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Research report

Neural basis of psychosis-related behaviour in the infection model of schizophrenia

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ABSTRACT

Maternal infection during pregnancy is a notable risk factor for the offspring to develop severe neuropsychiatric disorders, including schizophrenia. One prevalent hypothesis suggests that infection-induced disruption of early prenatal brain development predisposes the organism for long-lasting structural and functional brain abnormalities, leading to the emergence of psychopathological behaviour in adulthood. The feasibility of this causal link has received considerable support from several experimental models established in both rats and mice. In this review, we provide an integrative summary of the long-term neuropathological consequences of prenatal exposure to infection and/or inflammation as identified in various experimental models of prenatal immune challenge. In addition, we highlight how abnormalities in distinct brain areas and neurotransmitter systems following prenatal immune activation may provide a neural basis for the emergence of specific forms of psychosis-related behaviour. Specifically, we suggest that prenatal infection-induced imbalances in the mesolimbic and mesocortical dopamine pathways may constitute critical neural mechanisms for disturbances in sensorimotor gating, abnormalities in selective associative learning and hypersensitivity to psychostimulant drugs. On the other hand, the emergence of working memory deficiency following prenatal immune challenge may be crucially linked to the concomitant disruption of GABAergic and glutamatergic functions in prefrontal cortical and hippocampal structures. Notably, many of the identified neuronal abnormalities are directly implicated in the neuropathology of schizophrenia. The findings from prenatal infection models of schizophrenia thus provide considerable experimental evidence for the assumption that prenatal exposure to infection and/or inflammation is a relevant environmental link to specific neuronal abnormalities underlying psychosis-related behaviour in humans.

1. Introduction

Schizophrenia is a major form of psychotic illness characterised by impaired thinking, emotions, and behaviour. 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 [133,149,155,184]. Together with a strong genetic contribution [78], various environmental factors appear to increase the risk of schizophrenia and other psychosis-related disorders [48,111,142]. 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.

Maternal infection during pregnancy is one of the environmental factors that significantly increases the risk of schizophrenia and related disorders in the offspring [25,33,34,144]. This association does not appear to be limited to a single pathogen. Indeed, a multitude of infectious agents seems to be involved, including influenza [30,105,112,166], rubella [31], toxoplasma gondii [32,128], measles [173], polio [167], herpes simplex [35], and genital and/or reproductive infections [10]. One implication is that factors common to the immune response to a multitude of infectious agents may be the critical mediators of the association between prenatal infection and risk of schizophrenia. As extensively reviewed elsewhere [69,116,122], abnormal expression of pro-inflammatory cytokines and other mediators of inflammation in the maternal host and eventually in the foetal brain may interfere with normal foetal brain development [9,117,162]. This early inflammatory insult may predispose the offspring to long-lasting changes in subsequent brain and behavioural development and ultimately lead to

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adult neuropathology and associated psychosis-related behaviour in adolescence or early adulthood.

The feasibility of a causal link between maternal infection during pregnancy and higher risk of brain and behavioural pathology in the offspring has received considerable support from several experimental models established in both rats and mice. In these models, pregnant rats or mice are exposed to specific viral pathogens, immune-stimulating agents or pro-inflammatory cytokines, and the long-term brain and behavioural effects of the prenatal maternal manipulations are then evaluated in the offspring. A multitude of behavioural, cognitive and pharmacological abnormalities has been detected in adult mice and rats following prenatal exposure to human influenza virus [160], the viral mimic polyriboinosinic–polyribocytidilic acid (PolyI:C) [109,114–122,143,160,162,191,198–200], the bacterial endotoxin lipopolysaccharide (LPS) [26,65,66,71,153,154], and the pro-inflammatory cytokine interleukin (IL)-6 [158,162]. The spectrum of the functional deficits induced by the various prenatal immunological insults is summarised in Table 1.

The multiplicity of the adult behavioural, cognitive and pharmacological dysfunctions observed in prenatally immune challenged offspring suggests that the perturbations caused by the prenatal immunological manipulation are widespread, and fundamental to a range of normal neuropsychological functions. Importantly, many of the prenatal infection-induced behavioural, cognitive and pharmacological dysfunctions in adult rats and mice are implicated in some of the most critical phenotypes of schizophrenia and other psychosis-related disorders [7,106,115]. These include sensorimotor gating deficiency, abnormalities in selective associative learning, working memory impairment, enhanced sensitivity to psychostimulant drugs, and deficits in social behaviour (Table 1). The prenatal immune activation models thus enjoy a high level of face validity to schizophrenia-like psychopathology. The long-term effects of prenatal immune activation in rodents also mimic the characteristic maturational delay in disease onset of schizophrenia [133,149,155,184], because the full spectrum of prenatal infection-induced behavioural, cognitive, and pharmacological abnormalities emerges only after the post-pubertal stage of development [119,121,143,154,198,200]. Furthermore, some of the behavioural and cognitive deficits induced by *in utero* immune challenge in rats and mice can be normalized by acute and/or chronic antipsychotic drug treatment [160,143,153,198], suggesting that the prenatal immune activation models are also valid models of schizophrenia-like dysfunctions with respect to predictive validity.

One plausible account of the neural bases underlying the emergence of a wide spectrum of behavioural, cognitive and pharmacological dysfunctions after prenatal immune activation may be that they are indicative of multiple structural brain abnormalities. In fact, given that the immunological insult takes place early in development, it can be expected that foetal brain inflammation leads to wide-ranging neurodevelopmental sequelae, eventually leading to multiple neuroanatomical and neurochemical abnormalities in adult life. Direct support for this suggestion is yielded by numerous immunohistochemical, gene expression and neurochemical analyses in rats and mice, which demonstrate a wide spectrum of neuroanatomical and neurochemical changes in the adult CNS following prenatal exposure to infection and/or inflammation.

In this review, we provide an integrative summary of the long-term neuropathological consequences of prenatal exposure to infection and/or inflammation as identified in various experimental models of prenatal immune activation in rats and mice. In addition, we highlight how infection-induced abnormalities in distinct brain areas and/or neurotransmitter systems may provide a neural basis for specific forms of psychosis-related behaviour.

Table 1
Summary of current animal models demonstrating psychosis-related behavioural and pharmacological long-term consequences of prenatal exposure to various immunostimulatory agents, including human influenza virus, polyriboinosinic–polyribocytidilic acid (PolyI:C), lipopolysaccharide (LPS), turpentine, and interleukin-6 (IL-6).

Immunogen	Species	Gestation period	Psychosis-related behavioural and pharmacological abnormalities in adulthood						References
			Prepulse inhibition	Latent inhibition	Sensitivity to DA-R agonists	Sensitivity to NMDA-R antagonist	Working memory	Reversal learning effect	
Influenza virus	Mouse	Early/middle	→	ND	ND	↑	ND	ND	[160]
PolyI:C	Mouse	Early/middle	→	→	↑	↑	(↓)	–	[109,114,115,117,119–121,160,162]
	Mouse	Middle → late	→	ND	↑	ND	→	ND	[143]
	Mouse	Late	–	–	↑	↑	→	↑	[114,118,120]
	Rat	Middle/late	→	→	↑	↑	ND	→	[191,198–200]
LPS	Rat	Early → late	→	ND	↑	ND	ND	ND	[26,153,154]
	Rat	Middle	→	ND	ND	ND	ND	ND	[66]
	Rat	Late	→	ND	↑	ND	ND	ND	[65,66]
Turpentine	Rat	Middle	→	ND	ND	ND	ND	ND	[66]
IL-6	Mouse	Early/middle	→	→	ND	ND	ND	ND	[162]
	Rat	Early → middle	→	→	ND	ND	(↓)	ND	[158]
	Rat	Middle → late	ND	ND	ND	ND	→	ND	[158]

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 parentheses 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. ND = not determined; DA-R = dopamine receptor; NMDA-R = *N*-methyl-D-aspartate receptor.

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Since the behavioural effects of prenatal immune activation reach their prominence in adulthood [119,121,143,154,198,200], a special emphasis is put on the brain and behavioural relationships at the adult stage of development.

2. The long-term neuropathological consequences of prenatal infection

Exposure to infection and/or inflammation during critical periods of prenatal life can be considered an "immunological lesion" of the developing brain, which is characterised by the presence of virulent pathogens in the foetal brain [8,62,187] and/or abnormal foetal expression of pro-inflammatory cytokines [9,36,71,117,118] and activated microglia [85,137,157]. This early lesion of the brain does not remain static, but rather, it is progressive in nature. That is, the infection-induced disruption of early foetal brain development may significantly affect subsequent postnatal brain development and maturation, and subsequently lead to structural and functional deficits that are dependent on postnatal maturational processes. Hence, the prenatal immune activation models incorporate developmental aspects of abnormal brain structure and function in adulthood. This feature of the prenatal immune activation models is particularly relevant to the neurodevelopmental perspective of schizophrenia, because the disorder's pathophysiological and neuropathological mechanisms are assumed to be progressive in nature [149].

The neuropathological deficits induced by prenatal immune challenge include pre- and post-synaptic changes in various neurotransmitter systems such as the central dopamine (DA), γ-aminobutyric acid (GABA), glutamate (GLU), and serotonin (5-HT) systems, together with alterations in neuronal and glial cell number, structure and positioning. As highlighted in more detail in the following sections, many of the long-term neuropathological effects of prenatal immune challenge appear to be critically influenced by the precise timing of the infectious event as well as by the specificity of the immunogen present in the maternal host during pregnancy.

2.1. Effects on the central DA system

It has long been recognised that abnormalities in the central DA system play a major role in the pathophysiology of schizophrenia and psychosis-related behaviour [38,50,51,73,113,159,163]. According to the revised DA hypothesis of schizophrenia, the central DA system in this disorder may be characterised 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 prefrontal cortex (PFC) may be hypoactive [3,76,87,100,190]. 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.

Considering the prominent role of central DA in the pathophysiology of schizophrenia, numerous experimental investigations in rats and mice have explored whether prenatal immune challenge would lead to long-term changes in the central DA system relevant to schizophrenia. Experimental studies using the bacterial endotoxin LPS or the viral mimic PolyI:C have indeed found direct evidence for a causal relationship between prenatal immune activation and emergence of dopaminergic abnormalities in postnatal life. For example, chronic LPS treatment throughout pregnancy in rats increases the immunoreactivity (IR) for tyrosine hydroxylase (TH) in the nucleus accumbens (NAc) of the adult offspring, especially in the NAc shell subregion [26]. 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 [11]. 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 [153]. Interestingly, the effects of prenatal LPS exposure on accumbal DA and DOPAC levels are clearly dependent on the postnatal stage of the offspring: whilst enhanced accumbal DA and DOPAC levels are observed in adult (>170 days old) rats prenatally exposed to LPS, DA and DOPAC levels are highly comparable between control and prenatally immune challenged rats in early adulthood (70 days of age). Furthermore, DA and DOPAC levels are even significantly decreased in peri-adolescent (40 days old) rats prenatally exposed to LPS relative to control subjects [154]. This highlights the developmental origin and progressive nature of emerging dopaminergic abnormalities following prenatal exposure to the bacterial endotoxin LPS.

Similar to the findings in the chronic LPS model in rats, acute treatment with the viral mimic PolyI:C in early/middle gestation (gestation day [GD] 9) in mice leads to enhanced TH-IR in the NAc in adulthood [119]. This effect of early/middle gestational immune challenge does not appear to be accompanied by enhanced basal DA levels in this mesolimbic brain structure [188]. However, the null effect of acute PolyI:C treatment on basal striatal DA levels is consistent with the findings by Zuckerman et al. [198], who 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. On the other hand, a single exposure to PolyI:C in early/middle gestation in mice is sufficient to increase accumbal levels of the DA metabolite homovanillic acid (HVA), and to enhance DA and DOPAC contents in the globus pallidus (GP) and PFC [188]. Importantly, the increase in basal DA levels in the PFC following prenatal PolyI:C exposure is associated with a significant decrease in DA D1 (D1R) and D2 (D2R) receptors in this brain area [119,120], which may reflect a counter-regulatory post-synaptic mechanism for increased basal DA levels in the PFC.

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 GD 12 to 17 [143]. 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 [143].

Taken together, there is clear evidence that prenatal immune activation by exposure to inflammatory agents such as LPS or PolyI:C can negatively affect the normal development of the mesocorticolimbic and mesostriatal 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 [108,174,175]. Interestingly, the abnormal basal levels of DA and its metabolites appear to be linked to increased TH activity in these brain regions [174,175], similar to the effects reported in experimental models of prenatal immune challenge. In addition, 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 [139,140] (but see also [2,3]). Finally, several (but not all) studies demonstrate that receptor binding of DA D2-like receptors is decreased in the striatum of drug-free schizophrenic patients [47,108,150].

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2.2. Effects on the central GABA system

Converging evidence indicates that deficits in GABAergic interneurons are also crucially involved in the neuropathology of schizophrenia [20–23,53,80,81,102,103,151,181,192,193]. In fact, deficient GABAergic signalling in the dorsolateral PFC is among the best-replicated neuropathological findings in schizophrenia. Prefrontal GABAergic abnormalities in schizophrenic patients include reductions in the GABA-synthesising enzyme glutamic acid decarboxylase (GAD_{67}) [5,75,181], fewer GABA membrane transporter (GAT-1) cartridges in the GABAergic chandelier neurons [193], as well as decreased expression of the calcium-binding protein parvalbumin (PV) [20,80,81,102,103] and the secretory glycoprotein Reelin [86,75,63,64]. In addition, a number of post-synaptic GABAergic abnormalities have been described in the PFC and hippocampus (HPC) of patients with schizophrenia. These include up-regulation of $GABA_A$ receptor sites in general [22,23,46,77], and marked increases in $\alpha 2$ subunit levels at axon initial segments of pyramidal neurons in particular [103,183]. The up-regulation of the $GABA_A$ receptor $\alpha 2$ subunits may represent a compensatory response to the selective loss of pre-synaptic input provided by the PV-containing interneurons in the PFC and HPC of schizophrenic patients [53,103,151,183]. Considering the crucial importance of appropriate GABAergic inhibition in neuronal circuits of normal brain functions, including executive functioning and working memory, deficits in GABAergic interneurons are likely to contribute to the cognitive impairments and other clinical symptoms of schizophrenia [103,171,182].

In order to test whether prenatal exposure to infection may represent a significant environmental risk factor for schizophrenia-related GABAergic deficits, several animal models have explored the long-term effects of prenatal immune challenge on the postnatal expression of GABAergic markers in various brain areas. Fatemi et al. have provided the first evidence that maternal infection during pregnancy can lead to abnormalities in the central GABA system of the resulting offspring [58]: Neonatal mice of mothers infected with human influenza virus in early/middle gestation (GD 9) display a marked reduction of Reelin-positive cells in several cortical and hippocampal areas. Infection-induced Reelin reduction may also be responsible for some of the morphological changes noted in the neonatal brains of offspring born to influenza-infected mothers (see Section 2.4).

Subsequent studies in mice went on to show that mid-gestational maternal exposure to a viral-like acute phase response induced by acute PolyI:C treatment on GD 9 is similarly capable of suppressing Reelin expression in the offspring's HPC and PFC at pre-adolescent [118] and adult age [120]. In addition, prenatal PolyI:C exposure in mice is sufficient to markedly reduce the expression of the calcium-binding protein PV in prefrontal and hippocampal areas [120]. Interestingly, the latter effect (i.e., reduction in hippocampal PV expression following prenatal PolyI:C exposure) is more readily seen following prenatal immune challenge in late gestation (GD 17), but only marginally so following immunological stimulation in early/middle gestation (GD 9) [120]. This shows that the precise timing of the prenatal immune activation can, at least in part, critically influence the vulnerability to specific GABAergic abnormalities in the postnatal CNS.

In addition to the effects on central Reelin and PV, prenatal immune challenge also leads to long-lasting changes in $GABA_A$ receptor expression. In a first study, Nyffeler et al. [138] have shown that maternal treatment with the viral mimic PolyI:C on GD 9 increases the expression of the $\alpha 2$ subunit of $GABA_A$ receptors specifically in the HPC and basolateral amygdala (BLA) of the adult offspring compared to control offspring. It was further demonstrated that the up-regulation of $GABA_A$ receptor $\alpha 2$ subunits at the axon initial segments of hippocampal pyramidal neurons constitutes a compensatory response to a reduction in proximal inhibitory input provided by PV-expressing neurons in prenatally immune challenged animals [120].

Together, these data confirm a causal relationship between prenatal immune challenge and the emergence of multiple pre- and post-synaptic GABAergic deficits in the adult CNS. Since many of the reported GABAergic abnormalities are implicated in the neuropathology of schizophrenia, the experimental findings obtained in various prenatal immune activation models in rodents strongly support the hypothesis that prenatal exposure to infection and/or inflammation may be a significant etiopathological factor in GABAergic abnormalities in schizophrenia and related disorders.

2.3. Effects on the central GLU and 5-HT systems

In addition to the dopaminergic and GABAergic dysfunctions described above, abnormalities in the central GLU and 5-HT systems also appear to be involved in the neuropathology and pathophysiology of schizophrenia. According to the GLU hypothesis of schizophrenia, signalling via the *N*-methyl-D-aspartate (NMDA) receptor is compromised in this disease, and this may play an important role especially in the etiopathology of negative symptoms and cognitive impairments associated with the disorder [54,70,100,131,178]. Acute NMDA receptor blockade (e.g., by acute phencyclidine [PCP] or ketamine treatment) can also produce psychosis-like behaviour in healthy human subjects akin to the positive florid symptoms of schizophrenia, and it exacerbates existing psychoses in patients with schizophrenia [54,88,94,97]. This suggests that impaired signalling at NMDA receptors may also contribute to the emergence of positive symptoms of schizophrenia, an effect that may involve intricate interactions between NMDA-receptor functions and central DA neurotransmission [37,100].

Similarly, enhanced serotonergic signalling (especially via 5-HT_{2A} receptors) may be involved specifically during the early phases of schizophrenic psychoses and precipitate behavioural dysfunctions linked especially to the positive symptoms of this disorder (for a recent review see [68]). In contrast, deficient central 5-HT functions may underlie some of the negative symptoms in patients with schizophrenia [1,4]. However, it needs to be emphasized that despite much research, a clear picture of specific serotonergic alterations in schizophrenia has not yet emerged. According to the prevailing view, serotonergic signalling may have a modulatory influence on central DA transmission in schizophrenia, which may significantly contribute to the therapeutic effects of atypical antipsychotics [4].

Despite the suggested contributions of glutamatergic and serotonergic dysfunctions to psychosis-related behaviour, the long-term consequences of prenatal infection for the central GLU and 5-HT systems remain largely unexplored to date. However, initial evidence from experimental investigations in rats and mice suggest that prenatal exposure to infection and/or inflammation may indeed negatively affect the normal development of the glutamatergic and serotonergic systems. In mice, maternal administration of the viral mimic PolyI:C leads to a decrease in the expression of the NMDA-receptor subunit 1 (NR1) in the dorsal HPC of the adult offspring [120]. NR1 is ubiquitously expressed in the adult mammalian brain throughout pre- and postnatal development [183,107], and it is a prerequisite for the formation of functional NMDA receptors, together with the other known subunits NR2 and NR3 [43,92]. Interestingly, the effect of prenatal PolyI:C-induced immune challenge on hippocampal NR1 expression is observed only if the immunological manipulation is conducted in late (GD 17) but not early/middle (GD 9) gestation [120]. This indicates that the vulnerability to prenatal infection-mediated disturbances in hippocampal NR1 expression may increase as foetal development progresses from early to late gestation. This suggestion is also supported by

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the recent findings in rats that repeated prenatal exposure to the pro-inflammatory cytokine IL-6 during late gestation (i.e., on GDs 16, 18 and 20), but not during early-to-middle gestation (i.e., on GDs 8, 10 and 12), leads to significant changes in hippocampal NR1 expression at adult age [158]. However, prenatal exposure to IL-6, and prenatal exposure to the viral mimic PolyI:C each produce a different direction of change in adult hippocampal NR1 expression: Whereas prenatal treatment with PolyI:C decreases hippocampal NR1 expression [120], maternal treatment with IL-6 during pregnancy increases the expression of NR1 subunits in the HPC of adult offspring [158]. One possible explanation for these discrepancies may be that – in addition to the precise timing of prenatal immune activation – the immune stimulus specificity can critically influence the nature of the long-term neuropathological consequences of prenatal infection. Indeed, recent experimental findings in rats and mice clearly show that specific forms of adult brain and behavioural pathology emerging after prenatal immune challenge depend both on the specificity of the immunogen and on the precise prenatal timing of the infectious event [116,122].

In contrast to its effects on NMDA receptor subunits in the adult CNS [120,158], prenatal immune challenge in mice does not seem to markedly affect the basal CNS levels of GLU during neonatal, peri-adolescent or adult stages of development: neither maternal exposure to human influenza virus [60] nor the viral mimic PolyI:C [188] leads to significant changes in central GLU contents in the resulting offspring. Hence, prenatal immune activation may lead to specific abnormalities in hippocampal NMDA receptor expression in the absence of compensatory changes at the neurochemical level.

Evidence for serotonergic dysfunctions following prenatal immune activation is yielded by recent investigations in mice, which show that prenatal exposure to influenza virus or the viral mimic PolyI:C leads to reduced basal levels of 5-HT in various brain areas in postnatal life, including cerebellum, HPC, and NAc [60,188,189]. Interestingly, this association does not appear to be influenced by the precise timing of the prenatal immune challenge: Reduced central 5-HT levels have similarly been described in peri-adolescent or adult mice subjected to prenatal immune challenge either in early/middle [188] or late [60,189] gestation. Since the central 5-HT system has so far received little attention in the infection model of schizophrenia, evidence for additional serotonergic dysfunctions in prenatally immune challenged animals is still lacking.

2.4. Effects on neuronal and glial cell morphology

Besides the identified changes in various neurotransmitters systems, the long-term neuropathological consequences of prenatal infection also include abnormalities in neuronal and glial cell morphology. As with the infection-mediated neurochemical disturbances outlined above, the long-term changes in neuronal and glial cell morphology also appear to be critically determined by both the specificity of the immune stimulus and the precise prenatal timing. In addition, the extent to which abnormal cell morphology can be observed following *in utero* exposure to infection and/or inflammation is also influenced by the actual postnatal developmental stage of the offspring.

The detailed morphological analyses by Fatemi et al. have provided compelling evidence that prenatal exposure to human influenza in mice can induce numerous abnormalities in CNS morphology in postnatal life. In a first study, these authors have demonstrated that prenatal viral infection in early/middle gestation (GD 9) causes marked decreases in neocortical and hippocampal thickness in neonatal brains, an effect that may be attributable, at least in part, to neuronal migration deficits via infection-mediated reduction in Reelin expression during foetal brain development [58]. Fatemi et al. went on to show that influenza infection on GD 9 in the mouse leads to maturation dependent morphological abnormalities in postnatal hippocampal and cortical brain structures [57]: whilst pyramidal cell density is increased significantly in influenza-exposed offspring both at birth and in adulthood, non-pyramidal cell density is reduced only in the neonatal period but exceeds normal levels in adulthood. Furthermore, prenatal infection with influenza virus on GD 9 leads to pyramidal cell atrophy, which is evident already at birth and persists throughout development up to adulthood; and it leads to macrocephaly in adulthood despite smaller hippocampal and cortical thickness during the neonatal period [57,58]. These morphological abnormalities induced by prenatal influenza infection in early/middle gestation are paralleled by maturation-dependent changes in the expression of neuronal nitric oxide synthase (nNOS) in the postnatal CNS: Enhanced nNOS expression is observed in influenza-infected offspring during the neonatal [61] and peri-adolescent [56] stage of development, but reduced nNOS expression is noted in the brains of influenza-infected offspring in early adulthood [56]. Again, this highlights the developmental aspects of the neuronal deficits induced by prenatal exposure to infection, and it further suggests that abnormal nNOS expression may significantly contribute to the emergence of morphological changes following prenatal immune challenge.

Interestingly, prenatal exposure to influenza virus in late gestation (GD 18) in mice has recently been shown to lead to significant atrophy in several brain areas and white matter thinning in corpus callosum in early adulthood [60]. Notably, these effects are distinct from the morphological effects of influenza infection in early/middle pregnancy described above. The differential effects of early/middle and late gestational influenza infection on postnatal brain structures (e.g., adult macrocephaly following GD 9-infection *versus* adult microcephaly following GD 18-infection) supports the hypothesis that the neurodevelopmental impact of prenatal infection critically differs between early/middle and late gestational periods [118,120,122].

Unlike prenatal influenza infection, prenatal exposure to a viral-like acute phase response induced by a single administration of PolyI:C in early/middle gestation (GD 9) in mice does not seem to cause gross brain morphological changes in the pre-adolescent [118] or adult [138] brain. Hence, influenza infection during early/middle foetal development is likely to exert a more extensive impact on postnatal brain morphology compared to the viral mimic PolyI:C. However, it needs to be emphasized that prenatal exposure to PolyI:C in middle/late gestation (GD 15) in rats results in a moderate to severe adult hippocampal cell loss, with many of the remaining neurons exhibiting a pyknotic-like profile [198,200]. These findings are consistent with the study by Samuelsson et al. [158], who demonstrated that sub-chronic exposure to the pro-inflammatory cytokine IL-6 specifically during late gestation (i.e., on GDs 16, 18 and 20) but not during early-to-middle gestation (i.e., on GDs 8, 10 and 12) in rats leads to a pronounced pyramidal cell loss in adult hippocampal structures.

Loss of neurons is often followed by reactive gliosis, that is, the replacement of neuronal cells by glial cells. It would thus be expected that reactive gliosis is also a characteristic morphological sign following prenatal immune challenge, particularly following late gestational immune activation. Indeed, sub-chronic prenatal exposure to IL-6 in rats [158], chronic prenatal exposure to the endotoxin LPS in rats [26], as well as prenatal influenza infection in early/middle gestation in mice [55,59] have all been shown to result in enhanced number and/or activation of astrocytes and microglia in various brain regions during postnatal life. Given that astrocytes and microglia are the main source of cytokine production in the CNS [24], the prenatal infection-induced over-activation of glial cells is often paralleled by enhanced production and release of pro-inflammatory cytokines in the postnatal brain [158]. However, consistent with its null effect on neuronal cell loss in the

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postnatal brain, prenatal exposure to a viral-like acute phase by PolyI:C administration in early/middle gestation (GD 9) does not lead to reactive gliosis [138] or markedly enhanced production of CNS cytokines [117] in early adulthood.

A recent experimental study has provided initial *in vivo* evidence that maternal immune activation by PolyI:C in early/middle pregnancy delays myelination and axonal development in mice [109]: Offspring born to PolyI:C-treated mothers displayed a significant reduction in the oligodendrocyte marker myelin basic protein (MBP) and a decrease in myelination of hippocampal neurons during the early postnatal periods. This was accompanied by a reduction in axonal diameters in hippocampal neurons [158]. However, these abnormalities reverted to normal levels when the animals reached the adult stage of development, suggesting that the prenatal inflammation-induced changes in myelination and axonal development may represent transient neuropathological deficits during early postnatal brain development and maturation.

3. Linking specific neuronal dysfunctions with distinct forms of psychosis-related behaviour

Animal models are indispensable experimental tools in the study of possible causal links between specific neuronal dysfunctions and distinct forms of abnormal behaviour. They are therefore valuable in the exploration of specific brain and behavioural relationships in complex neuropsychiatric disorders such as schizophrenia, which is characterised by multiple behavioural, cognitive and pharmacological pathologies that are likely to involve neuronal disturbances beyond one single brain region and neurotransmitter system. As outlined above, the prenatal immune activation models have been shown to capture a wide spectrum of structural and functional abnormalities implicated in schizophrenia and psychosis-related disorders. An essential feature of the prenatal infection models of schizophrenia is that they do not rely on any specific presumption of the disorder's neuronal substrates. This is because they are not based on any specific neurological or pathophysiological features of the disorder, but rather, they are designed to interfere with early neurodevelopmental processes long before the onset of psychosis-related abnormalities. This allows a multi-faceted, longitudinal monitoring of the disease process as it unfolds during the course of neurodevelopment from early postnatal through to adult life, thus enabling the identification of intricate brain and behavioural relationships at distinct postnatal developmental stages. Furthermore, given that prenatal immune activation in rodents leads, at least in part, to differential brain and behavioural pathological outcomes, depending on the precise prenatal timing and immune stimulus specificity [116,122], the prenatal infection models provide a unique opportunity to link specific neuronal dysfunctions with distinct forms of psychosis-related behaviour.

It is well known that a given behavioural 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. Given that infection-induced interference with early brain development leads to abnormalities in multiple brain areas and neurotransmitter systems (see Section 2), it seems unlikely that a specific psychopathological phenotype seen in prenatally immune challenged animals is accounted for by dysfunctions in isolated brain structures. Rather, interactions and additive effects between different neuronal dysfunctions in multiple brain areas are likely to be involved in the precipitation of specific forms of psychosis-related behaviour following prenatal exposure to infection/inflammation. The following sections provide a detailed outline of the putative brain and behavioural associations in the infection model of schizophrenia.

3.1. Mesolimbic and mesocortical DA abnormalities: relevance to disturbances in sensorimotor gating, abnormalities in selective associative learning and hypersensitivity to psychostimulant drugs

It has long been suggested that disturbances in the mesolimbic and mesocortical DA systems play a crucial role in psychosis-related behaviour [38,50,51,73,76,113,159,163]. The mesolimbic DA system originates primarily from dopaminergic cell bodies located in the ventral tegmental area (VTA). These DA cells send prominent projections to the medial and ventral parts of the striatum, hippocampus and amygdala [42,89], forming the mesolimbic DA pathways. On the other hand, dopaminergic projections form the VTA to the PFC form the mesocortical DA pathway [16]. It is well known that pharmacological, genetic, or lesion-based experimental manipulations targeting the mesolimbic and/or mesocortical DA pathways can induce a set of behavioural, cognitive, and pharmacological dysfunctions implicated in psychosis-like behaviour (for a review see [17,42,50,73,135,168,169,186]). As highlighted in detail below, one plausible account for at least some of the behavioural, cognitive and pharmacological abnormalities emerging after prenatal immune challenge may be that they are causally linked to disturbances in mesolimbic and mesocortical DA pathways.

3.1.1. Sensorimotor gating and selective associative learning

Numerous independent investigations in rats and mice have provided compelling evidence 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 [17,90,91,168,169,186]). PPI refers to the reduction in the reaction to an intense startle-eliciting stimulus (pulse) when it is shortly preceded by a weak stimulus (prepulse); and LI is a form of selective learning, in which non-reinforced pre-exposures to a to-be-conditioned stimulus (CS) retards subsequent conditioning between the same CS and the unconditioned stimulus (US). Both paradigms have clear relevance to schizophrenia, because LI and PPI are deficient in at least some subsets of schizophrenic patients [169,186]. Deficient PPI and LI in adulthood are also two commonly observed pathological phenotypes emerging following prenatal exposure to a variety of immunogens, including influenza virus or the viral mimic PolyI:C [114–121,143,160,162,191,198–200], the bacterial endotoxin LPS [26,66,153,154], and the pro-inflammatory cytokine IL-6 [162]. Importantly, in many models of prenatal immune challenge, impaired PPI and LI are paralleled by significant neuroanatomical and neurochemical changes indicative of an overactive mesolimbic DA system, especially in ventral striatal regions (i.e., NAc core and shell). This includes enhanced accumbal TH immunoreactivity, enhanced accumbal DA levels, and increased striatal DA turnover (see Section 2.1). Hence, enhanced dopaminergic activity in mesolimbic (especially meso-accumbal) systems may be one of the critical neural bases of PPI and LI deficiency following prenatal immune activation. Additional support for this hypothesis is derived from the findings that pharmacological treatment with the preferential D2R blocker haloperidol, which targets dopaminergic neurotransmission particularly in striatal regions [152,156], is sufficient to normalize the prenatal infection-induced PPI and LI deficits in adulthood [26,153,198].

In addition to enhanced DA activity in mesolimbic structures, altered DA-associated signalling in the PFC may further contribute to the emergence of sensorimotor gating deficits following prenatal immune challenge. We have recently shown in mice that prenatal PolyI:C exposure in early/middle (GD 9) but not late (GD 17) gestation leads to adult sensorimotor gating impairment that is linked to a marked reduction in prefrontal D1Rs [120]. Furthermore, basal DA contents in the PFC are significantly increased following prenatal

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immune challenge in early/middle [188] but not late [60] gestation. Hence, experimental analyses of the impact of the precise timing of prenatal immune activation suggest that dopaminergic abnormalities in the PFC may provide a critical neural basis of PPI deficiency in adult animals exposed to *in utero* immune activation in early/middle gestation, but not in those subjected to prenatal immune challenge in late gestation. Several findings from previous experimentation in rodents can be taken as additional support for this hypothesis. First, pharmacological blockade of D1Rs in the mPFC significantly attenuates PPI in rats, indicating that impaired prefrontal D1R-mediated signalling can lead to sensorimotor gating deficiency [52,161]. Second, 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 [28,95]. Interestingly, this effect can be enhanced by simultaneous blockade of D1Rs in the PFC [45]. Taken together, besides enhanced dopaminergic activity in mesolimbic pathways (see above), specific dopaminergic abnormalities in the PFC may also significantly contribute to the neural substrates of PPI deficiency emerging following prenatal immune challenge in early/middle gestation.

To what extent may prefrontal DA dysfunctions also be involved in the precipitation of LI deficiency following prenatal immune challenge? The potential contribution of prefrontal cortical dysfunctions on LI abnormalities has been investigated in numerous independent studies using lesion-based or pharmacological approaches [28,52,95,96,186]. The findings derived from these studies suggest that neither the damage to intrinsic cells residing in the PFC nor pharmacologically induced changes in the PFC, which may eventually also affect subcortical mesolimbic DA functions, significantly affect the development and/or expression of LI. This also appears to be the case with particular respect to dopaminergic manipulations of the PFC: infusion of dopaminergic compounds into the PFC, which is known to affect PPI of the acoustic startle reflex, fail to exert significant effects on LI [28,52,95]. This highlights that the neural substrates of LI and PPI are clearly different in terms of the involvement of the prefrontal DA system (and its descending connections to the mesolimbic DA system). Even though a potential contribution of prefrontal DA dysfunctions to LI impairment cannot yet be completely ruled out in the prenatal infection model of schizophrenia, this possibility seems unlikely, based on the findings from many previous experimental investigations in rodents [186].

3.1.2. Sensitivity to psychostimulant drugs

One of the critical pharmacological abnormalities in schizophrenia and other psychosis-related disorders is enhanced sensitivity to psychostimulant drugs, including dopamine receptor agonists and NMDA receptor antagonists [88,97–99,104]. Prenatal immune challenge by various immunological stimuli successfully mimics these schizophrenia-related pharmacological abnormalities by increasing the behavioural sensitivity to low doses of the indirect dopamine receptor agonist amphetamine (AMPH) and the non-competitive NMDA-receptor antagonist dizocilpine (MK-801) and ketamine [65,115,117,119,120,143,160,198,199]. Prenatal infection-induced increases in the sensitivity to acute psychostimulant drug treatment are often indexed by a potentiation of the locomotor-enhancing effects of these drugs (see e.g. [115]).

It is well known that the locomotor enhancing effects of low doses of systemic AMPH (~1 mg/kg for rats, ~2 mg/kg for mice) are mediated by increased (impulse-dependent) DA transmission in the NAc [41,146], especially in its shell subregion [82,185]. Enhanced reaction to low doses of AMPH is therefore often suggestive of functional imbalance in mesolimbic (and especially accumbal) DA transmission. Consistent with this interpretation, adult rats and mice exposed to prenatal immune challenge display several DA abnormalities in dorsal and ventral striatal regions, which are indicative of enhanced DA activity in these areas (see Section 2.1). Hence, dopaminergic imbalances, especially in the NAc, may represent one of the critical neural substrates underlying the emergence of AMPH potentiation following prenatal immune challenge.

Since non-competitive NMDA-receptor antagonists such as MK-801 or ketamine increase DA release in the NAc [93,110,194] and stimulate the activity of VTA neurons [67,132], the efficacy of MK-801 to increase locomotor activity has also been attributed to increased dopaminergic transmission in mesolimbic structures. The neural substrates of the prenatal infection-induced potentiation of the locmotor-enhancing effects of acute treatment with non-competitive NMDA-receptor antagonists may thus also critically involve enhanced DA activity in mesolimbic structures. However, hyperlocomotor activity following acute pharmacological blockade of NMDA-receptors can also occur in the absence of endogenous dopamine [39,40]. An alternative explanation for locmotor hyperactivity following blockade of NMDA receptors may be that NMDA-receptor blockade may facilitate the inhibition of the corticostriatal glutamatergic pathway and eventually result in excessive activation of cortical and subcortical structures, thereby stimulating locomotor activity [37]. This raises the question whether the critical neural basis of the potentiation of the locmotor-enhancing effects of non-competitive NMDA-receptor antagonists seen in prenatally immune challenged animals may rather involve abnormalities in corticostriatal glutamatergic systems. Thus far, however, there is no direct evidence supporting this possibility. No signs of cortical and/or corticostriatal glutamatergic abnormalities have yet been detected in the brains of prenatally immune challenged animals. One possibility would therefore be that the apparent changes in DA-related neurochemical markers (see Section 2.1) may not only account for the potentiation of AMPH sensitivity in prenatally immune-challenged offspring, but they may also contribute to the enhancement of the locomotor-stimulating effects of systemic treatment with NMDA-receptor antagonist.

Besides the well-known functions of the meso-accumbal DA system in the mediation of locomotor activity, several other brain structures and neurotransmitter systems critically modulate spontaneous and drug-induced locomotor activity, especially the PFC and HPC [6,17,84,123,124]. The PFC regulates the activity of the NAc either through direct excitatory (glutamatergic) inputs on GABA projecting neurons in the NAc [27,126] or indirectly through the effects on other neurons involving different neurotransmitters systems in this same nucleus (for a recent review [49]). The NAc also receives prominent afferent fibers from the HPC and its allied structure entorhinal cortex [74,176,177], which together can critically influence DA activity in the NAc and thereby gain modulatory control over basal and drug-induced locomotor activity [18,19,145,170,195,197].

Considering the essential roles of PFC and HPC in the regulation and modulation of locomotor activity, it is reasonable to assume that neuroanatomical and neurochemical changes in these brain areas are likely to contribute to the potentiation of the locomotor-enhancing effects of psychostimulant drugs following prenatal immune challenge. For example, impairment in prefrontal D1R and D2R expression emerging in adult mice after prenatal immune challenge in early/middle gestation (see Section 2.1) may play a significant role in the potentiation of AMPH sensitivity. Indeed, several previous findings in rats can be taken as indirect evidence for this possibility. In the first place, selective blockade of D1Rs in the PFC has been shown to potentiate the locomotor-enhancing effects of intra-accumbal AMPH administration in rats [179,180]. Secondly, stimulation of prefrontal D2Rs attenuates the release of accumbal DA [49] and inhibits GLU-mediated excitatory drive on VTA DA neurons, which further inhibits mesolimbic dopaminergic activity [79]. Reduced D2R-mediated signalling in the PFC is thus also expected to

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enhance the locomotor-stimulating effects of systemic AMPH due to impaired inhibition of mesolimbic dopaminergic activity.

On the other hand, abnormal hippocampal functions may contribute to the emergence of enhanced behavioural sensitivity to psychostimulant drugs following prenatal immune challenge specifically in late gestation. As described above (see Section 2.2), prenatal immune challenge in late gestation leads to a marked loss of inhibitory inputs to the axon initial segment (AIS) of ventral hippocampal pyramidal neurons, which may ultimately decrease the inhibition of ventral hippocampal functions [148,183]. It is well known that decreased inhibition and/or stimulation of the vHIP can result in enhanced locomotor activity via increasing DA transmission in the NAc [18,19,101,145]. A decrease in the GABAergic inhibition of the vHIP in adult animals exposed to prenatal immune challenge in late gestation may thus lead to enhanced dopaminergic activity in accumbal structures upon pharmacological stimulation, thereby potentiating the behavioural reaction to DA-stimulating drugs such as PCP, MK-801, ketamine [93,110,194] and AMPH [41,82,146,185].

3.2. Prefrontal and hippocampal GABAergic and glutamatergic abnormalities: relevance to working memory impairment

The encoding and retrieval of memory are both thought to require the activation of a short-term memory buffer with a limited capacity, which is often referred to as working memory. It is used to hold the relevant information active for on-going behaviour including comprehension, reasoning and problem solving [12,13,72]. Working memory is known to be dependent on the integrity of both prefrontal and hippocampal functions: Deleterious effects of hippocampal damage on working memory function have been described for decades [15,29,129,130,141,147,196]; and current consensus further emphasizes the role of the prefrontal cortices and their interconnections with the hippocampus in mnemonic and executive controls in working memory [29,72].

At the molecular levels, several lines of evidence suggest that GABAergic and glutamatergic neurotransmission in prefrontal and hippocampal structures is crucial for intact working memory. Firstly, GABA-mediated inhibition, particularly through $GABA_A$ receptors, is an essential component in the regulation of neuronal rhythms and oscillatory activity, which is important for normal brain functions [125,164,165]. Impairments in prefrontal cortical GABAergic neurons and the resulting deficits in peri-somatic inhibition of pyramidal cells are believed to significantly contribute to working memory deficits in psychiatric disorders, especially in schizophrenia (see Section 2.2). Secondly, glutamatergic signalling via (hippocampal) NMDA receptors is critically involved in the encoding and retrieval of spatial and temporal memory [44,127,172], including working memory [14,134,136]. Hence, one plausible account of the neural bases underlying the emergence of working memory deficiency following prenatal immune challenge (see Table 1) would be that it is related to GABAergic and/or glutamatergic abnormalities. Support for this suggestion is yielded by recent immunohistochemical analyses demonstrating that prenatal immune activation can lead to various GABAergic and glutamatergic deficits in relevant brain areas, including PFC and HPC (see Section 2.2). Importantly, the efficacy of prenatal immune challenge to induce working memory deficits in adulthood noticeably differs between early/middle and late gestational periods [115,120,158]: whereas prenatal immune challenge during early/middle foetal development leads to adult spatial working memory deficits only when the demand on temporal retention is high, prenatal immune activation in late gestation induces adult spatial working memory impairments even when the demand on temporal retention is low. One expectation emerging from this contrast would be that prenatal immune challenge in late gestation can exert a more extensive neurodevelopmental impact on the relevant neural substrates underlying the disruption of spatial working memory, compared to prenatal immune challenge in early/middle gestation.

We have recently confirmed this expectation with respect to GABAergic and glutamatergic abnormalities in prefrontal and hippocampal structures. As already mentioned above (see Section 2.2), adult mice prenatally exposed to PolyI:C-induced immune challenge in late gestation display a pronounced GABAergic deficit in the PFC together with concomitant GABAergic and glutamatergic abnormalities in the HPC. In contrast, the GABAergic deficits which emerge following prenatal PolyI:C-induced immune activation appear to be restricted to PFC, and the hippocampal GLU system at adult age appears to be spared by early/middle prenatal immune challenge in mice. Hence, prefrontal (GABAergic) and hippocampal (glutamatergic and GABAergic) dysfunctions may have additive effects in the disruption of spatial working memory following prenatal immune challenge in late gestation. Accordingly, the concomitant disruption of hippocampal and prefrontal functions may severely impair mnemonic processing after late prenatal immune activation, thereby leading to the emergence of working memory deficits even when the demand on temporal retention is low. On the other hand, the existence of prefrontal pathology in the absence of parallel hippocampal neuropathology may result in working memory deficiency only in situations, in which the demand on temporal retention is high.

4. Conclusions

Based on the human epidemiological association between maternal infection during pregnancy and higher risk of schizophrenia in the offspring [25,33,34,144], an increasing number of experimental studies in rats and mice demonstrate that prenatal immune challenge is causally linked to the emergence of psychosis-related behaviour and pharmacological dysfunctions in adulthood. The infection-induced functional deficits are associated with multiple neuroanatomical, morphological and neurochemical abnormalities in various brain areas and neurotransmitter systems. These include pre- and post-synaptic changes in the central DA, GABA, GLU, and 5-HT systems, together with alterations in neuronal and glial cell number, structure and positioning. Experimental investigations in rats and mice thus confirm the expectation that infection-mediated interference with normal foetal brain development can disrupt the integrity of neuronal systems in postnatal life. Importantly, many of the identified neuronal abnormalities are directly implicated in the neuropathology of schizophrenia. Hence, there is considerable experimental evidence for assuming that prenatal exposure to infection and/or inflammation is a relevant environmental link to specific neuronal abnormalities implicated in schizophrenia and related psychosis-associated disorders.

Parallel functional and structural analyses suggest that prenatal infection-induced imbalances in the mesolimibic and mesocortical DA pathways may constitute critical neural mechanisms for disturbances in sensorimotor gating, abnormalities in selective associative learning and hypersensitivity to psychostimulant drugs. On the other hand, the emergence of working memory deficiency following prenatal immune challenge may be crucially linked to the concomitant disruption of GABAergic and glutamatergic functions in prefrontal cortical and/or hippocampal structures. These putative brain and behavioural relationships in the infection model of schizophrenia are illustrated in Fig. 1.

The causality of these brain and behavioural relationships schizophrenia should be further confirmed by additional structural and functional investigations. This would also help to develop and evaluate effective therapeutic treatments against psychosis-

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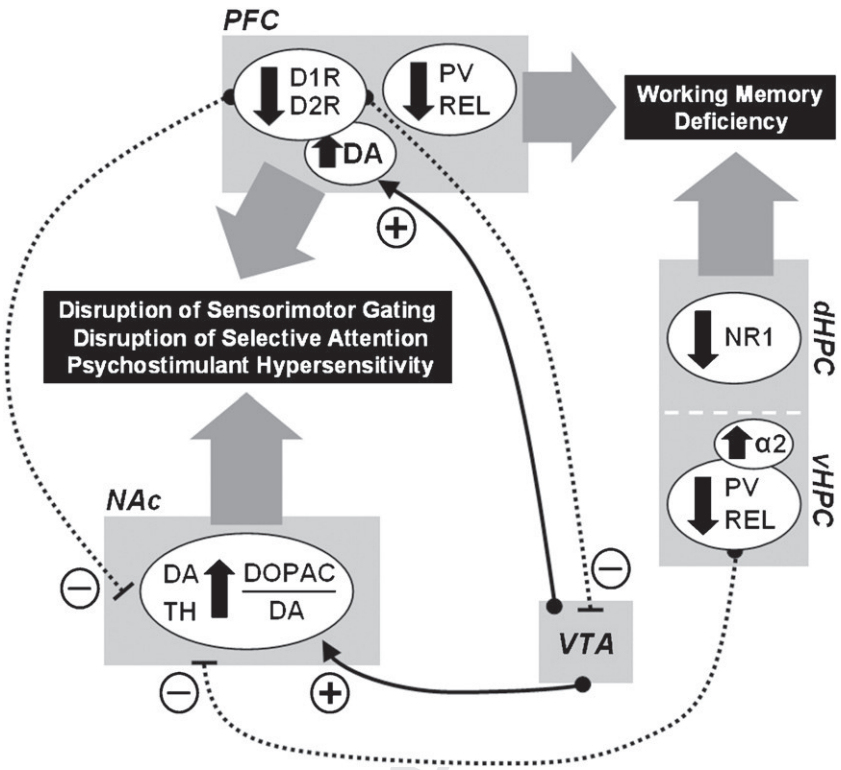

Fig. 1. Hypothesised neural basis of psychosis-related behaviour emerging in adult life following prenatal immune challenge. Hyperactivity of the meso-accumbal DA system includes enhanced tyrosine hydroxylase (TH) activity and DA release in the nucleus accumbens (NAc), as well as increased accumbal DA turnover (as indexed by the increased ratio between dihydroxyphenylacetic acid [DOPAC] and DA). Enhanced dopaminergic activity in the NAc may be critically involved in the precipitation of sensorimotor gating deficits, disruption of selective attention and hypersensitivity to psychostimulant drugs. Dopaminergic imbalances in the NAc may partly stem from diminished inhibitory control (indicated in dashed lines) from prefrontal cortex (PFC) and the ventral hippocampus (vHPC). The reduction in prefrontal inhibitory control of the NAc may arise from decreased DA D1 and D2 receptor (D1R and D2R) expression in the PFC, which may disrupt the activation of prefrontal excitatory (glutamatergic) inputs on inhibitory (GABAergic) neurons in the NAc. Likewise, decreased D1R and D2R expression in the PFC may attenuate the prefrontal inhibitory control of DA neurons in the ventral tegmental area (VTA), thereby facilitating hyperactivity of the meso-accumbal and meso-cortical DA pathways (indicated by the black arrows). Note that decreased prefrontal D1R and D2R expression may further contribute to the emergence of disrupted sensorimotor gating and increased sensitivity to psychostimulant drugs. The reduction in the inhibitory control of the NAc from the vHPC may stem from a loss of GABAergic inhibition of the vHPC, resulting from deficits in Parvalbumin (PV) and Reelin (REL) expression, which is accompanied by a compensatory up-regulation of the $GABA_A$ receptor subunit α2 at the axon initial segments of pyramidal neurons. The emergence of working memory impairment may be accounted for by the concomitant disruption of both hippocampal and prefrontal functions. The former includes impaired glutamatergic signalling at NMDA receptors in the dorsal hippocampus (dHPC), resulting from reduced expression of the NMDA receptor subunit 1 (NR1); and the latter involves a severe prefrontal GABAergic deficit marked by reduced PV and REL expression in the PFC. Note that the illustrated brain and behavioural relationships are influenced by both the specificity of the immune stimulus and the precise prenatal timing of the infectious event (see main text).

related behaviour emerging following prenatal immune challenge. Importantly, the longitudinal monitoring of prenatal infection-induced brain and behavioural abnormalities from pre-adolescent to adult life may significantly contribute to our understanding of the etiopathological mechanisms in schizophrenia, and it may help to establish early preventive interventions in individuals identified as being prodromally symptomatic of psychotic disorders.

Disclosure

The authors have no conflicts to disclose.

Uncited reference

[83].

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