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Review article

Non-invasive biomarkers of fetal brain development reflecting prenatal stress: An integrative multi-scale multi-species perspective on data collection and analysis

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ABSTRACT

Prenatal stress (PS) impacts early postnatal behavioural and cognitive development. This process of 'fetal programming' is mediated by the effects of the prenatal experience on the developing hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system (ANS). We derive a multi-scale multi-species approach to devising preclinical and clinical studies to identify early non-invasively available pre- and postnatal biomarkers of PS. The multiple scales include brain epigenome, metabolome, microbiome and the ANS activity gauged via an array of advanced non-invasively obtainable properties of fetal heart rate fluctuations. The proposed framework has the potential to reveal mechanistic links between maternal stress during pregnancy and changes across these physiological scales. Such biomarkers may hence be useful as early and non-invasive predictors of neurodevelopmental trajectories influenced by the PS as well as follow-up indicators of success of therapeutic interventions to correct such altered neurodevelopmental trajectories. PS studies must be conducted on multiple scales derived from concerted observations in multiple animal models and human cohorts performed in an interactive and iterative manner and deploying machine learning for data synthesis, identification and validation of the best non-invasive detection and follow-up biomarkers, a prerequisite for designing effective therapeutic interventions.

1. Introduction

By 2010, 250 million children (43%) younger than 5 years in low-income and middle-income countries are at risk of not reaching their developmental potential (Black et al., 2017; Lu et al., 2016). This is mostly due to exposure to biological and psychosocial factors that might alter brain function (Grantham-McGregor et al., 2007; Walker et al., 2007). It is now widely accepted that maternal distress including depression, anxiety, stress, fears and worries have been identified as key risk factors affecting child development that requires urgent intervention with major health-economic benefits (Persson and Rossin-Slater, 2018; Fontein-Kuipers et al., 2014; Rakers et al., 2017; Walker et al., 2007). Early postnatal care was shown to partially reverse the effects of prenatal stress (PS) on brain reprogramming in animal models

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(Barros et al., 2004, 2006b; Weaver et al., 2005). Early interventions promoting mother-infant bonding and cognitive stimulation, mainly based on education and maternal support programs and which are accessible in developing countries, might improve developmental outcomes in PS-exposed children, decreasing liability for psychopathology (Fontein-Kuipers et al., 2014; Nolvi et al., 2016).

The concept of stress was originally defined by Selye in 1950 as the "non-specific response of the body to any noxious stimulus", and was later thoroughly revised and refined in the literature by distinguishing between 'stressor' and 'stress response' (Selye, 1950). A recent revision by (Lucassen et al., 2014) proposes that a stressor is "any environmental demand that exceeds the physiological regulatory capacity of an organism", and, as suggested by (Koolhaas et al., 2011), "during situations of unpredictability and uncontrollability". During the gestational period, women like any other subject can be exposed to endogenous and exogenous challenges that may be perceived as unpleasant, aversive or threatening in such a way that the homeostasis, wellbeing, overall health or survival are threatened (Glover, 2015a).

PS impacts early behavioral and cognitive development in human infants (Beydoun and Saftlas, 2008; Mulder et al., 2002). As a result, infants may develop attention-deficit hyperactivity disorder (ADHD) and sleep disturbances (Weinstock, 1997). Longer-term persistence of these disorders may lead to depression and vulnerability to psychotic disorders in adulthood (van Os and Selten, 1998). The underlying mechanisms of this fetal programming of adult diseases are thought to be mediated by the impact of PS on the developing hypothalamic–pituitary–adrenal (HPA) axis, an essential homeokinetic system capable of responding to stressors (Van den Hove et al., 2006). HPA axis is highly sensitive to adverse early life experiences (Meaney, 2001). Animal studies show that PS results in vulnerability to anxiety and impaired learning, memory and locomotor dysfunction (Huizink et al., 2004; Weinstock, 2001). Exposure to PS results in increased responsiveness of the HPA axis to stress, and reductions of glucocorticoid receptor (GR) expression in the hippocampus of adult offspring (Zuena et al., 2008). In humans, prenatal depressed/stressed maternal mood is associated with higher rates of preterm delivery and lower birth weight (Van den Bergh et al., 2005; Wadhwa et al., 1993), elevated cortisol (Field et al., 2004), impaired subsequent working memory performance in young women (Entringer et al., 2009) and changes in the epigenetic regulation of GR expression (Mulder et al., 1997).

A possible therapeutic avenue to counteract the effects of PS-induced fetal programming is given by postnatal stimulation. This can be accomplished by changes in the postnatal environment, such as care and early adoption. The positive effects of such treatment include better cognitive performance of adult offspring (Meaney et al., 1988) and reduction of stress-induced corticosterone secretion (Wallen et al., 1999).

The first step in devising and testing early interventions to prevent PS effects on offspring is the identification of changes of the intrauterine environment using reliable and robust biomarkers of stress-related epigenetic reprogramming. We propose a conceptual multi-species multi-scale framework to discover early biomarkers of PS in the exposed infants. First, we review the experimental animal models and human cohort approaches for study of PS. We deliberately focus on two very different animal models: pregnant rat and sheep. The former lends itself to efficient studies of generational effects PS exerts on the offspring. The latter is *de facto* the only model of fetal physiology that allows fetal instrumentation and chronic monitoring with direct translational relevance to obstetrical practice. We conclude from this section of the review that a combination of such animal models and human cohorts into one systematic multi-species approach holds the key for a comprehensive and clinically relevant modeling of the PS effects. Second, we derive from these observations that such multi-species approach also needs to consider within one paradigm the multiple physiological scales of complexity which all are affected by the PS. Lastly, we review the mathematical instruments which are needed to tackle the complexity of data sets such studies would generate.

2. PS rewires the brain: a multi-species approach

Key question: what are the species used to model PS?

Various mammalian species have been used to document the multifarious effects of PS on brain development and function ranging from rats to human cohorts. In spite of the wealth of careful retrospective and prospective studies on PS, there are still several confounding factors that cannot be controlled in human studies such as genetic and environmental factors, as well as the social environment (Weinstock, 2001, 2008). For these reasons, studies in this field continue to rely on animal experiments, due mainly to their shorter life span and short breeding cycles, and because they offer the possibility to control the type, intensity, duration and timing of the stressor applied to the dam, the long term behavioral outcomes, as well as the interaction of the mother with her offspring in a controlled environment. The effects of PS on brain development in animal models have been mainly conducted in Sprague-Dawley, Wistar and Long-Evans rat strains, but also in Rhesus macaques, guinea pigs, sheep and mice (Arnsten, 2000; Braun et al., 2017; Kapoor and Matthews, 2008; Weinstock, 2008).

Most of the prenatal stress rodent models have been performed in rats and these studies have generated a large body of evidence towards the understanding of the mechanisms of developmental programming, especially in relation to the possibility of exploring the brain regions involved in neurogenesis and neuronal plasticity (Fatima et al., 2017).

Chronically instrumented non-anesthetized fetal sheep is an appropriate and uniquely suited animal model for studying the effects of in utero insults on fetal development, because of its recognized physiological and pathophysiological similarities to human fetal developmental profile and the unique ability to chronically instrument and monitor the fetus while manipulating the intrauterine environment.

Despite the diversity of findings, studies performed in human cohorts have shown the profound impact of PS on the cognitive development of the infants. However, research in humans has mainly been restricted to behavioural studies and to the macroscopic neuroanatomical analyses, while the genetic/epigenetic analysis has been limited to peripheral tissues due to the obvious inaccessibility of the brain (Braun et al., 2017).

The following will focus on the recent work in rodents, sheep and humans to provide an insight into some of the conceptual framework of mechanisms of perinatal and transgenerational programming.

1) ***Studies in pregnant rat models of PS***

Up to date, the most comprehensive behavioural, morphological and histological information comes from studies in rodent models (Boersma and Tamashiro, 2015; Weinstock, 2017). For many years, the outcomes were analysed in the first generation offspring only, but more recently a multigenerational paradigm has been established (Babenko et al., 2015).

a) *Single-generational studies*

In rodents, various PS protocols have been deployed ranging from saline injections, suspension, crowding, hypoxia, electric foot shock and placental insufficiency to unpredictable stress, noise and REM sleep deprivation (Huizink et al., 2004; Mastorci et al., 2009). A frequently used protocol is a modified version of Ward and Weisz model consisting of restraining the mothers during the last week of gestation (Ward and Weisz, 1984). This model induces a robust psychoneuroendocrine stress activation in the mothers (Mastorci et al., 2009). Abundant evidence demonstrates that exposure to different stressful events during the last week of pregnancy in rats interferes with the physiological progeny development inducing anomalies in neurogenesis and brain morphology that directly affect offspring behavior (Charil et al., 2010; Mastorci et al., 2009; Weinstock, 2001). PS induces low birth weight, learning and attention deficits, impaired adaptation to stressful conditions, vulnerability to anxiety and depressive-like behaviors, reduced social interaction and some of the characteristic neuronal changes of

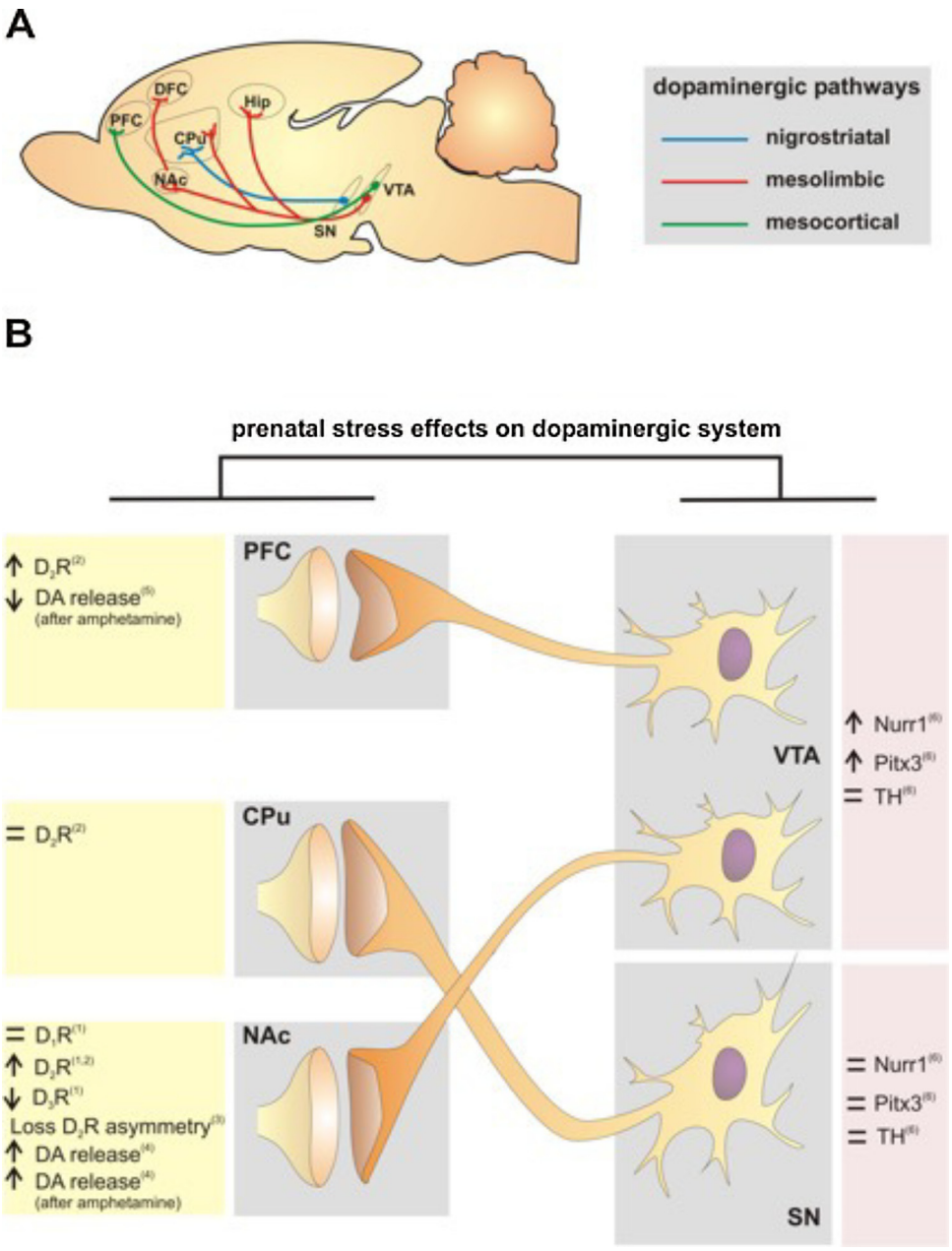


Fig. 1. A schematic representation of the dopaminergic pathways in the rat brain. Dopaminergic neurons can be divided into four groups: nigrostrial, mesolimbic, mesocortical, and tuberohypophyseal systems (see text for details). b Schematic representation of the alterations in the dopaminergic system in the adult rat brain of prenatally restrained stressed rat males. Note that impairments of the dopaminergic system are observed mainly in limbic areas of prenatally stressed rats. From Baier et al. (2015).

schizophrenia (Alonso et al., 1991; Darnaudery and Maccari, 2008; Huizink et al., 2004; Koenig et al., 2005; Weinstock, 2001, 2008; Yaka et al., 2007; Yang et al., 2006). At the morphological level, there is a reduced dendritic arborization and astroglial hypertrophy with synaptic loss suggesting a possible alteration of glutamate (Glu) metabolism. In fact, we found that metabotropic group III Glu receptors increase in cortical regions while *N*-methyl D-aspartate (NMDA) receptors increased both in cerebral cortex and basal ganglia of PS adult rats (Berger et al., 2002) and glutamate transporters were altered in frontal cortex and hippocampus of PS offspring (Adrover et al., 2015; Barros et al., 2006a). Furthermore, dopamine (DA) D2 receptors were found to increase in cortical areas and Nucleus Accumbens Core (NAcC) in PS adult male offspring (Berger et al., 2002). PS alters the asymmetry in D2 type receptors in the NAc, an area associated with impulsivity (Fig. 1). DA-related transcription factors were found to be disrupted in PS offspring and amphetamine or nicotine stimulation produces an increase in DA levels in NAc-Shell of adult PS male rats and PS produces a decreased DA release after amphetamine stimulation in PFC of adult offspring, suggesting that the cortical dopaminergic deficit might be triggering a NAc hyperfunction and an overall dopaminergic imbalance in the PS brain (Adrover et al., 2007; Barros et al., 2004, 2006b; Berger et al., 2002; Carboni et al., 2010; Katunar et al., 2010; Silvagni et al., 2008; Weaver et al., 2005). Adoption at birth reverses the receptor increase, reflecting the high vulnerability of the DA system to variations in both prenatal and postnatal environments (Barros et al., 2004). Together, these results show that the DA system development is sensitive to disruption by exposure to early stressors.

However, DA and Glu are not the only neurotransmitter pathways altered due to PS. We have also observed that α7-nicotinic acetylcholine receptor (α7nAChR) decreased in cortical areas, CA3 and the

dentate gyrus of the hippocampus in male adult PS offspring (Baier et al., 2015). Moreover, the major inhibitory neurotransmitter system, $GABA_A$/BDZ (Gamma aminobutyric acid/ Benzodiazepine) was found to be influenced by maternal care (Caldji et al., 2000) and we found that PS offspring showed a decrease in the number of BDZ receptors in the central amygdaloid nucleus and the dentate gyrus of the hippocampus, a result that correlates well with the increased anxiety state observed in PS offspring (Barros et al., 2006b).

Furthermore, enhanced propensity to self-administer drugs such as amphetamine and nicotine was observed in PS rats (reviewed in (Pastor et al., 2017)). PS induced delays in motor development and alterations in locomotor and exploratory activities that depend on the age and the sex of the offspring (Diaz et al., 1997; Henry et al., 1995). PS also affects sexual behavior of adult offspring and gonadal dysfunction. Studies report a reduction in the number of adult male copulations, decreased number of ejaculations, enhanced lordotic-like behaviors and increased male partner preference over receptive females (Gerardin et al., 2005; Kapoor and Matthews, 2011; Shono and Suita, 2003). Additionally, a persistent lack of tonic gonadotropin secretion and altered testosterone secretion profiles were shown (Gerardin et al., 2005; Rodriguez et al., 2007; Shono and Suita, 2003). Alterations in sexual morphological parameters, such as the anogenital distance length and the timing of testicular descent, were also found (Barros et al., 2004). Moreover, PS induces long-term imbalance of male sexual hormones concentrations in serum, advanced spermatogenesis development and age-dependent misbalance of alpha-receptor expression in prefrontal cortex and hippocampus (Pallares et al., 2013a,b).

Many studies have associated prenatal and perinatal early life adversity with changes in the global methylation status as well as at particular loci. For example, differential rearing (maternal versus surrogate-peer rearing) of rhesus macaques results in genome-wide differential methylation in both prefrontal cortex and T cells (Provencal et al., 2012). Variations in maternal care behavior modified the methylation pattern in a region of the glucocorticoid receptor Nr3c1 promoter responsible for controlling its hippocampal expression (Weaver et al., 2004). Similarly, in hypothalamic neurons, maternal separation was associated with arginine vasopressin gene hypomethylation (Murgatroyd et al., 2009), and a decreased DNA methylation of the corticotropin-releasing hormone (CRH) gene was related to gestational stress (Mueller and Bale, 2008). The expression of the gene *gpm6a* (which encodes membrane glycoprotein M6A participating in the establishment of neuronal morphology) is increased in the hippocampus of the PS rats' brains. The pattern of methylation in a CpG island of the first intron of the gene gpm6a was altered in rats subjected to PS (Monteleone et al., 2014). In mice, sex-specific changes were found in the levels of DNA methyltransferase (DNMT) 1 protein, the levels of histone H3 acetylation (AcH3) in the hippocampus, and serum corticosterone concentration. PS also induces spatial memory deficits and epigenetic changes in the hippocampus associated with gene repression and heterochromatin conformation (Benoit et al., 2015).

There is a consensus on the importance of the timing and the severity of the stressor during pregnancy which likely reflect the poorly understood interplay between the vulnerability windows of the developing fetus as a whole, the developing organ systems and the specific cell types on one hand and the stressor on the other hand (Weinstock, 2007). Male juvenile recovery of the reduced expression of mature oligodendrocytes and reactive astrocytes in the fetus was only observed in late gestation PS exposure as opposed to mid gestation (Bennett et al., 2016). Likewise, recovery of the fetus reduced circulating allopregnanolone concentrations was only observed in late gestation PS exposure in a model of guinea pig (Kapoor and Matthews, 2005). The effect of acute PS was studied during two critical phases of the guinea pig pregnancy: during the fetal brain growth spurt [gestational day 50–52 (PS50)] or during the period of rapid brain myelination [gestational day 60–62 (PS60)]. The adult PS50 male guinea pigs exhibited increased basal plasma cortisol levels. In contrast, PS60 male guinea pig offspring exhibited a higher plasma cortisol response to activation of the HPA axis. Moreover, PS50 male offspring exhibited a reduction in GR mRNA in the CA3 region of the hippocampus and increased POMC mRNA in the pituitary, consistent with the observed increase in basal HPA axis activity (Kapoor et al., 2008). Only PS60 females exhibited lower plasma estradiol levels, reduced ovary weight, and increased GR mRNA in the paraventricular nucleus (Kapoor and Matthews, 2008). PS60 offspring appeared to exhibit enhanced spatial learning, while PS50 male offspring exhibited impaired spatial learning (Kapoor et al., 2009). PS exposure of rats at mid-gestation increased offspring's perinatal mortality and the surviving animals showed memory and cognitive impairments when compared to late gestation PS exposure (Lordi et al., 2000).

Overall, these animal studies demonstrate the complex multi-scale effects of PS timing on perinatal and postnatal development within a single parent-offspring generation.

b) *Multi-generational studies*

The lifetime risk of mental illness is greater if an individual has family history of a similar condition. Therefore, most efforts during the past decades have focused on the identification of genetic associations, but the results were often met with disappointment, as the associations with genetic variations were weak. In the post-genomic era, the focus has shifted to identify associations between epigenetic regulators that can be modified by environmental factors, such as stress. Importantly, epigenetic marks are potentially heritable.

Key question: what are the differences between the single-generational and multi- or trans-generational PS?

Compared to single-generation PS, the multigenerational stress has somewhat different consequences: it facilitates adaptation to the recurrent maternal stress across generations, thus generating stress resilience. This causes new behavioral traits and better brain activity coherence. Based on the mismatch hypothesis, the multigenerational stress leads to better adaptation because the offspring is bred for a stressful environment and the stress is indeed occurring again when the daughters get pregnant. The transgenerational cohort faces the mismatch problem because they are bred for a stressful environment, but there is no more stress during pregnancy or any other time.

What are the key effects of multi- or trans-generational PS on neurodevelopment?

1. **PS elevates stress responses and the risk of mental illness**. PS (F1 generation) impedes developmental milestones in rats, thus desynchronizing brain development along with epigenetic signatures of human anxiety, depression, and adverse brain development (Zucchi et al., 2014). Interestingly, PS-induced anxiety-like and depression-like behaviours become most evident at the most vulnerable periods in life, early development and old age (Erickson et al., 2014).

2. **PS programs risk of anxiety and depression in future generations**. In a rat model of trans- and multigenerational experience, PS induces increased risk of gestational diabetes, preterm birth, and delayed brain development across generations. These manifestations are linked to microRNA (miRNA) and mRNA signatures of preterm birth (Yao et al., 2014) and mental illness, in particular anxiety and depression-like symptoms, and altered brain connectivity in adulthood (McCreary et al., 2016b). Interestingly, these studies revealed striking sex differences, with stressed females displaying partial stress resilience until the F3 generation, suggesting truly epigenetic inheritance.

3. **Stress-induced epigenetic and metabolic changes propagate across generations**. Some of the first studies that showed the propagation of epigenetic marks across generations via changes to gametes and the gestational uterine environment are the studies by Rachel Yehuda group (reviewed in (Bowers and Yehuda, 2016)). They showed that in both parents and offspring, Holocaust exposure had an effect on FKBP5 methylation, demonstrating the association of preconceptual parental trauma with epigenetic intergenerational alterations (Yehuda et al., 2016). Stress alters miRNA expression patterns in the brain (Babenko et al., 2012; Zheng et al., 2016) thus generating potentially

heritable biomarkers of disease. Numerous miRNA regulatory pathways have been identified in recent years, some of which are involved in signal transmission and neurodevelopment (Babenko et al., 2015; Dias et al., 2014), providing a mechanistic link to mental and cognitive disorders. Furthermore, altered epigenetic regulation of gene expression is also accompanied by altered metabolic footprints, which can be assessed in animals and humans using body hair, bio-fluids or solid tissues using NMR spectroscopy and inductively coupled plasma mass spectroscopy (Ambeskovic et al., 2013). Thus, altered epigenetic regulation of gene expression up-stream by PS is reflected in quantifiable metabolic end products down-stream which also may serve as predictive and diagnostic biomarkers (Ambeskovic et al., 2013; Kiss et al., 2016). These findings suggest that PS induces stable transgenerational specific epigenetic and metabolic alterations that can also be found in human disease.

miRNAs have become appreciated as a means for transgenerational epigenetic inheritance due to their small size, as they can translocate easily during meiosis and fertilization. miRNAs were suggested as robust biomarkers of common psychiatric and neurological disorders, and inflammatory responses (Huang et al., 2018; Lett et al., 2013; Metz et al., 2015; Srivastava et al., 2017). For example, rodent studies showed that ancestral stress generates miRNA signatures that can also be found in human psychiatric diseases and are associated with corresponding changes in the behavioural phenotype (Gapp et al., 2017; McCreary et al., 2016a; Zucchi et al., 2013). A recent series of studies in mice found that PS persistently alters miRNA expression leading to trans-generational behavioural and metabolic alterations in offspring (Gapp et al., 2017, 2014). In addition, miRNA biomarkers are able to predict the therapeutic response, as is the case for antidepressant treatment, and thus they serve as candidates for personalized medicine approaches (Labermaier et al., 2013).

Aside from miRNAs, major other epigenetic regulators have been identified. Due to the epigenetic mark erasure in the germ line cells, the chromatin remodelling mechanisms represent a more controversial way of transmitting environmental cues across generations. However, there are some reports indicating that certain genomic regions are not demethylated. Thus, they could retain the information to be transmitted to descendants (Lim and Brunet, 2013). Dias et al. have shown the transmission of odor aversion. In the sperm, the authors identified the hypomethylation in the Olfr151 gene that codes a known odor receptor (Dias and Ressler, 2014). In addition, histone methylation at particular loci in the sperm can be affected by paternal diet and has been associated to an altered cholesterol and lipid metabolism in the offspring (Carone et al., 2010).

In summary, trans-generational studies are uniquely suited to reveal mechanisms of trans-generational programming by inheritance of epigenetic, metabolomic and phenotypic traits. The multi-generational stress resembles human populations living in chronic stress conditions, e.g., several generations exposed to residential school, war or poverty (Laplante et al., 2016) (Santavirta et al., 2017).

We return to the PS studies in human cohorts in the following section of this review, but first we wish to discuss another animal model of PS from multi-scale multi-species perspective, the pregnant sheep.

2) ***Studies in pregnant sheep models of PS***

Fetal sheep and guinea pig (Iqbal et al., 2012) in particular have been used extensively for studies of effects of antenatal synthetic glucocorticoid (sGC) treatment on fetal brain development. Many studies showed detrimental acute and transgenerational effects on neurodevelopment and HPA axis responsiveness to stress (Anegroaie et al., 2016; Antonow-Schlorke et al., 2009; Iqbal et al., 2012; McCallum et al., 2008; Schwab et al., 2012, 2001). It is not clear whether the postnatal brain can fully compensate for these changes. Consequently, despite the acute benefits of the antenatal sGC treatment to the fetus during labour and in the early postnatal period, further studies are needed to delineate the long-term effects of repeated sGC courses on postnatal brain development. For such fetal/postnatal experimental paradigms, the guinea pig model has been instrumental, although it is possible to do similar work in larger mammals such as sheep or non-human primate. To the extent that sGCs represent a stress stimulus to the fetus and can be injected directly intravenously to the fetus, this experimental approach also represents a possible paradigm for mimicking human fetal stress exposure to maternal stress hormones without accounting for the interindividual and interspecies differences in the placental transfer dynamics. A pharmacological form of PS, antenatal GCs alter the set point of the HPA axis, which matures during late gestation. Taken together, as an iatrogenic stressor or a model for stress-induced fetal programming, sGC-driven studies in guinea pig and sheep have shown the potential of fetal stress exposure to alter organ development, in particular that of the brain (Moisiadis and Matthews, 2014a,b).

A more “human-like”, but also technically more complex experimental paradigm involves isolation of pregnant ewes because they are flock animals and experience such isolation as stress. Such an approach results in acute and chronic stress-induced adaptations and represents the most comprehensive animal experimental model of human fetal stress exposure (Rakers et al., 2013). Acute stress responses included the sympathetic and HPA axis activation with increases in heart rate and blood pressure, plasma cortisol and norepinephrine. Importantly, these changes were accompanied by a transient norepinephrine-mediated reduction of the uterine blood flow. These acute responses on the maternal side were reflected by a protracted increase of norepinephrine on the fetal side accompanied by a lactacidosis. Chronic maternal stress during the first and second trimesters may impede the placental catecholamine clearance, perhaps via the observed prolonged reduction of the uterine blood flow, thus elevating fetal catecholamine levels with hyperactive HPA axis and sympathetic nervous system revealed by heightened fetal responses to acute stress (Dreiling et al., 2017). Interestingly, unlike acute maternal stress, the chronic stress was accompanied by a fetal adaptation with regard to acid-base status and an improved oxygenation. The postnatal developmental sequelae of these adaptations remain to be elucidated.

Uniquely, pregnant sheep also allows chronic instrumentation and manipulation of the fetal vagus nerve (Frasch et al., 2018b). We return to the role of the vagus nerve and brain cholinergic signaling in the PS pathophysiology in the second part of this review.

Taken together, these results suggest that PS insults are critical in the development of biochemical responses and behavior in adults, and that maternal care is crucial both during pregnancy and in the first weeks of life (Fontein-Kuipers et al., 2014; Nolvi et al., 2016).

It has been postulated that several psychiatric disorders that manifest themselves in the adult human, such as schizophrenia, depression, anxiety and drug abuse, are imbalances of dopaminergic, glutamatergic and GABAergic systems as a consequence, among other reasons, of alterations in the early development of the corticostriatal pathway.

Rat and guinea pig models of gestational stress will provide clues to understanding the mechanisms by which a PS insult in early life contributes to the breakdown of the balance in neurotransmission and the formation of aberrant cortical connections, which would entail the establishment of abnormal cognitive behaviors. Meanwhile, pregnant sheep models enable direct fetal monitoring of the effects of PS and a more integrated study of complex physiological effects of PS on mother and the fetus (Frasch et al., 2018a).

From a multi-scale multi-species perspective, the biochemical, genomic and physiological biomarkers obtained in the above-reviewed preclinical models of PS can be tested in the human cohorts for their ability to predict altered developmental trajectories and health outcomes.

3) ***Studies in humans***

Key question: does PS exert lasting effects on the offspring’s development?

There is now a large consensus that different types of PS in pregnant women are associated with altered outcomes for the child.

The types of stress include maternal anxiety and depression, bereavement, daily hassles, bad relationship with the partner, and

exposure to acute man-made or natural disasters. Several independent retrospective and prospective studies (Glover, 2015b; Silveira and Manfro, 2015) have shown that PS is associated with lower birthweight and reduced gestational age (Wadhwa et al., 2011), a poorer performance on the Neonatal Behavioral Assessment Scale (Rieger et al., 2004), more difficult temperament (Davis et al., 2007; Werner et al., 2007), sleep problems (O'Connor et al., 2007), lower cognitive performance and increased fearfulness associated with higher maternal stress during pregnancy (Bergman et al., 2007).

A well-established cohort is based on the 1998 Quebec Ice Storm which follows the consequences of maternal stress induced by this natural disaster. By studying natural disasters, such as the Project Ice Storm, the impact of maternal objective and subjective distress on genetic and epigenetic biomarkers can be estimated (Cao-Lei et al., 2014). Project Ice Storm revealed correlation between exposure to prenatal stress and differential DNA methylation of 957 genes in 13 year old offspring (Cao-Lei et al., 2016a,b). The majority of the differentially methylated genes were related to immune function and metabolism. The methylation patterns seemed to mainly correspond to the degree of objective maternal stress rather than subjective stress reported by the mothers during pregnancy.

There are other human cohorts that allowed studies across the generations. In the Överkalix population in northern Sweden, the researchers found a relation between grandparent food availability and the grandchild's longevity. A food excess at ages 9–12 years of grandfathers correlated with short survival of grandsons. These effects might be triggered by methylation of epigenetic marks (Bygren et al., 2001). Famines during the first and second war (Germany, 1916–18) (Van den Berg and Pinger, 2014) and Amsterdam, 1944-45 (Roseboom et al., 2001) also showed that exposure to adverse environment during the early developmental stages changes the outcomes of the next generations.

Going deeper yet, several studies in human cohorts demonstrated that the child's developmental outcome depends on the *type, severity and timing* of the stress exposure during gestation. In relation to timing of exposure, natural disasters have been very useful to assess the effects of pregnant women's exposure to stress at different times of pregnancy on child development. If the PS exposure occurred in the first trimester, the changes were mainly in head circumference, cognitive development at two years of age, and subclinical autistic symptoms at six years of age (King et al., 2012). In the second trimester, the same study identified the effects on cognitive and language development at two years of age and on fingerprint asymmetry. If the PS was suffered in the third trimester, changes were related to motor development. Moreover, outcomes related to the onset of asthma-related phenotypes (Rosa et al., 2018), Leukocyte telomere length (Wang et al., 2017), cortisol increase (Yong Ping et al., 2015), ADHD (Zhu et al., 2015) and the risk of a small for gestational age (Khashan et al., 2014) were also related to the gestational week of the PS exposure.

In sum, there is large body of evidence for the complexity of PS effects on the individual's physiology and the heterogeneity in the stress responses. Because of the interplay between genes and environment, finding PS biomarkers requires a multi-species approach. Rodent models serve well to obtain single and transgenerational markers, sheep fetuses resemble closer human physiology and allow in utero monitoring while the human cohorts allow the analysis of the reliability of the putative biomarkers.

3. A multi-scale approach to discovery of biomarkers and treatment strategies

Key question: how can we weave together the multiple models of PS into a cohesive framework that has a high potential for discovery of early biomarkers relevant for detecting and treating the PS effects in humans?

Epigenetic markers may be correlated with maternal stress, depression and anxiety and with infants' cognitive development thus serving as novel biomarkers of PS. The animal model-centered review of the PS effects points to the impact of the PS on multiple physiological scales, from molecular level to complex system's level patterns. This dictates that *to derive meaningful, translational biomarkers from preclinical and clinical studies, PS effects should be studied on those molecular and integrative levels in a unified multi-scale paradigm.* Such unification can be achieved when multiple pertinent animal models and human cohorts studied are designed in concert, rather than as separate studies.

In following, we review the physiological scales relevant to gauging the PS effects comprehensively. We propose that such approach will yield clinically relevant PS biomarkers. Aside of biomarkers discovery, studying all physiological scales combined holds the potential to provide insights into therapeutic interventions to recover the PS brain phenotype. Such multi-scale paradigm requires novel mathematical methods of pattern discovery and integration. As we conclude below, rapid developments in machine learning hold the key to this methodology (Marschik et al., 2017).

1) ***PS influences brain development epigenetically***

Key questions: what are the epigenetic mechanisms mediating the PS effects and how can such mechanisms be gauged as biomarkers?

Studies on single, multi- and transgenerational stress inheritance mechanisms have been conducted mostly using pregnant rat model of inescapable stress (Monteleone et al., 2014; Yao et al., 2014). Other studies (reviewed in (Blaze and Roth, 2015; Ho and Burggren, 2010)) used maternal separation (Pusalkar et al., 2016) or alterations in maternal behavior (Weaver et al., 2004) or diet (Berardino et al., 2017) as early-life stressors and found changes in DNA methylation, histone modifications and microRNA expression.

We propose that PS may result in patterns of co-variation between DNA methylation and levels of microRNA between brain, blood and saliva in rodent and sheep models of PS. This would serve as a model to validate saliva as the clinically easily accessible peripheral fluid serving as a biomarker of PS exposure and to correlate methylation levels with behavioral outcomes and stress responsiveness.

a) ***PS inheritance via DNA methylation***

Epigenetic changes can persistently alter gene transcription affecting physiology and behavior and are thought to underlie these long-term effects of PS (Caldji et al., 2011; Mulligan et al., 2012; Weaver et al., 2004). Increased HPA stress reactivity in the offspring of low maternal care rats is associated with higher DNA methylation at the promoter of NR3C1 (which encodes GR) (Francis et al., 1999; Liu et al., 1997; Weaver et al., 2004). More recently, Braithwaite et al, (2015) reported that maternal prenatal depressive symptoms significantly predicted increased NR3C1 1F DNA methylation in buccal cells of male infants (Braithwaite et al., 2015). In mice, levels of both OGT (O-linked-N-acetylglucosamine (O-GlcNAc) transferase) and its biochemical mark, O-GlcNAcylation, were significantly lower in males and further reduced by prenatal stress (Howerton et al., 2013). In humans, differential methylation is associated with prenatal exposure to maternal depression (O'Connor et al., 2003; Teh et al., 2014), PS and birth weight (Filiberto et al., 2011; Mulligan et al., 2012; Vidal et al., 2014).

Preconceptual or intra-gestational stress may result in increased cerebral and placental expressions of the *CRH* gene stimulating fetal cortisol and adrenocorticotropic hormone (ACTH) and signaling premature maturation of fetal tissue (Horan et al., 2000; Moog et al., 2016). Repeated stress exposure may dysregulate HPA axis and increase CRH and cortisol levels which in turn sensitizes women to stress experienced during pregnancy. Pre-gestational stress increased the expression of CRH type 1 (CRH1) messenger RNA in the brains of mothers and offspring, suggesting an epigenetic route of transgenerational transmission (Zaidan et al., 2013). Pre-gestational stress to female rats two weeks prior to mating resulted in reduced anxiety, enhanced fear learning, and improved adaptive learning for second generation offspring (Zaidan and Gaisler-Salomon, 2015). Levels of the stress hormone corticosterone (an indicator of HPA axis functioning) were altered across the three generations in a sex-dependent manner (Zaidan and Gaisler-Salomon, 2015). Maternal stress during the third, but not

the second, week of gestation in rats was associated with alterations in stress reactivity behaviors and prolonged elevations in glucocorticoid levels among adult male offspring (Koenig et al., 2005). Heightened anxiety was associated with greater CRH mRNA gene expression in the amygdala, and attenuated stress responses were associated with greater glucocorticoid mRNA expression in the hippocampus and impaired feedback to the HPA axis (Grundwald and Brunton, 2015). The offspring of rats exposed to either a daily injection of corticosterone or prenatal stress during the third week of gestation all displayed decreased GR protein levels in the medial prefrontal cortex, hippocampus, and hypothalamus, as compared to controls (Bingham et al., 2013). Similarly to the pre-gestational dysregulatory effects of stress on responsiveness to stress during pregnancy, increased CRH levels during stressful pregnancy act on the CRH receptor 1 (CRH-R1) to mediate increased maternal vulnerability after delivery with a suppressed HPA axis increasing the risk for postpartum depression (Engineer et al., 2013; Meltzer-Brody et al., 2011). Overall, changes in maternal and offspring HPA axis function are modified via stress-induced changes to CRH expression (Zaidan et al., 2013) and often accompanied by behavioral effects.

Most studies have been focused on the effects of PS on the HPA axis at the expense of other physiological systems affected by PS, such as the autonomic nervous system (ANS). There is however a growing recognition that psychosocial stress in pregnancy may program the fetus through mechanisms other than altering maternal cortisol levels (Bleker et al., 2017). No association between maternal cortisol and infant DNA methylation was found in a recent study of the effects of maternal depression on offspring suggesting that such effects may not be mediated directly by glucocorticoids; instead, sympathetic nervous system activity, a component of the fetal ANS, may be the mediating pathway (Braithwaite et al., 2015).

The Table 1 *attempts an overview of the key genes that have been implicated in the stress response in relation to the HPA axis and to the ANS. Further studies are needed to delineate temporal and tissue-specific expression profiles of these genes, their epigenetic regulation and interactions with the environmental exposures that can modify their activity such as nutrition. Such studies may open avenues to therapeutic interventions to help reduce long-term impact of PS on the offspring* (Togher et al., 2014).

b) *PS inheritance via miRNA signaling*

Experimental paradigms of PS in animal or human cohorts allow for blood sampling and extraction of T cells and PBMCs to analyze microRNA profiles from cellular RNA. These microRNA patterns can be compared to those measured in animal studies yielding data from the relevant brain structures such as prefrontal cortex and dentate gyrus of the hippocampus. PS modified the expression of several microRNAs in the hippocampus and prefrontal cortex of prepubertal and adult rat offspring, microRNA-133b being altered most significantly (Monteleone et al., 2014).

In animal studies, it is important to account for microRNA spatial expression variation and co-localization. microRNA targets of interest are those related to HPA axis function such as GR, MR, 11ß-HSD type 1 and type 2, FKBP5, STAT5B and MHC II, Hsp70 and Hsp90, and to neuronal plasticity and psychopathologies, such as cortical BDNF and glial cell-derived neurotrophic factor (GDNF). Previous analyses have shown that differentially regulated microRNAs included miR-34 (anxiety), and miR-132, 142-5p, 146a, 181b, 486-5p, 650 (depression), miR-124 (regulates GR expression) (Babenko et al., 2015) and the miR-200 family.

2) ***PS on the G x E interface: genetic variance – epigenetic interactions***

Any attempt to analyse variations across the epigenome should include a genotype study since genetic variations can moderate the relationship between environmental factors and the epigenetic status.

In this context, the acetylcholinesterase gene (AChE) is known to undergo long-lasting transcriptional and alternative splicing changes after stress (Sailaja et al., 2012). In this study, Sailaja et al. identified histone deacetylase4 (HDAC4) as the mediator of the stress-inducible changes in AchE promoter in mice hippocampus. In a multiethnic cohort study of mothers and infants delivered at Mount Sinai Hospital in New York City, Berkowitz et al. showed that maternal levels of the organophosphate pesticide chlorpyrifos coupled with low maternal paraoxonase (PON1) activity were associated with a significant but small reduction in the infant head circumference implying that chlorpyrifos may have a detrimental effect on fetal neurodevelopment among mothers who exhibit low PON1 activity (Berkowitz et al., 2004). In fact, Browne et al. found that specific paraoxonase genotypes were associated with exposure-related changes in blood enzyme activities and abnormal EEG patterns (Browne et al., 2006). Thus, gene-

Table 1
Activity of genes involved in HPA axis and ANS functioning and altered by PS.

	Genes	Function	Role in PS
HPA axis	Exon 1_7 of *nr3c1*	Encodes the GR, which can function both as a transcription factor that binds to glucocorticoid response elements (GRE sites) in the promoters of glucocorticoid responsive genes to activate their transcription and as a regulator of other transcription factors.	Associated to a lower GR expression in hippocampus and with an exacerbated response to stress (Hackman et al., 2010; Kertes et al., 2016; Murgatroyd et al., 2009; Weaver et al., 2004).
	Intron 1 of *FKBP5*	Contains GRE sites. The protein FKBP51 belongs to the immunophilin protein family playing a role in immune-regulation and basic cellular processes involving protein folding and trafficking. Functions as a co-chaperone that interacts with the GR protein.	Chronically-administered glucocorticoids reduce methylation at *FKBP5* locus (Lee et al., 2010). In humans, war trauma modified methylation of this gene (Kertes et al., 2016).
	HSD11B2	Encodes the enzyme corticosteroid 11-beta-dehydrogenase, a microsomal enzyme complex responsible for the interconversion of cortisol and cortisone. Essential regulator of the cortisol flux from the mother to the fetus.	Placental expression of this gene controls the degree of fetal exposure to maternal glucocorticoids. This process is epigenetically regulated and modulated by PS via DNA methylation (Palma-Gudiel et al., 2015; Togher et al., 2014) which may reflect PS-induced alterations in the fetal brain (Jensen Pena et al., 2012).
	CRH	Major HPA regulator.	Changes in *CRH* methylation have been associated with chronic stress in animal models (Mueller and Bale, 2008) and in humans (Kertes et al., 2016).
ANS	*GNAS1*	Encodes the alpha-subunit of the Gs protein (Gsa), which binds GTP and stimulates adenylyl cyclase.	This GNAS1 subunit has been associated with ANS (Yasuda et al., 2004) and, more recently, with prenatal maternal stress.(Vangeel et al., 2015).
	ELP1/ IKBKAP	Encodes a scaffold protein and a regulator for three different kinases involved in pro-inflammatory signaling. This protein can bind NF-kappa-B-inducing kinase (NIK) and IKKs through separate domains and assemble them into an active kinase complex.	Mutations in this gene have been associated with familial dysautonomia (Jackson et al., 2014).
	IGF2	Member of the insulin growth factor family involved in fetal development and growth, epigenetically regulated on H19 promoter.(St-Pierre et al., 2012; Williams-Wyss et al., 2014)	An association was reported between DNA methylation in one of the *IGF2* differentially methylated regions (DMR0) and pregnancy-related anxiety (Vangeel et al., 2015).

environment interactions involving the ACHE/PON1 locus may be causally involved in determining the physiological response to organophosphate pesticides exposure.

The so called gene and environment interactions (G x E) and their influence on the interindividual variation in the methylome at birth were clearly demonstrated by Teh et al. who found that the best explanation for 75% of variably methylated regions (VMRs) was the interaction of the genotype with different *in utero* environments, including maternal smoking, maternal depression, maternal BMI, infant birth weight, gestational age, and birth order (Teh et al., 2014). Lin et al. provided further evidence that developmental pathways to adiposity begin before birth and are influenced by the environmental, genetic and epigenetic factors (Lin et al., 2017).

Since the influence of prenatal environment on the subsequent risk of illness is intensely studied, *the results mentioned above underscore the importance of assessing the degree to which environmental influences are moderated by the genotype*.

Various animal models are characterized by variable G x E interactions due to their individual degree of genetic similarity, for example in rodents compared to the larger mammalian organisms used in PS studies. This should be considered when translating findings from preclinical studies into clinical realm, on one hand. On the other hand however, the iterative multi-species multi-scale framework we propose here should aid somewhat to alleviate the biomarker bias coming from the one-way and separately conceived translational animal-to-human paradigms.

3) ***PS and metabolome***

Even mild maternal stress induces epigenetic and metabolomic alterations across four subsequent generations of rats. Notably, many of the epigenetic and metabolic signatures altered by transgenerational stress in this rat model have been also identified as markers of mental illness in humans (Zucchi et al., 2014).

Future studies can expand these findings with deep sequencing and ^{1}H nuclear magnetic resonance (NMR) spectroscopy to identify DNA methylation and microRNA signatures linked to impaired mental health using blood across species such as human, fetal sheep and rat cohorts and *link epigenetic and metabolomic profiles to endocrine markers of elevated stress response and adverse mental health outcomes*. The multi-species approach would allow to search for similarities between metabolomic patterns to identify possibly predictive epigenetic and metabolomic signatures of PS and transgenerational inheritance that are phylogenetically preserved. Corresponding epigenetic, genetic, behavioral and pathophysiological data can then be correlated with metabolomic outcomes. Determining metabolic linkages to brain development, mental health and wellness outcomes throughout the life-span and across generations has the potential to revolutionize the future of health care by transforming the current trends of curative care to personalized and preventive medicine.

We speculate that prenatal and transgenerational stress, through altered epigenetic regulation, programs the maternal, infant and child stress response and lifetime mental health trajectories.

We predict that stress response and mental health status will be associated with distinct metabolic signatures in clinically accessible tissues such as saliva or placenta.

4) ***PS and microbiome***

A surprising recent result that may help understand PS and perhaps even allow monitoring and treating it involved the gut microbiome.

The discovery of the placental microbiome re-fueled the debate whether fetus is exposed to and interacts with bacteria during development (Aagaard et al., 2014; Chu et al., 2016). It remains controversial whether the fetal compartment is colonized (Boersma and Tamashiro, 2015), but the notion continues to attract attention (Van den Bergh et al., 2017; Walker et al., 2017), because such physiological mechanism would have profound impact on brain-gut communication, for example via the vagus nerve (Liu et al., 2015) hence influencing the fetal brain development (Garzoni et al., 2013; Leclercq et al., 2017). Gut microbiota are essential to human health, playing a major role in the bidirectional communication between gut and brain (Borre et al., 2014; Haberman et al., 2014). The significance and influence of the fetal intestinal microbiome on stress responses, epigenetic modifications and brain development remain to be explored. Interactions between the microbial community and the developing brain likely contribute to pathological brain development after birth (Borre et al., 2014; Haberman et al., 2014).

Future studies will test PS effects on microbiomes of fetal gut and placenta in animal studies and in human placenta (clinical cohorts) to derive predictive biomarkers of PS. Conversely, maternal nutrition and lactation may be considered as therapeutic avenues to modify the effects of PS on fetal development via modulation of maternal-fetal microbiota transmission which, in turn, affect fetal programming due to PS (Chu et al., 2016).

5) ***PS and ANS***

Most PS-induced alterations have been described for hippocampal and prefrontal cortex neurons (Fujioka et al., 2006; Negron-Oyarzo et al., 2015). However, changes in the morphology and the connectivity of the autonomic nervous system (ANS) neurons due to PS have been poorly studied. Like the cortical neurons, those from the ANS may also be affected during PS exposure. In the guinea pig, it has been observed that enteric neurons (i.e., peripheral ANS neurons) respond to CRH (Liu et al., 2005). Patients suffering from panic disorder provide a clinical model of stress. These patients show changes in the sympathetic nervous system also observed in patients with essential hypertension. A reduced neuronal noradrenaline reuptake is present in both disorders and epigenetic changes mediate them (Esler et al., 2008).

During pregnancy, two lines of investigations have indicated a role of the ANS in mediation of stress effects on fetal physiology and development.

First, maternal corticosteroid administration during pregnancy - frequently used for fetal lung maturation in cases of threatening preterm delivery and an iatrogenically administered pharmacological stressor - has shown to affect autonomic balance *in utero* (Dawes et al., 1994; Derks et al., 1995; Mulder et al., 1997; Senat et al., 1998). This effect is transient, but repeated fetal administration of betamethasone alters nervous system maturation.

Second, the vagus nerve influences brain function and body metabolism in a pleiotropic manner (Pavlov and Tracey, 2012, 2015). A new field of bioelectronic medicine is emerging. It aims to devise therapeutic approaches using vagus nerve stimulation (VNS) to modify the endogenous salutory signaling of the vagus nerve (Borovikova et al., 2000; Kwan et al., 2016; Pavlov and Tracey, 2017). VNS reduced sympathetic tone, stress-induced anxiety behaviors and depression symptoms in animal models and in clinical studies (Caliskan and Albrecht, 2013; Clancy et al., 2014; George et al., 2008; Liu et al., 2013; O'Keane et al., 2005; Pena et al., 2014; Ylikoski et al., 2017). VNS is thought to facilitate tonic inhibition of the basolateral amygdala by the infralimbic region of the medial prefrontal cortex, which results in reduced fear response (Caliskan and Albrecht, 2013). VNS increases CRH expression in hypothalamus (Hosoi et al., 2000) and CRH-R1 agonism increases vagal modulation of heart rate variability (HRV) (Farrokhi et al., 2007; Porges, 1995, 2009). This reciprocal CRH - vagus nerve circuitry provides an important diagnostic and therapeutic link between stress and the ANS.

Notably, novel non-invasive methods of VNS are being developed which will not require surgical cervical VNS implants, have minimal to no side effects, and are low-cost (Clancy et al., 2014; Frangos et al., 2015; Liu et al., 2013; Ylikoski et al., 2017). It is now possible to conceive of VNS treatment of neonates. Of course, the optimal duration of such treatment and its long-term effects of such treatment will have to be explored as usual with new treatment approaches. There is reason for optimism considering the track record of some 100,000 patients treated with implanted VNS devices over 25 years and their relatively low side-effect profile (Revesz et al., 2016). An alternative to VNS or a complementary modality of sensory enrichment and reduction of stress effects could be the Kangaroo care (Conde-Agudelo and Diaz-Rossello,

2016; Head, 2014; Mooney-Leber and Brummelte, 2017; Pineda et al., 2017).

Together, there is strong evidence that vagus nerve activity is a key player in PS-induced brain programming, can be monitored using innovative fetal heart rate (FHR) analysis techniques (reviewed in detail below) and used as endogenous homeostatic mechanism to potentially recover the PS induced phenotype early postnatally. This offers another pillar of interventions, complementary to the neurobehavioural strategies such as enrichment mentioned in the introduction (Meaney et al., 1988;Wallen et al., 1999). These treatment possibilities invoke the need for continuous non-invasive assessment of the effects of such ANS manipulation. We discuss below how this can be accomplished with heart rate monitoring.

Fetal ANS function can be studied longitudinally using FHR analyses to measure biomarkers of PS-induced epigenetic reprogramming in human fetuses. Mothers and fetuses identified as having been "stressed" and controls can be monitored with abdominal non-invasive maternal and fetal electrocardiography (ECG) (fECG; mECG) for ANS assessment. This approach also permits quantification and correlation of ANS and behavioral data to the epigenetic biomarkers from salivary DNA obtained from the neonates and young infants.

Advanced FHR monitoring techniques such as phase-rectified signal averaging (PRSA) or multidimensional FHR analysis are sensitive to detecting an impairment of fetal ANS (Casati et al., 2014; Frasch et al., 2014; Graatsma et al., 2012; Huhn et al., 2011; Li et al., 2015a; Lobmaier et al., 2012; Rivolta et al., 2014; Stampalija et al., 2015). Future studies will test their ability to identify fetuses affected by PS.

Advanced analysis of FHR patterns specifically assessing changes in the autonomic regulation of FHR may identify fetus at increased risk for pathological fetal programming. Early signs of hypoxemia are found in changes in the autonomic regulation of the FHR. This can be assessed by the relatively new PRSA method measured by cardiotocography (CTG) or ECG (Bauer et al., 2006; Kantelhardt et al., 2007) in fetuses (Stampalija et al., 2016).

a) *Phase-rectified signal averaging method*

Initially, PRSA has been described in adult cardiology for prediction of mortality after myocardial infarction and has been found to be superior to other methods (Bauer et al., 2006). PRSA can eliminate signal artifacts and noise and extract areas of interest. In contrast to other methods of analysis of FHR variability, PRSA permits the detection of quasi-periodicities in non-stationary data. PRSA has been successfully applied in fetal medicine, despite the challenges of a non-stationary signal, with more disturbance in the signal than in the adult after a myocardial infarction. The novel parameter referred to as cardiac average acceleration and deceleration capacity is more specific than the conventional FHR analyses (e.g. computerized CTG and short term variation) in identifying intrauterine growth restriction (IUGR) antepartum (Graatsma et al., 2012; Huhn et al., 2011; Lobmaier et al., 2012, 2016) and strongly correlates with acid-base biomarkers during acute hypoxic stress in humans during labour (Georgieva et al., 2014) and the fetal sheep model (Rivolta et al., 2014). Even more interestingly, it has been shown that IUGR fetuses with brain sparing (fetal adaptive mechanism to chronic hypoxemia) have a lower acceleration and deceleration capacities than growth restricted foetuses without brain sparing (Stampalija et al., 2016). This intimate inter-relation between brain perfusion and FHR is thought to be mediated via ANS (aortic chemoreceptors and carotid baro- and chemoreceptors). Newer data also show an activation of ANS in fetuses affected by maternal gestational diabetes which could not be seen using conventional techniques (Lobmaier et al., 2017).

To evaluate the ANS influence on FHR the beat-to-beat information (R-R intervals) should be analysed. As we discuss below, this is distinct from the ultrasound-based FHR monitoring which lacks the precision of beat-to-beat variability needed to capture the brain-body communication (Durosier et al., 2014; Frasch, 2018; Gold et al., 2017; Li et al., 2015b). The new generation of the trans-abdominal fECG monitors (such as Monica AN24, Monica Healthcare, Nottingham, UK) allow for a completely non-invasive and passive recording of fetal and maternal ECG: it only records electrophysiological signals from the women's abdomen without hampering mobility or other diagnostic procedures (Stampalija et al., 2012).

This high precision fECG signal can be then used for a more sophisticated analysis of FHR such as PRSA or the multidimensional FHR analysis.

b) *Maternal-fetal heart rate entrainment and multidimensional fetal FHR variability analysis in fetal sheep and human cohorts*

Although the evidence of maternal-fetal heart rate entrainment, also referred to as synchronization, has been demonstrated (Van Leeuwen et al., 2009), its clinical potential as easily obtainable diagnostic or prognostic tool has remained untapped. We propose that both approaches should be explored both in large animal models and clinical studies to test their potential to predict maternal and fetal stress.

Complex signals bioinformatics approaches have been recently developed (Herry et al., 2016) that will allow examination of the putative correlations between the measures derived from all heart rate analyses techniques and epigenetic markers, based on the assumption that PS imprints both phenotypic modalities permitting a mutual inference.

HRV analysis can be performed via a series of automated algorithms that process a waveform recording into a comprehensive multivariate characterization of its degree of variability and complexity (See for example, the Continuous Individualized Multiorgan Variability Analysis (CIMVA) software engine, Fig. 2) (Seely and Newman, 2016). First, individual heartbeats are identified from the ECG waveform, using commonly used QRS delineation algorithms a time series of R-peak to R-peak time intervals (RRI) is formed. A thorough automated assessment is performed on the quality of the ECG signal and RRI time series. Movement artefacts, noise, disconnections and saturations are identified on the ECG waveform. A beat-by-beat signal quality index can be derived, using continuity and morphology analyses. In addition, the RRI time series is filtered to exclude or correct non-sinus beats and non-physiologically plausible data. The signal complexity and degree of variability are then assessed using the cleaned RRI time series.

FHR variability monitoring requires tracking HRV over time and a moving window analysis is typically employed, whereby a window of fixed duration (or fixed number of RR intervals) is shifted in time across the entire duration of the RRI time series. A comprehensive set of linear and nonlinear variability metrics are calculated within each window, as each technique provides a unique perspective on the data and no single method can provide a complete characterization of the biologic signals. Rather, a combination of multiple techniques stands to deliver the most complete evaluation (Table 2; for detailed description of the HRV measures see Table 3) (Bravi et al., 2011; Goldberger et al., 2002). Variability metrics include measures characterizing the statistical properties (e.g. standard deviation, RMSSD), the informational complexity (e.g. entropy measures), the pattern of variations across time scales (e.g. fractal measures, power law exponents) or the energy contained in the signal (e.g. spectral measures). Only high quality variability estimates are used in subsequent modelling. The output of the FHR variability analysis is a multivariate representation of variability tracked over time, where the temporal relation between subsets of fetal HRV measures can help characterize the fetal innate immune system's response to endotoxin and monitor fetal inflammatory response. For example, in a fetal sheep model of inflammation Durosier et al. (2015)) calculated a large set of fetal HRV measures to track variability changes and the impact of LPS injection and resulting inflammation over time. Using population-based Principal Component Analysis (PCA) derived from LPS-injected animals, animal-specific fetal HRV temporal profiles were created, which tracked pro-inflammatory cytokine IL-6 profiles (Fig. 3A).

In the fetal sheep model, FHR variability reflects maturation and activation of the parasympathetic branch of the ANS involved in sensing and control of fetal acidemia, hypoxia and inflammation (Durosier et al., 2013; Frasch et al., 2009, 2007). In human cohorts and in the fetal sheep model of human labor and fetal inflammation,

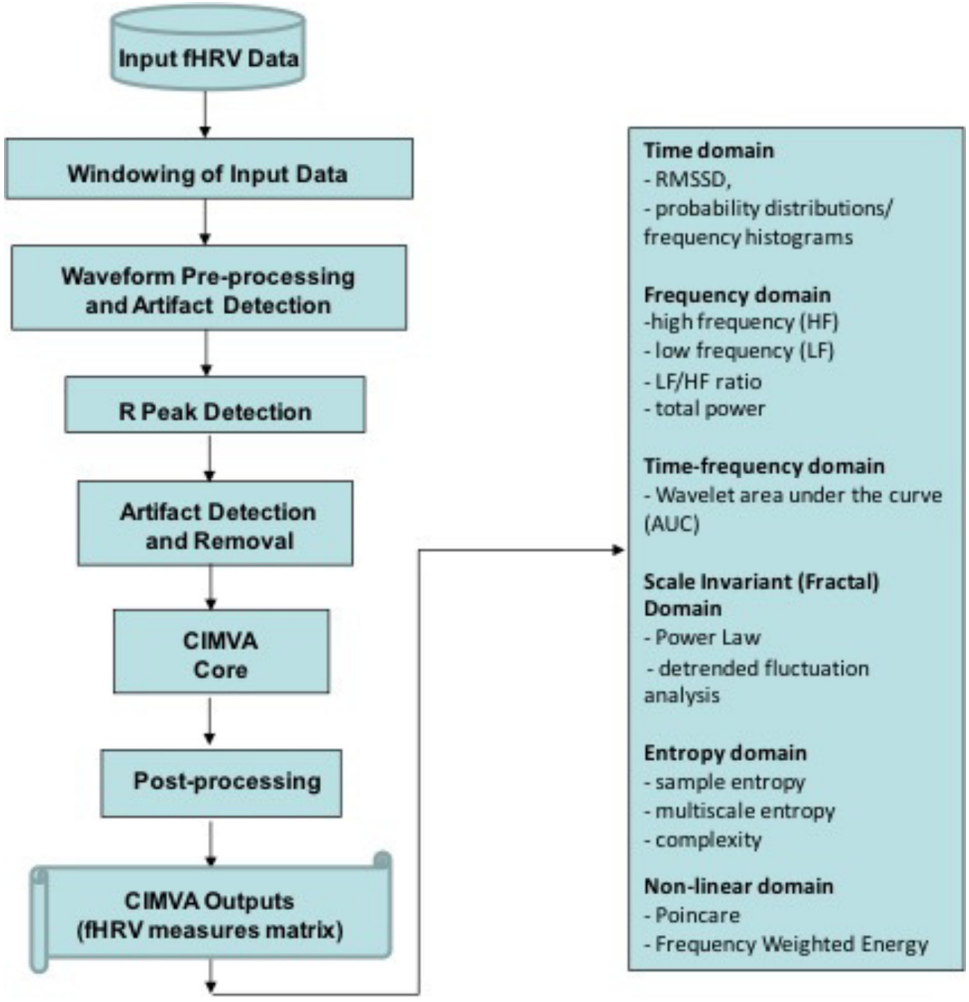


Fig. 2. Analytical flow for the derivation of a heart rate variability time series.

multidimensional FHR variability analysis can predict clinical outcomes after birth (Durosier et al., 2013; Liu et al., 1997). The teams of Hoyer, Schneider and van Leeuwen have demonstrated in human fetal magnetocardiogram (fMCG) studies of fetal HRV its potential to serve as an index of fetal brain development in health and disease, with particular focus on IUGR (Hoyer et al., 2014, 2012; Hoyer et al., 2015, 2013). While application of fMCG is currently limited to few specialized centers, these studies along with others reviewed here highlight the unique strength of high precision MCG or ECG to capture beat-to-beat fluctuations reflecting brain-body communication.

Interestingly, a closer look at the underlying structure of the "HRV inflammatory index" shown in Fig. 3A revealed a complex structure of various, complementary HRV measures behaving in concert in response to LPS (Fig. 3B). This study highlighted the potential of HRV to capture stimulus-specific brain-body communication suggesting that conceptually similar behaviour of HRV can be observed in response to acute or chronic stress. Indeed, in elephants, a highly complex social species with brains similar to humans, HRV-based techniques have been suggested to distinguish stressed versus non-stressed animals (Vezina-Audette et al., 2016).

From translational perspectives it should be stressed that to build such predictive FHR acquisition systems, certain types of FHR monitors are required, such as the AN24 monitor. Such monitors have the advantage over traditional ultrasound now used for FHR monitoring in that they sample FHR at a frequency high enough (900 Hz) to enable detection of the more subtle fluctuations of FHR variability which reflect integrative pathophysiological

Table 2
Description of heart rate variability domains.[a]

Domain	Features
Statistical	The statistical domain consists of statistical measures (mean, standard deviation, Gaussian, and so on) describing the data distribution. It assumes the data originates from a stochastic process.
Geometric	The geometric domain describes the properties related to the shape of the dataset in space. This includes, in a deterministic system, grid counting, heart rate turbulence, spatial filling index, and Poincaré and recurrence plots.
Energetic	The energetic domain describes the features related to the energy or the power of the data, such as frequency, periodicity, and irreversibility in time.
Informational	The informational domain describes the degree of complexity and irregularity in the elements of a time series, such as distance from periodicity or from a reference model. It includes various measures of entropy (compression, fuzzy, multiscale, and so on).
Invariant	The invariant domain describes the properties of a system that demonstrate fractality or other attributes that do not change over either space or time. Included are scaling exponents, fluctuation analysis, and multifractal exponents.

[a] Domains suggested for continuous individualized multiorgan variability analysis (CIMVA platform). Reproduced with permission from Durosier et al., 2015.

Table 3
Measures included in each domain of fetal heart rate variability for continuous individualized multiorgan variability analysis.

Domain	Fetal heart rate variability measure
Statistical	Coefficient of variation (based on intervals)
	Form factor
	Interquartile range
	Kurtosis
	Lee parameter
	Mean value
	Mean rate
	Mean of the differences
	Root mean square of successive differences of R-R intervals
	Skewness
	Standard deviation
	Standard deviation of the differences
	Symbolic dynamics: modified conditional entropy, non-uniform case
	Symbolic dynamics: modified conditional entropy, uniform case
	Symbolic dynamics: forbidden words, non-uniform case
	Symbolic dynamics: forbidden words, uniform case
	Symbolic dynamics: Shannon entropy, non-uniform case
	Symbolic dynamics: Shannon entropy, uniform case
	Symbolic dynamics: percentage of 0 variations sequences, non-uniform case
	Symbolic dynamics: percentage of 0 variations sequences, uniform case
	Symbolic dynamics: percentage of 1 variations sequences, non-uniform case
	Symbolic dynamics: percentage of 1 variations sequences, uniform case
	Symbolic dynamics: percentage of 2 variations sequences, non-uniform case
	Symbolic dynamics: percentage of 2 variations sequences, uniform case
Geometric	Dynamic moment of the second order
	Dynamical moment of the third order along the principal bisector
	Dynamical moment of the third order along the secondary bisector
	Dynamical moment of the third order along the x-axis
	Dynamical moment of the third order along the y-axis
	Finite growth rates
	Grid transformation feature: grid count
	Poincaré plot SD1
	Poincaré plot SD2
	Poincaré plot cardiac sympathetic index
	Poincaré plot cardiac vagal index
	Recurrence quantification analysis: average diagonal line
	Recurrence quantification analysis: maximum diagonal line
	Recurrence quantification analysis: maximum vertical line
	Recurrence quantification analysis: determinism/recurrences
	Recurrence quantification analysis: percentage of determinism
	Recurrence quantification analysis: percentage of laminarity
	Recurrence quantification analysis: percentage of recurrences
	Recurrence quantification analysis: Shannon entropy of the diagonals
	Recurrence quantification analysis: Shannon entropy of the vertical lines
	Recurrence quantification analysis: trapping time
Energetic	Low frequency/high frequency ratio
	Low frequency (LF) power*
	High frequency (HF) power**
	Hjorth parameters: activity
	Hjorth parameters: complexity
	Hjorth parameters: mobility
	Multifractal spectrum cumulant of the first order
	Multifractal spectrum cumulant of the second order
	Multifractal spectrum cumulant of the third order
	Multiscale time irreversibility asymmetry index
	Plotkin and Swamy energy operator: average energy
	Teager energy operator: average energy
	Very low frequency power***
	Wavelet area under the curve
Informational	Allan factor distance from a Poisson distribution
	Fano factor distance from a Poisson distribution
	Fuzzy entropy
	Grid transformation feature: AND similarity index
	Grid transformation feature: time delay similarity index
	Grid transformation feature: weighted similarity index
	Index of variability distance from a Poisson distribution
	Kullback-Leibler permutation entropy
	Multiscale entropy
	Predictive feature: error from an autoregressive model
	Sample entropy
	Shannon entropy
	Similarity index of the distributions
Invariant	Correlation dimension global exponent
	Detrended fluctuation analysis: a1
	Detrended fluctuation analysis: a2
	Detrended fluctuation analysis: area under the curve
	Detrended fluctuation analysis: overall a
	Diffusion entropy
	Embedding scaling exponent
	Kolmogorov-Sinai entropy
	Higuchi scaling exponent
	Largest Lyapunov exponent
	Power Law (based on frequency) slope x2
	Power Law (based on frequency) y-intercept x2
	Power Law (based on frequency) x-intercept x2
	Power Law (based on frequency) goodness of fit x2
	Power Law (based on histogram) slope
	Power Law (based on histogram) y-intercept
	Power Law (based on histogram) x-intercept
	Power Law (based on histogram) goodness of fit
	Rescaled detrended range analysis
	Scale-dependent Lyapunov exponent slope
	Scale-dependent Lyapunov exponent mean value
	Scaled windowed variance

* LF = [0.04–0.2 Hz].
** HF = [0.2–2 Hz].
*** VLF = [0.001–0.04 Hz].

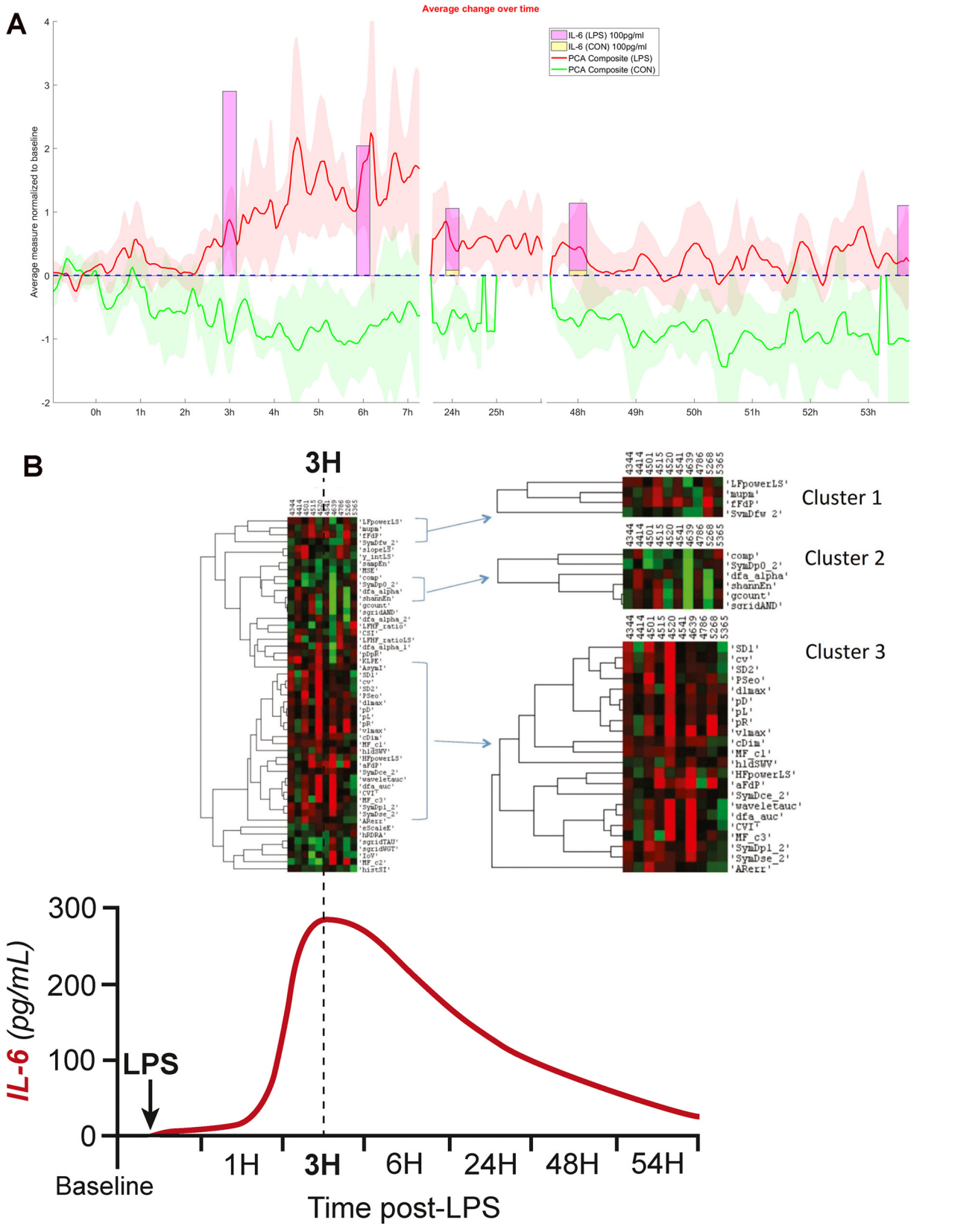
fetal responses such as those to acidemia and likely also to stress (Durosier et al., 2014; Frasch et al., 2014; Frasch, 2018; Gold et al., 2017; Li et al., 2015b).

4. Machine learning approaches

Key question: which mathematical tools do we require to synthesize the complex multi-modal data characterizing the PS effects on neurodevelopment into a cohesive predictive multi-species multi-scale framework?

The advances in data gathering technologies provide us with more ways to observe and accumulate data from the world. The relationship between PS and its impact on early postnatal behavioural and cognitive development is no exception. We can collect data representing direct or indirect measurements of the PS, for example, the DNA methylation, metabolome, microbiome, and the ANS activity. Due to the complex nature of such data, machine learning is an ideal approach to make sense of them. It encompasses a range of mathematical theories, statistical tools and computational techniques that are designed to extract relevant patterns of information and generate specific models from the data to gain a better understanding of that data (Friedman et al., 2001). There are several categories of machine learning algorithms, such as supervised versus unsupervised learning. Overall, two main analytical steps are commonly encountered in all these categories: feature extraction and learning. These two main steps are included in the overall data analysis framework in the following way:

1) The initial data cleaning/pre-processing is usually what takes the most time and is critical for the machine learning process;
2) Feature extraction and/or selection;
3) Learning/regression/classification, including testing and validation
4) Presentation of the results in a form that is easily interpreted by the



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We summarize an overall machine learning framework in Fig. 4. The available data for PS have at least the following properties:

- The data are collected from multimodal equipment and are of heterogeneous types;
- The data captured from the physiological systems affected by the PS are nonlinear and non-stationary;

Fig. 3. Fetal HRV and the fetal inflammatory response induced by an intravenous injection of lipopolysaccharide (LPS). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)
A. Temporal profile of a fetal HRV composite measure (principal component analysis, PCA) tracks accurately the pro-inflammatory cytokine IL-6 (pink bars). The red line represents the PCA for IL-6 deviations from baseline in response to LPS at 0 h (LPS, n = 10 fetal lambs); LPS is the immune stimulus from gram negative bacteria ("infection"). The green line represents the PCA for IL-6 deviations from baseline for control (saline-injected) animals (CON, n = 7). Lightly shaded areas correspond to the confidence intervals around the mean. The baseline value is represented by the dotted blue line.
B. A look under the hood: The rapid rise of IL6 in plasma induced by LPS (BOTTOM) is accompanied by the emergence of a complex HRV pattern (TOP) rendered here as a hierarchically clustered heatmap. This approach, widely used in genomic studies, visualizes the existence of distinct subsets of HRV measures that are changed in concert (increased or decreased) at the 3 h peak of the inflammatory response. Modified from Herry et al. (2016). See there for details.

- The data volume could be large and inconsistent across different facilities;
- Data quality could vary greatly and data collection velocity could be unpredictable;
- Although much has been learned about PS effects, there are still many uncertainties. In other words, the "label" provided by different field experts may have an unsatisfactory agreement rate due to the lack of the overall consensus what constitutes a PS phenotype.

Based on these facts, traditional approaches may not be adequate and choosing proper modern machine learning tools that are accurate in the prediction, stable to noise and computationally affordable can be challenging.

We now take a closer look at the different kinds of machine learning algorithms suitable for different objectives. While there are several measurements available from different aspects of the PS, designing and selecting proper features from these measurements (Guyon and Elisseeff, 2003) is the key step toward successful machine learning. The first typical challenge is the dimension reduction: as the data complexity and the measurements' diversity rise, we need more sophisticated approaches to identify useful parameters. In addition to traditional linear approaches, such as principal component analysis, several nonlinear tools have been developed for this purpose, for example, locally linear embedding (Roweis and Saul, 2000), ISOMAP (Tenenbaum et al., 2000) and diffusion map (Coifman et al., 2005).

Another challenge is the combination of heterogeneous data types, such as time-series, imaging, microbiome gene expression profile (operational taxonomic unit, OTU, frequencies), and blood biomarkers. While there are several naïve approaches to merge information from multimodal datasets, for example, a direct concatenation of features from different modalities, they may be insufficient to capture the nonlinearity and non-stationarity inherited in this kind of dataset. Development of suitable learning methods for multi-modal datasets is therefore needed. See Talmon and Wu (2017) for a discussion. To this end, a manifold learning technique called alternating diffusion, based on the low-dimensional geometric structure assumption, has been shown to be useful in fusing information from different modalities in a nonlinear fashion. It allows us to preserve the nonlinear/non-stationary underlying structure and remove the sensor-specific unwanted nuisance, before the learning procedure is applied (see, for example Talmon and Wu, 2017).

The above-mentioned dimensional reduction algorithms and sensor fusion algorithms fall into the unsupervised learning category and can be understood as the "feature extraction" step. For the learning step, there are many techniques available, ranging from the traditional linear/logistic regression to the modern support vector machine, boosting and random forest, etc (Friedman et al., 2001). We call these techniques supervised learning techniques, which means that we are learning the system based on the experts' labeling or truth. How to choose a proper learning tool depends on the knowledge of the target problem.

A recently active research field in machine learning is the deep

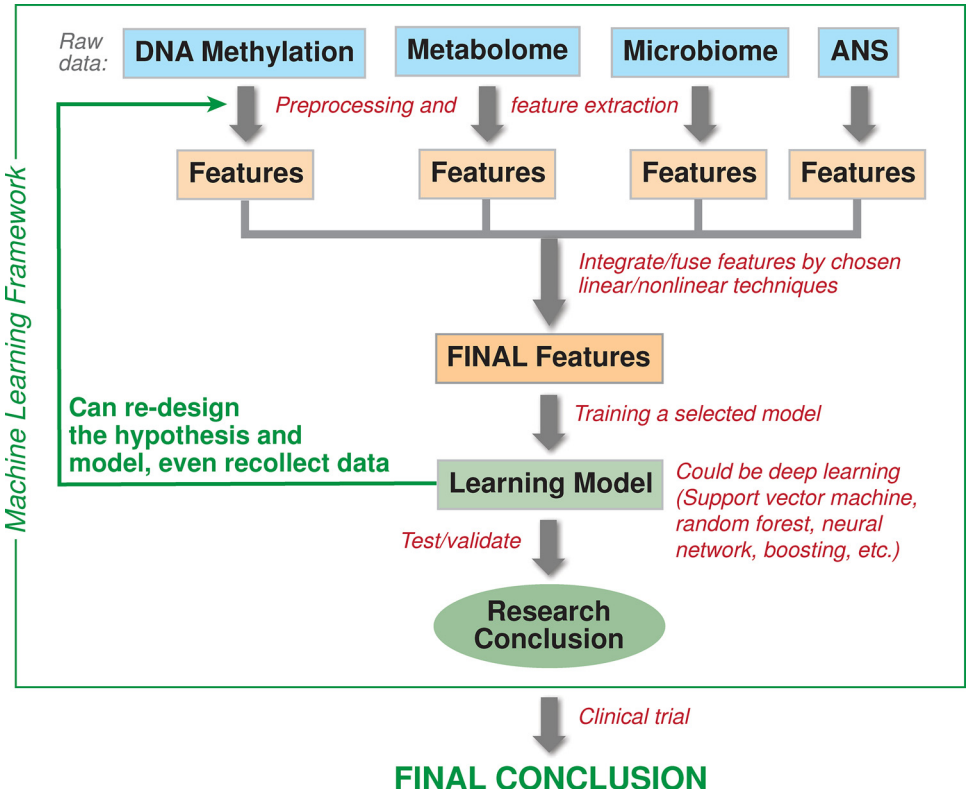

Fig. 4. Proposed framework for future studies of PS effects in a hybrid animal/human experimental design to accelerate biomarker discovery and validation. Note the multi-scale approach spanning several species and data acquisition techniques with varying spatio-temporal resolution. This requires machine learning techniques to derive at risk assessment algorithms for detection of PS exposure and prediction of neurodevelopmental outcomes.

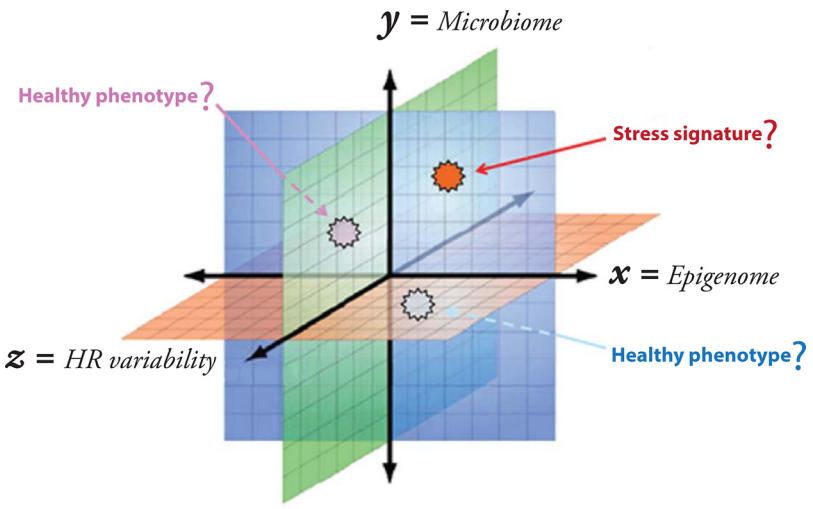

Fig. 5. A complex multi-scale phenotype of the healthy or prenatally stressed individual. Can the rapidly advancing machine learning techniques help distinguish such individual phenotypes based on all its features across the scales of observations, from microbiome, over to epigenetic landscape to the heart rate (HR) time series?

learning framework, which in brief is a generalization of the single layer neural network framework to multiple layers (and hence the nomination deep) (LeCun et al., 2015). One main feature of deep learning is the ability to combine the feature selection and learning steps in a unified framework. However, up to now, there is little theoretical understanding of how it works. How to design an efficient neural network topology for a given problem still remains an art, and a lot of trial and error and *ad hoc* experience are needed. Moreover, without theoretical understanding, it might be difficult to derive physiological insights from the established neural network, even if it provides a powerful prediction accuracy. Also, a lot of high quality data is typically required to make it work properly, which may limit its application to the clinical settings. Specifically, it is not always possible to obtain high quality data in clinical setting, for example, when there is a low agreement rate among experts. Several studies in healthcare nowadays take advantage of this kind of clinical uncertainty to claim "perfect results", which should be interpreted carefully, because the deep neural network learns both correct and incorrect labels. For instance, there is a low agreement rate among experts when diagnosing conditions such as pneumonia from the anterior-posterior chest X ray (Young and Marrie, 1994) or arrhythmia from single lead electrocardiogram signal. Thus, learning "expert labels" under the existence of clinical uncertainty with the deep neural network, and claiming that experts cannot do better than the trained model may be not meaningful.

Despite its theoretical limitations, the deep learning approach has obtained many successes in practical problems, when it is properly applied under suitable scenarios. Many variations have been developed in domains such as algorithms to combine audio and video, or the recognition of emotion from multiple modalities (Kahou et al., 2016; Mroueh et al., 2015) and using auto-encoders for auto-classification of the EEG-EMG data (Said et al., 2017) to name but a few.

While it is possible to learn features from the collected raw data by designing a suitable deep neural network, in the clinical setting it may be beneficial to combine the above-mentioned machine learning techniques in different ways. For example, unsupervised learning techniques could help extract intrinsic genuine features out of the raw data without being influenced by the quality of labels provided by experts, and allow the neural network to focus on the feature organization for the prediction purpose. By doing so, we may render the machine learning framework more interpretable, and can reduce the chance of over-interpreting the prediction accuracy. An example of combining supervised and unsupervised learning methods is that in multiple studies of young infants time series (Feldman et al., 2011; Weisman et al., 2011), where it has been shown that neonatal behavior can predict trajectories of neurobehavioral, emotional, and cognitive growth (Weisman et al., 2011). The effect of early childhood conditions on adult behavior can be translated through time series analysis and machine learning into clear prediction of the adult state, based on the observed neonatal features (Fig. 4). On the other hand, in a clinical setup, we may consider a multi-stage approach (e.g. (Basu Roy et al., 2015)): first, high-risk candidate will be detected using standard tests (e.g. microbiome or FHR monitoring). For high-risk candidates, more complex measures, such as metabolome, could be combined with microbiome data and other methods to produce better classifiers (Larsen and Dai, 2015).

In summary, although it is desirable to have a unified universal framework suitable for analyzing versatile medical data, particularly those for the prediction of PS effects, in practice a careful design of the machine learning framework based on the physiological knowledge and clinical setup is needed.

5. Outlook

As evidenced in this review, multiple preclinical studies in rodent and fetal sheep models of prenatal stress can now be translated into clinical studies involving pregnant mothers and infants. Methylation and microRNA levels can be correlated with maternal stress, depression and anxiety and with infant's cognitive development to assess the sensitivity of this novel biomarker. Similar data now begin to emerge for histone acetylation in the offspring as a function of maternal stress. We propose that increased stress, depression, and anxiety will have a positive relationship with increased methylation and distinct signatures of histone acetylation. Similarly, there is a growing body of literature on clinical studies validating the advanced FHR techniques for example to detect or predict fetal chronic hypoxia or acidemia at birth. This approach can now be extended to test if these monitoring techniques are useful for detecting PS. We attempted a visualization of the complex multi-scale PS or healthy phenotype in Fig. 5. We stress the limitations of our approach within the machine learning framework which arise from the dangers of overinterpreting the prediction accuracy and from the need for careful model calibration.

The immediate translational potential of the proposed framework into clinical practice can be realized by integrating multiple non-invasively obtainable sources of information using novel epigenetic, electrophysiological and biochemical approaches using machine learning techniques. The proposed framework could then yield progress well beyond the maternal–fetal medicine, especially in psychiatry, psychology and sociology, offering a more precise and truly personalized prediction and new possibilities for designing interventions to improve neurodevelopmental outcomes of pregnancy affected by PS. Such approach can also inform and help track the success of policy efforts by the private philanthropy and public funding agencies. The

urgent need to prioritize policy level actions is justified by the major social and health-economic benefits of reducing the persistent burden of generational PS effects on our societies (Persson and Rossin-Slater, 2018).

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