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Epigenetics of the developing and aging brain: Mechanisms that regulate onset and outcomes of brain reorganization

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ABSTRACT

Brain development is a life-long process that encompasses several critical periods of transition, during which significant cognitive changes occur. Embryonic development, puberty, and reproductive senescence are all periods of transition that are hypersensitive to environmental factors. Rather than isolated episodes, each transition builds upon the last and is influenced by consequential changes that occur in the transition before it. Epigenetic marks, such as DNA methylation and histone modifications, provide mechanisms by which early events can influence development, cognition, and health outcomes. For example, parental environment influences imprinting patterns in gamete cells, which ultimately impacts gene expression in the embryo which may result in hypersensitivity to poor maternal nutrition during pregnancy, raising the risks for cognitive impairment later in life. This review explores how epigenetics induce and regulate critical periods, and also discusses how early environmental interactions prime a system towards a particular health outcome and influence susceptibility to disease or cognitive impairment throughout life.

1. Introduction

Transition states represent critical periods during development and aging when systems undergo significant changes. These "critical periods" are highly dynamic and may span several years, such as in the case of puberty and reproductive senescence (perimenopause in women and andropause in men) (Petricka and Benfey, 2011). The effects of these transition periods are also accompanied by a neurological component, suggesting that the two are intimately linked (Brinton et al., 2015). Brain development is a life-long process that is sensitive to both genetic and environmental factors. Perturbations that occur during critical periods can result in lasting epigenetic alterations that have the potential to lie dormant before playing out later in life (Dominguez-Salas et al., 2014; Gali Ramamoorthy et al., 2015; Bhandari et al., 2015; Gore et al., 2011; Rzeczkowska et al., 2014; Gabory et al., 2011).

Although a cell's underlying DNA remains relatively unchanged throughout life, the epigenome is constantly changing. While a single epigenetic change may not result in an altered phenotype, accumulation of many changes over time has the potential to alter health trajectories and outcomes. With time and continuous exposure, diverse environmental insults can sensitize brain systems and increase the likelihood that a subsequent environmental trigger will induce a disease phenotype (Brinton et al., 2015; Chen et al., 2012). Dysregulation of the brain epigenome has been linked to a number of neurological dysfunctions and aberrant DNA methylation and histone modifications have been seen in Autism (Abdolmaleky et al., 2015; Berko and Greally, 2015), Alzheimer's disease (AD) (Bennett et al., 2015; Herrmann and Obeid, 2011a; Marques et al., 2012; Mastroeni et al., 2010; Nagata et al., 2015; Wang et al., 2008), Schizophrenia (Brucato et al., 2014; Milekic et al., 2014), and post-traumatic stress disorder (PTSD) (Schmidt et al., 2011; Roth, 2014). In this review, we refer to epigenetics broadly, but focus mainly on DNA methylation and histone modifications, which are the best-characterized mechanisms of epigenetic regulation.

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2. Methyl-donor molecules and one-carbon metabolism build and maintain the epigenome throughout life

Establishment, maintenance, and reorganization of the epigenome rely on the availability of methyl-donor molecules that are produced in the one-carbon cycle. One-carbon metabolism utilizes co-factors such as folate, choline, and various other B vitamins (B_6, B_{12}, riboflavin), to produce S-adenosylmethionine (SAM), the universal methyl-donor that provides methyl-groups used for DNA, histone, and other protein methylation (Fig. 1). Evidence of impaired one-carbon cycling, either due to decreased enzymatic activity or co-factor deficiency, is the accumulation of the intermediate molecule homocysteine (Hcy) (Herrmann and Obeid, 2011a; Tomizawa et al., 2015). Methyl-donor synthesis from Hcy relies on the bioavailability of the B vitamins (Fig. 1). Disruption of this process can result in epigenome dysregulation, setting the stage for long-term health consequences.

Prevalence and severity of impairments associate with B12 deficiencies are largely determined by a complex series of interactions between genetic variants, nutrition, and lifestyle (de Bree et al., 2001; Refsum et al., 2006; Steegers-Theunissen and Steegers, 2003; Steegers-Theunissen et al., 2013). In particular, lifestyle factors such as smoking, and coffee and alcohol consumption have been linked to perturbations in one-carbon metabolism and elevated levels of Hcy (Refsum et al., 2006).

How these effects are mediated through epigenetics can be demonstrated in the agouti mouse model. Experimentally, the agouti mouse serves as an "epigenetic sensor," allowing for easy visualization of epigenome perturbations. Hypomethylation of the agouti gene, which determines coat color, results in a yellow coated mouse. Conversely, animals that exhibit agouti gene hypermethylation are brown in color. Intermediate levels of methylation in the agouti gene result in a mottled coat, with the degree of methylation directly corresponding to mottle intensity (Jirtle and Skinner, 2007). Pregnant agouti mice fed a diet supplemented with one-carbon metabolites, such as FA, B12, and choline, give birth to mice with altered coat color, indicating that these molecules have the ability to directly influence DNA methylation patterns in the periphery (Cooney et al., 2002; Waterland and Jirtle, 2003; Rakyan et al., 2002). Furthermore, transgenerational effects that persisted to the F2 generation were observed (Cropley et al., 2010). Interestingly, these offspring were also less prone to obesity and other diseases (Waterland and Jirtle, 2003).

One-carbon metabolism and methyl-donor production remain vital to epigenetic maintenance throughout life, particularly during "critical periods" of transition. Despite this however, B-vitamin supplementation is only encouraged during pregnancy (and shortly after breastfeeding). Although an increased intake of folate during pregnancy has the potential to prevent the miscarriage and birth defects associated with deficiency, this practice has fostered an increase in individuals harboring genetic polymorphisms that compromise folate usage (Shea and Rogers, 2014). These individuals, in particular, may have an increased requirement for additional folate that may not be met during adolescence and adulthood and could predispose them to early neuroendocrine aging and cognitive impairments later in life. Just as all mothers are encouraged to increase their folate intake during pregnancy, B-vitamin supplements may be beneficial for young children (Hassan et al., 2019) and adolescents (Tomizawa et al., 2015; Kanani and Poojara, 2000) whose brains are still developing.

Complicating this discussion, however, are reports that folate supplementation may both suppress or facilitate progression of certain cancers, depending on the timing of administration (Baggott et al., 1992; Kim, 2004; Kotsopoulos et al., 2003; Song et al., 2000a, b). Furthermore, many scientists have begun to stress the importance of distinguishing between naturally occurring folates and folic acid, a synthetic compound that is added to supplements and fortified foods (Ulrich and Potter, 2006). More research is necessary to identify specific gene networks that are impacted by both methyl-donor deficiency and B12 supplementation at different stages of life and brain development, and how this relates to disease pathogenesis down the line.

3. Epigenetics regulate learning and memory

3.1. DNA methylation modulates transcription during learning events

In recent years, the epigenetic mechanisms that regulate learning and memory have been characterized. It is now widely accepted that DNA methylation regulates neuroplasticity, learning, and memory by playing a dual role in memory formation; serving as both a transient modulator of transcription during learning, as well as a static marker involved in remote memory maintenance (Creighton et al., 2020).

Memory formation during a learning event requires the coordination of transcriptional changes in a number of genes. Transcriptional patterns vary at different stages of memory formation and early perturbation can disrupt downstream events. For example, inhibition of transcription and protein synthesis during the first few hours after a learning event disrupts long-term potentiation (LTP), but not short-term memory.

Epigenetic modulators, such as and DNA methyltransferases (DNMT) and ten-eleven-translocation proteins (TETs), are abundant in neurons, where active methylation and demethylation occur during learning (Antunes et al., 2019). *In vivo* studies have demonstrated that treatment with DNMT inhibitors disrupts DNA methylation, resulting in altered transcription, LTP suppression, and impaired memory formation (Miller and Sweatt, 2007; Levenson et al., 2006).

The process of memory formation occurs in two distinct waves, where the first wave of altered transcription triggers the second. Included in the second wave of transcriptional changes are a number of genes that encode epigenetic modulating proteins involved in memory

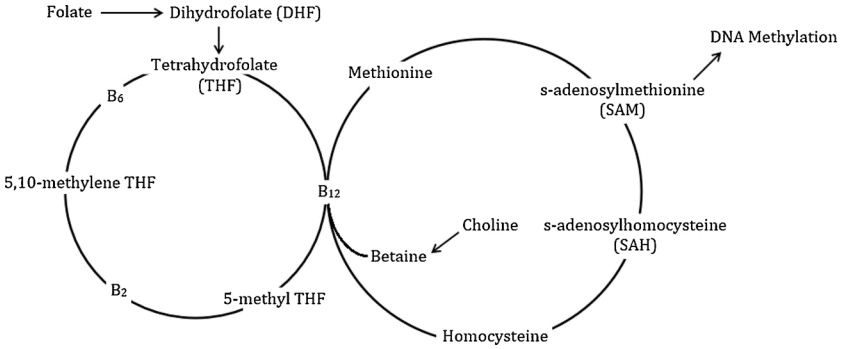

Fig. 1. One-carbon metabolism utilizes co-factors such as folate, choline, and various other B vitamins (B6, B12, riboflavin), to produce S-adenosylmethionine (SAM), the universal methyl-donor that provides methyl-groups used for DNA, histone, and other protein methylation. Impaired one-carbon metabolism results in loss of SAM production, an accumulation of homocysteine, and can lead to dysregulation of the epigenome.

maintenance (Duke et al., 2017). It is during these events that DNA methylation influences memory by altering transcriptional outcomes that impact memory formation and maintenance within the hippocampus, prefrontal cortex, and amygdala (Miller and Sweatt, 2007; Duke et al., 2017; Holliday, 1999; Miller et al., 2010).

3.2. One-carbon metabolism is intimately linked to learning, and memory

Methyl-donor deficiency can impair the dynamic regulation of DNA methylation that is required to modulate transcription during learning and memory in neurons. Indeed, mice with methyl-donor deficiency show reduced memory consolidation, poor performance in novel object recognition memory tests, and differential methylation and expression of the glutamate receptor gene, Gria1, which is involved in synaptic plasticity (Tomizawa et al., 2015). In addition to one-carbon metabolites, fetal deficiency of other micronutrients have epigenetic consequences linked to learning and memory impairments that persist into adulthood (Tran et al., 2015). Iron deficiency is associated with reduced brain-derived neurotrophic factor (BDNF) expression in the hippocampus that is accompanied by a loss of DNA methylation, an increase in histone deacetylase 1 (HDAC1) binding, and decreased ribonucleic acid (RNA) polymerase II binding at the BDNF promoter (Tran et al., 2015), all of which are involved in learning and memory. However, these effects of iron deficiency can be reversed by choline supplementation during late gestation, further implicating one-carbon metabolism as essential for both neuro-development and long-term cognitive function.

4. Both maternal and paternal preconception environments impact offspring health via epigenetic mechanisms

4.1. Imprinting

Offspring health outcomes can be impacted prior to conception through non-genetic mechanisms such as epigenetic imprinting, which is established in parental gamete cells during the maturation process from the primordial germ line. Gamete imprinting primarily occurs in a sex-specific manner and ensures that certain genes are preferentially expressed from either the maternal or paternal allele. Immediately after fertilization, the embryonic genome experiences dramatic and widespread loss of DNA methylation and histone modifications. This eraser of epigenetic information is seemingly a “reset” for the newly created genome. However, *some* epigenetic information must be maintained from the original egg and sperm in order to initiate the subsequent reprogramming of the methylome. These retained epigenetic characteristics are referred to as being “imprinted” onto the new genome. Imprinting control regions (ICR) that survive reprogramming are retained through cellular differentiation and are ubiquitously present in the adult organism’s somatic tissues. Only primordial germ cells are exempt from the process of imprinting (Bartolomei and Ferguson-Smith, 2011; Luedi et al., 2007); this exemption ensures that sex-specific epigenetic patterns can be appropriately re-established in both male and female offspring during gamete maturation.

The imprinting process is particularly important in genes where a double dose is toxic (Gendrel and Heard, 2014; Lyon, 1998). For example, the insulin-like growth factor 2 gene (IGF2) is maternally imprinted by epigenetic markers and is transcriptionally silenced. In health offspring, only the paternal copy of IGF2 is actively expressed. Re-activation of the maternally inherited IGF2, due to loss of imprinting, can impact mitochondrial function in offspring (Bjornsson et al., 2007). Similarly, improper imprinting of the Insulin (INS) and Guanine Nucleotide Binding Protein (G Protein), Alpha Stimulating Activity antisense RNA (GNASAS) genes are associated with an increased risk in coronary heart disease in adulthood (Talens et al., 2012). Disrupted imprinting at fertilization has been associated with a number of cognitive and developmental disorders that emerge later in life, including schizophrenia (Brucato et al., 2014; Marsit et al., 2012), Angelman syndrome (Clayton-Smith and Laan, 2003), Beckwith-Wiedemann syndrome (Viljoen and Ramesar, 1992), Prader-Willi syndrome (Cassidy et al., 2000), as well as multiple types of cancers (Feinberg and Tycko, 2004; Feinberg and Vogelstein, 1983; Yuan et al., 2003; Feng et al., 2008; Cui et al., 2002; Nakano et al., 2006; Kuerbitz et al., 2002).

4.2. Paternal environment before conception influences epigenetic programing during spermatogenesis

It is now widely accepted that the paternal preconception environment plays an important role in the imprinting process, early embryonic development, and both long term physical and cognitive health of offspring. As studies investigating paternal environmental factors begin to accumulate, the epigenetic mechanisms driving offspring traits are coming into better focus. Not surprisingly, it is the continuous nature of spermatogenesis that allows for environmental interactions, that influence the testis and sperm epigenomes, to subsequently impact the epigenetic programing of offspring.

A number of animal studies have investigated the effects of paternal stress on offspring stress response and anxiety behaviors. Results are somewhat mixed, with some reporting offspring with reduced anxiety (Mychasiuk et al., 2013; Rodgers et al., 2013; He et al., 2016), blunted stress response (Mychasiuk et al., 2013; Rodgers et al., 2013; Dias and Ressler, 2014; Dietz et al., 2011; Gapp et al., 2014), and improved behavioral flexibility (Mychasiuk et al., 2013; Rodgers et al., 2013), and others finding a general increase in anxiety and depressive behaviors (Rodgers et al., 2013; Dietz et al., 2011; Gapp et al., 2014; Azizi et al., 2019). Changes in DNA methylation and/or gene expression patterns in various regions of the brain have been identified in offspring born to stressed fathers (Mychasiuk et al., 2013; He et al., 2016; Dias and Ressler, 2014). Many of these alterations occurred in a sex-specific manner, with male and female offspring exhibiting divergent neurological and epigenetic effects (Mychasiuk et al., 2013; Rodgers et al., 2013; Dietz et al., 2011; Gapp et al., 2014; Azizi et al., 2019).

A study investigating physical exercise found global decrease in hippocampal DNA methylation and improved spatial learning in male rat offspring. Curiously, the authors found no changes in sperm DNA methylation were detected, suggesting that alternative epigenetic mechanisms play a role in transmission, such as histone modifications or sncRNA (Rodgers et al., 2013; Beeler et al., 2019; Krawetz et al., 2011).

Although extensively studied by number of groups, the biological consequences of paternal alcohol use is complicated. Findings across studies are mixed in terms of learning and behavioral patterns, as well as incidence of affective disorders in offspring (Beeler et al., 2019; Nieto and Kosten, 2019; Finegersh and Homanics, 2014; Liang et al., 2014; Rompala et al., 2017). Similarly, observed epigenetic perturbations are not consistent across studies. These inconsistencies are likely due to differences in species, strain, experimental paradigms, and the technical methods used.

Undeniably however, EtoH is a known epigenetic modifier in both adult (Cervera-Juanes et al., 2017) and developing tissues (Garro et al., 1991). Animal studies have demonstrated EtOH-induced alterations in DNA methylation, histone acetylation, and sncRNAs in both testis and developing sperm cells. In humans, alcohol use can produce hypomethylation of typically-hypermethylated ICR in sperm cells (Ouko et al., 2009). Animal studies have similarly demonstrated decreased methylation at paternally imprinted genes in offspring of EtOH-exposed fathers (Liang et al., 2014). In addition to imprinting alterations, other non-imprinting changes have been observed (Chang et al., 2017). How these epigenetic changes directly impact offspring health and development are only beginning to be understood. A recent study by Conner et al. identified abnormal patterns of gene expression in offspring neocortex and subtle alternations in patterns of intraneocortical connections (Conner et al., 2020). Cognitively, both male and female offspring exhibited changes in sensorimotor integration, decreased balance, coordination, and short-term motor learning. Consistent with

other studies(Kim et al., 2014), the authors observed a sex-specific increase of activity level in male offspring, a clinically relevant observation as the incidence of ADHD is increased in children born to alcoholic fathers (Knopik et al., 2005).

Several groups have begun to investigate other paternal factors. A recent retrospective clinical analysis revealed that non-allergic asthma was more common in offspring of fathers who either smoked, or had exposure to occupational welding, prior to conception (Mychasiuk et al., 2012). Paternal mental "enrichment" has been demonstrated to influence cognitive performance, reduce brain weight, and induce changes in global DNA methylation in the hippocampus and prefrontal cortex of both male and female offspring (Mychasiuk et al., 2012). Finally, other studies have shown that paternal diet alters glucose metabolism and brain development of offspring (Anderson et al., 2006; Kim et al., 2013; Ng et al., 2010) and is associated with changes in DNA methylation, possibly mediated through one carbon metabolism (Kim et al., 2013).

Both B12 vitamin deficiency and gene mutations impacting one-carbon metabolism are associated with low sperm count and poor viability (Bezold et al., 2001; Boxmeer et al., 2009; Dhillon et al., 2007; Safarinejad et al., 2011). Preliminary animals studies demonstrate altered sperm DNA methylation patterns in males with methylenetetrahydrofolate reductase (MTHFR) genetic variants, suggesting that perturbations in once carbon metabolism can directly impact epigenetic programing during spermatogenesis (Chan et al., 2010; Chen et al., 2001).

4.3. Maternal environment before conception influences the oocyte maturation processes and offspring health

The oocyte maturation process is period of epigenetic reorganization that is poorly understood but demonstratively sensitive to a variety of environmental factors, including alcohol(VandeVoort et al., 2015), endocrine disrupting chemicals (EDCs)(Susiarjo et al., 2013), diabetes (Ge et al., 2013), diet(Hou et al., 2016), as well as fertility treatments such as assisted reproductive technologies (ARTs)(Manipalviratn et al., 2009). It is likely that these factors influence maturation through epigenetic mechanisms (Steegers-Theunissen et al., 2013; Whitelaw et al., 2014; Zhang et al., 2010). Improper or disrupted epigenetic patterns in the oocyte genome can lead to subsequent disturbances in embryonic epigenetic reprograming at fertilization, setting the stage for the offspring's subsequent responses to environmental perturbations and influences epigenetic remodeling later in life. Indeed, preconception exposure to many of these factors have been linked to offspring neurological and health outcomes in both humans and animal models (Bhandari et al., 2015; Gore et al., 2011; Zhang et al., 2010; Collier et al., 2020; Allen et al., 2006).

Although few studies have directly investigated the role of one-carbon metabolism and in regulating epigenetic programing in the maturing oocyte, one-carbon biomarkers in follicular fluid (FF) are associated with fertility, oocyte and embryo quality, and pregnancy outcome (Boxmeer et al., 2009, 2008a; Boxmeer et al., 2008b; Ebisch et al., 2006; Pacchiarotti et al., 2007; Jerzak et al., 2003). Increased levels of FF Hcy is associated with endometriosis, and subfertility in women (Ebisch et al., 2006). Animal models have demonstrated that impaired one-carbon metabolism leads to a reduction of FF methionine and SAM, and an increase in Hcy (Kanakkaparambil et al., 2009; Sinclair and Singh, 2007). In couples undergoing IVF or ICSI, those who adhere to a diet rich in B12 vitamins have increased chance of successful pregnancy (Twigt et al., 2012; Vujkovic et al., 2010). These evidences demonstrate the importance of one-carbon status prior to conception and suggest the involvement of epigenetic mechanisms in driving the effects preconception environmental factors have on offspring.

5. The embryonic environment and implications later in life

5.1. Early embryonic reorganization of the epigenome

Undeniably, early embryonic development is a period of dramatic change and cellular reprogramming. Although each differentiated cell has a unique epigenetic signature that cannot be easily reversed, successful reproduction requires a "reset" of this signature to allow for totipotency to be restored to a fertilized zygote. Genome-wide studies mapping the DNA methylation patterns of mouse oocytes, sperm, and fertilized zygote cells through early development provide evidence for two major epigenetic reprogramming phases during early embryonic development (Smith et al., 2012). Upon fertilization, the zygote undergoes global de-methylation of the genome. DNA methylation levels continue to drop during the first few rounds of cellular division before genome re-methylation begins and global levels stabilize. In contrast to somatic tissues, where high CpG-density is correlated with low DNA methylation, the early pre-implantation phase of a developing embryo is a period during which DNA methylation is differentially positioned and maintained (Deaton and Bird, 2011). During early development, non-CpG methylation and higher levels of hydroxymethylation have been observed (Kinde et al., 2015). Little is known about the regulatory role of non-CpG methylation and hydroxymethylation; however, this may suggest that the pre-implantation phase is highly plastic and hypersensitive to environmental perturbations that have an increased potential to influence the health outcomes of the developing organism.

5.2. Prenatal one-carbon status contributes to the developing epigenome, and impacts neurodevelopment and cognition

The critical role of B-vitamin micronutrients during embryonic neuro-development is well documented. Elevated maternal Hcy is associated with small gestational age and congenital heart disease (Verkleij-Hagoort et al., 2006). In humans, maternal folic acid (FA) and choline deficiencies are linked to neural tube defects (spina bifida) and an increased risk for autism (Barua et al., 2014; Gillberg et al., 1986; Suren et al., 2013; Tamura and Picciano, 2006). Furthermore, maternal FA status correlates with preeclampsia, fetal growth restriction and other congenital malformations in offspring (Herrmann and Obeid, 2011b). In rats, choline deficiency is linked to a reduction of neural progenitor cell proliferation and an increase in apoptosis in developing brain tissues (Albright et al., 1999a, b). Choline-deprived offspring also show diminished visuospatial and auditory memory that persists throughout life (Meck and Williams, 1999). Conversely, offspring of choline-supplemented mothers exhibit an accelerated rate of neurogenesis, a reduction in apoptosis (Albright et al., 1999a; Craciunescu et al., 2003), and an increase in visuospatial and auditory memory that is not subject to decline during normal aging, suggesting that supplemental choline *in utero* may protect against age-related cognitive decline later in life (Meck and Williams, 1997a, b; Meck and Williams, 1997c; Meck et al., 1988; Meck and Williams, 2003).

Other studies have further demonstrated the interactions of B-vitamins with epigenetic patterns and neurodevelopment *in utero*. Choline deficiency is associated with changes in the DNA methylation of genes related to the cell cycle (Niculescu et al., 2006, 2004), and maternal FA regulates DNA methylation in a sex-specific manner (Barua et al., 2014). Male offspring, of mice fed a high FA diet, exhibited reduced expression and methylation patterns of Ror2(receptor tyrosine kinase like orphan receptor 2) (Barua et al., 2014), a gene involved in neurogenesis and development of the neocortex (Endo et al., 2012). Conversely, female offspring from these mothers exhibited hypomethylation and over expression of the Mtap4 (microtubule-associated protein 4) gene, which plays a role in the central nervous system (CNS) and in microtubule-dependent transport (Tokuraku et al., 2010).

Sex specific effects of maternal FA were also observed in several health-related imprinting genes in the offspring. Female offspring of

HMFA mothers showed altered methylation patterns in the Dio3 (Deiodinase, Iodothyronine, Type III) gene which has been implicated in insulin-related diseases. Males however showed no such effect in Dio3. Lastly, both male and female HMFA offspring demonstrated brain hypermethylation of several autism candidate genes, suggesting that maternal folic acid's protective effects against autism is mediated through epigenetic mechanisms (Gillberg et al., 1986; Suren et al., 2013; Tamura and Picciano, 2006).

5.3. Epigenetic patterns established in utero remain sensitive to the postnatal environment

Environmental perturbations during embryonic development can result in epigenetic modifications that correlate with alterations in the gene expression profiles seen in many adult-onset diseases (Gali Ramamoorthy et al., 2015; Gabory et al., 2011). Adverse maternal environments, such as poor nutrition, substance abuse, diabetes, and poor mental health, can also have life-long consequences for offspring (Dominguez-Salas et al., 2014; Barua et al., 2014). Maternal under-nutrition is known to cause intrauterine growth restriction (IUGR) and low birth weight (Vieau, 2011). Conversely, maternal over-nutrition, as well as gestational diabetes, has been linked to macrosomia or high birth weight (Vieau, 2011). Both IUGR and macrosomia have been linked to an increased risk of adult-onset obesity and metabolic disorders (Curhan et al., 1996; Pettitt and Jovanovic, 2001; Ong, 2006). Moreover, the fetal programming of the hypothalamus, which controls food intake and energy expenditure, is also influenced by maternal nutrition. Over- or under- nutrition can negatively impact the hypothalamic appetite regulatory systems and predispose offspring to metabolic disorders in adulthood (McMillen et al., 2005; Bouret, 2009; Ross and Desai, 2014).

Mechanistically, the loss of the pancreatic and duodenal homeobox (Pdx1) gene expression in IUGR is associated with adult-onset diabetes. Under conditions of poor maternal nutrition during fetal development the histone deacetylase complex mSin3/HDAC is recruited to the Pdx1 promoter in the pancreas. The loss of the histone acetylation at the Pdx1 promoter results in the loss of the transcription factor binding required for Pdx1 gene expression (Pinney and Simmons, 2010). Postnatally, a loss of the activating histone mark on histone 3 (H3) lysine 4 (K4) tri-methylation (me3) (H3K4me3), and an increase of the repressive H3 Lysine 9 (K9) di-methylation (me2) (H3K9me2), are seen at the Pdx1 gene promoter. While at this point, repression is still considered to be "reversible," the accumulating H3K9me2 marks soon recruit the DNA methyltransferase DNMT3A, which then methylates and permanently silences Pdx1 expression (Gabory et al., 2011).

Although IUGR does not immediately result in Pdx1 gene silencing through DNA methylation *in utero*, it establishes a chromatin state that is sensitive to further environmental impact, and raises the likelihood that the gene will be silenced later in life. This same principle can be applied to neurodevelopment, where the early environment can influence the likelihood of a particular cognitive outcome and modify the risk of neurodegenerative diseases later in life.

5.4. Toxic in utero exposures and negative health risks

EDCs are chemicals that can interfere with the endocrine system and produce adverse effects on development, health, and reproduction. EDCs are mostly synthetic and have been used widely in industry to produce plastics, pesticides, and oral contraceptive birth control. In recent years, EDCs have come under intense scrutiny as they have been linked to birth defects, behavioral issues, cancer, and immune system and metabolic dysfunction (Kim, 2004). EDCs are harmful to organisms both pre- and post-natally, and are able to disrupt proper genomic imprinting. Maternal exposure to bisphenol A (BPA) during late oocyte and early embryo development has been shown to modify gene expression in mouse embryos and placentas through the alteration of DNA methylation patterns and contribute to abnormal placental development (Kotsopoulos et al., 2003; Song et al., 2000a). The transgenerational effects of *in utero* EDC exposure are well documented (Bhandari et al., 2015; Gore et al., 2011; Susiarjo et al., 2013; Gore, 2008; Jandegian et al., 2015). Between the years 1958 and 1976, diethylstilbestrol (DES) was a common medicine given to pregnant women to prevent miscarriage. Both male and female offspring exposed to this chemical have been documented as having a dramatically increased risk for cancers and reproductive issues as adults (Hoover et al., 2011), and a number of studies have also observed third generation health risks (Blatt et al., 2003; Brouwers et al., 2006; Chantrain et al., 2009; Newbold et al., 2006; Ruden et al., 2005). Interestingly, these adverse health effects appear during puberty, suggesting that DES may alter the epigenetic mechanisms involved in puberty programming.

In animal models, prenatal alcohol exposure (PrEE) has also been linked to adiposity (Dobson et al., 2012), beta cell dysfunction, and glucose intolerance in adulthood (Chen and Nyomba, 2003). Neurologically, PrEE is associated with reduced brain weight and cortical length, abnormalities in intraneocortical circuitry, DNA hypomethylation of the neocortex and behavioral abnormalities (Bottom et al., 2020). Remarkably, co-administration of supplemental choline in alcohol exposed pregnancies successfully minimized or prevented many of these developmental abnormalities in offspring and experimentally reducing histone deacetylase expression has been shown to reverse glucose intolerance in alcohol-exposed offspring (Bottom et al., 2020). These experimental strategies highlight the potential for developmental disease intervention if the specific epigenetic perturbations can be identified (Yao et al., 2014).

5.5. Placental epigenetics

The placenta plays a critical role in development and facilitates nutrient and waste exchange between mother and fetus. Additionally, the placenta provides the fetus with protection and responds to maternal cues via epigenetic mechanisms regulating gene expression (Appleton et al., 2013; Gheorghe et al., 2010; Nugent and Bale, 2015). Epigenetic changes in the placenta, that occur in response to environmental perturbations, have the potential to alter long-term neurodevelopment and fetal programming (Nugent and Bale, 2015; Bale et al., 2010). These topics have been reviewed in detail by several groups, including Nugent and Bale (Nugent and Bale, 2015).

6. Puberty is a window period for long-term neurocognitive health consequences and is regulated by epigenetics

6.1. Pubertal timing and health outcomes

In mammals, initiation of puberty by activation of the hypothalamic-pituitary-gonadal (HPG) system relies on the functional organization of the hypothalamic GnRH neural network - a process that takes place early in development (Gore, 2008), suggesting that the transition to puberty is a process that begins *in utero* and is manifested later in life (Tena-Sempere, 2013). Timing of puberty varies between individuals as well as by sex, with females reaching sexual maturity earlier than males (McCarthy, 2013). Females are more likely to experience precocious, or early, puberty, while males are more likely to transition later (Rzeczkowska et al., 2014; McCarthy, 2013). The age of puberty onset can be modified by environmental factors, and is associated with multiple health and cognitive outcomes later in life. In girls, early menarche has been associated with an increased risk of breast cancer, cardiovascular disease, depression, eating and behavioral disorders, diabetes and obesity, as well as an overall increase risk of mortality (Rzeczkowska et al., 2014). Conversely, late menarche has been associated with a decreased risk of ischemic heart disease, but an increased risk of osteoporotic fracture (Rzeczkowska et al., 2014). In boys, initiation of puberty can be difficult to identify due to lack of a quantitative

measurements, such as age of menarche in girls; however, age of voice breaking is commonly used as a qualitative measurement of puberty onset in males (Day et al., 2015). Early male puberty has been linked to an increased risk for testicular cancer, whereas late puberty has been linked to both biological and social outcomes such as depression and low self-esteem (Rzeczkowska et al., 2014; Day et al., 2015; Golub et al., 2008). In both sexes, it is difficult to determine whether mistiming in puberty directly causes the associated health conditions, or if these health conditions are due to the underlying factors controlling puberty onset in the first place. Nevertheless, the transition through puberty is a critical period when environmental factors can permanently alter developmental and health trajectories.

6.2. Onset of puberty onset is epigenetically controlled

As many as 106 distinct parent-of-origin alleles have been implicated in the regulation of puberty, suggesting that puberty is at least partly controlled by classic, Mendelian genetics (Perry et al., 2014). However, variable onset is present in monozygotic twins, as well as inbred rodent strains raised in similar environments, suggesting that epigenetics may be involved. Indeed, several groups have identified the KISS1 gene, which regulates puberty in all mammals, to be under epigenetic control (Lomniczi et al., 2013; Wyatt et al., 2013; Semaan and Kauffman, 2013; Garcia-Galiano et al., 2012; Roa et al., 2008; Tena-Sempere, 2008).

The initiation of puberty begins with the expression of KISS1's protein product kisspeptin. Subsequent signaling through the Kiss1 receptor in gonadotrophin-releasing hormone (GnRH) neurons activates the neuroprotective and hypothalamic-pituitary-adrenal (HPA) axes. Mutations in KISS1, or its receptor KISS1R, can result in a failure to transition into puberty (Wyatt et al., 2013). Differential expression of KISS1 is thought to contribute to sex differences in the timing of puberty and in the secretion of Luteinizing hormone (LH) in adulthood (Semaan and Kauffman, 2013). Indeed, studies have found sex-specific differences in KISS1 messenger RNA (mRNA) expression as well as differences in DNA methylation along the KISS1 promoter (Semaan et al., 2012; Kauffman, 2009; Semaan and Kauffman, 2010). Furthermore, neonatal exposure to EDCs can alter the activation and function of the HPG axis (Tena--Sempere et al., 2000) and the timing of the hypothalamic expression of Kiss1 (Navarro et al., 2004, 2009), demonstrating how early environment can influence transition periods and health outcomes later in life.

Prior to puberty, the hypothalamus expresses the genes embryonic ectoderm development (Eed) and chromobox 7 (Cbx7), which bind to the KISS1 promoter and recruit polycomb repressive complex 2 (PRC2) (Lomniczi et al., 2013; Wyatt et al., 2013). PRC2 is responsible for silencing the KISS1 promoter through chromatin reorganization by trimethylating H3 on lysine 27 (H3K27me3) (Lomniczi et al., 2013). At the onset of puberty, DNA methylation increases at the Eed and Cbx7 gene promoter regions. The increase of DNA methylation is accompanied by a decrease in the expression of the two genes, and a subsequent loss of their binding at the KISS1 promoter (Lomniczi et al., 2013; Wyatt et al., 2013). Loss of Eed and Cbx7 binding, resulting in a loss of KISS1 repression, is accompanied by an increase in transcription-activating histone marks, H3K4me3, H3K9ac, and H3K14ac along the KISS1 promoter (Lomniczi et al., 2013). Thus the KISS1-mediated onset of puberty is set into motion through the epigenetic silencing of repressive factors (Lomniczi et al., 2013). Over-expression of Eed or treatment with 5-azadine, a DNA methylation inhibitor, is able to block puberty in female rats, further supporting the role of epigenetic programming in the pubertal transition (Lomniczi et al., 2013).

Considering the complexity of puberty and the wide range of systemic changes associated with the transition, it is probable that epigenetic mechanisms are involved in orchestrating the cooperation of many gene networks during this period. A series of studies have demonstrated that epigenetic mechanisms directly regulate GnRH transcription, both *in vitro* and *in vivo* (Kurian and Terasawa, 2013; Kurian et al., 2010; El Majdoubi et al., 2000). During puberty, a rise in GnRH mRNA is accompanied by a change in the DNA methylation status of the gene promoter (Kurian and Terasawa, 2013). Additionally, specific patterns of histone modifications at the GnRH gene are associated with differential levels of transcription (Iyer et al., 2011). Immature GnRH neuronal cells, which do not yet produce GnRH, possess mostly repressive H3K9me2 histone marks along the GnRH gene, while mature GnRH neuronal cells possess permissive H3K9ac and H3K4me3 histone marks (Iyer et al., 2011).

Lominiczi et al. surveyed genome-wide changes in DNA methylation and RNA transcription across different points of the female puberty transition and found that several genes with changes in expression were involved in chromatin and histone modification (Lomniczi et al., 2013). Expression changes of many of these genes were also accompanied by changes in DNA methylation. However, hormones are also known modifiers of the chromatin landscape. Estrogen induces changes in KISS1 promoter histone acetylation, possibly contributing to the positive feedback that is involved in generating the preovulatory surge in females (Tomikawa et al., 2012). More research is needed to explore the details of the cause-effect relationship between epigenetic programing and hormone signaling during puberty.

6.3. Brain changes that occur during puberty are sex-specific

In addition to the maturation of reproductive tissues, puberty is a time of widespread maturation and reorganizational in the brain (Spear, 2013). White matter volume in the frontal and parietal lobes peak at puberty (and subsequently declines thereafter) (Giedd et al., 1999; Perrin et al., 2008; Pfefferbaum et al., 1994), the limbic areas finish developing (Isgor et al., 2004; Bock et al., 2014), and task-dependent brain activity changes (Adleman et al., 2002; Kwon et al., 2002). Many of these aspects of normal brain development require organizational augmentation that is dependent on the sex-steroid surge which occurs during puberty (Morrison et al., 2014). These changes often occur in a sex-specific manner and can be blunted by gonadectomy, highlighting the role of sex steroids in brain development and reorganization during this period (Ahmed et al., 2008; Sex On Brain European Research Group et al., 2013).

6.4. Environmental perturbations during puberty can have long lasting and sexually dimorphic effects, and are likely regulated by epigenetics

Alcohol use during adolescence is associated with an increased risk of alcohol abuse in adulthood (DeWit et al., 2000). Curiously, children who first used alcohol at ages 11–14 had the highest risk for developing alcohol disorders later in life (DeWit et al., 2000), while those who first used alcohol at an older or younger age did not carry this same risk. These findings indicate that ages associated with the pubertal window might be more sensitive to environmental perturbations. Indeed, periods of hormonal flux, such as puberty, pregnancy, and perimenopause, have been identified as hypersensitive to environmental perturbations (Brinton et al., 2015; Dahl and Gunnar, 2009; Morrison et al., 2017).

Curiously, onset of many neuropsychiatric disease symptoms often occurs during or immediately following puberty (Arborelius et al., 1999; Corbett et al., 2009; Moghaddam, 2002; Nestler et al., 2002; Walker et al., 2008) and adverse childhood experiences are predictive for affective disorders in women (Morrison et al., 2017). Dysregulation of stress neurocircuitry in the HPA axis is a key endophenotype observed across affective disorders as well as many other psychiatric diseases (Arborelius et al., 1999; Corbett et al., 2009; Moghaddam, 2002; Nestler et al., 2002; Walker et al., 2008).

The HPA axis, which regulates responsivity to stress, is further developed during puberty, under the guidance of the sex steroids. Furthermore, the impact that estrogen and testosterone have on stress reactivity is different in adult versus pre-pubertal animals (Foilb et al., 2011; Romeo et al., 2004a, 2013). It is now understood that stress neurocircuitry in the HPA axis is augmented by the sex steroids during

puberty to elicit the reactivity response patterns observed in adulthood (Romeo et al., 2004a; Goldman et al., 1973; Lui et al., 2012; Romeo et al., 2006; Viau et al., 2005). In male rats for example, prepubertal animals take longer to recover from stress tests and demonstrate a prolonged stress response. In adulthood, testosterone reduces the stress response through mechanism that cannot be recapitulated through steroid treatment of prepubertal animals (Romeo et al., 2004a). Sex-specific differences in response to stress also exist. Female rats exposed to chronic stress during puberty have demonstrated blunted neurogenesis in the dentate gyrus and changes in hippocampal plasticity in adulthood (Barha et al., 2011). However, these effects were not observed in males.

Reorganization of the HPA's stress neurocircuitry that occurs during puberty suggests the involvement of epigenetic regulation (Carey et al., 1995; Handa et al., 1994; McCormick et al., 2002; Romeo et al., 2004b). Similarly, chronic stress or adversity during puberty likely exploits epigenetic mechanisms to elicit adult neurobiological deficits (Morrison et al., 2014). Recent studies have begun to investigate these mechanisms. Chronic stress during puberty increases visceral pain behaviors in rats and leads to an increase in the DNA methylation of the glucocorticoid receptor and a decrease in the DNA methylation of corticotrophin-releasing factor in the amygdala (Tran et al., 2013). Additionally, exposure to estrogenic compounds during early puberty has been demonstrated to alter the population of neurons expressing estrogen receptor alpha in the female rat hypothalamus (Ceccarelli et al., 2007), implicating the importance of epigenetic-hormone crosstalk.

In addition to biological programing, behavioral and social development also occurs during early adolescence under the influence of pubertal hormones. Animal models have demonstrated that during puberty, the presence of sex steroids augments hormone-induced behavioral response patterns towards those observed in adulthood, in a sex-specific manner (Schulz and Sisk, 2006). Pubertal hormones also program sex steroid-independent behavioral responses in the adult brain, further implicating epigenetic-hormone interactions as a key player during this developmental period. Perturbations in the timing of hormonal flux in the adolescent brain are likely to have long-lasting consequences on adult social and reproductive behavior (Schulz and Sisk, 2006).

7. Epigenetic shifts during aging and reproductive senescence contribute to age-related diseases and cognitive decline

7.1. Normal aging

Only 20–30 % of the individual variation in average human life span can be attributed to genetic variation, implying that longevity is largely due to environmental factors (Herskind et al., 1996; Mitchell et al., 2001; Zampieri et al., 2015). At birth, monozygotic twins have nearly identical epigenomes. Over time however, their epigenomes diverge due to environmental interactions and spontaneous errors in epigenetic maintenance (Zampieri et al., 2015). At older ages, the epigenomes of monozygotic twins can be dramatically different, explaining why many have remarkably different medical histories and health outcomes (Zampieri et al., 2015; Feil and Fraga, 2011; Poulsen et al., 2007). This kind of alteration in epigenetic patterning is referred to as epigenetic drift.

In contrast to epigenetic drift, which is a seemingly random accumulation of epigenetic changes over time, there is strong evidence for the existence of an "epigenetic clock," suggesting that many age-related changes in the epigenome may be "programmed" as a natural part of aging. Many groups have identified trends in DNA methylation that changes in predictable manners with increasing age (Horvath, 2013; Day et al., 2013; Weidner et al., 2014). In general, global DNA methylation declines with age, with region specific hypermethylation. Age related global DNA hypomethylation is mainly associated with repeating regions in the genome, such as Long interspersed nuclear elements (LINEs) and Alu elements (Bollati et al., 2009; Christensen et al., 2009; Jintaridth and Mutirangura, 2010; Heyn et al., 2013). Global hypomethylation results in the loss of chromatin regulatory proteins such as polycomb repression complexes and histone modifications which, subsequently, results in the global remodeling of chromatin and genome instability (McClay et al., 2014; Vijg and Dolle, 2007). However, DNA hypermethylation at CpG islands (CGIs) results in reduced expression in many genes involved in tumor suppression, genomic stability and repair, metabolism, cell differentiation and growth, and regulation of the immune system (Zampieri et al., 2015). Over time, accumulated changes in DNA methylation and gene expression in networks involved in age-related diseases predispose an individual to either susceptibility or resiliency to disease pathogenesis (Zampieri et al., 2015; Florl et al., 2004; Neuhausen et al., 2006; Shen et al., 2005; Siegmund et al., 2007).

7.2. Reproductive senescence and dysregulated GnRH signaling is linked to neurological disease pathogenesis in both men and women

In both males and females, reproductive senescence is not merely characterized by the loss of sex steroids, but instead is a function of both gonadal failure and hypothalamic-pituitary aging. The HPG axis, which is activated during puberty, is a negative feedback system in which pulsatile GnRH, produced in the hypothalamus, stimulates LH and follicle-stimulating hormone (FSH) production and secretion by the pituitary. LH and FSH stimulate estrogen and testosterone production in the ovaries and testes respectively. Systemic estrogen and testosterone then feedback onto the pituitary and hypothalamus and modulate GnRH, LH, and FSH production and secretion (Davis et al., 2015). The pituitary response to GnRH, and the gonadal response to LH and FSH simultaneously decline with age resulting in the diminished sex steroid

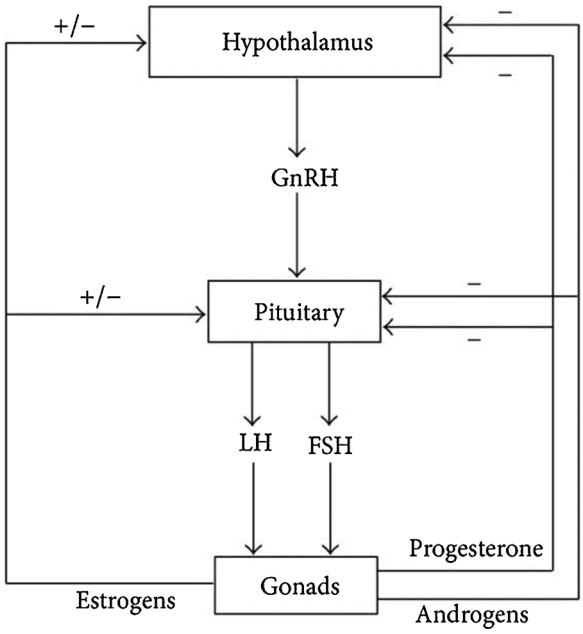

Fig. 2. The hypothalamic-pituitary-gonadal axis is activated during puberty by the epigenetic silencing of repressive factors. Kisspeptin expression in the hypothalamus activates GnRH-releasing neurons that signal to the pituitary to synthesize and release LH and FSH. LH and FSH then stimulate estrogen and testosterone production in the ovaries and testes, respectively. During reproductive senescence, pituitary responsiveness to GnRH decreases and LH pulses become desynchronized leading to an impaired sex steroid production and a loss of negative feedback onto the hypothalamus and pituitary. Luteinizing hormone (LH), Follicle stimulating hormone (FSH), Gonadotropin-releasing hormone (GnRH).

production characteristic of menopause and andropause, and a loss of negative feedback resulting in increased GnRH, LH, and FSH production (Fig. 2) (Davis et al., 2015; Meethal et al., 2005; Bottner et al., 2007; Wang et al., 2010).

LH and GnRH receptors are present in neurons throughout the brain, and changes in concentrations of these gonadal hormones during reproductive senescence have the potential to influence the structure and function of their neuronal targets. In the hippocampus, LH receptors are highly expressed (Meethal et al., 2005), and GnRH receptor concentrations increase with age and castration (Badr et al., 1989, 1988). Interestingly, increased LH levels are seen during the same time period that age-related cell cycle alterations and the upregulation of oxidative markers are observed (Nunomura et al., 2001; Ogawa et al., 2003).

In AD patients, increased levels of LH and GnRH are also observed in hippocampal pyramidal neurons (Meethal et al., 2005; Bowen et al., 2000; Short et al., 2000), suggesting that their altered signaling activity during reproductive senescence might be involved in disease pathogenesis. Indeed, LH has been implicated in the re-activation of mitotic signaling pathways seen in early AD pathogenesis (Harris et al., 2002; Mattson et al., 2004) and shown to promote the amyloidogenic pathway in amyloid precursor protein (APP) processing (Meethal et al., 2005), providing a direct link to the progression of AD pathology.

In the hippocampal pyramidal neurons, activation of GnRH receptors results in a long-lasting enhancement of synaptic transmission via glutamate receptors in CA1 & CA3 (Lu et al., 1999; Osada and Kimura, 1995). Normally, GnRH receptor activation is modulated by estrogen (Gore et al., 2004). The loss of estrogen negative feedback on the HPG axis, due to ovarian senescence, results in increased GnRH signaling that may play a role in driving neurodegeneration in AD (Wang et al., 2010; Badr et al., 1989, 1988). Conversely, men who have undergone GnRH agonist therapy for prostate cancer (which ultimately reduces LH production) show a decreased incidence of neurodegenerative diseases (Almeida et al., 2004; Gandy et al., 2001)

A series of studies have demonstrated that epigenetic mechanisms directly regulate GnRH transcription, both *in vitro* and *in vivo* (Kurian and Terasawa, 2013; Kurian et al., 2010; El Majdoubi et al., 2000). For example, during puberty a rise in GnRH mRNA is accompanied by a change in the DNA methylation status of the gene promoter (Kurian and Terasawa, 2013). Additionally, specific patterns of histone modifications at the GnRH gene are associated with differential levels of transcription (Iyer et al., 2011): immature GnRH neuronal cells, which do not yet produce GnRH, possess mostly repressive H3K9me2 histone marks along the GnRH gene, while mature GnRH neuronal cells possess permissive H3K9ac and H3K4me3 histone marks (Iyer et al., 2011). Better understanding of epigenetic control of GnRH expression patterns during aging may provide insights on how to clinically manage aberrant signaling pathways during reproductive senescence in the hopes of reducing negative neurological outcomes.

7.3. Epigenetic control of female reproductive senescence

The heritability of menopause timing is 44–66 % and similar to puberty, variability is present in monozygotic twins and inbred rat strains, suggesting that epigenetics and environmental factors are involved (Bennett et al., 2015). While recent studies have begun to compare the pre- and post- menopause epigenome, no studies have directly investigated specific epigenetic mechanisms involved in driving the transition itself.

In humans, menopause has been associated with accelerated epigenetic patterns of aging, including global hypomethylation (Levine et al., 2016) in blood and Repetitive Element DNA Methylation (Lu et al., 2018) (Fig. 3). Furthermore, women with an earlier age of menopause onset have been found to be "epigenetically older" than women with a later onset (Levine et al., 2016). The cause-effect relationship between epigenetics and menopause has been challenging to understand as differences in epigenetic patterns seen across the perimenopause transition consist of both age-related changes that initiate onset of reproductive senescence, as well as changes that occur as a direct result of endocrine status and loss of circulating sex hormones. Untangling these relationships are particularly important, as differential outcomes of menopause have been associated with a risk for neurodegenerative and autoimmune diseases (Fenichel and Sosset, 1997; Farage et al., 2012).

Recently in our own lab, we demonstrated that neuroendocrine aging precedes onset of perimenopause and is directly regulated by DNA methylation and one carbon metabolism, using a rat model that recapitulates characteristics of the human perimenopause (Bacon et al., 2019). In the hypothalamus, the majority of age-related changes in gene expression occurred while animals were still cycling regularly, indicating that hypothalamic aging begins before the phenotypic manifestation of perimenopause. Alongside these transcriptional changes, we

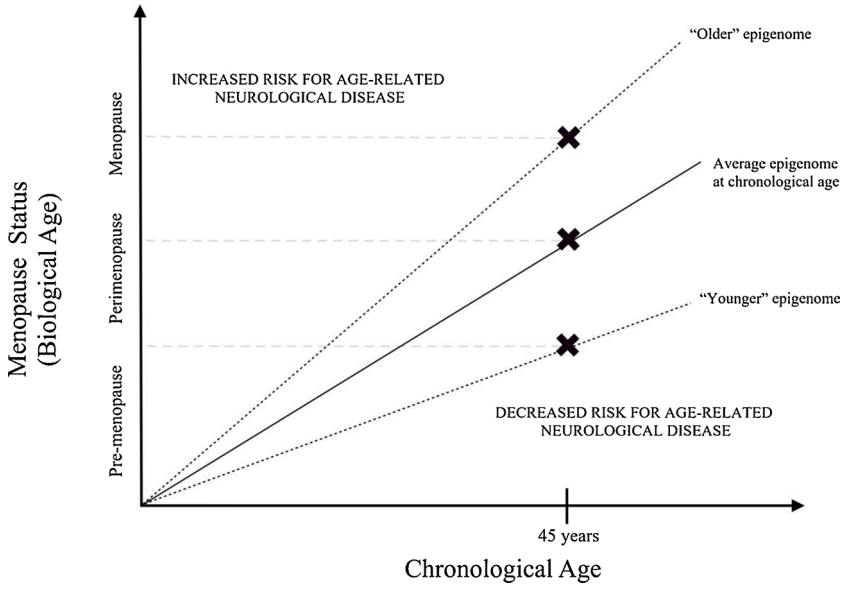

Fig. 3. In humans, menopause is strongly associated with the accelerated epigenetic patterns of aging in blood. Post-menopausal women are "biologically and epigenetically" older than pre-menopausal women of the same chronological age (hypothetically marked along each trajectory as "X"). Epigenetic changes prior to and during the perimenopause transition may provide an explanation for the age-related negative health and cognitive outcomes associated with early menopause.

observed decline in global DNA methylation with both age and reproductive senescence. Interestingly, within the young, regularly cycling animals we observed two distinct populations with "high" and "low" global DNA methylation levels suggesting that individual animals appear to be aging at various rates, suggesting that individual epigenetic differences that are present before perimenopause onset predispose an individual toward a particular outcome (late vs. early menopause). To interrogate mechanisms driving these observations, we treated young, regularly cycling animals with the DNA-methyltransferase-1 inhibitor, 5-aza-20-deoxycytidine, and monitored DNA methylation over time via blood. Treated animals exhibited loss of DNA methylation and an accelerated transition to reproductive senescence, as characterized by loss of estrus cycling, compared to non-treated animals. Conversely, we also supplemented young, regularly cycling animals with methionine, a SAM precursor, displayed delayed onset of reproductive senescence, highlighting the role that one-carbon metabolisms plays in neuroendocrine aging. Finally, genome-wide epigenetic profiling revealed changes in DNA methylation in genes required for hormone signaling, glutamate signaling, and melatonin and circadian pathways, providing insight into the origin of perimenopause-associated neurological symptoms.

7.4. Menopause is associated with an increased risk for neurodegeneration in some women

Perimenopause refers to the transition into female reproductive senescence. Menopause, the completion of the perimenopause transition, is characterized by the exhaustion of oocytes, amenorrhoea, and the loss of circulating estrogen (Brinton et al., 2015; Harlow et al., 2012). Loss of estrogen during female reproductive aging has profound effects in nearly all tissues, including breast, bone, cardiovascular, and brain. Menopause in humans is also marked by an increased risk for stroke, coronary heart disease, and neurological dysfunction in some women (Rocca et al., 2012; Weber et al., 2014; Silva and Naftolin, 2013; Wellons et al., 2012). Although a majority of women have no long-term health consequences, many women experience neurological symptoms during and after the perimenopause transition (Brinton et al., 2015). Furthermore, early menopause has been associated with adverse cognitive outcomes later in life, and the loss of estrogen during the perimenopause transition is considered to be a risk factor for developing AD (Geerlings et al., 2001; Henderson and Sherwin, 2007; Rocca et al., 2011).

The neurological consequences of menopause have been largely attributed to the dramatic loss of circulating estrogen. Estrogen-centered therapies have been used to treat many diseases, including breast, uterine, and ovarian cancers, as well as neurodegenerative diseases. However, cellular response and sensitivity to estrogen has been shown to decline following long-term hormonal deprivation (Gibbs, 2000), and although hormone therapy (HT) has been proposed as a possible treatment in reducing the risk and symptoms of AD (Paganini-Hill and Henderson, 1994; Ohkura et al., 1994), to date no studies have shown HT to be beneficial once AD symptoms have already presented (Almeida et al., 2006; Gurney et al., 2014). Furthermore, recent meta-analyses have suggested that HT may actually worsen cognitive dysfunction if initiated too late (O'Brien et al., 2014; Winkler and Fox, 2013), suggesting that there may be a "critical window" after menopause during which HT may be effective in preventing negative neurocognitive outcomes. Non-clinical studies in rodent models have shown a similar age-related loss of estrogen sensitivity (Selvamani and Sohrabji, 2010; Suzuki et al., 2007). While estrogen promotes neurotrophic support in neonatal, glial cultures (Arimoto et al., 2013; Rozovsky et al., 2002), these effects are lost in "aging" glial cultures originated from older male animals or from middle-aged females with irregular estrus cycles - implying that these changes occur across both age and the perimenopause transition and somehow alter cellular properties and influence responses to estrogen (Arimoto et al., 2013).

The molecular basis for age- and perimenopause- related loss or dysregulation of estrogen sensitivity is poorly understood. However, evidence suggests that changes in estrogen signaling may originate from changes in the DNA-binding profiles of the ERs. The ability of a transcription factor to modulate gene transcription depends upon the accessibility of the target region in the DNA. Response to estrogen is context dependent and differs between tissues and cell type, suggesting possible epigenetic mechanisms (Arimoto et al., 2013; Bourdeau et al., 2004; Foster, 2012). Indeed, local chromatin structure governs the context dependent ER-DNA-binding by controlling access to binding sites along the DNA (Miranda et al., 2013). Epigenetic modifications that occur with age and across the perimenopause transition may inhibit the ability of ERs to interact with the appropriate target regions of DNA. Development of better technologies to combat estrogen-related diseases hinges upon a better understanding of the molecular mechanisms behind age-related dysregulation of estrogen signaling. Further exploration of these details will allow us to more clearly define, the "window period" for beneficial hormone therapy in the prevention of AD as well as other estrogen-related diseases associated with increased age, such as various kinds of cancer, cardio-vascular disease, osteoporosis, and insulin sensitivity.

7.5. Deficiencies in one-carbon metabolism during perimenopause links female reproductive senescence to age-related diseases

One-carbon metabolism has the potential to modify the relationship between sex hormones and methylation in a bi-directional manner (Ulrich et al., 2012), further contributing to the complexity of endocrine aging and related health outcomes. The efficiencies of one-carbon metabolism vary among individuals, and can fluctuate over time and with menopause status (Zeisel, 2009). Estrogen stimulates the expression of phosphatidylethanolamine N-methyltransferase (PEMT), a gene involved in the endogenous production of choline (Resseguie et al., 2007). The loss of estrogen during menopause results in a decreased ability to produce choline and dramatically increases the need for exogenous choline intake. Demonstratively, postmenopausal women are much more sensitive to choline deficiency and are more likely to suffer from deficiency-induced fatty liver and muscle damage than are pre-menopausal women (da Costa et al., 2004, 2005). Conversely, dietary supplementation of folate has been shown to increase luteal progesterone levels in pre-menopausal women and to decrease the risk of sporadic anovulation (Gaskins et al., 2012), suggesting that folate may be able to regulate the initiation of the perimenopause transition through one-carbon metabolism.

Dietary differences in folate and other one-carbon metabolites, in addition to individual differences in sex hormone levels, may explain some of the individual differences seen in menopausal age, risk for cognitive impairment, and response to intervention therapies. Systemic decline in estrogen combined with nutrient deficiencies resulting in impaired epigenetic maintenance creates a hyper-plastic state that sensitizes the perimenopausal brain to environmental insults and modifies an individual's health trajectory (Fig. 3).

Elevated plasma Hcy is observed in post-menopausal women (Hak et al., 2000), as well as in AD patients, indicating impaired one-carbon metabolism. High levels of Hcy are additionally associated with an increased risk for developing AD (Shen and Ji, 2015; Nazef et al., 2014), and impaired one-carbon metabolism has been linked to AD, Parkinson's disease, and other psychiatric disorders (Lucock, 2000; Moat et al., 2004; Mattson and Shea, 2003; Kronenberg et al., 2009; Tangney et al., 2011; de Jager et al., 2012; Wald et al., 2011; Kronenberg et al., 2008; Nilsson et al., 2002; Clarke et al., 1998; Fuso et al., 2012, 2008; Lee et al., 2012). Coincidently, dysregulation of the epigenome in many of these same disorders are well established (Marques et al., 2012; Mastroeni et al., 2010; Wang et al., 2008; Lardenoije et al., 2015; Xu, 2015; Julien et al., 2009; Chen et al., 2009; Chouliaras et al., 2012). Thus, estrogen loss and impaired one-carbon metabolism, resulting in the dysregulation of the epigenome, provides a causal link between the

perimenopause transition and a risk for cognitive impairment later in life (Fig. 3).

8. Conclusion

Brain development is a life-long process that is sensitive to both genetic and environmental factors. While the genetic code is mostly invariant, environmentally-induced epigenetic alterations that occur during critical periods in the brain can cause phenotypic changes that manifest later in life. While traditionally only associated with early brain development, "critical periods" occur throughout life: gamete formation, development *in utero*, puberty, and reproductive senescence are all periods of transition that are hypersensitive to environmental perturbations. Changes that occur during these sensitive periods are then able to influence subsequent critical periods. For example, choline deficiency *in utero* may lead to epigenetic patterns associated with aberrant glutamate signaling that leaves the pubescent brain hypersensitive to stressors which impair brain plasticity and increase the risk for cognitive decline later in life. Similarly, initiation of sexual maturation is tightly regulated by epigenetic mechanisms, and the transition through puberty is a dynamic process that is influenced by environmental factors. If early events *in utero* are able to alter the HPG axis to impact puberty onset, it is likely that environmental conditions during the pubertal transition continue to influence other still-developing brain networks. Alterations in histone modifications and DNA methylation are mechanisms by which environmental factors during puberty can sensitize the brain towards specific neurological outcomes and aging phenotypes later in life. Rather than being isolated episodes, each event builds upon the last and to manifests a phenotype that is the culmination of a complex series of events that begin *in utero* and progress throughout life.

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