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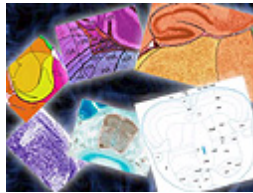
WHAT'S HOT IN... BIOLOGY , May/June 2009

Atlas Supports a New World of Neurogenomics

by *Jeremy Cherfas*



One of the delights of scanning the most highly cited papers is the opportunity to be at least vaguely aware of a huge range of subjects. One of the drawbacks is that it is impossible to be more than vaguely aware. Sometimes a paper is so astonishing that it is difficult not to be struck dumb. Such a paper is at #10.



From the Allen Mouse Brain Atlas. Details

[+ credit & details](#)

"Genome-wide atlas of gene expression in the adult mouse brain" beggars belief. It maps, in three dimensions, which of more than 20,000

genes is expressed where in the mouse brain. Not a vague hand-waving where, like "the neo-cortex," but a precise location that might be no more than a few cells in volume. A raft of scientists, mostly at the Allen Institute for Brain Science in Seattle, adopted an assembly-line approach that integrates several technologies and where the numbers tell only part of the story. The effort hinges on an inbred mouse strain that shows minimal variance across individuals. This is not the absolute cellular determinism of the nematode worm *Caenorhabditis elegans*, where each cell develops in exactly the same way in every non-mutant individual. The individual mice are, however, sufficiently alike that the researchers could, as they report, "treat the

Biology Top Ten Papers

Rank	Papers	Cites This Period Nov-Dec 08	Rank Last Period Sep-Oct 08
1	K. Takahashi, et al., "Induction of pluripotent stem cells from adult human fibroblasts by defined factors," <i>Cell</i> , 131(5): 861-72, 30 November 2007. [Kyoto U., Japan; CREST, Kawaguchi, Japan; Gladstone Inst. Cardio. Dis., San Francisco, CA] *243MG	93	1
2	The ENCODE Project Consortium (E. Birney, et al.), "Identification and analysis of functional elements in 1% of the human genome by the ENCODE pilot project," <i>Nature</i> , 447(7146): 799-816, 14 June 2007. [80 institutions worldwide] *178FV	68	4
3	Intl. HapMap Consortium (K.A. Frazer, et al.), "A second generation human haplotype map of over 3.1 million SNPs," <i>Nature</i> , 449(7164): 854-61, 18 October 2007. [72 institutions worldwide] *221LY	61	3
4	A. Barski, et al., "High-resolution profiling of histone methylations in the human genome," <i>Cell</i> , 129(4): 823-37, 18 May 2007. [NHLBI, NIH, Bethesda, MD; U. Calif., Los Angeles] *172FA	50	†

brain essentially as a complex but highly reproducible three-dimensional tissue array."



Not one three-dimensional array but 21,500—one per gene—plus a reference atlas that holds them all together. Each mouse brain was sliced into around 130 slices 25 μ M thick in which activated genes were sought using a staining technique called in-situ hybridization. The automated staining procedure dealt with the million sections of brain at a rate of 16,000 a week, and each image was then photographed at high and low magnifications by another automated system to result in 85 million images. A final system judged the quality of images, which were then assembled into a three-dimensional viewer that will show the locations in which a particular gene is expressed and what genes are expressed in a particular location.

Perhaps the most surprising result is that about 80% of the genes assayed were expressed in some part of the brain. This is higher than had been predicted by expression microarray analysis of larger chunks of brain tissue. It means that many genes are expressed either at low levels overall or at higher levels but in a small number of cells. Either way, studies of larger brain regions had missed them.



The corollary of this is that most genes are expressed in relatively few cells; 70.5% of the genes are expressed in fewer than 20% of the cells. The expression pattern, not surprisingly, reveals something about function. Among the near-ubiquitous genes, found in all cell types throughout the brain, are basic housekeeping genes for things like inter-cellular signalling and general cellular metabolism. Other genes are associated with particular cell types. For example, oligodendrocytes, which provide the insulating myelin sheath around nerve axons, are rich in genes for lipid synthesis and myelination. And, pleasingly, there is no evidence for genes one would not expect to be present, such as those involved in the immune response, meiosis, or blood coagulation.

Physical regions of the brain also have characteristic patterns of gene expression. One of the most complex analyses in the *Nature* paper looks at the pattern of gene expression in voxels—the 3-D equivalent of a pixel. The Allen Mouse Brain Atlas makes it possible to ask which genes are active or suppressed in each voxel and then to organize the voxels in search of patterns. If the voxels are grouped according to the large brain structure they belong to, then there are strong correlations in expression patterns among voxels in the same structure—no surprise there—and "complex but distinct correlations" between brain regions. Group the voxels by their correlations with other voxels, however, and a different pattern emerges. Large anatomical regions that are more or less undifferentiated, such as the cerebral cortex, give a single tight cluster of voxels. By contrast, structures with discrete anatomically distinct nuclei, such as the hypothalamus, have smaller local clusters that are intermingled.

5	V. Cherezov, <i>et al.</i> , "High-resolution crystal structure of an engineered human β_2 -adrenergic G protein-coupled receptor," <i>Science</i> , 318(5854): 1258-65, 23 November 2007. [Scripps Res. Inst., La Jolla, CA; Stanford U., CA] *233JG	45	2
6	M. Wernig, <i>et al.</i> , "In vitro reprogramming of fibroblasts into a pluripotent ES-cell-like state," <i>Nature</i> , 448(7151): 318-24, 19 July 2007. [5 U.S. institutions] *191GC	43	9
7	K. Okita, T. Ichisaka, S. Yamanaka, "Generation of germline-competent induced pluripotent stem cells," <i>Nature</i> , 448(7151): 313-7, 19 July 2007. [Kyoto U., Japan; Japan Sci. Tech. Agency, Kawaguchi] *191GC	41	†
8	T.S. Mikkelsen, <i>et al.</i> , "Genome-wide maps of chromatin state in pluripotent and lineage-committed cells," <i>Nature</i> , 448(7153): 553-60, 2 August 2007. [6 U.S. institutions] *195XV	39	10
9	S. Vasudevan, Y. Tong, J.A. Steitz, "Switching from repression to activation: MicroRNAs can up-regulate translation," <i>Science</i> , 318(5858): 1931-4, 21 December 2007. [Howard Hughes Med. Inst., Yale U. Sch. Med., New Haven, CT] *243HE	38	†
10	E.S. Lein, <i>et al.</i> , "Genome-wide atlas of gene expression in the adult mouse brain," <i>Nature</i> , 445(7124): 168-76, 11 January 2007. [Allen Inst. Brain Sci., Seattle, WA; Baylor Coll. Med., Houston, TX; Max Planck Inst. Biophys. Chem., Goettingen, Germany] *124QF	35	†


SOURCE: Thomson Reuters Hot Papers Database. Read the Legend.

There's a great deal more neuroanatomical richness in the paper, which uses gene expression to redefine aspects of brain structure and which is revitalizing efforts to understand the brain. Astonishing though its contents are, even more magical is the publicly available window on the masses of accumulated data. Go to brain-map.org and I guarantee that unless you are a neuroscientist (in which case none of this will be news to you) the richness of the data and the ease with which it can be manipulated and visualized will combine to occupy hours of your life. Alas, the impossibility of formulating even a mildly interesting question to ask of all those data will reinforce any feelings of inadequacy you might have had on first reading the paper. ■

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KEYWORDS: NEUROGENOMICS, MOUSE BRAIN, GENE EXPRESSION, GENOME-WIDE ATLAS, ALLEN INSTITUTE FOR BRAIN SCIENCE, IN SITU HYBRIDIZATION, ALLEN MOUSE BRAIN ATLAS.

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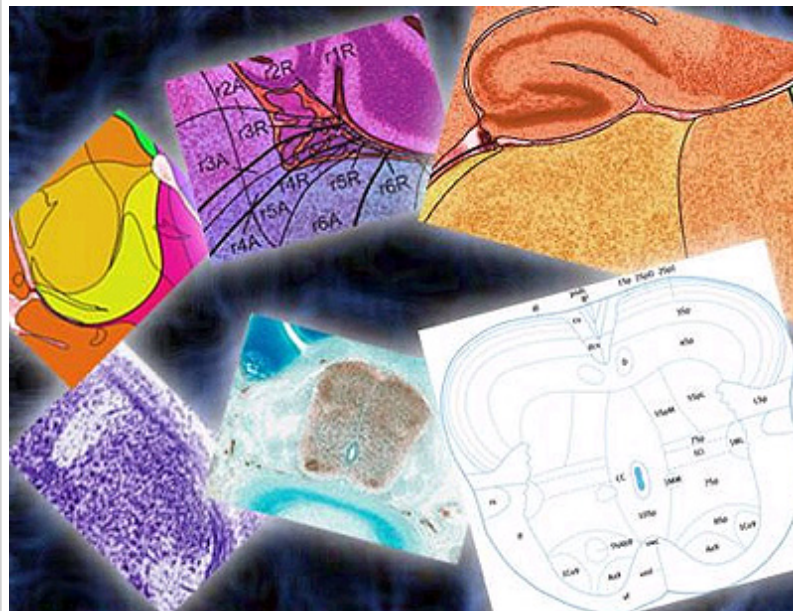
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WHAT'S HOT IN... BIOLOGY , May/June 2009

Atlas Supports a New World of Neurogenomics

by Jeremy Cherfas

Figure Description and Credit



ALLEN MOUSE BRAIN ATLAS (previously Allen Brain Atlas)

This image was used with permission, and downloaded from the Site:

Allen Mouse Brain Atlas [Internet]. Seattle (WA): Allen Institute for Brain Science. ©2009. Available from: <http://mouse.brain-map.org>.

The Institute's primary publication describing the Site:

Lein, E.S. *et al.*, Genome-wide atlas of gene expression in the adult mouse brain, *Nature* 445: 168-176 (2007), doi: 10.1038/nature05453.

KEYWORDS: NEUROGENOMICS, MOUSE BRAIN, GENE EXPRESSION, GENOME-WIDE ATLAS, ALLEN INSTITUTE FOR BRAIN SCIENCE, IN SITU HYBRIDIZATION, ALLEN MOUSE BRAIN ATLAS.



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