Neurodevelopmental effects of *SCN2A* loss of function

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SCN2A offers a unique opportunity

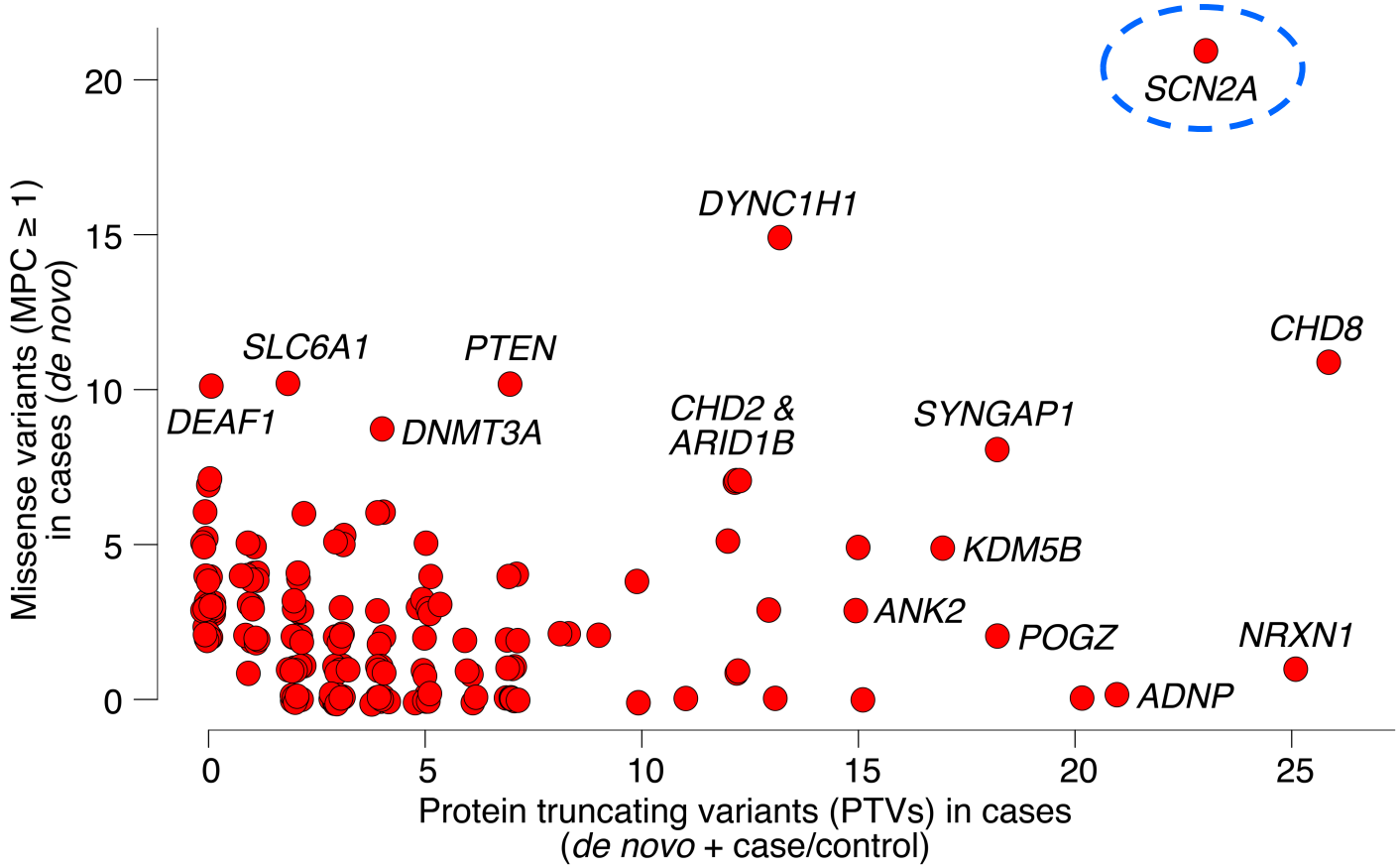
SCN2A gene

$Na_V1.2$ channels

Brain cells & circuits

Animal models

Children with *SCN2A*



SPARK
Simons Powering Autism Research

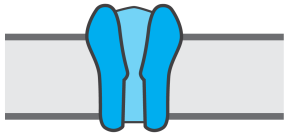
ASC
AUTISM SEQUENCING CONSORTIUM

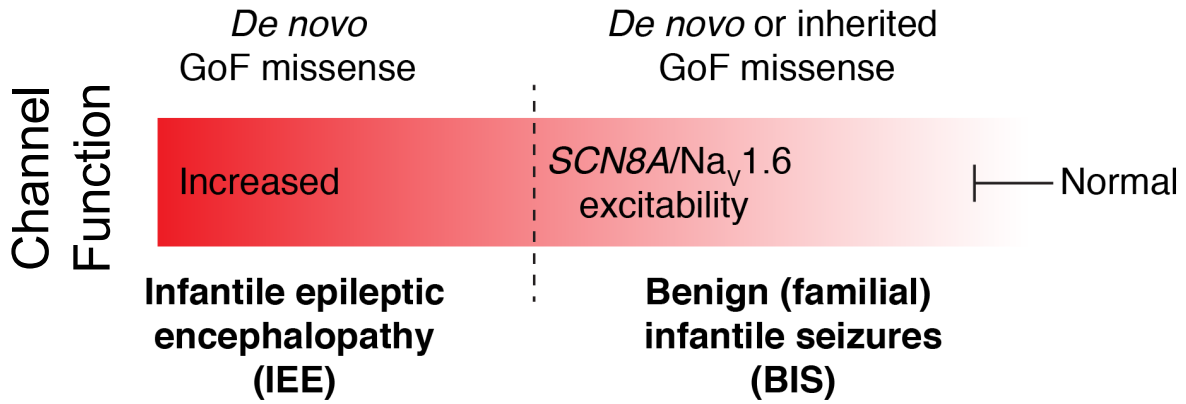
61,789 total samples; 20,029 ASD cases
184 genes with exome-wide significance
Satterstrom et al., 2020

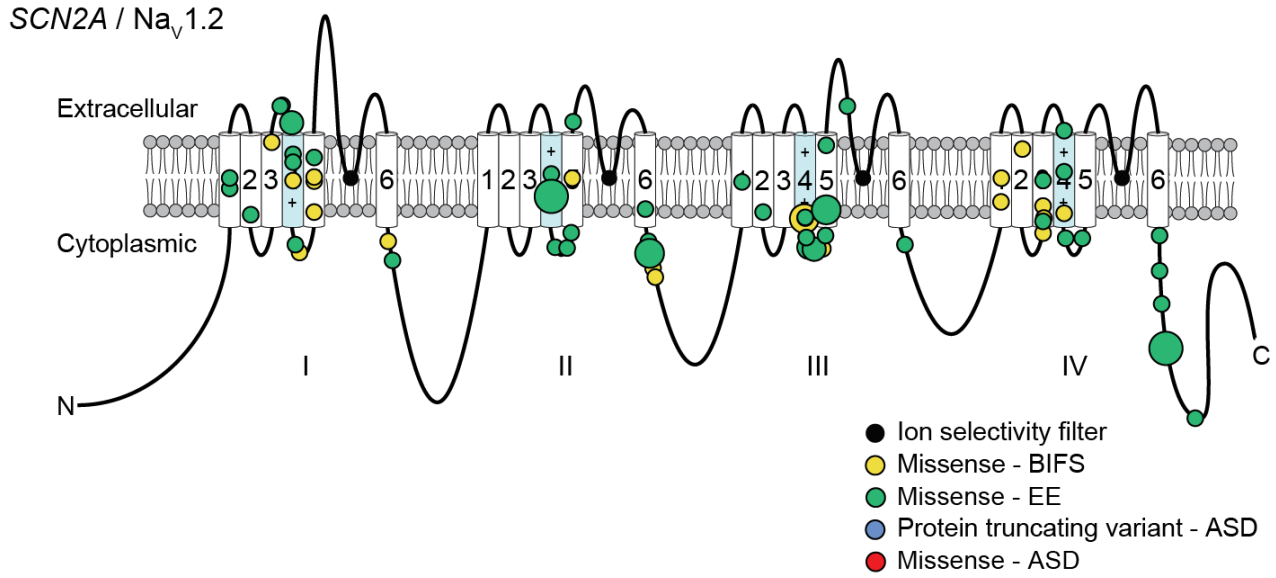
General model for *SCN2A* Disorders

***SCN2A* gene**

$Na_V1.2$ channels







Brain cells & circuits

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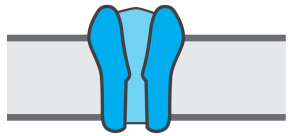
Children with *SCN2A*

Sanders et al., 2017; Ben-Shalom et al., 2017

General model for *SCN2A* Disorders

***SCN2A* gene**

$Na_V1.2$ channels



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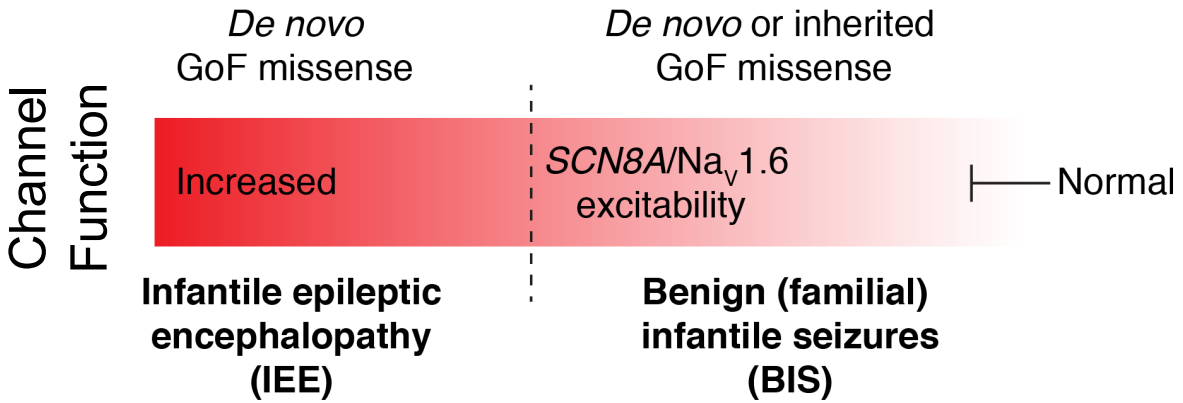

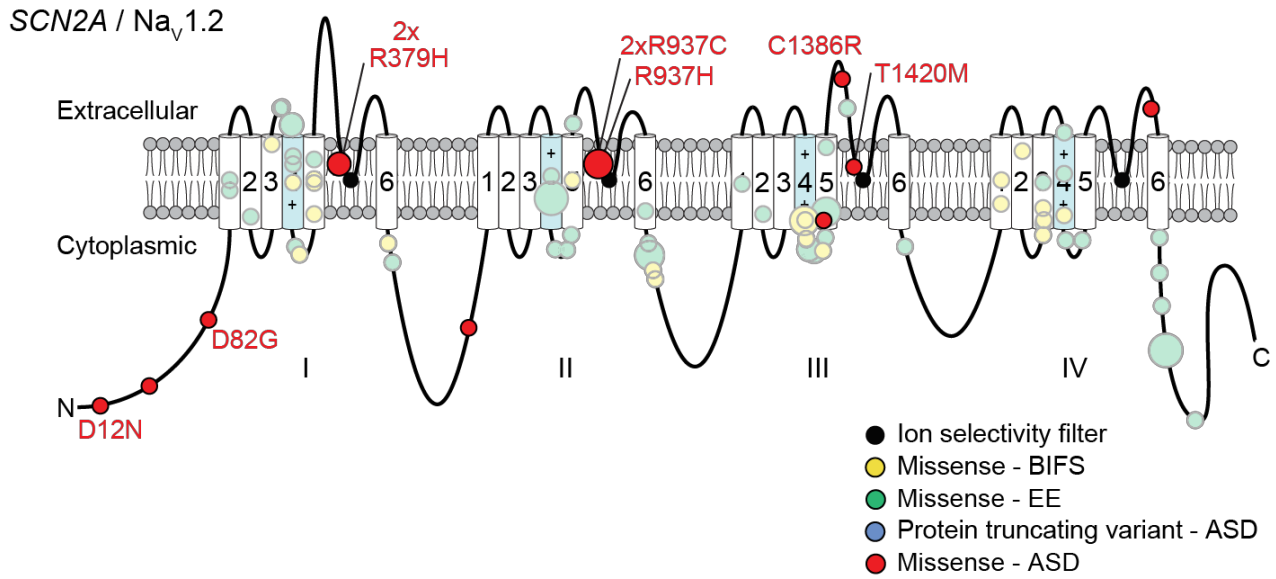

Sanders et al., 2017; Ben-Shalom et al., 2017

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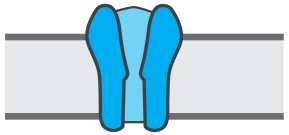
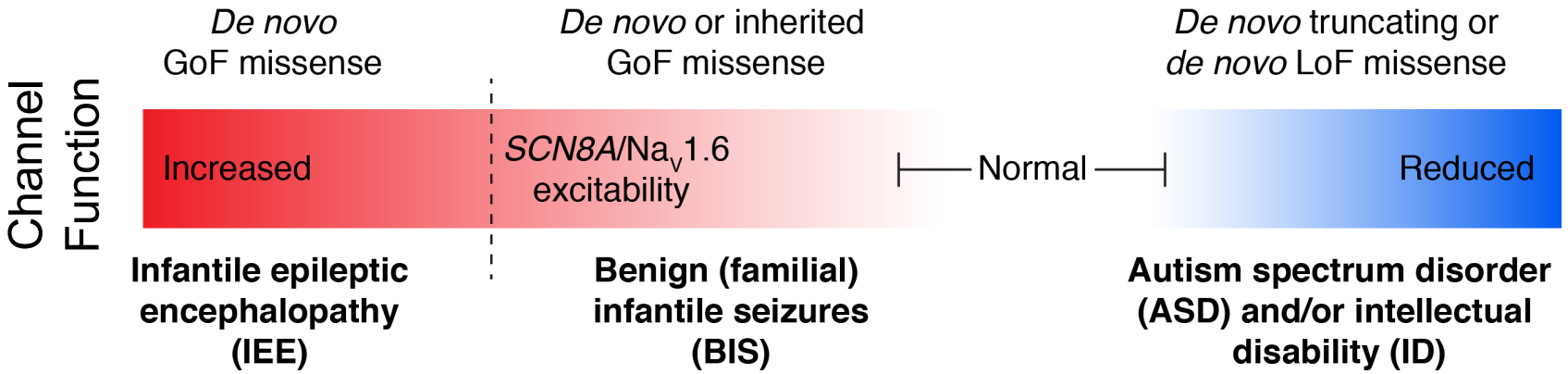
***SCN2A* gene**

$Na_V1.2$ channels



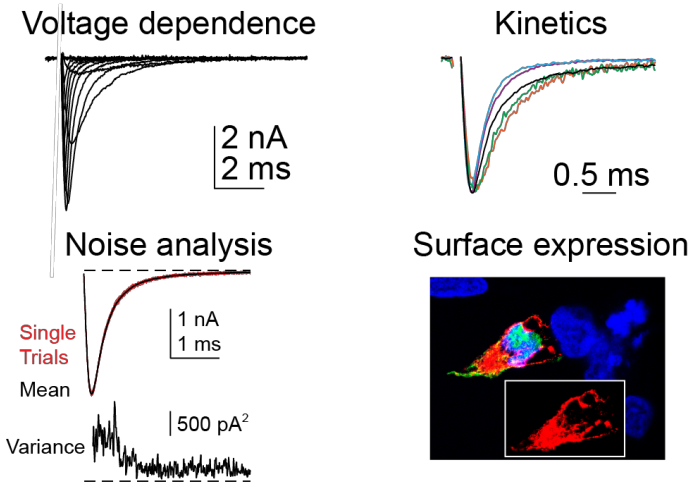


Brain cells & circuits

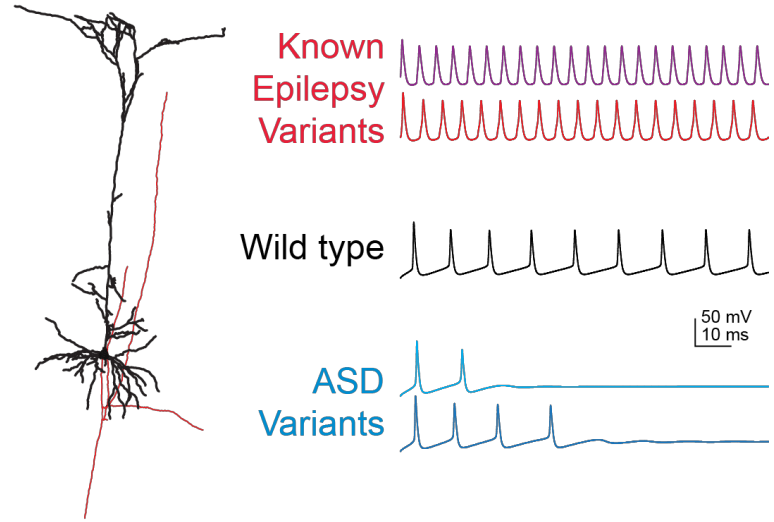
Animal models

Children with *SCN2A*

Biophysical assays



Compartmental modeling



Sanders et al., 2017; Ben-Shalom et al., 2017

General model for *SCN2A* Disorders

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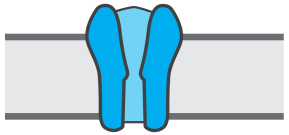
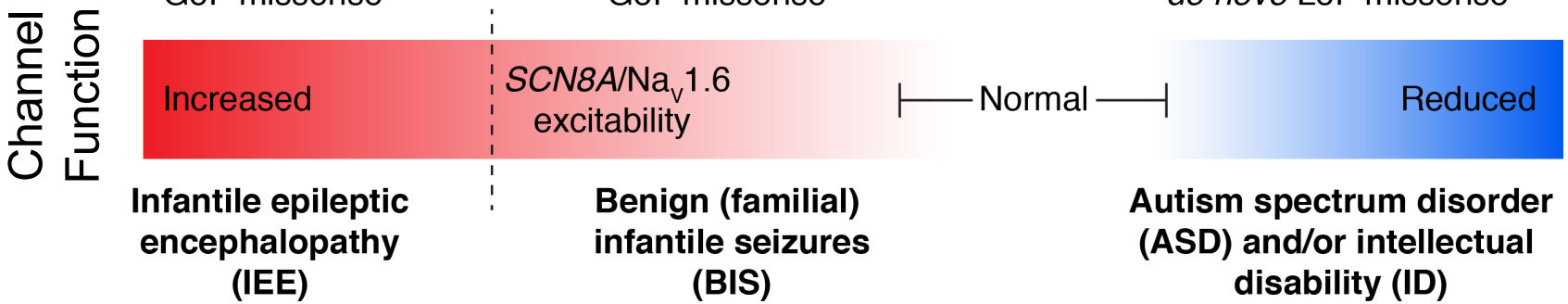
$Na_V1.2$ channels





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Sanders et al., 2017; Ben-Shalom et al., 2017

SCN2A is expressed across the brain

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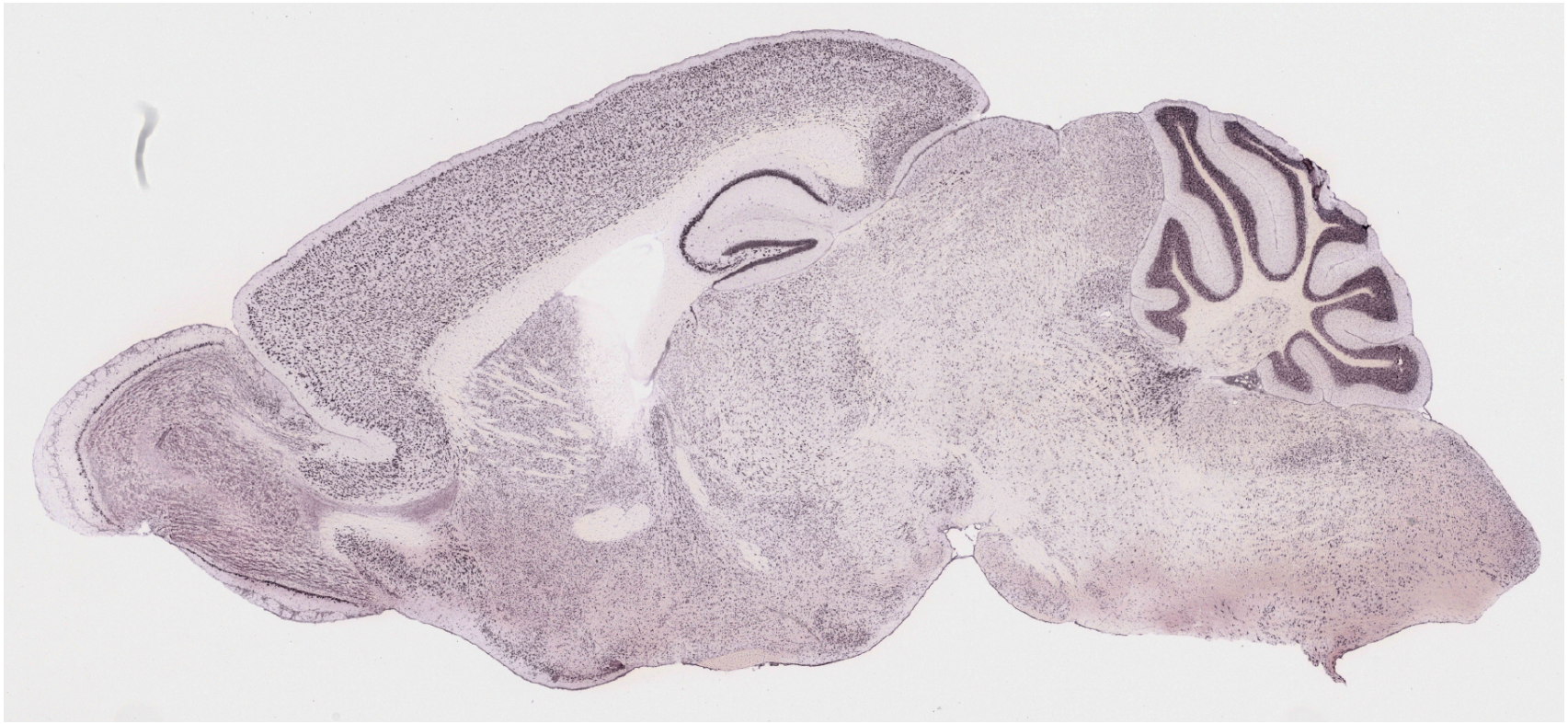
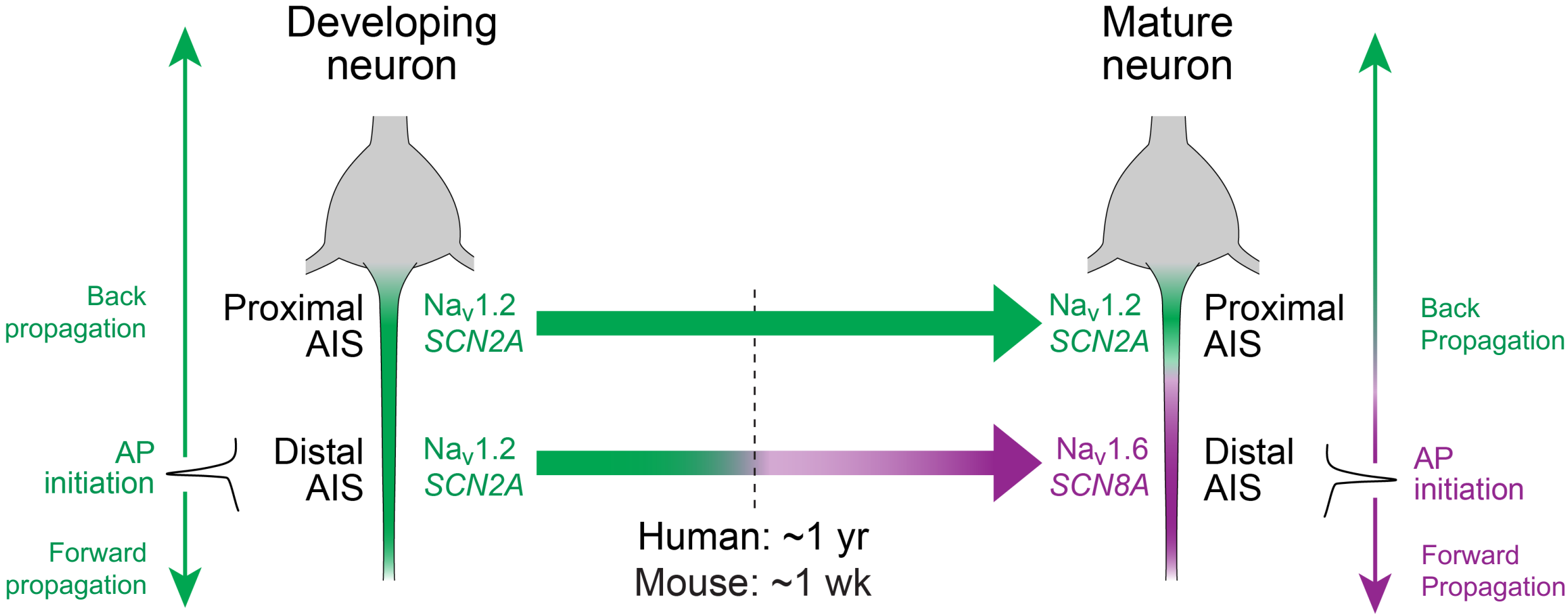


Allen Brain Atlas

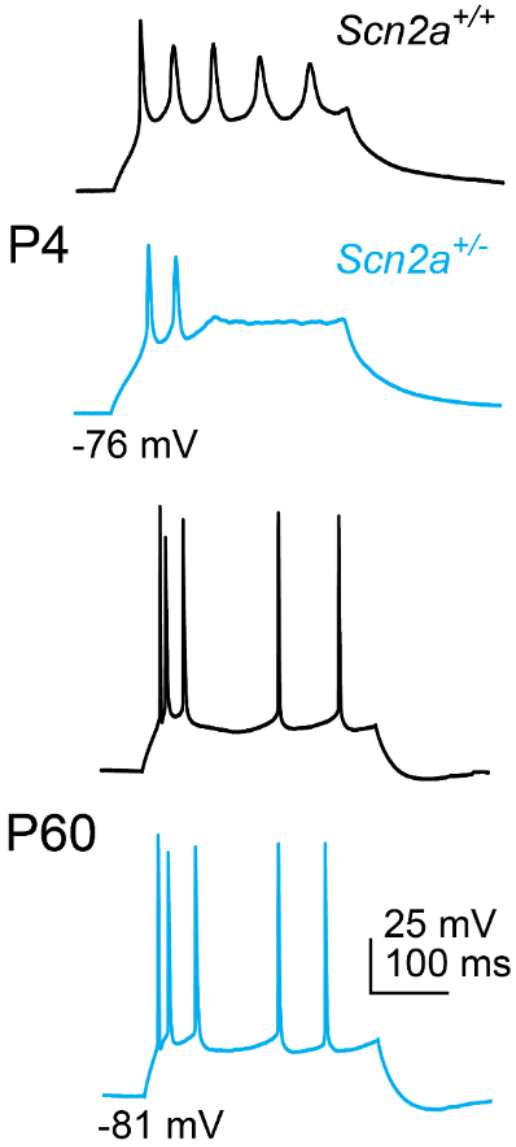
The role of *SCN2A* / $Na_V1.2$ changes during development

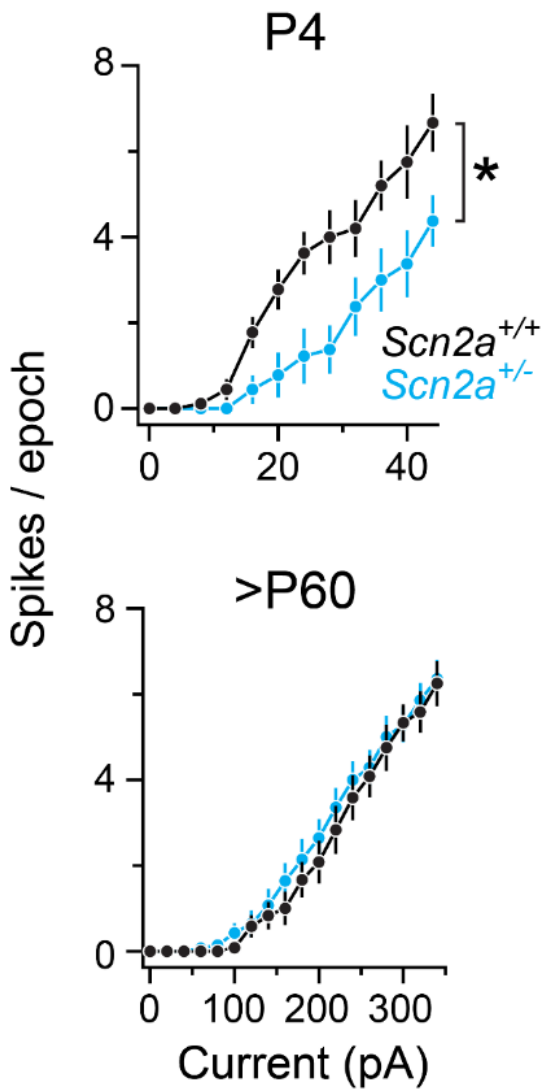


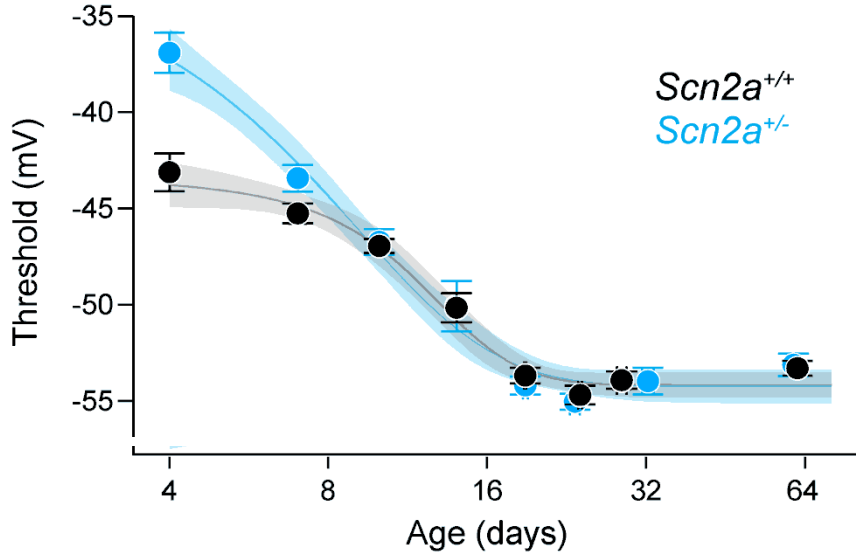
Gazina et al., 2014

Hu et al., 2009

Excitability recovers as non-$Na_V1.2$ channel expression increases

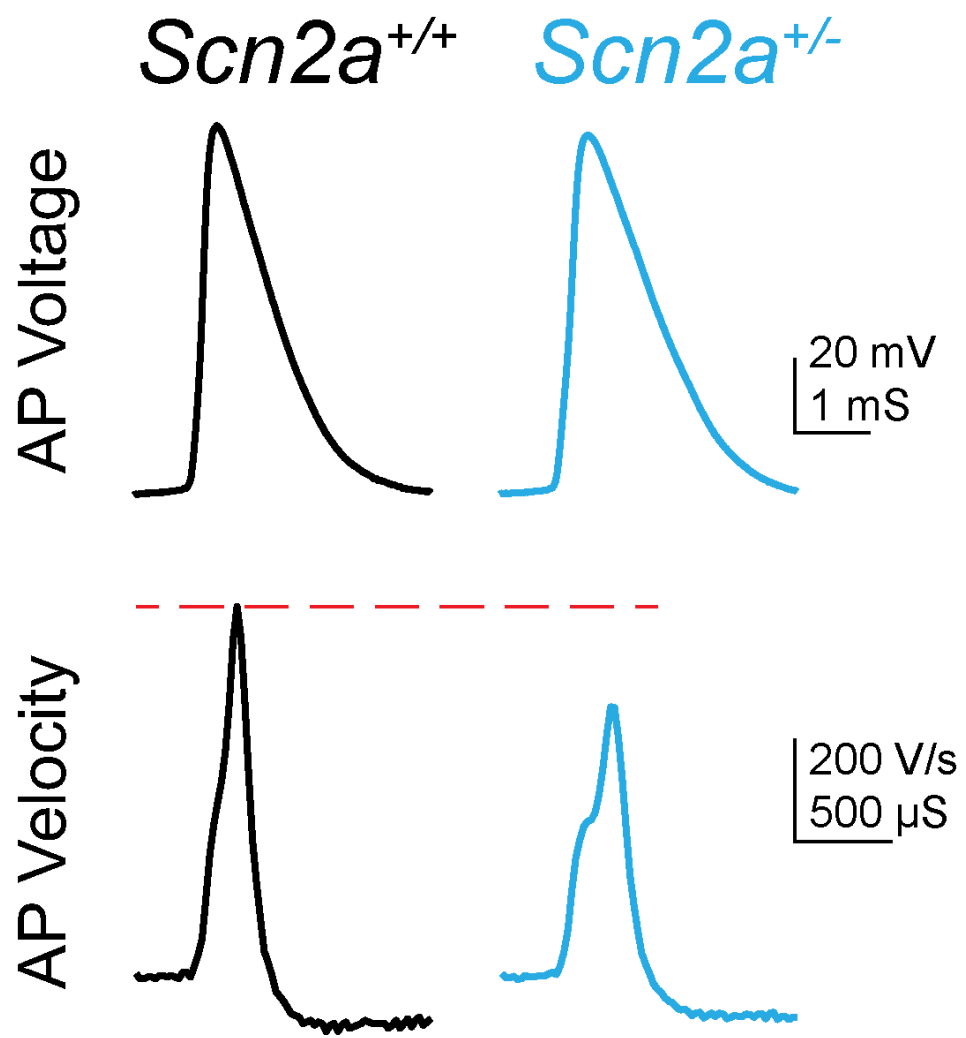


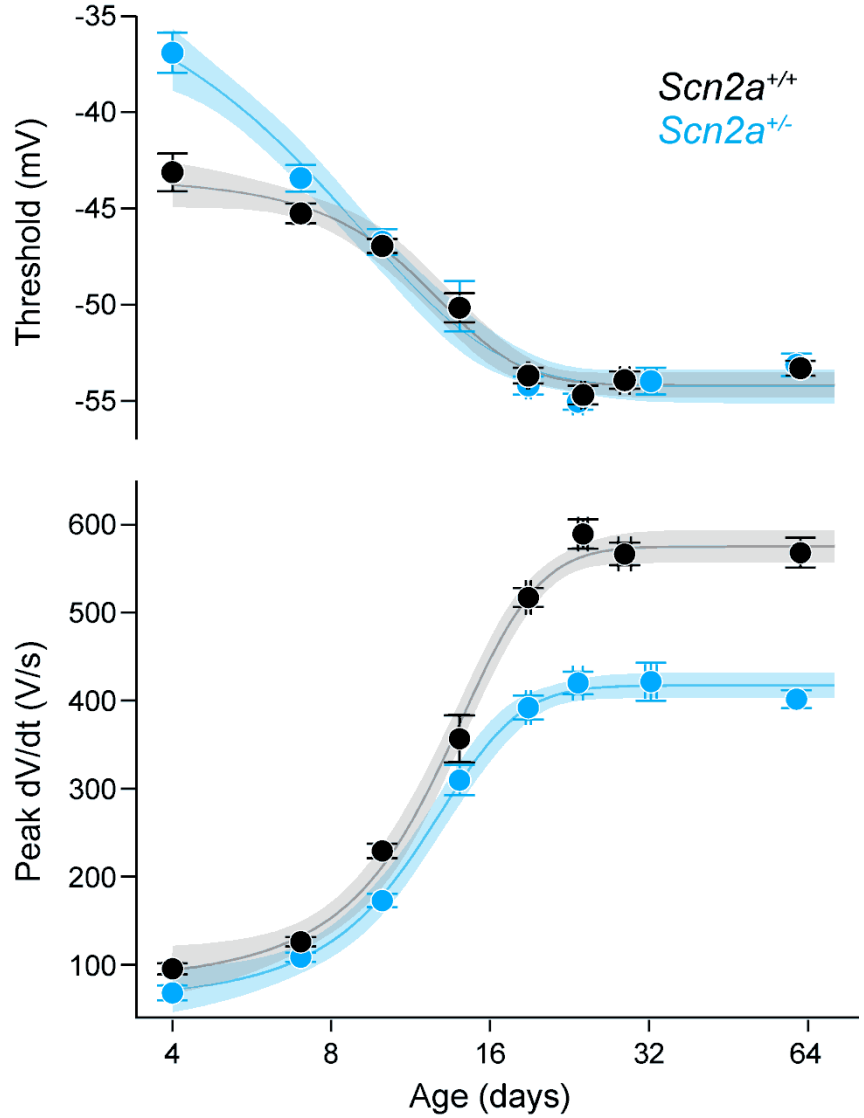




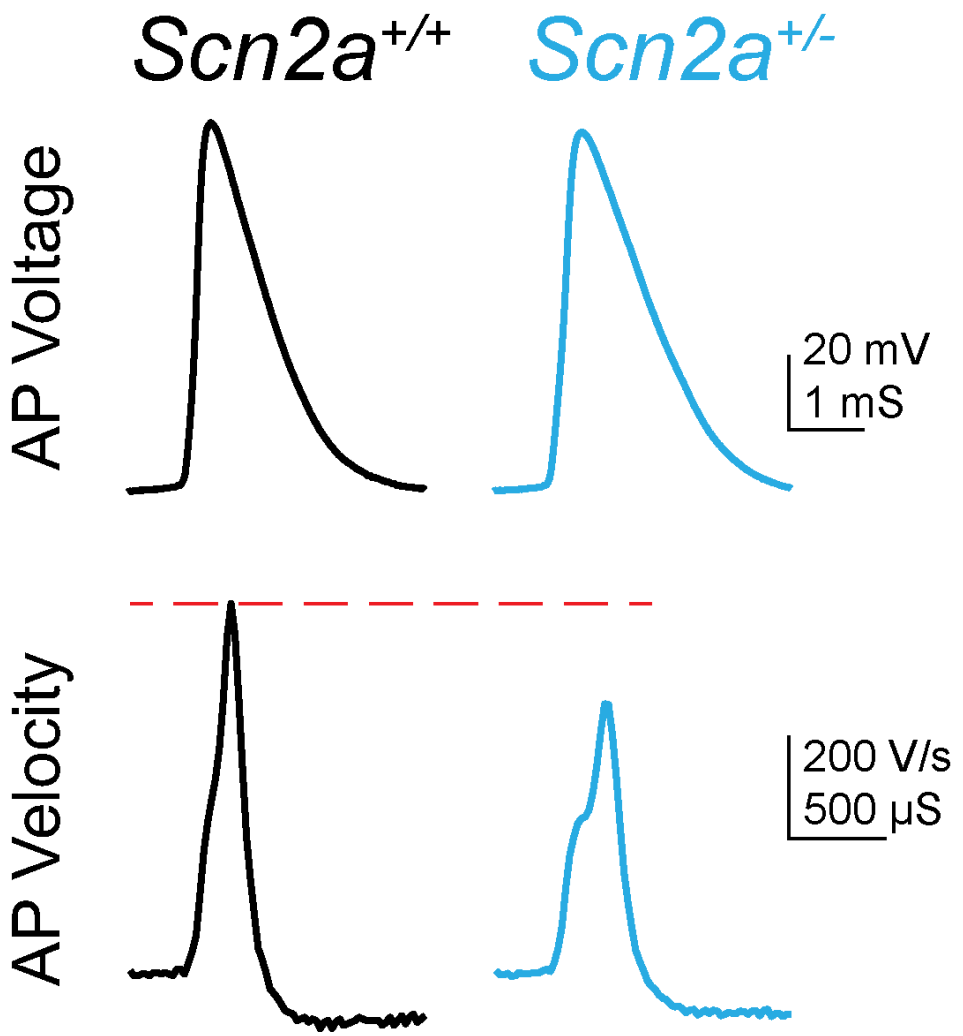
Spratt et al., Neuron 2019

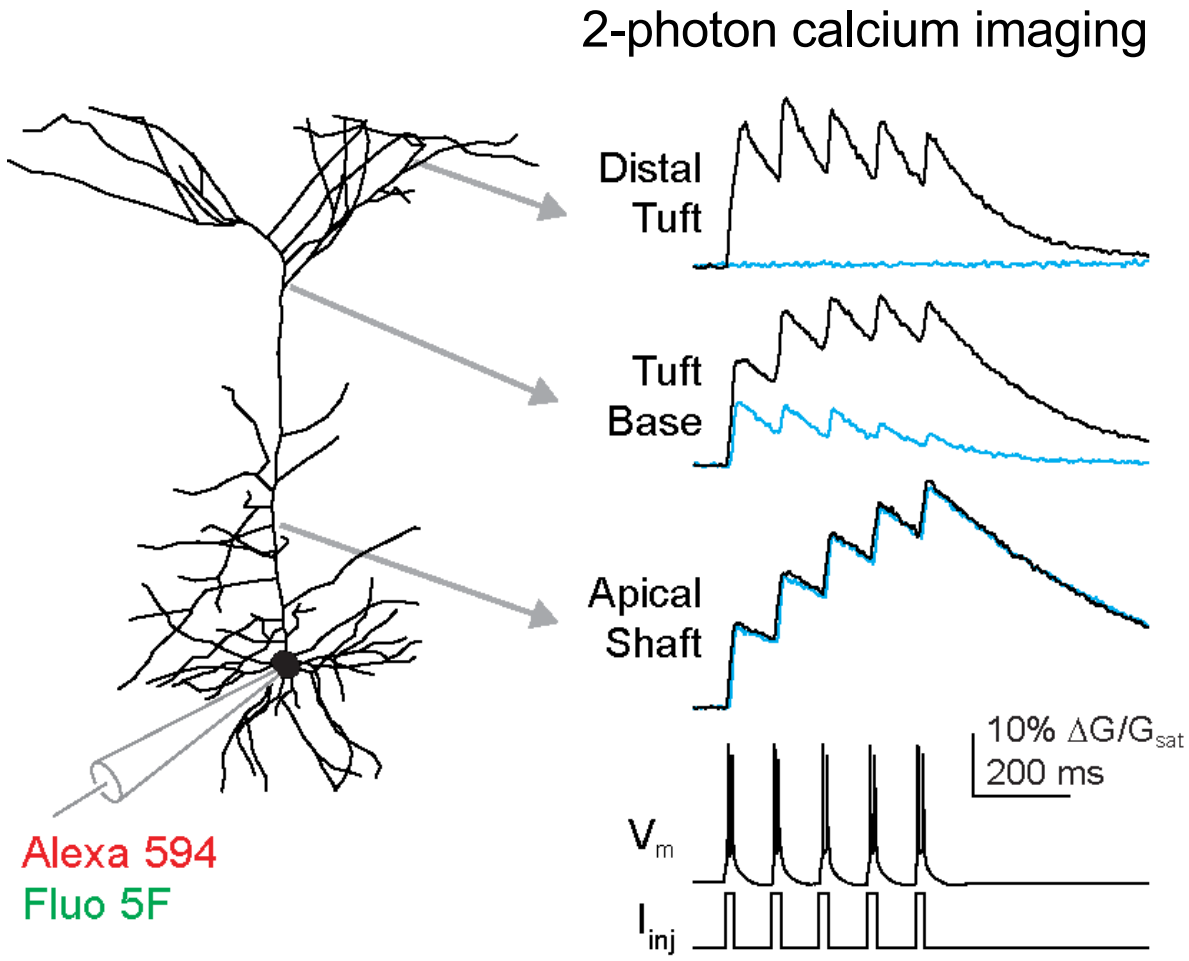
But another aspect of the spike—velocity—is affected throughout life





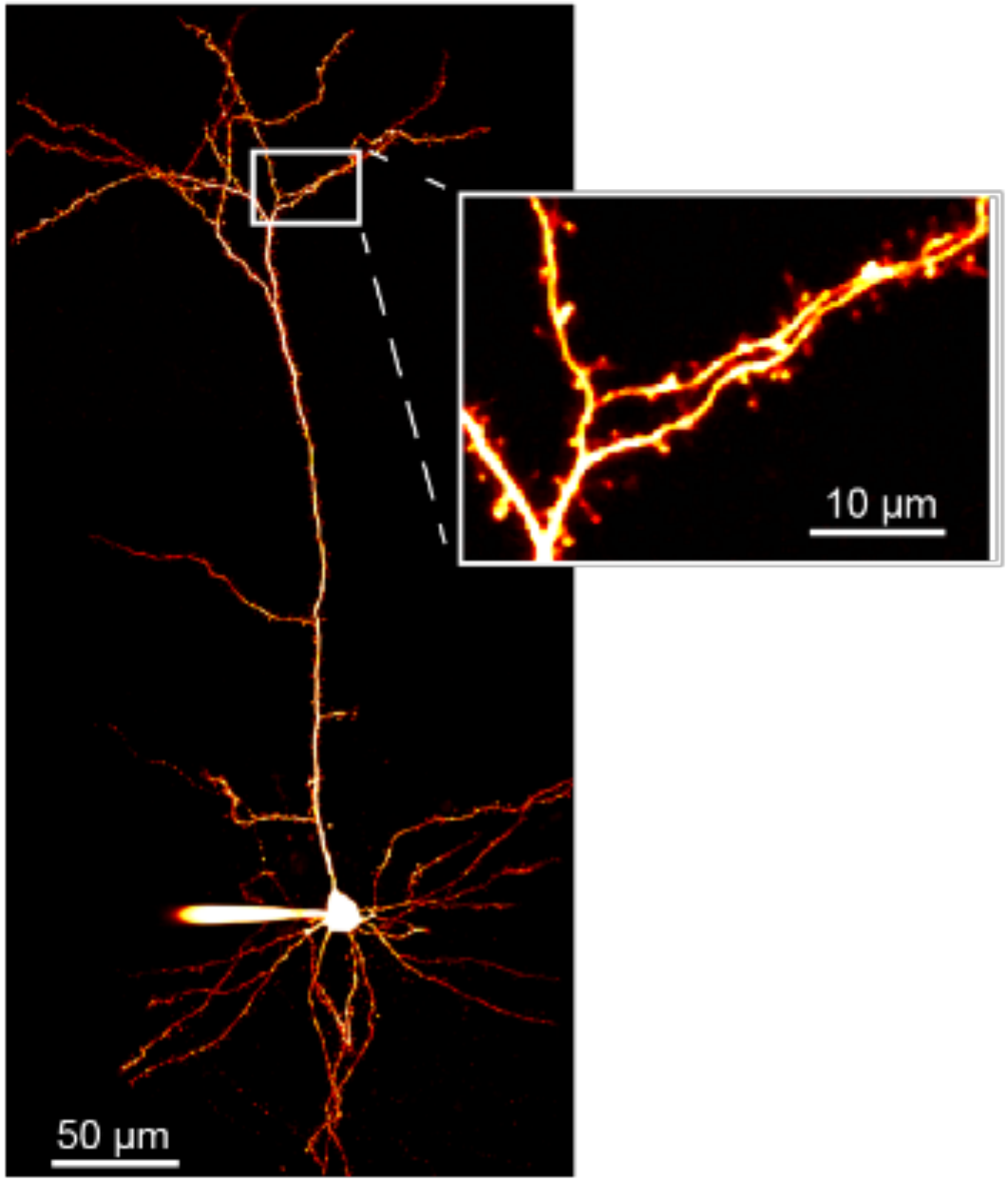
AP speed deficit is associated with impaired dendritic excitability

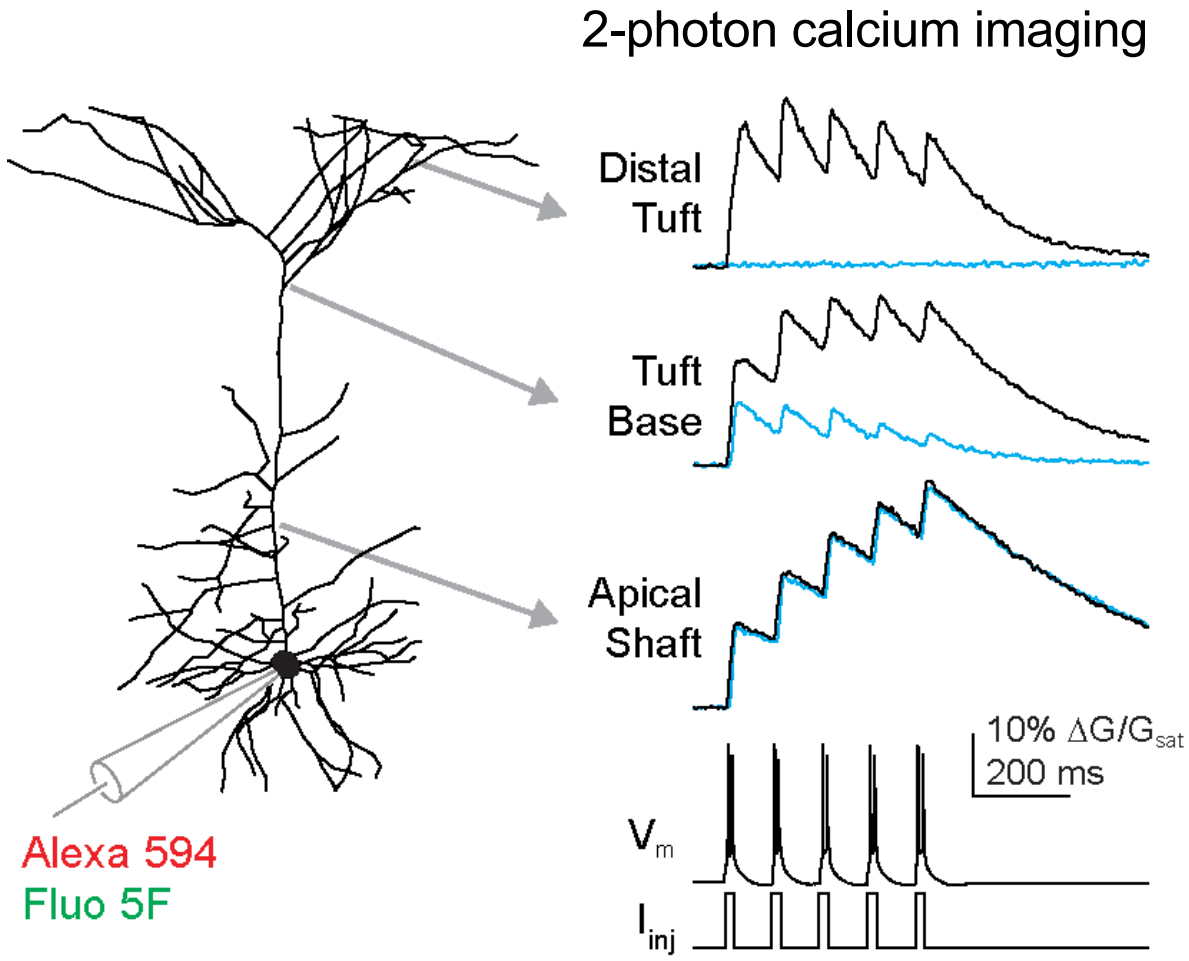




Spratt et al., 2019

Dendritic excitability can alter synaptic strength





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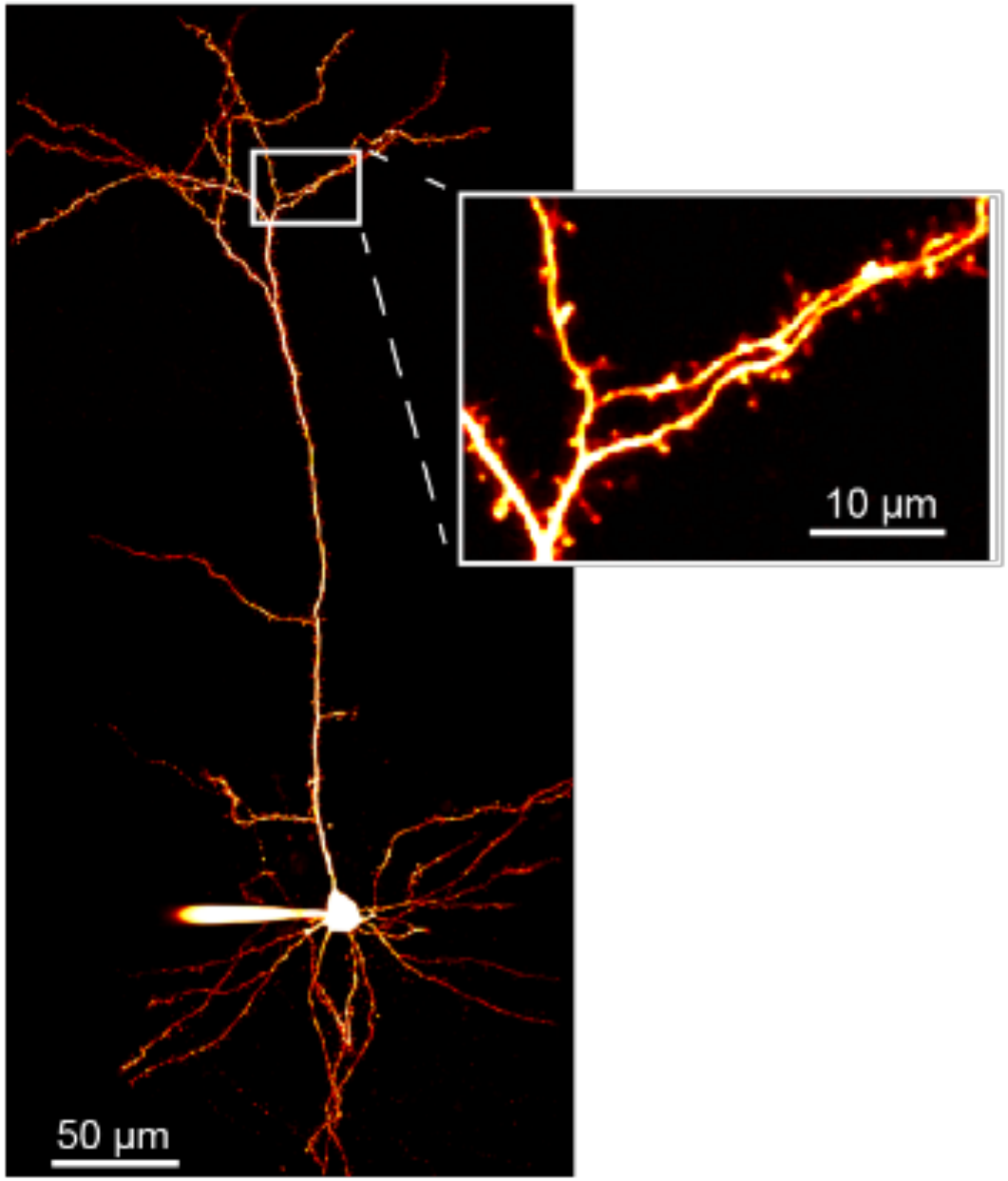

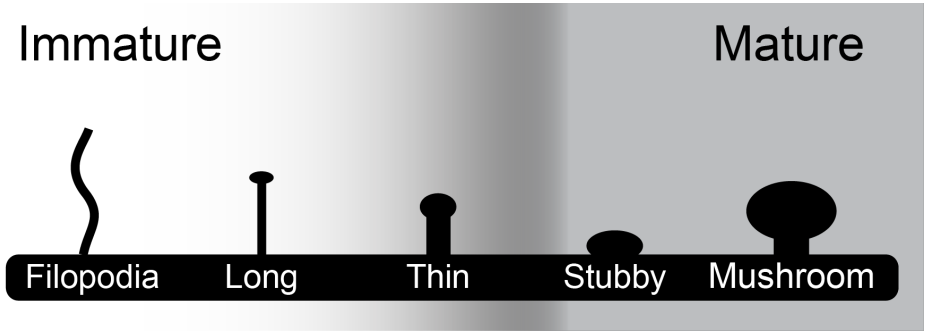

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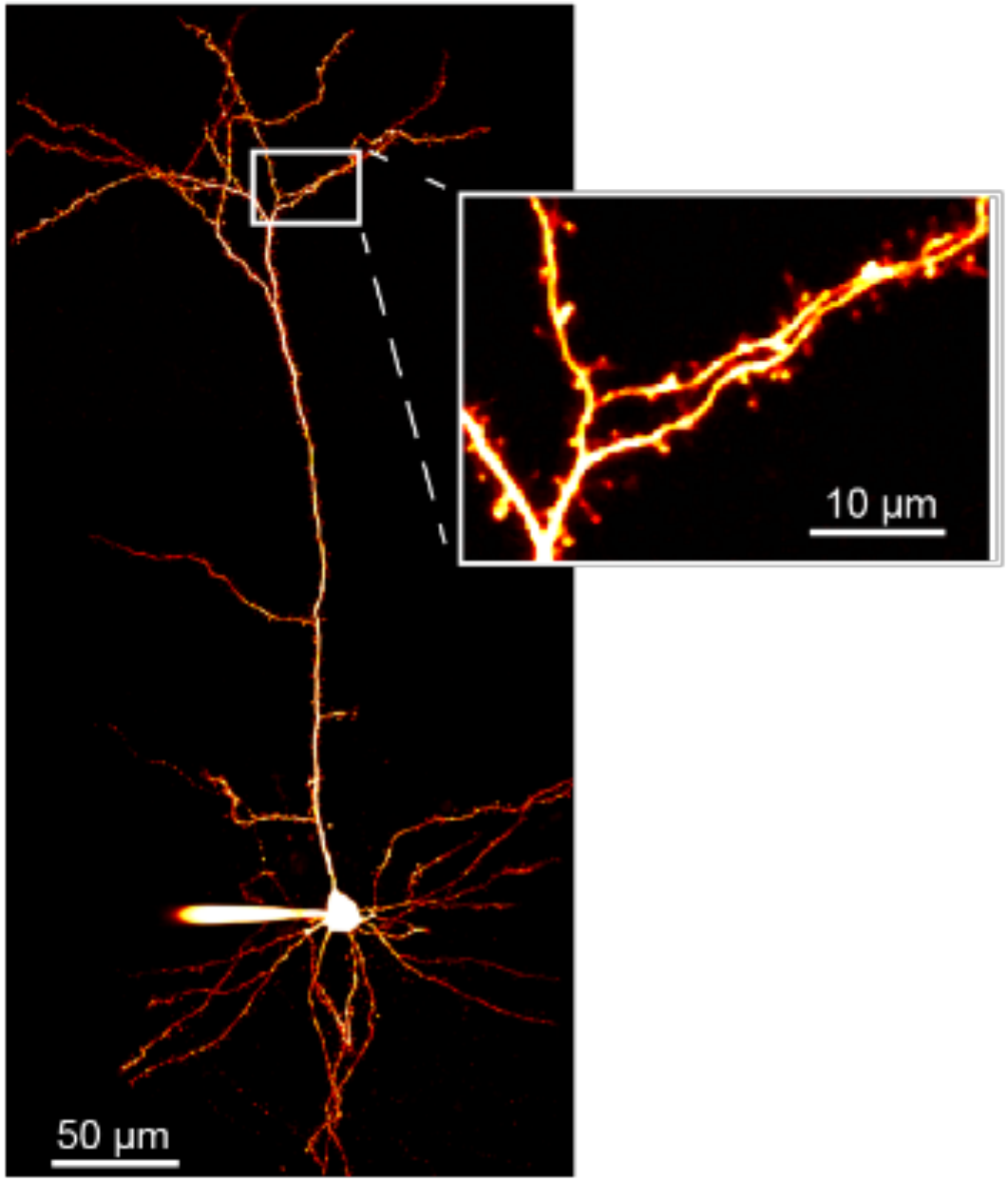

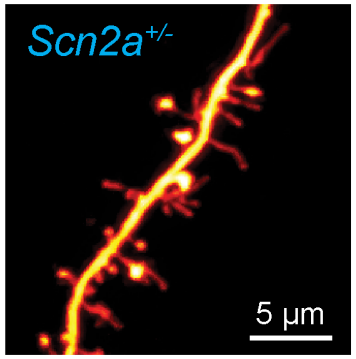

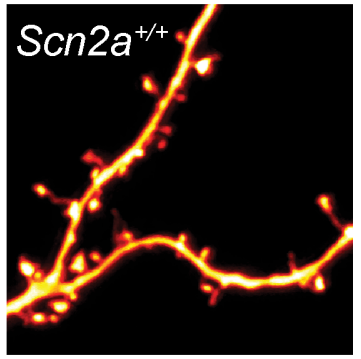

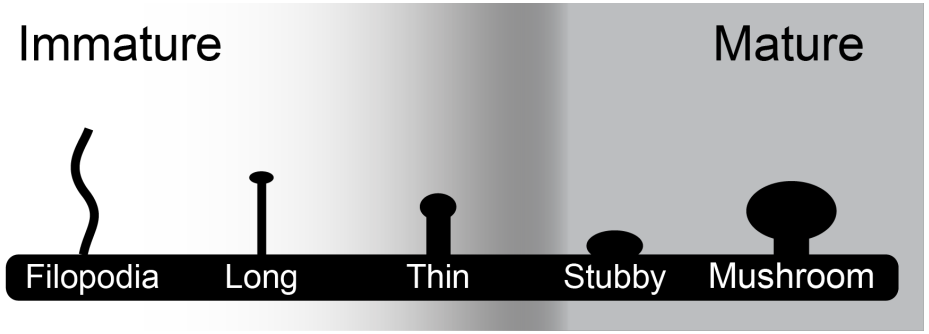

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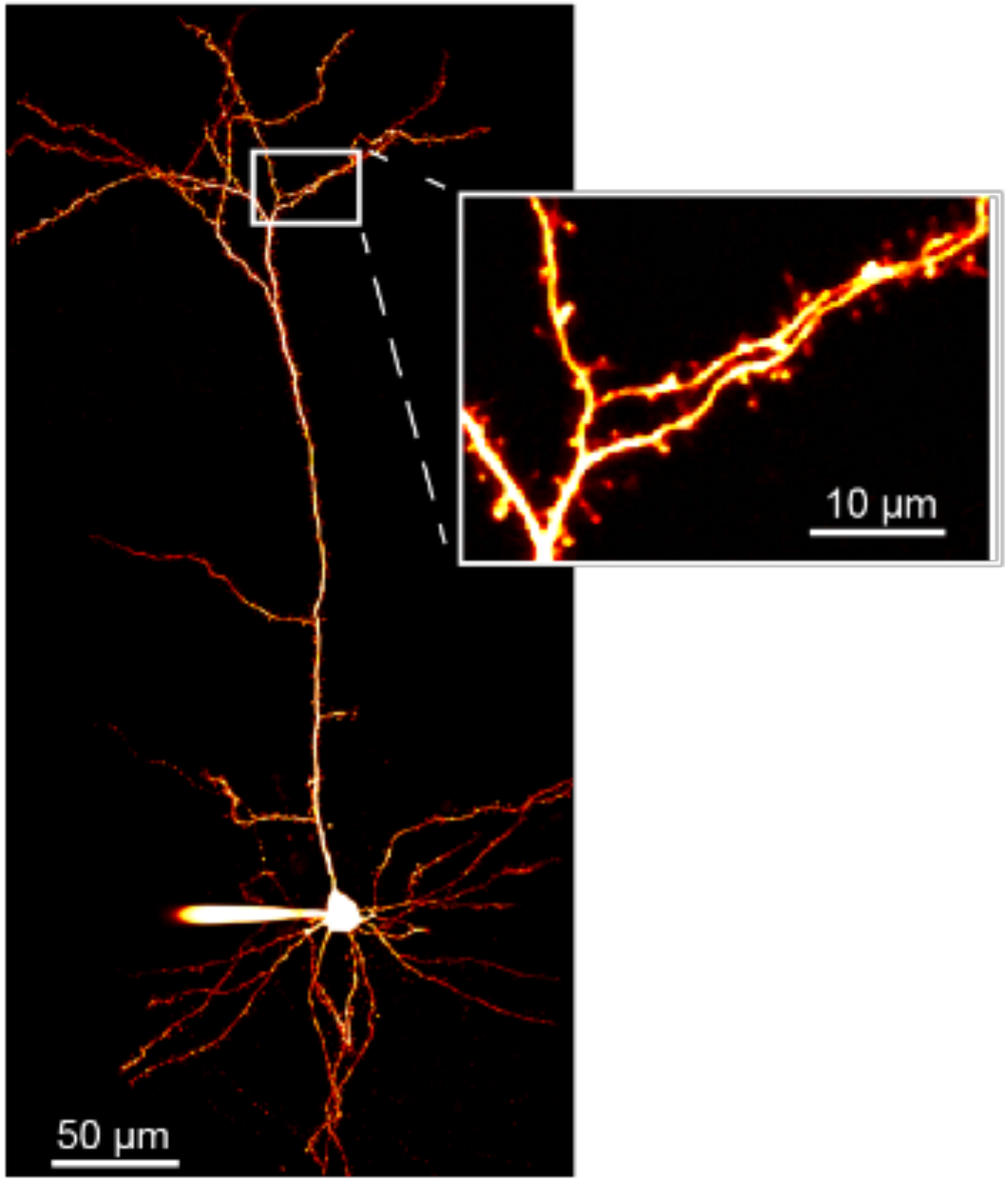
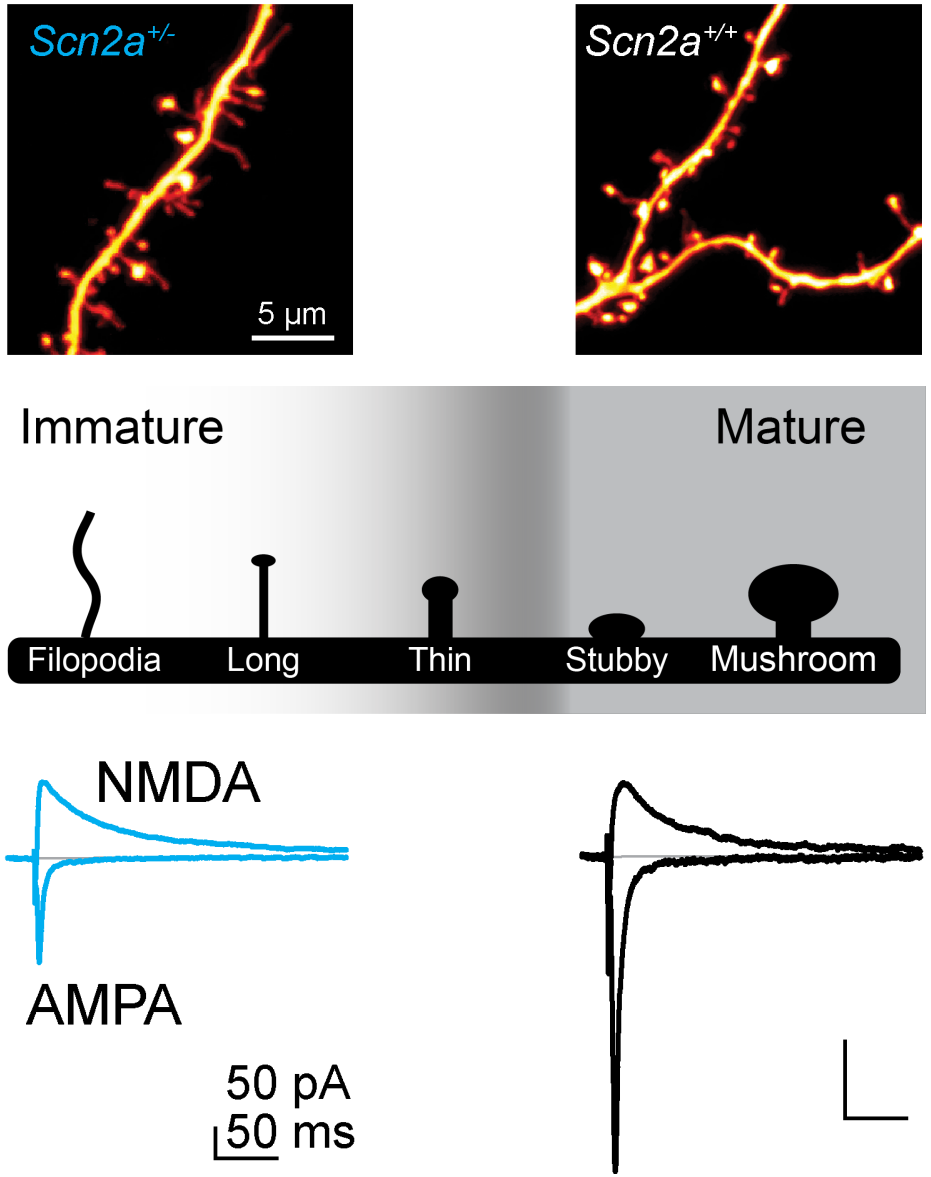
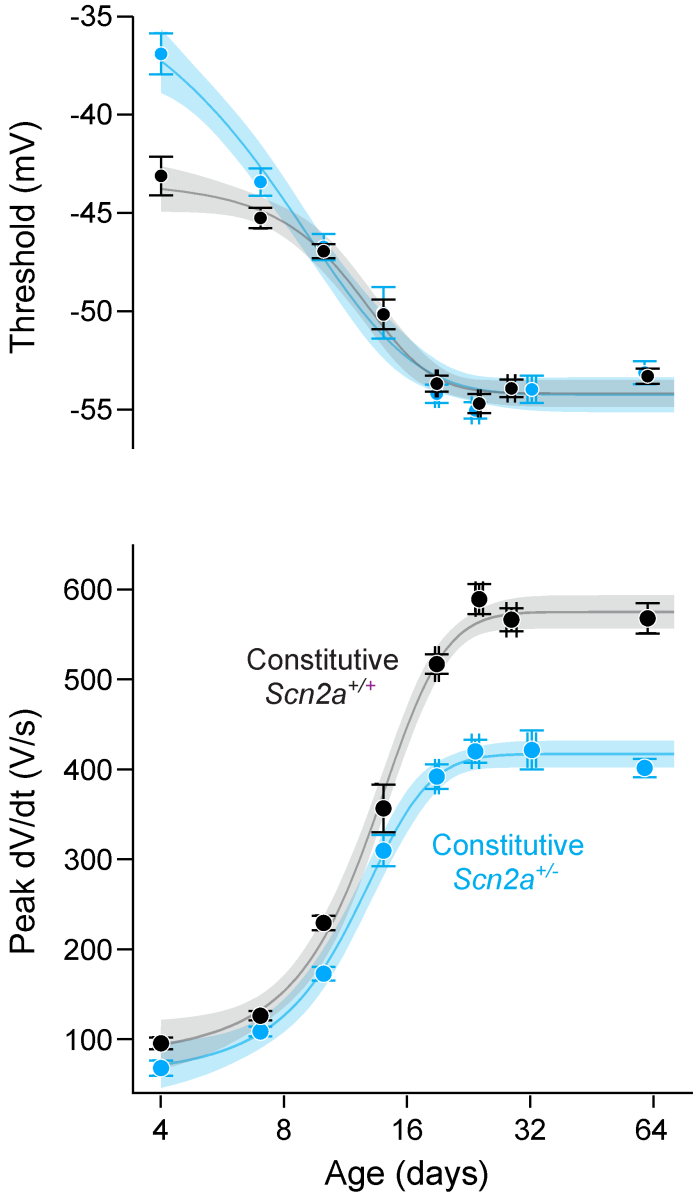
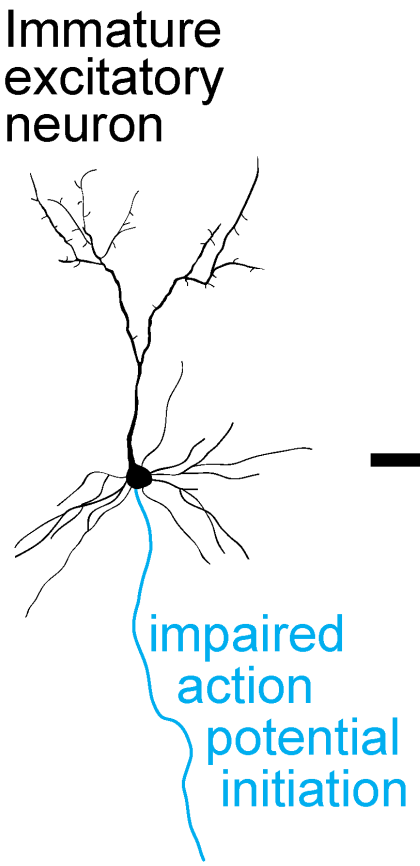
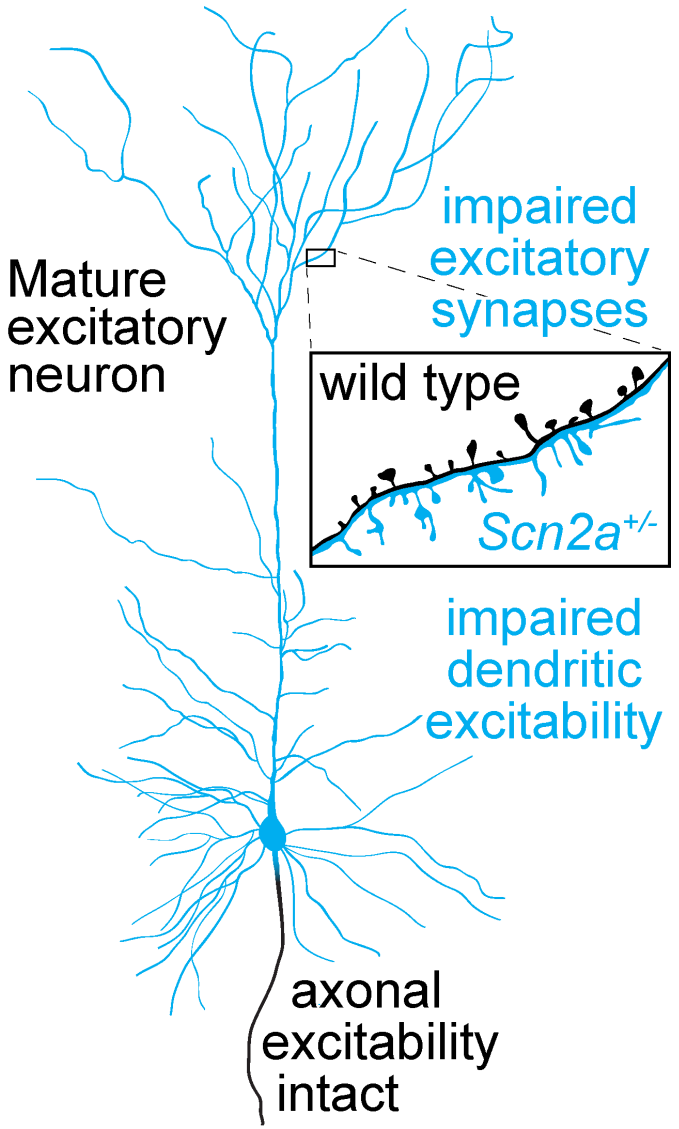




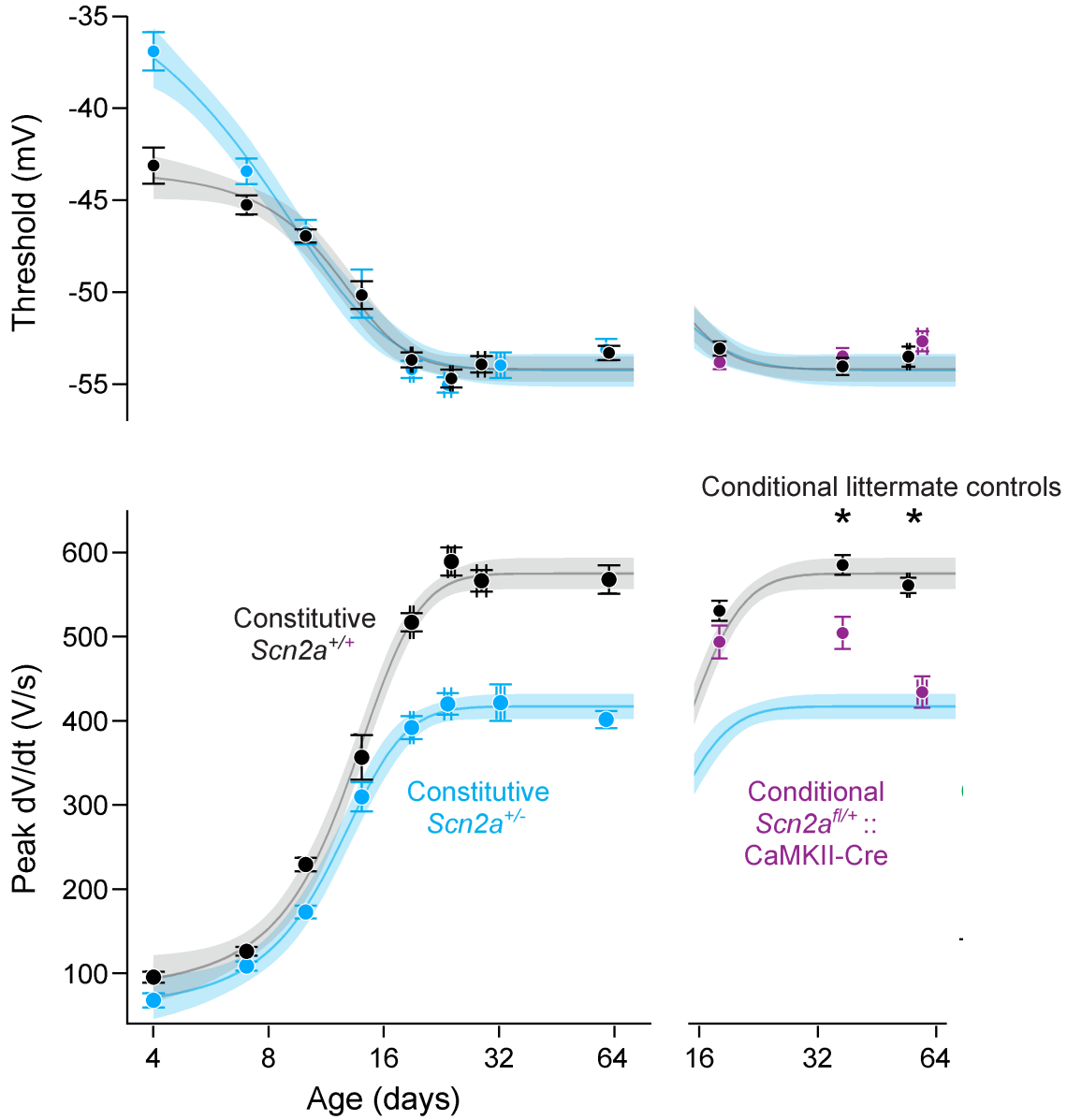
Scn2a function changes over development

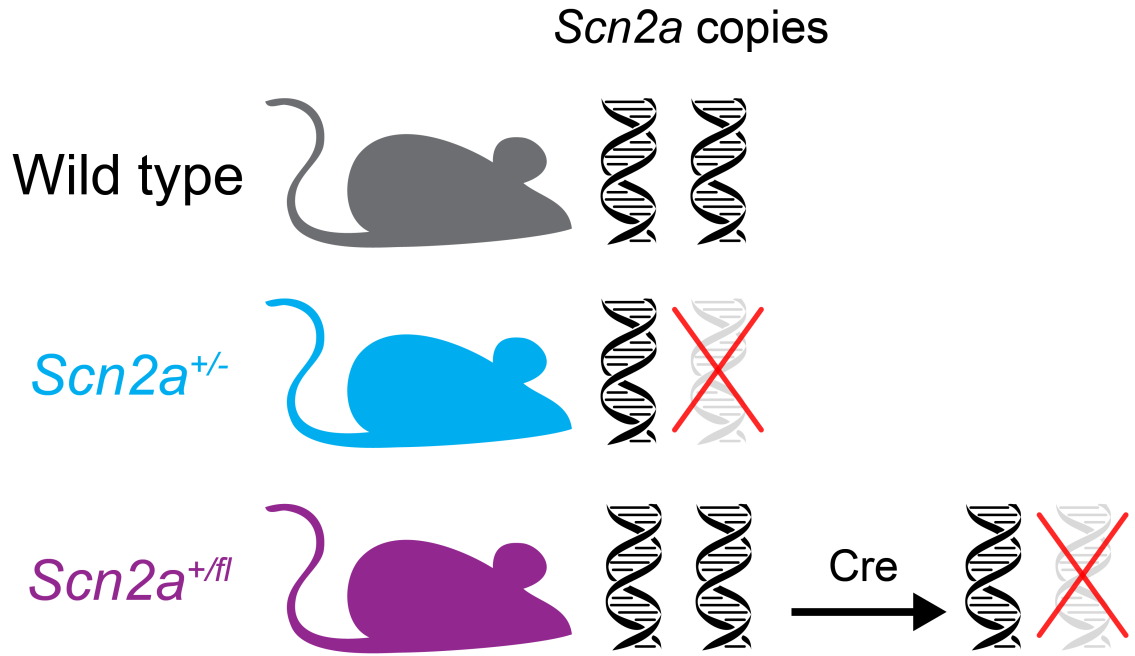




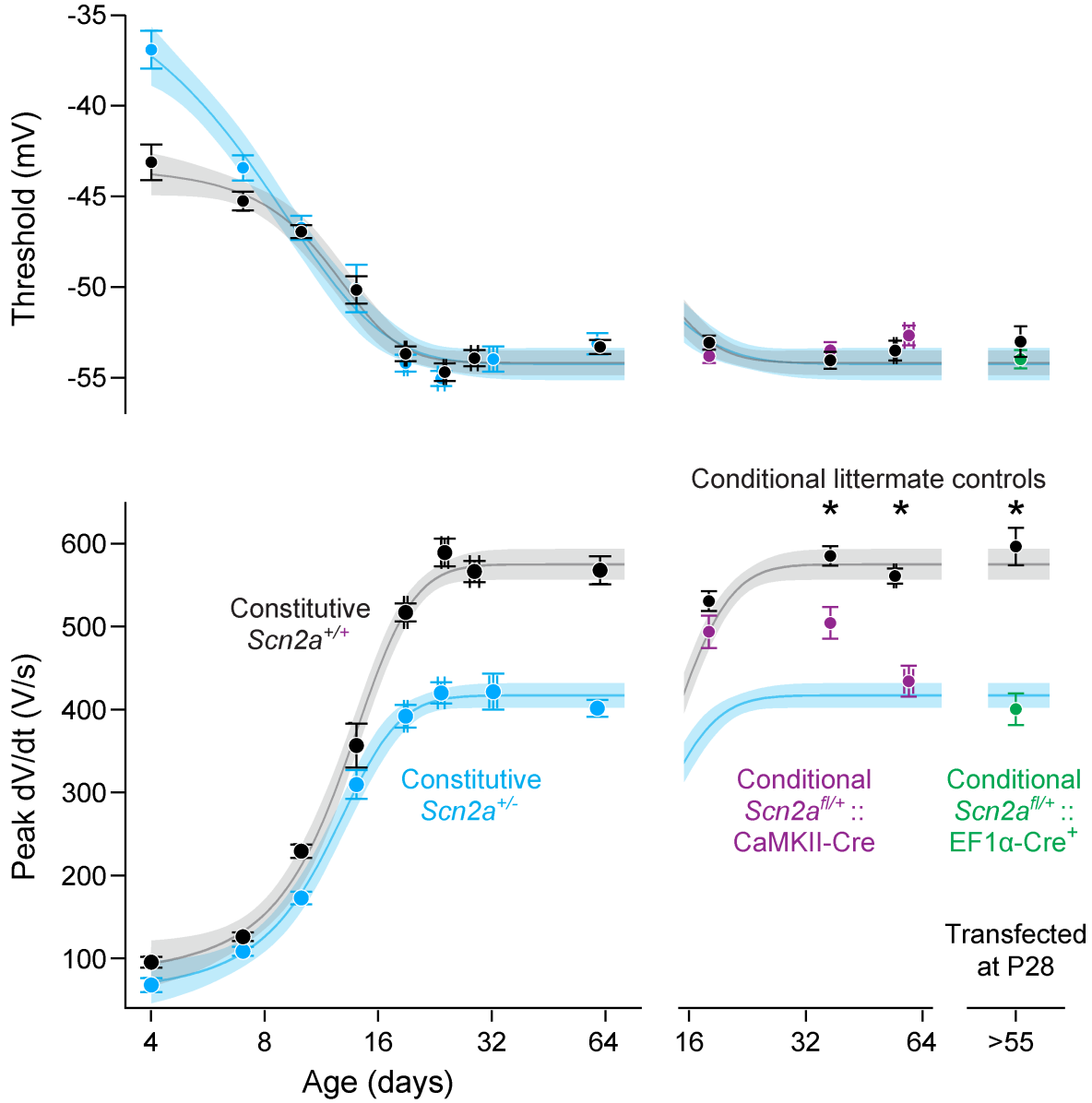


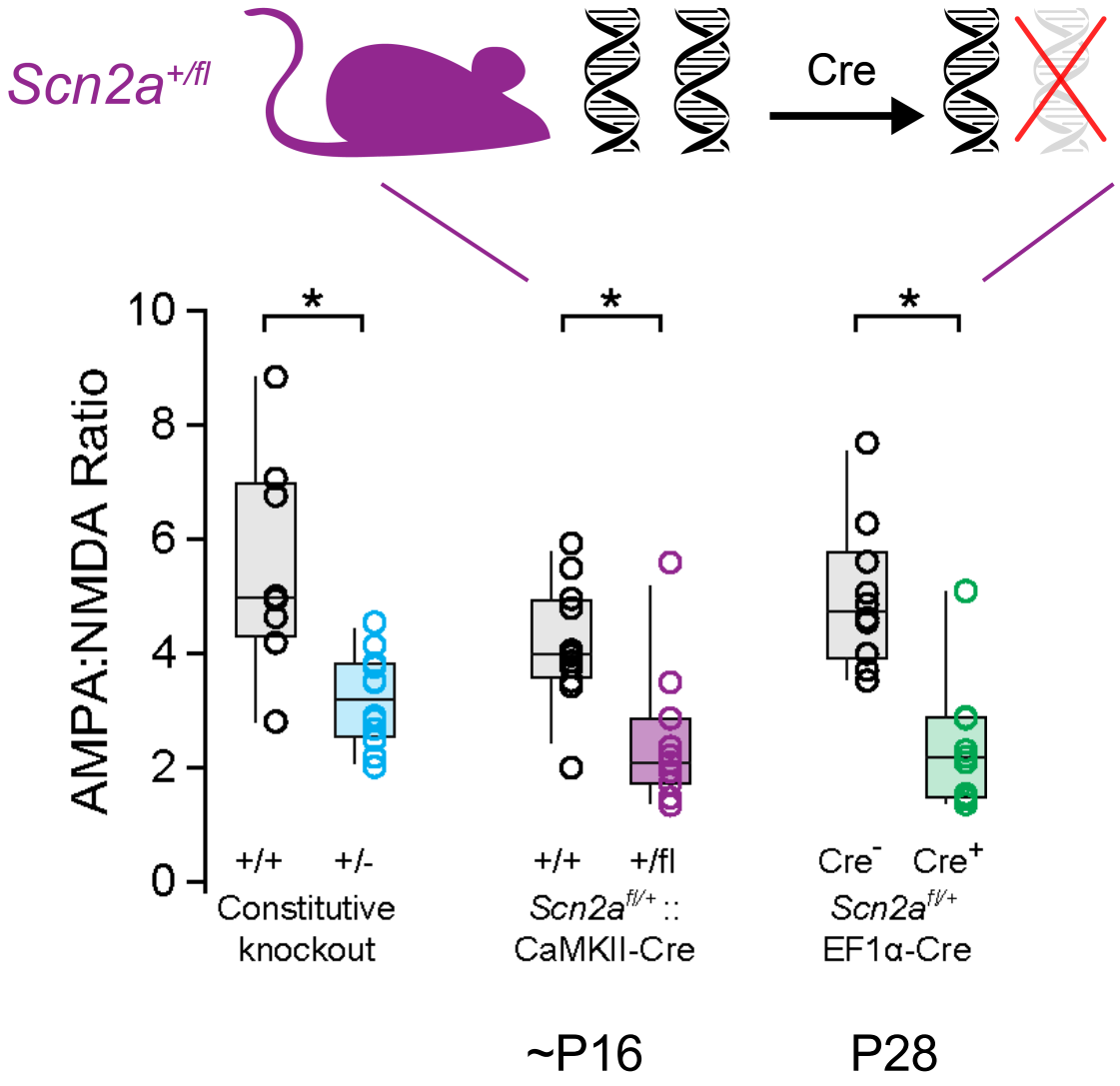
Engineered mouse that can switch from wild type to *Scn2a*$^{+/-}$





Synapse strength actively maintained by proper $Na_V1.2$ levels





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