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Prenatal exposure to infection: a primary mechanism for abnormal dopaminergic development in schizophrenia

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Abstract

Rationale Prenatal exposure to infection is a notable environmental risk factor in the development of schizophrenia. One prevalent hypothesis suggests that infection-induced disruption of early prenatal brain development predisposes the organism to long-lasting structural and functional brain abnormalities. Many of the prenatal infection-induced functional brain abnormalities appear to be closely associated with imbalances in the mesocorticolimbic dopamine system in adult life, suggesting that disruption of functional and structural dopaminergic development may be at the core of the developmental neuropathology associated with psychosis-related abnormalities induced by prenatal exposure to infection.

Objectives In this review, we integrate recent findings derived from experimental models in animals with parallel research in humans which supports this hypothesis. We thereby highlight the developmental perspective of abnormal DA functions following in-utero exposure to infection in relation to the developmental and maturational mechanisms potentially involved in schizophrenia.

Results Experimental investigations show that early prenatal immune challenge can lead to the emergence of early structural and functional alterations in the mesocorticolimbic DA system, long before the onset of the full spectrum of psychosis-associated behavioral and cognitive abnormalities in adulthood.

Conclusions Dopaminergic mal-development in general, and following prenatal immune activation in particular, may represent a primary etiopathological mechanism in the

development of schizophrenia and related disorders. This hypothesis differs from the view that dopaminergic abnormalities in schizophrenia may be secondary to abnormalities in other brain structures and/or neurotransmitter systems. The existence of primary dopaminergic mechanisms may have important implications for the identification and early treatment of individuals prodromally symptomatic for schizophrenia.

Keywords Animal model · Cytokines · Dopamine · Limbic system · Neurodevelopment · NMDA · Prefrontal cortex · Prodromal · Psychosis · Striatum

Introduction

Schizophrenia is a major form of psychotic disorder that affects approximately 1% of the population worldwide (Tamminga and Holcomb 2005; Ross et al. 2006). It is characterized by profound disturbances in mental functions, emotions, and behavior. Multiple lines of evidence suggest that this disabling brain disorder is of neurodevelopmental origin, in which the primary cerebral insult or pathological process occurs during early brain development, long before the illness is clinically manifest (Weinberger 1987; Murray et al. 1992; Rapoport et al. 2005). According to this hypothesis, an interaction between early neurodevelopmental disturbances and peri-adolescent brain maturation seems to be necessary in order to trigger the onset of full-blown psychotic behavior, which typically emerges during adolescence or early adulthood. A recent refinement of this hypothesis emphasizes the progressive nature of the changes which occur during and subsequent to the onset of full-blown psychosis (Pantelis et al. 2005a, b; Wood et al. 2008).

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It has long been recognized that schizophrenia is a heritable disorder that probably involves multiple genes with relatively modest effects across large populations (Harrison and Weinberger 2005; Ross et al. 2005). At least some of the early neurodevelopmental disturbances may be accounted for by abnormal expression of genes that are essential for early neurodevelopmental processes. Indeed, many of the recently identified susceptibility genes are known to have essential functions in early neurodevelopment, including neuronal differentiation, survival, synaptogenesis, and apoptosis (Harrison and Weinberger 2005; Ross et al. 2005). Besides genetic etiopathological contributions, various environmental factors can increase the risk of schizophrenia and other psychosis-related disorders (McDonald and Murray 2000; Dean and Murray 2005; Opler and Susser 2005). Many of these factors operate at prenatal or early postnatal stages of life, that is, during the critical periods of early central nervous system (CNS) development. Environmental insults targeting early brain development may thus bring additional risk towards altering neurodevelopmental trajectories and long-term brain functions relevant to schizophrenia.

Maternal infection during pregnancy is one of the known environmental factors that can significantly increase the risk of schizophrenia and related disorders in the offspring (for recent reviews, see Brown and Susser 2002; Fatemi 2005; Brown 2006; Patterson 2007; Boksa 2008). A large body of epidemiological data has provided compelling evidence for enhanced risk of schizophrenia following prenatal exposure to infection with various viral pathogens, including influenza (Mednick et al. 1988; Brown et al. 2004), rubella (Brown et al. 2001), toxoplasma gondii (Brown et al. 2005; Mortensen et al. 2007), measles (Torrey et al. 1988), polio (Suvisaari et al. 1999), herpes simplex (Buka et al. 2001), as well as infection with bacterial pathogens (Sørensen et al. 2008) and genital and/or reproductive infections (Babulas et al. 2006). Considering the wide variety of infectious agents involved, it has been suggested that factors common to the immune response to a multitude of pathogens may be the critical mediators of the association between prenatal infection and enhanced risk of schizophrenia. As discussed in detail elsewhere (Gilmore and Jarskog 1997; Ashdown et al. 2006; Meyer et al. 2007, 2008a), abnormal expression of pro-inflammatory cytokines and other mediators of inflammation in the maternal host and eventually in the fetal brain may interfere with normal fetal brain development. This early inflammatory insult may predispose the offspring to long-lasting changes in subsequent brain and behavioral development and ultimately lead to adult neuropathology and associated psychosis-related behavior in adolescence or early adulthood. However, there are several alternative (but not mutually exclusive) mechanisms whereby prenatal exposure to infection can bring about changes in brain and behavioral development (Fatemi 2005; Meyer et al. 2008a).

These include infection-induced stimulation of maternal/fetal stress response systems (Welberg and Seckl 2001; Koenig et al. 2002), placental insufficiency (Patterson 2007) and maternal/fetal nutritional deprivation (Brown et al. 1996; Brown and Susser 2008; Susser et al. 2008), as well as penetration of viral pathogens and/or antibodies to the fetal brain (Whitley and Stagno 1997; Aronsson et al. 2002).

Hence, there are several plausible mechanisms through which maternal infection during pregnancy can induce an immunological lesion to the developing fetal brain. Given that the immuno-precipitated brain lesion takes place early in development, it can be expected that this leads to wide-ranging neurodevelopmental sequelae and to multiple structural and functional brain abnormalities in adult life. Numerous experimental models of prenatal immune activation in rats and mice provide direct support for this hypothesis by demonstrating a wide spectrum of behavioral, pharmacological, neuroanatomical, and neurochemical changes in adult offspring born to immune-challenged mothers (for recent reviews, see Nawa and Takei 2006; Sullivan et al. 2006; Meyer et al. 2007, 2008a; Meyer and Feldon 2009). Importantly, many of the functional deficits induced by prenatal immune challenge in rats and mice are implicated in some of the most critical phenotypic symptoms of schizophrenia (Table 1). Furthermore, some of the behavioral and cognitive deficits induced by in-utero immune challenge in rats and mice can be normalized by acute and/or chronic antipsychotic drug treatment in the adult offspring (Borrell et al. 2002; Shi et al. 2003; Zuckerman et al. 2003; Zuckerman and Weiner 2005; Ozawa et al. 2006; Romero et al. 2007), suggesting that the prenatal immune activation models also fulfill predictive validity for psychosis-related dysfunctions.

Combined structural and functional investigations in experimental rodent models indicate that the prenatal infection-induced functional brain abnormalities at adult age are closely associated with imbalances in the mesolimbic and/or mesocortical dopamine (DA) system (Table 1). Abnormalities in these neurotransmitter systems are known to be critically involved in the pathophysiology of schizophrenia and related psychotic disorders (see below). Hence, disruption of dopaminergic development may be at the core of the developmental neuropathology associated with psychosis-related dysfunctions induced by prenatal exposure to infection. In this review, we integrate findings derived from experimental models in animals and parallel research in humans supporting this hypothesis. We first provide a brief overview of the development and neuroanatomy of the mesocorticolimbic DA system and its interconnected brain structures, and summarize the role of altered DA functions in schizophrenia. Next, we review experimental findings showing that prenatal immune activation can lead to long-lasting neuroanatomical and

Table 1 A sample of behavioral, cognitive, and pharmacological phenotypes disrupted by prenatal exposure to infection

Immunogen	Species	Gestation period	Schizophrenia-related functional abnormalities in adult offspring exposed to prenatal immune challenge			
			Prepulse inhibition	Latent inhibition	Sensitivity to AMPH	Working memory
Influenza virus	Mouse	Early/middle	↓	ND	ND	ND
PolyI:C	Mouse	Early/middle	↓	↓	↑	(↓)
	Mouse	Middle → late	↓	ND	↑	↓
	Mouse	Late	–	–	↑	↓
	Rat	Middle/late	↓	↓	↑	ND
	Rat	Early → late	↓	ND	↑	ND
LPS	Rat	Middle	↓	ND	ND	ND
	Rat	Late	↓	ND	↑	ND
	Rat	Middle	↓	ND	ND	ND
Turpentine	Rat	Middle	↓	ND	ND	ND
IL-6	Mouse	Early/middle	↓	↓	ND	ND
	Rat	Early → middle	↓	↓	ND	(↓)
	Rat	Middle → late	ND	ND	ND	↓
Involvement of mesolimbic DA system			++	+++	+++	+
Involvement of mesocortical DA system			++	-/+	+	+++

The table summarizes current animal models demonstrating schizophrenia-related long-term abnormalities emerging following prenatal exposure to various immunostimulatory agents, including human influenza virus, polyriboinosinic–polyribocytidilic acid (PolyI:C), lipopolysaccharide (LPS), turpentine, and interleukin-6 (IL-6). The table specifies the precise timing of the prenatal maternal 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. Arrows in brackets denote that only modest changes are induced by the prenatal immunological manipulation. The hyphens indicate that no significant changes were detected relative to the corresponding control treatment. The table also highlights the relative contribution of dopaminergic imbalances in the mesolimbic and/or mesocortical dopamine (DA) system to each of the listed phenotypic abnormalities: -/+, weak contribution; +, moderate contribution; ++, substantial contribution; +++, strong contribution. *AMPH* amphetamine, *ND* not determined

neurochemical changes in the mesocorticolimbic DA system, and discuss the dopamine-associated neural substrates of psychosis-related behavioral, cognitive, and pharmacological disturbances induced by prenatal immune challenge. Finally, we highlight the developmental perspective of abnormal DA functions following in-utero exposure to infection in relation to the developmental and maturational mechanisms potentially involved in schizophrenia, and speculate on the possibility that infection-induced mal-development of the mesocorticolimbic DA system may be primary to dysfunctions in other cortical and subcortical brain areas and/or neurotransmitter systems implicated in this disorder.

Anatomy and development of the mesocorticolimbic DA system

In the adult mammalian brain, the vast majority of dopaminergic cell bodies are located in discrete mesencephalic structures, namely, the substantia nigra (SN) and the ventral tegmental area (VTA). Dopaminergic cell bodies of the VTA project to the medial and ventral parts of the caudate putamen, nucleus accumbens, hippocampus, and amygdala. These projections form the mesolimbic DA

system. On the other hand, dopaminergic projections from the VTA to cortical structures, including medial and dorsolateral parts of the prefrontal cortex (PFC) and temporal, parietal, and occipital cortices, give rise to the mesocortical DA pathways. It is well known that both the mesolimbic and mesocortical DA systems play crucial roles in the regulation and modulation of cognitive, attentional, emotional, and reward-related behaviors (reviewed in Spanagel and Weiss 1999; Nieoullon 2002; Pezze and Feldon 2004). Dopaminergic cell bodies located in the SN project primarily to dorsolateral and dorsomedial parts of the caudate putamen, representing the mesostriatal dopaminergic pathway. Integrated in a complex network that includes other subthalamic and cortical areas, the mesostriatal DA system is fundamental to the control of voluntary movements and body posture (Groenewegen 2003). A detailed review of the neuroanatomy and pharmacology of the mesolimbic, mesocortical, and mesostriatal DA pathways can be found elsewhere (Joel and Weiner 2000; Tzschentke 2001; Van den Heuvel and Pasterkamp 2008).

Mesencephalic DA neurons arise from a common set of precursor cells early in fetal development. In mice, proliferation of dopaminergic progenitor cells starts

around gestation day (GD) 9.5–10.5 within the caudal region of the developing mesencephalon and peaks between GD 12 and 13 (Bayer et al. 1995; Marti et al. 2002). Subsequently, genesis of DA neurons declines. These cells then migrate to the rostral part of the mesencephalon during which they continue to develop as their axons and dendrites form and consolidate connections with their targets (GD 14 through early postnatal life) (Riddle and Pollock 2003; Sillitoe and Vogel 2008). In rats, the same developmental phases occur approximately 2 days later (Altman and Bayer 1981; Voorn et al. 1988). DA synthesizing neurons in the human fetal brain are also established very early in development, namely, at around 5 weeks post-conception (Pickel et al. 1980; Brana et al. 1996; Aubert et al. 1997). Hence, the cascade of developmental events that leads to the establishment of the mesocorticolimbic and mesostriatal DA systems starts early in fetal life. In most mammalian species, including humans, monkeys, and rodents, the central DA system also undergoes significant development and maturation in the postnatal period. As reviewed elsewhere (Riddle and Pollock 2003; Burbach and Smidt 2006; Smidt and Burbach 2007; Van den Heuvel and Pasterkamp 2008), this includes target selection and collateralization of DA neurons into the targeted areas as well as pruning and the programmed cell death of DA innervations.

Altered DA functions in schizophrenia

It has long been recognized that abnormalities in the central DA system play a major role in the pathophysiology of schizophrenia and psychosis-related behavior (for a recent review, see Goto and Grace 2007; Guillin et al. 2007; Howes et al. 2007). The original formulation of the DA hypothesis of schizophrenia was based on evidence that the therapeutically effective antipsychotic drugs act, at least in part, by blocking DA receptors, especially the DA D2 receptor (D2R) subclass (Van Rossum 1966; Carlsson 1974; Meltzer and Stahl 1976; Snyder 1976; Seeman 1987, 2006). Further support for this hypothesis has been yielded by the findings that DA-stimulating drugs can induce psychosis-like behavior in non-psychotic human subjects (Angrist and Gershon 1970; Gardner and Connell 1972; Bell 1973) and aggravate the symptoms in patients with schizophrenia (Lieberman et al. 1987; Laruelle et al. 1999). This has led to the original hypothesis that the psychotic symptoms in schizophrenia are associated with a hyperdopaminergic state, especially in mesolimbic structures, and that normalizing enhanced mesolimbic DA activity by DA-receptor blocking agents is critical for the therapeutic efficacy of antipsychotic drugs.

Subsequently, the putative impact of a hypofunctioning cortical DA system has been incorporated into the theories of altered DA functions in schizophrenia. According to the revised DA hypothesis of schizophrenia, the central DA system in this disorder may be characterized by an imbalance between subcortical and cortical DA systems. More specifically, it has been suggested that the subcortical mesolimbic DA system may be hyperactive whilst mesocortical DA projections to the PFC may be hypoactive (Carlsson et al. 2001; Abi-Dargham and Moore 2003; Laruelle et al. 2003; Winterer and Weinberger 2004; Goto and Grace 2007; Guillin et al. 2007; Jarskog et al. 2007). The former abnormalities may be involved in the precipitation of positive symptoms such as hallucinations, delusions, and paranoia, whereas the latter deficits may critically underlie the emergence of negative and cognitive symptoms such as social withdrawal, anhedonia, and impairments in executive functions and working memory.

Prenatal infection: an environmental link to long-term abnormalities in mesocorticolimbic DA functions relevant to schizophrenia

In-vivo animal models of prenatal immune activation are indispensable experimental tools to test the hypothesis of causality and biological plausibility of the human epidemiological association between prenatal exposure to infection and enhanced risk of schizophrenia-related disorders. They also provide unique opportunities to explore the underlying neuroimmunological and neuropathological mechanisms. Considering the critical role of the mesocorticolimbic DA system in the pathophysiology of schizophrenia, several experimental investigations in rats and mice have explored whether prenatal immune challenge may cause long-term changes in this neurotransmitter system.

The first direct experimental evidence for prenatal infection-induced alterations in the mesolimbic DA system has been provided by the studies of Borrell and colleagues, who have used a chronic prenatal immune activation model in rats (Borrell et al. 2002; Romero et al. 2007, 2008). In this model, pregnant rats are exposed to the bacterial endotoxin lipopolysaccharide (LPS) throughout gestation, and the brain and behavioral effects of the prenatal immunological manipulation are then compared to corresponding control treatment. LPS is recognized by a specific class of pathogen recognition receptors referred to as toll-like receptor (TLR) 2 and 4 (Triantafilou and Triantafilou 2002). Upon binding to these TLRs, LPS stimulates the production and release of many pro-inflammatory cytokines, including interleukin (IL)-1 β , IL-6, and tumor necrosis factor (TNF)- α (e.g., Kimura et al. 1994; Ashdown et al. 2006). Hence, administration of LPS to mammalian species mimics the

innate immune response that is typically seen after infection with Gram-negative bacteria (Triantafilou and Triantafilou 2002).

Using the prenatal LPS model in rats, Borrell and colleagues have shown that chronic activation of the maternal immune system increases the immunoreactivity (IR) of tyrosine hydroxylase (TH) in the nucleus accumbens (NAc) of the adult offspring, especially in the NAc shell subregion (Borrell et al. 2002). TH is the rate-limiting enzyme of DA (and noradrenaline) synthesis *in vivo*, and it can therefore be used as a pre-synaptic dopaminergic marker (Bacopoulos and Bhatnagar 1977). The increase in NAc TH-IR in adult rats prenatally exposed to LPS is paralleled by enhanced basal levels of DA in this brain area as well as by increased levels of the DA metabolite dihydroxyphenylacetic acid (DOPAC) in more dorsal parts of the striatum (Romero et al. 2007, 2008).

A causal link between prenatal immune challenge and the emergence of long-term abnormalities in the mesocorticolimbic DA system has also been found in experimental rodent models that are based on prenatal treatment with the viral mimic polyriboinosinic–polyribocytidilic acid (PolyI:C). PolyI:C is a synthetic analogue of virus-specific double-stranded RNA, which is recognized by the pathogen recognition receptor TLR3 (Alexopoulou et al. 2001; Takeuchi and Akira 2007). In addition to stimulating pro-inflammatory cytokine responses, PolyI:C is a potent inducer of the type I interferons IFN- α and IFN- β . Administration of PolyI:C to mammalian species can thus be used to mimic the acute phase response to viral infection (Fortier et al. 2004b; Traynor et al. 2004; Cunningham et al. 2007).

Consistent with the findings in the LPS model in rats (Borrell et al. 2002), acute prenatal treatment with the viral mimic PolyI:C in early/middle gestation (GD 9) in mice leads to enhanced TH-IR in the NAc at adult age (Meyer et al. 2008c). Importantly, the implementation of neonatal cross-fostering procedures in this model suggests that the effects of prenatal immune activation on altered accumbal TH expression are attributable to prenatal but not postnatal maternal effects on the offspring. This is because enhanced accumbal TH-IR was found in prenatally PolyI:C-treated offspring regardless of whether they were raised by surrogate mothers, which had experienced PolyI:C treatment during pregnancy, or whether they were adopted by sham-treated control surrogate mothers (Meyer et al. 2008c). The prenatal PolyI:C-induced effects on accumbal TH expression are paralleled by a marked increase in the basal levels of the DA metabolite homovanillic acid (HVA) in the NAc, but not by altered accumbal DA levels or its metabolite DOPAC (Winter et al. 2008). The null effect of acute prenatal PolyI:C treatment on basal striatal DA levels in mice corroborates the findings by Zuckerman et al. (2003), who have demonstrated that a single exposure to

PolyI:C in middle/late gestation (GD 15) in rats does not affect basal striatal DA release *in vitro* but leads to enhanced striatal DA release only following KCl-induced stimulation. DA-related abnormalities have also been detected in adult mice following sub-chronic treatment with the viral mimic PolyI:C on six consecutive days from GDs 12 to 17 (Ozawa et al. 2006). This prenatal immunological manipulation has been shown to result in a striatal dopaminergic hyperfunction at adult age, which manifests itself in increased striatal DA turnover (as indexed by the DOPAC+HVA/DA ratio) and decreased receptor binding of DA D2-like receptors in striatal regions.

In addition to abnormalities in the accumbal DA system, experimental studies using the PolyI:C model in mice have provided evidence that prenatal immune challenge can lead to long-lasting changes in the prefrontal cortical DA system. Post-mortem immunohistochemical investigations have revealed a significant decrease in the expression of D1R and D2R in the PFC of adult mice born to PolyI:C-treated mothers compared with offspring born to control mothers (Meyer et al. 2008c, d). Again, cross-fostering procedures in this model have verified the prenatal nature of these DA-related deficits in the PFC (see Meyer et al. 2008c). At the neurochemical level, prenatal PolyI:C-induced immune challenge has been shown to significantly increase the basal levels of DA in prefrontal cortical areas (Winter et al. 2008). One implication would therefore be that the decrease in prefrontal D1Rs and D2Rs induced by prenatal immune activation may reflect a counter-regulatory mechanism for increased basal DA levels in this brain area.

Taken together, there is considerable evidence derived from experimental models in animals that prenatal immune activation can negatively affect the normal development of the mesocorticolimbic DA system. The reported effects have clear relevance to schizophrenia, because similar neuropathological deficits have also been noted in patients suffering from this disorder. For example, there is biochemical evidence of enhanced levels of DA and its metabolites DOPAC and HVA in dorsal and ventral striatal regions (e.g., Mackay et al. 1982; Toru et al. 1982, 1988). Interestingly, the abnormal basal levels of DA and its metabolites appear to be linked to increased TH activity in these brain regions (Toru et al. 1982, 1988), similar to the effects reported in experimental models of prenatal immune challenge (Borrell et al. 2002; Meyer et al. 2008c). In addition to these pre-synaptic abnormalities, adult rats and mice exposed to prenatal immune challenge also display enhanced striatal DA release following KCl-induced stimulation (Zuckerman et al. 2003) and increased behavioral sensitivity to acute treatment with low doses of the indirect DA receptor agonist amphetamine (AMPH; see below). These dopaminergic abnormalities are suggestive of some of the most consistent pre-synaptic abnormalities observed in patients with schizophrenia, namely elevated

striatal DA release following acute AMPH challenge (Laruelle et al. 1996, 1999; Breier et al. 1997; Abi-Dargham et al. 1998) and elevated striatal DA synthesis capacity (Hietala et al. 1995, 1999; Lindstrom et al. 1999; for a recent review, see Howes et al. 2007). Furthermore, some of the DA receptor changes emerging in adult offspring born to immune-challenged mothers are also reminiscent of critical neuropathological signs in schizophrenia. For example, there is evidence from brain imaging studies that prefrontal D1Rs are reduced at least in a subgroup of schizophrenic patients, especially in those with marked negative symptoms (Okubo et al. 1997a, b; but see also Abi-Dargham et al. 2002, Abi-Dargham and Moore 2003). In addition, some studies demonstrate that receptor binding of DA D2-like receptors is decreased in the striatum of drug-free schizophrenic patients (Reynolds et al. 1980; Mackay et al. 1982; Dean et al. 2004). However, it needs to be emphasized that the findings of striatal D2R alterations in schizophrenia remain highly controversial. Indeed, in contrast to studies reporting decreased receptor binding of DA D2-like receptors in the striatum (Reynolds et al. 1980; Mackay et al. 1982; Dean et al. 2004), several studies found an increase (e.g., Crawley et al. 1986; Wong et al. 1986) or no changes (Farde et al. 1990; Martinot et al. 1990) in D2R binding in the striatum of patients with schizophrenia relative to healthy controls (for a recent review, see Howes et al. 2007).

DA-related brain and behavioral relationships in prenatal infection-induced psychotic behavior

The DA-related neuropathological changes in adult offspring born to immune-challenged rats and mice are accompanied by a wide spectrum of behavioral, cognitive, and pharmacological abnormalities implicated in psychotic disorders (for a summary, see Table 1). This includes disruption of sensorimotor gating (Borrell et al. 2002; Shi et al. 2003; Meyer et al. 2005, 2008b, d; Ozawa et al. 2006; Fortier et al. 2007; Romero et al. 2007, 2008; Smith et al. 2007; Wolff and Bilkey 2008), abnormalities in selective learning and attentional control (Zuckerman et al. 2003; Zuckerman and Weiner 2005; Meyer et al. 2005, 2006a, c, 2008b; Smith et al. 2007), enhanced sensitivity to psychostimulant drugs (Zuckerman et al. 2003; Zuckerman and Weiner 2005; Fortier et al. 2004a; Meyer et al. 2005, 2008b, c, d), as well as deficits in working memory (Meyer et al. 2005, 2008d), and reversal learning (Zuckerman and Weiner 2005; Meyer et al. 2006b). It is well known that the mesocorticolimbic DA system plays a prominent role in the expression and modulation of these neuropsychological, neurocognitive, and neurochemical functions, and disturbances within this neurotransmitter system are believed to be a critical pathophysiological mechanism for their

disruption in schizophrenic patients (Creese and Iversen 1975; Gray et al. 1991; Deutch 1992; Goldman-Rakic 1996, 1998; Swerdlow and Geyer 1998, 2001; Nieoullon 2002; Weiner 2003; Robbins 2005; Williams and Castner 2006; Goto and Grace 2008) (Table 1). For example, numerous experimental investigations in rats and mice demonstrate that manipulations leading to enhanced activity in the mesolimbic DA system, especially in the NAC, robustly disrupt sensorimotor gating in the form of prepulse inhibition (PPI) of the acoustic startle reflex and selective associative learning in the form of latent inhibition (LI) (reviewed in Koch and Schnitzler 1997; Koch 1999; Swerdlow and Geyer 1998, 2001; Moser et al. 2000; Weiner 2003). Furthermore, enhanced behavioral reactions to low doses of the dopaminergic psychostimulant drug AMPH are often suggestive of functional overactivity of mesolimbic (and especially mesoaccumbal) DA pathways (Creese and Iversen 1975; Pijnenburg et al. 1976; Weiner et al. 1996; Heidbreder and Feldon 1998). Hence, the prenatal infection-induced changes in the mesolimbic DA system may provide a plausible neuronal mechanism for some of the pathological core symptoms in adult offspring born to immune-challenged mothers. This hypothesis is further supported by the findings that pharmacological treatment with the preferential D2R blocker haloperidol is sufficient to normalize some of the prenatal infection-induced functional disturbances linked to a hyperdopaminergic state in mesolimbic structures, including disruption of sensorimotor gating and latent inhibition (Borrell et al. 2002; Zuckerman et al. 2003; Zuckerman and Weiner 2005; Romero et al. 2007).

In addition to the suggested involvement of abnormal mesolimbic DA functions, morphological and neurochemical alterations in the prefrontal DA system may also significantly contribute to some of the behavioral and cognitive disturbances in adult offspring born to immune-challenged mothers. It is known that normal working memory functions are crucially dependent on the integrity of the prefrontal cortical DA system (Goldman-Rakic 1996, 1998). Interestingly, DA signaling at D1R in the PFC exhibits an inverted U-shape relationship: Both insufficient and excessive prefrontal DA signaling can lead to working memory deficits, especially in the spatial domain (reviewed in Williams and Castner 2006). Reduced expression of prefrontal D1Rs (Meyer et al. 2008c, d), together with the concomitant changes in basal DA levels in this area (Winter et al. 2008), may thus be one of the critical neuronal substrates of working memory deficiency in prenatally immune-challenged subjects.

Altered DA-associated signaling in the PFC may also play an important contribution to the emergence of sensorimotor gating deficits in adult offspring born to immune-challenged mothers. Although the precise role of the prefrontal DA

system in the regulation and modulation of PPI still remains to be explored (Koch and Bubser 1994; Bast et al. 2002; Swerdlow et al. 2005, 2006), several findings from previous experimentation in rodents can be taken as additional support for this hypothesis: Pharmacological blockade of D1Rs in the PFC significantly attenuates PPI in rats, indicating that impaired prefrontal D1R-mediated signaling can lead to sensorimotor gating deficiency (Ellenbroek et al. 1996; Shoemaker et al. 2005). Furthermore, selective enhancement of dopaminergic activity in the PFC by micro-infusion of the direct dopamine receptor agonist apomorphine has been shown to disrupt PPI in rats (Broersen et al. 1999; Lacroix et al. 2000). Interestingly, this effect is enhanced by simultaneous blockade of D1Rs in the PFC (de Jong and van den Buuse 2006). The concomitant reduction in prefrontal D1Rs (Meyer et al. 2008c, d) and increase in basal DA levels (Winter et al. 2008) may thus provide an additional neural basis for sensorimotor gating dysfunctions in adult offspring born to immune-challenged mothers.

Developmental perspective of abnormal DA functions following prenatal immune challenge

The onset of full-blown psychopathological symptoms in schizophrenia typically occurs in adolescence or early adulthood (Weinberger 1987; Rapoport et al. 2005; Tamminga and Holcomb 2005). One prevalent hypothesis suggests that this maturational dependency is related to the functional maturation of intracortical connectivity, especially within prefrontal–temporolimbic cortical pathways (Weinberger 1987; Weinberger and Lipska 2005; Keshavan and Hogarty 1999). Early developmental defects of the temporolimbic cortex and its connectivity may subsequently affect mesolimbic DA functions and induce DA-dependent psychotic abnormalities (Weinberger 1987; Weinberger and Lipska 2005). However, prior to adult life, the impact of developmental lesions to the temporolimbic system on behavioral functions may be compensable, partly because dysfunctions of the subcortical neural circuits affected by the lesion do not critically disrupt dopaminergic functions. This further implies that subcortical dopaminergic systems come under more extensive control as intracortical neural circuitries mature, so that dysfunctions of this circuitry will have a greater influence on dopaminergic activity after it has reached the critical developmental stage after puberty (Weinberger 1987; Weinberger and Lipska 2005; Keshavan and Hogarty 1999). Taken together, enhanced mesolimbic (especially striatal) dopaminergic activity as seen in schizophrenic patients may be induced by early developmental defects of (non-dopaminergic) prefrontal–temporolimbic cortical pathways and may thus emerge secondarily to disturbances in other brain regions, particularly in prefrontal

(Feinberg 1982; Weinberger 1987; Deutsch 1992; Weinberger and Lipska 2005; Laruelle et al. 2003; Grace 2004) and/or hippocampal (Weiner 1990; Gray et al. 1991, Gray 1998; Grace 2000; Velakoulis et al. 2000; Phillips et al. 2006) structures (see Fig. 1a). Experimental studies in rats support this hypothesis by showing that early disruption of prefrontal–temporolimbic cortical pathways by neonatal lesion of the ventral hippocampus leads to the post-pubertal emergence of numerous DA-associated behavioral and neurochemical abnormalities implicated in schizophrenia (reviewed in Lipska and Weinberger 2000; Lipska 2004). Subsequent theories have further refined this hypothesis by emphasizing the potential contribution of a hypoglutamatergic state to mesolimbic and mesocortical DA imbalances. More specifically, it has been suggested that the critical DA abnormalities in schizophrenia (i.e., striatal excess and cortical deficiency of DA) might be secondary to hypofunctions of glutamatergic signaling at *N*-methyl-D-aspartate (NMDA) receptors in the PFC (for a review, see Carlsson et al. 2001; Laruelle et al. 2003).

Consistent with the post-pubertal onset of full-blown psychotic behavior in schizophrenia, most of the psychosis-related functional brain effects of prenatal immune challenge appear to be dependent on post-pubertal maturational processes. Experimental investigations in rats and mice show that various DA-related behavioral, cognitive, and pharmacological abnormalities induced by prenatal exposure

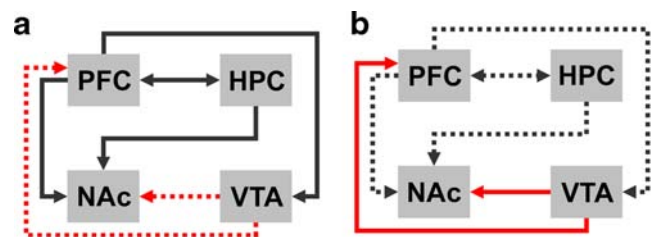


Fig. 1 Primary versus secondary neuronal contributions to mesocorticolimbic dopamine dysfunctions in psychosis-related disorders. Primary and secondary mechanisms are represented in *solid* and *dashed lines*, respectively. **a** Abnormalities in the mesoaccumbal (VTA → NAc) and mesocortical (VTA → PFC) dopamine systems (highlighted in *red*) may be secondary to dysfunctions in other neurotransmitter systems and/or brain areas. According to this model, the primary mechanisms for imbalances in the mesocorticolimbic dopamine systems involve diminished inhibitory control of the VTA and/or NAc from PFC and/or HPC (for a detailed discussion, see Carlsson et al. 2001 and Laruelle et al. 2003). **b** Alternatively, abnormalities in the mesoaccumbal and mesocortical dopamine systems may stem from primary developmental defects and may thus exist prior to alterations in other neurotransmitter systems and/or brain areas. Primary defects in the mesocorticolimbic dopamine system may induce subsequent changes in PFC and/or HPC structure and function, which in turn may further modulate the activity of mesoaccumbal and mesocortical dopaminergic functions. Primary defects in the mesocorticolimbic dopamine may arise from neurodevelopmental defects associated with (but not limited to) prenatal exposure to infection during early stages of fetal life. *HPC*, hippocampus; *NAc*, nucleus accumbens; *PFC*, prefrontal cortex; *VTA*, ventral tegmental area

to the viral mimic PolyI:C, or the bacterial endotoxin LPS, only emerge at post-pubertal but not juvenile or pre-pubertal stages of life (Zuckerman et al. 2003; Zuckerman and Weiner 2003; Meyer et al. 2006c, 2008c; Ozawa et al. 2006; Romero et al. 2008). In keeping with the developmental mechanisms outlined above, one possible explanation for this delayed onset of symptoms would be that the underlying mesocorticolimbic DA disturbances are only secondary to maturation-dependent dysfunctions in other brain regions and/or neurotransmitter systems. According to this interpretation, maternal infection during pregnancy would not directly affect the development and functioning of the offspring's DA system, but would lead instead to a developmental disruption of other neurotransmitter systems, which would then trigger subsequent functional imbalances in the mesocorticolimbic DA system and precipitate DA-associated psychotic disturbances in adulthood.

Contrary to this suggestion, however, several experimental investigations in rats and mice highlight that at least some of the prenatal infection-induced brain and behavioral abnormalities may stem from primary developmental defects of the mesocorticolimbic DA system (see Fig. 1b). The first line of evidence is derived from the recent findings that prenatal immune challenge can lead to enhanced behavioral sensitivity to acute dopaminergic stimulation by AMPH treatment already at the pre-pubertal stage of development (Meyer et al. 2008c), provided that prenatal immunological insult takes place during early fetal development (for a comparison in mice, see Ozawa et al. 2006 and Meyer et al. 2008c; for rats, see Zuckerman et al. 2003). Hence, distinct forms of schizophrenia-related psychopathology are manifested at different stages of postnatal development after early prenatal exposure to immune challenge in mice: Whilst abnormal selective associative learning (Meyer et al. 2006c), disrupted sensorimotor gating (Meyer, Vuillermot, Feldon; unpublished observation), and enhanced responding to acute NMDA-receptor antagonism by systemic dizocilpine (MK-801) treatment (Meyer et al. 2008c) only appear at adult age, early fetal brain inflammation leads to enhanced AMPH sensitivity already in pre-adolescence (Meyer et al. 2008c). Considering the known involvement of the mesolimbic (especially mesoaccumbal) DA system in mediating the behavioral effects of acute AMPH exposure (Creese and Iversen 1975; Pijnenburg et al. 1976; Weiner et al. 1996; Heidbreder and Feldon 1998), the potentiation of AMPH sensitivity emerging in pre-pubertal offspring born to gestationally immune-challenged mothers points to the existence of subcortical DA imbalances before (prefrontal) cortical structures reach maximal control over subcortical DA systems in adulthood (Feinberg 1982; Weinberger 1987; Weinberger and Lipska 2005; Keshavan and Hogarty 1999; Finlay 2001; Tsujimoto 2008). One implication is that immune activation in early fetal life may induce DA-associated endogenous

sensitization mechanisms during peri-adolescent development, which precede the onset of the full spectrum of schizophrenia-related abnormalities in adulthood. This idea is indeed central to the endogenous sensitization theory of schizophrenia, which suggests that dopaminergic transmission in psychosis-prone individuals may already function in a sensitized state before the onset of full-blown psychotic behavior (Laruelle 2000; Howes et al. 2004, 2007, 2009; Collip et al. 2008).

A second line of evidence for primary dopaminergic disturbances in the development of prenatal infection-induced, psychotic abnormalities is derived from experimental investigations designed to study the acute effects of early gestational maternal immune activation on fetal dopaminergic development: Using the PolyI:C model of prenatal immune challenge, we have recently shown that maternal immunological stimulation in early/middle pregnancy (GD 9) increases the number of mesencephalic DA neurons in the fetal VTA/SN at middle/late (GD 13) and late (GD 17) stages of prenatal development (Meyer et al. 2008e). This effect is paralleled by changes in fetal expression of several genes known to be involved in DA 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. 2008e). Notably, these findings do not provide a direct link between altered fetal dopaminergic development and the emergence of dopamine-associated structural and functional abnormalities in the postnatal period. However, these results highlight the possibility that postnatal dopaminergic abnormalities emerging after prenatal immune challenge are of developmental origin starting early in fetal life. In particular, infection-induced abnormalities in the development of fetal VTA/SN DA neurons may represent an important primary mechanism for the postnatal emergence of psychosis-related functional and structural changes associated with imbalances in the mesocorticolimbic DA system.

The feasibility and biological plausibility of primary dopaminergic mechanisms in the development of schizophrenia-related dysfunctions is also supported by several additional experimental investigations in mice. Rojas and colleagues (2007) have recently demonstrated that genetically induced reductions in the expression of the transcription factor *Nurr1* lead to adult behavioral and neurochemical dysfunctions with potential relevance to schizophrenia. At the neurochemical level, these include reduced DA turnover in striatal regions and enhanced DA turnover in the PFC; at the behavioral level, adult mice with reduced *Nurr1* expression display enhanced stress or drug-induced locomotor activity as well as deficient retention in emotional memory (Eells et al. 2002; Bäckman et al. 2003; Rojas et al. 2007). Similar findings have also been found following genetic disruption of the *Fgf receptor-1* (*Fgfr1*)

in mice (Klejbor et al. 2006). As already mentioned, both *Nurr1* and *Fgf* are critically involved in early dopaminergic development, and disruption of *Nurr1*- and/or *Fgf*-mediated signaling can lead to profound and persistent disturbances in the development of midbrain DA systems (Zetterström et al. 1997; Smits et al. 2003; Burbach and Smidt 2006; Smidt and Burbach 2007). Therefore, the identified neurochemical and behavioral abnormalities in *Nurr1*- and *FgfR1*-deficient mice (Eells et al. 2002; Bäckman et al. 2003; Klejbor et al. 2006; Rojas et al. 2007; Moore et al. 2008) provide a genetic link between primary developmental disturbances in the central DA system and the emergence of long-lasting brain and behavioral changes relevant to schizophrenia.

Another line of evidence for primary dopaminergic mechanisms in the development of psychosis-related abnormalities is obtained by the findings of Kellendonk and colleagues (2006), who have demonstrated that transient and selective overexpression of D2Rs in the striatum induces persistent abnormalities in PFC functioning. These include deficits in working memory and behavioral flexibility, increased basal DA levels and reduced DA turnover in the PFC, and altered D1R-mediated signaling in the PFC (Kellendonk et al. 2006). The great relevance of this study is that it clearly demonstrates that schizophrenia-related abnormalities involving PFC-dependent functions can emerge secondarily to changes in striatal DA receptor expression during pre- to postnatal brain development. Indeed, switching off striatal D2R overexpression in adult animals does not reverse the alterations in PFC functions, suggesting that the deficits result from early developmental but not concurrent functioning of enhanced striatal D2Rs (Kellendonk et al. 2006).

Predictions and opportunities associated with primary dopaminergic mechanisms in schizophrenia

If psychotic dysfunctions emerging at post-pubertal stages of life were indeed accounted for by primary defects in the development and/or functioning of the mesocorticolimbic DA system, then one immediate expectation would be that the onset of post-pubertal abnormalities can be prevented by appropriate interventions targeting abnormal development and/or maturation of the mesocorticolimbic DA system. Our recent experimental investigations designed to study the preventive effects of peri-adolescent pharmacological interventions in an infection-based neurodevelopmental mouse model of schizophrenia-like disorder fulfilled this expectation. We have shown that peri-adolescent treatment with the preferential D2R antagonist haloperidol is sufficient to prevent the emergence of multiple psychosis-related behavioral and pharmacological abnormalities in mice predisposed to adult brain pathology by

exposure to prenatal immune challenge (Meyer et al. 2008f). In this study (Meyer et al. 2008f), pregnant mice were exposed to PolyI:C or corresponding control treatment on GD 9, and the resulting offspring were then subjected to chronic haloperidol (or other antipsychotic or antidepressant drug) treatment during the peri-adolescent stage of development (i.e., between postnatal days 35 and 65). Adult behavioral and pharmacological functions in drug-treated PolyI:C and control offspring were then compared to corresponding offspring receiving placebo treatment during the peri-adolescent stage of development. Importantly, all the phenotypic characterization of drug- and placebo-treated offspring was conducted in a drug-free state following a drug wash-out period of 3 weeks, thus avoiding possible confounds arising from acute drug effects. We found that peri-adolescent haloperidol treatment in PolyI:C offspring was effective for the prevention of numerous abnormalities known to be associated with imbalances in the mesocorticolimbic DA system, namely deficiency in selective associative learning in the form of latent inhibition disruption and increased sensitivity to acute treatment with the indirect dopamine receptor agonist AMPH and the non-competitive NMDA-receptor antagonist MK-801 (Meyer et al. 2008f). Hence, in the absence of preventive pharmacotherapy, offspring born to PolyI:C-challenged mothers developed multiple schizophrenia-related abnormalities in adulthood, whereas PolyI:C offspring treated with haloperidol for preventive reasons did not. Even though the precise underlying molecular mechanisms remain to be elucidated, these findings indicate that the efficacy of peri-adolescent haloperidol treatment to block the emergence of prenatal PolyI:C-induced deficits in adulthood may be associated with the drugs' effects on processes occurring during peri-adolescent development of the mesocorticolimbic DA system.

Another prediction associated with the hypothesis of primary defects in the development and/or functioning of the mesocorticolimbic DA system would be that the extent and nature of the deficits may critically differ as a function of the timing of the infection-induced early brain lesion. More specifically, given that mesencephalic DA neurons forming the fetal VTA are established very early in prenatal development (see above), one would expect that primary defects in the mesocorticolimbic DA system would be more readily seen following immune activation during early stages of fetal life compared to late fetal immune challenge. Direct evidence for this possibility is still lacking. However, this expectation is not unprecedented, because the precise timing of prenatal immune challenge is known to critically determine the specificity of adult brain and behavioral dysfunctions (Meyer et al. 2006a, b, 2007, 2008d; Fortier et al. 2007; Fatemi et al. 2008).

The possible existence of primary etiopathological dopaminergic mechanisms in the development of psychosis-related abnormalities in general, and following prenatal immune activation in particular, may also have important implications for the identification of individuals at high risk for full-blown psychotic disorders. It has long been recognized that the full spectrum of psychotic symptoms in schizophrenia is preceded by a muted form of psychosis-related behavior. This early phase of the disorder is commonly referred to as the (initial) prodromal phase (McGlashan 1996; Klosterkötter et al. 2001; Lieberman et al. 2001; Cornblatt and Auther 2005). During this phase, subjects often display relatively unspecific pathological symptoms, including anxiety, depression, social withdrawal, and subtle neurocognitive deficits. Individuals prodromally symptomatic for schizophrenia also appear to suffer from attenuated forms of psychopathology typically seen in schizophrenic patients with marked positive symptoms. These include phases of hallucinations, delusions, and paranoia, which are not as frequent and/or severe as in patients with schizophrenia (McGlashan 1996; Klosterkötter et al. 2001; Lieberman et al. 2001; Cornblatt and Auther 2005). However, a relatively unknown factor is the conversion rate amongst individuals identified as being at high risk for full-blown psychosis. Based on the existing identification criteria, only 20–50% of the subjects identified as being at high risk go on to develop the full-blown psychotic disorder within 1–2 years (Yung et al. 1998, 2003; Corcoran et al. 2005).

Given that increased behavioral and neurochemical responses to acute treatment with low doses of AMPH is one of the critical pathological phenotypes associated with the positive symptoms of schizophrenia (Laruelle et al. 1996, 1999), enhanced sensitivity to acute AMPH exposure in individuals assumed to be at high risk of schizophrenia may be used as prodromal phenotype predicting the subsequent progression into full-blown psychotic disorder. Following our experimental findings (see Meyer et al. 2008c), one prediction would be that prodromal patients converting to the full-blown disorder may already display enhanced behavioral and/or neurochemical responses to acute dopaminergic stimulation by systemic AMPH treatment. This is in line with the hypothesis put forward by Howes and colleagues (2007) suggesting that the at-risk mental state existing in the prodromal phase of schizophrenia may be associated with striatal hyperdopaminergia. Howes and colleagues have recently found direct evidence for this hypothesis by showing that striatal overactivity precedes the onset of schizophrenia in individuals with prodromal psychotic symptoms (Howes et al. 2009). Furthermore, there is recent evidence indicating that individuals at high risk of psychosis display enhanced stress-induced DA release in ventral striatal regions (Soliman et al. 2008). Since stress exposure is known to stimulate dopaminergic transmission

in the mesocorticolimbic DA system in a similar way to acute AMPH treatment (Finlay and Zigmond 1997), this may additionally point to the existence of (mesocorticolimbic) dopaminergic hyperfunctions preceding the onset of full-blown psychotic disorder.

Summary and conclusions

Recent experimental investigations have provided considerable evidence that prenatal immune challenge can negatively affect normal mesocorticolimbic DA functions and lead to DA-dependent behavioral, cognitive, and pharmacological abnormalities implicated in schizophrenia. Imbalances in the mesocorticolimbic DA system appear to be among the core neuronal deficits underlying the emergence of psychosis-related symptoms following prenatal exposure to infection. Prenatal exposure to infection may thus be a significant environmental risk factor for dopaminergic dysfunctions in this disorder. This is consistent with the hypothesis that many of the developmental risk factors which increase the risk of schizophrenia appear to act by facilitating dopamine dysregulations (Di Forti et al. 2007; Murray et al. 2008).

The existence of core dysfunctions in the mesocorticolimbic DA system does not exclude the possibility that dysfunctions in other neurotransmitter systems may also significantly contribute to the emergence of psychosis-related behavior following prenatal exposure to infection. Indeed, a given behavioral trait is typically regulated by multiple interconnected brain structures, and disturbances at many sites within a complex neuronal circuitry can give rise to a similar pathological phenotype (O'Donnell and Grace 1998). Considering that infection-induced interference with early brain development can lead to abnormalities in multiple brain areas and neurotransmitter systems (reviewed in Meyer et al. 2007; Meyer and Feldon 2009), it seems unlikely that a specific pathological phenotype at the functional level is accounted for by dysfunctions in isolated brain structures. Therefore, disturbances in other neurotransmitter systems, including the GABAergic, glutamatergic, and serotonergic systems, may modulate the impact of mesocorticolimbic DA abnormalities on prenatal infection-induced psychotic disorders (for a detailed discussion, see Meyer and Feldon 2009). However, given that infection-induced abnormalities in the mesocorticolimbic DA system seem to start very early in brain development, mal-development in this neurotransmitter system may represent the primary etiopathological mechanism in the development of psychotic disorders following in-utero exposure to infection (Fig. 1b). This hypothesis differs from the view that dopaminergic abnormalities in schizophrenia may be secondary to abnormalities in other brain areas and/or

neurotransmitter systems, including deficient NMDA-mediated signaling in prefrontal and hippocampal structures (Fig. 1a).

The precise developmental mechanisms whereby primary dopamine dysregulations can lead to secondary abnormalities in other brain areas and neurotransmitter systems relevant to schizophrenia remain to be elucidated. However, one possibility would be that dopaminergic abnormalities existing during the course of postnatal brain development may alter the organism's sensitivity to environmental stimuli, including reward and stress. Such stimuli are well known to activate mesocorticolimbic DA transmission (Horger and Roth 1996; Finlay and Zigmond 1997; Spanagel and Weiss 1999; Pani et al. 2000). Primary dysfunctions in the mesocorticolimbic dopamine system may significantly alter the responsiveness to rewarding and stressful stimuli; and this may, in turn, induce secondary structural adaptations in cortical and subcortical brain areas, including hippocampus and prefrontal cortex. Indeed, as extensively reviewed elsewhere (McEwen 2001, 2007; Romeo and McEwen 2006), both hippocampus and PFC undergo stress-induced structural remodeling, which can ultimately precipitate hippocampal and prefrontal cortical dysfunctions relevant to schizophrenia and related disorders (Hains and Arnsten 2008). Hence, the hypothesis of primary dysfunctions in the mesocorticolimbic DA system may not only provide an important environmental link between prenatal exposure to infection and enhanced risk of schizophrenia but it may also explain abnormalities in other brain areas implicated in this disorder. Further investigations of the underlying cellular and molecular mechanisms are thus clearly warranted in order to verify whether the hypothesis of primary DA dysfunctions may be specific to individuals predisposed to psychotic disorders by prenatal infection or whether this may represent a general etiopathological mechanism involved in the development of schizophrenia and other psychotic disorders.

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References

- Abi-Dargham A, Moore H (2003) Prefrontal DA transmission at D1 receptors and the pathology of schizophrenia. *Neuroscientist* 9:404–416
- Abi-Dargham A, Gil R, Krystal J, Baldwin RM, Seibyl JP, Bowers M, van Dyck CH, Charney DS, Innis RB, Laruelle M (1998) Increased striatal dopamine transmission in schizophrenia: confirmation in a second cohort. *Am J Psychiatry* 155:761–767
- Abi-Dargham A, Mawlawi O, Lombardo I, Gil R, Martinez D, Huang Y, Hwang DR, Keilp J, Kochan L, Van Heertum R, Gorman JM, Laruelle M (2002) Prefrontal dopamine D1 receptors and working memory in schizophrenia. *J Neurosci* 22:3708–3719
- Alexopoulou L, Holt AC, Medzhitov R, Flavell RA (2001) Recognition of double-stranded RNA and activation of NF-kappaB by Toll-like receptor 3. *Nature* 413:732–738
- Altman J, Bayer SA (1981) Development of the brain stem in the rat. V. Thymidine-radiographic study of the time of origin of neurons in the midbrain tegmentum. *J Comp Neurol* 198:677–716
- Angrist BM, Gershon S (1970) The phenomenology of experimentally induced amphetamine psychosis—preliminary observations. *Biol Psychiatry* 2:95–107
- Aronsson F, Lannebo C, Paucar M, Brask J, Kristensson K, Karlsson H (2002) Persistence of viral RNA in the brain of offspring to mice infected with influenza A/WSN/33 virus during pregnancy. *J Neurovirol* 8:353–357
- Ashdown H, Dumont Y, Ng M, Poole S, Boksa P, Luheshi GN (2006) The role of cytokines in mediating effects of prenatal infection on the fetus: implications for schizophrenia. *Mol Psychiatry* 11:47–55
- Aubert I, Brana C, Pellevoisin C, Giros B, Caille I, Carles D, Vital C, Bloch B (1997) Molecular anatomy of the development of the human substantia nigra. *J Comp Neurol* 379:72–87
- Babulas V, Factor-Litvak P, Goetz R, Schaefer CA, Brown AS (2006) Prenatal exposure to maternal genital and reproductive infections and adult schizophrenia. *Am J Psychiatry* 163:927–929
- Bäckman C, You ZB, Perlmann T, Hoffer BJ (2003) Elevated locomotor activity without altered striatal dopamine contents in *Nurr1* heterozygous mice after acute exposure to methamphetamine. *Behav Brain Res* 143:95–100
- Bacopoulos NG, Bhatnagar RK (1977) Correlation between tyrosine hydroxylase activity and catecholamine concentration or turnover in brain regions. *J Neurochem* 29:639–643
- Bast T, Pezze MA, Feldon J (2002) Dopamine receptor blockade in the rat medial prefrontal cortex reduces spontaneous and amphetamine-induced activity and does not affect prepulse inhibition. *Behav Pharmacol* 13:669–673
- Bayer SA, Wills KV, Triarhou LC, Ghetti B (1995) Time of neuron origin and gradients of neurogenesis in midbrain dopaminergic neurons in the mouse. *Exp Brain Res* 105:191–199
- Bell DS (1973) The experimental reproduction of amphetamine psychosis. *Arch Gen Psychiatry* 29:35–40
- Boksa P (2008) Maternal infection during pregnancy and schizophrenia. *J Psychiatry Neurosci* 33:183–185
- Borrell J, Vela JM, Arévalo-Martin A, Molina-Holgado E, Guaza C (2002) Prenatal immune challenge disrupts sensorimotor gating in adult rats. Implications for the etiopathogenesis of schizophrenia. *Neuropsychopharmacology* 26:204–215
- Brana C, Caille I, Pellevoisin C, Charron G, Aubert I, Caron MG, Carles D, Vital C, Bloch B (1996) Ontogeny of the striatal neurons expressing the D1 dopamine receptor in humans. *J Comp Neurol* 370:23–34
- Breier A, Su TP, Saunders R, Carson RE, Kolachana BS, de Bartolomeis A, Weinberger DR, Weisenfeld N, Malhotra AK, Eckelman WC, Pickar D (1997) Schizophrenia is associated with elevated amphetamine-induced synaptic dopamine concentrations: evidence from a novel positron emission tomography method. *Proc Natl Acad Sci U S A* 94:2569–2574
- Broersen LM, Feldon J, Weiner I (1999) Dissociative effects of apomorphine infusions into the medial prefrontal cortex of rats on latent inhibition, prepulse inhibition and amphetamine-induced locomotion. *Neuroscience* 94:39–46
- Brown AS (2006) Prenatal infection as a risk factor for schizophrenia. *Schizophr Bull* 32:200–202
- Brown AS, Susser ES (2002) In utero infection and adult schizophrenia. *Ment Retard Dev Disabil Res Rev* 8:51–57

- Brown AS, Susser ES (2008) Prenatal nutritional deficiency and risk of adult schizophrenia. *Schizophr Bull* 34:1054–1063
- Brown AS, Susser ES, Butler PD, Richardson Andrews R, Kaufmann CA, Gorman JM (1996) Neurobiological plausibility of prenatal nutritional deprivation as a risk factor for schizophrenia. *J Nerv Ment Dis* 184:71–85
- Brown AS, Cohen P, Harkavy-Friedman J, Babulas V, Malaspina D, Gorman JM, Susser ES (2001) A.E. Bennett Research Award. Prenatal rubella, premorbid abnormalities, and adult schizophrenia. *Biol Psychiatry* 49:473–486
- Brown AS, Begg MD, Gravenstein S, Schaefer CA, Wyatt RJ, Bresnahan M, Babulas VP, Susser ES (2004) Serologic evidence of prenatal influenza in the etiology of schizophrenia. *Arch Gen Psychiatry* 61:774–780
- Brown AS, Schaefer CA, Quesenberry CP Jr, Liu L, Babulas VP, Susser ES (2005) Maternal exposure to toxoplasmosis and risk of schizophrenia in adult offspring. *Am J Psychiatry* 162:767–773
- Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH (2001) Maternal infections and subsequent psychosis among offspring. *Arch Gen Psychiatry* 58:1032–1037
- Burbach JP, Smidt MP (2006) Molecular programming of stem cells into mesodiencephalic dopaminergic neurons. *Trends Neurosci* 29:601–603
- Carlsson A (1974) Antipsychotic drugs and catecholamine synapses. *J Psychiatr Res* 11:57–64
- Carlsson A, Waters N, Holm-Waters S, Tedroff J, Nilsson M, Carlsson ML (2001) Interactions between monoamines, glutamate, and GABA in schizophrenia: new evidence. *Annu Rev Pharmacol Toxicol* 41:237–260
- Collip D, Myin-Germeys I, Van Os J (2008) Does the concept of “sensitization” provide a plausible mechanism for the putative link between the environment and schizophrenia? *Schizophr Bull* 34:220–225
- Corcoran C, Malaspina D, Hercher L (2005) Prodromal interventions for schizophrenia vulnerability: the risks of being “at risk”. *Schizophr Res* 73:173–184
- Cornblatt BA, Auther AM (2005) Treating early psychosis: who, what, and when? *Dialogues Clin Neurosci* 7:39–49
- Crawley JC, Crow TJ, Johnstone EC, Oldland SR, Owen F, Owens DG, Smith T, Veall N, Zanelli GD (1986) Uptake of ⁷⁷Br-spiroperone in the striata of schizophrenic patients and controls. *Nucl Med Commun* 7:599–607
- Creese I, Iversen SD (1975) The pharmacological and anatomical substrates of the amphetamine response in the rat. *Brain Res* 83:419–436
- Cunningham C, Campion S, Teeling J, Felton L, Perry VH (2007) The sickness behavior and CNS inflammatory mediator profile induced by systemic challenge of mice with synthetic double-stranded RNA (poly I:C). *Brain Behav Immun* 21:490–502
- de Jong IE, van den Buuse M (2006) SCH 23390 in the prefrontal cortex enhances the effect of apomorphine on prepulse inhibition of rats. *Neuropharmacology* 51:438–446
- Dean K, Murray RM (2005) Environmental risk factors for psychosis. *Dialogues Clin Neurosci* 7:69–80
- Dean B, Pavey G, Scarr E, Goeringer K, Copolov DL (2004) Measurement of dopamine D2-like receptors in postmortem CNS and pituitary: differential regional changes in schizophrenia. *Life Sci* 74:3115–3131
- Deutch AY (1992) The regulation of subcortical dopamine systems by the prefrontal cortex: interactions of central dopamine systems and the pathogenesis of schizophrenia. *J Neural Transm (Suppl)* 36:61–89
- Di Forti M, Lappin JM, Murray RM (2007) Risk factors for schizophrenia—all roads lead to dopamine. *Eur Neuropsychopharmacol* 17(Suppl 2):S101–S107
- Eells JB, Lipska BK, Yeung SK, Misler JA, Nikodem VM (2002) Nurr1-null heterozygous mice have reduced mesolimbic and mesocortical dopamine levels and increased stress-induced locomotor activity. *Behav Brain Res* 136:267–275
- Ellenbroek BA, Budde S, Cools AR (1996) Prepulse inhibition and latent inhibition: the role of dopamine in the medial prefrontal cortex. *Neuroscience* 75:535–542
- Farde L, Wiesel FA, Stone-Elander S, Halldin C, Nordström AL, Hall H, Sedvall G (1990) D2 dopamine receptors in neuroleptic-naive schizophrenic patients. A positron emission tomography study with [¹¹C]raclopride. *Arch Gen Psychiatry* 47:213–219
- Fatemi SH (2005) Neuropsychiatric disorders and infection. Dunitz–Taylor & Francis, London
- Fatemi SH, Reutiman TJ, Folsom TD, Huang H, Oishi K, Mori S, Smee DF, Pearce DA, Winter C, Sohr R, Juckel G (2008) Maternal infection leads to abnormal gene regulation and brain atrophy in mouse offspring: implications for genesis of neurodevelopmental disorders. *Schizophr Res* 99:56–70
- Feinberg I (1982) Schizophrenia: caused by a fault in programmed synaptic elimination during adolescence? *J Psychiatr Res* 17:319–334
- Finlay JM (2001) Mesoprefrontal dopamine neurons and schizophrenia: role of developmental abnormalities. *Schizophr Bull* 27:431–442
- Finlay JM, Zigmond MJ (1997) The effects of stress on central dopaminergic neurons: possible clinical implications. *Neurochem Res* 22:1387–1394
- Fortier ME, Joobar R, Luheshi GN, Boksa P (2004a) Maternal exposure to bacterial endotoxin during pregnancy enhances amphetamine-induced locomotion and startle responses in adult rat offspring. *J Psychiatr Res* 38:335–345
- Fortier ME, Kent S, Ashdown H, Poole S, Boksa P, Luheshi GN (2004b) The viral mimic, polyinosinic:polycytidylic acid, induces fever in rats via an interleukin-1-dependent mechanism. *Am J Physiol Regul Integr Comp Physiol* 287:R759–R766
- Fortier ME, Luheshi GN, Boksa P (2007) 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* 181:270–277
- Gardner R, Connell PH (1972) Amphetamine and other non-opioid drug users attending a special drug dependence clinic. *Br Med J* 2:322–325
- Gilmore JH, Jarskog LF (1997) Exposure to infection and brain development: cytokines in the pathogenesis of schizophrenia. *Schizophr Res* 24:365–367
- Goldman-Rakic PS (1996) Regional and cellular fractionation of working memory. *Proc Natl Acad Sci U S A* 93:13473–13480
- Goldman-Rakic PS (1998) The cortical dopamine system: role in memory and cognition. *Adv Pharmacol* 42:707–711
- Goto Y, Grace AA (2007) The dopamine system and the pathophysiology of schizophrenia: a basic science perspective. *Int Rev Neurobiol* 78C:41–C68
- Goto Y, Grace AA (2008) Limbic and cortical information processing in the nucleus accumbens. *Trends Neurosci* 31:552–558
- Grace AA (2000) Gating of information flow within the limbic system and the pathophysiology of schizophrenia. *Brain Res Brain Res Rev* 31:330–341
- Grace AA (2004) Developmental dysregulation of the dopamine system and the pathophysiology of schizophrenia. In: Keshavan MS, Kennedy J, Murray R (eds) *Neurodevelopment and schizophrenia*, 2nd edn. Cambridge University Press, Cambridge, pp 273–294
- Gray JA (1998) Integrating schizophrenia. *Schizophr Bull* 24:249–266
- Gray JA, Feldon J, Rawlins JNP, Hemsley DR, Smith AD (1991) The neuropsychology of schizophrenia. *Behav Brain Sci* 14:1–84

- Groenewegen HJ (2003) The basal ganglia and motor control. *Neural Plast* 10:107–120
- Guillin O, Abi-Dargham A, Laruelle M (2007) Neurobiology of dopamine in schizophrenia. *Int Rev Neurobiol* 78:1–39
- Hains AB, Arnsten AF (2008) Molecular mechanisms of stress-induced prefrontal cortical impairment: implications for mental illness. *Learn Mem* 15:551–564
- Harrison PJ, Weinberger DR (2005) Schizophrenia genes, gene expression, and neuropathology: on the matter of their convergence. *Mol Psychiatry* 10:40–68
- Heidbreder C, Feldon J (1998) Amphetamine-induced neurochemical and locomotor responses are expressed differentially across the anteroposterior axis of the core and shell subterritories of the nucleus accumbens. *Synapse* 29:310–322
- Hietala J, Syvälahti E, Vuorio K, Rökköläinen V, Bergman J, Haaparanta M, Solin O, Kuoppamäki M, Kirvelä O, Ruotsalainen U et al (1995) Presynaptic dopamine function in striatum of neuroleptic-naive schizophrenic patients. *Lancet* 346:1130–1131
- Hietala J, Syvälahti E, Vilkman H, Vuorio K, Rökköläinen V, Bergman J, Haaparanta M, Solin O, Kuoppamäki M, Eronen E, Ruotsalainen U, Salokangas RK (1999) Depressive symptoms and presynaptic dopamine function in neuroleptic-naive schizophrenia. *Schizophr Res* 35:41–50
- Horger BA, Roth RH (1996) The role of mesoprefrontal dopamine neurons in stress. *Crit Rev Neurobiol* 10:395–418
- Howes OD, McDonald C, Cannon M, Arseneault L, Boydell J, Murray RM (2004) Pathways to schizophrenia: the impact of environmental factors. *Int J Neuropsychopharmacol* 7(Suppl 1): S7–S13
- Howes OD, Montgomery AJ, Asselin MC, Murray RM, Grasby PM, McGuire PK (2007) Molecular imaging studies of the striatal dopaminergic system in psychosis and predictions for the prodromal phase of psychosis. *Br J Psychiatry* 191:13–s18
- Howes OD, Montgomery AJ, Asselin MC, Murray RM, Valli I, Tabraham P, Bramon-Bosch E, Valmaggia L, Johns L, Broome M, McGuire PK, Grasby PM (2009) Elevated striatal dopamine function linked to prodromal signs of schizophrenia. *Arch Gen Psychiatry* 66:13–20
- Jarskog LF, Miyamoto S, Lieberman JA (2007) Schizophrenia: new pathological insights and therapies. *Annu Rev Med* 58:49–61
- Joel D, Weiner I (2000) The connections of the dopaminergic system with the striatum in rats and primates: an analysis with respect to the functional and compartmental organization of the striatum. *Neuroscience* 96:451–474
- Kellendonk C, Simpson EH, Polan HJ, Malleret G, Vronskaya S, Winiger V, Moore H, Kandel ER (2006) Transient and selective overexpression of dopamine D2 receptors in the striatum causes persistent abnormalities in prefrontal cortex functioning. *Neuron* 49:603–615
- Keshavan MS, Hogarty GE (1999) Brain maturational processes and delayed onset in schizophrenia. *Dev Psychopathol* 11:525–543
- Kimura M, Toth LA, Agostini H, Cady AB, Majde JA, Krueger JM (1994) Comparison of acute phase responses induced in rabbits by lipopolysaccharide and double-stranded RNA. *Am J Physiol* 267:R1596–R1605
- Klejbor I, Myers JM, Hausknecht K, Corso TD, Gambino AS, Morys J, Maher PA, Hard R, Richards J, Stachowiak EK, Stachowiak MK (2006) Fibroblast growth factor receptor signaling affects development and function of dopamine neurons—inhibition results in a schizophrenia-like syndrome in transgenic mice. *J Neurochem* 97:1243–1258
- Klosterkötter J, Hellmich M, Steinmeyer EM, Schultze-Lutter F (2001) Diagnosing schizophrenia in the initial prodromal phase. *Arch Gen Psychiatry* 58:158–164
- Koch M (1999) The neurobiology of startle. *Prog Neurobiol* 59:107–128
- Koch M, Bubser M (1994) Deficient sensorimotor gating after 6-hydroxydopamine lesion of the rat medial prefrontal cortex is reversed by haloperidol. *Eur J Neurosci* 6:1837–1845
- Koch M, Schnitzler HU (1997) The acoustic startle response in rats—circuits mediating evocation, inhibition and potentiation. *Behav Brain Res* 89:35–49
- Koenig JJ, Kirkpatrick B, Lee P (2002) Glucocorticoid hormones and early brain development in schizophrenia. *Neuropsychopharmacology* 27:309–318
- Lacroix L, Broersen LM, Feldon J, Weiner I (2000) Effects of local infusions of dopaminergic drugs into the medial prefrontal cortex of rats on latent inhibition, prepulse inhibition and amphetamine induced activity. *Behav Brain Res* 107:111–121
- Laruelle M (2000) The role of endogenous sensitization in the pathophysiology of schizophrenia: implications from recent brain imaging studies. *Brain Res Brain Res Rev* 31:371–384
- Laruelle M, Abi-Dargham A, van Dyck CH, Gil R, D'Souza CD, Erdos J, McCance E, Rosenblatt W, Fingado C, Zoghbi SS, Baldwin RM, Seibyl JP, Krystal JH, Charney DS, Innis RB (1996) Single photon emission computerized tomography imaging of amphetamine-induced dopamine release in drug-free schizophrenic subjects. *Proc Natl Acad Sci U S A* 93:9235–9240
- Laruelle M, Abi-Dargham A, Gil R, Kegeles L, Innis R (1999) Increased dopamine transmission in schizophrenia: relationship to illness phases. *Biol Psychiatry* 46:56–72
- Laruelle M, Kegeles LS, Abi-Dargham A (2003) Glutamate, dopamine, and schizophrenia: from pathophysiology to treatment. *Ann N Y Acad Sci* 1003:138–158
- Lieberman JA, Kane JM, Alvir J (1987) Provocative tests with psychostimulant drugs in schizophrenia. *Psychopharmacology* 91:415–433
- Lieberman JA, Perkins D, Belger A, Chakos M, Jarskog F, Boteva K, Gilmore J (2001) The early stages of schizophrenia: speculations on pathogenesis, pathophysiology, and therapeutic approaches. *Biol Psychiatry* 50:884–897
- Lindström LH, Gefvert O, Hagberg G, Lundberg T, Bergström M, Hartvig P, Långström B (1999) Increased dopamine synthesis rate in medial prefrontal cortex and striatum in schizophrenia indicated by L-(beta-11C) DOPA and PET. *Biol Psychiatry* 46:681–688
- Lipska BK (2004) Using animal models to test a neurodevelopmental hypothesis of schizophrenia. *J Psychiatry Neurosci* 29:282–286
- Lipska BK, Weinberger DR (2000) To model a psychiatric disorder in animals: schizophrenia as a reality test. *Neuropsychopharmacology* 23:223–239
- Mackay AV, Iversen LL, Rossor M, Spokes E, Bird E, Arregui A, Creese I, Synder SH (1982) Increased brain dopamine and dopamine receptors in schizophrenia. *Arch Gen Psychiatry* 39:991–997
- Marti J, Wills KV, Ghetti B, Bayer SA (2002) A combined immunohistochemical and autoradiographic method to detect midbrain dopaminergic neurons and determine their time of origin. *Brain Res Brain Res Protoc* 9:197–205
- Martinot JL, Peron-Magnan P, Huret JD, Mazoyer B, Baron JC, Boulenger JP, Loc'h C, Maziere B, Caillard V, Loo H et al (1990) Striatal D2 dopaminergic receptors assessed with positron emission tomography and [⁷⁶Br]bromospiperone in untreated schizophrenic patients. *Am J Psychiatry* 147:44–50
- McDonald C, Murray RM (2000) Early and late environmental factors for schizophrenia. *Brain Res Rev* 31:130–137
- McEwen BS (2001) Plasticity of the hippocampus: adaptation to chronic stress and allostatic load. *Ann N Y Acad Sci* 933:265–277
- McEwen BS (2007) Physiology and neurobiology of stress and adaptation: central role of the brain. *Physiol Rev* 87:873–904

- McGlashan TH (1996) Early detection and intervention in schizophrenia: research. *Schizophr Bull* 22:327–345
- Mednick SA, Machon RA, Huttunen MO, Bonett D (1988) Adult schizophrenia following prenatal exposure to an influenza epidemic. *Arch Gen Psychiatry* 45:189–192
- Meltzer HY, Stahl SM (1976) The dopamine hypothesis of schizophrenia: a review. *Schizophr Bull* 2:19–76
- Meyer U, Feldon J (2009) Neural basis of psychosis-related behaviour in the infection model of schizophrenia. *Behav Brain Res*, in press (Epub ahead of print [PMID: 19154759])
- Meyer U, Feldon J, Schedlowski M, Yee BK (2005) Towards an immuno-precipitated neurodevelopmental animal model of schizophrenia. *Neurosci Biobehav Rev* 29:913–947
- Meyer U, Feldon J, Schedlowski M, Yee BK (2006a) Immunological stress at the maternal–foetal interface: a link between neurodevelopment and adult psychopathology. *Brain Behav Immun* 20:378–388
- Meyer U, Nyffeler M, Engler A, Urwyler A, Schedlowski M, Knuesel I, Yee BK, Feldon J (2006b) The time of prenatal immune challenge determines the specificity of inflammation-mediated brain and behavioral pathology. *J Neurosci* 26:4752–4762
- Meyer U, Schwendener S, Feldon J, Yee BK (2006c) Prenatal and postnatal maternal contributions in the infection model of schizophrenia. *Exp Brain Res* 173:243–257
- Meyer U, Yee BK, Feldon J (2007) The neurodevelopmental impact of prenatal infections at different times of pregnancy: the earlier the worse? *Neuroscientist* 13:241–256
- Meyer U, Feldon J, Yee BK (2008a) A review of the fetal brain cytokine imbalance hypothesis of schizophrenia. *Schizophr Bull*, 2008; in press (Epub ahead of print [PMID: 18408229])
- Meyer U, Murray PJ, Urwyler A, Yee BK, Schedlowski M, Feldon J (2008b) Adult behavioral and pharmacological dysfunctions following disruption of the fetal brain balance between pro-inflammatory and IL-10-mediated anti-inflammatory signaling. *Mol Psychiatry* 13:208–221
- Meyer U, Nyffeler M, Schwendener S, Knuesel I, Yee BK, Feldon J (2008c) Relative prenatal and postnatal maternal contributions to schizophrenia-related neurochemical dysfunction after in utero immune challenge. *Neuropsychopharmacology* 33:441–456
- Meyer U, Nyffeler M, Yee BK, Knuesel I, Feldon J (2008d) Adult brain and behavioral pathological markers of prenatal immune challenge during early/middle and late fetal development in mice. *Brain Behav Immun* 22:469–486
- Meyer U, Engler A, Weber L, Schedlowski M, Feldon J (2008e) Preliminary evidence for a modulation of fetal dopaminergic development by maternal immune activation during pregnancy. *Neuroscience* 154:701–709
- Meyer U, Spoerri E, Yee BK, Schwarz MJ, Feldon J (2008f) Evaluating early preventive antipsychotic and antidepressant drug treatment in an infection-based neurodevelopmental mouse model of schizophrenia. *Schizophr Bull*, in press (Epub ahead of print [PMID: 18845557])
- Moore TM, Brown T, Cade M, Eells JB (2008) Alterations in amphetamine-stimulated dopamine overflow due to the *Nurr1*-null heterozygous genotype and postweaning isolation. *Synapse* 62:764–774
- Mortensen PB, Nørgaard-Pedersen B, Waltoft BL, Sørensen TL, Hougaard D, Torrey EF, Yolken RH (2007) *Toxoplasma gondii* as a risk factor for early-onset schizophrenia: analysis of filter paper blood samples obtained at birth. *Biol Psychiatry* 61:688–693
- Moser PC, Hitchcock JM, Lister S, Moran PM (2000) The pharmacology of latent inhibition as an animal model of schizophrenia. *Brain Res Brain Res Rev* 33:275–307
- Murray RM, O'Callaghan E, Castle DJ, Lewis SW (1992) A neurodevelopmental approach to the classification of schizophrenia. *Schizophr Bull* 18:319–332
- Murray RM, Lappin J, Di Forti M (2008) Schizophrenia: from developmental deviance to dopamine dysregulation. *Eur Neuropsychopharmacol* 18(Suppl 3):S129–S134
- Nawa H, Takei N (2006) Recent progress in animal modeling of immune inflammatory processes in schizophrenia: implication of specific cytokines. *Neurosci Res* 56:2–13
- Nieoullon A (2002) Dopamine and the regulation of cognition and attention. *Prog Neurobiol* 67:53–83
- O'Donnell P, Grace AA (1998) Dysfunctions in multiple interrelated systems as the neurobiological bases of schizophrenic symptom clusters. *Schizophr Bull* 24:267–283
- Okubo Y, Suhara T, Sudo Y, Toru M (1997a) Possible role of dopamine D1 receptors in schizophrenia. *Mol Psychiatry* 2:291–292
- Okubo Y, Suhara T, Suzuki K, Kobayashi K, Inoue O, Terasaki O, Someya Y, Sassa T, Sudo Y, Matsushima E, Iyo M, Tateno Y, Toru M (1997b) Decreased prefrontal dopamine D1 receptors in schizophrenia revealed by PET. *Nature* 385:634–636
- Opler MG, Susser ES (2005) Fetal environment and schizophrenia. *Environ Health Perspect* 113:1239–1242
- Ozawa K, Hashimoto K, Kishimoto T, Shimizu E, Ishikura H, Iyo M (2006) Immune activation during pregnancy in mice leads to dopaminergic hyperfunction and cognitive impairment in the offspring: a neurodevelopmental animal model of schizophrenia. *Biol Psychiatry* 59:546–554
- Pani L, Porcella A, Gessa GL (2000) The role of stress in the pathophysiology of the dopaminergic system. *Mol Psychiatry* 5:14–21
- Pantelis C, Yücel M, Wood SJ, Velakoulis D, Sun D, Berger G, Stuart GW, Yung A, Phillips L, McGorry PD (2005a) Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr Bull* 31:672–696
- Pantelis C, Yücel M, Wood SJ, Velakoulis D, Sun D, Berger G, Stuart GW, Yung A, Phillips L, McGorry PD (2005b) Structural brain imaging evidence for multiple pathological processes at different stages of brain development in schizophrenia. *Schizophr Bull* 31:672–696
- Patterson PH (2007) Maternal effects on schizophrenia risk. *Science* 318:576–577
- Pezze MA, Feldon J (2004) Mesolimbic dopaminergic pathways in fear conditioning. *Prog Neurobiol* 74:301–320
- Phillips LJ, McGorry PD, Garner B, Thompson KN, Pantelis C, Wood SJ, Berger G (2006) Stress, the hippocampus and the hypothalamic–pituitary–adrenal axis: implications for the development of psychotic disorders. *Aust N Z J Psychiatry* 40:725–741
- Pickel VM, Specht LA, Sumal KK, Joh TH, Reis DJ, Hervonen A (1980) Immunocytochemical localization of tyrosine hydroxylase in the human fetal nervous system. *J Comp Neurol* 194:465–474
- Pijnenburg AJ, Honig WM, Van der Heyden JA, Van Rossum JM (1976) Effects of chemical stimulation of the mesolimbic dopamine system upon locomotor activity. *Eur J Pharmacol* 35:45–58
- Rapoport JL, Addington AM, Frangou S, Psych MR (2005) The neurodevelopmental model of schizophrenia: update 2005. *Mol Psychiatry* 10:434–449
- Reynolds GP, Reynolds LM, Riederer P, Jellinger K, Gabriel E (1980) Dopamine receptors and schizophrenia: drug effect or illness. *Lancet* 2:1251
- Riddle R, Pollock JD (2003) Making connections: the development of mesencephalic dopaminergic neurons. *Brain Res Dev Brain Res* 147:3–21
- Robbins TW (2005) Chemistry of the mind: neurochemical modulation of prefrontal cortical function. *J Comp Neurol* 493:140–146
- Rojas P, Joodmardi E, Hong Y, Perlmann T, Ogren SO (2007) Adult mice with reduced *Nurr1* expression: an animal model for schizophrenia. *Mol Psychiatry* 12:756–766

- Romeo RD, McEwen BS (2006) Stress and the adolescent brain. *Ann N Y Acad Sci* 1094:202–214
- Romero E, Ali C, Molina-Holgado E, Castellano B, Guaza C, Borrell J (2007) Neurobehavioral and immunological consequences of prenatal immune activation in rats. Influence of antipsychotics. *Neuropsychopharmacology* 32:1791–1804
- Romero E, Guaza C, Castellano B, Borrell J (2008) Ontogeny of sensorimotor gating and immune impairment induced by prenatal immune challenge in rats: implications for the etiopathology of schizophrenia. *Mol Psychiatry*, 2008; in press (Epub ahead of print [PMID: 18414405])
- Ross CA, Margolis RL, Reading SA, Pletnikov M, Coyle JT (2006) Neurobiology of schizophrenia. *Neuron* 52:139–153
- Seeman P (1987) Dopamine receptors and the dopamine hypothesis of schizophrenia. *Synapse* 1:133–152
- Seeman P (2006) Targeting the dopamine D2 receptor in schizophrenia. *Expert Opin Ther Targets* 10:515–531
- Shi L, Fatemi SH, Sidwell RW, Patterson PH (2003) Maternal influenza infection causes marked behavioral and pharmacological changes in the offspring. *J Neurosci* 23:297–302
- Shoemaker JM, Saint Marie RL, Bongiovanni MJ, Neary AC, Tochen LS, Swerdlow NR (2005) Prefrontal D1 and ventral hippocampal N-methyl-D-aspartate regulation of startle gating in rats. *Neuroscience* 135:385–394
- Sillitoe RV, Vogel MW (2008) Desire, disease, and the origins of the dopaminergic system. *Schizophr Bull* 34:212–219
- Smidt MP, Burbach JP (2007) How to make a mesodiencephalic dopaminergic neuron. *Nat Rev Neurosci* 8:21–32
- Smith SE, Li J, Garbett K, Mirmics K, Patterson PH (2007) Maternal immune activation alters fetal brain development through interleukin-6. *J Neurosci* 27:10695–10702
- Smits SM, Ponnio T, Conneely OM, Burbach JP, Smidt MP (2003) Involvement of Nurr1 in specifying the neurotransmitter identity of ventral midbrain dopaminergic neurons. *Eur J Neurosci* 18:1731–1738
- Snyder SH (1976) The dopamine hypothesis of schizophrenia: focus on the dopamine receptor. *Am J Psychiatry* 133:197–202
- Soliman A, O'Driscoll GA, Pruessner J, Holahan AL, Boileau I, Gagnon D, Dagher A (2008) Stress-induced dopamine release in humans at risk of psychosis: a [¹¹C]raclopride PET study. *Neuropsychopharmacology* 33:2033–2041
- Sørensen HJ, Mortensen EL, Reinisch JM, Mednick SA (2008) Association between prenatal exposure to bacterial infection and risk of schizophrenia. *Schizophr Bull*, in press (Epub ahead of print [PMID: 18832344])
- Spanagel R, Weiss F (1999) The dopamine hypothesis of reward: past and current status. *Trends Neurosci* 22:521–527
- Sullivan R, Wilson DA, Feldon J, Yee BK, Meyer U, Richter-Levin G, Avi A, Michael T, Gruss M, Bock J, Helmeke C, Braun K (2006) The International Society for Developmental Psychobiology annual meeting symposium: impact of early life experiences on brain and behavioral development. *Dev Psychobiol* 48:583–602
- Susser E, St Clair D, He L (2008) Latent effects of prenatal malnutrition on adult health: the example of schizophrenia. *Ann N Y Acad Sci* 1136:185–192
- Suvisaari J, Haukka J, Tanskanen A, Hovi T, Lonnqvist J (1999) Association between prenatal exposure to poliovirus infection and adult schizophrenia. *Am J Psychiatry* 156:1100–1102
- Swerdlow NR, Geyer MA (1998) Using an animal model of deficient sensorimotor gating to study the pathophysiology and new treatments of schizophrenia. *Schizophr Bull* 24:285–301
- Swerdlow NR, Geyer MA, Braff DL (2001) Neural circuit regulation of prepulse inhibition of startle in the rat: current knowledge and future challenges. *Psychopharmacology* 156:194–215
- Swerdlow NR, Shoemaker JM, Bongiovanni MJ, Neary AC, Tochen LS, Saint Marie RL (2005) Reduced startle gating after D1 blockade: effects of concurrent D2 blockade. *Pharmacol Biochem Behav* 82:293–299
- Swerdlow NR, Shoemaker JM, Kuczenski R, Bongiovanni MJ, Neary AC, Tochen LS, Saint Marie RL (2006) Forebrain D1 function and sensorimotor gating in rats: effects of D1 blockade, frontal lesions and dopamine denervation. *Neurosci Lett* 402:40–45
- Takeuchi O, Akira S (2007) Recognition of viruses by innate immunity. *Immunol Rev* 220:214–224
- Tamminga CA, Holcomb HH (2005) Phenotype of schizophrenia: a review and formulation. *Mol Psychiatry* 10:27–39
- Torrey EF, Rawlings R, Waldman IN (1988) Schizophrenic births and viral diseases in two states. *Schizophr Res* 1:73–77
- Toru M, Nishikawa T, Mataga N, Takashima M (1982) Dopamine metabolism increases in post-mortem schizophrenic basal ganglia. *J Neural Transm* 54:181–191
- Toru M, Watanabe S, Shibuya H, Nishikawa T, Noda K, Mitsushio H, Ichikawa H, Kurumaji A, Takashima M, Mataga N et al (1988) Neurotransmitters, receptors and neuropeptides in post-mortem brains of chronic schizophrenic patients. *Acta Psychiatr Scand* 78:121–137
- Traynor TR, Majde JA, Bohnet SG, Krueger JM (2004) Intratracheal double-stranded RNA plus interferon-gamma: a model for analysis of the acute phase response to respiratory viral infections. *Life Sci* 74:2563–2576
- Triantafilou M, Triantafilou K (2002) Lipopolysaccharide recognition: CD14, TLRs and the LPS-activation cluster. *Trends Immunol* 23:301–304
- Tsujimoto S (2008) The prefrontal cortex: functional neural development during early childhood. *Neuroscientist* 14:345–358
- Tzschentke TM (2001) Pharmacology and behavioral pharmacology of the mesocortical dopamine system. *Prog Neurobiol* 63:241–320
- Van den Heuvel DM, Pasterkamp RJ (2008) Getting connected in the dopamine system. *Prog Neurobiol* 85:75–93
- Van Rossum JM (1966) The significance of dopamine receptor blockade for the action of neuroleptic drugs. In: Brill J (ed) *Neuro-psycho-pharmacology*. Excerpta Medica Foundation, Amsterdam, pp 321–329
- Velakoulis D, Wood SJ, McGorry PD, Pantelis C (2000) Evidence for progression of brain structural abnormalities in schizophrenia: beyond the neurodevelopmental model. *Aust N Z J Psychiatry* 34 (Suppl):S113–S126
- Voom P, Kalsbeek A, Jorritsma-Byham B, Groenewegen HJ (1988) The pre- and postnatal development of the dopaminergic cell groups in the ventral mesencephalon and the dopaminergic innervation of the striatum of the rat. *Neuroscience* 25:857–887
- Weinberger DR (1987) Implications of normal brain development for the pathogenesis of schizophrenia. *Arch Gen Psychiatry* 44:660–669
- Weinberger DR, Lipska BK (2005) Cortical maldevelopment, anti-psychotic drugs, and schizophrenia: a search for common ground. *Schizophr Res* 16:87–110
- Weiner I (1990) Neural substrates of latent inhibition: the switching model. *Psychol Bull* 108:442–461
- Weiner I (2003) The “two-headed” latent inhibition model of schizophrenia: modeling positive and negative symptoms and their treatment. *Psychopharmacology* 169:257–297
- Weiner I, Gal G, Rawlins JN, Feldon J (1996) Differential involvement of the shell and core subterritories of the nucleus accumbens in latent inhibition and amphetamine-induced activity. *Behav Brain Res* 81:123–133
- Welberg LA, Seckl JR (2001) Prenatal stress, glucocorticoids and the programming of the brain. *J Neuroendocrinol* 13:113–128
- Whitley RJ, Stagno S (1997) Perinatal infections. In: Scheld WM, Whitley RJ, Durack DT (eds) *Infections of the central nervous system*. Lippincott-Raven, New York, pp 223–253

- Williams GV, Castner SA (2006) Under the curve: critical issues for elucidating D1 receptor function in working memory. *Neuroscience* 139:263–276
- Winter C, Djodari-Irani A, Sohr R, Morgenstern R, Feldon J, Juckel G, Meyer U (2008) 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*, in press (Epub ahead of print [PMID: 18752727])
- Winterer G, Weinberger DR (2004) Genes, dopamine and cortical signal-to-noise ratio in schizophrenia. *Trends Neurosci* 27:683–690
- Wolff AR, Bilkey DK (2008) Immune activation during mid-gestation disrupts sensorimotor gating in rat offspring. *Behav Brain Res* 190:156–159
- Wong DF, Wagner HN Jr, Tune LE, Dannals RF, Pearlson GD, Links JM, Tamminga CA, Broussolle EP, Ravert HT, Wilson AA, Toung JK, Malat J, Williams JA, O'Tuama LA, Snyder SH, Kuhar MJ, Gjedde A (1986) Positron emission tomography reveals elevated D2 dopamine receptors in drug-naive schizophrenics. *Science* 234:1558–1563
- Wood SJ, Pantelis C, Velakoulis D, Yücel M, Fornito A, McGorry PD (2008) Progressive changes in the development toward schizophrenia: studies in subjects at increased symptomatic risk. *Schizophr Bull* 34:322–329
- Yung AR, Phillips LJ, McGorry PD, McFarlane CA, Francey S, Harrigan S, Patton GC, Jackson HJ (1998) Prediction of psychosis. A step towards indicated prevention of schizophrenia. *Br J Psychiatry* 172:14–20
- Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M, McGorry PD (2003) Psychosis prediction: 12-month follow up of a high-risk (“prodromal”) group. *Schizophr Res* 60:21–32
- Zetterström RH, Solomin L, Jansson L, Hoffer BJ, Olson L, Perlmann T (1997) Dopamine neuron agenesis in *Nurr1*-deficient mice. *Science* 276:248–250
- Zuckerman L, Weiner I (2005) Maternal immune activation leads to behavioral and pharmacological changes in the adult offspring. *J Psychiatr Res* 39:311–323
- Zuckerman L, Rehavi M, Nachman R, Weiner I (2003) 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* 28:1778–1789