

Insights from spatially mapped gene expression in the mouse brain

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The growing number of publicly available databases of murine gene expression arising from genomic-scale transcriptome/proteome profiling projects allows open access to information about genes potentially involved in diseases and disorders of the brain. The use of various methodologies by myriad projects provides complementary types of information, ranging from easily quantifiable microarray data for gross brain regions, to transcript tag analysis and proteomic characterization. One mode of gene expression analysis that has recently been widely adopted is the utilization of colorimetric *in situ* hybridization. This approach is adaptable for high throughput production, and provides a reproducible, scaleable platform for large datasets. The Allen Brain Atlas in particular has utilized this technology to produce a genomic-scale anatomical digital atlas of gene expression in the adult male mouse brain. The availability of global datasets with cellular level spatial resolution, which can be easily parsed due to accessible informatics-derived image analysis tools, can provide both high level and detailed insights into gene regulation. This article reviews various gene expression profiling projects in the mouse brain, how these data sets are increasingly used to complement other studies and applications of these datasets to further understanding of neurological disease.

INTRODUCTION

The mammalian brain is a structure of astounding complexity, with hundreds of different regions that have highly specialized functions and nuclei. Within these regions are a vast array of different cell types contributing to the functional properties of each distinct neuroanatomical area. Morphological, physiological, chemical, cytoarchitectural and myeloarchitectural characteristics are routinely studied to define these distinct cell populations in the central nervous system (CNS). Complementing these attributes is the recent advent of spatially mapped gene expression data. Elucidation of detailed gene expression profiles in the normal state will lead to a better understanding of the phenotypes of various CNS disorders such as schizophrenia, autism and epilepsy, many of which have poorly defined disease etiologies.

Developments in automation of histological procedures, microscopy and image analysis, as well as the availability of the mouse genome sequence (1) have facilitated the rapid production of expression data from the mouse brain with spatial and cellular resolution. These expression modalities include *in situ* hybridization (ISH) (2), reporter gene methods (3)

and immunohistochemistry (4). In this review, we briefly describe several projects that are delineating gene expression with a variety of methodologies in the mouse brain, and the utilization of these large-scale expression data sets in diverse applications. In addition, global findings from the Allen Brain Atlas (ABA), a genome-scale spatially resolved gene expression atlas, are discussed. Using the ABA dataset, the expression profiles of example genes implicated in autism, epilepsy or schizophrenia are analysed in the context of their expression patterns in the mouse brain.

Spatially resolved expression projects

Several large-scale projects have applied a range of technologies to identify gene expression patterns in the mouse brain (Table 1). Microarray analysis on discrete brain regions has been used on one (<http://symatlas.gnf.org/SymAtlas/>) (5) and several adult mouse strains (<http://www.teragenomics.com/>) (6). Microarrays have been combined in the adult mouse with voxelation and gene expression tomography in which volumetric maps of gene expression are produced from images (<http://vox.pharmacology.ucla.edu/datadownload.html>)

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Table 1. Mouse brain gene expression databases

Project ^a	Web site	Data modality	Age
GNF	http://symatlas.gnf.org/SymAtlas/	Microarray	P70 to P94
Teragenomics	http://www.teragenomics.com/	Microarray	P56
Voxelation map ^b	http://vox.pharmacology.ucla.edu/datadownload.html (microarray data)	Voxelation	P56
	http://vox.pharmacology.ucla.edu/home.html (image data)		
Mouse atlas of gene expression	http://www.mouseatlas.org/	SAGE	E0.5-P84
WebQTL	http://www.genenetwork.org	QTL	Various
MNED	http://mouse.bio.brandeis.edu/	Microarray on cell types	P57 to P106
BGEM	http://www.stjudebgem.org/web/mainPage/mainPage.php	Radioactive ISH	E11.5, E15.5, P7, P42
GENSAT	http://www.gensat.org/ or http://www.ncbi.nlm.nih.gov/projects/gensat/	GFP reporter transgenics	E10.5, E15.5, P7, adult
GenePaint.org	http://www.genepaint.org/ (http://www.genetlas.org for P7)	Colorimetric ISH	E10.5, E14.5, E15.5, P7, P56
EurExpress	http://www.eurexpress.org/ee/	Colorimetric ISH	E14.5
Embryo gene expression patterns	http://www.sanger.ac.uk/Teams/Team39/	Colorimetric ISH	E10.5, E12.5, E14.5
EMBLYS	TBD	Colorimetric ISH	E9.5, E10.5, E11.5
TF and RNA-binding proteins ^c	http://mahoney.chip.org/mahoney/	Colorimetric ISH	E10.5, E13.5, P0
EMAP/EMAGE	http://genex.hgu.mrc.ac.uk/	Various	TS1-TS28
GXD	http://www.informatics.jax.org/mgihome/GXD/aboutGXD.shtml	Various	Various
ABA	http://www.brain-map.org	Colorimetric ISH	P56

ABA, Allen Brain Atlas; BGEM, Brain Gene Expression Map; E, embryonic day; EMBLYS, Embryonic Mouse in Bioinformative Lyceum System; EMAGE, Edinburgh Mouse Atlas Gene-Expression Database; EMAP, Edinburgh Mouse Atlas Project; GENSAT, Gene Expression Nervous System Atlas; GNF, Genomics Institute of the Novartis Research Foundation; GXD, Gene Expression Database; ISH, *in situ* hybridization; MNED, Mouse Neuronal Expression Database; P, postnatal day; QTL, quantitative trait loci; SAGE, serial analysis of gene expression; TBD, to be determined; TS, Theiler stage and TF, transcription factors.

^aDatabases/projects are listed in order of appearance in the text.

^bEntire project name: Voxelation Map of Gene Expression in a Coronal Section of the Mouse Brain.

^cEntire project name: ISH Database of Transcription Factors and RNA-binding proteins.

(7,8). Unlike microarrays, which are based on sequences of known transcripts, expression analysis beyond known transcripts is obtained by serial analysis of gene expression (SAGE) in numerous brain structures and developmental stages by the Mouse Atlas of Gene Expression (<http://www.mouseatlas.org/>) (9,10). Combinations of phenotypic data, which includes microarray expression analysis and genotype are available for mapping quantitative trait loci (QTL) by GeneNetwork (<http://www.genenetwork.org>) (11). Utilizing microarray analysis in assaying cell-type specific expression profiles, Sugino *et al.* (12) have analysed 12 distinct neuronal populations that include excitatory projection neurons and inhibitory interneurons with the resulting cell type expression data available at the Mouse Neuronal Expression Database (MNED) (<http://mouse.bio.brandeis.edu/>). All these gene expression data sets lack comprehensive coverage and neuro-anatomic specificity throughout the brain; however, they do provide valuable expression information on a finite number of discrete brain regions or cell types.

Several projects have gene expression data with high levels of spatial mapping in the developing nervous system (13,14). Each project contributes publicly available data to the community across a wide range of developmental timepoints with various degrees of resolution and anatomical mapping/annotation. Two closely related projects use two different data modalities to generate neuroanatomically mapped data. The Brain Gene Expression Map (BGEM) (<http://www.stjudebgem.org/web/mainPage/mainPage.php>) (15,16) utilizes radioactive ISH to identify gene candidates for the Gene Expression Nervous System Atlas (GENSAT) enhanced green fluorescent protein

reporter transgenic mouse pipeline (<http://www.gensat.org/> or <http://www.ncbi.nlm.nih.gov/projects/gensat/>) (3,17,18).

Non-isotopic ISH is another technique that has been widely employed. GenePaint (<http://www.genepaint.org/>) and EurExpress (<http://www.eurexpress.org/ee/>) (19,20) use a colorimetric ISH platform on primarily embryonic day 14.5 (E14.5). Postnatal day 7 (P7) ISH data is available at <http://www.genetlas.org> (21). Various developmental stages are assayed by colorimetric ISH by the Embryo Gene Expression Patterns project (<http://www.sanger.ac.uk/Teams/Team39/>). The Embryonic Mouse in Bioinformative Lyceum System (EMBLYS), a project of the National Research Institute for Children Health and Development of Japan, is initially generating data for transcription factor related genes, followed by genomic-scale ISH expression profiling. Colorimetric ISH on transcription factor and RNA-binding proteins in development is available at <http://mahoney.chip.org/mahoney/> (22,23). Complementing these large-scale projects is the Edinburgh Mouse Atlas Project (EMAP) (<http://genex.hgu.mrc.ac.uk/>), which contains substantial spatial and temporal data, including a digital mouse embryonic developmental atlas linked to a gene expression database, EMAGE (24,25). EMAGE collaborates with the Gene Expression Database (GXD) of Mouse Genome Informatics (MGI) (<http://www.informatics.jax.org/mgihome/GXD/aboutGXD.shtml>) (26) to acquire and map gene expression patterns throughout development (25).

Insights from the ABA

In addition to the database projects described above, a comprehensive survey of gene expression patterns obtained by

colorimetric ISH has been completed by the Allen Institute for Brain Science. The ABA (<http://www.brain-map.org>) contains the expression patterns of approximately 20 000 genes in 56-day-old (P56) C57Bl/6J male brains from the hybridization of non-isotopic digoxigenin labeled riboprobes to uniformly spaced 25- μ m thick fresh-frozen tissue sections (27). High resolution images are captured in which signal detection algorithms identify signal intensity and convert this spatial information to segmented digital representations of expressing cells (28). To create a searchable anatomical gene expression database, colorimetric ISH image data for each gene is aligned in the same three-dimensional coordinate space through registration to a reference atlas (27–29). Finally, three-dimensional representations of gene expression superimposed on the reference atlas are illustrated with the stand-alone online Brain Explorer application (C. Lau *et al.* submitted for publication).

From this genome-scale survey of expression in the mouse brain, one unexpected finding is that a high percentage of genes (~80%) display expression above background (27). This percentage of genes expressed in the brain is significantly higher than that predicted from microarray analysis (30), though a definitive cross platform comparison of microarray and ISH data has yet to be published. Surprisingly, relatively few genes appear to be expressed in all cells (i.e. genes with ubiquitous expression profiles). Gene expression does delineate major cell classes in the brain such as neurons, astrocytes and oligodendrocytes. At the opposite end of the expression spectrum is the very small number of genes expressed only in a single structure or nuclei.

Shifting from global to regional analyses, cellular expression patterns in defined brain structures such as the cerebral cortex may delineate potential gene markers for neuroanatomical regions and cell types. The cortex has a laminar pattern and is divided into several layers as well as motor and sensory areas. Genes with restricted expression can be found in different cortical layers (layers I, II/III, IV, V, VI and VIb) and in functionally discrete cortical regions such as the somatosensory cortex (27). However, the majority of genes expressed in the cortex are found to display relatively consistent expression patterns within a layer throughout the neocortex (27). Abnormalities of the cortex, such as cognitive impairment, degeneration and aberrant neurological wiring contribute to many neurological and degenerative nervous system disorders.

Heterogeneous gene expression profiles are also apparent in areas such as the subregions of the hippocampus (CA1, CA2, CA3, dentate gyrus and hilus) and in all hippocampal cardinal axes, with common delineations seen along the dorsal/ventral (septotemporal) axis (27). The hippocampus has been shown to be essential in certain types of learning and memory (31,32) and its relevance in several disease states has been well-described. For example, significantly larger hippocampal volumes have been correlated with autism (33,34) and smaller hippocampal volumes have been documented with schizophrenia and epilepsy (33,35). How gene expression profile diversity in the hippocampus corresponds to the function and connectivity of this structure and its role in various neurological disorders is an exciting avenue for further investigation.

Utilization of spatially resolved expression data

As the majority of large-scale expression data is recent, it is difficult to ascertain the full extent of their use by the scientific community; however, there are several published studies that showcase diverse applications addressing important biological questions in mice and humans. Papassotiropoulos *et al.* (36) have identified KIBRA (alias WWC1, WW and C2 domain containing 1) during a genome-wide screen of >500 000 single-nucleotide polymorphisms to find memory-related gene variants in humans. Expression of KIBRA in CA1 and the dentate gyrus of the mouse hippocampus is high in the ABA, supporting the importance of KIBRA in memory. Petyuk *et al.* (37) have developed a methodology for spatial proteome mapping of the mouse brain that starts with tissue voxelation and ends with peptide identification and quantitation. GENSAT and ABA data have been used to corroborate the protein abundance data from this proteomics technique (37). Mozhui *et al.* (38) have performed a genetic and structural analysis of the basolateral amygdala complex (BLAc) in BXD recombinant inbred mice in which BLAc volume and cell populations were quantified. A QTL for BLAc size has been identified with WebQTL (39) and the ABA expression profiles of the resulting candidate genes have been examined (38). In a study by Dugas *et al.* (40) in which gene expression profiles during oligodendrocyte differentiation were assessed from microarrays, ABA, BGEM and GENSAT data have been applied to validate the expression patterns of candidate genes in white matter. The majority of candidate genes (55 out of 70) are expressed in white matter in at least one database. In a study by Ponomarev *et al.* (41), MNED and ABA datasets have been employed to define cell type-specific expression of GABA A (gamma-aminobutyric acid) α 1 mutation-associated genes in the cortex and cerebellum, respectively. Microarray expression data have been used to identify differentially expressed genes between knock-out and wild-type lines. Then, the spatially resolved expression profiles of the candidate genes have been assessed in MNED and ABA in different types of neurons and glial cells (41). In a study about corticotrophin releasing factor (CRF) and its receptors, GENSAT data confirms RT-PCR data that shows low expression levels of Type 2 CRF receptor (CRF-R2 α) in the vermis and hemisphere of the cerebellum (42). A study by Morales and Hatten (43) has used GENSAT data to identify numerous genes with restricted expression in cerebellar progenitor populations, including Purkinje cell and cerebellar nuclear precursors. Finally, a study by Yaylaoglu *et al.* (44) has compared expression patterns of fibroblast growth factors and their receptors in E14.5 mice.

In addition to applying existing gene expression data to verify candidate genes, confirm gene expression data from microarrays, SAGE, RT-PCR, or proteomics, or ascertain cell type expression, spatially mapped expression data has been employed for comparison between wild-type and mutant states. This application of spatially mapped data can lead to a better understanding of gene regulation, cell type specificity, disease and neurodevelopment. One such example is the study of the developing hippocampus of *Emx2* mutant mice by several techniques, one of which was ISH (45). In addition to examining the neuroanatomical differences in the hippocampal fissure

region between wild-type and *Emx2*^{-/-} mice, the downstream implications of the absence of *Emx2* have been examined, specifically the effects on hippocampal *Reln* expressing cells (45). Continuing the study of the *Emx2* mutant, Skutella *et al.* (46) has performed microarray analysis on wild-type and *Emx2*^{-/-} hippocampus. Many microarray candidate genes that differed in expression between wild-type and mutant *Emx2* hippocampus have been assayed by ISH.

Expression analysis of genes associated with neurological disorders

Cellular resolution of gene expression patterns (e.g. neuroanatomical selectivity, cell type expression and identification of co-expressed genes) in the wild-type state provides a foundation to begin to understand phenotypes in the diseased condition. In the next sections, we utilize publicly available ABA data to examine expression profiles in the cortex, hippocampus and striatum of some orthologs associated with autism, epilepsy or schizophrenia (Table 2). The list shown in Table 2 is not comprehensive, but does contain numerous candidate genes that are strongly supported in the literature (47–53). One application of spatially mapped gene expression data is assessment of the presence/absence of a candidate gene in a brain region associated with a particular disorder. In many cases, the nature of the involvement of a particular candidate gene in the pathophysiology and phenotype of neurological disease is poorly understood. While using neuroanatomical gene expression analysis for this purpose is complicated by the simultaneous needs to assess complex global expression patterns and detailed cellular resolution, insight may be gained about the circuitry affected by these disorders.

Autism

Autism spectrum disorders (ASDs) are characterized by impairments in social, communicative and behavioral development, often accompanied by abnormal cognitive functioning, learning, attention and sensory processing (54). Autism is considered one of multiple ASDs (55) and has a prevalence of about one in every 150 children (56). Abnormalities in neural development are widely recognized as the underlying neuropathological causes of ASDs (57). Post-mortem studies of autistic brains show a variety of neuropathologies including decreased programmed cell death and/or increased cell proliferation, abnormal cell differentiation with smaller neuronal size, altered cell migration with disrupted cortical and subcortical cytoarchitectonics and modified synaptogenesis (57,58).

Table 2 lists 12 genes associated with autism. From the mouse ortholog expression profiles, 12, 11 and 10 genes are expressed in the cortex, hippocampus and striatum, respectively, although the expression is markedly lower in the striatum compared with the other two structures. Three genes, *Adcyap1*, *Nrcam* and *Reln*, have enriched expression in cortical layer V, but also have interesting expression profiles in other cortical layers. *Reln* is expressed in GABAergic interneurons, *Nrcam* has widespread expression in cortical layers II through VIb and *Adcyap1* is enriched in cortical layers II/III (see Fig. 1 and Table 2). Expression of these

genes in cortical layer V is intriguing since cortical layer V pyramidal cells are the major cortical neurons that send projections to striatal, pallidal and brainstem regions as well as projecting to other cortical layers (59). The expression of *Reln* in GABAergic interneurons is interesting since an imbalance between excitation and inhibition characterizes the cortex of autistic individuals, leading to hyperexcitability and unstable activity of cortical networks following sensory stimulation (60).

Epilepsy

Epilepsies are characterized by recurrent and often unpredictable seizures (61). Approximately 3% of the population is affected by epilepsies, with peak incidences in children and the elderly (62). Epilepsies can be caused by both acquired and genetic factors, with almost half of all epilepsies having some genetic basis (63); however, only a small percentage appears to have Mendelian inheritance. Largely genetic, idiopathic epilepsies comprise ~30% of all epilepsies (62,64).

A number of genes, including several ion channels, have been associated with rare monogenic idiopathic epilepsies (49,61). Table 2 lists 13 genes associated with epilepsy. Expression analysis of the mouse orthologs shows that 13, 13 and 12 genes are expressed in the cortex, hippocampus and striatum, respectively. Several of these epilepsy-associated genes exhibit discrete hippocampal expression patterns. Figure 1 shows the hippocampal expression of *Abat*, *Gabrb2* and *Grik1*. Interestingly, all three genes are expressed in GABAergic interneurons, but differ in their distribution and expression level in hippocampal pyramidal cells (i.e. *Abat* has moderate expression at the CA2/CA3 boundary with heterogeneous expression levels throughout CA3 and *Gabrb2* has moderate expression in CA1). In the epilepsy phenotype, memory impairment in the temporal lobe is well documented, as is hippocampal cell loss and gliosis (65,66). In addition, GABA-mediated inhibition in the hippocampus is impaired in epilepsy (67,68).

Schizophrenia

Schizophrenia is a complex, heritable psychiatric disorder with an incidence of ~1% of the population. Dysfunctions in the prefrontal and mesial temporal cortices, and in the glutamate and GABA neurotransmitter systems have been implicated in schizophrenia (69). In addition, several studies suggest a strong link with dopamine (70), hence the dopamine hypothesis (71–73). It has been suggested that delusions, a hallmark of schizophrenia psychosis, are produced by abnormally reinforced/rewarded thoughts and associations (74–76). One neuroanatomical region that has an important role in the learning of associations is the ventral striatum (77,78). In schizophrenia, aberrant striatal dopamine function has been described (79).

Several putative schizophrenia susceptibility genes have been identified (52,80). Table 2 lists 13 genes associated with schizophrenia: 13, 12 and 12 genes are expressed in the cortex, hippocampus and striatum, respectively. Figure 1 shows striatal expression profiles of mouse ortholog of *PDYN*, *PPP1R1B* and *RGS4*. All three genes exhibit robust expression

Table 2. Expression analysis of genes associated with neurological disorders

Gene symbol ^a	Gene name	Reference	Mouse ortholog	Cortex expression ^b	Hippocampus expression ^b	Striatum expression ^b
Genes associated with autism						
<i>ADCYAP1</i>	Adenylate cyclase activating polypeptide 1	(93)	<i>Adcyap1</i>	Medium D, Moderate L, Enriched in layers 2/3 & 5	Scattered D, High L, Enriched in DG	Negative
<i>CENTG2</i>	Centaurin, gamma 2	(94)	<i>Centg2</i>	Medium D, Low L	High D, Moderate L in DG	Medium D, Low L
<i>DVLI</i>	Disheveled, dsh homolog 1 (<i>Drosophila</i>)	(95)	<i>Dvl1</i>	Medium D, Moderate L	High D, High L	Medium D, Low L
<i>GABRA4</i>	Gamma-aminobutyric acid (GABA) A receptor, alpha 4	(96)	<i>Gabra4</i>	Medium D, Moderate L, Enriched in layers 2/3	Medium D, High L, Enriched in DG	High D, Moderate L
<i>GABRA5</i>	GABA-A receptor, alpha 5	(97)	<i>Gabra5</i>	Medium D, Moderate L, Enriched in layer 6b	High D, Very high L	Scattered D, Low L
<i>GABRB1</i>	GABA-A receptor, beta 1	(96)	<i>Gabrb1</i>	Medium D, Low L	Medium D, Low L, Enriched in CA2	Scattered D, Low L
<i>GABRG1</i>	GABA-A receptor, gamma 1	(98)	<i>Gabrg1</i>	Sparse D, Low L	Negative	Negative
<i>GABRG3</i>	GABA-A receptor, gamma 3	(99)	<i>Gabrg3</i>	Scattered D, Moderate L	Scattered D, Moderate L	Scattered D, Moderate L
<i>GLO1</i>	Glyoxalase I	(100)	<i>Glo1</i>	Medium D, Moderate L	High D, High L	Scattered D, Moderate L
<i>NRCAM</i>	Neuronal cell adhesion molecule	(101)	<i>Nrcam</i>	Medium D, High L, Enriched in layer 5	High D, High L, Enriched in CA2, CA3	Scattered D, High L
<i>NRXN1</i>	Neurexin 1	(102)	<i>Nrxn1</i>	High D, High L, Enriched in layers 2 & 6b	High D, High L	Medium D, Moderate L
<i>Reln</i>	Reelin	(103,104)	<i>Reln</i>	Scattered D, High L, Enriched in layer 5	Scattered D, High L	High D, High L
Genes associated with epilepsy						
<i>ABAT</i>	4-aminobutyrate aminotransferase	(105)	<i>Abat</i>	Medium D, High L	Scattered D, High L, Enriched in CA2 & subgranular DG	High D, Moderate L
<i>CACNA1H</i>	Calcium channel, voltage-dependent, T type, alpha 1H subunit	(106,107)	<i>Cacna1h</i>	Medium D, Moderate L, Enriched in layer 5	Medium D, High L, Enriched in DG	Medium D, Moderate L
<i>CHRNA2</i>	Cholinergic receptor, nicotinic, alpha 2 (neuronal)	(108)	<i>Chrna2</i>	Medium D, Low L	Scattered D, Low L	Scattered D, Low L
<i>CHRN2</i>	Cholinergic receptor, nicotinic, beta 2 (neuronal)	(109,110)	<i>Chrn2</i>	Scattered D, Low L	Medium D, Low L	Scattered D, Low L
<i>CLCN2</i>	Chloride channel 2	(111)	<i>Clcn2</i>	Medium D, High L, Enriched in layer 5	Medium D, Moderate L	Scattered D, Low L
<i>GABBR2</i>	GABA-B receptor, 2	(112,113)	<i>Gabbr2</i>	High D, Very high L, Enriched in layers 2/3	High D, Very high L	Medium D, Moderate L
<i>GABRA1</i>	GABA-A receptor, alpha 1	(114)	<i>Gabra1</i>	High D, High L, Enriched in layers 2/3	High D, High L, Enriched in CA1	Scattered D, Low L
<i>GABRB2</i>	GABA-A receptor, beta 2	(115)	<i>Gabrb2</i>	Medium D, Moderate L	Scattered D, Moderate L, Enriched in subgranular DG	Scattered D, Low L
<i>GABRB3</i>	GABA-A receptor, beta 3	(116,117)	<i>Gabrb3</i>	Medium D, Moderate L	High D, Very high L	Medium D, Moderate L
<i>GABRG2</i>	GABA-A receptor, gamma 2	(118)	<i>Gabrg2</i>	Medium D, Moderate L	Medium D, Moderate L	Scattered D, Low L
<i>GRIK1</i>	Glutamate receptor, ionotropic, kainate 1	(119)	<i>Grik1</i>	Scattered D, High L	Scattered D, High L, Enriched in subgranular DG	Scattered D, Low L
<i>NOS1</i>	Nitric oxide synthase 1 (neuronal)	(120,121)	<i>Nos1</i>	Scattered D, High L, Enriched in layers 5 & 6	Medium D, High L	Scattered D, Very high L
<i>VIP</i>	Vasoactive intestinal peptide	(122,123)	<i>Vip</i>	Scattered D, Very high L, Enriched in layers 2/3	Sparse D, Very high L	Negative

Continued

Table 2. Continued

Gene symbol ^a	Gene name	Reference	Mouse ortholog	Cortex expression ^b	Hippocampus expression ^b	Striatum expression ^b
Genes associated with schizophrenia						
<i>BDNF</i>	Brain-derived neurotrophic factor	(124)	<i>Bdnf</i>	Medium D, Moderate L, Enriched in layers 2/3 & 6	Medium D, High L, Enriched in CA3	Negative
<i>CHRNA7</i>	Cholinergic receptor, nicotinic, alpha 7	(125)	<i>Chrna7</i>	Scattered D, Low L, Enriched in layer 1	Medium D, Moderate L	Scattered D, Low L
<i>COMT</i>	Catechol-O-methyltransferase	(126)	<i>Comt</i>	Medium D, Moderate L	Medium D, High L, Enriched in CA3	Medium D, Moderate L
<i>DTNBP1</i>	Dystrobrevin binding protein 1	(127)	<i>Dtnbp1</i>	Medium D, Moderate L, Enriched in layer 5	High D, High L, Enriched in CA1	Scattered D, Low L
<i>ERBB4</i>	v-erb-a erythroblastic leukemia viral oncogene homolog 4 (avian)	(128)	<i>ErbB4</i>	Medium D, High L	Scattered D, High L	Scattered D, High L
<i>NRG1</i>	Neuregulin 1	(129)	<i>Nrg1</i>	Scattered D, Moderate L, Enriched in layer 5	Negative	Scattered D, Low L
<i>NTRK3</i>	Neurotrophic tyrosine kinase, receptor, type 3	(130,131)	<i>Ntrk3</i>	Scattered D, Low L	Scattered D, Low L	Scattered D, Low L
<i>PAFAH1B1</i>	Platelet-activating factor acetylhydrolase, isoform Ib, alpha subunit 45 kDa	(132)	<i>Pafah1b1</i>	High D, Very high L	High D, Very high L	High D, High L
<i>PDYN</i>	Prodynorphin	(133,134)	<i>Pdyn</i>	Scattered D, High L, Enriched in layer 2	Medium D, High L, Enriched in DG	Medium D, Very high L, Enriched in ACB
<i>PPP1R1B</i>	Protein phosphatase 1, regulatory (inhibitor) subunit 1B (dopamine and cAMP regulated phosphoprotein, DARPP-32)	(135)	<i>Ppp1r1b</i>	High D, High L, Enriched in layers 2/3 & 6	Medium D, Moderate L, Enriched in CA1	High D, Very high L
<i>PRODH</i>	Proline dehydrogenase (oxidase) 1	(136)	<i>Prodh</i>	Scattered D, Low L, Glial cells	Scattered D, Low L, Glial cells	Scattered D, Low L, Glial cells
<i>PVALB</i>	Parvalbumin	(137)	<i>Pvalb</i>	Medium D, Very high L	High D, Very high L	Medium D, High L
<i>RGS4</i>	Regulator of G-protein signaling 4	(138)	<i>Rgs4</i>	High D, High L, Enriched in layers 2/3	High D, High L, Enriched in CA2	High D, Very high L

ACB, nucleus accumbens; D, density; DG, dentate gyrus and L, level.

^aIn certain cases, a gene is associated with more than one disorder [e.g. *Reln* has been associated with autism (103,104) and schizophrenia (139,140)], but for this review the genes are classified in only one disorder.

^bCortex, hippocampus, striatum expression: for each structure analysed in the adult mouse brain, an expression score for density and level is provided. Expression density (density, D) is divided into four categories: sparse (<5% of cells contain expression in the structure), scattered (5–20% of cells), medium (20–70% of cells) and high (>70% of cells). Expression level (L) is calibrated to the expression heat maps for each gene (27,28). The expression level is divided into four categories: very high (range red to orange on heat mask), high (range orange to yellow on heat mask), moderate (green on heat mask), low (blue on heat mask) and negative (undetectable). In addition, regional enrichment in cortical layers (e.g. layer 1, layers 2/3, layer 6), hippocampus (e.g. CA1, CA2, dentate gyrus) or striatum (e.g. nucleus accumbens) or a cell type such as glial cells is described.

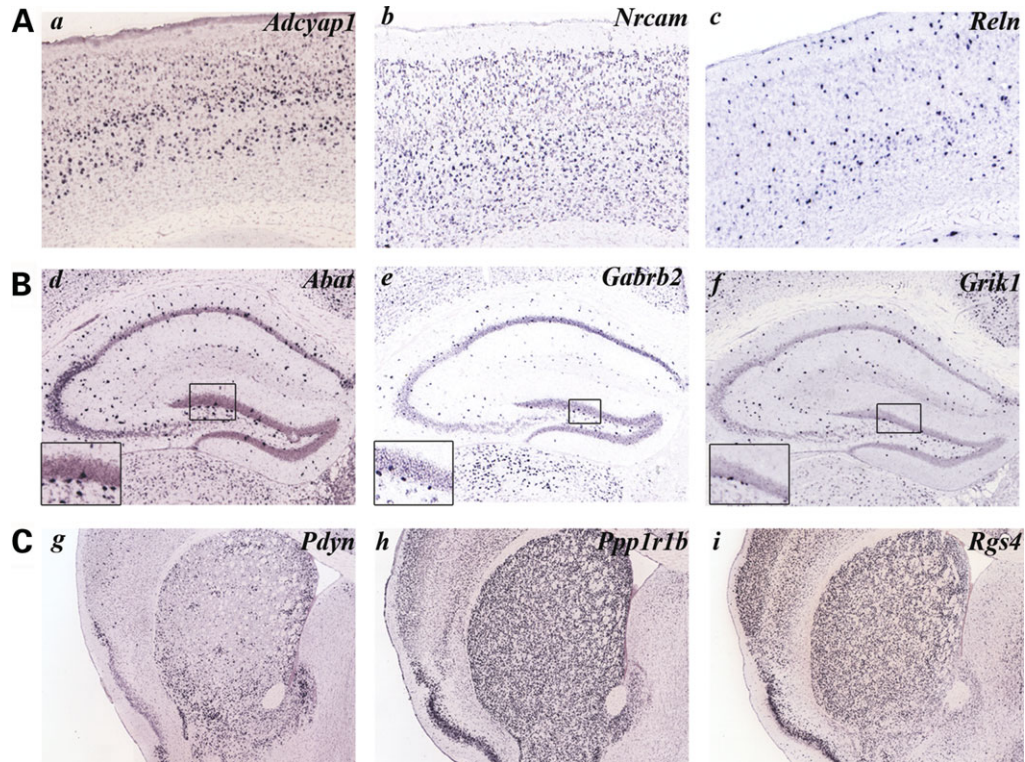


Figure 1. Expression profiles in the mouse brain of genes associated with autism, epilepsy or schizophrenia. **(A)** Examples of cortical expression patterns of genes associated with autism. a, *Adcyap1* (adenylate cyclase activating polypeptide 1) (sagittal image series ID 70523740); b, *Nrcam* (neuronal cell adhesion molecule) (sagittal image series ID 173) and c, *Reln* (reelin) (sagittal image series ID 892). Each gene has enriched expression in cortical layer 5 in addition to expression in other cortical layers. **(B)** Expression in hippocampal subregions of genes associated with epilepsy. d, *Abat* (4-aminobutyrate aminotransferase) (coronal image series ID 72079931); e, *Gabrb2* (gamma-aminobutyric acid (GABA) A receptor, beta 2) (coronal image series ID 472) and f, *Grik1* (glutamate receptor, ionotropic, kainate 1) (coronal image series ID 75749751). Each gene is strongly expressed in GABAergic interneurons throughout the hippocampus, but differs in their distribution and expression level in hippocampal pyramidal cells. Inset shows magnified view of expression in dentate gyrus and subgranular zone. **(C)** Examples of striatal expression patterns in genes associated with schizophrenia. g, *Pdyn* (prodynorphin) (coronal image series ID 71717084); h, *Ppp1r1b* [protein phosphatase 1, regulatory (inhibitor) subunit 1B (dopamine and cAMP regulated phosphoprotein, DARPP-32)] (coronal image series ID 73732146) and i, *Rgs4* (regulator of G-protein signaling 4) (coronal image series ID 74511884). Each gene is strongly expressed in the striatum with either a widespread expression pattern (*Ppp1r1b* and *Rgs4*) or a pattern with strong foci of expression (*Pdyn*).

throughout the striatum. *RGS4* modulates the signaling activity of G-protein coupled receptors, which feedback to regulate *RGS4* expression via dopamine receptors (81–83). Expression analysis of *RGS4* in normal human brain tissue reveals dense expression in most cortical layers and lower expression in the basal ganglia (striatum), thalamus and hippocampus (pyramidal layers) (84). Examination of schizophrenia samples from medicated patients shows a decrease in *RGS4* mRNA levels in the caudate (striatum) (85). *PPP1R1B* (DARPP-32) has a critical role in regulating dopamine signaling in the striatum (86). Previous studies have shown that *PPP1R1B* is strongly expressed in the mouse striatum (87,88) and the ABA ISH data concurs with this report. *PDYN* is the precursor for dynorphin opioid peptides and the opioid system has important functions in addiction, reward and controlling pain. Interestingly, there is a high degree of overlap between schizophrenia and addictive disorders (89). *PDYN* has been shown to be highly expressed in the patch/striosome compartment compared with the matrix of the dorsal caudate-putamen (90,91) and the ABA data are consistent with this description of patchy expression in the striatum.

CONCLUSION

A new era of neurogenomics has begun. With increasing amounts of publicly available gene expression data in the mouse, we are just beginning to reap the benefits of applying these data sets to numerous biological questions, particularly regarding neurological disease, gene regulation and cell type specificity. Expression profiling of single neurons from the rat somatosensory neocortex by multiplex RT–PCR has shown that the expression of any single gene cannot define an anatomical cell type; however, combinatorial expression profiles can predict anatomical cell types with a higher degree of accuracy (92). Further defining the molecular profile of cell types will be possible using these data sets as a starting point to define candidate cell type markers for double or multiplex fluorescent ISH studies, which can identify the extent of coexpression between marker genes. A logical extension of the mouse studies described in this review will be the future availability of cellular resolution datasets using human brain tissue in both normal and disease states, which would accelerate our understanding of neurological disorders.

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REFERENCES

- Waterston, R.H., Lindblad-Toh, K., Birney, E., Rogers, J., Abril, J.F., Agarwal, P., Agarwala, R., Ainscough, R., Alexandersson, M., An, P. *et al.* (2002) Initial sequencing and comparative analysis of the mouse genome. *Nature*, **420**, 520–562.
- Carson, J.P., Thaller, C. and Eichele, G. (2002) A transcriptome atlas of the mouse brain at cellular resolution. *Curr. Opin. Neurobiol.*, **12**, 562–565.
- Gong, S., Zheng, C., Doughty, M.L., Losos, K., Didkovsky, N., Schambra, U.B., Nowak, N.J., Joyner, A., Leblanc, G., Hatten, M.E. *et al.* (2003) A gene expression atlas of the central nervous system based on bacterial artificial chromosomes. *Nature*, **425**, 917–925.
- Anderson, C.N. and Grant, S.G. (2006) High throughput protein expression screening in the nervous system—needs and limitations. *J. Physiol.*, **575**, 367–372.
- Su, A.I., Cooke, M.P., Ching, K.A., Hakak, Y., Walker, J.R., Wiltshire, T., Orth, A.P., Vega, R.G., Sapinoso, L.M., Moqrich, A. *et al.* (2002) Large-scale analysis of the human and mouse transcriptomes. *Proc. Natl. Acad. Sci. USA*, **99**, 4465–4470.
- Zapala, M.A., Hovatta, I., Ellison, J.A., Wodicka, L., Del Rio, J.A., Tennant, R., Tynan, W., Broide, R.S., Helton, R., Stoveken, B.S. *et al.* (2005) Adult mouse brain gene expression patterns bear an embryologic imprint. *Proc. Natl. Acad. Sci. USA*, **102**, 10357–10362.
- Liu, D. and Smith, D.J. (2003) Voxelation and gene expression tomography for the acquisition of 3-D gene expression maps in the brain. *Methods*, **31**, 317–325.
- Chin, M.H., Geng, A.B., Khan, A.H., Qian, W.J., Petyuk, V.A., Boline, J., Levy, S., Toga, A.W., Smith, R.D., Leahy, R.M. *et al.* (2007) A genome-scale map of expression for a mouse brain section obtained using voxelation. *Physiol. Genomics*. (in press).
- Siddiqui, A.S., Khattrra, J., Delaney, A.D., Zhao, Y., Astell, C., Asano, J., Babakaiff, R., Barber, S., Beland, J., Bohacec, S. *et al.* (2005) A mouse atlas of gene expression: large-scale digital gene-expression profiles from precisely defined developing C57BL/6J mouse tissues and cells. *Proc. Natl. Acad. Sci. USA*, **102**, 18485–18490.
- Khattrra, J., Delaney, A.D., Zhao, Y., Siddiqui, A., Asano, J., McDonald, H., Pandoh, P., Dhalla, N., Prabhu, A.L., Ma, K. *et al.* (2007) Large-scale production of SAGE libraries from microdissected tissues, flow-sorted cells, and cell lines. *Genome Res.*, **17**, 108–116.
- Rosen, G.D., La Porte, N.T., Diechtiareff, B., Pung, C.J., Nissanov, J., Gustafson, C., Bertrand, L., Gefen, S., Fan, Y., Tretiak, O.J. *et al.* (2003) Informatics center for mouse genomics: the dissection of complex traits of the nervous system. *Neuroinformatics*, **1**, 327–342.
- Sugino, K., Hempel, C.M., Miller, M.N., Hattox, A.M., Shapiro, P., Wu, C., Huang, Z.J. and Nelson, S.B. (2006) Molecular taxonomy of major neuronal classes in the adult mouse forebrain. *Nat. Neurosci.*, **9**, 99–107.
- Hatten, M.E. and Heintz, N. (2005) Large-scale genomic approaches to brain development and circuitry. *Annu. Rev. Neurosci.*, **28**, 89–108.
- Sunkin, S.M. (2006) Towards the integration of spatially and temporally resolved murine gene expression databases. *Trends Genet.*, **22**, 211–217.
- Brumwell, C.L. and Curran, T. (2006) Developmental mouse brain gene expression maps. *J. Physiol.*, **575**, 343–346.
- Magdaleno, S., Jensen, P., Brumwell, C.L., Seal, A., Lehman, K., Asbury, A., Cheung, T., Cornelius, T., Batten, D.M., Eden, C. *et al.* (2006) BGEM: an *in situ* hybridization database of gene expression in the embryonic and adult mouse nervous system. *PLoS Biol.*, **4**, e86.
- Heintz, N. (2004) Gene expression nervous system atlas (GENSAT). *Nat. Neurosci.*, **7**, 483.
- Geschwind, D. (2004) GENSAT: a genomic resource for neuroscience research. *Lancet Neurol.*, **3**, 82.
- Visel, A., Thaller, C. and Eichele, G. (2004) GenePaint.org: an atlas of gene expression patterns in the mouse embryo. *Nucleic Acids Res.*, **32**, D552–D556.
- Alvarez-Bolado, G. and Eichele, G. (2006) Analysing the developing brain transcriptome with the GenePaint platform. *J. Physiol.*, **575**, 347–352.
- Carson, J.P., Ju, T., Lu, H.C., Thaller, C., Xu, M., Pallas, S.L., Crair, M.C., Warren, J., Chiu, W. and Eichele, G. (2005) A digital atlas to characterize the mouse brain transcriptome. *PLoS Comput. Biol.*, **1**, e41.
- Gray, P.A., Fu, H., Luo, P., Zhao, Q., Yu, J., Ferrari, A., Tenzen, T., Yuk, D.I., Tsung, E.F., Cai, Z. *et al.* (2004) Mouse brain organization revealed through direct genome-scale TF expression analysis. *Science*, **306**, 2255–2257.
- McKee, A.E., Minet, E., Stern, C., Riahi, S., Stiles, C.D. and Silver, P.A. (2005) A genome-wide *in situ* hybridization map of RNA-binding proteins reveals anatomically restricted expression in the developing mouse brain. *BMC Dev. Biol.*, **5**, 14.
- Baldock, R.A., Bard, J.B., Burger, A., Burton, N., Christiansen, J., Feng, G., Hill, B., Houghton, D., Kaufman, M., Rao, J. *et al.* (2003) EMAP and EMAGE: a framework for understanding spatially organized data. *Neuroinformatics*, **1**, 309–325.
- Christiansen, J.H., Yang, Y., Venkataraman, S., Richardson, L., Stevenson, P., Burton, N., Baldock, R.A. and Davidson, D.R. (2006) EMAGE: a spatial database of gene expression patterns during mouse embryo development. *Nucleic Acids Res.*, **34**, D637–D641.
- Smith, C.M., Finger, J.H., Hayamizu, T.F., McCright, I.J., Eppig, J.T., Kadin, J.A., Richardson, J.E. and Ringwald, M. (2007) The mouse gene expression database (GXD): 2007 update. *Nucleic Acids Res.*, **35**, D618–D623.
- Lein, E.S., Hawrylycz, M.J., Ao, N., Ayres, M., Bensinger, A., Bernard, A., Boe, A.F., Boguski, M.S., Brockway, K.S., Byrnes, E.J. *et al.* (2007) Genome-wide atlas of gene expression in the adult mouse brain. *Nature*, **445**, 168–176.
- Ng, L.L., Pathak, S.D., Kuan, C.L., Lau, C., Dong, H., Sodt, A.J., Dang, C.N., Avants, B., Yushkevich, P., Gee, J.C. *et al.* (2007) Neuroinformatics for genome-wide 3D gene expression mapping in the mouse brain. *IEEE Trans. Comput. Biol. Bioinform.* (in press).
- Dong, H.W. (2007) *The Allen Atlas: A Digital Brain Atlas of C57BL/6J Male Mouse*, Hoboken, NJ, John Wiley & Sons.
- Sandberg, R., Yasuda, R., Pankratz, D.G., Carter, T.A., Del Rio, J.A., Wodicka, L., Mayford, M., Lockhart, D.J. and Barlow, C. (2000) Regional and strain-specific gene expression mapping in the adult mouse brain. *Proc. Natl. Acad. Sci. USA*, **97**, 11038–11043.
- Zola-Morgan, S., Squire, L.R. and Amaral, D.G. (1986) Human amnesia and the medial temporal region: enduring memory impairment following a bilateral lesion limited to field CA1 of the hippocampus. *J. Neurosci.*, **6**, 2950–2967.
- Scoville, W.B. and Milner, B. (2000) Loss of recent memory after bilateral hippocampal lesions, 1957. *J. Neuropsychiatry Clin. Neurosci.*, **12**, 103–113.
- Geuze, E., Vermetten, E. and Bremner, J.D. (2005) MR-based *in vivo* hippocampal volumetrics: 2. Findings in neuropsychiatric disorders. *Mol. Psychiatry*, **10**, 160–184.
- Rojas, D.C., Peterson, E., Winterrowd, E., Reite, M.L., Rogers, S.J. and Tregellas, J.R. (2006) Regional gray matter volumetric changes in autism associated with social and repetitive behavior symptoms. *BMC Psychiatry*, **6**, 56.
- Heckers, S. and Konradi, C. (2002) Hippocampal neurons in schizophrenia. *J. Neural Transm.*, **109**, 891–905.
- Papassotiropoulos, A., Stephan, D.A., Huentelman, M.J., Hoerndli, F.J., Craig, D.W., Pearson, J.V., Huynh, K.D., Brunner, F., Corneveaux, J., Osborne, D. *et al.* (2006) Common Kibra alleles are associated with human memory performance. *Science*, **314**, 475–478.
- Petyuk, V.A., Qian, W.J., Chin, M.H., Wang, H., Livesay, E.A., Monroe, M.E., Adkins, J.N., Jaitly, N., Anderson, D.J., Camp, D.G., II. *et al.* (2007) Spatial mapping of protein abundances in the mouse brain by voxelation integrated with high-throughput liquid chromatography-mass spectrometry. *Genome Res.*, **17**, 328–336.

38. Mozhui, K., Hamre, K.M., Holmes, A., Lu, L. and Williams, R.W. (2007) Genetic and structural analysis of the basolateral amygdala complex in BXD recombinant inbred mice. *Behav. Genet.*, **37**, 223–243.
39. Chesler, E.J., Wang, J., Lu, L., Qu, Y., Manly, K.F. and Williams, R.W. (2003) Genetic correlates of gene expression in recombinant inbred strains: a relational model system to explore neurobehavioral phenotypes. *Neuroinformatics*, **1**, 343–357.
40. Dugas, J.C., Tai, Y.C., Speed, T.P., Ngai, J. and Barres, B.A. (2006) Functional genomic analysis of oligodendrocyte differentiation. *J. Neurosci.*, **26**, 10967–10983.
41. Ponomarev, I., Maiya, R., Harnett, M.T., Schafer, G.L., Ryabinin, A.E., Blednov, Y.A., Morikawa, H., Boehm, S.L., 2nd., Homanics, G.E., Berman, A.E. *et al.* (2006) Transcriptional signatures of cellular plasticity in mice lacking the alpha 1 subunit of GABA A receptors. *J. Neurosci.*, **26**, 5673–5683.
42. Bishop, G.A., Tian, J.B., Stanke, J.J., Fischer, A.J. and King, J.S. (2006) Evidence for the presence of the type 2 corticotropin releasing factor receptor in the rodent cerebellum. *J. Neurosci. Res.*, **84**, 1255–1269.
43. Morales, D. and Hatten, M.E. (2006) Molecular markers of neuronal progenitors in the embryonic cerebellar anlage. *J. Neurosci.*, **26**, 12226–12236.
44. Yaylaoglu, M.B., Titmus, A., Visel, A., Alvarez-Bolado, G., Thaller, C. and Eichele, G. (2005) Comprehensive expression atlas of fibroblast growth factors and their receptors generated by a novel robotic *in situ* hybridization platform. *Dev. Dyn.*, **234**, 371–386.
45. Zhao, T., Kraemer, N., Oldekamp, J., Cankaya, M., Szabo, N., Conrad, S., Skutella, T. and Alvarez-Bolado, G. (2006) Emx2 in the developing hippocampal fissure region. *Eur. J. Neurosci.*, **23**, 2895–2907.
46. Skutella, T., Conrad, S., Hooge, J., Bonin, M. and Alvarez-Bolado, G. (2007) Microarray analysis of the fetal hippocampus in the Emx2 mutant. *Dev. Neurosci.*, **29**, 28–47.
47. Yang, M.S. and Gill, M. (2007) A review of gene linkage, association and expression studies in autism and an assessment of convergent evidence. *Int. J. Dev. Neurosci.*, **25**, 69–85.
48. Santangelo, S.L. and Tsatsanis, K. (2005) What is known about autism: genes, brain, and behavior. *Am. J. Pharmacogenomics*, **5**, 71–92.
49. Mulley, J.C., Scheffer, I.E., Harkin, L.A., Berkovic, S.F. and Dibbens, L.M. (2005) Susceptibility genes for complex epilepsy. *Hum. Mol. Genet.*, **14**, R243–R249. Spec No. 2.
50. Ottman, R. (2005) Analysis of genetically complex epilepsies. *Epilepsia*, **46** (Suppl. 10), 7–14.
51. Gutierrez-Delgado, E. and Serratosa, J.M. (2004) Genetics of the epilepsies. *Curr. Opin. Neurol.*, **17**, 147–153.
52. Ross, C.A., Margolis, R.L., Reading, S.A., Pletnikov, M. and Coyle, J.T. (2006) Neurobiology of schizophrenia. *Neuron*, **52**, 139–153.
53. Carter, C.J. (2006) Schizophrenia susceptibility genes converge on interlinked pathways related to glutamatergic transmission and long-term potentiation, oxidative stress and oligodendrocyte viability. *Schizophr. Res.*, **86**, 1–14.
54. Yeargin-Allsopp, M., Rice, C., Karapurkar, T., Doernberg, N., Boyle, C. and Murphy, C. (2003) Prevalence of autism in a US metropolitan area. *Jama*, **289**, 49–55.
55. Van Naarden Braun, K., Pettygrove, S., Daniels, J., Miller, L., Nicholas, J., Baio, J., Schieve, L., Kirby, R.S., Washington, A., Brocksen, S. *et al.* (2007) Evaluation of a methodology for a collaborative multiple source surveillance network for autism spectrum disorders—Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2002. *MMWR Surveill. Summ.*, **56**, 29–40.
56. (2007) Prevalence of autism spectrum disorders—autism and developmental disabilities monitoring network, 14 sites, United States, 2002. *MMWR Surveill. Summ.*, **56**, 12–28.
57. Persico, A.M. and Bourgeron, T. (2006) Searching for ways out of the autism maze: genetic, epigenetic and environmental clues. *Trends Neurosci.*, **29**, 349–358.
58. Bauman, M.L. and Kemper, T.L. (2005) Neuroanatomic observations of the brain in autism: a review and future directions. *Int. J. Dev. Neurosci.*, **23**, 183–187.
59. Feldmeyer, D. and Sakmann, B. (2000) Synaptic efficacy and reliability of excitatory connections between the principal neurones of the input (layer 4) and output layer (layer 5) of the neocortex. *J. Physiol.*, **525**, 31–39.
60. Polleux, F. and Lauder, J.M. (2004) Toward a developmental neurobiology of autism. *Ment. Retard. Dev. Disabil. Res. Rev.*, **10**, 303–317.
61. Berkovic, S.F., Mulley, J.C., Scheffer, I.E. and Petrou, S. (2006) Human epilepsies: interaction of genetic and acquired factors. *Trends Neurosci.*, **29**, 391–397.
62. Hauser, W.A., Annegers, J.F. and Kurland, L.T. (1993) Incidence of epilepsy and unprovoked seizures in Rochester, Minnesota: 1935–1984. *Epilepsia*, **34**, 453–468.
63. Annegers, J.F., Rocca, W.A. and Hauser, W.A. (1996) Causes of epilepsy: contributions of the Rochester epidemiology project. *Mayo. Clin. Proc.*, **71**, 570–575.
64. Jallon, P., Loiseau, P. and Loiseau, J. (2001) Newly diagnosed unprovoked epileptic seizures: presentation at diagnosis in CAROLE study. Coordination Active du Réseau Observatoire Longitudinal de l'Épilepsie. *Epilepsia*, **42**, 464–475.
65. Leritz, E.C., Grande, L.J. and Bauer, R.M. (2006) Temporal lobe epilepsy as a model to understand human memory: the distinction between explicit and implicit memory. *Epilepsy Behav.*, **9**, 1–13.
66. Blume, W.T. (2006) The progression of epilepsy. *Epilepsia*, **47** (Suppl. 1), 71–78.
67. Magloczky, Z. and Freund, T.F. (2005) Impaired and repaired inhibitory circuits in the epileptic human hippocampus. *Trends Neurosci.*, **28**, 334–340.
68. Lerche, H., Weber, Y.G., Jurkat-Rott, K. and Lehmann-Horn, F. (2005) Ion channel defects in idiopathic epilepsies. *Curr. Pharm. Des.*, **11**, 2737–2752.
69. Lewis, D.A. and Hashimoto, T. (2007) Deciphering the disease process of schizophrenia: the contribution of cortical GABA neurons. *Int. Rev. Neurobiol.*, **78**, 109–131.
70. Iversen, S.D. and Iversen, L.L. (2007) Dopamine: 50 years in perspective. *Trends Neurosci.*, **30**, 188–193.
71. Carlsson, A. and Lindqvist, M. (1963) Effect of chlorpromazine or haloperidol on formation of 3-methoxytyramine and normetanephrine in mouse brain. *Acta Pharmacol. Toxicol. (Copenh)*, **20**, 140–144.
72. Matthyse, S. (1973) Antipsychotic drug actions: a clue to the neuropathology of schizophrenia? *Fed. Proc.*, **32**, 200–205.
73. Snyder, S.H., Banerjee, S.P., Yamamura, H.I. and Greenberg, D. (1974) Drugs, neurotransmitters, and schizophrenia. *Science*, **21**, 1243–1253.
74. Jensen, J., Willeit, M., Zipursky, R.B., Savina, I., Smith, A.J., Menon, M., Crawley, A.P. and Kapur, S. (2007) The formation of abnormal associations in schizophrenia: neural and behavioral evidence. *Neuropsychopharmacology*.
75. King, R., Barchas, J.D. and Huberman, B.A. (1984) Chaotic behavior in dopamine neurodynamics. *Proc. Natl. Acad. Sci. USA*, **81**, 1244–1247.
76. Shaner, A. (1999) Delusions, superstitious conditioning and chaotic dopamine neurodynamics. *Med. Hypotheses*, **52**, 119–123.
77. O'Doherty, J.P., Dayan, P., Friston, K., Critchley, H. and Dolan, R.J. (2003) Temporal difference models and reward-related learning in the human brain. *Neuron*, **38**, 329–337.
78. O'Doherty, J., Dayan, P., Schultz, J., Deichmann, R., Friston, K. and Dolan, R.J. (2004) Dissociable roles of ventral and dorsal striatum in instrumental conditioning. *Science*, **304**, 452–454.
79. Laruelle, M., Kegeles, L.S. and Abi-Dargham, A. (2003) Glutamate, dopamine, and schizophrenia: from pathophysiology to treatment. *Ann. N.Y. Acad. Sci.*, **1003**, 138–158.
80. Harrison, P.J. and Weinberger, D.R. (2005) Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol. Psychiatry*, **10**, 40–68.
81. Geurts, M., Hermans, E. and Maloteaux, J.M. (2002) Opposite modulation of regulators of G protein signalling-2 RGS2 and RGS4 expression by dopamine receptors in the rat striatum. *Neurosci Lett*, **333**, 146–150.
82. Schwendt, M., Gold, S.J. and McGinty, J.F. (2006) Acute amphetamine modulation-regulates RGS4 mRNA and protein expression in rat forebrain: distinct roles of D1 and D2 dopamine receptors. *J. Neurochem.*, **96**, 1606–1615.
83. Taymans, J.M., Leysen, J.E. and Langlois, X. (2003) Striatal gene expression of RGS2 and RGS4 is specifically mediated by dopamine D1 and D2 receptors: clues for RGS2 and RGS4 functions. *J. Neurochem.*, **84**, 1118–1127.

84. Erdelyi, H.A., Lahti, R.A., Lopez, M.B., Myers, C.S., Roberts, R.C., Tamminga, C.A. and Vogel, M.W. (2004) Regional expression of RGS4 mRNA in human brain. *Eur. J. Neurosci.*, **19**, 3125–3128.
85. Erdelyi, H.A., Tamminga, C.A., Roberts, R.C. and Vogel, M.W. (2006) Regional alterations in RGS4 protein in schizophrenia. *Synapse*, **59**, 472–479.
86. Greengard, P. (2001) The neurobiology of slow synaptic transmission. *Science*, **294**, 1024–1030.
87. Zachariou, V., Sgambato-Faure, V., Sasaki, T., Svenningsson, P., Berton, O., Fienberg, A.A., Nairn, A.C., Greengard, P. and Nestler, E.J. (2006) Phosphorylation of DARPP-32 at Threonine-34 is required for cocaine action. *Neuropsychopharmacology*, **31**, 555–562.
88. Yan, L., Bobula, J.M., Svenningsson, P., Greengard, P. and Silver, R. (2006) DARPP-32 involvement in the photic pathway of the circadian system. *J. Neurosci.*, **26**, 9434–9438.
89. Batel, P. (2000) Addiction and schizophrenia. *Eur. Psychiatry*, **15**, 115–122.
90. Gerfen, C.R. (1992) The neostriatal mosaic: multiple levels of compartmental organization. *Trends Neurosci.*, **15**, 133–139.
91. Hurd, Y.L. and Herkenham, M. (1995) The human neostriatum shows compartmentalization of neuropeptide gene expression in dorsal and ventral regions: an *in situ* hybridization histochemical analysis. *Neuroscience*, **64**, 571–586.
92. Toledo-Rodriguez, M., Goodman, P., Illic, M., Wu, C. and Markram, H. (2005) Neuropeptide and calcium-binding protein gene expression profiles predict neuronal anatomical type in the juvenile rat. *J. Physiol.*, **567**, 401–413.
93. Nicot, A., Otto, T., Brabet, P. and Dicicco-Bloom, E.M. (2004) Altered social behavior in pituitary adenylate cyclase-activating polypeptide type I receptor-deficient mice. *J. Neurosci.*, **24**, 8786–8795.
94. Wassink, T.H., Piven, J., Vieland, V.J., Jenkins, L., Frantz, R., Bartlett, C.W., Goedken, R., Childress, D., Spence, M.A., Smith, M. *et al.* (2005) Evaluation of the chromosome 2q37.3 gene CENTG2 as an autism susceptibility gene. *Am. J. Med. Genet. B Neuropsychiatr. Genet.*, **136**, 36–44.
95. Lijam, N., Paylor, R., McDonald, M.P., Crawley, J.N., Deng, C.X., Herrup, K., Stevens, K.E., Maccaferri, G., McBain, C.J., Sussman, D.J. *et al.* (1997) Social interaction and sensorimotor gating abnormalities in mice lacking DVL1. *Cell*, **90**, 895–905.
96. Ma, D.Q., Whitehead, P.L., Menold, M.M., Martin, E.R., Ashley-Koch, A.E., Mei, H., Ritchie, M.D., DeLong, G.R., Abramson, R.K., Wright, H.H. *et al.* (2005) Identification of significant association and gene-gene interaction of GABA receptor subunit genes in autism. *Am. J. Hum. Genet.*, **77**, 377–388.
97. McCauley, J.L., Olson, L.M., Delahanty, R., Amin, T., Nurmi, E.L., Organ, E.L., Jacobs, M.M., Folstein, S.E., Haines, J.L. and Sutcliffe, J.S. (2004) A linkage disequilibrium map of the 1-Mb 15q12 GABA(A) receptor subunit cluster and association to autism. *Am. J. Med. Genet. B Neuropsychiatr. Genet.*, **131**, 51–59.
98. Vincent, J.B., Horike, S.I., Choufani, S., Paterson, A.D., Roberts, W., Szatmari, P., Weksberg, R., Fernandez, B. and Scherer, S.W. (2006) An inversion inv(4)(p12-p15.3) in autistic siblings implicates the 4p GABA receptor gene cluster. *J. Med. Genet.*, **43**, 429–434.
99. Hogart, A., Nagarajan, R.P., Patzel, K.A., Yasui, D.H. and Lasalle, J.M. (2007) 15q11-13 GABA A receptor genes are normally biallelically expressed in brain yet are subject to epigenetic dysregulation in autism-spectrum disorders. *Hum. Mol. Genet.*, **16**, 691–703.
100. Junaid, M.A., Kowal, D., Barua, M., Pullarkat, P.S., Sklower Brooks, S. and Pullarkat, R.K. (2004) Proteomic studies identified a single nucleotide polymorphism in glyoxalase I as autism susceptibility factor. *Am. J. Med. Genet. A*, **131**, 11–17.
101. Sakurai, T., Ramoz, N., Reichert, J.G., Corwin, T.E., Kryzak, L., Smith, C.J., Silverman, J.M., Hollander, E. and Buxbaum, J.D. (2006) Association analysis of the NrCAM gene in autism and in subsets of families with severe obsessive-compulsive or self-stimulatory behaviors. *Psychiatr. Genet.*, **16**, 251–257.
102. Feng, J., Schroer, R., Yan, J., Song, W., Yang, C., Bockholt, A., Cook, E.H., Jr., Skinner, C., Schwartz, C.E. and Sommer, S.S. (2006) High frequency of neurexin Ibeta signal peptide structural variants in patients with autism. *Neurosci. Lett.*, **409**, 10–13.
103. Persico, A.M., D'Agruma, L., Maiorano, N., Totaro, A., Militerni, R., Bravaccio, C., Wassink, T.H., Schneider, C., Melmed, R., Trillo, S. *et al.* (2001) Reelin gene alleles and haplotypes as a factor predisposing to autistic disorder. *Mol. Psychiatry*, **6**, 150–159.
104. Fatemi, S.H., Snow, A.V., Stry, J.M., Araghi-Niknam, M., Reutiman, T.J., Lee, S., Brooks, A.I. and Pearce, D.A. (2005) Reelin signaling is impaired in autism. *Biol. Psychiatry*, **57**, 777–787.
105. Arion, D., Sabatini, M., Unger, T., Pastor, J., Alonso-Nanclares, L., Ballesteros-Yanez, I., Garcia Sola, R., Munoz, A., Mirnics, K. and DeFelipe, J. (2006) Correlation of transcriptome profile with electrical activity in temporal lobe epilepsy. *Neurobiol. Dis.*, **22**, 374–387.
106. Chen, Y., Lu, J., Pan, H., Zhang, Y., Wu, H., Xu, K., Liu, X., Jiang, Y., Bao, X., Yao, Z. *et al.* (2003) Association between genetic variation of CACNA1H and childhood absence epilepsy. *Ann. Neurol.*, **54**, 239–243.
107. Khosravani, H., Altier, C., Simms, B., Hamming, K.S., Snutch, T.P., Mezeyova, J., McRory, J.E. and Zamponi, G.W. (2004) Gating effects of mutations in the Cav3.2 T-type calcium channel associated with childhood absence epilepsy. *J. Biol. Chem.*, **279**, 9681–9684.
108. Aridon, P., Marini, C., Di Resta, C., Brilli, E., De Fusco, M., Politi, F., Parrini, E., Manfredi, I., Pisano, T., Pruna, D. *et al.* (2006) Increased sensitivity of the neuronal nicotinic receptor alpha 2 subunit causes familial epilepsy with nocturnal wandering and ictal fear. *Am. J. Hum. Genet.*, **79**, 342–350.
109. De Fusco, M., Becchetti, A., Patrignani, A., Annesi, G., Gambardella, A., Quattrone, A., Ballabio, A., Wanke, E. and Casari, G. (2000) The nicotinic receptor beta 2 subunit is mutant in nocturnal frontal lobe epilepsy. *Nat. Genet.*, **26**, 275–276.
110. Phillips, H.A., Favre, I., Kirkpatrick, M., Zuberi, S.M., Goudie, D., Heron, S.E., Scheffer, I.E., Sutherland, G.R., Berkovic, S.F., Bertrand, D. *et al.* (2001) CHRNB2 is the second acetylcholine receptor subunit associated with autosomal dominant nocturnal frontal lobe epilepsy. *Am. J. Hum. Genet.*, **68**, 225–231.
111. Haug, K., Warnstedt, M., Alekov, A.K., Sander, T., Ramirez, A., Poser, B., Maljevic, S., Hebeisen, S., Kubisch, C., Rebstock, J. *et al.* (2003) Mutations in CLCN2 encoding a voltage-gated chloride channel are associated with idiopathic generalized epilepsies. *Nat. Genet.*, **33**, 527–532.
112. Princivalle, A.P., Richards, D.A., Duncan, J.S., Spreafico, R. and Bowery, N.G. (2003) Modification of GABA(B1) and GABA(B2) receptor subunits in the somatosensory cerebral cortex and thalamus of rats with absence seizures (GAERS). *Epilepsy Res.*, **55**, 39–51.
113. Princivalle, A.P., Duncan, J.S., Thom, M. and Bowery, N.G. (2003) GABA(B1a), GABA(B1b) AND GABA(B2) mRNA variants expression in hippocampus resected from patients with temporal lobe epilepsy. *Neuroscience*, **122**, 975–984.
114. Cossette, P., Liu, L., Brisebois, K., Dong, H., Lortie, A., Vanasse, M., Saint-Hilaire, J.M., Carmant, L., Verner, A., Lu, W.Y. *et al.* (2002) Mutation of GABRA1 in an autosomal dominant form of juvenile myoclonic epilepsy. *Nat. Genet.*, **31**, 184–189.
115. Kang, J.Q. and Macdonald, R.L. (2004) The GABAA receptor gamma2 subunit R43Q mutation linked to childhood absence epilepsy and febrile seizures causes retention of alpha1beta2gamma2S receptors in the endoplasmic reticulum. *J. Neurosci.*, **24**, 8672–8677.
116. DeLorey, T.M., Handforth, A., Anagnostaras, S.G., Homanics, G.E., Minassian, B.A., Asatourian, A., Fanselow, M.S., Delgado-Escueta, A., Ellison, G.D. and Olsen, R.W. (1998) Mice lacking the beta3 subunit of the GABAA receptor have the epilepsy phenotype and many of the behavioral characteristics of Angelman syndrome. *J. Neurosci.*, **18**, 8505–8514.
117. Wagstaff, J., Knoll, J.H., Fleming, J., Kirkness, E.F., Martin-Gallardo, A., Greenberg, F., Graham, J.M., Jr., Menninger, J., Ward, D., Venter, J.C. *et al.* (1991) Localization of the gene encoding the GABAA receptor beta 3 subunit to the Angelman/Prader-Willi region of human chromosome 15. *Am. J. Hum. Genet.*, **49**, 330–337.
118. Baulac, S., Huberfeld, G., Gourfinkel-An, I., Mitropoulou, G., Beranger, A., Prud'homme, J.F., Baulac, M., Brice, A., Bruzzone, R. and LeGuern, E. (2001) First genetic evidence of GABA(A) receptor dysfunction in epilepsy: a mutation in the gamma2-subunit gene. *Nat. Genet.*, **28**, 46–48.
119. Sander, T., Hildmann, T., Kretz, R., Furst, R., Sailer, U., Bauer, G., Schmitz, B., Beck-Mannagetta, G., Wienker, T.F. and Janz, D. (1997) Allelic association of juvenile absence epilepsy with a GluR5 kainate receptor gene (GRIK1) polymorphism. *Am. J. Med. Genet.*, **74**, 416–421.

120. Murashima, Y.L., Yoshii, M. and Suzuki, J. (2000) Role of nitric oxide in the epileptogenesis of EL mice. *Epilepsia*, **41** (Suppl. 6), S195–S199.
121. Dun, N.J., Dun, S.L., Wong, R.K. and Forstermann, U. (1994) Colocalization of nitric oxide synthase and somatostatin immunoreactivity in rat dentate hilar neurons. *Proc. Natl. Acad. Sci. USA*, **91**, 2955–2959.
122. Kanamatsu, T. and Hirano, S. (1988) Differences in ME-LI and VIP-LI in discrete brain regions of seizure-naïve and seizure-experienced El mice. *Neurochem Res*, **13**, 983–988.
123. de Lanerolle, N.C., Gunel, M., Sundaresan, S., Shen, M.Y., Brines, M.L. and Spencer, D.D. (1995) Vasoactive intestinal polypeptide and its receptor changes in human temporal lobe epilepsy. *Brain Res.*, **686**, 182–193.
124. Takahashi, M., Shirakawa, O., Toyooka, K., Kitamura, N., Hashimoto, T., Maeda, K., Koizumi, S., Wakabayashi, K., Takahashi, H., Someya, T. *et al.* (2000) Abnormal expression of brain-derived neurotrophic factor and its receptor in the corticolimbic system of schizophrenic patients. *Mol. Psychiatry*, **5**, 293–300.
125. Waterworth, D.M., Bassett, A.S. and Brzustowicz, L.M. (2002) Recent advances in the genetics of schizophrenia. *Cell Mol. Life Sci.*, **59**, 331–348.
126. Shifman, S., Bronstein, M., Sternfeld, M., Pisante-Shalom, A., Lev-Lehman, E., Weizman, A., Reznik, I., Spivak, B., Grisaru, N., Karp, L. *et al.* (2002) A highly significant association between a COMT haplotype and schizophrenia. *Am. J. Hum. Genet.*, **71**, 1296–1302.
127. Straub, R.E., Jiang, Y., MacLean, C.J., Ma, Y., Webb, B.T., Myakishev, M.V., Harris-Kerr, C., Wormley, B., Sadek, H., Kadambi, B. *et al.* (2002) Genetic variation in the 6p22.3 gene DTNBP1, the human ortholog of the mouse dysbindin gene, is associated with schizophrenia. *Am. J. Hum. Genet.*, **71**, 337–348.
128. Silberg, G., Darvasi, A., Pinkas-Kramarski, R. and Navon, R. (2006) The involvement of ErbB4 with schizophrenia: association and expression studies. *Am. J. Med. Genet. B Neuropsychiatr. Genet.*, **141**, 142–148.
129. Stefansson, H., Sigurdsson, E., Steinthorsdottir, V., Bjornsdottir, S., Sigmundsson, T., Ghosh, S., Brynjolfsson, J., Gunnarsdottir, S., Ivarsson, O., Chou, T.T. *et al.* (2002) Neuregulin 1 and susceptibility to schizophrenia. *Am. J. Hum. Genet.*, **71**, 877–892.
130. Schramm, M., Falkai, P., Feldmann, N., Knable, M.B. and Bayer, T.A. (1998) Reduced tyrosine kinase receptor C mRNA levels in the frontal cortex of patients with schizophrenia. *Neurosci. Lett.*, **257**, 65–68.
131. Weickert, C.S., Ligons, D.L., Romanczyk, T., Ungaro, G., Hyde, T.M., Herman, M.M., Weinberger, D.R. and Kleinman, J.E. (2005) Reductions in neurotrophin receptor mRNAs in the prefrontal cortex of patients with schizophrenia. *Mol. Psychiatry*, **10**, 637–650.
132. Lipska, B.K., Peters, T., Hyde, T.M., Halim, N., Horowitz, C., Mitkus, S., Weickert, C.S., Matsumoto, M., Sawa, A., Straub, R.E. *et al.* (2006) Expression of DISC1 binding partners is reduced in schizophrenia and associated with DISC1 SNPs. *Hum. Mol. Genet.*, **15**, 1245–1258.
133. Ventriglia, M., Bocchio Chiavetto, L., Bonvicini, C., Tura, G.B., Bignotti, S., Racagni, G. and Gennarelli, M. (2002) Allelic variation in the human prodynorphin gene promoter and schizophrenia. *Neuropsychobiology*, **46**, 17–21.
134. Zhang, C.S., Tan, Z., Lu, L., Wu, S.N., He, Y., Gu, N.F., Feng, G.Y. and He, L. (2004) Polymorphism of prodynorphin promoter is associated with schizophrenia in Chinese population. *Acta Pharmacol. Sin.*, **25**, 1022–1026.
135. Meyer-Lindenberg, A., Straub, R.E., Lipska, B.K., Verchinski, B.A., Goldberg, T., Callicott, J.H., Egan, M.F., Huffaker, S.S., Mattay, V.S., Kolachana, B. *et al.* (2007) Genetic evidence implicating DARPP-32 in human frontostriatal structure, function, and cognition. *J. Clin. Invest.*, **117**, 672–682.
136. Gogos, J.A., Santha, M., Takacs, Z., Beck, K.D., Luine, V., Lucas, L.R., Nadler, J.V. and Karayiorgou, M. (1999) The gene encoding proline dehydrogenase modulates sensorimotor gating in mice. *Nat. Genet.*, **21**, 434–439.
137. Hashimoto, T., Volk, D.W., Eggan, S.M., Mirnics, K., Pierri, J.N., Sun, Z., Sampson, A.R. and Lewis, D.A. (2003) Gene expression deficits in a subclass of GABA neurons in the prefrontal cortex of subjects with schizophrenia. *J. Neurosci.*, **23**, 6315–6326.
138. Mirnics, K., Middleton, F.A., Stanwood, G.D., Lewis, D.A. and Levitt, P. (2001) Disease-specific changes in regulator of G-protein signaling 4 (RGS4) expression in schizophrenia. *Mol. Psychiatry*, **6**, 293–301.
139. Guidotti, A., Auta, J., Davis, J.M., Di-Giorgi-Gerevini, V., Dwivedi, Y., Grayson, D.R., Impagnatiello, F., Pandey, G., Pesold, C., Sharma, R. *et al.* (2000) Decrease in reelin and glutamic acid decarboxylase67 (GAD67) expression in schizophrenia and bipolar disorder: a postmortem brain study. *Arch. Gen. Psychiatry*, **57**, 1061–1069.
140. Impagnatiello, F., Guidotti, A.R., Pesold, C., Dwivedi, Y., Caruncho, H., Pisu, M.G., Uzunov, D.P., Smalheiser, N.R., Davis, J.M., Pandey, G.N. *et al.* (1998) A decrease of reelin expression as a putative vulnerability factor in schizophrenia. *Proc. Natl. Acad. Sci. USA*, **95**, 15718–15723.