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Models of Neurodevelopmental Abnormalities in Schizophrenia

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Abstract

The neurodevelopmental hypothesis of schizophrenia asserts that the underlying pathology of schizophrenia has its roots in brain development and that these brain abnormalities do not manifest themselves until adolescence or early adulthood. Animal models based on developmental manipulations have provided insight into the vulnerability of the developing fetus and the importance of the early environment for normal maturation. These models have provided a wide range of validated approaches to answer questions regarding environmental influences on both neural and behavioral development. In an effort to better understand the developmental hypothesis of schizophrenia, animal models have been developed, which seek to model the etiology and/or the pathophysiology of schizophrenia or specific behaviors associated with the disease. Developmental models specific to schizophrenia have focused on epidemiological risk factors (e.g., prenatal viral insult, birth complications) or more heuristic models aimed at understanding the developmental neuropathology of the disease (e.g., ventral hippocampal lesions). The combined approach of behavioral and neuroanatomical evaluation of these models strengthens their utility in improving our understanding of the pathophysiology of schizophrenia and developing new treatment strategies.

Keywords

Development; Immune; Social isolation; Stress; Neonatal ventral hippocampal lesion; Protein deprivation; Prenatal; Neonatal; Postnatal; Animal model; Schizophrenia; Toxin; Obstetric complications; Behavior

1 Neurodevelopmental Models of Schizophrenia

1.1 Developmental Theory of Schizophrenia

Over the past two decades, development of the central nervous system has become critical in understanding the neurobiology of schizophrenia (Fatemi and Folsom 2009; Lewis and Levitt 2002; Murray and Lewis 1988; Weinberger 1987). The neurodevelopmental hypothesis of schizophrenia asserts that the underlying pathology of schizophrenia has its roots in brain development and that these brain abnormalities do not manifest themselves until adolescence or early adulthood (Fatemi and Folsom 2009; Rapoport et al. 2005). In addition to the course of illness, support for a neurodevelopmental etiology comes from neuroanatomical and cytoarchitectural abnormalities in the brains of patients with schizophrenia. For example, ventricular enlargement and decreased cortical, hippocampal, and amygdalar volumes are present without any evidence of gliosis (i.e., trauma or neurodegeneration, Arnold et al. 1997; Fatemi and Folsom 2009; Weinberger 1987). Additionally, misplaced and clustered neurons, particularly in the entorhinal cortex, indicate problems of neuronal migration and suggest an early developmental anomaly (Arnold et al. 1991; Falkai et al. 2000; Jakob and Beckmann 1986). Pyramidal neurons in the hippocampus and neocortex have smaller cell bodies and fewer dendritic spines and dendritic arborizations (reviewed in Harrison and Weinberger 2005). Additionally,

decreased presynaptic proteins such as synapto-physin, SNAP-25, and complexin II have been observed in schizophrenia brains as well as decreased density of interneurons (e.g., parvalbumin-immunoreactive cells) (Harrison and Weinberger 2005). There are also reports of decreases in cell numbers in the thalamus and a decreased number of oligodendrocytes. Neuroimaging data and postmortem studies have shown that *N*-acetylaspartate (NAA), a marker of neuronal integrity, is decreased in first episode and in never-medicated patients (Bertolino and Weinberger 1999; Nudmamud et al. 2003). On the basis of these neuropathological changes, investigators have conceptualized schizophrenia as a disease of functional "dysconnectivity" (Friston and Frith 1995; McGlashan and Hoffman 2000; Weinberger et al. 1992) or a "disorder of the synapse" affecting the machinery of the synapse (Frankle et al. 2003; reviewed in Harrison and Weinberger 2005; Mirnics et al. 2001). Recent evidence from MRI studies of reduced white matter supports the disconnection model of schizophrenia (Fatemi and Folsom 2009).

Epidemiological studies support the notion that environmental factors contribute to the incidence of schizophrenia (Cannon et al. 2003; Rapoport et al. 2005). For example, season of birth is a risk factor, with late winter/early spring births associated with an increased risk of schizophrenia (Boyd et al. 1986; Machon et al. 1983; Mino and Oshima 2006; Torrey et al. 1997). Recent studies showed that social factors such as urbanicity, immigrant status, and social isolation are associated with an increased risk for schizophrenia (Cannon et al. 2008; Dean et al. 2003; Marcelis et al. 1998). Hence, the developmental hypothesis of schizophrenia has led to the examination of environmental and epigenetic factors associated with schizophrenia, asserting that an early environmental insult, such as a viral exposure to the developing fetus (Brown and Susser 2002; Mednick et al. 1988; O'Callaghan et al. 1991; Takei et al. 1996) or obstetric complications (Owen and Lewis 1988), causes dysfunction in neural systems that normally reach maturity in late adolescence and early adulthood. Thus, the symptoms of schizophrenia would not express themselves until the point in development in which these brain areas (e.g., dorsal prefrontal cortex) mature (Weinberger 1987).

1.2 Animal Models of Developmental Hypothesis

Several animal models are being used to understand neurobiological processes relevant to the developmental hypothesis of schizophrenia (Fatemi and Folsom 2009; Lipska and Weinberger 2000; Meyer and Feldon 2009a, b; Powell and Geyer 2002). Although recreating a uniquely human condition such as schizophrenia is not feasible in animals, animal models have been useful in aiding our understanding of the pathophysiology of the disease (Geyer and Markou 2002; Powell and Geyer 2007; Swerdlow et al. 1994) (Young et al. 2010). These animal models are evaluated based on their face, construct, and predictive validity, and involve both the manipulations (e.g., pharmacological, developmental insult) and measures (e.g., prepulse inhibition, cognitive flexibility). For a more detailed description of the differences in various forms of validity, see Young et al. this text, Geyer and Markou (2002), Swerdlow et al. (1994). When evaluating the relevance of the model to schizophrenia, one should consider both the manipulations and the measures.

Developmental models specific to schizophrenia have focused on the intrauterine environment [e.g., viral insult, exposure to neurotoxins, prenatal maternal stress; (Fatemi et al. 2005; Meyer et al. 2009)], birth complications [e.g., cesarean section, hypoxia; (Boksa and El-Khodor 2003; Vaillancourt and Boksa 2000; Wakuda et al. 2008)], perinatal insult [e.g., ventral hippocampal lesions (Tseng et al. 2009)], prenatal stress (Koenig et al. 2002), and postnatal maternal and/or social deprivation (Ellenbroek et al. 1998; Fone and Porkess 2008; Powell and Geyer 2002). Additionally, genetic models, particularly those targeting developmental genes or those that display age-dependent emergence of a phenotype, can also address neurodevelopmental aspects of schizophrenia (Powell et al. 2009). The combined approach of behavioral and neuroanatomical evaluation of these models

strengthens their utility in improving our understanding of the pathophysiology of schizophrenia and developing new treatment strategies (Meyer and Feldon 2009a) including prophylaxis (Meyer et al. 2008d; Powell et al. 2003).

There are several specific experimental factors that need to be considered when conducting developmental studies such as comparisons of the time course of CNS maturation across species, timing of the environmental manipulation, litter effects, and cross-fostering. For a more detailed review of these experimental considerations, see Meyer and Feldon (2009a). Rats and mice differ greatly from humans in the timing of brain development, with brain development in rodents occurring at a much faster pace than that in humans. Considering the proportion of time relative to the lifespan of the organism and the timing of specific neuronal processes, late gestation in humans most likely corresponds to the early postnatal period in rats and mice (Clancy et al. 2001, 2007). Comparisons in brain development between species can be estimated using an algorithm, originally described by (Finlay and Darlington 1995), which is now accessible through a web site (http://translatingtime.net/) (Clancy et al. 2007). Thus, the nature of the schizophrenia-relevant risk factor or neuropathology being modeled and the timing of insult are important factors to consider when evaluating neurodevelopmental models of schizophrenia.

Other important experimental considerations to take into account are in utero environment and maternal behavior. In prenatal challenge models, cross-fostering involves transferring pups from one dam to another lactating surrogate dam to account for any effects the challenge had on mother–pup interactions. For example, in order to confirm significant effects of your manipulation (e.g., prenatal immune activation) it is important to rule out effects of maternal behavior on the observed experimental results. An additional experimental consideration in developmental experiments is litter effects. In multiparous species such as rats and mice, there are often anywhere from 6 to 12 pups born at the same time. This fecundity, while one of the main reasons that rodents are the preferred laboratory species, presents problems to experimental design and statistical analyses, particularly in developmental studies (reviewed in Zorrilla 1997). Owing to shared genes, intrauterine environment, and common postnatal environment, littermates are more similar to each other than nonlittermates and are thus not independent observations. This interdependence complicates statistical analyses and, when each littermate is treated as an independent sample in the ANOVA, inflates the sample size and increases the likelihood of observing a false positive or a false negative (Zorrilla 1997). There are several ways to handle litter effects in the experimental design and statistical analysis, which are discussed in the final section of this chapter and in Zorrilla (1997).

2 Behavioral Measures

Several behavioral measures with certain degrees of validity have been used to assess neurodevelopmental manipulations of relevance to schizophrenia. In this chapter, we will focus primarily on the developmental manipulations themselves and report on the subsequent behavioral and neuronal abnormalities produced by the manipulation. For a more complete review of the “measures” or behavioral tasks used in animal models of schizophrenia, the reader is referred to Jones et al. (2008), Powell and Geyer (2007), Young et al. (2009), Young et al. this text. Briefly, developmental models have been evaluated across several behaviors of relevance to schizophrenia. Generally, these measures fall into four categories: locomotor activity (e.g., spontaneous and drug-induced), gating (e.g., prepulse inhibition of startle, auditory gating), cognitive (e.g., learning and memory, behavioral flexibility), and social (e.g., social interaction, social recognition).

2.1 Spontaneous and Drug-Induced Locomotor Activity

Measures of locomotion and stereotypy in animals have been useful in the identification of drugs that treat the positive symptoms of schizophrenia (e.g., dopamine D2 receptor antagonists). Typically, these experiments involve administering a psychostimulant such as amphetamine to a rat or mouse and observing both the quantity and quality of motor activity produced (reviewed in Segal and Geyer 1985; Segal et al. 1981; Swerdlow et al. 1986). In the absence of a pharmacological manipulation, as is the case with developmental models, spontaneous locomotor activity is often used to evaluate exploratory behavior and unconditioned anxiety produced by a developmental insult. Many of the developmental models reviewed here have also been evaluated for drug-induced locomotor activity (e.g., response to amphetamine, phencyclidine) to probe the functional integrity of the dopamine and glutamate systems, respectively. The measurement of amphetamine-induced locomotor activity is based on the more general dopamine hyperactivity hypothesis of schizophrenia and more specifically, the finding that patients with schizophrenia show exaggerated dopamine release and an exacerbation of symptoms in response to amphetamine (Laruelle et al. 1996).

2.2 Gating Deficits

Deficient gating of sensory input or intrusive thoughts in schizophrenia patients has been recognized for a number of years (Kietzman et al. 1985). In experimental animal studies, gating deficits are evaluated using three primary measures: prepulse inhibition (PPI) of startle, auditory gating, and latent inhibition (LI). Perhaps, the most common behavioral measure assessed in animal models of schizophrenia is PPI of the startle response, an operational measure of sensorimotor gating [reviewed in (Swerdlow and Geyer 1998; Swerdlow et al. 2008)]. PPI is disrupted in schizophrenia patients (Braff et al. 2001) (See Braff 2010) and in pharmacological, developmental, and genetic animal models of schizophrenia (Geyer et al. 2001; Powell and Geyer 2002; Powell et al. 2009). PPI is reliable, can be tested repeatedly in the same animal and has demonstrated face, construct, and predictive validity in animal models of schizophrenia (Geyer and Moghaddam 2002; Swerdlow et al. 1994, 2008). The ability to test the same behavior in the same animals repeatedly is a particularly attractive feature for developmental models that involve the assessment of behaviors both pre- and postpuberty. Together with amphetamine stimulated locomotor activity, sensorimotor gating, as measured by PPI, is often the “gold standard” behavioral endpoint in neurodevelopmental models of schizophrenia research.

The auditory “sensory gating” paradigm in animal studies is based on a similar paired-stimulus paradigm in humans in which the P50 event-related potential (ERP) elicited by the second of two audible clicks is normally reduced relative to the ERP elicited by the first click (Freedman et al. 1999). Because schizophrenia patients do now show the normal reduction in ERP to the second click, a rodent version based on the N40 ERP generated from the hippocampus has been evaluated in animal models of schizophrenia (Freedman et al. 1999; Stevens et al. 1997). LI is conceptually related to the gating theories of schizophrenia disorders and refers to the observation that repeated exposures to a sensory stimulus (i.e., habituation) retards the rate at which a subject will subsequently acquire a stimulus–response association based on this stimulus (Weiner and Arad 2009; Weiner et al. 1988). Meyer et al. (2005) hypothesized that decreases in LI may reflect increased distraction by irrelevant stimuli.

2.3 Attention

Attentional problems in schizophrenia are among the core features of the disease (Addington et al. 1997). In laboratory tests, schizophrenia patients show deficits in the continuous performance task (CPT), which measures sustained attention (Nestor and O’Donnell 1998;

Orzack and Kornetsky 1966). Rodent models of attention include the 5-choice serial reaction time task (5-CSRTT) developed by Robbins and colleagues (Chudasama and Robbins 2004; Robbins 2002). Other rodent tasks of attention include the sustained attention task pioneered by Sarter and colleagues (Sarter et al. 2001). For a more complete review of attentional tasks in animal models of schizophrenia, see Young et al. (2009).

2.4 Cognitive Deficits

Because cognitive deficits in schizophrenia are part of the core features of the illness, are associated with poor quality of life, and are relatively resistant to current treatments, there is a renewed focus on defining and treating cognitive deficits (Green et al. 2004; Nuechterlein et al. 2004). The cognitive deficits in schizophrenia include impairments in working memory as well as problem solving, social cognition, and learning and memory (Cannon et al. 2005; Hagan and Jones 2005; Nuechterlein et al. 2004). Animal models mapping onto the specific cognitive domains deficient in schizophrenia are extensively reviewed elsewhere (Young et al. 2009). Briefly, rodent models have focused primarily on assessments of learning and memory (e.g., novel object recognition, Morris water maze; fear conditioning), working memory (e.g., delayed alternation in T-maze), and cognitive flexibility (e.g., set shifting, reversal learning; (Floresco et al. 2009). These tasks are outlined in the previous section (Young et al. this text) and in a recent review paper (Young et al. 2009). Important to developmental models of schizophrenia is the observation that cognitive deficits (e.g., processing speed, working memory, executive function, verbal memory) often predate the onset of psychotic symptoms (Eastvold et al. 2007). This early emergence of cognitive deficits in the prodromal phase should be considered in relation to the postpubertal emergence criteria adopted by many neurodevelopmental animal models. Thus, the emergence of early deficits in cognitive function in an animal model could strengthen its usefulness, particularly in relation to early intervention studies aimed at modeling prodromal treatments.

2.5 Social Interaction

Social withdrawal is included among the negative symptoms of schizophrenia and is often one of the earliest symptoms to occur (Johnstone et al. 2005; McClellan et al. 2003; Miller et al. 2002). Animal models of social impairments fall into three primary categories: social interaction allowing contact between the animal, social approach without contact, and social recognition/social novelty. Social interaction models involve exposing a rat to a nonaggressive conspecific and scoring the amount and type of social interaction [e.g., rough and tumble play, allogrooming; (Sams-Dodd 1996, 1998)]. Rodent social interaction tests such as these have shown their usefulness as a screen for putative antipsychotic medications (e.g., Bruins Slot et al. 2005). A simple test of social approach and novelty was established recently by Crawley, Moy, and colleagues. In this paradigm, test mice are placed in a three-chambered arena, in one chamber, a “stranger” mouse is placed under a wire cup, and in the opposite chamber there is an empty wire container (Crawley 2007; Moy et al. 2004). Exploratory behavior of the test mouse is quantified for 10 min, with social approach measured by comparing the number of contacts and time spent at the container with the “stranger” mouse compared to the empty container. After 10 min, social novelty is tested by putting a new mouse into the previously empty container, and comparing the exploration of the stranger mouse explored in the approach test and the new mouse. This measure of “social novelty” is very similar to other social recognition tests, which involve assessing the time spent investigating a novel, unfamiliar conspecific in the presence of a familiar conspecific (Engelmann et al. 1995; Ferguson et al. 2002; Thor and Holloway 1981; Winslow and Camacho 1995).

3 Epidemiologic-Based Developmental Manipulations

Historically, the manipulations used to produce animal models involved assessment of drug-induced changes in behavior, particularly in response to psychotomimetic drugs (e.g., amphetamine-induced hyperactivity, phencyclidine-induced PPI disruptions). While pharmacological models have proven useful in the evaluation of antipsychotics, developmental manipulations offer the unique ability to probe etiological factors associated with schizophrenia and provide models for the assessment of novel therapeutics (Meyer and Feldon 2009a). For example, assessment of drugs in amphetamine-induced hyperactivity model will tend to screen for compounds predominantly on dopamine antagonist properties similar to currently available antipsychotics. Neurodevelopmental models can be either epidemiologic and focus on the specific risk factors in the human populations (e.g., prenatal infection) (for review, see Meyer and Feldon 2009a) or be heuristic models of developmental neuropathology observed in schizophrenia (e.g., neonatal ventral hippocampal lesion) (for review, see Tseng et al. 2009). Hence, for the purposes of this discussion, the relevant neurodevelopmental animal models of schizophrenia are divided into two categories: epidemiologic and heuristic models (Table 1). Of course, there is some overlap between the two categories and it can be debated how well each model represents the epidemiological risk factor and/or neuropathology it attempts to address. Nevertheless, this distinction is used to guide the discussion of the developmental models reviewed in this chapter.

3.1 Viral and Immune-Activating Models of Schizophrenia

Epidemiological studies have linked prenatal exposure to viral and bacterial infections during early to mid-gestation with an increased risk for schizophrenia (reviewed in Brown and Susser 2002; Fatemi and Folsom 2009; Patterson 2009; but see also Selten et al. 1999a). Early studies focused on the link between influenza and schizophrenia (Mednick et al. 1988; O'Callaghan et al. 1991), but other infectious agents such as toxoplasmosis (Brown et al. 2005) and bacterial infections (Sorensen et al. 2009) have also been associated with the disease. Epidemiological findings have been corroborated by serologic evidence of gestational influenza infection during early to mid-pregnancy increasing the risk of schizophrenia threefold (Brown et al. 2004a). In addition to influenza, there is also serologic evidence of increased maternal levels of cytokines such as TNF-alpha (Buka et al. 2001) and IL-8 (Brown et al. 2004b) during pregnancy in mothers of patients with schizophrenia. Additional evidence for alterations in immune function in schizophrenia comes from the observation that higher levels of antibodies and alterations in other measures of immune function are reported in schizophrenia patients (reviewed in Patterson 2009; Schwarz et al. 2001). To examine and identify the causal relationship between the neural and behavioral consequences of prenatal exposure and immune challenges, the effects of maternal challenges with influenza virus (Shi et al. 2003), as well as other viruses [e.g., borna disease virus, lymphocytic choriomeningitis, cytomegalovirus; (Lipska and Weinberger 2000)], and immune activating agents have been investigated in animal models (for more thorough reviews, see Meyer and Feldon 2009a, b; Patterson 2009). When given at the appropriate time during gestation, these viruses or immune-activating agents can have rather selective effects on neuronal development and behavior. These prenatal immune paradigms, conducted in both rats and mice, have emerged over the last decade as some of the most important neurodevelopmental models of schizophrenia. These animal models involve exposure of pregnant rats or mice to an immune challenge with either influenza, the bacterial endotoxin lipopolysaccharide (LPS), or the viral mimic polyriboinosinic–polyribo-cytidilic acid (PolyI:C) during gestation and corresponding assessment of brain and behavioral effects in the offspring.

3.1.1 Prenatal Viral Exposure—Exposure of mice to influenza virus on gestation day 9 results in behavioral and brain abnormalities reminiscent of schizophrenia (Fatemi et al. 1998). Specifically, influenza-exposed mice showed deficits in PPI, decreased exploratory behavior, and decreased social interaction (Shi et al. 2003). Neuroanatomical abnormalities associated with in utero exposure to influenza include pyramidal cell atrophy and macrocephaly, increased glial fibrillary acidic protein (GFAP) immunoreactivity, increased glutamic acid decarboxylase (GAD) 65 and 67 proteins (Fatemi et al. 2002a, b, 2004). Prenatal exposure to influenza also results in decreased size of the lateral ventricles, disrupted corticogenesis, and reduced Reelin immunoreactivity in the frontal cortex and hippocampus (Fatemi et al. 1999).

3.1.2 Prenatal PolyI:C Exposure—Interestingly, the behavioral impairments (specifically PPI) in influenza-exposed offspring appeared to be associated with the *maternal* immune response and not with the viral infection per se because similar alterations in behavior were observed when the pregnant dam was treated with PolyI:C, which elicits an immune response in the mother similar to that observed with influenza (Shi et al. 2003). PolyI:C has been extensively studied in both rats and mice with varying outcomes based on the timing of exposure (Meyer and Feldon 2009b; Meyer et al. 2006b). Additional behavioral, neuropathological, and neurochemical studies further supported the prenatal PolyI:C model as a valid model of schizophrenia. Specifically, behavioral impairments in PPI, LI, reversal learning, novel object recognition, and working memory in addition to an increased sensitivity to dopamine agonists and glutamate antagonists are all observed in the offspring of mice and rats exposed to gestational PolyI:C (see also Fortier et al. 2007; Meyer et al. 2006a; Ozawa et al. 2006; Shi et al. 2003; Smith et al. 2007; Wolff and Bilkey 2008; Zuckerman et al. 2003; Zuckerman and Weiner 2003, 2005). Using MRI, a recent study showed increased lateral ventricle size and PPI deficits in mice exposed to PolyI:C in utero (Li et al. 2009). Several neuropathological studies revealed alterations in dopamine, gamma-aminobutyric acid (GABA), and glutamate systems and decreased Reelin expression in the PFC and hippocampus (reviewed in Meyer and Feldon 2009b). Alterations in dopamine neurocircuitry in the PolyI:C model include increased tyrosine hydroxylase (TH) immunoreactivity in the nucleus accumbens (NAC), decreased dopamine receptors in the prefrontal cortex (PFC), and alterations in basal and stimulated dopamine release depending on the timing of insult (Meyer et al. 2008b, c; Winter et al. 2009). Similar to the observation of decreased calcium-binding protein parvalbumin (PV) immunoreactivity in schizophrenia brain (Beasley et al. 2002; Reynolds et al. 2004), mice exposed to PolyI:C in utero have decreased PV staining in hippocampus and PFC (Meyer et al. 2008c). Increased limbic GABA-A receptor immunoreactivity in brains of PolyI:C-exposed mice further support a role for GABA in the neuropathology of the immune insult (Nyffeler et al. 2006). Prenatal PolyI:C also leads to alterations in the glutamate system, as evidenced by decreased expression of the *N*-methyl-D-aspartate (NMDA) receptor subunit 1 (NR1) (Meyer et al. 2008c).

3.1.3 Prenatal LPS Exposure—Administration of the bacterial endotoxin LPS to mammalian species mimics the innate immune response that is typically seen after infection with gram-negative bacteria. Hence, neurodevelopmental animal models of schizophrenia have also utilized LPS as an infectious agent during gestation. Initial studies with prenatal LPS conducted by Borrell and Romero and colleagues administered LPS every other day throughout pregnancy (Borrell et al. 2002; Romero et al. 2007). Similar to prenatal viral exposure, when pregnant rats were exposed to LPS, their offspring exhibited PPI deficits that emerged postpuberty and were reversed by administration of antipsychotics (Borrell et al. 2002; Romero et al. 2007, 2008). The offspring also showed increased TH immunoreactivity and basal dopamine levels in the NAC as well as decreased DARP-32 in

frontal cortex and increased synaptophysin in hippocampus and cortex (Borrell et al. 2002; Romero et al. 2007, 2008). Subsequent studies revealed that discrete administration of LPS during gestation (embryonic days 15–16 or 18–19) disrupts PPI and increases amphetamine-induced locomotor activity in the offspring (Fortier et al. 2004, 2007). Additional CNS abnormalities in adult offspring include morphological changes in pyramidal neurons of the hippocampus and PFC (Baharnoori et al. 2009; Nolan et al. 2003).

LPS administered to pregnant rats has been shown to increase cytokines in the amniotic fluid (Urakubo et al. 2001) and in fetal plasma (Ashdown et al. 2006). Borrell et al. (Borrell et al. 2002) showed that serum levels of the cytokines IL-6 and IL-2 were significantly higher in adult offspring of LPS-infected dams. These authors suggest that elevated cytokine levels in the adult offspring may contribute to the PPI deficits observed following prenatal LPS. These data are in line with reports describing elevated levels of cytokines in the CSF and plasma of schizophrenia patients (Licinio et al. 1993; Mittleman et al. 1997).

3.1.4 Role of Cytokines in Prenatal Immune Models—Studies with PolyI:C indicated that the maternal immune response was responsible for the schizophrenia-like behavioral and neuronal effects of prenatal immune challenge but the specific elements of the immune response contributing to these impairments was not known. Subsequent studies went on to examine the role of specific cytokines in the prenatal immune models. PolyI:C administration increases both proinflammatory (IL-6, IL-1β, TNF alpha) and anti-inflammatory (IL-10) cytokines. Both IL-6 and IL-10 play an important role in mediating the effects of prenatal PolyI:C administration. For example, many of the behavioral and neuropathological effects of prenatal PolyI:C are mimicked by gestational administration of IL-6 and blocked in IL-6 knockout mice (Smith et al. 2007). Conversely, over-expression of the anti-inflammatory cytokine IL-10 blocked the emergence of behavioral abnormalities in the offspring exposed to PolyI:C in utero but lead to some behavioral abnormalities when overexpressed on its own in the absence of any immunogenic agent (Meyer et al. 2008a).

3.1.5 Neonatal Immune Activation—In addition to prenatal immune activation, other immune-based developmental models have focused on neonatal exposure of rat or mouse pups to a viral or immunogenic agent (Nawa et al. 2000). These neonatal infections are thought to model infection during the late second/early third trimester. Earlier work showed that rats with neonatal exposure to cytomegalovirus show an increased sensitivity to the PPI-disruptive effects of apomorphine (Rothschild et al. 1999). Neonatal influenza administered on postnatal day 3 or 4 resulted in PPI deficits in adult *Tap1*−/−(transporter associated with antigen processing 1) mice expressing reduced levels of MHC Class I (Asp et al. 2009). The PPI deficits were accompanied by increases in transcripts encoding indoleamine-pyrrole 2,3-dioxygenase (IDO) and transient increases in other enzymes in the kynurenine pathway of tryptophan metabolism and kynurenic acid (KYNA) (Asp et al. 2009; Holtze et al. 2008). These studies raise the possibility that elevations in KYNA, an endogenous NMDA antagonist and nicotinic acetylcholine (nAch) alpha-7 antagonist, may mediate in part the behavioral effects of neonatal immune activation. Neonatal exposure to PolyI:C also results in behavioral and neurochemical abnormalities later in life (Ibi et al. 2009). Again, the effects of these immune-activating agents may be mediated through increases in cytokines. Administration of cytokines (e.g., IL-1α, leukemia inhibitory factor [LIF]) to neonatal rat or mouse pups also results in locomotor hyperactivity, decreased PPI, impaired social interaction, and neuroanatomical abnormalities such as increased TH and dopamine metabolism (Tohmi et al. 2004; Tsuda et al. 2006; Watanabe et al. 2004). Similar to effects of prenatal PolyI:C treatment in mice, administration of LPS on postnatal day 7 and 9 to rat pups also produced decreased PV immunoreactivity in the hippocampus (Jenkins et al. 2009).

3.1.6 Discussion of Immune Models—Like all the studies of epidemiological risk factors, one important aspect to consider is that the risk factor of prenatal or neonatal viral infection only confers a modest increased risk for developing the disorder. Obviously, not all individuals exposed to an infection in utero subsequently develop schizophrenia. One advantage to the environmental risk factors outlined here is the possibility to study gene–environment interactions. Inducing an effect of immune activation in genetically compromised or genetically susceptible animal but not in the wildtype animal would be extremely compelling and useful to our understanding of gene–environment interactions in schizophrenia. These gene–environment interactions are beginning to be explored in relation to immune challenge models (reviewed in Ayhan et al. 2009). Examples of these gene–environment interactions include the neonatal exposure to influenza in TAP1−/− mice described above (Asp et al. 2009) and recent studies examining the effects of neonatal PolyI:C administration in DISC1 dominant-negative (DISC1 DN) mutant mice (Ibi et al. 2010). Specifically, DISC1 DN mice displayed a more pronounced response to the behavioral effects of neonatal PolyI:C compared to wildtype mice (Ibi et al. 2009). Hence, immune models are ripe for studies of gene–environment interactions and may prove useful in our understanding of the dynamic interplay between susceptibility genes and environmental risk factors.

As mentioned previously, the role of maternal behavior in the effects of prenatal immune activation need to be taken into account. In studies, in which cross-fostering was employed, mother–pup behavioral interactions accounted for some of the observed effects (Meyer et al. 2006c, 2008b). One additional consideration in studies of prenatal immune activation is that the immune challenge may produce a nutritional deficiency in the mom, which can have significant effects on the offspring (see Sect. 3.2). Dams do tend to lose weight in response to the immune-activating agent.

3.2 Maternal Malnutrition

Epidemiological studies suggest that prenatal nutritional deficiency increases the risk of developing schizophrenia (Brown and Susser 2008; Susser et al. 1996). Perhaps the most robust examination of this relationship comes from the two periods of famine, one during 1944–1945 in The Netherlands termed “The Dutch Hunger Winter” and the other during the “Chinese Famine” that took place during 1959–1961. Those offspring exposed to the famine during early gestation had a twofold increase of developing schizophrenia as adults (Susser et al. 1996; Xu et al. 2009). Candidate micronutrients that may be responsible for these abnormalities include folate, vitamin D, essential fatty acids, retinoids, and iron, all of which play a role in normal fetal brain development (reviewed in Brown and Susser 2008). In order to determine the mechanism responsible for altered brain development in response to early gestational malnutrition, several animal models have been developed: prenatal protein deficiency (or protein–calorie malnutrition) and prenatal vitamin D deficiency (reviewed in Meyer and Feldon 2009a).

3.2.1 Prenatal Protein Deficiency—Prenatal protein deficiency typically involves depriving the dam of protein prior to and during pregnancy and comparing the behavioral effects in the offspring to that of control rats that received normal levels of protein during gestation (e.g., low casein diets (6%) or adequate casein diets (25%)). Protein deprivation in rats leads to many alterations in brain development consistent with an animal model of schizophrenia including structural differences in the hippocampus, alterations in dopamine and serotonin release, and changes in glutamate receptor binding (Meyer and Feldon 2009a for review). As far as behavioral effects of prenatal protein deficiency, several alterations have been reported. Namely, female rats that underwent prenatal protein deprivation display a postpubertal emergence of PPI deficits (Palmer et al. 2004), an increased responsiveness to

dopamine agonists and NMDA receptor antagonists (Palmer et al. 2008; Tonkiss et al. 1998). Impairments in working memory measured in a radial arm maze have been reported in rats exposed to prenatal protein deprivation (Ranade et al. 2008); whereas other studies have shown no difference in working memory as measured in a T-maze alternation task and in an operant delayed alternation task (Tonkiss and Galler 1990). There have yet to be any report showing reversal of the functional impairments in prenatal protein deficiency with drug treatment. Such future studies would clarify the predictive validity of the prenatal protein deficiency model of schizophrenia.

3.2.2 Prenatal Vitamin D Deficiency—Maternal vitamin D deficiency has also been examined in animal models for its role in the development of schizophrenia (Eyles et al. 2009). McGrath (1999) argues that Vitamin D deficiency may explain several risk factors for schizophrenia including maternal malnutrition, increased winter births in schizophrenia, urbanicity, and dark-skinned immigrants in cold climates. The hypothesis of vitamin D deficiency is intriguing because vitamin D is important for normal fetal brain development and deficiencies (e.g., rickets) can have profound impact on health (Eyles et al. 2009). The epidemiological evidence for this link is mixed. While maternal vitamin D supplementation reduced the risk of schizophrenia in an examination of data from a Finnish Birth Cohort (McGrath et al. 2004), other studies have supported the link only weakly (McGrath et al. 2003) or not at all (Kendell and Adams 2002; Özer et al. 2004). Nevertheless, animal models of maternal vitamin D deficiency have supported a link between the deficiency and brain and behavioral abnormalities related to schizophrenia (reviewed in Eyles et al. 2009). For example, prenatal vitamin D deficiency in rats is associated with enlarged lateral ventricles and smaller neocortical width (Eyles et al. 2003), decreased neurotrophin levels (Eyles et al. 2003; Feron et al. 2005), altered neurogenesis (Cui et al. 2007), and increased long-term potentiation (LTP) (Grecksch et al. 2009). Maternal vitamin D deficiency also produces changes in PFC, hippocampal, and NAC gene and protein expression in pathways involved in oxidative stress, synaptic plasticity, calcium homeostasis, and neurotransmission (Almeras et al. 2007; Eyles et al. 2007; McGrath et al. 2008).

Maternal vitamin D deficiency is associated with several behavioral impairments with validity for schizophrenia. For example, rats exposed to prenatal vitamin D deficiency demonstrate heightened locomotor activity in a novel environment (Burne et al. 2004a, 2006) and increased sensitivity to the NMDA antagonist MK-801 and the dopamine D2 receptor antagonist haloperidol (Kesby et al. 2006). Deficits in PPI are observed when the prenatal vitamin D deficiency is continued through the tenth postnatal week, but not when exposed in utero only (Burne et al. 2004b). Regarding cognitive tasks, rats exposed to prenatal vitamin D deficiency show impaired habituation in the hole board but no differences in spatial learning in the radial arm maze or active avoidance learning in the shuttle box (Becker et al. 2005). The normal learning abilities are not surprising, considering the reported increase in LTP (Grecksch et al. 2009). Although most studies produce vitamin D deficiency throughout gestation, there is some evidence that the detrimental effects of maternal vitamin D deficiency may be more pronounced when the deficiency occurs during the late gestational period (O'Loan et al. 2007). Initial studies of maternal vitamin D deficiency in mice suggest that while adult offspring displayed increased locomotor activity, vitamin D-deprived and control mice did not differ in PPI or social behavior (Harms et al. 2008).

3.3 Obstetric Complications

Another set of prenatal and perinatal risk factors that have been well documented are obstetric complications. As Rapoport et al. (2005) point out, the relative risk for schizophrenia-associated obstetric complications is low, with an odds ratio for the exposure

to obstetric complications increasing the risk of schizophrenia estimated at 2.0 (Rapoport et al. 2005). Nevertheless, obstetric complications have been well documented and linked to schizophrenia in several independent studies. Specifically, birth complications such as pre-eclampsia, cesarean section, and perinatal hypoxia are associated with an increased risk of schizophrenia (Cannon et al. 2002; Hultman et al. 1997; Zornberg et al. 2000). These birth complications have all been modeled in animals (reviewed in Boksa 2004; Meyer and Feldon 2009a).

3.3.1 Cesarean Section—For Cesarean section (C-section), the experimental litter is removed from the uterus and kept warm until being placed with a foster mom (El-Khodor and Boksa 1997). In rats and the more precocious species, guinea pigs, C-section is associated with heightened sensitivity to the locomotor-activating effects of amphetamine and stress, deficits in PPI, and decreased and increased dopamine in the PFC and NAC, respectively (Brake et al. 1997, 2000; El-Khodor and Boksa 1998, 2000; Juarez et al. 2005; Vaillancourt and Boksa 2000). Additionally, rats born by C-section demonstrate a postpubertal increase in dopamine D1 receptor binding and increased functional response to D1 agonists (Boksa et al. 2002).

3.3.2 Perinatal Hypoxia—Both intrauterine and neonatal hypoxia have been tested in rats, mice, and guinea pigs. Both manipulations lead to widespread effects on brain morphology and neurochemistry, specifically with decreased hippocampal volume or neuronal cell loss coupled with reduced dendritic spine density and/or elongation (reviewed in Meyer and Feldon 2009a). Intrauterine hypoxia typically involves removing the intact uterus from the dam and placing it in a 37°C water bath for a certain period of time (typically around 15 min) (El-Khodor and Boksa 1997). Hence, perinatal hypoxia manipulations in practice also involve C-section. Neonatal hypoxia involves placing a pup in a chamber without oxygen or with very low levels of oxygen (e.g., 8%) for a specified period of time (Fendt et al. 2008; Nadri et al. 2007). Some methods combine the low-oxygen environment with occlusion of the carotid artery (Rice et al. 1981). The behavioral effects of intrauterine and neonatal hypoxia are mixed (reviewed in Meyer and Feldon 2009a). Whereas the near-term intrauterine hypoxia produced deficits in PPI and working memory in guinea pigs (Becker and Donnell 1952; Vaillancourt and Boksa 2000) and impairments in spatial learning in the water maze in rats(Boksa et al. 1995), no impairments in working memory as measured by spontaneous alternation in the T maze were reported in rats (Boksa et al. 1995). Rats exposed to intrauterine hypoxia did display decreased social and exploratory behavior and increased response to stress and dopamine agonists (Brake et al. 1997; reviewed in Meyer and Feldon 2009a).

Neonatal hypoxia is associated with reference and working memory impairments in the water maze and decreased hippocampal volume (Huang et al. 2009; Pereira et al. 2007). Interestingly, environmental enrichment blocked the memory impairments and hippocampal volume reduction produced by neonatal hypoxia (Pereira et al. 2007). Depending on the timing and severity of postnatal hypoxia, differing effects on PPI have been reported. Although hypoxia at postnatal day 9 altered mesolimbic dopamine neurochemistry, it did not produce differences in PPI (Sandager-Nielsen et al. 2004). Subsequent studies using subchronic exposure to hypoxia during postnatal day 4–8 did result in PPI deficits in the adult rat (Fendt et al. 2008). These animal studies of hypoxia are useful for our understanding of perinatal complications as a risk factor as they have shown many neuroanatomical abnormalities consistent with schizophrenia. The behavioral abnormalities, on the other hand, are less consistent thus making the model less useful for pharmacological intervention studies.

3.3.3 Placental Insufficiency—Placental insufficiency is another prenatal risk factor for schizophrenia (Cannon et al. 2002) which involves loss of blood flow to the developing fetus. Placental insufficiency is achieved experimentally in guinea pigs by ligation of the uterine artery and results in decreased PPI, enlargement of the lateral ventricles, reduced volume of the basal ganglia and septum, and reduced hippocampal BDNF (Dieni and Rees 2003, 2005; Mallard et al. 1999, 2000; Rehn et al. 2004). The neuroanatomical abnormalities, without any evidence of gliosis, together with the observation of deficient PPI, suggest that placental insufficiency may have face validity for schizophrenia. However, further behavioral tests and pharmacological interventions are warranted in this model (Meyer and Feldon 2009a).

3.4 Prenatal/Postnatal Stress

There is some evidence that psychological stressors during pregnancy increase the risk for schizophrenia in offspring. This association comes from the studies examining the occurrence of schizophrenia in offspring whose mothers were exposed to a stressful experience during pregnancy (reviewed in Koenig 2006; Koenig et al. 2002). Because assessing psychological stress retrospectively is very difficult, studies have focused on discrete events for the individual (e.g., death of a relative) or periods of “stress” for an entire community (e.g., war, flood). In a retrospective study of the 5-day Nazi invasion of the Netherlands in 1940, schizophrenia risk was increased when exposed to the traumatic event during the first trimester (van Os and Selten 1998). Additionally, the risk of schizophrenia was increased in offsprings whose mothers experienced the death of a relative during the first trimester pregnancy (Khashan et al. 2008). Other studies, however, have failed to report a relationship between prenatal stress and the later development of schizophrenia. For example, there was no relationship between a deadly 1953 flood in Holland and the later development of schizophrenia in exposed offspring (Selten et al. 1999b).

3.4.1 Prenatal Stress—On the basis of the association between prenatal stress and risk for schizophrenia and the observation that maternal stress may alter the programming of the fetal brain (Weinstock 2008), consequences of prenatal stress have been evaluated for their effects on behavior and neurochemical alterations associated with schizophrenia. The effects of prenatal stress on schizophrenia-related behaviors have been mixed. Rats exposed to prenatal stress show hyperactivity in a novel environment (Son et al. 2007) and an increased sensitivity to amphetamine (reviewed in Meyer and Feldon 2009a). Pups born to dams that had been restrained three times a day for 30 min during gestational days 15–22 did not exhibit deficits in PPI or LI when tested as adults (Lehmann et al. 2000). These rats actually showed slight increases in PPI, which was normalized by the combination of prenatal stress and maternal separation. Subsequent studies, however, did show impaired LI in the offspring of dams exposed to more severe stress of repeated electric foot shock. Prenatal repeated variable stress paradigm, on the other hand, produce behavioral alterations relevant to schizophrenia in the exposed offspring (Koenig 2006). Repeated variable stress described in these studies involved exposing the pregnant rat to several different stressors including 60 min restraint stress, cold exposure (4°C) for 6 h, overnight food deprivation, overcrowding during dark phase of cycle, swim stress, and lights on for 24 h. Rats are exposed to 2–3 of these stressors each day from gestation day 14 until parturition, i.e., the third week of pregnancy. Rats exposed to repeated variable stress showed impaired social interaction (Lee et al. 2007), PPI deficits, and increased sensitivity to amphetamine challenge postpuberty (Koenig et al. 2005). Interestingly, prenatally stressed rats also showed a trend toward deficits in N40 gating (Koenig et al. 2005). Thus, repeated variable stress appears to exert more robust effects on gating measures than does prenatal restraint stress.

Cognitive deficits, on the other hand, have been well documented in offspring of dams exposed to prenatal stress. Specifically, prenatal restraint stress leads to impairments in spatial learning in the water maze in rats (Lemaire et al. 2000; Szuran et al. 2000; Wu et al. 2007; Yang et al. 2006) and guinea pigs (Kapoor et al. 2009). Prenatally stressed rats also show impaired reversal learning in the water maze (Szuran et al. 2000). Additional impairments in working memory in the radial arm maze in mice (Son et al. 2006) and in the T maze delayed alternation test in rats have been associated with prenatal stress (Gue et al. 2004). Importantly, the working memory deficits in the T maze delayed alternation task were observed in prepubertal rats. The early emergence of working memory impairments is interesting to schizophrenia models because of the observation of early development of cognitive deficits in prodromal patients (Eastvold et al. 2007). Many sex differences in the behavioral effects of prenatal stress have been reported, with prenatal stress conferring more profound cognitive disruptions in males and more affective or anxiety disturbances in females (reviewed in Meyer and Feldon 2009a; Weinstock 2008). Few pharmacological studies have been conducted in the prenatal stress model, with the exception of oxytocin reversing impairments in social interaction in the model (Lee et al. 2007). Thus, further pharmacological studies should be conducted to evaluate the predictive validity of the model.

In addition to the behavioral abnormalities, prenatal stress alters brain development. Many studies report increased HPA axis activity and corresponding decreases in glucocorticoid and mineralcorticoid receptors (Szuran et al. 2000). Hippocampal abnormalities are consistently reported in mice exposed to prenatal stress. These abnormalities include decreased neurogenesis and decreased density of granule cells in the hippocampus (Lemaire et al. 2000), decreased LTP and enhanced LTD in hippocampal CA1 region (Son et al. 2006; Yang et al. 2006), and reduced NR2A and NR2B subunits of NMDA receptor in hippocampus (Son et al. 2006). Alterations in dopamine function including increased DA turnover and alterations in DA receptors and DA transporter (reviewed in Meyer and Feldon 2009a; Son et al. 2007).

In conclusion, although the prenatal stress model was developed primarily to examine factors contributing to anxiety and depressive disorders (Weinstock 2008), many of the behavioral and neurochemical abnormalities suggest that the model may prove useful for schizophrenia research (Koenig 2006).

3.4.2 Maternal Deprivation—Stress manipulations in the early postnatal period have also been assessed for their effects on schizophrenia-related behaviors. These experiments typically involve removing the pups from the dam during the first few weeks of life for various lengths of time, with shorter periods of time (3–15 min; early handling) resulting in *decreased* HPA axis response and longer periods of time (3 h or 24 h; maternal separation, MS) resulting in *increased* HPA axis activity (Meaney et al. 1991, 1993). Although early handling (i.e., brief separations) affects neuroendocrine and anxiety-related behavior, it does not appear to affect PPI (Pryce et al. 2001). Early handling increases LI when compared to nonhandled rats (Feldon et al. 1990; Weiner et al. 1985). PPI following more prolonged periods of maternal separation in rats has also been assessed (for review see Weiss and Feldon 2001). Ellenbroek et al. (1998) showed that separation from the dam for 24 h at PND 3, 6, and 9 produced deficits in PPI on PND 69 in male and female rats of the Wistar strain (Ellenbroek and Cools 2000). Maternal separation for shorter periods of time (e.g., 1–4 h/day) did not affect PPI in rats (Finamore and Port 2000; Weiss et al. 2001) or mice (Millstein et al. 2006), but did impair acoustic startle habituation (Finamore and Port 2000). These data indicate that longer periods of maternal separation (e.g., 24 h) at one point during the preweanling period may have a greater effect on PPI than shorter, repeated separations from the mother, suggesting that a certain amount of nutritional deprivation may be

necessary to observe the effects of MS on PPI. Maternal separation does, however, result in cognitive deficits in adulthood. Specifically, MS rats display learning impairments in the water maze and the NORT (Aisa et al. 2007, 2008). These behavioral impairments are consistent with the observed alterations in hippocampal development (Huot et al. 2002) among other neurochemical and neuroanatomical differences (Holmes et al. 2005). In conclusion, MS produces cognitive impairments but does not consistently alter PPI. This observation, together with the lack of a clear epidemiological link between postnatal stress and schizophrenia, suggests that the MS model may not be a particularly useful model for schizophrenia research.

3.5 Postweaning Social Isolation

Social withdrawal and isolation are common features of schizophrenia that have received recent attention because of the role social factors play in the risk for schizophrenia and conversion to psychosis in prodromal patients (Addington et al. 2008). Indeed, social functioning, among other factors, predicts conversion to psychosis in patients at a high risk of developing psychosis (Cannon et al. 2008). Because of this observation, coupled with social factors contributing to the etiology of schizophrenia, we have categorized social isolation rearing as an epidemiological model in this review. When evaluating animal models of schizophrenia, one should consider both proximate and distal risk factors to the development of the disease. Thus far, we have discussed distal risk factors for the development of schizophrenia. Postweaning social isolation can be considered a model of a more proximal risk factor – social isolation.

Social isolation rearing of rodents is a developmental model relevant to schizophrenia that involves more subtle environmental manipulations leading to profound effects on behavior and brain development. Social isolation rearing of young rodents provides a nonpharmacologic method of inducing long-term alterations reminiscent of several symptoms seen in schizophrenia patients (Geyer et al. 1993; Powell and Geyer 2002). Rearing animals in social isolation is particularly consequential for species that rely on social contact after being weaned from the mother. Specifically, isolation rearing deprives rodents of social interactions during a developmental period in which play behavior emerges (Einon and Morgan 1977). Thus, as a consequence of social isolation, animals are deprived of stimuli critical to behavioral and neurobiological development (reviewed in Hall 1998). The lack of early social contact provides a model of the social isolation and social withdrawal which occurs early in the course of schizophrenia and predicts conversion to psychosis in patients at a high risk of developing psychosis (Cannon et al. 2008). Behavioral and neurochemical changes after isolation rearing in rats provide a nonlesion and nonpharmacological model to enhance our understanding of the developmentally linked emergence of neural and behavioral abnormalities in schizophrenia patients (Geyer et al. 1993; Powell and Geyer 2002).

3.5.1 Isolation Rearing: Neuroanatomical Abnormalities—Rats reared in social isolation exhibit profound abnormalities in behavior, drug responses, and neurochemistry compared to rats reared in social groups (Fone and Porkess 2008; Hall 1998; Powell and Geyer 2002). The most well documented set of studies are those that support isolation-reared rats as a model for dopamine hyper-reactivity associated with schizophrenia, such as (1) increased behavioral sensitivity to dopamine agonists (Bowling and Bardo 1994; Jones et al. 1990, 1992; Sahakian et al. 1975), (2) reduced responsivity to dopamine antagonists (Sahakian et al. 1977), (3) elevated basal and amphetamine-stimulated dopamine release in the NAC (Hall et al. 1998; Jones et al. 1992), and (4) elevated dopamine concentrations (Jones et al. 1992) and altered dopamine turnover (Blanc et al. 1980) in the frontal cortex. In addition to alterations in dopamine function, isolation-reared rats display abnormalities in

the hippocampus and frontal cortex. Isolation-reared rats have increased density of 5-HT_{1A} receptors in the hippocampus (Del-Bel et al. 2002; Preece et al. 2004). Synaptophysin is a synapse-specific protein involved in neuro-transmitter release and its expression is reduced within certain hippocampal sub-fields in schizophrenia (Eastwood and Harrison 1995). Varty et al. (1999) also reported reduced synaptophysin immunoreactivity in the dentate gyrus of isolation-reared rats. There is also evidence of reduced BDNF in the hippocampus (Scaccianoce et al. 2006) and decreased spine density in isolation-reared rats (Silva-Gomez et al. 2003b). More recent studies have pointed to further alterations in the hippocampus of isolation-reared rats. Loss of PV-positive GABA interneurons observed in isolation-reared rats (Harte et al. 2007; Schiavone et al. 2009) is very similar to that reported in the hippocampus and frontal cortex of schizophrenia patients (Reynolds et al. 2004; Reynolds and Beasley 2001). Isolation-reared rats show abnormalities in the PFC including (1) abnormal firing of pyramidal cells in the PFC upon dopamine stimulation from VTA neurons (Peters and O'Donnell 2005), (2) decreased volume of PFC (Day-Wilson et al. 2006; Schubert et al. 2009; Silva-Gomez et al. 2003b), and (3) decreased dendritic arborization in the PFC (Pascual et al. 2006; Silva-Gomez et al. 2003b).

3.5.2 Isolation Rearing: Behavioral Abnormalities—Rats reared in social isolation show deficits in PPI (Cilia et al. 2001, 2005; Geyer et al. 1993; Varty and Geyer 1998; Varty and Higgins 1995) and slow rates of startle habituation (for reviews, see Geyer et al. 1993, 2001; Powell and Geyer 2002; Weiss and Feldon 2001). More recent studies have also shown that several different strains of mice (e.g., ddY, 129T2, C57BL/6) exhibit deficits in PPI when reared in social isolation from weaning (Dai et al. 2004; Sakaue et al. 2003; Varty et al. 2006; see also Pietropaolo et al. 2008). Deficits in PPI produced by isolation rearing are developmentally specific in that they only appear when social isolation occurs early, during the postnatal period, and not in rats isolated as adults (Wilkinson et al. 1994). PPI deficits in isolation-reared rats can be reversed with both typical (Geyer et al. 1993; Varty and Higgins 1995) and atypical (Bakshi et al. 1998; Cilia et al. 2001; Varty and Higgins 1995; but see Barr et al. 2006) antipsychotic drugs. Thus, several investigators have shown predictive validity of the PPI deficits in the isolation-rearing model (summarized in Geyer et al. 2001). In addition to PPI deficits, isolated rats also exhibit abnormalities in motor activity. When tested in novel environments, isolated rats show elevated levels and slowed habituation of locomotor activity (Hall 1998; Jones et al. 1989, 1990; Lapiz et al. 2000; Paulus et al. 1998; Sahakian et al. 1975; Varty et al. 2000), increased investigatory behavior (e.g., rearings, holepokes; Lapiz et al. 2000; Paulus et al. 1998), and an increased preference for a novel environment (Hall et al. 1997). Additionally, isolation-reared rats and mice show increased anxiety-like behavior (Da Silva et al. 1996; Wright et al. 1991), deficits in fear learning (Voikar et al. 2005; Weiss et al. 2004), impaired recognition memory (e.g., novel object recognition; Bianchi et al. 2006; McLean et al. 2010; Voikar et al. 2005), reduced spatial memory (Ibi et al. 2008), and cognitive inflexibility as demonstrated by deficits in reversal learning (Krech et al. 1962; Schrijver et al. 2004) and extradimensional set-shifting tasks (McLean et al. 2010; Schrijver and Wurbel 2001). Thus, isolation rearing of rats and mice is associated with impaired sensorimotor gating, cognitive inflexibility, reductions in PFC volume and hippocampal synaptic plasticity, hyper-function of mesolimbic dopaminergic systems, and hypofunction of mesocortical dopamine, strikingly similar behavioral and neuroanatomical abnormalities as those observed in schizophrenia. Taken together, these results point towards the usefulness of the social isolation model in mimicking some behavioral, neurochemical, and neuropathological phenomena characteristic of schizophrenia.

Few studies have directly tested the mechanism by which isolation rearing exerts its effects on brain and behavioral development. Recently, a clear role for nicotinamide adenosine dinucleotide phosphate (NADPH) oxidase 2 (Nox2)-dependent oxidative mechanisms in the

loss of PV interneurons and development of schizophrenia-like behavior in the isolation-rearing model was demonstrated (Schiavone et al. 2009). Corroborating our earlier work (Harte et al. 2007), Schiavone et al. (2009) found decreased PV immunoreactivity in the brains of rats reared in social isolation. This loss of PV interneurons was associated with elevations in Nox2, and the decrease in PV-staining and deficits in novel object recognition were blocked by treatment with the Nox2 inhibitor apocynin (Schiavone et al. 2009). Recent studies in mice have shown reductions in the expression of two developmental genes, Nurr1 and Npas4, in mice reared in social isolation (Ibi et al. 2008).

3.5.3 Discussion of Isolation-Rearing Model—There are several advantages to the isolation-rearing model that make it an appealing preclinical model of schizophrenia. First, the isolation-rearing model has shown a high degree of predictive validity for antipsychotic drugs. Second, there is a wealth of data on the relevant behavioral and neurochemical/neuroanatomical differences associated with postweaning social isolation, and many of these findings have been reported in both rats and mice. Finally, isolation rearing is a relatively easy procedure to conduct but does require ample housing space for individual cages. There are also several disadvantages to the model. Since the insult is ongoing, it is difficult to determine the precise timing of the effects since age is confounded with duration of isolation. Thus, there is a need for more discrete manipulations of the duration of isolation (e.g., early postnatal, pubertal). Relative to most of the other models reviewed here, isolation rearing occurs rather late in development and may thus only be relevant to early childhood and pubertal insults. Like the nVH lesion model discussed below, it can also be considered as a heuristic model to guide future studies into the pathophysiology of and treatments for schizophrenia.

4 Heuristic Neurodevelopmental Models

4.1 Neonatal Ventral Hippocampal Lesion Model

One of the first and most widely studied neurodevelopmental models of schizophrenia is the neonatal ventral hippocampal lesion (nVH) model. On the basis of the observation of developmental abnormalities in the hippocampus of schizophrenia patients, attempts to model the developmental perturbation and delayed behavioral symptomatology, similar to that of schizophrenia, have been undertaken (Lipska and Weinberger 2000; Tseng et al. 2009).

4.1.1 Neonatal Ventral Hippocampal Lesion Model: Behavioral Studies—Rats with nVH lesions show increased responsiveness (e.g., hyperlocomotion, increased stereotypy) to dopamine agonists (Lipska et al. 1993; Lipska and Weinberger 1993, 1994a; Sams-Dodd et al. 1997) and NMDA antagonists (Al-Amin et al. 2000, 2001), deficits in PPI (Francois et al. 2009a; Le Pen et al. 2003; Le Pen and Moreau 2002; Lipska et al. 1995), and more recently alterations in N40 gating (Swerdlow et al. 2007; Vohs et al. 2009). The locomotor sensitivity to stimulants and PPI deficits in rats with nVH lesions exhibit a delayed temporal pattern and do not appear until postpuberty (Lipska et al. 1993, 1995; Lipska and Weinberger 1993; but see Swerdlow et al. 2007). Additionally, nVH lesions produce social and cognitive impairments, strengthening the relationship to this model and schizophrenia symptomatology (Lipska 2004). Rats with nVH lesions display decreased social interactions, which emerge prepuberty (Becker et al. 1999; Flores et al. 2005; Sams-Dodd et al. 1997), and impaired social recognition memory (Becker and Grecksch 2000).

Cognitive deficits associated with nVH lesions encompass many of the cognitive domains deficient in schizophrenia. For example, rats sustaining nVH lesions display deficits in spatial learning in the water maze and radial arm maze (Chambers et al. 1996; Le Pen et al. 2000; Silva-Gomez et al. 2003a) as well as impaired avoidance learning (Le Pen et al. 2000)

and novel object recognition. Continuous spatial delayed alternation task and discrete paired-trial variable-delay task were impaired in rats that sustained nVH lesions but not in rats sustaining adult VH lesions, lending further support to the neurodevelopmental construct validity of the nVH lesion model (Lipska et al. 2002a). Subsequent studies aimed at dissecting the relative contribution of the hippocampus and the PFC to the impairments on working memory tasks showed that nVH lesions lead to impairments in T maze delayed alternation and discrimination learning (Marquis et al. 2006). Impairments in T maze delayed alternation (Marquis et al. 2006) and in the radial arm maze (Chambers et al. 1996) were apparent at the juvenile age, suggesting early cognitive impairments in this model. Marquis et al. (2006) argue that the distinction of whether a given task is delay-dependent or not is critical to dissecting the relative contribution of mPFC and the hippocampus to working memory impairment. For example, lesions of the PFC impair performance when no delay is involved; whereas dorsal hippocampal lesions impair performance only when there are delays introduced (Winocur 1991). In several of the working memory tasks reviewed here, nVH lesions produced deficits independent of delay suggesting impaired PFC function. Additional probes of PFC function are set-shifting tasks, which probe cognitive flexibility or problem solving (Young et al. 2009). nVH lesions were associated with set-shifting deficits in the ASST (Marquis et al. 2008) and T maze set shifting (Brady 2009), with set-shifting impairments in the ASST occurring prepuberty.

Transient inactivation of the hippocampus during a critical developmental period produces many of the behavioral alterations observed in the nVH lesion model (Lipska 2004). Tetrodotoxin (TTX), which blocks voltage-gated sodium channels, infused into the VH on PND7 produced increased sensitivity to amphetamine and MK-801-induced locomotor activity in adulthood (Lipska et al. 2002b). These data suggest that the neonatal blockade during a critical period alters the development of hippocampal and related neurocircuits.

Important for the predictive validity of the nVH lesion neurodevelopmental model, some of the behavioral effects are reversed with antipsychotic drugs and putative antipsychotics. Antipsychotics blocked stress- and drug-induced hyperactivity (Al-Amin et al. 2000; Lipska and Weinberger 1994b; Rueter et al. 2004; Sams-Dodd et al. 1997) and PPI deficits (Le Pen and Moreau 2002; Rueter et al. 2004) but failed to block social impairments (Rueter et al. 2004; Sams-Dodd et al. 1997; but see Becker and Grecksch 2003) produced by nVH lesions. The nVH lesion model has also been used to test the efficacy of putative antipsychotics. For example, glycine and the glycine transporter inhibitor ORG24598 reverse PPI deficits associated with nVH lesions (Le Pen et al. 2003), and the AMPA antagonist LY293558 blocked MK-801-induced hyperactivity (Al-Amin et al. 2000). Thus, the nVH lesion model has shown predictive validity for schizophrenia pharmaco-therapy.

4.1.2 Neonatal Ventral Hippocampal Lesion Model: Neuropathological Studies

—In the outset of the model, the ventral hippocampus and subiculum were targeted because of the consistent alterations in hippocampus in schizophrenia patients and because the ventral hippocampus has important connections with the PFC and NAC (Lipska 2004). Indeed, lesions of the ventral hippocampus on PND7 result in many neuropathological changes that mirror many of the brain alterations observed in schizophrenia, particularly alterations in the PFC. O'Donnell, Tseng and colleagues have suggested that reorganization occurs within the PFC following nVH lesions (reviewed in O'Donnell et al. 2002; Tseng et al. 2009). These PFC changes are indicated by a postpubertal emergence of altered dopamine–glutamate interactions (Tseng et al. 2007; Tseng and O'Donnell 2007). The inhibitory GABA interneuron system is dysregulated in response to nVH lesion. For example, several studies have shown decreased expression of GAD67 and PV in the PFC (Francois et al. 2009a; Lipska et al. 2003). Other studies, however, did not report changes in GAD67 or PV mRNA but did report abnormal responses to D2 stimulation in these

interneurons (Tseng et al. 2008). While the development of a "noisy" circuit in the PFC may occur postpuberty, there is evidence of decreased dendritic spine densities in the PFC as early as PND36 (Marquis et al. 2008) and increased glucose metabolism as early as PND21 (Francois et al. 2009b). These changes in interneurons are supported by regional changes in $GABA_A$ receptor expression (Endo et al. 2007). Other neuroanatomical alterations include compromised neuronal function as evidenced by reduced NAA and glycogen synthase kinase-3β (GSK-3β), as well as reduced expression of BDNF mRNA, glutamate receptor GluR3, and glutamate transporter EAAC1 (reviewed in Lipska 2004).

4.1.3 Conclusions for nVH Lesion Model—While not modeling an epidemiological risk factor per se, the nVH model has proven extremely useful in preclinical animal studies of schizophrenia. Perhaps because it was one of the early neurodevelopmental models, there is a wealth of neuroanatomical and behavioral data on the model. While the cardinal measure of the nVH lesion model has been the postpubertal emergence of an increased sensitivity to amphetamine-induced locomotor activation, many other behavioral deficits are apparent including some that emerge prepuberty (e.g., social impairments, cognitive deficits). This prepubertal emergence of behavioral abnormalities may be very relevant to schizophrenia as early social and cognitive deficits continue to be recognized as symptoms occurring early in the progression of the disease. As reviewed here, the nVH lesion model has been used in preclinical drug development with some success. Additionally, changes in gene expression in PFC in the nVH lesion model may reveal new targets for schizophrenia genetic studies, thus offering a hypothesis-generating model for schizophrenia genetics (Wong et al. 2005). While there are many strengths to the nVH lesion model, there are also a few weaknesses. The procedure itself is technically challenging and often requires extra animals in the lesion group because some have to be excluded postmortem for improper placement or lack of a significant lesion. Many laboratories have, of course, successfully implemented the nVH lesion procedure as evidenced by the large number of publications on the topic. Additionally, recent advancements in MRI technology offer the ability to detect lesion size and regional extent *in vivo*, saving time and animals in a procedure that typically requires postmortem confirmation of lesion size and location (Bertrand et al. 2010). Thus, the nVH lesion model has shown face, predictive, and construct validity as an animal model of schizophrenia and is proving to be a useful tool in preclinical schizophrenia research.

4.2 Prenatal Toxin

Evidence of cytoarchitectural abnormalities in the brains of individuals with schizophrenia has led to the creation of models focused on disrupted neurogenesis (for a more complete review, see Lipska and Weinberger 2000; Lodge and Grace 2009). For example, rats exposed to the mitotic toxin methylazoxymethanol acetate (MAM) during gestation exhibit morphological abnormalities in brain regions implicated in schizophrenia (e.g., hippocampus, frontal, and entorhinal cortices; reviewed in Lodge and Grace 2009; Talamini et al. 1998, 1999) and behavioral abnormalities including deficits in PPI (Le Pen et al. 2006; Moore et al. 2006; with other reports of only modest effects, Talamini et al. 2000) and LI (Flagstad et al. 2005; Lodge et al. 2009). MAM-treated rats also show increased locomotor response to dopamine and glutamate psychostimulants (Lena et al. 2007; Moore et al. 2006) and impaired social interaction (Le Pen et al. 2006). The increased locomotor activity and PPI deficits emerged postpuberty (Le Pen et al. 2006; Moore et al. 2006). Gestational MAM also produces several cognitive deficits including impaired spatial recognition memory (Le Pen et al. 2006) and reversal learning (Flagstad et al. 2005; Moore et al. 2006). These behavioral differences produced by gestational MAM are associated with alterations in mesolimbic and mesocortical dopamine systems (Lodge and Grace 2007; Flagstad et al. 2004) and decreased PV interneuron number in the dorsolateral PFC and the hippocampus (Lodge et al. 2009; Penschuck et al. 2006). Experiments have administered MAM either

during mid-gestation (E9–12) or late gestation (E17–18), with the more consistent behavioral effects occurring at the later gestational time point.

Other disruptors of neurogenesis have been evaluated for their effects on brain and behavioral development. For example, adult-onset PPI deficits are observed from disturbing neurogenesis with the antimitotic cytosine arabinocide (Ara-C) at embryonic days 19.5 and 20.5 (Elmer et al. 2004). Additionally, neonatal exposure of rats to the NOS inhibitor (L-nitroarginine) induces locomotor hypersensitivity to amphetamine and deficits in PPI (Black et al. 1999). Thus, gestational exposure to neurotoxins can have profound effects on brain development. Regarding its use as a neurodevelopmental model of schizophrenia, the MAM model has shown a certain degree of face and construct validity. Few studies, however, have tested the ability of antipsychotics or other compounds to reverse the behavioral effects. Thus, the pharmacological predictive validity of this model is yet to be determined.

4.3 Postnatal/Neonatal NMDA Antagonists

Accumulating evidence shows that perinatal NMDA-R antagonist exposures (pNM) can produce persistent behavioral and neurochemical deficits and the loss of PV interneurons (Andersen and Pouzet 2004; du Bois et al. 2008, 2009; Nakatani-Pawlak et al. 2009; Sircar and Rudy 1998; Stefani and Moghaddam 2005; Wang et al. 2008; Wiley et al. 2003). Blockade of NMDA receptors in the postnatal period leads to a range of behavioral abnormalities relevant to schizophrenia from enhancement of exploration to impaired working memory in the delayed alternation task (reviewed in Mouri et al. 2007). Perinatal NMDA receptor antagonist exposure also leads to impairments in sensorimotor gating, spatial memory, social interaction behavior, and cognitive flexibility in adulthood (Boctor and Ferguson 2009; Broberg et al. 2008, 2009; Lei et al. 2009; Mouri et al. 2007; Secher et al. 2009; Wang et al. 2003). In addition to cognitive deficits, typical of schizophrenia, rats treated postnatally with NMDA receptor antagonists also showed higher level of fear exhibited in the elevated plus maze (Wedzony et al. 2008) and impairments in conditioned fear (Hunt 2006). A decrease in the number of PV-positive cells and spine density in the frontal cortex, NAC and hippocampus was also shown in both rats (Wang et al. 2008) and mice (Nakatani-Pawlak et al. 2009) when analyzed in adulthood. Oxidative mechanisms in this model were suggested by results showing that antioxidants can prevent the appearance of behavioral disruptions in adulthood (Wang et al. 2003).

5 Discussion

Over the last two decades, several neurodevelopmental animal models of schizophrenia have emerged to assess the pathophysiology associated with schizophrenia risk factors, the consequence of early brain insult, and the efficacy of putative antipsychotics. Many of these models reviewed here have convincingly shown face, construct, and predictive validity for schizophrenia. These models support the developmental hypothesis of schizophrenia by demonstrating similar behavioral and neuropathological abnormalities to those observed in the clinical condition. Many of these models converge on several key behavioral and neuropathological abnormalities. The two most common and consistent behavioral phenotypes are deficits in sensorimotor gating as measured by PPI and increased sensitivity to the locomotor-activating effects of amphetamine. The question is then whether these behavioral abnormalities emerge out of a common pathway or are they merely the most sensitive to multiple neurocircuit abnormalities? Increased mesolimbic dopamine activity is common to most of the models which exhibit PPI deficits and increased sensitivity to amphetamine. In addition to overactive mesolimbic dopamine, one of the most consistent findings in the models is that of decreased PV immunoreactivity in either the PFC or hippocampus, indicating abnormalities in the GABAergic inhibitory circuits that are critical to normal neuronal activity. Indeed, Behrens and Sejnowski argue that these GABA

interneurons are slow to develop and are particularly sensitive to early environmental insult, particularly oxidative stress (Behrens and Sejnowski 2009).

The recent progress in developing and characterizing neurodevelopmental models, combined with the progress in genetic models of schizophrenia (reviewed by Young et al. this text), offer a unique opportunity to study gene–environment interactions. Additionally, neurodevelopmental models also offer the ability to explore the "2-hit" model described by Keshavan et al. (Keshavan and Hogarty 1999) in which maldevelopment during two critical time periods, early brain development and then adolescence, may lead to the development of schizophrenia. While animal models offer us the ability to probe in more depth the underlying pathology associated with an early environmental manipulation, *in vivo* animal imaging techniques such as MRI are emerging as a useful tool to evaluate structural changes in brain in the developing animal. Initial studies using MRI have been applied to social isolation rearing (Schubert et al. 2009), nVHs (Bertrand et al. 2010), and prenatal PolyI:C (Li et al. 2009; Piontkewitz et al. 2009). Future neurodevelopmental studies may benefit from this approach which allows for the determination of the ontogeny of structural abnormalities produced by the developmental manipulations.

Findings from neurodevelopmental animal models may also aid in our understanding of the processes leading to the development of schizophrenia during the prodromal phase of the disease and inform the debate on prophylactic treatments aimed at thwarting the progression to psychosis (Powell et al. 2003). Hence, several exciting pharmacological intervention studies have been conducted in which both antipsychotics and antidepressants have shown efficacy as preventive treatments in several neurodevelopmental models (Meyer et al. 2008d; Piontkewitz et al. 2009; Richtand et al. 2006). Specifically, risperidone administered from PND35–56 prevented amphetamine-induced locomotor sensitivity in the nVH lesion model (Richtand et al. 2006). In the PolyI:C model, periadolescent clozapine and fluoxetine (PND35–65) blocked the emergence of schizophrenia-like behavioral profile (PPI, LI, amphetamine-induced hyperlocomotion) in mice (Meyer et al. 2008d), and adolescent (PND34–47) administration of clozapine blocked LI deficits and amphetamine-induced hyperlocomotion in PolyI:C-exposed rats (Piontkewitz et al. 2009). Interestingly, the structural abnormalities observed with prenatal PolyI:C, enlarged lateral ventricles and reduced hippocampal volume as measured by MRI, were also prevented with adolescent clozapine treatment in this same study (Piontkewitz et al. 2009). Thus, neurodevelopmental models may aid in the debate on the efficacy and safety of early preventive treatments during the prodromal phase of illness.

As alluded to in the introductory sections, there are several experimental considerations to take into account when conducting developmental studies such as these, with the two primary concerns being cross-fostering and litter effects. Cross-fostering can be done in one of two ways. One method for determining the effect of the prenatal manipulation on maternal behavior is to give dams of each treatment group litters of both control and prenatally exposed neonates. The other method would be to use control lactating surrogate dams that had not been exposed to either treatment. Indeed, there is evidence in some of the neurodevelopmental models reviewed here that the mother–pup behavioral interaction accounts for some of the observed effects (Meyer et al. 2006c, 2008b). Litter effects can pose statistical problems for the analysis because of the interdependence of individual animals from one litter. Often, the entire litter is used and each animal is treated as an independent observation in the ANOVA. In order to avoid this problem of artificially inflating the sample size, one common practice is to sample only one animal from each litter for the experimental analyses. As Zorilla (Zorrilla 1997) argues, using a representative animal from each litter (or "two-stage sampling") also poses problems for statistical analyses when the within litter variability on a given measure is high. One solution is to

average at least two pups per litter, with additional observations not necessarily adding much more power (Zorrilla 1997). Another option is to try to minimize litter effects in the design by using a stud for multiple dams assigned to different treatment groups or using inbred strains (Zorrilla 1997). One easy approach for postnatal manipulations is to randomize treatment conditions within litter. In addition to these experimental design considerations, the effect of litter can be handled somewhat at the analysis step. Covarying for litter in the ANOVA is an option, but it requires at least two littermate observations for each between-litter effect (i.e., two littermates per sex per treatment condition). Perhaps the best way to deal with litter effects is to combine the experimental design suggestions with a within litter statistical analysis in which litter is nested within the treatment condition (reviewed in Zorrilla 1997).

In conclusion, developmental models focused on epidemiological risk factors and neurodevelopmental anomalies have contributed to our understanding of the developing brain, the neuropathology of schizophrenia, and treatment approaches for this debilitating disease. Future studies in this area should continue to examine the 2-hit hypothesis of schizophrenia through the combination of genetic and environmental manipulations and early plus late environmental manipulations. The manipulations used to study secondary or “late hits” could be based on recent findings of putative risk factors that may increase the conversion to psychosis in high-risk individuals (Cannon et al. 2008), many of which occur during adolescence (e.g., social isolation, substance abuse, etc.). Lastly, these models are uniquely suited for epigenetic studies aimed at determining the mechanism by which these manipulations exert long-term effects on brain and behavioral development.

Abbreviations

ASST	Attentional set-shifting task
DA	Dopamine
GABA	Gamma-aminobutyric acid
IL-1α	Interleukin-1alpha
IL-6	Interleukin-6
LI	Latent inhibition
LPS	Lipopolysaccharide
NMDA	*N*-methyl-D-aspartate
NORT	Novel object recognition
Nox2	NADPH oxidase 2
nVH	Neonatal ventral hippocampal lesion
PCP	Phencyclidine
PFC	Prefrontal cortex
PND	Postnatal day
pNM	Perinatal NMDA antagonist
PolyI:C	Polyriboinosinic–polyribocytidilic acid
PPI	Prepulse inhibition
PV	Parvalbumin

TH Tyrosine hydroxylase

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Table 1

Overview of neurodevelopmental models

Risk factor/pathology	Rodent model	References
Epidemiological models		
Maternal infection	Prenatal viral infection	Shi et al. (2003), Fatemi et al. (1998, 2002a, b, 2004)
	Prenatal PolyI:C	Shi et al. (2003), Meyer et al. (2009)[a], Meyer and Feldon (2009b)[a]
	Prenatal LPS	Borrell et al. (2002), Romero et al. (2007, 2008), Fortier et al. (2004)
	Prenatal cytokine	Smith et al. (2007)
Neonatal infection	Neonatal viral infection	Asp et al. (2009), Rothschild et al. (1999)
	Neonatal cytokine exposure	Tohmi et al. (2004), Tsuda et al. (2006), Watanabe et al. (2004)
	Neonatal PolyI:C	Ibi et al. (2009)
	Neonatal LPS	Jenkins et al. (2009)
Prenatal stress/maternal deprivation	Prenatal restraint stress	Gue et al. (2004), Kapoor et al. (2009), Lemaire et al. (2000), Son et al. (2006), Szuran et al. (2000), Wu et al. (2007), Yang et al. (2006)
	Prenatal repeated variable stress	Koenig (2006)[a], Koenig et al. (2005), Lee et al. (2007)
	Postnatal maternal deprivation	Ellenbroek et al. (1998), Ellenbroek and Cools (2000)
Obstetric complications	Cesarean section	Brake et al. (1997, 2000), El-Khodor and Boksa (1998, 2000), Juarez et al. (2005), Vaillancourt and Boksa (2000)
	Hypoxia/anoxia	El-Khodor and Boksa (1997), Huang et al. (2009), Pereira et al. (2007), Sandager- Nielsen et al. (2004), Fendt et al. (2008)
	Placental insufficiency	Dieni and Rees (2003, 2005), Mallard et al. (1999), Rehn et al. (2004)
Nutritional deficiency	Prenatal protein deprivation	Palmer et al. (2004, 2008), Tonkiss et al. (1998), Ranade et al. (2008)
	Vitamin D deficiency	Eyles et al. (2009)[a], Burne et al. (2004a, b), O'Loan et al. (2007)
Social isolation	Postweaning social isolation rearing	Fone and Porkess (2008)[a], McLean et al. (2010), Powell and Geyer (2002)[a], Schiavone et al. (2009)
Heuristic models		
Developmental hippocampal pathology	Neonatal ventral hippocampal lesion	Bertrand et al. (2010), Lipska and Weinberger (2000)[a], Tseng et al. (2009)[a]
Disruption in neuronal migration	Prenatal MAM	Le Pen et al. (2006), Lodge and Grace (2009)[a], Moore et al. (2006)
Disruption in perinatal brain development	Neonatal NMDA antagonist	du Bois et al. (2008), Mouri et al. (2007)[a], Nakatani-Pawlak et al. (2009), Wang et al. (2008)

[a]Indicates review article; refer to the text for a more complete overview of the models