

Description of Structure:

LOCATION and STRUCTURAL ANATOMY:

The hierarchical relationship within the brain is depicted below in the structure [legend](#). The Allen Reference Atlas (based on Nissl-stained sections scanned at 10X) was the primary resource for the following descriptions.

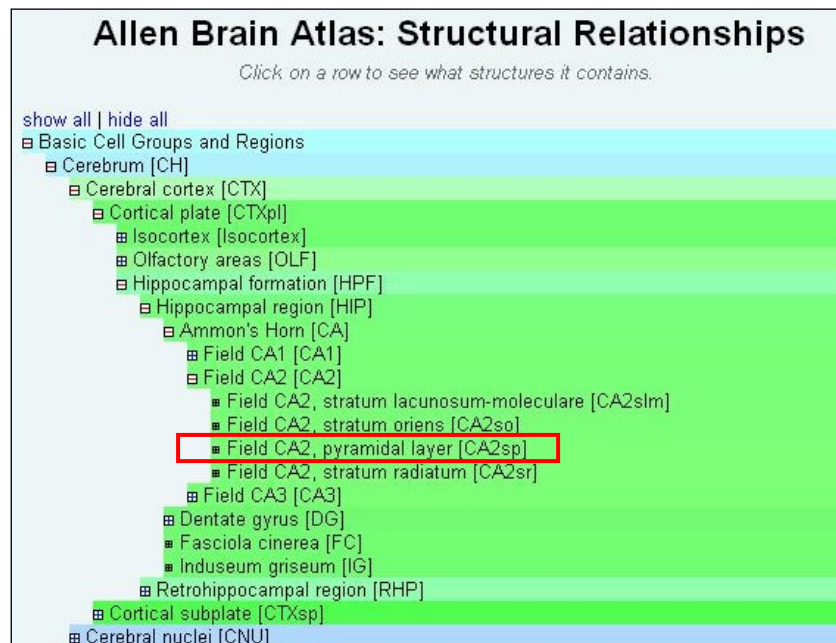
For additional information please refer to the [Allen Reference Atlas white paper](#).
[BrainInfo](#) houses a search engine that allows searches for structure name aliases.

The CA2 pyramidal cell layer lies within Ammon's horn, a subdivision of the hippocampus. Coronally, the hippocampus emerges just caudal to the septum, medial to the lateral ventricles, and dorsal to the thalamus; it extends caudally and laterally, separating the cortex from the thalamus and brainstem. At its caudal aspect, the hippocampus occupies a more ventral position in the brain, located medial to the cortical plate and the subiculum. Within the hippocampus lies the dentate gyrus; the two structures exist as an interlocking "C" structure. The pyramidal cells of the hippocampus have been divided into three subdivisions: CA1, CA2 and CA3. The pyramidal cells of the CA2 (CA2sp) appear prior to the formation of the lateral blade of the dentate gyrus. Proceeding along the septotemporal axis, two portions of the CA2sp layer (medial and lateral) can be visualized, separated by the pyramidal cells of CA1. At the most medial aspect of the CA2 lies the Fasciola cinerea (FC). Moving caudally, the medial aspect of CA2sp fades and only the lateral portion remains, situated between CA1 and CA3 pyramidal cell layers.

The CA2 pyramidal cells are densely packed, though less so than CA1, making the distinction between these two regions fairly apparent. On Nissl stained sections, the boundary between CA2 and CA3 is difficult to distinguish. As the hippocampal region begins to curve to form its temporal pole, CA2sp remains bound between CA1sp and CA3sp; however, moving caudally CA2sp becomes interposed between two regions of CA1sp, then disappears entirely at the level at which the hypothalamus can no longer be seen.

In the sagittal perspective the CA2 pyramidal cells first appear laterally at the same level that the granule layer of the dentate gyrus becomes apparent. In sagittal sections, CA2sp is present throughout the majority of the sections containing dorsal hippocampus, and remains until just before the midline.

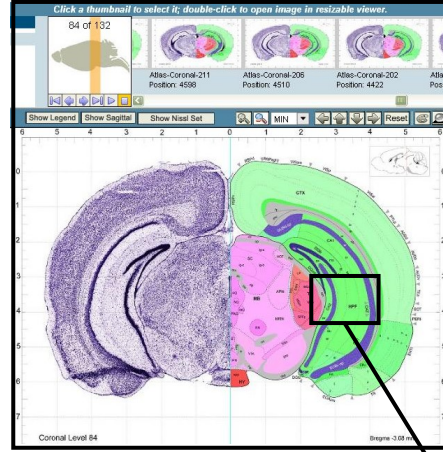
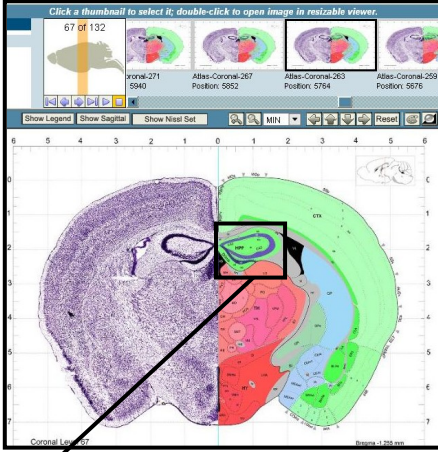
The appearance and location of the CA2sp can be appreciated on the following two pages. Nissl-stained sections and Allen Reference Atlas plates reveal the cytoarchitecture and extent of the CA2 pyramidal layer, and its location in relation to surrounding structures.



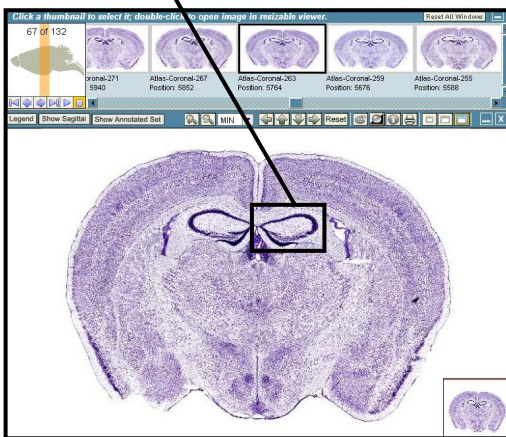
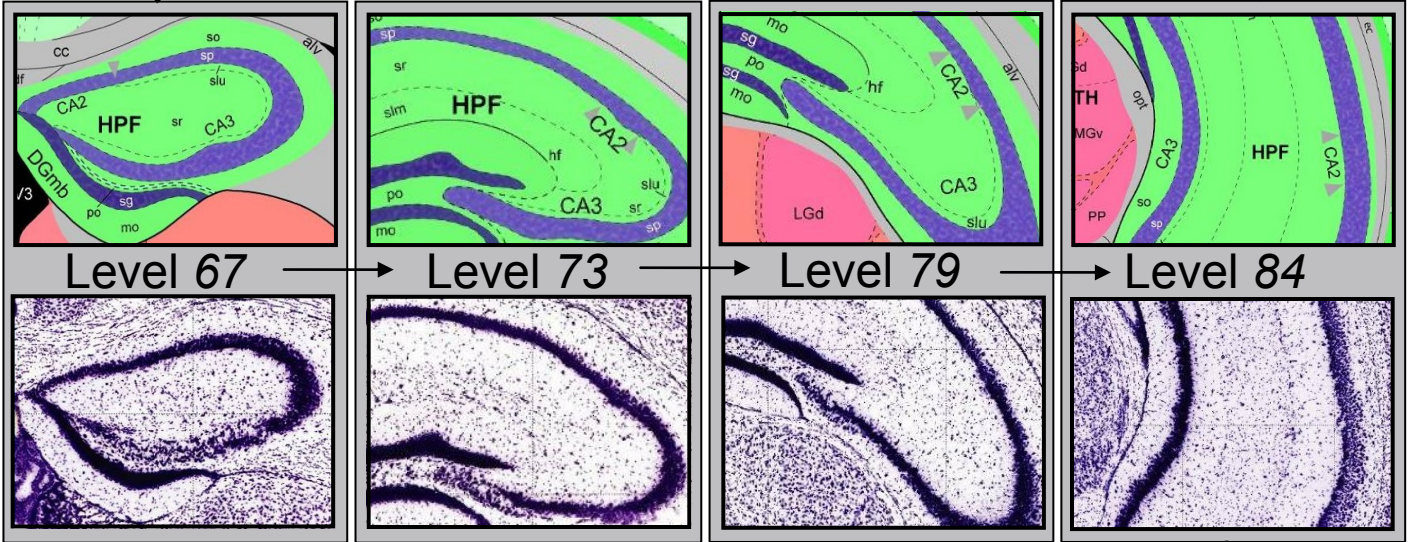
Atlas and Nissl:
Coronal:

Rostral

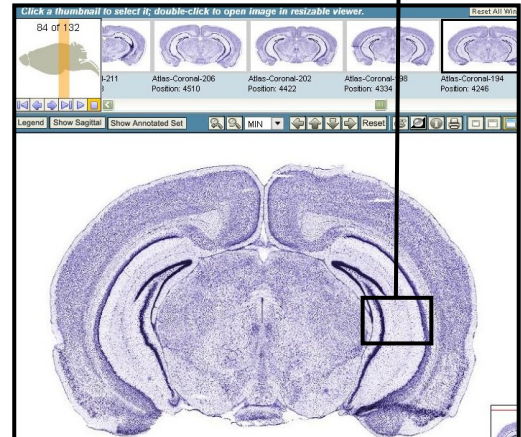
Caudal



Reference
Atlas



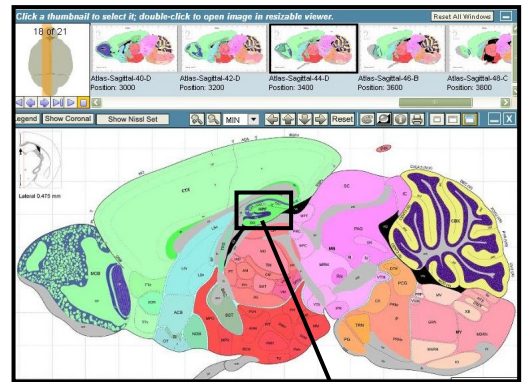
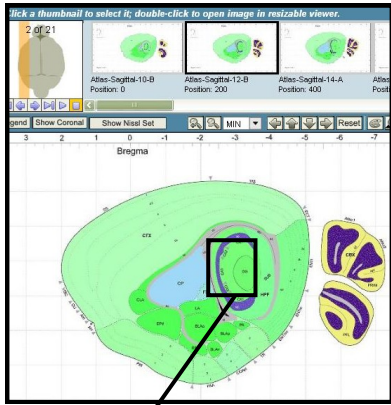
Nissl



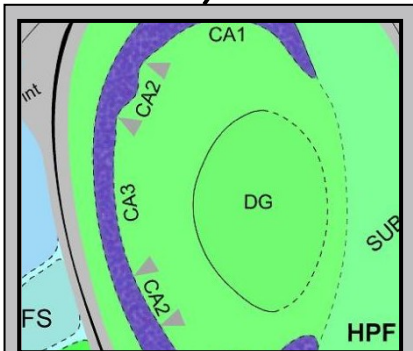
Atlas and Nissl:
Sagittal:

Lateral

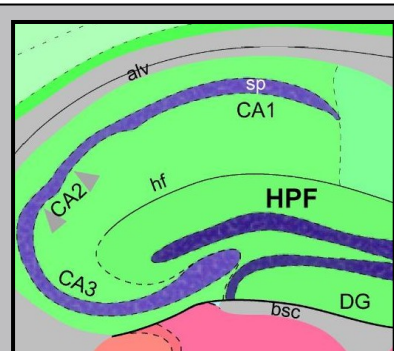
Medial



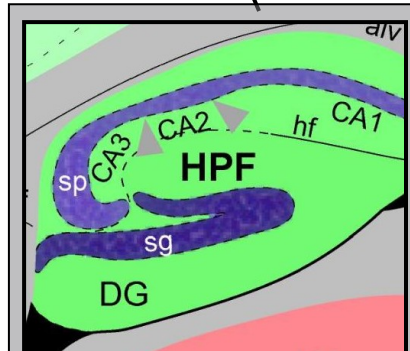
Reference Atlas



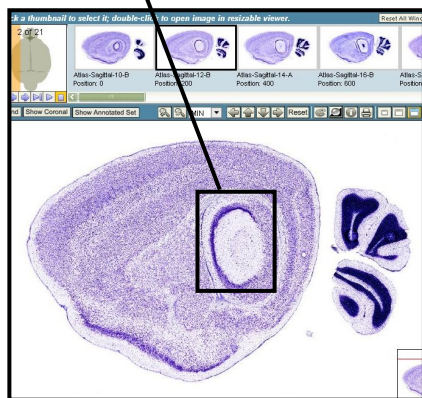
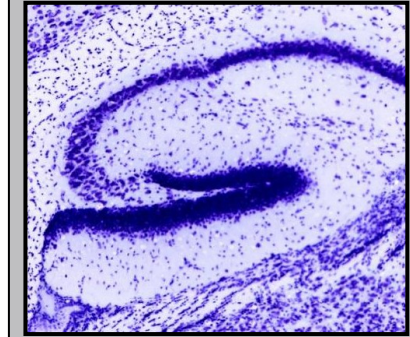
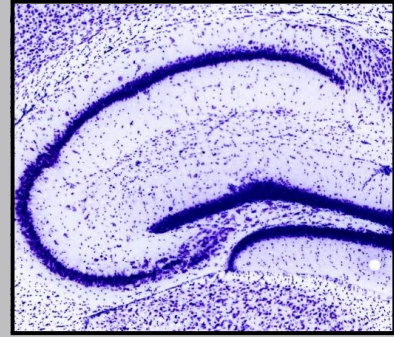
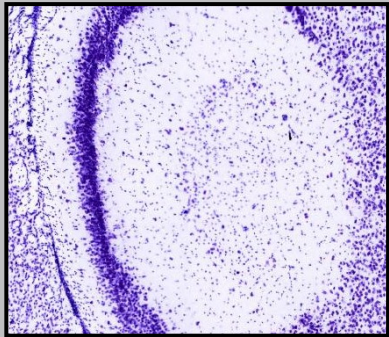
Level 2



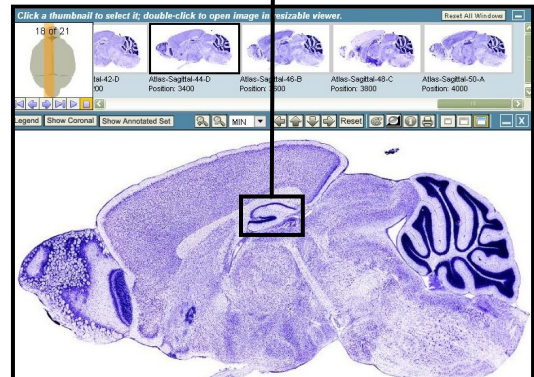
Level 10



Level 18



Nissl



In Situ Hybridization Expression Patterns of 50 Select Genes:

The in situ hybridization (ISH) data below presents the CA2 pyramidal layer's anatomical and cytoarchitectural characteristics in the context of actual gene expression. In addition to presenting molecularly defined borders, ISH gene expression patterns also aid in phenotyping cell populations that otherwise can not be differentiated on purely morphological grounds.

The 50 genes in this section were selected based on a mathematical algorithm to identify gene expression patterns that allow selective identification of the CA2sp. The gene expression patterns were then verified manually. As such, these genes do not represent the only genes found in this structure, genes specific to this structure, or genes expressing at the highest level within this structure.

Please refer to our protocol in the [Data Production Processes white paper](#).

To read about heat map conversion, refer to the [Informatics Data Processing white paper](#).

The expression data subsequently presented can be further explored, in coronal and sagittal planes, at brain-map.org.

This survey of 50 Select Genes shows distinct expression patterns within the CA2 pyramidal layer. Two categories of expression are outlined. The first category contains genes whose expression is relatively specific to CA2sp. The second category of expression includes genes that show enriched expression in CA2sp along with expression in CA1sp and/or CA3sp. Almost all genes that are expressed in CA2sp are also expressed in FC, regardless of which category the gene falls into. Although in coronal sections CA2sp appears physically separated into the medial and lateral portions, there were no genes in this set that distinguished these two segments.

Consistent with the Nissl stained sections, differentiation of CA2sp from that of CA3sp in the following ISH gene expression data is often difficult, especially in the second expression category. The border between CA2sp and CA1sp, however, is easier to discern in both sections labeled for Nissl and those labeled by ISH. Gene expression patterns also show that CA2sp may appear more rostrally than shown in the Allen Reference Atlas.

Cellular density expression key		Cellular intensity expression key	
None	No expression	No color	Very low intensity
Sparse	Very few cells expressing	Blue	Low intensity
Scattered	Less than 10% of cells expressing in scattered pattern	Green	Medium intensity
Medium	10-80% of cells expressing	Yellow	High intensity
High	Greater than 80% of cells expressing	Red	Very high intensity

To view heat map at brain-map.org, right click on the ISH image and select "Show Expression Analysis."

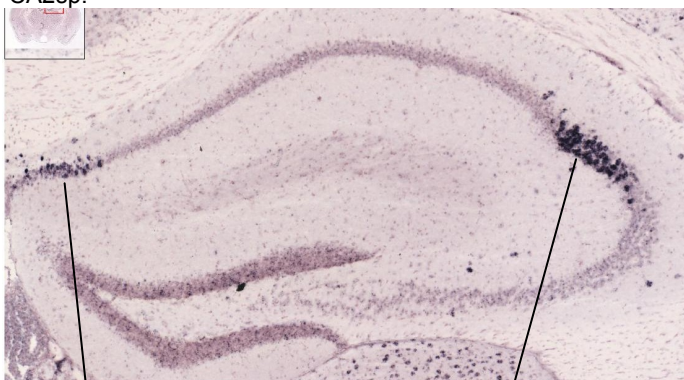
ISH DATA The images below were selected to highlight various expression patterns of the CA2sp.

ISH

[Cacng5](#)

Coronal:

Cacng5 shows an expression pattern that is restricted to CA2sp.



Medial CA2sp

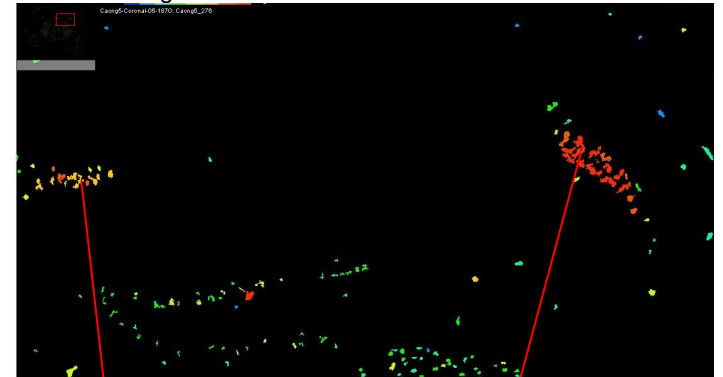
Lateral CA2sp

Heat map

[Cacng5](#)

Coronal:

A high density and very high intensity expression pattern can be seen for Cacng5.

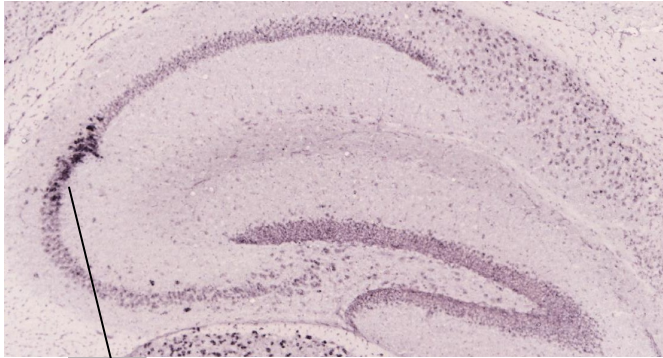


Medial CA2sp

Lateral CA2sp

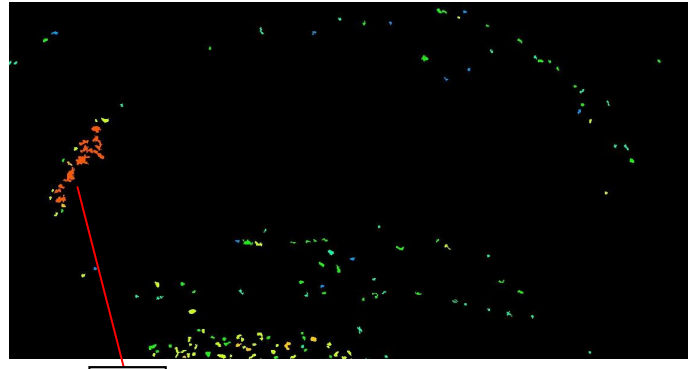
ISH
[Cacng5](#)
Sagittal:

In the sagittal view, Cacng5 expression is specific to CA2sp.



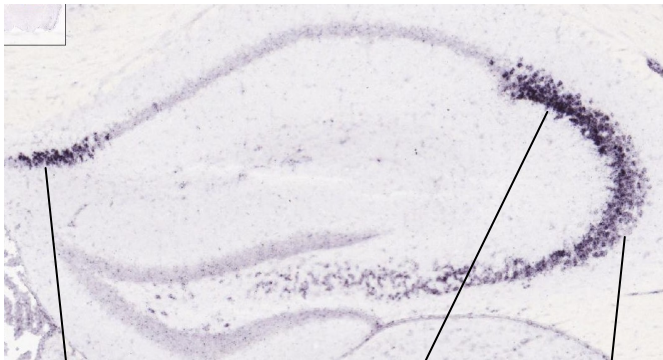
Heat map
[Cacng5](#)
Sagittal:

In the sagittal view the expression for Cacng5 shows high density and very high intensity.



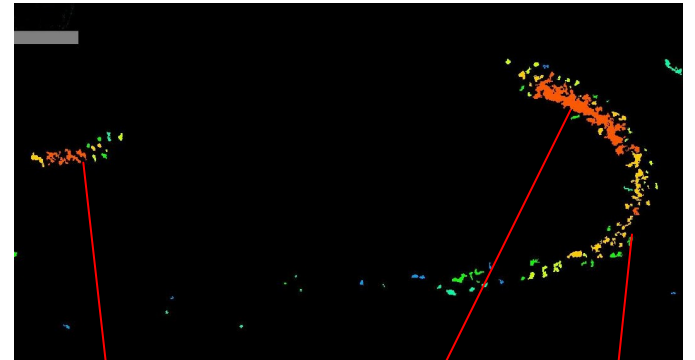
ISH
[Ccadc3](#)
Coronal:

Ccadc3 shows preferential expression in CA2sp with extension to CA3sp.



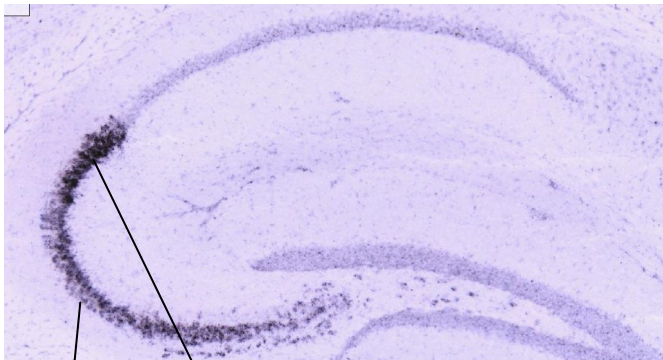
Heat map
[Ccadc3](#)
Coronal:

A high density, very high intensity expression pattern in CA2sp with decreased density and intensity in CA3sp.



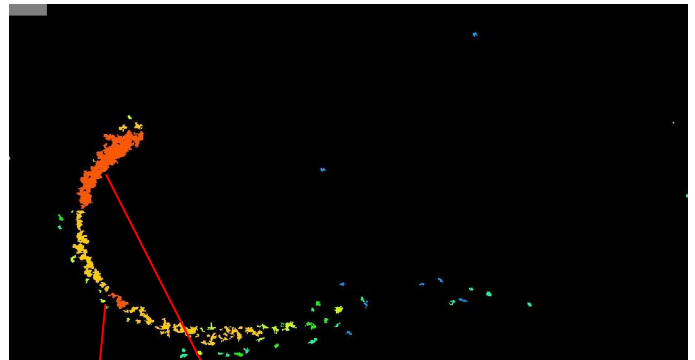
ISH
[Ccadc3](#)
Sagittal:

Preferential expression pattern in CA2sp with extension to CA3sp.



Heat map
[Ccadc3](#)
Sagittal:

A high density and very high intensity expression pattern in CA2sp with decreased density and intensity in CA3sp.

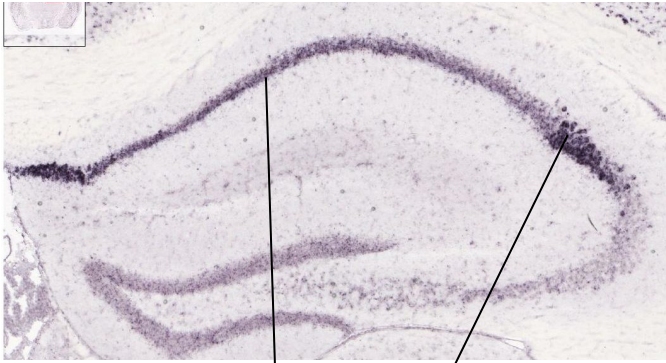


ISH

Kcnk2

Coronal:

Kcnk2 shows preferential expression in CA2sp with expression in CA1sp.



CA1sp

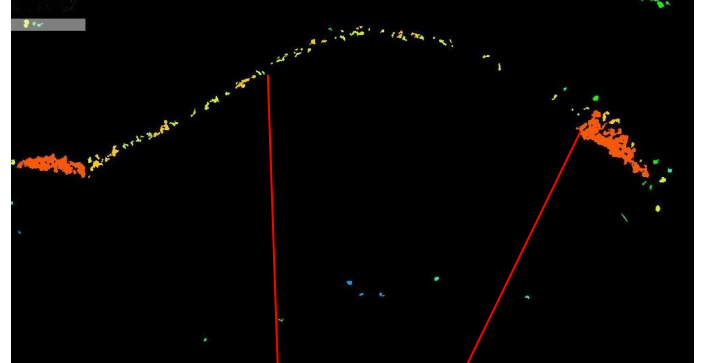
Lateral CA2sp

Heat map

Kcnk2

Coronal:

A high density and very high intensity expression pattern in CA2sp with decreased density and intensity in CA1sp.



CA1sp

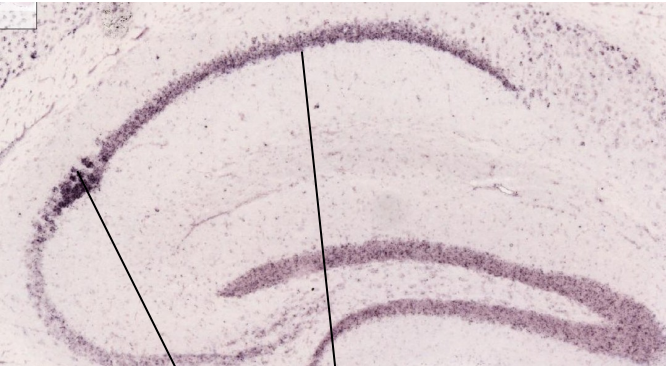
Lateral CA2sp

ISH

Kcnk2

Sagittal:

Preferential expression pattern in CA2sp with expression in CA1sp.



CA2sp

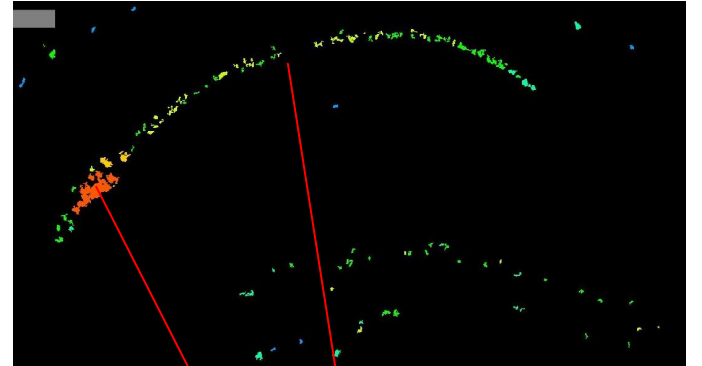
CA1sp

Heat map

Kcnk2

Sagittal:

A high density and very high intensity expression pattern in CA2sp with decreased density and intensity in CA1sp.



CA2sp

CA1sp

50 SELECT GENES:

This gene list was generated by manual curation of an [algorithmically](#) derived list that compared gene expression values of CA2sp to those of the pyramidal layer of Ammon's Horn. Categories of expression are subjectively grouped by relative expression characteristics.

Curation of 50 Select Genes List: April 2008

Expression patterns specific to the CA2 pyramidal layer

Number	Gene Symbol	Gene Name	Expression Pattern
1	Cacng5	calcium channel, voltage-dependent, gamma subunit 5	High density and very high intensity
2	Map3k15	mitogen-activated protein kinase 15	Medium density and very high intensity
3	Aimgo2	adhesion molecule with Ig like domain 2	High density and very high intensity
4	s100b	S100 protein, beta polypeptide, neural	Medium density and very high intensity
5	Mmp14	matrix metalloproteinase 14 (membrane-inserted)	High density and intensity
6	Tiam2	T-cell lymphoma invasion and metastasis 2	High density and very high intensity
7	Stard5	StAR-related lipid transfer (START) domain containing 5	High density and very high intensity, staining predominates in lateral portion
8	9930021J17Rik	RIKEN cDNA 9930021J17 gene	Medium density and high intensity

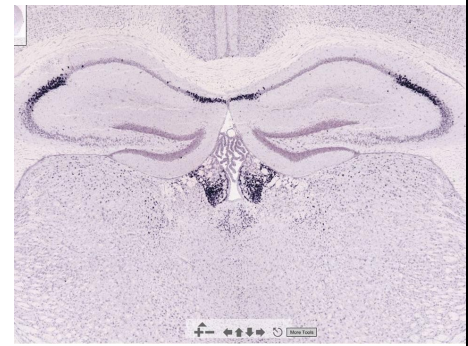
[1.Cacng5](#)



[2.Map3k15](#)



[3.Aimgo2](#)



[4.s100b](#)



[5.Mmp14](#)



[6.Tiam2](#)



[7.Stard5](#)



[8.9930021J17Rik](#)



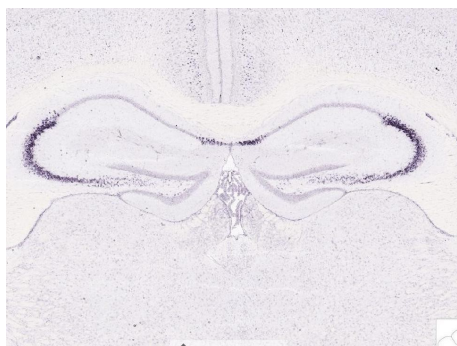
Preferential expression in CA2sp with expression in CA1sp and/or CA3sp

Number	Gene Symbol	Gene Name	Expression Pattern
9	Ccdc3	coiled-coil domain containing 3	High density and very high intensity, with expression in CA3sp
10	D330017J20Rik	RIKEN cDNA D330017J20 gene	High density and very high intensity, with expression in CA1/CA3sp
11	Sh3kbp1	SH3-domain kinase binding protein 1	Medium density and intensity, with expression in CA3sp
12	8430436L14Rik	RIKEN cDNA 8430436L14 gene	High density and intensity, with expression in CA3sp
13	Pqlc1	PQ loop repeat containing 1	Medium density and high intensity, with expression in CA3sp
14	Stard13	serologically defined colon cancer antigen 13	High density and intensity, with expression in CA3sp
15	Sms	spermine synthase	High density and very high intensity, with expression in CA3sp
16	BB146404	expressed sequence BB146404	High density and intensity, with expression in CA3sp
17	Kcnk2	potassium channel, subfamily K, member 2	High density and very high intensity, with expression in CA1sp
18	Efcfbp2	EF hand calcium binding protein 2	High density and very high intensity, with expression in CA3sp
19	LOC433485	similar to chromosome 20 open reading frame 39	High density and intensity, with expression in CA3sp
20	Prss23	protease, serine, 23	Medium density and very high intensity, with expression in CA3sp
21	Btbd3	BTB (POZ) domain containing 3	High density and very high intensity, with expression in CA1/CA3sp
22	Dusp4	dual specificity phosphatase 4	High density and intensity, with expression in CA1/CA3sp
23	Rgs14	regulator of G-protein signaling 14	High density and very high intensity, with expression in CA1sp
24	Sema7a	sema domain, immunoglobulin domain (Ig), and GPI membrane anchor, (semaphorin) 7A	High density and intensity, with expression in CA1/CA3sp
25	Zdhhc23	zinc finger, DHHC domain containing 23	High density and very high intensity, with expression in CA1/CA3sp
26	C630007C17Rik	RIKEN cDNA C630007C17 gene	High density and very high intensity, with expression in CA1/CA3sp
27	4930572J05Rik	RIKEN cDNA 4930572J05 gene	High density and very high intensity, with expression in CA1/CA3sp
28	Gsto1	glutathione S-transferase omega 1	High density and very high intensity, with expression in CA1/CA3sp
29	Sostdc1	sclerostin domain containing 1	High density and very high intensity in lateral portion, with expression in CA1/CA3sp.
30	Dnahc9	dynein, axonemal, heavy chain 9	High density and very high intensity, with expression in CA1sp
31	Gpr12	G-protein coupled receptor 12	High density and very high intensity, with expression in CA1/CA3sp
32	Trib2	tribbles homolog 2 (Drosophila)	High density and very high intensity, with expression in CA1/CA3sp
33	4631427C17Rik	RIKEN cDNA 4631427C17 gene	High density and very high intensity, with expression in CA3sp
34	Lman2	lectin, mannose-binding 2	High density and very high intensity, with expression in CA1/CA3sp
35	Pvr1	poliovirus receptor-related 1	High density and very high intensity, with expression in CA1/CA3sp
36	Centd1	centaurin, delta 1	Medium density and high intensity, with expression in CA1/CA3sp
37	st8sia6	ST8 alpha-N-acetyl-neuraminide alpha-2,8-sialyltransferase 6	Medium density and high intensity, with expression in CA3sp

Preferential expression in CA2sp with expression in CA1sp and/or CA3sp

Number	Gene Symbol	Gene Name	Expression Pattern
38	Fabp3	fatty acid binding protein 3, muscle and heart	Medium density and high intensity, with expression in CA1sp
39	Accn1	amiloride-sensitive cation channel 1, neuronal (degenerin)	High density and very high intensity, with expression in CA1/CA3sp
40	Fhod3	formin homology 2 domain containing 3	Medium density and intensity, with scattered expression in CA1/CA3sp
41	Hs3st1	heparan sulfate (glucosamine) 3-O-sulfotransferase 1	High density and intensity, with expression in CA1/CA3sp
42	TC1517215	TIGR MGI TC1517215	High density and medium intensity, with expression in CA3sp
43	Osbp10	oxysterol binding protein-like 10	High density and intensity, with expression in CA1sp
44	Nab1	Ngfi-A binding protein 1	High density and very high intensity, with expression in CA1/CA3sp
45	Mgst3	microsomal glutathione S-transferase 3	High density and very high intensity, with expression in CA1/CA3sp
46	Nptx2	neuronal pentraxin 2	Medium density and high intensity, with expression in CA1/CA3sp
47	Dip2a	DIP2 disco-interacting protein 2 homolog A (Drosophila)	Medium density and high intensity, with scattered expression in CA1/CA3sp
48	Ptgs1	prostaglandin-endoperoxide synthase 1	Medium density and high intensity, with expression in CA1/CA3sp
49	Ptpn5	protein tyrosine phosphatase, non-receptor type 5	High density and very high intensity, with expression in CA1/CA3sp
50	Dtna	dystrobrevin alpha	High density and intensity, with expression in CA1/CA3sp

[9.Ccdc3](#)



[10.D330017J20Rik](#)



[11.Sh3kbp1](#)



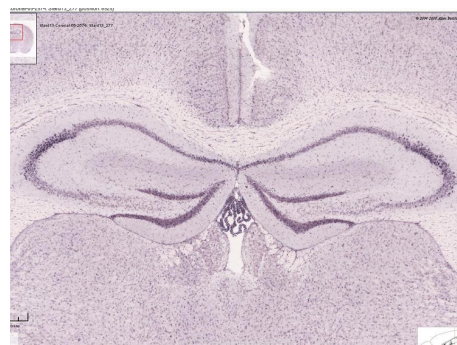
[12.8430436L14Rik](#)



[13.Pqlc1](#)



[14.Stard13](#)



Preferential expression in CA2sp with expression in CA1sp and/or CA3sp

[15.Sms](#)



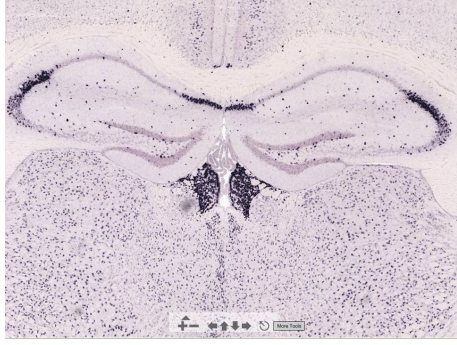
[16.BB146404](#)



[17.Kcnk2](#)



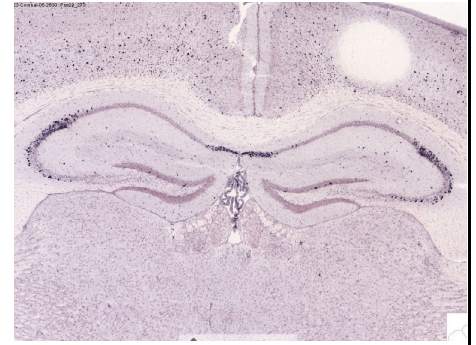
[18.Efcab2](#)



[19.LOC433485](#)



[20.Prss23](#)



[21.Btbd3](#)



[22.Dusp4](#)



[23.Rgs14](#)



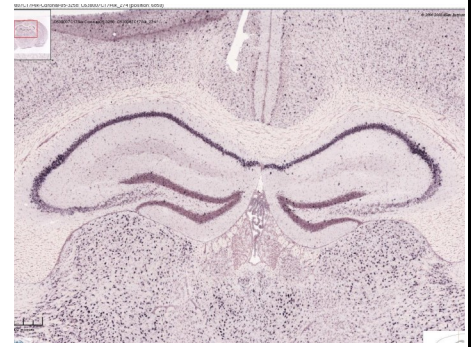
[24.Sema7a](#)



[25.Zdhhc23](#)



[26.C630007C17Rik](#)



[27.4930572J05Rik](#)



[28.Gsto1](#)



[29.Sostdc1](#)



Preferential expression in CA2sp with expression in CA1sp and/or CA3sp

[30.Dnahc9](#)



[31.Gpr12](#)



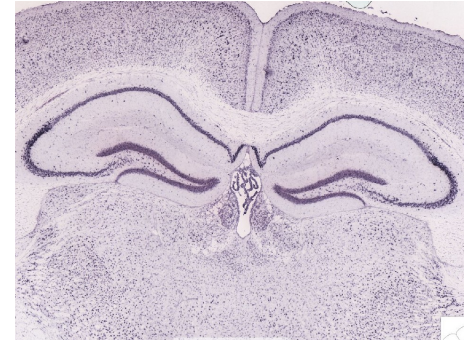
[32.Trib2](#)



[33.4631427C17Rik](#)



[34.Lman2](#)



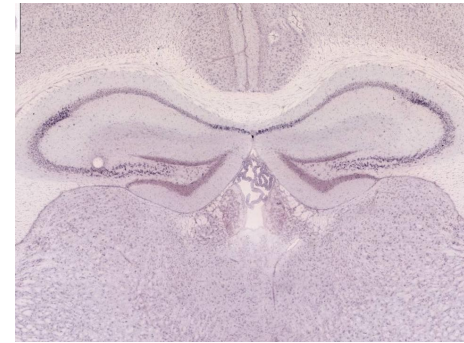
[35.Pvr11](#)



[36.Centd1](#)



[37.st8sia6](#)



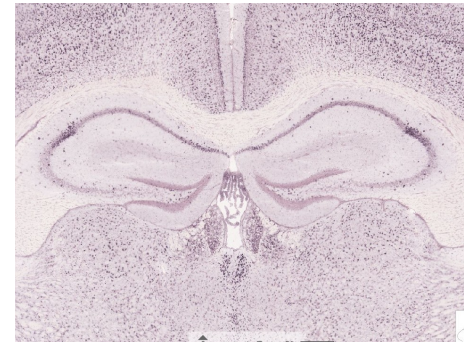
[38.Fabp3](#)



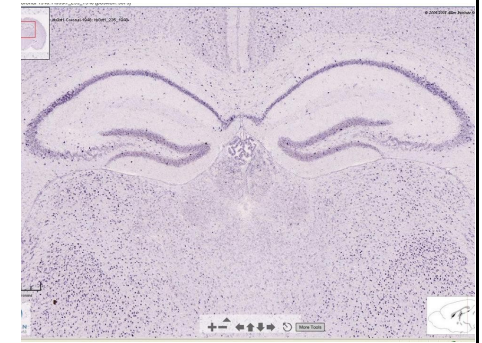
[39.Accn1](#)



[40.Fhod3](#)



[41.Hs3st1](#)



Preferential expression in CA2sp with expression in CA1sp and/or CA3sp

[42.TC1517215](#)



[43.Osbpl10](#)



[44.Nab1](#)



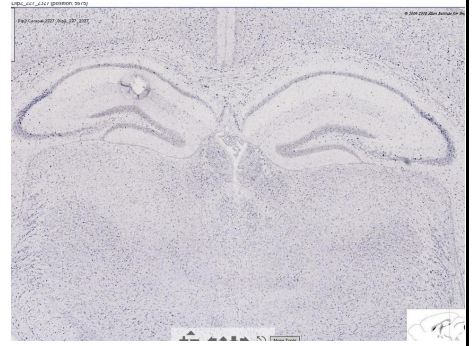
[45.Mgst3](#)



[46.Nptx2](#)



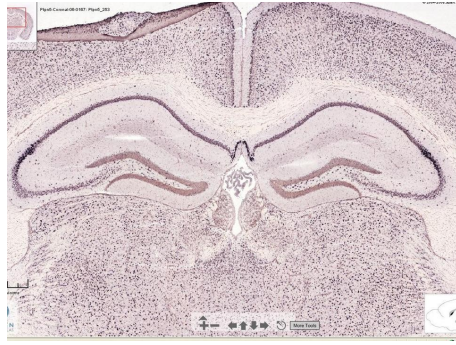
[47.Dip2a](#)



[48.Ptgs1](#)



[49.Ptpn5](#)



[50.Dtna](#)



Correlated Expression:

The ABA coronal set contains many genes of known scientific interest as well as genes exhibiting combinatorial or unique expression patterns. A correlation analysis of all available ABA coronal experiments (4376) was performed by comparing the expression value of the CA2sp to expression values in other regions of the brain. Following [image analysis](#), the data values for each experiment were mapped to a 3-D reference brain at $(200\mu\text{m})^3$ voxel resolution. Then, each voxel was assigned a single expression value based on the product of density and intensity of expression. Values from all 4376 experiments were computed, and the likelihood of co-expression between any two voxels or regions are reported as a Pearson's correlation coefficient.

For the purposes of determining correlated expression between the CA2sp and other brain regions, expression values from all voxels within the CA2sp were aggregated to form a single expression value. Two types of comparisons were then made. First, the aggregate expression values of the CA2sp and those of other anatomically defined regions (~200 structures) were compared within the 3-D reference brain (structure vs. structure; table below). Second, a color map was then generated to display the correlation between the CA2sp and each of the ~53,000 voxels of the reference volume (structure vs. voxel; correlation map on the following page).

STRUCTURE vs. STRUCTURE

The expression value of the CA2sp was compared to expression values for all other defined atlas regions. Degree of correlation is displayed as a comparative fraction, with self-correlation = 1.000. Correlation between the CA2sp and macro/parent-structures are presented, as well as correlation between the CA2sp and the 25 highest ranking substructures. The most highly correlated macro/parent-structures don't always contain the 25 top most correlated substructures. Columns match the Allen Reference Atlas palette.

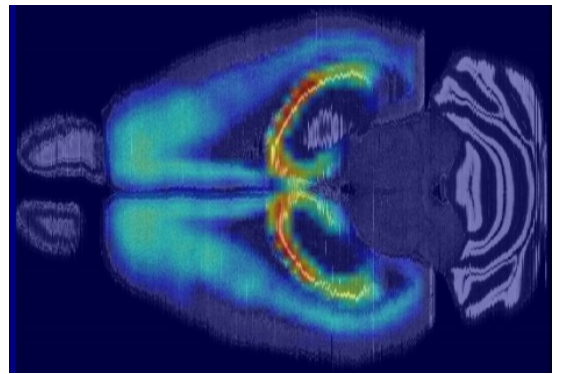
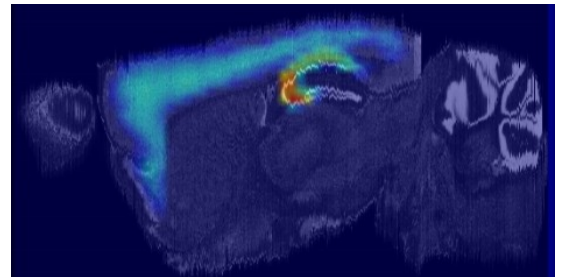
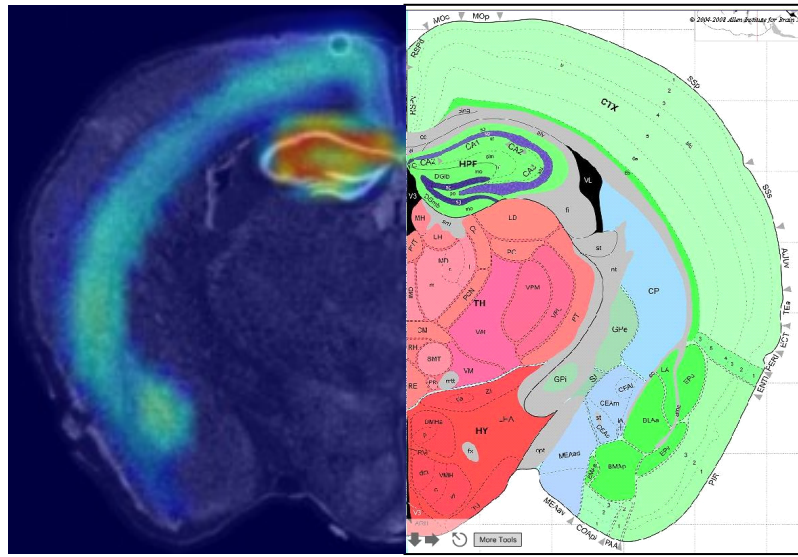
Correlation of CA2sp with macro structures:

Macro Structure	Correlation
OLF (Olfactory areas)	0.855275
STR (Striatum)	0.769116
PAL (Pallidum)	0.784862
CTX (Cerebral cortex)	0.873141
HY (Hypothalamus)	0.746973
TH (Thalamus)	0.793763
HIP (Hippocampal region)	0.946172
RHP (Retrohippocampal formation)	0.876928
MB (Midbrain)	0.773827
P (Pons)	0.760953
MY (Medulla)	0.759982
CB (Cerebellum)	0.639773

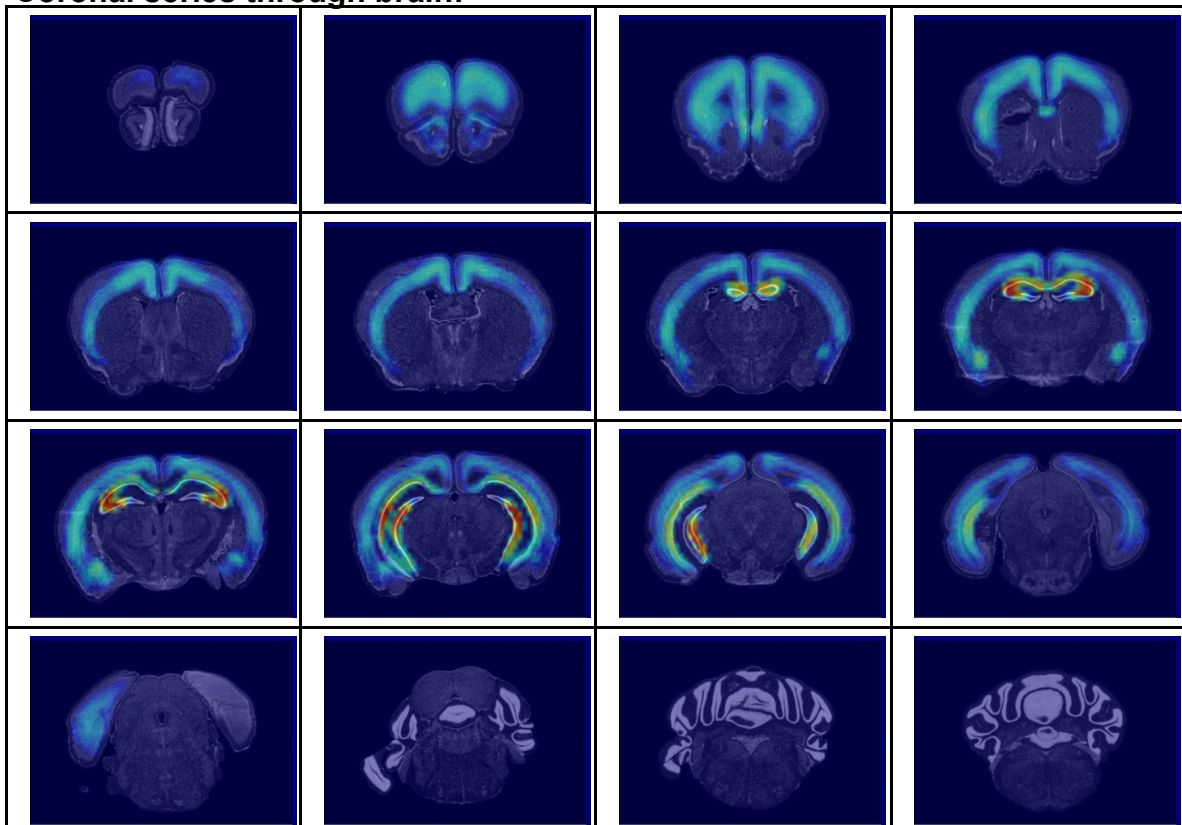
Substructure	Correlation
Field CA2, pyramidal layer	1
Field CA3, pyramidal layer	0.974648
Ammon's Horn	0.964114
Field CA1, pyramidal layer	0.929573
Cortical plate	0.906448
Subiculum	0.887004
Basolateral amygdalar nucleus	0.885938
Basolateral amygdalar nucleus, anterior part	0.885414
Cortical subplate	0.88072
Basolateral amygdalar nucleus, posterior part	0.876218
Cerebral cortex, layer 5	0.875995
Agranular insular area, dorsal part, layer 5	0.875406
Ectorhinal area/Layer 6a	0.874851
Gustatory areas, layer 5	0.874601
Secondary motor area, layer 5	0.874117
Dorsal peduncular area, layer 2/3	0.873816
Perirhinal area, layer 6a	0.873688
Primary motor area, Layer 5	0.8735
Perirhinal area, layer 6b	0.872883
Perirhinal area	0.872607
Perirhinal area, layer 5	0.872431
Agranular insular area	0.872394
Cerebral cortex, layer 6a	0.8723
Taenia tecta	0.871908
Ectorhinal area/Layer 5	0.871702

STRUCTURE vs. VOXEL:

Correlation between the CA2sp and all other $(200\mu\text{m})^3$ voxels in the brain. Degree of correlation assessed for each voxel is provided visually (lower value = the correlation value of the 25th ranked substructure reported on the previous page) using the "jet" color scale at rostrocaudal levels throughout the brain.



Coronal series through brain:



Gene Ontology (GO) Analysis:

GO TABLE:

Below is an ontological analysis of the 50 Select Genes, using [DAVID](#) Bioinformatics Resources. The functional terms that follow were returned using these constraints:

Category	Definition	Constraints
P-value	Probability that the term is over-represented in this 50 Select Genes list relative to the mouse genome	when $p \leq 0.05$
Gene Count	The minimum number of genes that must fall into an ontological category to be considered a group	5 genes per term group
GO Level	The level of functional specificity for GO functional categories: Molecular Function (mf), Biological Process (bp) and Cellular Components (cc)	Level GO_All
# of DAVID IDs	Number of unique DAVID gene IDs from user's input list	47 DAVID gene IDs / 50 input genes

Date of table completion: April 2008

GO Category	GO Term	Gene Count	% of Genes	p-value
GOTERM_MF_ALL	calcium ion binding	7	14.89%	0.007638
GOTERM_MF_ALL	enzyme regulator activity	6	12.77%	0.009724
GOTERM_BP_ALL	cellular lipid metabolism	5	10.64%	0.01256
GOTERM_MF_ALL	cation binding	13	27.66%	0.020525
GOTERM_BP_ALL	lipid metabolism	5	10.64%	0.023131
GOTERM_CC_ALL	extracellular region	11	23.40%	0.025515
GOTERM_CC_ALL	extracellular space	10	21.28%	0.032773
GOTERM_MF_ALL	ion binding	13	27.66%	0.034763
GOTERM_MF_ALL	metal ion binding	13	27.66%	0.034763
GOTERM_CC_ALL	cellular component unknown	7	14.89%	0.049803

Glynn Dennis Jr., Brad T. Sherman, Douglas A. Hosack, Jun Yang, Michael W. Baseler, H. Clifford Lane, Richard A. Lempicki. "DAVID: Database for Annotation, Visualization, and Integrated Discovery." *Genome Biology*. 2003 4(5): P3.

CA2 PYRAMIDAL LAYER Summary:

Anatomy

- The CA2 pyramidal layer lies within Ammon's horn and is most often interposed between CA1 and CA3 pyramidal layers.
- The pyramidal cells of the CA2 region are large and densely packed. The distinction between CA1sp and CA2sp can be readily appreciated on Nissl stained sections by the shift in the packing density of the cells, while the boundary between CA2sp and CA3sp is somewhat harder to identify.
- Although a single structure, two distinct portions of CA2sp are identifiable in rostral coronal sections, separated by the pyramidal cells of CA1.

Expression Patterns of the 50 Select Genes

- Only a few genes, including *Stard5* and *Sosdc1*, suggested subdivisions within the CA2sp region.
- Gene expression in CA2sp often extends into CA3sp, especially at the rostral aspects of Ammon's horn, suggesting that CA2sp may extend more rostrally than shown in the Allen Reference Atlas.
- A subset of genes show specific expression in CA2sp, independent of surrounding pyramidal cells in CA1 and CA3, while another subset show expression in CA2sp along with expression in CA1sp and/or CA3sp.
- With the exception of *S100b*, the genes presented here also express in FC.

Correlation

- The cerebral cortex, specifically layers 5 and 6, correlated most strongly with CA2sp.
- Limbic and paralimbic areas showed gene expression that correlated strongly with CA2sp.
- Correlation of CA2sp with individual voxels highlights the concordance in gene expression between CA2sp and FC.

We encourage you to reply with any comments or questions by email to [!Annotation@alleninstitute.org](mailto:Annotation@alleninstitute.org). To further explore the gene expression data and analytical tools referred to in this report, please access our genome-wide data set at brain-map.org.

Other Tools:

NEUROBLAST:

Many of the 50 genes listed in this report can be used to explore the NeuroBlast tool. This unique mining tool works seamlessly from within brain-map.org to produce a list of genes that share similar expression patterns to any gene in the coronal data set. Search for and select any gene, then select one of several brain regions from the NeuroBlast drop-tab to explore a ranked list of similarly expressed genes for that region.

To learn more about this function, please refer to the [NeuroBlast white paper](#).

BRAIN EXPLORER:

To compare gene expression levels across anatomical structures in 3-D detail, download the [Brain Explorer](#) desktop application. This program is used to view gene expression in 3-D view (coronal, sagittal, horizontal and everywhere in between) across all brain structures and allows for simultaneous viewing of multiple expression profiles.

The NeuroBlast spatial homology function and an anatomic search tool are also available from within Brain Explorer to allow the user to search for and visualize genes with similar expression patterns.