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The impact of early-life environment on absence epilepsy and neuropsychiatric comorbidities

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ABSTRACT

This review discusses the long-term effects of early-life environment on epileptogenesis, epilepsy, and neuropsychiatric comorbidities with an emphasis on the absence epilepsy. The WAG/Rij rat strain is a well-validated genetic model of absence epilepsy with mild depression-like (dysthymia) comorbidity. Although pathologic phenotype in WAG/Rij rats is genetically determined, convincing evidence presented in this review suggests that the absence epilepsy and depression-like comorbidity in WAG/Rij rats may be governed by early-life events, such as prenatal drug exposure, early-life stress, neonatal maternal separation, neonatal handling, maternal care, environmental enrichment, neonatal sensory impairments, neonatal tactile stimulation, and maternal diet. The data, as presented here, indicate that some early environmental events can promote and accelerate the development of absence seizures and their neuropsychiatric comorbidities, while others may exert anti-epileptogenic and disease-modifying effects. The early environment can lead to phenotypic alterations in offspring due to epigenetic modifications of gene expression, which may have maladaptive consequences or represent a therapeutic value. Targeting DNA methylation with a maternal methyl-enriched diet during the perinatal period appears to be a new preventive epigenetic anti-absence therapy. A number of caveats related to the maternal methyl-enriched diet and prospects for future research are discussed.

1. Introduction

Generalized epilepsies have a strong genetic component. The variety of mutations and involvement of different combinations of genes, the genetic heterogeneity, and the heterogeneousness of the various epileptic phenotypes hamper quick progress and understanding of the different pathologies underlying generalized genetic epilepsies (GGE). Absence epilepsy is classified as an epilepsy syndrome with a genetic cause according to the current International League Against Epilepsy (ILAE) classification system (Scheffer et al., 2017). In previous versions of the classification system, absence epilepsies were referred to as idiopathic syndrome.

The GGE represents 15–35 % of the population of people with epilepsy (Jallon and Latour, 2005). Absence epilepsy is the most common form of generalized epilepsies during childhood. In large cohorts, the frequency of the most prevalent type of absence epilepsy, childhood absence epilepsy (CAE), varies from 1.5 % to 12.1 % among the genetic generalized epilepsies, and this large difference depends largely on the mode and source of the case definition. The incidence of CAE has been estimated to range from 0.7 to 8 per 100,000 persons, and the prevalence rates of CAE in children's cohorts ranged from 0.1 to 0.7 per 1000 persons (Jallon and Latour, 2005; Matricardi et al., 2014). In adults (> 17 years), the average GGE incidence is much lower: only 2.9/100 000 inhabitants per year and the prevalence of absence epileptic patients is 0.3 among 1000 persons (Gesche et al., 2020). Therefore, the absence epilepsy is most commonly, although not exclusively, considered a pediatric disease.

For a long time, CAE was considered to be a benign form of epilepsy given the high (60–70%) complete remission rate (Berg et al., 2014; Bouma et al., 1996) and the absence of comorbid pathologies. However, subsequent studies have shown that CAE is associated with cognitive impairments, among other things, attention disturbances, and psychiatric comorbidities, such as attention-deficit/hyperactivity disorder (ADHD), anxiety, and depression (Barone et al., 2020; Cheng et al., 2017; Gruenbaum et al., 2021; Masur et al., 2013; Tenney et al., 2013; Tenney and Glauser, 2013; Vega et al., 2011). Cognitive impairments, including recognition memory and attention disturbances, were also found in the WAG/Rij model of CAE (Fedosova et al., 2022, 2021; Leo

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et al., 2019).

Two animal models are at the forefront of neurobiological research towards mechanisms and processes that govern generalized absence epilepsy. The GAERS and WAG/Rij models, both models first discovered in the eighties of the last century (van Luijtelaar and Coenen, 1986; Vergnes et al., 1982), are well described and considered as models with a high predictive, construct and face validity (Coenen and van Luijtelaar, 2003; Depaulis and Charpier, 2018; Marescaux and Vergnes, 1995). The WAG/Rij strain was already fully inbred before the discovery that they showed spontaneous SWDs concomitant with clinical signs (van Luijtelaar and Coenen, 1986), while the GAERS, originally a selection line, were later fully inbred. Current theories on the origin of absence epilepsy in humans have been molded by discoveries in these models (Meeren et al., 2002; Polack et al., 2007), have led to the cortical focus theory on absence epilepsy, and inspired research in other species (Ding et al., 2019; Zobeiri et al., 2019) and absence epileptic patients (Crunelli et al., 2020; Gupta et al., 2011; Miao et al., 2014; Moeller et al., 2008; Ossenblok et al., 2019; Tenney et al., 2013; Westmijse et al., 2009; Youssofzadeh et al., 2018).

When the animals of these two inbred strains are born, they do not have seizures. The spike-wave discharges (SWDs) are expressed age-dependently in both WAG/Rij rats (Coenen and van Luijtelaar, 1987; Gabova et al., 2020) and GAERS (Jarre et al., 2017). In WAG/Rij rats, the number of animals expressing SWDs, the number of SWDs per hour, as well as the mean duration of individual SWDs increases with age from about 2 months of age (Coenen and van Luijtelaar, 1987; Gabova et al., 2020; Schridde and van Luijtelaar, 2005). SWDs in the rodent rat models have a frequency of about 7–11 Hz, mean duration of about 5 s, and the number of daily SWDs in 6-month-old WAG/Rij rats is about 16–18 per hour (van Luijtelaar and Coenen, 1986; van Luijtelaar and van Oijen, 2020). GAERS have more and longer SWDs, as well as an earlier onset of the fully developed SWDs (Akman et al., 2010). However, the SWDs incidence, number and mean duration may vary in different colonies of WAG/Rij rats, as has been found in GAERS (Powell et al., 2014). In WAG/Rij rats, age-dependent increases in the number and mean duration of SWDs occurred unevenly: from 2 to 6 months of age, these SWDs characteristics increase by 20 and 6 times, respectively, and from 6 to 12 months of age only by 1.5 times. In general, the epileptic phenotype in WAG/Rij rats is fully expressed by 6–7 months of age. However, the SWDs amplitude and asymmetry index continues to increase up to 8–9 months of age, indicating that the evolution of SWDs in WAG/Rij rats is completed by 8–9 months of age (Gabova et al., 2020). It is not excluded that age-related dynamics of SWDs development in other colonies of WAG/Rij rats may have some differences as well.

Detailed recent studies in GAERS (Jarre et al., 2017) and WAG/Rij rats (Gabova et al., 2020) have described the precursors of SWDs, and not mature SWDs were retrospectively present as early as 2 months (WAG/Rij) and 30 days (GAERS) of age. Then, with age, immature discharges successfully undergo three stages of "maturation" (Gabova et al., 2020; Jarre et al., 2017), which reflects progressive electrophysiological changes in the somatosensory cortex (Jarre et al., 2017), a brain region that is related with the initiation, spreading and generalization of SWDs in the WAG/Rij and GAERS models (Meeren et al., 2002; Polack et al., 2007).

The vulnerability of the immature developing rat brain towards external influences has been known for a long time, including the age-dependent decrease during ontogeny (Wasterlain and Plum, 1973), and these external environmental factors might have long-term consequences, including the phenotypic expression of genetically determined epilepsies. Early quantitative genetic studies, a complete Mendelian cross-breeding study between WAG/Rij rats and another fully inbred strain, Agouti Copenhagen Irish (ACI), not only confirmed a genetic transmission of genes responsible for the occurrence of SWDs, but equally demonstrated epigenetic and early environmental influences, including maternal effects, for SWD characteristics such as incidence, mean duration, and number of SWDs. Maternal effects were evident since rats of the F1 generation raised by ACI versus WAG/Rij mothers showed different characteristics of SWDs (Peeters et al., 1992, 1990). The contribution of maternal effects on SWDs was confirmed in a second Mendelian cross-breeding study between BN and F344 rats (Vadasz et al., 1995). Later, the role of maternal behaviour as an early environmental factor contributing to the development of absence epileptic phenotype in WAG/Rij rats was established (Sarkisova and Gabova, 2018) and will be discussed further in Section 3.5 "Maternal care".

Previous data have shown that WAG/Rij rats develop also a mild depression-like (dysthymia) phenotype in parallel with spontaneous absences (Sarkisova et al., 2003), and, importantly, that prevention of epileptogenesis by early and chronic drug administration also prevented the development of a mild depression-like phenotype, suggesting a close and causal relationship between them (Russo et al., 2016, 2011; Sarkisova and van Luijtelaar, 2011; Sarkisova et al., 2010; van Luijtelaar et al., 2013). Interestingly, no phenotypic expression of behavioural depressive-like symptoms was found in pre-symptomatic (36-day-old) WAG/Rij rats. Behavioural depression-like symptoms appear at the age of 3 months when SWDs start to be clearly expressed. Then, with age, depressive symptoms increase, as far as absence epileptic seizures aggravate (Sarkisova et al., 2014). In all, both aspects of the phenotype, the spontaneous absence seizures combined with the depressive-like behaviour, are co-occurring in this model and are under the influence of external factors, including chronic drug administration.

Since the early nineties, quite a number of studies have been done regarding the effects of environmental factors on the phenotypic expression of SWDs and psychiatric comorbidities in WAG/Rij rats, here we will review these studies, and we will emphasize studies in WAG/Rij rats, but not exclusively. Moreover, early intervention studies in other epilepsy models might be discussed as well, since they may point towards putative environmental factors that might play a role in the epigenetic effects on SWDs and comorbid depression-like behaviour in WAG/Rij rats.

2. The impact of the environment on the development of the adult phenotype

This review will discuss prenatal, perinatal, and postnatal factors, with an emphasis on early postnatal influences, considering that most studies were done in the most vulnerable period of the immature brain. Environmental exposures must occur during the window of susceptibility (at specific times for different cell types' maturation) to produce alterations in offspring, which can persist throughout life. This differential sensitivity to environmental factors during development is a well-known fact, which is based, among other things, on an early observation (Wasterlain and Plum, 1973). These authors compared the effects of a supramaximal electroconvulsive seizure per day for 10 days between days 2 and 11, days 9 and 18, and days 19–28 of their postnatal life (Post Natal Day, PND). The seizures as presented in the youngest group had a larger effect on brain weight, and brain cell number, the slightly older treated group had a smaller reduction in brain weight, brain protein, and brain RNA without a fall in brain DNA, suggesting a reduction of cell size without a change in cell number. The brains of the oldest shocked group showed no change in brain weight, cell number, or cell size. All this suggested that the immature rat brain is more vulnerable to seizures than the older brain. Now it is widely accepted that the brain growth spurt in rats and mice occurs postnatally, with peak growth velocity on PND7-PND10, and ends in the third week, suggesting that these early weeks of life are the most sensitive to disturbances due to adverse environmental factors. The fact that the brain in the offspring is vulnerable during the perinatal period is important clinically since it is now established that the majority of anti-seizure medications (ASMs) cause apoptotic neurodegeneration in the developing rat brain at doses and plasma concentrations relevant for the anticonvulsant treatment of the pregnant mothers with epilepsy (Ikonomidou, 2010).

Prenatal and early postnatal exposure to environmental factors

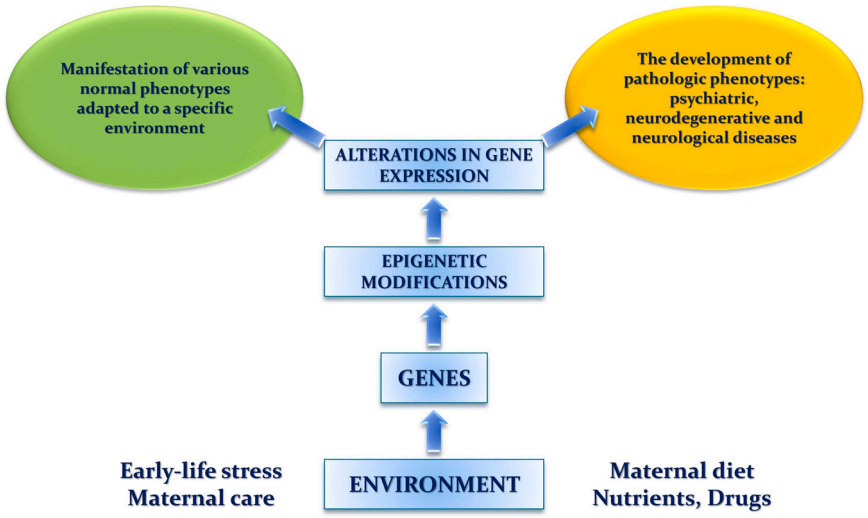

Fig. 1. The epigenetic basis for the development of normal (indicated in green) and pathologic (indicated in yellow) phenotypes. See details in the text.

primarily associated with the mother and including early-life stress, maternal care, and nutrition, taking pharmaceutical drugs or medication can exert adverse effects on offspring and promote the development of different diseases later in life (Tchernitchin and Gaete, 2015). These early environmental factors that affect an organism's phenotype result from gene-environment interactions, which are mediated by epigenetic modifications of the genome. Epigenetic modifications regulate gene expression without altering the DNA sequence. Epigenetic modifications can include DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA, as well as more recently identified mechanisms such as hydroxymethylcytosine residues (Gräff et al., 2011; Kriaucionis and Heintz, 2009; Skinner et al., 2010). DNA methylation refers to the process by which a methyl group attaches to DNA via cytosine at specific locations in the genome called CpG sites (Razin, 1998). DNA methylation causes a stable but potentially reversible change in gene expression. DNA methylation usually results in the silencing of a gene, but recent evidence indicates that methylation may also be associated with gene activation (Métivier et al., 2008).

Epigenetic modifications of the genome provide a mechanism that allows the stable propagation of gene activity from one generation of cells to the next (Jaenisch and Bird, 2003). Unlike genetic changes, epigenetic modifications are more dynamic and are often reversible, and allow the phenotype to adapt to alterations in the environment throughout life; it is the ultimate solution of nature for proper adaptation to different circumstances in normal neurodevelopmental processes in all living species. However, variations in epigenetic modifications can contribute not only to phenotypic diversity (variability of normal phenotypes adapted to a specific environment) but also to the development of pathologic phenotypes such as psychiatric, neurodegenerative, and neurological diseases, including epilepsy and associated behavioural comorbidities in predisposed individuals (Fig. 1).

Early environmental factors may impact brain cell programming and through epigenetic mechanisms can produce susceptibility or, on the contrary, resistance to the development of various neurological and neuropsychiatric diseases, including epilepsy and its comorbidities. Therefore, knowledge of epigenetic mechanisms of the different disorders could lead to the development of new preventive or protective therapeutic strategies. Epigenetics of epileptic and psychiatric diseases is a new promising area of research. Genomic analysis is very important to understand the risk for the development of any pathology. However, it should be emphasized that the genome may be altered by epigenetic mechanisms, which can modify the susceptibility to develop diseases.

3. Effects of early-life factors on absence seizures and comorbidities

3.1. Prenatal drug exposure

Prenatal effects of substances, behavioural procedures, and the occurrence of seizures may lead to modifications in various neurotransmitter systems, neural excitability, and seizures. Well-known are the prenatal cocaine administration studies of Baraban et al. (1997) and Keller and Snyder-Keller (2000). They found that prenatally administered cocaine reduced the cocaine-induced seizure threshold later in life in a sex-dependent manner since only females showed an increased sensitivity to cocaine-induced seizures. This sex difference was not present in the same pretreated dams when the seizures in adulthood were induced by acute injection of pentylenetetrazole (PTZ), indicating that their increased seizure susceptibility was specific to cocaine. It was thought that limbic structures such as the piriform cortex, amygdala, and hippocampus are heavily involved since the PTZ seizure was associated with intense c-fos induction in these limbic structures.

Ethanol is a psychoactive substance that exerts a detrimental effect on the brain, especially during neurodevelopment. Prenatal exposure to alcohol can cause a number of physiological, cognitive, and behavioural abnormalities in offspring, called Fetal Alcohol Syndrome (FAS), which is also associated with increased susceptibility to convulsive seizures (Cho et al., 2017) and predisposition to neuropsychiatric disorders, in particular, to anxiety and depression (Easey et al., 2019). The degree to which alcohol affects offspring's development depends of a variety of factors, such as timing, level of alcohol exposure, and genetic background. Recent studies have shown that epigenetic modifications, such as DNA methylation and post-translational histone modifications, can mediate the effects of prenatal alcohol exposure on gene expression in the brain structures and, as a consequence, on the phenotype of offspring. There is evidence that persistent changes of DNA methylation profiles and histone modifications may be associated with the long-term physiological and neurobehavioural alterations observed in FAS (Lussier et al., 2018; Mandal et al., 2017; Zhang et al., 2015).

Human and animal studies indicate that prenatal alcohol exposure results in devastating neuropathological consequences in the offspring, including suppression of the migration of cortical GABAergic interneurons, a reduction in the number of cortical neurons, as well as alterations in radial glial cells (Luhmann, 2016). In postnatal studies in humans, aplasia or hypoplasia of the corpus callosum, reduced cortical thickness, profound changes in the frontal cortex, cerebellum, and a reduced fronto-thalamic distance were detected (Kfir et al., 2009; Riley

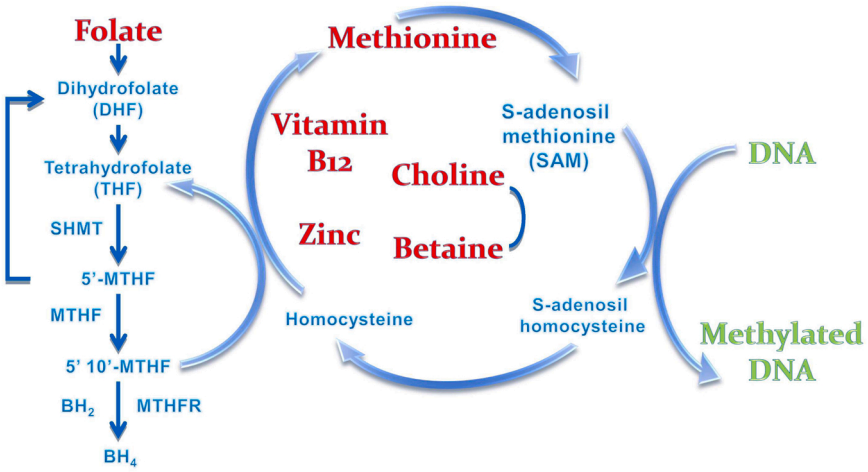

Fig. 2. Nutritional methyl group donors and cofactors of the one-carbon cycle (indicated in red) and the DNA methylation. SHMT – serine hydroxymethyltransferase, BH_2 – quinonoid dihydrobiopterin, BH_4 – tetrahydrobiopterin, MTHF – methyltetrahydrofolate, MTHFR – methylenetetrahydrofolate reductase. (adapted from Cooney et al., 2002).

et al., 2004; Sowell et al., 1996). Interestingly, all these brain structures are involved in genetic generalized epilepsy of the absence type. Few studies have described the effects of prenatal exposure to alcohol on epileptic seizures in genetic models. We found the only study of the effect of perinatal alcohol exposure on genetic models of generalized epilepsy (Russo et al., 2008). In this research, the effects of ethanol given during the last 2 weeks of gestation and for 1 week after delivery were compared between Genetically Epilepsy Prone Rats (GEPR), a genetic epilepsy model with convulsive seizures elicited by audiogenic stimulation (Ribak, 2017), and WAG/Rij rats with genetic absence epilepsy. Two non-epileptic strains were used as controls. In addition, susceptibility to PTZ-induced seizures was assessed in ethanol-treated and control animals. It was found that perinatal exposure to ethanol increases the number and intensity of audiogenic seizures in GEPR, but does not affect the susceptibility to PTZ-induced seizures in a non-epileptic control group. In WAG/Rij rats, the effects were opposite: perinatal exposure to ethanol decreased the number of SWDs, their mean and total duration. Control Wistar rats were virtually without SWDs. In Wistar rats exposed to ethanol, SWDs were completely absent. Perinatal ethanol exposure had a protective effect on PTZ-induced seizures in WAG/Rij rats. This effect was the most prominent following administration of PTZ at a dose of 50 mg/kg. The authors suggest that the disruption in the cortico-thalamo-cortical circuit and specifically alterations in the somatosensory cortex may underlie a reduction in the number and duration of SWDs in WAG/Rij rats perinatally exposed to ethanol. The increased sensitivity to audiogenic seizures in GEPR prenatally exposed to ethanol can be attributed to GABAergic abnormalities in the inferior colliculus contributing to initiation and spread seizure activity during audiogenic stimulation (Ribak, 2017). The data of Russo et al. (2008) demonstrate a clear gene-environment interaction, namely the opposite effect of the same treatment on 2 genetic epilepsy models, one convulsive and another non-convulsive. The second interesting fact is that the long-term effects of perinatal alcohol exposure on PTZ-induced seizures were the same irrespective of the genotype: in both cases, antiepileptic, similar to the effect of perinatal alcohol exposure on SWDs. This suggests that non-convulsive absence seizures and PTZ-induced convulsive seizures may use some of the same cortico-thalamo-cortical circuits.

ASMs are often used to treat epilepsy and neuropsychiatric disorders in women during prenatal, perinatal, and postnatal periods because these illnesses almost always require continued pharmacological treatments. The evidence that some of the ASMs, and certainly valproic acid (VPA), are causing adverse neurodevelopmental effects is overwhelming (Daugaard et al., 2020; Wlodarczyk et al., 2012). ASMs cross the placenta, producing substantial fetal medication exposure. Preclinical studies showed that some ASMs, such as phenobarbital, phenytoin, vigabatrin, and VPA can induce neuronal apoptosis and impaired neurogenesis in the immature brain (Bittigau et al., 2002). Lamotrigine, VPA, and vigabatrin may impair neuronal migration in the developing brain (Manent et al., 2008). Prenatal VPA produces alterations of multiple gene expressions in offspring by affecting epigenetic mechanisms such as histone acetylation and DNA methylation, participating in fundamental developmental and regulatory processes. VPA acts through several mechanisms including an increase of gamma-aminobutyric acid (GABA) in the brain due to the inhibition of its catabolism, the suppression of voltage-sensitive channels, and the inhibition of histone deacetylase. VPA is a powerful epigenetic modifier that mainly affects brain development in offspring (Ornoy et al., 2020). VPA interferes with one-carbon metabolism (Fig. 2), including the transport of methylfolate into the brain and placenta, and the effect of VPA on folate metabolism is thought to be associated with increased risk for VPA-induced fetal developmental abnormalities. However, genetic factors, notably polymorphisms related to one-carbon metabolism, contribute to the vulnerability to VPA-induced developmental risks (Bottiglieri et al., 2000; Reynolds and Green, 2020). Decreased DNA methylation was found in neonates of mothers who took ASMs during pregnancy (Smith et al., 2012). Epigenetic modifications of gene expression induced by prenatal ASMs exposure might underlie increased susceptibility to seizures and epilepsy in offspring later in life.

Prenatal exposure to VPA was shown to increase susceptibility to kainic acid-induced seizures in adult mice offspring due to aberrant and/or ectopic hippocampal neurogenesis associated with significant alterations in the expression of neuron differentiation and nervous system development-related genes. VPA disrupted the expression of multiple genes, including neural stem/progenitor cells genes associated with cell migration, consequently producing ectopic localization of newborn neurons in the hilus (Sakai et al., 2018). Ectopically located granular cells in the hilus of the hippocampal dentate gyrus are more excitable than those located normally in the granular cell layer (Zhan et al., 2010). VPA also influenced another cell type in the immature brain: it selectively suppressed inhibitory synaptic formation by repressing the expression of a vesicular GABA transporter and glutamate decarboxylases in neurons, leading to a shift in balance towards more excitation in rat cortical neurons (Fukuchi et al., 2009; Kumamaru et al., 2014). VPA exposure resulted in distinct defects in synaptic differentiation of neocortical neurons and retardation of axonal growth specific to GABAergic neurons (Iijima et al., 2016). Disturbance of the excitatory and inhibitory balance resulting from neurodevelopmental dysfunction

in GABAergic circuitry might be a common cause not only of increased seizure susceptibility and epilepsy but also of multiple comorbid behavioural, emotional, and cognitive impairments, autistic spectrum disorder (ASD) and ADHD (Christensen et al., 2013; Genovesi et al., 2011; Gesche et al., 2020; Iijima et al., 2016; Williams et al., 2016).

Prenatal VPA administration in Wistar rats modified the susceptibility to generalized tonic-clonic seizures induced by PTZ, but not to status epilepticus (SE) induced by lithium-pilocarpine in the 2-week-old offspring. Two subgroups, with different PTZ-induced seizure susceptibility, were found after prenatal exposure to VPA. The highly susceptible subgroup exhibited an increased duration of generalized tonic-clonic seizures and developed SE, while the low susceptible subgroup exhibited only minimal seizures. The authors speculate that the seizure protective effect of prenatal VPA may be due to an increase in fetal levels of GABA and changes in drug metabolism promoting an increased degradation of PTZ. The reason for being highly susceptible to PTZ was thought to be an under-development of the GABAergic system (Puig-Lagunes et al., 2016).

Very few studies were done on the genetic epilepsy models. A recent study showed that exposure to VPA for 2 weeks before conception that was continued during pregnancy in GAERS, Non-Epileptic Controls (NEC), and random bred non-epileptic Wistars caused a significant reduction in birth weight and length via C-birth born pups in which the mothers were VPA-treated. Moreover, there were altered intravertebral distances and a delay in the development of the vertebral arches in the VPA groups. These neurodevelopmental and vertebrate impairments were not affected by strain (Jazayeri et al., 2020). The outcomes showed, besides the well-known teratogenicity of VPA, that the epileptic genotype was not a contributing factor in this adverse effect.

Kliouéva et al. (2001) investigated the effects of daily subconvulsive (40 mg/kg) injections of PTZ (7–10 injections) in pregnant WAG/Rij dams on the susceptibility to spontaneous occurring SWDs in offspring when they were 4–5 months old. EEG recordings in the adult offspring showed that prenatally treated rats have three times fewer SWDs during a two-hour recording period at PND130. The authors proposed that the decrease in SWDs in prenatally treated subjects is due to reduced functional GABAergic activity. Evidence for this came a few years later from a study from Naseer et al. (2009): they showed that maternal PTZ-induced seizures indeed decreased GABAB1 receptors, next to neuronal death via caspases-3 in hippocampal neurons. The hippocampus is not a primary brain region in the typical absence epilepsy (Inoue et al., 1993; Onat et al., 2013), although it may modulate the occurrence of SWDs (Tolmacheva and van Luijtelaar, 2007), and during SWDs there is an increased network coupling between the somatosensory cortex, containing the SWD initiation site, and the hippocampal dentate gyrus (Papp et al., 2018). However, a decrease in SWDs was obtained when the GABA reuptake blocker tiagabine was locally administered in the hippocampus, suggesting that an increased GABAergic hippocampal functioning, not a diminished GABAergic functioning, could be the cause of a reduced number of SWDs in the offspring of prenatally PTZ-treated dams. Therefore, it is more likely that functional disturbances are the key players in the absence epilepsy essential circuits, the networks between cortex and thalamus affected by prenatal administration of PTZ-induced decreases in SWDs. It is not known, however, whether there is also a decreased functional activity of GABAB receptors, induced by prenatal PTZ exposure, in the cortex and thalamus. GABAB receptors are not only highly expressed in the hippocampus, but also cortex and thalamus (Bischoff et al., 1999).

A role of GABAB receptors in the increased cortical excitability has been demonstrated in WAG/Rij rats: levels of mRNA for most GABAB receptors are diminished in the neocortex of WAG/Rij rats, and higher doses of the GABAB agonist baclofen are required to depress pharmacologically isolated, stimulus-induced IPSPs generated by cortical neurons. It is therefore thought that a decreased function of presynaptic GABAB receptors in the neocortex may contribute to neocortical hyperexcitability and the occurrence of SWDs (Inaba et al., 2009). Given the functional deficiency of GABAB receptors in the somatosensory cortex in WAG/Rij rats (Merlo et al., 2007), it is not likely that the diminishment in SWDs in WAG/Rij rats found by Kliouéva et al. (2001) after prenatal PTZ exposure is due to a further cortical deficiency of GABAB receptors. The last major candidate to explain the decrease in SWDs by prenatal PTZ administration is the thalamus. GABAB receptors in the thalamus may underlie the generation of SWDs since they play a role in burst firing by activating low-threshold calcium currents (LTCC) (Crunelli and Leresche, 1991). Moreover, Liu et al. (1992) showed that injections of the selective GABAB agonist R-baclofen into the ventrolateral thalamus increased the number of SWDs in GAERS in a dose-dependent way, whereas the same but also systemic injections with the GABAB antagonist CGP 35–348 decreased SWDs in old Wistar rats with lots of SWDs (Puigcerver et al., 1996). This might imply that a diminished GABAB receptor function in the thalamus may indeed be responsible for the reduction in SWDs after prenatal administration of PTZ in the pregnant dams.

Nowadays it is widely assumed that an increased tonic inhibition in the thalamus is a major subcortical determinant of SWDs in various genetic absence epilepsy and seizure models, including the GAERS, stargazer, and lethargic mice models (Cope et al., 2009; Crunelli et al., 2020). In case prenatal PTZ is indeed causing a functional deficiency of GABAB receptors in the thalamus in the offspring, this may lead to a diminishment of tonic inhibition and fewer SWDs. Although GABAA receptors are the constituent receptor types for tonic inhibition, studies in rat brain slices have shown that activation of postsynaptic GABAB receptors enhances the magnitude of the tonic GABAA current recorded in thalamocortical cells. This demonstrates postsynaptic crosstalk between GABAB and GABAA receptors. A consequence of this cross-talk could be that also GABAB receptors contribute to tonic GABAergic inhibition, allowing an explanation for the modulatory effects of GABAB agonists and antagonists in increasing and decreasing SWDs respectively, and for the prenatal effects of PTZ (Connelly et al., 2013).

The direction of the prenatally-induced effects of PTZ on SWDs, specifically a reduction in SWDs, is opposite to the commonly reported pro-epileptic effects of prenatal seizures in the offspring later in life. Once more, a reduction of thalamic and/or hippocampal GABAergic functioning might explain both the effects of an increase in limbic convulsive seizures and the decrease in SWDs in adult rats.

3.2. Early-life stress

Early-life stress is one of the strongest environmental factors that can produce epigenetic modifications that persisted into adulthood and could be transmitted across generations. Abnormal epigenetic modifications, in particular DNA methylation, are thought to be a cause of many diseases in humans (Gräff et al., 2011; Kiss et al., 2016; Liu et al., 2008; Nilsson et al., 2018; Robertson, 2005; Skinner et al., 2010). It has been shown that early-life stress-induced epigenetic modifications, leading to behavioural disorders in adult animals, can be transmitted across generations (Franklin et al., 2011, 2010; Razoux et al., 2017; Stenz et al., 2018). Neonatal maternal separation, neonatal handling, neonatal isolation, poor maternal care, or exposure neonates to aggressive foster mothers and/or fathers (early-life maltreatment models) can be regarded as powerful early-life stressors, and therefore all of them could produce epigenetic modification of DNA and, as a consequence, trigger and/or provoke (in genetically susceptible individuals) seizures, epilepsy and comorbid behavioural abnormalities later in life. There is no conclusive evidence on whether early-life stress can provoke epileptic seizures and comorbidities in humans possibly because most human studies were based on retrospective self-repots. Only a single study was found in which epileptic children raised in warzones and non-warzones in Croatia were compared and showed that in the warzone the assumed higher stress levels in children were accompanied by a greater number of generalized seizures (both absence and tonic-clonic seizures), while in non-warzone a much smaller

increase in the number of partial seizures was seen. Moreover, a first epileptic seizure during the war (without a subsequent diagnosis of epilepsy) was directly linked in time to a stressful event, suggesting that severe stress can potentially provoke epileptic insults without a primary process of epileptogenesis or predisposition (Bosnjak et al., 2002). Early in development, the brain is thought to be more prone to seizures, probably caused by an age-related imbalance between excitation and inhibition, which may be associated, among other things, with the initially excitatory effects of the neurotransmitter GABA (Holmes, 1997). Because of this, the effect of stress on epilepsy and epileptogenesis is expected to be more apparent during brain development.

The brain structures, which regulate the stress response, among others the hippocampus, are also often involved in epilepsy, and therefore stress, especially strong, long-lasting, and acting very early in life (in a critical window for epigenetic modifications) could play a role in triggering seizures (Huang, 2014). Early-life stress can affect brain excitability (Dubé et al., 2015) and/or connectivity (Nephew et al., 2017; Razoux et al., 2017) and can provoke seizure generation and epilepsy (Dubé et al., 2015; Gunn and Baram, 2017; Salzberg et al., 2007). In animal studies, using the amygdala kindling model of limbic epileptogenesis, it has been shown that burst firing in the thalamic reticular nucleus was significantly increased in kindled rats previously subjected to maternal separation-induced early-life stress compared to kindled rats previously subjected to neonatal handling. Maternal separation also enhanced the burst firing of hippocampal pyramidal neurons. Following kindling-induced seizures, somatosensory cortical neurons exhibited a more pronounced increase in burst firing in rats subjected to early maternal separation than in rats subjected to neonatal handling. Results suggest that early-life stress enhances vulnerability to limbic epilepsy in adulthood, as evidenced by changes in firing patterns in thalamocortical and hippocampal regions (Ali et al., 2013) and by reduced electrical seizure thresholds and prolonged seizure duration during kindling epileptogenesis (Koe et al., 2014). Thus, an early stressful environment appears to promote a vulnerability to epilepsy development due to alterations in brain excitability (Jones and O'Brien, 2013). It may be assumed that early-life stress-induced changes in brain connectivity (Liu et al., 2016; Nephew et al., 2017) and region-specific structural abnormalities and dysfunction (Yang et al., 2015) could underlie behavioural impairments, including anxiety and depression, associated with epilepsy. Early-life social isolation stress (single housing) was shown to produce increased seizure susceptibility, epileptogenesis, and neurochemical alterations leading to anxiety and depression (Mumtaz et al., 2018). Socially isolated mice had a higher network degree, suggesting higher overall connectivity, as well as abnormal network structure and white matter microstructure (Liu et al., 2016). Changes in the resting functional connectivity were found in the genetic absence epilepsy both in humans and animal models. However, it is unknown whether early-life stress induced by insufficient maternal care provided by depressive WAG/Rij mothers (see Section 3.5) could contribute to the alterations of network structure in adult WAG/Rij rats genetically predisposed to absence epilepsy. Absence seizures in the WAG/Rij rat model were associated with changes in network resting functional connectivity. A high degree of cortical-cortical correlations (when SWDs were present), but not in non-epileptic controls was observed. The strongest connectivity was seen between regions involved in seizures, mainly in the somatosensory and adjacent cortices. Resting inter-hemispheric cortical-cortical correlations were significantly higher in WAG/Rij rats compared to non-epileptic Wistar rats (Mishra et al., 2013). Microstructural changes in white matter pathways interconnecting the regions of seizure discharges were reported in two genetic models of absence epilepsy (WAG/Rij and GAERS) (Chahboune et al., 2009). In human patients with typical childhood absence epilepsy, abnormally increased resting connectivity between the two hemispheres, most evident in cortical areas, was also found (Bai et al., 2011).

Stress and elevated level of corticosteroid hormones affect neuronal excitability in various brain regions (Joëls et al., 1995) and can increase susceptibility not only for convulsive seizures but also for non-convulsive absence seizures (Tolmacheva et al., 2012; Schridde and van Luijtelaar, 2004b). WAG/Rij rats showed elevated resting corticosterone concentration compared to age-matched Wistar rats, a larger and quicker rise after foot-shock stress than Wistars, and a decline to the lower than baseline corticosterone level 60 min after exposure to a stressor. The results suggest that the hypothalamic-pituitary-adrenal (HPA) axis in epileptic WAG/Rij rats is rather different from non-epileptic Wistar rats (Tolmacheva et al., 2012). These data indicate that stress reactivity of the HPA axis might be involved in the regulation of the genetic absence epilepsy. Because maternal care affects the development of HPA stress reactivity in the offspring (Liu et al., 1997), there is a reason to assume that larger HPA stress responses in adult WAG/Rij rats were programmed early in life by poor maternal care (see Section 3.5). More studies are needed to elucidate this issue further.

Although various preclinical epilepsy models have shown increased seizure susceptibility in naive rodents after prenatal and early postnatal stress exposure, a causal relationship between stress and epileptogenesis in epileptic patients has not been fully resolved for a long time. However, subsequent studies have shown that early-life stress can be a seizure precipitant and a risk factor for epileptogenesis in humans as well (Novakova et al., 2013; van Campen et al., 2014), but only in people with a stress-sensitive type of epilepsy. Stress sensitivity is more common in children who experienced early-life stress. Children with stress-sensitive seizures also show an altered release of cortisol in response to stress (van Campen et al., 2015b).

A negative correlation of cortisol level with global functional connectivity was found only in people with stress-sensitive seizures, not in those without stress-sensitivity of seizures (den Heijer et al., 2018). Based on the data that epilepsy is associated with enhanced functional connectivity, authors speculate that increased functional connectivity in epilepsy is somehow a protective mechanism against seizure generation, which fails in a stress-sensitive subgroup of subjects as cortisol level increases. Put in other words, a change in the brain's functional connectivity induced by stress hormones can facilitate the generation of seizures. In stress-sensitive individuals, early-life stress can be a risk factor for childhood epilepsy as well (van Campen et al., 2012).

HPA-related stress hormones can affect excitatory and inhibitory processes in the brain structures that are critically involved in seizure generation. Early-life stress might provoke vulnerability to seizure generation and epileptogenesis via altering glucocorticoids level (Kumar et al., 2007), HPA-axis (Joëls, 2009), membrane receptors, for instance, GABA (Reddy, 2013), NMDA and AMPA (Olney et al., 1991; Rogawski, 2013), neurogenesis (McCabe et al., 2001), brain structures connectivity (Nephew et al., 2017; Wang and Meng, 2016), monoaminergic brain systems (Matthews et al., 2001), dendritic spine morphology (Wang et al., 2013; Wong and Guo, 2013), and ion channels (Jones et al., 2011; Russo et al., 2016). Ion channels are a class of gene products that influence neuronal and network excitability. Channelopathies occur in epilepsy, leading to the disruption of neuronal and network function. The hyperpolarization-activated cyclic nucleotide-gated (HCN) ion channels, particularly the major isoform, HCN1, have been reported to accompany, and perhaps contribute to, the epileptogenic processes in many temporal lobe epilepsy (TLE) models (McClelland et al., 2011). HCN1 ion channels in the somatosensory cortex play a special role in the pathogenesis of absence epilepsy in the WAG/Rij and GAERS genetic models, and they are very sensitive to environmental manipulations (see Sections 3.3, 3.4, 3.6, 4.2).

Early-life stress-induced region-specific abnormalities in dendritic spine formation (Wong and Guo, 2013) may alter synaptic differentiation and lead to impaired synaptic function/plasticity and abnormal network connectivity, which could underlie the development of epilepsy and related comorbid behavioural abnormalities. In rodents, HPA axis formation, differentiation, and maturation of many brain structures, including cortex and hippocampus, synaptogenesis, neurotransmitter systems development as well as the establishment of connectivity

between brain structures, take place during early postnatal life, and that is why this period of ontogeny is so susceptible to environmental influences. The favorable early environment promotes good self-regulation of the HPA axis later in life, but early-life adversity disrupts normal HPA axis development and "programs" poor HPA self-regulation, which plays an important role in the pathogenesis of epilepsy and its psychiatric comorbidities, depression, and anxiety in particular. Interestingly, corticotropin-releasing factor (CRF) and its type 1 receptor were shown to play a critical role in modulating adverse effects of early-life stress such as dendritic remodeling in the cortex and hippocampus and memory impairment (Martin and Wellman, 2011; Wang et al., 2013; Yang et al., 2015). The role of particular genes, including the CRF gene, has been demonstrated in triggering early adversity-associated pathological conditions such as anxiety and depression (Vaiserman and Koliada, 2017).

Early-life stress may be a shared causal environmental factor for both epilepsy and psychiatric comorbidities often accompanying it. Dysregulation of HPA activity is one of the most commonly observed neuroendocrine symptoms of depression in humans (Holsboer, 2000). HPA dysregulation was found in different animal epilepsy models (Daniels et al., 1990; Mazarati et al., 2009; Szafarczyk et al., 1986; Tolmacheva et al., 2012) and human studies (Zobel et al., 2004), as well as in depressive disorders (Keller et al., 2017). Therefore, hyper(re)activity of the HPA axis, which develops in epilepsy, could be regarded as one of the possible mechanisms underlying the co-morbidity between epilepsy and depression. Put into other words, the dysregulation of the HPA system might be proposed as a common pathophysiological mechanism of epilepsy and depression co-morbidity (Mazarati et al., 2009). Recently it was found that the neuropeptide hormone ghrelin is altered in children with generalized epilepsies (Costa et al., 2022) and is associated with stress response (Meyer et al., 2014; Stark et al., 2016). Ghrelin regulates the HPA axis and associated stress-related mood disorders, such as fear, anxiety, and depression (Spencer et al., 2015). This suggests that ghrelin could serve as a common pathophysiological mechanism of epilepsy and its neuropsychiatric comorbidities.

Epigenetic modifications, particularly DNA methylation, could be implicated as a molecular mechanism underlying the impact of early-life stress on epilepsy and its behavioural comorbidities. Accumulating evidence suggests that early-life stress can induce region-specific dysregulation of the DNA methylation pattern of multiple genes in the brain, which can lead to anxiety (Elliott et al., 2016) and depression-like behaviour (Zhang et al., 2019), and these changes in DNA methylation can be transmitted across generations (Murgatroyd et al., 2009; Roth et al., 2009). Interestingly, a substantial body of evidence also indicates that dysregulation of epigenetic mechanisms occurs in several human epilepsy syndromes (Kobow and Blümcke, 2018). DNA methylation has been highlighted as the methylation hypothesis of epileptogenesis (Kobow and Blümcke, 2012). Epigenetic mechanisms can influence the expression profile of candidate genes that persist in epilepsy. Epigenetic modifications can impact seizures and epilepsy in several ways (Lubin, 2012; Roopra et al., 2012). Firstly, seizure activity can be a result of histone acetylation-induced gene expression changes, including alterations in mRNA levels, for glutamate receptors 2 (GluR2 and GRIA2) and BDNF, the well-characterized epileptogenesis-related genes. For instance, histone acetyltransferase-mediated increases in histone acetylation levels at the promoter regions of the glutamate receptor 2 and BDNF genes have been found to correlate with these gene expression changes associated with seizures in an experimental animal TLE model (Huang et al., 2002). Histone acetylation is also involved in epileptogenesis in human epileptic disorders (Qureshi and Mehler, 2010), and may have a crucial role in the development of absence epilepsy and depression-like comorbidity in the WAG/Rij rat model (Citraro et al., 2020). Secondly, seizures can be a result of gene expression changes induced by alterations in the DNA methylation level. DNA methyltransferase enzymes 1 and/or 3a were shown to increase in the brain of patients with TLE (Zhu et al., 2012) and a rat model of TLE (Williams-Karnesky et al., 2013). The DNA methyltransferase (DNMT) enzyme DNMT3a in the prefrontal cortex and nucleus accumbens has also been shown to affect anxiety (Elliott et al., 2016) and depression-like behaviour (LaPlant et al., 2010). Ethosuximide treatment results in alterations in the expression of DNMT enzymes that catalyze DNA methylation, leading to reduction of epileptogenesis and behavioural comorbidity (elevated anxiety) in the GAERS model (Dezsi et al., 2013), indicating that the absence epilepsy and its behavioural comorbidity may share common epigenetic mechanisms. Thirdly, seizures and epileptogenesis might be mediated by transcription factors both in epileptic patients and epilepsy models. Repressor element-1 silencing transcription factor (REST) and neuronal restrictive silencer factor (NRSF) repress gene expression through dynamic recruitment of epigenetic complexes (Qureshi and Mehler, 2009). Of note, REST is involved in the regulation of multiple epileptogenesis-associated factors, including growth factors, neurotransmitter receptors, ion channels, circuit excitability, and neurogenesis (McClelland et al., 2014, 2011; Roopra et al., 2012). Fourthly, methyl-CpG-binding protein 2 can regulate neuronal activity (Roopra et al., 2012).

The expression of several ion channels has been identified to contribute to the aetiology of epilepsy. These channels are critical for electrical signaling between neurons and are responsible for the regulation of neuronal excitability. Dysregulation of ion channel expression is highly associated with epilepsy. Although the molecular mechanisms that underlie these changes in gene expression are not understood yet, it is known that many of these genes can be regulated by NRSF (McClelland et al., 2014, 2011). Epileptogenesis causes the downregulation of genes that are involved in epilepsy, for instance, the HCN1 ion channel gene in both TLE (McClelland et al., 2011) and genetic absence epilepsy (Nishitani et al., 2019; Strauss et al., 2004) models. Dysregulation of NRSF seems to be associated with epilepsy. However, specific mechanisms are still unknown. There is evidence that HCN1 channelopathy derives from NRSF-mediated transcriptional repression that may contribute to epileptogenesis Thus, therapeutic interventions targeting NRSF to restore HCN1 gene expression can slow down the progression of epilepsy, as has been shown in a mouse model of TLE (McClelland et al., 2011). Whether targeting NRSF to restore HCN1 gene expression could slow down the development of genetic absence epilepsy in the WAG/Rij rat model remains to be investigated.

Taken together, early-life stress can prime seizure occurrence and epileptogenesis. In addition, epigenetic modifications can be regarded as a shared pathogenic mechanism underlying the impact of early-life stress on epilepsy and its psychiatric comorbidities.

3.3. *Neonatal maternal separation*

The separation between offspring or children from their mothers has been seminal for understanding the development of psychopathology (Bowlby, 1951), and Bowlby's ideas have brought about significant changes in perceptions of separations between children and their mothers. Later, maternal separation was introduced on a large scale in the biological and biopsychological literature. It is one of the most commonly used laboratory methods to manipulate and study early-life stress effects on the development of neurological and psychiatric disorders in adulthood. Maternal separation has been induced in several ways, ranging from a single 24 h separation to repeated episodes of separation lasting 3, 6, or 12 h. There was a considerable amount of variability between studies likely related to the differences in the maternal separation protocol due to the lack of standardization (Wang et al., 2020). For instance, the number of days for which the mother was separated from their pups varied in different experiments. A most common procedure is to keep the newborns together as a litter in their familiar environment and remove the mother. This procedure leaves the pups without care but in a familiar environment and the presence of their siblings. According to another procedure, the litter is transferred into a new environment in which pups are deprived not only of the

mother but also of their familiar environment, the mother remains in the home cage. The former procedure is usually called "maternal separation" in contrast with the more stressful for pups "maternal deprivation". Of interest, the maternal separation protocol, which is more stressful for mothers, leads to increased maternal motivation and maternal care after reunion (Bailoo et al., 2014), while maternal deprivation is more stressful for newborn pups, leading to more adverse and long-lasting consequences in later life (Zimmerberg and Sageser, 2011). Studies have shown that maternal separation of sufficient duration (typically 3 h/day during the first 2 postnatal weeks of life) increases anxiety- and depressive-like behaviour in rats during adulthood (Kambali et al., 2019; Lee et al., 2007; Matthews and Robbins, 2003). Neonatal maternal separation is considered as a model of human depression as evidenced by rodent (Vetulani, 2013) and primate (Sánchez et al., 2001) studies. However, other studies in both rats and mice have shown considerable variability of behavioural outcomes induced by neonatal maternal separation. Although most of the reports highlight the harmful effects, such as the increased risk for psychopathology, several studies showed no effects of maternal separation on anxiety- and depression-related phenotypes in different mouse strains (Millstein and Holmes, 2007) or even positive effects: reduced anxiety and improved cognitive ability (Savignac et al., 2011) or increased resilience to later-life stressful events (Santarelli et al., 2017). Inconsistency of the data could be related to differences in genetic background and protocol parameters used. Interestingly, in Wistar-Kyoto rats, known for their stress reactivity, anxiety, and depression-like phenotype, neonatal maternal separation (3 h/day from PND1 to PND14) induced anxiolytic and antidepressant-like behavioural effects in adult offspring. Positive behavioural effects of maternal separation were associated with DNA hypermethylation specifically in the hippocampus. Of note, enhancing DNA methylation in Wistar-Kyoto rats by using dietary methyl-donor supplementation improved anxiety/depression-like phenotype similar to neonatal maternal separation (McCoy et al., 2016). Negative behavioural effects of neonatal maternal separation are thought to be associated with abnormal HPA axis development (Sheng et al., 2021), persistent alterations in the monoaminergic and GABAergic brain systems (Arborelius and Eklund, 2007; Caldji et al., 2000), and epigenetic modifications of genes affected by early-life stress - corticotrophin-releasing hormone (Chen et al., 2012), glucocorticoid receptor (Park et al., 2017), BDNF (Park et al., 2018) and GABAR (Hsu et al., 2003), specifically in the hippocampus. In addition, another variable that should also be taken into account is the so-called "stress hyporesponsive period", when the adrenocortical response to stress-inducing stimuli is still hypofunctional (the first week of life). This means that separation from the mother and/or siblings during the first postnatal week could have consequences different from those occurring when protocols with the separation in the second week of life are used. For instance, neonatal maternal separation during the first postnatal week was found to modify the expression of glucocorticoid receptors in the CA1 hippocampal subfield to promote increased secretion of corticosterone later in life, indicating an impairment of adrenocortical control and persistence of HPA-axis stimulation (Biagini et al., 1998).

Neonatal maternal separation strongly modifies the stress response, a critical factor involved not only in the development of behavioural impairments such as anxiety and depression, but also in seizure induction. However, it should be noted that most attention in this area of investigation was paid to behavioural impairments induced by neonatal maternal separation, and very little research has been done on the effects of maternal separation on epileptogenesis and epilepsy. The effect of neonatal maternal separation on genetic absence epilepsy was studied in the WAG/Rij rat model. WAG/Rij dams were separated from their pups daily for 3 h from PND1 to PND21 to establish the effects of maternal separation on SWDs later in life. At the age of 4–5 months, rats separated from the mother showed 35 % fewer SWDs compared to untreated controls, with no effect on the mean duration of SWDs. The morphology of the SWDs was different in the separated from the mother group as well: reduced amplitude of the peaks of the SWDs, less energy in the 7–12 Hz band, next to a lower peak frequency (Schridde et al., 2006). In sharp contrast to this anti-absence action in adult WAG/Rij rats are the effects of maternal separation (3 h/day from PND2 to PND14) in Wistar rats: separation from the mother increased the vulnerability to limbic epilepsy (Kumar et al., 2011; Salzberg et al., 2007). Neonatal maternal separation in Wistar rats led to accelerated kindling rates in young adulthood, heightened corticosterone responses during and after kindling in females and a similar trend in males, and a reduced number of pyramidal cells in CA3 post-kindling, as well as significantly increased dentate granule cell neurogenesis in female rats subjected to maternal separation compared to their control group (early handling). The enhanced amygdala kindling rate after 3 h maternal separation at PND2-PND17 was confirmed in prepubertal rats at PND18 (Zhou et al., 2010). Kumar and coworkers concluded that these data showed that early life stress results in enduring enhancement of HPA axis responses to limbic seizures, with increased hippocampal CA3 cell loss and augmented neurogenesis, in a sex-dependent manner. This implicates important hippocampal candidate mechanisms through which early-life stress may promote vulnerability to limbic epileptogenesis in rats, as well as to human MTLE and its associated psychiatric disorders. Next, the Kumar et al. (2011) and Schridde et al. (2006) data once more illustrate the opposite effects of maternal separation in limbic versus absence epilepsy. How neonatal maternal separation may have pro-epileptic effects regarding TLE and at the same time an anti-absence epilepsy action is not quite clear. The hippocampus is not a part of the cortico-thalamo-cortical network in which SWDs are initiated and maintained (Tancredi et al., 2000). However, the hippocampus plays a modulatory role in the occurrence of SWDs, as intrahippocampal administration of GABA-mimetic drugs reduces the occurrence of SWDs (Tolmacheva and van Luijtelaar, 2007). A more excitable hippocampus, as obtained through maternal separation, might facilitate the occurrence of SWDs, similar to facilitating the hippocampal kindling rate. However, this mechanism is less likely, considering that maternal separation reduces SWDs instead of enhances SWDs.

Schridde et al. (2006) proposed that changes within the cortico-thalamo-cortical system may be responsible for the maternal separation-induced reduction of SWDs. Considering that WAG/Rij rats have marked impairment in I_h in the somatosensory cortex, as has been established in pyramidal neurons, using RT-PCR, in situ hybridization, immunohistochemistry and Western blot (Strauss et al., 2004), and the crucial role of I_h in cortical and thalamic bursting (Gloor and Fariello, 1988; Lüttjohann and Pape, 2019; Pape, 1996; Pinault and O'Brien, 2005) and neural excitability (Poolos et al., 2002), the authors focused on I_h. Maternal separation caused an upregulation of the fast component of I_h and HCN1in the somatosensory cortex in the experimental group of WAG/Rij rats compared to the control group. No group differences in HCN2 and HCN4 proteins or changes in mRNA of any of the channel subunits were found. These data are in agreement with the results of a comparative study by Strauss et al. (2004), indicating that only cortical HCN1 channels seem to be critical for SWDs (Strauss et al., 2004). Therefore, it can be proposed that maternal separation rescues the genetic deficit in I_h channel functions in the somatosensory cortex, causing less cortical excitability and, as a result, a reduction in the number of SWDs. Kole et al. (2007) confirmed the important role of cortical HCN1 in WAG/Rij rats in a developmental study and showed that the changes in cortical I_h precede the onset of SWDs. Blumenfeld et al. (2008) not only confirmed the contribution of HCN1 in cortical excitability in WAG/Rij rats but also demonstrated that antiepileptogenesis by chronic and early treatment prevents the impairment of cortical I_h and age-dependent increase in SWDs. In all, the results of Schridde et al. (2006) provided the first evidence that relatively mild changes in the neonatal environment have a long-term impact on the absence seizures, I_h, and HCN1 and suggested that an increase in I_h and HCN1 is associated with absence seizure reduction. These findings demonstrate that genetically determined SWDs are quite sensitive to early interventions

and that the evidence for cortical I_h as a controlling mechanism for SWDs seems to be strong. The direction of the maternal separation effects in WAG/Rij rats is a reduction in SWDs, while in TLE models the effects are opposite. This might point towards the role of GABA, since GABA also acts both as a pro-absence and anticonvulsant agent.

Considering that dams display increased maternal care and attentiveness to pups upon reunion after separation (Bailoo et al., 2014) and that a heightened level of maternal care reduces SWDs in WAG/Rij offspring (Sarkisova and Gabova, 2018; see also Section 3.5), we cannot exclude the role of improved maternal care in anti-absence effects of neonatal maternal separation. The genetic background of the WAG/Rij rats may also contribute to this effect. Maternal care can program HPA axis development (Sheng et al., 2021) and thereby can dampen a hyper-activation of the HPA axis leading to the prevention of the development of adverse effects, which could be induced by neonatal maternal separation. Although the effect of maternal separation on comorbid depression has not been studied, it can be assumed that maternal separation may not only reduce SWDs but also improve depression-like behaviour in WAG/Rij rats. The fact that neonatal maternal separation reduced depression-like behaviour in innately depressive Wistar-Kyoto rats (McCoy et al., 2016) supports this assumption. However, further studies are needed to find out if this is the case in WAG/Rij rats.

3.4. Neonatal handling

The developing brain is extremely sensitive to even minor environmental perturbations. Neonatal handling is a form of early-life impact which can result in long-term consequences. The procedure commonly involves removing the mother and then the rat pups from their cage, placing the pups in a small container with sawdust, and returning all of them after 15 min back to their cage and this is followed by the return of their mother (Caldji et al., 2000). However, in different studies, the duration of the handling procedure may be different (1, 3, or 15 min), as well as can be repeated a different number of times (for 10, 15, or 21 days). Despite this variability in the parameters of the procedure, the main effects of neonatal handling, such as long-term alterations in brain functions, reduced anxiety/emotionality, and reduced stress responses later in life are robust and well-reproducible (Raineki et al., 2014). The most common duration of the manipulation, 15 min, is much shorter than for maternal separation, typically 3 h.

Although this manipulation is short, it may induce changes in the brain and behaviour that persist long into adulthood (Pryce et al., 2001). Repetitive brief handling in neonatal rats has been shown to cause decreased glucocorticoid responses to stress due to a permanent increase in glucocorticoid receptors density and binding in the hippocampus, a critical region for HPA regulation, especially for the negative-feedback inhibition of adrenocortical activity. Moreover, hippocampal cell loss and spatial memory impairments, which emerged with age in the non-handled rats, were almost absent in the handled rats, indicating that neonatal handling can retard the development of age-related pathological processes (Meaney et al., 1988). The molecular mechanisms underlying neonatal handling-induced behavioural and cognitive changes are not fully understood. However, it is assumed that alterations in GABA, the major inhibitory neurotransmitter, which regulates both behavioural and neuroendocrine responses to stress, may contribute to the effects of neonatal handling (Hsu et al., 2003). Abnormalities in GABAergic function have been observed in acquired and genetic models of epilepsy (Treiman, 2001). Acquired alterations or genetic defects in GABA receptor channels cause epilepsy (Chuang and Reddy, 2018). This means that neonatal handling which can modulate the GABAergic brain system may also modify acquired or genetic epilepsy. Neonatal handling-induced changes are reported not only in the GABAergic (Caldji et al., 2000) brain system, but also in monoaminergic (Durand et al., 1998; Papaioannou et al., 2002a,b), cholinergic (Pondiki et al., 2006), and opioid neurotransmitter systems (Ploj et al., 1999), all known to modulate epilepsies, including the frequency of occurrence of SWDs in WAG/Rij rats (van Luijtelaar and Zobeiri, 2014; Russo et al., 2016). Neonatal handling could modify the development of the HPA axis and, as a consequence, its response to different stressors. It has been shown that neonatal handling induces better regulation of HPA axis activity due to the increased negative feedback efficacy (Myers et al., 2012). When performed daily during the first 14 or 21 days of postnatal life, it causes in adult animals a reduced release and production of ACTH and corticosterone due to an enhanced glucocorticoid negative feedback sensitivity, meditated by an increased hippocampal glucocorticoid receptor mRNA expression. This leads to a reduced ACTH and corticosterone response to stressors later in life (Meaney et al., 1993; Raineki et al., 2014). Of interest, not only neonatal handling but also long-lasting (6 weeks) handling in adolescent rats may also produce beneficial effects. Improvements in learning and memory, including spatial memory impairments caused by neurodegeneration, and decreases in anxiety levels have been reported (Costa et al., 2012; Stara et al., 2018). Of note, handling for 7 days, 5 min per day in 60-days-old Wistar rats reduced time spent in the dark box as a measure of anxiety in the light-dark choice test (Aulich et al., 1974).

One of the most frequently described effects of neonatal handling is a reduction in anxiety-like behaviour, which is most often established in the open field (more time spent in the center area), in the elevated plus, or zero mazes (more time spent in the open sections (Caldji et al., 2000; Durand et al., 1998; Meerlo et al., 1999; Río-Alamos et al., 2015; (2017)). It is generally accepted that early postnatal handling has beneficial consequences, such as the ability to cope with stressors and improved adaptation to the environment. However, other behaviours may show negative effects of early handling. For instance, neonatal handling negatively affected neurocircuitry that supports social behaviour leading to deficits in social and play behaviours (Raineki et al., 2014).

The effects of early neonatal handling on epileptogenesis and seizure susceptibility were most often studied regarding the assumption that early handling is stressful, for an overview see Jones et al. (2014). The effects of neonatal handling in comparison with standard husbandry or completely undisturbed group on epileptiform activity were rarely studied, and if studied, the focus was on hippocampal-related epilepsies and the role of the HPA-axis. And in that case, early handling was proconvulsive since it decreased seizure onset time in the lithium-pilocarpine model (Persinger et al., 2002). In a genetic absence epilepsy model, it has been found that neonatal handling for 15 min per day during PND1-PND22 reduced (35 %) the number of SWDs in adult WAG/Rij rats, while the mean duration of SWDs was not affected. The morphology of the SWDs was also changed as a consequence of neonatal handling: the power of the 7–12 Hz and beta (12.5–25 Hz), as well of the peak frequency, were reduced compared to the untreated control group, while the background EEG showed no group differences (Schridde et al., 2006). It is not easy to attribute the reduction in number and changes in the morphology of SWDs to a certain mechanism; several non-exclusive mechanisms might be proposed, such as the role of the monoamine system, GABA, for the HPA-axis via a reduction in GABAA receptor function and expression in the hippocampal dentate gyrus (Hsu et al., 2003). However, another possibility is considering that the morphological changes were reminiscent of SWDs seen in young WAG/Rij rats, indicating that the process of epileptogenesis is delayed and that changes in the cortico-thalamo-cortical pathways are involved or caused these changes.

Schridde et al. (2006) also analyzed HCN channels, previously demonstrated to play a role in the increased focal excitability at the initiation site, the somatosensory cortex, in the WAG/Rij model (Strauss et al., 2004), and showed that in brain slices of neonatally handled rats the typical HCN response was more pronounced and faster in onset compared to a control group that was exposed to a single disturbance in the weaning period for cage maintenance. Importantly, the decreased HCN function is a marker for cortical epileptogenesis in this model, and this decrease was rescued by an antiepileptogenic treatment

(Blumenfeld et al., 2008). The combined results allow us to suggest that neonatal handling delayed epileptogenesis, considering that less number of SWDs was initiated and that also the less mature morphology of the SWDs pointed in that direction, and that cortical focal I_h channels are a mediating factor in this process. In line with this role of HCN channels is that HCN channel blocker ZD7288 increased the input resistance, diminished the HCN typical voltage sag, and prevented the rebound depolarization, and this effect was again more pronounced in neonatally handled animals (Schridde et al., 2006). Current-density analyses showed h-channel availability in neonatally handled rats. In situ hybridization and Western blot analyses showed that HCN1 protein expression was increased in the somatosensory cortex, and not the mRNA expression. This implies that post-transcriptional or post-translational factors are playing a role, affecting the location or amount of HCN1 proteins. Other HCN subunits were not affected by neonatal handling. The electrophysiological and molecular evidence strongly suggests a selective increase of HCN1 subunits in layer V of the somatosensory cortex in neonatally handled WAG/Rij rats. Subsequent studies showed that the age-dependent increase in SWDs was accompanied or even caused by the age-dependent decrease in HCN1 channels, which preceded the increase in SWDs (Blumenfeld et al., 2008; Kole et al., 2007). It is therefore suggested that the reduction in the number of SWDs, as reported here, as well as the morphological changes (less mature SWDs were found) induced by neonatal handling, are caused by a smaller reduction in HCN channel functioning and by a diminished increase in cortical excitability. Epigenetic modifications of HCN1 channel gene expression might contribute to these effects (see Section 4.2).

The seminal work of Meaney and coworkers showed that differences in maternal care after neonatal handling rather than the handling procedure itself may be the critical factor in inducing neuroplastic changes, among those that are involved in the reduced endocrinological and behavioural response to stressors later in life (Caldji et al., 2000; Hsu et al., 2003). Handling of the pups altered the behaviour of the mother: it increased the level of licking and grooming of pups (Garoflos et al., 2008; Pryce et al., 2001; Reis et al., 2014; Villescas et al., 1977) and did not change substantively the arched-back nursing (de Azevedo et al., 2010). Mothers of non-handled pups demonstrated stable maternal care, including licking/grooming behaviour. Of interest, in the tactile stimulation group, in which the mother was removed from the nest and the pups remained in their home cages and were stimulated with a brush for 10 min/day within the nest, no changes in maternal care were observed after her return to the nest (de Azevedo et al., 2010). This indicates that tactile stimulation, which mimics normal maternal care, prevents neonatal handling-induced increases in pup licking. Taken together, the findings allow us to assume that increased maternal care and the immediate effects of infantile tactile stimulation (see Section 4.1) following the return of pups to the nest could be considered as a mediating mechanism for the beneficial effects of neonatal handling on behaviour, as well as on epileptogenesis in a genetic absence epilepsy model. Therefore, maternal behaviour will be discussed in the next paragraph.

3.5. Maternal care

Maternal care is the most relevant environmental factor influencing the later-life phenotype in offspring. Deficits in maternal care can induce epigenetic modifications in the offspring leading to neurologic and psychiatric diseases, including epilepsy and depression. Increased risk for epilepsy and psychiatric disorders in offspring may be due to genetic predisposition. However, maternal care has also been shown to be very important. Likely, a combination of genetic, epigenetic, and environmental factors could more accurately explain the link between maternal care and the development of epilepsy and psychiatric disorders in offspring.

Maternal anxiety and depression may lead to unresponsive or inconsistent care by the mother toward the child leading to insecure attachment (Campbell et al., 2004) which has been linked to increased risk for anxiety and depression in the offspring (Brumariu and Kerns, 2010; Wan and Green, 2009). Clinical data suggest that reduced maternal care associated with maternal depression increases several times the risk of the development of depression and epilepsy in offspring (Asselmann et al., 2015; Ekinci et al., 2009; Sellers et al., 2013). Animal studies support these findings indicating that the early maternal environment is critical for the later-life phenotype of offspring (Champagne et al., 2003; Francis et al., 1999a; Weaver et al., 2004). So, in the rat, it has been shown that variations in maternal care, particularly in licking/grooming, influence the growth and survival of the offspring, as well as the development of an endocrine, emotional and cognitive response to stress (Champagne et al., 2003). Interestingly, individual differences in maternal behaviour can be transmitted from the mother to her female offspring (Champagne et al., 2003; Francis et al., 1999b). Depressive rat mothers, similarly to humans, exhibit reduced maternal care compared with non-depressive dams, as was found in Flinders Sensitive (Lavi-Avnon et al., 2008) and WAG/Rij (Sarkisova et al., 2017a) rat strains. Poor mothering behaviour can be also observed in the anxious BALB strain of mice (Prakash et al., 2006). Females of BALB mice performed less arched-back nursing and licking/grooming pups and have longer latencies to retrieve pups to the nest (Tarantino et al., 2011), similar to depressive WAG/Rij females genetically predisposed to absence epilepsy (Dobriakova et al., 2014; Sarkisova and Gabova, 2018).

In mammals, the quality of early life is primarily dependent on maternal care. In rats and mice, maternal care is manifested in the form of arched-back nursing, non-arched-back nursing (non-nutritive contacts with the pups) in 'blanket' or passive posture, and licking/grooming. Arched-back nursing and licking-grooming pups are thought to be the most important types of maternal behaviour exhibited by most rodent species with a great variation between different strains (Champagne et al., 2003). It has been found that these two types of maternal care expressions critically influence the offspring's later-life phenotype and shape their responsiveness to stress and their level of anxiety (Sakhai et al., 2013). However, recent studies have shown that non-arched-back nursing, which represents tactile (skin-to-skin) contact with pups, in addition to licking/grooming, is also an important or even more important component of maternal care compared with arched-back nursing (see also Section 4.1). This view is supported by the fact, that rearing by foster Wistar mothers with a high level of non-arched-back nursing normalized the absence epileptic phenotype in WAG/Rij rat offspring (Sarkisova et al., 2017a; Sarkisova and Gabova, 2018) and the schizophrenia-like phenotype in apomorphine-susceptible (APO-SUS) rat offspring (van Vugt et al., 2014), as was established in cross-fostering studies. The WAG/Rij mothers exhibited depression-like behavioural symptoms and a low level of the active type of maternal care compared with control Wistar dams irrespective of the specificity of their pups (own or foster): a longer latency to retrieve pups to the nest, a shorter duration of the tactile non-nutritive contacts with pups (non-arched-back nursing), a lesser number of licking/grooming episodes, and a longer duration of arched-back nursing in immobile/passive posture (Sarkisova and Gabova, 2018). Moreover, WAG/Rij dams did not show a preference for a pup-associated compartment in the place preference test (Sarkisova et al., 2017b), indicating that reduced maternal care in WAG/Rij mothers might be due to depression-associated deficits in pup-induced maternal reward. Similarly, the APO-SUS mothers provided less maternal care than their control, apomorphine-unsusceptible (APO-UNSUS) dams. Pups of APO-SUS mothers had a reduced body weight. The APO-SUS mothers were more involved in self-grooming, spent less time in contact with pups and, like the WAG/Rij mothers, exhibited less non-arched-back nursing. The APO-SUS rats had, besides the schizophrenia-like phenotype, also many SWDs (Cools and Peeters, 1992; De Bruin et al., 2000). Therefore, it can be assumed that, although the effects of cross-fostering on EEG and SWDs were not investigated, improved maternal care given by APO-UNSUS mothers might reduce the

epileptic phenotype in APO-SUS rats similar to WAG/Rij rats. Further studies are needed to verify this assumption.

The responsiveness to stress is regulated by glucocorticoids and glucocorticoid receptors. High levels of circulating glucocorticoids increase the stress response, while lower levels attenuate it. Conversely, high levels of glucocorticoid receptors in the forebrain, in particular in the hippocampus, provide negative feedback that reduces the production of glucocorticoids and thereby dampens the stress response (Seckl, 2007). Interestingly, offspring of mothers with a high level of arched-back nursing and licking-grooming show increased glucocorticoid receptors expression and reduced reactivity to stress, whereas offspring of mothers with a low level of arched-back nursing and licking-grooming demonstrate decreased glucocorticoid receptors expression and increased stress reactivity (Liu et al., 1997). Glucocorticoids act via mineralocorticoid and glucocorticoid receptors, the first of them is involved in stress response onset but the second one participates in response termination and is essential for stress-coping strategy (active or passive). The imbalance between mineralocorticoid and glucocorticoid receptors is thought to be associated with stress vulnerability leading to the development of pathologic phenotypes (Franklin et al., 2012). Put in other words, a high level of active maternal behaviours, such as licking/grooming and arched-back nursing, has beneficial effects on the later-life phenotypes of offspring, but a low level can lead to stress vulnerability, depressive-like behaviour, anxiety, and altered cognitive and social behaviours (Myers-Schulz and Koenigs, 2012). Similarly in humans, maternal attachment to, the favorable environment in childhood predisposes individuals to stress resilience (Jaffee, 2007), while maternal neglect, physical maltreatment, and abuse or traumatic early-life events increase the risk for affective disorders later in life (Dietz et al., 2011; Hulme, 2011).

Changes in maternal care can occur naturally due to individual variability in maternal care but can also be produced experimentally using specific manipulations in rodents. One of the ways to change maternal care to investigate the contribution of maternal care to seizure susceptibility and epileptogenesis is a cross-fostering procedure. The procedure of cross-fostering includes the removal of newborn pups from their biological mother and placing them with a foster mother with a different from the biological mother's manifestation of maternal behaviour, commonly with a higher level of expression. To control whether a cross-fostering procedure per se can cause its own effect, an in-fostering procedure is usually used (pups are cross-fostered to foster mothers of the same strain with approximately the same expression of maternal care). Of interest, the cross-fostering approach was effective in improving depressive phenotype in Flinders Sensitive line rats fostered by Flinders Resistant dams with a higher level of arched-back nursing and licking/grooming (Malkesman et al., 2008). Anxious BALB mice fostered by non-anxious B6 mothers have been reported to express decreased anxiety levels in the elevated plus-maze test (Priebe et al., 2005). Cross-fostering was also found can ameliorate the expression of genetically determined pathologies, such as arterial hypertension in NISAG rats (Yakobson et al., 2001), catalepsy in genetic cataleptic GK rats (Kolpakov et al., 2002), and high anxiety in high responders to novelty (bHR) selection line (Cohen et al., 2015). However, cross-fostering did not exert a substantial effect on the expression of pathologic phenotypes, such as hyperactivity in spontaneously hypertensive (SHR) rats (Howells et al., 2009) and in hyperactive (High--Active) rats (Majdak et al., 2016), in two animal models of ADHD. Females of seizure-prone EL mice exhibit a reduced level of maternal care. They are slower than the control to initiate pup retrieval and spend less time in arched-back nursing but longer time in non-maternal behaviours, such as exploration and self-grooming (Bond et al., 2003). Cross-fostering of genetically susceptible to seizures El pups to seizure-resistant CD-1 mothers with a higher level of maternal care delayed seizure onset and seizure frequency, indicating that the maternal environment plays an important role in shaping the adult seizure phenotype (Leussis and Heinrichs, 2009). Paradoxically, El pups reared in the biparental environment, in which they received more parental care from both biological parents compared with El pups raised by only the El mothers, showed earlier development of seizures and increased seizure susceptibility later in life (Orefice and Heinrichs, 2008). Results indicate that the presence of a second care provider in addition to the dam constitutes a form of stressor exposure in El pups and, as a consequence, accelerates the development of seizures in genetically susceptible offspring.

Cross-fostering of WAG/Rij pups genetically predisposed to absence epilepsy with comorbid depression to control Wistar mothers with a high level of maternal care showed that improvement of early caregiving environment can exert disease-modifying effects on epileptogenesis and behavioural comorbidities in genetic absence epilepsy. WAG/Rij offspring reared by Wistar dams with a high level of non-arched-back nursing and licking/grooming exhibited less and shorter SWDs and reduced depression-like behaviour (immobility in the forced swimming test) in adulthood compared with age-matched WAG/Rij offspring reared by their own or foster WAG/Rij mothers with a low level of maternal care. Moreover, a high level of maternal care of foster Wistar mothers decelerated the absence epilepsy appearance and its progression in WAG/Rij offspring, indicating an anti-epileptogenic effect. In 30% of adult (7–8 month old) WAG/Rij offspring reared by foster Wistar mothers no typical well-developed (mature) SWDs were found. Only immature SWDs, which were similar to immature SWDs commonly recorded in young (2–3 month old) WAG/Rij rats, were observed. Of note, adult WAG/Rij rats, adopted by Wistar dams, were behaviourally undistinguishable from aged-matched normal Wistar rats reared by their own or foster Wistar mothers, indicating the absence of behavioural symptoms of comorbid depression. Interestingly, the adoption by WAG/Rij dams with a low level of maternal care did not change EEG and behaviour in Wistar offspring (Sarkisova et al., 2017a; Sarkisova and Gabova, 2018). Results of these studies suggest that early-life environment can interact with a genetic predisposition to shape later-life seizure phenotype and associated behavioural comorbidities in the offspring. Disease-modifying effects of improved maternal care on genetic absence epilepsy and comorbid depression persisted into adulthood suggesting a possible role of epigenetic mechanisms, such as DNA methylation, which affects gene expression.

Mounting evidence suggests that maternal care leads to epigenetic modifications of gene expression in the offspring. So, adult rat offspring exposed to poor maternal care early in development exhibited increased methylation in the promoter region of the hippocampal glucocorticoid receptor gene (GR 1_7) that resulted in decreased gene expression and enhanced response to stress. Conversely, a high level of maternal care was associated with decreased promoter methylation of the hippocampal GR 1_7 gene and increased gene expression (Weaver et al., 2004). Significantly elevated levels of methylation were detected in the estrogen receptor alpha gene promoter region in adult offspring of low licking/grooming dams compared with offspring of high licking/grooming dams, and cross-fostering reversed this effect (Champagne et al., 2006). Epigenetic modulation of gene expression has been implicated in the long-lasting impact of positive caregiver experiences on the offspring's adult phenotype, namely, on stress reactivity and maternal behaviour (Weaver et al., 2004). It has been shown that gene expression differences induced by distinct epigenetic (specifically DNA hypomethylation) patterning in the amygdala might underlie downstream behavioural differences such as anxiety and depression-like phenotype (McCoy et al., 2017). Cross-fostering to foster mothers with a different style of maternal care shifted developmental gene expression in the amygdala (not hippocampus) and reduced adult anxiety and depression-like behaviours (Cohen et al., 2015).

It might be hypothesized that a high level of maternal care of foster Wistar mothers counteracts the manifestation of pathologic phenotype in adult WAG/Rij offspring by changes in the activity of DNA methyltransferases (DNMTs), enzymes that catalyze DNA methylation, leading to epigenetic modifications in the expression of genes pathogenetically

relevant for absence epilepsy and comorbid depression in certain brain structures. In favor of this assumption, there is evidence that a maternal methyl-enriched diet, which impacts DNA methylation, increased DNMT1 and HCN1 ion channel gene expression in the somatosensory cortex responsible for the generation of SWDs, and reduced absence seizures and depression-like comorbidity in adult offspring of WAG/Rij rats (see Section 4.2). We can also assume that changes in DNA methylation induced by a high level of maternal care could prevent the age-related development of the mesolimbic DA deficiency responsible for the manifestation of behavioural symptoms of comorbid depression in adult offspring of WAG/Rij rats. A reduced DAergic tone has been suggested to be a neurochemical mechanism of comorbid depression-like behaviour in WAG/Rij rats (Sarkisova et al., 2013; Sarkisova et al., 2014). Moreover, the absence epileptogenesis could also be associated with a reduced DAergic tone. Decreased tonic release of DA has been suggested to act as a facilitating and self-sustaining factor, which may lead to increased excitability of the somatosensory cortex (Cavarec et al., 2019) and thereby contribute to the generation of SWDs. Interestingly, neurochemical alterations of the DAergic brain system begin to appear before the occurrence of SWDs in WAG/Rij rats (Sarkisova et al., 2014). Maternal care was found to affect the development of the midbrain DA pathway. Tyrosine hydroxylase (TH) immunoreactivity in the ventral tegmental area was elevated by PND6 in response to maternal licking/grooming, and this effect was sustained into adulthood. The differences in the TH cell counts in the ventral tegmental area associated with different levels of postnatal maternal care suggest that the developing DAergic brain system is shaped by maternal care. Maternal licking/grooming altered the expression of genes critical for midbrain DA neuron differentiation and maintenance. Moreover, the offspring of mothers with a high level of licking/grooming had elevated DA receptor mRNA in the nucleus accumbens. TH gene DNA methylation increased with age but did not vary as a function of maternal licking/grooming (Peña et al., 2014). Whether the development of the mesolimbic DAergic brain system, in particular TH gene expression, is shaped by maternal care in the WAG/Rij rat model of absence epilepsy with comorbid depression-like behaviour remains to be established.

Due to epigenetic mechanisms, variations in postnatal maternal care can predispose to or, on the contrary, prevent offspring from developing later-life pathologies, including the absence epilepsy and psychiatric comorbidities. Taken together, results suggest that maternal care can make a significant contribution to the trajectory of brain development and thereby substantively impact the adult phenotype of the offspring, even in the case of genetically determined pathology, such as the absence epilepsy and comorbid depression.

3.6. Environmental enrichment

Donald O. Hebb, dated back to 1947, observed that rats reared in an enriched environment performed generally better on behavioural tasks than those reared under standard laboratory conditions. This observation allowed him to formulate the scientific concept of an ‘enriched environment’. In animal studies, environmental enrichment refers to housing conditions designed to enhance sensory, motor, social, and cognitive stimulation, compared to control conditions. ‘Environmental enrichment’ implies that the interaction of various factors, not a single contributing factor, is an essential element of housing conditions (van Praag et al., 2000). Cage enrichment has a long tradition in inducing neuroplastic changes and is commonly applied in rats post-weaning for several weeks, 24 h/day. It is very well established that housing condition has long-lasting and profound effects across the lifespan on a variety of brain-behavior-related variables. Living in an enriched environment stimulates neurogenesis, increases the expression of neurotrophic factors, modifies brain structure and circuitry, improves cognitive functions, favors alterations in brain chemistry, and may protect against seizures or against the effects of seizures (Kempermann et al., 2002; Rosenzweig and Bennett, 1972; van Praag et al., 2000; Young et al., 1999). The seminal review (Dhanushkodi and Shetty, 2008) contained a small section regarding the effects of enrichment strategies for functional recoveries in TLE. The section was small due to the limited literature on this topic. They concluded based on two studies that animals reared in environmentally enriched conditions show a decreased susceptibility to seizures and hippocampal degeneration when acutely challenged with kainic acid (Young et al., 1999) or showed an increased threshold for amygdala kindling, also after prior housing in an enriched environment (Auvergne et al., 2002). A third study examined whether exposure to an enriched environment after the induction of acute seizures or SE is efficacious for preventing chronic epilepsy. Rutten et al. (2002) used the lithium-pilocarpine SE model in 20-day-old rats, but the effect of post-SE 30-day enriched housing on seizure prevention was not conclusive, perhaps due to the young age of the animals (Rutten et al., 2002). We identified a few more studies, all in TLE models. In the kainic acid seizure model, 20–25 days old animals were used, and the effects of early life environment on seizure-induced behavioral deficits, neuronal injury, and the inflammatory reaction in young rats were investigated. Two rearing conditions, maternal separation for 3 h daily during the first 2 weeks of their lives followed by single housing versus maternal care in an enriched environment for 7–10 days, followed by group housing in an enriched environment, were compared. A significant reduction in DNA fragmentation and microglial activation in the enriched compared to maternally separated animals. These results suggested that a nurturing early enriched environment can enhance the ability of the developing brain to recover from seizures and provide a buffer against their damaging effects (Kazl et al., 2009). The same group of authors showed earlier that environmental enrichment may reverse the adverse effects of early-life seizures on exploratory behaviour and the expression of genes involved in synaptic plasticity (Koh et al., 2005). Of note, not only kainic acid-induced seizures but also depression-like behaviour in the forced swimming test was reduced in juvenile rats reared in an enriched environment. Changes in 5-HT receptor gene expression were paralleled by decreased mobility in the forced swimming test, but environmental enrichment reversed both depression-like behaviour and gene expression. This means that seizures lead to increased susceptibility to depression through transcriptional regulation, while environmental enrichment can interact with gene expression to influence the behavioural comorbidity in epilepsy (Koh et al., 2007).

Vrinda et al. (2017) used the lithium pilocarpine SE model in young adult Wistar rats. 6 weeks after SE, rats have been housed 6 h/day in an enriched cage or their regular home cages. Depression-like behaviour, anxiety, spatial learning, and memory were assessed using the sucrose preference test, elevated plus maze, and Morris water maze, respectively. Enriched housing significantly reduced seizure episodes and seizure duration in epileptic rats, next to normalization of hippocampal delta and theta power. In addition, environmental enrichment alleviated depression-like behaviour and hyperactivity. However, environmental enrichment neither ameliorated epilepsy-induced spatial learning and memory deficits nor restored cell density in the hippocampal CA1 region. In another study, it has been shown that environmental enrichment significantly improves hippocampal neurogenesis (increases cell proliferation and survival, extends the apical dendrites), decreases long-term seizure activity, and improves cognitive impairments in adult rats after SE (Zhang et al. (2015)).

Positive effects of environmental enrichment were found in other epilepsy models, such as the AY-9944 mouse model of childhood atypical absence epilepsy (Stewart et al., 2012) and the Q54 transgenic mouse model of TLE (Manno et al., 2011). Enriched Q54 mice displayed a reduced frequency of epileptic discharges and reduced hippocampal damage (Manno et al., 2011). Another study demonstrated that AY-9944 mice from enriched housing conditions exhibited less behavioural hyperactivity and anxiety, improved olfactory recognition and spatial learning, but no significant reduction in the number of epileptic discharges in comparison with their non-enriched cohorts (Stewart et al.,

2012). Environmental enrichment may facilitate amygdala kindling, but reduce kindling-induced anxiety (Young et al., 2004), indicating the opposite effects on epileptic seizures and behavioural comorbidity. On the other hand, in a genetic model, El mice, enriched housing from PND21 to PND 49, produced a 100 % decrease in seizure susceptibility relative to El controls (Korbey et al., 2008).

Thus, the vast majority of the evidence shows positive effects of a post-weaning enriched environment on seizure characteristics in TLE models, both regarding the reduction of seizure susceptibility or inhibition of epileptogenesis. Moreover, there is evidence that the positive effects of environmental enrichment are not restricted to only the post-weaning SE models, or to the manipulations in the silent period, but that also later in life environmental effects can be found.

In sharp contrast are the outcomes of enriched housing in the WAG/Rij rat model of absence epilepsy (Schridde and van Luijtelaar, 2005, 2004a). The enriched/impoverished housing conditions resembled those used by Rosenzweig and Bennett (Rosenzweig and Bennett, 1972), comprising a pool of weekly changed objects and providing social and inanimate enrichment in a large cage with 8–10 animals per cage, whereas impoverished housing implied a singly housed rat in a standard colony cage. ACI rats were used as a control: they have very few SWDs and are mainly of type II. For the differences between type I and type II SWDs see Midzianovskaia et al. (2001) and van Luijtelaar and Coenen (1986). Half of the rats of each strain (group size n = 20) were housed from post-weaning day 30 to PND90 in the enriched environment, and the other half of the animals were housed in impoverished conditions. EEG recording showed, at PND90, that enriched housing increased the mean duration of the SWDs type I (the classical SWDs), and the number of type II SWDs. Then, half of each group was transferred to the other environment and stayed there for another 60 days, and half of the rats remained in their original housing condition, also for 60 more days. EEG recordings after the second housing period revealed that again the mean duration of type I was increased in the groups of WAG/Rij rats that have spent two or four months in the enriched conditions, and again the number of type II SWDs was enhanced in the WAG/Rij's that were housed during the last 60 days in the enriched environment (Schridde and van Luijtelaar, 2005). The results are striking because of three reasons: first, the effects are opposite to the literature on the TLE models that found a positive effect of an enriched environment, here a negative, implying an increase in the mean duration (type I) and number (type II) of SWDs. Second, the effects on the number and mean duration of either type I or type II was different. The increase in the mean duration of SWDs might point towards a role of the thalamic reticular nucleus (RTN), a structure involved in determining the duration of SWDs (Lüttjohann and Van Luijtelaar, 2015; Sohal et al., 2000). Third, the lack of an increase in the number of types I SWDs excludes the role of the somatosensory cortex, the trigger zone of SWDs (Meeren et al., 2002). The number of type II SWDs was increased, type II has a more occipital and localized spatial distribution and is, therefore, less generalized compared to type I SWDs, however, the source of this type of SWDs is not known. Therefore, but not based on strong evidence, it is thought that the RTN is a primary candidate for the effects of enriched housing post-weaning on SWDs.

The effects of enriched housing were also studied in the GAERS model of absence epilepsy (Dezsi et al., 2016): cage enrichment started immediately the following weaning at PND21, the end of week 3. At weeks 9, 10, 11, 14, and 20, the EEG was recorded and the rats were tested in the open field. Enrichment delayed the onset of epilepsy, as evidenced by a reduced proportion of GAERS who had developed epilepsy by 9 weeks of age. Moreover, recording sessions over weeks showed that enriched GAERS had a lower SWD incidence, and a shorter mean duration compared with standard housed controls. Enrichment also reduced the indices of anxiety as obtained from a brightly lit open field (increased the number of entries into the inner area, as well as the total time spent in the inner area). In addition, it was investigated whether environmental enrichment could improve disease outcomes in adult symptomatic GAERS when absence epilepsy had already developed. Six weeks of housing in an enriched environment reduced the incidence of SWDs, not the mean duration. The authors established as well that the effects of environmental enrichment on SWDs and anxiety were genetically transmitted through the male germ line into the next generation, which also benefitted from the enriched experience of the father. Reduced CRH mRNA expression was associated with these phenotypic improvements, but this was not due to changes in DNA methylation (Dezsi et al., 2016). The reduction in SWDs and CRH, as found in this study, agrees with that cortisol enhances SWDs in the WAG/Rij model (Schridde and van Luijtelaar, 2004b).

The reasons for the different effects of enrichment in the two genetic absence models are not immediately clear, but there were some differences between the experiment in GAERS and the WAG/Rij model. The enriched cages were much smaller in the GAERS study and the number of rats in the enriched cage was not mentioned, next the GAERS's impoverished condition contained two rats, in the WAG/Rij study impoverished housing implied single housing, while the WAG/Rij enrichment cages, measuring 75 × 150 × 80 cm contained 8–10 rats. Therefore, the reasons for the results at variance are difficult to pinpoint considering a large number of differences. It clear is as well, that there are some differences between GAERS and WAG/Rij rats regarding the epileptic phenotype, for a direct comparison see (Akman et al., 2010) regarding the number of SWDs per hour, the frequency of the SWDs, the age of onset, and the genes involved. Epilepsy in both models is genetically determined but driven by different chromosomal locations in the WAG/Rij strain compared to GAERS (Gauguier et al., 2004; Rudolf et al., 2004), and single nucleotide (G to C) mutation in the Cav 3.2 T-type calcium channel gene (Cacna1h) was found in GAERS and not in rats of the WAG/Rij strain (Powell et al., 2009). It is therefore rather likely that not only differences between the type of enrichment and impoverishment, but also different genetic causes are interacting with the environmental factors in contrasting manners to differentially alter SWD characteristics. In general, inconsistency of data concerning the effects of environmental enrichment on epileptogenesis and psychiatric comorbidities may be explained not only by differences in epilepsy models but also by differences in experimental protocols used (Harland and Dalrymple-Alford, 2020). Possibly due to differences in experimental procedures environmental enrichment can not only reduce seizures, but also exaggerate them, and not only absence seizures, as in the WAG/Rij model, but also other types of seizures, for instance, seizures induced by PTZ kindling in Wistar rats. Environmental enrichment improved learning and memory in the Morris water maze test, but lead to the exaggeration of PTZ-induced seizures (Keloglan, 2016). One of the reasons for the seizure aggravation effects of enriched housing could be the stress caused by the change from the familiar and safe environment to a new unfamiliar one enriched with a variety of multimodal stimuli. Multi-sensory stimulation or intense and repeated stimulation of a single modality may be stressful for animals and can lead to seizure aggravation. Stress-induced seizure aggravation effects in epilepsy models are well known (Joëls, 2009), including WAG/Rij rats (Tolmacheva et al., 2012).

There is a single paper in which it was demonstrated that exposure to intense 20–40 strobe trains per day for 3 days in adult Sprague-Dawley rats changes the common response to strobe trains in 34/36 rats (Uhlrich et al., 2005). Over the stimulation sessions, a high-amplitude spike-wave response developed not seen before the onset of stimulation, and this spike-wave response emerged fully by the third day of photic exposure, first at the occipital cortex, later it spread to the frontal cortex, and by the end of treatment, the oscillations were mimicking SWDs. The results indicate that visual stimulation, by itself, can induce in adult rats an enduring sensitization of visual response with epileptiform characteristics. The site or origin of these SWD-like oscillations, also sensitive to ETX, is topographically different from the classical SWDs in WAG/Rij and GAERS, which have an initiation site at the somatosensory cortex (Meeren et al., 2002; Polack et al., 2007). Here the visual cortex,

interconnected with the visual thalamus seems to be the excitable area and it might be the initiation site of SWDs. Next, the visual pathways between the visual cortex, and the visual thalamus, including the higher-order nuclei, might be the primary circuit for the visual stimulation-induced SWDs. The data, as obtained by Uhlrich, raise the question of whether intense stimulation of other sensory modalities might have the same proepileptic effect, and or whether this is only in epilepsy-prone subjects. Although Sprague-Dawley (SD) rats are not considered as a genetic absence model, there are indications that SD rats are not devoid of SWDs (Komoltsev et al., 2021; Pearce et al., 2014; Willoughby and Mackenzie, 1992). Therefore, it might be possible that the vulnerability to cortico-thalamo-cortical oscillations primes SD rats for SWDs in case they are challenged and exposed to repetitive and intense visual stimulation. Whether similar intense stimulation in young GAERS or WAG/Rij rats may have similar neuroplastic effects remains to be investigated.

3.7. Neonatal sensory impairments

Sensory experience during early postnatal life modulates cortical development, including morphological and functional characteristics of neurons. Brain circuits are particularly sensitive to alterations produced by sensory stimuli during a certain time window called a critical period (Reha et al., 2020). Deprivation of sensory inputs during the critical period, when functional and structural characteristics of cortical neurons are most susceptible to alterations, can induce substantial impairments of axonal and dendritic morphology, and synaptic connectivity of neural circuits (Briner et al., 2010; Lee et al., 2009). The main regulator of the experience-dependent activity of sensory systems is the balance of excitation and inhibition. In some cases, sensory deprivation may potentiate inhibition, which can suppress responses to deprived sensory inputs. In other cases, sensory deprivation may weaken the inhibition, leading to the restoration of sensory responsiveness (House et al., 2011). The time course of experience-dependent sensory development is specific for each sensory system. The critical period of the somatosensory system precedes the critical periods of the visual and auditory systems (Li et al., 2009). However, postnatal deprivation of sensory input in one modality can result in compensatory cross-modal plasticity that increases activity in the remaining intact senses (Dooley and Krubitzer, 2019; Merabet and Pascual-Leone, 2010; Mezzera and López-Bendito, 2016; Rauschecker, 1995). Cross-modal plasticity implies not only physiological changes such as the increased activity of the non-deprived sensory system but also the recruitment of the deprived area for compensatory senses (Voss and Zatorre, 2012).

An important part of normal development is also proper sensory integration: the environment is experienced as a combination of a variety of within a single sensory modality stimulus features and between different sensory modalities. The surrounding of an organism is complex and comprises sensory inputs from several senses at the same time. Only very few day-to-day life events and stimuli present themselves as unimodal, rather as multisensory experiences, deriving from a combination of information acquired through several different sensory modalities. The brain has to integrate multisensory information to provide a complete and coherent picture of events to allow a proper and adapted behavioural response. Deprivation of one sensory modality may therefore also affect proper sensory integration (Dionne-Dostie et al., 2015).

Insufficient or abnormal sensory experience early in life could lead to sensory integration dysfunction when multisensory integration is not adequately processed to provide an appropriate response to the environmental impacts. Sensory processing abnormalities (increased or decreased sensory sensitivity) were found in several neurological and neuropsychiatric disorders including schizophrenia, bipolar disorder, ASD, ADHD, and depression (Harrison et al., 2019). Altered sensory sensitivity can also be linked to seizure susceptibility. Impairments of sensory sensitivity and sensory modulation (behavioural responses to regulate sensory input, e.g., to reduce or prevent exposure to stimuli) were found in childhood epilepsy. Sensory modulation disorders were reported in 49 % of the 158 children with epilepsy. Increased behavioural responses in epileptic children were associated with sensory "sensitivity" and "sensory avoidance", but not with "sensory seeking". Comorbidity of childhood epilepsy with ASD and ADHD was associated with more severe sensory modulation dysfunction, although 27 % of children with epilepsy without comorbid disorders also showed a sensory processing impairment (van Campen et al., 2015a). There is no evidence of sensory impairment in childhood absence epilepsy. However, a hypersensitivity to a gentle tactile touch in the WAG/Rij rat pups with a genetic predisposition to absence epilepsy was found (see also Section 4.1). Most of the WAG/Rij pups (64 %) compared with age-matched Wistar pups (23 %) showed an active avoidance response to tactile touch (Malyshev et al., 2014). In both pre-symptomatic and symptomatic WAG/Rij rats an increased sensitivity to painful stimuli as measured in four different and commonly used pain tests was found, indicating an early deviant somatosensory system (De Caro et al., 2020). This also demonstrates that the changes in the somatosensory system precede the onset of SWDs and can be considered as a causative contributing factor to their development.

The somatosensory system, especially the tactile sensations from whiskers, plays a key role in the perception of the environment in rodents. Layer IV of the primary somatosensory cortex (S1), called the barrel cortex contains a topographic representation of each facial whisker. The whisker map in the barrel cortex is established during the critical period that extends along the first postnatal week when activity-dependent development and balance of excitatory and inhibitory inputs are formed (Che et al., 2018). Neonatal sensory deprivation in rodents induces long-lasting changes in the structure and function of the somatosensory system. For instance, neonatal whisker trimming leads to enlarged excitatory and weakened inhibitory receptive fields in layer IV barrel neurons (Shoykhet et al., 2005), as well as to morphological changes in the spiny stellate neurons (larger dendritic spines and greater spine density) and behavioural alterations (higher explorative activity and more frequent social interactions) in adult rats (Lee et al., 2009). Neonatal deprivation in whisker-dependent tactile perception impaired fear/anxiety-related emotional systems of the amygdala (greater stress-induced c-fos expression) and social behaviours in the social preference and social dominance tests in mice as adults (Soumiya et al., 2016).

There is convincing evidence that primary sensory cortices are anatomically interconnected. Anatomical studies in rodents revealed direct cortico-cortical projections from S1 and the auditory cortex (A1) to the visual cortex (V1). Conversely, V1 was shown to connect to S1 and only weakly to A1 (Henschke et al., 2015). Such anatomical connections indicate the presence of a functional multimodal interplay between the primary sensory cortices. These functional multimodal connections between cortical areas can cause a perceptual improvement of one sensory modality when the other sensory modality is lost. For example, blind individuals compensate the lack of visual inputs by responding to somatosensory or auditory inputs with improved sensitivity. In rats, which were visually deprived at postnatal 4 weeks (PND26-PND30), but not later (PND58-PND66), increased sensitivity of the somatosensory system involved in the whisker-dependent tactile perception was found (Abe and Yawo, 2018). It has been well-documented that the somatosensory cortex plays a crucial role in the pathogenesis of absence seizures in genetic rodent models (Ding and Gallagher, 2016; Meeren et al., 2002; Polack et al., 2007). Of interest, absence seizures models, WAG/Rij rats (Meeren et al., 2002), and GAERS (Polack et al., 2007), are albinos, and, as a result, they may have visual impairments which are characteristic of albinism. Genetic epileptic mice modeling juvenile myoclonic epilepsy are not albino, suggesting that there are other causative factors for the seizures in this model (Ding and Gallagher, 2016).

Both GAERS and WAG/Rij strains originate from Wistar rats. Wistar rats are albinos: they have a lower number of rod photoreceptors (Donatien and Jeffery, 2002) and night blindness (retinopathy), starting

around three months of age and getting worse in the next 3 months (Lai et al., 1975). One of the symptoms is the slow adaptation to darkness (Behn et al., 2003). Visual electrophysiological studies, both electroretinography (ERG) and evoked potentials, comparing albino (Wistar) and pigmented (Long-Evans) rats at the ages of 1.5, 4, 7, and 10 months showed markedly decreased ERG b-wave amplitudes in Wistar rats, as well as tendencies for reduced amplitudes of the VEP (visual evoked potential). Markers for post-receptor processing revealed impairments in Wistar rats as well (Heiduschka and Schraermeyer, 2008). Therefore, it can be safely assumed that albino rats have problems with their visual system and, in particular, with seeing in the dark, during their behaviourally active period.

As we have already mentioned, when a sensory modality is lost or impaired, as in blindness or deafness, the adaptive reorganization will take place, associated with neuroplasticity affecting both the sensory modality that is impaired, in our case the visual one, and those that remain intact: sensory loss of one modality has striking effects on the development and function of the remaining modalities (Chabot et al., 2008; Merabet and Pascual-Leone, 2010). Problems with the visual system in albino rats are likely to cause rearrangements in other sensory systems: in rodents, the collection of information from the environment is much more dependent on their whisking touch system than in rats with normal vision. The trigeminal pathway in albino rats is stimulated by the animals using this system, consisting of the micro (short and thin hairs around the nose tip), and macro - vibrissae (long stiff mystacial hairs) projecting via the brainstem and ventro-posterior medial (VPM) nucleus of the thalamus to the cortical S1 (Adibi, 2019). Interestingly, whisking consists of rhythmic cyclic vibrissae sweeping actions, consisting of repetitive forward (protraction) and backward (retraction) movements at an average frequency of about 8 Hz (Adibi, 2019; Semba et al., 1980), the same frequency as can be found in the SWDs in thalamus and cortex, accompanying the absence seizures. There is evidence from animal studies that even partial afferent signal loss leads to paroxysmal cortical activity, including SWDs that can progress to electrographic seizures (Nita et al., 2006; Topolnik et al., 2003).

Given this, it is perhaps not surprising that highly excitable cells were found in the S1 in GAERS (Polack et al., 2007), and that the somatosensory cortex was hyper-excitable in symptomatic WAG/Rij rats (D'Antuono et al., 2006; Lüttjohann et al., 2011), and that there are changes in cerebral blood flow in brain regions involved in the generation and expression of SWDs in WAG/Rij rats (Tsenov et al., 2019). Furthermore, trigeminal inputs originating from the snout and vibrissae, but not the input from the nervus facialis, are necessary for the initiation of the spontaneous SWDs (Abbasova et al., 2010) in the cortical somatosensory projection area, specifically, this region is the cortical focus of SWDs generation in both WAG/Rij rats and GAERS. Not only from the Wistar lines obtained WAG/Rij strain and GAERS, but also other Wistar lines, e.g. those obtained from Winkelmann, Germany, tested at 84–94 weeks, and Harlan Wistar rats at a much younger age, show a high number of SWDs (Perescis et al., 2019; van Luijtelaar et al., 1994). Agouti and hooded strains showed much fewer SWDs in a strain comparative study (Inoue et al., 1990). In all, we can assume that all albino lines are at least partly sensory (visual) deprived. It is therefore proposed that the increase in excitability and other neural changes observed in the cortical areas of sensory-deprived individuals, such as an increase in arborization of pyramidal cells in S1 (Karpova et al., 2005), are due to increased experience-dependent neuronal activity of the intact sensory system, in this case, the touch system during postnatal life. According to this hypothesis (Singh et al., 2018), the anatomical reorganization of cortical areas in sensory-deprived animals would be the result of heightened use of the intact senses from birth onwards and during the rest of their lives. This view would predict that sensory deprivation of the whisking touch system would further enhance the process of epileptogenesis. This hypothesis was tested in the WAG/Rij model of absence epilepsy (Sitnikova, 2011). Trimming of the whiskers from postnatal day 1–21 led to predicted increases in both the number and duration of the spontaneously occurring SWDs when the rats were 5 and 8 months old in comparison to sham-trimmed WAG/Rij control rats, showing that sensory deprivation of the whisking touch system accelerates epileptogenesis. Mechanisms, regarding the type and nature of the changes in SWDs induced by early sensory deprivation in the cortex and thalamus, await to be explored, as well as whether in adult WAG/Rij rats whisker trimming would lead to quick changes in excitability and, as a consequence, changes in the number of SWDs.

Sensory deprivation and epilepsy were not often studied, there is some literature regarding the role of hearing impairments on audiogenic seizure susceptibility (Sun et al., 2011). Tympanic membrane (TM) damage in young rats showed that 2 weeks later more than 80% of the rats showed audiogenic seizure (AGS) when exposed to a loud sound (120 dB sound pressure level white noise), while none of the control animals showed this. The susceptibility to AGS lasted at least 16 weeks after the TM damage, and even the hearing loss recovered. The seizures were controlled by the GABA transaminase inhibitor vigabatrin, suggesting a role of reduced GABAergic inhibition in this process. C-fos staining showed strong staining in the inferior colliculus (IC) in the TM-damaged rats, not in the control rats, after exposure to a loud sound, indicating a hyper-excitability in the IC during AGS. These results indicate that early-age conductive hearing loss can impair sound tolerance by reducing GABA inhibition in the IC. Interestingly, many Wistar rats and also 30% of the WAG/Rij rats show increased sensitivity to audiogenic seizures (Kuznetsova et al., 1996), perhaps because their partial blindness might have caused adaptations in other sensory modalities.

In the absence models, the cortex and thalamus are the main key players. Changes in excitability that are occurring in parvalbumin (PV)-containing inhibitory interneurons located in the deprived barrel columns can occur very rapidly, in some instances within hours after the initial whisker plucking (Marik et al., 2010). PV-containing neurons were found to be decreased in the neocortex of WAG/Rij rats (Arkan et al., 2019), suggesting that their gradual decrease might play a role in both epileptogenesis and its increased speed after sensory deprivation. However, this suggestion awaits experimental verification.

4. Epigenetic treatments of absence epilepsy and comorbidities

4.1. Neonatal tactile stimulation

Emerging evidence suggests that an early environmental factor such as maternal care can improve or prevent the development of several pathologic phenotypes in offspring: stress vulnerability, fear, anxiety-like and depression-like behaviours (Champagne et al., 2008; Freitas et al., 2015; Masís-Calvo et al., 2013; Singh-Taylor et al., 2018; Weaver et al., 2004), genetically determined absence epilepsy with depression-like comorbidity (Sarkisova and Gabova, 2018), and schizophrenia-relevant features of behaviour (van Vugt et al., 2014).

In rats, individual differences in maternal behaviour, primarily in licking/grooming and arched-back nursing, were shown to exert multilevel effects on physiological, morphological, behavioural, and neurochemical characteristics in the offspring (Champagne et al., 2008, 2004, 2003; Masís-Calvo et al., 2013; Peña et al., 2014; Weaver et al., 2004; Zhang et al., 2005) Although most studies of maternal care have focused on a special role of arched-back nursing for pups' development (Champagne et al., 2003), non-arched-back nursing or non-nutritive contact with pups was found to be also a very important component of maternal behaviour, which can exert a beneficial phenotypic effect on the offspring (Sarkisova and Gabova, 2018; van Vugt et al., 2014). Well-caring rat mothers commonly express higher levels of licking-grooming, arched-back, and/or non-arched-back nursing compared with poor-caring rat mothers. Maternal licking-grooming represents naturally occurring sensory stimulation to the skin of pups, but non-arched-back nursing or non-nutritive contact with pups constitutes warmth from skin-to-skin tactile contacts with pups or

thermotactile stimulation to most of the pup body (Kojima and Alberts, 2011). The mother's arched-back nursing is the best posture for milk delivery compared with the non-arched-back posture (Lonstein et al., 1998). However, skin-to-skin tactile contact with pups is greater during non-arched-back nursing. Although suckling stimulation and receipt of milk are effective reinforcers for rat pups, these nutritive rewards did not contribute to the development of social attachments, as seen in the rat pups' filial huddling. Interestingly, the frequency with which mother rats exhibit non-nutritive skin-to-skin contact with pups (hovering posture over the pups) did, however, correlate with the subsequent filial preference (Kojima and Alberts, 2011), which can be regarded as a form of social attachment. Depressive WAG/Rij mothers exhibited shorter non-nutritive skin-to-skin tactile contacts with pups (non-arched-back nursing) and pup licking-grooming, but even longer arched-back nursing compared with control Wistar rats (Sarkisova et al., 2017b; Sarkisova and Gabova, 2018); see also Section 3.5). This is probably the reason why the WAG/Rij pups compared to Wistar pups showed less attachment to their mothers (mother-oriented test), despite a normal nest-seeking response caused by olfactory stimuli (olfactory discrimination test) and the same level of locomotor activity (gait reflex test) (Malyshev et al., 2014). Newborn WAG/Rij pups also exhibited hypersensitivity to a gentle tactile touch (touching the ear with a cotton swab), which may be due to insufficiency of tactile stimulation and tactile skin-to-skin tactile contacts provided by their depressive mothers and may represent a kind of tactile deafferentation. On the other hand, a hypersensitivity to a tactile touch in the WAG/Rij pups can be a manifestation of increased stress reactivity or enhanced anxiety due to reduced maternal tactile stimulation and tactile contacts early in life. It is known that poor maternal care (insufficient contact with the mother) early in development leads to increased corticosterone levels and to a hyper-reactivity to stress in the offspring (Raineki et al., 2010). Recent studies have shown that the rewarding sensation of touch in affiliative interactions could be underpinned by a specialized system of nerve fibers called C-tactile afferents, which respond optimally to slowly moving, gentle touch (McGlone et al., 2014; Pawling et al., 2017). Interestingly, it has been shown in rodents that tactile stimuli activate hypothalamic oxytocin neurons (Okabe et al., 2015). This suggests that C-tactile afferent stimulation may cause oxytocin release during affiliative tactile interactions (Walker et al., 2017). Oxytocin is released when a mother cares for her child, making the interaction pleasurable. In this context, it could not be excluded that hypersensitivity to a gentle, non-painful tactile touch in WAG/Rij pups (Malyshev et al., 2014) may be due to tactile allodynia (pain hypersensitivity) associated with a reduced C-tactile hedonic touch experience early in life. Insufficient tactile contact with the mother induced by maternal separation was shown to cause mechanical allodynia in the whisker pad skin in adulthood (Dubner et al., 2016).

In several studies, tactile stimulation (stroking a pup's body with a soft brush) was used to "mimic'' maternal licking and grooming behaviour. It has been demonstrated that neonatal tactile stimulation improves the maturation of premature infants and newborn rats (Schanberg and Field, 1987). Additional research has reported the beneficial effects of tactile stimulation on neonatal isolation-induced anxiety-like behaviour and pain sensitivity in adult rats (Imanaka et al., 2008), and the ability of tactile stimulation to attenuate amphetamine sensitization (Muhammad et al., 2011) and improve responsiveness to diazepam (Boufleur et al., 2012). Neonatal tactile stimulation can also decrease depression-like behaviour and potentiate antidepressant sertraline action in rats (Freitas et al., 2015). It has been demonstrated that symptoms of emotional and behavioural disorders in infants, caused by maternal pre- and postnatal anxiety and depression, can be modified by tactile stimulation assessed by mothers' self-reported stroking of their babies during the first week of life. Of note, the positive effect of maternal stroking was associated with a reduction of the glucocorticoid receptor NR3C1 gene methylation (Pickles et al., 2017; Sharp et al., 2015), leading to a reduced HPA reactivity mediated via increased glucocorticoid receptor gene expression (Murgatroyd et al., 2015). These studies provide evidence that maternal stroking in infancy has a similar beneficial effect to that reported in rodents.

A recent study reported that neonatal tactile stimulation affects the genetic absence epilepsy and comorbid depression-like behaviour in the WAG/Rij model (Balikci et al., 2020). From postnatal days 3–21, neonatal tactile stimulation (by a soft baby brush) was carried out for 15 min three times per day. The tactile stimulation protocol from a video article by Mychasiuk et al., (2013) was used. The effect of tactile stimulation was compared with that of deep touch pressure and maternal separation. Rat pups that were not subjected to any stimulation were used as a control. At the age of 5 months, WAG/Rij males were tested in the open field, sucrose consumption, and forced swimming tests. At the age of 6 months, EEG recordings were carried out. The number and total duration of SWDs per hour were assessed. Tactile stimulation, deep touch pressure, and maternal separation did not change substantially locomotor activity, and the amount of 20% sucrose consumed for 15 min. The tactile stimulation and deep touch pressure significantly increased the number of approaches to the drinking bottle in the sucrose consumption test. Tactile stimulation and deep touch pressure increased the latency to immobility, but only tactile stimulation decreased the immobility time and increased the duration of active swimming in the forced swimming test. Tactile stimulation and deep touch pressure reduced the number and total duration of SWDs compared with the control group. Results show that neonatal tactile stimulation can ameliorate the genetic absence epilepsy and comorbid depression-like behaviour in adult WAG/Rij rats. Of note, deep touch pressure similar to tactile stimulation reduced the number and duration of SWDs in adult rats. However, the effect of the tactile stimulation on depressive-like behaviour in the forced swimming test was greater compared with that of the deep touch pressure. Thus, tactile stimulation decreased immobility time and increased latency to immobility and the duration of active swimming, while the deep touch pressure increased only the immobility latency (Balikci et al., 2020). The authors believed that the deep tactile pressure resembles maternal non-arched back nursing. However, deep tactile pressure mimicked only one parameter of maternal non-arched-back nursing, such as hovering over the pups associated with tactile pressure, but not a rather significant parameter of maternal care, the warmth from skin-to-skin tactile contacts with pups or thermotactile stimulation. That's probably why the effect of the deep tactile pressure on the depressive-like phenotype in WAG/Rij rats was substantially weaker compared with that of the tactile stimulation (produced by a soft baby brush), which, was more like a maternal licking-grooming than deep tactile pressure resembled maternal non-arched-back nursing. This assumption is supported by the fact that licking-grooming and non-arched-back nursing, naturally provided by the foster Wistar mother, exerted an equally strong effect on both the absence seizures and depression-like comorbidity in adult WAG/Rij offspring (Sarkisova and Gabova, 2018).

The mechanism underlying the beneficial effects of neonatal tactile stimulation on the brain is not yet known. However, it has been assumed that the fibroblast growth factor-2 (FGF-2) may be a key modulator of these effects. For example, it has been demonstrated that tactile stimulation leads to an increase in the production of FGF-2 in both skin and brain (Richards et al., 2012). As FGF-2 is known to be a potent neurotrophic growth factor, increased production of FGF-2 in response to tactile stimulation might contribute to cortical plasticity and positive outcomes. Neonatal tactile stimulation can also affect other neurotrophic factors, including BDNF, which is very essential for structural and functional plasticity during development (Lu and Naggapan, 2014). BDNF increases neuronal excitability and is localized in the brain areas implicated in epileptogenesis. Moreover, seizure activity increases the expression of BDNF mRNA and protein, indicating that BDNF may contribute to the lasting structural and functional changes underlying epilepsy development and progression. BDNF modulates neuronal excitability in the hippocampus, but it also promotes neuronal survival

in models of SE. In the pilocarpine model of SE, it has been shown that the BDNF-expressing vector injected in the hippocampus increases neurogenesis, limits neuronal damage, and reduces the occurrence of spontaneous seizures (Simonato and Zucchini, 2010). BDNF regulates synaptogenesis during development and has been shown to enhance axonal branching in the hippocampus and dendritic branching in the cortex (Binder et al., 2001). Glutamate release is enhanced, whereas inhibitory transmission is diminished by BDNF. Of note, the BDNF signaling pathway is impaired in GAERS after the onset of absence seizures. Intracerebroventricular injection of BDNF significantly reduces the occurrence of SWDs in GAERS (Landweer, 2010). BDNF is known to modulate the expression of neurotransmitters, which have a potential role in epileptic seizures and affective behaviours. BDNF may be dysregulated in depression (Nestler et al., 1968). Of note, neonatal tactile stimulation can increase BDNF levels (Antoniazzi et al., 2017). Thus, converging evidence suggests that deficits in BDNF signaling may contribute to the pathogenesis of both absence epilepsy and depressive-like comorbidity, and can underlie positive phenotypic effects of the neonatal tactile stimulation.

Tactile stimulation early in life affects the neuroanatomical organization, dendritic morphology, and synaptic connectivity during brain development (Kolb and Gibb, 2010; Mychasiuk et al., 2013; Richards et al., 2012). Neonatal tactile stimulation was shown to increase dendritic branching, dendritic length, and spine density in the prefrontal cortex and amygdala (Richards et al., 2012). At the same time, it was found that tactile stimulation early in life led to decreases in spine density and dendritic length in the parietal cortex (Kolb and Gibb, 2010). This means that tactile stimulation may differentially affect the synaptic organization in different cerebral regions. Morphometric analysis of neurons in epileptic WAG/Rij and non-epileptic ACI rats revealed distinctive differences between somatosensory and motor cortex. The shape of dendritic arborization, the branching, and the orientation of dendrites in the somatosensory cortex where SWDs are thought to originate were different in epileptic WAG/Rij and non-epileptic ACI rats. The number of free terminations of apical dendrites was greater in the somatosensory cortex compared to the motor cortex in non-epileptic rats. In epileptic rats, there was also a difference between the two cortical areas, however in the opposite direction (Karpova et al., 2005). Put in other words, morphometric characteristics of dendrites in the cortical focal area of WAG/Rij rats were at variance with dendritic characteristics outside the focal areas, which were functionally similar to the areas in non-epileptic controls. These morphological features might reflect the hyper-excitability of somatosensory neurons, which underlie the initiation and spreading of SWDs in WAG/Rij rats. Thus, these results allow us to assume that the seizure-reducing effect of neonatal tactile stimulation in WAG/Rij rats (Balikci et al., 2020) can be mediated by its influence on the morphologic characteristics of dendrites in the somatosensory cortex leading to a decrease in the excitability of the epileptogenic cortical focus. It cannot be excluded that artificial neonatal tactile stimulation in WAG/Rij rats, like a natural mother's care, might affect the development of the mesolimbic DA pathway (Peña et al., 2014), which is impaired in young WAG/Rij rats (Malyshev et al., 2014) and insufficiency of which is implicated both in absence epileptogenesis (Cavarec et al., 2019) and in the expression of depression-like symptoms in adult WAG/Rij rats (Sarkisova et al., 2013).

Altogether, these findings indicate that tactile stimulation in early life plays an important role in preventing the development of many disorders in the offspring, including genetically determined absence epilepsy and depression-like comorbidity.

4.2. Maternal diet

One of the most important environmental factors that can have a significant impact on the later-life phenotype in offspring is the maternal diet. Numerous epidemiological studies and data from animal models indicate that maternal undernutrition, protein restriction, or, on the contrary, energy-rich diets during the perinatal period can lead to cardiometabolic diseases such as obesity, insulin resistance, hypertension, and raised serum cholesterol levels in the offspring (Bertram and Hanson, 2001; Samuelsson et al., 2008). Interestingly, several studies have shown that a paternal low-protein or high-fat diet can also influence future metabolic disease risk in the offspring (Carone et al., 2010; Ng et al., 2010), providing experimental evidence for non-genetic intergenerational paternal transmission of metabolic phenotypes (cholesterol and lipid metabolism) to offspring. The mechanism by which alterations in maternal or paternal diet may induce a long-term trans-generational effect on metabolism and phenotype in the offspring has been suggested to involve the altered epigenetic regulation of metabolic genes (Ferguson-Smith and Patti, 2011).

It has been found that a high-fat diet in dams during pregnancy and lactation induces epigenetic and phenotypic changes in the offspring, increases expression of the μ-opioid receptor and preproenkephalin in the reward-related brain structures (nucleus accumbens, prefrontal cortex, hypothalamus), and this was accompanied by the hypomethylation of the promoter regions of genes in association with long-term alterations in gene expression (DA and opioids) and behaviour (preference for palatable foods) (Pitman and Borgland, 2015; Thanos et al., 2018; Vucetic et al., 2010). Maternal obesity and diabetes have also been reported to induce changes in DNA methylation in the liver and metabolic defects in the offspring (Li et al., 2013).

Although most studies have concentrated on changes in DNA methylation associated with alterations in maternal diet, there is growing evidence that early-life nutrition can also induce substantial changes in other epigenetic mechanisms, such as histone modifications and miRNAs (Sandovici et al., 2011). Alterations in the paternal diet in rodents have also been shown to produce epigenetic changes in the offspring. Protein-restricted diet of male rats before mating can produce widespread changes in DNA methylation in the liver of the offspring compared to the control. Differences in paternal diet may be transmitted to offspring through epigenetic modifications of histone code and miRNA as well (Carone et al., 2010; Lillycrop and Burdge, 2015), indicating that histone and miRNAs may also play a role in the transmission of obesity and impaired metabolic state from the high-fat-fed fathers to the offspring.

Evidence that maternal diet in humans can induce long-term epigenetic and phenotypic changes in the offspring is more limited. However, persistent epigenetic alterations in the DNA methylation of a number of genes in individuals who were prenatally exposed to famine during the Dutch Hunger Winter have been reported (Heijmans et al., 2008; Roseboom et al., 2006). More recent studies have indicated widespread gender-related changes in the epigenome of offspring associated with maternal periconceptional micronutrient supplementation intake (Khulan et al., 2012).

Maternal high-fat or high-fructose diet during pregnancy and lactation can affect not only metabolic state but also emotional and cognitive behaviour in offspring (Coulibaly et al., 2017; Peleg-Raibstein et al., 2012; Winther et al., 2018) Increased anxiety (reduction of entries and time spent in open arms in the elevated plus-maze test), depression-like behaviour (increased immobility time in the forced swimming test), and cognitive impairments (episodic memory in the novel object recognition task and spatial working memory in Y-maze) have been reported. Males were more affected than females (Coulibaly et al., 2017).

Clinical and animal model data indicate the contribution of maternal diet to susceptibility to adult-onset disease in offspring. Emerging evidence indicates the role of DNA methylation, the best-studied epigenetic mechanism, in the pathogenesis of many neurological and psychiatric diseases, including epilepsy (Kobow et al., 2013; Kobow and Blümcke, 2012) and depression (Fuchikami et al., 2011). The process of DNA methylation depends on the availability of dietary methyl group donors. A metabolic pathway that integrates nutrients from the environment to produce multiple epigenetic modifications through DNA methylation is

the one-carbon cycle (Mentch and Locasale, 2016). Its simplified scheme is illustrated in Fig. 2.

S-adenosyl-L-methionine (SAM) is the end product of a one-carbon cycle and serves as the universal methyl group donor for DNA methylation. DNA methyltransferase requires SAM to establish or maintain DNA methylation patterns. The synthesis of SAM is dependent on the availability of dietary folic acid, vitamin B12, methionine, betaine, and choline (Cooney et al., 2002). Developmental choline deficiency alters SAM levels and global and gene-specific DNA methylation (Niculescu et al., 2006). Prenatal choline availability has been shown to impact neural cell proliferation during early development and learning and memory in adult rodents (Glenn et al., 2007; Meck and Williams, 2003). Additional dietary cofactor such as zinc influence the availability of methyl groups for SAM formation, and thereby affects CpG methylation (Danchin et al., 2020). Vitamin B12 (cobalamin) is a cofactor of 5-methyltetrahydrofolate-homocysteine methyltransferase (MTHF) that catalyzes the conversion of homocysteine into methionine, the direct precursor of SAM. Folic acid in the form of tetrahydrofolate is a cofactor that is used in a number of biochemical reactions such as the biosynthesis of amino acids, DNA synthesis, and repair. It is also necessary for the conversion of homocysteine to methionine. If vitamin B12 is unavailable, tetrahydrofolate is "trapped" and cannot be used to convert homocysteine to methionine (Mattson and Haberman, 2005). The bioavailability of these cofactors may influence DNA methylation by modification of the one-carbon cycle activity and production of SAM (Feil and Fraga, 2012). Moreover, methyl donors are necessary for some neurotransmitter synthesis (DA, NA, 5-HT), impairment of which plays an important role in the pathogenesis of affective disorders, including depression (Gao et al., 2018). The neurotransmitters DA and NA are synthesized from the amino acid tyrosine in a series of chemical reactions dependent on tyrosine hydroxylase. 5-HT is synthesized from the amino acid tryptophan, and the rate-limiting step is catalyzed by tryptophan hydroxylase. SAM functions as a methyl-donating cofactor in the rate-limiting step of the synthesis of the monoamines DA and 5-HT (Mischoulon and Fava, 2002; Otero Losada and Rubio, 1989). Enhancement of SAM levels permits it to act as a cofactor of COMT, decreasing COMT enzyme activity and thereby degradation of catecholamines (Tsao et al., 2011). Therefore SAM can be regarded as a treatment option for depressive disorders that increase monoamines: low levels of SAM, elevated homocysteine, and low 5-HT, DA, and NA are usually found in depressive patients (Bottiglieri et al., 2000). Moreover, it has been also demonstrated antiepileptic and memory-enhancing effects of SAM administration in a PTZ-induced kindling model of epilepsy (Dhediya et al., 2016).

A maternal diet with insufficient content of methyl donors can cause impairment of DNA methylation and alteration in gene expression leading to the development of various disorders in offspring (Geoffroy et al., 2019). Maternal (McCoy et al., 2017) and paternal (McCoy et al., 2018) methyl donors-depleted diets lead to increased anxiety and depression-like behaviour in adult rat offspring. In this context, of particular interest is the use of methyl-enriched maternal diets for correction or prevention of later pathologic phenotypes in the offspring. It has been found that the maternal high fructose diet with supplementation of methyl donors and cofactors of the one-carbon cycle (folic acid, choline, betaine, L-methionine, and vitamin B12) improves anxiety-like and depression-like behaviours and induces better performance in spatial and recognition memory tests in adult rat offspring (Coulibaly et al., 2017). Supplementation of the maternal diet with methyl donors during critical periods of brain development (in utero and pre-weaning stage) counteracted the development of some of the adverse effects seen in mice offspring from dams fed a high-fat diet: excessive weight gain, increased fat preference, changes in gene expression, and global hypomethylation in the prefrontal cortex. Sex differences in the effects of the maternal diet were observed. So, fat preference and DA transporter mRNA expression in the reward-associated ventral tegmental area were significantly increased only in male offspring born to mothers fed a high-fat diet, as compared to control offspring. Methyl donors-supplemented maternal diet normalized these measures. Maternal high-fat diet-induced global hypomethylation was more pronounced in male offspring than in female offspring. This adverse effect of the maternal high-fat diet was corrected by methyl supplementation. On the contrary, μ-opioid receptor mRNA expression changes were more pronounced in female offspring compared to male offspring: in females, mRNA expression was increased both in the prefrontal cortex and nucleus accumbens, while in males only in the prefrontal cortex (Carlin et al., 2013).

Although the effect of the maternal diet on the epigenome of offspring is best investigated in the field of metabolic diseases, the effect of the maternal diet on the epigenome of offspring in the area of epilepsy and associated behavioural comorbidities has only recently begun to be investigated.

It has been found in rats of the Krushinsky-Molodkina strain (KM) that maternal methyl-enriched diet during the prenatal and early postnatal ontogeny decreased the intensity of the audiogenic seizure in the progeny of both sexes (Poletaeva et al., 2014). Positive effects of maternal methyl-enriched diet on the genetically-based epileptic phenotype in offspring of KM rats were associated with changes in the methylation status of several genes, which were previously shown to be hypermethylated after epileptic tolerance procedure (Miller-Delaney et al., 2012). Maternal methyl-enriched diet induced different changes (increases or decreases) in the methylation status of different genes in adult offspring depending on the animal group that differs in the intensity of audiogenic seizures ("0" – no seizures and "4" – intense seizures). The majority of these genes were related to nuclear functions, such as DNA binding and transcriptional regulation. The epileptic tolerance procedure (seizure preconditioning) decreased the intensity of SE provoked by kainate in mice. Surprisingly, genes that were hypermethylated after epileptic tolerance did not match mostly the genes that were hypomethylated after the development of epilepsy (Miller-Delaney et al., 2012). Whether maternal methyl-supplemented diet can improve behavioural comorbidities (elevated anxiety and depression-like behaviour) described in KM rats (Sarkisova et al., 2017c) remains to be investigated.

The effect of maternal methyl-enriched diet on pathologic phenotype and gene expression in WAG/Rij rats was studied (Sarkisova et al., 2021; Sarkisova et al., 2020). The methyl-enriched diet contained methyl group donors (choline, betaine, L-methionine) and cofactors of the one-carbon cycle (folic acid, vitamin B12, zinc), which are highlighted in red in Fig. 2.

The methyl-supplemented diet, as used in these studies, modified other genetically determined pathologic phenotypes, such as audiogenic seizures in KM rats (Poletaeva et al., 2014) and agouti coat color in mice (Cooney et al., 2002) and rats (Prasolova et al., 2009). Correction of pathological phenotypes was accompanied by changes in the methylation profile of certain genes (Cooney et al., 2002; Prasolova et al., 2009; Poletaeva et al., 2014).

In WAG/Rij rats, maternal methyl-enriched diet during the perinatal period (a week before mating, during mating, pregnancy, and a week after parturition) reduced SWDs and comorbid depression in an adult 7-month-old offspring (Sarkisova et al., 2020). This beneficial phenotypic effect was greater expressed in males compared to females. In WAG/Rij males, maternal methyl-enriched diet reduced the number and total duration of SWDs, but it did not affect the mean duration of SWDs. In contrast, in WAG/Rij females, maternal methyl-enriched diet reduced the mean and total duration of SWDs, but not the number of SWDs. The reduction in the number of mature SWDs in males was accompanied by the appearance of a large number of immature discharges, which are typical for young 2–3 month old rats of this strain (Gabova et al., 2020), indicating an anti-epileptogenic effect. Of note, in 50 % of WAG/Rij males born to mothers fed methyl-supplemented diet, mature SWDs were absent, and they were replaced by immature discharges commonly recorded in young (pre-symptomatic) WAG/Rij rats. At the same time, in

100 % of age-matched males born to mothers fed a control diet mature SWDs were observed. In other words, maternal methyl-enriched diet during the perinatal period decelerated the age-related process of the progressive development of epileptic activity in WAG/Rij males. In WAG/Rij females, the anti-epileptogenic effect of maternal methyl-enriched diet was less pronounced. Maternal methyl-enriched diet caused substantial changes in the averaged power spectra of SWDs, as was established with Fast Fourier Transform analysis, only in males: a decrease in the spectral power at the fundamental frequency, and the first and second harmonics. Maternal methyl-enriched diet did not significantly affect the averaged spectral power of SWDs in female offspring. No significant differences were found between male and female offspring born to mothers fed a control diet in the number, mean and total duration of SWDs, as well as in the averaged spectral power of SWDs. The methyl-enriched maternal diet had no substantial effect on the averaged spectral power of the background EEG, indicating a selective effect on SWDs.

In male and female WAG/Rij offspring born to mothers fed a methyl-enriched diet, the duration of immobility in the forced swimming test was shorter and the duration of climbing was longer compared with the corresponding values in WAG/Rij offspring born to mothers fed the control diet. Moreover, maternal methyl-enriched diet increased the duration of swimming only in females, and the number of divings only in males. Maternal methyl-enriched diet increased sucrose preference (anti-anhedonic effect) only in males and did not substantially affect the preference for sucrose in females (Sarkisova et al., 2020). The beneficial effect of maternal methyl-supplemented diet on SWDs and depression-like comorbidity in WAG/Rij offspring was associated with increases in the DNA methyltransferase 1 (DNMT1) and HCN1 ion channel gene expression in the somatosensory cortex (Sarkisova et al., 2021). Epigenetic modifications induced by maternal methyl-enriched diet in the offspring at the early stages of ontogenesis were supposed to be a possible mechanism underlying the correction of genetically determined pathologic phenotype in WAG/Rij rats. Of note, maternal methyl-supplemented diet-induced increases in the expression of the DNMT1 gene in the somatosensory cortex of WAG/Rij offspring were similar to the effect of early long-term ethosuximide treatment, a first choice anti-absence drug (Dezsi et al., 2013). Put in other words, maternal methyl-enriched diet during the perinatal period produced the same alterations in the DNMT1 gene expression in the somatosensory cortex of offspring as pharmacological long-term anti-absence therapy. Reduced expression of the HCN1 ion channel in the somatosensory cortex in WAG/Rij rats is thought to be associated with the genesis of SWDs (Blumenfeld et al., 2008; Kole et al., 2007; Schridde et al., 2006; Strauss et al., 2004). Moreover, loss of HCN1 in HCN1-knockout rats caused spontaneous bilateral SWDs accompanied by behavioural arrest, both of which were suppressed by ethosuximide (Nishitani et al., 2019), providing evidence of a causal relationship between HCN1 and absence epilepsy. A rapid decline in the expression of HCN1 channels precedes the onset of absence seizures (Kole et al., 2007). This suggests that the reduced expression of HCN1 facilitates the initiation and propagation of spontaneous generalized seizures. Given this, increased expression of the HCN1 gene in the somatosensory cortex in WAG/Rij offspring is supposed to be associated with the beneficial phenotypic effects of methyl-supplemented maternal diet. These findings are the first to indicate a new preventive therapeutic strategy based on the maternal diet during the perinatal period, targeting DNA methylation in the initiation site of SWDs, to correct symptoms of genetic absence epilepsy and comorbid depressive-like behaviour in offspring, (Sarkisova et al., 2021; 2020). We can assume that the maternal methyl-supplemented diet prevents the decline in the expression of HCN1 in the somatosensory cortex, and therefore epileptogenesis, leading to the prevention of the development of depression-like comorbidity. Maternal methyl-enriched diet increased the expression of HCN1 and DNMT1 genes not only in the somatosensory cortex, but also in the hippocampus, as well as the expression of the TH gene in the nucleus accumbens (Sarkisova et al., 2021), a brain region critically involved in the pathophysiology of depression. Moreover, maternal methyl-supplemented diet also increased DAergic tone of the mesolimbic brain system, which contributes to epileptogenesis and comorbid depression in WAG/Rij rats (Sarkisova et al., 2022). Further studies are necessary to understand epigenetic mechanisms by which maternal dietary supplementations during the perinatal period prevent epileptogenesis and the development of depression-like comorbidity in offspring genetically predisposed to absence epilepsy.

Another possible mechanism for the beneficial effect of the methyl-enriched diet on absence epilepsy and comorbid depression in the offspring of WAG/Rij rats could be its effect on the gut microbiota. It is now well established that maternal diet during the perinatal period affects the development of gut microbiota in the offspring (Al Rubaye et al., 2021) leading to specific epigenetic signatures that may predispose or prevent the development of later-life pathology. Experimental evidence suggests that maternal supplementation of dietary methyl groups is critical for the neurodevelopment of offspring (Emmerson and Jadavji, 2016). Furthermore, folate and vitamin B12 deficient diets may negatively impact both the microbiome and the brain function such as memory (Park et al., 2022). A number of studies have clearly demonstrated that the gut microbiota can modulate or contribute to neurological and psychiatric diseases, including epilepsy (Gong et al., 2020; Mengoni et al., 2021) and depression (Eltokhi and Sommer, 2022). The gut-brain axis has been shown to be able to affect the excitability in the brain and thereby modulate seizure susceptibility (Darch and McCafferty, 2022; Mengoni et al., 2021). Differences in the gut microbiota have been reported in patients with epilepsy compared to healthy controls (Gong et al., 2020) and in the WAG/Rij absence model (Citraro et al., 2021). Interestingly, microbiota transplantation from non-epileptic Wistar rats or ethosuximide-treated WAG/Rij rats induced a significant reduction in the number and duration of SWDs. Transplantation from ethosuximide-treated WAG/Rij rats was more effective than that from Wistar rats (Citraro et al., 2021). The link between depression-like behaviour and microbiota has also been described (Eltokhi and Sommer, 2022). For example, the transplantation of fecal matter from depressed patients into microbiota-depleted rats led to depressive-like behaviour (Kelly et al., 2016). Clinical evidence for the role of the microbiota in depression is provided by an alteration in the number of microbiota and their diversity in individuals with depression when compared to healthy controls. Moreover, the role of the microbiota-gut-brain axis in regulation of DAergic signaling, the dysfunction of which leads to depressive disorders, has been established (Hamamah et al., 2022). Taken together, these data allow us to assume that the maternal methyl-enriched diet leads to a balanced and diverse composition of the microbiota in the offspring, which may contribute to a favorable phenotypic effect. Further research is needed to find out whether the maternal methyl-enriched diet affects the composition of microbiota in the offspring of WAG/Rij rats and whether this really makes a significant contribution to the positive phenotypic effect of the methyl-enriched diet.

Positive effects of maternal methyl-supplemented diets on the pathologic phenotype in offspring were also shown for other genetic animal models of neurological disorders, such as the Alzheimer's disease model (Ash et al., 2014; Velazquez et al., 2020), atherosclerosis model (Delaney et al., 2013), Down syndrome model (Moon et al., 2010), and Rett syndrome model (Nag and Berger-Sweeney, 2007) in mice. Maternal choline supplementation ameliorated Alzheimer's disease pathology in old offspring by reducing brain homocysteine levels and changing 27 genes expression related to inflammation, histone modification, and neuronal death. The maternal diet reduced amyloid-ß load, and microglia activation, and improved cholinergic signaling in the brain and cognitive deficits in old mice. A transgenerational benefit of a methyl donor-supplemented maternal diet on the development of Alzheimer-like symptoms in mice was shown (Velazquez et al., 2020). Human studies are very limited and inconsistent, some of them point to

positive effects, such as the prevention of neural tube defects and mental health problems (O'Neil et al., 2014a) in offspring, but others are inconclusive (Bekdash, 2019).

Although animal model studies that examined how maternal methyl-supplemented diets impact epigenome and phenotype in offspring have reported a favorable outcome, it should be emphasized that excessive or inadequate intake of methyl donors can have adverse effects (Bekdash, 2019; De Crescenzo et al., 2021; O'Neill et al., 2014b). For instance, a higher folic acid-supplemented maternal diet during pregnancy led to disruptive gene and protein expression changes in the cerebral hemispheres, as well as behavioural abnormalities in neonatal C57Bl6J mice, including increased ultrasonic vocalizations, greater anxiety-like behaviour, and hyperactivity (Barua et al., 2014). Excess folic acid-supplemented diet during pregnancy can alter cortical neurodevelopment in mouse offspring. Paradoxically, changes in the brain due to very high amounts of folic acid mimicked those associated with a deficiency of folic acid (De Crescenzo et al., 2021). Women who have given birth to a child with neural tube defects (O'Neill et al., 2014a,b) or who have epilepsy and take anticonvulsants (Moore, 2005) have generally been advised to take high doses of folic acid. However, a very high amount of folic acid can be harmful to the brain development of the fetus. Human epidemiological studies showed a strong correlation (0.87) between maternal consumption of prescription prenatal vitamins (containing $>$ 1 mg of folic acid) and ASD incidence in offspring (Beard et al., 2011). Too much folic acid might disrupt brain development and thus increase the risk of ASD (Leeming and Lucock, 2009; Rogers, 2008). However, consumption of folic acid by women beginning at the periconceptional period was associated with a reduced risk of ASD in children of mothers with inefficient folate metabolism (for example, MTHFR gene variant). A greater risk for ASD was also observed for children whose mothers had other one-carbon metabolism pathway gene variants and reported no prenatal vitamin intake (Schmidt et al., 2011).

Based on the available evidence, it can be concluded that intake of dietary methyl donors and cofactors during the perinatal period may alter fetal development, thus establishing a link between early environment and disease development in the offspring later in life. However, the results presented here suggest the importance of 'optimal' methylation status during the perinatal period, particularly due to maternal diet, not only for reproducing healthy offspring but also for preventing the development of pathological phenotypes, even if they are genetically determined. The composition of the maternal diet, dose and duration of methyl donor supplementation at critical stages of neurodevelopment as well as genetic contribution to the components of one-carbon metabolism (for example, MTHFR gene variant) seem to be very important factors to consider. Other factors also may interact with maternal diet to influence the phenotypic outcome in the offspring: genetic background, gender, developmental windows of exposure, and tissue-specific susceptibility. It should also be taken into account that changes in the methylation status on the global level, as most likely occurs when methyl supplements are used, can affect both "beneficial" and "harmful" genes. The disease promotion or prevention may depend on the combined genes that will be affected.

Of note, the beneficial phenotypic effect of the maternal methyl-enriched diet on absence epilepsy and depression-like comorbidity was associated with epigenetic modifications in the expression of genes relevant to this pathology. Therefore, we can assume that the methyl-supplemented maternal diet can be regarded as a potential new epigenetic therapeutic strategy for the treatment of human absence epilepsy and its comorbidities.

5. Conclusions and perspectives for future research

This review presents the current findings indicating that environmental perturbations during the perinatal period have a major impact on the development of absence epilepsy and psychiatric comorbidities in the offspring.

The developing brain is very sensitive to environmental impacts and therefore it is not surprising that the prenatal administration of drugs that directly or indirectly affect the balance of excitatory and inhibitory processes in different brain regions, often resulting from neurodevelopmental dysfunction in GABAergic cortico-thalamo-cortical and extra-thalamic limbic circuitries, might be a common cause not only of increased seizure susceptibility and epilepsy but also of multiple comorbid behavioural, emotional and cognitive impairments.

Accumulating evidence suggests that early-life stress can prime seizure occurrence and epileptogenesis (Huang, 2014). Moreover, early-life stress is a major risk factor for anxiety and depression in adulthood and may contribute to neuropsychiatric comorbidities in epilepsy (Mumtaz et al., 2018). In addition, epigenetic modifications can be regarded as a shared pathogenic mechanism underlying the effect of various types of early-life stress on epilepsy and its psychiatric comorbidities. In general, the literature on early-life interventions and their impact on epilepsy and its comorbidities for a large part is aimed at the HPA axis and hippocampus, and, indeed, many changes in the limbic system are widely acknowledged. However, little attention is commonly paid to other brain structures. Early life stress has a broader impact than only on the hippocampus and the limbic system. It can also affect the excitatory/inhibitory balance in the medial prefrontal cortex (Ohta et al., 2020). Next, disruptions or alternations in network activity in one brain region could impact other networks and connected brain regions (Onat et al., 2007), which may directly or indirectly contribute to psychiatric disorders co-existing with epilepsy. Another important issue is that long-term consequences induced by early-life interventions may not be the same in various brain regions, especially in the case of GABA with its diversity of subunit compositions. So, an upregulation of the numbers of a specific type of receptors in one brain region could be accompanied by a downregulation in another part of the brain (Citraro et al., 2006; Tong et al., 2009). It is clear by now that early interventions may work oppositely in different brain regions (Ohta et al., 2020). It may be assumed that early interventions-induced changes in the brain connectivity/network activity and region-specific structural, neurochemical, and molecular abnormalities and dysfunctions could underlie psychiatric comorbidities of epilepsy, including anxiety and depression. Changes in the network functional connectivity were found in genetic absence epilepsy both in human and animal models.

WAG/Rij mothers do not seem to be the best moms, at least when they are compared to Wistar mothers. In addition to absence seizures and comorbid depression-like state, WAG/Rij dams were found to exhibit reduced maternal care, as evidenced by the smaller number of tactile contacts with pups and licking/grooming or tactile stimulations. Rearing by foster Wistar mothers with a high level of maternal care reduced the number and duration of SWDs and comorbid depression in adult offspring of WAG/Rij rats (Sarkisova and Gabova, 2018). However, it is unknown whether less good and perhaps insufficient maternal care provided by depressive WAG/Rij mothers (Sarkisova et al., 2017b) causes early-life stress in offspring, and how much this could contribute to the alterations of network structure in adult WAG/Rij rats.

Neonatal maternal separation is one of the commonly used laboratory methods to study early-life stress effects on the development of neurologic and psychiatric disorders in adulthood. However, there was a considerable amount of variability between studies related to the behavioural outcomes induced by neonatal maternal separation: no effects, harmful effects, or positive effects on anxiety and depression-like behaviour. In the same way, opposite results were obtained, indicating the anti-absence action of neonatal maternal separation in WAG/Rij rats (Schridde et al., 2006) and pro-convulsive effects in limbic epilepsy models (Kumar et al., 2011; Salzberg et al., 2007). This inconsistency in the data is probably related to differences in the maternal separation protocol and the lack of standardization (Wang et al., 2020). However, the opposite effects of neonatal maternal separation on absence epilepsy and TLE may also be due to the specificity of the models used, the differences in vulnerability of the affected networks in the genetic models

and the induced seizure models, and the opposite effects of neonatal maternal separation in different regions of the brain. Of interest is that GABA mimetic drugs have also opposite effects in TLE and absence epilepsy, and therefore the opposite effects reported might also be region-specific and GABA-related. The effects of the neonatal maternal separation on the psychiatric comorbidities of epilepsy have not been investigated in any experimental seizure or epilepsy model, including absence epilepsy models. However, since other antiepileptogenic effects may affect the comorbidities as well, it cannot be excluded that neonatal maternal separation may also have an impact on the comorbidities.

Neonatal handling is also usually used as a form of early-life intervention which can result in long-term consequences. In different studies, the duration of handling is variable, and this procedure can be repeated a different number of times. The effects of neonatal handling on epileptogenesis and seizure susceptibility were rarely studied and, if studied, these investigations were based on the assumption that this early-life intervention is stressful, and the focus was on hippocampus-related epilepsies and the role of the HPA-axis. In this case, early-life handling was pro-convulsive in the lithium-pilocarpine model (Persinger et al., 2002). However, beneficial effects of neonatal handling such as reduced anxiety/emotionality and stress responses later in life were also reported (Raineki et al., 2014), as well as the antiepileptogenic effect in the WAG/Rij rat model (Schridde et al., 2006). It is still unknown what causes the opposite effect of neonatal handling in different animal models of epilepsy: pro-convulsive in the TLE model and anti-epileptogenic in the absence epilepsy model, but see our suggestions above regarding the opposite effects of neonatal maternal separation.

It is well documented that neonatal handling of the pups changes the behaviour of the mother: it increases licking and grooming and does not change the arched-back nursing (de Azevedo et al., 2010; Reis et al., 2014). The increase in licking/grooming was exactly the type of maternal care that prevented the development of absence epilepsy and comorbid depression in WAG/Rij offspring in a cross-fostering study (Sarkisova and Gabova, 2018). This allows us to conclude that increased maternal care and immediate effects of infantile tactile stimulation following the return of pups to the nest could be considered as a mediating mechanism for the beneficial effects of neonatal handling on behaviour (Raineki et al., 2014), as well as on epileptogenesis in the WAG/Rij model (Schridde et al., 2006). Further research is needed to find out the role of maternal care in the development of epilepsy and its psychiatric comorbidities, and in particular in the effects of neonatal maternal separation and neonatal handling on epileptogenesis and psychiatric comorbidities in the absence epilepsy. In addition, inconsistency of data concerning the effects of neonatal maternal separation and handling in the absence epilepsy and TLE suggests that the effects of these environmental manipulations should be more carefully investigated, considering the time period of these manipulations during the postnatal development (the first weeks of life) with special attention to which of the sensory systems is currently being formed and what effects do these manipulations have on maternal behaviour.

Early sensory deprivation, as induced by neonatal whisker trimming, can lead to neuroplastic changes (enlarged excitation and weakened inhibition) in the somatosensory cortex and behavioural alterations, including measures of anxiety in adults, next to accelerated epileptogenesis, as was demonstrated in the WAG/Rij model. Moreover, WAG/Rij rats and GAERS are albinos with a relative insufficiency of the visual system. This may imply that there will be neuroplastic changes in other sensory systems, namely in the somatosensory cortex, resulting in a hyper-excitability of neural cells and an increased sensitivity to painful stimuli. Both results were reported in the genetic rat models (De Caro et al., 2020; Polack et al., 2007). Mechanisms regarding the type and nature of the early sensory deprivation-induced changes in SWDs in the cortex and thalamus await to be investigated, as well as whether in adult WAG/Rij rats whisker trimming would lead to alterations in excitability and, as a consequence, the changes in the number of SWDs.

Not only sensory deprivation but also intense sensory (visual) stimulation has been shown to have dramatic effects, as was found in Sprague-Dawley rats. Visual stimulation, by itself, can induce in adult rats an enduring sensitization of visual response with epileptiform SWD-like characteristics, not seen before the onset of stimulation. This work deserves to be replicated and extended, also earlier in the development. Moreover, it is necessary to investigate the consequences of intense visual stimulation early in life both in the visual system and in the somatosensory system, considering that plastic changes in one sensory system may have large consequences for other sensory systems.

A recent study demonstrated rather large differences between WAG/Rij and Wistar rats in pain thresholds, indicating hypersensitivity to mechanical and thermal noxious and non-noxious stimuli in WAG/Rij rats (De Caro et al., 2020). This is important, considering that the pain system involves the same thalamic nuclei, somatosensory cortex, and thalamo-cortical circuitry as the networks in which SWDs are generated. Therefore, a study of pain thresholds in GAERS is relevant. Interestingly, hypersensitivity to a gentle, non-painful tactile touch has earlier been detected in newborn WAG/Rij pups (Malyshev et al., 2014). The fact that the changes in pain threshold were occurring in pre-symptomatic WAG/Rij rats, that is before SWDs are emerging, is important and may point toward the cause of SWDs in the genetic rat models. Pain sensitivity is known to be heritable. Therefore, research on gene expression of pain sensitivity in WAG/Rij rats seems to be the way to proceed. Hypersensitivity to a non-painful tactile touch in WAG/Rij pups may be due to tactile allodynia (pain hypersensitivity) associated with a reduced C-tactile hedonic touch experience provided early in life by depressive WAG/Rij mothers. Insufficient tactile contact with the mother induced by maternal separation caused mechanical allodynia in the whisker pad skin in adulthood (Dubner et al., 2016). Consequently, it is also necessary to investigate in the future whether early-life environmental factors, especially maternal care, might contribute to abnormal pain sensitivity in the WAG/Rij model and whether the administration of anti-pain medication early in development could be an effective way to prevent SWDs. In addition, whether neonatal tactile stimulation can correct abnormal pain sensitivity in WAG/Rij rats and whether the beneficial effect of neonatal tactile stimulation on the absence epilepsy and comorbid depression-like behaviour in WAG/Rij rats is associated with epigenetic modifications of gene expression relevant for this pathology remains to be investigated.

Mounting evidence suggests that maternal care leads to epigenetic modifications of gene expression, specifically by changes in DNA methylation, which might be a cause of the long-lasting impact of maternal care on the offspring's phenotype. Given this, a maternal methyl-enriched diet was used as an epigenetic treatment to affect DNA methylation, leading to changes in gene expression, and, as a consequence, causing correction of genetic absence epilepsy and depression-like comorbidity in WAG/Rij rats. Maternal methyl-enriched diet during the perinatal period delayed epileptogenesis: it decelerated the age-related process of the progressive development of epileptic activity and reduced depression-like comorbidity in WAG/Rij offspring (Sarkisova et al., 2020). Antiepileptogenic and disease-modifying effects of the maternal methyl-enriched diet were associated with increases in the DNMT1 and HCN1 gene expression in the somatosensory cortex (Sarkisova et al., 2021), indicating a new preventive therapeutic strategy to correct genetic absence epilepsy and comorbid depression in the offspring (Sarkisova et al., 2021; Sarkisova et al., 2020). Of note, the beneficial effect of the maternal methyl-enriched diet was accompanied by the same alterations in gene expression in the somatosensory cortex as pharmacological treatment with ethosuximide, a first-choice anti-absence drug (Dezsi et al., 2013). Therefore, the methyl-supplemented maternal diet can be regarded as a potential new epigenetic therapeutic strategy for the treatment of human absence epilepsy and its comorbidities. Whether the maternal methyl-enriched diet can alter the pain sensitivity in adult WAG/Rij offspring needs to be established.

The expression of several ion channels has been identified to contribute to the aetiology of epilepsy, including absence epilepsy.

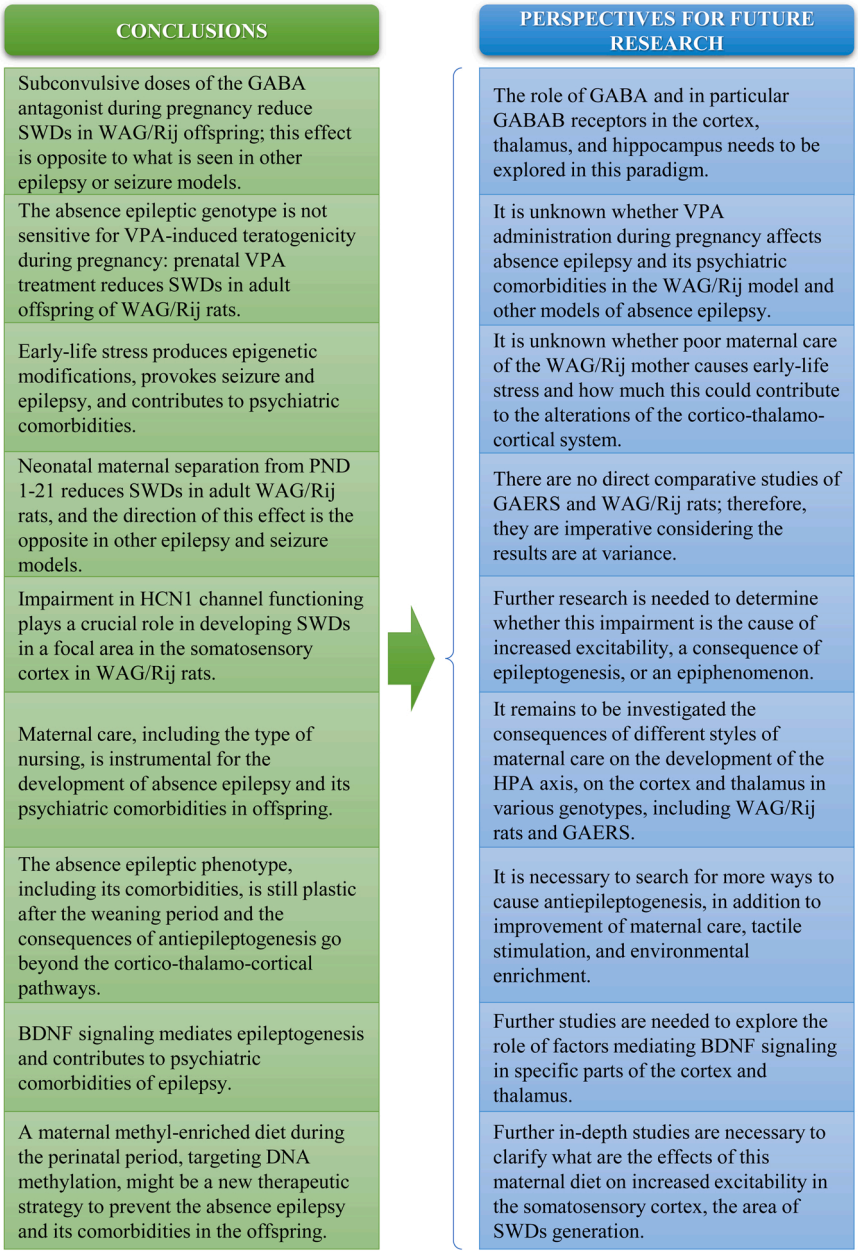

Fig. 3. Summarizing of conclusions and perspectives for future research.

These channels are critical for electrical signaling between neurons and are responsible for the regulation of neuronal excitability. Dysregulation of ion channel gene expression is highly associated with epilepsy. Although the molecular mechanisms that underlie these changes are not understood yet, it is known that many of these ion channel genes can be regulated by NRSF (McClelland et al., 2014, 2011). Epileptogenesis causes downregulation of genes that are involved in epilepsy, for instance, the HCN1 ion channel gene in both genetic absence epilepsy (Nishitani et al., 2019; Strauss et al., 2004) and in various TLE models (McClelland et al., 2011). However, specific mechanisms are still unknown although there is evidence that HCN1 channelopathy derives from NRSF-mediated transcriptional repression contributing to epileptogenesis. This means that therapeutic interventions targeting NRSF to restore HCN1 gene expression can slow down the progression of epilepsy, as was shown in a TLE mouse model (McClelland et al., 2011). However, it remains to be investigated whether targeting NRSF to restore HCN1 gene expression could slow down the development of absence epilepsy in genetic absence epilepsy models.

Reduced expression of HCN1 ion channels in the somatosensory cortex is thought to be associated with the genesis of absence epilepsy in the WAG/Rij model. Data presented in this review indicate that pathologic phenotype in WAG/Rij rats can be modified by early-life environmental interventions leading to epigenetic modifications of the HCN1 channel expression in the somatosensory cortex (Sarkisova et al., 2021; Schridde et al., 2006). Neonatal maternal separation and neonatal handling, presumably leading to increased maternal care, neonatal artificial tactile stimulation, mimicking maternal licking/grooming (Balikci et al., 2020), and improved maternal care of healthy foster mothers (Sarkisova and Gabova, 2018) exerted disease-modifying effects on the pathologic phenotype in WAG/Rij offspring. Increased I_h and HCN1 expression at the SWD initiation site was associated with the absence seizure reduction (Schridde et al., 2006). I_h drives the repetitive firing in nociceptive neurons mediated by HCN1, and HCN channel blockers have an analgesic action on peripheral pain (Ramírez et al., 2018). Finally, changes in I_h/HCN1 were already reported in pre-symptomatic WAG/Rij rats (Kole et al., 2007), suggesting that the

reduced I_h currents and the HCN1 channel expression may be an initiating factor in the pathogenesis of SWDs in WAG/Rij rats. Therefore, it is thought that I_h/HCN1 might play a role in both epileptogenesis and pain transmission. It can be assumed that maternal separation and neonatal handling, known to affect HCN1 expression and I_h, may exert anti-epileptogenic effects via alterations in maternal behaviour that the mothers display in response to environmental changes. Whether maternal care can alter HCN1 gene expression in the somatosensory cortex needs to be found out.

Epigenetic modifications of relevant genes expression induced by the maternal methyl-enriched diet in the offspring at the early stages of ontogenesis are also assumed to be a possible molecular mechanism underlying the correction of genetically determined pathologic phenotype in WAG/Rij rats (Sarkisova et al., 2021). Further in-depth studies are necessary to better understand epigenetic mechanisms by which maternal dietary supplementations during the perinatal period prevent epileptogenesis and the development of depression-like comorbidity in offspring genetically predisposed to absence epilepsy. Epigenetic therapy based on maternal diet, in general, is a new promising area of research. However, many questions still need to be addressed and answered, regarding the composition of the maternal diet, dose and duration of methyl-donors supplementation at critical stages of neurodevelopment as well as genetic contribution to the components of one-carbon metabolism (for example, MTHFR gene variant). Other factors also may interact with the maternal diet to influence the phenotypic outcome in the offspring: genetic background, sex, developmental windows of exposure, and tissue-specific susceptibility.

Finally, the genetic absence epilepsy models with their clear and easy quantification of EEG-based epileptic seizures are rather suitable for the study of how early environmental factors shape the brain not only in relation to epileptogenesis but also in relation to other associated phenotypic alterations, such as neuropsychiatric disorders. Epigenetic interventions for the absence epilepsy and its comorbidities are a new area of research. Results presented in this review highlight DNA methylation as an epigenetic mechanism in controlling and/or modulating absence seizures and their comorbidities, and might insight into epigenetic treatment based on a maternal methyl-enriched diet. The main conclusions and perspectives for future research are summarized in Fig. 3.

CRediT authorship contribution statement

Sarkisova K.Yu.: Conceptualization, Methodology, Writing – Original draft preparation, Reviewing and Editing;**Van Luijtelaar G.**: Supervision, Writing – Original draft preparation, Reviewing and Editing.

Conflicts of interest

The authors declare no conflict of interest.

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