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Review

The first decade and beyond of transcriptional profiling in schizophrenia

P. Adolfo Sequeira, Maureen V. Martin, Marquis P. Vawter *

Functional Genomics Laboratory, Department of Psychiatry and Human Behavior, School of Medicine, University of California, Irvine, Irvine CA 92697-4260, USA

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ABSTRACT

Gene expression changes in brains of individuals with schizophrenia (SZ) have been hypothesized to reflect possible pathways related to pathophysiology and/or medication. Other factors having robust effects on gene expression profiling in brain and possibly influence the schizophrenia transcriptome such as age and pH are examined. Pathways of curated gene expression or gene correlation networks reported in SZ (white matter, apoptosis, neurogenesis, synaptic plasticity, glutamatergic and GABAergic neurotransmission, immune and stress-response, mitochondrial, and neurodevelopment) are not unique to SZ and have been associated with other psychiatric disorders. Suggestions going forward to improve the next decade of profiling: consider multiple brain regions that are carefully dissected, release large datasets from multiple brain regions in controls to better understand neurocircuitry, integrate genetics and gene expression, measure expression variants on genome wide level, peripheral biomarker studies, and analyze the transcriptome across a developmental series of brains. Gene expression, while an important feature of the genomic landscape, requires further systems biology to advance from control brains to a more precise definition of the schizophrenia interactome.

Contents

Introduction

A better understanding of the implication of genetic variation in complex neuropsychiatric disorders from the numerous GWAS findings

* Corresponding author.
E-mail address: mvawter@uci.edu (M.P. Vawter).
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recently published requires translation into functional effects, a possibility that postmortem brain gene studies offer. As an example, the recent genetic association for a handful of candidate genes in schizophrenia (SZ) of DISC1, NRG1, GRM3, AKT, RGS4, ERBB4, GAD1, ZNF804A, and genes in the MHC loci, suggests that association of these candidate genes might be partially accounted for by gene expression changes in postmortem brain. Instead of relying on genetic information alone and dichotomous diagnosis, gene expression which can vary in quantity and structure, can constitute a useful endophenotype to understand translated RNA and non-translated RNA regulatory functions. Gene expression is a RNA expression quantitative trait phenotype that is intermediate between DNA and protein. This review of gene expression studies identifies genes in networks or biological pathways involved in schizophrenia. Besides genetic variation there are also interacting factors that account for much larger share of the variance in gene expression across the transcriptome than diagnosis, such as tissue pH and aging (Choi et al., 2009; Colantuoni et al., 2008; Mistry and Pavlidis, 2010; Torkamani et al., 2010).

One of the authors (MPV) previously compiled postmortem microarray data from 2000 to 2008 literature (Altar et al., 2009), the purpose of this review is to update that last review to comprehensively cover the first decade of work beginning with the initial SZ transcriptional profiling paper (Mirnics et al., 2000) and include peripheral blood-based discovery studies that have the advantage to provide biological material from living clinical populations for the study of biomarkers. Although the field of biomarker discovery in SZ is in a nascent stage, a significant overlap between blood and brain gene expression has been described confirming the utility of biomarkers for the study of brain maladies (Rollins et al., 2010). We recently examined the relationship between postmortem brain gene expression and whole blood gene expression by exon array in human subjects and reported that 23% of transcripts were co-expressed at similar levels in blood and brain from the same subjects (Rollins et al., 2010).

Studies of gene expression in bipolar disorder (BD) will not be extensively described, for review (Altar et al., 2009). Individuals with BD are often treated with similar drug regimens as SZ, and do provide a useful comparison for diagnostic specificity of gene expression findings but for space limitations will not be considered in this review.

Technical factors contributing to brain gene expression variability in schizophrenia between studies

Many factors can have a significant effect on brain gene expression levels and mask the biological signatures of complex disorders. In the following sections, we will discuss the influence of factors such as the type of array platform utilized, age, pH, gender, suicide status, and mRNA quality on gene expression findings (Table 1). Our review of technical factors in postmortem gene expression could not address all the important issues affecting RNA, such as postmortem interval, RNA quality, and subject characteristics such as ethnicity. Instead, there are interesting articles that focus on these specific factors (Barton et al., 1993; Burke et al., 1991; Harrison et al., 1995; Johnson et al., 1986; Kobayashi et al., 1990; Leonard et al., 1993; Li et al., 2004a; Perrett et al., 1988; Perry et al., 1982; Preece and Cairns, 2003; Spielman et al., 2007; Tomita et al., 2004; Wester et al., 1985). We have chosen two major issues to be considered in detail in this review of gene expression, the brain tissue pH which is believed to be a tissue quality indicator, and also dependent upon agonal factors, and age.

Tissue source

The source of the samples utilized in microarray studies constitutes one source of variability between studies since the different brain banks have different sample collections in terms of age, pH, hemisphere dissected, and dissection method (Table 1). The most widely used brain bank in microarray studies of SZ is the Stanley Medical Research Institute (SMRI) brain bank (Torrey et al., 2000). Two of the SMRI collections, microarray brain collection and neuropathology consortium have been used in at least 11 major microarray papers on SZ (Altar et al., 2005; Aston et al., 2004; Choi et al., 2008; Chu et al., 2009; Iwamoto et al., 2005; Kim and Webster, 2010a; Middleton et al., 2005b; Prabakaran et al., 2004; Shao and Vawter, 2008; Tkachev et al., 2003b; Vawter et al., 2001). The Stanley brain collection contains relatively young subjects with schizophrenia and gender and age matched controls (average age is around 45). This brain bank has several sample sets with low average pH (SZ = 6.1; controls = 6.3), and a few individual brains that have pH as low as 5.8 and a wide range of post mortem interval (PMI), up to 61 h (http://sncid.stanleyresearch.org/Demographics.aspx).

The University of Pittsburgh brain bank also has a sample of young individuals with SZ and matched controls (average age is about 45), with low PMI and high pH (higher than 6.5), sampled from one hemisphere (right), mainly ascertained from the coroner's office as opposed to a hospital or hospice based ascertainment, all factors that should help reduce the noise due to RNA degradation and sample to sample variability (Mirnics et al., 2001).

The Mount Sinai brain bank sample was used in several microarray studies (Hakak et al., 2001; Haroutunian et al., 2006, 2007; Katsel et al., 2005a, 2005b; Kerns et al., 2010). This is a large sample of chronic and elderly in-patients with schizophrenia hospitalized for more than 35 years (average age >70), and with short post-mortem interval (PMI). As an example, the largest brain gene expression study in SZ profiling by this group used a total of 15 brain regions in this sample, the average age is 80.7 ± 3.0 for the controls and 74.7 ± 2.3 for the subjects with SZ (Katsel et al., 2005a). This cohort was consistently sampled from left hemisphere and gray matter was preferably sampled in these studies.

Although matching samples within a study helps to reduce variability introduced by demographic variables, such as age and gender (Erraji-Benchekroun et al., 2005; Galfalvy et al., 2003; Vawter et al., 2004a) it is apparent that there are large differences between the ages of subjects with SZ studied from different brain banks. The factor of age in SZ gene expression will be described later in this review.

Tissue heterogeneity (multiple cell types, various regions, dissection techniques and LCM)

Tissue heterogeneity from each brain bank can also play a central role in gene expression results, some studies were conducted using blocks of brain tissue containing variable amounts of gray and white matter, while others dissected specifically gray matter from cortical ribbons (Table 1). More homogeneous tissue sample preparations were collected in studies using laser capture microdissection (LCM) of specific brain regions such as the dentate gyrus (Altar et al., 2005a); cortical layers of the prefrontal cortex (Arion et al., 2010) and hippocampal subregions (Benes et al., 2007). LCM has also been used to specifically microdissect neurons in thalamic subregions (Chu et al., 2009), or from layers of the entorhinal cortex (Hemby et al., 2002) and both neurons and endothelial cells for cell-specific comparisons of gene expression in schizophrenia (Harris et al., 2008).

Microarray platform and labeling techniques

The development of microarrays allowed for whole genome exploration of gene expression alterations (Lockhart et al., 1996; Schena et al., 1995) of complex disorders such as schizophrenia that are not limited to candidate target genes. Early microarray studies in prefrontal cortex areas of subjects with schizophrenia revealed several differentially expressed genes such as a robust decreases in genes for GABA function including glutamic acid decarboxylase, HINT1, glutamate transport and receptors, 14-3-3 family members, and decreases in genes for CNS synaptic and metabolic functions as reviewed by Altar et al. (2009).

Table 1
Microarray profiling of gene expression in schizophrenia in the past decade by brain bank, brain region, type of array, and sample characteristics.

Study	Brain regions	Dissection	Ctrl	SZ	Hemisphere	Array	Sample	Confirm	Reference
1	BA9	Block	11	11	Right	cDNA (UniGEM V)	UPCNMDBB	ISH	(Mirnics et al., 2000)
2	BA46	Gray	12	12	Left	HuGeneFL (Affy)	MSBB		(Hakak et al., 2001)
3	BA9	Block	11	11	Right	cDNA (UniGEM V)	UPCNMDBB	ISH	(Mirnics et al., 2001)
4	CB, BA9,BA21	Block	8	8	NS	cDNA (NIA-Neuroarray, pool)	SMRI		(Vawter et al., 2001)
5	EC	SCGE	9	8	NS	cDNA (custom)	MHCRCS	IHC	(Hemby et al., 2002)
6	BA9, BA10	Block	10	10	Right	cDNA (UniGEM V or V2)	UPCNMDBB	IHC	(Middleton et al., 2002)
7	PFC	Block	10	10	NS	cDNA (custom)	Japan/New Zealand	qPCR, ISH	(Mimmack et al., 2002)
8	DLPFC	Block	15	15	NS	cDNA (NIA-Neuroarray, pool)	NIMH		(Vawter et al., 2002)
9	BA9	Block	15	15	Alternate	U133A	SMRI	qPCR	(Tkachev et al., 2003b)
10	BA21	Block	14	12	NS	U95A	SMRI	qPCR	(Aston et al., 2004)
11	BA9	Block	50	54	Alternate	U133A	SMRI	LC-MS/MS	(Prabakaran et al., 2004)
12	BA47	Block?	6	6	Right	cDNA (Clontech)	BRINU		(Sugai et al., 2004)
13	Dentate gyrus	LCM	24	22	Alternate	cDNA (Agilent)	SMRI	qPCR	(Altar et al., 2005)
14	BA46	Block	35	35	Alternate	U133A	SMRI	qPCR	(Iwamoto et al., 2005)
15	15 regions	Gray	13	13	Left	U133AB	MSBB		(Katsel et al., 2005a, 2005b)
16	Hippocampus	Gray	12	12	Random	U95Av2	SRCBB	qPCR, WB	(Mexal et al., 2005)
17	BA9	Block	10	10	Right	cDNA (UniGEM V or V2)	SMRI	PCR, IHC	(Middleton et al., 2005a)
18	15 regions	Block	18	21	Left	U133AB	MSBB	qPCR	(Haroutunian et al., 2006)
19	BA9	Block	14	14	Right	Nimblegen (custom)	UPCNMDBB	qPCR	(Arion et al., 2007)
20	Hippocampus	LCM	7	7	Alternate	U133A	HBB	qPCR	(Benes et al., 2007)
21	15 regions	Gray	13	13	Left	U133AB	MSBB		(Haroutunian et al., 2007)
22	BA8,9, SFG	Block	55	55	Alternate	cDNA (pool)	MBB, HBB, SMRI	qPCR	(Saetre et al., 2007)
23	PFC, BA46	Block	82[a]	81[a]	Alternate	U133(Plus2.0 and A), U95Av2	SMRI		(Choi et al., 2008)
24	BA9	LCM	12	12	Alternate	U133Plus2.0 and Codelink	SMRI		(Harris et al., 2008)
25	BA9	Block	14	14	Right	Nimblegen (custom)	UPCNMDBB	qPCR	(Hashimoto et al., 2008)
26	ACC	Gray	19	16	Left	U133AB	MSBB	qPCR, WB	(Katsel et al., 2008)
27	BA46	Block	30	30	Left	U133Plus2.0	VBBN	qPCR	(Narayan et al., 2008)
28	BA46	Block	35	35	Alternate	Codelink	SMRI	qPCR	(Shao and Vawter, 2008)
29	Thalamus	LCM	15	15	Alternate	U133Plus2.0	SMRI	qPCR	(Chu et al., 2009)
30	BA10	Block	23	28	NS	U133(Plus2.0 and A)	CCH and HBB	qPCR	(Maycox et al., 2009)
31	BA46	Block	30	30	Left	GLYCOv2	VBBN	qPCR	(Narayan et al., 2009)
32	BA46	LCM	8	8	Right	U133plus2.0	CCNMDBB		(Arion et al., 2010)
33	PFC	Block	15	14	Alternate	U133A	SMRI		(Kim and Webster, 2010a, 2010b)
34	BA46, BA9	Block	54	47	NS	U133Plus2.0 and U95A	VBBN and HBB		(Torkamani et al., 2010)

CCNMDBB	Conte Center for the Neuroscience of Mental Disorders Brain Bank
MBB	Maudsley Brain Bank
CCH	Charing Cross Hospital
UPCNMDBB	University of Pittsburgh's Center for the Neuroscience of Mental Disorders Brain Bank
SMRI	Stanley Medical Research Institute
VBBN	Victorian Brain Bank Network
HBB	Harvard Brain Bank
NZNFHBB	New Zealand Neurological Foundation Human Brain Bank
TMMH	Tokyo Metropolitan Matsuzawa Hospital
MHCRCS	Mental Health Clinical Research Center on Schizophrenia at the University of Pennsylvania
BRINU	Brain Research Institute, Niigata University
PPC	Pilgrim Psychiatric Center
SRCBB	Schizophrenia Research Center Brain Bank
SCGE	Single-cell gene expression
LCM	Laser capture microdissection
MSBB	Mount Sinai Brain Bank
SFG	Superior frontal gyrus
NS	Not specified
ACC	Anterior cingulate cortex

[a] This study compares non-psychotic vs psychotic subjects.

Platform differences in microarray studies conducted on different custom or commercial cDNA arrays (UniGem, NIA-Neuroarray, Clontech, Agilent) or oligonucleotide arrays (Affymetrix, Nimblegen) could contribute to differences in replicability. Earlier studies were conducted with cDNA arrays mainly and later studies with oligonucleotide arrays (Table 1). Table 1 shows the major microarray studies involving SZ using different microarray platforms and several brain bank samples while highlighting common characteristics and differences.

Array platform comparability might account for low reproducibility of results, shown even when comparing different generations of commercial arrays from the same manufacturer (Nimgaonkar et al., 2003), from different manufacturers (Barnes et al., 2005) and when comparing commercial (UnigeGEM V) and custom (Clontech) arrays containing different families of genes or focused genes as in the case of the NIA-Neuroarray (1128 neuro-related genes) (Vawter et al., 2001, 2002) or the GLYCOv2 Gene Chip (Narayan et al., 2009). Some early microarray studies used a co-hybridization of a disease sample paired with a single control sample on the same array using different dyes, usually Cy3 and Cy5 (Schena et al., 1995). Newer studies have been conducted using focused custom arrays to investigate functional groups of genes such as the GLYCOv2 Gene Chip (Narayan et al., 2009) or the GABA-related transcriptome using a Nimblegen custom array (Hashimoto et al., 2008). Commercial, mainly oligonucleotide based arrays (Affymetrix, Nimblegen, Codelink, Agilent), with more consistent chemistries, more probesets, and better statistical analysis procedures tend to yield higher reproducibility across laboratories (Shi et al., 2006). Additionally, some of these early studies employed case–control pairing without taking into account the confounding effects of gender, age, RNA quality, and pH (Hakak et al., 2001; Middleton et al., 2002; Mimmack et al., 2002;

Mirnics et al., 2000, 2001) and in some cases with pooled RNA (Vawter et al., 2001, 2002).

Other sources of variability (pH and age as examples)

Brain transcript expression profiles are moderately consistent across 11 studies for pH, sex, and age in control brain tissue (Mistry and Pavlidis, 2010). These individual 'drivers' had been previously published by many investigators as covariates, so the meta-analysis result was reassuring when using unaggregated postmortem brain transcript data (Mistry and Pavlidis, 2010). This analysis suggests that mismatch of any of these three drivers in case–control analysis will be detected in the microarray measurements, assuming the rest of the experimental methods are conducted without bias (Mistry and Pavlidis, 2010). The driver that influences the largest number of genes appears to be pH, as confirmed in multiple studies (Elashoff et al., 2007; Li et al., 2004a; Mexal et al., 2006; Mistry and Pavlidis, 2010; Munakata et al., 2005; Vawter et al., 2006a). An example of tissue pH, that does not involve gene expression, was an increase in cerebellar granular cell layer necrosis that was reported in lower pH brains (Weis et al., 2007), suggesting a relationship of cerebellar acidosis and neuronal atrophy. In control subjects with obvious cerebellar granular cell layer necrosis (CGCLN) compared to controls subjects without CGCLN, the average pH was decreased 0.4 (Weis et al., 2007). However, when comparing histopathological abnormalities, CGCLN+ to CGCLN− in schizophrenia groups, the pH was reduced only 0.04 pH units, which was not significant. This interaction of pH with Diagnosis × CGCLN is one example of how difficult it is to control for the association or interaction of pH upon postmortem findings overall using an example that measures a histopathological abnormality. While we cannot conclude that pH is causing this CGCLN difference, we can infer that as a surrogate for tissue quality, the pH in fact does correlate well with obvious histopathological findings in controls, but not in cases with SZ only. An additional comparison in the Weis et al. study that would have been interesting is to divide up the subjects into high and low pH groups, and determine if the number of CGCLN+ and CGCLN− percentage of subjects were different. There was little pH difference between SZ cases with and without cerebellar degeneration; the main point is that the effect was robust in controls but not apparent in SZ for some unknown reason.

Brain pH appears to be lower among BD and SZ groups by 0.08 pH units compared to controls (Weis et al., 2007) using a large number of subjects for SZ (n = 120), controls (n = 116), and BD (n = 113). However, one must be careful in the interpretation of postmortem pH which is an excellent surrogate for tissue quality and agonal factors, and thus a careful interpretation would be made if the subjects were matched on agonal factors. Mitochondrial DNA SNPs can explain low and high pH postmortem brain differences (Rollins et al., 2009). Further, lactate concentration increases during hypoxia and lactate may also increase as a result of drug treatments (Halim et al., 2008), both of which can lower brain pH. Implicit in most of these observations is a linear model; however, instances of non-linear effects of pH, such as bi-stable levels of gene expression have been observed (Vawter, M.P, unpublished data).

Inferring that pH differences in patient and control groups are due to pathophysiology might be erroneous, as direct effects on pH could be due to hypoxia and mitochondrial uncoupling, and anaerobic respiration of the brain at the time of death due to differences in agonal factors (Li et al., 2007, 2004b; Tomita et al., 2004). Complicating this picture further is that agonal-pH measures (Atz et al., 2007) correlate with RNA quality measures leading to expression sample error. A method to study covariate interaction in schizophrenia was recently reported by (Munakata et al., 2005; Vawter et al., 2006a) using postmortem brain from controls, devoid of psychiatric medications (Halim et al., 2008) and other psychiatric related illness complications which might complicate pH. In these analyses, gene expression was measured in postmortem brain in low pH controls and compared to gene expression in a group of high pH controls in order to find pH sensitive genes (Munakata et al., 2005; Vawter et al., 2006a). The gene expression profiles developed across three brain regions showed 350 genes differentially expressed in high pH and low pH subjects (Vawter et al., 2006a) and the full list of genes affected by differences in pH in or more brain regions is available (http://www.vawterlab.com/data.html).

There were 144 genes significantly dysregulated by pH, reported between both studies using DLPFC (Munakata et al., 2005; Vawter et al., 2006a) and concordance in fold change between both studies was high (95.8%, 138/144 genes agreed in direction between low and high pH groups). This highly consistent list of pH sensitive genes from Vawter et al. (2006a) also overlaps significantly (86% of genes) with the results of the meta-analysis concerning pH (Mistry and Pavlidis, 2010).

The emphasis on pH differences that is caused by agonal factors is one interpretation of how differences arise between cases and controls, other interpretation suggests that pH is part of the pathophysiology. The list of genes from Table 2 that were sensitive to pH differences was intersected with a list of SZ dysregulated genes from a study in which cases had no reported agonal factors (Arion et al., 2007). This exercise was done to show that using all subjects that had rapid deaths and obtained from the same source, i.e. not extensively hospitalized prior to death would yield a list of genes that intersected beyond chance with pH sensitive genes. The expression findings were pH independent—i.e. there was no significant correlation between any of the genes and the subject's pH and expression levels (Karoly Mirnics, personal communication) and further the paired data analysis used similarly matched subjects on pH. *This would rule out uncontrolled agonal factors in the Arion study, especially at the lower pH range.* The intersection of pH sensitive genes with SZ differentially expressed genes from the same brain region is shown in Table 3.

There were 175 genes that overlap between 1210 pH sensitive genes (Vawter et al., 2006a) and the 1664 SZ candidate genes studied by Arion et al., 2007 with a custom-designed Nimblegen array Arion (Arion et al., 2007). The expected p-value for 21 genes that overlap when drawing 53 genes is given by the formula $p = \binom{M}{x} * \binom{N-M}{n-x} \div \binom{N}{n}$ where M = total number of marked genes (175), N = total population size (1664), n = number of genes drawn or sample size (53), and x = number of marked genes in sample (21).

$$p = \binom{175}{21} * \binom{1664-175}{53-21} \div \binom{1664}{53} = 1.07^{-08}$$

The result shows a small probability (10^{-8}) associated with the overlap of the SZ and pH significant gene lists and suggests that it is highly unlikely to occur by random drawing of 53 genes, taking into account fold change consistency lowers the probability further of concordant fold change direction.

This statistical finding cannot show a cause and effect relationship. The intersection of a candidate gene list enriched for schizophrenia genes with a second gene list enriched in pH genes can be speculated as due to a) the enriched schizophrenia list overlaps with pH genes as part of the pathophysiology or b) the enriched schizophrenia list mimics changes in pH related pathology due to medication effects or c) the schizophrenia list is composed of genes that have some pH-agonal effects but unrelated to pathophysiology. When the schizophrenia and control subjects are exquisitely matched on agonal factors and pH and other important expression experimental and subject factors are controlled, the pH sensitive genes that overlap the SZ associated gene list might be part of the ante-mortem pathophysiology of schizophrenia. If this is true, then essentially it postulates that even with matching, we can detect a gene signature that apparently manifests as aberrant matching of subjects on pH; however we know that cases are matched

Table 2
Partial list of 350 genes sensitive to agonal pH differences across controls in three brain regions (DLPFC, anterior cingulate cortex, and cerebellum). The list of dysregulated genes represents the results of a 0.4 pH mean difference in controls without psychiatric drug treatment.

Gene symbol	Gene title	Fold change-anterior cingulate	Rank anterior cingulate (T-values)	Fold change-DLPFC	Rank DLPFC (T-values)	Fold change-cerebellum	Rank cerebellum (T-values)
ATP6V1A	ATPase, H+ transporting, lysosomal 70 kDa, V1 subunit A	2.37	7	2	13	1.76	3
CRYM	Crystallin, mu	2.88	9	2.28	23	1.91	10
SLC17A7	Solute carrier family 17 (sodium-dependent inorganic phosphate cotransporter), member 7	2.05	15	1.79	37	1.42	57
ATP2A2	ATPase, Ca++ transporting, cardiac muscle, slow twitch 2	2.07	19	1.76	36	1.48	49
PTTG1IP	Pituitary tumor-transforming 1 interacting protein	0.5	20	0.54	27	0.66	88
TM4SF1	Transmembrane 4 L six family member 1	0.46	25	0.4	3	0.53	6
ATP2B2	ATPase, Ca++ transporting, plasma membrane 2	2.16	26	2.28	10	1.87	12
DCLK1	Doublecortin-like kinase 1	2.59	31	2.11	46	2.27	18
GAD1	Glutamate decarboxylase 1 (brain, 67 kDa)	2.48	32	2.37	11	1.76	71
MCL1	myeloid cell leukemia sequence 1 (BCL2-related)	0.53	36	0.56	47	0.73	170
TAZ	tafazzin	0.47	41	0.54	89	0.51	14
RGS7	regulator of G-protein signaling 7	2.24	46	1.85	43	1.38	466
AQP1	Aquaporin 1 (Colton blood group)	0.41	51	0.66	347	0.53	44
NSF	N-ethylmaleimide-sensitive factor	2.15	53	1.6	127	1.47	93
PMP22	Peripheral myelin protein 22	0.52	54	0.63	180	0.79	639
CDC42	Cell division cycle 42 (GTP binding protein, 25 kDa); cell division cycle 42 pseudogene 2	2.24	56	1.94	73	1.78	40
GLRB	Glycine receptor, beta	2.1	65	1.5	382	1.38	274
PALLD	Palladin, cytoskeletal associated protein	0.53	66	0.52	33	0.73	210
SYN2	Synapsin II	2.46	76	2.49	92	1.66	74
HMGB2	High-mobility group box 2	0.52	87	0.58	143	0.65	207
CLIC4	Chloride intracellular channel 4	0.51	91	0.7	574	0.59	64
MOAP1	Modulator of apoptosis 1	2.27	96	2	42	1.43	358
ZFP36	Zinc finger protein 36, C3H type, homolog (mouse)	0.42	103	0.43	71	0.58	75
VSNL1	Visinin-like 1	2.09	112	1.51	368	1.55	114
NPTN	Neuroplastin	2	114	1.53	145	1.33	381
ZIC1	Zic family member 1 (odd-paired homolog, *Drosophila*)	0.53	119	0.6	174	1.4	378
CNN3	Calponin 3, acidic	0.46	122	0.5	53	0.67	221
GOT1	Glutamic-oxaloacetic transaminase 1, soluble (aspartate aminotransferase 1)	2.13	125	1.74	110	1.83	54
MT1X	Metallothionein 1X	0.5	129	0.47	44	0.52	86
CHGB	Chromogranin B (secretogranin 1)	2.28	130	2.06	68	1.72	124
PLOD2	Procollagen-lysine, 2-oxoglutarate 5-dioxygenase 2	0.51	132	0.58	278	0.61	63
TXNIP	Thioredoxin interacting protein	0.49	138	0.5	86	0.52	45
HPRT1	hypoxanthine phosphoribosyltransferase 1	2.07	154	1.68	206	1.65	43
FGF1	Fibroblast growth factor 1 (acidic)	0.51	164	0.73	764	0.64	103
RTN1	Reticulon 1	2.02	167	1.66	194	1.35	463
NEFL	Neurofilament, light polypeptide	2.13	172	1.64	282	1.53	491
MAFF	v-maf musculoaponeurotic fibrosarcoma oncogene homolog F (avian)	0.37	187	0.36	80	0.41	33
PCP4	Purkinje cell protein 4	2.01	188	1.62	398	1.78	195
C10orf10	Chromosome 10 open reading frame 10	0.46	226	0.43	58	0.65	138
SYT1	Synaptotagmin I	1.98	227	1.64	181	1.52	127
SCG2	secretogranin II (chromogranin C)	2.07	245	2.04	108	1.5	575
EFEMP1	EGF-containing Fibulin-like extracellular matrix protein 1	0.52	257	0.52	165	0.69	355
S100A8	S100 calcium binding protein A8	0.49	267	0.41	61	0.54	67
IL1R1	Interleukin 1 receptor, type I	0.5	281	0.56	266	0.64	252
F3	Coagulation factor III (thromboplastin, tissue factor)	0.47	283	0.39	32	0.66	419
PVALB	Parvalbumin	2.12	303	1.96	84	1.6	314
IFI16	Interferon, gamma-inducible protein 16	0.5	308	0.63	511	0.57	174
CNR1	Cannabinoid receptor 1 (brain)	2.02	325	1.73	344	1.58	339
ZFP36L1	Zinc finger protein 36, C3H type-like 1	0.5	624	0.61	637	0.54	246
DDX3Y	DEAD (Asp-Glu-Ala-Asp) box polypeptide 3, Y-linked	2.61	685	2.89	286	3.43	157
ATP5B	ATP synthase, H+ transporting, mitochondrial F1 complex, beta polypeptide	2.14	722	2.36	598	2.22	231
PRG1	p53-responsive gene 1	0.48	990	0.49	150	0.49	52

well with controls on pH and without agonal factors. Essentially the problem is whether the covariate is actually part of the pathophysiology, or part of the effect due to having the illness, again we cannot directly solve the cause and effect dilemma. Another way to frame the question is whether pH sensitive genes in controls are the same pH sensitive genes in SZ.

Effects of age on brain gene expression

A series of imaging studies have challenged the view of the static nature of brain pathophysiology in schizophrenia by showing progressive alterations in cortical structure (for a review (Cannon, 2008)). Repeated measures of the same subjects' might show a shift in imaging phenotypic characteristics in subjects with SZ, such as brain volumetric changes that are independent of age effects. Because it is impossible to separate the age from the disease stage, i.e. chronic patients are older than young patients, gene expression evaluation with age in individual postmortem brains from patients with SZ is difficult to isolate. In the case of neuro-imaging and other phenotypic studies longitudinal studies can evaluate age and medication and phenotypic changes. Age dependent or disease stage dependent alterations in gene expression profiles have also pointed to common genes and pathways involved

Table 3
There was an overlap of 21 genes of the 53 genes from Arion et al., 2007 (third and fourth columns are from Arion et al., 2007) and Vawter et al., 2006a (fifth, sixth, and seventh columns (Vawter et al., 2006a). Of these 21 genes, the fold change direction suggested that the SZ subjects had a lower pH than controls, i.e. SZ subjects showed dysregulation in the same directions as low pH controls except for two genes (ATP5A1 and LMO2).

Gene symbol	Gene title	SZ mALR (Arion et al., 2007)	P (Arion et al., 2007)	Fold change-DLPFC (Low pH compared to high pH)	Fold change-anterior cingulate (low pH compared to high pH)	Fold change-cerebellum (low pH compared to high pH)
ATP5A1	ATP synthase, H+ transporting, mitochondrial F1 complex, alpha subunit 1, cardiac muscle	0.52	0.0014	−1.76	−1.97	−1.96
CAP2	CAP, adenylate cyclase-associated protein, 2 (yeast)	−0.55	0.0357	−1.6	−1.8	−1.28
CDK5R1	Cyclin-dependent kinase 5, regulatory subunit 1 (p35)	−0.62	0.0087	−1.2	−1.23	−1.11
CHI3L1	Chitinase 3-like 1 (cartilage glycoprotein-39)	1.12	0.0039	1.93	1.85	1.55
CRYM	Crystallin, mu	−0.64	0.0068	−2.28	−2.88	−1.91
GOT1	Glutamic–oxaloacetic transaminase 1, soluble (aspartate aminotransferase 1)	−0.5	0.0029	−1.74	−2.13	−1.83
HSPA8	Heat shock 70 kDa protein 8	−0.52	0.0135	−1.42	−1.31	−1.16
IFITM1	Interferon induced transmembrane protein 1 (9–27)	0.77	0.0013	1.73	1.87	1.84
KCNK1	Potassium channel, subfamily K, member 1	−0.6	0.0045	−1.64	−1.68	−1.16
KIFAP3	Kinesin-associated protein 3	−0.47	0.0162	−1.63	−1.84	−1.24
LMO2	LIM domain only 2 (rhombotin-like 1)	−0.47	0.0147	1.14	1.29	1.3
MAPK1	Mitogen-activated protein kinase 1	−0.73	0.007	−1.46	−1.39	−1.3
NDUFS4	NADH dehydrogenase (ubiquinone) Fe–S protein 4, 18 kDa (NADH-coenzyme Q reductase)	−0.47	0.0259	−1.51	−1.36	−1.41
NME1	Non-metastatic cells 1, protein (NM23A) expressed in; NME1–NME2 readthrough transcript; non-metastatic cells 2, protein (NM23B)	−0.4	0.0135	−1.39	−1.44	−1.31
PAFAH1B1	Platelet-activating factor acetylhydrolase, isoform Ib, subunit 1 (45 kDa)	−0.5	0.0021	−1.68	−1.7	−1.39
RGS4	Regulator of G-protein signaling 4	−0.99	0.0016	−2.48	−2.67	−1.01
SCAMP1	Secretory carrier membrane protein 1	−0.71	0.0073	−1.24	−1.22	−1.07
SPOCK3	Sparc/osteonectin, cwcv and kazal-like domains proteoglycan (testican) 3	−0.63	0.0129	−1.31	−1.09	−1.32
SYN2	Synapsin II	−0.43	0.0023	−2.49	−2.46	−1.66
SYNJ1	Synaptojanin 1	−0.6	0.0038	−1.54	−1.59	−1.23
TF	Transferrin	−0.86	0.0253	−1.37	−0.82	−1.37

both in normal brain aging and in schizophrenia (Choi et al., 2009; Colantuoni et al., 2008; Erraji-Benchekroun et al., 2005; Mistry and Pavlidis, 2010; Torkamani et al., 2010).

For instance, a robust effect of age on gene expression was observed in "modules" that differentiates normal subjects from those with schizophrenia (Torkamani et al., 2010). Those age-related neuron modules underlined by Torkamani et al. included genes previously associated with schizophrenia and involved in GABA/glutamate neurotransmission as well as synaptic functioning supporting earlier microarray studies (Hakak et al., 2001; Mirnics et al., 2000; Vawter et al., 2001, 2002). In another study aiming to explore how schizophrenia related genes play a role in normal structural aging in the human brain using custom cDNA arrays and qPCR in the frontal pole (BA10) and DLPFC (BA9/46) of 72 normal controls, there was a significant correlation between expression and age for genes previously associated with schizophrenia (DARPP-32, PRODH, RGS4, and GRM3) and a change in expression correlation with age after age 30 for ERBB3, NRG1, and NGFR (Colantuoni et al., 2008). Several other SZ associated genes, such as NRG1, RGS4, BDNF, GAD67, and NTRK2, were also shown to be affected by age in a recent meta-analysis of 11 microarray datasets (Mistry and Pavlidis, 2010). Similarly, in a study aiming to detect genes altered in the late adolescent period, between ages 15 to 25, 2000 genes were identified, including a number of genes previously associated with SZ like NRG1, as well as genes involved in energy metabolism, lipid synthesis, glutamate and neuropeptide signaling and neuronal development/plasticity age (Harris et al., 2009). In another study of normal human brain aging, many genes previously shown to be altered in subjects with schizophrenia were significantly altered at different ages, from 1 month to 49 years (Choi et al., 2008). Thus GRIA1, GRIK1, GRIK2, GRIN2D, GRIP1, GRM5, GRM7, and SLC1A6 are significantly downregulated across age in normal human brain, which sets a baseline for studies of SZ compared to controls.

Despite efforts to match subjects by age in a study, the severity and stage of the illness may also play a role in decreasing the number of common genes across gene expression studies of schizophrenia. In current study designs, age, stage of the disease or age of onset, as well as years under medication are confounded and brain collections sometimes vary significantly in terms of average age as discussed in the brain bank section. This is particularly true for the effect of medication on a normal human brain and in SZ brains over long periods of time which is mainly unknown and confounded with age related alterations. This collinearity issue can at least be avoided by the study of control brains only. It was recently shown that the expression of certain major schizophrenia susceptibility genes in the human prefrontal cortex of normal controls is age dependent and therefore probably plays a role in normal aging independently of their involvement in SZ (Colantuoni et al., 2008; Mistry and Pavlidis, 2010). Also, only four genes (SAMSN1, CDC42BPB, DSC2 and PTPRE) overlap when comparing differentially expressed genes in brains from patients with schizophrenia at different stages of the disease (short, intermediate, and long duration of illness) (Narayan et al., 2008, 2009), suggesting that SZ related alterations are also age dependent and also possibly influenced by medication over long periods of time. Notably, the highest number of altered transcripts (1306) were observed in the short duration of illness group, compared to 487 and 279 transcripts for the intermediate and long term groups (Narayan et al., 2008, 2009). This study confirmed the alterations in myelin/oligodendrocyte related genes but only in the short duration of illness group (2.88 years in average) in which individuals were young, 26.1 and 28.8 years old respectively for SZ and controls (Narayan et al., 2008, 2009). Future studies should include age, medication duration and stage of the disease as co-factors to reveal genes involved in the different stages of the development of the "schizophrenic" phenotype. However, it would also be interesting to explore gene expression differences that are present at the beginning of the disorder separately from those present in chronic elderly cases that had years of medication.

Taken together, the gene expression evidence suggests that schizophrenia susceptibility genes undergo age-dependent and possibly

medication dependent expression changes in the human brain. How far backwards in development we can observe alterations in those genes during the critical period of development will require the study of gene expression changes in young SZ patients versus young controls. The study of pre-adolescent postmortem brains at a high risk for schizophrenia would be an ideal group to study the hypothesis of the neurodevelopmental basis of schizophrenia (Rapoport et al., 2005) but such a cohort would be extremely difficult to collect. The molecular age of brains from individuals with SZ thus are different across the lifespan compared to controls, but not in a stable pattern, being also affected by medication, further complicating the comparison of this illness between studies of cohorts with different ages (Colantuoni et al., 2008; Mistry and Pavlidis, 2010; Narayan et al., 2009).

Schizophrenia altered gene pathways in the brain

White matter and oligodendrocyte associated genes

One of the most consistent alterations observed in post-mortem gene expression studies using brains from patients with schizophrenia is a decrease in expression in white matter and oligodendrocyte pathway related genes (Table 4). Hakak et al. (2001) initially observed a decrease in the BA46 of myelin associated genes (MAG, MAL, CNP, HERR3, gelsolin, and transferrin) in a sample of 12 chronic elderly subjects with schizophrenia that had at least 35 years of hospitalization and an average age >70 (Hakak et al., 2001). Several groups confirmed alterations in this family of genes using different platforms and younger samples (Aston et al., 2004; Prabakaran et al., 2004; Tkachev et al., 2003b). In BA9 a reduction of key oligodendrocyte-related and myelin-related genes in SZ but also in subjects with BD was observed using the Stanley Foundation sample and Affymetrix U133A arrays (Tkachev et al., 2003a). Significant reductions of myelin/oligodendrocyte genes such as MAG, MBP, and MOP were also confirmed using U95A Affymetrix arrays in BA21 (Aston et al., 2004). Finally, using the U133A array, Prabakaran et al. (2004) observed decreases in key myelination genes (MAG, MPZ, PMP22 and MBP). Interestingly, all these initial studies used Affymetrix arrays (HuGeneFL, U133A and U95A) and Stanley foundation brain samples or brain samples from the Mount Sinai group brain bank (Aston et al., 2004; Hakak et al., 2001; Prabakaran et al., 2004; Tkachev et al., 2003a) possibly explaining at least in part the concordance of these studies concerning myelin and oligodendrocyte alterations in gene expression (Table 1). A group from Japan however, also observed oligodendrocyte- and astrocyte-related genes to be differentially expressed in the prefrontal cortex from patients with SZ from Japan and using a different platform, the Clontech Atlas Human Neurobiology Array and Atlas Human Cancer Array (Sugai et al., 2004).

Because several myelin and oligodendrocyte associated genes (particularly MAG, ERBB, TF, PLP1, MOG, MOBP, and MOG) have also been shown to be altered not only in SZ but also in major depressive disorder and BD post-mortem brain tissue, as reviewed by Sokolov (2007), these alterations point to possible common mechanisms involved in psychiatric disorders or common drivers of expression that might confound studies of psychiatric disorders.

Since these initial findings using microarrays, decreased expression in myelin and oligodendrocyte related genes in post-mortem brain tissue from patients with SZ has been confirmed by qPCR and ISH by many groups in cortical and sub-cortical region (Barley et al., 2009; Katsel et al., 2008; Kerns et al., 2010) . Interestingly, it was recently shown that the quaking gene (QKI), a member of the signal transduction and activation of RNA (STAR) protein family, is a regulator of the expression of oligodendrocyte related genes and that alterations observed in QKI splice-variants expression might explain altered expression of myelin-related genes in subjects with SZ. This is interesting as a decrease expression of QKI in seven cortical regions and hippocampus by microarrays and qPCR was observed (Haroutunian et al., 2006).

Reductions in expression of MAG and CNP in SZ in schizophrenia is a highly replicable finding in SZ gene expression, however there are some negative reports recently been published using qPCR, immunoblotting, and microarrays. Changes in gene expression of MAG, CNP, and OLIG2 were not observed in the DLPFC from subjects with SZ (Mitkus et al., 2008). However, the authors observed an effect of genetic polymorphisms in the expression levels of CNP and OLIG2, raising the question of the role played by genetics in the expression alterations previously observed in this family of genes in brain cohorts with diverse genetic backgrounds (Mitkus et al., 2008). Lastly, Maycox et al. (2009), using two separate cohorts from the Harvard Brain Bank and the Charing Cross Hospital (Table 1), did not observe a dysregulation of myelin related genes, astrocyte or microglial markers, or metabolic genes in either cohort (Maycox et al., 2009).

GABA and glutamate neurotransmission

Many emerging pharmacological therapeutic strategies involve GABAergic and glutamatergic neurotransmitter pathways (Karam et al., 2010). This is in agreement with gene expression studies that have consistently confirmed the involvement of GABAergic and glutamatergic neurotransmission in the pathophysiology of SZ as reviewed in this section.

Gamma-aminobutyric acid (GABA) is the main inhibitory neurotransmitter in the central nervous system. Initial evidence of a decreased expression in SZ of the glutamate decarboxylase 1 gene

Table 4
Main pathways differentially expressed in microarray studies and validated in follow-up studies of schizophrenia.

Pathway	Direction	Replicated findings — examples	Studies
Myelin and Oligodendrocyte	Decrease	MAG, MOG, CNP, QKI	(Aston et al., 2004; Barley et al., 2009; Hakak et al., 2001; Haroutunian et al., 2007; Katsel et al., 2008; Kerns et al., 2010; Prabakaran et al., 2004; Sugai et al., 2004; Tkachev et al., 2003a)
GABA	Decrease	GAD1, CB1R, CCK	(Conde et al., 1994; Dracheva et al., 2004; Duncan et al., 2010; Hakak et al., 2001; Hashimoto et al., 2008, 2003; Mirnics et al., 2000; Straub et al., 2007; Vawter et al., 2001)
Glutamate	Increase	VGLUT1, VGLUT2, EAAT1, EAAT2, NR2B	(Bauer et al., 2008, 2010; Bitanihirwe et al., 2009; Dracheva et al., 2005; Hammond et al., 2010; Kristiansen et al., 2010a, 2010b; Oni-Orisan et al., 2008; Uezato et al., 2009)
Signaling and Synaptic	Decrease/Increase	RGS4, Semaphorins, 14-3-3, KCNH2, SYN1	(Altar et al., 2005; Iwamoto et al., 2005; Maycox et al., 2009; Middleton et al., 2005b; Mirnics et al., 2000; Prabakaran et al., 2004; Shao et al., 2008; Vawter et al., 2001)
Mitochondria	Decrease	mtDNA and nuclear DNA encoded transcripts related to mitochondria	(Altar et al., 2005; Iwamoto et al., 2005; Khaitovich et al., 2008; Middleton et al., 2005b; Prabakaran et al., 2004; Shao et al., 2008; Shao and Vawter, 2008)
Immune	Increase	SERPINA3, IFITM2, IFITM3	(Arion et al., 2007; Saetre et al., 2007)
Stress	Increase	MT1X, MT2A	(Arion et al., 2007; Choi et al., 2008; Chu et al., 2009; Kim et al., 2007; Saetre et al., 2007; Shao and Vawter, 2008)

(GAD1), responsible for the synthesis of GABA from glutamate, came from studies using ISH, qPCR and Western blot analysis (Akbarian et al., 1995; Guidotti et al., 2000; Impagnatiello et al., 1998). In the first published schizophrenia microarray study, a global decrease was observed in the expression of presynaptic genes in a sample of relatively young subjects with SZ (average age for controls 45.1 and 46.5 for SZ), including decreases in genes involved in GABAergic neurotransmission such as GAD1 (Mirnics et al., 2000). Other early microarray papers also reported alterations in genes involved in GABAergic and glutamatergic neurotransmission (Hakak et al., 2001; Vawter et al., 2001). The direction of the changes were in disagreement however for some of the specific genes, GAD1 mRNA was decreased in Mirnics et al. (2000) but increased in Hakak et al. using a sample of elderly chronic patients with an average age of 72 years old (Hakak et al., 2001), possibly reflecting differences in age and chronicity of the illness (collinear with years of medication) between the two cohorts used and gender imbalance in case–control comparisons. GAD1 reductions were later confirmed in the brains of patients with SZ by microarrays (Hashimoto et al., 2008) and by other techniques (Duncan et al., 2010; Straub et al., 2007). Interestingly, the reported increase of GAD1 in the brains of patients with SZ (Hakak et al., 2001), was also confirmed in the occipital cortex using a cohort of elderly cases and controls, suggesting that while in younger subjects GAD1 is decreased (Dracheva et al., 2004), in elderly cohorts this gene is increased in SZ. Layer specific changes observed in subjects with schizophrenia of PV mRNA accompanied by significant GAD1 reductions in PV immunoreactive neurons suggest that this population of neurons specifically have a reduction of GAD1 and possibly reduced levels of GABAergic neurotransmission (Conde et al., 1994; Hashimoto et al., 2003). Interestingly, cannabinoid 1 receptor (CB1R), highly expressed in the DLPFC, was found to be significantly decreased, both mRNA and protein, in subjects with schizophrenia and correlated with levels of GAD1 and cholecystokinin (CCK) suggesting a compensatory mechanism for the impaired GABA neurotransmission in a subpopulation of GABAergic neurons (Eggan et al., 2008).

Multiple lines of evidence, pharmacological, imaging, clinical and post-mortem studies, tend to demonstrate the link between alterations in glutamate neurotransmission (Table 4), the main excitatory neurotransmitter in the human brain, with schizophrenia (Lewis et al., 2003). Microarray gene expression studies have identified several genes involving glutamatergic neurotransmission including transporters and receptors are differentially expressed in schizophrenia. These findings have been pursued by independent qPCR and ISH studies. The vesicular glutamate transporter 2 (VGLUT2) mRNA was shown to be increased in the inferior temporal gyrus of subjects with schizophrenia, the vesicular type of glutamate transporter is involved in the packaging of glutamate, a critical step for the release of glutamate at the synapse (Oni-Orisan et al., 2008; Uezato et al., 2009). However, a layer specific decrease in vGluT1-immunoreactive boutons in the PFC has also been observed suggesting a decrease in the expression of the transporter or a decrease in the number of neurons expressing it (Bitanihirwe et al., 2009). Finally, an increase in expression and a decrease in glycosylation of excitatory amino acid transporters EAAT1 and EAAT2 in schizophrenia was also reported recently, suggesting abnormal expression levels and posttranslational modification of glutamate transporters in schizophrenia, because excitatory amino acid transporters (EEATs) are responsible for the termination of the glutamatergic signaling by removing glutamate from the synapse, alterations in their expression might lead to a decreased capacity for glutamate reuptake (Bauer et al., 2008, 2010). Alterations have been observed in mRNA trafficking and protein expression of AMPA and NMDA receptors in the frontal cortex of elderly subjects with schizophrenia (Dracheva et al., 2005; Hammond et al., 2010; Kristiansen et al., 2010a). More specifically, Kristiansen et al. observed alterations of the NR2B-NMDA receptor subunit and its Tbr-1/CINAP regulatory proteins in subcellular compartments suggesting alterations in the processing of these molecules (Kristiansen et al., 2010b). NMDA receptor associated proteins have also been shown to be altered in SZ, PSD95 protein levels were found to be decreased specifically in the anterior cingulate cortex of patients with SZ off antipsychotic medications (Funk et al., 2009), confirming previous changes reported in postsynaptic density (PSD) proteins and NMDA receptor subunits (Kristiansen et al., 2006).

However, not all studies have confirmed alterations of glutamatergic genes in certain brain areas of subjects with schizophrenia (Dracheva et al., 2008; McCullumsmith et al., 2007). Using ISH to assess expression levels in the hippocampus of NMDA receptor subunits NR1, 2A, 2B, 2C and 2D as well as the NMDA receptor associated PSD proteins PSD-95, PSD-93, NF-L and SAP102 there were no significant changes in the hippocampus of patients with SZ (McCullumsmith et al., 2007) while abnormalities in the expression of ionotropic glutamate receptor subunit transcripts were found in medial temporal cortex in schizophrenia (Beneyto et al., 2007). The category of NMDA-PSD gene expression was significant in an over-representation analysis for smokers compared to non-smokers. Since more patients with SZ smoke compared to controls, this effect also will need to be considered in evaluation of findings not only in glutamatergic pathways, but other diverse pathways such as immune and cholinergic (Mexal et al., 2005).

Signaling and synaptic related genes

Pathway alterations in signaling and synaptic gene alterations (Table 4) have been consistent in some microarray studies (Altar et al., 2005a; Iwamoto et al., 2005; Middleton et al., 2005b; Mirnics et al., 2000; Prabakaran et al., 2004) as recently reviewed (Altar et al., 2009). An initial report showing a decrease in the gene coding for the regulator of G-protein signaling 4 (RGS4) in subjects with schizophrenia (Mirnics et al., 2001), was confirmed, along with the alterations of other synaptic genes such as SYN2, SYNJ1 and MAPK1 by other groups (Arion et al., 2007). However, some studies failed to replicate the association between RGS4 variants and SZ or the changes in gene expression of RGS4 in the brains of SZ subjects (Ishiguro et al., 2007; Rethelyi et al., 2010; Stuart Gibbons et al., 2008; Vilella et al., 2008). Discordances in RGS4 expression changes in SZ might also be due to specific changes in only some splice variants of RGS4 as shown in the prefrontal cortex of subjects with SZ (Ding and Hegde, 2009) or by genetic polymorphisms possibly influencing RGS4 expression (Buckholtz et al., 2007; Chowdari et al., 2008; Emilsson et al., 2006).

Recent reports have shown new families of signaling and synaptic related genes as being altered in SZ (Table 4). Netrins, membrane-bound axon guidance molecules that play a role in synaptic formation and maintenance, are both associated with schizophrenia in family based genetic studies and have altered expression in certain brain areas of subjects with schizophrenia (Aoki-Suzuki et al., 2005; Ohtsuki et al., 2008). The signaling proteins involved in axon guidance, semaphorins, previously shown to be altered in the cerebellum of subjects with SZ (Eastwood et al., 2003), were also shown to be altered in BA46 infragranular layers of subjects with SZ, with several semaphorin genes (SEMA3E, SEMA3C, SEMA6D, SEMA3A and SEMA4D) being altered (Arion et al., 2010).

Previous reports implicating important synaptic vesicle genes such as VAMP2 and SYT5 and alterations in signal transduction genes such as CACNB3, CACNG3, CAPNS1, CMKK2 and PIK4CB were confirmed (Maycox et al., 2009) in two independent cohorts (HBB and CCH). A primate specific isoform of the KCNH2 gene, involved in neuronal repolarization and spike frequency, was identified as a new candidate gene for schizophrenia using a combination of genetic association and gene expression investigation (Huffaker et al., 2009). Examples of other signaling related alterations were reported in Altar et al. (2009) such as the decreased expression of the 14-3-3 family of genes (Altar et al., 2009).

Mitochondrial function

The initial microarray evidence of altered mitochondrial function gene expression in post-mortem tissue from brains of patients with SZ was provided in the SMRI sample of 50 controls and 54 persons with SZ (Prabakaran et al., 2004) in BA9. Mitochondrial function genes were confirmed to be also altered in SZ by other groups using different platforms and samples (Altar et al., 2005a; Iwamoto et al., 2005; Middleton et al., 2005b). Furthermore, down-regulation of some nuclear encoded mitochondrial related genes, such as those encoding respiratory chain components, was reported in samples of both SZ and BD (Iwamoto et al., 2005). This not only suggests a similar mechanism involved in both disorders, and as was discussed in the section on pH effects on gene expression, pH seems to be relevant to mitochondrial brain expression alterations.

Notwithstanding the potential role of pH considerations, additional studies have found energy metabolism alterations in the brains of SZ as well as in normal brain development. For instance, genes and metabolites relating to energy metabolism and energy-expensive brain functions are altered in brains of subjects with SZ (Khaitovich et al., 2008). Changes in late adolescence for genes associated with energy metabolism, protein and lipid synthesis, as well as decreases in genes involved in glutamate and neuropeptide signaling and neuronal development/plasticity were observed in SZ (Harris et al., 2009). Thus, some critical genes and pathways involved in schizophrenia also play a pivotal role in brain development of normal subjects.

Expression of mitochondrial expressed genes, i.e. transcribed from mitochondrial DNA (mtDNA), was studied in DLPFC samples from UCI Brain Bank (Shao et al., 2008). After adjusting for pH, there were 10 of 13 mtDNA encoded transcripts decreased in SZ (MTATP6, MTATP8, MTCO3, MTCYB, MTND1, MTND2, MTND3, MTND4, MTND5 and MTND6) (Shao et al., 2008). Interestingly, BD showed no alterations in mtDNA transcribed genes in the same report.

Immune and stress-response genes

Several studies have reported alterations in the immune and stress-response genes in subjects with schizophrenia using microarrays and mostly PFC samples (Arion et al., 2007; Saetre et al., 2007; Shao and Vawter, 2008). Arion et al. reported a 50% increase in several immune and stress-response related genes (SERPINA3, IFITM1, IFITM2, IFITM3, CHI3L1, MT2A, CD14, HSPB1, HSPA1B and HSPA1A) (Arion et al., 2007). An up-regulation of genes involved in immune and stress-response (SERPINA3, IFITM2, IFITM3, HLA-A, MT1X and GBP1) was also observed in the BA8, 9 and superior frontal gyrus in schizophrenia by microarrays and qPCR (Saetre et al., 2007). Three genes, SERPINA3, IFITM2, and IFITM3 were altered in both studies (Arion et al., 2007; Saetre et al., 2007).

Stress is thought to play a role in the development of schizophrenia; recent studies have shown that metallothioneins, a family of genes involved in the response to stress, several members are expressed in response to glucocorticoid levels, play a role in neuroprotection (Hidalgo et al., 2001). Interestingly, several stress related metallothionein genes were shown to be altered in prefrontal cortex areas in several studies of SZ. MT2A was up-regulated in two studies (Arion et al., 2007; Saetre et al., 2007) and another member of the metallothionein family of genes, MT1X, was up-regulated in two studies (Saetre et al., 2007; Shao and Vawter, 2008). MT1X was also identified as one of the top genes in the DLPFC in a linear discriminant analysis aiming to differentiate SZ and BD from controls (Shao and Vawter, 2008) and appeared to be increased with lifetime exposure to antipsychotic medication. MT2A was also shown to be significantly increased, more than 3 fold, in schizophrenia using LCM to harvest neurons from the mediodorsal nucleus of the thalamus, a region known to have extensive reciprocal connections to the DLPFC (Chu et al., 2009), suggesting metallothionein alterations are common to the DLPFC and functionally interacting regions.

Metallothioneins are small single chain proteins with a high content of cysteine residues organized in specific sequences enabling the formation of thiolate cluster and the binding of certain metals in response to oxidative stress, glucocorticoid, and inflammatory mediators (Coyle et al., 2002). This family of genes has also been suggested to be involved in suicide and might in part explain some of the changes observed in cohorts containing SZ and many suicide victims. This is a particularly important issue since some brain collections have an important number of suicide victims among the cases, making impossible to separate the suicide effects from effects of SZ and/or medication. A combined analysis of a large microarray data set to investigate gene expression in changes in patients with SZ who did and did not commit suicide showed that several members of the metallothionein subfamily 1 (MT1X, MT1M, MT1E, MT1H, MT1F, and MT1G) were specifically down-regulated in the prefrontal cortex (BA10/46), among those subjects with schizophrenia who committed suicide (Kim et al., 2007).

Finally, a large meta-analysis of seven microarray studies that used three different Affymetrix platforms with two different post-mortem brain collections from the SMRI confirmed the involvement of metallothionein genes schizophrenia (Choi et al., 2008). There was a general up-regulation of specific metallothionein subfamilies (MT1E, MT1F, MT1H, MT1K, MT1X, MT2A and MT3) in SZ, confirming the implication of this family of genes in sub-phenotypes of psychiatric disorders relevant to stress response (Choi et al., 2008). Taken together, an increased metallothionein gene expression in brain might be specifically associated with psychosis (Choi et al., 2008) and a down-regulation with suicide (Kim et al., 2007).

Peripheral derived gene expression in schizophrenia

While it is ideal to examine gene expression using postmortem brain tissue in studies of psychiatric or neurological disorders, there are limited numbers of brains available for postmortem studies. Assessment of peripheral blood gene expression has several advantages, including practical availability of blood compared to brain tissue in human subjects and reduced confounds such as PMI, pH, and agonal factors, and can be examined at multiple time points to assess the effects of disease progression, disease state or experimental manipulations such as drug treatment. Moreover, twin or siblings studies of peripheral blood gene expression can be designed to increased power and to differentiate between heritable differences and disease-specific differences. While there are brain specific mRNAs by definition that are unlikely to be meaningful candidates for disease associated changes in the blood, there is a high correlation ($r = 0.98$) of selected transcripts coexpressed in brain and blood (Rollins et al., 2010) and a large and more accessible pool of subjects that can be readily tested from blood samples. Finally, blood samples can be used to induce pluripotent stem cells for studying different cellular phenotypes.

Peripheral gene expression of schizophrenia candidate genes

Recent studies of peripheral expression of schizophrenia candidate genes are summarized in this section (Table 5). Neuregulin-1 (NRG1) expression was examined in peripheral blood of subjects with first onset SZ and their siblings and controls. The results of this study showed decreased NRG1 expression in subjects with SZ compared to their unaffected siblings and controls, but expression increased following four weeks of antipsychotic treatment. NRG1 GGF2 isoform was decreased in expression in immortalized lymphocytes before and after antipsychotic (olanzapine) stimulation in subjects with schizophrenia compared to controls. The down-regulation of NRG1 expression in blood and lymphocytes is inconsistent with findings of increased brain NRG1 expression (Chong et al., 2008). The NRG1 risk allele identified in

Table 5
Peripheral studies of gene expression alterations in schizophrenia sorted by candidate gene.

Gene	mRNA	Peripheral tissue	Reference
AHI1	Increased in early onset SZ compared to C	Lymphocytes	(Slonimsky et al., 2010)
AHI1	NS in late onset SZ compared to C	Lymphocytes	(Slonimsky et al., 2010)
ApoER2	Decreased in medicated SZ but not drug-naïve SZ	Lymphocytes	(Suzuki et al., 2008)
CHRNA7	Decreased in SZ compared to C	Lymphocytes	(Perl et al., 2003)
DRD2	Increased in SZ compared to C	Lymphocytes	(Zvara et al., 2005)
DRD3	Decreased in SZ compared to C	Lymphocytes	(Vogel et al., 2004)
DTNBP1	Decreased in SZ compared to C	Lymphocytes	(Chagnon et al., 2008)
NRG1	Decreased in SZ compared to siblings and C	Whole Blood	(Zhang et al., 2008)
NRG1	Increased after AP treatment	Whole Blood	(Zhang et al., 2008)
NRG1 (GGF isoform)	NS between SZ and C	Lymphocytes	(Chagnon et al., 2008)
NRG1 (GGF isoform)	Decreased after AP treatment	Lymphocytes	(Chagnon et al., 2008)
NRG1 (GGF2 isoform)	Decreased in SZ compared to C	Lymphocytes	(Chagnon et al., 2008)
SELENBP1	Increased in SZ compared to C	Whole Blood	(Glatt et al., 2005)
TGFBR2	Increased in AP-free SZ compared to C	Leukocytes	(Numata et al., 2007)
TGFBR2	Decreased after AP treatment	Leukocytes	(Numata et al., 2007)
VLDLR	Decreased in drug-naïve SZ but not medicated SZ compared to C	Lymphocytes	(Suzuki et al., 2008)

Abbreviations: SZ — schizophrenia, C — control, AP — antipsychotic, NS — not significant.

association studies has also been associated with increased postmortem brain gene expression (Law et al., 2006).

Dystrobrevin binding protein 1 (DTNBP1) has been shown to be decreased in the brain and variants have been identified in association with schizophrenia (Kirov et al., 2004; van den Oord et al., 2003; Williams et al., 2004). DTNBP1 was decreased approximately 30% in immortalized lymphocytes of subjects with schizophrenia before and after olanzapine stimulation compared to controls, suggesting decreased DTNBP1 may be a stable biomarker of schizophrenia (Chagnon et al., 2008) requiring further study in other illnesses.

Reelin, which plays an important role in brain development, has been implicated in the etiology of schizophrenia by postmortem studies that have shown decreased reelin mRNA in the prefrontal cortex (Impagnatiello et al., 1998), and by mouse models of reelin deficiency that display schizophrenia associated behaviors and anatomical features (Guidotti et al., 2000). Reelin receptors VLDLR and APOER2 were examined in peripheral blood lymphocytes from drug-naïve and medicated subjects with schizophrenia compared to controls and VLDLR mRNA levels were found to be decreased in drug-naïve patients but not medicated patients, while APOER2 expression was decreased in medicated but not drug-naïve patients. There was a positive correlation between VLDLR mRNA and the duration of illness and a negative correlation between APOER2 mRNA levels and duration of illness drug-naïve and medicated patients (Suzuki et al., 2008).

The α7 nicotinic acetylcholine receptor was found to be decreased in expression in peripheral blood lymphocytes of subjects with schizophrenia compared to controls, and was unlikely to be related to the effects of smoking as non-smoking healthy controls did not differ from smoking healthy controls in α7 nicotinic acetylcholine receptor expression (Perl et al., 2003). This is consistent with postmortem studies showing decreases in α7 nicotinic acetylcholine receptor in the brains of subjects with schizophrenia who possess neuregulin risk alleles compared to controls (Mathew et al., 2007).

Selenium binding protein 1 (SELENBP1) was selected for examination in peripheral whole blood in subjects with schizophrenia compared to controls based on microarray findings showing an increase in SELENBP1 in postmortem dorsolateral prefrontal cortex of subjects with schizophrenia compared to controls (Glatt et al., 2005). There was a significant increase in SELENBP1 expression peripheral blood from subjects with schizophrenia compared to controls.

Overall, these studies (Table 5) support the value of single gene focused investigations of peripheral gene expression changes associated with schizophrenia but more work is needed to confirm positive findings in larger cohorts and other illnesses to determine whether peripheral gene expression alterations may mirror brain gene expression alterations, or could be useful for diagnostic purposes, or for prediction of drug response.

Microarray analyses of gene expression in schizophrenia derived from blood

A second strategy, to identify groups of gene expression alterations by microarray, queries sets of biologically related gene expression alterations in pathways and undiscovered networks. One advantage of this strategy is that a group of genes can be used as gene expression classifiers, and diagnostic and treatment response classification ability may be improved. The overview of nine recent microarray studies of peripheral blood gene expression changes in schizophrenia are summarized in Table 6. This section briefly describes the outcomes of these studies.

Gene expression profiling has been conducted by microarray in subjects with schizophrenia compared to controls using blood RNA (Table 6). Tsuang et al. (2005) identified 567 genes, eight of which were validated by qPCR. A whole blood RNA biomarker study in subjects with schizophrenia and other psychotic disorders identified 50 candidate biomarker genes for hallucinations and 107 candidate biomarkers for delusions (Kurian et al., 2009). Untreated first episode subjects with schizophrenia were compared to healthy controls, identifying 180 significantly altered gene probes (Kuzman et al., 2009). Examination of 52 antipsychotic-free subjects with schizophrenia and schizophreniform and 49 normal controls (Takahashi et al., 2010) identified eleven genes previously associated with schizophrenia, including NRG1, NTF3, CHRNB2, CCKAR, DAOA, DAO, L1CAM, NEUROG1, ZNF74, PRODH, and CHGA.

Transcript expression in schizophrenia and their non-psychotic were examined in 33 schizophrenia sib pairs using leukocytes (Middleton et al., 2005a). In a study of expression in immortalized lymphoblasts of subjects with schizophrenia and unaffected relatives, Vawter et al. (2004b) confirmed by real-time PCR (Vawter et al., 2004b) two genes, GNAO1 and NPY1R, that were significantly decreased in expression in subjects with schizophrenia. Several subjects from this study (Vawter et al., 2004b) were repeated with SNP markers (Vawter et al., 2004b) and seven differentially expressed genes were validated with qPCR (ADAM9, ADH1B, CTLA4, HCK, NR2F2, SMARCA2, and WSB2). The effects of glucose deprivation on lymphoblastic cell lines from subjects with schizophrenia and their unaffected relatives was examined using exon arrays (Martin et al., 2009). There were eight genes with significant glucose deprivation × diagnosis × exon effects, including glutaminase, which was decreased in expression in the DLPFC, and there was an over-representation of functional categories including molecular transport, protein trafficking, and cellular function and maintenance.

These recent microarray studies of peripheral blood gene expression in schizophrenia show little if any overlap in terms of specific genes identified or enriched biological pathways. This may be related to heterogeneity in subjects, a high false positive rate or the exclusion

Table 6
Recent studies using blood derived RNA and screened by microarray.

Tissue	Number of altered transcripts reported	Genes validated by qPCR and/or over-represented functional groups.	Reference
Whole blood	567	APOBEC3B, ADSS, ATM, CLC, CTBP1, DATF1, CXCL1, and S100A9 confirmed by qPCR.	Tsuang et al., 2005
Whole blood	180	Transcription/RNA processing, ubiquitin, lipid/glucose/protein metabolism, signal transduction and cytoskeleton	Kuzman et al., 2009
Whole blood	50 candidate biomarker genes for hallucinations 107 candidate biomarkers for delusions	Candidate biomarkers for delusions included schizophrenia candidate genes DRD2 Candidate markers for hallucinations included RHOBTB3	Kurian et al., 2009.
Whole blood	792	Cell adhesion, nervous system development, and neurotransmitter binding and receptor activity.	Takahashi et al., 2010
Whole blood	557 in sample 1 2182 in sample 2	ARF1, BAT1 and GDI2 confirmed by qPCR. Glutamate metabolism, hypoxia signaling in the cardiovascular system, chondroitin sulfate biosynthesis and calcium-induced T lymphocyte apoptosis.	Kuzman et al., 2009
Lymphoblastic cell lines	122	Molecular transport, protein trafficking, and cellular function and maintenance. ERO1L, DSC2, MCCC2, CR1, IRF5, GLS, DSC3, and ADCY1 confirmed by qPCR.	Martin et al., 2009
Leukocyte	200	Pathways involved eye morphogenesis, glycosaminoglycan binding, and hyaluronic acid binding. Decreased expression of genes implicated in included adenylate cyclase, CCAAT-binding transcription factor subunit B and fibroblast growth factor receptors in subjects with schizophrenia compared to controls.	Middleton et al., 2005b
Lymphoblastic cell lines	29	GNAO1 and NPY1R confirmed by qPCR	Vawter et al., 2004b
Lymphoblastic cell lines	1529	ADAM9, ADH1B, CTLA4, HCK, NR2F2, SMARCA2, and WSB2 confirmed by qPCR	Vawter et al., 2006b

of true findings based on over-stringent multiple comparison corrections, different types of blood derived preparations used in each study, and inherent noise in microarray results using different platforms. Further research in larger samples using a more stable method such as RNA-sequencing to count transcripts could avoid some of the pitfalls, but more uniform blood collection methods would be useful in this developing field. Interestingly, Ingenuity Pathway Analysis (IPA) was run on the gene symbols from peripheral blood microarray and candidate gene studies reviewed above that were confirmed by qPCR. The IPA revealed an over-representation of reelin signaling in neurons (Benjamini Hochberg $p = 0.0002$), although the reelin gene itself was not entered into the analysis. The six reelin pathway genes over-represented were: APOE, ARHGEF9, ATM, HCK, LRP8, and VLDLR. Genes of interest expressed in peripheral derived RNA sources are also expressed in brain, and are a useful probe of CNS expression within certain limitations.

Future research directions

Collaborative studies and combinations of large datasets can maximize the results obtained from the limited and valuable brain tissue available for research. For collaborative studies, currently operational brain banks, as well as researchers using the tissue should standardize quality control measurements (pH, RIN, 5′/3′ ratios, RNADeg slope, etc.) and extraction methods for RNA, DNA, and protein to improve comparability of results (Atz et al., 2007). Also, if raw data is made publicly available after publication this would allow the compilation of large datasets, like in the model developed by the Stanley Foundation (Kim and Webster, 2010b). Large data sets have far more power in discovering genes involved in schizophrenia and are relatively easy to compile by combining all available and published gene expression data.

Large collaborative studies have been privately and publicly funded lately. The Allen Institute for Brain Science recently released gene expression data from two control brains analyzed across 1000 structures per brain, including cortical, subcortical, cerebellar and brainstem structures (http://human.brain-map.org/) and will extend this to at least ten normal control brains. This effort should allow whole brain mapping of gene expression and show connectivity between regions to allow correlation tracing between neuroanatomical locations in the Human Transcriptome Map. A new developmental series of brains will enlarge the number of individuals at each decade of life. This recently funded NIMH "Transcriptional Atlas of Human Brain Development" will also lay deep foundations upon which to build a more complete and deep interactome analysis that will include additional data layers from next generation sequencing studies, multiple brain regions that are connected neurocircuits, methylation, analysis of the effect of genetics on gene expression, and most importantly from careful screening of controls.

These experiments are not without challenge(s) and the different approaches for generating the transcriptome, genome, and methylome datasets come with drastically different noise and reliability levels. Development of novel methods to integrate the heterogeneous datasets and to automatically account for different noise levels will be difficult and a test of 'truth', i.e. whether the inferred interactome is true due to the lack of a true reference interactome for comparing against is a challenge, however the control interactome could be a reference. One step towards building a true interactome is to use the large support of 'drivers' of gene expression, and look across datasets for that signature in control brains. This experiment would then be conducted on subjects with SZ to determine if the same gene expression drivers were consistent with control patterns. We argue that systems biology approach makes sense to unravel the complex interactome in schizophrenia, for examples (Banerjee et al., 2010; Camargo et al., 2007; Guo et al., 2009; Yang et al., 2008). Schizophrenia interactome was identified in a recent NIMH challenge grant series as a salient topic. The present review has identified genes and pathways as candidates for understanding a complex psychiatric disorder that could be placed in the SZ interactome. The field of gene expression has adopted use of pathway support and the next advance predicted is comprehensive interactome across many interconnected layers.

Summary

Postmortem brain and peripheral tissue gene expression alterations have been reliably observed in glutamate–glutamine shuttling, oligodendrocyte — white matter, mitochondrial metabolic processes, NRG1-ERBB4 signaling, immune and stress response genes, and synaptic plasticity networks. Recent studies have also revealed specific changes in gene expression related to age or stage of the disease, as well as the involvement of the metallothionein family of genes in SZ and in suicide victims with SZ. The overlap of many of these biological pathways with BD or MDD, suggests however that the same networks could be implicated in diverse diseases of adult onset psychiatric disorders

consistent with the genetic evidence of complex disorders. It is unlikely that there are specific genes that only cause schizophrenia, rather there are genes with specific brain function that have altered expression patterns from the perspective of normal transcriptome profiles at a certain neurodevelopment epoch which can predispose to schizophrenia.

SZ associated genes are pH sensitive and age regulated (Mistry and Pavlidis, 2010), which raises the question whether the pathophysiology is related to: a) genes altered in the immune and bioenergetics/metabolic pathways as some have suggested, b) whether these changes are perhaps coincidental to premortem differences in schizophrenia but not causative of schizophrenia such as environmental factors, stress, nutrition and medication, or c) whether there are interactions that explain the phenomenon such as genetics of gene expression. The data remain purely statistical, and as such, cause and effect are difficult to disentangle. Experiments will be required to perturb these networks and then look for similar changes in other expression traits that may produce features of a SZ related phenotype. The way forward will certainly require larger control brain datasets, generation and use of genetic information controlling expression, sharing of data for integration, and then experimental validation of the interactome. By a full understanding of the control interactome, we will have a basis to discover the exact differences in the interactome from individuals with SZ.

Conflict of interest disclosures

Dr. Marquis Vawter is a co-inventor on two patents regarding gene expression for genes in pathways related to those described in this article.

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