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Journal of Bioanalysis & Biomedicine

Open Access

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The Autism risk gene *Met* controls neural development and circuit formation

Shenfeng Qiu

Basic Medical Sciences
College of Medicine-Phoenix
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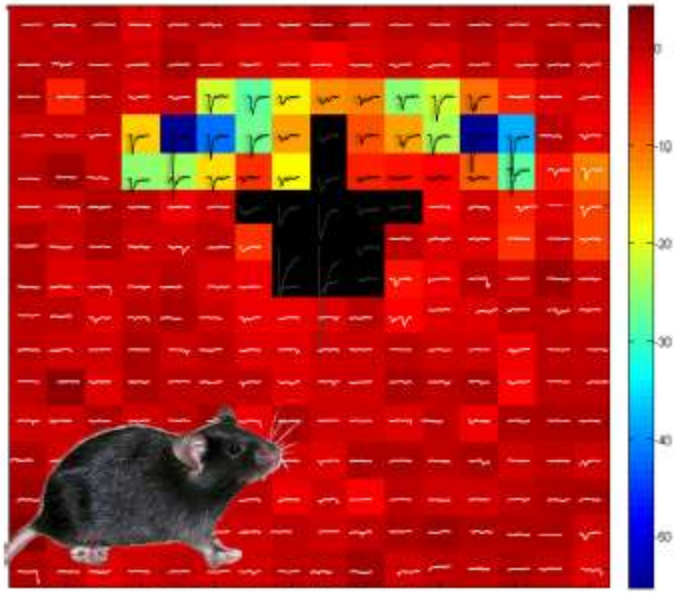


Major areas of interest in the lab:

Neurodevelopmental disorders (NDDs)

- Disease onset is during periods of ongoing brain development and maturation.
- Often begin early in life, associated with complex neuropsychiatric features.
- Caused by a wide range of genetic and environmental factors.
- Highly prevalent, contribute substantially to the disease burdens worldwide.

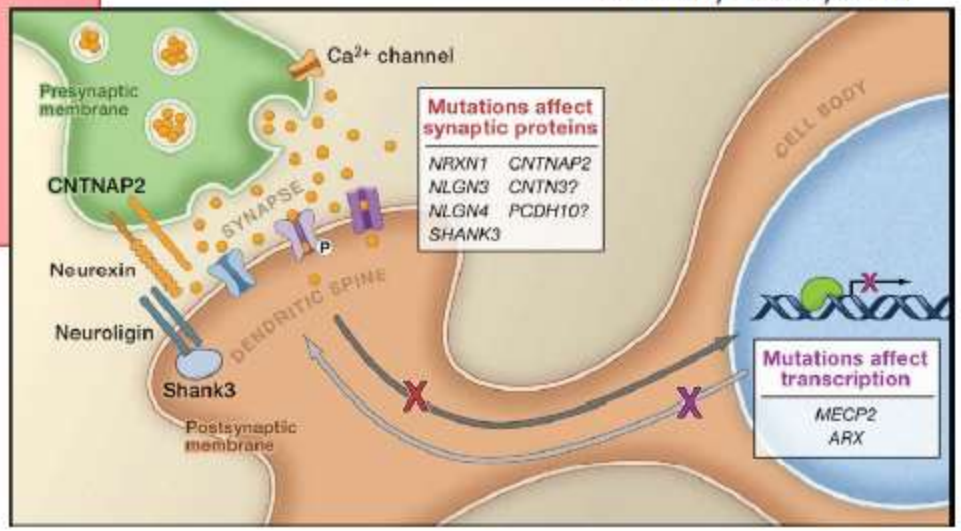
Autism as a neurodevelopmental disorder

- Autism is a neurodevelopmental syndrome showing impairments in reciprocal social interaction, communication, repetitive and restricted patterns of behavior and interests.
- Prevelance is 1:110 in the general population.
- 4:1 male to female ratio
- Recognized as a highly heterogenous genetic disorder, only 10% ASD cases are associated with a recognized genetic cause.

Molecules (risk genes) implicated in Autism

- **Glutamatergic Synapses and Connectivity**
  - Neurexins/neuroligin
  - *CNTNAP2*
  - *SHANK3*

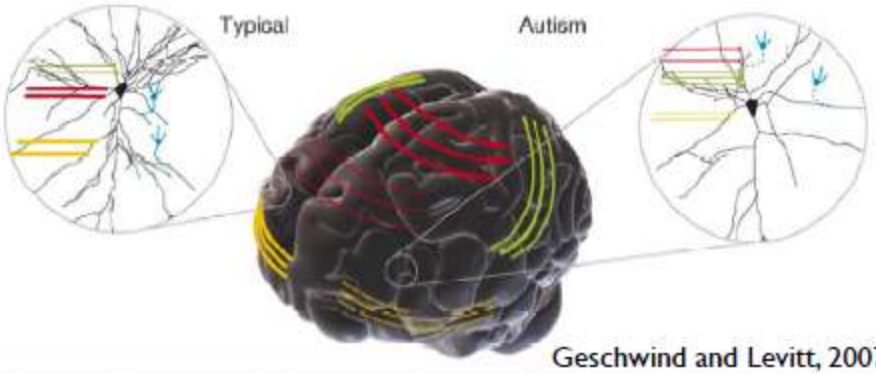
Walsh, 2008, Cell



- **Gene Transcription and Protein Synthesis**
  - *FMR1*
  - *PTEN, TSC1, TSC2*
  - *MeCP2*

- **Neuronal Migration, growth &excitability**
  - *GABAa R*
  - *Dlx*

Autism pathophysiology



Geschwind and Levitt, 2007

- Impaired neurogenesis, migration (Wegiel, 2010)
- Dysregulation of dendritic spines and synaptic proteins (Kelleher, 2008; Bear, 2008)
- Unbalanced excitatory/inhibitory network (Persico, 2006; Südhof, 2008)
- Early neuronal overgrowth and hyperconnectivity (Courchesne, 2007)
- Reduced long range connectivity (Just, 2004; Frith, 2004)

MET emerges as an Autism risk gene

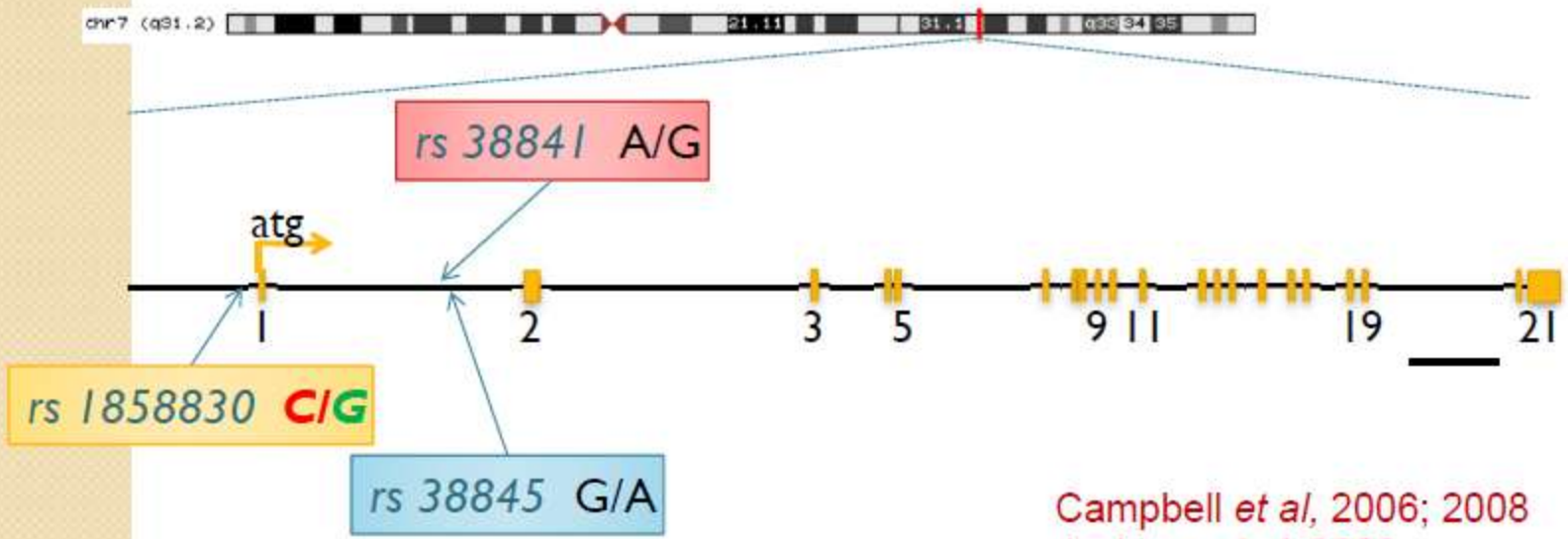
PNAS

A genetic variant that disrupts *MET* transcription is associated with autism

Daniel B. Campbell*, James S. Sutcliffe*†, Philip J. Ebert*, Roberto Militerni‡, Carmela Bravaccio§, Simona Trillo§, Maurizio Elia‖, Cindy Schneider**, Raun Melmed††, Roberto Sacco‡‡§§, Antonio M. Persico‡‡§§, and Pat Levitt*†¶

Departments of *Pharmacology and †Molecular Physiology and Biophysics and ¶Vanderbilt Kennedy Center for Research on Human Development, Vanderbilt University, Nashville, TN 37203; ‡Department of Child Neuropsychiatry, II University of Naples, I-80131 Naples, Italy; §Associazione Anni Verdi ONLUS, 00148 Rome, Italy; ‖Unit of Neurology and Clinical Neurophysiopathology, Scientific Institutes for Research, Hospitalization and Health Care (IRCCS) Oasi Maria SS, 94018 Troina, EN, Italy; **Center for Autism Research and Education, Phoenix, AZ 85012; ††Southwest Autism Research and Resource Center, Phoenix, AZ 85006; ‡‡Laboratory of Molecular Psychiatry and Neurogenetics, University Campus Bio-Medico, I-00155 Rome, Italy; and §§IRCCS Fondazione Santa Lucia, 00179 Rome, Italy

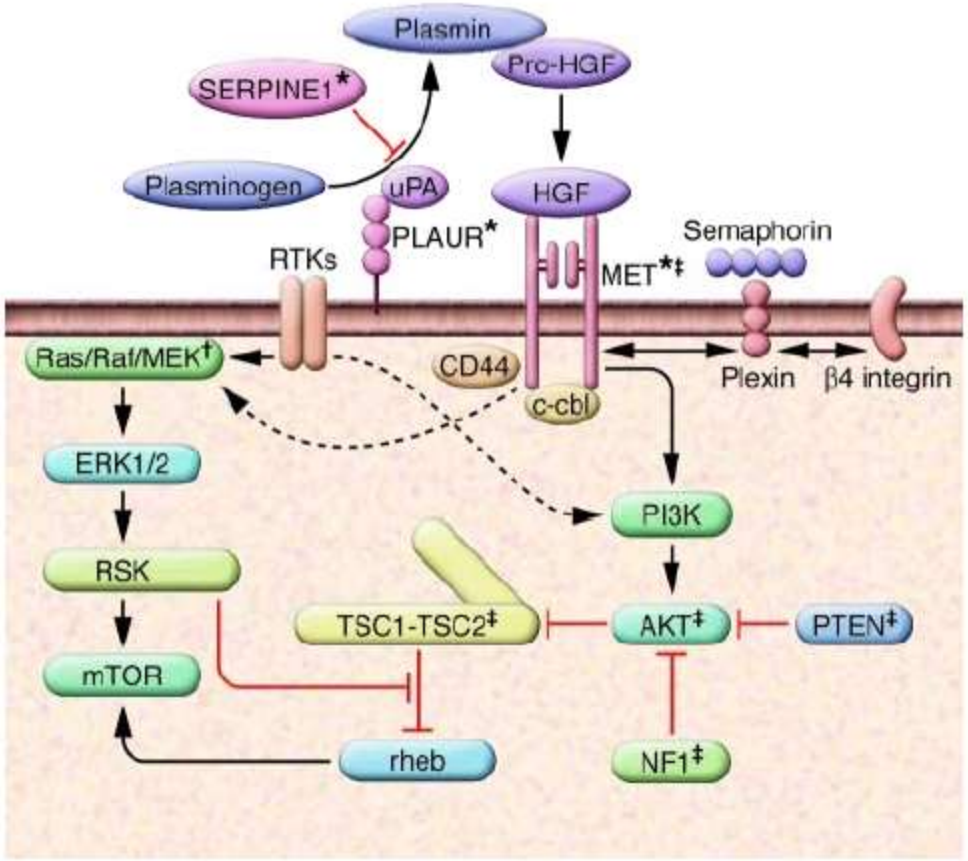
Human MET locus genomic structure



rs 1858830 ***Relative Risk*** (CC/GG) = 2.27 (95% CI: 1.41-3.65)

Campbell *et al*, 2006; 2008
Jackson *et al*, 2009
Sousa *et al*, 2008
Thanseem *et al*, 2010
Marshall *et al*, 2008 (CNVs)

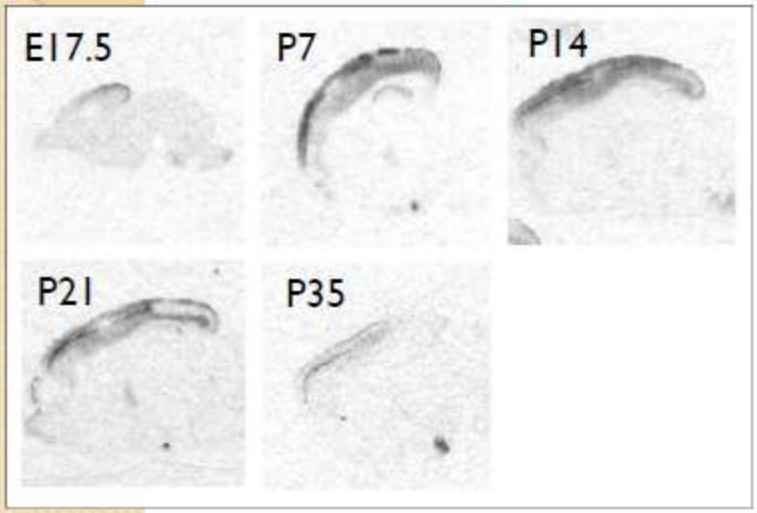
Met mediated signaling pathways



Levitt and Campbell, JCI 2009

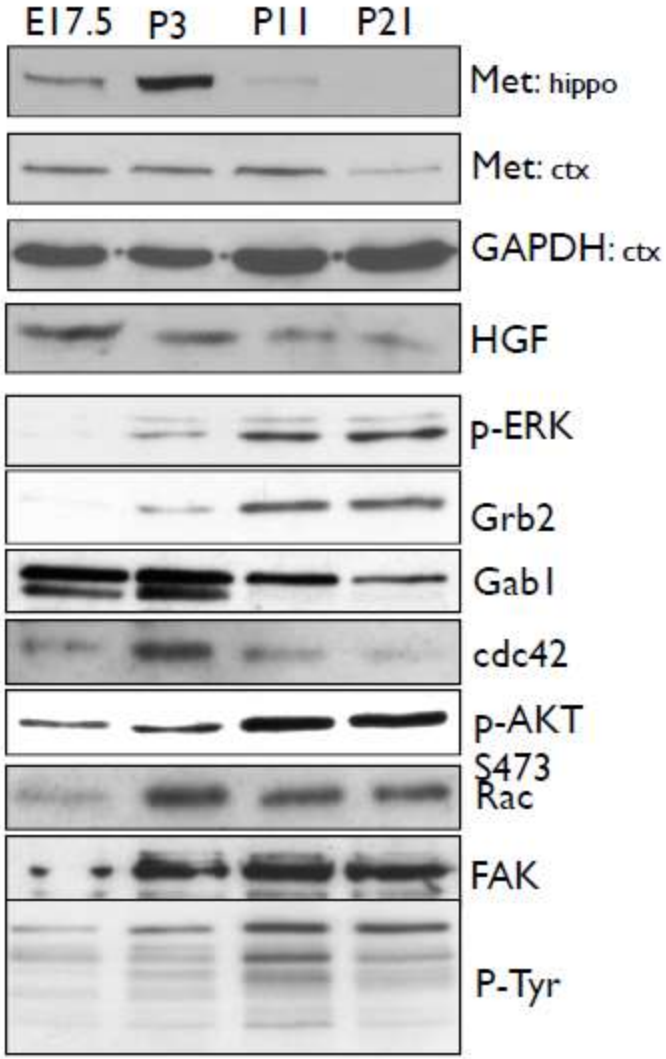
Developmental expression of Met receptor tyrosine kinase

Met In Situ Hybridization



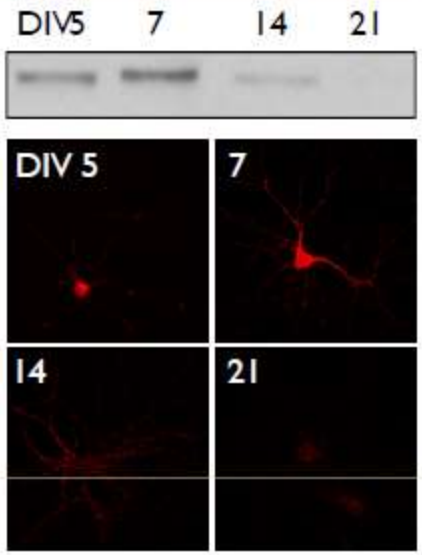
Judson et al 2010

WB: mouse brain tissue

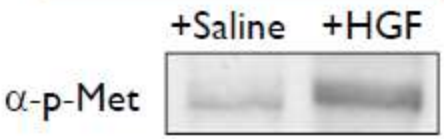


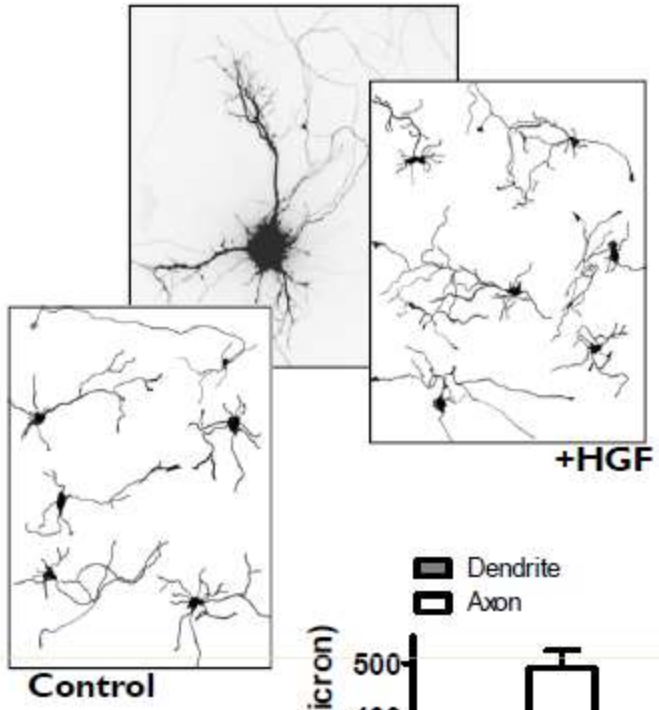
Qiu & Levitt, manuscript in prep

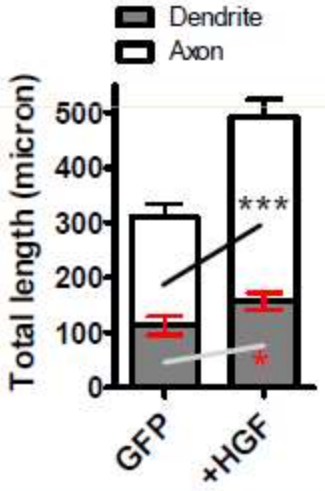
cultured hippo neuron



DIV 7 cultured neuron



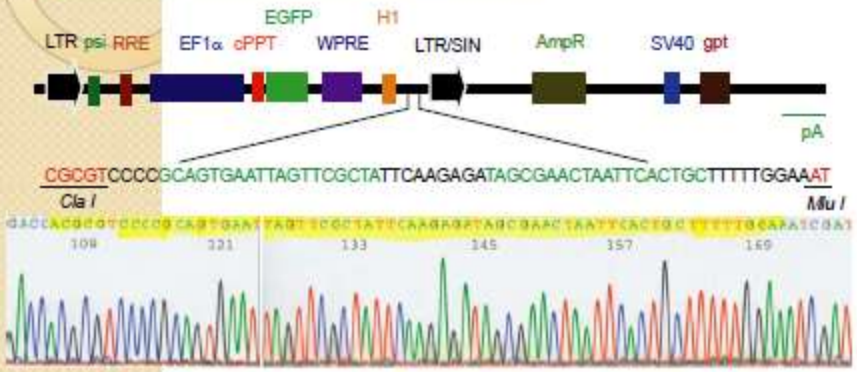




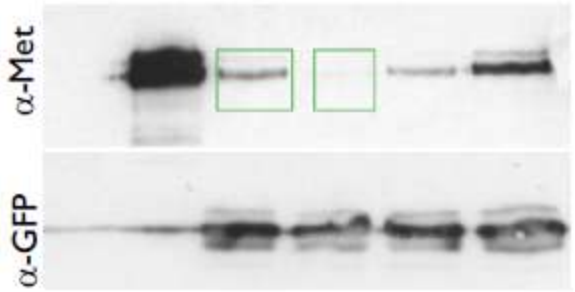
HGF promoted neurite growth

Anti-sense knockdown of Met using small interference RNA

siRNA vector and sequence

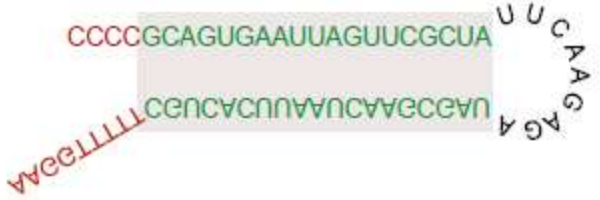


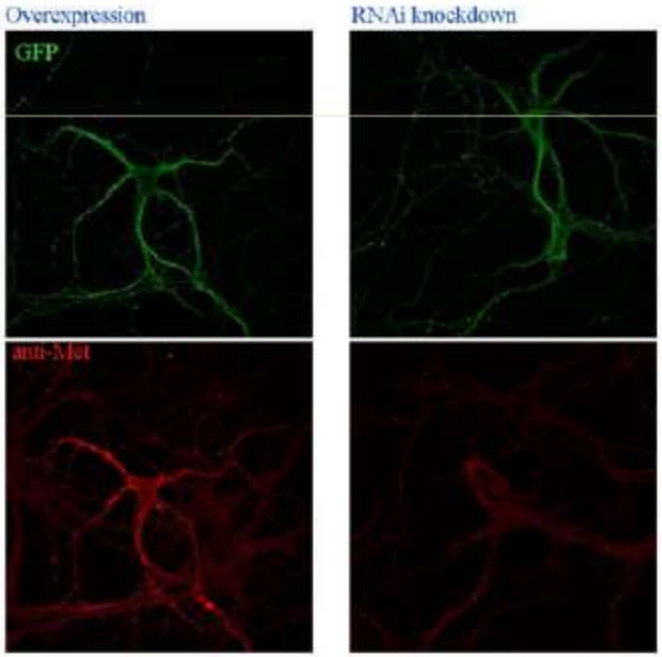
Verification of efficacy



SiMet1 GCACAAAGCAAGCCAGATT
SiMet2 GCAGTGAATTAGTTCGCTA
SiMet3 GCAGCCTGATTGTGCATTT

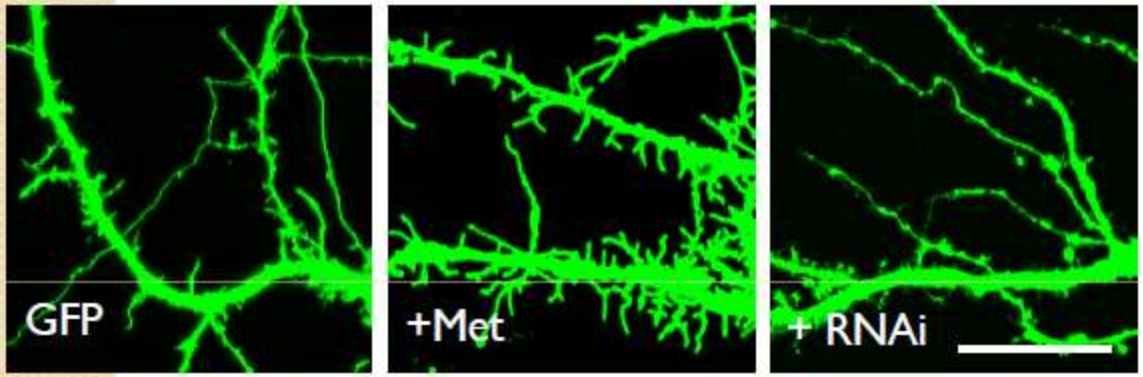
siRNA



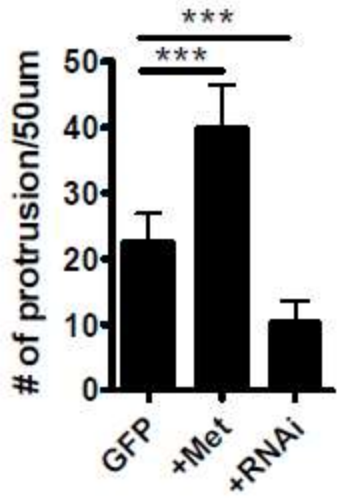


Met signaling affects neuronal growth and morphology

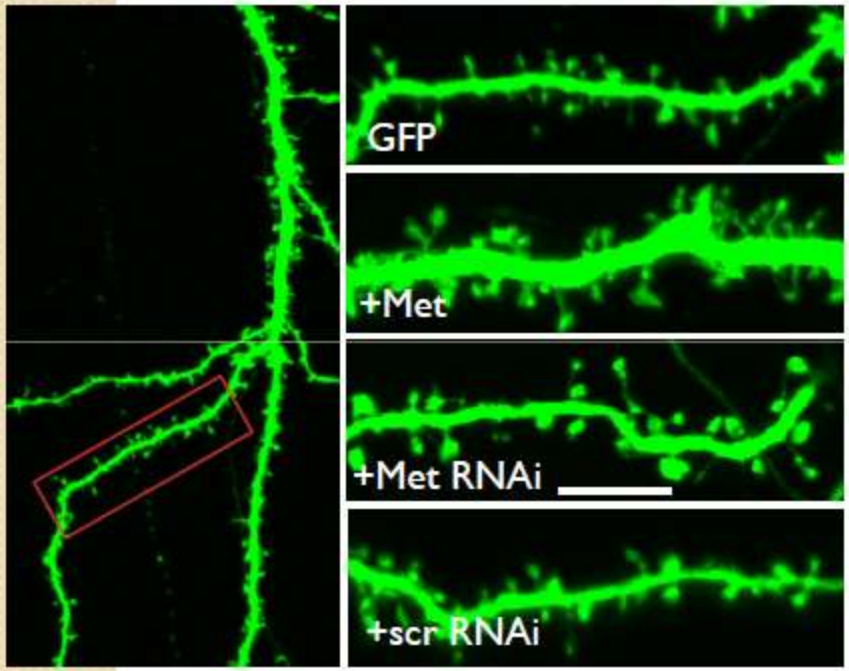
*Manipulating Met expression alters **dendritic protrusions***



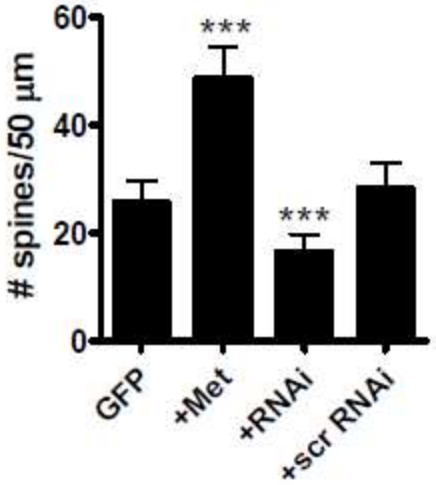
DIV 11 + 4 d

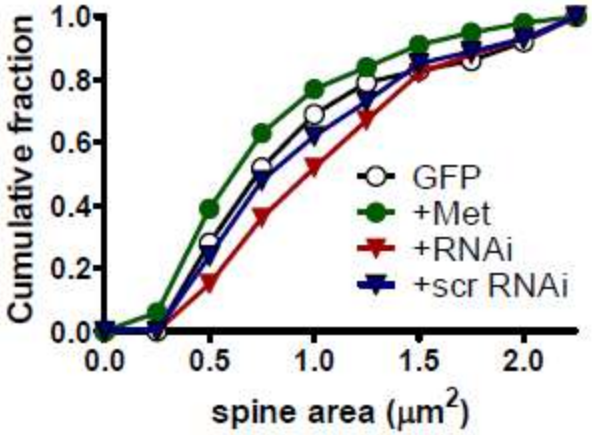


*Manipulating Met expression alters **dendritic spine** development*



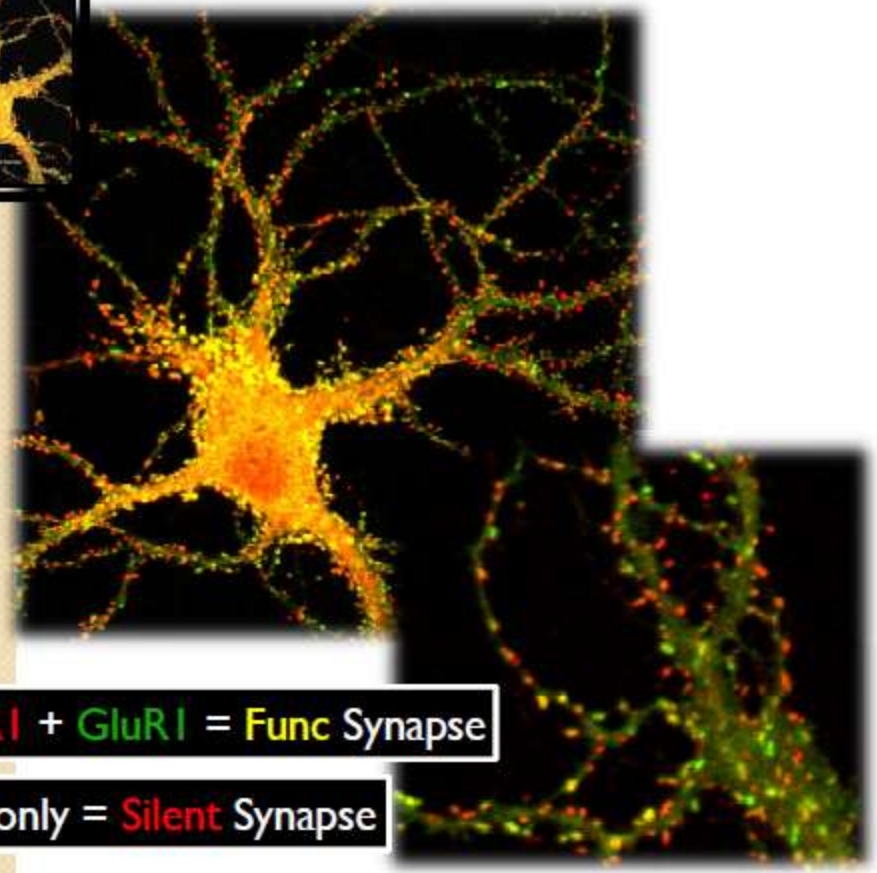
DIV 14 + 7 d





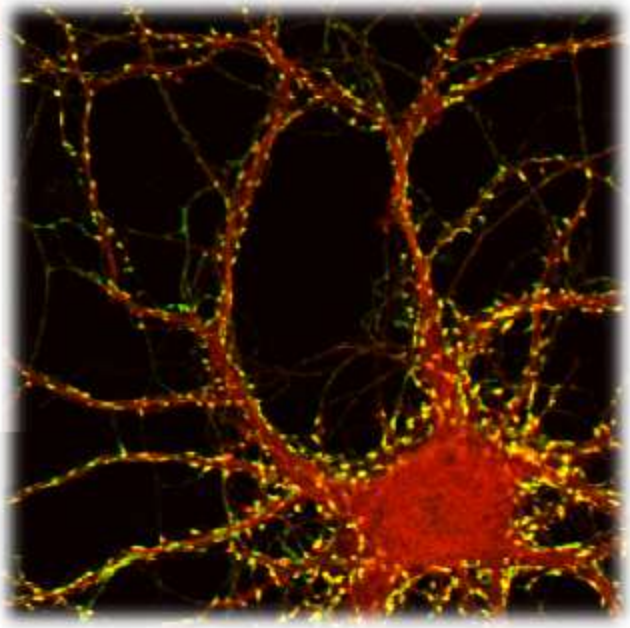
Quantification of excitatory synapses using fluorescent immunocytochemistry

Confocal imaging of functional synapses in cultured hippocampal neurons



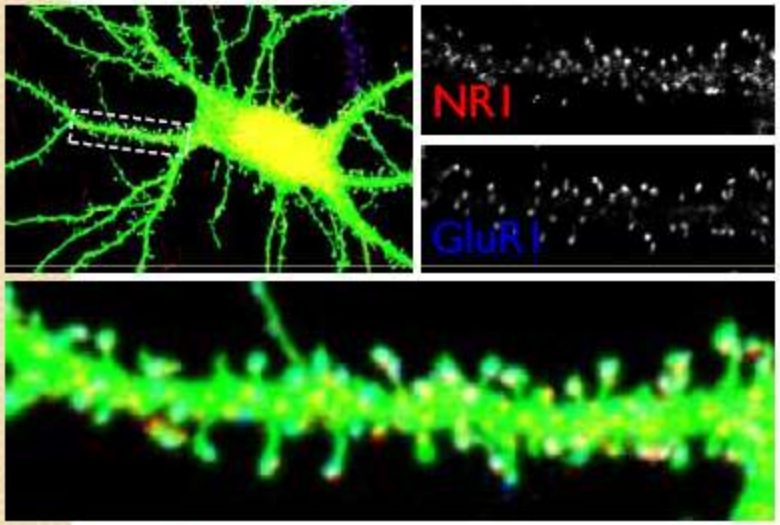
NR1 + GluR1 = Func Synapse

NR1 only = Silent Synapse



PSD95 + Syn I = Synaptic site

Met signaling affects excitatory synapse formation



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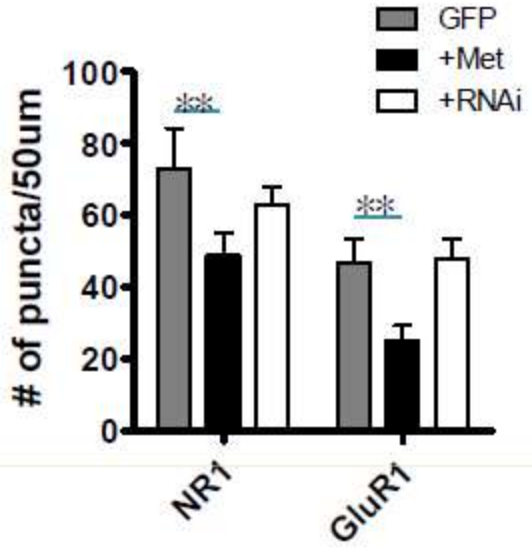
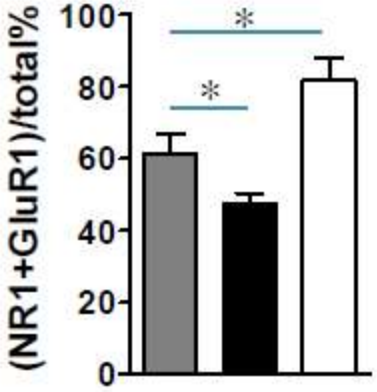
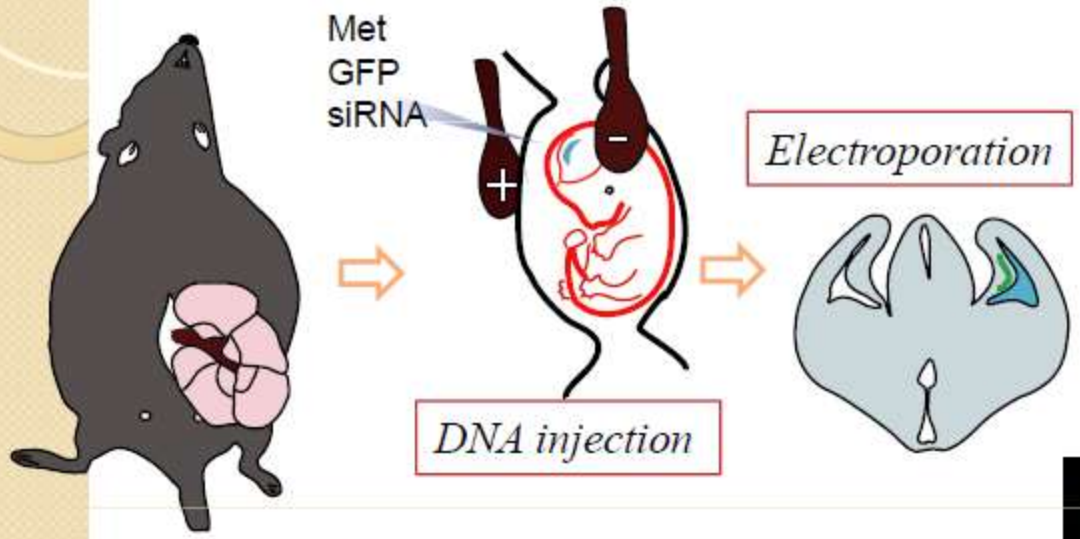
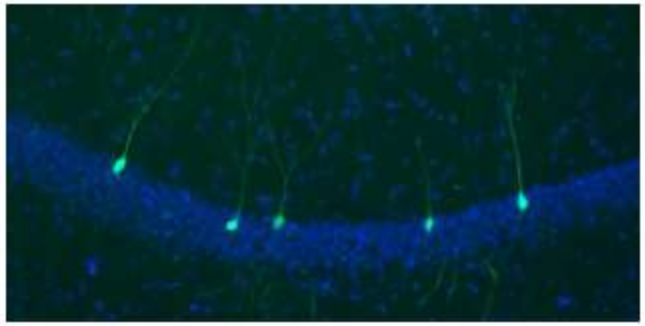


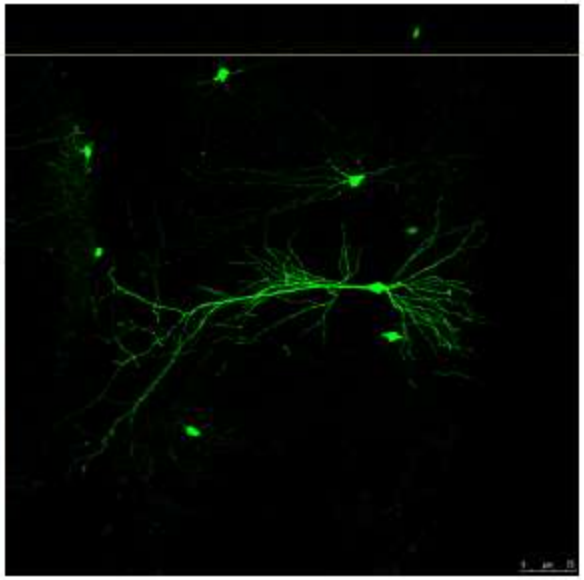


Manipulating Met expression *in vivo* using *In Utero* Electroporation (IUEP)



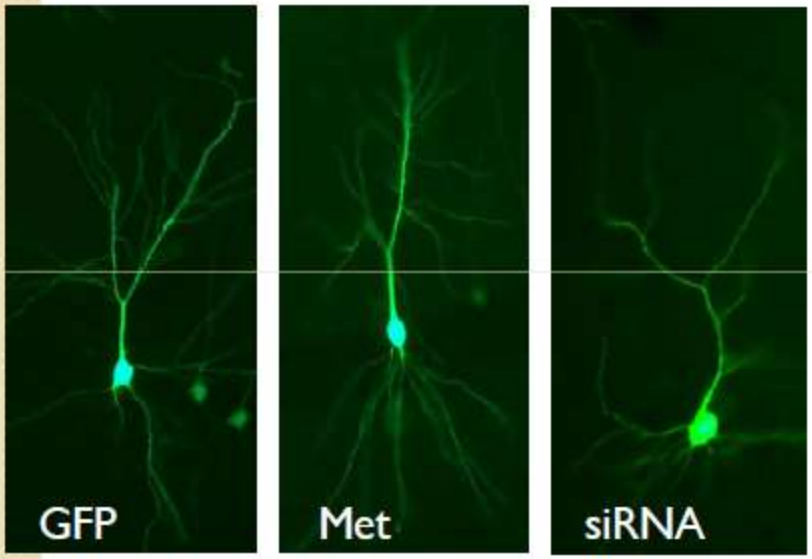
Postnatal morphology and function

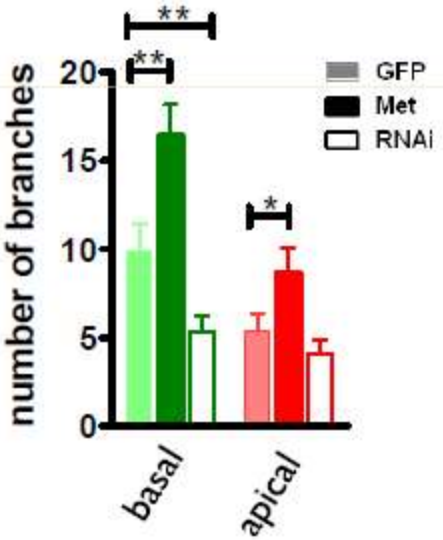




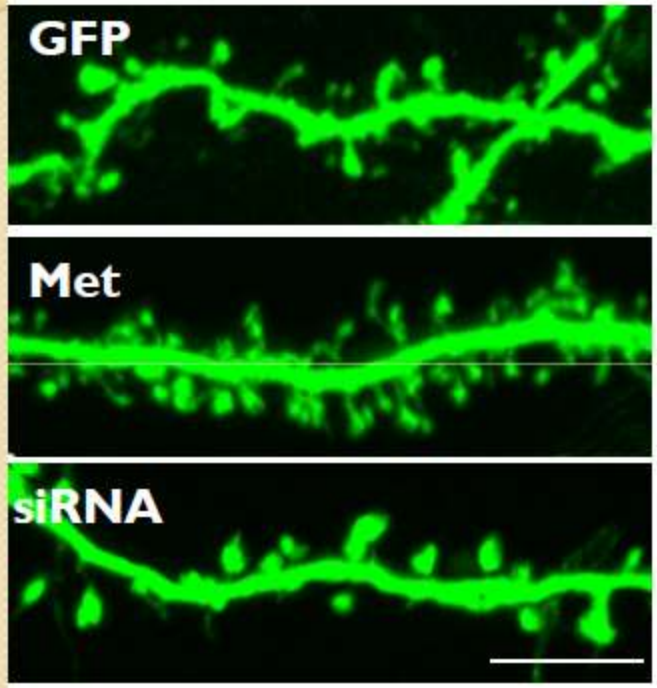
Altered Met expression by IUEP changes CA1 neuronal morphology

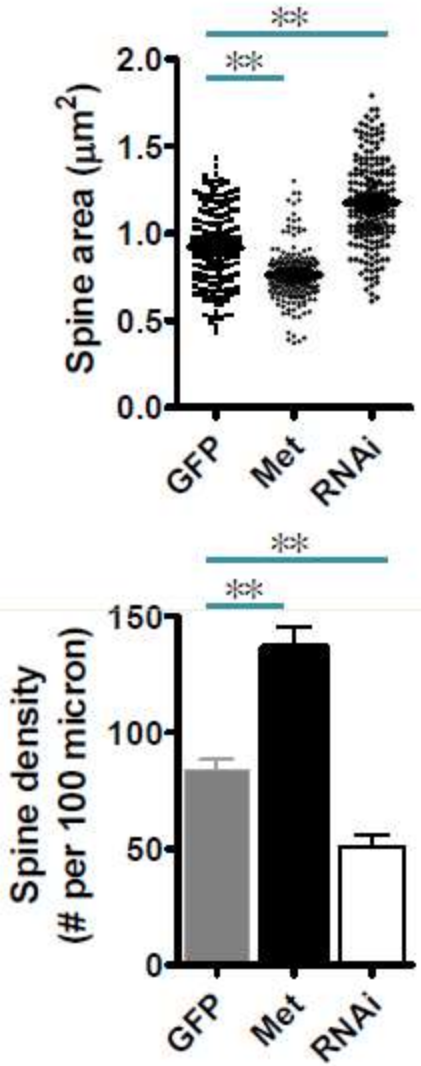
Morphology of electroporated CA1 neurons





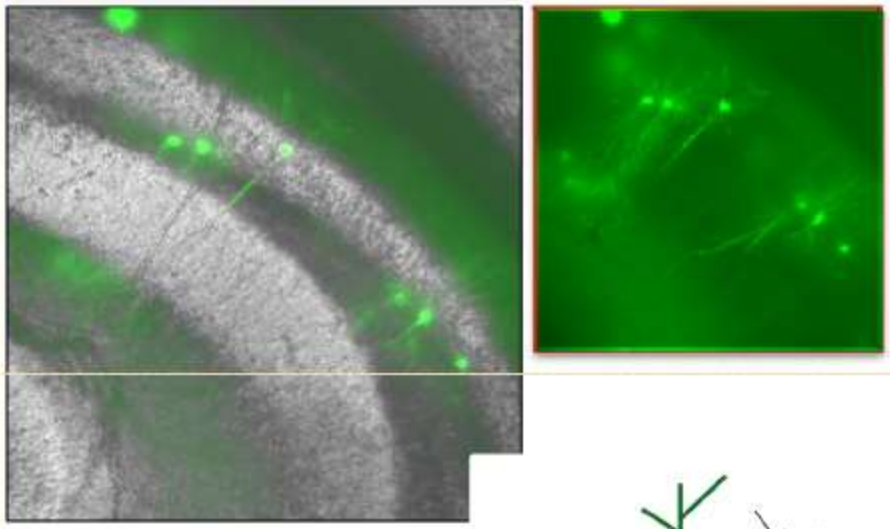
Dendritic spines of electroporated CA1 neurons



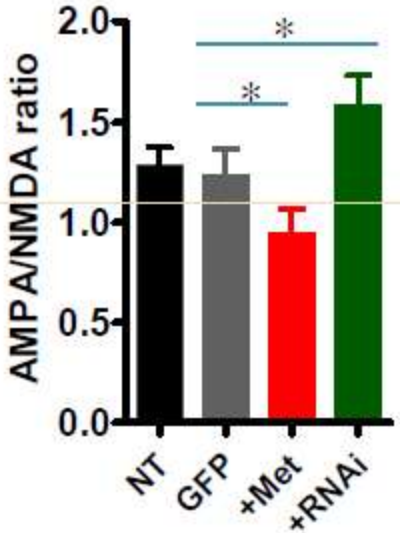


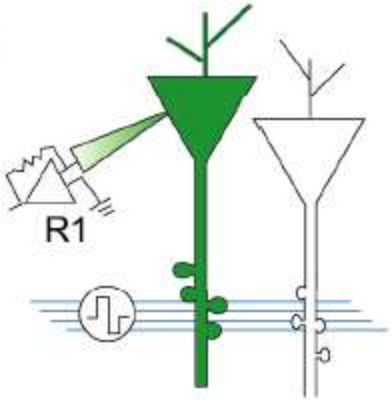
Altered Met signaling in *vivo* affects neuronal function

IUEP hippocampal slice



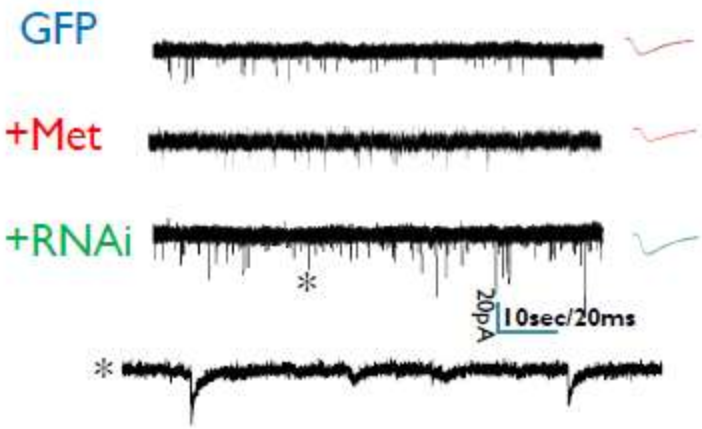
Postnatal day 21-30

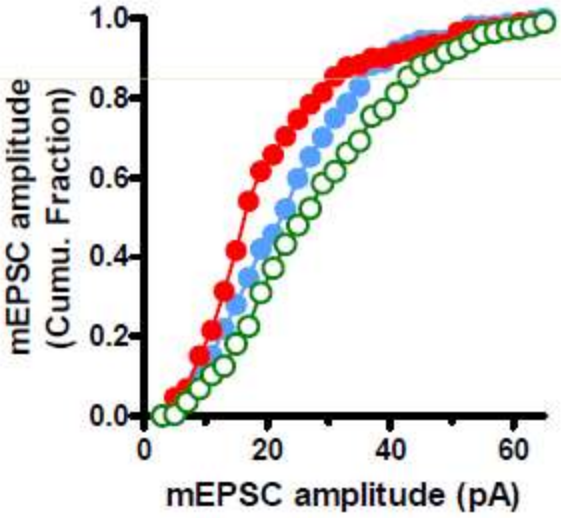


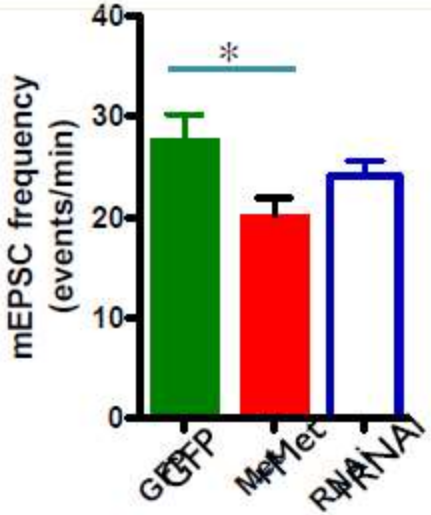


Changed AMPA/NMDA R current ratio

Changed mEPSC amplitude and frequency

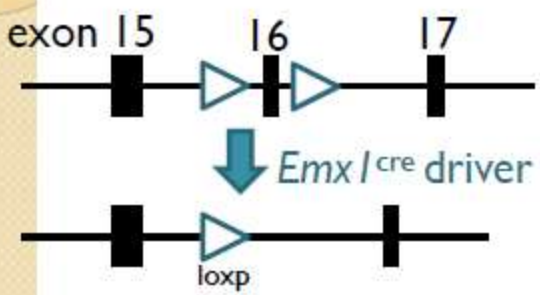


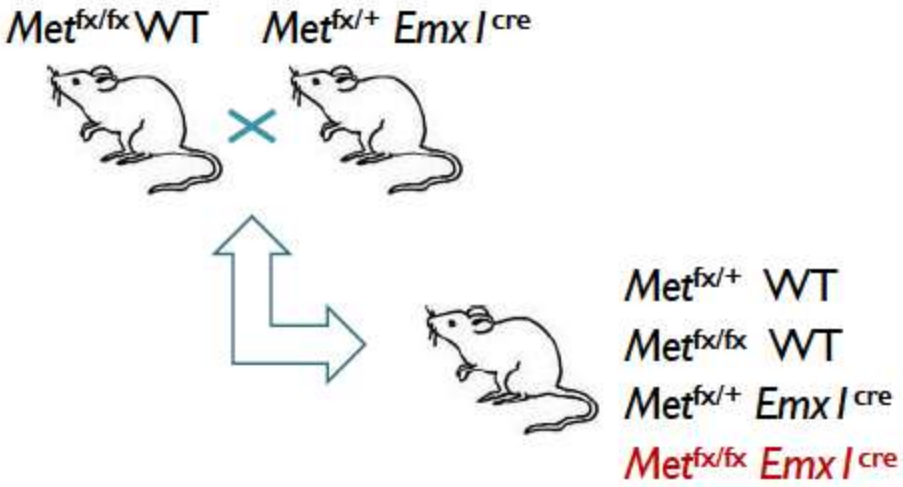




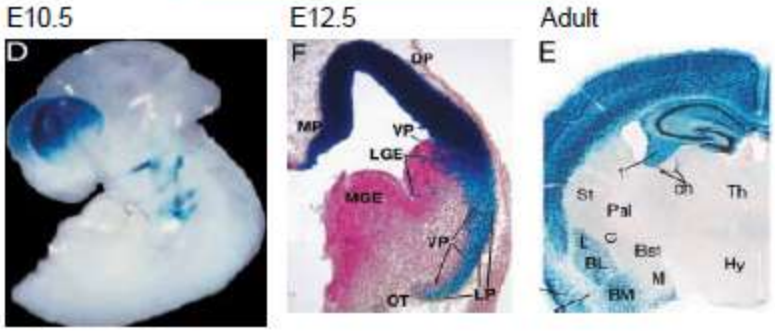
A conditional Met knockout mouse model (*Met*$^{fx/fx}$; *Emx1*^{cre})

cKO mice breeding scheme





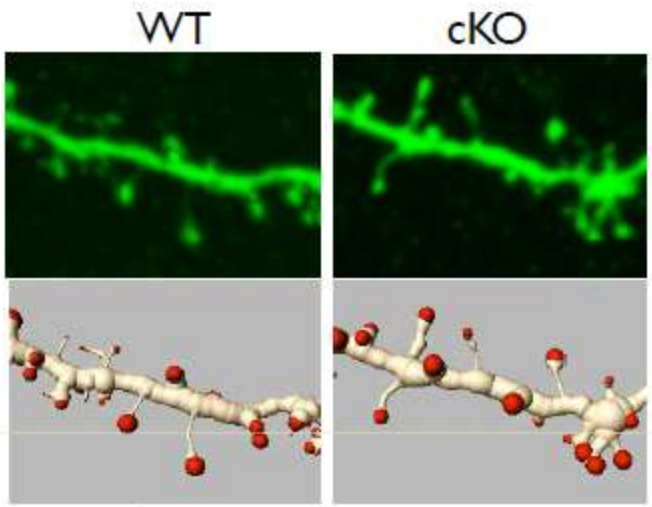
Emx1^{cre} driver line

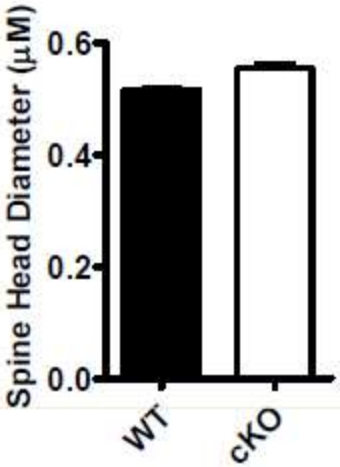


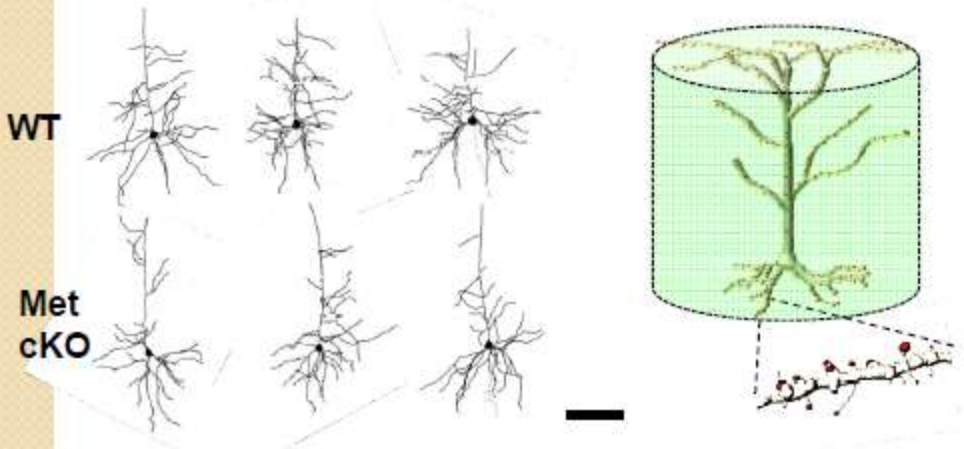
Gorski et al., (2002) J. Neurosci 22(15): 6309

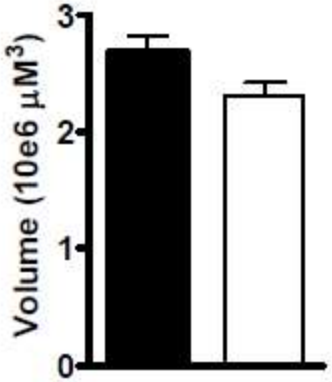
A conditional Met knockout mouse model (*Met*$^{fx/fx}$; *Emx1* ^{cre})

Judson et al., 2009, 2010





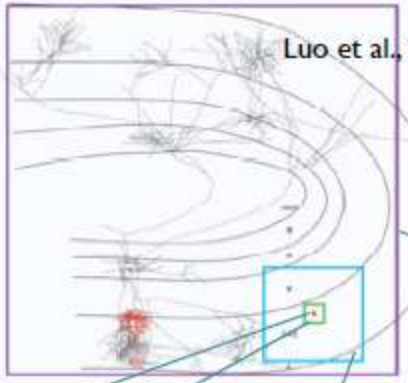


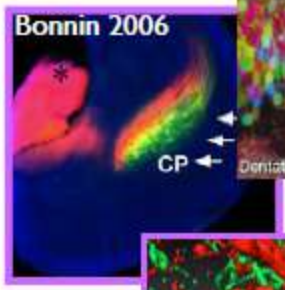


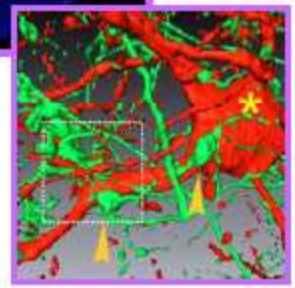
How do we study functional circuits?

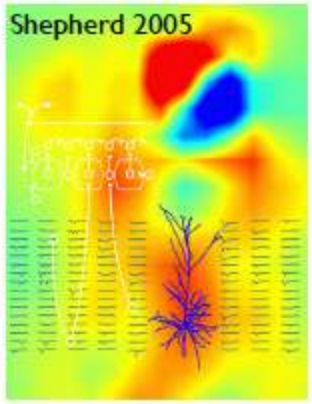
Connectome of c. elegans

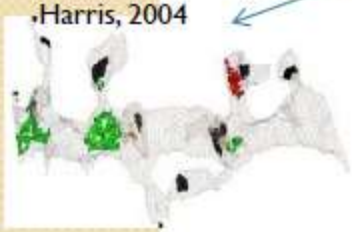
Spatial ranges of circuitry mapping techniques











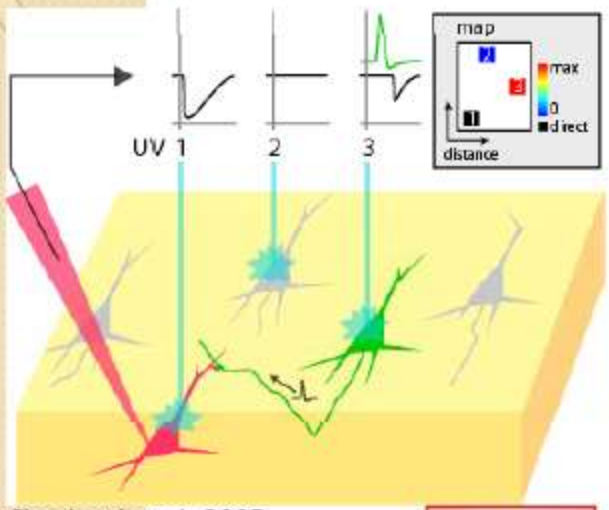
3D EM
Reconstructions
20 micron

Paired recordings
200 micron

LSPS
2000 micron

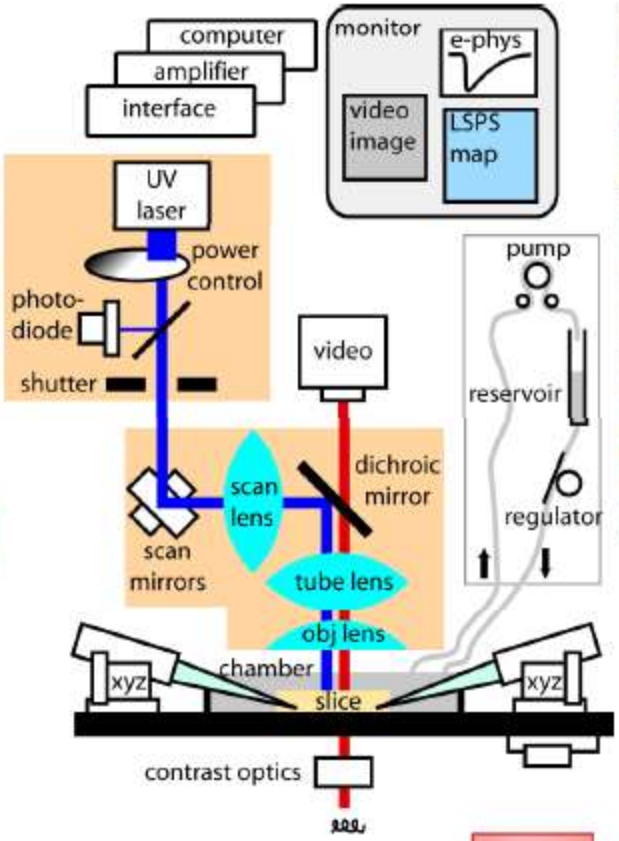
Axon tracing
ChR2 assisted mapping
Potentially **entire brain**

Functional circuit mapping using Laser Scanning Photostimulation (LSPS)

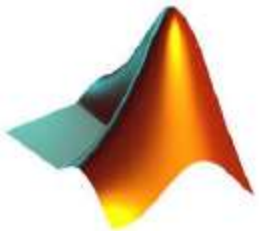


Shepherd et al., 2005

Principle

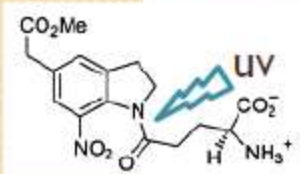


Setup



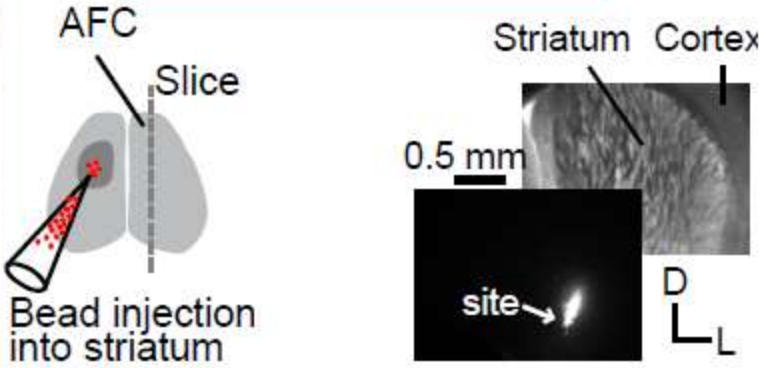
System control
Data management

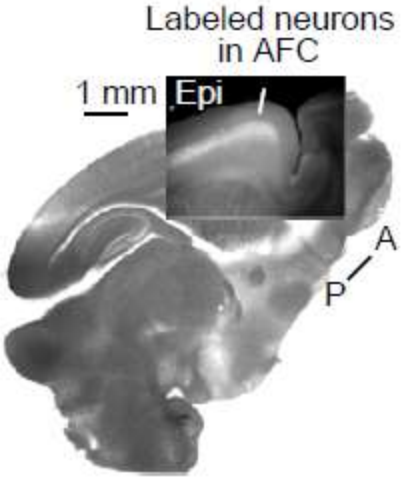
MNI-caged glutamate:

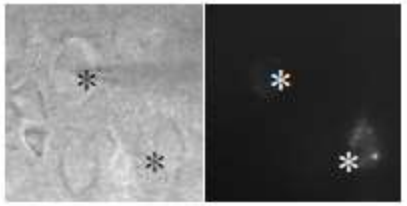


LSPS mapping: focusing on prefrontal circuits

Selective labeling of corticostriatal neurons

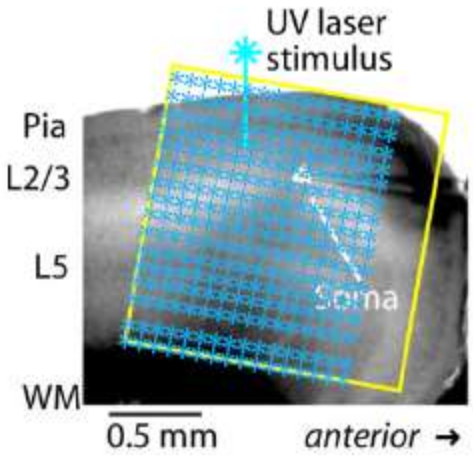


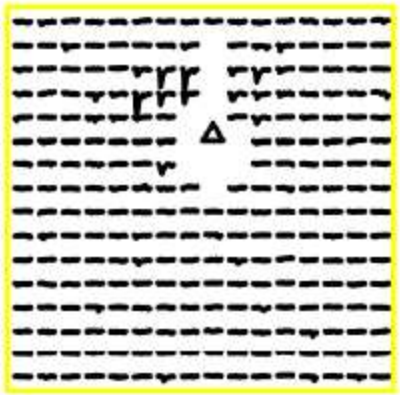




Qiu, Anderson et al., J Neurosci 2011

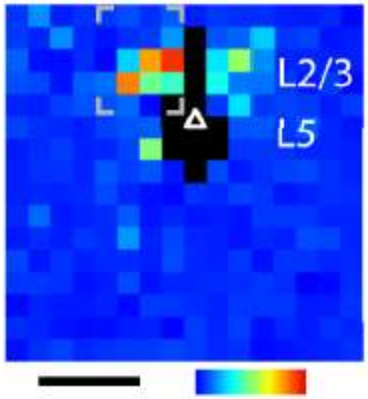
LSPS mapping of L5 CS neuron inputs



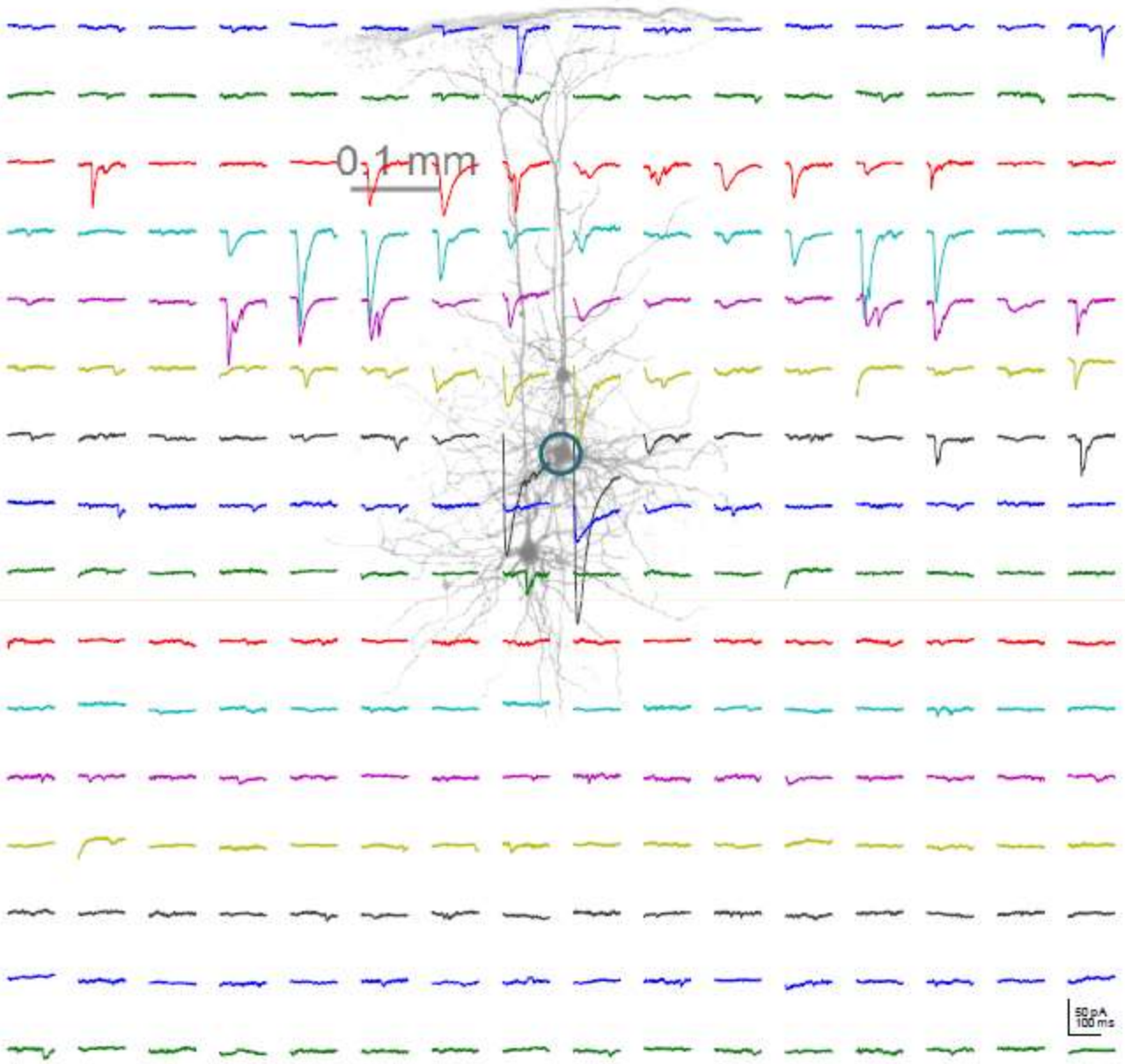


50 pA, 100 msec

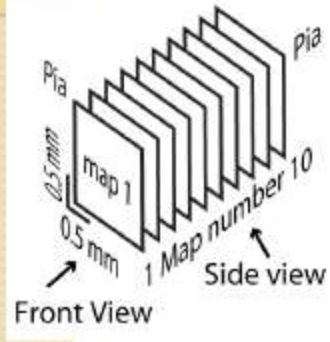
Color coded map



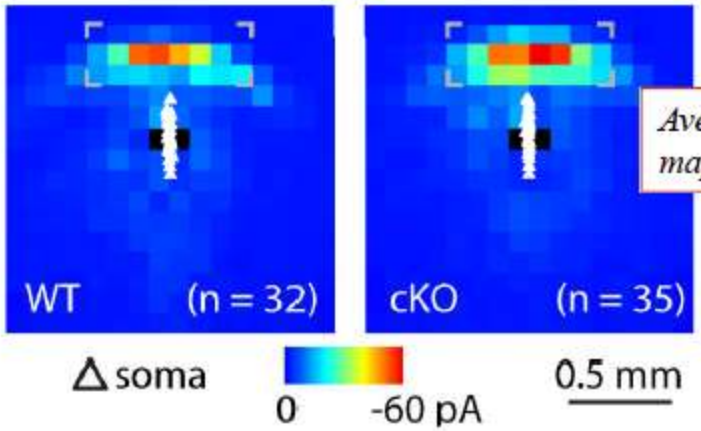
25 pA, 50 msec


0,1 mm
50 pA
100 ms

Increased excitatory inputs in Layer 5B corticostriatal neurons: sublayer specific



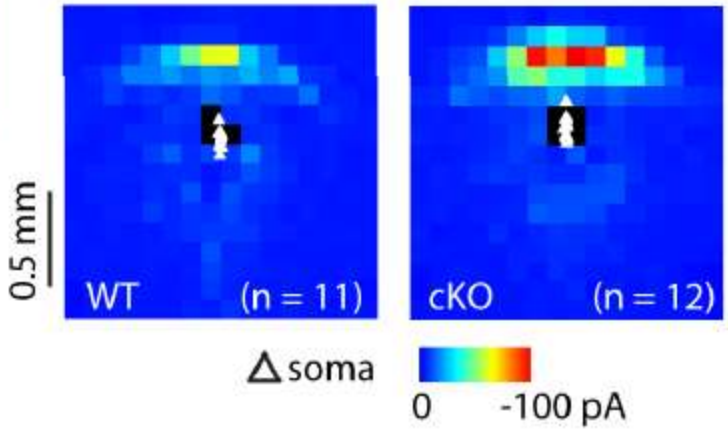
Avg maps, all corticostriatal neurons



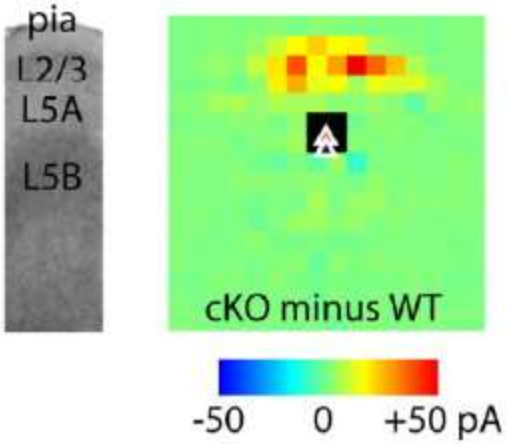
*Averaged **L5** CS neuron input map show no overall difference*

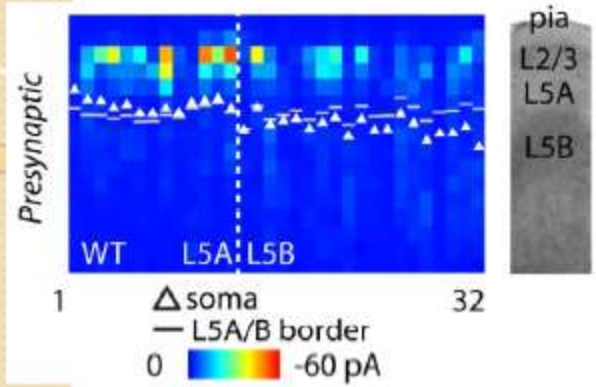
*Significance is revealed for the input onto **L5B** neurons*

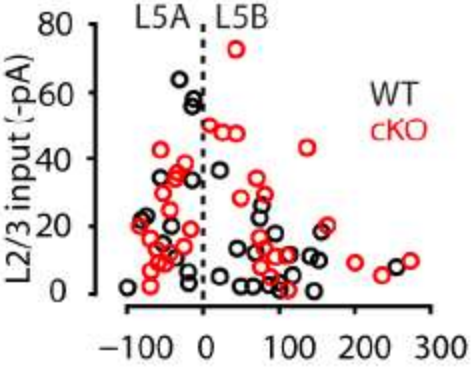
Avg maps, upper L5B neurons

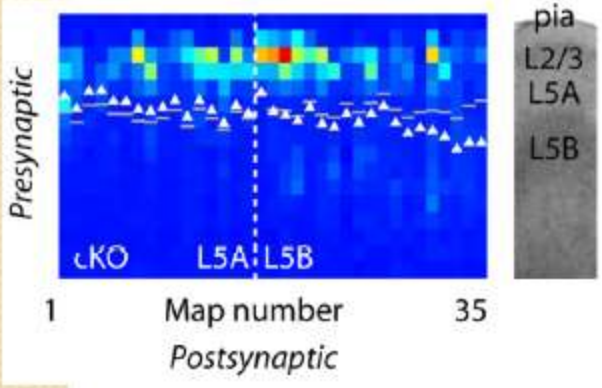


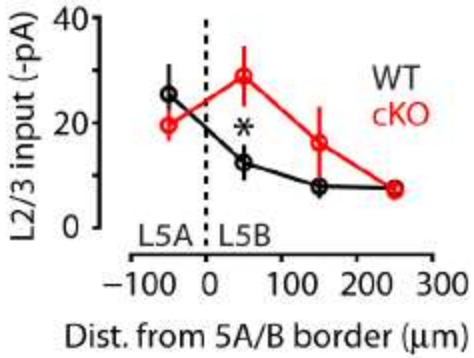
Difference

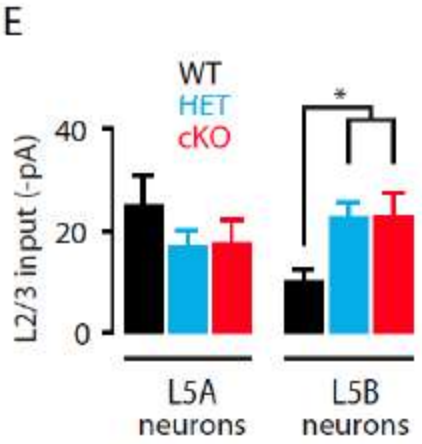



Presynaptic
WT
L5A
L5B
pia
L2/3
L5A
L5B
1
32
Δ soma
L5A/B border
0
-60 pA

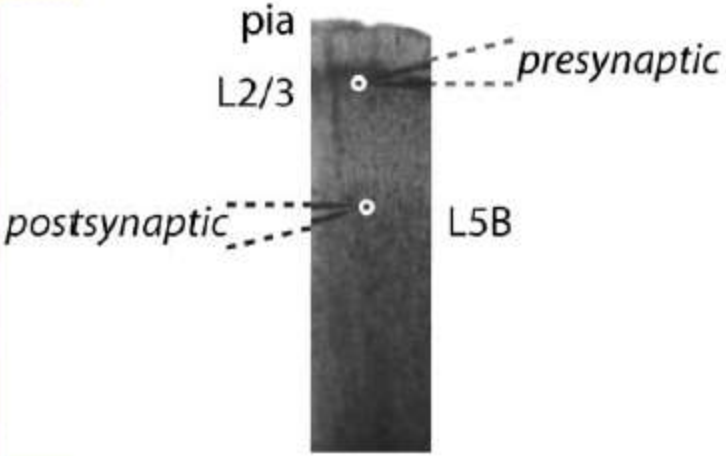

L5A
L5B
WT
cKO
L2/3 input (-pA)
80
60
40
20
0
−100
0
100
200
300

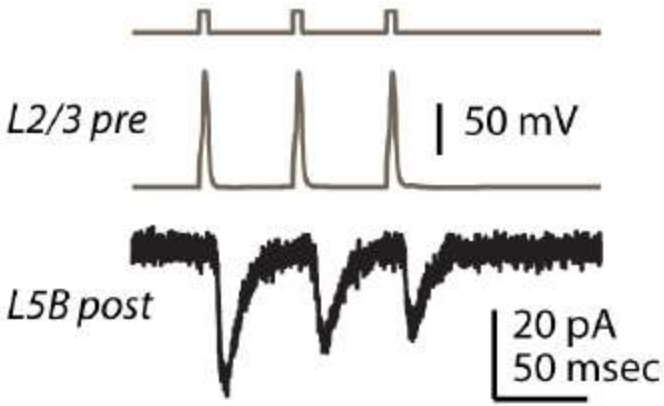

Presynaptic
cKO
L5A
L5B
pia
L2/3
L5A
L5B
1
Map number
35
Postsynaptic

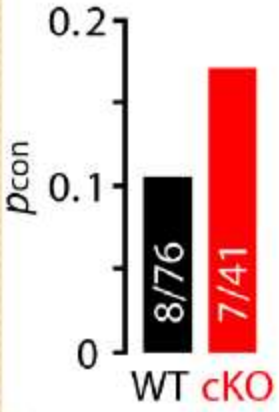

L2/3 input (-pA)
40
20
0
WT
cKO
*
L5A
L5B
−100
0
100
200
300
Dist. from 5A/B border (µm)

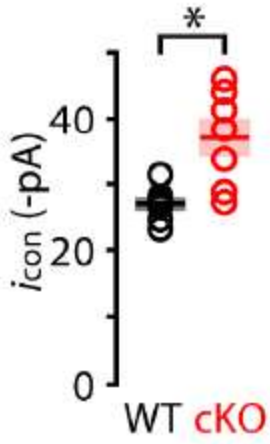

E
WT
HET
cKO
L2/3 input (-pA)
40
20
0
*
L5A
neurons
L5B
neurons

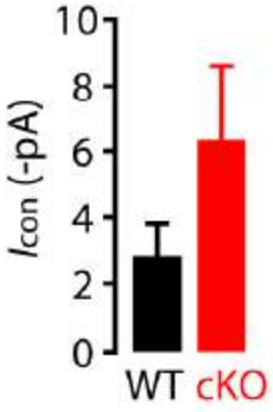
Increased unitary connection at L2/3->L5B CS neurons: paired recording

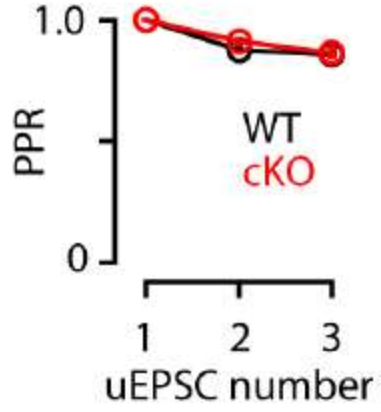






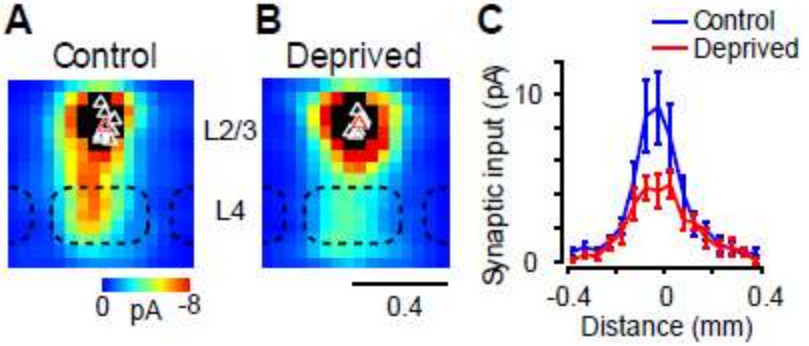


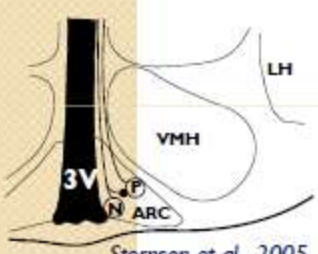




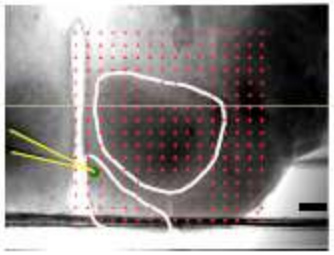
LSPS is a useful tool to resolve circuit changes in physiological/pathological states

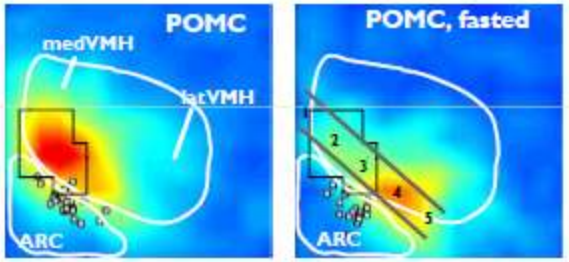
Shepherd et al., 2003

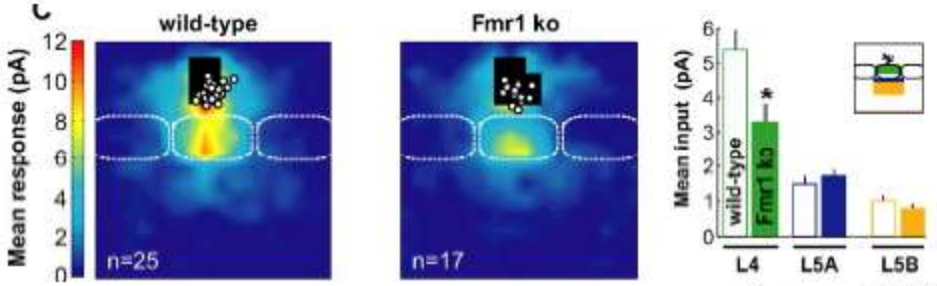




Sternson et al., 2005







Bureau et al., 2008

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