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Expression profiling in neuropsychiatric disorders: Emphasis on glutamate receptors in bipolar disorder

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ABSTRACT

Functional genomics and proteomics approaches are being employed to evaluate gene and encoded protein expression changes with the tacit goal to find novel targets for drug discovery. Genome-wide association studies (GWAS) have attempted to identify valid candidate genes through single nucleotide polymorphism (SNP) analysis. Furthermore, microarray analysis of gene expression in brain regions and discrete cell populations has enabled the simultaneous quantitative assessment of relevant genes. The ability to associate gene expression changes with neuropsychiatric disorders, including bipolar disorder (BP), and their response to therapeutic drugs provides a novel means for pharmacotherapeutic interventions. This review summarizes gene and pathway targets that have been identified in GWAS studies and expression profiling of human postmortem brain in BP, with an emphasis on glutamate receptors (GluRs). Although functional genomic assessment of BP is in its infancy, results to date point towards a dysregulation of GluRs that bear some similarity to schizophrenia (SZ), although the pattern is complex, and likely to be more complementary than overlapping. The importance of single population expression profiling of specific neurons and intrinsic circuits is emphasized, as this approach provides informative gene expression profile data that may be underappreciated in regional studies with admixed neuronal and non-neuronal cell types.

1. Introduction

Psychotic disorders are characterized clinically by hallucinations and/or delusions and are categorized as primary psychiatric/psychotic disorders due to precipitants including substance abuse, psychoactive medications, and head trauma or secondary to conditions that affect the central nervous system (CNS) including brain tumors, cerebral infarcts, epilepsy, HIV-AIDS, multiple sclerosis, and neurodegenerative disorders, among others. Disorders in which psychosis is a primary symptom include schizophrenia (SZ), schizoaffective disorder, and schizophreniform disorder as well as delusional disorder and brief and shared psychotic disorders. In addition, psychoses can present in major depressive disorder (MDD) and in bipolar disorder (BP). Unfortunately, psychotic disorders significantly impair the ability of the affected individual to communicate effectively, have clear mentation, and behave in a socially appropriate and consistent manner, which negatively impacts the ability to conduct a normal lifestyle. SZ-related disorders affect approximately 2.4 million people, or 1.1% of the USA population >18 years old each year (Gejman et al., 2010; Regier et al., 1993) while the spectrum of BP affect approximately 5.7 million people, or 2.6% of the USA population >18 years old each year (Kessler et al., 2005a, 2005b; Vieta and Morralla, 2010). These disorders place a profound emotional, financial, and social burden on the individual, their families, and society at large.

To date, the majority of medications receiving FDA approval for neuropsychiatric disorders are modifications of drugs that were developed several decades ago based upon clinical observations, as well as trial and error. Unfortunately, *bona fide* targets for neuropsychiatric and neurodegenerative disorders are relatively scarce, and there is a paucity of proof-of-concept studies for novel drugs in psychiatric and neurological practice. Clearly, there is an urgent need to identify relevant neurobiological mechanisms that can be translated into treatments for amelioration of psychotic disorders. SZ, MDD, and BP are posited to be multigenic, multifactorial diseases that likely converge in final common pathogenic mechanisms that manifest as psychosis.

Current understanding of the mechanisms of psychotic disorders emanate in part from the identification of genetic loci in defined homogeneous populations (ideally replicated in an unrelated cohort)

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which harbor disease-causing and disease-modifying genes. Discovery of affected genotypes and kindreds has proven beneficial for elucidation of the molecular pathogenesis for these complex neuropsychiatric disorders, and will likely be invaluable tools for genetic counseling as well as diagnosis and selection of medications for affected individuals as the field of translational molecular psychiatry matures into clinical practice. The utilization of human postmortem brain tissues from affected individuals in combination with their respective clinical diagnoses and pathological records relative to appropriate age-matched controls provide a powerful means for investigating disease-related processes related to psychosis. However, mechanisms underlying psychosis remain poorly understood in SZ, BP, and related disorders, effectively impeding the development of relevant and valid animal and cellular models. Traditionally, animal and cellular models have proven useful in relating the role of specific genes, gene targets, and affected pathways with various behavioral indices associated with psychotic disorders. Thus, there are currently few alternatives for studying the etiology and mechanisms for these diseases besides the use of well-characterized human postmortem brains, which places a huge demand on the maintenance and growth of high quality tissue repositories and brain banks that specialize in accrual of brains from neuropsychiatric patients as well as unaffected age-matched normal subjects.

2. Bipolar disorder

Individuals diagnosed with BP present initially with either a manic or depressive episode. A diagnosis of BP type I occurs if a distinct mood change occurs (elevated, expansive, or irritable) for a period of at least a week, or shorter depending if hospitalization is necessitated (DSM-IV criterion A) (Baldessarini et al., 2010; DSM-IV, 2000). A manic episode involves at least three or more symptoms including altered speech patterns, decreased sleep, distractibility, excessive talking, grandiosity, increased goal directed activity, inflated self esteem, overindulgence in pleasurable activities, and racing thoughts (DSM-IV criterion B) (DSM-IV, 2000). A diagnosis of BP type II, a depressive state, typically occurs with a relatively short duration and severity of manic symptoms, and the occurrence of at least one depressive episode. Therefore, a diagnosis of BP may require several years of monitoring, because a manic episode may not occur for quite some time after initial presentation. A gradation and combination of these diverse symptoms has made diagnosis even more difficult, and categories such as bipolar spectrum disorder (BPS) and subthreshold BP are recognized by the World Health Organization. Current estimated worldwide prevalence of BP include an aggregate lifetime prevalence of 2.4% for BPS, 1.4% for subthreshold BP, 0.6% for BP type I, and 0.4% for BP type II (Merikangas et al., 2011). Estimated one year prevalence of 1.5% for BPS, 0.8% for subthreshold BP, 0.4% for BP type I, and 0.3% for BP type II (Merikangas et al., 2011). Unfortunately, suicide rates of BP patients are among the highest of any neuropsychiatric disorder, including an approximate 10-fold increase in the risk of suicide above the general population (Cassidy, 2011). Persons with BP also tend to abuse drugs and alcohol, increasing suicide and overall mortality levels (Baldessarini et al., 2010; McDonald et al., 2011; Oquendo et al., 2010). Neuroimaging studies implicate volumetric changes in several brain relevant limbic brain regions including the amygdala, anterior cingulate, and hippocampus in BP, suggesting some form of connectivity-based degeneration in BP, but these findings are inconsistent and difficult to differentiate from similar changes seen in other neuropsychiatric disorders (Cherlyn et al., 2010; Friedman et al., 2006; Usher et al., 2010). In summary, treating BP is a public health issue that requires improved diagnosis and treatment, particularly for those individuals that may attempt suicide, and a pharmacogenomic approach awaits identification of suitable targets for development.

3. Genome-wide association studies (GWAS) in bipolar disorder: identification of several glutamatergic neurotransmission susceptibility candidates

Twin studies have established that BP is a highly heritable condition (Barnett and Smoller, 2009), and research aimed at finding susceptibility genes have been undertaken worldwide. GWAS investigations are well-recognized high-throughput functional genomics assessments that evaluate genes and single nucleotide polymorphisms (SNPs) from affected and unaffected individuals. GWAS studies are useful to identify candidate genes that can be evaluated further in microarray and qPCR based studies. There have been several GWAS studies performed on cohorts of subjects with BP, including large multi-institution evaluations with thousands of subjects with BP compared to age-matched non-psychiatric controls (Belmonte Mahon et al., 2011; Scott et al., 2009; Sklar et al., 2008). Several BP susceptibility loci have been found, including myosin 5B (MYO5B), voltage-dependent calcium channel, L-type, α1C subunit (CACNA1C) and ankyrin 3 (ANK3), the latter in which the specific identified, SNP (rs10994336) has been replicated in several independent studies (Ferreira et al., 2008; Ruberto et al., 2011; Scott et al., 2009; Sklar et al., 2008; Takata et al., 2011). Unfortunately, the majority of risk factors for BP remain unknown, likely due to the heterogeneity of this multigenic neuropsychiatric disorder. This was evidenced in a recent GWAS analysis of three large cohorts (two from the USA and one from Germany) where the collaborative research group failed to identify any genome-wide significance for any SNPs, even with a breakout of two BP phenotypes, age at onset and psychotic symptoms, which can be interrogated with relatively high power to detect genetic variation (Belmonte Mahon et al., 2011).

Despite these tangible setbacks, there is a serviceable website with a current, annotated database of genetic studies of BP (http://bioprogramming.bsd.uchicago.edu/BDStudies/) (Piletz et al., 2011) that includes several candidate genes related to glutamatergic neurotransmission that are worthy of mention. Both positive and negative findings are cited. Specific glutamatergic neurotransmission candidate susceptibility genes include citron (CIT) positive (Lyons-Warren et al., 2005) and negative (Yosifova et al., 2009), D-amino acid oxidase (DAO) positive (Fallin et al., 2005; Prata et al., 2008) and negative (Shi et al., 2008), and the nitric oxide synthase (NOS) genes NOS1 (neuronal) positive (Fallin et al., 2005; Yosifova et al., 2009) and negative (Buttenschon et al., 2004; Gratacos et al., 2009; Okumura et al., 2010), and NOS3 (endothelial) positive (Reif et al., 2006) and negative (Gratacos et al., 2009; Sklar et al., 2002). GluRs identified as BP candidate genes include the ionotropic α-amino-3-hydroxy-5-methylisoxazolepropionic acid (AMPA) receptor subunits GRIA1 positive (Kerner et al., 2009; Shi et al., 2008) and negative (Gratacos et al., 2009), GRIA2 positive (Perlis et al., 2009) and negative (Shi et al., 2008; Sklar et al., 2002), kainate (KA) receptor subunit GRIK4 positive (Pickard et al., 2006, 2008) and negative (Gratacos et al., 2009), N-methyl-D-aspartate (NMDA) receptor subunits GRIN1 positive (Mundo et al., 2003; Shi et al., 2008; Yosifova et al., 2009) and negative (Georgi et al., 2006), GRIN2A positive (Itokawa et al., 2003) and negative (Gratacos et al., 2009; Shi et al., 2008), GRIN2B positive (Avramopoulos et al., 2007; Fallin et al., 2005; Lorenzi et al., 2010; Martucci et al., 2006; Zhao et al., 2011) and negative (Gratacos et al., 2009; Shi et al., 2008), GRIN2C positive (Shi et al., 2008), and GRIN2D positive (Shi et al., 2008), and metabotropic glutamate receptors (mGluRs) GRM1 positive (Baum et al., 2008; Frank et al., 2011) and negative (Fan et al., 2010; Shi et al., 2008), GRM3 positive (Fallin et al., 2005; Sklar et al., 2008) and negative (Gratacos et al., 2009; Marti et al., 2002; Shi et al., 2008; Yosifova et al., 2009), GRM4 positive (Fallin et al., 2005) and negative (Shi et al., 2008; Sklar et al., 2002), GRM7 positive (Gratacos et al., 2009) and negative (Baum et al., 2008; Shi et al., 2008; Sklar et al., 2002; Yosifova et al., 2009), among other glutamatergic neurotransmission candidates

(Cherlyn et al., 2010; Piletz et al., 2011). A high percentage of these glutamatergic neurotransmission/GluR candidate genes also overlap in susceptibility with SZ (Cherlyn et al., 2010; Fallin et al., 2005; Frank et al., 2011; Marti et al., 2002; Martucci et al., 2006; Pickard et al., 2006), highlighting the complex, multigenic, multifactorial nature of these neuropsychiatric disorders and the difficulty teasing apart genes that might discriminate these two conditions. As evidenced by a nearly equal amount of positive and negative association findings of glutamatergic neurotransmission and GluR genes, the apparent lack of agreement across cohorts and studies emphasizes the high likelihood that susceptibility alleles are moderate in effect size and require very large, homogeneous populations for presence detection.

4. Expression profiling in neuropsychiatric disorders

Due to a paucity of transformative therapy for neuropsychiatric disorders, the majority of current drugs being approved in the present environment are modifications of therapeutics that were identified by investigators in previous generations. Actual targets for neuropsychiatric disorders are difficult to validate, and proof-of-concept studies for novel drugs are rare in molecular psychiatry. The implementation of gene expression profiling methods, including microarray technology and hopefully next generation sequencing technologies in the near future, enables researchers to generate a relative quantitative index of multiple genes simultaneously from postmortem human brain tissue samples as well as optimally prepared brain tissues or cells from relevant animal and/or cellular models in either a high-throughput or moderate-throughput format (Ginsberg and Mirnics, 2006; Hakak et al., 2001; Mimmack et al., 2002; Mirnics et al., 2000). Molecular fingerprinting is performed by extracting RNAs from identified regions or cells, followed by RNA amplification, and hybridizing labeled RNA to desired array platforms. Our research group favors the study of individual populations of neurons for microarray analysis, as this approach enables an assessment of gene expression alterations that occur in one relevant cell type {*e.g.*, entorhinal cortex stellate cells (Fig. 1), neocortical pyramidal and GABAergic interneurons, cholinergic basal forebrain neurons, and CA1 pyramidal neurons, among others} without the confound of admixed adjacent neuronal and non-neuronal (*e.g.*, astrocytes, microglia, oligodendrocytes, vascular, and epithelial) cell types (Ginsberg et al., 2006, 2010, in press, 2011; Hemby et al., 2002, 2003). Assessing gene expression patterns in targeted neuronal populations is important since reliance on regional assessment of expression may emphasize genes contained in the majority of the neurons and/or those in highest abundance in the region, or those in glial and vascular epithelial cell populations. Regional assessment does not adequately reflect the alterations in gene expression occurring in target neurons due to masking and/or dilution effects caused by changes in the total neuronal population of that region. Such differences are highlighted in Fig. 1 where gene expression is compared between microdissected neurons and the region from which the neurons were extracted in normal subjects, providing a clear example of differential expression patterns between the two approaches. These results suggest that, when targeting neurons in heterogeneous neuronal populations for analysis, it is informative to refine the level of molecular analysis to a single neuronal population as well as to analyze the surrounding tissue sample. Quantification of hybridization signal intensity is performed to assess the relative expression level of each feature on an array. Gene expression is determined using bioinformatics software and statistical approaches, enabling coordinate expression level analyses which can be correlated with other variables including age, gender, and antipsychotic medication levels, among others (Altar et al., 2009; Deep-Soboslay et al., 2011; Ginsberg et al., 2010; Ginsberg and Mirnics, 2006). As the majority of neuropsychiatric disorders, including BP, are treated with a combination of antipsychotic and mood stabilizing medications, it is often difficult to determine whether gene expression level changes in postmortem brain tissues are caused organically by the disorder or whether they are a side effect of chronic drug treatments. Unfortunately, antipsychotic medications such as haloperidol and clozapine and mood stabilizers including lithium, valproate, and carbamazepine are notorious for interacting with a wide number of targets and downstream signaling pathways and may have neurodegenerative effects independent of the neuropsychiatric disorder they are being used to treat (Altar et al., 2003, 2009; Bachmann et al., 2005; Gould et al., 2004; Lewis, 2011). The implementation of animal models (principally nonhuman primates and rodents) for drug treatment studies has been helpful to ascertain specific effects of antipsychotic/mood stabilizer treatment on gene and encoded protein expression within a few systems (notably catecholaminergic, cholinergic, GABAergic, and glutamatergic) (Cheng et al., 2008; Fasulo and Hemby, 2003; Fatemi et al., 2006; Lewis et al., 2008; Melchitzky and Lewis, 2008; O'Connor et al., 2007). For example, select AMPA GluRs are differentially regulated in monkeys chronically treated with antipsychotic drugs, as clozapine treatment significantly decreases GRIA1 and increases GRIA3 mRNA levels, whereas both clozapine and haloperidol increase expression of GRIA2 (O'Connor and Hemby, 2007). Importantly, these AMPA receptor alterations were found pyramidal neurons microdissected from layers II/III and V of dorsolateral prefrontal cortex, but not when regional assessment of dorsolateral prefrontal cortex was performed (O'Connor and Hemby, 2007), indicating these changes are likely to be pyramidal neuron specific. In contrast, delivery of the mood stabilizers lithium, valproate, and carbamazepine has been shown to downregulate mRNA and protein levels of the KA receptor GRIK2 in astrocytes but not in neurons (Li et al., 2009), indicating the importance of assaying

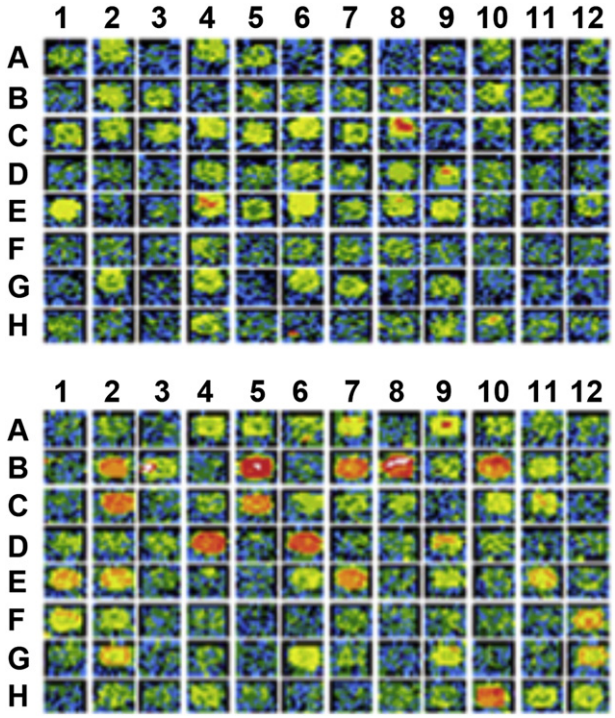

Fig. 1. Representative expression profiling of entorhinal stellate neurons (top panel) and regional entorhinal cortex (lower panel) obtained from normal control human postmortem tissue using the Incyte UniGEM V platform. Several genes expressed in stellate cells were also expressed in entorhinal cortex at differing abundance levels (*e.g.*, compare B2, C5, and B10 between the two panels). mRNAs detectable in stellate cells and not in the regional entorhinal cortex dissection was exemplified in G7 and E4. In contrast, several genes present in the entorhinal cortex dissection were below the limit of detection in stellate cells, likely due to the heterogeneity of admixed cell types within the entorhinal cortex (*e.g.*, compared B5, D4, and H10 between panels). Color coded expression levels depict red as high expression and blue as low expression.

both neuronal and non-neuronal populations in neuropsychiatric disorders and when considering the possibly confounding effects of antipsychotic/mood stabilizing therapeutics. Notably, moderate- and high-throughput, fairly unbiased mRNA methodologies including microarrays provide a cost-effective, simultaneous assessment of gene expression levels. These approaches are somewhat technically challenging, and require high quality RNA to measure the relatively small (20–40%) changes in brain gene expression that typify neuropsychiatric disease (Altar et al., 2009; Atz et al., 2007; Eberwine et al., 2001; Ginsberg, 2008; Ginsberg and Mirnics, 2006; Jurata et al., 2004; Mirnics et al., 2006). They also require validation by independent methods, including real-time quantitative PCR (qPCR) (Bustin, 2010; Nolan et al., 2006) and/or *in situ* hybridization (Bernard et al., 2011; Hashimoto et al., 2008; Mirnics et al., 2000, 2006) as well as analytical measurements of their respective encoded protein products.

5. Gene expression analysis in bipolar disorder

Published microarray analyses of neuropsychiatric disorders have focused mainly on employing postmortem brain samples from SZ subjects, and studies employing brains accrued from MDD subjects are emerging. To date, only a few postmortem brain studies have evaluated expression level changes in BP. Although a comprehensive assessment of all the genes altered in BP is beyond the scope of this review, classes of transcripts that display differential regulation (principally downregulation) in BP *versus* age-matched controls include 14–3–3 family genes (*e.g.*, YWHAQ and YWHAZ; which also overlap with changes observed in SZ) (Altar et al., 2009; Elashoff et al., 2007; Klempan et al., 2009; Konradi et al., 2004; Sequeira et al., 2007; Sibille et al., 2004), neuropeptides {*e.g.*, cholecystokinin (CCK), tachykinin precursor 1 (TAC1), proenkephalin (PENK)}, protein kinases {*e.g.*, calcium/calmodulin-dependent protein kinase kinase 2, beta (CAMKK2), and cyclin-dependent kinase 5 regulatory subunit 1 (CDK5R1)}, ubiquitin pathway genes, and G-protein coupled receptor signaling, among others (Altar et al., 2009; Le-Niculescu et al., 2007; Ogden et al., 2004; Ryan et al., 2006). In addition, several studies that employ subregional microarray/qPCR analyses are highlighted because they illustrate the power of discriminating gene expression levels from presumably affected cell types and/or regions. Specifically, a study of cell cycle regulation markers in SZ and BP within subregions of the hippocampal formation indicates complex, region-specific alterations in genes associated with DNA repair mechanisms. For example, mRNA for the methyl-CpG binding domain protein (MBD4) is upregulated in the stratum oriens region of the CA1 and CA2/CA3 hippocampal sectors (Benes et al., 2009). Moreover, related genes involved in the transcriptional complex, G1 and G2 checkpoints, and neurotrophin/neurogenesis classes are dysregulated in a disease-specific, regionally-specific manner, including downregulation of neuregulin 1 (NRG1), neurotrophin-3 (NT-3), and several fibroblast growth factor subtypes (FGF3 and FGF9) within CA1 of BP subjects, whereas upregulation of neuropilin 1 (NRP1), the neurotrophin-3 receptor TrkC, and the roundabout axon guidance receptor subtype 1 (ROBO1) is found in the same subjects within the CA2/CA3 sector (Benes et al., 2009). These hippocampal subregional results are consistent with *post hoc* analyses of regional hippocampal investigations that show upregulation of 19/44 genes in the apoptotic pathway in BP (Benes et al., 2006). Within the brainstem, a regional study of the locus coeruleus combining laser capture microdissection (LCM) with microarray analysis found several genes related to glutamatergic neurotransmission in astrocytes, including glial high affinity glutamate transporter member 2 (SLC1A2), glial high affinity glutamate transporter member 3 (SLC1A3), and glutamine synthetase (GLUL) differentially regulated in subjects with MDD compared to BP (Bernard et al., 2011). Specifically, dysregulation of these genes were found via microarray analysis in MDD but not BP subjects, which was validated via qPCR and *in situ* hybridization (Bernard et al., 2011). These observations point to the importance of studying neuronal as well as non-neuronal populations in multiple interconnected brain regions (*i.e.*, not simply restricting analyses to forebrain structures such as the hippocampal formation and dorsolateral prefrontal cortex) and enabling comparisons between and across neuropsychiatric disorders including BP, MDD, and SZ.

6. Glutamatergic neurotransmission gene expression analysis in bipolar disorder

Glutamatergic signaling, in particular through ionotropic AMPA and NMDA receptors, plays a crucial role in excitatory neurotransmission, synaptic function, neuroplasticity, and development. Dysfunction of the glutamatergic system, notably within excitatory circuits driven by AMPA and NMDA receptors, as well as within non-neuronal cells such as astrocytes and oligodendrocytes, has been implicated in the pathogenesis of several neuropsychiatric disorders, including BP, MDD, and SZ (Javitt, 2007; Marsden, 2011; Sequeira and Turecki, 2006). Although relatively little information has been published on expression level differences of transcripts related to glutamatergic neurotransmission and/or GluRs to date in BP relative to the ongoing work being performed in SZ and MDD, the data that is available is worth summarizing. Specifically, high-density oligonucleotide microarray analyses within postmortem BP brains have identified differential regulation of several genes, including GluRs. Specifically, downregulation of the KA receptor GRIK1 and mGluR receptor GRM1 are observed in a study where a total of 53 genes are differentially regulated (Iwamoto et al., 2004; Kato et al., 2007). Importantly, GRIK1 downregulation has been replicated in an independent study where the research group hypothesized that a significant portion of the expression level changes occur on glial cells (Choudary et al., 2005), consistent with a larger body of regional microarray studies in SZ where glial alterations have been reported by several research groups (Hakak et al., 2001; Haroutunian et al., 2007; Mirnics et al., 2000; Tkachev et al., 2003). Cell type-specific decrements in GluRs within BP and SZ have been investigated, including significant loss of KA receptors GRIK1 and GRIK1 and NMDA receptor GRIN2A in GAD67-positive GABAergic interneurons within the cingulate cortex of subjects with BP and SZ (Woo et al., 2004, 2007). These studies point to the importance of evaluating specific cell types within forebrain regions to determine specific changes in relevant classes of transcripts. Importantly, these observations in BP are consistent with regional and single population expression profiling studies in SZ that indicate frank glutamatergic dysfunction as a mechanism underlying pathophysiology (Hemby et al., 2002; Mirnics et al., 2000). Specifically, downregulation of select AMPA and NMDA receptor subunits via microarray analysis are consistent with *in situ* hybridization and PCR-based observations of decreased GluR and glutamate transporter expression within the hippocampus as well as frontal and temporal neocortex (Beneyto and Meador-Woodruff, 2008; Eastwood and Harrison, 1999, 2005; Humphries et al., 1996; McCullumsmith et al., 2007; Mueller and Meador-Woodruff, 2004; Rao et al., 2010; Uezato et al., 2009). Downregulation of the GluR-interacting partners SAP102 and α-internexin have also been reported in BP (McCullumsmith et al., 2007; Pennington et al., 2008). The general finding of decreased GluR expression is consistent with increased glutamate levels in BP cerebral cortex (Hashimoto et al., 2007; Kim and Webster, 2010). Overall, downregulation of ionotropic (as well as metabotropic) GluRs on both pyramidal neurons and calbindin-immunoreactive, parvalbumin-immunoreactive, and calretinin-immunoreactive GABAergic interneurons may have profound downstream effects upon excitatory neurotransmission and subsequent behavioral and cognitive sequelae.

Future studies are warranted in postmortem BP brain tissues to characterize further potential expression level dysregulation of markers of glutamatergic neurotransmission and GluRs. Importantly,

next generation technologies are now being employed in conjunction with the use of postmortem brains obtained from neuropsychiatric patients (including those with BP) to comprehend the functional genomics/genetic variant imbalances that underlie these disorders from a population-based perspective (Lin et al., 2011; Tang et al., 2011). Recent studies include high-throughput microRNA (miRNA) profiling of human miRNAs, which revealed dysregulation of 7 miRNAs in SZ subjects and an additional 15 miRNAs in BP subjects (Kim et al., 2010). Interestingly, all 22 of these miRNAs were determined via *in silico* mining techniques to regulate brain specific genes that are classified within neurodevelopment and behavior hubs (Kim et al., 2010), potentially impacting the development of SZ and BP. Copy number variation (CNV) analysis in rare variants has also generated significant interest for studying the complex genetic susceptibility of multigenic diseases, including neuropsychiatric disorders (Chen et al., 2010; Grozeva et al., 2010; Saus et al., 2010). Preliminary candidate genes with likely CNVs related to SZ, MDD, and BP include mGluR GRM7 (Saus et al., 2010), consistent with a GWAS study in BP (Gratacos et al., 2009). Next generation deep sequencing and epigenetic approaches will likely help the neuropsychiatric disorder field by uncovering rare genetic variants which may be exploited to understand mechanisms underlying the disease process. Although these new functional genomics technologies generate significant excitement, each has caveats and limitations that have to be acknowledged (Chen et al., 2010; Tang et al., 2011), particularly to their applicability to populations of subjects, and integration of these results with existing microarray, GWAS, and biochemical studies are critical for mechanistic studies of these complex disorders. Moreover, current microarray and qPCR-based studies illustrate the importance of studying subregions and individual cell types for future gene discovery studies in neuropsychiatric disorders even though these approaches are more technically challenging than regional and global tissue based endeavors (Ginsberg et al., in press).

7. Conclusions

The search for genes underlying the pathophysiology of BP has been complicated by a limited understanding of pathogenesis, a paucity of animal models, and the genetic and phenotypic complexity of this debilitating neuropsychiatric disorder. This review has illustrated small, but significant breakthroughs in GWAS and expression profiling pertinent to glutamatergic neurotransmission and GluR expression. Glutamatergic dysfunction has been implicated in SZ, MDD, and BP, and differentiating these changes poses a challenge for the field. We posit that expression profiling via subregional and/or homogeneous population approaches will be more informative than global or regional studies with admixed neuronal and non-neuronal cell types that may have complex alterations occurring throughout disease onset and progression. Strategic emphasis is required to continue efforts for the systematic accrual of clinically characterized BP brain tissue and age-matched unaffected control subjects to further neuropathological analyses as well as proposed state-of-the-art connectome and circuit driven approaches that enable highly targeted functional genomic and proteomic assessments. In conclusion, GWAS and population-directed microarray and qPCR interrogative strategies along with exciting next generation sequencing technologies may help develop novel agents that target systems and/or circuits adversely affected specifically during BP pathogenesis, potentially reducing the problems of drug interactions and unwanted side effects that currently plague the treatment approach.

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