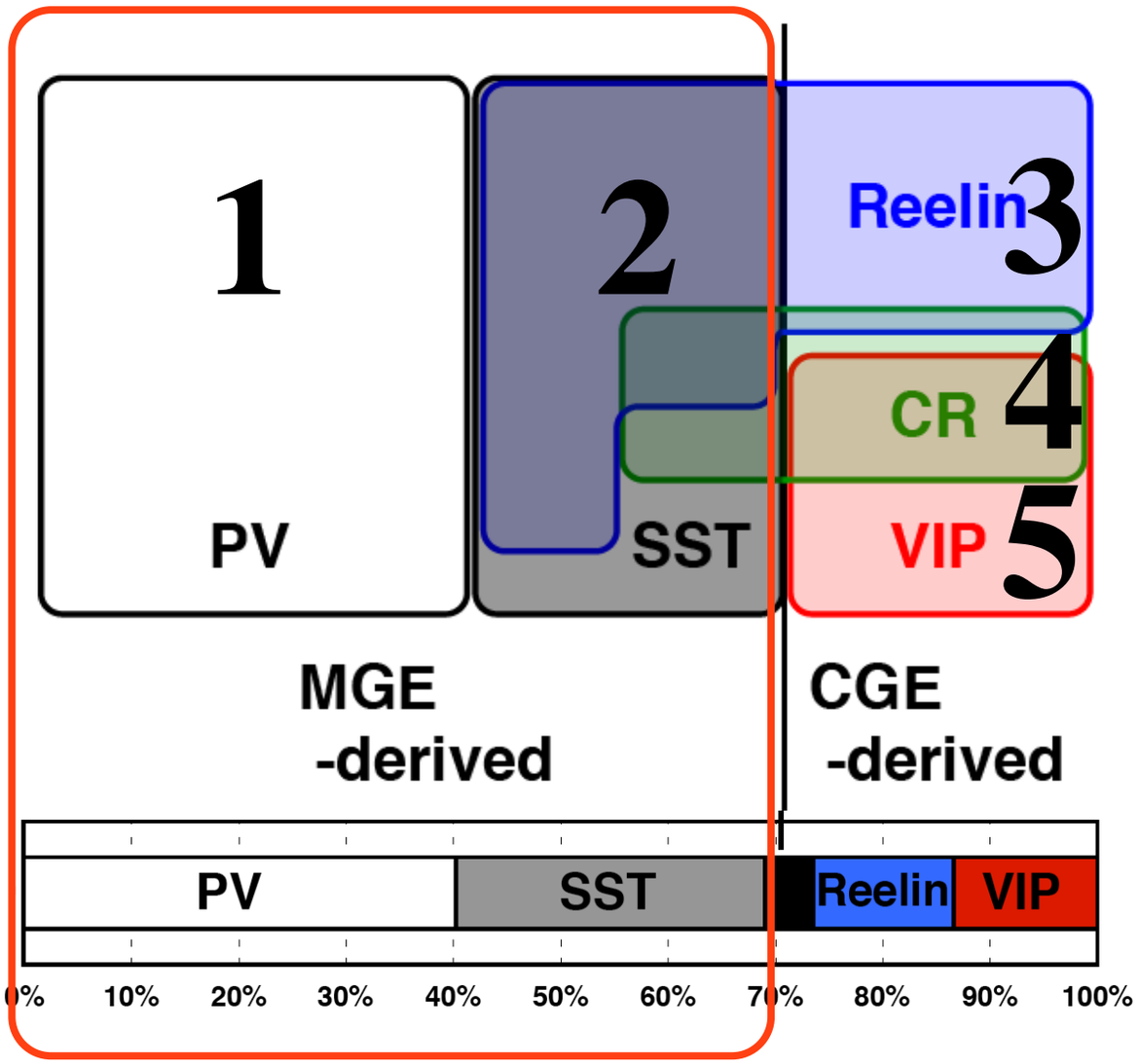

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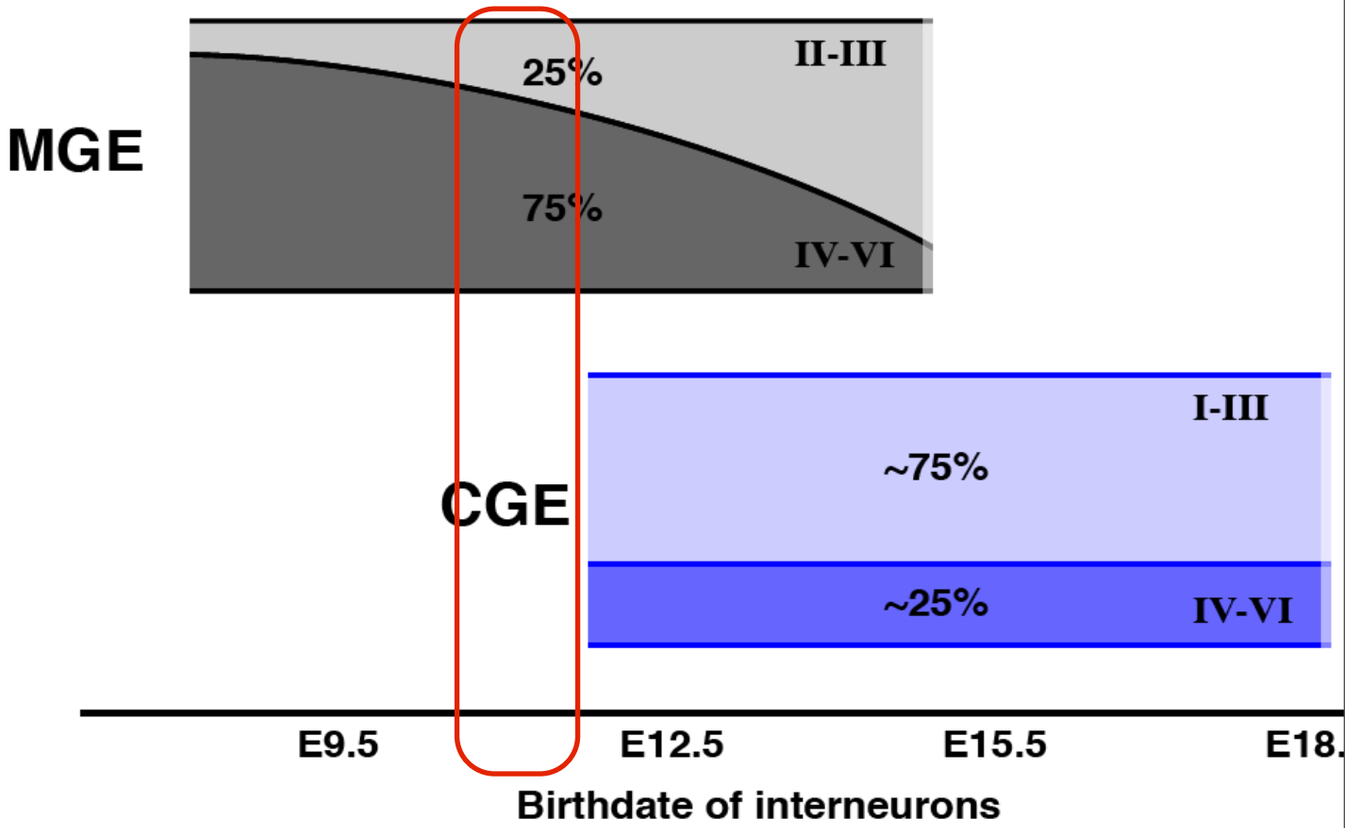

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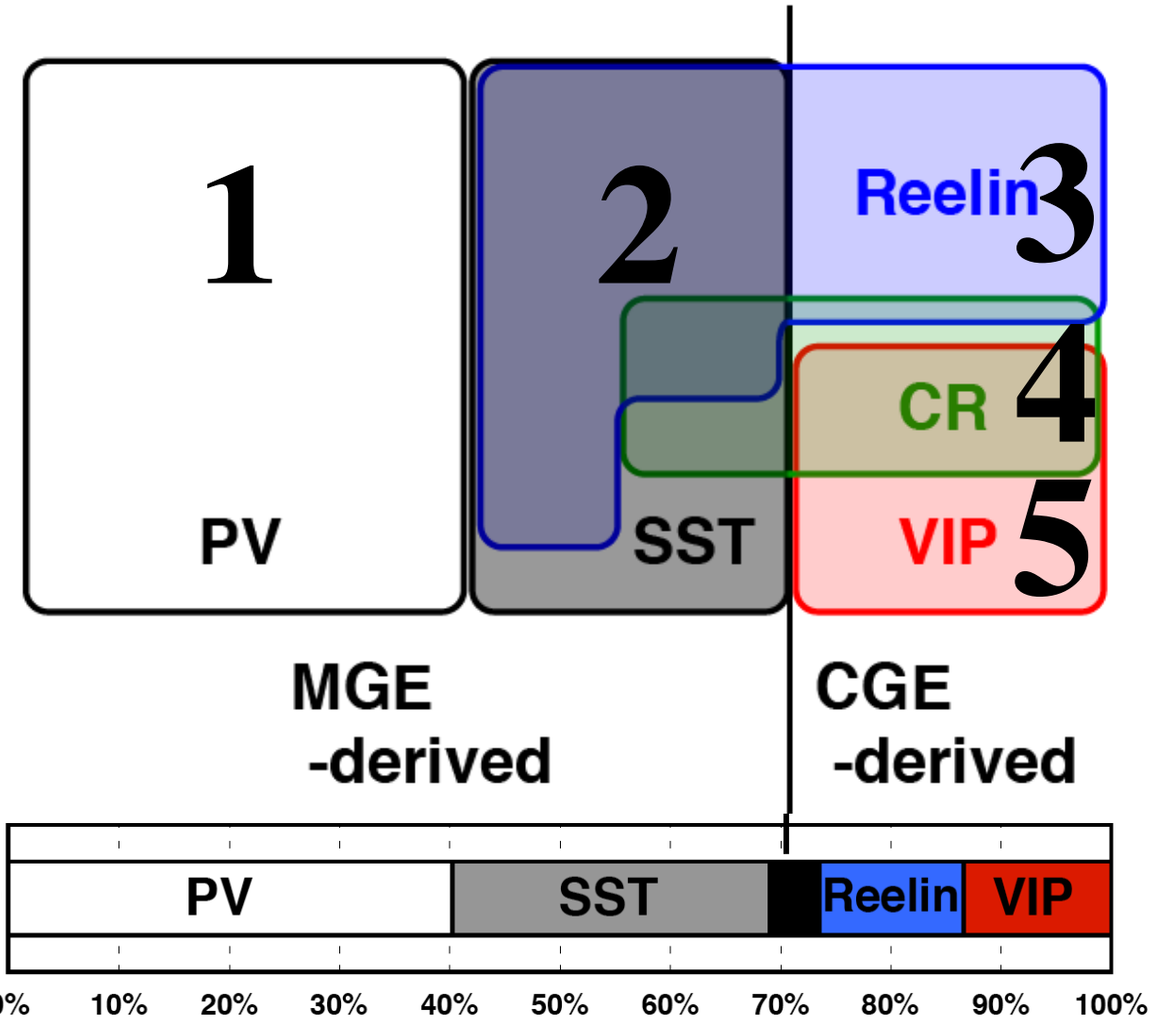

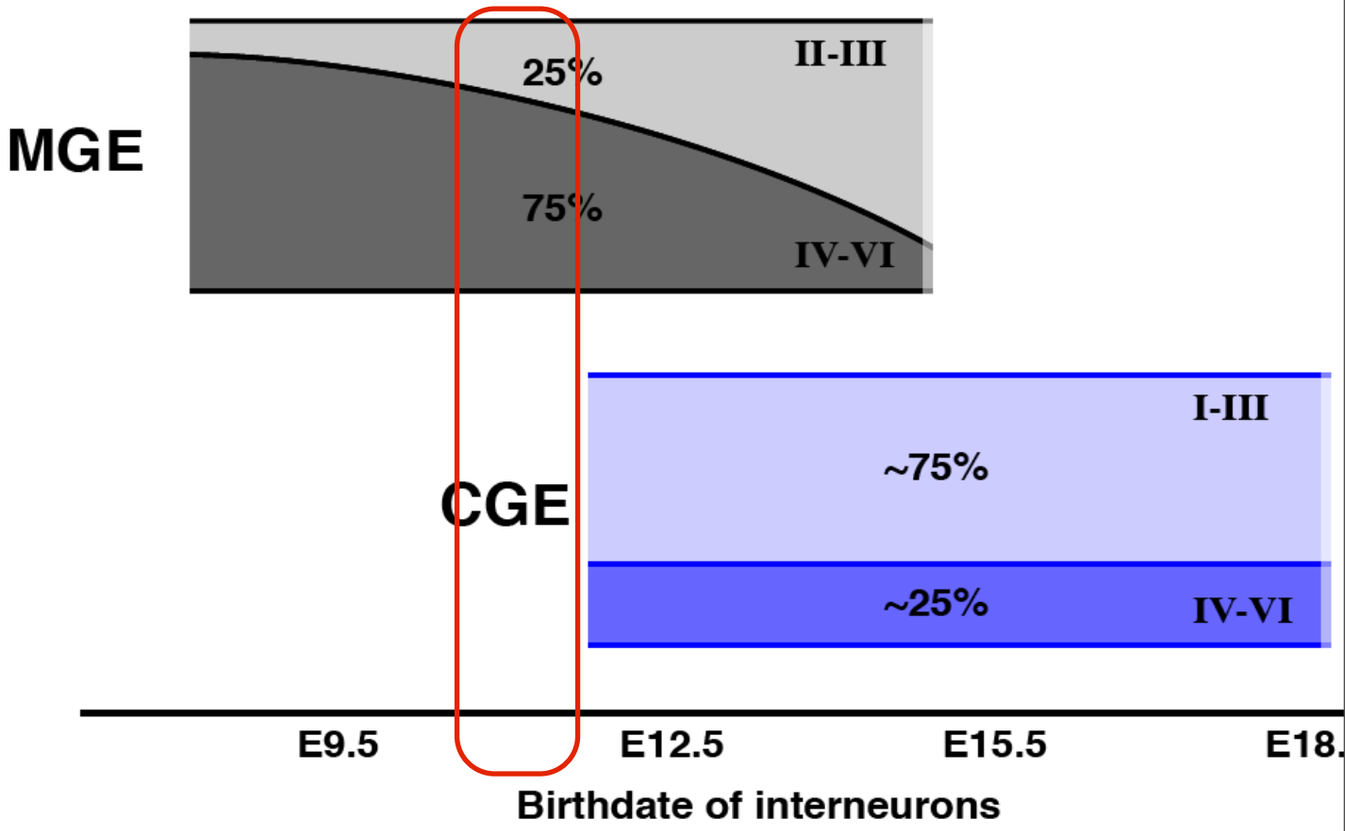

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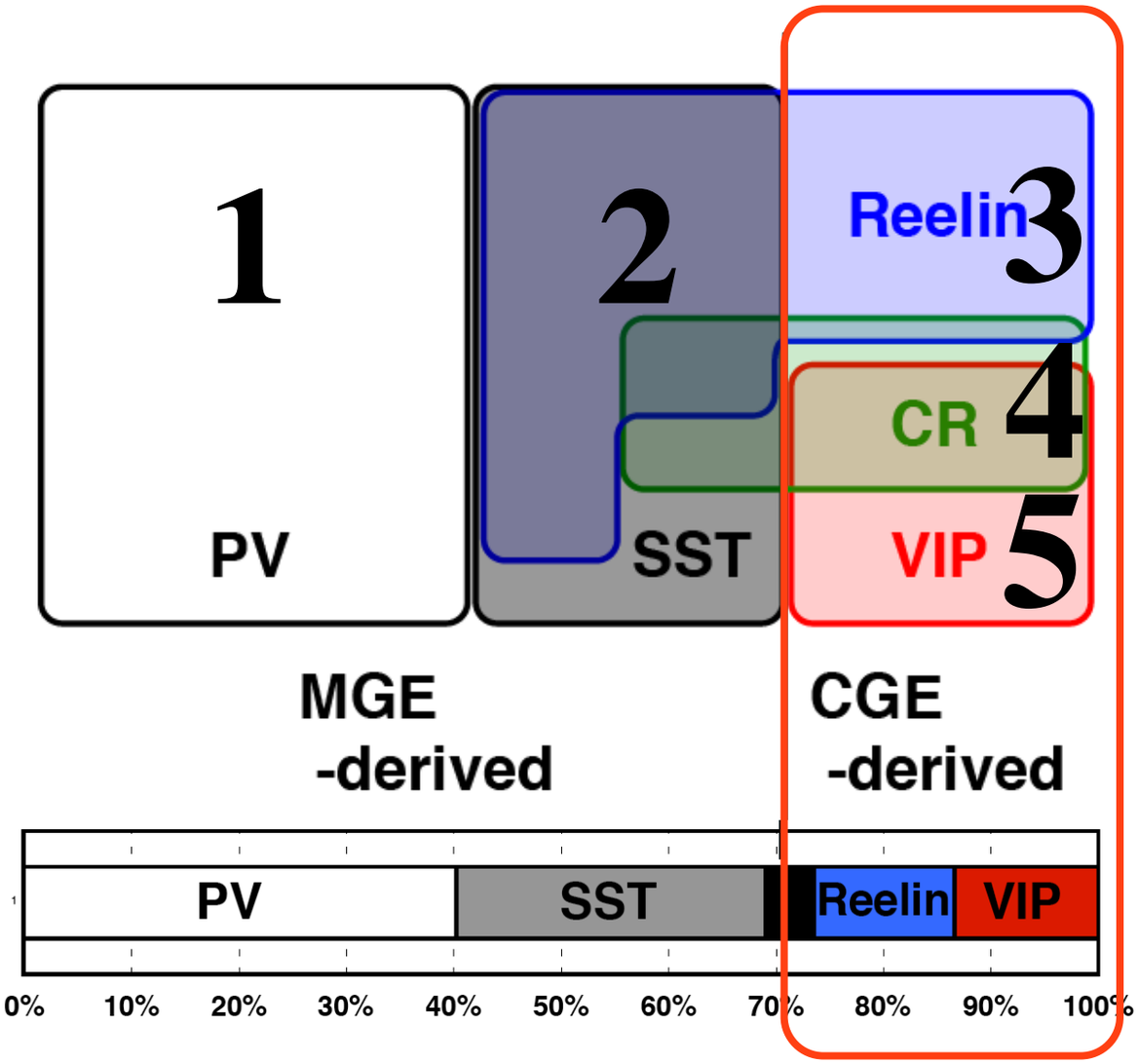

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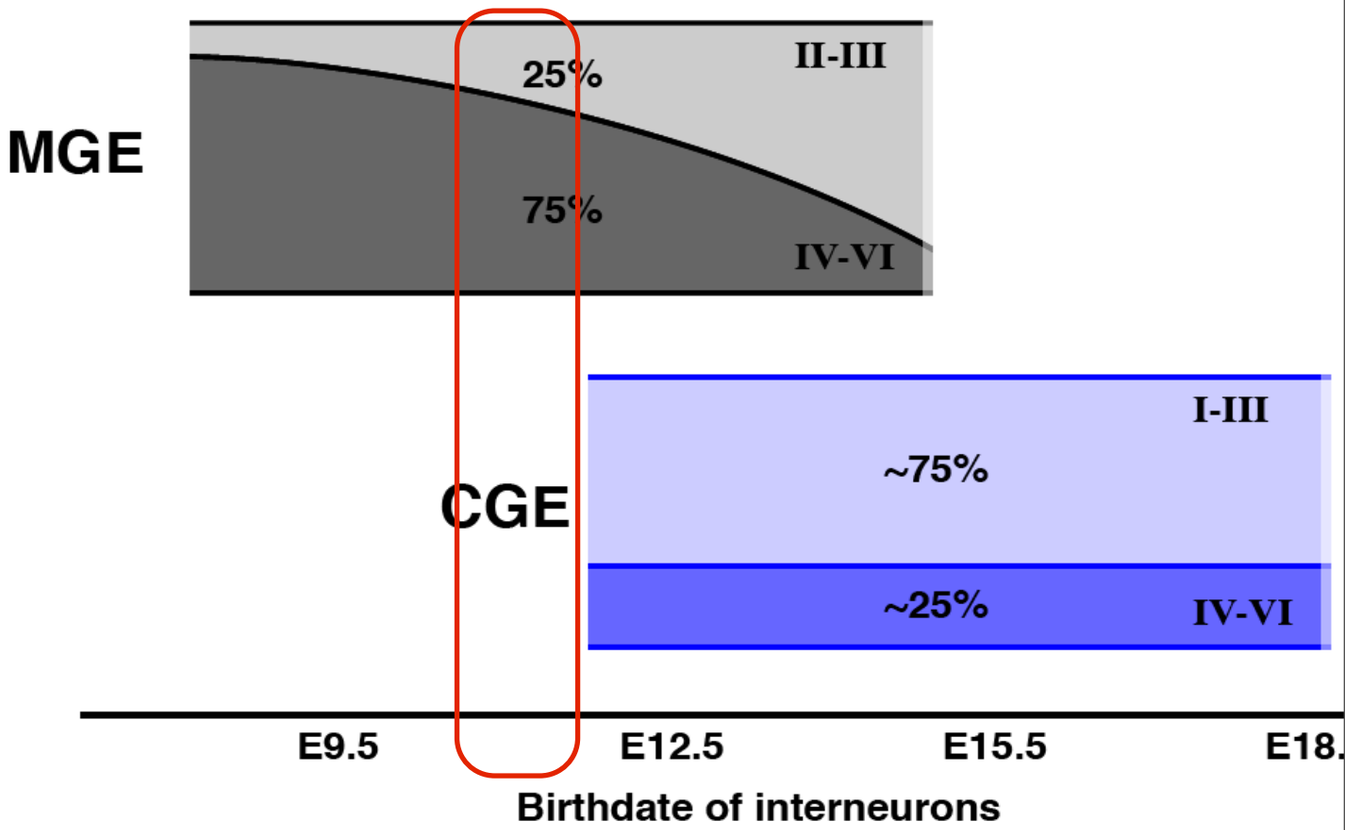

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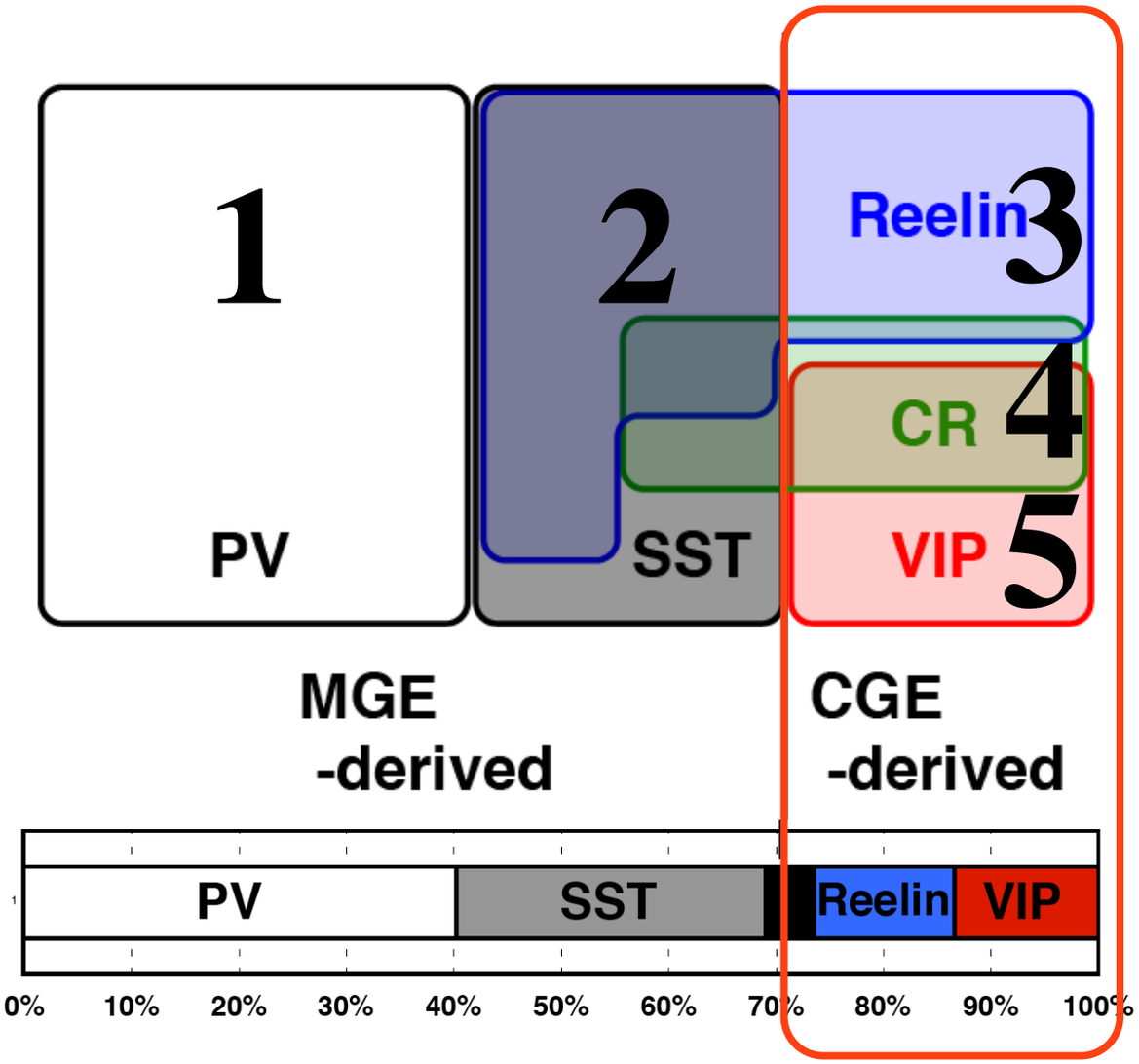

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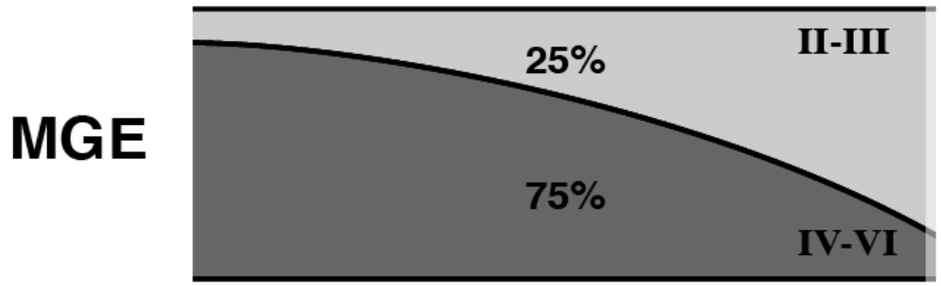

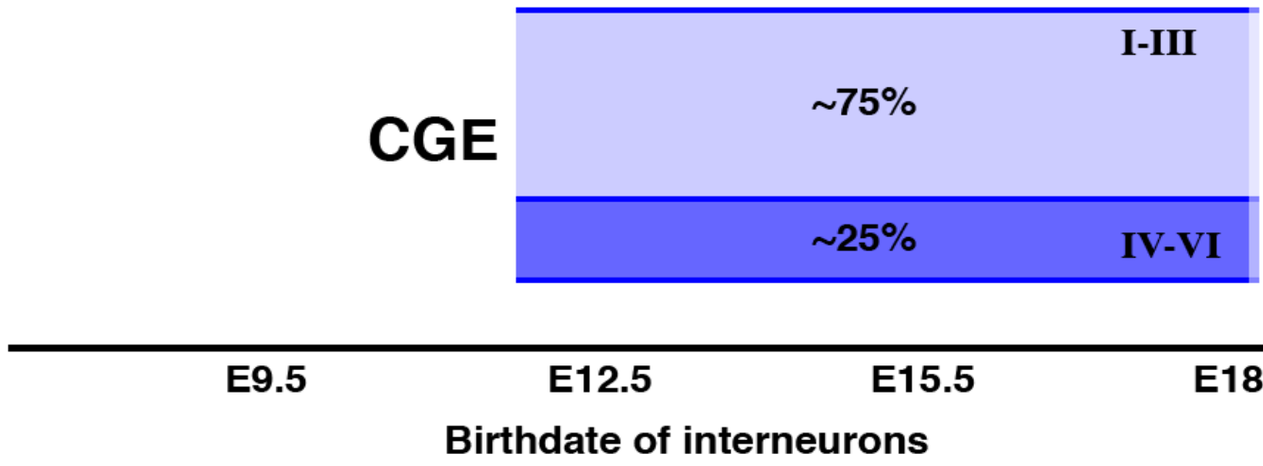

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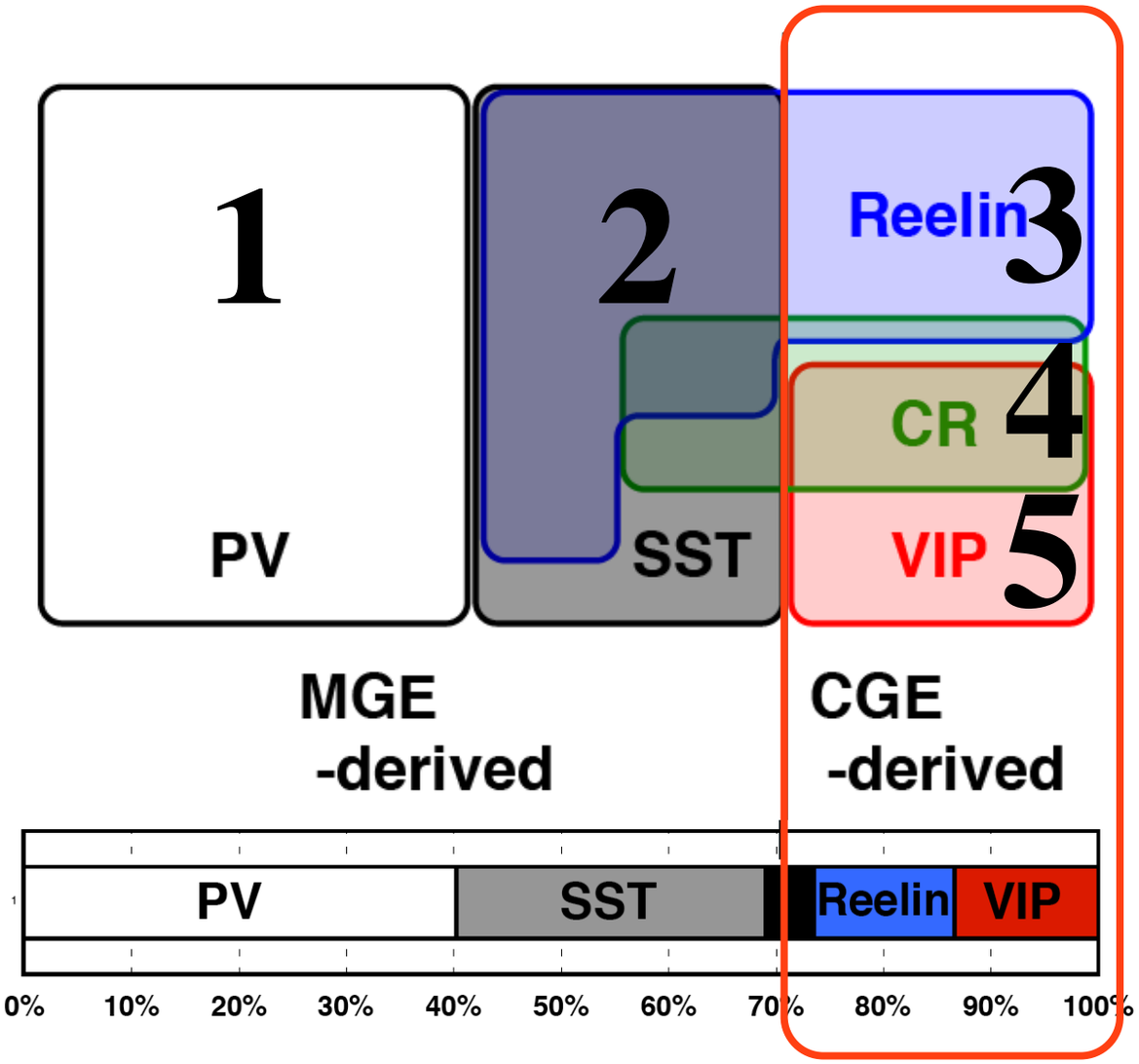

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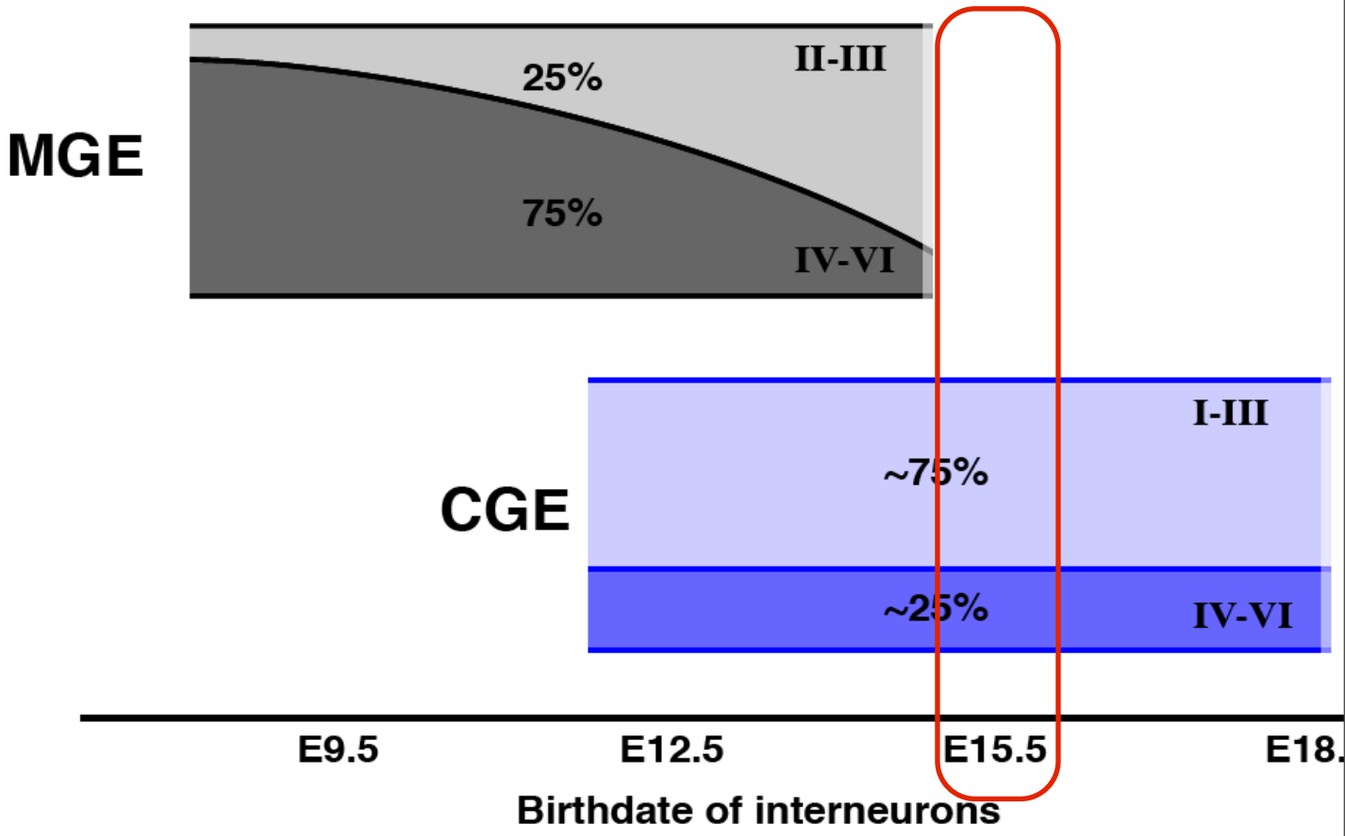
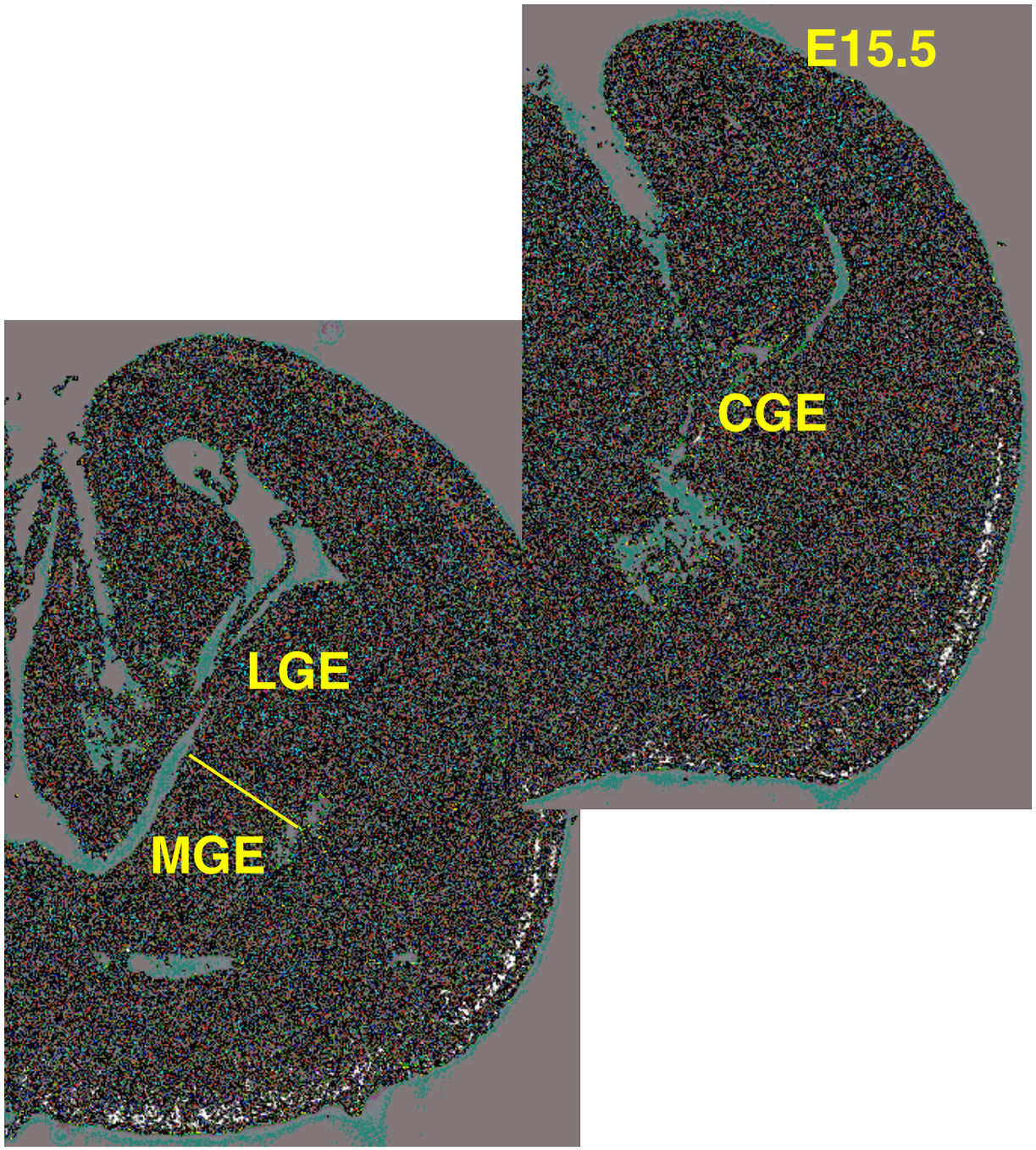
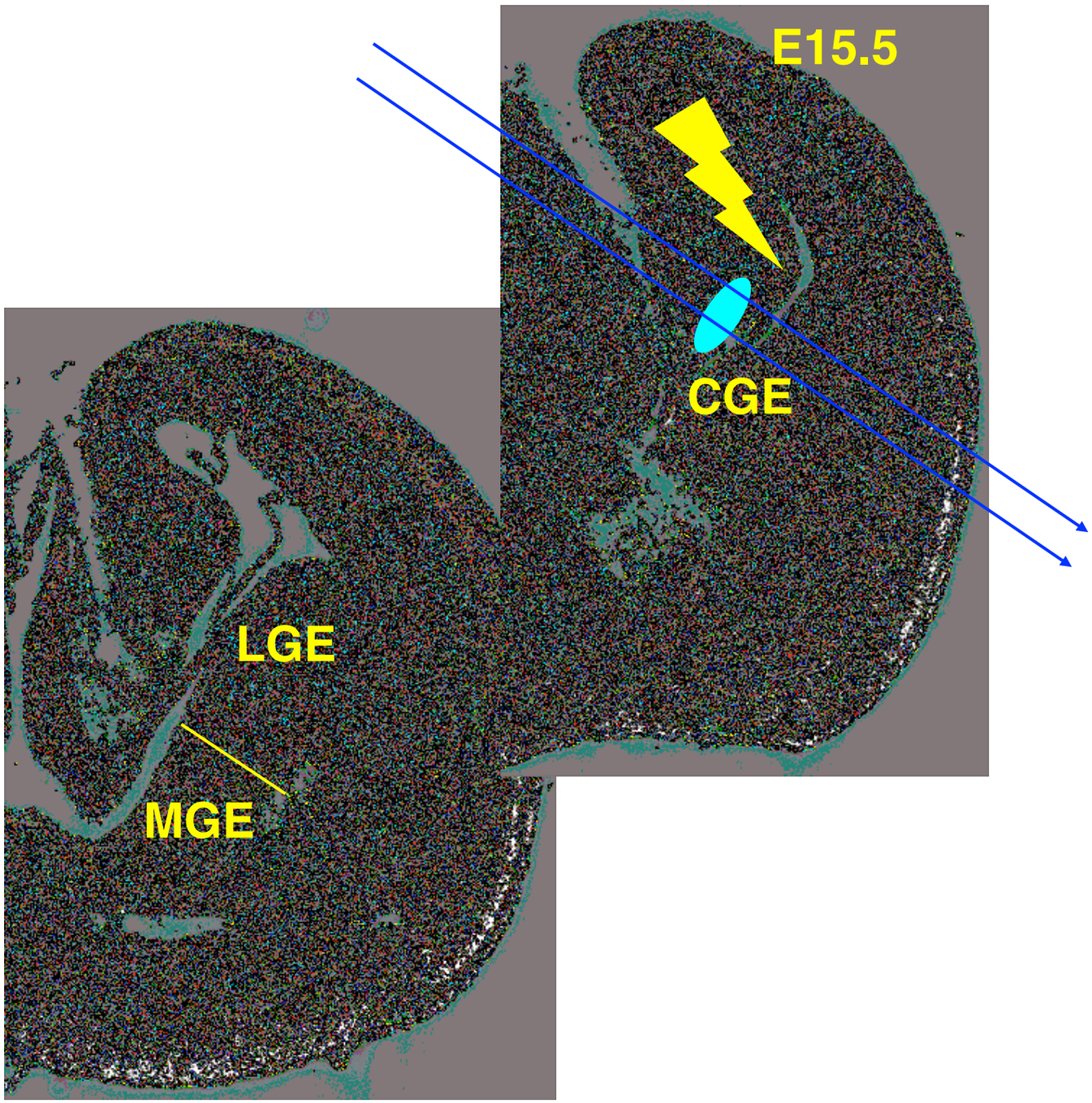


In vivo manipulation of CGE-derived interneurons
Method



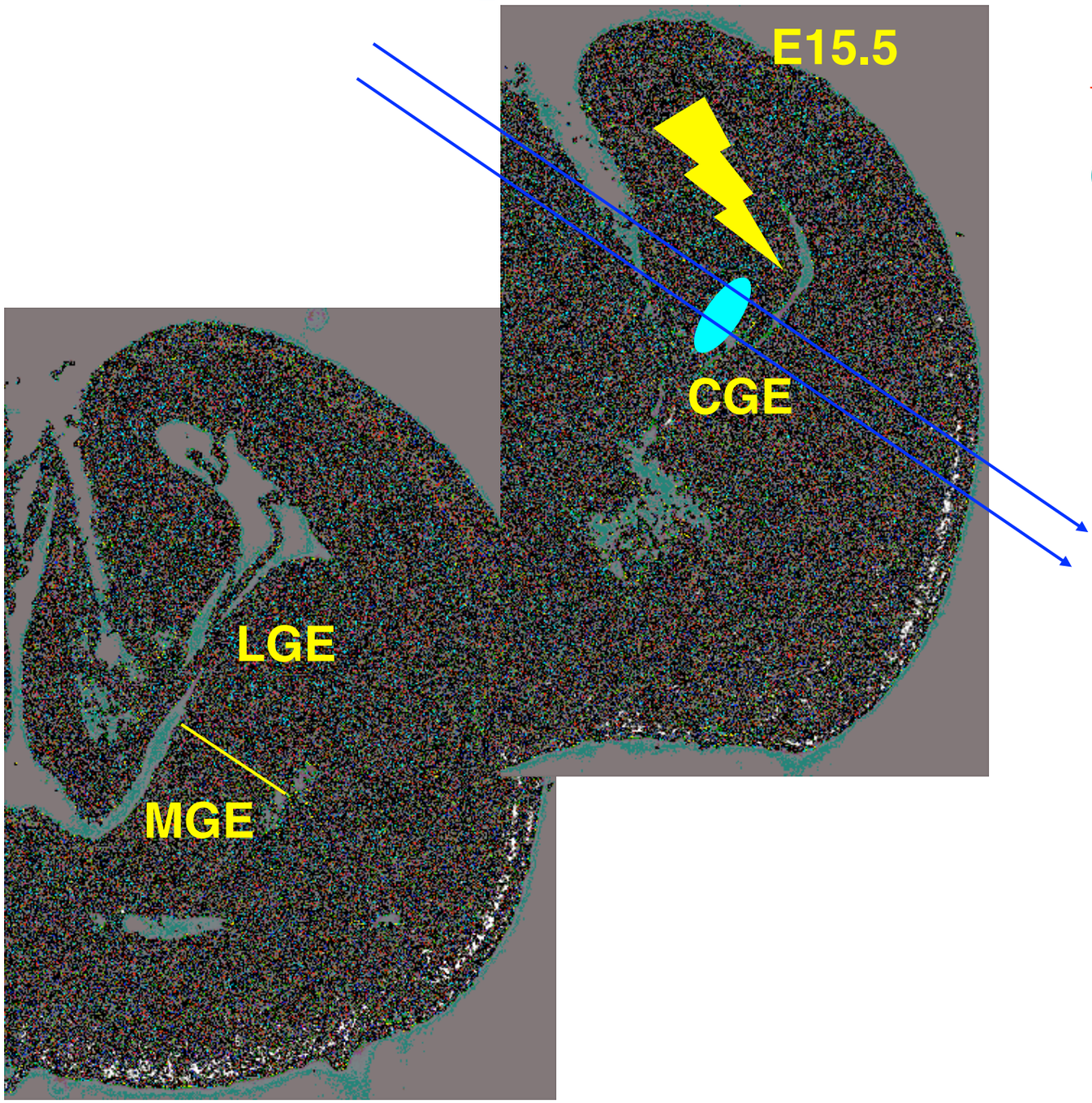
In vivo manipulation of CGE-derived interneurons
Method

In utero Electroporation



In vivo manipulation of CGE-derived interneurons
Method

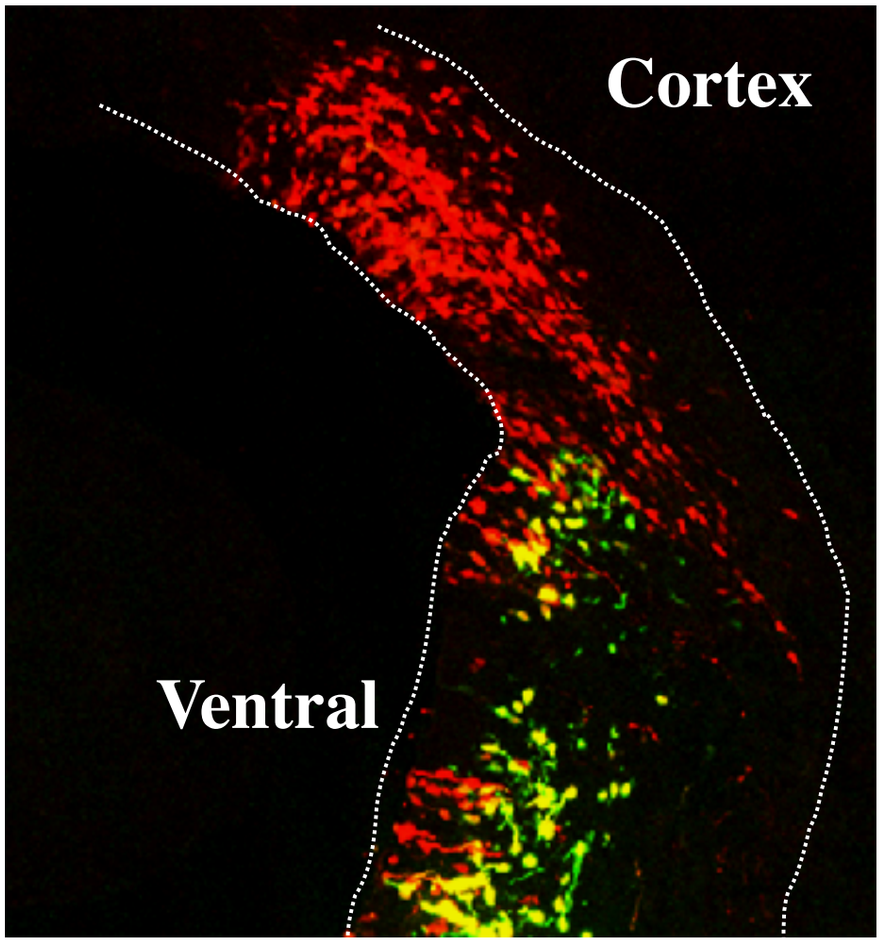
In utero Electroporation



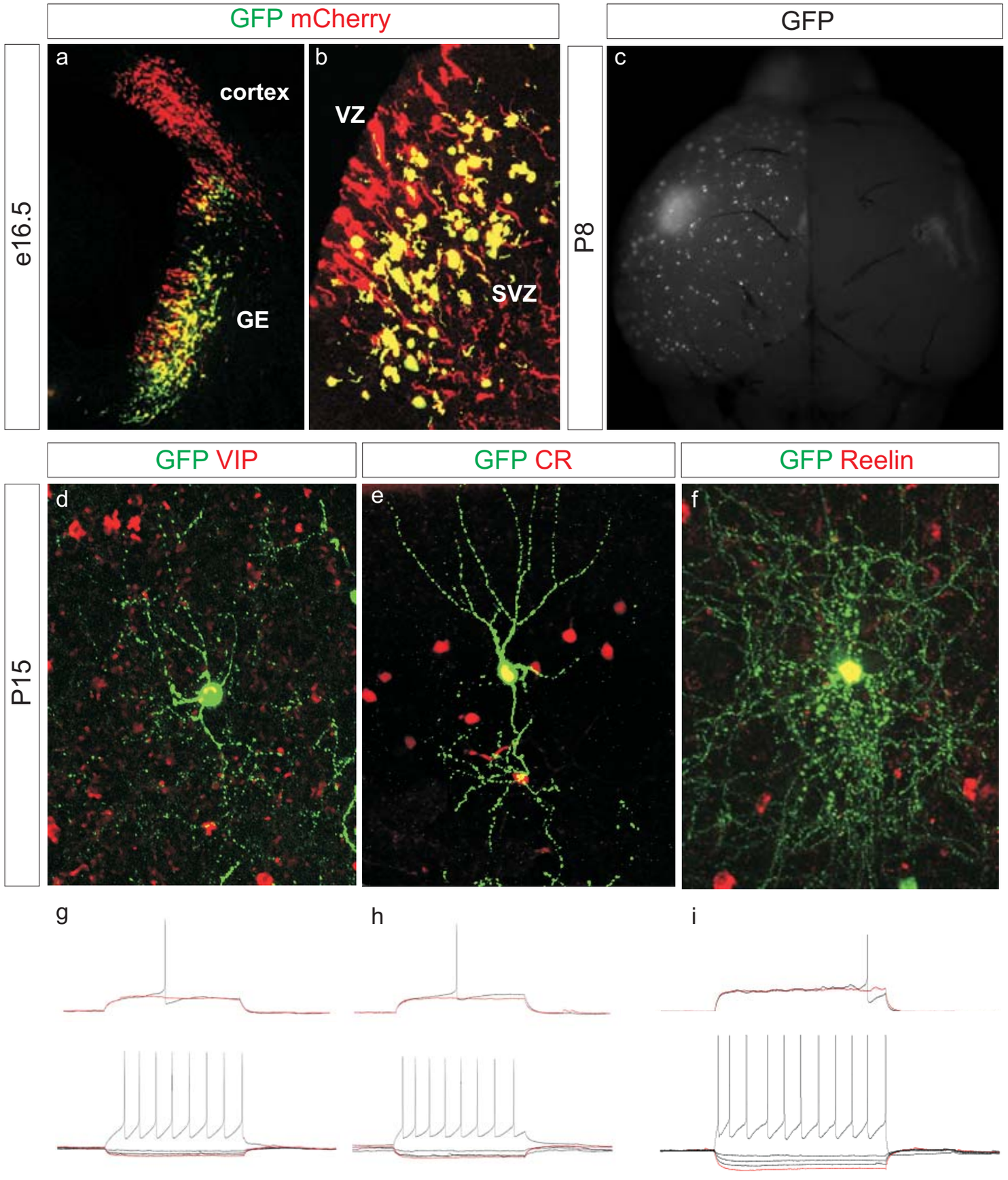
GABAergic-specific enhancer (*Dlx5/6*)

Ubiquitous ***CAG-mCherry***

GABAergic ***Dlx5/6 enhancer-EGFP***

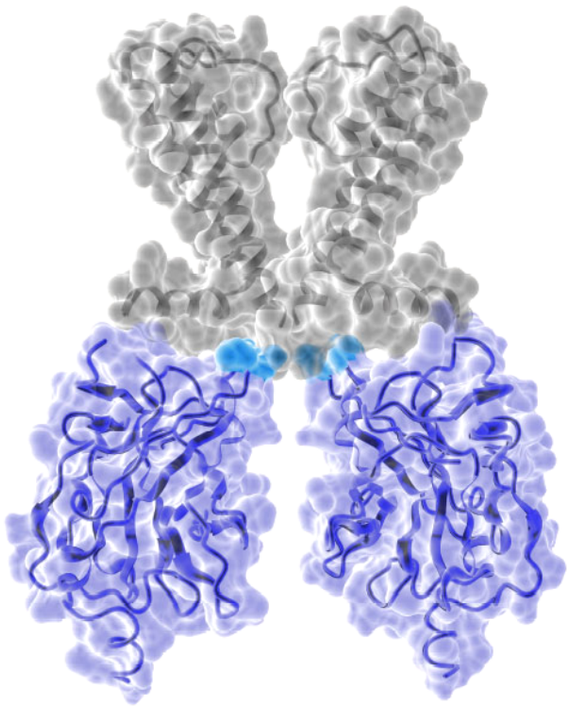


Selective targeting of specific CGE-derived interneuron subclasses

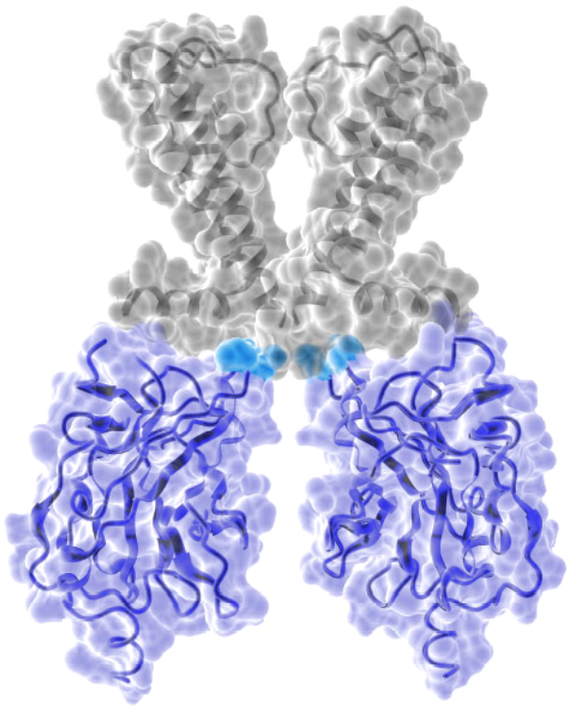


Kir2.1 eliminates the activity

Kir2.1
Inwardly rectifying potassium channel



Kir2.1
Inwardly rectifying potassium channel



Kir2.1 eliminates the activity

Olfactory sensory neurons

Neuron, Vol. 42, 553–566, May 27, 2004, Copyright ©2004 by Cell Press

Spontaneous Neural Activity Is Required for the Establishment and Maintenance of the Olfactory Sensory Map

C. Ron Yu,[1,2] Jennifer Power,[2] Gilad Barnea,[2] Sean O'Donnell,[3] Hannah E.V. Brown,[4] Joseph Osborne,[3] Richard Axel,[2,3,4,*] and Joseph A. Gogos[2,5,*]

Thalamo-cortical targeting

Interplay between Laminar Specificity and Activity-Dependent Mechanisms of Thalamocortical Axon Branching

Naofumi Uesaka,* Yasufumi Hayano,* Akito Yamada, and Nobuhiko Yamamoto
Neuroscience Laboratories, Graduate School of Frontier Biosciences, Osaka University, Suita, Osaka 565-0871, Japan

Callosal axon targeting

Evidence for Activity-Dependent Cortical Wiring: Formation of Interhemispheric Connections in Neonatal Mouse Visual Cortex Requires Projection Neuron Activity

Hidenobu Mizuno,[1,2] Tomoo Hirano,[1,2] and Yoshiaki Tagawa[1,2]
[1]Department of Biophysics, Kyoto University Graduate School of Science, Kitashirakawa-Oiwake-cho, Sakyo-ku, Kyoto 606-8502, Japan, and [2]Core Research for Evolutional Science and Technology, Japan Science and Technology Agency, Kawaguchi, Saitama 332-0012, Japan

Activity-Dependent Development of Callosal Projections in the Somatosensory Cortex

Chun-Lei Wang,* Lei Zhang,* Yang Zhou, Jing Zhou, Xiu-Juan Yang, Shu-min Duan, Zhi-Qi Xiong, and Yu-Qiang Ding
Institute of Neuroscience and Key Laboratory of Neurobiology, Shanghai Institutes for Biological Sciences, Chinese Academy of Sciences, Shanghai 200031, China

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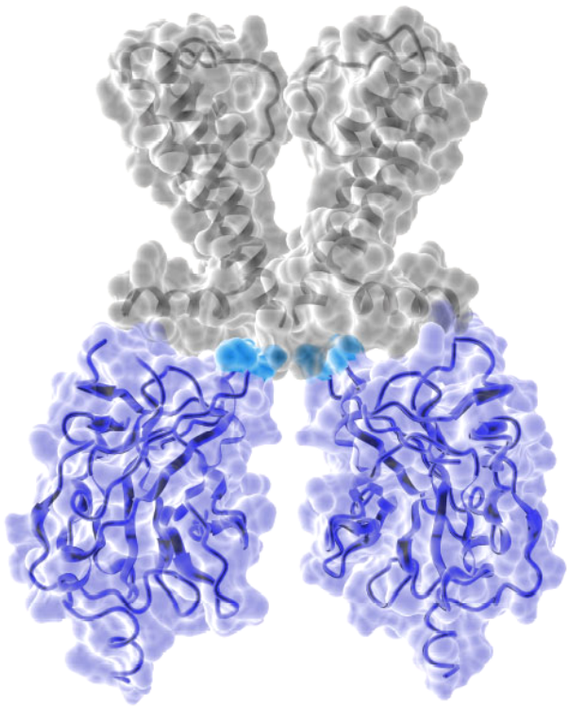
Kir2.1
Inwardly rectifying potassium channel



Excitatory GABA Action Is Essential for Morphological Maturation of Cortical Neurons *In Vivo*

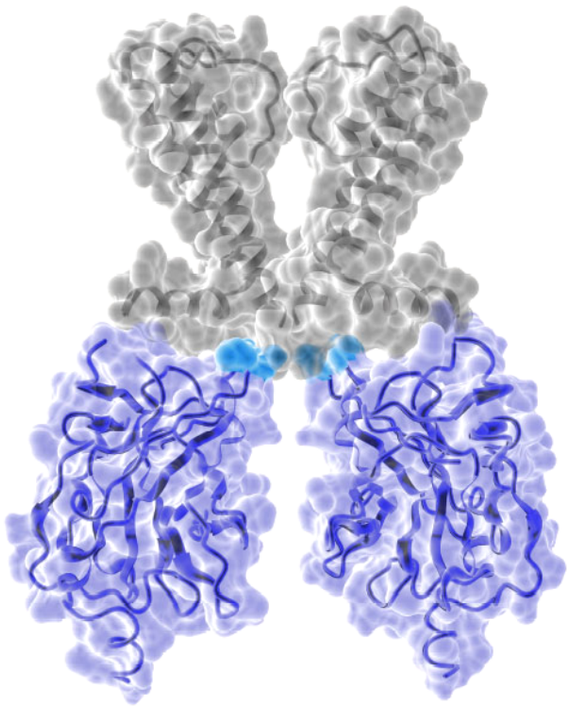
Laura Cancedda,* Hubert Fiumelli,* Karen Chen, and Mu-ming Poo
Division of Neurobiology, Department of Molecular and Cell Biology, Helen Wills Neuroscience Institute, University of California at Berkeley, Berkeley, California 94720-3200

(Cancedda et al., 2007)

Pyramidal neurons (superficial layers)

Kir2.1 eliminates the activity

Kir2.1
Inwardly rectifying potassium channel



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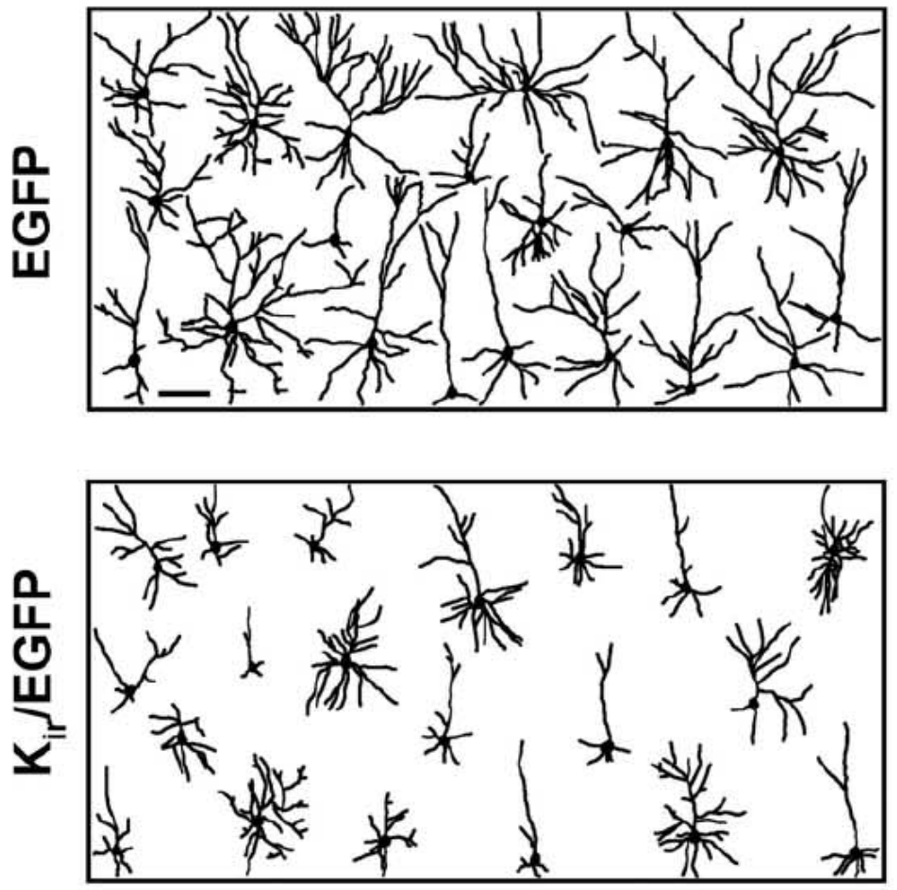
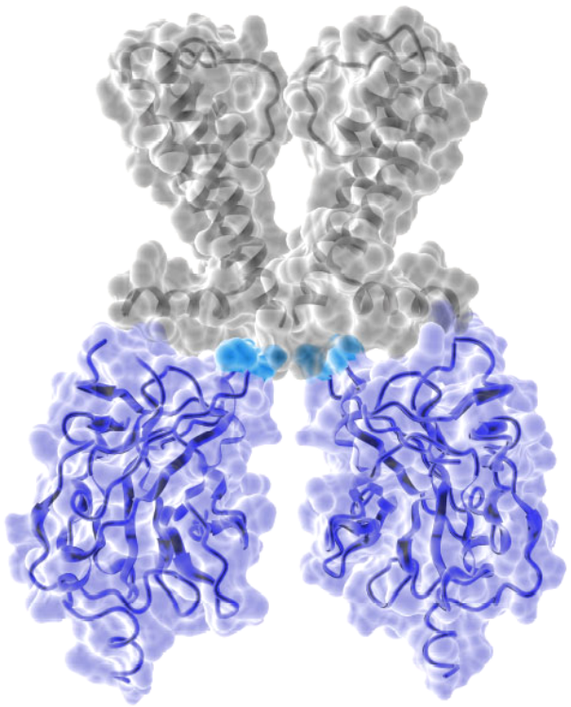
Pyramidal neurons (superficial layers)

Morphological defects



Kir2.1 eliminates the activity

Kir2.1
Inwardly rectifying potassium channel



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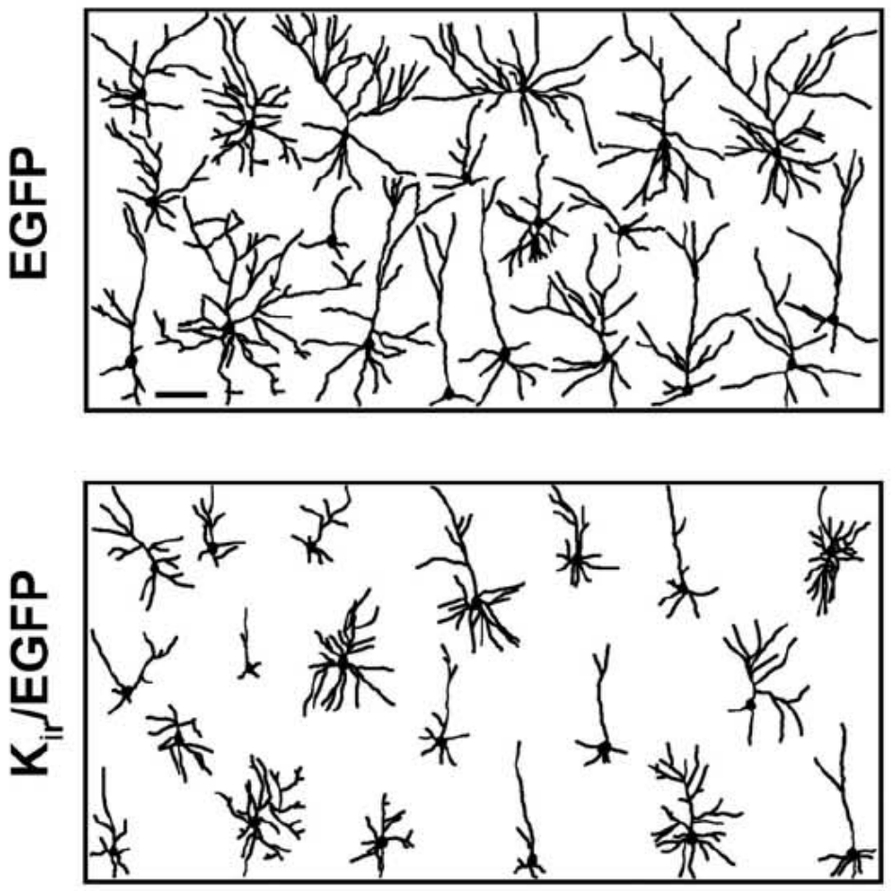
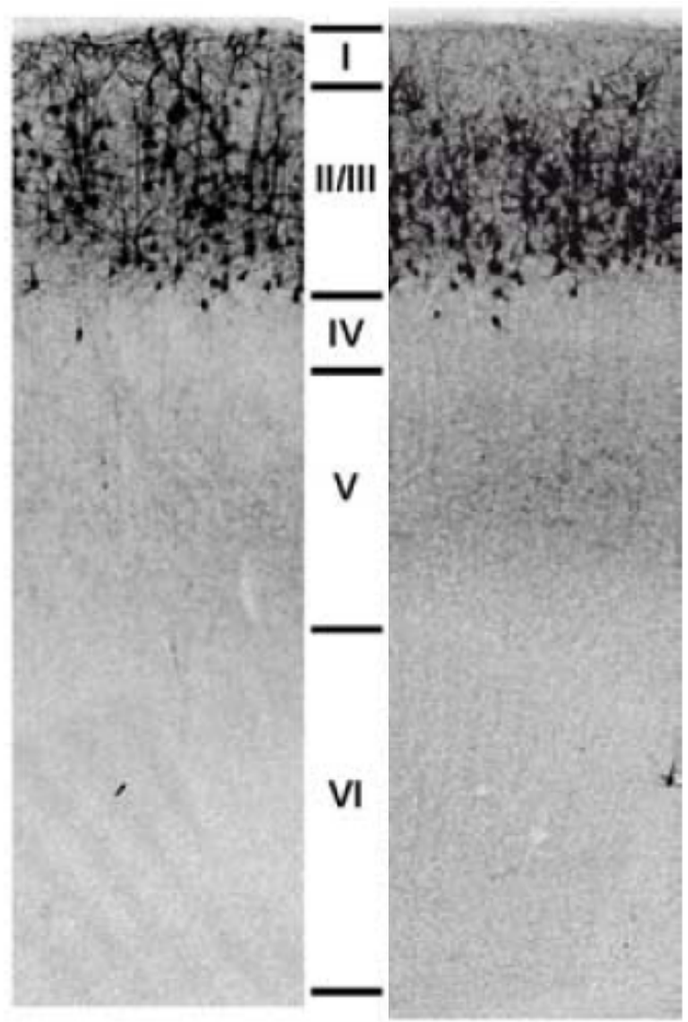
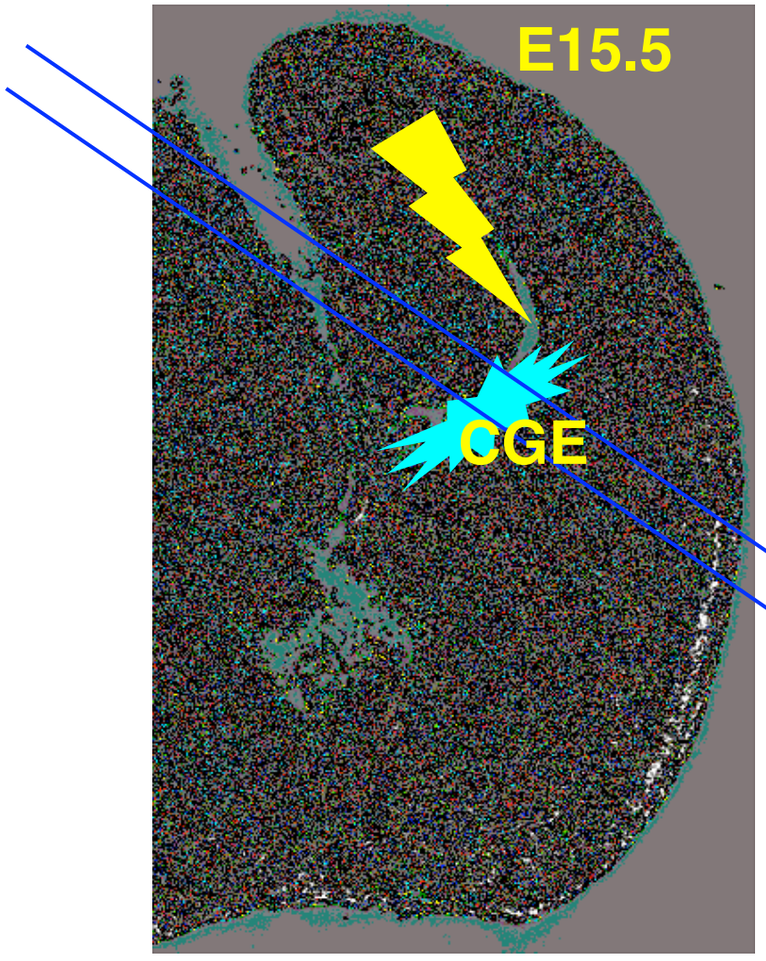
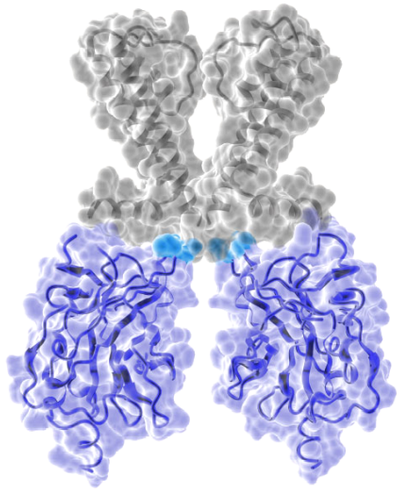


No effect in layering



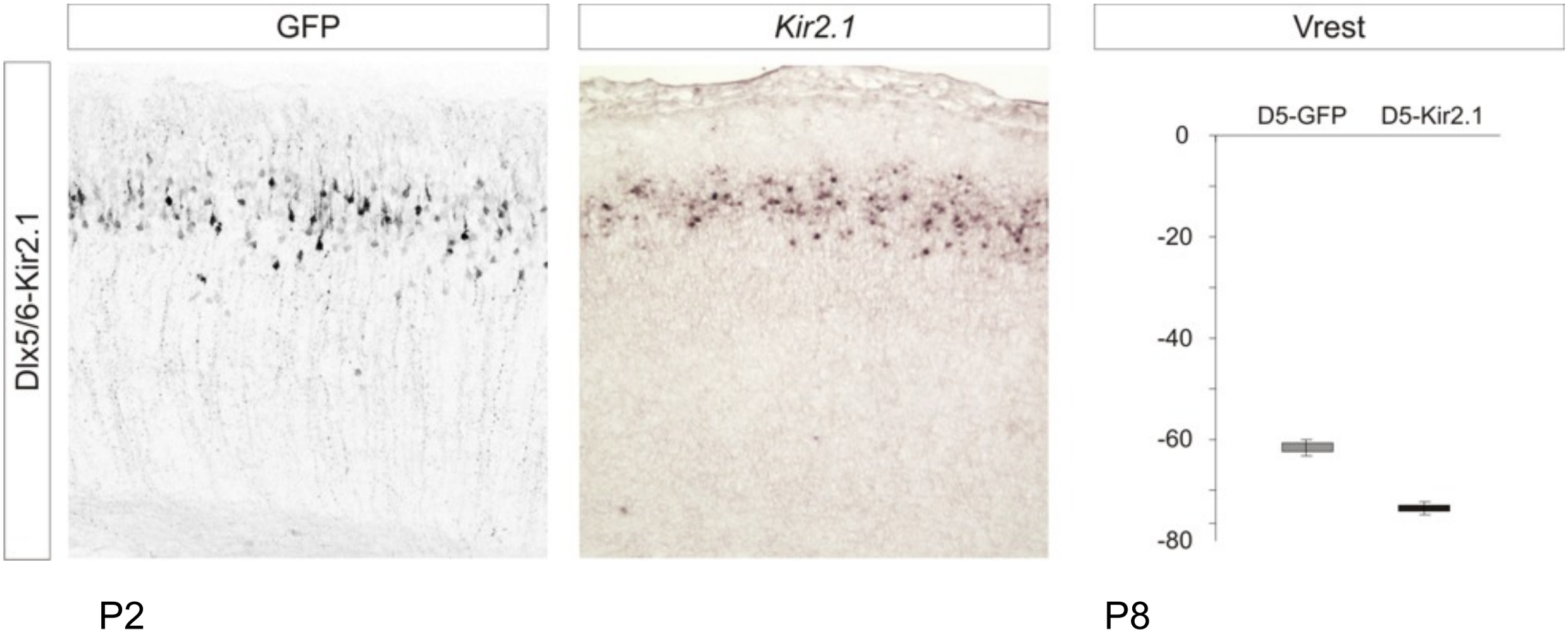
Electroporation



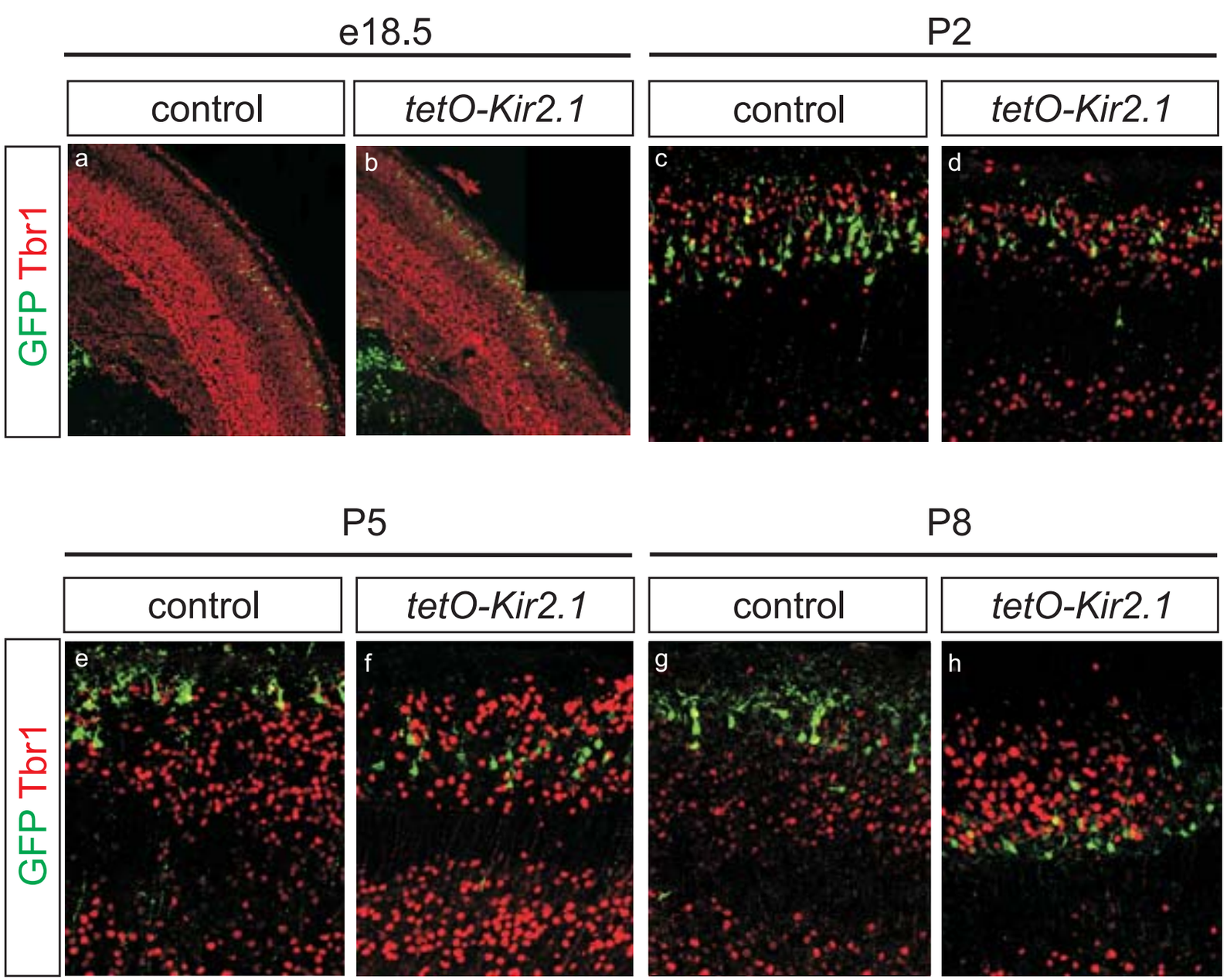


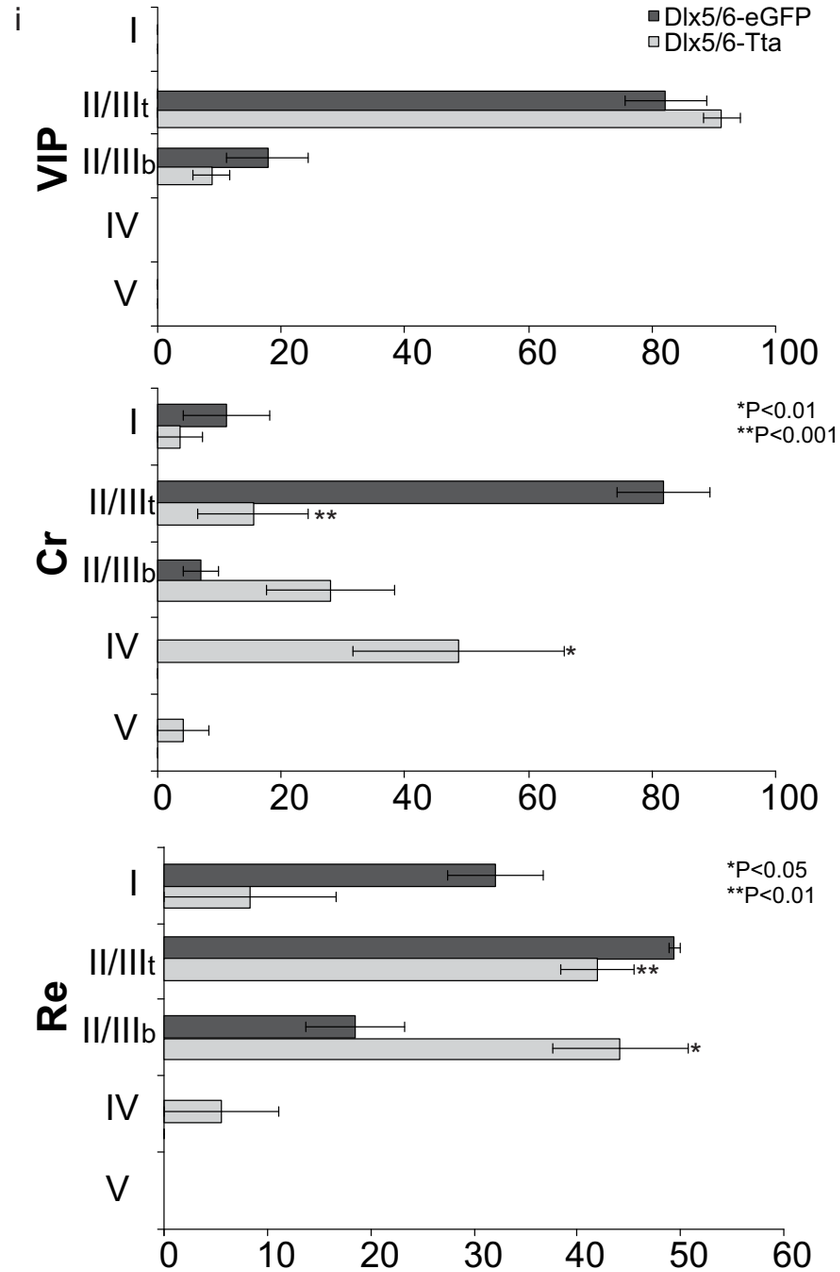
Express *Kir2.1* in CGE-derived interneurons and eliminate the activity

Kir2.1 expression significantly decreases Vrest

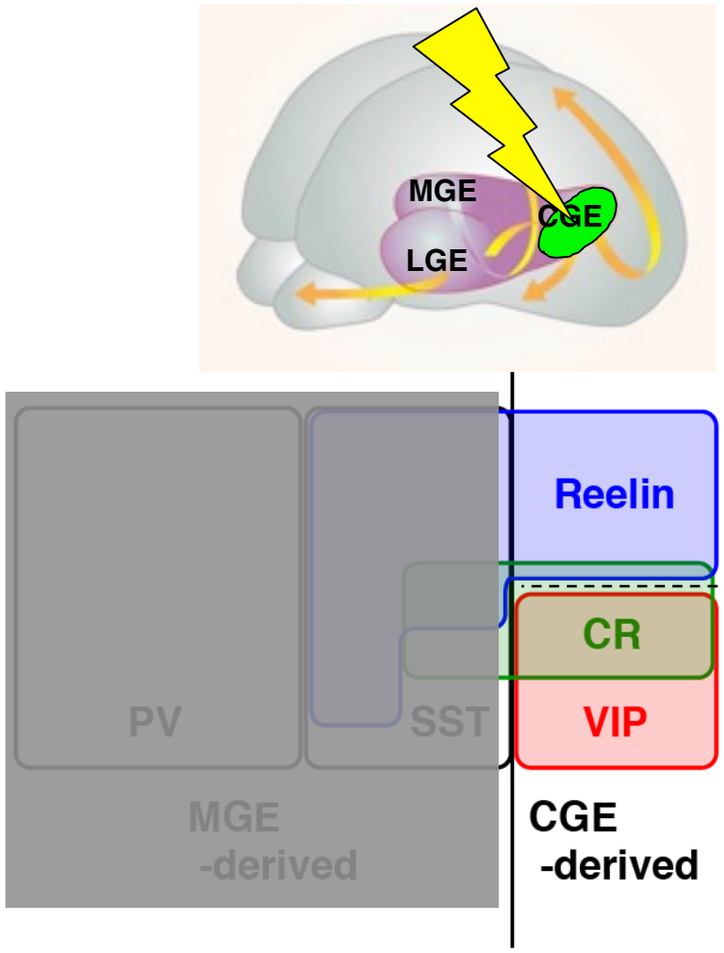


Activity-dependent defects in the laminar positioning of CGE-derived interneurons are subtype specific.



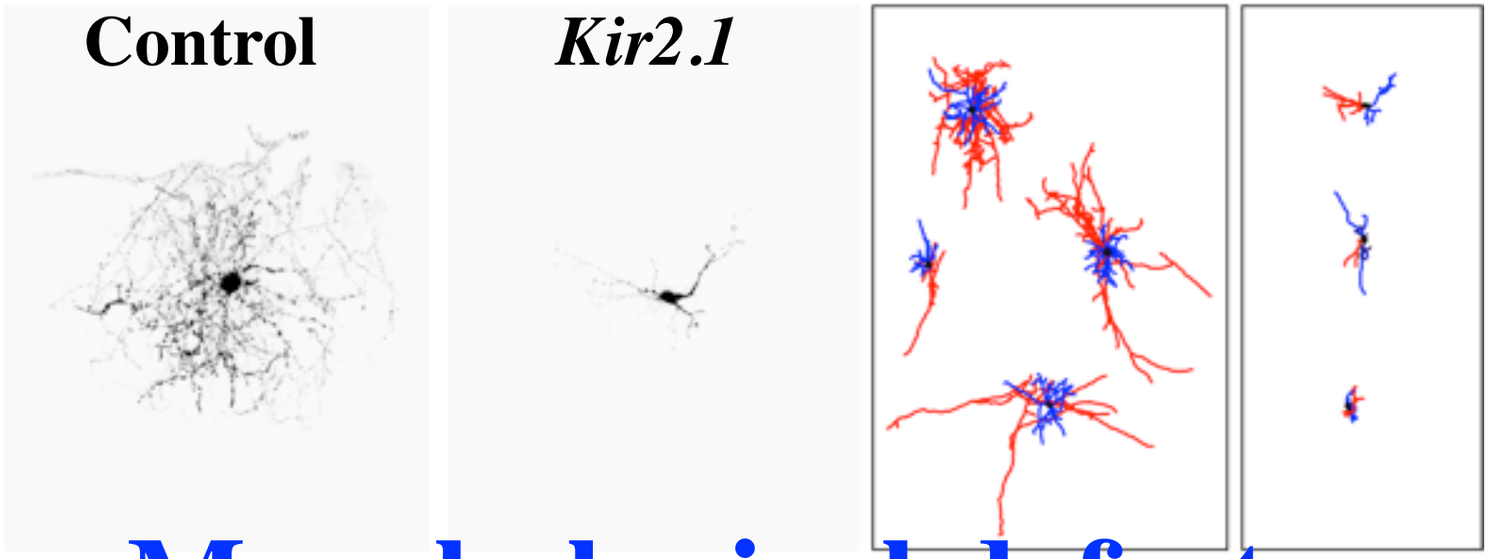


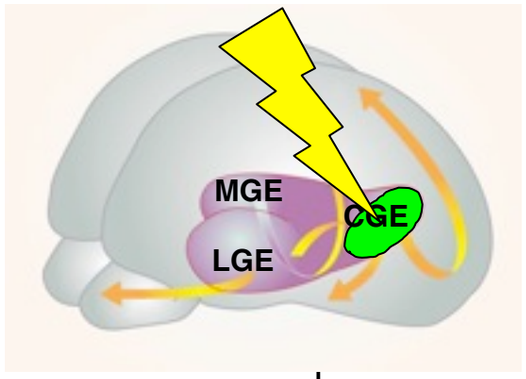
Effect of *Kir2.1* expression in CGE-derived interneurons Morphologies

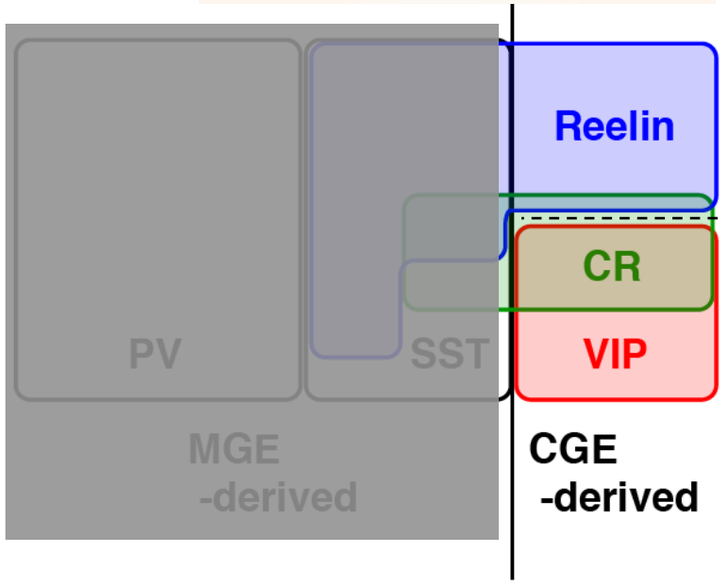


Effect of *Kir2.1* expression in CGE-derived interneurons

Morphologies



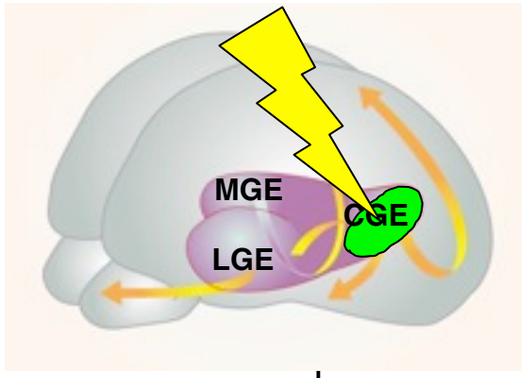


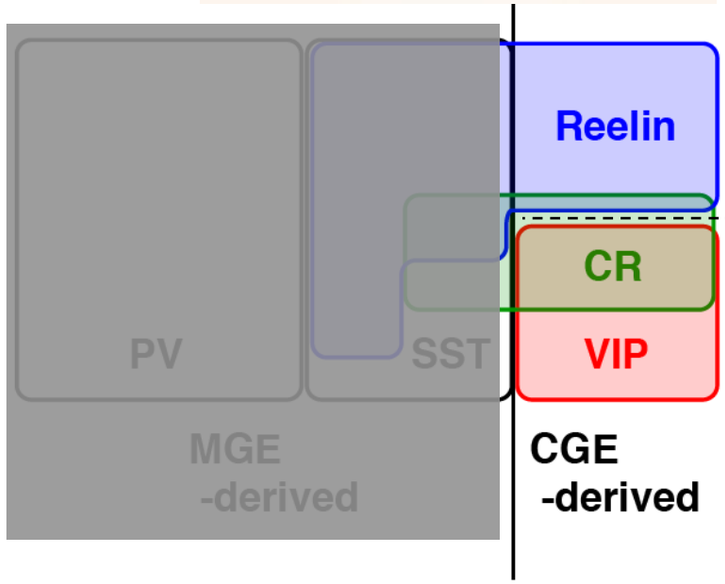


Morphological defects

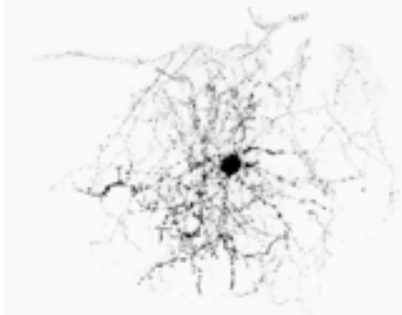
Effect of *Kir2.1* expression in CGE-derived interneurons

Morphologies



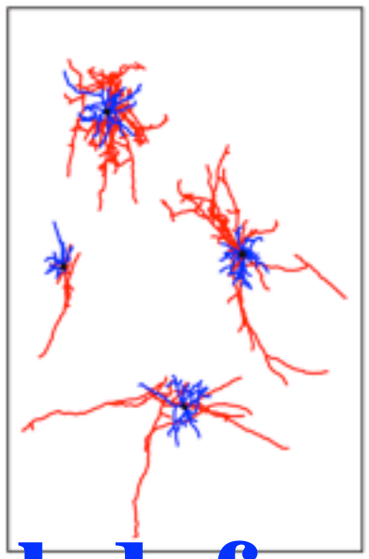


Control

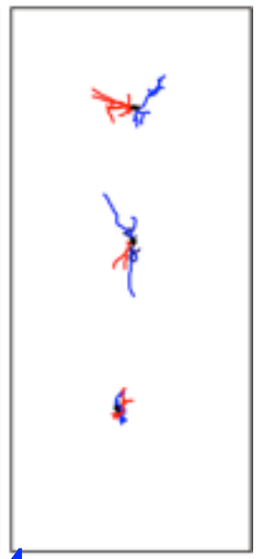


Kir2.1

Control



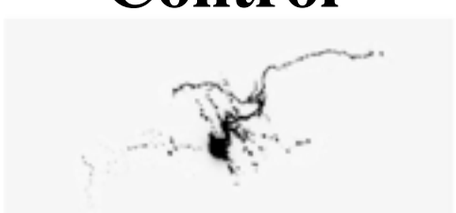
Kir2.1



Morphological defects

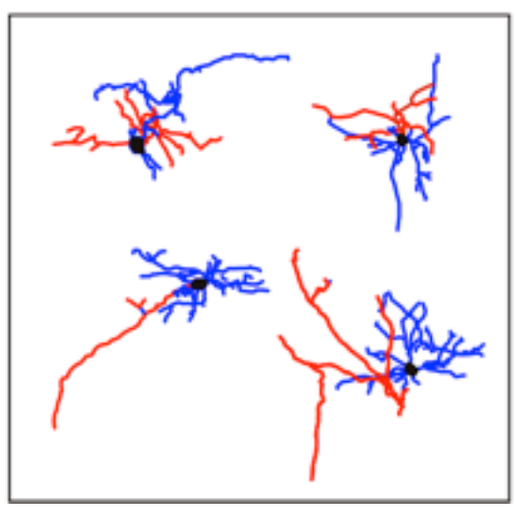
No obvious defects

Control

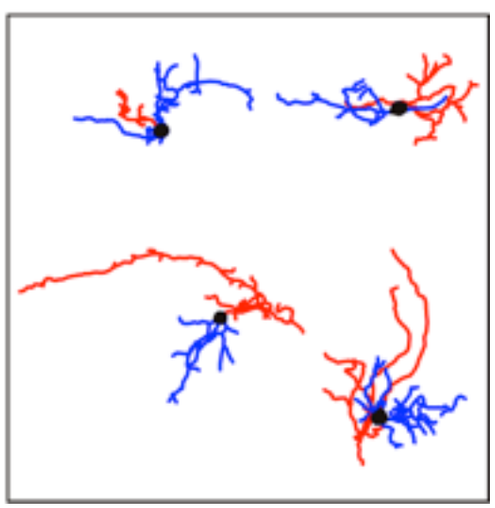


Kir2.1

Control



Kir2.1

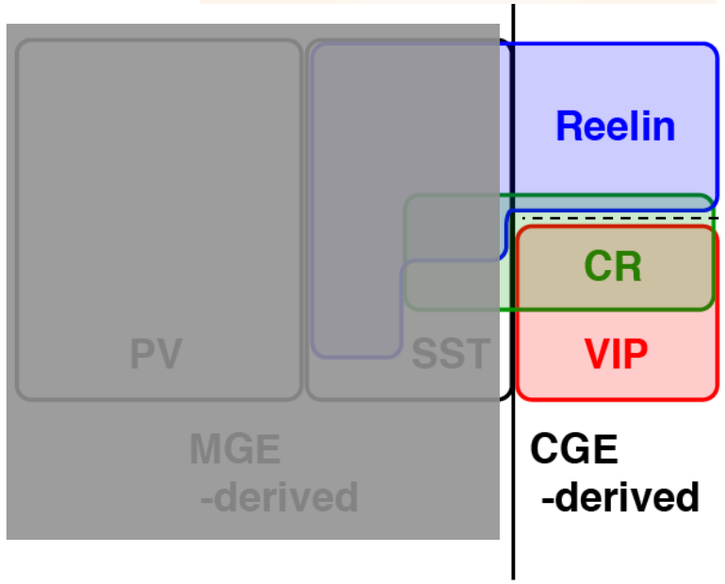


Effect of *Kir2.1* expression in CGE-derived interneurons

Morphologies

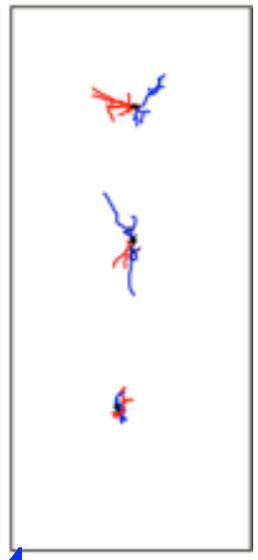
Control

Kir2.1



Control

Kir2.1

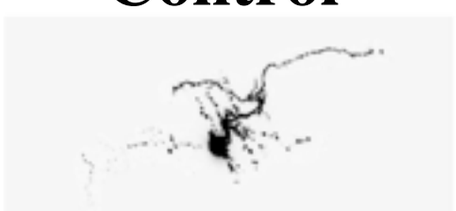


Class-specific effect

Morphological defects

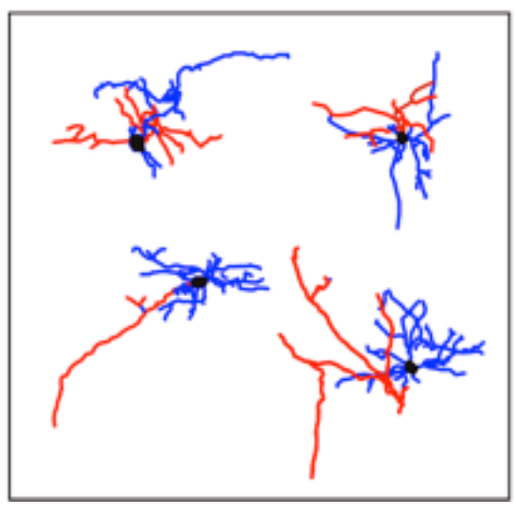
No obvious defects

Control

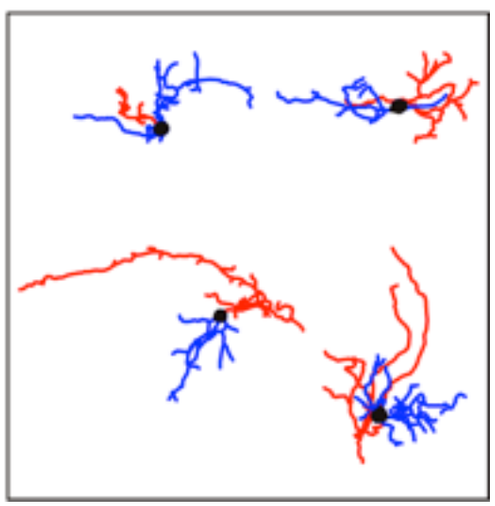


Kir2.1

Control



Kir2.1



Defects in axonal and dendritic development in NPY and CR interneurons persist beyond P15

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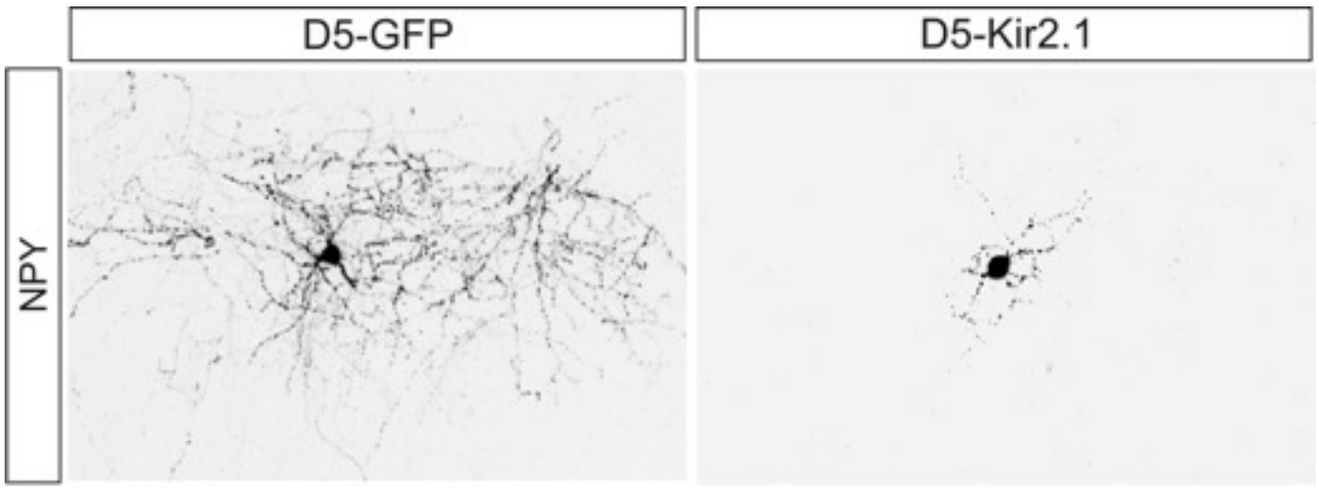
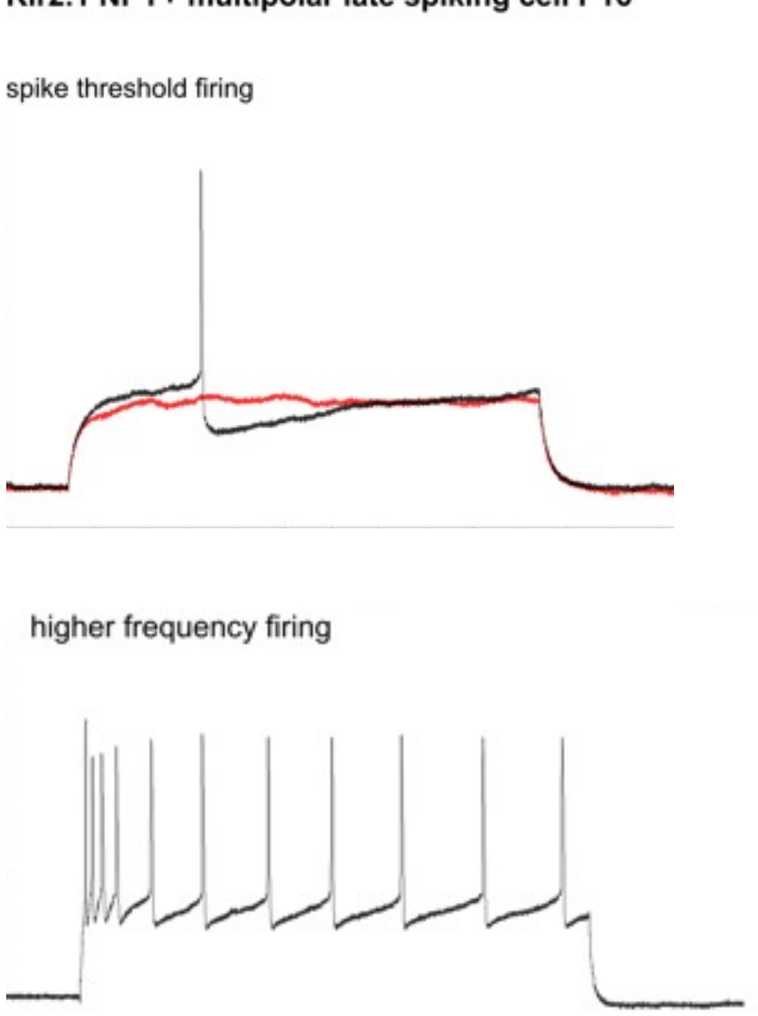
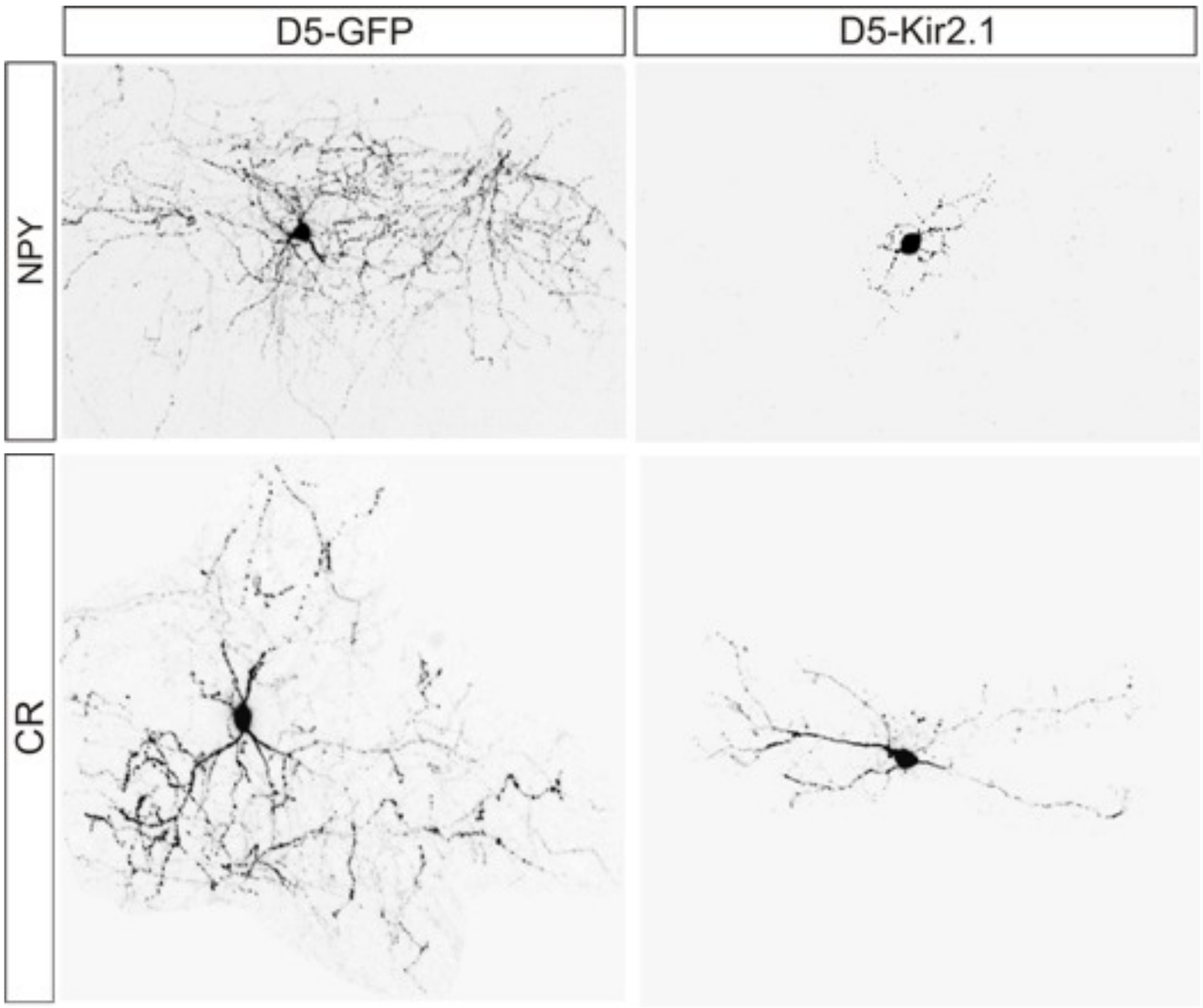


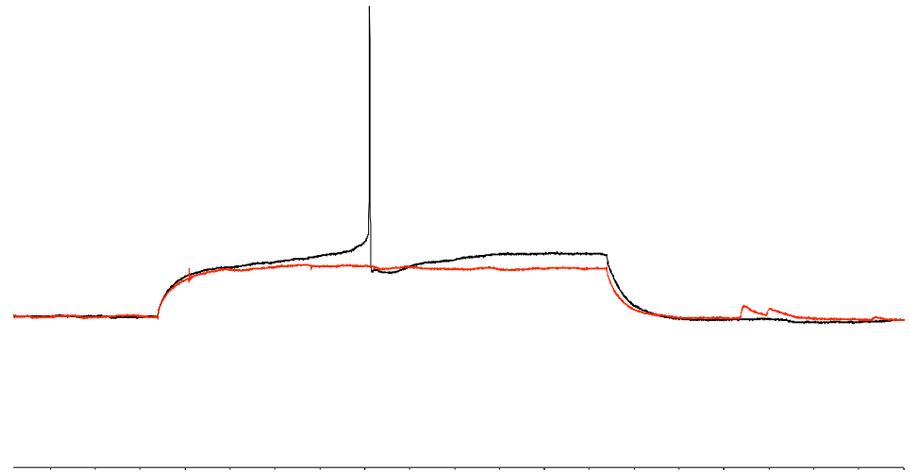
Kir2.1 NPY multipolar cell at P16



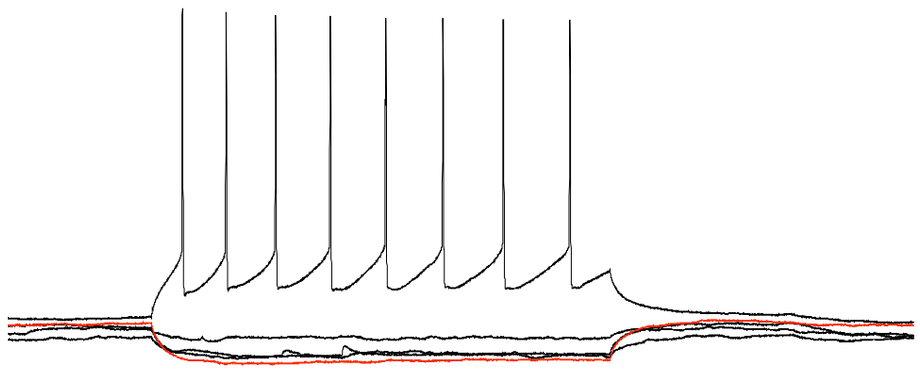
Defects in axonal and dendritic development in NPY and CR interneurons persist beyond P15



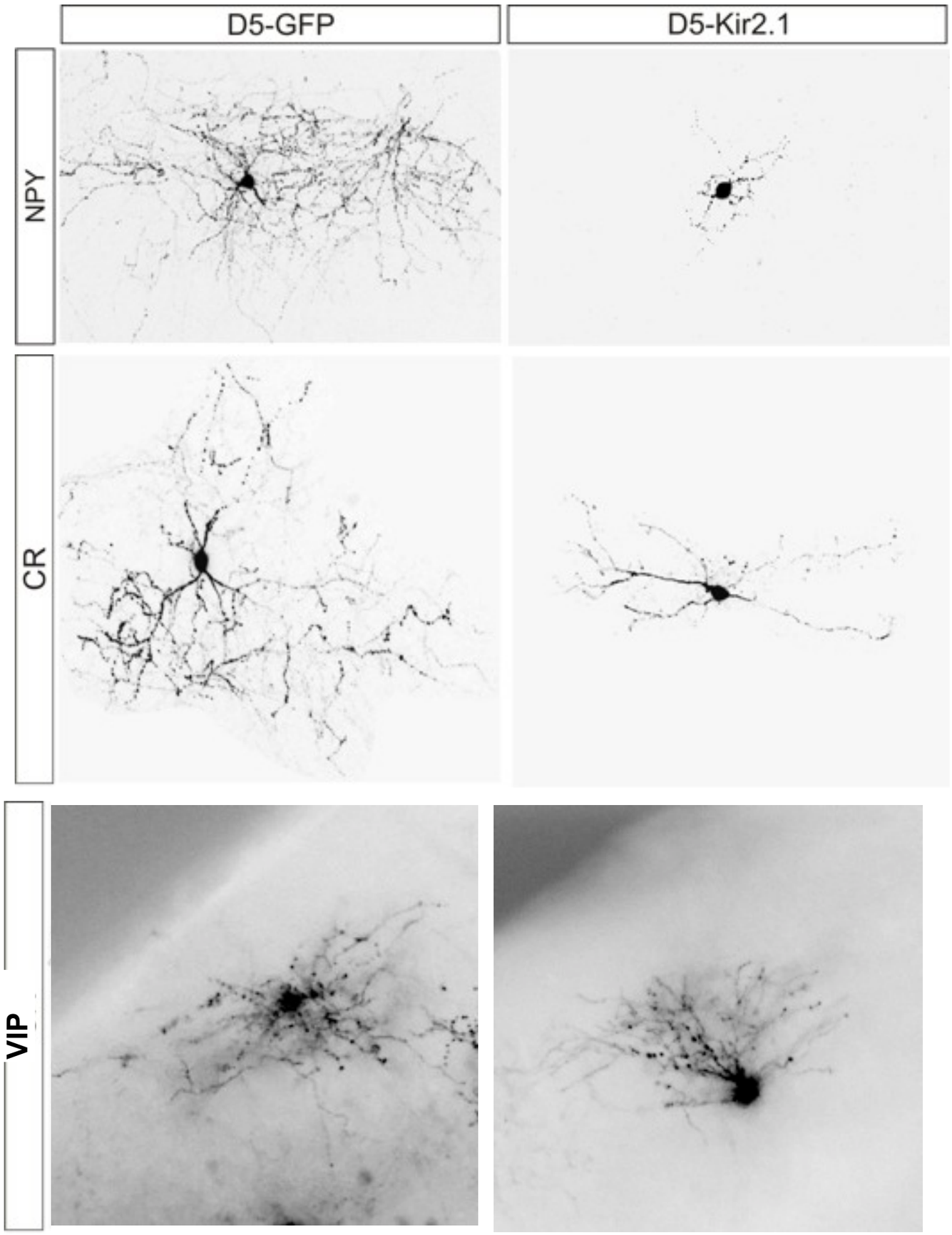
Kir2.1 CR cell at P18



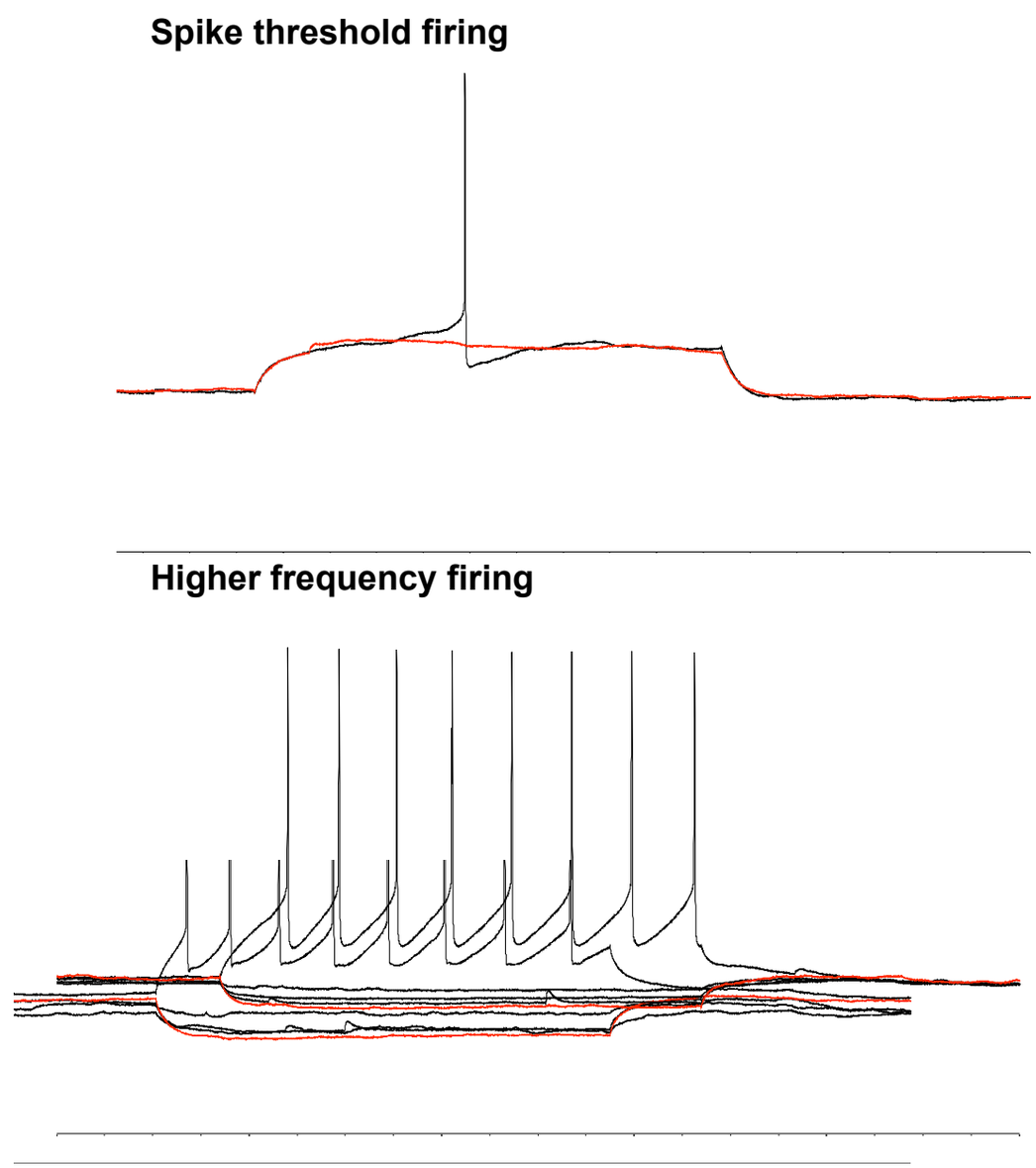
Higher frequency firing



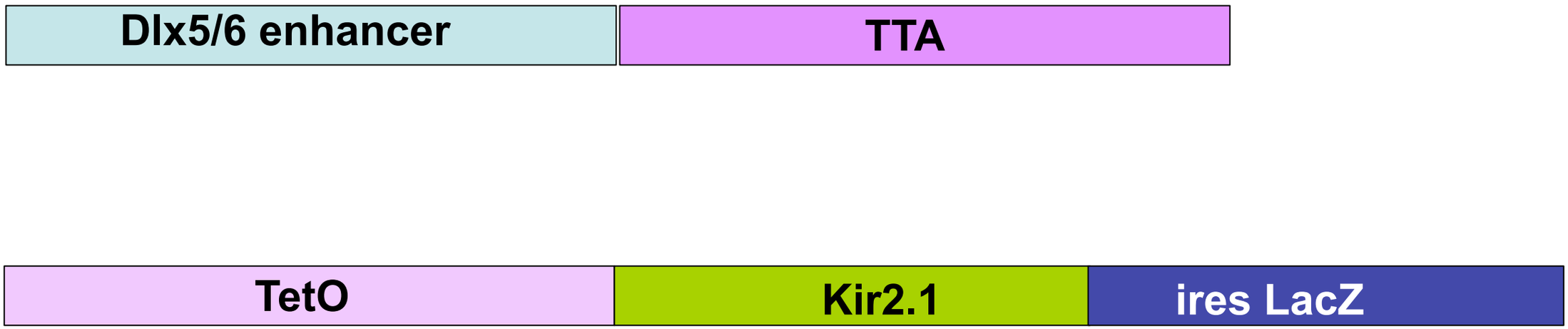
Defects in axonal and dendritic development in NPY and CR interneurons persist beyond P15



Kir2.1 VIP multipolar cell at P16



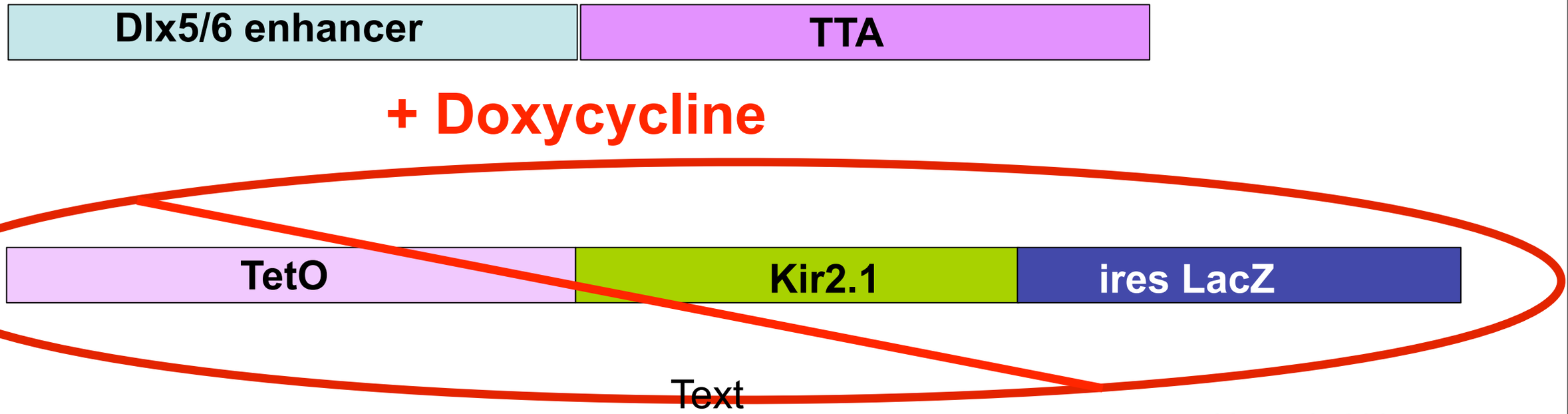
Temporal control of neuronal excitability



Text

Yu et al., 2004

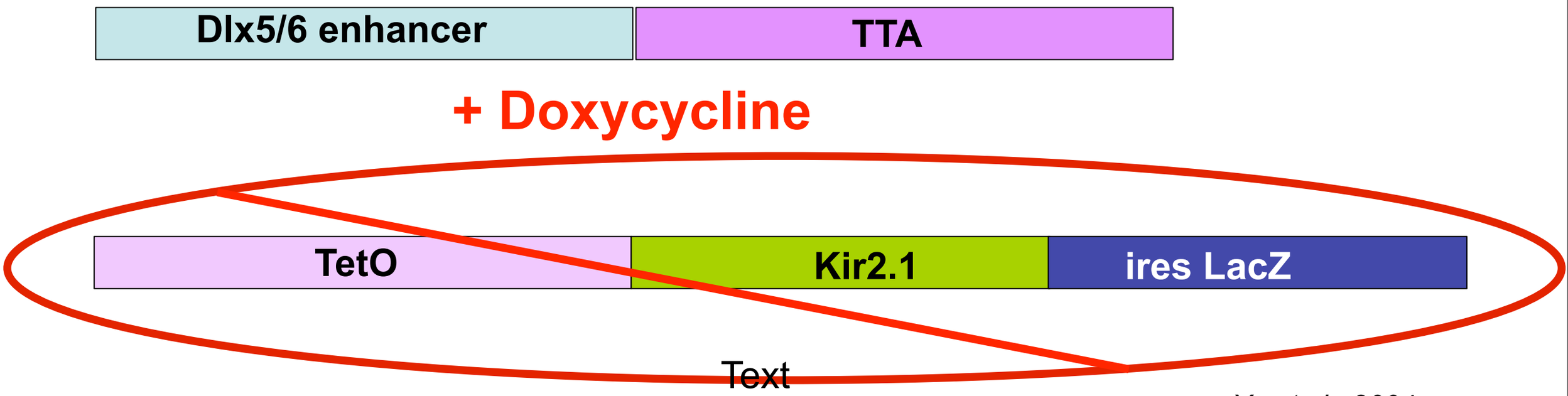
Temporal control of neuronal excitability



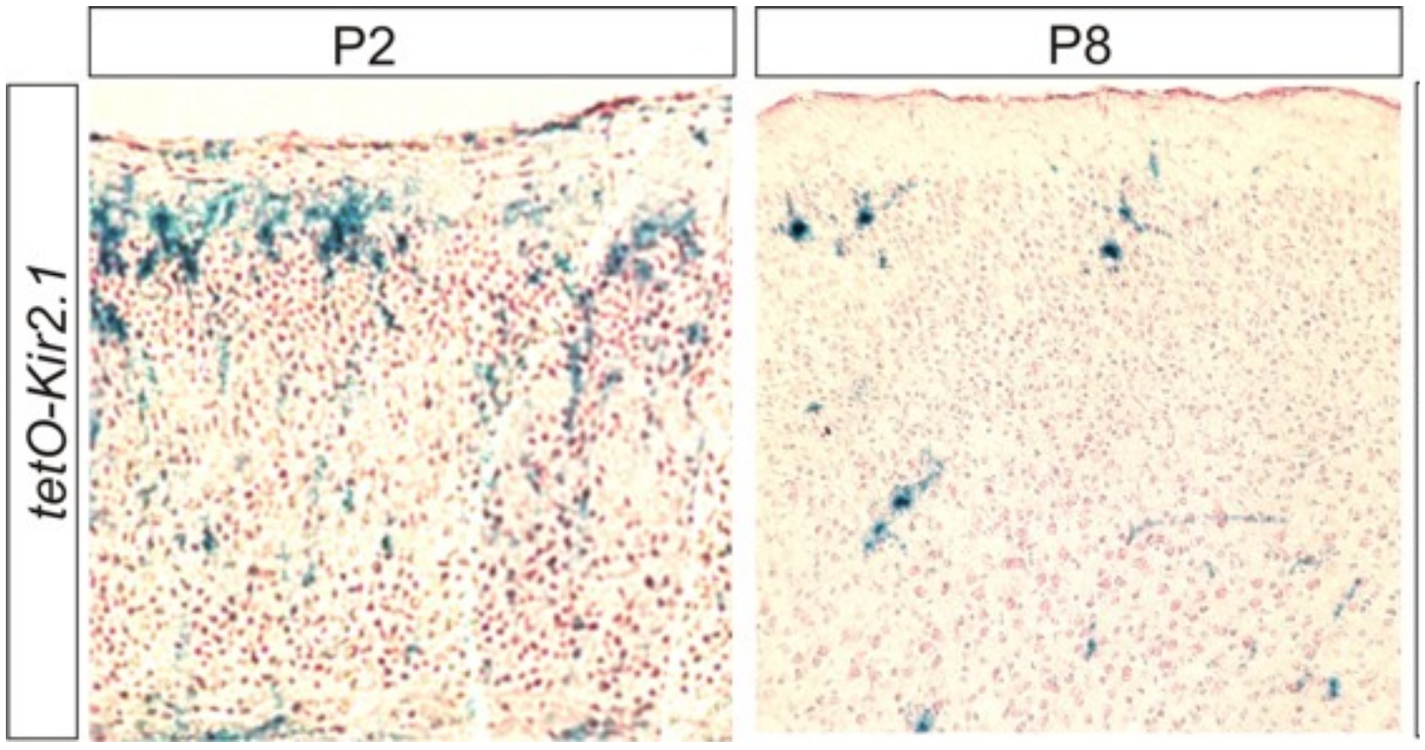
Text

Yu et al., 2004

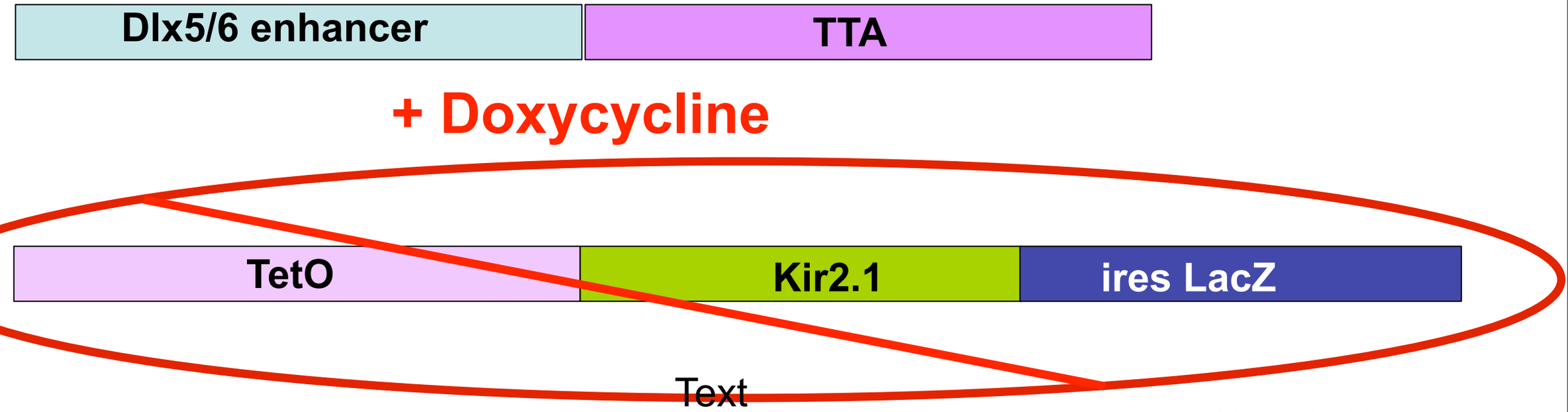
Temporal control of neuronal excitability



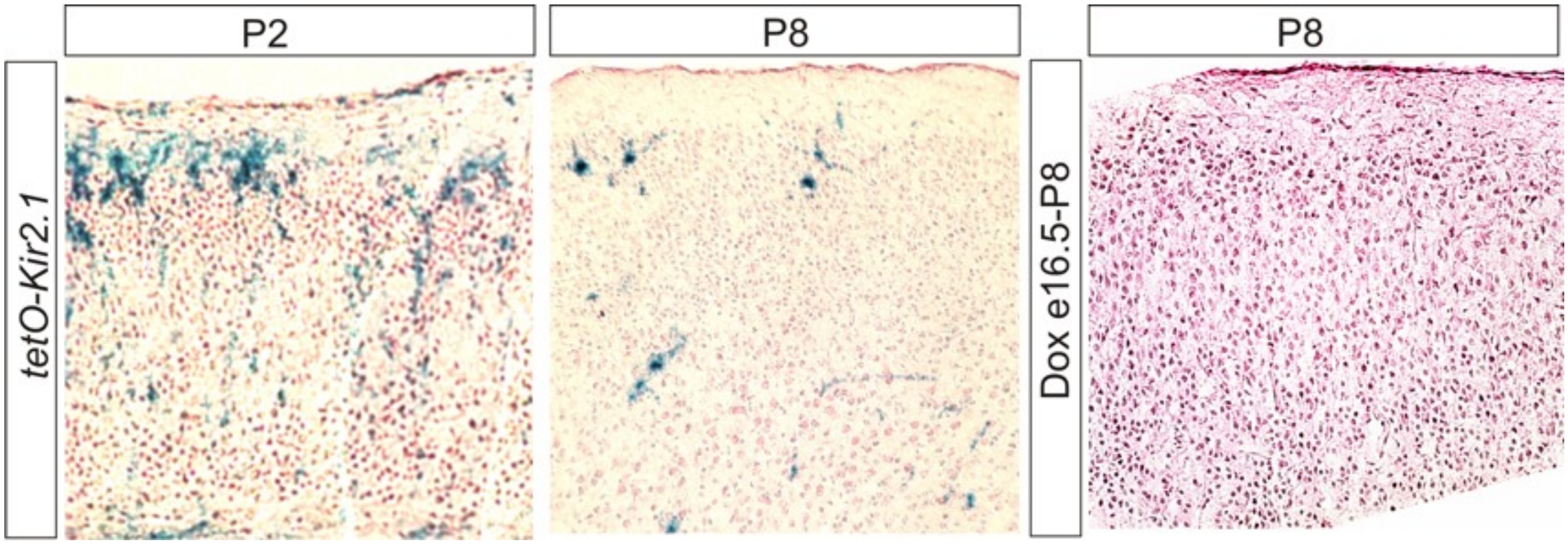
Yu et al., 2004



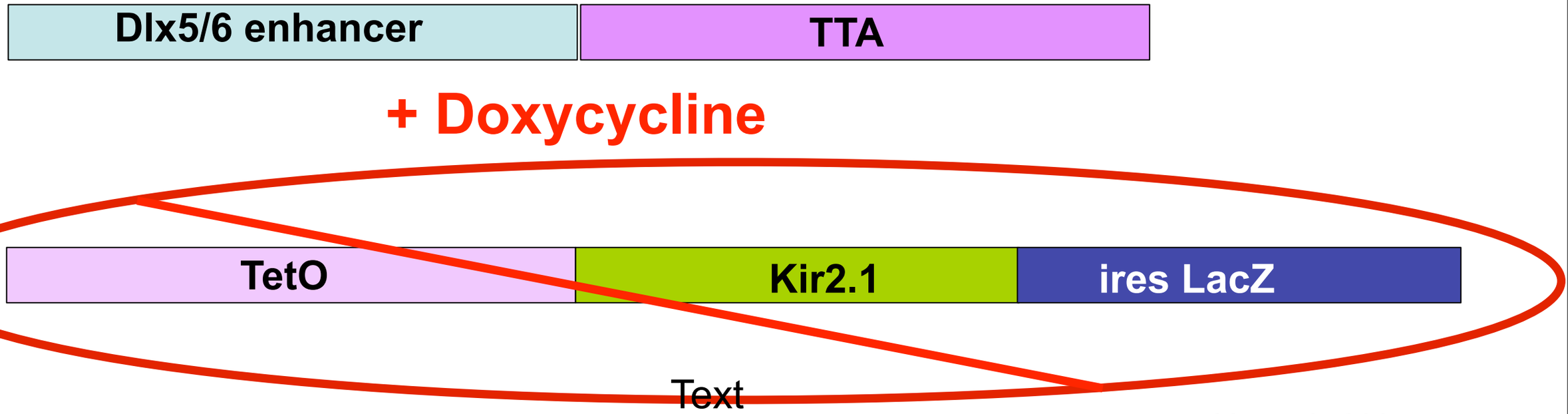
Temporal control of neuronal excitability



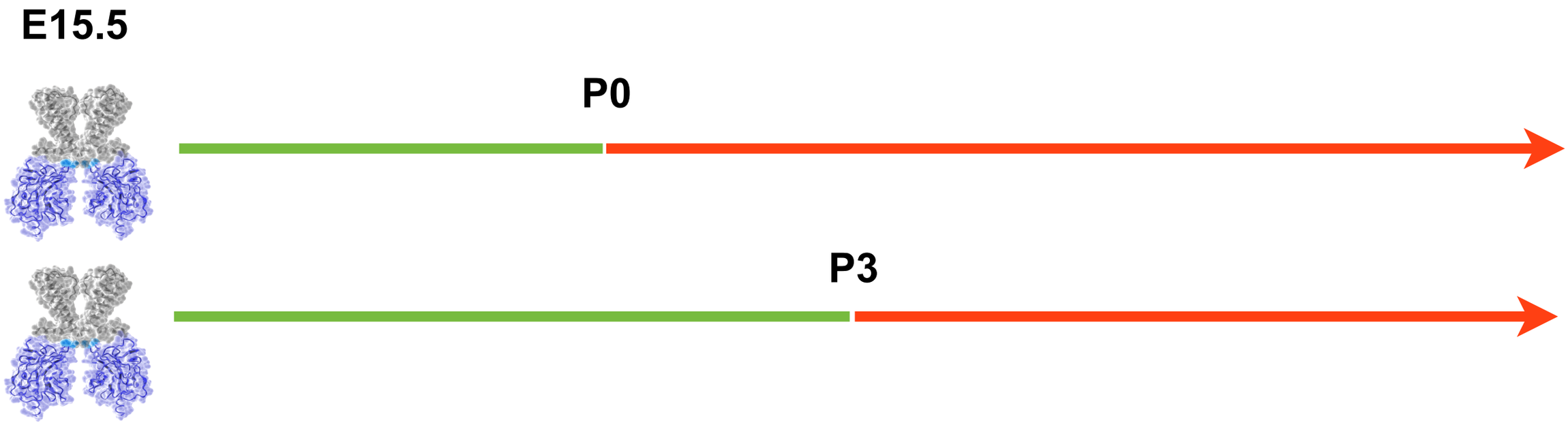
Yu et al., 2004

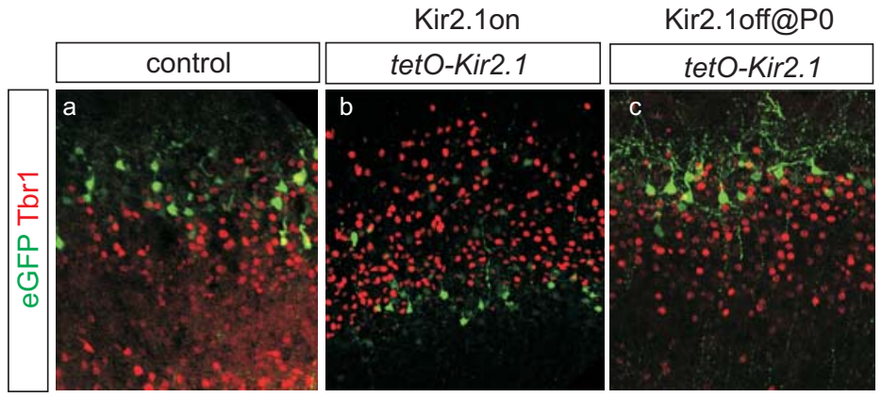


Temporal control of neuronal excitability



Yu et al., 2004




Kir2.1on
Kir2.1off@P0
control
tetO-Kir2.1
tetO-Kir2.1
a
b
c
eGFP Tbr1

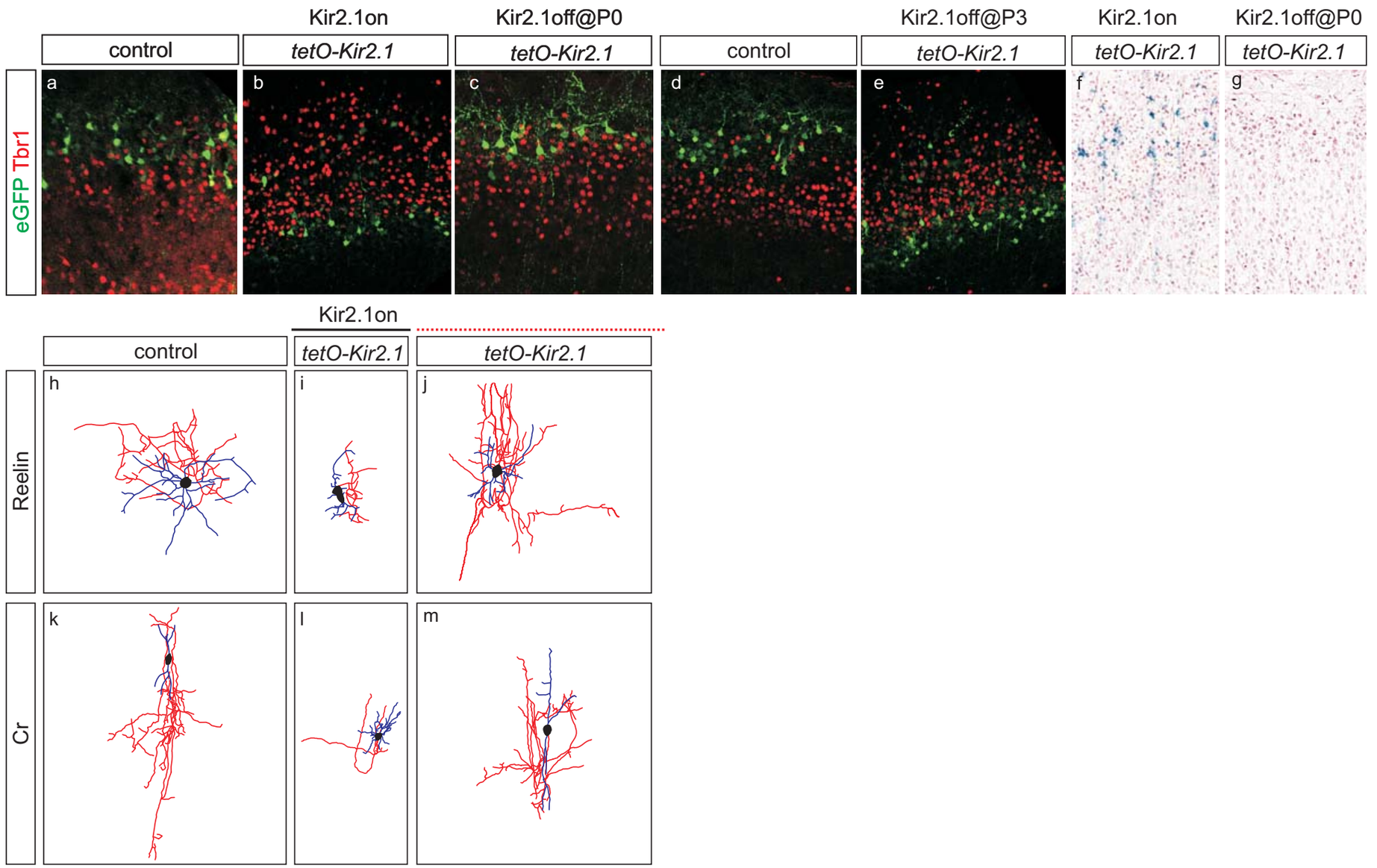


Figure 4. Specific interneuron subtypes require activity for migration and morphological maturation at two distinct stages of development.

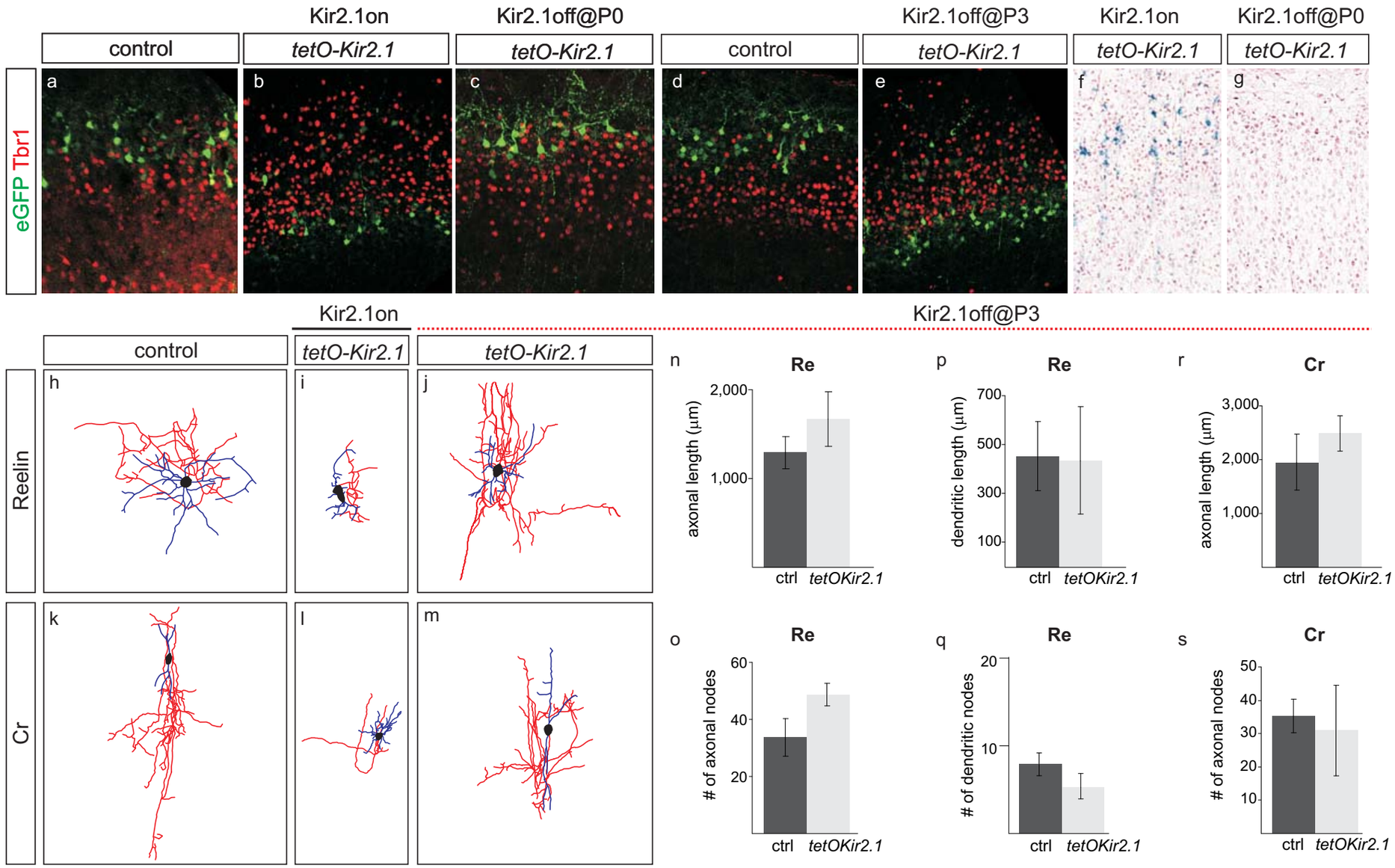
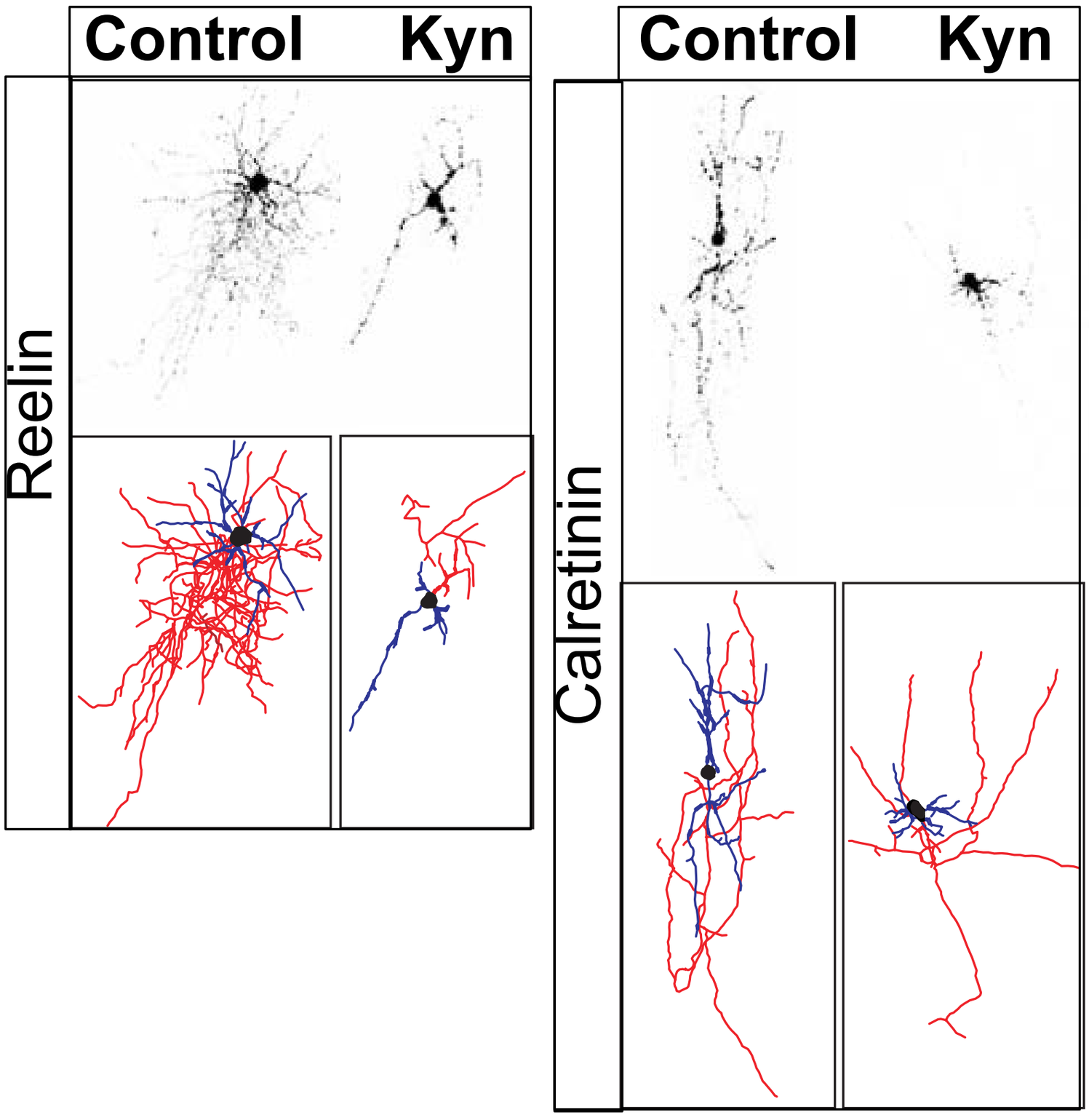


Figure 4. Specific interneuron subtypes require activity for migration and morphological maturation at two distinct stages of development.

Glutamate signaling is selectively required for morphology <u>but not</u> laminar positioning.



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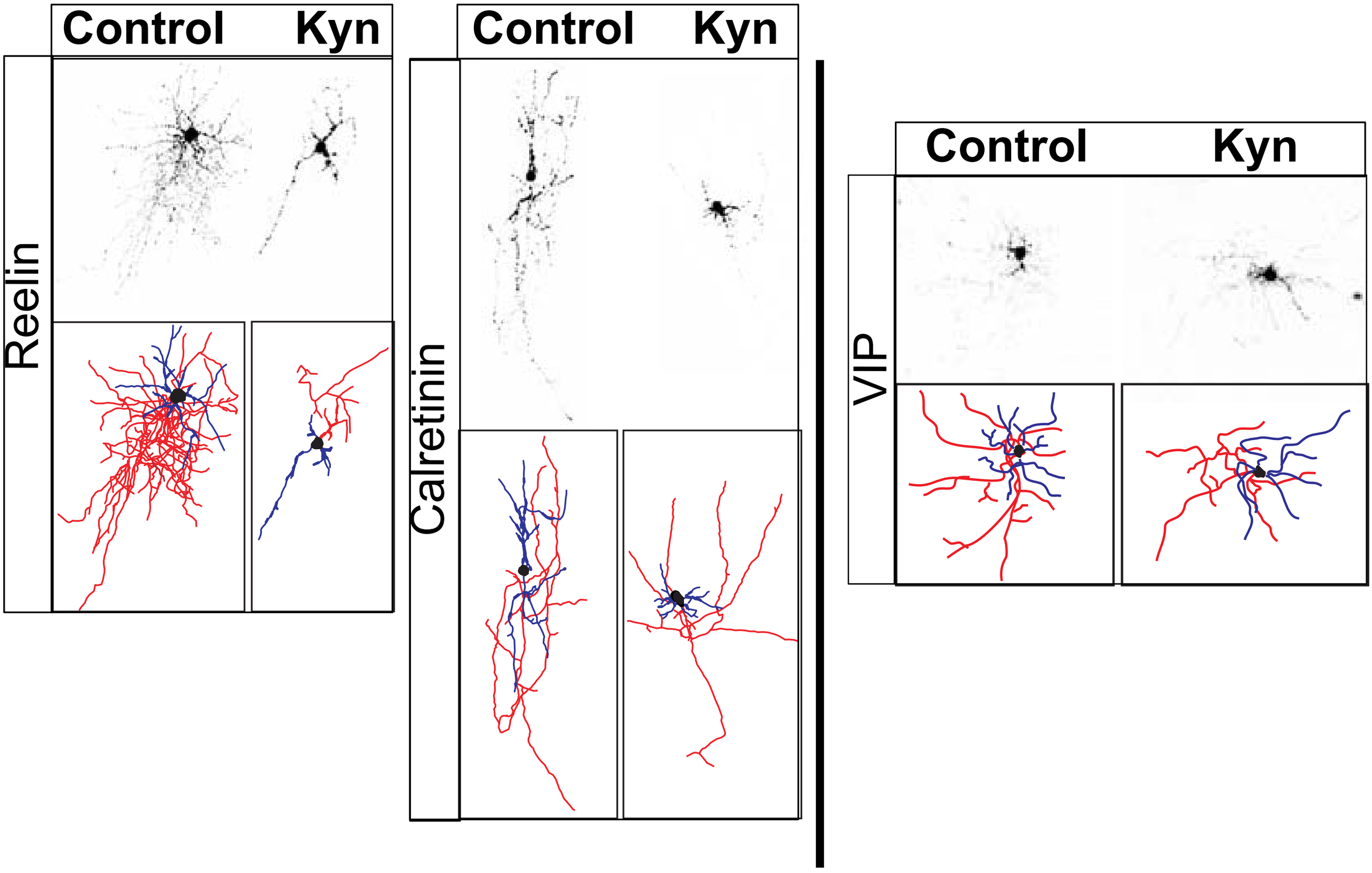

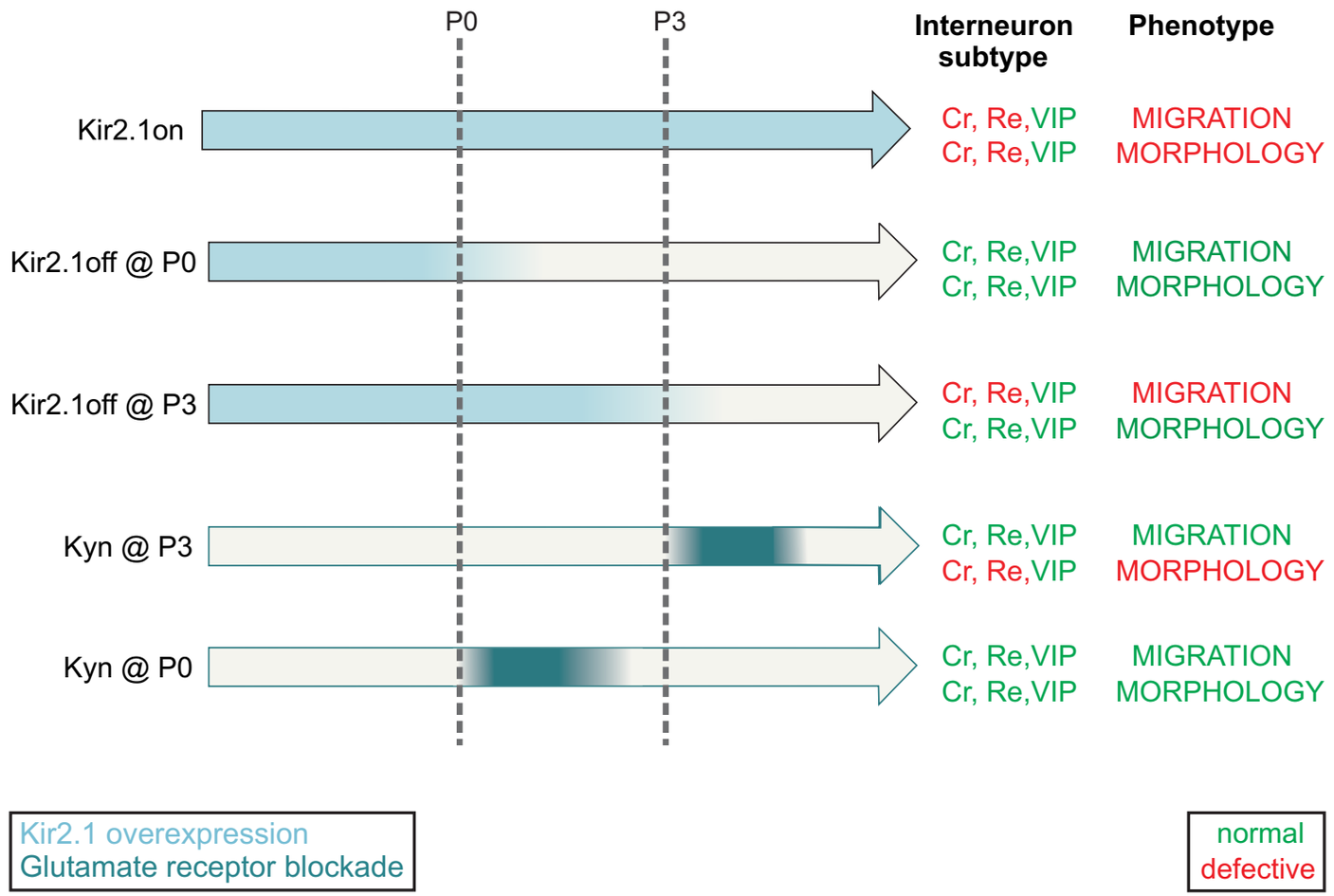

Supplementary Figure 1. Activity-dependent development of Cr- and Re-expressing interneuron subtypes

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