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Mitochondria, oligodendrocytes and inflammation in bipolar disorder: evidence from transcriptome studies points to intriguing parallels with multiple sclerosis

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Abstract

Gene expression studies of bipolar disorder (BPD) have shown changes in transcriptome profiles in multiple brain regions. Here we summarize the most consistent findings in the scientific literature, and compare them to data from schizophrenia (SZ) and major depressive disorder (MDD). The transcriptome profiles of all three disorders overlap, making the existence of a BPD-specific profile unlikely.

Three groups of functionally related genes are consistently expressed at altered levels in BPD, SZ and MDD. Genes involved in energy metabolism and mitochondrial function are downregulated, genes involved in immune response and inflammation are upregulated, and genes expressed in oligodendrocytes are downregulated. Experimental paradigms for multiple sclerosis demonstrate a tight link between energy metabolism, inflammation and demyelination. These studies also show variabilities in the extent of oligodendrocyte stress, which can vary from a downregulation of oligodendrocyte genes, such as observed in psychiatric disorders, to cell death and brain lesions seen in multiple sclerosis. We conclude that experimental models of multiple sclerosis could be of interest for the research of BPD, SZ and MDD.

Keywords

mood disorders; transcriptome; microarrays; myelin; white matter; oligodendrocytes; mitochondria; inflammation; schizophrenia; multiple sclerosis

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Introduction

A subset of symptoms of bipolar disorder (BPD) overlaps with other psychiatric disorders such as major depressive disorder (MDD) and schizophrenia (SZ) (Berrettini, 2003; Moller, 2003). In concordance with the shared clinical symptoms, molecular and genetic findings show significant overlap across these disorders (Green et al., 2009; Huang et al., 2010; Knight et al., 2009). Thus, if we accept that any gene expression profile found in BPD might also be found in selected other psychiatric disorders and is not exclusive for BPD, a number of themes emerge from transcriptome studies. Given the complexities of psychiatric disorders, the overlap of findings in BPD, MDD, and SZ could be useful to correlate gene expression patterns with specific symptoms such as depression or psychosis, and advance the development of symptom-specific medications.

After an initial discussion of experimental limitations, essential for the proper consideration of the available literature, we will address the most consistent transcriptome findings in BPD. These findings point to abnormal bioenergetic function, myelin deficiencies, and increased activity of the immune system. Interestingly, this triad of pathological abnormalities is also the focus of multiple sclerosis (MS) research. We conclude that certain experimental models of MS are of potential use for the study of BPD and related psychiatric disorders.

Tissue sources for gene expression profiling

Human brain samples are the most proximal tissue for any kind of brain disorder, but are also the most difficult to obtain. Samples are collected post-mortem, and the lack of experimental control before samples enter a brain bank presents a number of limitations. These include significant lags between time of death and proper storage of tissue, heterogeneity in cause of death, adverse pre-mortem events, various medical interventions, advanced age of patients, comorbidity with other disorders, exposure to prescription drugs, dietary preferences, smoking habits, and potential addictions. Additionally, post-mortem samples cannot be collected in large numbers, limiting the statistical control for the influence of these complex factors on experimental outcomes.

Alternative tissue types that might be easier to collect on larger scales, and might permit tighter experimental control, are usually further removed from the brain. Blood samples and cell lines derived from various tissues such as lymphocytes or fibroblasts are the most frequent alternatives. These samples are collected from live patients at comparatively younger ages, are easier to harvest, and can be kept under defined culture conditions with ample time to overcome ('wash out') the effects of drug exposure and dietary influences. Peripheral cells can be transformed into cell lines, which can be multiplied and propagated, and the effects of various experimental manipulations such as drug treatments can be studied in parallel cultures of the same sample. Aside from valid questions regarding the comparability of gene expression patterns in peripheral tissues with gene expression patterns in brain tissue, general tissue culture issues have to be considered as well. These include the consequences of transforming cells programmed naturally for a finite number of mitotic divisions into cells that divide continuously, and the fact that over time cells with the fastest rate of division overgrow all other cells, creating a monoclonal culture that might not be representative of the original sample. Primary cultures, in which cells are not transformed, have a finite life span and limited quantities, but they can be helpful to circumvent the unwanted effects of cell immortalization.

The nature of psychiatric disorders makes them a uniquely human affliction, as these disorders affect complex behaviors that we are most adept to diagnose in humans. Animal models can be employed to determine the biological targets of therapeutic agents used to

treat BPD and to study the downstream effects of pathological conditions on biochemical pathways and behaviors. However, post-mortem gene expression profiling is essential to identify these pathological changes modeled in animals.

Although there is no optimal approach to gene expression profiling in BPD, by combining different approaches and by considering their shortcomings in the interpretation of the data, we have obtained novel hypotheses about the pathophysiological mechanisms of BPD.

Studies of the transcriptome

The sequencing of the human genome and the associated coding sequences, together with the rapid progression of biological technologies have led to new hopes for a better understanding of psychiatric disorders (Horvath et al.; Mirnics et al., 2006). ‘Transcriptome’ refers to the entirety of messenger ribonucleic acids (mRNAs) in a particular tissue. It is assumed that an altered expression level of an mRNA in a disease is an indication for an abnormality in either the encoded protein, or a biologically connected structure or function. In BPD, transcriptomes have been most thoroughly studied with microarrays, though methodological approaches are constantly evolving. Levels of almost all known transcripts of the genome can be examined on a single microarray, a particularly attractive option for the study of polygenic disorders (Konradi, 2005). More recently, sequence-based approaches have begun to replace microarray studies. These ‘deep sequencing’ approaches sequence the entire transcriptome multiple times and collect information on sequence variants and frequency of transcripts (Wang et al., 2009).

Owing to their large scale, transcriptome studies yield a fair number of false-positive and false-negative findings. A number of corrective algorithms have been developed to deal with the problem of multiple testing such as the commonly used Benjamini-Hochberg correction (Benjamini and Hochberg, 1995). Large-scale gene expression approaches are not well suited for the study of a small number of genes of interest. The strength of transcriptome studies lies in the ability to examine expression levels of groups of functionally or anatomically related genes, as the likelihood that an entire group of related genes is concordantly regulated by chance is exceedingly small (Konradi, 2005). Programs have been developed that use existing databases to determine the expected versus observed rates of regulated genes mapped to predefined groups of related genes (see for example Dennis et al., 2003; Huang et al., 2009; Salomonis et al., 2007; Subramanian et al., 2005; Zhang et al., 2005).

While analysis of the entire transcriptome represented a shift from the conventional hypothesis-driven approaches and was criticized by some as ‘high-priced fishing expeditions’, these studies have extended the boundaries of current knowledge and generated novel hypotheses (Gibson, 2003).

Transcriptome studies have the potential to yield valuable clues to the underlying pathology in BPD, and they can help to define novel research strategies (Konradi, 2005). For example, a downregulation of mRNA transcripts encoding mitochondrial genes could indicate a loss of mitochondria or a loss of a cell type that has particularly large numbers of mitochondria. Alternatively, the same molecular profile could arise from dysregulation of a genetic ‘master switch’ that regulates a group of genes expressed in mitochondria, or from dysregulation of epigenetic mechanisms such as histone modifications and DNA methylation (Petronis, 2010). Initial findings can be followed up with additional experimental approaches to clarify and extend our knowledge base.

Major gene groups of interest in bipolar disorder: Rounding up the usual suspects

For many psychiatric disorders, including BPD, a number of neurotransmitter systems were initially suspected of playing a role in the disease mechanism. Early studies were guided by available technology and pharmacological observations, with considerable elements of serendipity. For example, compounds that were initially used as anesthetics, or as solvents for drugs, had surprising effects on symptoms of psychiatric disorders (Cade, 1949; Lopez-Munoz et al., 2005). These observations led to testable hypotheses but they also set boundaries and created narratives in which what could not be imagined or measured remained unexplored. Discovery-driven studies and novel technologies changed that picture and created interesting new models.

Initial studies focused on known neurotransmitter systems such as biogenic amines (Cousins et al., 2009; Manji and Lenox, 2000; Schildkraut, 1974), glutamate, and GABA (Krystal et al., 2002; Post, 1990), and on altered regulation of glucocorticoids (Daban et al., 2005; Watson et al., 2004), with implications of an involvement of each system. Studies with lithium led to the hypothesis of a role of the glycogen synthase kinase 3 beta pathway (Ikonov and Manji, 1999; Klein and Melton, 1996), while studies with valproic acid introduced a role for epigenetic mechanisms in BPD (Phiel et al., 2001). Serotonin and norepinephrine became a focus because of their involvement in the mechanism of action of antidepressants (Owens, 2004). Overall, many different systems seemed to be implicated in BPD, with supportive evidence for each one.

Going beyond the usual suspects: Mitochondria, myelin and the immune system in BPD

In gene expression studies, groups of regulated genes are examined for shared biological, molecular, or structural functions as well as for mutual mechanisms of regulation. These studies are quite comprehensive and in the past led to novel discoveries, novel hypotheses and re-discovery of old hypotheses. Herein, we will focus on three gene groups that have raised particular attention in transcriptome studies: mitochondria, myelin and immune function (tables 1, 2). These systems are important throughout the brain and could explain the widespread pathological findings.

Abnormal patterns of mitochondrial genes in BPD

Gene and protein expression profiles in BPD show a decrease of mRNA and proteins involved in mitochondrial functions such as oxidative phosphorylation (OXPHOS) (Iwamoto et al., 2005; Konradi et al., 2004; Pennington et al., 2008; Washizuka et al., 2005). Downregulations were observed in the prefrontal cortex (PFC; Brodmann areas 9 and 46, table 1), (Iwamoto et al., 2005; Pennington et al., 2008; Sun et al., 2006), hippocampus (Konradi et al., 2004) and in lymphoblastoid cell lines (table 2), (Washizuka et al., 2005). Under compromised OXPHOS, ATP levels decrease and the activity of ATP-dependent ion pumps such as the Na⁺/K⁺-ATPase is slowed down, causing the membrane potential to shift toward hypopolarization. Neurotransmitters are released, and their uptake is delayed. The consequences of ATP loss have been studied in models of ischemia and ensuing glutamate toxicity, providing insights into the pathological mechanisms that in extreme cases lead to cell death (Calabresi et al., 1995; Nieber, 1999; Santos et al., 1996).

A confound in post-mortem studies of mRNA levels for proteins involved in mitochondrial function is a causality dilemma between degradation of mRNA under lower pH levels (Vawter et al., 2006; Washizuka et al., 2005), and reduced mRNA levels for mitochondrial

proteins reducing pH levels due to compromised OXPHOS (figure 1). Samples with low pH are considered to be affected by adverse agonal events and are excluded from RNA studies, which inadvertently leads to the exclusion of samples with genuine molecular abnormalities affecting bioenergetic function. Specifically, lower mRNA and protein levels of the electron transfer chain cause a shift from OXPHOS to glycolysis to retain ATP production, which leads to the accumulation of lactic acid, the acidification of tissue, and a decrease in pH (Clay et al., 2010). By excluding samples with lower pH, patients with pathologically reduced mitochondrial function are excluded. A correlation between mRNA levels of mitochondrial genes and pH has been demonstrated (Vawter et al., 2006), though cause and effect remain to be elucidated. Since low pH levels are also a function of agonal stress and should be observed throughout the brain (Vawter et al., 2006), we chose to match samples for pH levels in the cerebellum, while examining mRNA profiles in the hippocampus (Konradi et al., 2004). We reasoned that decreased mitochondrial mRNA levels in the hippocampus could not be due to agonal stress if pH levels in the cerebellum were in the normal range. By this approach, we found a large decrease of mRNA levels for proteins involved in OXPHOS in BPD.

In a transcriptome study of samples matched for pH, the downregulation of mitochondrial genes was still observed in the post-mortem PFC in BPD and SZ (Iwamoto et al., 2005). A study in cultured lymphocytes, which was not confounded by agonal stress, showed that cells from subjects with BPD responded to glucose deprivation with a downregulation of mRNA transcripts for the mitochondrial electron transfer chain, whereas cells from normal controls responded with a robust upregulation (Naydenov et al., 2007). This study showed that cells from BPD patients are unable to properly adjust bioenergetic output during glucose shortages, indicating problems with the molecular regulation of OXPHOS gene expression.

Corroborating *in vivo* evidence for mitochondrial involvement in BPD comes from magnetic resonance spectroscopy (MRS), an imaging technique that allows visualization of energy-related metabolite levels and pH in the brain. Kato et al. found reduced frontal lobe pH in medicated and unmedicated BPD patients (Kato et al., 1998; Kato et al., 1993), and two-dimensional proton echo-planar spectroscopic imaging of medication-free BPD patients showed a shift from OXPHOS to glycolysis (Dager et al., 2004), (figure 1).

Mitochondrial diseases are frequently comorbid with psychotic symptoms and misdiagnosed as BPD or SZ (Campos et al., 2001; Fattal et al., 2006; Grover et al., 2006; Mancuso et al., 2008; Prayson and Wang, 1998). Patients exhibiting classical mitochondrial disease symptoms in muscle tissue, such as ragged red fibers and electron transport chain deficiency, also commonly present with psychosis or depression (Fattal et al., 2006; Grover et al., 2006; Mancuso et al., 2008; Prayson and Wang, 1998). These observations make a particularly strong case for a role of mitochondria in the clinical symptoms of psychosis, since the primary disease-causing events in mitochondrial disorders are mutations in mitochondrial DNA or mRNAs coding for mitochondrial proteins.

In most studies of psychiatric populations, the majority of patients are on medication. Thus, medication effects on mitochondrial genes cannot be entirely excluded. In studies of medication effects, mood stabilizers provided partial protection for mitochondria under stress, whereas first-generation antipsychotic drugs had adverse effects on mitochondrial respiration (Bachmann et al., 2009; King et al., 2001; Maurer and Moller, 1997; Maurer et al., 2009; Pereira et al., 1992; Prince et al., 1997; Sagara, 1998; Struwing et al., 2007; Valvassori et al.; Washizuka et al., 2009). These findings suggest that mitochondrial pathology could be introduced by antipsychotic drugs, but not by mood stabilizers.

As with other studies, significant overlaps between BPD and SZ were seen. For example, Iwamoto et al. observed a tendency for the same expression changes in the two diseases and commented that the overall pattern of differential gene expression was very similar in BD and SZ (Iwamoto et al., 2005). In a study of hippocampal gene expression patterns, the downregulation of mitochondrial genes was restricted to subjects with BPD and was not observed in subjects with SZ (Konradi et al., 2004). These differences could be brain-area specific, or the result of false-negative or false-positive findings in SZ.

Abnormal patterns of oligodendrocyte markers in BPD

In the central nervous system, oligodendrocytes insulate long-range axons with myelin sheaths to form white matter tracts. Expression levels of oligodendrocyte-specific mRNAs were found to be downregulated in BPD and related disorders. For example, gene expression profiling of the PFC (Brodmann area 9) in 15 BPD samples from the Stanley Foundation showed a reduction of oligodendrocyte- and myelin-specific genes. These expression changes had a high degree of overlap with SZ (table 1), (Hakak et al., 2001; Tkachev et al., 2003). Gene expression profiling in the temporal cortex (Brodmann area 21) of patients with MDD, collected by the Stanley Foundation, also showed downregulation of oligodendrocyte-specific genes (Aston et al., 2005). Not surprisingly, the authors of the latter publication concluded that MDD may share common oligodendroglial abnormalities with SZ and BPD. Myelin abnormalities in BPD, SZ and MDD have been supported by histological observations as well as by imaging studies such as diffusion tensor imaging (for a review see Herring and Konradi, 2011), lending further credibility to the gene expression profiling observations.

Although oligodendrocyte abnormalities are not likely key to the pathology of all instances of BPD, they could be causal in some cases. For example, an increased incidence of psychiatric symptoms associated with BPD, MDD and anxiety disorders has been documented in multiple sclerosis (MS), an inflammatory disease of the central nervous system whose primary pathology is demyelination (Chwastiak and Ehde, 2007; Hogancamp et al., 1997). Although depression and anxiety might be normal responses to the diagnosis of a severe neurodegenerative disorder, this argument cannot explain the increased incidence of BPD in MS. Moreover, neuregulin (NRG), a gene involved in oligodendrocyte development and myelination of the central nervous system, is one of the genetic loci for BPD and SZ, (Tavaglia et al., 2008). NRG belongs to a family of epidermal growth factor-like ligands that interact with ErbB receptor tyrosine kinases. A loss of ErbB signaling in transgenic mice leads to changes in oligodendrocyte number and morphology, increased levels of dopamine receptors and transporters, and behavioral alterations consistent with neuropsychiatric disorders (Roy et al., 2007). Although most genetic NRG studies were carried out in SZ (Stefansson et al., 2003; Stefansson et al., 2002), NRG1 haplotypes were also associated with psychotic BPD (Goes et al., 2009).

Because training and experience influence white matter structure, it is possible that myelin deficiencies may result from, or cause some, cases of psychiatric disorders. On the positive side, training of working memory leads to white matter changes and facilitates connectivity in the corpus callosum, the white matter tract that connects both cerebral hemispheres and other brain areas (Takeuchi et al., 2010). On the negative side, sensory deprivation in mice prevents the developmental increase in myelin mRNA transcripts (Lyckman et al., 2008). These observations suggest that hypoactive brain structures have decreased myelination. Although we do not know whether the reduction in oligodendrocyte markers observed in psychiatric illnesses is a cause or symptom of disease, it seems a reasonable assumption that disruptions of connectivity due to myelin deficiencies could contribute to the clinical symptoms in BPD and related disorders.

Gene expression patterns indicative of inflammatory processes

Transcriptome analysis in the PFC (Brodmann area 9) and the orbitofrontal cortex (Brodmann area 11) of BPD subjects showed an upregulation of immune response genes (table 1), (Ryan et al., 2006). Independent studies confirmed these findings in the frontal cortex (Brodmann area not mentioned Rao et al., 2010) and in Brodmann area 46 (PFC), where a similar signature was seen in SZ patients (Arion et al., 2007; Shao and Vawter, 2008). Gene expression analysis in the PFC (Brodmann area 10) of MDD yielded the same pattern (Shelton et al., 2010). Such gene expression changes could be due to duration of illness, as changes in inflammatory genes were found in SZ patients only with long-term illness (Narayan et al., 2008). Monocytes of BPD patients and offspring of BPD parents showed increased inflammatory gene expression (table 2), (Padmos et al., 2008). Comparisons of the presence of this gene expression signature between monozygotic and dizygotic twins revealed the signature to be primarily the result of environmental factors (Padmos et al., 2009).

The transcriptome studies emphasize the role of the immune system in BPD, SZ and MDD, a role that has long been hypothesized (Goldstein et al., 2009). The upregulation of genes involved in immune response indicates inflammatory processes in the brain and suggest that models of multiple sclerosis (MS) might provide some insights into the pathophysiology of psychiatric disorders. Although the pathogenesis, disease course, and clinical symptoms of MS differ from those of BPD, animal models and strain-specific vulnerabilities in mice (Lynch et al., 2010), might be useful to examine how the genetic environment influences inflammatory processes in the brain (see below).

Limitations of transcriptome studies of brain samples

Assuming that the technology itself is flawless - which no technology is - a number of limitations in transcriptome studies need to be considered when interpreting data. While these factors should be kept in mind, they should not detract from the valuable information that can be obtained from transcriptome studies.

False-positive and false-negative errors

Transcriptome studies, by virtue of the large number of genes analyzed, have a high number of false-positive and false-negative findings (Konradi, 2005). Although algorithms have been developed to reduce the probability of false-discoveries (for example Benjamini and Hochberg, 1995), the false-negative errors go mostly unnoticed. The strength of transcriptome studies is their ability to examine groups of genes of similar function or location, providing information on pathological processes. The likelihood that an entire group of functionally related genes reaches significance by chance is much lower than the likelihood for any individual gene. The inverse argument applies for false-negative findings, where it seems unlikely that an entire group of functionally related genes will be invisible in the analysis.

Limited experimental control over human brain samples

RNA is not particularly stable and is rapidly degraded by RNases, which are ubiquitous in all tissues. Factors that cannot be experimentally controlled in human brain samples, such as pre-mortem events, cause of death, and post-mortem events affect RNA integrity (see discussion on pH, above). Due to the limited availability of human brain samples, overall sample sizes are small enough to be sensitive to these unavoidable variabilities. Studies might find false-positive results, though the chances of false-negative results are likely equally as high. Transcriptome studies are a good example of an instance where the absence of evidence cannot be interpreted as evidence of absence.

Brain-specific genes will be over-represented in the group of regulated genes

Each tissue type has a specific profile of expressed genes. The list of regulated genes in the brain will naturally be biased toward neuronal and glial markers expressed in the brain area examined. Although excitement might be high when a favorite pathway or neurotransmitter system emerges in the analysis, proper statistical approaches that correct for tissue bias are crucial. It is therefore necessary to determine if regulated genes are over-representative of any particular brain function. Fisher's exact test and variations thereof must be used to examine if the percentage of genes regulated in a specific category is statistically different from the percentage of genes regulated in all categories (for example, see Hosack et al., 2003).

Potential reasons for diverse findings in expression patterns

The relatively small sample sizes of post-mortem studies leads to inherent statistical errors, with false-positive and false-negative results. Still, the considerable overlap in the findings raises confidence in the value of these studies. A number of factors that might contribute to the variability between studies will be briefly discussed here.

First, it is likely that different brain areas have different disease signatures. Thus, it cannot be expected that all brain areas yield the same results. Second, differences in dissection methods could play a role. For example, abnormalities in oligodendrocyte genes might predominate in white matter and thus depend on the relative proportion of grey and white matter in a sample. Mitochondria predominate in synapses (neuropil), whereas glycolysis predominates in astroglia (Nehlig and Coles, 2007), further supporting the relevance of balancing grey and white matter. Thirdly, gender and race differences influence the data. Race differences are well known in mitochondria, where different haplogroups define genetic populations (Torroni and Wallace, 1994). Gender differences in brain structure, function and biology are also amply described (Cosgrove et al., 2007) and extend to gene expression profiles in the brain (Vawter et al., 2004). Fourthly, some gene expression profiles are likely the result of exposure to medication. Varying prescription practices, as well as geographically distinct dietary habits could distort the gene expression patterns. Finally, given the overlap between BPD, SZ and MDD, disease symptoms may be interpreted differently and nosology might vary (Blacker and Tsuang, 1992).

The common thread between myelin, mitochondria and inflammation

Multiple sclerosis research has long focused on pathological processes that link myelin, inflammation and mitochondrial function (figure 2), (Kalman et al., 2007). Experimental MS models can potentially provide insight into the pathophysiological mechanisms of BPD. For example, the copper chelator cuprizone (CPZ) induces demyelination in mice and serves as a murine model for MS (Herring and Konradi, 2011). We have shown that CPZ reduces the expression of oligodendrocyte genes in the rat PFC, and that this reduction is accompanied by deficits in PFC-mediated cognitive behaviors (Gregg et al., 2009). By carefully selecting the age of exposure – adolescence - and the concentration of CPZ, the PFC was specifically targeted without any effect on other brain areas and no decline in motor function. This study showed that MS-inducing drugs can affect higher cognitive function in the absence of motor deficits, presumably modulated by genetic background, force of impact, i.e. dose of CPZ, and periods of heightened vulnerability of different brain areas.

CPZ selectively injures oligodendrocytes (Matsushima and Morell, 2001). Inflammatory processes and mitochondrial stress are required to mediate oligodendrocyte toxicity by CPZ. CPZ causes the formation of megamitochondria in the liver, which are formed in the presence of free radicals and can lead to apoptosis (Wakabayashi, 2002). Transgenic mice

lacking neuronal nitric oxide synthase, an inhibitor of the electron transfer chain and inducing agent of oxidative stress, are relatively resistant to CPZ-induced demyelination (Linares et al., 2006).

In primary oligodendrocyte cultures, inflammatory cytokines are required for CPZ-mediated cell death (Pasquini et al., 2007), demonstrating the involvement of the immune system in cell death. Transgenic mice lacking the type 2 CXC chemokine receptor (CXCR2), expressed by neutrophil cells of the immune system, are resistant to CPZ-induced demyelination, although their initial response to CPZ is similar to the response of wild-type mice (Liu et al., 2010). Whereas wild-type mice progress from an initial downregulation of oligodendrocyte-specific genes to apoptosis and widespread demyelination, CXCR2 knockout mice recover from the initial insult with most of their oligodendrocytes spared. These observations demonstrate that the energy metabolism and the immune system control the mechanism and magnitude of demyelination.

Pathological connections between myelin loss, mitochondria and inflammation have been observed in other MS models as well. For example, the experimental autoimmune encephalomyelitis (EAE) model has been used for a long time to model MS, and it is well known that mitochondria and inflammation play a significant role in this model (Gold et al., 2006). Mice lacking cyclophilin D, a key regulator of the mitochondrial permeability transition pore, partially recovered in the EAE model, whereas wild-type mice progressed in the disease (Forte et al., 2007). Activation of the mitochondrial permeability transition pore seemed a critical factor in the disease progression. Similarly, suppressing the activation of microglia repressed the development of EAE, confirming a role for the immune system (Heppner et al., 2005).

MS models show that the genetic environment determines the extent of myelin stress and the range of pathological consequences (deLuca et al., 2010; Piehl and Olsson, 2009). Thus, the combination of polymorphisms in genes of immune system proteins, and/or genes of proteins involved in bioenergetic function, could determine which brain areas are affected, and to what extent (figure 2).

Concluding remarks

Despite many confounding factors, transcriptome profiling has produced results that have been verified in multiple studies. Similar molecular signatures have been observed in BPD, SZ and MDD, generating novel hypotheses on the pathophysiology of BPD and related disorders. The three factors we focused on, mitochondria, myelination and inflammation, are systemic in the brain and not circumscribed like the neurotransmitter systems of previous hypotheses. We propose that variant environmental influences together with genetic predispositions determine the degree to which different brain areas and functions are affected in individual patients, thus leading to variations in psychiatric symptoms and diagnoses. Introducing these hypotheses does not negate previous hypotheses, but can interdigitate with them. Mitochondrial vulnerabilities and myelination defects could be the disease cause in some cases, and a consequence of the disease processes in others. Similarly, inflammation could be secondary to demyelination and/or apoptotic processes in cells under mitochondrial stress, or it could be the primary cause of demyelination triggered by viral infections (Hart et al., 1999; Karlsson et al., 2001). Although we do not propose that BPD, SZ and MDD are variants of MS, the large knowledge base of MS research might provide some interesting and novel insights into disease mechanisms and treatment approaches in these disorders. Transcriptome studies have played an essential role in the development of these hypotheses, and further research of gene expression profiles in BPD will be helpful to deepen and expand our knowledge.

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Abbreviations

BPD	bipolar disorder
SZ	schizophrenia
MDD	major depressive disorder
OXPHOS	oxidative phosphorylation
ETTs	electron transfer mRNA transcripts
TCA cycle	tricarboxylic acid cycle

Gene Symbol/Gene Name

ATP5C1	ATP synthase gamma chain
ATP5G2	ATP synthase, c (subunit 9) isoform 2
ATP5G3	ATP synthase, c (subunit 9) isoform 3
ATP5H	ATP synthase, subunit d
ATP5J	ATP synthase subunit f6
ATP5J2	ATP synthase, subunit f, isoform 2
ATP5L	ATP synthase, g
ATP5O	ATP synthase, subunit O (OSCP)
ATP5S	ATP synthase, subunit s (factor B)
ATP6V1A	ATPase, lysosomal 70kDa, V1 subunit A, isoform 1
ATP6V1D	ATPase, lysosomal 34kDa, V1 subunit D
AZU1	Azurocidin 1 (cationic antimicrobial protein 37)
BCL2A1	BCL2-related protein A1
C8A	Complement component 8, alpha polypeptide
CD7	CD7 antigen (p41)
CD72	CD72 antigen
CLDN11	Claudin 11
CLPX	ClpX caseinolytic peptidase X
COQ7	coenzyme Q7 homolog, ubiquinone
COX11	COX11
COX15	COX15
COX4I1	Cytochrome c oxidase IV-isoform 1
COX5A	Cytochrome c oxidase polypeptide Va
COX6C	Cytochrome c oxidase polypeptide Vic

COX7A2	Cytochrome c oxidase subunit VIIa polypeptide 2 (liver)
COX7A2L	Cytochrome c oxidase VIIa 2 like
COX7B	Cytochrome c oxidase subunit VIIb
COX7C	Cytochrome c oxidase VIIc
CRIP1	Cysteine-rich protein 1 (intestinal)
DIABLO	Diablo homolog
DNM1L	Dynamin 1-like
EMP1	Epithelial membrane protein 1
ERBB2	v-erb-b2 erythroblastic leukemia viral oncogene homolog 2
ERBB3	Neuregulin receptor tyrosine kinase
FH	Fumarate hydratase
GALC	Galactosylceramidase
GBX2	Gastrulation brain homeo box 2
GPX4	Glutathione peroxidase 4
HLA-E	Major histocompatibility complex, class I, E
HMGCS2	3-hydroxy-3-methylglutaryl-CoA synthase 2
IL17RB	Interleukin 17 receptor B
IL1B	Interleukin 1 beta
IL1R2	Interleukin 1 receptor, type II
IL2RA	Interleukin 2 receptor, alpha
IL4	Interleukin 4
IL4R	Interleukin 4 receptor
IL5	Interleukin 5 (colony-stimulating factor, eosinophil)
IL6	Interleukin 6
IL8RB	Interleukin 8 receptor, beta
JARID2	Jumonji, AT rich interactive domain 2
KIR2DS1	Killer cell immunoglobulin-like receptor, two domains, short cytoplasmic tail, 1
KNG1	Kininogen 1
LGALS3	Lectin, galactoside-binding, soluble, 3
MAG	Myelin associated glycoprotein
MBP	Myelin basic protein
MCCC1	Methylcrotonoyl-CoA carboxylase 1 (alpha)
MCEE	Methylmalonyl CoA epimerase
MMAA	Methylmalonic aciduria (cobalamin deficiency) cblA typ
MOBP	Myelin-associated oligodendrocyte basic protein

MOG	Myelin oligodendrocyte glycoprotein
MPST	Mercaptopyruvate sulfurtransferase
MPZL1	Myelin protein zero-like 1
MRPL3	Mitochondrial ribosomal protein L3
MRPS12	Mitochondrial ribosomal protein S12
MS4A2	Fc fragment of IgE, high affinity I, receptor for; beta polypeptide
MSRB2	Methionine sulfoxide reductase B2
NDUFA1	NADH dehydrogenase 1, alpha, 1
NDUFA5	NADH dehydrogenase 1, alpha, 5
NDUFA6	NADH dehydrogenase 1, alpha, 6
NDUFAB1	NADH dehydrogenase 1, alpha/beta subcomplex, 1
NDUFB1	NADH dehydrogenase 1, beta, 1
NDUFS7	NADH dehydrogenase Fe-S protein 7
NDUFS8	NADH dehydrogenase Fe-S protein 8
NDUFV3	NADH dehydrogenase 1, flavoprotein 3
NFATC1	Nuclear factor of activated T-cells, cytoplasmic, calcineurin-dependent 1
NMU	Neuromedin U
OLIG1	Oligodendrocyte lineage transcription factor 1
OLIG2	Oligodendrocyte lineage transcription factor 2
ORM1/ORM2	Orosomucoid 1, orosomucoid 2
OXCT1	3-oxoacid CoA transferase
PBX4	Pre-B-cell leukemia homeobox 4
PDE4B	Phosphodiesterase 4B, cAMP specific
PFC	Properdin P factor, complement
PLP1	Lipophilin, primary constituent of myelin, proteolipid protein
PPARA	Peroxisome proliferator activated receptor alpha
PRLR	Prolactin receptor
PRSS25	HtrA serine peptidase 2
PTGS2	Prostaglandin-endoperoxide synthase 2
PTX3	Pentraxin 3, long
PVR	PDGF- and VEGF-receptor related
SLC25A16	Solute carrier family 25, member 16 (mitochondrial)
SLC25A4	Solute carrier family 25, member 4 (mitochondrial)
SOC5	Suppressor of cytokine signaling 5
SOX10	Transcription factor, regulates myelin-related genes, myelination deficiency

SSBP1	Single-stranded DNA binding protein
TF	Transferrin, transports iron, involved in myelin maintenance/formation
TNF	Tumor necrosis factor
TNFAIP3	Tumor necrosis factor, alpha-induced protein 3
TNFRSF17	Tumor necrosis factor receptor superfamily, member 17
TOMM40	Translocase of outer mitochondrial membrane 40
TXNIP	Thioredoxin interacting protein
UGP2	UDP-glucose pyrophosphorylase 2
UQCRB	Ubiquinol-cytochrome c reductase binding protein
UQCRC2	Ubiquinol-cytochrome c reductase complex core protein 2
UQCRH	Ubiquinol-cytochrome c reductase hinge protein
UQCRCQ	Ubiquinol-cytochrome c reductase, complex III subunit VII
VDAC1	Voltage-dependent anion channel 1; porin
VDAC1P1	VDAC1 pseudogene, porin protein, isoform 1
VDAC2	Voltage-dependent anion channel 2; porin
WWP1	WW domain containing E3 ubiquitin protein ligase 1

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Figure 1.

Relationship between electron transfer mRNA transcripts (ETTs), glycolysis and pH. A: In the normal functioning living cell, glycolysis feeds into the tricarboxylic acid (TCA) cycle followed by the electron transfer chain (gray boxes). Oxygen is consumed and water is produced. B: In a living cell with reduced expression of ETTs, the electron transfer chain and OXPHOS get compromised, causing a shift toward glycolysis. Lactic acid accumulates in the tissue and the pH drops. C: Agonal stress prior to death leads to a drop in pH of the brain tissue, which accelerates RNA degradation in the post-mortem tissue. Reduced levels of ETTs found in post-mortem brain could thus be either a function of agonal events, or an indication of inadequate synthesis of ETTs. ETTs - electron transfer mRNA transcripts; TCA - tricarboxylic acid cycle

Figure 2.

Hypothesis connecting mitochondria, myelin and immune function. Multiple sclerosis models have shown that mitochondria and the immune system play a role in demyelination, and that the genetic environment modulates the severity of oligodendrocyte stress and demyelination. Thus, under certain conditions mRNA levels of oligodendrocyte genes can be downregulated without causing overt cell death and MS symptoms. The downregulation of oligodendrocyte genes might be an indication of cell stress in BPD. Transcriptome studies have shown that genes involved in myelination, inflammation and energy metabolism are dysregulated in BPD. We hypothesize that these systems interact to reduce myelination and thereby hypopolarize the neuronal membrane potential, making it more susceptible to depolarization. Neuronal function and network activities get compromised, leading to symptoms associated with BPD and other psychiatric conditions.

Table 1

Publications of gene expression profiles in the brain of subjects with BPD.

Reference	group	# of samples	mean age	mean PMI	gender	tissue	markers of energy function	oligodendrocyte markers	markers of immune response/stress	collection site	Platform
(Tkachev et al., 2003)	BPD	15	42.3	32.5	9M, 6F	PFC - BA 9		<i>decreased levels</i> (BPD): OLIG2, SOX10, GALC, MAG, PLP1, CLDN11, MOG, ERBB3, TF		Stanley Foundation Brain Collection	Affymetrix HG-U133A
	SZ	15	44.2	33.7	9M, 6F			<i>increased levels</i> (SZ): MPZL1; <i>decreased levels</i> (SZ): OLIG1, OLIG2, SOX10, GALC, MBP, MAG, PLP1, MOBP, CLDN11, MOG, ERBB3, TF			
	control	15	48.1	23.7	9M, 6F						
(Konradi et al., 2004)	BPD	9	65.4 ± 5.8	18.4 / - 2.3 *	4 M, 5 F	Hippocampus	<i>decreased levels:</i> OXCT1, ATP5G3, ATP5H, ATP5J2, ATP5C1, ATP5O, ATP6V1D, ATP6V1A, COX7A2, COX7B, DNM1L, FH, MRPL3, NDUFB1, SSBP1, SLC25A4, UQCRC, UGP2, VDAC1P1, VDAC1, VDAC2			Harvard Brain Tissue Resource Center	Affymetrix HG-U95Av2
	SZ	8	62 ± 6.4	18.9 ± 1.8 *	4 M, 4 F						
	control	10	66.1 ± 4.8	19 ± 1.4 *	5 M, 5 F						
(Iwamoto et al., 2005)	BPD	33	43.8	36.4	16 M, 17 F	PFC - BA 46	a general downregulation of mitochondrial genes was observed in BPD and SZ			Stanley Foundation Array Collection	Affymetrix HG-U133A
	SZ	35	42.6	31.4	26 M, 9 F						
	control	34	44.1	29.6	25 M, 9 F						
(Ryan et al., 2006)	BPD	10	43.5 ± 10.7 **	33.8 ± 18.5 **	5 M, 5 F	OFC - BA 11			<i>increased levels:</i> AZU1, C8A, CD7, CD72, CRIP1, GBX2, HLA-E, IL1R2, IL2RA, IL4, IL4R, IL5,	Stanley Foundation Brain Collection	Affymetrix HG-U133A
	control	11	47.8 ± 11 **	23.1 ± 9.6 **	7 M, 4 F						

Reference	group	# of samples	mean age	mean PMI	gender	tissue	markers of energy function	oligodendrocyte markers	markers of immune response/stress	collection site	Platform
(Sun et al., 2006)	BPD	30	44.5 ± 10.7 **	37.2 ± 17.7 **	16 M, 14 F	PFC - BA 9	<i>increased levels:</i> MMAA, HMGCS2, MCCE, CLPX; <i>decreased levels:</i> COX6C, NDUFS8, NDUF57, COX5A, ATP5C1, ATP5J, ATP5G3, UQCRC2, SLC25A16, GPX4, PRSS25, DIABLO, MPST, MSRB2, TOMM40, MRPS12, MCCC1, COQ7		IL8RB, KIR2DS1, KNG1, MS4A2, ORMI/ORM2, PFC, PRLR, TNFRSF17; <i>decreased levels:</i> SOC55, WWPI		19K cDNA Array (University Health Network Microarray Centre, Toronto)
	control	31	43.8 ± 7.3 **	29.1 ± 13.1 **	24 M, 7 F						
	BPD	35	45 ± 11 **	38 ± 18 **	17 M, 18 F						
	control	35	44 ± 8 **	29 ± 13 **	26 M, 9 F						
(Shao and Vawter, 2008)	BPD	29	45.3 ± 9.8 **	39.1 ± 17.9 **	15 M, 12 F	PFC - BA 46	<i>increased levels:</i> ERBB2, IL17RB, IL2RA, JARID2, LGALS3, NFATC1, PBX4, PPARA, TXNIP; <i>decreased levels:</i> NMTU, PVR		increased levels: ERBB2, IL17RB, IL2RA, JARID2, LGALS3, NFATC1, PBX4, PPARA, TXNIP; <i>decreased levels:</i> NMTU, PVR	Stanley Foundation Array Collection	Stanley Foundation Array Collection
	SZ	32	42.9 ± 8.6 **	30.5 ± 15.1 **	23 M, 9 F						
	control	27	44.4 ± 6.5 **	28.9 ± 12.7 **	23 M, 6 F						
(Rao et al., 2010)	BPD	10	49 ± 7.2	21 ± 3.0	not listed	PFC (no BA listed)			increased mRNA and protein: IL-1beta, IL-1R, myeloid differentiation factor 88, NFkappaB subunits	Harvard Brain Tissue Resource Center	western blots, QPCR, immunohistochemistry
	control	10	43 ± 3.5	27 ± 1.5							

* SEM;

** SD;

BA = Brodmann area; PFC = prefrontal cortex; DLPFC = dorsolateral PFC; OFC = orbitofrontal cortex; for abbreviations see 'list of abbreviations'

Table 2

Publications of gene expression profiles in peripheral tissue of subjects with BPD.

Reference	group	# of samples	mean age	gender	tissue	markers of energy function	markers of immune response/stress	collection site	Platform
(Washizuka et al., 2005)	BPD I	13	52.5 ± 12.4	7 M, 6 F		<i>decreased levels:</i> NDUFA1, NDUFV3, NDUFA6, NDUFS7, COX6C		Brain Science Institute, RIKEN, Saitama	
	BPD II	8	57.0 ± 10.7	2 M, 6 F	Lymphoblastoids				
	control	11	51.1 ± 10.0	8 M, 3 F					
(Naydenov et al., 2007)	BPD	21	40.5 ± 2.3	10 M, 11 F		<i>decreased levels in low glucose:</i> ATP5G2, ATP5L, ATP5S, COX11, COX15, COX4H1, COX7A2L, COX7C, NDUFA5, NDUFA6, NDUFB1, UQCRB, UQCRC2, UQCRH		McLean Hospital	Affymetrix HG-U133A 2.0
	control	21	39.3 ± 2.9	12 M, 9 F	Glucose-deprived primary lymphocytes in culture				
(Padmos et al., 2008)	BPD	42	42	16 M, 26 F			<i>increased levels:</i> PDE4B, IL1B, IL6, TNF, TNFAIP3, PTGS2, PTX3, BCL2A1, EMP1	Erasmus Med. Center, University Utrecht	Affymetrix HG-U95Av2 (5 BPD subjects, 6 controls); Q-PCR (all subjects)
	control	25	40	11 M, 14 F			<i>increased levels:</i> PDE4B, IL1B, IL6, TNF, TNFAIP3, PTGS2, PTX3, BCL2A1, EMP1		
	BPD offspring	54	18	26 M, 28 F	Monocytes				
	control-children	70	16	33 M, 37 F					
(Padmos et al., 2009)	BPD - twin MZ/concordant	6 pairs	36	4 M, 8 F				Erasmus Med. Center, University Utrecht	QPCR
	BPD - twin DZ/discordant	12 pairs	41	6 M, 18 F					
	BPD - twin DZ/concordant	4 pairs	43	2 M, 6 F	Monocytes		<i>increased levels:</i> PDE4B, IL1B, IL6, TNF, TNFAIP3, PTGS2, PTX3, BCL2A1, EMP1		
	BPD - twin DZ/discordant	19 pairs	43	14 M, 24 F					
	control - twin MZ	18 pairs	40	6 M, 30 F					
	control - twin DZ	16 pairs	44	9 M, 23 F					