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Immune system gene dysregulation in autism & schizophrenia

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Abstract

Gene*environment interactions play critical roles in the emergence of autism and schizophrenia pathophysiology. In both disorders, recent genetic association studies have provided evidence for disease-linked variation in immune system genes and post-mortem gene expression studies have shown extensive chronic immune abnormalities in brains of diseased subjects. Furthermore, peripheral biomarker studies revealed that both innate and adaptive immune systems are dysregulated. In both disorders symptoms of the disease correlate with the immune system dysfunction; yet, in autism this process appears to be chronic and sustained, while in schizophrenia it is exacerbated during acute episodes. Furthermore, since immune abnormalities endure into adulthood and anti-inflammatory agents appear to be beneficial, it is likely that these immune changes actively contribute to disease symptoms. Modeling these changes in animals provided further evidence that prenatal maternal immune activation alters neurodevelopment and leads to behavioral changes that are relevant for autism and schizophrenia. The converging evidence strongly argues that neurodevelopmental immune insults and genetic background critically interact and result in increased risk for either autism or schizophrenia. Further research in these areas may improve prenatal health screening in genetically at-risk families and may also lead to new preventive and/or therapeutic strategies.

Keywords

schizophrenia; autism; immune; environment; maternal immune activation

INTRODUCTION

Autism spectrum disorder (ASD) is characterized by symptoms in the domains of social interaction, communication and restricted and repetitive interests and behaviors (Meyer et al., 2011; Noterdaeme, 2011; Ratajczak, 2011). In contrast, clinical manifestations of schizophrenia (SCZ) encompass positive symptoms, negative symptoms and cognitive deficits (Frangou and Murray, 2000; Tandon et al., 2009). Despite distinct clinical presentations, there are common pathophysiological underpinnings to both of these disorders. ASD and SCZ arise as a result of strong genetic and environmental risk factors that interact in complex ways to give rise to two distinct disease processes. Twin studies have provided estimates of heritability in ASD and SCZ as high as 90% and 80% respectively, suggesting that genetic differences play a pivotal role in the etiology of both disorders (Tandon et al., 2008; Geschwind, 2009). However, a recent twin study specifically

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examined possible effects of the environment in ASD and concluded that about 58% of the stated heritability could be attributed to environmental factors commonly affecting the twin pairs (Hallmayer et al., 2011). Likewise, a meta-analysis of twin-studies in schizophrenia found a strong environmental component (Sullivan et al., 2003). Furthermore, monozygotic twins who shared a placenta (monochorionic) had significantly higher concordance for schizophrenia than those with separate placentas (dichorionic), arguing that prenatal environmental factors confer risk for neurodevelopmental disorders even when the genetic makeup is identical (Davis et al., 1995).

It is clear that both genetics and environment contribute to the emergence of ASD and SCZ, but how could environmental factors alter genetically-encoded programs and lead to disease? “Environment” is most commonly referred to as a set of broad external influences affecting various homeostatic mechanisms of an organism. Environmental factors exert their influence directly by affecting specific cellular processes (e.g. toxins, short-term effects of drugs) or indirectly by manipulating the expression of genes (e.g. hormones, long-term effects of drugs, immune system activation and exercise (Russell, 2003)). These environment-triggered gene expression changes can be either beneficial or detrimental in disorders such as Alzheimer’s Disease (Lazarov et al., 2005; Radak et al., 2010), Parkinson’s Disease (Zigmond et al., 2009) or traumatic brain injury (Devine and Zafonte, 2009). For example, environmental conditions like exercise have been shown to impact biological systems through changes in the expression of various gene cascades (Mitchell et al., 2012). However, environmental influences on gene expression in both ASD and SCZ appear to be primarily detrimental and contribute to the disease process. So, what are the major environmental factors in the emergence of ASD and SCZ and how might they increase the risk for illness? Over 40 years ago, epidemiological studies identified maternal infection during early pregnancy as a significant risk factor for ASD (Chess, 1971). Likewise, an increased concordance rate of SCZ in monochorionic vs. dichorionic twins can be explained by shared blood circulation and a shared placenta, which suggests that an infection would affect both monchorionic twins similarly (Davis et al., 1995). In addition, various studies identified that exposure to a wide variety of bacterial and viral agents increases the risk for ASD and SCZ (Brown and Derkits, 2010; Ratajczak, 2011)**(Brown/ Pardo this issue?)**, arguing that a general immune system activation, and not a specific infectious agent is responsible for an increased risk in both diseases.

Recent genomics, genetics, functional and animal model studies of ASD and SCZ strongly support this interpretation. A meta-analysis of previous genome wide association study (GWAS) datasets identified variants of genes involved in the immune response that are significantly correlated with SCZ diagnosis (Ripke et al., 2011) and post-mortem expression studies have found dysregulated immune system gene transcripts in brains of patients with ASD (Lintas et al., 2012) and SCZ (Arion et al., 2007; Sequeira et al., 2012). Furthermore, in the brain of subjects with ASD, Vargas et al. observed a strong activation of microglia and astrocytes, as well as elevated cytokine levels, suggesting that ASD is characterized by a persistent immune system activation (Vargas et al., 2005). Microglial activation has also been suggested to play a role in SCZ, though the evidence remains to be comprehensively assessed (Bernstein et al., 2009; Monji et al., 2011). In addition, studies of peripheral blood revealed distinctly altered cytokine levels across both disorders (Chan et al., 2011; Onore et al., 2012). Finally, maternal immune activation (MIA) studies in rodents have provided evidence for anatomical, gene expression and behavioral changes related to ASD or SCZ (Patterson, 2009; Boksa, 2010; Müller and Schwarz, 2010)**(Boksa this issue?)**.

However, our understanding of immune system dysfunction in these two disorders remains incomplete to date. Currently we have a very limited understanding of how immune system dysfunction disrupts normal brain development and contributes to the emergence of a

disease. More specifically, we do not know 1) how the genetic elements and the environmental insults interact; 2) whether neuroimmune dysfunction is a primary or adaptive part of the disease process; 3) how immune system disturbances change during the course of each disease; and 4) whether immune system abnormalities are directly responsible for the behavioral phenotypes seen in patients and whether they represent good drug targets.

1. Genetic variation implicates immune system related genes

Genome wide association study (GWAS) is a DNA-based, hypothesis-free method which analyzes genetic variation between individuals in a large population. It is primarily designed to uncover genetic variation such as single-nucleotide polymorphisms (SNPs), micro-deletions, or copy number variations (CNVs) that are associated with a particular trait, condition, or disorder. With a large population and a good reference dataset, this technique is very powerful for identifying alleles and genomic regions not previously associated with illness (Raychaudhuri, 2011). However, this method is susceptible to type II errors (false negatives) and rare alleles occurring only in a small part of the population can remain undetected. In spectrum disorders like ASD and SCZ, this is compounded by considerable genetic heterogeneity in the patient population. Furthermore, the functional impact of the majority of identified SNPs has not been investigated comprehensively (especially non-coding SNPs). Nevertheless, GWA studies can be very useful in providing leads for follow up, hypothesis-driven studies with the primary goal of understanding the biological effects by which gene expression disturbances alter the development of the brain. Such hypothesis-based studies in turn have a higher analytical power and can readily analyze a particular signal with a minimal need for statistical correction.

In SCZ patients, GWA studies have uncovered an association between the major histocompatibility locus (MHC) and diagnosis. The MHC locus contains multiple conserved genes that are involved in the innate, adaptive and autoimmune systems (Traherne, 2008). Several patient populations of different geographical origins have been queried. Some studies reported significant associations of SNPs within the MHC locus (Sullivan et al., 2008; Need et al., 2009; Purcell et al., 2009; Shi et al., 2009; Stefansson et al., 2009; Yue et al., 2011) while others failed to replicate these findings (O'Donovan et al., 2008; Shifman et al., 2008; Walsh et al., 2008; Athanasiu et al., 2010; Ma et al., 2011; Yamada et al., 2011). However when these studies were combined into a meta-analysis, 129 disease-related polymorphisms were identified in the extended MHC locus (Ripke et al., 2011). Furthermore, a hypothesis-driven candidate gene approach revealed that polymorphisms in nuclear factor kappa B (NFκB) (Hashimoto et al., 2011), interleukin 2, 4 (Schwarz et al., 2006), 3 (Chen et al., 2007), 6 and 10 (Bocchio Chiavetto et al., 2002; Paul-Samojedny et al., 2010; Almoguera et al., 2011) were also linked to SCZ.

In contrast, GWA studies of ASD have not uncovered significant associations with genes implicated in immune function (Ma et al., 2009; Wang et al., 2009; Weiss et al., 2009; Anney et al., 2010). However, hypothesis-driven genetic assessments revealed that HLA A2 (MHC class I) and HLA DR4 (MHC class II) loci contained SNPs associated with ASD, suggesting that genomic variation in the MHC region is also associated with ASD (Lee et al., 2006; Torres et al., 2006; Guerini et al., 2009; Guerini et al., 2011). Therefore, genetic variation in immune system genes must be further evaluated as a potential risk factor for both ASD and SCZ.

Interestingly, GWA studies show overlapping risk genes associated with ASD/SCZ and immune system diseases. The involvement of the MHC locus for example appears to be one of the strongest findings in GWA studies of chronic inflammatory diseases (Wucherpfennig and Sethi, 2011). Furthermore, variation in the HLA DRB1 locus is associated with

rheumatoid arthritis, an autoimmune disease that appears to have reduced incidence in patients with SCZ and an increased incidence in mothers of children with ASD (Crespi and Thiselton, 2011). Finally, GWA studies also identified that certain neurexin alleles predispose to developing autoimmune diseases such as rheumatoid arthritis, Crohn's disease and multiple sclerosis (Baranzini, 2009) and neurexin has also been identified as an ASD and SCZ susceptibility gene (Gauthier et al., 2011).

Overall, GWA studies suggest that elements in critical immune response genes might contribute to the emergence of disease pathophysiology in both ASD and SCZ. The exact role(s) of these alleles will have to be addressed in future studies, especially considering that genes found on the MHC locus have a variety of functions in the immune and nervous systems.

2. Post-mortem gene expression changes

Genetic variations can directly give rise to gene expression changes, alter protein structure and function, modulate gene expression in concert with environmental factors, or have no effect. Gene expression changes that are found in postmortem brain tissue are the cumulative products of genetics, cause of death, duration of illness, treatment, and other biological events that are only peripherally associated with disease pathophysiology. Nevertheless, a well-controlled post-mortem gene expression study can identify gene expression changes and pathways that are specific to the disease.

In SCZ, transcriptome studies have uncovered immune system, synaptic, oligodendrocyte, and energy metabolism related disturbances (Faludi and Mirnics, 2011). These changes are likely to be related, although at the present time we have a limited understanding of how these domains interact. Clearly, disruption of the immune system might result in altered energy metabolism and synapse elimination, yet synaptic elimination or altered oligodendrocyte function might also trigger immune/chaperone responses. Although we do not fully understand the temporal sequence in which the transcriptome changes emerge, postmortem tissue of subjects with SCZ or ASD shows strong neuroimmune transcriptome dysregulation. In the brains of subjects with schizophrenia, Arion et al. and Saetre et al. provided converging evidence for a robust immune transcript upregulation in the prefrontal cortex consisting of SERPINA3, IFITM2 and IFITM3. Importantly, both studies observed gene expression changes that were independent of the patients' medication history (Arion et al., 2007; Saetre et al., 2007). Similarly, Garbett et al. (Garbett et al., 2008) found several immune related expression changes in Brodmann area (BA) 46 of patients, while Shao and Vawter reported an increased expression of humoral immune response genes in the same brain region (Shao and Vawter, 2008). However, Schmitt et al. observed a systemic repression of immune transcripts in BA22 of the temporal lobe, suggesting that neuroimmune disturbances might have a regional character in schizophrenia. This potentially regional specificity was also supported by the comprehensive brain mapping study of Katsel et al., who reported an interesting and very complex spatial pattern of immune dysregulation across the brain regions (Katsel et al., 2005).

In summary, converging SCZ postmortem studies suggest that immune system activation is a chronic, progressive process in a subpopulation of patients, and this appears to be a residual expression signature of early immune system activation. Furthermore, immune transcript induction is linked to other gene expression changes, particularly downregulation of synaptic marker transcripts and energy metabolism related transcripts. Lastly, immune system changes are complex and encompass both gene expression increases and decreases in a region-specific pattern, with the hippocampus and prefrontal cortex showing the most prominent neuroimmune transcript dysregulation.

The immune system activation in ASD is equally complex. Transcriptome studies have primarily revealed ASD-associated dysregulation of immune, synaptic and developmental transcripts. The study of Garbett et al. provided evidence for a strong induction of both the innate as well as adaptive immune systems (Garbett et al., 2008). Similarly, Voineagu et al. report a strong induction of gene expression involved in the immune and inflammatory response in the frontal and temporal cortices, but observed no significant correlation between alleles associated with ASD in GWAS and immune gene mRNA levels. The authors also found that regional specialization was significantly attenuated in subjects with ASD (Voineagu et al., 2011). Finally, Ziats and Rennert used a publicly available gene-expression atlas of 16 human brain regions ranging from 21 weeks of gestation to 40 years of age, looked for highly expressed ASD risk-genes in the developing brain and used pathway analysis to identify signaling hubs for risk gene convergence. They found that 219 previously identified putative ASD risk genes may converge on cytokine signaling pathways, suggesting that an early immune activation might be a core feature of ASD pathophysiology (Ziats and Rennert, 2011).

Combined, ASD transcriptome studies suggest that immune system induction is chronic, complex, and probably not of genetic origin. Rather, it is likely to be a result of environmental or adaptive processes arising from an early immune activation. Similar to changes in SCZ, immune system activation in ASD is linked tightly with synaptic transcript downregulation and encompasses innate as well as adaptive immune system transcripts. There is a notable overlap of specific gene expression patterns between these two disorders, including two interferon-inducible transcripts, IFITM2 and IFITM3 (Arion et al., 2007; Saetre et al., 2007; Garbett et al., 2008; Voineagu et al., 2011). However, in contrast to SCZ, immune system changes in ASD appear to be uniform across cortical regions. Importantly, these studies support the possibility that prenatal immune activation might be a common contributor to the emergence of ASD or SCZ. However since postmortem studies provide only snapshots of the transcriptome, the temporal emergence of immune system changes will have to be ascertained by other longitudinal methods.

3. Peripheral Biomarkers

Post-mortem transcriptome studies build a compelling case for neuroimmune disturbances in ASD and SCZ patients, but are these changes associated with peripheral biomarkers of inflammation that could potentially be used for aiding early diagnosis or monitoring treatment effectiveness? Several studies are informative in this regard.

Early studies of peripheral immune markers have provided variable results, but a recent meta-analysis by Miller and colleagues reported an increase in the inflammatory cytokines IL-1β, IL-6 and TGFβ specifically during acute episodes of the illness (Miller et al., 2011). This evidence suggests a state-specific induction of immune markers during active episodes of SCZ, which has been corroborated by Takahashi et al. who found that recent onset or active episodes result in the induction of inflammatory and immune related biological processes (Takahashi et al., 2010). Additionally, Kurian et al. reported that high hallucination and delusion scores correlate with interleukin-related expression in the serum of patients (Kurian et al., 2011), while Drexhage and colleagues found a significant up-regulation of IL 1β, IL-6 and TNFα in peripheral blood mononuclear cells in recent-onset patients (Drexhage et al., 2010). Further support comes from a study by Song et al., which confirmed increased TNFα and IL-1β mRNA and protein levels in unmedicated first episode patients (Song et al., 2009). Thus, it appears that in patients with SCZ, the acute phase of illness correlates with peripheral changes in both innate and adaptive immune systems.

In ASD, peripheral immune activation is equally complex and appears to involve both the innate and adaptive immune systems. Furthermore, altered levels of peripheral immune markers appear to indicate symptom severity. Multiple studies support this conclusion. First, TNFα signaling-related expression changes were correlated with diagnosis and severity of ASD (Hu et al., 2006; Hu et al., 2009). Similarly, levels of pro-inflammatory cytokines such as IL-1β, IL-6 and IL-8 were increased in patients with ASD and correlated with a more pronounced behavioral impairment (Ashwood et al., 2011). In addition, expression levels of the anti-inflammatory cytokine TGFβ decreased as behavioral symptoms worsened (Ashwood et al., 2008). Therefore, it appears that the balance of pro-inflammatory and anti-inflammatory cytokines is altered in ASD and that cytokine levels correlate with severity of symptoms including poor communication skills and impaired social behaviors.

In summary, serum biomarker studies of ASD and SCZ suggest several similarities between these two disorders. In both ASD and SCZ, immune dysfunction is systemic and not confined to the CNS. It is also important to note that both innate and adaptive immune markers show altered levels and that peripheral cytokine levels appear to correlate with disease symptomatology in both disorders (acute phase in schizophrenia and symptom severity in ASD).

If immune disturbances contribute to the manifestations of ASD/SCZ, can their treatment alleviate disease symptoms? Interestingly, it appears that antipsychotic medication counteracts the peripheral immune response in SCZ patients. For example, a four-week long treatment with risperidone reduced serum levels of IL-1β mRNA and protein which were correlated with a reduction of symptom severity (Song et al., 2009). It has been proposed recently that immune system regulation may be part of symptom alleviation (see also (Drzyzga et al., 2006; Strous and Shoenfeld, 2006; Miller et al., 2011)). Consequently several recent studies investigated whether direct treatment of immune dysfunction leads to an improvement of symptoms. These efforts revealed that anti-inflammatory therapy with aspirin (Laan et al., 2010) or a COX2 inhibitor (Müller et al., 2002; Müller et al., 2010) improved treatment response in SCZ patients with elevated levels of peripheral inflammatory markers or acute symptoms. In ASD, treatment with anti-inflammatory drugs moderately alleviated a subset of ASD symptoms (Rossignol, 2009). Furthermore, a recent study reported that fever reduces symptom severity in autistic children (Curran et al., 2007). The mechanisms underlying this effect are unclear, but one can speculate that altering cytokine balance might benefit brain function in these patients.

However, the central question of any biomarker study is: “can a set of peripheral molecules be predictive of diagnosis, descriptive of the progression of disease, or effective in monitoring treatment efficacy?” A reliable clinical test must be both specific (identify only subjects with the condition) and sensitive (identify all subjects with the condition). As a result, the utility of peripheral immune system biomarker-based diagnosis for ASD or SCZ is highly unlikely, since any disease-associated change is potentially masked by immune system responses to a host of internal (e.g. food, physical activity, sleep) and external (e.g. contact with chemicals or infectious agents) stimuli. In addition, the expression of peripheral immune system genes is primarily controlled by local events, not CNS triggered processes. Furthermore, the high incidence of co-morbid conditions in psychiatric patients makes it challenging to attribute immune marker changes to the primary disease, especially considering that some immune markers appear to lack disease-specificity across the various psychiatric disorders (Abdallah et al., 2011). However, while peripheral immune system markers alone are unlikely to be good diagnostic tools, integrated “-omics” based tests have a better chance of achieving the required diagnostic sensitivity and specificity. Continuously-monitored, integrative personal “-omics profiles” show promise in

distinguishing healthy versus disease states, although this approach is not ready to be adopted in clinical practice at the current time (Chen et al., 2012).

Overall, both post-mortem and peripheral blood studies in ASD have consistently identified immune abnormalities in a wide age-range of patients, suggesting a chronic immune activation which increases with the severity of symptoms. Indeed, the clinical profile of ASD patients is characterized by a relative continuity of symptoms as opposed to the episodic character of active psychosis in SCZ. In contrast to ASD, it appears that SCZ is characterized by peripheral inflammatory markers that are more robust during acute episodes. This suggests a chronic inflammatory profile in SCZ which exacerbates during active disease periods. Thus, external stimuli precipitating psychotic episodes in SCZ (e.g. stress) might act upon chronic immune abnormalities leading to a flaring up of inflammatory processes. Such an inflammatory response could lead to a progressive exacerbation of chronic immune abnormalities, which may underlie the detrimental effect of untreated psychotic episodes as well as the beneficial effect of prompt and continued use of medication (Frangou and Murray, 2000). However, the overall postmortem and biomarker data suggest that chronic immune transcript dysregulation might be characteristic of a patient subpopulation and this subpopulation remains poorly defined to date. Further studies will have to refine the relationship between the neuroimmune disturbances and disease symptoms. In the future, meta-analysis of postmortem gene expression data from patients at different stages of illness (duration of illness and symptom severity) may provide more information about the trajectory of transcriptome dysfunction.

4. Modeling immune disturbances

The data from Voineagu et al. suggest that post-mortem immune system transcript changes in ASD may not be caused by genetic variation (Voineagu et al., 2011). Furthermore, epidemiological studies suggest that a wide variety of bacterial and viral agents increase the risk for ASD and SCZ (Brown and Derkits, 2010; Ratajczak, 2011)**(Brown/Pardo this issue?)** and cytokine levels are reportedly increased in pregnant mothers whose children later develop ASD and SCZ (Brown et al., 2004; Goines et al., 2011). This raises two critical questions: what effect does maternal immune activation (MIA) have on the developing fetus and can such changes be investigated using animal models?

Animal studies addressing these questions revealed several ASD and SCZ related features. Following MIA, cytokine levels were elevated in the maternal serum as well as the fetal brain (Golan et al., 2005; Meyer et al., 2006) and offspring exhibited morphological brain abnormalities that mimicked those seen in ASD and SCZ (Boksa, 2010; Kneeland and Fatemi, 2012). Additionally, complex transcript changes were observed in the fetal brain with changes following maternal viral infection known to play a role in the pathophysiology of ASD and SCZ (Fatemi et al., 2009; Fatemi et al., 2009; Kneeland and Fatemi, 2012). Moreover, converging evidence showed that behavioral changes in the MIA-exposed offspring were reminiscent of ASD and SCZ (Boksa, 2010; Meyer, 2011)**(Boksa this issue?)**, and that some of these behavioral deficits were ameliorated after exposure to antipsychotic drugs (Piontkewitz et al., 2009; Meyer et al., 2010; Piontkewitz et al., 2011). These studies provide compelling evidence that MIA-exposed offspring in animal models exhibit several critical features that are also observed in patients with ASD or SCZ, suggesting that maternal immune activation plays a role in the pathogenesis of these disorders.

However, these studies also revealed that the infectious agents are not acting directly on the fetal brain, but rather through an activation of immune cascades. Early evidence showed that fetal brains exhibited no detectable levels of viral genes after maternal viral exposure (Shi et al., 2005). This finding was extended to show that exposure to an analogue of bacterial

infection (lipopolysaccharide - LPS) led to elevation of cytokine levels in the fetal brain and maternal circulation, but did not result in altered cytokine mRNA synthesis in the fetal brain, suggesting a maternal and not fetal immune response (Oskvig et al., 2012). Furthermore, maternal exposure to IL-6 alone led to behavioral and transcript changes comparable to those seen after exposure to the non-infective viral mimetic poly(I:C) (Smith et al., 2007; Garbett et al., 2012). Bringing these findings together, viral infection, poly(I:C) and IL-6 not only resulted in similar patterns of transcript changes in the fetal brain (Garbett et al., 2012), but behavioral and transcriptome changes were blocked by administration of IL-6 neutralizing antibodies following poly(I:C) exposure (Smith et al., 2007). Therefore, these results provide evidence that various infections cause a systemic maternal immune activation which affects the fetus via circulating cytokines, IL-6 in particular. Therefore, the IL-6 pathway might represent a promising target for preventing the detrimental effects of MIA on the developing brain.

The induction of acute phase immune response proteins is well-documented, but it is still mostly unclear how an immune system induction can impact the developing brain. Recent animal studies have also been instructive in this regard, providing evidence that the immune system interacts with neurodevelopmental mechanisms. Firstly, neurogenesis was found to be compromised in IL-6 knockout mice (Bowen et al., 2011). Furthermore, modulation of the pro-inflammatory cytokine TNFα altered the stabilization and pruning of synapses (Lee et al., 2010) and was shown to play a role in synaptic plasticity and synaptic pruning (Beattie et al., 2002; Stellwagen and Malenka, 2006). Additionally, IL1β was found to modify synaptic strength in GABAergic circuits (Serantes et al., 2006) and the MHC locus was found to play a critical role in activity dependent neuronal path-finding and stabilization of active connections (Shatz, 2009)**(Shatz this issue?)**. Finally, microglial activation was critical for the genesis, migration and selective stabilization of new neurons (Chung and Barres, 2011; Ekdahl, 2012), synaptic pruning (Paolicelli et al., 2011) and neuronal plasticity (Ben Achour and Pascual, 2010). This data provides convincing evidence that an altered immune function not only impacts neurogenesis but also leads to critical modifications in brain connectivity. Interestingly, the disease process in SCZ is characterized by overpruning of synapses (Faludi and Mirnics, 2011), while in ASD, a lack of appropriate pruning and/or a premature stabilization of synapses could lead to an excess of synaptic connections, ultimately resulting in the emergence of hyper-reactive and hyper-plastic neuronal circuits (Markram et al., 2007) and altered cortical minicolumns (Buxhoeveden et al., 2006; Casanova et al., 2006). This strongly argues that the gene*environment interaction in the human brain has a different outcome in SCZ as opposed to ASD. It is also important to note that the nature of the transcript changes, cytokine measures and structural abnormalities following MIA depended on the developmental stage of the fetus at the time of exposure, providing evidence that the exact timing of MIA can lead to distinct pathophysiological complications in animal models (Meyer et al., 2007; Fatemi et al., 2012; Kneeland and Fatemi, 2012). However, it should be pointed out that not every child of a bacterially or virally infected mother develops a neuropsychiatric condition (Selten et al., 2010; Brown, 2011). It is therefore likely that the effects of MIA depend on the strength of infection and/or gene*environment interaction, as well as developmental timing of the insult. Animal studies strongly support this view as MIA exposure of Nurr1 and DISC1 transgenic mouse models exacerbated anatomical and behavioral phenotypes. Furthermore, it is intriguing that these mice also exhibited an altered cytokine balance without MIA exposure, suggesting that certain mutations by themselves can also affect the immune system, possibly rendering the organism more sensitive to an immune insult (Abazyan et al., 2010; Vuillermot et al., 2012).

In summary, animal studies of MIA are essential for deciphering the ways the immune system alters brain structure, connectivity and function (Deverman and Patterson, 2009).

Integrating these data with human clinical and postmortem observations will be critical to understand the gene*environment interactions that give rise to ASD and SCZ pathophysiology. Clearly, genes are multifunctional and any classification of them into 'synaptic', 'immune' or 'glial' categories is highly artificial. Implementing interactome-based assessment such as weighted gene co-expression network analysis (WGCNA) (Mirnics, 2008; Oldham et al., 2008) will be the only way to understand the functional relationship between gene networks and how their disturbances can drive disease pathology.

CONCLUSION

Immune dysfunction is an integral part of ASD and SCZ pathophysiology. Epidemiological studies, GWAS, postmortem brain studies, peripheral biomarkers and MIA all provide converging evidence for a profound impact of immune system disturbances on neurodevelopment which are directly relevant for ASD/SCZ etiology. Furthermore, the enduring presence of immune disturbances in the brain during adult life argues that these changes are active contributors to the disease process. Yet ample unanswered questions remain. It is not known if the risk for developing disease requires multiple genetic/environmental hits or a specific combination of genetic*environmental hits. Furthermore, it remains to be established whether these changes are primary aspects of each disorder or whether they are adaptive/maladaptive mechanisms in response to a separate primary insult. Regardless of the origin of these changes, it is important that anti-inflammatory agents appear to be beneficial in both patient populations. Further research in these areas may improve prenatal health screening in genetically at-risk families and may also lead to new preventive and therapeutic strategies.

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