REVIEW ARTICLE

Adverse neuropsychiatric development following perinatal brain injury: from a preclinical perspective

Ivo Bendix[1], Martin Hadamitzky[2], Josephine Herz[1] and Ursula Felderhoff-Müser[1]

Perinatal brain injury is a leading cause of death and disability in young children. Recent advances in obstetrics, reproductive medicine and neonatal intensive care have resulted in significantly higher survival rates of preterm or sick born neonates, at the price of increased prevalence of neurological, behavioural and psychiatric problems in later life. Therefore, the current focus of experimental research shifts from immediate injury processes to the consequences for brain function in later life. The aetiology of perinatal brain injury is multi-factorial involving maternal and also labour-associated factors, including not only placental insufficiency and hypoxia–ischaemia but also exposure to high oxygen concentrations, maternal infection yielding excess inflammation, genetic factors and stress as important players, all of them associated with adverse long-term neurological outcome. Several animal models addressing these noxious stimuli have been established in the past to unravel the underlying molecular and cellular mechanisms of altered brain development. In spite of substantial efforts to investigate short-term consequences, preclinical evaluation of the long-term sequelae for the development of cognitive and neuropsychiatric disorders have rarely been addressed. This review will summarise and discuss not only current evidence but also requirements for experimental research providing a causal link between insults to the developing brain and long-lasting neurodevelopmental disorders.

INTRODUCTION

Over the past decades, it has become clear that the perinatal environment in conjunction with genetic factors shapes an individuals' predisposition to increased risk of disease[1]. Brain development is influenced by various intrauterine, prenatal and postnatal events interacting with the genotype to affect the neural systems related to emotions, cognitive and language abilities, which may also increase the risk for psychopathology later in life. Noxious stimuli include maternal infection yielding excess inflammation, maternal stress, obesity and metabolic disorders, many of them associated with intrauterine growth restriction (IUGR) and/or preterm birth. In addition to these foetal elements, the immature brain is at risk to be exposed to additional injurious stimuli during or early after birth, e.g. infection, foetal hypoxia, intrapartum oxygen deprivation, hyperoxia, stress from maternal separation and medical procedures, exposure to medication or anaesthesia further increasing the risk for the development of behavioural and neuropsychiatric brain diseases in later life.

Perinatal brain injury affects infants born at all gestational ages with a higher incidence in the most vulnerable very immature group of patients. Improved obstetric and neonatal care in conjunction with the use of preventive and/or therapeutic strategies such as antenatal steroids prior to preterm delivery and the introduction of hypothermia treatment for hypoxic–ischaemic encephalopathy (HIE) has led to increased survival rates and also reduction of severe neurological impairment. For instance, a recent meta-analysis of world-wide cohorts born after 2006 revealed that the pooled prevalence of cerebral palsy in infants born extremely preterm was with a rate of 6.8% (95% confidence interval 5.5–8.4) reduced compared to previous studies[2]. In the majority of cases suffering from an adverse perinatal environment, physiological brain maturational processes are affected leading to a variety of neurodevelopmental disorders in later life such as cognitive impairment, autism spectrum disorders (ASD), attention deficit (hyperactivity) disorder (ADHD) and psychiatric disease like schizophrenia (SZ)[3].

While these sequelae are frequently related to perinatal brain injury of various origins, investigations of the underlying anatomical and pathophysiological processes remain a major goal for research in neonatal neurology. In this review, we give an overview on multiple risk factors for the development of neuropsychiatric diseases focussing on recent findings derived from experimental models (Table 1). We further summarise shared cellular and molecular mechanisms across a variety of neurodevelopmental disorders. Finally, we discuss challenges for preclinical research focussing on the assessment of neuropsychiatric symptoms in experimental models.

RISK FACTORS FOR THE DEVELOPMENT OF NEUROPSYCHIATRIC DISEASES

Maternal and early postnatal stress

Human studies suggest a positive association between maternal stress and the risk of preterm delivery, foetal growth restriction, altered social behaviour, ADHD symptoms and impaired cognitive performance[4,5]. Furthermore, analysis in siblings demonstrated that exposure to high levels of cortisol in utero are associated with lower adult educational attainment and verbal cognition[6]. The

[1]Department of Paediatrics I, Neonatology and Experimental Perinatal Neuroscience, University Hospital Essen, University Duisburg-Essen, Essen, Germany and [2]Institute of Medical Psychology and Behavioural Immunobiology, University Hospital Essen, University of Duisburg-Essen, Essen, Germany
Correspondence: Ivo Bendix (ivo.bendix@uk-essen.de) or Ursula Felderhoff-Müser (ursula.felderhoff@uk-essen.de)

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Table 1. Modelling adverse neuropsychiatric development following perinatal insults

Models	(Neuropatho)physiology	Neuropsychiatric outcome/behavioural deficits	References
Maternal and early postnatal stress			
Prenatal restraint stress (pregnant Sprague–Dawley rats 45 min, 3×/day from embryonic day 11 (E11) until birth)	Male offspring, postnatal day 14 (PND14) and PND22: - reduced serum leptin levels - reduced expression of γ2 subunit of gamma-aminobutyric acid A receptors in amygdala - altered expression of metabotropic glutamate receptor 2/3/5 receptors in the amygdala and hippocampus PND30–300: - hypertrophic adrenal glands PND90–660: - reduced hippocampal cell proliferation	PND22: - increased anxiety (reduced time in open arms of elevated plus maze (EPM)) - more ultrasonic vocalization in response to isolation from their mothers and later suppression of ultrasonic vocalization after exposure to an unfamiliar male odour PND120: - delayed learning in a spatial memory task (Water maze)	9,10
Maternal separation (rat pups separated for 3 h/day between PND2–14)	PND60: - basal adrenocorticotropic hormone levels increased - reduced adrenocorticotropic hormone levels after restraint stress - decreased noradrenaline in limbic regions and increased 5-hydroxyindoleacetic acid levels in the frontal cortex and hippocampus	PND60: - increased anxiety (reduced number of entries into open arms and increased time in closed arms of EPM)	21
Maternal social behaviour deficits (Long–Evans rat dams had decreased nesting/bedding material between PND8 and 12)	PND20–22 and PND42–48: - reduced neural activation (cFos) in amygdala, medial prefrontal cortex and nucleus accumbens	PND20–22 and PND42–48: - social behaviour deficits (less time in the social chamber) PND75: - depressive-like behaviour in forced-swim test	22
Maternal separation (Sprague–Dawley rat pups, 3 h/day, PND3–21)	PND21–60: - hypomyelination and ultrastructural changes in medial prefrontal cortex in males and females - impaired oligodendrocyte precursor cell differentiation in medial prefrontal cortex via decreased the expression of histone deacetylases 1/2 and activation of Wnt signalling	PND21 and PND60: - increased anxiety (decreased time in centre of open field (OF)) - increased grooming and circling behaviour - cognitive deficits: (decreased response in nonmatching-to-place task in T maze) - social behaviour deficits (reduced social interaction with stranger rats)	23
Maternal obesity			
Maternal obesity (12-week-old C57BL/6 dams, high-fat diet, 60% calories from fat 6 weeks prior to mating, control diet: 10% calories from fat)	PND42: - increased microglia activation in amygdala in female but not in male offspring - increased cerebral pro-inflammatory cytokine levels (IL-1beta and TNFalpha) in female but not male offspring	PND32–35: - hyperactivity (increased distance travelled in open field in male offspring) - increased anxiety in female offspring (decreased distance in centre over total distance travelled in OF) PND39–42: - social behaviour deficits in female but not male offspring (reduced interest in stranger mice in three-chamber sociability test after prolongation of maternal high-fat diet into the lactation period)	31
Maternal high-fat diet (Long–Evans rats, 60% fat for 4 weeks prior mating until weaning, controls: standard chow (13.5% fat))	PND110: - heightened response to restraint stress and a slower return to baseline corticosterone levels - increased mineralocorticoid receptor mRNA expression in amygdala - increased glucocorticoid receptor mRNA expression in amygdala of females - higher levels of nuclear factor kappa B transcript in female offspring - increased abundance of IL-6	PND90: - increased anxiety in males (less time in centre of OF and decreased preference for open arms of EPM)	33
Maternal high fat diet (C57BL/6 dams, high-fat diet (32% fat) 6 weeks before mating and throughout pregnancy and lactation, controls: normal diet (4% fat))	PND21: - increased lipid peroxidation - decreased mRNA and protein levels of BDNF in the hippocampus PND35: - decreased dendritic length, number of branches and dendrite formation	PND21–28: - decreased number of readings in OF - cognitive deficits (increased distance to reach the target hole of the Barnes maze)	35
Maternal high-fat diet (C57BL/6 dams, 60% from fat, 3 weeks before mating prolonged until weaning, control: normal chow)	PND90: - reduced amino acid levels (glutamate, aspartate, GABA, taurine and tyrosine) in the medial prefrontal cortex and hippocampus	PND90 and PND540: - cognitive disabilities evident in a reference memory (T maze) and in an associative learning (two-way active avoidance) paradigm - potentiation of prepulse inhibition	36
Placental insufficiency/IUGR			
Intrauterine artery ligation (Dunkin–Hartley guinea pigs, E28–30)	PND56: - enlargement of lateral ventricles - atrophy of basal ganglia and septal region	PND84: - reduced prepulse inhibition	53
Maternal caloric undernutrition (ICR mice, 50% food restriction, E12–15 and PND0–21)	PND45, male offspring: - increased brain insulin receptor expression - reduced PSD95 expression	PND25–35 - learning disabilities (Morris water maze)	56
Meso-ovarian vessel cauterisation (Wistar rats, E17)	PND35: - reduced levels of PSD95 and synaptophysin in the hippocampus	PND25–35: - spatial memory deficits (water maze)	55

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Table 1 continued

Models	(Neuropatho)physiology	Neuropsychiatric outcome/behavioural deficits	References
Hypoxia–ischaemia			
Neonatal hypoxia–ischaemia (PND7 Sprague–Dawley rats, right common carotid artery ligation, 3 h hypoxia at 8% oxygen)	PND95: - macroscopic injury to the hippocampus, ranging from hippocampal atrophy and neuronal loss to severe reduction of the ipsilateral hemisphere with the loss of cerebral cortex and hippocampus	PND21: - increased motor activity PND36: - cognitive deficits (difference in spontaneous and forced alternation in T maze) PND50: - spatial memory deficits (increased error rates in water maze) PND90: - increased apomorphine-induced stereotypy in open field	74
Neonatal hypoxia–ischaemia (PND4 Sprague-Dawley rats, bilateral carotid artery occlusion followed by to hypoxia, 8% oxygen for 15 min)	PND21: - reduced white matter size, decrease in thickness of corpus callosum, reduction in numbers of mature oligodendrocytes and hypomyelination - enlarged ventricles, decrease in hippocampal axon dendrite length, reduced numbers of tyrosine hydroxylase-positive neurons - enhanced microgliosis	PND21: - hyperactivity (increased distance travelled in OF) - reduced anxiety/increased impulsivity (increased entries and time in open arms of the EPM)	69
Neonatal hypoxia–ischaemia (PND10 129T2xC57BL/6 F1 hybrid mice, right common carotid artery ligation followed by 1 h hypoxia at 10% oxygen)	PND94: - decreased brain weight and hippocampal injury	PND49: - deficits in novel object recognition PND56-91: - spatial memory deficits (water maze) - increased circling following apomorphine challenge	72
Neonatal hypoxia–ischaemia (PND9 C57BL/6 mice, occlusion of the right common carotid artery followed by 1 h hypoxia (8 or 10% oxygen)	PND16: - neuronal and axonal loss - hypomyelination and astrogliosis - microglia and endothelial activation - peripheral leukocyte infiltration - increased pro-inflammatory cytokine levels (IL-6, IL-1beta) PND51: - brain atrophy mainly affecting the cortex, hippocampus and striatum	PND28–49: - reduced anxiety (increased time in open arms in EPM) - cognitive deficits (reduced recognition memory in object recognition)	67,71
Neonatal hypoxic–ischaemia (left common carotid artery ligation in male PND9 C57BL/6 mice followed by 30 min hypoxia at 10% oxygen)	PND55: - increased reactive gliosis (GFAP, Iba1) in the hippocampus - hippocampal volume reduction by >50% - reduced neuronal density	PND50–54: - cognitive deficits (reduced recognition memory in object recognition)	70
Neonatal hypoxia–ischaemia (PND10 Wistar rats, occlusion of the right common carotid artery followed by 65 min hypoxia at 8% oxygen)	PND11, 24 and 94 - brain atrophy mainly affecting hippocampal and thalamo-striatal regions	PND50–70: - cognitive deficits (recognition memory in object recognition)	75
Prenatal transient systemic hypoxia–ischaemia, (Sprague–Dawley dams, E18, transient occlusion of uterine arteries for 60 min, shams: laparotomy for 60 min)	PND35–40: - diffusion tensor imaging abnormalities - impaired axonal integrity and reduced myelination	PND25–32: - hyperactivity (distance and velocity in OF) - social behaviour deficits (reduced social interaction)	77
Hyperoxia			
24 h 80% oxygen (Wistar rats, PND6)	PND7: - increased lipid peroxidation - increased microglia activation and pro-inflammatory cytokine expression - oligodendrocyte degeneration and impaired maturation - reduced mRNA expression of synaptic plasticity-related molecules PND11: - hypomyelination PND125: - microstructural white matter abnormalities in corpus callosum and external capsule	PND30 and PND90: - cognitive deficits (increased time to find escape hole, probe trial in Barnes maze, and recognition memory deficits in object recognition)	88,95
48 h 80% oxygen (C57BL/6 mice, PND6)	PND30 and PND53: - disturbed white matter diffusivity in corpus callosum	PND44–53: - hyperactivity (higher maximum velocity in wheel running) - impaired capacity to compensate complex motor challenge (irregularly spaced crossbars in running wheel)	96
Inflammation			
Maternal immune activation (MIA, YFP-H C57BL/6 mice, E12.5, 20 mg/kg poly I:C, i.p.)	PND17 and PND90: - reduced cortical spine density, dynamics PND17–19: - altered excitatory and inhibitory synaptic connectivity in offspring	PND60: - repetitive behaviour (increased marble burying)	104
MIA (C57BL6/N mice, E9, 5 mg/kg poly I:C, i.v.)	PND40 and PND90: - impaired expression of presynaptic and postsynaptic proteins in the hippocampus PND90: - increase in hippocampal IL-1β expression	PND90: - prepulse inhibition deficits	105

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Models	(Neuropatho)physiology	Neuropsychiatric outcome/behavioural deficits	References
MIA (C57BL/6, E15, 5 mg/kg poly I:C on E15, i.p.)	PND120, male offspring: - decreased cell proliferation and reduced dendritic intersections in dentate gyrus	PND120, male offspring: - prepulse inhibition deficits of the acoustic startle response - cognitive deficits (reduced spatial memory in the T and Morris water maze) - increased depressive like behaviour (tail-suspension test)	[106]
MIA (mice, E12.5, 20 mg/kg poly I:C, i.p)	E14.5: elevated IL-17Ra mRNA expression in the brain	PND9: - abnormal ultrasonic vocalisation PND56–360: - social interaction deficits in male mice - increased repetitive behaviour (marble burying)	[108]
Cytomegalovirus infection (BALB/c mice, PND0, 750 plaque-forming units, i.p.)	PND30: - brain atrophy and cerebellar hypoplasia	PND 30–40: - social behaviour deficits (lack of preference for social novelty)	[109]
MIA (rhesus monkeys; E43, 44, 46, 47, 49 and 50; 0.25, 0.5 and 1 mg/kg poly I:C, i.v.)	PND1280: - smaller apical dendrites and greater number of oblique dendrites in dorsolateral prefrontal cortex	PND180: increased whole-body stereotypies (pacing)	[112]
MIA (C57BL/6 mice, 5 mg/kg poly I:C, i.v. either at E9 or E17)	PND24 and PND180: MIA E9: - reduction of dopamine D1-receptors, Reelin and Parvalbumin in medial prefrontal cortex - reduced Reelin-positive cells in hippocampal and reduced doublecortin expression in dentate gyrus MIA E17: - reduction in NMDA-receptor subunit NR1 in dorsal hippocampus - decrease in postnatal Reelin- and Parvalbumin-positive cells in the medial prefrontal cortex - reduced doublecortin expression and enhanced apoptosis (caspase-3) in dentate gyrus	PND98–112: MIA E9: - reduced prepulse inhibition of acoustic startle response MIA E17: - impaired working memory - enhanced locomotor reaction to dizocilpine (MK-801) - perseverative behaviour (reversal learning in the T maze)	[114,117]
MIA (Sprague–Dawley rats, 50 µg/kg LPS, i.p., on E12 or E16)	E18: - decreased dopaminergic neurons in the midbrain (MIA at E16)	PND30 - reduced anxiety (more time in centre of the open field, MIA E16) - altered amphetamine response in reward processing (MIA E12)	[115]
Postnatal inflammation (Wistar rats, PND3, 0.25 mg/kg LPS)	PND5: - cellular degeneration, reactive gliosis - increased IL-1beta levels PND11: - hypomyelination PND120: - microstructural deficits in the white matter assessed by diffusion tensor imaging	P30 and P90: - cognitive deficits (latency in probe trial in the Barnes maze, recognition memory in object recognition)	[120]
Postnatal inflammation (Swiss mice, 10 µg/kg IL-1beta twice a day from PND1 to PND4 and once on PND5, i.p.)	PND15 and PND30: - increase of oligodendrocyte progenitors associated with a reduction of mature PND30: - reduced expression of myelin proteins PND35: - microstructural abnormalities in the white matter oligodendrocytes	PND29: - cognitive deficits (recognition memory in novel object recognition and in object location memory)	[121]
Postnatal inflammation (Sprague–Dawley rats, PND14, 100 µg/kg LPS)	PND14: increased cFos positive neurons in central amygdala	PND40: - increased anxiety (less time in open arms of EPM for females) PND65: - altered fear behaviour (increased freezing rate in auditory cued fear conditioning)	[122]
Multiple hit			
MIA (Lewis rats, 200 µg/kg LPS, i.p., every 12 h from E17 until end of gestation)+hypoxia–ischaemia at PND1 (occlusion of the right common carotid artery followed by 210 min hypoxia at 8% oxygen)	PND25: - enlarged right lateral ventricles - decreased thickness of corpus callosum - reactive astrogliosis and microgliosis - decreased number of dopaminergic neurons in substantia nigra	PND15, 20, 25: - reduced exploratory behaviour and increased immobility (decreased total distance travelled in OF, increased freezing)	[124]
transient systemic hypoxia–ischaemia (Sprague–Dawley rats, 60 min uterine artery occlusion at E18)+perinatal inflammation (intra-amniotic injection of 4 µg LPS after occlusion)	PND2: - ventricular enlargement - increased microglial and astroglial immunoreactivity PND15: - reduced myelin basic protein expression	PND28: - motor impairment and gait abnormalities in forelimbs and hindlimbs (DigiGait analysis)	[125]
MIA (1 mg/kg poly I:C i.v. E9, C57BL/6 mice)+stress in puberty (electric foot shock, restraint stress, swimming stress, water deprivation, repeated home cage changes, PND30–40)	PND41: - increased microglia activation and pro-inflammatory cytokine levels in the hippocampus PND70: - increased dopamine in the nucleus accumbens independent of stress - decreased serotonin in medial prefrontal cortex independent of MIA	PND70-PND100: - increased anxiety independent of MIA (increased time in open arms of EPM) - disruption of selective associative learning independent of MIA and stress (impaired latent inhibition in conditioned active avoidance paradigm) - synergistic effects in sensorimotor gating	[129]

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Table 1 continued

Models	(Neuropatho)physiology	Neuropsychiatric outcome/behavioural deficits	References
MIA (100 μg/kg LPS i.p., E18 and E19, Wistar rats) +systemic hypoxia (PND4, 8% oxygen, 140 min)	- synergistic effect for dopamine in the hippocampus PND18 and PND30: - hypomyelination PND18 and PND69: - impaired oligodendrocyte maturation PND18: - microglia activation and astrogliosis	deficiency (reduced PPI of the acoustic startle reflex) PND28: - reduced social play behaviour in males (pinning) PND35: - ASD-like symptoms (repetitive grooming) PND49: - increased anxiety (reduced transition inner–outer zone in open field)	[128]

underlying reasons for these effects are assumed to be stress-related alterations in brain structure. As such, it was shown that children born to mothers who experienced high levels of anxiety in the early second trimester of pregnancy or chronic perceived stress had region-specific reductions in grey matter volume in the cortex, hippocampus and cerebellum[7,8]. Nevertheless, information about the detailed cellular and molecular mechanisms is mainly limited to animal studies[4]. In experimental models, prenatal stress can be induced either by restraint under bright light, nest manipulation or predator stimuli, which alters the offsprings' anxiety-related behaviour, learning and memory and stress regulation[4,9–12]. Neuropathology includes alterations in hippocampal gene expression, cortical inhibitory neuron subtypes and hypothalamic–pituitary–adrenal axis responses or cortisol reactivity[13–15]. Furthermore, basic neurodevelopmental processes like cellular proliferation, differentiation and migration are delayed[16,17]. Importantly, maternal stress is supposed to interact with multiple genes involved in neurogenesis, serotonergic genes and genes involved in GABAergic transmission, implicated in both SZ and ASD[18]. For example, interaction between the serotonergic gene 5-hydroxytryptamine transporter (5-HTT aka. *sodium-dependent serotonin transporter and solute carrier family 6 member 4* (*SLC6A4*)) and stress was observed for ultrasonic vocalisation[19] and ASD-like stereotypic repetitive grooming behaviour[20]. In addition to maternal stress, early postnatal stress models have been developed with maternal separation being one of the most prominent causes leading to long-lasting increases in anxiety, depressive behaviour and disruption of stress responses. These changes are accompanied by reduced neural activation in the amygdala and other areas implicated in social functioning, including the medial prefrontal cortex and nucleus accumbens[21,22]. Recently, it was shown that long-lasting stress (i.e. 3 h maternal separation daily for the first 3 postnatal weeks) results in increased anxiety and reduced social interaction accompanied by impaired oligodendrocyte differentiation and myelination in the prefrontal cortex[23]. Nevertheless, often only single regions and single cell types were analysed. Other molecular events such as alteration not only in synaptic strength and neuron connections but also inflammatory processes may contribute to early stress-induced behavioural alterations in later life. The relationship between synaptogenesis, synaptic pruning and inflammation has been demonstrated in a variety of studies[24–26]. However, whether these mechanisms are associated with early-life stress and later life changes remains to be investigated.

Maternal obesity
Causal links between maternal obesity and the development of severe perinatal brain injury, e.g. periventricular leukomalacia, HIE or intraventricular haemorrhage are rather scarce[27,28]. In contrast, high amount of human studies indicate that it is associated with an increased risk for various mental health disorders, such as not only ADHD, ASD, depression and SZ but also cognitive impairments (reviewed elsewhere[29]). This is supported by animal research[30]. For instance, in a rodent model of maternal high-fat diet (HFD) it was shown that female offspring revealed decreased sociability and males presented with increased hyperactivity[31]. However, this seems to contradict other reports demonstrating that HFD leads to signs of anxiety and depression assessed in the elevated plus maze (EPM), open field (OF) and forced swim test in male offspring[32,33]. In addition to rodents, a non-human primate model was used demonstrating that adiposity in pregnancy increases the risk of impulsive and disruptive behaviour[34]. Besides alteration of emotions, cognitive function is reduced with delayed spatial learning, deficits in reference memory and associative learning accompanied by attenuated levels of amino acids in the medial prefrontal cortex and hippocampus[35,36]. Preclinical studies in rodents and primates suggest abnormal development of the serotonergic and dopaminergic system and obesity-induced inflammation as underlying mechanisms[29,34]. This is supported by human studies demonstrating that maternal obesity is associated with changes in cytokines, hormones and acute-phase proteins in the second trimester and with an increased risk of maternal infection or childhood asthma[37,38].

Placental insufficiency
IUGR often caused by placental insufficiency is a major contributor to neurodevelopmental deficits involving problems in motor skills, cognition and memory in school children[39]. It is assumed that deviant brain development and altered maturational processes may lead to increased chances of later cognitive, emotional and behavioural problems[40–42]. Neuroimaging studies revealed structural brain alterations and disturbed white matter organisation leading to impaired neurodevelopmental outcomes, which persist into young adulthood[43–45].

Growth-restricted foetuses due to placental insufficiency are chronically hypoxemic and hypoglycaemic. In rodents, placental dysfunction can be caused by reduced utero placental perfusion leading to hypertension and placental ischaemia[46,47] or genetic knockdown of the insulin receptor reflecting maternal diabetes[48]. Despite initial epidemiological evidence indicating a relationship between these maternal metabolic disorders (i.e. hypertension and diabetes) and the risk for the development of SZ[49,50], animal research in terms of long-term neuropsychiatric outcomes in above described experimental models is still lacking.

Most commonly applied models for evaluation of neurodevelopment in IUGR offspring include umbilical/uterine artery ligation or chronic hypoxia in sheep, piglets or rodents[39]. Neuropathological consequences include reductions in total brain volume, myelination deficits and impaired brain connectivity[39]. Furthermore, unilateral ligation of the uterine artery at mid-gestation was associated with ventriculomegaly, reduced basal ganglia volume, impaired synaptogenesis and altered cerebellar Purkinje cell development in the guinea-pig brain at adolescence, resembling anatomical changes found in some individuals with SZ[18,51–54]. Of note, prepulse inhibition (PPI) of the acoustic startle response (ASR) was reduced[53]. In addition to the PPI deficit that is supposed to parallel sensorimotor gating deficits observed in SZ, cognitive deficits have been observed in rodent models of IUGR induced

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either by maternal caloric undernutrition or by meso-ovarian vessel cauterisation leading to learning disabilities and spatial memory deficits in adolescent offspring[55,56].

Hypoxia–ischaemia (HI)
Another frequent insult in the perinatal period is term asphyxia with HIE affecting approximately 1.5–3 in 1000 live births[57]. Despite improvement of outcomes after introduction of hypothermia treatment mortality remains significant and severe motor and cognitive impairment may lead to cerebral palsy evident in the first 2 years of life. Beside the severe forms of brain injury children may also suffer from attention, memory and behaviour problems, requiring developmental surveillance beyond 2 years of age. Diversity of outcome across grades of HIE is reported but only few studies have addressed the milder consequences of HIE at school age both in the pre- and post-cooling period[58–60]. Furthermore, children with diagnosed stroke in the neonatal period, a disease with an incidence between 7.1 in 100.000 and 16 in 100.000 live births, may also present with poor neurological and psychosocial outcome, which is largely dependent on the lesion size[61–64]. Those deficits can be attributed to the pattern of injury and affected brain structures, such as hippocampus, cortex and striatum[65].

The most commonly used neonatal asphyxia model has been established in rodents by Rice–Vannucci in 1981 with unilateral common carotid artery (CCA) occlusion followed by systemic hypoxia (HI) leading to excitotoxicity, apoptosis, inflammation and subacute white and grey matter injury resulting in long-term brain atrophy mainly affecting cortex, hippocampus and striatum[66–68]. This type of injury leads to long-term sensorimotor deficits while general locomotor activity is only transiently increased resolving at 3 weeks of age[67,69,70]. This transient increase in locomotor activity may reflect hyperactivity, a major hallmark of ADHD. Furthermore, adolescent and young adult animals reveal reduced anxiety, an increased risk-taking behaviour, deficits in sustained attention and increases in impulsivity and compulsivity[67,69,71–73]. Together, these results suggest that HI contributes to the development of characteristics related to ADHD. In addition to alterations in impulsive behaviour, several groups also demonstrated deficits in cognitive abilities either in recognition or working memory or learning capability[67,69–71,74,75]. With regard to symptoms associated with SZ, discrepant results have been described. While unilateral HI in 10-day-old mice did not modulate sensorimotor gating[72], bilateral CCA ligation in 12-day-old rats revealed a significant deficit in this behavioural domain[76]. The variability of outcomes can be most likely explained by differences in experimental models, age and species.

In addition to postnatal HI in term-born equivalent rodents a prenatal hypoxic–ischaemic brain injury model has been recently developed. Offspring of dams exposed to transient intrauterine systemic HI have been shown to develop symptoms of ASD revealed by poor social interaction[77]. Subplate neuronal loss and impaired cortical maturation resulting in impaired thalamocortical connections have been discussed as potential underlying mechanisms[77].

Hyperoxia
While HI causes an acute disruption of oxygen supply reflecting asphyxia, preterm birth is frequently associated with exposure to non-physiological high oxygen concentrations. This is caused by a sudden rise in oxygen tension compared to intrauterine conditions and is further increased by intensive care[78,79]. Although our understanding of neuropathological hallmarks of hyperoxia-triggered brain injury has increased within the past decade[80], involving inflammatory responses and induction of reactive oxygen species associated with oligodendroglial cell death and hypomyelination triggering ultrastructural changes of the developing white matter[81–94], the evaluation of long-lasting functional deficits has only recently begun[88,95,96]. Neonatal hyperoxia is

associated with reduced motor-skill learning and memory deficits assessed in the complex running wheel, Barnes maze and novel object recognition that persist into late adulthood[88,95,96]. These findings resemble the difficulties observed in neurodevelopmental follow-up studies in ex-preterm infants, emphasising the importance of experimental preclinical research.

Inflammation
Early perinatal immune activation is associated with long-lasting consequences on cognitive and emotional health throughout life. Clinical studies have linked early- and late-onset infections to adverse outcome with development of cerebral palsy[97]. In addition, pattern of inflammatory markers have been related to neurological outcome in very immature infants as investigated up to 10 years of age[98,99]. Different models of immune activation have been established. The most common immunogens are the viral mimetic polyinosinic–polycytidylic acid (poly I:C) and the bacterial mimetic lipopolysaccharide (LPS). Poly I:C induces several symptoms of ASD and SZ, such as impaired cerebral communication, abnormal social and repetitive behaviour, decreased sensorimotor gating, working memory deficits and increased anxiety[100–102]. These behavioural abnormalities are associated with neuropathological alterations, e.g. not only reduced cortical thickness and decreased volumes of hippocampus, amygdala and striatum[103] but also ASD-associated aberrations in Purkinje cells and altered levels of synaptic proteins, as well as deficits, in synaptic transmission[102,104–106]. Furthermore, neurochemical alterations involving serotonergic and dopaminergic signalling have been linked to SZ and ASD pathology[101,107]. While LPS and poly I:C induce a general rise in pro-inflammatory cytokines, prenatal administration of selective cytokines such as interleukin-6 (IL-6) or IL-17 are sufficient to elicit ASD- and SZ-like behaviours[102,108]. Besides these artificial immune stimuli, models of congenital viral infections have been used, such as cytomegalovirus infection leading to delayed acquisition of neurological milestones (e.g. righting and grasping reflexes, cliff aversion and negative geotaxis) and disturbances in social behaviour and exploratory activity in adolescent animals[109]. Clinical signs were accompanied by brain atrophy, cerebellar hypoplasia and neuronal loss[109]. In spite of the huge number of available models altogether underpinning the detrimental impact of perinatal inflammation on long-term neurodevelopment, it needs to be critically emphasised that most outcome measures focus on distinct and selective behavioural domains, single brain regions and/or single analysis time points in a single animal model. Comprehensive systematic analyses identifying common neurobiological principles underlying distinct pathologies should be a future goal in this research field.

In addition to immune stimuli, several different species have been studied with various outcomes, i.e. while maternal treatment with poly I:C in mice leads to long-lasting deficits in sensorimotor gating in both male and female[102], Wistar rats seem to be less sensitive to maternal immune activation as sensorimotor deficits were only observed in males[110]. To overcome limitations regarding translation, non-human primate models of maternal immune activation have been developed[111,112] also recapitulating symptoms of neurodevelopmental disorders, e.g. abnormal repetitive behaviour.

Timing of immune challenge seems to be critical not only for foetal brain pathology[113] but also for long-term behavioural outcomes. For instance, maternal immune activation with poly I:C at late gestation is supposed to be more effective to induce working memory deficits compared to early gestation[110,114]. Similarly, maternal LPS injection at early gestation (i.e. embryonic day 12 (E12)) leads to impaired reward seeking behaviour while at late gestation (i.e. E16) impaired motor behaviour is induced[115]. Comparative analysis in the poly I:C model further demonstrated that prenatal immune activation at E9 but not at E17 reduces OF

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exploration, impairs the latent inhibition effect of associative learning and alters sensorimotor gating[82,114,116,117]. On the other hand, E17 but not E9 immune activation led to perseverative behaviour[117]. Considering the delay in rodent brain development compared to humans, with the first postnatal week in rodent brain development corresponding to the third trimester in humans[118,119], several postnatal models of inflammation have been developed. A single low-dose LPS injection at postnatal day 3 (PND3) or repetitive injections of IL-1beta over the first 5 PNDs impairs recognition memory, which is accompanied by long-lasting alterations of the white matter microstructure[120,121]. Interestingly, locomotor and anxiety-related behaviour were not modulated[120]. In addition to cognitive dysfunction, pain and conditioned fear responses can be modulated by neonatal inflammation as previously shown after immune challenge with LPS at PND14[122].

MULTIPLE HIT HYPOTHESIS

Epidemiological studies suggest that the probability to develop a neuropsychiatric disorder does not only rely on a single risk factor but also requires exposure to multiple "hits". For instance maternal immune activation is supposed to be a "disease primer" increasing susceptibility to effects of genetic mutations and postnatal risk factors that synergise to trigger mental diseases in later life[102,123]. This is supported by clinical and experimental data, e.g. the effect of maternal infection in increasing the risk for SZ is higher in families with SZ history[101]. In preclinical models, it was shown that low-dose poly I:C synergises with SZ- and ASD-related genes like DISC1, NRG1, NR4A2 and TSC2 inducing increased ASD- and SZ-related abnormalities compared to single insults[101,102,107].

In addition to the combination with genetic variations, animal models of prenatal inflammation have been combined with intrauterine or early postnatal HI[124–127]. However, the majority of studies mainly focussed either on analysis of acute inflammatory responses and/or pathological alterations involving for example myelination deficits[126,127]. Furthermore, correlations to behavioural changes have rarely been assessed and if so these analyses focussed on motor deficits that were similar in single intrauterine-induced hypoxic–ischaemic injury and in the combined setting[125]. Analysis of behaviours relevant to mental disorders have only recently been explored in more subtle models of white matter injury, e.g. by combination of foetal inflammation with postnatal hypoxia not involving severe lesions or gross anatomical changes. This combination led to long-term changes in oligodendrocyte maturation, which was associated with increased anxiety and signs of autism-like behaviour, i.e. reduced social play behaviour and increased repetitive grooming[128]. Besides episodes of hypoxia, exposure of preterm babies to high oxygen concentrations is critical in terms of brain development (see above). Combining an inflammatory stimulus (i.e. LPS) with hyperoxia (80% oxygen) results in long-lasting impairment of white matter microstructural integrity, which did not significantly differ compared to single insults. However, underlying mechanisms were different in so far that hyperoxia but not LPS predominantly induced apoptotic cell death while LPS rather impaired oligodendrocyte maturation[82]. Even though these pathophysiological processes are important to understand, analyses of behaviours potentially relevant to cognitive and neuropsychiatric disorders are lacking.

In addition to early prenatal and postnatal factors, events in later in life may also increase the risk for neurodevelopmental diseases. This was elegantly demonstrated in a translational mouse model that combined exposure to prenatal immune challenge and peripubertal stress resulting in synergistic effects on adult behavioural alterations associated with neuropsychiatric diseases[129].

In spite of a whole body of clinical and experimental evidence (with only a few selected here) confirming the multiple hit hypothesis for the development of mental illness, the underlying mechanisms remain obscure. Further research is necessary combining diverse prenatal and postnatal risk factors to characterise phenotypes and illuminate the cellular and molecular pathways for each factor.

SEXUAL DIMORPHISM

Compelling clinical and preclinical evidence demonstrates a pronounced sexual dimorphism across a huge variety of cognitive deficits and neuropsychiatric disorders. This is supported by experimental work since males display deficits in executive function and attention while females presented increased immobility in the forced swim test and reduced saccharin intake after immune activation in lactating dams[130]. These findings recapitulate the clinical situation where men have an increased risk for SZ and women for depression[131,132]. Of note, hippocampal and striatal volume reductions were similar in males and females. However, the inflammatory response, i.e. pro-inflammatory cytokine levels (i.e. IL-6, interferon-gamma) in the offsprings' brain were increased in males supporting the concept of cytokine-mediated perinatal programming of neuropsychiatric disorders. Similar sex differences were observed in a model of intrauterine inflammation induced by LPS injection at E15 demonstrating increased cytokine responses in males[133]. However, behavioural phenotypes were similar in that study contradicting the results by Arad et al., which might be explained by different behaviour tests applied but more likely by the different timing of perinatal immune activation[133]. This is supported by a recent report where postnatal LPS challenge between P5 and P7 resulted in differential behavioural responses in males and females suggesting that the sexual dimorphism in behavioural domains is more prominent after late immune challenges[134]. Even though divergent behavioural responses dependent on sex were confirmed, the kind of behavioural deficits differed comparing studies of Custodio et al. and Arad et al., i.e. depressive-like behaviour was observed in female but not in male mice after immune challenge by lactating dams[130] while direct immune challenge via intraperitoneal injection to neonatal animals at a similar time point resulted in the opposite with males but not females presenting depressive-like behaviour[134]. These different outcomes suggest that not only timing but also the mode of immune challenge may be decisive for final outcome and sexual dimorphism in adulthood. On the other hand, these differences might have been caused by alteration of maternal behaviour after injection of LPS to the lactating dam. Similar low levels of maternal care have been described when immune activation occurs in mid-gestation[135,136]. Besides long-lasting divergent outcomes in behaviour, emerging evidence suggests that inflammatory responses also differ between adult males and females. As such, males demonstrate increased myeloperoxidase activity in the hippocampus at P35 and P70[134]. Furthermore, cytokine responses to adult LPS challenge are increased in males at adulthood after intrauterine immune challenge[133].

In addition to perinatal immune challenges, neonatal HI induces long-lasting immune responses, which differ between genders. For instance, in adolescent male mice circulating levels of tumour necrosis factor (TNF)alpha were increased and males revealed more lymphocyte infiltration in injured brain hemispheres accompanied by reduced neurogenesis[137]. Regarding HI-induced atrophy and neurobehavioural deficits, gender differences were observed after neonatal HI in P9 mice with reduced brain atrophy in females while deficits in OF behaviour were increased, likely representing injury not detectable by volume measurements alone[138].

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Sex differences have also been observed in models of maternal obesity with female offspring of HFD-fed dams revealing increased anxiety in the OF but males being more hyperactive[31]. Furthermore, latency in initial and reverse Barnes maze trials were decreased in male but not in female offspring of HFD-fed dams[139].

The most obvious mechanism underlying sexually dimorphic outcomes seem to be sex hormones that is supported by epidemiological data revealing a higher incidence and earlier onset of SZ in males compared to females while incidence in females increases with age and outnumbers that of males after the age of 50 years[140]. The sex hormone hypothesis is in line with numerous reports on the neuroprotective effects of oestrogen[84,141–143]. Major target mechanisms of sex hormones are supposed to be regulation of neurotransmitter dysfunction and synaptic plasticity[144,145]. Nevertheless, preclinical reports demonstrating no sex differences in hormone levels but differences in outcome regarding early and late inflammatory responses and histological outcomes after neonatal HI[137,146] imply that additional intrinsic mechanisms may play a role in divergent susceptibility to the development of neurological deficits. This was demonstrated in in vitro cultures of isolated cells or brain slices revealing differences in cell death pathways and differentiation of specific hippocampal neuron subpopulations independent of the presence of hormones[147,148]. In view of the huge amount of epidemiological evidences for more than two decades, preclinical in vivo research is now beginning to include stratified analyses for sex across a huge variety of perinatal injury models.

MECHANISMS POTENTIALLY RELEVANT FOR THE DEVELOPMENT OF NEURODEVELOPMENTAL DISORDERS

In spite of the well-known heterogeneity of cognitive and neuropsychiatric symptoms, only some of them overlapping between different diseases and despite the obvious diversity of risk factors, several common molecular and cellular mechanisms have been proposed to underlie the pathology of neuropsychiatric disorders. Here we will focus on the most prominent molecular and cellular components.

Cytokines

The major hypothesis how maternal immune activation impairs neurodevelopment and potential consecutive development of neuropsychiatric symptoms is an alteration of the balance between pro- and anti-inflammatory cytokines. As such, blockade of IL-6 and IL-17 during maternal immune activation via poly I:C reverses behavioural abnormalities resembling ASD-like behaviour while an increase of IL-10 is protective[101,108]. Whether maternal increases in pro-inflammatory cytokines mediate direct effects on the foetal brains or rather indirectly through induction of placental inflammation leading to downstream effects such as oxidative stress and nutrient deficiency is still not entirely clear[149,150]. Of note, elevated cerebral cytokines levels may persist into adulthood in a region- and age-specific manner[114,117,151,152]. Changes in cerebral major histocompatibility complex-I expression and associated intracellular mammalian target of rapamycin signalling are proposed mechanisms underlying altered synaptic plasticity and function associated with neuropsychiatric disorders[100].

In addition to prenatal immune activation, hyperoxia also generates inflammatory responses in the developing brain, as demonstrated by a marked increase in mRNA and protein levels of caspase-1 and its downstream effectors IL-1beta, IL-18, and IL-18 receptor alpha (IL-18Ralpha) in PND6 rodents exposed to hyperoxia for 2–48 h[88,153]. Of note, both intraperitoneal injection of a specific inhibitor of IL-18 and genetic deficiency of IL-1 receptor-associated kinase 4, which is pivotal in both IL-1beta and IL-18 signal transduction, attenuated hyperoxic brain injury[153]. Even though a direct correlation to cognitive development and neuropsychiatric symptoms remains to be determined, these findings causally link inflammation triggered by pro-inflammatory cytokines such as IL-1beta and IL-18 to early hyperoxia-induced cell death resulting in long-lasting white matter structural abnormalities[86–89,95].

Similarly to hyperoxia, maternal obesity and neonatal HI increase cytokine levels in the offsprings' brain. This was demonstrated in rodent and non-human primate models of obesity[34,154,155]. Moreover, after neonatal hypoxic–ischaemic brain injury in rodents, cerebral levels pro-inflammatory proteins (e.g. IL-1beta and TNFalpha) were increased compared to sham-controls while anti-inflammatory cytokines (e.g. IL-10) were decreased 4 days after injury that was associated with long-term alteration of emotional and impulsive behaviour assessed in the EPM[71]. In addition to short-term regulation of brain cytokines, recent work also demonstrated a long-lasting increase in the pro-inflammatory cytokine TNFalpha up to 30 days after injury at least in males[137].

Taken together, these findings strongly suggest that cytokines are a contributing mechanism underlying the pathology of developmental neuropsychiatric disorders. Nevertheless, determination of molecular targets and dynamic changes of a larger number of cytokines across brain regions, developmental stages and animal models to identify immune signatures associated with specific neuropsychiatric symptoms will be a major goal for future.

Microglia

Microglia as resident immune cells of the brain play an important role during physiological brain development. Microglia functions during development include not only phagocytosis of synaptic elements and living and dying cells but also stimulation of myelination, neurogenesis and cell survival[24]. The majority of studies in early brain injury models propose a detrimental activation of microglia mainly based on their amoeboid morphology associated with increased pro-inflammatory cytokine release similar as in adult neurodegenerative diseases. However, these simple conclusions might be misleading because immature microglia differ from adult microglia for example in gene expression in response to LPS activation[156]. Microglia development proceeds through three distinct stages—early, pre-adult and adult—with characteristic gene expression and functional states. Therefore, it is not surprising that perturbations of this maturational process during early brain development modulate microglia. For instance, maternal immune activation results in a transcriptional shift of pre-microglia towards the more advanced developmental stage[157]. Thus analysis by morphology alone might provide limited information. Assessment of microglia function by gene expression, phagocytic activity or altered ultrastructure is suggested to be more accurate[24].

A major mechanism potentially relevant for the pathophysiology of developmental brain disorders is an alteration of microglia-mediated synaptic pruning. This is supported by a recent report using a model of prenatal inflammation by a single LPS stimulus at E15 resulting in symptoms reminiscent of ASD (e.g. increased stereotypic movements and reduced ultrasonic vocalisation, reduced social preference)[158]. Of note, these long-term behavioural alterations were accompanied by reduced hippocampal expression of the fractalkine receptor CX3CR1 at P15[158], the time point and structure where effects would be most readily detected for microglia-mediated synaptic pruning[159]. Even though microglia-specific CX3CR1 deletion studies are still missing, a causal relationship between CX3CR1 signalling and impaired social behaviour was recently demonstrated by Zhan et al.[160]. Deficient synaptic pruning due to CX3CR1 deletion (CX3CXR1 knockout mice) coincided with weak synaptic transmission and altered functional connectivity in the prefrontal cortex leading to deficits in social interaction and increased grooming behaviour[160]. Interestingly, CX3CR1 mRNA expression is only reduced in males after prenatal immune activation[158] suggesting that different microglia responses to perinatal insults might be a major cause for

observed sex differences in behavioural outcomes as described above.

While the importance of CX3CR1 is largely acknowledged by previous reports[159,160], recent work in a model of postnatal inflammation by repetitive IL-1beta injection very elegantly identified a potential new molecular player previously not linked to microglia function but rather considered as a marker of neuronal postsynaptic density[161]. Using complex gene network analysis of the microglial transcriptomic response to injury, it was demonstrated that discs large homologue 4 (DLG4, aka. postsynaptic density protein-95) is expressed in microglia of the immature mouse and human brain, which was developmentally regulated and modulated by inflammation[161]. Since DLG4 knockout mice reveal increased repetitive behaviour, abnormal communication and social behaviour[162], this might be a new important mechanism how microglia contribute neurodevelopmental disorders after perinatal infection. Even though the underlying mechanism of DLG4 action in microglia remains unclear, its involvement in crosstalk between oligodendrocytes, astrocytes and microglia or regulation of glutamatergic and GABAergic signalling was suggested[161]. Nevertheless, cell-specific deletion would be important to dissect the functional role of DLG4 on microglia for long-term neurodevelopmental outcome.

In addition to immune activation, early-life stress has also been implicated in perturbation of microglia function in the hippocampus[163]. Furthermore, neonatal HI and hyperoxia are known to result in increased abundance of the microglial cell marker Iba-1[71,88,164]. In-depth analysis in experimental neonatal HI revealed a change in microglia phenotypes even though no consistent classification could be made regarding the classical M1 and M2 polarisation states[165]. Furthermore, the classical view of detrimental microglia activation following perinatal insults is challenged by the growing number of evidence for a protective role of microglia under certain conditions, such as neonatal ischaemic brain injury[25]. It was shown that depletion of microglia enhances local inflammation induced by ischaemia–reperfusion and increases injury severity in the developing brain[166]. Taken together, the functional relevance of phenotypic and functional microglia differences associated with perinatal noxious insults for the development of cognitive and neuropsychiatric disorders in later life remains to be further investigated.

Oligodendrocytes
The development of the mammalian brain involves complex cellular processes, like migration, glial cell proliferation, axonal and dendritic outgrowth, synaptogenesis and myelination of axons[167]. Although neurogenesis is mostly completed around 24 weeks of gestation, i.e. at the border of viability of preterm infants, outgrowth and the formation of long-range connectivity supported by glia maturation and axonal myelination are still in progress[168,169]. Development of diffuse white matter alterations and a reduction of cortical and hippocampal grey matter volume are often associated with cognitive impairment, attention deficit disorder, behavioural problems, autism and development of psychiatric disease in later life[170–173].

Experimental work detecting long-lasting subtle alterations of white matter integrity and brain connectivity following perinatal insults like HI, hyperoxia, inflammation or IUGR[80,164,174,175] confirm reports about white matter abnormalities in psychiatric patients[176–178]. Oligodendrocyte development is characterised by different developmental stages, ranging from oligodendrocyte precursor cells to fully mature, myelinating oligodendrocytes. Whereas mature oligodendrocyte seem to be less sensitive to noxious stimuli, oligodendrocyte precursor cells and premyelinating oligodendrocytes, which are the most abundant oligodendrocyte populations around birth, are particularly vulnerable[174]. Hypoxia or hyperoxia-induced imbalances of the cellular redox system of developing, immature oligodendrocytes have

been suggested to cause cell death[84,179,180] while inflammation-triggered perinatal brain injury rather leads to maturational arrest of oligodendrocytes[82,121]. In spite of different underlying causes, both insults result in disturbed structural white matter development[82,86–89,120,121].

While most of these findings remain at a descriptive level, a causal link between minor myelination deficits and psychiatric symptoms has recently been reported. Using mice heterozygous for the oligodendroglial gene MBP, Poggi et al. demonstrated that very subtle hypomyelination without gross lesions and/or striking differences in basic and cognitive behaviour results in persistent defects of PPI of the startle response, as a surrogate marker of gating defects in SZ patients[181]. A similar association between myelin deficits and behaviour was demonstrated in CNP$^{-/-}$ mice that show signs of catatonia, a psychomotor syndrome observed across neuropsychiatric diseases[182]. Interestingly, these mice have increased inflammatory responses predominantly in white matter tracts. Furthermore, signs of catatonia were reversed after microglia depletion. These data demonstrate that altered myelin gene expression and minor structural abnormalities of central nervous system myelin trigger white matter inflammation as underlying cause of catatonic signs[182]. Even though experimental data are sparse in the field of neonatology, these basic findings strongly support the concept that perinatal injurious stimuli inducing subtle myelination deficits, e.g. by inflammation and/or oxygen disturbances, contribute to long-lasting neuropsychiatric consequences.

Epigenetics
Epigenetic mechanisms, i.e. the enzymatic regulation of transcription activity and gene expression without altering DNA sequence via acetylation, methylation, ubiquitination, phosphorylation and sumoylation on histones, DNA or via microRNA-mediated regulation of translation plays a pivotal role in normal and disturbed brain development and may be associated with neurodevelopmental and/or neuropsychiatric diseases later in life[183–185]. Interestingly, perinatal brain injury either induced by inflammatory triggers or by stress has been linked to sustained epigenetic alterations associated with adverse neurodevelopmental outcome[18,150]. Furthermore, maternal HFD-associated alteration of cognitive performance and anxiety-related behaviour were associated with increased brain-derived neurotrophic factor and Grin2b methylation and increased expression of DNA methyltransferases[186]. Whereas the latter reviews and reports rather focus on prenatal insults, several studies have also provided a direct link between early postnatal insults, epigenetic modifications and neuropsychiatric outcome. For instance, early-life stress-induced cognitive impairment and anxiety is attenuated by silencing of miRNA124a in the hippocampus of adult male rats[187]. Furthermore, maternal separation was associated with persistent dysregulation of histone modifiers in the medial prefrontal cortex, one of the key structures regulating stress responses and mood-related behaviour[188]. For perinatal brain injury induced by postnatal inflammation, alterations in miRNA expression and histone acetylation have been described, which potentially contribute to disturbed oligodendrocyte maturation[121,189,190] even though this hypothesis needs to be proven in cell- and region-specific analyses.

CHALLENGES FOR PRECLINICAL RESEARCH
Clinical and epidemiological studies are limited to establish a causal relationship between perinatal insults and the development of neuropsychiatric disorders. This may be attributed to impossible randomisation of handling or behaviour. Humans are ecologically and behaviourally heterogeneous limiting the associative power and thus necessitating large studies. Furthermore, symptoms often do not appear for many years after birth. The

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multiple hit scenario further impedes clear definitions of causal relationships. Therefore, animal models are essential to identify target mechanisms and therapeutics.

Challenges for experimental modelling and data analysis

Technical difficulties emerge from currently used animal models of perinatal brain injury that often induce severe cerebral lesions and associated motor deficits that may confound interpretation of results from behavioural analyses assessing emotional, social and cognitive tasks. Furthermore, owing to improvements in obstetric and neonatal care the number of infants suffering from rather subtle and late-onset cognitive and socio-emotional impairments in later life requires the development of additional more subtle injury models than the currently used severe injury models with high mortality and morbidity. First attempts have been made by combining prenatal immune challenge with postnatal hypoxia only, instead of combination with the more severe model of HI[128].

Nevertheless, even with refinement of experimental models, which are indispensable to increase our abilities for the design of therapies, most likely no single animal model can reflect all neuropathological alterations and behavioural deficits of a complex human disorder. For instance, while maternal immune activation has been shown to induce behavioural abnormalities resembling symptoms of ASD and SZ[100–102], neuropathological alterations do not always parallel observations in clinical studies. As such, while cortical thickness is reduced in the rat model of maternal immune activation, clinical studies demonstrated widespread increased cortical thickness in ASD patients[191]. Another example is neonatal encephalopathy related to HI that is modelled by induction of unilateral brain damage and thus is unlikely to fully model the global brain injury seen in humans. Nevertheless, work in this model has shown suppression of electroencephalogram power after unilateral HI, as is often seen in infants with HIE[192]. Thus, despite the unilateral nature of the injury, the HI model replicates at least some important aspects of the encephalopathy observed clinically. With regard to preterm-birth-related complications caused by high oxygen concentrations, the hyperoxia model has been developed. It is a postnatal model where experimental animals do not suffer from lung injury when exposed for 24–48 h to high oxygen concentrations in contrast to preterm infants. It also lacks the clinical fluctuation of oxygen concentrations observed in clinical practice of neonatal care[85,193]. However, it represents a very standardised and reproducible type of injury that can be combined with additional noxious stimuli, i.e. an inflammatory challenge can be easily added to closer mimic the clinical situation[82].

In addition to these difficulties, one has to keep in mind for all models with maternal targeting that this involves whole-litter manipulations where littermates share similar in utero and postnatal environments, which can produce considerable litter effects. Therefore, in experimental designs with maternal targeting, littermates may not be treated as fully independent in statistical analyses that would artificially increase sample size. It is rather suggested to randomly select only one subject from each litter and to allocate animals of one litter to different outcome measures to avoid ethical issues of wasting animals[194]. An alternative would be the use of appropriate statistical models as previously described[195]. Potential effects by altered maternal care and/or pain due to injections/interventions can also be confounders in studies with maternal targeting.

Challenges for assessment of neuropsychiatric symptoms in rodents

Symptoms like hallucination, delusions and major thought disorders are difficult to measure in primates and impossible to assess in small animals, such as rodents. Therefore, the aim should not be to fully mimic the entire syndrome but rather focus on distinct behavioural physiological and neuroanatomical phenotypes. Nevertheless, multi-task approaches are needed to model multi-symptomatic diseases and several studies have shown that neuropsychopathological deficits and disorders can be reliably modelled in animals with the help of a battery of neurological and neuropsychological tests screening behavioural abnormalities in rodents[196,197]. This chapter briefly presents and describes paradigms that are commonly used in rodents to screen for behavioural deficits frequently associated with certain neuropsychiatric disorders or after experimentally induced developmental manipulations[198,199]. However, rodent behaviours have limitations when compared to the complexity of human behaviour. Thus any tests used for the assessment of behavioural patterns in general are crucial to provide established face validity, construct validity and predictive validity[200].

Anxiety-related behaviours. The most commonly used unconditioned tests of anxiety comprise the OF test, the EPM, and the light/dark test (LD). All of them reveal the conflict between avoidance behaviour towards potentially dangerous spaces and the motivation to explore novel, unfamiliar areas[201].

Elevated plus maze: One prominent paradigm assessing anxiety-related behaviour is the EPM test. The apparatus consists of a centre platform with four branching arms, two open and two opposing closed arms. By placing the animal on the centre platform always facing an open arm, behaviour is assessed over a certain time. The dependent measures are usually the number of open arm entries, time spent in open/closed arms, the distance covered on the open/closed arms and head dips (the frequency of the animal protruding its head over the ledge of an open arm and down towards the floor). An increase in anxiety-like behaviour is characterised by reduced number of entries into the open arms and the increased time spent on the closed arms of the maze compared to controls[202–205]. Likewise, the reduction in head dips is suggested to reflect deteriorated risk assessment-related behaviour[206] and thus also supports the assumption that anxiety-like behaviour is apparent.

Rodents' sickness behaviour is in part reflected by reduced exploration and motor activity[207–212]. Thus observed changes in EPM performance may be simply explainable due to impaired locomotor activity induced by experimental interventions. Such an assumption can, however, be ruled out easily by quantifying the total distance covered on the maze between experimental groups. Second, analysing the number of entries into the closed arms is also considered as good indicator of locomotion rather than anxiety[213].

Open field: A simple rectangular acrylic box with black walls and a frosted floor with infrared backlighting can be used as an OF arena. For testing, animals are placed in the centre of the dimly lit OF arena[214] and movements are assessed by a video tracking system over 5, 10, 20 or more minutes. The dependent measures are usually general motor activity, that is covered distance and velocity, as well as straighten up-postures for vertical activity. Anxiety-like behaviour in this test is reflected as less time that is spent in the centre of the arena and vice versa more time spent at the borders of the arena. Like in the EPM, quantifying the total distance covered in this test may check simple effects on locomotor activity.

LD test: Another simple but meaningful setting to investigate decreased exploratory behaviour as an index for anxiogenic effects in laboratory rodents is provided by the LD. This plexiglas-made arena consists of two compartments, while two-thirds of the arena is white coloured and illuminated, one-third was black coloured and darkened. The two compartments are separated by a black partition equipped with photocells across the opening, as well as in the overall arena, to measure locomotor activity. Animals

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are placed in the centre of the bright chamber facing the separating wall. The total numbers of transitions between the two compartments and total locomotor activity, as well as time spent in the bright side are recorded[215]. In this test which is based on rodents innate aversion to brightly illuminated areas[216], less time exploring the lit compartment (risk assessments) and low latency to enter the lit compartment are usually interpreted as increased levels of anxiety[217].

While the aforementioned paradigms are frequently used to assess anxiety in rodents, there are drawbacks that need to be taken into consideration. First of all, the ideal animal model of anxiety does not exist, and the tests available (EPM, OF and the LD) are characterised by their originality. Second, using solely one task to measure anxiety-like effects is biased, since rodent behaviours have limitations when compared to the complexity of human behaviour[200]. Thus, to gain broader understanding about underlying mechanisms and to increase validity of data, multiple behavioural tests should be used to characterise the anxiogenic/anxiolytic impact of experimentally induced interventions[218,219], which also improve translation from animals to humans. Moreover, it is proposed that short-term, intra-individual variations in emotionality probably constitute an important factor for investigating anxiety-related behaviour that may differ between tests[220].

Deficits in sensorimotor gating, break point and stereotypic behaviour

Sensorimotor gating: The startle response is a fast twitch of eye-lid-closure, facial, neck and skeletal muscles evoked by a sudden and intense tactile, visual or acoustic stimulus[221,222]. This characteristic response pattern, best described as ASR, is observed in a variety of species such as rodents and humans and is thought to be a protective function against injury from a predator or harm and of the preparation of a flight-or-fight response[223]. However, when a distinctive non-startling stimulus (prepulse) is presented 30–500 ms prior to the actual startling stimulus, the response magnitude is naturally reduced. This mechanism of inhibited contemporaneous sensory or motor events that would interfere with the ongoing processing of the prepulse reflects a fundamental principle of the neuronal control of behaviour, which in turn is necessary for stimulus recognition and sequential organisation of the appropriate behaviour[224]. This phenomenon also known as PPI is considered to be a pre-attentive filter mechanism, reflecting the ability of an organism to gate out irrelevant sensory information[221,222,225–227]. PPI can be measured with almost identical procedures in humans (eye blink reflex) and rodents (startle chamber)[228,229]. Since PPI is disrupted in schizophrenic patients, animal models of sensorimotor gating may offer the possibility to investigate the neural mechanisms related to some characteristical impairment in SZ[230]. While lesioning the medial prefrontal cortex[198] or the ventral thalamus[231] in adults are known to induce deficits in sensorimotor gating, neonatal lesions of the entorhinal cortex did not impact PPI measured during adulthood[232]. However, multiple studies involving different forms of maternal immune activation demonstrated reduced PPI responses[105,108,117].

Break point: The so-called "break point" or progressive ratio (PR) test is an operant behaviour task that measures the instrumental effort a rat is willing to invest in order to obtain a reward[233,234]. In this paradigm, animals are initially trained to press a lever in order to obtain a reward. At the level of stable performance, the number of lever presses required for the reward is progressively increased[235], and at a certain point of instrumental effort, animals cease to "work" for the reward and stop responding. The "break point" is considered as operational measure for a shift in motivation, indicating that the value of the reward is lower than the effort the animal is willing to invest[236]. PR schedules have

been shown to provide a valuable method to measure the impact of experimental manipulations that might affect the perceived reinforcement value of gustatory stimuli[233]. Moreover, it was assumed that a reduced break point and hence a lower performance in the PR- test might serve as an animal model for anhedonia, a core negative symptom in SZ[236]. When adult rats were tested for motivation in the PR task following neonatal lesions of the entorhinal cortex, a reduced break point in operant responding was observed. These findings indicate that early-life brain injury reduced motivation during operant behaviour reflecting a state of anhedonia as also observed in SZ[232].

Stereotypy: Stereotypy is not only a fundamental feature of the behavioural syndrome induced by psychomotor stimulant drugs but also a cardinal feature of a broad range of neuropsychiatric disorders[237–240]. Behaviours of patients that typify stereotypy in clinical disorders range from repetitions of single or multiple movements (motor stereotypies) to repetitive, inflexible patterns of attention, emotion, planning and cognition[241]. Most commonly, video recordings of animals for a certain amount of time are evaluated for specific patterns, such as focussed sniffing, repetitive head and limb movements and oral movements (chewing, licking and biting)[242,243].

Cognitive deficits

Morris water maze: Neurodevelopmental disorders due to perinatal insults are often associated with cognitive deficits later in life[244]. A prominent task, which assesses spatial learning in rodents is the Morris water maze test[245]. This test is based upon the premise that animals have evolved an optimal strategy to explore their environment and escape from an unpleasant environment (the water tank) with a minimum amount of effort (swimming the shortest distance possible). The time the animals need to discover a hidden platform in the tank after previous exposure to the set-up with only external proximal and distal cues available is considered as an index for spatial memory[246,247].

Barnes maze: Similarly, but not as aversive, however, is the Barnes maze task, which also assesses spatio-temporal memory[248]. Here animals are placed in the centre of a brightly illuminated round board equipped with 20 holes at the border. Animals are required to escape from the very unpleasant environment by seeking an escape box that is attached to one of the 20 holes at the border region. After training, the latency to find the escape box is assessed after a couple of training days reflecting the memory performance[249].

Radial maze: Spatial memory abilities may also be assessed in an eight-arm radial maze using a reinforced alternation task. The maze consists of an octagonal central platform 48 cm in diameter connected to eight equally spaced arms projecting radially from the central platform with adjacent arms separated by 45°. At the distal end of each arm, food cups are located (2.5 cm high × 4 cm in diameter) that prevents the rodent from viewing the food reward. The test, usually in an experimental room equipped with several extra-maze visual cues, is initiated by placing the rodent into the centre of the maze with orientation varying from trial to trial towards distinct arms[232]. Four arms (alternating) of the maze are always baited with food rewards. The animals are placed in the centre of the maze, and arm choices are recorded when an animal collects the reward or reaches the end of an arm. Entering an arm that had never been baited reflects a reference memory error, while a re-entry into an arm that was baited indicates a working memory error[250]. Since a re-entry into a never-baited arm could be related to either process of working or reference memory, it is scored as a "perseveration error"[251].

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Novel object recognition: Another method to test cognitive functioning in rodents is provided by the novel object recognition test[252–254]. To verify that performance is less dependent on spatial information, an actual modified version of the task is performed in a Y-maze. Here no external cues are visible for the animal from inside the maze. Initially, three identical objects are placed at the end of the maze arms for familiarisation purposes. On testing days, one familiar object is replaced by a novel, differently shaped object, which is consistent in height material. As most reliable parameter for assessing recognition memory is the time spent in the distal half-arms during the first 2 min of the test. In healthy subjects, this should indeed be longer for the arm with the unfamiliar object[255].

Social behaviour
Social interaction: In humans, early prefrontal–cortical damage has been shown to impair cooperative behaviour and social interaction, as well as social cognition[256,257]. The so-called "unsocial" behaviour is also a characteristic outcome of neurodevelopmental psychiatric disorders, such as SZ and autism. Hence, social withdrawal and social isolation are most commonly seen as negative symptoms in SZ, while the core symptoms of autism comprise specific impairments of reciprocal social relationships, affected cooperative play with peers and atypical social behaviour[258,259].

Impairment of social behaviour in rodents can be measured using the social interaction test. This paradigm is based on the fact that active interaction reflects motivation to interact and does not necessarily reflect the behaviour of both animals, while passive interaction depends on the pair. Moreover, the evaluation of active and passive interaction separately and for each animal of the pair allow the investigation of social behaviours between animals of different strains or drug treatments, increasing the repertoire of information originated from this task[260–262]. Briefly, pairs of unfamiliar rats or mice are simultaneously but placed apart in an unfamiliar arena (e.g. OF). Over a certain time period, the time spent in active (sniffing and following) or passive behaviour (animals lie next to each other in distance) are scored[263]. Based on its predictive and face validities, a decrease in social interaction has been described in several animal models of SZ as a behavioural parameter that mirrors the negative symptoms of this disease[199,264–267] but need to be evaluated following subtle perinatal insults in the future.

Three chamber sociability test: A different method to analyse sociability in rodents is provided by the three chamber sociability test. Here the animal is placed in a roofless apparatus comprising three compartments, a small centre compartment and two equally sized end compartments. During testing, the subject is placed in the middle compartment. One end compartment hosts a strange, unfamiliar rodent in an inverted grid cup, while the other end compartment contains an identical but only an empty grid cup, sometimes with an object[268,269]. Restraining the unfamiliar rodent in a grid cup limits the mobility of this animal but still allows visual, olfactory and tactile contact to the testing subject. Moreover, possible aggressive responses between test and stranger animal are prevented[270]. However, rodents normally prefer to spend more time with an unfamiliar counterpart. Thus valid measures for *sociability* in this test are the amount of time the test subject spends in each compartment and the amount of exploration time (sniffing), as well as the transitions between the compartments. Besides sociability, social novelty may be assessed in a subsequent test setting[271]. Here a second stranger animal is placed in the former empty grid cup. In this phase, the test subject may choose whether to explore the rodent that was already present during the *sociability* phase (now a familiar animal) or the newly introduced one. Measures for *social novelty* during this testing phase are the same ones as described above.

Impulsive behaviour. Although not yet experimentally assessed following insults to the developing brain, high levels of impulsive behaviour are evident in a number of psychiatric disorders, such as obsessive–compulsive disorder, ADHD, SZ, antisocial and addictive behaviour[272,273]. Owing to the range of behaviours that the term impulsivity encompasses, it is proposed that impulsivity not as a unitary construct but rather as a set of diverse and complex phenomena that may have independent underlying biological mechanisms[274,275]. Common aspects of impulsivity comprise decreased inhibitory control, intolerance of delay to rewards and quick decision making due to lack of consideration, as well as poor attention ability and hyperactivity[276,277]. Despite this very broad range of symptomatology, it is possible to devise different paradigms to measure the various forms of impulsive behaviour in both humans and laboratory animals[278–280]. In general, impulsivity includes two major categories: behaviour that results from diminished ability to inhibit actions, often referred to as impulsive action, and behaviour that reflects impulsive decision making, for example intolerance to delay of gratification also known as delay aversion[277,281].

Impulsive action (inhibitory control): Impulse control is often described as active inhibitory mechanism, modulating internally and externally driven pre-potent desires for primary reinforcers, such as food, sex or other highly desirable rewards. This inhibitory control mechanism may provide lower cognitive mechanisms to guide behaviour, while rapid conditioned responses and reflexes are transiently suppressed[277,282]. The most popular clinical measure of sustained attention, vigilance and response inhibition in humans is the continuous performance task[281,283]. The preclinical analogue of the continuous performance task designed for rodents is the five-choice serial reaction time task, an operant-based test originally developed to measure visuo-spatial attention. In this 30–40 min task, animals are required to be attentive and withhold responding (nose poke) while monitoring five apertures for brief light stimuli (e.g. ≤1 s) presented randomly therein[284,285]. Subsequently, at the beginning of a trial and prior to presentation of a light stimulus, there is a 5-s inter-trial interval during which the animals have to withhold a response at all. Any responses made during this time are described as premature responses. Low levels of premature responses require the ability to inhibit actions, whereas high levels are seen as a measure of motoric impulsivity reflected by disturbances in the inhibition of behaviour[279,284].

Impulsive decision-making (delay aversion): Owing to the fact that impulsive patients are not able to take time to carry out appropriate evaluations of incoming information in order to choose behavioural responses on a detailed analysis of a given situation[286,287], the inability to tolerate delays of gratification or reward is also an important aspect of impulsive behaviour[288–290]. A well-established paradigm for testing sensitivity to delays of reward in laboratory animals is the delay-based decision-making task, carried out in random operant chambers with two retractable levers and a food pellet dispenser. Here the ability to wait for a food reward is taken as an operational measure of impulsive-like behaviour[275,291]. More specific, rats are given the choice between a small (one food pellet) and a large reinforcer (five food pellets). The programmed delay associated with the large reinforcer is increased stepwise from 0 to 60 s during the session. Trained rats begin each session by choosing the lever providing the larger reinforcer but then switch the preference to the smaller one as the delay increases. This switch from the large to the small reinforcer indicates an increase in impulsive choice[275,292].

CONCLUSION
Owing to the increasing amount of clinical neurodevelopmental follow-up studies in large cohorts confirming the increased risk

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for cognitive, neurobehavioural and neuropsychiatric problems following perinatal insults, the focus of translational experimental research has shifted from the sole analysis of the underlying pathophysiology to assessment of long-lasting neurobehavioural deficits reminiscent to typical neurodevelopmental disorders. However, several hurdles remain. While the multiple hit hypothesis is increasingly implemented in experimental research, underlying cellular and molecular mechanisms of each factor and potential synergistic actions remain largely unclear. Furthermore, stratified analyses for sex across a huge variety of perinatal injury models needs to be included in future studies. Major evidence for a direct link between perinatal insults and long-term neurodevelopmental disorders is derived from prenatally or postnatally induced inflammation while the impact of prenatal stress, IUGR and oxygen imbalances on long-lasting neuropsychological symptoms is less well explored. Moreover, most outcome measures focus on distinct and selective behavioural domains, single brain regions and/or single analysis time points in a single animal model. Thus comprehensive systematic analyses including multi-task behavioural tests and the identification of common neurobiological principles underlying distinct pathologies should be a future goal in this research field. This will need multidisciplinary experimental approaches combining knowledge from the field of basic neurobiology, neonatology, paediatrics, psychology and psychiatry to explore the full spectrum of perinatal programming of neurodevelopmental disorders.

ADDITIONAL INFORMATION

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