



Developmental neuroinflammation and schizophrenia

Urs Meyer*

Physiology and Behaviour Laboratory, Swiss Federal Institute of Technology (ETH) Zurich, Schorenstrasse 16, 8603 Schwerzenbach, Switzerland

ARTICLE INFO

Available online 15 November 2011

Keywords:

Cytokines
Infection
Inflammation
Microglia
Oxidative stress
Poly I:C

ABSTRACT

There is increasing interest in and evidence for altered immune factors in the etiology and pathophysiology of schizophrenia. Stimulated by various epidemiological findings reporting elevated risk of schizophrenia following prenatal exposure to infection, one line of current research aims to explore the potential contribution of immune-mediated disruption of early brain development in the precipitation of long-term psychotic disease. Since the initial formulation of the “prenatal cytokine hypothesis” more than a decade ago, extensive epidemiological research and remarkable advances in modeling prenatal immune activation effects in animal models have provided strong support for this hypothesis by underscoring the critical role of cytokine-associated inflammatory events, together with downstream pathophysiological processes such as oxidative stress, hypoferrremia and zinc deficiency, in mediating the short- and long-term neurodevelopmental effects of prenatal infection. Longitudinal studies in animal models further indicate that infection-induced developmental neuroinflammation may be pathologically relevant beyond the antenatal and neonatal periods, and may contribute to disease progression associated with the gradual development of full-blown schizophrenic disease. According to this scenario, exposure to prenatal immune challenge primes early pre- and postnatal alterations in peripheral and central inflammatory response systems, which in turn may disrupt the normal development and maturation of neuronal systems from juvenile to adult stages of life. Such developmental neuroinflammation may adversely affect processes that are pivotal for normal brain maturation, including myelination, synaptic pruning, and neuronal remodeling, all of which occur to a great extent during postnatal brain maturation. Undoubtedly, our understanding of the role of developmental neuroinflammation in progressive brain changes relevant to schizophrenia is still in infancy. Identification of these mechanisms would be highly warranted because they may represent a valuable target to attenuate or even prevent the emergence of full-blown brain and behavioral pathology, especially in individuals with a history of prenatal complications such as in-utero exposure to infection and/or inflammation.

© 2011 Elsevier Inc. All rights reserved.

1. Introduction

Schizophrenia is a chronic psychotic disorder that affects 0.5–1% of the population worldwide (Tandon et al., 2008). The onset of full-blown schizophrenic disease is typically in late adolescence or early adulthood, and the clinical manifestation involves expression of distinct but often co-existing symptom classes which are commonly referred to as positive, negative and cognitive symptoms (Carter et al., 2008; Möller, 2007; Tandon et al., 2009). Positive symptoms refer to clinical features that are normally not present in healthy individuals but appear as a result of the disease. These include visual and/or auditory hallucinations, delusions, paranoia, and major thought

disorders. Negative symptoms are features that are normally present in healthy individuals, but are reduced or absent in schizophrenic patients. This symptom category typically includes social withdrawal, apathy, anhedonia, alogia, and behavioral perseveration. Finally, cognitive symptoms of schizophrenia are characterized by disturbances in executive functions, working memory impairment, and inability to sustain attention.

Despite extensive research and remarkable advances in the neurobiological, neurochemical and genetic aspects of this disabling mental illness (Insel, 2010; Jaaro-Peled et al., 2009; Ross et al., 2006; van Os and Kapur, 2009), the underlying etiological processes remain a challenge for clinicians and basic researchers alike. Since its initial formulation in the late 1980's (Murray and Lewis, 1987; Weinberger, 1987), the neurodevelopmental hypothesis of schizophrenia has been one of the most enduring theoretical accounts of the disorder's etiology and has since then received converging support from various research fields, including epidemiology, neuroimaging and post-mortem analysis (Fatemi and Folsom, 2009; Lewis and Levitt, 2002; McGrath et al., 2003; Rapoport et al., 2005). In essence, this hypothesis suggests that the etiology of schizophrenia involves aberrant neurodevelopmental

Abbreviations: 3-OHXY, 3-hydroxykynurenine; CNS, central nervous system; EGF, epidermal growth factor; FGF, fibroblast growth factor; GABA, γ -aminobutyric acid; IFN, interferon; IL, interleukin; LPS, lipopolysaccharide; NAC, N-acetylcysteine; polyI:C, polyriboinosinic–polyribocytidilic acid; QUIN, quinolinic acid; RNS, reactive nitrogen species; ROS, reactive oxygen species; Shh, sonic hedgehog; TGF, transforming growth factor; TNF, tumor necrosis factor; TLR, toll-like receptor.

* Tel.: +41 44 655 7403; fax: +41 44 655 7203.

E-mail address: urmeyer@ethz.ch.

processes, in which primary cerebral insults occur during early brain development long before the illness is clinically expressed. Recent advances in brain imaging techniques have led to an important refinement of the neurodevelopmental hypothesis of schizophrenia by underlining the importance of progressive brain changes that occur during the early stages of the disease, i.e., before and/or during the transition to full-blown psychosis (Hulshoff Pol and Kahn, 2008; Pantelis et al., 2005; Wood et al., 2008). Brain changes in schizophrenia thus appear to be more dynamic than previously assumed, so that an interaction between early neurodevelopmental disturbances and pathological events occurring during postnatal brain maturation seems necessary to trigger the onset of overt schizophrenic disease (Cannon et al., 2003; Keshavan, 1999; Keshavan and Hogarty, 1999; Read et al., 2001; Walker et al., 1999).

There is increasing interest in and evidence for altered immune factors in the etiology and pathophysiology of schizophrenia (Drexhage et al., 2010; Meyer et al., 2011a,b; Müller and Schwarz, 2006, 2010; Müller et al., 2000; Steiner et al., 2010). Stimulated by various epidemiological findings reporting elevated risk of schizophrenia following prenatal exposure to infection (Brown, 2011; Brown and Derkits, 2010), one line of current research aims to explore the potential contribution of immune-mediated disruption of early brain development in the precipitation of long-term psychotic disease (McAlonan et al., 2010; Meyer and Feldon, 2010; Meyer et al., 2009a,b). One of the immunological mechanisms in this context is developmental neuroinflammation, which may predispose the organism to schizophrenia-relevant brain and behavioral abnormalities (Meyer et al., 2011a,c). The present article summarizes existing evidence for this hypothesis and discusses the role of developmental neuroinflammation in schizophrenia with regards to its impact on early brain development, disease progression and possible preventive interventions.

2. Epidemiological and translational studies of prenatal infection and schizophrenia

A significant association between prenatal maternal infection and increased risk of schizophrenia in the offspring has been demonstrated in a variety of retrospective epidemiological studies (reviewed in Brown and Derkits, 2010; Brown, 2011; Brown and Patterson, 2011), even though negative reports also exist (e.g., Crow and Done, 1992; Mino et al., 2000; Morgan et al., 1997). Interestingly, the link between prenatal exposure to infection and enhanced schizophrenia risk does not seem to be pathogen-specific. Indeed, numerous viral infectious agents have been implicated in this association, including influenza (Brown et al., 2004a; Mednick et al., 1988), rubella (Brown et al., 2001), measles (Torrey et al., 1988), polio (Suvisaari et al., 1999), herpes simplex (Buka et al., 2001a), as well as bacterial pathogens causing sinusitis, tonsillitis and pneumonia (Sørensen et al., 2009), genital and/or reproductive infections (Babulas et al., 2006), and the protozoan parasite *Toxoplasma gondii* (Brown et al., 2005; Mortensen et al., 2007). Importantly, the establishment of prospective epidemiological approaches has provided clear serologic evidence for at least some of the infectious agents implicated in the prenatal infectious etiology of schizophrenia (Brown et al., 2004a,b, 2005; Mortensen et al., 2007). Even though prenatal exposure to infection per se appears to have relatively modest effects across large populations (Morgan et al., 1997; Selten et al., 2010), it is likely to be a relevant factor interacting with other schizophrenia risk factors, including genetic predisposition. In support of this hypothesis, the effect of prenatal infection on elevating risk of schizophrenia is substantially increased in offspring with a positive family history of psychotic disorders (Clarke et al., 2009).

Epidemiological research is now also beginning to determine whether prenatal exposure to infection confers vulnerability to specific features of schizophrenia neuropathology and psychopathology.

Brown and colleagues have recently provided a first line of evidence showing that deficits in fine-motor coordination, verbal memory, executive functions and working memory are more pronounced in schizophrenic cases with a positive history of prenatal infection compared to schizophrenic cases without such a history (Brown et al., 2009b, 2011). Furthermore, a significant association between increased length of the cavum septum pellucidum and prenatal infection has been demonstrated in exposed schizophrenia cases compared to unexposed cases, indicating that in-utero exposure to infection may contribute to neurodevelopmental morphologic abnormalities frequently observed in schizophrenic patients (Brown et al., 2009a).

Based on the reported association between prenatal influenza infection and adult schizophrenia, Fatemi and colleagues have pioneered an experimental animal model of prenatal exposure to human influenza virus in mice (Fatemi et al., 1998, 1999, 2000, 2002a,b, 2004, 2005, 2008), which has recently been adopted by other laboratories (Moreno et al., 2011). In this model, pregnant mice are infused intranasally with a sublethal dose of a neurotropic strain of human influenza virus, and the long-term brain and behavioral effects are then evaluated in the resulting offspring relative to control offspring born to sham-treated mothers. Brain morphological and neuroanatomical investigations in this model have shown that maternal influenza infection leads to a variety of neuropathological signs in the offspring's brains postnatally, some of which are critically implicated in the neuropathology of schizophrenia (Fatemi et al., 1998, 1999, 2000, 2002a,b, 2004, 2005, 2008, 2009; Moreno et al., 2011; for a summary see Table 1). In addition to the identified neuropathological alterations (Table 1), prenatal exposure to influenza virus in mice also induces a set of behavioral and pharmacological changes in adulthood, which are implicated in both the positive and negative symptoms of schizophrenia (Moreno et al., 2011; Shi et al., 2003). This includes deficits in sensorimotor gating, reduced spatial exploration and social interaction, and enhanced sensitivity to pharmacological treatment with NMDA-receptor antagonists and hallucinogens (summarized in Table 2). Importantly, the prenatal infection-induced deficits in sensorimotor gating can be normalized by acute treatment with typical or atypical antipsychotic drugs (Shi et al., 2003), suggesting that at least some of the long-term behavioral changes induced by prenatal influenza exposure are sensitive to pharmacological compounds used in the symptomatic pharmacotherapy of schizophrenia.

The findings derived from the prenatal influenza mouse model have recently been completed with experimental investigations in rhesus monkeys demonstrating the emergence of reduced gray and white matter in distinct cortical and parieto-cortical brain regions of neonates born to influenza-infected mothers (Short et al., 2010). Notably, the extension of translational research to rhesus monkeys is especially relevant in the present context because prenatal corticogenesis is more advanced in primate as compared to rodent species, and therefore, primate models help to verify the relevance of the findings in animal models to the human condition. Taken together, the experimental data obtained in mouse and primate prenatal viral infection models can readily be taken as causal evidence to support human epidemiological studies suggesting that there may be a causal relationship between in-utero exposure to infection and emergence of postnatal brain dysfunctions pertinent to schizophrenic disease.

3. The role of inflammation in mediating the effects of maternal infection on the offspring

In the event of maternal infection during pregnancy, at least some infectious pathogens such as rubella are capable of penetrating the placental barrier and infiltrating the fetal environment, thereby causing direct damage to the growing organism by interfering with cell growth, protein synthesis and nutritional supply (Bale, 2009). Despite

Table 1

Summary of long-term morphological and neurochemical brain abnormalities relevant to schizophrenia as identified in various animal models of prenatal infection and/or inflammation. The models are based on prenatal exposure to human influenza virus, the viral mimic polyriboinosinic–polyribocytidilic acid (polyI:C), the bacterial endotoxin lipopolysaccharide (LPS), the pro-inflammatory cytokine interleukin-6 (IL-6), and the locally acting inflammatory agent turpentine. The table specifies the precise timing of the prenatal maternal infection and/or immune challenge as well as the rodent species used for the experimental investigations. Downward and upward arrows indicate an impairment or enhancement of the particular morphological or neurochemical parameter, respectively; the hyphens indicate that no changes were detected relative to the corresponding control treatment. ND = not determined. DA, dopamine; DA-R, dopamine receptor; GABA_A-R, γ -aminobutyric acid receptor subtype A; NMDA-R, N-methyl-D-aspartate receptor; PV, parvalbumin; TH, tyrosine hydroxylase.

Immunogen	Species	Gestational period	Morphological/neurochemical brain abnormalities in adolescent or adult offspring born to immune-challenged mothers												References
			Cortico-/neurogenesis	Neuronal morphology	Dendritic/synaptic structure and function	Lateral ventricles	Reelin	PV	TH	DA	DA-R	GABA _A -R	NMDA-R		
Influenza	Mouse	Early/middle	↓ ^{a,b}	Increased pyramidal and non-pyramidal cell density, pyramidal cell atrophy ^{a,b} ; reduced Purkinje cell density ^c	ND	↓	↓ ^{a,b,d}	ND	ND	—	ND	ND	ND	Fatemi et al. (1998, 1999, 2002a,b, 2004); Winter et al. (2008); Shi et al. (2009).	
	Mouse	Late	ND	Reduced brain volume ^{c,e,f} ; lower fractional anisotropy of corpus callosum	ND	—	ND	ND	ND	—	ND	ND	ND	Fatemi et al. (2008, 2009).	
PolyI:C	Mouse	Early/middle	↓ ^b	Reduced Purkinje cell density ^c ; lower fractional anisotropy throughout fronto-striatal-limbic circuits	Delayed postnatal myelination ^b	↑	↓ ^{a,b}	↓ ^a	↑ ^g	↑ ^a _h	↑ ^g _a	↑ ^{b,i}	—	Meyer et al. (2006b, 2008c); Nyffeler et al. (2006); Ozawa et al. (2008); Makinodan et al. (2008); Li et al. (2009, 2010); Winter et al. (2009); Shi et al. (2009); Wolf et al. (2011); Soumiya et al. (2011a,b).	
	Mouse	Late	↓ ^b	—	ND	—	↓ ^{a,b}	↓ ^a _b	ND	↓ ^a _b	ND	↑ ^b	↓ ^b	Meyer et al. (2006b, 2008c); Li et al. (2009); Bitanirwe et al. (2010a).	
	Rat	Middle/late	ND	Abundance of pyknotic neuronal cells ^b ; reduced volume of hippocampus and prefrontal cortex	Abnormal long-range neural synchrony ^{a,b}	↑	ND	ND	ND	↑ ^{g,j}	ND	ND	ND	Zuckerman et al. (2003); Piontkewitz et al. (2009, 2011a, 2011b); Dickerson et al. (2010).	
LPS	Rat	Early → late	ND	ND	ND	ND	ND	ND	↑ ^g	↑ ^g	ND	ND	ND	Borrell et al. (2002); Romero et al. (2007, 2010).	
	Rat	Middle/late	↓ ^b	ND	Reduced dendritic arborization and length ^{a,b} ; reduced spine density ^a ; abnormal excitatory postsynaptic potentials ^b ; impaired short-term potentiation ^b	ND	ND	ND	ND	ND	ND	ND	ND	Lowe et al. (2008); Baharnoori et al. (2009); Cui et al. (2009); Graciarena et al. (2010).	
	Mouse	Late	ND	Increased density; shrinkage of neuronal cells ^b	ND	ND	ND	ND	ND	ND	ND	ND	ND	Golan et al. (2005).	
IL-6	Rat	Early → late	ND	Abundance of pyknotic neuronal cells ^b ; neuronal cell loss ^b	ND	ND	ND	ND	ND	ND	—	—	—	Samuelsson et al. (2006).	
	Rat	Middle → late	ND	Abundance of pyknotic neuronal cells ^b ; neuronal cell loss ^b	ND	ND	ND	ND	ND	ND	↑ ^b	↑ ^b	—	Samuelsson et al. (2006).	
Turpentine	Rat	Middle/late	ND	ND	ND	ND	ND	ND	↑ ^g	↑ ^g	ND	ND	ND	Aguilar-Valles et al. (2010).	

^a Frontal cortex.

^b Hippocampus.

^c Cerebellum.

^d In neonatal offspring.

^e Whole brain.

^f Present only in peri-pubertal but not in adult offspring.

^g Striatum.

^h Globus pallidus.

ⁱ Amygdala.

^j Only following KCl-induced stimulation.

Table 2

Summary of long-term behavioral, cognitive and pharmacological dysfunctions relevant to schizophrenia as identified in various animal models of prenatal infection and/or inflammation. The models are based on prenatal exposure to human influenza virus, the viral mimic polyriboinosinic–polyribocytidilic acid (PolyI:C), the bacterial endotoxin lipopolysaccharide (LPS), the pro-inflammatory cytokine interleukin-6 (IL-6), and the locally acting inflammatory agent turpentine. The table specifies the precise timing of the prenatal maternal infection and/or immune challenge as well as the rodent species used for the experimental investigations. Downward and upward arrows indicate an impairment or enhancement of the particular phenotype, respectively; the hyphens indicate that no changes were detected relative to the corresponding control treatment; ND = not determined. DA-R, dopamine receptor; NMDA-R, N-methyl-D-aspartate receptor.

Immunogen	Species	Gestational period	Behavioral, cognitive and pharmacological abnormalities in adult offspring born to immune-challenged mothers								References
			Prepulse inhibition	Latent inhibition	Social behavior	Exploratory behavior	Working memory	Cognitive flexibility	Sensitivity to DA-R agonists	Sensitivity to NMDA-R agonists	
Influenza PolyI:C	Mouse	Early/middle	↓	ND	↓	↓	ND	ND	ND	↑	Shi et al. (2003); Moreno et al. (2011) Shi et al. (2003); Meyer et al. (2005, 2006a,b,c, 2008b,c,d, 2010b); Smith et al. (2007); Makinodan et al. (2008); Li et al. (2009); Vuillermot et al. (2010, 2011). Ozawa et al. (2008); Cardon et al. (2010); De Miranda et al. (2010); Wolf et al. (2011) Meyer et al. (2006b, 2006c, 2008c, 2010a, 2010b); Li et al. (2009); Bitanhirwe et al. (2010a,b). Zuckerman et al. (2003); Zuckerman and Weiner (2003, 2005); Wolff and Bilkey (2008); Piontkewitz et al. (2009, 2011a, 2011b); Dickerson et al. (2010); Bronson et al. (2011); Han et al. (2011); Richtand et al. (2011); Wolff et al. (2011); Zhang et al. (2011, in press). Borrell et al. (2002); Romero et al. (2007, 2010). Fortier et al. (2007). Fortier et al. (2004a, 2007); Graciarena et al. (2010). Coyle et al. (2009). Golan et al. (2005). Smith et al. (2007) Fortier et al. (2007); Aguilar-Valles et al. (2010); Aguilar-Valles and Luheshi (2011). Aguilar-Valles and Luheshi (2011).
	Mouse	Early/middle	↓	↓	↓	↓	↓	—	↑	↑	
	Mouse	Middle or middle → late	↓	ND	ND	↓	↓	ND	↑	ND	
	Mouse	Late	—	—/↑	↓	—	↓	↓	↑	↑	
	Rat	Middle/late	↓	↓	ND	—	↓	↓/↑	↑/↓	↑/↓	
LPS	Rat	Early → late	↓	ND	ND	ND	ND	ND	ND	ND	Fortier et al. (2007). Fortier et al. (2004a, 2007); Graciarena et al. (2010). Coyle et al. (2009). Golan et al. (2005). Smith et al. (2007) Fortier et al. (2007); Aguilar-Valles et al. (2010); Aguilar-Valles and Luheshi (2011). Aguilar-Valles and Luheshi (2011).
	Rat	Middle	↓	ND	ND	ND	ND	ND	ND	ND	
	Rat	Middle → late or late	↓	ND	ND	ND	↓	ND	↑	ND	
	Mouse	Early/middle	ND	ND	ND	—	↓	ND	ND	ND	
IL-6 Turpentine	Mouse	Late	ND	ND	↓	—	ND	ND	ND	ND	Fortier et al. (2007); Aguilar-Valles et al. (2010); Aguilar-Valles and Luheshi (2011). Aguilar-Valles and Luheshi (2011).
	Mouse	Early/middle	↓	↓	↓	↓	ND	ND	ND	ND	
	Rat	Middle/late	↓	ND	ND	ND	ND	ND	↑	ND	
	Rat	Late	—	ND	ND	ND	ND	ND	—	ND	

this, converging evidence from several lines of research indicates that the deleterious effects of maternal infection on the offspring are likely to be attributable to maternal/fetal inflammatory responses rather than direct viral effects on the developing fetus (Gilmore and Jarskog, 1997; Meyer et al., 2009b; Patterson, 2002). This issue is discussed in detail in subsequent sections (Sections 3.3 and 3.4) following a summary of the main components of the inflammatory response system (Section 3.1) and of known neurodevelopmental effects of cytokines (Section 3.2).

3.1. Main components of the inflammatory response system

Inflammation is one of the first defense mechanisms of the innate immune system to infection and other physiological insults such as tissue damage or stress (Gallin et al., 1999). Typically, it is characterized by redness and swelling of infected/wounded tissue and is promoted by a number of secreted pro-inflammatory factors, including prostaglandins, leukotrienes, pro-inflammatory cytokines and chemokines. Prostaglandins are important mediators of the febrile response and of blood vessel dilation, whereas leukotrienes together with chemokines are critical for attracting leukocytes to sites of infection and/or tissue damage (Gallin et al., 1999). Cytokines have wide-ranging roles in the innate and adaptive immune systems, where they help regulate the recruitment and activation of lymphocytes as well as immune cell differentiation and homeostasis (Curfs et al., 1997). In addition, some cytokines possess direct effector mechanisms, including induction of cell apoptosis and inhibition of protein synthesis (Curfs

et al., 1997). Members of the pro-inflammatory cytokine family, including interleukin (IL)-1 β , IL-6 and tumor necrosis factor (TNF)- α , are essential to the inflammatory response by contributing to febrile reactions, activating phagocytotic cells such as macrophages or dendritic cells, facilitating vascular permeability, and promoting the release of plasma-derived inflammatory mediators such as bradykinin and components of the complement system. In the periphery, pro-inflammatory cytokines are produced and released to a great extent by activated endothelial cells and cells of the mononuclear phagocyte system (monocytes, macrophages and monocyte-derived dendritic cells). The synthesis of pro-inflammatory molecules is strongly stimulated upon activation of the innate immune system. This most often occurs upon binding of microbe-specific components by a special class of receptors known as pathogen recognition receptors, or when damaged or infected cells send out alarm signals, many of which are recognized by the same receptors as those that recognize pathogens (Janeway and Medzhitov, 2002). Table 3 summarizes the major cellular sources and main biological activities of pro- and anti-inflammatory cytokines.

Under normal conditions, inflammation is controlled by various homeostatic processes that limit or counteract inflammation once it has been induced by a pro-inflammatory stimulus such as infection (Serhan and Savill, 2005). Such control mechanisms ensure that inflammatory processes efficiently remove invading pathogens and contribute to tissue repair and wound healing without inducing collateral damage to non-infected, healthy and unwounded tissue. Dysfunction of such surveillance mechanisms may lead to persistent

Table 3
Major immunological effects and known neurodevelopmental effects of selected inflammatory cytokines. The table summarizes the major cellular sources and immunological effects of selected pro- and anti-inflammatory cytokines (adapted from [Curfs et al., 1997](#) and [Meyer et al., 2011b](#)) and illustrates some of the known neurodevelopmental effects (corresponding references in the table).

Cytokine	Main cellular source	Main immunological effects	Known neurodevelopmental effects	References
IL-1 β	Activated monocytes/macrophages; endothelia cells; microglia.	Promotion of fever (endogenous pyrogen); stimulation of other pro-inflammatory cytokines and hematopoietic growth factors; induction of acute-phase proteins; stimulation of HPA axis; activation of T-, B- and endothelial cells.	Conversion of midbrain progenitor cells into dopaminergic phenotype; promotion of fetal midbrain dopamine cell survival; disruption of neuron dendrite development and outgrowth.	Kushima et al. (1992) ; Akaneya et al. (1995) ; Ling et al. (1998) ; Potter et al. (1999) ; Gilmore et al. (2004) .
sIL-1RA	Activated monocytes/macrophages; endothelia cells; fibroblasts, astrocytes.	Inhibition of IL-1 activity; homeostatic control of inflammation through anti-inflammatory actions.	Inhibition or promotion of neurogenesis depending on specificity of neuroinflammatory milieu and maturational stage.	Goshen et al. (2008) ; Ben Menachem-Zidon et al. (2008) ; Spulber et al. (2008) .
IL-6	Activated monocytes/macrophages; T cells (T _H 2 and T _H 17 cells); hepatocytes; osteoclasts; fibroblasts; astrocytes.	Promotion of fever (endogenous pyrogen); induction of acute-phase proteins; stimulation of immunoglobulin-G production; activation of T cells; stimulation of HPA axis.	Decreasing survival of fetal serotonin neurons; disruption of neuron dendrite development and outgrowth; promotion of fetal midbrain dopamine and dorsal root ganglion cell survival.	Kushima et al. (1992) ; Akaneya et al. (1995) ; Jarskog et al. (1997) ; Edoff and Jerregård (2002) ; Gilmore et al. (2004) .
sIL-6R	Activated monocytes/macrophages; hepatocytes; osteoclasts.	Augmentation of IL-6 responses by acting as an IL-6 agonist.	Enhancement of neuronal survival during development.	Edoff and Jerregård (2002) .
IL-8	Activated monocytes/macrophages; endothelia cells; fibroblasts.	Activation of neutrophils; chemotactic for neutrophils, T cells and basophils.	Largely unknown.	
IL-10	Activated monocytes/macrophages; T cells (T _H 2 cells); B cells.	Inhibition of pro-inflammatory cytokine synthesis; inhibition of sepsis; promotion of humoral immune responses involving antibody secretion.	Promotion of neuronal survival; trophic support to developing neurons.	Zhou et al. (2009a,b) .
TNF- α	Activated monocytes/macrophages; T cells (T _H 1 cells); natural killer cells; endothelia cells; microglia.	Promotion of fever (endogenous pyrogen) and sepsis; direct cytotoxic effects by inducing apoptosis; activation of monocytes, lymphocytes, and endothelial cells.	Neuronal apoptosis; disruption of neuron dendrite development and outgrowth.	Barker et al. (2001) ; Neumann et al. (2002) ; Gilmore et al. (2004) ; Doherty (2007) .
sTNFR	Virtually all nucleated cells.	Inhibition of TNF activity; homeostatic control of inflammation through anti-inflammatory actions.	Blocking neuronal apoptosis (mediated by TNF- α).	Yang et al. (2002) .
TGF- β	Megakaryocytes; T cells (T _H 3 cells).	Inhibition of pro-inflammatory cytokine synthesis; inhibition of natural killer cell activity and growth of T- and B-cells; in the presence of IL-6 stimulation of T _H 17 cells.	Ventral midbrain dopaminergic development by promotion of tyrosine hydroxylase expression; regulation of (neuromuscular) synapse formation.	Roussa et al. (2006) ; Feng and Ko (2008) .

inflammation, known from numerous pathological conditions such as rheumatoid arthritis, atherosclerosis, inflammatory bowel disease, and Crohn's disease ([Briand and Muller, 2010](#); [Serhan and Savill, 2005](#)).

In the central nervous system (CNS), microglia and astrocytes are the major immunocompetent cells regulating both the induction as well as limitation of inflammatory processes ([Ransohoff and Cardona, 2010](#); [Ransohoff and Perry, 2009](#); [Seth and Koul, 2008](#)). This is achieved through the synthesis of cytokines, up- or down-regulation of various cell surface receptors such as pathogen recognition receptors, cytokine receptors, and numerous receptors crucial for antigen presentation. Acting as the first and main form of active immune defense in the brain, microglia are considered to be the resident macrophages of the CNS, which constantly scavenge the CNS for damaged neurons, plaques, and infectious agents ([Ransohoff and Cardona, 2010](#); [Ransohoff and Perry, 2009](#)). Microglia appear to play crucial roles in both neuronal protection and pathology, and are often referred to as a “double-edged sword” ([Block et al., 2007](#)). On the one hand, they secrete neurotrophic factors pivotal for cellular repair, and recruit immune cells into the brain for clearance of infection or cellular debris. On the other hand, chronic or exaggerated microglial activation is linked to excessive secretion of pro-inflammatory factors and has been linked to (progressive) neurodegenerative processes ([Block et al., 2007](#)). With regards to astrocytes, it has been considered for long that the main roles of these glial cells are related to neuronal support functions. However, accumulating evidence suggests that astrocytes exert a much wider spectrum of functions, including regulation of neuronal differentiation, axonal guidance, synapse formation, and brain plasticity ([Seth and Koul, 2008](#)). Of note, astrocytes have

also become the focus of attention due to their modulatory effects on microglia cells. They seem to have noticeable inhibitory as well as stimulatory influences on microglia functions depending on the precise immune milieu in which astrocyte–microglia interactions take place ([Bianchi et al., 2011](#); [Wang, 2010](#); [Zhang et al., 2011, in press](#)).

3.2. Neurodevelopmental effects of cytokines

Many cytokines and cytokine receptors are constitutively expressed during fetal brain development ([Burns et al., 1993](#); [Mehler and Kessler, 1997](#); [Mousa et al., 1999](#); [Pousset, 1994](#)), suggesting essential roles for these molecules in the regulation and modulation of normal brain development. Indeed, besides their various roles in the peripheral immune system, cytokines have been recognized to exert a number of essential neurodevelopmental effects, including neuronal induction, proliferation, migration and survival. These effects have recently been reviewed in several excellent articles ([Bauer et al., 2007](#); [Deverman and Patterson, 2009](#); [Jonakait, 2007](#)), and some of the major neurodevelopmental effects of selected inflammatory cytokines are also summarized in [Table 3](#). In view of the essential roles of cytokines during normal brain development, it can readily be expected that abnormal levels of these molecules during critical periods of early brain development adversely affect neurodevelopmental processes and contribute to a higher susceptibility for complex brain disorders of developmental origin such as schizophrenia.

Notably, distinct classes of cytokines can exert differing effects in the developing CNS. For instance, among the variety of pro- and anti-inflammatory cytokines, IL-1 β is the most capable in inducing

the conversion of rat mesencephalic progenitor cells into a dopaminergic phenotype (Ling et al., 1998; Potter et al., 1999) and IL-6 is highly efficacious in decreasing the survival of fetal brain serotonin neurons (Jarskog et al., 1997). In contrast, IL-1 β and IL-6 (and to a lesser extent TNF- α) appear to have an equivalent capacity to negatively regulate the survival of fetal midbrain dopaminergic neurons at low to medium concentrations (Jarskog et al., 1997), whereas the same cytokines can promote survival of these cells at higher concentrations (Akaneya et al., 1995; Kushima et al., 1992). A similar dependency on cytokine specificity and/or concentration has also been found in a recent *in vitro* study by Gilmore et al. (2004) who have demonstrated that TNF- α can disrupt cortical neuron's dendrite development at low concentration while the same effects can be achieved by exposure of fetal cortical neurons to higher concentrations of IL-1 β , IL-6, or TNF- α .

The responsiveness and/or sensitivity of developing cells to many signaling cues, including cytokines, can also vary considerably as neurodevelopment progresses. For example, while TNF- α is neurotrophic to dopaminergic ventral mesencephalic neurons during early fetal development, the same molecule can exert neurotoxic effects on these cells at later stages of fetal brain development (Doherty, 2007). Similarly, embryonic cells cultured as progenitor neurospheres proliferate more robustly in response to basic fibroblast growth factor (bFGF) than to epidermal growth factor (EGF), whereas proliferation of postnatal and adult progenitor cells is enhanced more effectively by EGF than bFGF (Zhu et al., 1999). In the context of maternal infection during pregnancy, this highlights that the eventual neurodevelopmental impact of abnormal maternal/fetal cytokine expression is likely to be determined also by the precise stage of brain development (Meyer et al., 2006b, 2007, 2008c).

3.3. Epidemiological evidence for a role of inflammation in mediating the effects of maternal infection on the offspring

It has been widely recognized that intrauterine infection and subsequent maternal/fetal inflammatory responses are major contributors to periventricular leukomalacia (i.e., white matter damage) (Dammann and Leviton, 1997, 2000; Hagberg et al. 2005; Leviton et al., 2010; Shatrov et al., 2010). Periventricular leukomalacia is causally linked to subsequent development of cognitive and neurological disabilities, especially cerebral palsy (Leviton et al., 2010; Shatrov et al., 2010), and is characterized by enhanced pro-inflammatory cytokine secretion and microglial activation causing loss of oligodendrocyte progenitor cells and immature neurons in periventricular regions (Deng, 2010; Leviton and Gressens, 2007).

The fact that numerous infectious pathogens have been implicated in the association between prenatal infection and schizophrenia has led to the hypothesis that common immunological factors in general, and pro-inflammatory cytokines in particular, are the candidate mediators of this association (Gilmore and Jarskog, 1997). However, in contrast to the broad literature implicating inflammatory processes in the development of neonatal white matter damage and cerebral palsy (Dammann and Leviton, 1997, 2000; Deng, 2010; Hagberg et al. 2005; Leviton and Gressens, 2007), direct epidemiological evidence linking enhanced maternal/fetal expression of inflammatory markers and later development of schizophrenia is thus far limited to a small number of investigations. These include reports of a significant association between high maternal levels of the pro-inflammatory cytokines TNF- α (Buka et al., 2001b) and IL-8 (Brown et al., 2004b) and elevated risk of schizophrenia spectrum disorder in the offspring. In addition, Ellman et al. (2010) have recently provided a first line of evidence implicating increased prenatal maternal IL-8 levels with exacerbation of structural brain changes in schizophrenic offspring. More specifically, this study reported for the first time a significant association between higher prenatal IL-8 levels in the second/third trimester of pregnancy and greater ventricular

cerebrospinal fluid volume in adult schizophrenia spectrum cases (Ellman et al., 2010). In addition, higher prenatal IL-8 levels were correlated with lower volumes in the left entorhinal cortex and right posterior cingulate (Ellman et al., 2010). Even though these findings may be indicative of abnormal expression of specific inflammatory markers in the developmental course of schizophrenia and related disorders, such valuable epidemiological data need to be interpreted with some points of caution. First, all epidemiological studies are observational in nature and thus cannot prove causality. Second, the available epidemiological studies reporting a significant association between enhanced maternal cytokine levels and increased schizophrenia risk in the offspring have so far not been able to delineate the source of inflammatory mediators. Hence, they readily fall short in identifying whether the presence of enhanced maternal cytokine levels is attributable to prior or ongoing infectious processes, or to other adverse maternal conditions, such as preeclampsia, obesity and anemia. As discussed in the next section (Section 3.4), experimental research in animals provides a unique opportunity to overcome these limitations.

3.4. Experimental evidence for a role of inflammation in mediating the effects of maternal infection on the offspring

Several experimental approaches have been established with the aim to test the hypothesis that the detrimental long-term effects of prenatal infection on offspring brain and behavioral development may be mediated indirectly by effects associated with activation of the maternal/fetal inflammatory response systems (for recent reviews see Meyer et al., 2009a,b; Boksa, 2010; Meyer and Feldon, 2010). Two of the best established models are based on maternal exposure to the bacterial endotoxin, lipopolysaccharide (LPS), and the synthetic analog of double-stranded RNA, polyriboinosinic-polyribocytidilic acid (polyI:C). LPS is recognized by toll-like receptor (TLR) 4, whereas polyI:C is recognized primarily by TLR3 (Alexopoulou et al., 2001; Takeuchi and Akira, 2007; Triantafyllou and Triantafyllou, 2002). TLRs are a class of pathogen recognition receptors, which recognize invariant structures present on virulent pathogens. Upon binding to TLRs, LPS and polyI:C both stimulate the production and release of many pro-inflammatory cytokines, including IL-1 β , IL-6, and TNF- α , (Cunningham et al., 2007; Fortier et al., 2004b; Meyer et al., 2006a,b). In addition, polyI:C is a potent inducer of the type I interferons IFN- α and IFN- β (Alexopoulou et al., 2001; Takeuchi and Akira, 2007). Therefore, whereas LPS exposure leads to a cytokine-associated innate immune response that is typically seen after infection with Gram-negative bacteria (Triantafyllou and Triantafyllou, 2002), administration of polyI:C mimics the acute phase response to viral infection (Traynor et al., 2004).

Notably, maternal exposure to LPS or polyI:C during pregnancy is capable of enhancing pro-inflammatory cytokine levels in the three maternal-fetal compartments, namely, the placenta, the amniotic fluid, and the fetus, including the fetal brain (e.g., Cai et al., 2000; Urakubo et al., 2001; Paintlia et al. 2004; Ashdown et al., 2006; Meyer et al., 2006b, 2008b; Graciarena et al., 2010; reviewed in Boksa, 2010). In-utero exposure to such immunogens further leads to microglia activation and expression of pro-inflammatory transcription factors such as nuclear factor- κ B (NF- κ B) in fetal and neonatal brains (Briscoe et al., 2006; Hutton et al., 2008; Nitsos et al., 2006; Roumier et al., 2008; Saadani-Makki et al., 2008), and this is paralleled by white matter injury (as evident by oligodendrocyte precursor cell loss and hypomyelination) and neuronal apoptosis during fetal and neonatal brain development (Bell and Hallenbeck, 2002; Dean et al., 2009; Hagberg et al., 2002; Kumral et al., 2007; Nitsos et al., 2006; Svedin et al., 2005; Wang et al., 2006). Taken together, animal models using inflammatory agents such as LPS or polyI:C provide multiple lines of evidence that in-utero inflammation induces wide-

spread neuroinflammation during critical stages of fetal and neonatal brain development.

Furthermore, numerous behavioral, cognitive, neurochemical, and brain morphological abnormalities have been detected in adult animals following maternal gestational exposure to LPS or polyI:C. These long-term effects have been extensively reviewed elsewhere (Boksa, 2010; Meyer and Feldon, 2009a,b, 2010; Meyer et al., 2007, 2009a,b; Patterson, 2009) and are summarized in Tables 1 and 2. Importantly, many of the behavioral, cognitive and pharmacological dysfunctions in adult animals born to LPS- or polyI:C- exposed mothers are directly implicated in schizophrenia and other psychosis-related disorders, including abnormalities in sensorimotor gating, selective attention, working memory and sensitivity to psychotomimetic drugs (Tables 1 and 2), and at least some of these functional abnormalities can be normalized by acute and/or chronic antipsychotic drug treatment (Tables 1 and 2; reviewed in Meyer et al., 2007, 2009a,b; Meyer and Feldon, 2009a,b, 2010; Patterson, 2009; Boksa, 2010). Taken together, the efficacy of prenatal exposure to cytokine-releasing agents such as LPS or polyI:C to induce fetal and neonatal brain inflammation, together with its long-term impact on brain and behavioral abnormalities relevant to schizophrenia, strongly underscores the essential role of prenatal cytokine-associated inflammation in mediating the effects of maternal infection on the offspring. This notion is further supported by the findings that blocking the actions of the pro-inflammatory cytokine IL-1 β or IL-6 in the pregnant maternal host by genetic or pharmacological interventions prevents the long-term brain and behavioral consequences of prenatal polyI:C or LPS treatment (Girard et al., 2010; Smith et al., 2007), and that over-expression of the anti-inflammatory cytokine IL-10 prevents the emergence of multiple behavioral and pharmacological abnormalities typically seen after prenatal polyI:C-induced immune challenge (Meyer et al., 2008b).

Another valuable model to study the relative contribution of prenatal inflammation to the development of schizophrenia-related brain disease is based on maternal intramuscular injection of turpentine oil (Aguilar-Valles and Luheshi, 2011; Aguilar-Valles et al., 2010; Fortier et al., 2007). Following its intramuscular injection, turpentine remains confined at the site of administration and locally causes tissue damage, recruitment and activation of immune cells, and secretion of pro-inflammatory cytokines (Aguilar-Valles et al., 2007; Luheshi et al., 1997). This experimental approach offers the opportunity to study of the effects of circulating inflammatory mediators that are solely produced by the maternal immune system. Hence, in contrast to the systemic LPS and polyI:C models (Ashdown et al., 2006; Hsiao and Patterson, 2011), placental secretion of inflammatory markers is minimal, and this readily facilitates the delineation of the relative contribution of maternally produced versus placenta-derived inflammatory factors in the link prenatal inflammation and abnormal brain and behavioral development (Aguilar-Valles and Luheshi, 2011; Aguilar-Valles et al., 2010; Fortier et al., 2007). Importantly, prenatal turpentine treatment is efficacious in inducing long-term behavioral, pharmacological and neurochemical changes implicated in schizophrenic disease, including prepulse inhibition deficiency, amphetamine hypersensitivity, deficits in spatial memory, and dopaminergic imbalances in striatal structures (Fortier et al., 2007; Aguilar-Valles et al., 2010; Aguilar-Valles and Luheshi, 2011; summarized in Tables 1 and 2). The findings from the prenatal turpentine model thus provide further strong support for the hypothesis that induction of maternal inflammatory responses assumes a key role in mediating the association between maternal infection during pregnancy and enhanced risk of schizophrenia-related brain pathology in the offspring.

3.5. The roles of oxidative stress, hypoferrmia, and zinc deficiency

The preceding sections have emphasized a critical role of abnormal maternal/fetal pro-inflammatory cytokine expression in the disruption of normal brain and behavioral development following

prenatal infection/inflammation. Even though evidence for this notion is manifold, it should be noted that several alternative (but not mutually exclusive) mechanisms seem feasible in this context. In addition to its effects on pro-inflammatory cytokine secretion, infection and subsequent induction of inflammatory responses are strongly associated with numerous other pathophysiological effects, including oxidative stress, iron deficiency (hypoferrmia), and (temporary) zinc deficiency (Ferré and Clària, 2006; Ganz and Nemeth, 2009; Prasad, 2009; Scrimgeour and Condlin, 2009). Oxidative stress is referred to as an imbalance between the production and elimination of reactive oxygen species (ROS), some of which are highly cytotoxic and promote tissue injury (Kohen and Nyska, 2002). Upon activation, innate immune cells secrete ROS and reactive nitrogen species (RNS) as a central part of killing invading pathogens (Nathan and Shiloh, 2000). Production of ROS and RNS is thus an important downstream mechanism of inflammation-mediated immune responses. For these reasons, it has been speculated that at least parts of the detrimental neurodevelopmental effects associated with prenatal infection/inflammation could be accounted for by the cytotoxic effects of excess ROS and RNS in the course of fetal brain development. In support of this hypothesis, it has been shown that treatment of pregnant mice with N-acetylcysteine (NAC), a glutathione precursor with potent anti-oxidant (and additional anti-inflammatory) properties protects against LPS-induced adverse developmental outcomes including intrauterine fetal death and preterm labor (Buhimschi et al., 2003). Maternal NAC treatment has also been shown to prevent LPS-induced elevation of cytokines in maternal and fetal compartments, and to attenuate the deleterious effects of prenatal LPS exposure on hypomyelination in the developing rat brain (Beloosesky et al., 2006; Buhimschi et al., 2003; Lanté et al., 2007; Paintlia et al., 2004, 2008; Xu et al., 2005). In addition, maternal NAC administration in rats prevents prenatal LPS-induced impairments in spatial memory and hippocampal long-term potentiation in the offspring (Lanté et al., 2008).

In addition to the induction of oxidative stress, activation of the innate immune system also induces hypoferrmia. This process is mediated to a great extent by the pro-inflammatory cytokines IL-1 β and IL-6 (Lee et al., 2005; Nemeth et al., 2004) and serves to reduce the availability of this essential nutrient to the invading pathogens as part of the host's inherent defense system (Kluger and Rothenburg, 1979). Since iron is also pivotal for normal brain development (Kwik-Urbe et al., 2000a,b; Unger et al., 2007), inflammation-induced hypoferrmia may readily contribute to neurodevelopmental abnormalities caused by prenatal infection/inflammation. In an elegant recent study, Aguilar-Valles et al. (2010) have provided direct experimental support for this hypothesis by showing that maternal iron supplementation prevents the long-term brain and behavioral effects of prenatal inflammation using a model of maternal turpentine administration.

As part of the acute phase response to infection, pro-inflammatory cytokines also trigger the induction of the zinc-binding protein metallothionein (Vallee and Falchuk, 1993). In the course of pregnancy, this process leads to maternal and fetal zinc deficiency, which has further been associated with teratogenicity and abnormal brain development (Daston et al., 1994; Taubeneck et al., 1995). It can thus be expected that inflammation-induced zinc deficiency may, similarly to the aforementioned effects of hypoferrmia, contribute to altered brain and behavioral development following prenatal infection. Indeed, recent work by Coyle et al. (2009) supports this notion: Using a mouse model of prenatal maternal LPS exposure, the authors found that maternal dietary zinc supplementation was efficient in preventing the emergence of long-term cognitive abnormalities typically seen following prenatal LPS treatment.

4. Fetal brain development in the event of inflammation

As summarized in Tables 1 and 2, a plethora of findings have emerged with respect to long-term behavioral, cognitive, neurochemical, and

brain morphological abnormalities induced by prenatal infection or immune challenge. In contrast, there has so far been considerably less effort to study the effects of prenatal inflammation in terms of early alterations in fetal brain development. Using the mouse prenatal polyI:C model, neuroanatomical investigations have recently provided evidence that early prenatal immune challenge disrupts perinatal cortical laminar formation and comprises the normal development of upper-layer (but not deeper-layer) cortical neurons (Soumiya et al., 2011a). In addition, experimental work in this model shows that prenatal immune activation impedes the normal course of neurogenesis during fetal development (Soumiya et al., 2011b). The latter findings are especially intriguing in view of the fact that the effects of prenatal immune activation on reduced (hippocampal) neurogenesis persist postnatally and are even evident at adult stages of development (Cui et al., 2009; Graciarena et al., 2010; Meyer et al., 2006b; 2010a; Wolf et al., 2011). Together, it appears that the persistent impairments in postnatal neurogenesis following prenatal immune challenge are likely to be of developmental origin starting early in fetal life.

Our laboratory has recently begun to study the short-term effects of polyI:C-induced maternal immune challenge on the fetal development of the dopamine system, a neurotransmitter system highly implicated in schizophrenia and related psychotic disorders (Howes and Kapur, 2009). We have found that maternal immune stimulation by polyI:C in early/middle gestation (gestation day [GD] 9) increases the number of dopamine neurons in the fetal midbrain at middle/late (GD 13) and late (GD 17) stages of prenatal development (Meyer et al., 2008a; Vuillermot et al., 2010). This effect is paralleled by changes in fetal expression of several genes known to be involved in dopamine neuron development, including the inductive signals sonic hedgehog (Shh) and fibroblast growth factor 8 (FGF8), as well as the transcription factors Nurr1 and Pitx3 (Meyer et al., 2008a). Notably, these findings do not provide a direct link between altered fetal dopaminergic development and the emergence of the well described dopamine-associated structural and functional abnormalities in the postnatal period (Tables 1 and 2). However, these results highlight that postnatal dopaminergic abnormalities emerging after prenatal immune challenge are developmentally regulated and start early in-utero. In view of this, it seems that prenatal inflammation-induced abnormalities in fetal midbrain dopamine development may represent an important primary mechanism for the postnatal emergence of functional and structural changes associated with imbalances in the mesocorticolimbic dopamine system (Meyer and Feldon, 2009b).

In addition to its effects on the central dopamine system, the long-term neuropathological deficits induced by prenatal infection and/or inflammation include pre- and post-synaptic changes in various other neurotransmitter systems such as the γ -aminobutyric acid (GABA), glutamate, and serotonin systems, together with alterations in neuronal and glial cell number, structure and positioning (reviewed Meyer and Feldon, 2009a; Boksa, 2010; Table 1). In view of these multiple effects, it is feasible that maternal/fetal inflammation and associated physiological insults could directly induce primary defects in the early fetal development of various neurotransmitter systems and cell populations. However, direct evidence for this possibility is still lacking, so that it remains essentially unknown how early neurodevelopmental abnormalities induced by fetal neuroinflammation are converted into long-term brain and behavioral pathology in adulthood (Boksa, 2010).

5. Priming of long-term neuroinflammation by prenatal infection and inflammation

One of the pertinent questions is whether exposure to prenatal infection or inflammation can permanently alter immune functions across the postnatal life-span (Bilbo and Schwarz, 2009; Meyer et al., 2011b). This issue seems particularly relevant in view of the fact that schizophrenia is associated with various immunological abnormalities (Drexhage

et al., 2010; Müller and Schwarz, 2006, 2010; Müller et al., 2000; Steiner et al., 2010), including peripheral low-grade inflammation (Altamura et al., 1999; Fan et al., 2007; Miller et al., 2011; Potvin et al., 2008) and signs of microglia and astrocyte over-activation (Bernstein et al., 2009; Doorduyn et al., 2009; Rothermundt et al., 2009; van Berckel et al., 2008). Several lines of experimental evidence indicate that prenatal exposure to infection or inflammation can indeed lead to long-lasting immune abnormalities, including inflammatory changes in the periphery and CNS. Persistent increases in peripheral levels of pro-inflammatory cytokines, together with enhanced microglia and/or astrocyte activation, have been demonstrated in rodent models of prenatal viral influenza exposure (Fatemi et al., 2002b, 2004), chronic gestational LPS exposure (Borrell et al., 2002; Romero et al., 2007, 2010), sub-chronic prenatal IL-6 treatment in mid-to-late gestation (Samuelsson et al., 2006), and acute polyI:C treatment in early/middle gestation (Han et al., 2011; Juckel et al., 2011). In addition, sub-chronic maternal treatment with IL-2 from mid-to-late pregnancy in mice has been shown to elevate B- and T-cell counts in response to antigenic stimulation in the juvenile offspring (Ponzio et al., 2007).

Exposure to acute fetal inflammation may further induce latent neuroinflammatory abnormalities that can be unmasked by exposure to certain environmental stimuli throughout postnatal life (Meyer et al., 2011a). This idea of multiple hits with either sensitizing or priming effects is also central to several theories of prenatal immune priming, which have been put forward in the context of peripheral immunity, CNS inflammation and progressive neurodegeneration, perinatal brain damage, retinopathy, and various forms of learning and memory (Bilbo and Schwarz, 2009; Dammann et al., 2009; Perry et al., 2007). According to this scenario, inflammatory exposure in early (prenatal or neonatal) life causes the organism to respond differently (and often more vigorously) to subsequent immunological or non-immunological challenges such as stress (Bilbo et al., 2005; Rousset et al., 2008; Wang et al., 2009). Priming of exacerbated neuroinflammatory responses has perhaps been best established in the context of microglia biology, highlighting that microglia can be primed by initial infectious or inflammatory stimuli to induce exaggerated pro-inflammatory responses to secondary environmental stimuli such as peripheral inflammation (Cunningham et al., 2009; Field et al., 2010; Palin et al., 2008; Perry et al., 2007). As discussed in more detail in the next section (Section 6), such priming effects seem also highly relevant in the context of schizophrenia because the disorder's etiology most likely involves exposure to multiple environmental and/or genetic insults at various stages of brain development and maturation (Cannon et al., 2003; Keshavan, 1999; Keshavan and Hogarty, 1999; Read et al., 2001; Walker et al., 1999).

6. (Latent) Neuroinflammation and disease progression

Longitudinal studies in rat and mouse models of prenatal immune challenge demonstrate that many of the prenatal inflammation-induced behavioral, pharmacological and cognitive disturbances are progressive in nature: They are often dependent on maturational processes and are pathologically manifest only once the offspring reach adolescence or early adulthood (Meyer et al., 2006c, 2008c; Ozawa et al., 2008; Vuillermot et al., 2010; Zuckerman and Weiner, 2003; Zuckerman et al., 2003). This is consistent with the progression of symptoms in schizophrenia, which tend to progress from prodromal to prodromal signs and finally into overt psychotic disease. Recent longitudinal neuroanatomical and in-vivo brain imaging studies in rodent prenatal immune activation models have further shown that the maturation-dependent functional brain abnormalities are developmentally paralleled (and possibly also predicted) by progressive changes in brain morphology and neurochemistry (Piontkewitz et al., 2009, 2010, 2011a, 2011b; Romero et al., 2010; Vuillermot et al., 2010). Taken together, it appears that early-life inflammatory events

do not induce static effects on the brain, but instead, they cause progressive changes in brain and behavioral development.

The precise cellular and molecular mechanisms responsible for the progressive brain and behavioral pathology induced by fetal brain inflammation remain largely elusive. However, it is intriguing to note that in several models of prenatal immune challenge (Fatemi et al., 2002b; Graciarena et al., 2010; Juckel et al., 2011; Romero et al., 2010; Samuelsson et al., 2006), signs of activated central and peripheral inflammatory responses exist prior to the onset of the full spectrum of schizophrenia-related behavioral, cognitive and pharmacological dysfunctions. For instance, prenatal polyI:C exposure in early/middle gestation in mice leads to increased microglia activation in pubescence (i.e. on postnatal day 30) (Juckel et al., 2011), a maturational stage at which prenatally polyI:C-exposed and control offspring do not differ with respect to various schizophrenia-relevant behavioral and cognitive functions (Meyer et al., 2006c, 2008c; Ozawa et al., 2008; for rats see Zuckerman et al., 2003; Zuckerman and Weiner, 2003; Piontkewitz et al., 2009, 2011a, 2011b). Likewise, increased peripheral TNF- α levels have been shown to precede the onset of sensorimotor gating deficiency in a rat model of prenatal LPS exposure (Romero et al., 2010).

There are several important implications from these findings: First, despite the capacity of prenatal immune challenge to cause peripheral and central inflammation that persist into the postnatal life span, such inflammatory changes do not necessarily translate into overt behavioral manifestations. Second and perhaps even more intriguingly, the presence of activated inflammatory responses such as enhanced microglia activation or systemic pro-inflammatory cytokine elevation may play an important role in the progression of brain disease following prenatal exposure to infection and/or inflammation. As schematically illustrated in Fig. 1, one may speculate on a model in which exposure to prenatal immune challenge primes early pre- and postnatal alterations in peripheral and central inflammatory response systems, which in turn may promote developmental neuroinflammation and may disrupt the normal development and maturation of neuronal systems from juvenile to adult stages of life. Such developmental neuroinflammation may adversely affect processes that are pivotal for normal brain maturation, including myelination, synaptic pruning, and neuronal remodeling, all of which occur to a great extent during peri-pubertal brain maturation (de Graaf-Peters and Hadders-Algra, 2006; Paus et al., 2008). In this way, priming of

postnatal neuroinflammation by prenatal immune challenge may contribute to the development of progressive brain and behavioral pathology following prenatal immune challenge (Fig. 1).

As already mentioned before (Section 5), early-life exposure to infection and/or inflammation has also the potential to induce latent neuroinflammatory abnormalities that can be unmasked and become biologically relevant by additional exposure to certain environmental stimuli throughout postnatal life (Meyer et al., 2011a). Such latent effects may also be relevant for the hypothetical model illustrated in Fig. 1 because unleashing latent neuroinflammatory processes during critical periods of brain maturation can also be expected to further interfere with maturational trajectories of postnatal brain development (Knickmeyer et al., 2010). Related to this, it is of note that patients with schizophrenia frequently report phases of stress in the proximity of or during the transition to full-blown psychosis (Phillips et al., 2006), and exposure to physical or psychological stressors is well known to activate microglia cells and enhance the production and release of pro-inflammatory cytokines in the CNS (Frank et al., 2007; García-Bueno et al., 2008). Psychosocial and/or physical stress in the early-phase of schizophrenic disease may therefore be an important factor with the potential to unmask latent neuroinflammatory effects, and to unleash their detrimental impact on disease progression (Fig. 1). This concept would be consistent with “multiple-hit” theories of schizophrenia, suggesting that the disorder's etiology most likely involves exposure to multiple environmental and/or genetic insults at various stages of brain development and maturation (Cannon et al., 2003; Keshavan, 1999; Keshavan and Hogarty, 1999; Read et al., 2001; Walker et al., 1999).

According to the hypothetical model illustrated in Fig. 1, priming of (latent) neuroinflammatory responses by prenatal infection and/or inflammation may be relevant for the progressive reduction in gray matter volume that occurs in the proximity of or during the onset of full blown psychosis (Hulshoff Pol and Kahn, 2008; Pantelis et al., 2005; Wood et al., 2008). Such volume reduction seems to resemble an exaggeration of gray matter reduction occurring as a result of normal adult development (Hulshoff Pol and Kahn, 2008; Wood et al., 2008), and it is a matter of current debate whether or not this process may involve (transient) neurodegenerative processes (Archer, 2010; McGlashan, 2006; Pérez-Neri et al., 2006). A recent study by de la Fuente-Sandoval et al. (2011) shows increased brain glutamate levels in subjects with ultra-high risk for schizophrenia

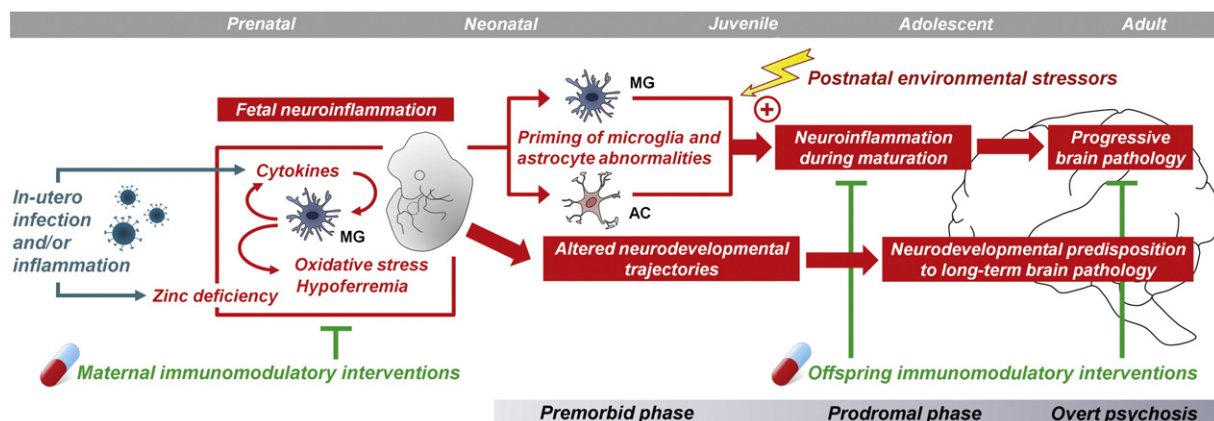


Fig. 1. Hypothetical model summarizing aspects of developmental neuroinflammation in schizophrenia. In-utero exposure to infection and/or inflammation leads to fetal neuroinflammation and associated pathophysiological changes. The former is characterized by enhanced levels of pro-inflammatory cytokines in the fetal brain together with fetal microglia activation, and the latter includes presence of oxidative stress, hypoferremia and zinc deficiency. Early fetal neuroinflammation changes neurodevelopmental trajectories, thereby inducing a neurodevelopmental predisposition to long-term brain pathology. Prenatal exposure to brain inflammation further primes postnatal microglia (MG) and astrocyte (AC) abnormalities, which developmentally coincide with (or even contribute to) premorbid symptoms such as subtle neurological and psychomotor deficits. Altered microglia and astrocyte functions may per se, or upon additional exposure to postnatal stressors, cause neuroinflammation during postnatal brain maturation and may contribute to progressive brain and behavioral pathology as seen in the proximity of overt psychosis (i.e., during the prodromal phase) and thereafter. Immunomodulatory interventions targeting early fetal brain inflammation and/or the functional consequences of persistent neuroinflammation in the postnatal life span may attenuate or even prevent the emergence of full-blown brain and behavioral pathology following prenatal immune challenge.

and first-episode patients. This has been taken as circumstantial evidence to support the possibility of (transient) processes of neurodegeneration in the early stages of schizophrenia (Lahti and Reid, 2011), primarily because excess synaptic glutamate levels are highly neurotoxic (Lau and Tymianski, 2010). In the present context it is highly interesting to point out that activated microglia release substantial levels of glutamate (Barger and Basile, 2001; Barger et al., 2007), and accumulating evidence suggests that such microglia-mediated toxicity contributes to neuronal damage in the event of neuroinflammation (Block et al., 2007; Perry et al., 2007; Ransohoff and Perry, 2009).

Microglia over-activation also leads to elevated production of quinolinic acid (QUIN) and 3-hydroxykynurenine (3-OHKY), both of which have potent neurotoxic properties too (Müller et al., 2011; Wonodi and Schwarcz, 2010). In a recent study, Condray et al. (2011) showed that drug-naïve first-episode schizophrenic patients displayed enhanced 3-OHKY levels, and that the levels of 3-OHKY predicted clinical improvement following anti-psychotic drug treatment in as much as the lowest concentrations of 3-OHKY were associated with the greatest improvement in symptoms. Taken together, the excess in glutamate and 3-OHKY release during the early (prodromal) stages of schizophrenic disease would fit with the hypothetical model illustrated in Fig. 1, which emphasizes a critical role of (prenatal infection/inflammation-induced) neuroinflammatory processes in the progressive development of overt schizophrenic disease.

7. Developmental neuroinflammation as a possible target for disease prevention

It has been proposed that prophylactic or symptomatic treatments targeting maternal infection and associated inflammatory processes may be efficient in reducing the incidence of schizophrenia and related disorders (Brown and Patterson, 2011). According to estimations put forward by Brown and Derkits (2010), such preventive efforts could reduce the number of schizophrenia cases by as much as one-third, depending on which infectious agents were to be considered and what population studied. Current investigations in animal models have already provided initial biological plausibility for this possibility by showing that at least parts of the deleterious neurodevelopment effects of prenatal infection/inflammation can be attenuated or even fully prevented by appropriate interventions targeting activated inflammatory response systems or associated physiologically processes such as oxidative stress, hypoferrremia and zinc deficiency (Aguilar-Valles et al., 2010; Coyle et al., 2009; De Miranda et al., 2010; Girard et al., 2010; Lanté et al., 2007, 2008; Pang et al., 2005; Robertson et al., 2007).

Besides prophylactic or symptomatic treatments targeting the maternal host, anti-inflammatory interventions may have the potential to attenuate progressive brain changes and development of psychosis when applied during early-phases of the developmental course of schizophrenia (Meyer et al., 2011b). Müller et al. (2010) have recently provided clinical evidence for this hypothesis in a double-blind, placebo-controlled clinical trial using the anti-inflammatory agent celecoxib (a preferential cyclooxygenase-2 inhibitor) given in conjunction with atypical antipsychotic drugs. The authors demonstrated superior beneficial treatment effects of such anti-inflammatory addition therapy (as compared with treatment outcomes using antipsychotic drugs alone) especially when the anti-inflammatory therapy was initiated in the early-phase of schizophrenia as opposed to later chronic stages (Müller and Schwarz, 2010; Müller et al., 2010, 2011). In another double-blind, randomized, placebo-controlled study in the early-phase of schizophrenia, administration of the broad-spectrum antibiotic minocycline in conjunction with standard antipsychotic drugs has been shown to exert superior effects in improving negative and cognitive symptoms compared with treatment outcomes using antipsychotic drugs alone (Levkovitz et al., 2010). In

contrast, such anti-inflammatory strategies may exert no superior effects in the treatment of schizophrenia when implemented in patients with a long duration of disease (Rapaport et al., 2005), suggesting that neuroinflammatory processes are especially relevant for the early-phase of the disease (Fig. 1).

It is also intriguing to point out that numerous antipsychotic drugs are known to exert inhibitory effects on immune functions in general, and on pro-inflammatory cytokine networks in particular (reviewed in Pollmächer et al., 2000; Drzyzga et al., 2006). Of special interest in the present context seem to be the recently identified microglia-inhibiting effects of antipsychotic drugs (Bian et al., 2008; Kato et al., 2007; Kato et al., 2008; Zheng et al., 2008). Hence, antipsychotic drugs may add to the therapeutic (or even preventive) effects in the pharmacotherapy of schizophrenia by dampening on-going inflammatory processes such as microglia over-activation.

8. Conclusions

In 1997, Gilmore and Jarskog proposed for the first time that “...cytokines generated by the maternal immune system (and/or the placental or fetal immune system) in response to infection may in part be responsible for the interaction between maternal infection during pregnancy, altered neuronal development, and schizophrenia” (Gilmore and Jarskog, 1997). Extensive epidemiological research and remarkable advances in modeling prenatal immune activation effects in animal models have since then provided strong support for this hypothesis by underscoring the critical role of cytokine-associated inflammatory events, together with downstream pathophysiological processes such as oxidative stress, hypoferrremia and zinc deficiency, in mediating the short- and long-term neurodevelopmental effects of prenatal infection. Longitudinal studies in animal models further indicate that developmental neuroinflammation induced by prenatal immune challenge may be pathologically relevant beyond the antenatal period, and may contribute to disease progression associated with the gradual development of full-blown schizophrenic disease. Undoubtedly, our understanding of the role of developmental neuroinflammation in progressive brain changes relevant to schizophrenia is still in infancy. Identification of these mechanisms would be highly warranted because they may represent a valuable target to attenuate or even prevent the emergence of full-blown brain and behavioral pathology, especially in individuals with a history of prenatal complications such as in-utero exposure to infection and/or inflammation.

Disclosure

The author declares that he has no conflicts of interest to disclose.

Acknowledgments

The author receives support from the European Union's Seventh Framework Programme (FP7/2007-2011) under grant agreement no. 259679.

References

- Aguilar-Valles A, Flores C, Luheshi GN. Prenatal inflammation-induced hypoferrremia alters dopamine function in the adult offspring in rat: relevance for schizophrenia. *PLoS One* 2010;5:e10967.
- Aguilar-Valles A, Luheshi GN. Alterations in cognitive function and behavioral response to amphetamine induced by prenatal inflammation are dependent on the stage of pregnancy. *Psychoneuroendocrinology* 2011;36:634–48.
- Aguilar-Valles A, Poole S, Mistry Y, Williams S, Luheshi GN. Attenuated fever in rats during late pregnancy is linked to suppressed interleukin-6 production after localized inflammation with turpentine. *J Physiol* 2007;583:391–403.
- Akaneya Y, Takahashi M, Hatanaka H. Interleukin-1 beta enhances survival and interleukin-6 protects against MPP+ neurotoxicity in cultures of fetal rat dopaminergic neurons. *Exp Neurol* 1995;136:44–52.
- Alexopoulou L, Holt AC, Medzhitov R, Flavell RA. Recognition of double-stranded RNA and activation of NF- κ B by toll-like receptor 3. *Nature* 2001;413:732–8.

- Altamura AC, Boin F, Maes M. HPA axis and cytokines dysregulation in schizophrenia: potential implications for the antipsychotic treatment. *Eur Neuropsychopharmacol* 1999;10:1–4.
- Archer T. Neurodegeneration in schizophrenia. *Expert Rev Neurother* 2010;10:1131–41.
- Ashtown H, Dumont Y, Ng M, Poole S, Boksa P, Luheshi GN. The role of cytokines in mediating changes in the morphology of pyramidal neurons of the prefrontal cortex and hippocampus in rats. *Schizophr Res* 2009;107:99–109.
- Bale JR Jr. Fetal infections and brain development. *Clin Perinatol* 2009;36:639–53.
- Barger SW, Basile AS. Activation of microglia by secreted amyloid precursor protein evokes release of glutamate by cystine exchange and attenuates synaptic function. *J Neurochem* 2001;76:846–54.
- Barger SW, Goodwin ME, Porter MM, Beggs ML. Glutamate release from activated microglia requires the oxidative burst and lipid peroxidation. *J Neurochem* 2007;101:1205–13.
- Barker V, Middleton G, Davey F, Davies AM. TNF α contributes to the death of NGF-dependent neurons during development. *Nat Neurosci* 2001;4:1194–8.
- Bauer S, Kerr BJ, Patterson PH. The neuropleiotic cytokine family in development, plasticity, disease and injury. *Nat Rev Neurosci* 2007;8:221–32.
- Bell MJ, Hallenbeck JM. Effects of intrauterine inflammation on developing rat brain. *J Neurosci Res* 2002;70:570–9.
- Beloosesky R, Gayle DA, Ross MG. Maternal N-acetylcysteine suppresses fetal inflammatory cytokine responses to maternal lipopolysaccharide. *Am J Obstet Gynecol* 2006;195:1053–7.
- Ben Menachem-Zidon O, Goshen I, Kreisel T, Ben Menahem Y, Reinhart E, Ben Hur T, et al. Intra-hippocampal transplantation of transgenic neural precursor cells overexpressing interleukin-1 receptor antagonist blocks chronic isolation-induced impairment in memory and neurogenesis. *Neuropsychopharmacology* 2008;33:2251–62.
- Bernstein HG, Steiner J, Bogerts B. Glial cells in schizophrenia: pathophysiological significance and possible consequences for therapy. *Expert Rev Neurother* 2009;9:1059–71.
- Bian Q, Kato T, Monji A, Hashioka S, Mizoguchi Y, Horikawa H, et al. The effect of atypical antipsychotics, perospirone, ziprasidone and quetiapine on microglial activation induced by interferon- γ . *Prog Neuropsychopharmacol Biol Psychiatry* 2008;32:42–8.
- Bianchi R, Kastrianaki E, Giambanco I, Donato R. S100B protein stimulates microglia migration via RAGE-dependent up-regulation of chemokine expression and release. *J Biol Chem* 2011;286:7214–26.
- Bilbo SD, Biedenkapp JC, Der-Avakian A, Watkins LR, Rudy JW, Maier SF. Neonatal infection-induced memory impairment after lipopolysaccharide in adulthood is prevented via caspase-1 inhibition. *J Neurosci* 2005;25:8000–9.
- Bilbo SD, Schwarz JM. Early-life programming of later-life brain and behavior: a critical role for the immune system. *Front Behav Neurosci* 2009;3:14.
- Bitanhiirwe BK, Peleg-Raibstein D, Mouttet F, Feldon J, Meyer U. Late prenatal immune activation in mice leads to behavioral and neurochemical abnormalities relevant to the negative symptoms of schizophrenia. *Neuropsychopharmacology* 2010a;35:2462–78.
- Bitanhiirwe BK, Weber L, Feldon J, Meyer U. Cognitive impairment following prenatal immune challenge in mice correlates with prefrontal cortical AKT1 deficiency. *Int J Neuropsychopharmacol* 2010b;13:981–96.
- Block ML, Zecca L, Hong JS. Microglia-mediated neurotoxicity: uncovering the molecular mechanisms. *Nat Rev Neurosci* 2007;8:57–69.
- Boksa P. Effects of prenatal infection on brain development and behavior: a review of findings from animal models. *Brain Behav Immun* 2010;24:881–97.
- Borrell J, Vela JM, Arévalo-Martin A, Molina-Holgado E, Guaza C. Prenatal immune challenge disrupts sensorimotor gating in adult rats. Implications for the etiopathogenesis of schizophrenia. *Neuropsychopharmacology* 2002;26:204–15.
- Briand JP, Muller S. Emerging peptide therapeutics for inflammatory autoimmune diseases. *Curr Pharm Des* 2010;16:1136–42.
- Briscoe T, Duncan J, Cock M, Choo J, Rice G, Harding R, et al. Activation of NF- κ B transcription factor in the preterm ovine brain and placenta after acute LPS exposure. *J Neurosci Res* 2006;83:567–74.
- Bronson SL, Ahlbrand R, Horn PS, Kern JR, Richtand NM. Individual differences in maternal response to immune challenge predict offspring behavior: contribution of environmental factors. *Behav Brain Res* 2011;220:55–64.
- Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, et al. Serologic evidence of prenatal influenza in the etiology of schizophrenia. *Arch Gen Psychiatry* 2004a;61:774–80.
- Brown AS, Cohen P, Harkavy-Friedman J, Babulas V, Malaspina D, Gorman JM, et al. A.E. Bennett Research Award. Prenatal rubella, perinatal abnormalities, and adult schizophrenia. *Biol Psychiatry* 2001;49:473–86.
- Brown AS, Deicken RF, Vinogradov S, Kremen WS, Poole JH, Penner JD, et al. Prenatal infection and cavum septum pellucidum in adult schizophrenia. *Schizophr Res* 2009a;108:285–7.
- Brown AS, Derkatis EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *Am J Psychiatry* 2010;167:261–80.
- Brown AS, Hooton J, Schaefer CA, Zhang H, Petkova E, Babulas V, et al. Elevated maternal interleukin-8 levels and risk of schizophrenia in adult offspring. *Am J Psychiatry* 2004b;161:889–95.
- Brown AS, Patterson PH. Maternal infection and schizophrenia: implications for prevention. *Schizophr Bull* 2011;37:284–90.
- Brown AS, Schaefer CA, Quesenberry Jr CP, Liu L, Babulas VP, Susser ES. Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring. *Am J Psychiatry* 2005;162:767–73.
- Brown AS, Vinogradov S, Kremen WS, Poole JH, Bao Y, Kern D, et al. Association of maternal genital and reproductive infections with verbal memory and motor deficits in adult schizophrenia. *Psychiatry Res* 2011;188:179–86.
- Brown AS, Vinogradov S, Kremen WS, Poole JH, Deicken RF, Penner JD, et al. Prenatal exposure to maternal infection and executive dysfunction in adult schizophrenia. *Am J Psychiatry* 2009b;166:683–90.
- Brown AS. The environment and susceptibility to schizophrenia. *Prog Neurobiol* 2011;93:23–58.
- Buhimschi IA, Buhimschi CS, Weiner CP. Protective effect of N-acetylcysteine against fetal death and preterm labor induced by maternal inflammation. *Am J Obstet Gynecol* 2003;188:203–8.
- Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH. Maternal infections and subsequent psychosis among offspring. *Arch Gen Psychiatry* 2001a;58:1032–7.
- Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Wagner RL, Yolken RH. Maternal cytokine levels during pregnancy and adult psychosis. *Brain Behav Immun* 2001b;15:411–20.
- Burns TM, Clough JA, Klein RM, Wood GW, Berman NE. Developmental regulation of cytokine expression in the mouse brain. *Growth Factors* 1993;9:253–8.
- Cai Z, Pan ZL, Pang Y, Evans OB, Rhodes PG. Cytokine induction in fetal rat brains and brain injury in neonatal rats after maternal lipopolysaccharide administration. *Pediatr Res* 2000;47:64–72.
- Cannon TD, van Erp TG, Bearden CE, Loewy R, Thompson P, Toga AW, et al. Early and late neurodevelopmental influences in the prodrome to schizophrenia: contributions of genes, environment, and their interactions. *Schizophr Bull* 2003;29:653–69.
- Cardon M, Ron-Harel N, Cohen H, Lewitus GM, Schwartz M. Dysregulation of kisspeptin and neurogenesis at adolescence link inborn immune deficits to the late onset of abnormal sensorimotor gating in congenital psychological disorders. *Mol Psychiatry* 2010;15:415–25.
- Carter CS, Barch DM, Buchanan RW, Bullmore E, Krystal JH, Cohen J, et al. Identifying cognitive mechanisms targeted for treatment development in schizophrenia: an overview of the first meeting of the Cognitive Neuroscience Treatment Research to Improve Cognition in Schizophrenia Initiative. *Biol Psychiatry* 2008;64:4–10.
- Clarke MC, Tanskanen A, Huttunen M, Whittaker JC, Cannon M. Evidence for an interaction between familial liability and prenatal exposure to infection in the causation of schizophrenia. *Am J Psychiatry* 2009;166:1025–30.
- Condray R, Dougherty GG, Keshavan MS, Reddy RD, Haas GL, Montrose DM, et al. 3-Hydroxykynurenine and clinical symptoms in first-episode neuroleptic-naïve patients with schizophrenia. *Int J Neuropsychopharmacol* 2011;14:756–67.
- Coyle P, Tran N, Fung JN, Summers BL, Rofe AM. Maternal dietary zinc supplementation prevents aberrant behaviour in an object recognition task in mice offspring exposed to LPS in early pregnancy. *Behav Brain Res* 2009;197:210–8.
- Crow TJ, Done DJ. Prenatal exposure to influenza does not cause schizophrenia. *Br J Psychiatry* 1992;161:390–3.
- Cui K, Ashtown H, Luheshi GN, Boksa P. Effects of prenatal immune activation on hippocampal neurogenesis in the rat. *Schizophr Res* 2009;113:288–97.
- Cunningham C, Campion S, Lunn K, Murray CL, Woods JF, Deacon RM, et al. Systemic inflammation induces acute behavioral and cognitive changes and accelerates neurodegenerative disease. *Biol Psychiatry* 2009;65:304–12.
- Cunningham C, Campion S, Teeling J, Felton L, Perry VH. The sickness behaviour and CNS inflammatory mediator profile induced by systemic challenge of mice with synthetic double-stranded RNA (poly I:C). *Brain Behav Immun* 2007;21:490–502.
- Curfs JH, Meis JF, Hoogkamp-Korstanje JA. A primer on cytokines: sources, receptors, effects, and inducers. *Clin Microbiol Rev* 1997;10:742–80.
- Dammann O, Brinkhaus MJ, Bartels DB, Dördelmann M, Dressler F, Kerk J, et al. Immaturity, perinatal inflammation, and retinopathy of prematurity: a multi-hit hypothesis. *Early Hum Dev* 2009;85:325–9.
- Dammann O, Leviton A. Maternal intrauterine infection, cytokines, and brain damage in the preterm newborn. *Pediatr Res* 1997;42:1–8.
- Dammann O, Leviton A. Role of the fetus in perinatal infection and neonatal brain damage. *Curr Opin Pediatr* 2000;12:99–104.
- Daston GP, Overmann GJ, Baines D, Taubeneck MW, Lehman-McKeeman LD, Rogers JM, et al. Altered Zn status by alpha-hederin in the pregnant rat and its relationship to adverse developmental outcome. *Reprod Toxicol* 1994;8:15–24.
- de Graaf-Peters VB, Hadders-Algra M. Ontogeny of the human central nervous system: what is happening when? *Early Hum Dev* 2006;82:257–66.
- de la Fuente-Sandoval C, León-Ortiz P, Favila R, Stephano S, Mamo D, Ramírez-Bermúdez J, et al. Higher levels of glutamate in the associative-striatum of subjects with prodromal symptoms of schizophrenia and patients with first-episode psychosis. *Neuropsychopharmacology* 2011;36:1781–91.
- De Miranda J, Yaddanapudi K, Hornig M, Villar G, Serge R, Lipkin WI. Induction of Toll-like receptor 3-mediated immunity during gestation inhibits cortical neurogenesis and causes behavioral disturbances. *MBio* 2010;1(4). pii: e00176–10.
- Dean JM, Farrag D, Zahkousk SA, El Zawahry EY, Hagberg H, Kjellmer I, et al. Cerebellar white matter injury following systemic endotoxemia in preterm fetal sheep. *Neuroscience* 2009;160:606–15.
- Deng W. Neurobiology of injury to the developing brain. *Nat Rev Neurol* 2010;6:328–36.
- Deverman BE, Patterson PH. Cytokines and CNS development. *Neuron* 2009;64:61–78.
- Dickerson DD, Wolff AR, Bilkey DK. Abnormal long-range neural synchrony in a maternal immune activation animal model of schizophrenia. *J Neurosci* 2010;30:12424–31.
- Doherty GH. Developmental switch in the effects of TNF α on ventral midbrain dopaminergic neurons. *Neurosci Res* 2007;57:296–305.

- Doorduyn J, de Vries EF, Willemsen AT, de Groot JC, Dierckx RA, Klein HC. Neuroinflammation in schizophrenia-related psychosis: a PET study. *J Nucl Med* 2009;50:1801–7.
- Drexhage RC, Knijff EM, Padmos RC, Heul-Nieuwenhuijzen L, Beumer W, Versnel MA, et al. The mononuclear phagocyte system and its cytokine inflammatory networks in schizophrenia and bipolar disorder. *Expert Rev Neurother* 2010;10:59–76.
- Drzyzga L, Obuchowicz E, Marciniowska A, Herman ZS. Cytokines in schizophrenia and the effects of antipsychotic drugs. *Brain Behav Immun* 2006;20:532–45.
- Edoff K, Jerregård H. Effects of IL-1 β , IL-6 or LIF on rat sensory neurons co-cultured with fibroblast-like cells. *J Neurosci Res* 2002;67:255–63.
- Ellman LM, Deicken RF, Vinogradov S, Kremen WS, Poole JH, Kern DM, et al. Structural brain alterations in schizophrenia following fetal exposure to the inflammatory cytokine interleukin-8. *Schizophr Res* 2010;121:46–54.
- Fan X, Goff DC, Henderson DC. Inflammation and schizophrenia. *Expert Rev Neurother* 2007;7:789–96.
- Fatemi SH, Araghi-Niknam M, Laurence JA, Stary JM, Sidwell RW, Lee S. Glial fibrillary acidic protein and glutamic acid decarboxylase 65 and 67 kDa proteins are increased in brains of neonatal BALB/c mice following viral infection in utero. *Schizophr Res* 2004;69:121–3.
- Fatemi SH, Cuadra AE, El-Fakahany EE, Sidwell RW, Thuras P. Prenatal viral infection causes alterations in nNOS expression in developing mouse brains. *Neuroreport* 2000;11:1493–6.
- Fatemi SH, Earle J, Kanodia R, Kist D, Emamian ES, Patterson PH, et al. Prenatal viral infection leads to pyramidal cell atrophy and macrocephaly in adulthood: implications for genesis of autism and schizophrenia. *Cell Mol Neurobiol* 2002a;22:25–33.
- Fatemi SH, Emamian ES, Kist D, Sidwell RW, Nakajima K, Akhter P, et al. Defective corticogenesis and reduction in Reelin immunoreactivity in cortex and hippocampus of prenatally infected neonatal mice. *Mol Psychiatry* 1999;4:145–54.
- Fatemi SH, Emamian ES, Sidwell RW, Kist DA, Stary JM, Earle JA, et al. Human influenza viral infection in utero alters glial fibrillary acidic protein immunoreactivity in the developing brains of neonatal mice. *Mol Psychiatry* 2002b;7:633–40.
- Fatemi SH, Folsom TD, Reutiman TJ, Abu-Odeh D, Mori S, Huang H, et al. Abnormal expression of myelination genes and alterations in white matter fractional anisotropy following prenatal viral influenza infection at E16 in mice. *Schizophr Res* 2009;112:46–53.
- Fatemi SH, Folsom TD. The neurodevelopmental hypothesis of schizophrenia, revisited. *Schizophr Bull* 2009;35:528–48.
- Fatemi SH, Pearce DA, Brooks AI, Sidwell RW. Prenatal viral infection in mouse causes differential expression of genes in brains of mouse progeny: a potential animal model for schizophrenia and autism. *Synapse* 2005;57:91–9.
- Fatemi SH, Reutiman TJ, Folsom TD, Huang H, Oishi K, Mori S, et al. Maternal infection leads to abnormal gene regulation and brain atrophy in mouse offspring: implications for genesis of neurodevelopmental disorders. *Schizophr Res* 2008;99:56–70.
- Fatemi SH, Sidwell R, Kist D, Akhter P, Meltzer HY, Bailey K, et al. Differential expression of synaptosome-associated protein 25 kDa [SNAP-25] in hippocampi of neonatal mice following exposure to human influenza virus in utero. *Brain Res* 1998;800:1–9.
- Feng Z, Ko CP. Schwann cells promote synaptogenesis at the neuromuscular junction via transforming growth factor- β 1. *J Neurosci* 2008;28:9599–609.
- Ferré N, Clària J. New insights into the regulation of liver inflammation and oxidative stress. *Mini Rev Med Chem* 2006;6:1321–30.
- Field R, Campion S, Warren C, Murray C, Cunningham C. Systemic challenge with the TLR3 agonist poly I:C induces amplified IFN α / β and IL-1 β responses in the diseased brain and exacerbates chronic neurodegeneration. *Brain Behav Immun* 2010;24:996–1007.
- Fortier ME, Joobar R, Luheshi GN, Boksa P. Maternal exposure to bacterial endotoxin during pregnancy enhances amphetamine-induced locomotion and startle responses in adult rat offspring. *J Psychiatr Res* 2004a;38:335–45.
- Fortier ME, Kent S, Ashdown H, Poole S, Boksa P, Luheshi GN. The viral mimic, polyinosinic:polycytidylic acid, induces fever in rats via an interleukin-1-dependent mechanism. *Am J Physiol Regul Integr Comp Physiol* 2004b;287:R759–66.
- Fortier ME, Luheshi GN, Boksa P. Effects of prenatal infection on prepulse inhibition in the rat depend on the nature of the infectious agent and the stage of pregnancy. *Behav Brain Res* 2007;181:270–7.
- Frank MG, Baratta MV, Sprunger DB, Watkins LR, Maier SF. Microglia serve as a neuroimmune substrate for stress-induced potentiation of CNS pro-inflammatory cytokine responses. *Brain Behav Immun* 2007;21:47–59.
- Gallin JI, Snyderman R, Fearon DT, Haynes BF, Nathan C. Inflammation: basic principles and clinical correlates. Philadelphia: Lippincott Williams & Wilkins; 1999.
- Ganz T, Nemeth E. Iron sequestration and anemia of inflammation. *Semin Hematol* 2009;46:387–93.
- García-Bueno B, Caso JR, Leza JC. Stress as a neuroinflammatory condition in brain: damaging and protective mechanisms. *Neurosci Biobehav Rev* 2008;32:1136–51.
- Gilmore JH, Jarskog LF, Vadlamudi S, Lauder JM. Prenatal infection and risk for schizophrenia: IL-1 β , IL-6, and TNF α inhibit cortical neuron dendrite development. *Neuropsychopharmacology* 2004;29:1221–9.
- Gilmore JH, Jarskog LF. Exposure to infection and brain development: cytokines in the pathogenesis of schizophrenia. *Schizophr Res* 1997;24:365–7.
- Girard S, Tremblay L, Lepage M, Sébire G. IL-1 receptor antagonist protects against placental and neurodevelopmental defects induced by maternal inflammation. *J Immunol* 2010;184:3997–4005.
- Golan HM, Lev V, Hallak M, Sorokin Y, Huleihel M. Specific neurodevelopmental damage in mice offspring following maternal inflammation during pregnancy. *Neuropharmacology* 2005;48:903–17.
- Goshen I, Kreisel T, Ben-Menachem-Zidon O, Licht T, Weidenfeld J, Ben-Hur T, et al. Brain interleukin-1 mediates chronic stress-induced depression in mice via adrenergic activation and hippocampal neurogenesis suppression. *Mol Psychiatry* 2008;13:717–28.
- Graciarena M, Depino AM, Pitossi FJ. Prenatal inflammation impairs adult neurogenesis and memory related behavior through persistent hippocampal TGF β 1 downregulation. *Brain Behav Immun* 2010;24:1301–9.
- Hagberg H, Mallard C, Jacobsson B. Role of cytokines in preterm labour and brain injury. *BJOG* 2005;112(Suppl 1):16–8.
- Hagberg H, Peebles D, Mallard C. Models of white matter injury: comparison of infectious, hypoxic-ischemic, and excitotoxic insults. *Ment Retard Dev Disabil Res Rev* 2002;8:30–8.
- Han X, Li N, Meng Q, Shao F, Wang W. Maternal immune activation impairs reversal learning and increases serum tumor necrosis factor- α in offspring. *Neuropsychobiology* 2011;64:9–14.
- Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: version III—the final common pathway. *Schizophr Bull* 2009;35:549–62.
- Hsiao EY, Patterson PH. Activation of the maternal immune system induces endocrine changes in the placenta via IL-6. *Brain Behav Immun* 2011;25:604–15.
- Hulshoff Pol HE, Kahn RS. What happens after the first episode? A review of progressive brain changes in chronically ill patients with schizophrenia. *Schizophr Bull* 2008;34:354–66.
- Hutton LC, Castillo-Melendez M, Smythe GA, Walker DW. Microglial activation, macrophage infiltration, and evidence of cell death in the fetal brain after uteroplacental administration of lipopolysaccharide in sheep in late gestation. *Am J Obstet Gynecol* 2008;198:117.e11–117.e11.
- Insel TR. Rethinking schizophrenia. *Nature* 2010;468:187–93.
- Jaaro-Peled H, Hayashi-Takagi A, Seshadri S, Kamiya A, Brandon NJ, Sawada A. Neurodevelopmental mechanisms of schizophrenia: understanding disturbed postnatal brain maturation through neuregulin-1-ErbB4 and DISC1. *Trends Neurosci* 2009;32:485–95.
- Janeway Jr CA, Medzhitov R. Innate immune recognition. *Annu Rev Immunol* 2002;20:197–216.
- Jarskog LF, Xiao H, Wilkie MB, Lauder JM, Gilmore JH. Cytokine regulation of embryonic rat dopamine and serotonin neuronal survival in vitro. *Int J Dev Neurosci* 1997;15:711–76.
- Jonakait GM. The effects of maternal inflammation on neuronal development: possible mechanisms. *Int J Dev Neurosci* 2007;25:415–25.
- Juckel G, Manitz MP, Brüne M, Friebe A, Heneka MT, Wolf RJ. Microglial activation in a neuroinflammatory animal model of schizophrenia—a pilot study. *Schizophr Res* 2011;131:96–100.
- Kato T, Mizoguchi Y, Monji A, Horikawa H, Suzuki SO, Seki Y, et al. Inhibitory effects of aripiprazole on interferon- γ -induced microglial activation via intracellular Ca $^{2+}$ regulation in vitro. *J Neurochem* 2008;106:815–25.
- Kato T, Monji A, Hashioka S, Kanba S. Risperidone significantly inhibits interferon- γ -induced microglial activation in vitro. *Schizophr Res* 2007;92:108–15.
- Keshavan MS, Hogarty GE. Brain maturational processes and delayed onset in schizophrenia. *Dev Psychopathol* 1999;11:525–43.
- Keshavan MS. Development, disease and degeneration in schizophrenia: a unitary pathophysiological model. *J Psychiatr Res* 1999;33:513–21.
- Kluger MJ, Rothenburg BA. Fever and reduced iron: their interaction as a host defense response to bacterial infection. *Science* 1979;203:374–6.
- Knickmeyer RC, Styner M, Short SJ, Lubach GR, Kang C, Hamer R, et al. Maturational trajectories of cortical brain development through the pubertal transition: unique species and sex differences in the monkey revealed through structural magnetic resonance imaging. *Cereb Cortex* 2010;20:1053–63.
- Kohen R, Nyska A. Oxidation of biological systems: oxidative stress phenomena, antioxidants, redox reactions, and methods for their quantification. *Toxicol Pathol* 2002;30:620–50.
- Kumral A, Baskin H, Yesilirmak DC, Ergur BU, Aykan S, Genc S, et al. Erythropoietin attenuates lipopolysaccharide-induced white matter injury in the neonatal rat brain. *Neonatology* 2007;92:269–78.
- Kushima Y, Hama T, Hatanaka H. Interleukin-6 as a neurotrophic factor for promoting the survival of cultured catecholaminergic neurons in a chemically defined medium from fetal and postnatal rat midbrains. *Neurosci Res* 1992;13:267–80.
- Kwik-Urbe CL, Gietzen D, German JB, Golub MS, Keen CL. Chronic marginal iron intakes during early development in mice result in persistent changes in dopamine metabolism and myelin composition. *J Nutr* 2000a;130:2821–30.
- Kwik-Urbe CL, Golub MS, Keen CL. Chronic marginal iron intakes during early development in mice alter brain iron concentrations and behavior despite postnatal iron supplementation. *J Nutr* 2000b;130:2040–8.
- Lahti AC, Reid MA. Is there evidence for neurotoxicity in the prodromal and early stages of schizophrenia? *Neuropsychopharmacology* 2011;36:1779–80.
- Lanté F, Meunier J, Guiramand J, De Jesus Ferreira MC, Cambonie G, Aimar R, et al. Late N-acetylcysteine treatment prevents the deficits induced in the offspring of dams exposed to an immune stress during gestation. *Hippocampus* 2008;18:602–9.
- Lanté F, Meunier J, Guiramand J, Maurice T, Cavalier M, de Jesus Ferreira MC, et al. Neurodevelopmental damage after prenatal infection: role of oxidative stress in the fetal brain. *Free Radic Biol Med* 2007;42:1231–45.
- Lau A, Tymianski M. Glutamate receptors, neurotoxicity and neurodegeneration. *Pflügers Arch* 2010;460:525–42.
- Lee P, Peng H, Gelbart T, Wang L, Beutler E. Regulation of hepcidin transcription by interleukin-1 and interleukin-6. *Proc Natl Acad Sci U S A* 2005;102:1906–10.
- Leviton A, Allred EN, Kuban KC, Hecht JL, Onderdonk AB, O'shea TM, et al. Microbiologic and histologic characteristics of the extremely preterm infant's placenta predict white matter damage and later cerebral palsy. The ELGAN study. *Pediatr Res* 2010;67:95–101.

- Leviton A, Gressens P. Neuronal damage accompanies perinatal white-matter damage. *Trends Neurosci* 2007;30:473–8.
- Levkovitch Y, Mendlovich S, Riwkes S, Braw Y, Levkovitch-Verbin H, Gal G, et al. A double-blind, randomized study of minocycline for the treatment of negative and cognitive symptoms in early-phase schizophrenia. *J Clin Psychiatry* 2010;71:138–49.
- Lewis DA, Levitt P. Schizophrenia as a disorder of neurodevelopment. *Annu Rev Neurosci* 2002;25:409–32.
- Li Q, Cheung C, Wei R, Cheung V, Hui ES, You Y, et al. Voxel-based analysis of postnatal white matter microstructure in mice exposed to immune challenge in early or late pregnancy. *Neuroimage* 2010;52:1–8.
- Li Q, Cheung C, Wei R, Hui ES, Feldon J, Meyer U, et al. Prenatal immune challenge is an environmental risk factor for brain and behavior change relevant to schizophrenia: evidence from MRI in a mouse model. *PLoS One* 2009;4(7):e6354.
- Ling ZD, Potter ED, Lipton JW, Carvey PM. Differentiation of mesencephalic progenitor cells into dopaminergic neurons by cytokines. *Exp Neurol* 1998;149:411–23.
- Lowe GC, Luheshi GN, Williams S. Maternal infection and fever during late gestation are associated with altered synaptic transmission in the hippocampus of juvenile offspring rats. *Am J Physiol Regul Integr Comp Physiol* 2008;295:R1563–71.
- Luheshi GN, Steffler A, Turnbull AV, Dascombe MJ, Brouwer S, Hopkins SJ, et al. Febrile response to tissue inflammation involves both peripheral and brain IL-1 and TNF-alpha in the rat. *Am J Physiol* 1997;272:R862–8.
- Makinodan M, Tatsumi K, Manabe T, Yamauchi T, Makinodan E, Matsuyoshi H, et al. Maternal immune activation in mice delays myelination and axonal development in the hippocampus of the offspring. *J Neurosci Res* 2008;86:2190–200.
- McAlonan GM, Li Q, Cheung C. The timing and specificity of prenatal immune risk factors for autism modeled in the mouse and relevance to schizophrenia. *Neurosignals* 2010;18:129–39.
- McGlashan TH. Is active psychosis neurotoxic? *Schizophr Bull* 2006;32:609–13.
- McGrath JJ, Féron FP, Burne TH, Mackay-Sim A, Eyles DW. The neurodevelopmental hypothesis of schizophrenia: a review of recent developments. *Ann Med* 2003;35:86–93.
- Mednick SA, Machon RA, Huttunen MO, Bonett D. Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry* 1988;45:189–92.
- Mehler MF, Kessler JA. Hematolymphopoietic and inflammatory cytokines in neural development. *Trends Neurosci* 1997;20:357–65.
- Meyer U, Engler A, Weber L, Schedlowski M, Feldon J. Preliminary evidence for a modulation of fetal dopaminergic development by maternal immune activation during pregnancy. *Neuroscience* 2008a;154:701–9.
- Meyer U, Feldon J, Dammann O. Schizophrenia and autism: both shared and disorder-specific pathogenesis via perinatal inflammation? *Pediatr Res* 2011a;69:26R–33R.
- Meyer U, Feldon J, Fatemi SH. In-vivo rodent models for the experimental investigation of prenatal immune activation effects in neurodevelopmental brain disorders. *Neurosci Biobehav Rev* 2009a;33:1061–79.
- Meyer U, Feldon J, Schedlowski M, Yee BK. Immunological stress at the maternal–foetal interface: a link between neurodevelopment and adult psychopathology. *Brain Behav Immun* 2006a;20:378–88.
- Meyer U, Feldon J, Schedlowski M, Yee BK. Towards an immuno-precipitated neurodevelopmental animal model of schizophrenia. *Neurosci Biobehav Rev* 2005;29:913–47.
- Meyer U, Feldon J, Yee BK. A review of the fetal brain cytokine imbalance hypothesis of schizophrenia. *Schizophr Bull* 2009b;35:959–72.
- Meyer U, Feldon J. Epidemiology-driven neurodevelopmental animal models of schizophrenia. *Prog Neurobiol* 2010;90:285–326.
- Meyer U, Feldon J. Neural basis of psychosis-related behaviour in the infection model of schizophrenia. *Behav Brain Res* 2009a;204:322–34.
- Meyer U, Feldon J. Prenatal exposure to infection: a primary mechanism for abnormal dopaminergic development in schizophrenia. *Psychopharmacology* 2009b;206:587–602.
- Meyer U, Knuesel I, Nyffeler M, Feldon J. Chronic clozapine treatment improves prenatal infection-induced working memory deficits without influencing adult hippocampal neurogenesis. *Psychopharmacology* 2010a;208:531–43.
- Meyer U, Murray PJ, Urwyler A, Yee BK, Schedlowski M, Feldon J. Adult behavioral and pharmacological dysfunctions following disruption of the fetal brain balance between pro-inflammatory and IL-10-mediated anti-inflammatory signaling. *Mol Psychiatry* 2008b;13:208–21.
- Meyer U, Nyffeler M, Engler A, Urwyler A, Schedlowski M, Knuesel I, et al. The time of prenatal immune challenge determines the specificity of inflammation-mediated brain and behavioral pathology. *J Neurosci* 2006b;26:4752–62.
- Meyer U, Nyffeler M, Schwendener S, Knuesel I, Yee BK, Feldon J. Relative prenatal and postnatal maternal contributions to schizophrenia-related neurochemical dysfunction after in utero immune challenge. *Neuropsychopharmacology* 2008c;33:441–56.
- Meyer U, Nyffeler M, Yee BK, Knuesel I, Feldon J. Adult brain and behavioral pathological markers of prenatal immune challenge during early/middle and late fetal development in mice. *Brain Behav Immun* 2008d;22:469–86.
- Meyer U, Schwarz MJ, Müller N. Inflammatory processes in schizophrenia: a promising neuroimmunological target for the treatment of negative/cognitive symptoms and beyond. *Pharmacol Ther* 2011b;132:96–110.
- Meyer U, Schwendener S, Feldon J, Yee BK. Prenatal and postnatal maternal contributions in the infection model of schizophrenia. *Exp Brain Res* 2006c;173:243–57.
- Meyer U, Spoerri E, Yee BK, Schwarz MJ, Feldon J. Evaluating early preventive antipsychotic and antidepressant drug treatment in an infection-based neurodevelopmental mouse model of schizophrenia. *Schizophr Bull* 2010b;36:607–23.
- Meyer U, Weiner I, McAlonan GM, Feldon J. The neuropathological contribution of prenatal inflammation to schizophrenia. *Expert Rev Neurother* 2011c;11:29–32.
- Meyer U, Yee BK, Feldon J. The neurodevelopmental impact of prenatal infections at different times of pregnancy: the earlier the worse? *Neuroscientist* 2007;13:241–56.
- Miller BJ, Buckley P, Seabolt W, Mellor A, Kirkpatrick B. Meta-analysis of cytokine alterations in schizophrenia: clinical status and antipsychotic effects. *Biol Psychiatry* 2011;70:663–71.
- Mino Y, Oshima I, Tsuda T, Okagami K. No relationship between schizophrenic birth and influenza epidemics in Japan. *J Psychiatr Res* 2000;34:133–8.
- Möller HJ. Clinical evaluation of negative symptoms in schizophrenia. *Eur Psychiatry* 2007;22:380–6.
- Moreno JL, Kurita M, Holloway T, López J, Cadagan R, Martínez-Sobrido L, et al. Maternal influenza viral infection causes schizophrenia-like alterations of 5-HT A and mGlu receptors in the adult offspring. *J Neurosci* 2011;31:1863–72.
- Morgan V, Castle D, Page A, Fazio S, Gurrin L, Burton P, et al. Influenza epidemics and incidence of schizophrenia, affective disorders and mental retardation in Western Australia: no evidence of a major effect. *Schizophr Res* 1997;26:25–39.
- Mortensen PB, Nørgaard-Pedersen B, Waltoft BL, Sørensen TL, Hougaard D, Volken RH. Early infections of *Toxoplasma gondii* and the later development of schizophrenia. *Schizophr Bull* 2007;33:741–4.
- Mousa A, Seiger A, Kjaeldgaard A, Bakhtiet M. Human first trimester forebrain cells express genes for inflammatory and anti-inflammatory cytokines. *Cytokine* 1999;11:55–60.
- Müller N, Krause D, Dehning S, Musil R, Schennach-Wolff R, Obermeier M, et al. Celecoxib treatment in an early stage of schizophrenia: Results of a randomized, double-blind, placebo-controlled trial of celecoxib augmentation of amisulpride treatment. *Schizophr Res* 2010;121:118–24.
- Müller N, Myint AM, Schwarz MJ. Kynurenine pathway in schizophrenia: pathophysiological and therapeutic aspects. *Curr Pharm Des* 2011;17:130–6.
- Müller N, Riedel M, Ackenheil M, Schwarz MJ. Cellular and humoral immune system in schizophrenia: a conceptual re-evaluation. *World J Biol Psychiatry* 2000;1:173–9.
- Müller N, Schwarz M. Schizophrenia as an inflammation-mediated dysbalance of glutamatergic neurotransmission. *Neurotox Res* 2006;10:131–48.
- Müller N, Schwarz MJ. Immune system and schizophrenia. *Curr Immunol Rev* 2010;6:213–20.
- Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *Br Med J* 1987;295:681–2.
- Nathan C, Shiloh MU. Reactive oxygen and nitrogen intermediates in the relationship between mammalian hosts and microbial pathogens. *Proc Natl Acad Sci U S A* 2000;97:8841–8.
- Nemeth E, Rivera S, Gabayan V, Keller C, Taudorf S, Pedersen BK, et al. IL-6 mediates hypoferrremia of inflammation by inducing the synthesis of the iron regulatory hormone hepcidin. *J Clin Invest* 2004;113:1271–6.
- Neumann H, Schweigreiter R, Yamashita T, Rosenkranz K, Wekerle H, Barde YA. Tumor necrosis factor inhibits neurite outgrowth and branching of hippocampal neurons by a rho-dependent mechanism. *J Neurosci* 2002;22:854–62.
- Nitosi I, Rees SM, Duncan J, Kramer BW, Harding R, Newnham JP, et al. Chronic exposure to intra-amniotic lipopolysaccharide affects the ovine fetal brain. *J Soc Gynecol Investig* 2006;13:239–47.
- Nyffeler M, Meyer U, Yee BK, Feldon J, Knuesel I. Maternal immune activation during pregnancy increases limbic GABA receptor immunoreactivity in the adult offspring: implications for schizophrenia. *Neuroscience* 2006;143:51–62.
- Ozawa K, Hashimoto K, Kishimoto T, Shimizu E, Ishikura H, Iyo M. Immune activation during pregnancy in mice leads to dopaminergic hyperfunction and cognitive impairment in the offspring: a neurodevelopmental animal model of schizophrenia. *Biol Psychiatry* 2008;59:546–54.
- Paintlia MK, Paintlia AS, Barbosa E, Singh I, Singh AK. N-acetylcysteine prevents endotoxin-induced degeneration of oligodendrocyte progenitors and hypomyelination in developing rat brain. *J Neurosci Res* 2004;78:347–61.
- Paintlia MK, Paintlia AS, Contreras MA, Singh I, Singh AK. Lipopolysaccharide-induced peroxisomal dysfunction exacerbates cerebral white matter injury: attenuation by N-acetyl cysteine. *Exp Neurol* 2008;210:560–76.
- Palin K, Cunningham C, Forse P, Perry VH, Platt N. Systemic inflammation switches the inflammatory cytokine profile in CNS Wallerian degeneration. *Neurobiol Dis* 2008;30:19–29.
- Pang Y, Rodts-Palenik S, Cai Z, Bennett WA, Rhodes PG. Suppression of glial activation is involved in the protection of IL-10 on maternal *E. coli* induced neonatal white matter injury. *Brain Res Dev Brain Res* 2005;157:141–9.
- Pantelis C, Yücel M, Wood SJ, Velakoulis D, Sun D, Berger G, et al. Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr Bull* 2005;31:672–96.
- Patterson PH. Immune involvement in schizophrenia and autism: etiology, pathology and animal models. *Behav Brain Res* 2009;204:313–21.
- Patterson PH. Maternal infection: window on neuroimmune interactions in fetal brain development and mental illness. *Curr Opin Neurobiol* 2002;12:115–8.
- Paus T, Keshavan M, Giedd JN. Why do many psychiatric disorders emerge during adolescence? *Nat Rev Neurosci* 2008;9:947–57.
- Pérez-Neri I, Ramírez-Bermúdez J, Montes S, Ríos C. Possible mechanisms of neurodegeneration in schizophrenia. *Neurochem Res* 2006;31:1279–94.
- Perry VH, Cunningham C, Holmes C. Systemic infections and inflammation affect chronic neurodegeneration. *Nat Rev Immunol* 2007;7:161–7.
- Phillips LJ, McGorry PD, Garner B, Thompson KN, Pantelis C, Wood SJ, et al. Stress, the hippocampus and the hypothalamic–pituitary–adrenal axis: implications for the development of psychotic disorders. *Aust N Z J Psychiatry* 2006;40:725–41.
- Piontkewitz Y, Arad M, Weiner I. Abnormal trajectories of neurodevelopment and behavior following in utero insult in the rat. *Biol Psychiatry* 2011a;70:842–51.

- Piontkewitz Y, Arad M, Weiner I. Risperidone administered during asymptomatic period of adolescence prevents the emergence of brain structural pathology and behavioral abnormalities in an animal model of schizophrenia. *Schizophr Bull*. 2011b;37:1257–69.
- Piontkewitz Y, Assaf Y, Weiner I. Clozapine administration in adolescence prevents postpubertal emergence of brain structural pathology in an animal model of schizophrenia. *Biol Psychiatry* 2009;66:1038–46.
- Pollmächer T, Haack M, Schuld A, Kraus T, Hinze-Selch D. Effects of antipsychotic drugs on cytokine networks. *J Psychiatr Res* 2000;34:369–82.
- Ponzio NM, Servatius R, Beck K, Marzouk A, Kreider T. Cytokine levels during pregnancy influence immunological profiles and neurobehavioral patterns of the offspring. *Ann N Y Acad Sci* 2007;1107:118–28.
- Potter ED, Ling ZD, Carvey PM. Cytokine-induced conversion of mesencephalic-derived progenitor cells into dopamine neurons. *Cell Tissue Res* 1999;296:235–46.
- Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E. Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. *Biol Psychiatry* 2008;63:801–8.
- Pousset F. Developmental expression of cytokine genes in the cortex and hippocampus of the rat central nervous system. *Dev Brain Res* 1994;81:143–6.
- Prasad AS. Zinc: role in immunity, oxidative stress and chronic inflammation. *Curr Opin Clin Nutr Metab Care* 2009;12:646–52.
- Ransohoff RM, Cardona AE. The myeloid cells of the central nervous system parenchyma. *Nature* 2010;468:253–62.
- Ransohoff RM, Perry VH. Microglial physiology: unique stimuli, specialized responses. *Annu Rev Immunol* 2009;27:119–45.
- Rapaport MH, Delrahim KK, Bresee CJ, Maddux RE, Ahmadpour O, Dolnak D. Celecoxib augmentation of continuously ill patients with schizophrenia. *Biol Psychiatry* 2005;57:1594–6.
- Rapoport JL, Addington AM, Frangou S, Psych MR. The neurodevelopmental model of schizophrenia: update 2005. *Mol Psychiatry* 2005;10:434–49.
- Read J, Perry BD, Moskowitz A, Connolly J. The contribution of early traumatic events to schizophrenia in some patients: a traumagenic neurodevelopmental model. *Psychiatry* 2001;64:319–45.
- Richtand NM, Ahlbrand R, Horn P, Stanford K, Bronson SL, McNamara RK. Effects of risperidone and paliperidone pre-treatment on locomotor response following prenatal immune activation. *J Psychiatr Res* 2011;45:1194–201.
- Robertson SA, Care AS, Skinner RJ. Interleukin 10 regulates inflammatory cytokine synthesis to protect against lipopolysaccharide-induced abortion and fetal growth restriction in mice. *Biol Reprod* 2007;76:738–48.
- Romero E, Ali C, Molina-Holgado E, Castellano B, Guaza C, Borrell J. Neurobehavioral and immunological consequences of prenatal immune activation in rats. *Influence of antipsychotics. Neuropsychopharmacology* 2007;32:1791–804.
- Romero E, Guaza C, Castellano B, Borrell J. Ontogeny of sensorimotor gating and immune impairment induced by prenatal immune challenge in rats: implications for the etiopathology of schizophrenia. *Mol Psychiatry* 2010;15:372–83.
- Ross CA, Margolis RL, Reading SA, Pletnikov M, Coyle JT. Neurobiology of schizophrenia. *Neuron* 2006;52:139–53.
- Rothermundt M, Ahn JN, Jörgens S. S100B in schizophrenia: an update. *Gen Physiol Biophys* 2009;28:F76–81.
- Roumier A, Pascual O, Béchade C, Wakselman S, Poncer JC, Réal E, et al. Prenatal activation of microglia induces delayed impairment of glutamatergic synaptic function. *PLoS One* 2008;3:e2595.
- Roussa E, Wiehle M, Dünker N, Becker-Katins S, Oehlke O, Kriegelstein K. Transforming growth factor beta is required for differentiation of mouse mesencephalic progenitors into dopaminergic neurons in vitro and in vivo: ectopic induction in dorsal mesencephalon. *Stem Cells* 2006;24:2120–9.
- Rousset CI, Kassem J, Olivier P, Chalou S, Gressens P, Saliba E. Antenatal bacterial endotoxin sensitizes the immature rat brain to postnatal excitotoxic injury. *J Neuropathol Exp Neurol* 2008;67:994–1000.
- Saadani-Makki F, Kannan S, Lu X, Janisse J, Dawe E, Edwin S, et al. Intrauterine administration of endotoxin leads to motor deficits in a rabbit model: a link between prenatal infection and cerebral palsy. *Am J Obstet Gynecol* 2008;199:651.e1–7.
- Samuelsson AM, Jennische E, Hansson HA, Holmäng A. Prenatal exposure to interleukin-6 results in inflammatory neurodegeneration in hippocampus with NMDA/GABA(A) dysregulation and impaired spatial learning. *Am J Physiol Regul Integr Comp Physiol* 2006;290:R1345–56.
- Scrimgeour AG, Condlin ML. Zinc and micronutrient combinations to combat gastrointestinal inflammation. *Curr Opin Clin Nutr Metab Care* 2009;12:653–60.
- Selten JP, Frissen A, Lensvelt-Mulders G, Morgan VA. Schizophrenia and 1957 pandemic of influenza: meta-analysis. *Schizophr Bull* 2010;36:219–28.
- Serhan CN, Savill J. Resolution of inflammation: the beginning programs the end. *Nat Immunol* 2005;6:1191–7.
- Seth P, Koul N. Astrocyte, the star avatar: redefined. *J Biosci* 2008;33:405–21.
- Shatrov JG, Birch SC, Lam LT, Quinlivan JA, McIntyre S, Mendz GL. Chorioamnionitis and cerebral palsy: a meta-analysis. *Obstet Gynecol* 2010;116:387–92.
- Shi L, Fatemi SH, Sidwell RW, Patterson PH. Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *J Neurosci* 2003;23:297–302.
- Shi L, Smith SE, Malkova N, Tse D, Su Y, Patterson PH. Activation of the maternal immune system alters cerebellar development in the offspring. *Brain Behav Immun* 2009;23:116–23.
- Short SJ, Lubach GR, Karasin AI, Olsen CW, Styner M, Knickmeyer RC, et al. Maternal influenza infection during pregnancy impacts postnatal brain development in the rhesus monkey. *Biol Psychiatry* 2010;67:965–73.
- Smith SE, Li J, Garbett K, Mirmics K, Patterson PH. Maternal immune activation alters fetal brain development through interleukin-6. *J Neurosci* 2007;27:10695–702.
- Sørensen HJ, Mortensen EL, Reinisch JM, Mednick SA. Association between prenatal exposure to bacterial infection and risk of schizophrenia. *Schizophr Bull* 2009;35:631–7.
- Soumiya H, Fukumitsu H, Furukawa S. Prenatal immune challenge compromises development of upper-layer but not deeper-layer neurons of the mouse cerebral cortex. *J Neurosci Res* 2011a;89:1342–50.
- Soumiya H, Fukumitsu H, Furukawa S. Prenatal immune challenge compromises the normal course of neurogenesis during development of the mouse cerebral cortex. *J Neurosci Res* 2011b;89:1575–85.
- Spulber S, Oprica M, Bartfai T, Winblad B, Schultzberg M. Blunted neurogenesis and gliosis due to transgenic overexpression of human soluble IL-1ra in the mouse. *Eur J Neurosci* 2008;27:549–58.
- Steiner J, Jacobs R, Panteli B, Brauner M, Schiltz K, Bahn S, et al. Acute schizophrenia is accompanied by reduced T cell and increased B cell immunity. *Eur Arch Psychiatry Clin Neurosci* 2010;260:509–18.
- Suvisaari J, Haukka J, Tanskanen A, Hovi T, Lönnqvist J. Association between prenatal exposure to poliovirus infection and adult schizophrenia. *Am J Psychiatry* 1999;156:1100–2.
- Svedin P, Kjellmer I, Welin AK, Blad S, Mallard C. Maturation effects of lipopolysaccharide on white-matter injury in fetal sheep. *J Child Neurol* 2005;20:960–4.
- Takeuchi O, Akira S. Recognition of viruses by innate immunity. *Immunol Rev* 2007;220:214–24.
- Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, “just the facts”: what we know in 2008. 2. Epidemiology and etiology. *Schizophr Res* 2008;102:1–18.
- Tandon R, Nasrallah H, Keshavan MS. Schizophrenia, “just the facts” 4. Clinical features and conceptualization. *Schizophr Res* 2009;110:1–23.
- Taubeneck MW, Daston GP, Rogers JM, Gershwin ME, Ansari A, Keen CL. Tumor necrosis factor- α alters maternal and embryonic zinc metabolism and is developmentally toxic in mice. *J Nutr* 1995;125:908–19.
- Torrey EF, Rawlings R, Waldman IN. Schizophrenic births and viral diseases in two states. *Schizophr Res* 1988;1:73–7.
- Traynor TR, Majde JA, Bohnet SG, Krueger JM. Intratracheal double-stranded RNA plus interferon- γ : a model for analysis of the acute phase response to respiratory viral infections. *Life Sci* 2004;74:2563–76.
- Triantafyllou M, Triantafyllou K. Lipopolysaccharide recognition: CD14, TLRs and the LPS-activation cluster. *Trends Immunol* 2002;23:301–4.
- Unger EL, Paul T, Murray-Kolb LE, Felt B, Jones BC, Beard JL. Early iron deficiency alters sensorimotor development and brain monoamines in rats. *J Nutr* 2007;137:118–24.
- Urakubo A, Jarskog LF, Lieberman JA, Gilmore JH. Prenatal exposure to maternal infection alters cytokine expression in the placenta, amniotic fluid, and fetal brain. *Schizophr Res* 2001;47:27–36.
- Vallee BL, Falchuk KH. The biochemical basis of zinc physiology. *Physiol Rev* 1993;73:79–118.
- van Berckel BN, Bossong MG, Boellaard R, Kloet R, Schuitmaker A, Caspers E, et al. Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11 C] PK11195 positron emission tomography study. *Biol Psychiatry* 2008;64:820–2.
- van Os J, Kapur S. Schizophrenia. *Lancet* 2009;374:635–45.
- Vuillermot S, Feldon J, Meyer U. Nurrl1 is not essential for the development of prepulse inhibition deficits induced by prenatal immune activation. *Brain Behav Immun* 2011;25:1316–21.
- Vuillermot S, Weber L, Feldon J, Meyer U. A longitudinal examination of the neurodevelopmental impact of prenatal immune activation in mice reveals primary defects in dopaminergic development relevant to schizophrenia. *J Neurosci* 2010;30:1270–87.
- Walker EF, Diforio D, Baum K. Developmental neuropathology and the precursors of schizophrenia. *Acta Psychiatr Scand Suppl* 1999;395:12–9.
- Wang J. Preclinical and clinical research on inflammation after intracerebral hemorrhage. *Prog Neurobiol* 2010;92:463–77.
- Wang X, Rousset CI, Hagberg H, Mallard C. Polysaccharide-induced inflammation and perinatal brain injury. *Semin Fetal Neonatal Med* 2006;11:343–53.
- Wang X, Stridh L, Li W, Dean J, Elmgren A, Gan L, et al. Lipopolysaccharide sensitizes neonatal hypoxic-ischemic brain injury in a MyD88-dependent manner. *J Immunol* 2009;183:7471–7.
- Weinberger DR. Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 1987;44:660–9.
- Winter C, Djodari-Irani A, Sohr R, Morgenstern R, Feldon J, Juckel G, et al. Prenatal immune activation leads to multiple changes in basal neurotransmitter levels in the adult brain: implications for brain disorders of neurodevelopmental origin such as schizophrenia. *Int J Neuropsychopharmacol* 2009;12:513–24.
- Winter C, Reutiman TJ, Folsom TD, Sohr R, Wolf RJ, Juckel G, et al. Dopamine and serotonin levels following prenatal viral infection in mice—implications for psychiatric disorders such as schizophrenia and autism. *Eur Neuropsychopharmacol* 2008;18:712–6.
- Wolf SA, Melnik A, Kempermann G. Physical exercise increases adult neurogenesis and telomerase activity, and improves behavioral deficits in a mouse model of schizophrenia. *Brain Behav Immun* 2011;25:971–80.
- Wolff AR, Bilkey DK. Immune activation during mid-gestation disrupts sensorimotor gating in rat offspring. *Behav Brain Res* 2008;190:156–9.
- Wolff AR, Cheyne KR, Bilkey DK. Behavioural deficits associated with maternal immune activation in the rat model of schizophrenia. *Behav Brain Res* 2011;225:382–7.
- Wonodi I, Schwarcz R. Cortical kynurenine pathway metabolism: a novel target for cognitive enhancement in schizophrenia. *Schizophr Bull* 2010;36:211–8.
- Wood SJ, Pantelis C, Velakoulis D, Yücel M, Fornito A, McGorry PD. Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. *Schizophr Bull* 2008;34:322–9.
- Xu DX, Chen YH, Wang H, Zhao L, Wang JP, Wei W. Effect of N-acetylcysteine on lipopolysaccharide-induced intra-uterine fetal death and intra-uterine growth retardation in mice. *Toxicol Sci* 2005;88:525–33.

- Yang L, Lindholm K, Konishi Y, Li R, Shen Y. Target depletion of distinct tumor necrosis factor receptor subtypes reveals hippocampal neuron death and survival through different signal transduction pathways. *J Neurosci* 2002;22:3025–32.
- Zhang L, Liu W, Alizadeh D, Zhao D, Farrukh O, Lin J, et al. S100B attenuates microglia activation in gliomas: possible role of STAT3 pathway. *Glia* 2011;59:486–98.
- Zhang Y, Cazakoff BN, Thai CA, Howland, JG. Prenatal exposure to a viral mimetic alters behavioural flexibility in male, but not female, rats. *Neuropharmacology*, in press (Epub ahead of print [PMID: 21376064]).
- Zheng LT, Hwang J, Ock J, Lee MG, Lee WH, Suk K. The antipsychotic spiperone attenuates inflammatory response in cultured microglia via the reduction of proinflammatory cytokine expression and nitric oxide production. *J Neurochem* 2008;107:1225–35.
- Zhou Z, Peng X, Insolera R, Fink DJ, Mata M. IL-10 promotes neuronal survival following spinal cord injury. *Exp Neurol* 2009a;220:183–90.
- Zhou Z, Peng X, Insolera R, Fink DJ, Mata M. Interleukin-10 provides direct trophic support to neurons. *J Neurochem* 2009b;110:1617–27.
- Zhu G, Mehler MF, Mabie PC, Kessler JA. Developmental changes in progenitor cell responsiveness to cytokines. *J Neurosci Res* 1999;56:131–45.
- Zuckerman L, Rehavi M, Nachman R, Weiner I. Immune activation during pregnancy in rats leads to a postpubertal emergence of disrupted latent inhibition, dopaminergic hyperfunction, and altered limbic morphology in the offspring: a novel neurodevelopmental model of schizophrenia. *Neuropsychopharmacology* 2003;28:1778–89.
- Zuckerman L, Weiner I. Maternal immune activation leads to behavioral and pharmacological changes in the adult offspring. *J Psychiatr Res* 2005;39:311–23.
- Zuckerman L, Weiner I. Post-pubertal emergence of disrupted latent inhibition following prenatal immune activation. *Psychopharmacology* 2003;169:308–13.