Research in Autism Spectrum Disorders 8 (2014) 312–316

Contents lists available at ScienceDirect

Research in Autism Spectrum Disorders

Journal homepage: http://ees.elsevier.com/RASD/default.asp

Review

# The role of prenatal immune activation in the pathogenesis of autism and schizophrenia: A literature review

Amanda Easson [a], Marc Woodbury-Smith [b,*]

[a] Faculty of Health Sciences, McMaster University, Canada
[b] Department of Psychiatry and Behavioural Neurosciences, McMaster University, Canada

ARTICLE INFO

*Article history:*
Received 17 September 2013
Received in revised form 5 December 2013
Accepted 10 December 2013

*Keywords:*
Autism
Schizophrenia
Prenatal
Immune activation
Neurodevelopment

ABSTRACT

Autism spectrum disorder (ASD) and schizophrenia (SZ) are two neurodevelopmental disorders that, despite having distinct diagnostic criteria, share certain clinical and etiological features. The genetic origin of the two disorders is beyond doubt, with evidence for unique and overlapping genetic risk factors. However, lower estimates of heritability have recently been reported for both disorders, lending support to a significant contribution from non-genetic factors. Notably, there is increasing evidence that immune activation during prenatal life may act as a risk factor for ASD and SZ. In this review, evidence supporting the hypothesis that prenatal immune activation (PIA) influences the onset and progression of ASD and SZ is analyzed. Results show that the detrimental effects of PIA on neurodevelopment include morphological changes in various brain regions, with perhaps the most notable being the hippocampus and prefrontal cortex, as well as altered activity of neurotransmitter systems such as the serotonergic system and impairments in working memory and prepulse inhibition. An examination of the risk factor of PIA offers new insight into the pathophysiology of ASD and SZ, and in this way opens up new possibilities for the treatment of these two disorders.



**Contents**



* Corresponding author at: McMaster Children's Hospital, Chedoke Site, EVEL Building, Room 457, 1200 Main Street West, Hamilton, Ontario L8N 3Z5, Canada. Tel.: +1 9055252100x77465.
*E-mail address:* woodbur@mcmaster.ca (M. Woodbury-Smith).

1750-9467/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.rasd.2013.12.007

Neurodevelopmental disorders involve disruptions of brain functioning that can negatively affect the processes of learning, memory, and emotion (McCary et al., 2012). Autism spectrum disorder (ASD) and schizophrenia (SZ) are perhaps two of the most significant neurodevelopmental disorders in terms of their relatively high prevalence (Centers for Disease Control and Prevention, 2012; National Institute of Mental Health, 2009) and negative impact on health-related quality of life (Eack & Newhill, 2007; Kuhlthau et al., 2010). ASD is characterized by social impairment, communication deficits, and certain stereotyped behavioral patterns (Wing, Gould, & Gillberg, 2011). Impairment in social interaction may present itself as early as infancy or may not develop until later in childhood (Volkmar & Klin, 2005). Due to difficulties understanding social cues such as facial expression, children with ASD may have trouble interpreting others' thoughts and feelings (Lai, Lombardo, & Baron-Cohen, 2013). SZ typically has its onset in adolescence; however, premorbid symptoms are often seen in earlier years (Fatemi & Folsom, 2009). SZ manifests in negative symptoms – those that cause reductions in a capacity – such as poor social functioning and apathy, and positive symptoms – excesses or distortions of normal functioning – such as hallucinations and delusions (Fatemi & Folsom, 2009). Abnormalities can develop as early as in utero and can lead to the activation of neural circuit pathology during adolescence or early adulthood (Fatemi & Folsom, 2009).

Genetic linkage studies have reported both similar and distinct loci associated with ASD and SZ. While high heritability estimates of at least 80% have been reported for ASD and SZ (Carroll & Owen, 2009), more recent studies have adjusted these estimates downwards. A recent study reported a heritability estimate of 37% for ASD (Hallmayer et al., 2011), while another study on key endophenotypic measures for SZ reported heritability estimates ranging from 24% to 55% (Greenwood et al., 2007). These reduced estimates support the idea that environmental factors may play a significant role in the pathogenesis of ASD and SZ.

The negative impact of early events only started receiving attention relatively recently, when in the early 1990s David J.P. Barker and his colleagues studied the effects of nutrition during the prenatal period on the risk of adulthood diseases such as coronary heart disease (Barker & Martyn, 1992). More recent research has emphasized the role of prenatal immune activation (PIA) in the psychopathology of neurodevelopmental disorders. Prenatal immune activation describes the response of a pregnant woman's immune system to infection, and, crucially, the impact her immune response may have on normal fetal brain development, including the risk of neurodevelopmental disorders in offspring (Smith, Li, Garbett, Mirnics, & Patterson, 2007). The purpose of this article is to (a) provide an overview of neuroanatomical, neurochemical, neuropsychological, and behavioral changes that can result from PIA, (b) discuss potential mechanisms by which these changes can occur, (c) describe the role of the timing of infection in PIA-induced changes in the offspring, (d) explain how PIA is implicated in ASD and SZ, and (e) suggest directions for future research in this field. The idea that PIA can lead to various psychopathologies warrants further exploration, especially seeing that the field of developmental origins of health and disease is relatively contemporary.

## 1. Methods

PubMed was searched using the keywords "autism", "autism spectrum disorder", "ASD", "Asperger Syndrome" and "schizophrenia". Results were restricted to articles published in the last ten years and to articles published in the English language. The search yielded 990 articles. The abstracts of these articles were screened by both authors for focussing on the role of maternal immune activation (MIA) in the onset and progression of psychopathologies in the developing infant. Articles were excluded if they did not pertain to both ASD and SZ. Following initial screening, articles were selectively chosen by both authors for the review based on the criterion of a focus on MIA-induced immunological, genetic, neuroanatomical, neurochemical, neuropsychological, and/or behavioral changes in offspring that have implications for the pathogenesis of ASD and SZ. The reference lists of included articles were searched for additional articles that were highly significant and relevant to the objectives of the review, and that met inclusion criteria but were not captured in the PubMed search.

## 2. Neuroanatomical, neurochemical, neuropsychological and behavioral sequelae of PIA

Morphological changes in the hippocampus are commonly reported in offspring exposed to prenatal infection. Changes include decreases in neurogenesis (Cui, Ashdown, Luheshi, & Boksa, 2009), axonal size (Makinodan et al., 2008), myelin thickness (Makinodan et al., 2008), dendritic branching (Baharnoori, Brake, & Srivastava, 2009), and the neuronal glycoprotein Reelin (Meyer, Nyffeler, Yee, Knuesel, & Feldon, 2008). Detrimental changes have also been observed in the prefrontal cortex (PFC), including decreases in dendritic branching (Baharnoori et al., 2009), Reelin (Meyer, Nyffeler, Yee, et al., 2008), and D1 and D2 dopamine receptors (Meyer, Nyffeler, Schwendener, Knuesel, Yee, & Feldon, 2008). Further, white matter thinning in the corpus callosum (Fatemi et al., 2008) and defective proliferation in cortical cells (De Miranda et al., 2010) has been observed. Hypofunctioning of N-methyl-D-aspartic acid (NMDA) receptors (Samuelsson, Jennische, Hansson, & Holmang, 2006) and decreases in cortical 5HT1A and 5HT1B mRNA (Baharnoori, Bhardwaj, & Srivastava, 2012) have also been detected. These morphological changes in the hippocampus and PFC can be especially detrimental to processes governed by these regions. In particular, impairments in learning and memory and the regulation of social behavior, which are largely governed by the hippocampus (Jarrard, 1993) and PFC (Anderson, Bechara, Damasio, Tranel, & Damasio, 1999) respectively, may be observed.

Animal studies have revealed a range of behaviors that are affected by PIA. Prepulse inhibition (PPI) was shown to be significantly reduced following PIA (Borrell, Vela, Arevalo-Martin, Molina-Holgado, & Guaza, 2002). PPI is a phenomenon in