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
Cells Drive Brain Function
Cells Drive Brain Function

Glutamateric principal cells
Glutamateric principal cells

Pyramidal neurons

80% of brain cells.

Cells Drive Brain Function
Pyramidal neurons
80% of brain cells.

Cells Drive Brain Function

Glutamateric principal cells

GABAergic interneurons
Glutamateric principal cells

GABAergic interneurons

Pyramidal neurons
80% of brain cells.

Cells Drive Brain Function

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
GABAergic cortical interneurons

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Excitatory network

Cajal, 1906
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Gating

Feedforward inhibition

Feedback inhibition

Rhythm generation

Cajal, 1906
The Cell Assembly Hypothesis

“The Organization of Behavior” Donald Hebb 1949

Donald Hebb 1904-1985
The Cell Assembly Hypothesis

“The Organization of Behavior” Donald Hebb 1949

Donald Hebb 1904-1985

Thursday, November 11, 2010
Linking affective brain disorders to their biological cause
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<th>Size (bp)</th>
<th>Type</th>
<th>Genes affected (SV breakpoints)</th>
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<td>198,573,215</td>
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<td>57,723,933</td>
<td>152,391</td>
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<td>1 LARGE</td>
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Controls (n = 268)

| 100,204,503 | 219,761 | del  | 2 FRRS1 |
| 8,581,679 | 410,026 | del  | 1 ROBO1 |
| 81,408,551 | 1,740,703 | del  | 1 MANE |
| 96,143,673 | 413,043 | del  | 1 FLY31810 |
| 84,699,929 | 363,921 | del  | 6 SND1, CTSD |
| 112,334,786 | 1,300,896 | dup  | 1 MPDZ |
| 127,422,401 | 338,843 | del  | 1 SOK5, LYR5, TMTC1 |
| 11,755,764 | 3,611,148 | del  | 20 HYDIN |
| 13,216,945 | 575,532 | dup  | 3 BPIF2 |
| 25,248,947 | 665,297 | dup  | 7 TMTC1, HYDIN |
| 29,990,037 | 196,994 | del  | 1 BPIF2 |
| 69,748,827 | 352,892 | del  | 2 TMTC1, HYDIN |
| 31,191,488 | 292,660 | dup  | 5 BPIF2 |
Linking affective brain disorders to their biological cause

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<td>31,191,488</td>
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Microarray analysis of Cortical Interneurons

Once dissociated cortical cells are obtained from Dlx5/6-Cre-GFP mice, GFP positive cells are FACS sorted followed by expression analysis by microarray.

Dlx5/6-Cre-EGFP mouse

Scheme of the brain.

Interneuron progenitors originate in the ganglionic eminences (purple) take migratory pathways (arrows) to reach the cortex. We dissected the cortex of this mouse at E13.5 and E15.5

FACS sorting

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

Microarray hybridization and scanning

E13.5

GFP

E15.5

GFP

GFP
Genes expressed in local projection neurons linked to psychiatric disorders

Thursday, November 11, 2010
Genes expressed in local projection neurons linked to psychiatric disorders

<table>
<thead>
<tr>
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<th>Human Disease</th>
<th>Ref.</th>
<th>Mouse Endophenotype</th>
<th>Ref.</th>
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<td>Transcription factors/ regulators</td>
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<td>(Pickard et al. 2005; Pickard et al. 2006)</td>
<td>Impaired prepulse inhibition;</td>
<td>(Erbel-Sieler et al. 2004)</td>
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<td>Hdas11</td>
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<td>(Sztatmari et al. 2007)</td>
<td>Impaired social recognition</td>
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15% of local projection neuron genes are linked to psychiatric disorders

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<td>Cacnb4</td>
<td>Autism; epilepsy</td>
<td>(Scagay, De Warrd, et al. 2000;</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Sztanai et al. 2007)</td>
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<td></td>
<td>Cacnb2</td>
<td>Schizophrenia; epilepsy</td>
<td>(Scagay et al. 2004);</td>
<td>Epileptic seizures</td>
<td>(Sztanai et al. 1998)</td>
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<td></td>
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<td>Mental retardation; epilepsy</td>
<td>(Escagay, De Warrd, et al. 2000;</td>
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<td>(Shigemori et al. 2007)</td>
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<td>Escagay et al. 2001;</td>
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<td>Inlow and Restiso 2004)</td>
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<td></td>
<td>Aet</td>
<td>Mental retardation; Autism; Schizophrenia</td>
<td>(Inlow and Restiso 2004);</td>
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<td>Barby et al. 2005;</td>
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<td>Zhang et al. 2006)</td>
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<td></td>
<td>Kon2</td>
<td>Autism</td>
<td>(Sztanai et al. 2007)</td>
<td>Kon2 deletion as an antidepressant behavioral</td>
<td>(Heurteaux et al. 2008)</td>
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<td>Dcx</td>
<td>Epilepsy; Mental retardation</td>
<td>(Reiner et al. 2006)</td>
<td>Deficient interneuron migration.</td>
<td>(Fiocourt et al. 2007)</td>
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<td></td>
<td>Mda5a1</td>
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<td>Defective tangential cell migration</td>
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<td></td>
<td>Nf2/F2</td>
<td>Autism</td>
<td>(Sztanai et al. 2007)</td>
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<td>(Tripodi et al. 2004)</td>
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<td>Shank3</td>
<td>Autism</td>
<td>(Durand et al. 2007;</td>
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<td>Sztanai et al. 2007)</td>
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<td>Sed62</td>
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<td>Gamp6</td>
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<td>Cenp2</td>
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</tbody>
</table>
...Versus 1% of genes expressed in long distance projection neurons.
In vivo transplantation study
The MGE and CGE give rise to cortical interneurons

UBM guided in vivo transplantation

The majority of cortical interneurons are generated in the MGE and CGE

Interneuron subtypes seems regionally specified

Wichterle et al., 2001

Nery et al., 2002

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Heterotopic transplantation study suggests that interneuron subtypes are intrinsically determined.

UBM guided in vivo transplantation

In vivo transplantation study
The MGE and CGE give rise to cortical interneurons

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Nery et al., 2002
Genetically Birthdating of the MGE or CGE

Olig2\textsuperscript{CreER} : Temporal MGE fate mapping
Mash1 : Temporal CGE fate mapping

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

Butt et al., Neuron 2005
Complementary assays for interneuron subtype

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

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Neocortical GABAergic interneurons are ventrally derived

(Aizawa et al., 2004)
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Interneurons are ventrally derived

(Aizawa et al., 2004)
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A cladistic approach to classifying cortical interneurons
A cladistic approach to classifying cortical interneurons

GABAergic Neurons
A cladistic approach to classifying cortical interneurons

GABAergic Neurons

Projection Interneuron
A cladistic approach to classifying cortical interneurons

GABAergic Neurons

Projection

Interneuron

MGE

CGE
A cladistic approach to classifying cortical interneurons

GABAergic Neurons

- **Projection**
  - MGE
    - Basket
  - CGE
    - Martinotti

- **Interneuron**
  - Neurogliaform
  - Bipolar
A cladistic approach to classifying cortical interneurons

GABAergic Neurons

Projection

MGE
- Basket
  - PV
  - CCK
- Martinotti
  - SOM/CR

Interneuron

CGE
- Neurogliaform
- Bipolar
  - ?
  - VIP
- SOM

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A cladistic approach to classifying cortical interneurons

GABAergic Neurons

Projection

Interneuron

Genetic

MGE

Basket
PV
CCK
SOM/CR
SOM

Martinotti

Neurogliaform

Bipolar

VIP
CR

CGE

? ?
A cladistic approach to classifying cortical interneurons

GABAergic Neurons

Projection

Interneuron

Genetic

MGE

Basket
PV
FS

Martinotti
CCK
dFS

SOM/CR
?

SOM
?

Environmental

Projection

Interneuron

GABAergic Neurons

Neurogliaform
VIP

Bipolar
CR

FS
dFS

iIB
?

rIB
?
A cladistic approach to classifying cortical interneurons

GABAergic Neurons

Projection

Interneuron

Genetic

MGE

Basket

Martinotti

PV  CCK  SOM/CR  SOM

FS  dFS                      iIB  rIB

Environmental

CGE

Neurogliaform  Bipolar

VIP  CR

Activity

Thursday, November 11, 2010
John Rubenstein, Butt et al., Neuron 2008
MGE
Nkx2.1  John Rubenstein, Butt et al., Neuron 2008
↓
Lhx6  Vassilis Pachnis, Stewart Anderson

CGE
MGE
Nkx2.1  John Rubenstein, Butt et al., Neuron 2008
  ↓
Lhx6  Vassilis Pachnis, Stewart Anderson
  ↓
Sox6  Azid et al. (Macklis Lab) Nature Neuroscience 2009
       Batista-Brito et al., Neuron 2009
MGE

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CGE
Gli1/2

\[ \downarrow \]

CoupTF1/2
MGE

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CGE

Gli1/2

CoupTF1/2

Ets1
MGE
Nkx2.1  John Rubenstein, Butt et al., Neuron 2008
   ↓
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CGE
Gli1/2
   ↓
CoupTF1/2
    ↓
Ets1

All Interneurons
MGE

Nkx2.1  John Rubenstein, Butt et al., Neuron 2008

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CGE

Gli1/2

\[ \downarrow \]

CoupTF1/2

Ets1

All Interneurons

MGE  CGE
MGE
Nkx2.1
John Rubenstein, Butt et al., Neuron 2008

Lhx6
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Azid et al. (Macklis Lab) Nature Neuroscience 2009
Batista-Brito et al., Neuron 2009

CGE
Gli1/2

CoupTF1/2

Ets1

All Interneurons

Basket Cells

NGF Cells

bipolar Cells

Martinotti Cells

multipolar Cells
MGE
Nkx2.1  John Rubenstein, Butt et al., Neuron 2008

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CGE
Gli1/2

CoupTF1/2

Ets1

All Interneurons

Basket Cells

NGF Cells

bipolar Cells

Martinotti Cells

multi-polar Cells

???

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Contextual Iterative Analysis
Contextual Iterative Analysis

As applied to cortical interneurons:
Contextual Iterative Analysis

As applied to cortical interneurons:

• Genes expressed in adult cortical interneurons (AIBS)
Contextual Iterative Analysis

As applied to cortical interneurons:

• Genes expressed in adult cortical interneurons (AIBS)

• Genes expressed in embryonic cortical interneurons (Batista-Brito et al., 2008)
Contextual Iterative Analysis

As applied to cortical interneurons:

• Genes expressed in adult cortical interneurons (AIBS)
• Genes expressed in embryonic cortical interneurons (Batista-Brito et al., 2008)
• Genes expressed in temporal cohorts of MGE-driven interneurons (Miyoshi et al.)
Contextual Iterative Analysis

As applied to cortical interneurons:

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- Genes expressed in CGE-derived cortical interneurons.
Contextual Iterative Analysis

**As applied to cortical interneurons:**

- Genes expressed in adult cortical interneurons (AIBS)
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- Genes expressed in temporal cohorts of MGE-driven interneurons (Miyoshi et al)
- Genes lost in cortical interneuron progenitors lacking \textit{Nkx2.1} gene function
- 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

CGE-derived

Reelin

Calretinin

VIP

Miyoshi et al. JN 07
Butt et al. Neuron 05
Sousa et al., CC 09
Miyoshi et al. JN 10

Nery et al. NN 02

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Cortical interneuron subtypes derived from the MGE and CGE

MGE

25% II-III
75% IV-VI

CGE

~75% I-III
~25% IV-VI

Birthdate of interneurons

E9.5 E12.5 E15.5 E18.5
### MGE-derived

<table>
<thead>
<tr>
<th>Origin</th>
<th>Molecular marker</th>
<th>Functional properties</th>
<th>Laminar distribution</th>
<th>Morphology</th>
<th>Diversity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast-spiking basket cells</td>
<td>MGE</td>
<td>Fast spiking firing pattern: Low input resistance and fast membrane time constant. Mediated fast, powerful and precise IPSPs.</td>
<td>Layers II/III: highest proportion in layer IV.</td>
<td>Mostly multipolar, occasionally bifurcated 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.</td>
<td>1. Variations in expression of channels and receptors; e.g., Erg1 X receptors in cingulate CR &amp; hippocampus. 2. Layer-specific differences in threshold firing: delayed or onset spike and in degree of adaptation during large depolarizations. 3. Variations in axonal transcalamin and transcalamin and somatic-dendritic size. 4. Facilitating inputs from corticostriatal axons, other excitatory inputs are depressing. 5. Fire early or late.</td>
</tr>
</tbody>
</table>

| Chandelier cells (see also: aspyny cells) | MGE | Spiking resembles FS basket cells, with higher input resistance & slower membrane time constant. | Layers III/IV, most often in layer I/II. | Multipolar, or bifurcated dendrites. Pre-terminal axon branches form short vertical rows of boutons resembling dendrites, making synapses on the axonal initial segment of pyramidal cells. | 1. Calcium positive and negative. 2. Variations in expression of other markers: reelin, NPY+. 3. Variations in location and extent of distal axonal tuft. |

| Martiretti cells | MGE | Often called L5 cells (low threshold spiking). Some fire 2 or more spikes on slow depolarizing hump 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/IV | Multipolar, bifurcated or bipolar dendrites; ascending axon that typically leads to a dense axonal arborisation in layer I. Target distal and tuft dendrites. | 1. Calcium positive and negative. 2. Variations in expression of other markers: reelin, NPY+ |

### CGE-derived

<table>
<thead>
<tr>
<th>Origin</th>
<th>Molecular marker</th>
<th>Functional properties</th>
<th>Laminar distribution</th>
<th>Morphology</th>
<th>Diversity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slow-firing basket cells</td>
<td>CGE</td>
<td>Slow spiking firing pattern: Low input resistance and slow membrane time constant. Mediated slow, powerful and precise EPSPs.</td>
<td>Layers II/III: highest proportion in layer IV.</td>
<td>Mostly multipolar, occasionally bifurcated 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.</td>
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</table>

| X-94 like SST neurons | CGE | 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 mGluR. | Layers II/IV | Multipolar, or bifurcated dendrites. Axon ramifies extensively in layer IV. |

| Neurogliaform cells | CGE | Ca2+ spikes: Delayed firing preceded by a slow depolarizing ramp at threshold and low current injections. Regular adapting firing during large current injections. Mediate combined slow GABAergic and GABAergic synaptic responses. Target dendritic spines but also produce non-synaptic “volume” GABA release. | Layers V/VI | Multipolar, short highly branched dendritic and axonal arbor around cell body. |

| LS2 | CGE | Ca2+ spikes: Delayed spiking less robust than neurogliaform cells. | Layers V/VI | Multipolar, wider and less branched dendritic and axonal arbor than neurogliaform cells. |

| CCX-expressing interneurons | CGE | Ca2+ Two populations: VIP+ and VIP-. BSNs or RSNs. | Layers I/II | Typically in upper layers. |

<table>
<thead>
<tr>
<th>Neocortex</th>
<th>Hippocampus</th>
<th>Paleocortex/Periform Cortex</th>
<th>Striatum</th>
<th>Basolateral Amygdala</th>
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<tbody>
<tr>
<td>Fast-spiking basket cells</td>
<td>Basket PV cells</td>
<td>Fast-spiking multipolar cells</td>
<td>Fast-spiking cells</td>
<td>Fast spiking cells with diverse firing patterns resembling the diversity observed in neocortex</td>
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<tr>
<td>Chandelier cells (aco-axonic cells)</td>
<td>Chandelier or aco-axonic cells</td>
<td>Chandelier cells PMID: 15679039</td>
<td></td>
<td>Chandelier cells (PMID: 6185547)</td>
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<tr>
<td>Martinotti cells</td>
<td>O-LM cells</td>
<td>Regular-spiking multipolar cells (somatostatin expressing neurons)</td>
<td>Low threshold spiking (LTS or pLTS: persistent low threshold spiking) SST-expressing interneurons</td>
<td>SST-expressing BLA interneurons</td>
</tr>
<tr>
<td>X-94 like SST neurons</td>
<td>Neurogliaform and ivy cells. Most express NOS and are MGE derived.</td>
<td>Neurogliaform cells</td>
<td></td>
<td>Neurogliaform cells PMID: 6199387</td>
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<tr>
<td>CCX-expressing interneurons</td>
<td>CCX basket cells (+VIP and VIP-/VGLUT3+)</td>
<td>Horizontal cells which resemble the interneurons described in somatosensory cortex as LS2</td>
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<td></td>
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<tr>
<td>LS2</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Bilaterally irregulated Spiking</td>
<td>CR+/VIP interneuron targeting (cN7) (2)</td>
<td>CGE derived VIP neurons are known to be present in BLA but have not been much characterized</td>
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<td>Bursting bipolar cells (bNA2)</td>
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<tr>
<td>Projecting GABAergic neurons</td>
<td>Projecting GABAergic neurons: Back projection cells; hippocampus to septum projecting cells; double projection; oriens-retrohippocampal projection</td>
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<tr>
<td>Striatofugal cells</td>
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<tr>
<td>Other CCX/INs: Schaffer collateral associated cells and Lecunosum-moleculare/Perforant- Pathway (LM-PP) associated cells and the Lecunosum-moleculare/Radialium/Perforant- Pathway (LM-R-PP) associated cells</td>
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<tr>
<td>Tolaminac cells</td>
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<td>CR (VIP-)/N targeting cells</td>
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<td>Large calbindin</td>
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<tr>
<td>Age Group</td>
<td>Number of Cases</td>
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<tr>
<td>E10-18</td>
<td>P0</td>
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<td>P0-7</td>
<td>P7-14</td>
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<tr>
<td>P21+</td>
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HYPOTHETICAL MODEL

Immature INs arrive in developing cortex

Migration

In vitro slice preparation
<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>E10-18</td>
<td>Neurons start to extend processes</td>
</tr>
<tr>
<td>P0</td>
<td>Axon/dendrite pathfinding</td>
</tr>
<tr>
<td>P0-7</td>
<td>In vitro slice preparation slice</td>
</tr>
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<td>P7-14</td>
<td></td>
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<td>P21+</td>
<td></td>
</tr>
</tbody>
</table>

**HYPOTHETICAL MODEL**

- Immature INs arrive in developing cortex
- Migration
- In vitro slice preparation
- In vitro slice preparation tau-GFP
HYPOTHETICAL MODEL

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

Immature INs arrive in developing cortex

Migration

In vitro slice preparation

Neurons start to extend processes

Axon/dendrite pathfinding

Early development of inhibitory network?

Synapse refinement

In vitro slice preparation tau-GFP

Dual recording - GABA dynamics and modulation.
Test PYR-IN connectivity
HYPOTHETICAL MODEL

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

Immature INs arrive in developing cortex
Migration

Neurons start to extend processes
Axon/dendrite pathfinding

Early development of inhibitory network?
Synapse refinement

Network formation
Cortical microcircuit

In vitro slice preparation
Dual recording - GABA dynamics and modulation. Test PYR-IN connectivity

Thursday, November 11, 2010
### HYPOTHETICAL MODEL

<table>
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<tr>
<th>Time</th>
<th>Event Description</th>
<th>Method/Technique</th>
</tr>
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<tr>
<td>E10-18</td>
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<tr>
<td>P21+</td>
<td>Network refinement and plasticity</td>
<td>PYR&gt;IN and IN&gt;PYR connectivity, network activity, Behavioral network, Cortical columns, 2-photon imaging of tau-GFP</td>
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HYPOTHETICAL MODEL

E10-18

Slow Ca++ Oscillations

P0

P0-7

P7-14

P21+

Immature INs arrive in developing cortex

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Dual recording - GABA dynamics and modulation. Test PYR-IN connectivity

PYR>IN and IN>PYR connectivity, network activity

Cortical columns, 2-photon imaging of tau-GFP

In vitro slice preparation
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**HYPOTHETICAL MODEL**

**Slow Ca++ Oscillations**

**SPAs/cENOS**

**Cortical columns, 2-photon imaging of tau-GFP**
**HYPOTHETICAL MODEL**

**E10-18**
- Immature INs arrive in developing cortex
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- In vitro slice preparation

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**SPAs/cENOS**

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HYPOTHETICAL MODEL

E10-18

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SPAs/cENOS

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In vitro slice preparation

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Figure 1: Local circuit control of developing columnar architecture in the neocortex.
Manipulate the activity of developing interneurons

Natalia DeMarco

Theo Karayannis
Manipulate the activity of developing interneurons

Natalia DeMarco

Theo Karayannis

Introduction of $Kir2.1$ into CGE-derived interneurons
CGE-derived interneurons express Reelin or VIP

Mouse somatosensory cortex at P21

~ 70% ~ 30%
CGE-derived interneurons express Reelin or VIP

Mouse somatosensory cortex at P21

~ 70%  ~ 30%

Thursday, November 11, 2010
CGE-derived interneurons express Reelin or VIP

Mouse somatosensory cortex at P21

1. PV
2. SST
3. Reelin
4. CR
5. VIP

MGE-derived

CGE-derived

E9.5  E12.5  E15.5  E18.

Birthdate of interneurons

~ 70%
~ 30%
CGE-derived interneurons express Reelin or VIP

Mouse somatosensory cortex at P21

~ 70%  ~ 30%
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Mouse somatosensory cortex at P21

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Mouse somatosensory cortex at P21

- MGE-derived interneurons:
  - PV
  - SST
  - CR
  - Reelin
  - VIP

- CGE-derived interneurons:
  - ~70%
  - ~30%

Birthdate of interneurons:
- E9.5
- E12.5
- E15.5
- E18.

- MGE:
  - II-III: 25%
  - IV-VI: 75%

- CGE:
  - I-III: ~75%
  - IV-VI: ~25%
CGE-derived interneurons express Reelin or VIP

Mouse somatosensory cortex at P21

1. PV
2. SST
3. Reelin
4. CR
5. VIP

MGE-derived

CGE-derived

~ 70%  ~ 30%

Birthdate of interneurons

E9.5  E12.5  E15.5  E18.5

25%  75%  IV-VI

~75%  ~25%  I-III  IV-VI
CGE-derived interneurons express Reelin or VIP

Mouse somatosensory cortex at P21

MGE-derived

CGE-derived

~ 70%  
~ 30%
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

GABAergic-specific enhancer (Dlx5/6)

In utero Electroporation

Ubiquitous CAG-mCherry

GABAergic Dlx5/6 enhancer-EGFP

Cortex

Ventral
Selective targeting of specific CGE-derived interneuron subclasses
Kir2.1 eliminates the activity

Kir2.1
Inwardly rectifying potassium channel
Kir2.1 eliminates the activity

Kir2.1
Inwardly rectifying potassium channel

Olfactory sensory neurons

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

C. Ron Yu, Jennifer Power, Gilad Barnea, Sean O'Donnell, Hannah E.V. Brown, Joseph Osborne, Richard Axel, and Joseph A. Gogos

Thalamo-cortical targeting

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

Naofumi Ucsaka, Yasufumi Hayano, Akiro 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, Tomoe Hirano, and Yoshiaki Tagawa
Department of Biophysics, Kyoto University Graduate School of Science, Kitashirakawa-Oiwake-cho, Sakyo-ku, Kyoto 606-8502, Japan, and 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
Kir2.1 eliminates the activity

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

Pyramidal neurons (superficial layers)

(Cancedda et al., 2007)
**Kir2.1 eliminates the activity**

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

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(Cancedda et al., 2007)

**Pyramidal neurons (superficial layers)**

**Morphological defects**
Kir2.1 eliminates the activity

Excitatory GABA Action Is Essential for Morphological Maturation of Cortical Neurons \textit{In Vivo}

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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)

Morphological defects

No effect in layering
Electroporation

Express *Kir2.1* in CGE-derived interneurons and eliminate the activity
Kir2.1 expression significantly decreases Vrest

Dlx5/6 enhancer

Kir2.1

GFP

Kir2.1

Vrest

P2

P8

D5-GFP  D5-Kir2.1

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

**Figure 3.** Subtype-specific defects in laminar targeting of CGE-derived interneurons.
Effect of *Kir2.1* expression in CGE-derived interneurons

Morphologies

![Diagram showing brain regions and neurotransmitters related to CGE-derived interneurons with labels for PV, SST, MGE-derived, CGE-derived, Reelin, CR, and VIP.]
Effect of *Kir2.1* expression in CGE-derived interneurons

Morphologies

Control  *Kir2.1*

Morphological defects

PV
SST
MGE
CGE-derived

MGE
LGE
CGE

Reelin
CR
VIP

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

**Morphologies**

<table>
<thead>
<tr>
<th>Control</th>
<th><em>Kir2.1</em></th>
</tr>
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<tbody>
<tr>
<td><img src="image1.png" alt="Control" /></td>
<td><img src="image2.png" alt="Kir2.1" /></td>
</tr>
</tbody>
</table>

**Morphological defects**

- No obvious defects

![Morphological defects](image3.png)

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

### Morphologies

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<thead>
<tr>
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<th><em>Kir2.1</em></th>
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<tbody>
<tr>
<td>Class-specific effect</td>
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<tr>
<td>Morphological defects</td>
<td><img src="image3" alt="Control" /> <img src="image4" alt="Kir2.1" /></td>
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<tr>
<td>No obvious defects</td>
<td><img src="image5" alt="Control" /> <img src="image6" alt="Kir2.1" /></td>
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Defects in axonal and dendritic development in NPY and CR interneurons persist beyond P15
Defects in axonal and dendritic development in NPY and CR interneurons persist beyond P15.

Kir2.1 NPY multipolar cell at P16
Kir2.1 NPY+ multipolar late spiking cell P16

spike threshold firing

higher frequency firing
Defects in axonal and dendritic development in NPY and CR interneurons persist beyond P15.
Defects in axonal and dendritic development in NPY and CR interneurons persist beyond P15

<table>
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<tr>
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<th>D5-Kir2.1</th>
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<tr>
<td>NPY</td>
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<tr>
<td>CR</td>
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</tr>
<tr>
<td>VIP</td>
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Kir2.1 VIP multipolar cell at P16

- Spike threshold firing
- Higher frequency firing

Thursday, November 11, 2010
Temporal control of neuronal excitability

Yu et al., 2004
Temporal control of neuronal excitability

Yu et al., 2004

Dlx5/6 enhancer + TTA

+ Doxycycline

TetO Kir2.1 ires LacZ

Text

Yu et al., 2004
Temporal control of neuronal excitability

+ Doxycycline

Dlx5/6 enhancer  
Kir2.1  
ires LacZ

Yu et al., 2004
Temporal control of neuronal excitability

+ Doxycycline

Yu et al., 2004

E15.5

P0

P3
Figure 4. Specific interneuron subtypes require activity for migration and morphological maturation at two distinct stages of development.

- **Kir2.1on**
  - control
  - tetO-Kir2.1

- **Kir2.1off@P0**
  - tetO-Kir2.1

**eGFP**

<table>
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<tr>
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<th>Kir2.1off@P0</th>
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<tbody>
<tr>
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**Reelin**

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<tbody>
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**# of axonal nodes**

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<th>Kir2.1off@P3</th>
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**# of dendritic nodes**

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Glutamate signaling is selectively required for morphology but not laminar positioning.
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Supplementary Figure 1. Activity-dependent development of Cr- and Re-expressing interneuron subtypes.