Title

Fetal programming of human energy homeostasis brain networks: Issues and considerations

Permalink

https://escholarship.org/uc/item/1tm8r0cn

Authors

Rasmussen, Jerod M
Thompson, Paul M
Entringer, Sonja
et al.

Peer reviewed

Fetal Programming of Human Energy Homeostasis Brain Networks: Issues and Considerations

Jerod M. Rasmussen[a,b,*], **Paul M. Thompson**[c], **Sonja Entringer**[a,b,d,e], **Claudia Buss**[a,b,d,e], **Pathik D. Wadhwa**[a,b,e,f,g,*]

[a]Development, Health and Disease Research Program, University of California, Irvine, California, USA 92697.

[b]Department of Pediatrics, University of California, Irvine, California, USA 92697.

[c]Imaging Genetics Center, Mark and Mary Stevens Institute for Neuroimaging and Informatics, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA 90033.

[d]Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Department of Medical Psychology, Augustenburger Platz 1, 13353 Berlin

[e]Departments of Psychiatry and Human Behavior, Obstetrics & Gynecology, Epidemiology, University of California, Irvine, California, USA 92697.

[f]Department of Obstetrics & Gynecology, University of California, Irvine, California, USA 92697.

[g]Department of Epidemiology, University of California, Irvine, California, USA 92697.

Abstract

In this paper we present a transdisciplinary framework and testable hypotheses regarding the process of fetal programming of energy homeostasis brain circuitry. Our model proposes that key aspects of energy homeostasis brain circuitry already are functional by the time of birth (with substantial inter-individual variation); that this phenotypic variation at birth is an important determinant of subsequent susceptibility for energy imbalance and childhood obesity risk; and that this brain circuitry exhibits developmental plasticity, in that it is influenced by conditions during intrauterine life, particularly maternal-placental-fetal endocrine, immune/inflammatory and metabolic processes and their upstream determinants. We review evidence that supports the scientific premise for each element of this formulation, identify future research directions, particularly recent advances that may facilitate a better quantification of the ontogeny of energy homeostasis brain networks, highlight animal and *in-vitro* based approaches that may better address the determinants of inter-individual variation in energy homeostasis brain networks, and

*Corresponding Authors:** Pathik D. Wadhwa, MD, PhD., Development, Health and Disease Research Program, University of California, Irvine, 3117 Gillespie Neuroscience Research Facility (GNRF), 837 Health Sciences Road, Irvine, CA 92697, Tel: (949) 824-8238, Fax: (949) 824-8218, pwadhwa@uci.edu, Jerod M. Rasmussen, PhD., Development, Health and Disease Research Program, University of California, Irvine, 3117 Gillespie Neuroscience Research Facility (GNRF), 837 Health Sciences Road, Irvine, CA 92697, Tel: (949) 824-8238, Fax: (949) 824-8218, rasmussj@uci.edu.

discuss the implications of this formulation for the development of strategies targeted towards the primary prevention of childhood obesity.

Keywords

Childhood Obesity; Fetal Programming; Energy Balance Homeostasis; Brain Circuitry; Reward; Interoception; Satiety; Salience

1.   Introduction and Overview

Obesity represents among the most urgent national and global health challenges due to its high prevalence and established health risks[1–4]. Childhood obesity is a particularly grave concern as obese children are substantially more likely to have obesity as adults[5,6] and to develop obesity-related disorders at earlier ages[7,8] and of greater severity[9–11]. Understanding the causal origins of obesity requires not only the consideration of the multi-factorial interplay between genetic and environmental risk factors, but also the temporal sequence of conditional probabilities underlying its emergence. That is, the effects of any given risk factor at any given stage of the life span are conditioned upon the enduring effects of prior exposures at prior life stages.

Over the past several years there has been substantial interest in the role of developmental processes, over and above those of genetic and lifestyle factors, in shaping individual differences in susceptibility for developing obesity[12–16]. Indeed, a rapidly growing and convergent body of epidemiological, clinical and experimental evidence in humans and animals suggests that the origins of obesity can be traced, in part, back to developmental processes occurring during the intrauterine period of life, at which time the developing embryo/fetus responds to 'suboptimal' conditions by producing structural and functional changes in cells, tissues and organ systems that persist across the life span and modulate susceptibility for many complex common disorders (*i.e.*, the concept of fetal, or developmental, programming of health and disease risk). To date, research on fetal programming of obesity has focused largely on processes and mechanisms within peripheral cells, tissues and organ systems, such as adipocyte[17], pancreas[18], liver[19–21] and muscle[22,23] biology. While this focus is entirely justified, we suggest there is yet another system of critical importance that also warrants attention in the context of fetal programming: the brain circuitry that underlies energy balance homeostasis.

Energy balance homeostasis refers to the phenomenon that governs homeostatic regulation, or synchronization, between energy intake (EI) and energy expenditure (EE). The importance of the brain, and specifically hypothalamic-limbic-cortical brain circuitry, in the regulation of energy homeostasis is well-established. Differences have been described in this brain circuitry between normal-weight individuals and those diagnosed with obesity, however, it is not yet clear whether these differences are a cause, consequence, or both, of the obese state. In light of this fundamental gap in our understanding, and based on the growing evidence that supports the phenomenon of fetal programming of the brain (but has not yet focused specifically on energy balance homeostasis circuitry, particularly beyond the hypothalamus), we propose here a conceptual, trans-disciplinary framework and articulate

testable hypotheses regarding the process of fetal programming of energy homeostasis brain circuitry along the developmental trajectory to obesity (excess adiposity) (see Figure 1). This framework is built on converging evidence that overlapping mechanisms of fetal programming of the brain and peripheral systems may play a substantial role in explaining inter-individual variation in the structure, function, and connectivity of energy homeostatic-relevant brain circuitry at birth, and its subsequent implications for the trajectory and magnitude of fat gain. Our conceptual model proposes that *a*) key aspects of energy homeostasis brain circuitry already are established and functional by the time of birth; *b*) there is substantial structural and functional inter-individual variation in this circuitry by the time of birth; *c*) this phenotypic variation at birth is a determinant of subsequent susceptibility for energy imbalance and is hypothesized to be prospectively associated with markers of childhood and adult obesity risk (*e.g.*, change in adiposity over the early postnatal period and persistence of the effect into childhood); and *d*) this newborn brain circuitry exhibits developmental plasticity, in that it is influenced by conditions during the intrauterine life, particularly key maternal-placental-fetal endocrine, immune/inflammatory, metabolic and oxidative processes across gestation and their upstream determinants.

In this perspectives paper, we first review the concept of energy balance and provide a brief description of the role of the brain in regulating energy balance. We then review and synthesize evidence that examines the premise that energy homeostasis-related brain circuitry is already established and functional by the time of birth, with meaningful inter-individual variation. Next, we review and synthesize evidence underlying the fetal programming of energy homeostasis-related brain circuitry hypothesis. Finally, we identify questions, issues and research directions aimed at testing key elements of our model and discuss their potential implications for the development of strategies ultimately targeted towards the primary prevention of childhood obesity.

2. The Concept of Energy Balance Homeostasis

Human physiology conforms to the first law of thermodynamics, which states that energy cannot be created or destroyed; it can only be transformed from one form to another. It then follows that the rate of change in the body's energy stores (ES) is equal to the difference between the effective rates of energy intake (EI) and energy expenditure (EE). EI occurs primarily via the consumption of the three major macronutrient food groups - carbohydrate, protein, and fat[24]. Absorbed carbohydrates, proteins, and fats are then transformed *in vivo* to substrates that ultimately are either oxidized to produce metabolically useful energy that drives biological processes such as growth, maintenance, physical activity, etc., (EE) or they are stored (ES). Any imbalance between the intake (EI) and utilization (EE) of these macronutrients results in a non-zero balance (ES) that will lead to an alteration in body composition in the form of tissue contraction/expansion via triglycerides in adipocytes (dominant form), and protein and intracellular glycogen in skeletal muscle. Thus, the long-term stability of body weight and composition is considered a marker of being in a state of energy balance. The development of obesity necessitates positive energy imbalance over and above that required for normal growth and development from conception through adolescence. In lean individuals and those diagnosed with obesity, a state of energy balance

ultimately occurs over the long term, but in individuals with obesity this steady state is simply achieved with a higher amount of body fat.

In the context of an acute reduction in EI relative to EE it also is clear that evolutionary adaptations over time have favored a number of physiological responses acting against weight loss to promote weight regain towards a homeostatic set point[25]. Such weight-preserving mechanisms are thought to be equally present in lean individuals and those with obesity *despite* the over-abundance of energy stores present in obesity. Thus, once established, the condition of excess adiposity is difficult to reverse. In contrast to the oversimplified "eat less move more" solution to addressing the problem of unwanted weight gain and obesity, the U.S. Endocrine Society has taken the position, based on the convergence of evidence, that *obesity should now be conceptualized as a disorder of the energy homeostasis system, rather than simply arising from the accumulation of excess weight*. Moreover, the Society's position paper on this issue has emphasized the need to elucidate underlying mechanisms, with a major focus on the influence of developmental processes[26].

3. Components of the Energy Balance Homeostasis System

Energy homeostasis is centrally regulated within the central nervous system (CNS), with peripheral inputs and outputs (see Figure 2)[27]. Communication within and between the central and peripheral systems occurs via afferent and efferent signaling involving endocrine and other effectors. The CNS relies on long- (tonic) and short-term (episodic) peripheral inputs to obtain information regarding the state of energy intake (nutrients) and energy stores (body composition). Outputs from the CNS guide the adjustments to energy expenditure and caloric intake that are needed to achieve energy balance. Ultimately, the majority of peripheral signals converge on the hypothalamus where, in concert with other cortical and subcortical regions, these signals are integrated with gustatory (e.g., olfaction), interoceptive (e.g., gastric expansion), behavioral (e.g., stress) and social (e.g., peer pressure) contextual information. Below, we briefly review the role of the brain in maintaining energy homeostasis, beginning with the hypothalamus and then vertically expanding beyond the hypothalamus to include higher-order brain structures critical to feedback and feed-forward energy homeostasis signaling, including the ventral striatum, limbic, insula and anterior cingulate. Because these individual structures do not operate in isolation, we organize the discussion into four canonical energy homeostasis brain networks: satiety, visceral, reward, and salience networks. Finally, we frame the development of these systems in the context of the effects of the fetal programming process, with a focus on those elements of this circuitry that exhibit developmental plasticity (wherein maternal-placental-fetal biological processes during fetal life forecast its observed variation at the time of birth).

3.1 The satiety network

Hypothalamic nuclei constitute the principal CNS regulators of energy balance homeostasis[28–30]. Early lesion studies were instrumental in establishing the key satiety network nuclei underlying hyperphagic (i.e., paraventricular, dorsomedial and ventromedial nuclei) and hypophagic (i.e., lateral nuclei) behaviors. The melanocortin system of peptide

hormones functioning within the hypothalamus is the key regulator of energy intake (i.e., promotion or suppression of appetite signaling) via the sensing of current energy status in peripheral organs[31]. Hormonal signaling from adipose tissue (leptin, representing satiety) and the gastrointestinal tract (ghrelin, representing hunger) confers homeostatic status to melanocortin receptors in orexegenic (agouti-related peptide/neuropeptide Y [AgRP/NPY]) and anorexigenic (proopiomelanocortin [POMC]) neurons residing in the arcuate nucleus of the hypothalamus. Ghrelin promotes AgRP/NPY activation and inhibits POMC activation, providing higher order brain systems with an increased appetite signal. Conversely, leptin inhibits AgRP/NPY activity and promotes POMC activation, decreasing the CNS's motivation for energy intake while increasing signaling to upregulate energy expenditure. In coordination with the hypothalamus, the brainstem (*e.g.,* nucleus of the solitary tract [NTS]) acts as a co-regulator of energy balance through the peripheral sensing of nutrients[32], descending projections from the hypothalamus[33], and interoceptive (see Section 3.3 Visceral network below) and nutrient signaling ascending from the gastrointestinal tract[34].

The importance of POMC (appetite suppressing, expenditure promoting) and AgRP (appetite promoting, expenditure suppressing) neurons in the modulation and regulation of energy balance is well established. However, the full relevance of direct communication *between* these cell types is not yet well understood, as AgRP neurons do not appear to contribute to spontaneous input to POMC neurons[35], and while optogenetic stimulation of AgRP does inhibit POMC neurons, such inhibition is not necessary for the induction of feeding behaviors[36]. It is clear, however, that other intrahypothalamic signaling pathways are of relevance to energy homeostasis as postprandial POMC signaling to the paraventricular nucleus (PVN) via α-melanocyte-stimulating hormone and melanocortin 3 and 4 receptors results in decreased appetite and increased energy expenditure[37], and AgRP signaling to the PVN promotes appetite and decreases energy expenditure[38].

Central regulation of energy expenditure to meet the demands of thermoregulation, basal metabolism and physical activity also is accomplished, in part, via hormonal signaling to the hypothalamus. For example, thermoregulation in response to exogenous cold exposure is achieved through the activation of the hypothalamic-thyroid-adrenal axis and the downstream effects of thyroid (T3/T4) hormones in upregulating cellular metabolism and heat production in peripheral tissues[39]. The hypothalamus also modulates cellular metabolism in response to endogenous conditions reflecting over-nutrition. For example, increased diet induced thermogenesis occurs in response to high-caloric intake, whereas fasting produces a reduction in energy expenditure. As noted previously, these energy balance mechanisms are asymmetric, in that they are more sensitive to weight loss than weight gain, thus emphasizing the importance of higher cognitive regulation of energy intake in the context of the abundance of western diets (whose influence is believed to further mask or reduce the effectiveness of energy balance set points[40,41]).

3.2 Reward network

Over and beyond the hypothalamus, the ultimate 'decision' of what, when, and how much to eat implicates the recruitment of several inter-linked cortical and subcortical structures (see Figure 3), of which the mesolimbic dopaminergic (reward) pathway plays a crucial

role[42–46]. The reward network is the catalyst for motivated behavior in the context of feeding, in that learned associations with foods that are high in energy content provide positive reinforcement through the release of dopamine[47]. Direct evidence comes from lesion studies demonstrating a decreased desire for food after experimental damage to reward areas[48]. The reward network relies on projections between dopaminergic neurons in the ventral tegmentum area (VTA) and the nucleus accumbens, but also relies on modulatory connections between the amygdala[49], hippocampus[50,51], insula[52], prefrontal[49]/orbitofrontal cortex, caudate[53], putamen, thalamus and pituitary gland[54]. Upon novel exposure to food rewards, dopamine is released in the nucleus accumbens. Prolonged exposure habituates such a response, ultimately transferring the reward response on to food-related stimuli (e.g., images, smells), and thus becoming a potent predictor of reward[55–58]. From an evolutionary perspective, environmental stimuli motivating food seeking behaviors clearly are adaptive. Yet, in the modern obesogenic environment, in which such stimuli are ubiquitous, they have often become a liability. Because dopamine and the reward network play such a prominent role in motivating food intake behaviors[59], it has been suggested in the context of the problem of obesity that this feature may now constitute an affliction similar to other addictive behaviors including narcotics abuse[60] and reflect an inherent obstacle to weight loss.

3.3 Visceral network

The visceral/gustatory/interoception network represents another key component[61] of the brain circuitry implicated in caloric intake. This network integrates sensory information about internal bodily states (e.g., insula activation via gastric distension[62]), food-related cues (e.g., olfactory/gustatory cortex activation via olfaction/taste), and their interaction[63], enabling feedback (setpoint error detection and correction) and feedforward (anticipation of future energy availability) input[64]. The olfactory system consists of signaling from smell receptors (chemosensation) in the nasal cavity to the primary/secondary olfactory cortex via the olfactory bulb. Conversely, the gustatory system consists of an ascending pathway originating from taste receptors in the tongue through to the rostral division of the NTS, the ventroposterior medial nucleus of the thalamus (VPMpc), and terminating in the gustatory cortex located within the insula. The role of the insula in modulating complex feeding behaviors in the context of obesity is well established[65–68]. In addition to gustation, the insula plays an essential role in somatosensation, interoception, reward/addiction and emotion[69]. Thus, the insula is believed to integrate multisensory input[66,70]. Further, the insula has dense, reciprocal structural connections to the amygdala[71], a brain structure involved in taste and textural coding[72], and therefore hypothesized to mediate the processing of taste and reward[73,74].

3.4 Salience network

The salience network (anterior cingulate cortex [ACC], anterior insula[75]), in concert with satiety-related input from the hypothalamus, is believed to underlie the drive for the prioritization of sustenance and the de-prioritization of other functional tasks of less importance[76]. The salience network is centered on bilateral orbital frontoinsular and dorsal anterior cingulate cortices[77], with connectivity to the VTA, thalamus, hypothalamus and amygdala. This network is also likely important for switching between internal (default

mode network) and external (central executive network) modes of thought[78,79], a property consistent with and necessary in the context of feeding behaviors[80]. Critically, structural and functional variation in the salience network has been shown to predict food intake under stressful conditions, has been associated with familial obesity risk, and differences have been described between normal-weight and individuals with obesity[81]. This then suggests that the integrity of the salience network is functionally relevant in the context of energy homeostasis.

4. The Ontogeny of Inter-individual Variation in Energy Homeostasis Brain Networks

Our framework postulates that energy homeostasis brain networks are already established at the time of birth, albeit further maturation and finetuning occurs postnatally, and that the inter-individual variation in their functional variation is prospectively associated with key markers of subsequent obesity risk (e.g., postnatal feeding behaviors and infant weight/fat gain). In this section we describe animal and, where available, human evidence that supports the scientific premise of these postulates (see Table 1 for summary).

4.1 Ontogeny of the Satiety Network

As reviewed above in Section 3.1, the hypothalamus represents the hub of *the* primary appetite regulatory network. A considerable body of evidence, primarily in rodents, suggests that the hypothalamus takes shape beginning with the formation of neuronal progenitor cells appearing shortly after the closure of the neural tube, and this is followed within days by cellular specification into hypothalamic neurons (e.g., POMC, VMH neurons). Axonal growth occurs throughout gestation from differentiated cell types to various target regions. Importantly, inter-individual variation is evident in hypothalamic expression of genes encoding extracellular matrix (ECM) protein production (e.g., Col1a1, Col3a1) at postnatal day 10 in rodents (roughly equivalent to the human newborn period), accompanied by subsequent variation in postnatal body fat accrual, thus indicating *functionally* meaningful inter-individual phenotypic variation at this early life[82,83] stage. Interestingly, while the rodent hypothalamus responds functionally at birth[84–87] to metabolic stimuli, appetite is not yet modulated by acute injections of leptin or ghrelin[84,88]. Further, a functional response to food deprivation (i.e., NPY expression) is not observed until between 10 to 20 days postnatal age. However, in rodents structural connectivity originating within and between the hypothalamus is largely incomplete at birth, whereas in precocial species such as non-human primates[89] and humans these connections are comparatively mature at birth[90]. In contrast to the ontogeny of the rodent satiety network, fetal hypothalamic NPY and POMC have been shown to be well expressed in baboons in late gestation, even prior to birth. Moreover, an appetite-promoting functional phenotype (i.e., increased NPY and decreased POMC expression in the hypothalamus) is established by late gestation in fetuses exposed to *in utero* caloric restriction. Thus, collectively, this evidence suggests that in precocial species the satiety network exhibits structural and functional maturity by the time of birth.

4.2   Ontogeny of the Reward Network

In rodents, dopaminergic projections from the VTA to the Nucleus Accumbens are in place by the time of birth and rapidly expand over the first few weeks of postnatal life[91–93]. Recent evidence in rodents also supports substantial inter-individual variation in Dopamine Receptor D2 expression within the VTA and the Nucleus Accumbens as early as postnatal day 10[94]. In humans, the connections of the reward network are largely in place by the end of the gestational period, with dopamine transporter immunoreactivity reaching a functional state by 40-weeks gestation[95]. And based on the presence of a diverse set of human infant behaviors in response to gustatory and olfactory stimuli, it appears that key aspects of learned behaviors and reward-based anticipatory responses to food cues are established and functional by birth. For example, it is well established that breast milk odor produces an analgesic effect on term and preterm newborns[96]. Based on the consideration that the aversiveness of pain is encoded by reward mesocorticolimbic circuitry[97], it seems reasonable to suggest that aspects of this circuitry, particularly in the context of feeding, are established and functional in humans by late gestation. Moreover, the olfaction of fatty acids from maternal amniotic fluid is sufficient to elicit appetitive responses within 24 hours of birth[98,99]. Here, mesocorticolimbic circuitry appears to underlie such responses, as maternal colostrum and novel odorant[100] olfaction is sufficient for the activation of orbitofrontal cortical regions in newborns[101–104]. Thus, these findings support the premise that key aspects of conditioned learned associations[50] with stimuli are present during gestation and are functional at the time of birth. Moreover, it is clear that there is inter-individual variation in newborns in behavioral preferences for flavors (e.g., garlic, anise) consumed by the mother with volatile compounds present in the amniotic fluid during pregnancy[105–110], further supporting the premise of functional maturity in its underlying neurocircuitry. In addition to flavor preference, recent evidence suggests fetal growth conditions (small for gestational age and intrauterine growth restriction) are associated with variation in early life dopamine signaling in the nucleus accumbens[111,112] and newborn hedonic responses to sweet stimuli[113] with long term consequences on the preference for highly palatable foods (e.g., high fat and sugar content) [114,115]. While more complex reward-based feeding behaviors begin to emerge around the weaning period[116,117], we suggest that reward circuitry in humans in response to gustatory and olfactory cues is functional by birth and acts in coordination with limbic regions through dopamine release.

4.3   Ontogeny of the Visceral Network

In rodents, visceral network connectivity between the gastrointestinal tract and the gustatory pathway are structurally in place as early as the first postnatal day of life[118–120], with evidence of the presence of direct control of ingestive behavior (e.g., postingestive but preabsorptive signaling). The visceral network continues to mature postnatally through changing biochemical signaling[121] and further synaptic organization[122] and appears to play a clear role in energy homeostasis. In a recent report in human newborns, we demonstrated a prospective, inverse association between the volume of the newborn insula (a key component for sensing the physiological state of visceral organs) and fat gain during early life (a key marker of childhood obesity risk) [123]. We note this finding is consistent with those evident in human adults linking insula gray matter volume and activity with gastric distension, the

obese state[124–127] or future risk of developing obesity[128], and metabolic factors associated with obesity, including blood leptin concentration[129].

4.4 Ontogeny of the Salience Network

Although the developmental ontogeny in prenatal life of the salience network in the context of feeding and childhood obesity risk has yet to be described, we suggest, based on three lines of evidence, that it likely is structurally and functionally intact by the time of birth, with meaningful inter-individual variation in the context of obesity risk. First, as discussed previously in Section 3.4, inter-individual variation in adults in the functional connectivity of the salience network has consistently been shown to be associated with several obesity-related phenotypes[130]. Second, the salience network is structurally supported by multiple white matter pathways[131], (e.g., Uncinate Fasciculus[132], corpus callosum[131]) that develop in humans during the mid-gestation period. And third, the functional connectivity of the salience network is evident by birth[133], and the strength of its connectivity is associated with maternal BMI[134] and inflammation[135] during pregnancy, supporting the premise that it exhibits meaningful inter-individual variation at birth.

Table 1 provides a summary of the above evidence supporting the presence of structural and functional inter-individual variation in brain circuitry at birth and its prospective associations with offspring obesity risk. It is organized by network and depicts the model species studied and the presence or absence of evidence.

5. Fetal Programming of Energy Homeostasis Brain Networks

A rapidly growing and convergent body of epidemiological, clinical and experimental evidence in humans and animals suggests that the origins of obesity can be traced, in part, back to developmental processes occurring during the intrauterine period of life, at which time the developing embryo/fetus responds to 'suboptimal' conditions by producing structural and functional changes in cells, tissues and organ systems that persist across the life span and modulate susceptibility for many complex common disorders. This process, commonly referred to as fetal programming, is adaptive from an evolutionary perspective, but at the individual level may confer a trade-off favoring short-term survival/reproductive fitness at the long-term cost of susceptibility to complex common disorders. The importance of fetal programming is supported by evidence that exposures to suboptimal maternal nutrition, suboptimal maternal metabolic health, excess maternal stress, and excess maternal inflammation during intrauterine life have the potential to alter neurodevelopmental outcomes and obesity risk throughout the life course. Specifically, several convergent lines of evidence suggest that key brain structures involved in energy homeostasis (e.g., hypothalamus, amygdala and hippocampus) exhibit plasticity in response to maternal conditions during pregnancy. However, with the exception of the hypothalamus, this literature has, to date, largely focused on observations in the context of neuropsychiatric disorder risk[136]. For the remainder of this section, we highlight standing and recent developments in which maternal states and conditions influence offspring body composition *and* energy homeostasis relevant brain circuitry in a manner consistent with one another.

These findings support our premise that fetal programming of energy homeostasis brain circuitry may, in part, mediate the influence of maternal conditions on offspring obesity risk.

5.1.1 Sociodemographic factors

In humans, offspring adiposity risk is associated with several sociodemographic factors, including maternal age at conception, race/ethnicity, and socioeconomic status. Younger maternal age at conception has been linked with child outcomes including low birthweight[137], an increased obesity risk[138], and increased risk for central adiposity[139]. Race and ethnicity are also associated with birthweight[140], newborn adiposity[141], and early life feeding behaviors. It is likely that economic deprivation may explain some of the racial and ethnic disparities in infant birth outcomes (e.g., birthweight), feeding behaviors, and subsequent childhood obesity[142–145] prevalence.

In addition to obesity risk, sociodemographic states and conditions have been associated with energy homeostasis-relevant brain circuitry and development. For example, it is well established that children from high socioeconomic status (SES) families perform better on a number of cognitive tasks[146], including executive functioning tasks believed to underlie aspects of childhood obesity[147]. In addition, current evidence suggests that structural brain development (e.g., insula, frontal cortex) is SES-dependent and mediates the association between SES and cognitive performance, particularly in executive function domains[148]. Further, the effects of SES on brain development can be traced back to well before childhood because SES has been shown to influence growth and functional connectivity of the frontal cortex already in human infancy[149,150]. In fact, recent evidence has emerged that the effects of SES can be traced back to fetal brain development[151], particularly in the amygdala, a structure highly integrated into the central control of energy homeostasis. Certainly, because SES could not exert a *direct* effect on the fetal brain, these findings motivate the needs for a mechanistic understanding of the role of putative mediators such as gestational biology on programming homeostasis-relevant brain circuitry throughout the life course.

5.1.2 Biophysical/clinical factors

Maternal biophysical and clinical factors such as obesity, excess gestational weight gain and gestational diabetes are associated with greater offspring birth weight and fat mass. The metabolic consequences of over-nutrition during the fetal period are also believed to track beyond infancy, as children born to mothers with obesity or diabetes continue to have increased obesity risk[152–154]. Additionally, not only are offspring of over-nutrition pregnancies larger at birth and in later life[155], they are also more likely to suffer from adverse metabolic conditions such as hypertension and diabetes[156,157] as adults. While genetic variation (DNA base pair variation) certainly plays a role in the intergenerational transmission of obesity and obesity-related outcomes, it is clear that the intrauterine milieu plays an important role above and beyond genetics. For example, one Swedish national cohort study of pregnancy following bariatric surgery found a marked decrease in pre-pregnancy BMI (from roughly 44 to 30, on average) accompanied by a reduced risk of gestational diabetes and excessive fetal growth[158]. Importantly though, the Swedish study and others[159,160] have found an increased risk for small-for-gestational-age offspring

following gastric bypass, suggesting that such restrictive surgery may result in a milieu of nutritional deficiency during pregnancy. In a recent meta-analysis of natural weight gain between successive pregnancies[161], it was estimated that a BMI increase of greater than three units between pregnancies was associated with a 63% higher risk (adjusted odds ratio) of large-for-gestational age offspring.

In addition to offspring obesity outcomes across the lifespan, there is emerging evidence that maternal obesity is associated with offspring cognitive[162 163 164,165] and neurodevelopmental disorder[166] outcomes, and plays a specific role in shaping newborn functional and structural brain connectivity patterns within key aspects of the satiety, salience, and reward networks. Indeed, recent neuroimaging evidence supports a direct role for the hypothalamus as a mediator between maternal nutrition status and susceptibility to weight gain in childhood[167]. Within interoception, salience and reward systems[134,168,169], maternal obesity has also been linked with fetal and newborn human offspring functional and structural connectivity. Because salience and reward networks play a requisite role in assigning motivation and importance based on integrated input from the hypothalamus by de-prioritizing other[76] functional tasks of less importance, it is plausible that maternal obesity (through associated gestational biological factors) also plays a meaningful role in programming aspects of central feeding behaviors that then contribute to obesity throughout the human life-course.

5.1.3 Maternal Diet/Nutrition

The influence of maternal nutrition on offspring brain function in the context of obesity is well established. In rodents, a maternal high fat diet alters offspring feeding behavior and predisposes to an obese phenotype[170–172]. This effect is partially mediated by POMC expression in the hypothalamus and likely programmed via CpG methylation in a POMC promoter region. Other recent findings support endoplasmic reticulum stress brought on by fetal exposure to maternal free fatty acid concentrations as a cause of altered hypothalamic development, with metabolic consequences in postnatal life[173]. Beyond the hypothalamus, maternal diet-induced obesity models have demonstrated altered feeding behavior in rodent offspring, favoring highly palatable foods (e.g., high-fat, high-sugar) accompanied by altered aspects of limbic[174] and reward[175–179] circuitry. Strikingly, maternal under-nutrition during pregnancy also promotes an increased appetite for high fat foods in offspring[180]. Because preference for high fat foods is commonly considered to be associated with reward circuitry function[181], it is likely that under-/over-nutrition models share a common programming target in reward circuitry, albeit through a different mechanism (e.g., differential epigenetic modification)[182] of nutrition status. Potentially, this may also be attributed to separate motivational mechanisms where exposure to excess nutrition could influence offspring hedonic liking (opioid and cannabinoid) via *in utero* priming, whereas exposure to undernutrition could influence the fetal development of circuitry underlying homeostatic wanting (dopamine)[183] in preparation for an *ex utero* environment limited in food resources.

In humans, higher maternal protein intake (relative to carbohydrate or fat intake) in mid-pregnancy is associated with lower visceral adiposity in neonates[184]. In the same cohort, maternal sugar intake was positively associated with peak BMI in infancy, and maternal

carbohydrate and sugar intakes were positively associated with BMI between two to four years of age[185]. In a separate study, an imbalance in maternal micronutrient intake (excess folic acid in a B_{12} deficient diet) during pregnancy was associated with whole-brain oxidative stress. In addition, in a large prospective mother-child cohort study, researchers documented a negative association between maternal depression during pregnancy and offspring IQ, mediated by the maternal diet at 32-weeks gestation[186]. Collectively, these findings support the plausibility that aspects of maternal behavior (e.g., diet and nutrition) influence early life adiposity outcomes through changes to appetite regulating networks (e.g., satiety, limbic and reward circuitry) during fetal brain development.

5.1.4 Maternal-Placental-Fetal Metabolic, Endocrine and Immune/Inflammatory Biology

The effects of maternal states and conditions during pregnancy on fetal programming of the brain and peripheral systems are ultimately mediated *via* gestational biology. Over and above the role of gestational biology in mediating the effects of maternal diet/nutrition during pregnancy (as discussed above) it is evident that aspects of gestational biology also may mediate the effects of other key prenatal states and conditions on fetal brain energy homeostasis-related phenotypes. Here, we discuss these offspring outcomes in relation to fetal exposures to three key aspects of maternal-placental-fetal biology: metabolic, endocrine, and immune/inflammatory gestational state.

5.1.4.1 Maternal Metabolic State—Glucose and insulin are important markers of maternal metabolic state, and of consequence to offspring health and development, including the brain. In humans, recent evidence supports the notion that maternal gestational diabetes status and insulin sensitivity[187] are associated with fetal brain function (auditory evoked response latency) following a maternal oral-glucose stimulus[188]. While maternal insulin does not cross the placental barrier, glucose constitutes a predominant form of energy substrate provided to the developing fetus by crossing the placenta. The mechanisms that regulate the differential effect of maternal insulin sensitivity on the fetal brain response to glucose administration are not well established. However, Linder et al observed that insulin-resistant mothers have higher glucose levels accompanied by increased insulin levels in the postprandial state and go on to suggest that as glucose transfer across the placenta increases, hyperinsulinemia (e.g., increased pancreatic insulin production) in the fetus may be induced (Pedersen hypothesis) [189]. As a result, increased insulin levels in the mother correspond with increased insulin levels in the fetal brain compartment. Importantly, insulin within the brain compartment appears sufficient for modulating energy homeostasis brain networks both *in utero* and postnatally, with ramifications on food intake, body weight, and ultimately obesity[190–193]. For example, intravenous insulin elicits changes in brain activity measured using magnetoencephalography[194], and insulin reactivity is associated with limbic activation as measured by fMRI in response to visual food cues[195]. Further, recent evidence in animals supports a specific role for brain-based control of glucose homeostasis in Type-2 diabetes[196], further supporting the role of the brain as both a sensor and effector of energy homeostasis. To summarize, the fetus experiences variation in glucose concentration exposure that is dependent on variation in maternal metabolism, which in turn is sufficient to elicit differential brain function *in utero*[197] likely *via* fetal insulin production. Thus, because the brain is a regulator of energy homeostasis, the above collectively suggests

a pathway through which maternal insulin sensitivity status programs offspring metabolic health, mediated through fetal brain development and function.

5.1.4.2 Maternal endocrine state—Stress plays an important role in obesity; it alters metabolism, affects appetite, and influences dietary intake[198,199]. During pregnancy, excess stress has been associated with adverse developmental outcomes[200] including obesity risk[201] and atypical brain development[202–205]. The stress hormone cortisol is perhaps the most robust biological indicator of response to a diverse range of stressors, including low socioeconomic status, psychosocial distress, inter-personal conflict, performance pressure, and lack of social support[206–209]. Indeed, cortisol's importance in effecting appetite and metabolism is well established. For example, differentiation of human adipocyte precursor cells in the presence of insulin is promoted by cortisol in a dose-dependent manner and occurs at physiological concentrations *in vitro*[210,211]. Consistent with this observation, prenatal maternal cortisol levels have been positively associated with early life adipose tissue accumulation in human newborns[212].

With respect to the brain and appetite, several studies have reported associations between fetal cortisol exposure and alterations in brain development in energy homeostasis-relevant brain regions including the amygdala[213], hippocampus, insula[214], frontal cortex[215], and anterior cingulate[216]. For example, in rodents, dexamethasone treatment during pregnancy has been shown to affect offspring birth weight, and glucocorticoid receptor mRNA expression in the amygdala and hippocampus in a time-dependent manner[217]. More specifically to appetite, induction of corticotropin releasing factor (a hypothalamic precursor of cortisol production) in the maternal brain during late pregnancy predisposes rodent offspring, in a sex-specific manner, to episodes of binge eating[218] when subjected to a limited-access food paradigm[219]. Such binge eating behavior is accompanied by hypothalamic adaptation in the offspring, as evidenced by hypomethylation of miR1-a and downstream dysregulation of the melanocortin system. Collectively these findings suggest that stress during pregnancy may play a meaningful role in setting up obesity susceptibility by influencing fetal brain development of energy homeostasis-relevant networks.

In addition to nutrition (see above Section 5.1.3), maternal stress during pregnancy is one of the most commonly-studied factors in the context of the fetal programming of brain development. However, the effects of maternal nutrition and stress on offspring brain development are often studied separately despite evidence of a bi-directional relationship between them[220,221]. The limited literature that does consider the combined effect of diet and stress seems to point to a high fat diet, or higher dietary intake of targeted nutrients (e.g., antioxidants), as being neurodevelopmentally protective with respect to high levels of stress exposure during pregnancy[222]. However, at least one recent study suggests synergistic effects between maternal stress and diet on offspring body weight, food-motivated behaviors, and reward center functioning[223]. Importantly, the interaction between diet and stress during pregnancy appears to consistently affect regions in the brain that are of high relevance to energy homeostasis, including hippocampal morphology[224], nucleus accumbens dopamine release[223], and the morphology of the prefrontal cortex[225].

In humans, psychosocial stress is positively associated with oxidative stress (OS) [226,227]. Further, correlative studies during pregnancy have demonstrated positive associations of maternal and umbilical cord blood oxidative stress markers[228] with maternal and neonatal oxidative status in small-for-gestational age newborns[229]. However, the precise mechanisms are not yet fully understood[230,231]. While a moderate increase in OS is an expected physiological component of pregnancy[232,233], excessive maternal OS during pregnancy has been linked with a number of adverse pregnancy outcomes (e.g., growth restriction[234] and gestational diabetes[235]) that have a demonstrable influence on offspring metabolic health in later life. In support of the role of OS in fetal programming of energy homeostasis relevant brain regions, several rodent studies have established negative effects of maternal OS on offspring neurogenesis, hippocampal glucocorticoid receptor density, and cognitive functioning, that can be ameliorated by antioxidant administration to the pregnant dam[236–238]. Interestingly, in humans, excess maternal adiposity is associated with increased OS[239,240] and has been shown to alter DNA methylation sites relevant for CNS development and appears to reduce limbic white matter microstructure in offspring[169]. Thus, OS represents an additional pathway between maternal stressors and alterations to offspring energy homeostasis-relevant neurocircuitry. It should be noted, however, that because direct maternal-fetal transfer of reactive oxygen species is unlikely, OS should be considered as part of a broader pathway involving physiological mediating correlates (e.g., inflammatory processes, elevated glucocorticoid concentrations) [241].

5.1.4.3 Maternal immune/inflammatory state

Maternal inflammation is another potentially critical factor in programming of newborn energy homeostasis-relevant brain circuitry (e.g., salience, fronto-limbic). Animal studies have established that prenatal exposure to pro-inflammatory cytokines results in increased fat depots in offspring postnatally[242]. Further, adult male offspring of lipopolysaccharide-exposed dams have been shown to have higher caloric intake, fat mass, circulating leptin and up-regulation of hippocampal glucocorticoid receptor proteins[243]. While healthy fetal brain development and metabolic programming requires a rich set of cell-signaling mechanisms, the literature suggests that both are susceptible to excessively abundant inflammatory cytokines. Animal models demonstrate maternal immune activation (MIA) alone is sufficient to alter early neurodevelopment with long term consequences on the susceptibility to developing neuropsychiatric disorder (e.g., autism, schizophrenia[244]). In humans, recently emerging evidence points to the importance of interleukin-6 (IL-6) in programming energy homeostasis relevant brain circuitry and behavior. For example, maternal IL-6 concentrations during pregnancy are associated with newborn amygdala volume and connectivity[245], fronto-limbic white matter structural connectivity[246], and the functional connectome[135]. Importantly, each of these studies used inter-individual variation in the newborn brain circuitry to demonstrate prospective associations with cognitive outcomes that are relevant for feeding behavior including impulse control, cognition, and working memory (a cognitive domain associated with obesity[247]).

5.1.5 Summary of Fetal Programming of Energy Homeostasis Brain Networks

Based on the above-discussed findings, it is apparent that variation in metabolic function and in brain development share considerable overlap in terms of their developmental origins.

Yet, a comprehensive understanding of the relationship between these two domains has not yet been mapped and is potentially of high value to the field of fetal programming of obesity. The recent explosion of research on the fetal origins of obesity has focused primarily on peripheral cells, tissues and organ systems. It is plausible that fetal programming of energy homeostasis brain circuitry likely and additionally plays an important role in mediating the influence of maternal states and conditions on offspring obesity risk.

Table 2 summarizes the above-discussed evidence supporting the developmental plasticity of newborn brain energy homeostasis regulating networks and structures in humans and rodents. It is organized by maternal risk factors that, on one hand, have been prospectively associated with offspring obesity risk, and, on the other hand, have separately been associated with the development of key offspring brain phenotypes that are known to underlie energy homeostasis.

6. Questions, Issues, Considerations, and Future Research Directions

We outline below issues, considerations, and opportunities for future research directions. We begin by discussing recent advances that may facilitate a better quantification in the human newborn brain of the ontogeny of energy homeostasis brain networks at a systems level. Second, we discuss state-of-the-art approaches (recent and proposed) for phenotyping energy expenditure and energy intake in the human newborn. Third, we consider optimal approaches to phenotyping the *consequences* of variation in newborn energy homeostasis brain networks. Finally, we highlight several novel animal and *in-vitro*-based approaches that may advance our understanding of the *determinants* of inter-individual variation in energy homeostasis brain networks (through experimental models that trade off translational generalizability for mechanistic specificity).

6.1.1 Advances in neonatal brain imaging

The key variables of interest in neonatal brain imaging in the context of fetal programming are resolving the structural morphometry (size/shape), structural connectivity (integrity of the physical connections between brain structures/regions/networks), and functional connectivity (the degree to which structures/regions/networks covary in activity) within and between brain networks.

Over the course of the last decade, there has been a dramatic increase in the ability to non-invasively image the developing *human* brain using non-invasive MRI-based techniques[133,249,250]. This methodological advancement holds great promise in increasing our understanding of the developmental ontogeny of energy homeostasis-relevant brain circuitry and its *prospective* role in shaping propensity for childhood obesity. Specifically, differences are well established between normal weight adults and those with obesity in MRI-based (gray matter (GM) structure, white matter (WM) fiber integrity, and functional connectivity) measures of the hypothalamic-limbic-cortical brain circuitry that regulate energy homeostasis. It is, however, unclear whether the observed difference in this brain circuitry between normal-weight and individuals with obesity is a cause or consequence of the obese state. Identifying neural correlates of childhood obesity risk that predate the influence of the postnatal obesogenic environment and their fetal determinants

would advance scientific understanding of the neurobiological underpinnings of obesity. In this section, we summarize and identify potential MRI-based biomarkers of human energy homeostasis brain circuitry in infancy, including structural morphometry, structural connectivity and functional connectivity. Finally, we discuss the importance of and the opportunities in longitudinal imaging of early life neurodevelopment with MRI.

6.1.1.1   Structural Morphometry—GM/WM volume is an indirect measure of the amount and size of neurons, glial cells, and dendritic processes. Decreased GM and WM volume has been regionally associated with excess weight/obesity in adolescents and adults[124,126]. Adiposity effects neurotrophic factors such as leptin, insulin and pro-inflammatory cytokines, whose long-term influence may lead to excessive burden on the brain, as evident in elderly populations[251]. Alternatively, it is plausible that volume reductions in areas within energy homeostasis networks may also effect feeding behaviors. Insula volume serves as an ideal example because its importance in obesity is well established[65–67], and it is a brain region known to independently modulate complex-feeding behaviors[64,68]. Furthermore, reduced insula GM in adult individuals identified as obese-prone, relative to those categorized as obese-resistant, supports the notion that reduced insula volume is itself a risk factor for future weight gain[128]. This is further supported by data in newborns demonstrating a prospective association between newborn insula volume and increased gains in body fat percentage in the first six-months of postnatal life[123]. Collectively, these findings support the premise that structural morphometry of the newborn brain represents a promising neurophenotype underlying the functional consequences of variation in energy homeostasis brain circuitry.

6.1.1.2   Structural Connectivity—Diffusion Tensor Imaging (DTI) directly measures the isotropy of water diffusion in the brain and, indirectly, the capacity to transmit efferent and afferent signals between cortical nodes in the brain. In adults, hypothalamic mean diffusion[252], and WM anisotropy and volume[253] are associated with obesity. However, the directions of these WM associations are inconsistent and brain-region/tract-dependent[254]. In normal-weight children relative to those with obesity, Ou *et al* demonstrated *increased* fractional anisotropy in tracts related to food intake (e.g., forceps minor, inferior fronto-occipital fasciculus)[255], and they suggest fatty acid presence in the extracellular space surrounding the axons as a cause. In contrast to their findings in children, Ou *et al* have also demonstrated *reduced* anisotropy in neonatal offspring of mothers with obesity[169]. Analogous with obesity-related GM changes, it is possible that the WM deficits observed in adult individuals with obesity are a consequence, as opposed to a cause, of long-term exposures to obesity-related factors. To date, there are no studies characterizing the association between newborn WM phenotypes and postnatal obesity -related outcomes.

6.1.1.3   Functional Connectivity—Resting state functional MRI provides information about how the brain is organized, with "connected" brain regions working more closely in synchrony. Alterations in functional connectivity in and between energy homeostasis brain networks have been observed in overweight and adults with obesity[256–258]. In one early study of MR-based hypothalamic connectivity, Wijngaarden *et al* observed hypothalamic-insula connectivity differences in adult subjects with obesity[259]. A second

study of hypothalamic connectivity identified deficits in overweight/obese adults between both the orbitofrontal cortex and ventral striatum and the medial hypothalamus[260,261]. Since these two early studies, several others support nutritional status-dependent connectivity between the hypothalamus and the insula, striatum, and hippocampus[262–265]. In the salience network, adult obesity[261,266] and fat intake after sleep deprivation[267] have been associated with deficits in ACC-putamen connectivity. Importantly, similar circuitry (ACC-prefrontal) in the human newborn appears to be associated with maternal obesity state (weight[134]). One recent report has further identified effects of maternal weight status on newborn offspring functional brain connectivity strength within sensory, reward, executive, and motor control networks[268]. Collectively, these results suggest altered connectivity patterns across multiple homeostasis-regulating networks in the obese relative to lean state. However, little is known about the developmental ontogeny or integrity of these specific networks in obesity prone newborns.

6.1.1.4   Longitudinal Imaging—In both humans and rodents, the mechanisms motivating the initiation and cessation of feeding transition from visceral/gustatory/interoceptive dominated in early life, to satiety/reward-dominated control in post-pubertal life[116]. However, these dominant networks act in concert with other cortical and subcortical networks that regulate feeding decisions, justifying a more systems level approach that includes and integrates feedback and feed-forward input in order to understand energy homeostasis relevant neurodevelopment. Yet, despite acknowledgement of the likelihood of its developmental importance[269], little attention has been paid to the ontogeny of the system of networks as a whole, the maternal influences during pregnancy on this ontogeny, or the postnatal consequences of variation in this ontogeny for later obesity. MRI-based techniques present a unique and timely opportunity to address this current knowledge gap. Specifically, MRI provides a maximally non-invasive approach suitable for longitudinal observation of systems-based neurodevelopment across species. In neonatal/infant human research that likely requires natural sleep during scanning, this is largely limited to passive observation of anatomical morphology, and functional/structural connectivity within and between systems. However, recent evidence supports the plausibility of odorant delivery and functional response recorded using MRI in infants[100]. In contrast to human research, stimuli in early rodent life can likely be extended to include nutritive gastric distension and hormonal inputs (e.g., leptin administration), though care should be taken in experimental design as most hormonal stimuli-of-interest are known effectors of development. In later stages of development, when human children are old enough for compliance, the opportunity for more complex stimuli (e.g., tasteants) and challenge protocols (e.g., stressors) would allow gaining a greater understanding of the gestational influence on specific systems including reward, satiety, visceral and salience networks.

6.2.1   Advances in the quantification of energy expenditure during the early postnatal life period/phase.

The key variables of interest in the quantification of energy expenditure during early postnatal life are focused on the constituents of total energy expenditure (TEE): basal metabolic rate (BMR), diet induced thermogenesis (DIT) and physical activity levels (PAL).

Doubly labeled water (DLW) is the most widely-used method for measuring infant TEE[270–273] owing to its minimal invasiveness, high accuracy, and repeatability[274]. Indirect calorimetry is a complimentary measure capable of further delineating the two components of TEE that compromise BMR: sleeping metabolic rate (SMR) and wakeful resting energy (WEE) [275,276]. DIT is also typically measured via indirect calorimetry, however, is measured using pre- and postprandial conditions[277]. DIT is then defined as the post-ingestion increase in BMR divided by the energy content of the food. Thus, there exists a challenge and opportunity with respect to refined measures of intake for normalization (see Section 6.2.2). With respect to PAL, actigraphy devices are a common method for determination in pediatric samples as they are relatively inexpensive, reliable, and convenient, making them highly accessible in a research context. Recent improvements in wearable devices for infants have also begun to provide insights into the role of early life PAL in typical growth trajectories[278,279]. As a proxy, when included with TEE, SMR can also be used to objectively estimate PAL[280,281] in early life by assuming that variation in WEE is principally driven by variation in PAL. In ideal study conditions, frequent measures of energy intake quantity and quality (see Section 6.2.2) would be coupled with repeated measures of energy expenditure (e.g., TEE, DIT, PAL, and BMR), and longitudinal measures of body composition (see Section 6.3.1) in order to provide high temporal resolution measures of early life energy balance.

6.2.2 Advances in quantification of energy intake during the early postnatal life period/ phase.

The key variables of interest in the quantification of energy intake during early postnatal life can be categorized as indirect (frequency of intake, nutritional biomarkers) and direct (breastmilk/formula composition and volume) measures.

In children and adults, self-reported measures of dietary intake are commonly used despite their susceptibility to day-to-day variation in diet (e.g., 24-hour recall) and recall error[282,283]. Recent advances in smartphone applications have helped address this by allowing for high frequency intake assessments over long periods of time at minimal cost and subject burden[284,285] yet remain susceptible to rater bias and perception. Alternatively, nutritional biomarkers (e.g., plasma carotenoid[286], lipid profiles[287], urinary sucrose[288], plasma alkylresorcinol[289]) hold the potential to reduce error from day-to-day diet variation and rater bias by providing objective measures of energy intake over varying time scales dependent on the tissue being sampled[290] (e.g., blood, hair, adipose tissue). Further towards this aim, recent biosensor advances are enabling sweat-based continuous monitoring of metabolites and protein concentrations using wearable micropatch arrays[291–293]. While the majority of developments in the electronic recording of feeding behaviors[294] and nutritional biomarkers have thus far focused on older populations, emerging evidence suggests they provide similar advantages in studies focused on early life[295] behaviors designed for the detailed characterization of energy intake.

Early life assessments of energy intake reflect a relatively stable and simple dietary intake (breast milk/formula). However, objective and accurate quantification of intake volume and composition during breastfeeding in an accessible and minimally invasive manner remains

challenging[296]. In addition to the challenges of accurate volume measures, there exists variability in the composition of breast milk temporally across a single feed. For example, hind milk has higher lipid content relative to fore milk, and such a difference in composition appears to be of consequence to early life growth in very premature infants[297]. For this reason, assessment of breast milk composition (e.g., lipid content) *across feeding duration* would advance current understanding of the influence of intake on energy intake/imbalance in early life. Towards this, limiting study recruitment to maternal cohorts identified as suboptimal infant breastfeeding behavior[298] (SIBB) would enrich for exclusively bottle fed infants, thus allowing for easy, frequent and accurate quantification of homogeneous intake by objectively and precisely weighing bottles before and after feeding. While this would result in a comprehensive, precise and well-controlled measure of intake, it would generalize poorly (e.g., to breastfed individuals) and limit understanding with respect to heterogeneity in breast milk/formula composition. Nipple shields[299], while controversial with respect to its level of invasiveness, are instrumental in SIBB populations and could address such a shortcoming by leveraging negative pressure[300–302] to proportionally sample volume. Minimal fluidic mixing is a feature of microfluidic devices[303], and if incorporated into a nipple shield design, could allow for the retention of temporal composition profiles, providing valuable information about the interaction between breast milk temporal composition dynamics, feeding behaviors and subsequent growth. Accurate and precise characterization of both breast and bottle feeding is particularly relevant to understanding early life feeding behaviors including cessation, duration and intensity of feeding. Because variation in these feeding behaviors[304,305] is likely driven by variation in energy homeostasis brain circuitry, they are of high relevance to the context of the current framework.

6.3.1 Advances in quantification of the biophysical, metabolic and clinical consequences (outcomes) of variation in newborn energy homeostasis brain circuitry

The key variable of interest in furthering our understanding of the clinical consequences of variation in newborn energy homeostasis brain circuitry is the magnitude and trajectory of adiposity and its regional distribution.

The consequence of positive imbalance in energy homeostasis above and beyond normal growth is excess tissue deposition. Mounting evidence suggests child size and growth velocity during early infancy represent the most reliable, valid, and strongest predictors of childhood obesity risk. Rapid size increase, and weight or fat gain during early life is associated with increased infant cardiovascular risk factors[306], increased childhood (and adult) obesity risk[307] and related outcomes[308–314] including type 1 diabetes[315], metabolic disorders[316], hypertension[317], and asthma[318] in later life. Recent evidence supports the notion that change in infant fat mass during early infancy is a much stronger predictor of childhood obesity risk than weight gain alone[308]. More specifically, the phase of rapid fat accrual in the first three months of life has been identified as a critical window for adiposity growth[319].

However, it should be noted that early life growth is highly non-linear, suggesting that two single-measure time points insufficiently characterize growth features including tempo, peak magnitude/velocity[320,321], and age at peak magnitude/velocity, particularly in relation to

later health risks[322]. It therefore seems imperative that studies using growth as an outcome ought to record frequent measures (e.g., skinfold, length, weight) and, when possible, anchor them to more informative measures of body-composition including MRI, DXA, or air displacement plethysmography. One emerging technology that promises to deliver frequent, precise and, most importantly, convenient quantification of body composition is 3d structured light imaging[323,324]. Commercially available structured light scanners are now affordable and can be packaged with user-friendly software, enabling research participants to obtain in-home surface and volume measures of their growing child, independent of support staff. Coordinated measurements of volume and weight allow for body composition (e.g., body fat percentage) estimates in a manner consistent with those derived from air displacement plethysmography at a fraction of the cost and inconvenience. Serial measures utilizing structured light imaging would also reduce the effect of measurement bias (*via* repeated measures) while simultaneously enabling true non-linear modeling of early life growth patterns.

While frequent serial longitudinal measures will provide a greater understanding of growth, it is likely that proxy measures of total body fat will only provide a partial picture of metabolic health and disease risk. For example, it has recently been argued that it is the spatial and class distribution of lipids in fat deposits that determines metabolic risk[325,326]. Importantly, emerging MRI-based techniques allow for the precise quantification of fat composition throughout the whole body under free breathing conditions[327,328]. The importance of this development lies in the lack of compliance observed during the traditional breath-holding protocols in pediatric populations. The application of these emerging techniques would provide whole-body proton density fat fraction maps, thus allowing for the precise quantification of lipid distribution and density throughout the body. Important deposits of interest include the liver and classical Brown Adipose Tissue sites[329,330]. In addition to such detailed measures, combining them with frequent longitudinal (serial) assessments would not only provide a more complete picture of body composition but could provide important anchor points in longitudinal curve fitting, as they would represent a more accurate and precise measurement of total body fat.

Collectively, these findings and considerations support the critical importance of longitudinal and detailed cross-sectional assessments of body composition during the period of rapid tissue expansion in early life and the validity of their use as outcomes in the context of research pertaining to fetal programming of energy homeostasis brain circuitry.

6.3.2 The role of postnatal conditions in assessing the consequences of altered newborn energy homeostasis brain circuitry

Prenatal states, conditions, and biological factors that influence newborn energy homeostasis brain networks can also influence brain networks postnatally. For example, as suggested above, maternal stress may influence the intrauterine development of limbic brain circuitry implicated in several aspects of food intake. Moreover, it is evident that sequelae of maternal stress, including depression[331], anxiety[332], and obesity[333], are associated with reduced breastfeeding initiation and/or duration. This then creates a scenario in which susceptibility to stress exposure may be established *in utero* (altered brain development),

only to then encounter adverse postnatal exposures that are themselves conditioned on the same stress exposure. The infant microbiome is an additional postnatal factor increasingly acknowledged to play a role in postnatal brain development[334,335]. Further, infant microbiome composition and activity are believed to be susceptible to maternal conditions (e.g., inflammation) [336] that may also alter fetal brain development. Because most maternal conditions with the potential to alter fetal brain development during pregnancy are likely to persist through the postnatal period, they then may potentiate the adverse effects of prenatal exposures. Indeed, our model recognizes that the effects of prenatal and postnatal states and conditions may not be mutually exclusive, and that in many instances the effects of postnatal exposures may, in part, be conditioned upon the effects of prenatal exposures and that these effects may be additive or multiplicative in nature.

6.4 Advances in the use of animal models and in vitro approaches for studies of the determinants and consequences of variation in newborn energy homeostasis brain circuitry

Till this point we have focused on currently-available opportunities for human research on fetal programing of energy homeostasis brain circuitry. Now, we briefly provide a perspective on animal and *in vitro* research opportunities, with a specific focus on how they can complement and inform human research.

First, recent advances in optogenetics[337] allows for high temporal and spatial resolution control of living neural tissue. Thus, this method provides an *in vivo* basis for experimentally validating the behavioral/physiological consequences of activating specific brain regions that have been identified in human cohorts as susceptible to developmental programming and prospectively relevant to early life energy imbalance. Further, combining optogenetic methods with fMRI[338–340] could facilitate assessment of the functional connectivity of *precise* neural circuitry, particularly in the context of variation in fetal exposures (e.g., stress/inflammation). For instance, one could vary maternal exposures like diet (e.g., saturated fats) during pregnancy and then characterize the inter-individual variation in offspring functional connectivity to the arcuate nucleus by optically exciting virally transfected cells during fMRI acquisition. The advantage of this approach combines features of optogenetics not available using conventional MRI techniques (precise neural control) while obtaining whole brain function on a scale translatable to that observed in human studies. Yet several challenges remain in establishing its utility in a developmental context when considering the time necessary to establish the virus necessary for light-based excitation relative to the pace of early life development, and its invasive nature relative to the plasticity of the developing brain. In contrast, manganese enhanced MRI (MEMRI) has recently emerged as a powerful but minimally invasive (administration of $MnCl_2$ through the tail) tool for understanding neural recruitment in rodents. MEMRI is considered non-toxic at viable doses, validated with histology and gene expression, has been used to map pain circuitry in newborn rodents[341], and most relevantly, has been instrumental in recent gains in the fundamental understanding of early life neurodevelopment at a systems level[342–344]. Further, it is compatible with more conventional MR imaging (DTI and resting state functional connectivity) techniques allowing for its use as a complimentary measure[345,346]. Finally, MEMRI has the demonstrated ability to map neural dynamics in the hypothalamus

during administration of leptin. Because MEMRI and optogenetics provide precise neural control and inference observable at a macroscopic scale, these tools promise maximal translation from rodent to human research in a developmental context. In particular, they present a unique opportunity to gain insight into the early life transition from visceral-based control of feeding to reward-based feeding, as well as its gestational determinants and later consequences on the obese state.

Second, the placenta (and placental biology) represents the key interface between the maternal and fetal compartments. A number of questions remain regarding when, what, and how circulating maternal factors (e.g., lipids, cytokines) are able to cross the placental barrier. Recently, MRI techniques have been developed to non-invasively detect complement activation in the placenta using C-3 targeted ultrasmall paramagnetic iron oxide (USPIO) nanoparticles to bind within inflamed placenta and fetal cortex[347,348]. USPIO is an MR contrast agent that locally increases field inhomogeneity and thereby decreases T2* relaxation time (signal void). Ultimately this technique could be leveraged to gain a greater understanding of the impact of maternal inflammation (e.g., resulting from maternal obesity) on the placenta and fetal brain. While this technique is potentially viable in humans (as Ferumoxytol is FDA-approved for human use), it is unlikely to see applications in pregnancy research in the near future and therefore should be considered for rodent models only.

Finally, tissue engineering methods represent an additional opportunity to gain a greater understanding of the role of the gestational milieu on neurodevelopment. Specifically, lab-on-a-chip and organoid models allow for well-controlled environments in which to perturb living tissues with metabolic, inflammatory or endocrine challenges. One recently micro-engineered placenta-on-a-chip[349] provided an *in vitro* testbed for assessing the structural and functional complexities of the placental barrier under varying conditions. Importantly, this placenta-on-a-chip was able to recapitulate maternal-to-fetal glucose transfer properties found in *ex-vivo* perfused human placentas. Similarly, brain organoids are continually improving in both complexity and function with respect to their respective target tissues[350,351]. Specifically, four recent advances have allowed for the development of highly complex functions in brain organoids including: 1) fine scale transcriptional mappings[352], 2) photo-responsive retinal networks[353], 3) inter-neuronal migration[354], and 4) enhancement of forebrain and cortical plate formation[355]. By perturbing the microenvironment with physiologically relevant levels of inflammatory and stress-related factors during development of lab-on-a-chip devices and/or brain organoids, one could gain a highly detailed understanding of the impact of the gestational milieu on tissue development at the cellular level.

6.5 The scientific and clinical relevance of characterizing variation in newborn energy homeostasis brain circuitry

The scientific relevance of characterizing variation in the newborn brain derives from the logic that energy homeostasis brain circuitry near birth represents a relatively (to children/adults) simple model of the neurobiology of energy homeostasis, and that brain circuitry at this time largely precedes influence by the postnatal obesogenic environment. The conceptual framework discussed above includes several brain networks that have

downstream behavioral analogues to feeding in later life (e.g., reward/motivation, learned associations), however in infancy, there are also several external pressures and networks found in adulthood that are not yet relevant. For example, brain networks associated with conscious inhibition[356], food-related monetary economic decision making[357] (*i.e.,* the balance between food costs and nutrition), and susceptibility to food advertising[358] are not of direct relevance to infant feeding. In addition, given the extreme nutritional requirements during infancy (several times the caloric requirements, per kg, in adulthood) it is likely that feeding behaviors are especially salient during infancy, and are thus more readily measurable. Finally, because the state of the brain at birth reflects the cumulative sum of influences by in utero exposures during fetal brain development, yet precedes influence by the postnatal environment under which the brain further adapts, the inter-individual variation present at birth provides the most unconfounded characterization of in utero influences possible. Therefore, we assert that the time of birth is of scientific importance as it enables a more complete understanding of the temporality and sequence of effects in fetal programming than observations made in later life alone (*e.g.,* early childhood).

The clinical importance (*i.e.,* effect size) of inter-individual variation in human energy homeostasis brain networks at birth (*i.e.,* initial setting) is largely unknown. While it is unlikely that any single conceptualization of the causal origins of obesity will be of major consequence to the global obesity crisis, obesity has been labeled a "heritable neurobehavioral disorder that is highly sensitive to environmental conditions" [359]. This then suggests that pre- and postnatal environmental exposures play a critically important role in expressing inter-individual variation in the developing brain. Further, because fetal brain development happens at such a rapid pace culminating with the formation, segregation (differentiation/specialization) and integration (forming a network of networks) of brain networks by the time of birth, it is likely that the foundational setting of these brain networks plays a meaningful role in the ontogeny of downstream feeding behaviors in later life. However, because brain development in humans is especially protracted in order to further adapt to the postnatal environment, we assert that the proposed framework should largely be viewed in the context of susceptibility. That is, future efforts also focusing on the postnatal ontogeny (*e.g.,* cascading effects, reversibility) of these brain networks under the influence of the postnatal obesogenic environment, as well as potential interventions and positive influences[360], are critical in further contributing to the current understanding of the clinical importance of fetal programming of human energy homeostasis brain networks.

7 . Summary/Conclusion

Here, we have provided an overview of the concept of energy balance and the role of the brain in regulating energy balance. We have described evidence supporting the premise that energy homeostasis relevant brain circuitry is established and functional by the time of birth, with contextually-meaningful variation across individuals. We have advanced a novel conceptual framework placing fetal brain development on the putative pathway between maternal conditions during pregnancy and offspring susceptibility for obesity. Specifically, we describe a model by which classes of exposure *in utero* (sociodemographic, maternal biophysical, metabolic, endocrine, and inflammation) may influence the development of brain networks (satiety, reward, visceral, salience) that are ultimately for responsible for

regulating downstream feeding behaviors. Further, we have identified questions, issues, considerations, and research directions relevant to our proposed model. By identifying determinants of childhood obesity that are already present at birth (i.e., predating the influence of postnatal conditions), this conceptual framework seeks to lay the groundwork for primary prevention strategies. In addition, through the identification of neural correlates of childhood obesity risk that predate the influence of the postnatal obesogenic environment and their fetal determinants, this framework aims to advance the current scientific understanding of the neurobiological underpinnings of obesity in humans.

Acknowledgments

References

1. Lim SS, Flaxman AD, Danaei G, et al. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. The Lancet 380, 2224–2260 (2012).

2. McPherson K Reducing the global prevalence of overweight and obesity. The Lancet 384, 728–730 (2014).

3. Kelly AS, Barlow SE, Rao G, et al. Severe obesity in children and adolescents: Identification, associated health risks, and treatment approaches: A scientific statement from the American Heart Association. Circulation 128, 1689–1712 (2013). [PubMed: 24016455]

4. Tylavsky FA. Ferrara A, Catellier DJ, et al. Understanding childhood obesity in the US: the NIH environmental influences on child health outcomes (ECHO) program. Int J Obes (Lond) 44, 617–627 (2020). [PubMed: 31649277]

5. Serdula MK, Ivery D, Coates RJ, Freedman DS, Williamson DF, & Byers T Do obese children become obese adults? A review of the literature. Prev Med 22, 167–177 (1993). [PubMed: 8483856]

6. Whitaker RC, Wright JA, Pepe MS, Seidel KD & Dietz WH Predicting obesity in young adulthood from childhood and parental obesity. New England Journal of Medicine 337, 869–873 (1997). [PubMed: 9302300]

7. Freedman DS, Khan LK, Dietz WH, Srinivasan SR & Berenson GS Relationship of childhood obesity to coronary heart disease risk factors in adulthood: the Bogalusa Heart Study. Pediatrics 108, 712–718 (2001). [PubMed: 11533341]

8. Dabelea D & Harrod CS Role of developmental overnutrition in pediatric obesity and type 2 diabetes. Nutr. Rev. 71 Suppl 1, S62–7 (2013). [PubMed: 24147926]

9. Forgat-Campagna A & Narayan KV Type-2 diabetes in children: Exemplifies the growing problem of chronic diseases. BMJ. 322(7283): 377–378 (2001). [PubMed: 11179142]

10. Doak CM, Visscher TLS, Renders CM, & Seidell JC The prevention of overweight and obesity in children and adolescents: a review of interventions and programmes. Obesity 7(1):111–136 (2006).

11. Ghoorah K, Campbell P & Kent A Obesity and cardiovascular outcomes: a review. European Heart Journal: Acute Cardiovascular Care 5(1): 77–85 (2016). [PubMed: 24526749]

12. Castro-Rodríguez DC, Rodríguez-González GL, Menjivar M & Zambrano E Maternal interventions to prevent adverse fetal programming outcomes due to maternal malnutrition: Evidence in animal models. Placenta 102, 49–54 (2020). [PubMed: 33218579]

13. Lindsay KL, Entringer S, Buss C & Wadhwa PD Intergenerational transmission of the effects of maternal exposure to childhood maltreatment on offspring obesity risk: A fetal programming perspective. Psychoneuroendocrinology 116, 104659 (2020). [PubMed: 32240906]

14. Bond TA, Karhunen V, Wielscher M, et al. Exploring the role of genetic confounding in the association between maternal and offspring body mass index: evidence from three birth cohorts. Int J Epidemiol 49, 233–243 (2020). [PubMed: 31074781]

15. Kisioglu B & Nergiz-Unal R Potential effect of maternal dietary sucrose or fructose syrup on CD36, leptin, and ghrelin-mediated fetal programming of obesity. Nutr Neurosci 23, 210–220 (2020). [PubMed: 29961406]

16. anlı E & Kabaran S Maternal obesity, maternal overnutrition and fetal programming: Effects of epigenetic mechanisms on the development of metabolic disorders. Curr Genomics 20, 419–427 (2019). [PubMed: 32476999]

17. Chang E, Hafner H, Varghese M, et al. Programming effects of maternal and gestational obesity on offspring metabolism and metabolic inflammation. Sci Rep 9, 16027–15 (2019). [PubMed: 31690792]

18. Moullé VS & Parnet P Effects of nutrient intake during pregnancy and lactation on the endocrine pancreas of the offspring. Nutrients 11, 2708 (2019). [PubMed: 31717308]

19. Du JE, You YA, Kwon EJ, et al. Maternal malnutrition affects hepatic metabolism through decreased hepatic taurine levels and changes in HNF4A methylation. Int J Mol Sci 21, 9060 (2020). [PubMed: 33260590]

20. Dumolt JH, Ma M, Mathew J, Patel MS & Rideout TC Gestational hypercholesterolemia alters fetal hepatic lipid metabolism and microRNA expression in Apo-E-deficient mice. Am. J. Physiol. Endocrinol. Metab. 317, E831–E838 (2019). [PubMed: 31453710]

21. He B. Wen Y, Hu S, et al. Prenatal caffeine exposure induces liver developmental dysfunction in offspring rats. J Endocrinol 242, 211–226 (2019). [PubMed: 31340202]

22. Kislal S, Shook LL & Edlow AG Perinatal exposure to maternal obesity: Lasting cardiometabolic impact on offspring. Prenat Diagn 40, 1109–1125 (2020). [PubMed: 32643194]

23. Campodonico-Burnett W, Hetrock B, Wesolowski SR, et al. Maternal Obesity and Western-Style Diet Impair Fetal and Juvenile Offspring Skeletal Muscle Insulin-Stimulated Glucose Transport in Nonhuman Primates. Diabetes 69, 1389–1400 (2020). [PubMed: 32354857]

24. Hall KD, Heymsfield SB, Kemnitz JW, Klein S, Schoeller DA, & Speakman JR Energy balance and its components: implications for body weight regulation. The American journal of clinical nutrition 95(4): 989–994 (2012). [PubMed: 22434603]

25. Speakman JR The evolution of body fatness: trading off disease and predation risk. J Exp Biol 221, jeb167254 (2018). [PubMed: 29514887]

26. Schwartz MW, Seeley RJ, Zeltser LM, et al. Obesity Pathogenesis: An Endocrine Society Scientific Statement. Endocr. Rev. 38, 267–296 (2017). [PubMed: 28898979]

27. Gonzalez-Campoy JM, Richardson B, Richardson C, et al. Bariatric Endocrinology: Principles of Medical Practice. International journal of endocrinology (2014).

28. Augustine V, Lee S & Oka Y Neural control and modulation of thirst, sodium appetite, and hunger. Cell 180, 25–32 (2020). [PubMed: 31923398]

29. Andermann ML & Lowell BB Toward a wiring diagram understanding of appetite control. Neuron 95, 757–778 (2017). [PubMed: 28817798]

30. Augustine V, Gokce SK, Lee S, et al. Hierarchical neural architecture underlying thirst regulation. Nature 555, 204–209 (2018). [PubMed: 29489747]

31. Waterson MJ & Horvath TL Neuronal regulation of energy homeostasis: Beyond the hypothalamus and feeding. Cell Metabolism 22, 962–970 (2015). [PubMed: 26603190]

32. Blouet C & Schwartz GJ Brainstem nutrient sensing in the nucleus of the solitary tract inhibits feeding. Cell Metabolism 16, 579–587 (2012). [PubMed: 23123165]

33. Kishi T, Aschkenasi, Lee CE, Mountjoy KG, Saper CB, Elmquist JK Expression of melanocortin 4 receptor mRNA in the central nervous system of the rat. J Comp Neurol 457, 213–235 (2003). [PubMed: 12541307]

34. Travagli RA, Hermann GE, Browning KN & Rogers RC Brainstem circuits regulating gastric function. Annu Rev Physiol 68, 279–305 (2006). [PubMed: 16460274]

35. Rau AR & Hentges ST The relevance of AgRP Neuron-Derived GABA inputs to POMC neurons differs for spontaneous and evoked release. J Neurosci 37, 7362–7372 (2017). [PubMed: 28667175]

36. Atasoy D, Betley JN, Su HH & Sternson SM Deconstruction of a neural circuit for hunger. Nature 488, 172–177 (2012). [PubMed: 22801496]

37. Könner AC, Klöckener T & Brüning JC Control of energy homeostasis by insulin and leptin: targeting the arcuate nucleus and beyond. Physiol. Behav. 97, 632–638 (2009). [PubMed: 19351541]

38. Timper K & Brüning JC Hypothalamic circuits regulating appetite and energy homeostasis: pathways to obesity. Dis Model Mech 10, 679–689 (2017). [PubMed: 28592656]

39. Mullur R, Liu Y-Y & Brent GA Thyroid hormone regulation of metabolism. Physiol Rev 94, 355–382 (2014). [PubMed: 24692351]

40. Haas VK, Gaskin KJ, Kohn MR, Clarke SD & Müller MJ Different thermic effects of leptin in adolescent females with varying body fat content. Clin Nutr 29, 639–645 (2010). [PubMed: 20452104]

41. Müller MJ, Bosy-Westphal A & Heymsfield SB Is there evidence for a set point that regulates human body weight? F1000 Med Rep 2, 59 (2010). [PubMed: 21173874]

42. Lee PC & Dixon JB Food for thought: Reward mechanisms and hedonic overeating in obesity. Curr Obes Rep 6, 353–361 (2017). [PubMed: 29052153]

43. Ferrario CR, Labouèbe G, Liu S, et al. Homeostasis meets motivation in the battle to control food intake. Journal of Neuroscience 36, 11469–11481 (2016). [PubMed: 27911750]

44. Leigh S-J, Lee F & Morris MJ Hyperpalatability and the generation of obesity: Roles of environment, stress exposure and individual difference. Curr Obes Rep 7, 6–18 (2018). [PubMed: 29435959]

45. Bogdanov VB et al. Reward-related brain activity and behavior are associated with peripheral ghrelin levels in obesity. Psychoneuroendocrinology 112, 104520 (2020). [PubMed: 31786481]

46. Han P, Mohebbi M, Seo H-S & Hummel T Sensitivity to sweetness correlates to elevated reward brain responses to sweet and high-fat food odors in young healthy volunteers. NeuroImage 208, 116413 (2020). [PubMed: 31837472]

47. Lenoir M, Serre F, Cantin L & Ahmed SH Intense sweetness surpasses cocaine reward. PLoS ONE 2, e698 (2007). [PubMed: 17668074]

48. Wise RA & Rompré PP Brain dopamine and reward. Annu Rev Psychol 40: 191–225(1989). [PubMed: 2648975]

49. Land BB, Narayanan NS, Liu R, et al. Medial prefrontal D1 dopamine neurons control food intake. Nature Neuro 17, 248–253 (2014).

50. Kanoski SE & Grill HJ Hippocampus contributions to food intake control: mnemonic, neuroanatomical, and endocrine mechanisms. Biological Psychiatry 81(9):748–756(2015). [PubMed: 26555354]

51. Kullmann S, Heni M, Veit R, et al. Intranasal insulin enhances brain functional connectivity mediating the relationship between adiposity and subjective feeling of hunger. Sci Rep 7, 1627–10 (2017). [PubMed: 28487570]

52. Avery JA, Powell JN, Breslin FJ, et al. Obesity is associated with altered mid-insula functional connectivity to limbic regions underlying appetitive responses to foods. Journal of Psychopharmacology 31, 1475–1484 (2017). [PubMed: 28944718]

53. Nakamura Y & Ikuta T Caudate-Precuneus functional connectivity is associated with obesity preventive eating tendency. Brain Connect 7, 211–217 (2017). [PubMed: 28260392]

54. Bassareo V & Di Chiara G Differential responsiveness of dopamine transmission to food-stimuli in nucleus accumbens shell/core compartments. Neuroscience 89, 637–641 (1999). [PubMed: 10199600]

55. Norgren R, Hajnal A & Mungarndee SS Gustatory reward and the nucleus accumbens. Physiol. Behav. 89, 531–535 (2006). [PubMed: 16822531]

56. Epstein LH, Temple JL, Roemmich JN & Bouton ME Habituation as a determinant of human food intake. Psychol Rev 116, 384–407 (2009). [PubMed: 19348547]

57. Schultz W Dopamine signals for reward value and risk: basic and recent data. Behav Brain Funct 6, 24–9 (2010). [PubMed: 20416052]

58. Epstein LH, Rodefer JS, Wisniewski L & Caggiula AR Habituation and dishabituation of human salivary response. Physiol. Behav. 51, 945–950 (1992). [PubMed: 1615055]

59. Volkow ND, Wise RA & Baler R The dopamine motive system: implications for drug and food addiction. Nat. Rev. Neurosci. 18, 741–752 (2017). [PubMed: 29142296]

60. Volkow ND & Wise RA How can drug addiction help us understand obesity? Nat. Neurosci. 8, 555–560 (2005). [PubMed: 15856062]

61. Simmons WK & DeVille DC Interoceptive contributions to healthy eating and obesity. Curr Opin Psychol 17, 106–112 (2017). [PubMed: 28950955]

62. Tomasi D, Wang GJ, Wang R, Backus W & Geliebter A Association of body mass and brain activation during gastric distention: implications for obesity. PLoS One 4(8):e6847 (2009). [PubMed: 19718256]

63. Gutierrez R, Fonseca E & Simon SA The neuroscience of sugars in taste, gut-reward, feeding circuits, and obesity. Cell Mol Life Sci 77, 3469–3502 (2020). [PubMed: 32006052]

64. Livneh Y, Sugden AU, Madara JC, et al. Estimation of current and future physiological states in insular cortex. Neuron 105, 1094–1111.e10 (2020). [PubMed: 31955944]

65. Morton GJ, Meek TH & Schwartz MW Neurobiology of food intake in health and disease. Nat. Rev. Neurosci. (2014).

66. Simon SA, de Araujo IE, Gutierrez R & Nicolelis MAL The neural mechanisms of gustation: a distributed processing code. Nat. Rev. Neurosci. 7, 890–901 (2006). [PubMed: 17053812]

67. Volkow ND, Wang GJ, Tomasi D & Baler RD Obesity and addiction: neurobiological overlaps. Obesity Reviews (2013).

68. Peng Y, Gillis-Smith S, Jin H, et al. Sweet and bitter taste in the brain of awake behaving animals. Nature 1–12 (2015). doi:10.1038/nature15763

69. Kurth F, Zilles K, Fox PT & Laird AR A link between the systems: functional differentiation and integration within the human insula revealed by meta-analysis. Brain Struct Funct 214(5–6):519–34 (2010). [PubMed: 20512376]

70. Small DM & Prescott J Odor/taste integration and the perception of flavor. Exp Brain Res 166, 345–357 (2005). [PubMed: 16028032]

71. Mufson EJ, Mesulam MM & Pandya DN Insular interconnections with the amygdala in the rhesus monkey. Neuroscience 6, 1231–1248 (1981). [PubMed: 6167896]

72. Kadohisa M Neuronal representations of stimuli in the mouth: The primate insular taste cortex, orbitofrontal cortex and amygdala. Chemical Senses 30, 401–419 (2005). [PubMed: 15829609]

73. Morton GJ, Cummings DE, Baskin DG & Barsh GS Central nervous system control of food intake and body weight. Nature (2006).

74. Baxter MG & Murray EA The amygdala and reward. Nat. Rev. Neurosci. (2002).

75. Carnell S, Benson L, Chang KV, et al. Neural correlates of familial obesity risk and overweight in adolescence. NeuroImage 159, 236–247 (2017). [PubMed: 28754348]

76. Berthoud H-R, Münzberg H & Morrison CD Blaming the brain for obesity: Integration of hedonic and homeostatic mechanisms. Gastroenterology 152, 1728–1738 (2017). [PubMed: 28192106]

77. Ham T, Leff A, de Boissezon X, Joffe A & Sharp DJ Cognitive control and the salience network: an investigation of error processing and effective connectivity. Journal of Neuroscience 33, 7091–7098 (2013). [PubMed: 23595766]

78. Uddin LQ Salience processing and insular cortical function and dysfunction. Nat. Rev. Neurosci. 16, 55–61 (2015). [PubMed: 25406711]

79. Seeley WW, Menon V, Schatzberg AF, et al. Dissociable intrinsic connectivity networks for salience processing and executive control. Journal of Neuroscience 27, 2349–2356 (2007). [PubMed: 17329432]

80. Sewaybricker LE, Melhorn SJ, Askren MK, et al. Salience network connectivity is reduced by a meal and influenced by genetic background and hypothalamic gliosis. Int J Obes (Lond) 44, 167–177 (2020). [PubMed: 30967608]

81. Farruggia MC, van Kooten MJ, Perszyk EE, et al. Identification of a brain fingerprint for overweight and obesity. Physiol. Behav. 222, 112940 (2020). [PubMed: 32417645]

82. Barrand S, Crowley TM, Wood-Bradley RJ, De Jong KA & Armitage JA Impact of maternal high fat diet on hypothalamic transcriptome in neonatal Sprague Dawley rats. PLoS ONE 12, e0189492 (2017). [PubMed: 29240779]

83. Plagemann A, Harder T, Rake A, et al. Observations on the orexigenic hypothalamic neuropeptide Y-system in neonatally overfed weanling rats. J. Neuroendocrinol. 11, 541–546 (1999). [PubMed: 10444311]

84. Steculorum SM & Bouret SG Developmental effects of ghrelin. Peptides 32, 2362–2366 (2011). [PubMed: 21736909]

85. Baquero AF, de Solis AJ, Lindsley SR, et al. Developmental switch of leptin signaling in arcuate nucleus neurons. Journal of Neuroscience 34, 9982–9994 (2014). [PubMed: 25057200]

86. Caron E, Sachot C, Prevot V & Bouret SG Distribution of leptin-sensitive cells in the postnatal and adult mouse brain. J Comp Neurol 518, 459–476 (2010). [PubMed: 20017211]

87. Bouret SG, Bates SH, Chen S, Myers MG & Simerly RB Distinct roles for specific leptin receptor signals in the development of hypothalamic feeding circuits. Journal of Neuroscience 32, 1244–1252 (2012). [PubMed: 22279209]

88. Piao H, Hosoda H, Kangawa K, Murata T, Narita K, & Higuchi T Ghrelin stimulates milk intake by affecting adult type feeding behaviour in postnatal rats. J. Neuroendocrinol. 20, 330–334 (2008). [PubMed: 18194428]

89. Grayson BE, Allen SE, Billes SK, Williams SM, Smith MS, & Grove KL Prenatal development of hypothalamic neuropeptide systems in the nonhuman primate. Neuroscience 143, 975–986 (2006). [PubMed: 17029798]

90. Gali Ramamoorthy T, Begum G, Harno E & White A Developmental programming of hypothalamic neuronal circuits: impact on energy balance control. Front Neurosci 9, 126 (2015). [PubMed: 25954145]

91. Antonopoulos J, Dori I, Dinopoulos A, Chiotelli M & Parnavelas JG Postnatal development of the dopaminergic system of the striatum in the rat. Neuroscience 110, 245–256 (2002). [PubMed: 11958867]

92. Van den Heuvel DMA & Pasterkamp RJ Getting connected in the dopamine system. Prog. Neurobiol. 85, 75–93 (2008). [PubMed: 18304718]

93. Tepper JM, Sharpe NA, Koós TZ & Trent F Postnatal development of the rat neostriatum: electrophysiological, light- and electron-microscopic studies. Dev Neurosci 20, 125–145 (1998). [PubMed: 9691188]

94. Rossetti MF, Schumacher R, Gastiazoro MP, et al. Epigenetic dysregulation of dopaminergic system by maternal cafeteria diet during early postnatal development. Neuroscience 424, 12–23 (2020). [PubMed: 31682820]

95. Meng SZ, Ozawa Y, Itoh M & Takashima S Developmental and age-related changes of dopamine transporter, and dopamine D1 and D2 receptors in human basal ganglia. Brain Research 843, 136–144 (1999). [PubMed: 10528120]

96. Loos HM, Reger D & Schaal B The odour of human milk: Its chemical variability and detection by newborns. Physiol. Behav. 199, 88–99 (2019). [PubMed: 30414885]

97. Navratilova E & Porreca F Reward and motivation in pain and pain relief. Nature Neurosci 17, 1304–1312 (2014). [PubMed: 25254980]

98. Contreras CM, Gutiérrez-Garcia AG, Mendoza-López R, et al. Amniotic fluid elicits appetitive responses in human newborns: fatty acids and appetitive responses. Dev. Psychobiol. 55, 221–231 (2013). [PubMed: 22315200]

99. Contreras CM, Rodríguez-Landa JF, García-Rios RI, et al. Myristic acid produces anxiolytic-like effects in Wistar rats in the elevated plus maze. Biomed Res Int 2014, 492141–8 (2014). [PubMed: 25328885]

100. Adam-Darque A, Grouiller F, Vasung L, et al. fMRI-based Neuronal Response to New Odorants in the Newborn Brain. Cerebral Cortex 28, 2901–2907 (2018). [PubMed: 29106509]

101. Bartocci M, Winberg J, Ruggiero C, et al. Activation of olfactory cortex in newborn infants after odor stimulation: a functional near-infrared spectroscopy study. Pediatr. Res. 48, 18–23 (2000). [PubMed: 10879795]

102. Arichi T, Gordon-Williams R, Allievi A, et al. Computer-controlled stimulation for functional magnetic resonance imaging studies of the neonatal olfactory system. Acta Paediatr. 102, 868–875 (2013). [PubMed: 23789919]

103. Aoyama S, Toshima T, Saito Y, et al. Maternal breast milk odour induces frontal lobe activation in neonates: a NIRS study. Early Human Development 86, 541–545 (2010). [PubMed: 20675084]

104. Frie J, Bartocci M & Kuhn P Neonatal cortical perceptions of maternal breast odours: A fNIRS study. Acta Paediatr. 109, 1330–1337 (2020). [PubMed: 31782829]

105. Lipchock SV, Reed DR & Mennella JA The gustatory and olfactory systems during infancy: implications for development of feeding behaviors in the high-risk neonate. Clin Perinatol 38, 627–641 (2011). [PubMed: 22107894]

106. Mennella JA, Jagnow CP & Beauchamp GK Prenatal and postnatal flavor learning by human infants. Pediatrics 107, e88–e88 (2001). [PubMed: 11389286]

107. Bloomfield FH, Alexander T, Muelbert M, & Beker F Smell and taste in the preterm infant. Early Human Develop. 114, 31–34 (2017).

108. Schaal B, Marlier L, senses RSC Human foetuses learn odours from their pregnant mother's diet. Chemical senses, 25(6), 729–737 (2000). [PubMed: 11114151]

109. Hepper PG Adaptive fetal learning: prenatal exposure to garlic affects postnatal preferences. Animal behaviour 36, 935–936 (1988).

110. Faas AE, Spontón ED, Moya PR & Molina JC Differential responsiveness to alcohol odor in human neonates: Efects of maternal consumption during gestation. Alcohol 22, 7–17 (2000). [PubMed: 11109023]

111. Laureano DP, Dalle Molle R, Alves MB, et al. Intrauterine growth restriction modifies the hedonic response to sweet taste in newborn pups – Role of the accumbal μ-opioid receptors. Neuroscience 322, 500–508 (2016). [PubMed: 26926962]

112. Dalle Molle R, Laureano DP, Alves MB, et al. Intrauterine growth restriction increases the preference for palatable foods and affects sensitivity to food rewards in male and female adult rats. Brain Research 1618, 41–49 (2015). [PubMed: 26006109]

113. Ayres C, Agranonik M, Portella AK, et al. Intrauterine growth restriction and the fetal programming of the hedonic response to sweet taste in newborn infants. International Journal of Pediatrics 2012, (2012).

114. Fetal growth interacts with multilocus genetic score reflecting dopamine signaling capacity to predict spontaneous sugar intake in children. Appetite 120, 596–601 (2018). [PubMed: 29038017]

115. Dalle Molle R, Bischoff AR, Portella AK, Silviera PP The fetal programming of food preferences: Current clinical and experimental evidence. Journal of Developmental Origins of Health and Disease. 222–230 (2015). [PubMed: 26412563]

116. Zeltser LM Feeding circuit development and early-life influences on future feeding behaviour. Nat. Rev. Neurosci. 19, 302–316 (2018). [PubMed: 29662204]

117. Zeltser LM Developmental influences on circuits programming susceptibility to obesity. Frontiers in Neuroendocrinology 39, 17–27 (2015). [PubMed: 26206662]

118. Rinaman L Ontogeny of hypothalamic-hindbrain feeding control circuits. Dev. Psychobiol. 48, 389–396 (2006). [PubMed: 16770760]

119. Rinaman L, Roesch MR & Card JP Retrograde transsynaptic pseudorabies virus infection of central autonomic circuits in neonatal rats. Brain Res Dev Brain Res 114, 207–216 (1999). [PubMed: 10320760]

120. Swithers SE & Hall WG A nutritive control of independent ingestion in rat pups emerges by nine days of age. Physiol. Behav. 46, 873–879 (1989). [PubMed: 2516909]

121. Rinaman L Postnatal development of catecholamine inputs to the paraventricular nucleus of the hypothalamus in rats. J Comp Neurol 438, 411–422 (2001). [PubMed: 11559897]

122. Elson AE & Simerly RB Developmental specification of metabolic circuitry. Frontiers in Neuroendocrinology 39, 38–51 (2015). [PubMed: 26407637]

123. Rasmussen JM, Entringer S, Kruggel F, et al. Newborn insula gray matter volume is prospectively associated with early life adiposity gain. Int J Obes (Lond) 41, 1434–1439 (2017). [PubMed: 28487552]

124. Kurth F, Levitt JG, Luders E, et al. Relationships between gray matter, body mass index, and waist circumference in healthy adults. Hum Brain Mapp 34, 1737–1746 (2012). [PubMed: 22419507]

125. Janowitz D, Wittfeld K, Terock J, et al. Association between waist circumference and gray matter volume in 2344 individuals from two adult community-based samples. NeuroImage 122, 149–157 (2015). [PubMed: 26256530]

126. Pannacciulli N, Del Parigi A, Le DSNT, et al. Brain abnormalities in human obesity: A voxel-based morphometric study. NeuroImage 31, 1419–1425 (2006). [PubMed: 16545583]

127. Carnell S, Gibson C, Benson L, Ochner CN & Geliebter A Neuroimaging and obesity: current knowledge and future directions. Obesity Reviews 13, 43–56 (2011). [PubMed: 21902800]

128. Smucny J, Cornier M, Eichman LC, Thomas EA, Bechtell JL, Tregellas JR,. Brain structure predicts risk for obesity. Appetite 59, 859–865 (2012). [PubMed: 22963736]

129. Pannacciulli N, Le DSNT, Chen K, Reiman EM & Krakoff J Relationships between plasma leptin concentrations and human brain structure: A voxel-based morphometric study. Neurosci. Lett. 412, 248–253 (2007). [PubMed: 17123711]

130. Olivo G, Wiemerslage L & Nilsson EK Resting-state brain and the FTO obesity risk allele: Default mode, sensorimotor, and salience network connectivity underlying different somatosensory. Front Hum Neurosci 10:52 (2016). [PubMed: 26924971]

131. Figley TD, Bhullar N, Courtney SM & Figley CR Probabilistic atlases of default mode, executive control and salience network white matter tracts: an fMRI-guided diffusion tensor imaging and tractography study. Front Hum Neurosci 9, 585 (2015). [PubMed: 26578930]

132. Menon V & Uddin LQ Saliency, switching, attention and control: a network model of insula function. Brain Struct Funct 214, 655–667 (2010). [PubMed: 20512370]

133. Gao W, Lin W, Grewen K & Gilmore JH Functional Connectivity of the Infant Human Brain: Plastic and Modifiable. Neuroscientist (2016). doi:10.1177/1073858416635986

134. Li X, Andres A, Shankar K, et al. Differences in brain functional connectivity at resting state in neonates born to healthy obese or normal-weight mothers. Int J Obes (Lond) 40, 1931–1934 (2016). [PubMed: 27677619]

135. Rudolph MD, Graham AM, Feczko E, et al. Maternal IL-6 during pregnancy can be estimated from newborn brain connectivity and predicts future working memory in offspring. Nature Neurosci 21, 765–772 (2018). [PubMed: 29632361]

136. Shook LL, Kislal S & Edlow AG Fetal brain and placental programming in maternal obesity: A review of human and animal model studies. Prenat Diagn 40, 1126–1137 (2020). [PubMed: 32362000]

137. Fall CHD, Sachdev HS, Osmond C, et al. Association between maternal age at childbirth and child and adult outcomes in the offspring: a prospective study in five low-income and middle-income countries (COHORTS collaboration). Lancet Glob Health 3, e366–77 (2015). [PubMed: 25999096]

138. Myrskylä M & Fenelon A Maternal age and offspring adult health: evidence from the health and retirement study. Demography 49, 1231–1257 (2012). [PubMed: 22926440]

139. Savage T et al. Increasing maternal age is associated with taller stature and reduced abdominal fat in their children. PLoS ONE 8, e58869 (2013). [PubMed: 23527040]

140. Davis KE, Li X, Adams-Huet B & Sandon L Infant feeding practices and dietary consumption of US infants and toddlers: National Health and Nutrition Examination Survey (NHANES) 2003–2012. Public Health Nutr 21, 711–720 (2018). [PubMed: 29166968]

141. Tint MT, Fortier MV, Godfrey KM, et al. . Abdominal adipose tissue compartments vary with ethnicity in Asian neonates: Growing Up in Singapore Toward Healthy Outcomes birth cohort study. The American Journal of Clinical Nutrition 5: 1311–1317 (2016).

142. Evans-Campbell T Historical trauma in American Indian/Native Alaska communities: a multilevel framework for exploring impacts on individuals, families, and communities. J Interpers Violence 23, 316–338 (2008). [PubMed: 18245571]

143. Muhlhausler BS, Gugusheff JR, Ong ZY & Vithayathil MA Nutritional approaches to breaking the intergenerational cycle of obesity. Can J Physiol Pharmacol 91, 421–428 (2013). [PubMed: 23745987]

144. Braveman P, Krieger N & Lynch J Health inequalities and social inequalities in health. Bull World Health Organ 78, 232–4– discussion 234–5 (2000). [PubMed: 10743295]

145. Braveman PA Monitoring equity in health and healthcare: a conceptual framework. J Health Popul Nutr 21, 181–192 (2003). [PubMed: 14717564]

146. Hackman DA & Farah MJ Socioeconomic status and the developing brain. Trends in Cognitive Sciences 13, 65–73 (2009). [PubMed: 19135405]

147. Reinert KRS, Po'e EK & Barkin SL The relationship between executive function and obesity in children and adolescents: a systematic literature review. J Obes 2013, 820956–10 (2013). [PubMed: 23533726]

148. Noble KG, Houston SM, Brito NH, et al. Family income, parental education and brain structure in children and adolescents. Nature Neurosci 18, 773–778 (2015). [PubMed: 25821911]

149. Hanson JL, Hair N, Shen DG, et al. Family poverty affects the rate of human infant brain growth. PLoS ONE 8, e80954 (2013). [PubMed: 24349025]

150. Ramphal B, Whalen DJ, Kenley JK, et al. Brain connectivity and socioeconomic status at birth and externalizing symptoms at age 2 years. Dev Cogn Neurosci 45, 100811 (2020). [PubMed: 32823180]

151. Qiu A, Shen M, Buss C, et al. Effects of antenatal maternal depressive symptoms and socio-economic status on neonatal brain development are modulated by genetic risk. Cerebral Cortex 27, 3080–3092 (2017). [PubMed: 28334351]

152. Josey MJ, McCullough LE, Hoyo C & Williams-DeVane C Overall gestational weight gain mediates the relationship between maternal and child obesity. BMC Public Health 19, 1062–9 (2019). [PubMed: 31391077]

153. Lahti-Pulkkinen M, Bhattacharya S, Wild SH, et al. Consequences of being overweight or obese during pregnancy on diabetes in the offspring: a record linkage study in Aberdeen, Scotland. Diabetologia 62, 1412–1419 (2019). [PubMed: 31214738]

154. Heslehurst N, Vieria R, Akhter Z, et al. The association between maternal body mass index and child obesity: A systematic review and meta-analysis. PLoS Med 16, e1002817 (2019). [PubMed: 31185012]

155. Martorell R, Stein AD & Schroeder DG Early nutrition and later adiposity. J. Nutr. 131, 874S–880S (2001). [PubMed: 11238778]

156. Curhan GC, Chertow GM, Willett WC, et al. Birth weight and adult hypertension and obesity in women. Circulation 94, 1310–1315 (1996). [PubMed: 8822985]

157. Curhan GC, Willett WC, Rimm EB, et al. Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. Circulation 94, 3246–3250 (1996). [PubMed: 8989136]

158. Johansson K, Cnattingius S, Näslund I, et al. Outcomes of pregnancy after bariatric surgery. N Engl J Med 372, 814–824 (2015). [PubMed: 25714159]

159. Akhter Z, Rankin J, Ceulemans D, et al. Pregnancy after bariatric surgery and adverse perinatal outcomes: A systematic review and meta-analysis. PLoS Med 16, e1002866 (2019). [PubMed: 31386658]

160. Falcone V, Stopp T, Feichtinger M, et al. Pregnancy after bariatric surgery: a narrative literature review and discussion of impact on pregnancy management and outcome. BMC Pregnancy Childbirth 18, 507–13 (2018). [PubMed: 30587161]

161. Teulings NEWD, Masconi KL, Ozanne SE, Aiken CE & Wood AM Effect of interpregnancy weight change on perinatal outcomes: systematic review and meta-analysis. BMC Pregnancy Childbirth 19, 386–15 (2019). [PubMed: 31660893]

162. Monthé-Drèze C, Rifas-Shiman SL, Gold DR, Oken E & Sen S Maternal obesity and offspring cognition: the role of inflammation. Pediatr. Res. 85, 799–806 (2019). [PubMed: 30420706]

163. Coo H, Fabrigar L, Davies G, Fitzpatrick R & Flavin M Are observed associations between a high maternal prepregnancy body mass index and offspring IQ likely to be causal? J Epidemiol Community Health 73, 920–928 (2019). [PubMed: 31358534]

164. Contu L & Hawkes CA A Review of the impact of maternal obesity on the cognitive function and mental health of the offspring. Int J Mol Sci 18, 1093 (2017). [PubMed: 28534818]

165. Álvarez-Bueno C, Cavero-Redondo I, Lucas-de la Cruz L, Notario-Pacheco B, & Martínez-Vizcaíno V Association between pre-pregnancy overweight and obesity and children's

neurocognitive development: a systematic review and meta-analysis of observational. International journal of epidemiology. 46(5), 1653–1666 (2017). [PubMed: 29040611]

166. Rivera HM, Christiansen KJ & Sullivan EL The role of maternal obesity in the risk of neuropsychiatric disorders. Front Neurosci 9, (2015).

167. Page KA, Luo S, Wang X, et al. Children exposed to maternal obesity or gestational diabetes mellitus during early fetal development have hypothalamic alterations that predict future weight gain. Diabetes Care 42, 1473–1480 (2019). [PubMed: 31332028]

168. Norr ME, Hect JL, Lenniger CJ, van den Heuvel M & Thomason ME An examination of maternal prenatal BMI and human fetal brain development. J Child Psychol & Psychiat 62, 458–469 (2021). [PubMed: 32779186]

169. Ou X, Thakali KM, Shankar K, Andres A & Badger TM Maternal adiposity negatively influences infant brain white matter development. Obesity 23(5): 1047–1054 (2015). [PubMed: 25919924]

170. Marco A, Kisliouk T, Tabachnik T, Weller A & Meiri N DNA CpG Methylation (5-Methylcytosine) and its derivative (5-Hydroxymethylcytosine) alter histone posttranslational modifications at the Pomc promoter, affecting the impact of perinatal diet on leanness and obesity of the offspring. Diabetes 65, 2258–2267 (2016). [PubMed: 27217481]

171. Auguste S, Sharma S, Fisette A, et al. Perinatal deficiency in dietary omega-3 fatty acids potentiates sucrose reward and diet-induced obesity in mice. International Journal of Developmental Neuroscience 64, 8–13 (2018). [PubMed: 28919371]

172. Klein MO, MacKay H, Edwards A, et al. POMC and NPY mRNA expression during development is increased in rat offspring brain from mothers fed with a high fat diet. International Journal of Developmental Neuroscience 64, 14–20 (2018). [PubMed: 28323039]

173. Park S, Jang A & Bouret SG Maternal obesity-induced endoplasmic reticulum stress causes metabolic alterations and abnormal hypothalamic development in the offspring. PLOS Biology 18, e3000296 (2020). [PubMed: 32163401]

174. Bilbo SD & Tsang V Enduring consequences of maternal obesity for brain inflammation and behavior of offspring. The FASEB Journal 24, 2104–2115 (2010). [PubMed: 20124437]

175. Alfaradhi M & Ozanne S Developmental programming in response to maternal overnutrition. Front. Genet. 2, (2011).

176. Bayol SA, Farrington SJ & Stickland NC A maternal 'junk food' diet in pregnancy and lactation promotes an exacerbated taste for "junk food" and a greater propensity for obesity in rat offspring. British Journal of Nutrition 98, 843–851 (2007). [PubMed: 17697422]

177. Vucetic Z, Kimmel J, Totoki K, Hollenbeck E, & Reyes TM Maternal high-fat diet alters methylation and gene expression of dopamine and opioid-related genes. Endocrinology, 151(10), 4756–4764 (2010). [PubMed: 20685869]

178. Ong ZY & Muhlhausler BS Maternal 'junk-food' feeding of rat dams alters food choices and development of the mesolimbic reward pathway in the offspring. The FASEB Journal 25, 2167–2179 (2011). [PubMed: 21427213]

179. Mühlhäusler BS, Adam CL & McMillen IC Maternal nutrition and the programming of obesity. Organogenesis 4, 144–152 (2008). [PubMed: 19279726]

180. Nielsen MO et al. Late gestation undernutrition can predispose for visceral adiposity by altering fat distribution patterns and increasing the preference for a high-fat diet in early postnatal life. Br. J. Nutr. 109, 2098–2110 (2013). [PubMed: 23069212]

181. Stice E & Yokum S Gain in body fat is associated with increased striatal response to palatable food cues, whereas body fat Stability is associated with decreased striatal response. Journal of Neuroscience 36, 6949–6956 (2016). [PubMed: 27358453]

182. Sookoian S, Gianotti TF, Burgueño AL & Pirola CJ Fetal metabolic programming and epigenetic modifications: a systems biology approach. Pediatr. Res. 73, 531–542 (2013). [PubMed: 23314294]

183. Volkow ND, Wang G-J & Baler RD Reward, dopamine and the control of food intake: implications for obesity. Trends in Cognitive Sciences 15, 37–46 (2011). [PubMed: 21109477]

184. Chen LW, Tint MT, Fortier, et al. Maternal macronutrient intake during pregnancy is associated with neonatal abdominal adiposity: the Growing Up in Singapore Towards healthy Outcomes (GUSTO) Study. The Journal of nutrition, 146(8), 1571–1579 (2016). [PubMed: 27385763]

185. Chen LW, Aris IM, Bernard JY, et al. Associations of maternal macronutrient intake during pregnancy with infant BMI peak characteristics and childhood BMI. The American journal of clinical nutrition, 105(3), 705–713 (2017). [PubMed: 28179222]

186. Barker ED, Kirkham N, Ng J & Jensen SKG Prenatal maternal depression symptoms and nutrition, and child cognitive function. Br J Psychiatry 203, 417–421 (2013). [PubMed: 24115347]

187. Linder K, Schleger F, Kiefer-Schmidt I, et al. Gestational diabetes impairs human fetal postprandial brain activity. J. Clin. Endocrinol. Metab. 100, 4029–4036 (2015). [PubMed: 26465393]

188. Schleger F, Linder K, Fritsche A & Preissl H Maternal insulin sensitivity and fetal brain activity. Diet, Nutrition, and Fetal Programming 49, 67–78 (Humana Press, Cham, 2017).

189. Goldstein H The pregnant diabetic and her newborn: Problems and management. Arch Intern Med 122, 92–92 (1968).

190. Heni M, Kullmann S, Preissl H, Fritsche A & Häring H-U Impaired insulin action in the human brain: causes and metabolic consequences. Nat Rev Endocrinol 11, 701–711 (2015). [PubMed: 26460339]

191. Kullmann S, Heni M, Hallschmid M, et al. Brain insulin resistance at the crossroads of metabolic and cognitive disorders in humans. Physiol Rev 96, 1169–1209 (2016). [PubMed: 27489306]

192. Chen W, Balland E & Cowley MA Hypothalamic Insulin Resistance in Obesity: Effects on Glucose Homeostasis. Neuroendocrinology 104, 364–381 (2017). [PubMed: 28122381]

193. Kullmann S, Kleinridders A, Small DM, et al. Central nervous pathways of insulin action in the control of metabolism and food intake. Lancet Diabetes Endocrinol 8, 524–534 (2020). [PubMed: 32445739]

194. Tschritter O, Preissl H, Hennige AM, et al. The cerebrocortical response to hyperinsulinemia is reduced in overweight humans: a magnetoencephalographic study. PNAS 103, 12103–12108 (2006). [PubMed: 16877540]

195. Kroemer NB, Krebs L, Kobiella A, et al. (Still) longing for food: Insulin reactivity modulates response to food pictures. Hum Brain Mapp 34, 2367–2380 (2013). [PubMed: 22461323]

196. Brown JM, Scarlett JM & Schwartz MW Rethinking the role of the brain in glucose homeostasis and diabetes pathogenesis. Journal of Clinical Investigation 129, 3035–3037 (2019). [PubMed: 31329157]

197. Hege MA, Kullman S, Heni M, et al. Electro/magnetoencephalographic signatures of human brain insulin resistance. Current Opinion in Behavioral Sciences 9, 163–168 (2016).

198. Scott KA, Melhorn SJ & Sakai RR Effects of chronic social stress on obesity. Curr Obes Rep 1, 16–25 (2012). [PubMed: 22943039]

199. Pecoraro N, Reyes F, Gomez F, Bhargava A & Dallman MF Chronic stress promotes palatable feeding, which reduces signs of stress: feedforward and feedback effects of chronic stress. Endocrinology 145, 3754–3762 (2004). [PubMed: 15142987]

200. Huizink AC, Robles de Medina PG, Mulder EJH, Visser GHA & Buitelaar JK Stress during pregnancy is associated with developmental outcome in infancy. J Child Psychol Psychiatry 44, 810–818 (2003). [PubMed: 12959490]

201. Entringer S Impact of stress and stress physiology during pregnancy on child metabolic function and obesity risk. Curr Opin Clin Nutr Metab Care 16, 320–327 (2013). [PubMed: 23400210]

202. Buss C, Entringer S, Swanson JM & Wadhwa PD The role of stress in brain development: The gestational environment's long-term effects on the brain. Cerebrum 2012, 4 (2012). [PubMed: 23447790]

203. Buss C, Davis EP, Muftuler LT, Head K & Sandman CA High pregnancy anxiety during mid-gestation is associated with decreased gray matter density in 6–9-year-old children. Psychoneuroendocrinology 35, 141–153 (2010). [PubMed: 19674845]

204. Buss C, Davis EP, Hobel CJ & Sandman CA Maternal pregnancy-specific anxiety is associated with child executive function at 6–9 years age. Stress 14, 665–676 (2011). [PubMed: 21995526]

205. Paternain L, Batlle MA, De la Garza AL, et al. Transcriptomic and epigenetic changes in the hypothalamus are involved in an increased susceptibility to a high-fat-sucrose diet in prenatally stressed female rats. Neuroendocrinology 96, 249–260 (2012). [PubMed: 22986707]

206. McEwen BS & Gianaros PJ Central role of the brain in stress and adaptation: links to socioeconomic status, health, and disease. Ann. N. Y. Acad. Sci. 1186, 190–222 (2010). [PubMed: 20201874]

207. Cohen S Keynote Presentation at the Eight International Congress of Behavioral Medicine: the Pittsburgh common cold studies: psychosocial predictors of susceptibility to respiratory infectious illness. Int J Behav Med 12, 123–131 (2005). [PubMed: 16083315]

208. Steptoe A, Feldman PJ, Kunz S, et al. Stress responsivity and socioeconomic status: a mechanism for increased cardiovascular disease risk? Eur Heart J 23, 1757–1763 (2002). [PubMed: 12419295]

209. Wang JL Perceived work stress, imbalance between work and family/personal lives, and mental disorders. Soc Psychiatry Psychiatr Epidemiol 41, 541–548 (2006). [PubMed: 16572273]

210. Hauner H, Schmid P & Pfeiffer EF Glucocorticoids and insulin promote the differentiation of human adipocyte precursor cells into fat cells. J. Clin. Endocrinol. Metab. 64, 832–835 (1987). [PubMed: 3546356]

211. Campbell JE, Peckett AJ, D'souza AM, Hawke TJ & Riddell MC Adipogenic and lipolytic effects of chronic glucocorticoid exposure. Am J Physiol Cell Physiol 300, C198–209 (2011). [PubMed: 20943959]

212. Entringer S, Buss C, Rasmussen JM, et al. Maternal cortisol during pregnancy and infant adiposity: A prospective investigation. J. Clin. Endocrinol. Metab. 102, 1366–1374 (2017). [PubMed: 28009530]

213. Buss C, Davis EP, Shahbaba B, et al. Maternal cortisol over the course of pregnancy and subsequent child amygdala and hippocampus volumes and affective problems. Proc. Natl. Acad. Sci. U.S.A. 109, E1312–9 (2012). [PubMed: 22529357]

214. Graham AM, Rasmussen JM, Entringer S, et al. Maternal cortisol concentrations during pregnancy and sex-specific associations with neonatal amygdala connectivity and emerging internalizing behaviors. Biological Psychiatry 85, 172–181 (2019). [PubMed: 30122286]

215. Davis EP, Head K, Buss C & Sandman CA Prenatal maternal cortisol concentrations predict neurodevelopment in middle childhood. Psychoneuroendocrinology 75, 56–63 (2017). [PubMed: 27771566]

216. Davis EP, Sandman CA, Buss C, Wing DA & Head K Fetal glucocorticoid exposure is associated with preadolescent brain development. Biological Psychiatry 74, 647–655 (2013). [PubMed: 23611262]

217. Welberg LA, Seckl JR & Holmes MC Prenatal glucocorticoid programming of brain corticosteroid receptors and corticotrophin-releasing hormone: possible implications for behaviour. Neuroscience 104, 71–79 (2001). [PubMed: 11311532]

218. Schroeder M, Jakovcevski M, Polacheck T, et al. A methyl-balanced diet prevents CRF-induced prenatal stress-triggered predisposition to binge eating-like phenotype. Cell Metabolism 25, 1269–1281.e6 (2017). [PubMed: 28576418]

219. Czyzyk TA, Sahr AE & Statnick MA A model of binge-like eating behavior in mice that does not require food deprivation or stress. Obesity 18, 1710–1717 (2010). [PubMed: 20300082]

220. Rao TSS, Asha MR, Ramesh BN & Rao KSJ Understanding nutrition, depression and mental illnesses. Indian Journal of Psychiatry 50, 77–82 (2008). [PubMed: 19742217]

221. Groesz LM, McCoy S, Carl J, et al. What is eating you? Stress and the drive to eat. Appetite 58, 717–721 (2012). [PubMed: 22166677]

222. Lindsay KL, Buss C, Wadhwa PD, et al. , The interplay between nutrition and stress in pregnancy: Implications for fetal programming of brain development. Biological Psychiatry 85, 135–149 (2019). [PubMed: 30057177]

223. Romani-Perez M, Lépinay AL, Alonso L, et al. Impact of perinatal exposure to high-fat diet and stress on responses to nutritional challenges, food-motivated behaviour and mesolimbic dopamine function. Int J Obes (Lond) 41, 502–509 (2017). [PubMed: 28025577]

224. Huang CF, Du JX, Deng W, et al. , Effect of prenatal exposure to LPS combined with pre- and post-natal high-fat diet on hippocampus in rat offspring. Neuroscience 286, 364–370 (2015). [PubMed: 25498225]

225. Rincel M, Lépinay AL, Janthakin Y, et al. Maternal high-fat diet and early life stress differentially modulate spine density and dendritic morphology in the medial prefrontal cortex of juvenile and adult rats. Brain Struct Funct 223, 883–895 (2018). [PubMed: 29022091]

226. Sivonová M, Žitnanová I, Hlin íková, et al. Oxidative stress in university students during examinations. Stress 7, 183–188 (2004). [PubMed: 15764015]

227. Lesgards JF, Durand P, Lassarre M, et al. Assessment of lifestyle effects on the overall antioxidant capacity of healthy subjects. Environ Health Perspect 110, 479–486 (2002). [PubMed: 12003751]

228. Argüelles S, Machado MJ, Ayala A, Machado A & Hervías B Correlation between circulating biomarkers of oxidative stress of maternal and umbilical cord blood at birth. Free Radic Res 40, 565–570 (2006). [PubMed: 16753833]

229. Saker M, Mokhtari NS, Merzouk SA, et al. Oxidant and antioxidant status in mothers and their newborns according to birthweight. Eur J Obstet Gynecol Reprod Biol 141, 95–99 (2008). [PubMed: 18760523]

230. Rakers F, Rupprecht S, Dreiling M, et al. Transfer of maternal psychosocial stress to the fetus. Neuroscience and Biobehavioral Reviews (2017). doi:10.1016/j.neubiorev.2017.02.019

231. Thompson LP & Al-Hasan Y Impact of oxidative stress in fetal programming. J Pregnancy 2012, 582748–8 (2012). [PubMed: 22848830]

232. Hung TH, Lo LM, Chiu TH, et al. A longitudinal study of oxidative stress and antioxidant status in women with uncomplicated pregnancies throughout gestation. Reprod Sci 17, 401–409 (2010). [PubMed: 20167745]

233. Little RE & Gladen BC Levels of lipid peroxides in uncomplicated pregnancy: a review of the literature. Reprod Toxicol 13, 347–352 (1999). [PubMed: 10560582]

234. Turpin CA, Sakyi SA, Owiredu WKBA, Ephraim RKD & Anto EO Association between adverse pregnancy outcome and imbalance in angiogenic regulators and oxidative stress biomarkers in gestational hypertension and preeclampsia. BMC Pregnancy Childbirth 15, 189–10 (2015). [PubMed: 26303772]

235. Zhu C, Yanh H, Geng Q, et al. Association of oxidative stress biomarkers with gestational diabetes mellitus in pregnant women: a case-control study. PLoS ONE 10, e0126490 (2015). [PubMed: 25915047]

236. Zheng A, Li H, Cao K, et al. Maternal hydroxytyrosol administration improves neurogenesis and cognitive function in prenatally stressed offspring. The Journal of Nutritional Biochemistry 26, 190–199 (2015). [PubMed: 25442671]

237. Feng Z, Jia H, Li X, et al. A milk-based wolfberry preparation prevents prenatal stress-induced cognitive impairment of offspring rats, and inhibits oxidative damage and mitochondrial dysfunction in vitro. Neurochem Res 35, 702–711 (2010). [PubMed: 20131093]

238. Feng Z, Zou X, Jia H, et al. Maternal docosahexaenoic acid feeding protects against impairment of learning and memory and oxidative stress in prenatally stressed rats: possible role of neuronal mitochondria metabolism. Antioxid Redox Signal 16, 275–289 (2012). [PubMed: 21905985]

239. Gallardo JM, Gómez-López J, Medina-Bravo P, et al. Maternal obesity increases oxidative stress in the newborn. Obesity 23, 1650–1654 (2015). [PubMed: 26193060]

240. Negro S, Boutsikou T, Briana DD, et al. Maternal obesity and perinatal oxidative stress: the strength of the association. J Biol Regul Homeost Agents 31, 221–227 (2017).

241. Buss C Maternal oxidative stress during pregnancy and offspring neurodevelopment. Brain, Behavior, and Immunity 93, 6–7 (2021). [PubMed: 33454300]

242. Dahlgren J, Nilsson C, Jennische E, et al. Prenatal cytokine exposure results in obesity and gender-specific programming. Am. J. Physiol. Endocrinol. Metab. 281, E326–34 (2001). [PubMed: 11440909]

243. Nilsson C, Larsson BM, Jennische E, et al. Maternal endotoxemia results in obesity and insulin resistance in adult male offspring. Endocrinology 142, 2622–2630 (2001). [PubMed: 11356713]

244. Estes ML & McAllister AK Maternal immune activation: Implications for neuropsychiatric disorders. Science 353, 772–777 (2016). [PubMed: 27540164]

245. Graham AM, Rasmussen JM, Rudolph MD, et al. Maternal systemic Interleukin-6 during pregnancy is associated with newborn amygdala phenotypes and subsequent behavior at 2 years of age. Biological Psychiatry (2017). doi:10.1016/j.biopsych.2017.05.027

246. Rasmussen JM, Graham AM, Entringer S, et al. Maternal Interleukin-6 concentration during pregnancy is associated with variation in frontolimbic white matter and cognitive development in early life. NeuroImage 185, 825–835 (2019). [PubMed: 29654875]

247. Wu N, Chen Y, Yang J & Li F Childhood obesity and academic performance: The role of working memory. Front Psychol 8, 611 (2017). [PubMed: 28469593]

248. Page KA, Luo S, Wang X, et al. Children exposed to maternal obesity or gestational Diabetes mellitus during early fetal development have hypothalamic alterations that predict future weight gain. Diabetes Care 42, 1473–1480 (2019). [PubMed: 31332028]

249. Qiu A, Mori S & Miller MI Diffusion tensor imaging for understanding brain development in early life. Annu Rev Psychol 66, 853–876 (2015). [PubMed: 25559117]

250. Makropoulos A, Counsell SJ & Rueckert D A review on automatic fetal and neonatal brain MRI segmentation. NeuroImage (2017). doi:10.1016/j.neuroimage.2017.06.074

251. Raji CA, Ho AJ, Parikshal NN, et al. Brain structure and obesity. Hum Brain Mapp NA–NA (2009). doi:10.1002/hbm.20870

252. Thomas K, Beyer F, Lewe G, et al. Higher body mass index is linked to altered hypothalamic microstructure. Sci Rep 9, 17373 (2019). [PubMed: 31758009]

253. Karlsson HK, Tuulari JJ, Hirvonen J, et al. Obesity is associated with white matter atrophy: a combined diffusion tensor imaging and voxel-based morphometric study. Obesity 21, 2530–2537 (2013). [PubMed: 23512884]

254. Verdejo-Román J, Björnholm L, Muetzel RL, et al. Maternal prepregnancy body mass index and offspring white matter microstructure: results from three birth cohorts. Int J Obes (Lond) 43, 1995–2006 (2019). [PubMed: 30518826]

255. Ou X, Andres A, Pivik RT, Cleves MA & Badger TM Brain gray and white matter differences in healthy normal weight and obese children. (2015). doi:10.1002/jmri.24912

256. Steward T, Miranda-Olivos R, Soriano-Mas C & Fernández-Aranda F Neuroendocrinological mechanisms underlying impulsive and compulsive behaviors in obesity: a narrative review of fMRI studies. Rev Endocr Metab Disord 20, 263–272 (2019). [PubMed: 31654260]

257. Zhang Y, Ji G, Li G, et al. Ghrelin reductions following bariatric surgery were associated with decreased resting state activity in the hippocampus. Int J Obes (Lond) 43, 842–851 (2019). [PubMed: 29915363]

258. Mokhtari F, Rejeski WJ, Zhu W, et al. Dynamic fMRI networks predict success in a behavioral weight loss program among older adults. NeuroImage 173, 421–433 (2018). [PubMed: 29471100]

259. Wijngaarden MA, Veer IM, Rombouts S, et al. Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience. Behav. Brain Res. 287, 127–134 (2015). [PubMed: 25779924]

260. Kullmann S, Heni M, Linder K, et al. Resting-state functional connectivity of the human hypothalamus. Hum Brain Mapp 35, 6088–6096 (2014). [PubMed: 25131690]

261. Zhang B, Tian D, Yu C, et al. Altered baseline brain activities before food intake in obese men: a resting state fMRI study. Neurosci. Lett. 584, 156–161 (2015). [PubMed: 25459293]

262. Al-Zubaidi A, Iglesias S, Stephan KE, et al. Effects of hunger, satiety and oral glucose on effective connectivity between hypothalamus and insular cortex. NeuroImage 217, 116931 (2020). [PubMed: 32417450]

263. Li P, Shan H, Nie B, et al. Sleeve gastrectomy rescuing the altered functional connectivity of lateral but not medial hypothalamus in subjects with obesity. Obes Surg 29, 2191–2199 (2019). [PubMed: 30895508]

264. Rucker P & Ikuta T Pituitary gland functional connectivity and BMI. Front Neurosci 13, 120 (2019). [PubMed: 30881281]

265. Martín-Pérez C, Contreras-Rodríguez O, Vilar-López R & Verdejo-García A Hypothalamic networks in adolescents with excess weight: Stress-related connectivity and associations with emotional eating. Journal of the American Academy of Child & Adolescent Psychiatry 58, 211–220.e5 (2019). [PubMed: 30738548]

266. García-García I et al. Alterations of the salience network in obesity: a resting-state fMRI study. Hum Brain Mapp 34, 2786–2797 (2013). [PubMed: 22522963]

267. Fang Z, Spaeth AM, Ma N, et al. Altered salience network connectivity predicts macronutrient intake after sleep deprivation. Sci Rep 5, 8215 (2015). [PubMed: 25645575]

268. Salzwedel AP, Gao W, Andres A, et al. Maternal adiposity influences neonatal brain functional connectivity. Front Hum Neurosci 12, 514 (2018). [PubMed: 30662399]

269. Harris RBS Appetite and Food Intake. CRC Press. doi:10.1201/9781315120171

270. Wong WW, Butte NF, Garza C & Klein PD Comparison of the doubly labeled water (2H2 18O) method with indirect calorimetry and a nutrient-balance study for simultaneous determination of energy expenditure, water intake, and metabolizable energy intake in preterm infants. Am. J. Clin. Nutr. 45, 1543–1548 (1987). [PubMed: 3591734]

271. Jones PJH, Winthrop AL, Schoeller DA, et al. Validation of doubly labeled water for assessing energy expenditure in infants. Pediatr. Res. 21, 242–246 (1987). [PubMed: 3104873]

272. Jensen CL, Butte NF, Wong WW & Moon JK Determining energy expenditure in preterm infants: comparison of 2H(2)18O method and indirect calorimetry. Am J Physiol 263, R685–92 (1992). [PubMed: 1415659]

273. Westerterp KR, Lafeber HN, Sulkers EJ & Sauer PJ Comparison of short term indirect calorimetry and doubly labeled water method for the assessment of energy expenditure in preterm infants. Biol Neonate 60, 75–82 (1991).

274. Wong WW, Roberts SB, Racette SB, et al. The doubly labeled water method produces highly reproducible longitudinal results in nutrition studies. J. Nutr. 144, 777–783 (2014). [PubMed: 24523488]

275. Bines JE & Truby HD Measurement of resting energy expenditure in infants. J Paediatr Child Health 40, 380–383 (2004). [PubMed: 15228567]

276. Duro D, Mitchell PD, Mehta NM, et al. Variability of resting energy expenditure in infants and young children with intestinal failure-associated liver disease. J Pediatr Gastroenterol Nutr 58, 637–641 (2014). [PubMed: 24361903]

277. Westerterp KR Diet induced thermogenesis. Nutr Metab (Lond) 1, 5 (2004). [PubMed: 15507147]

278. Benjamin-Neelon SE, Bai J, Østbye T, et al. Physical activity and adiposity in a racially diverse cohort of US infants. Obesity 28, 631–637 (2020). [PubMed: 31944621]

279. Pitchford EA, Ketcheson LR, Kwon H-J & Ulrich DA minimum accelerometer wear time in infants: A generalizability study. J Phys Act Health 14, 421–428 (2017). [PubMed: 28290739]

280. Butte NF, Wong WW, Hopkinson JM, et al. Energy requirements derived from total energy expenditure and energy deposition during the first 2 y of life. Am. J. Clin. Nutr. 72, 1558–1569 (2000). [PubMed: 11101486]

281. de Bruin NC, Degenhart HJ, Gàl S, et al. Energy utilization and growth in breast-fed and formula-fed infants measured prospectively during the first year of life. Am. J. Clin. Nutr. 67, 885–896 (1998). [PubMed: 9583846]

282. Frobisher C & Maxwell SM The estimation of food portion sizes: a comparison between using descriptions of portion sizes and a photographic food atlas by children and adults. J Hum Nutr Diet 16, 181–188 (2003). [PubMed: 12753111]

283. Thompson FE, Subar AF, Loria CM, Reedy JL & Baranowski T Need for technological innovation in dietary assessment. J Am Diet Assoc 110, 48–51 (2010). [PubMed: 20102826]

284. Wharton CM, Johnston CS, Cunningham BK & Sterner D Dietary self-monitoring, but not dietary quality, improves with use of smartphone app technology in an 8-week weight loss trial. J Nutr Educ Behav 46, 440–444 (2014). [PubMed: 25220777]

285. Hutchesson MJ, Rollo ME, Callister R & Collins CE Self-monitoring of dietary intake by young women: online food records completed on computer or smartphone are as accurate as paper-based food records but more acceptable. J Acad Nutr Diet 115, 87–94 (2015). [PubMed: 25262244]

286. Natarajan L, Pu M, Fan J, et al. Measurement error of dietary self-report in intervention trials. Am. J. Epidemiol. 172, 819–827 (2010). [PubMed: 20720101]

287. King IB, Lemaitre RN & Kestin M Effect of a low-fat diet on fatty acid composition in red cells, plasma phospholipids, and cholesterol esters: investigation of a biomarker of total fat intake. Am. J. Clin. Nutr. 83, 227–236 (2006). [PubMed: 16469979]

288. Cook CM, Alvig AL, Liu YQD & Schoeller DA The natural 13C abundance of plasma glucose is a useful biomarker of recent dietary caloric sweetener intake. J. Nutr. 140, 333–337 (2010). [PubMed: 20018804]

289. van Baak MA & Astrup A Consumption of sugars and body weight. Obes Rev 10 Suppl 1, 9–23 (2009).

290. Potischman N Biologic and methodologic issues for nutritional biomarkers. J. Nutr. 133 Suppl 3, 875S–880S (2003). [PubMed: 12612173]

291. Munje RD, Muthukumar S, Jagannath B & Prasad S A new paradigm in sweat based wearable diagnostics biosensors using Room Temperature Ionic Liquids (RTILs). Sci Rep 7, 1950–12 (2017). [PubMed: 28512341]

292. Hooton K & Li L Nonocclusive sweat collection combined with chemical isotope labeling LC-MS for human sweat metabolomics and mapping the sweat metabolomes at different skin locations. Anal Chem 89, 7847–7851 (2017). [PubMed: 28679039]

293. Agrawal K, Sivamani RK & Newman JW Noninvasive profiling of sweat-derived lipid mediators for cutaneous research. Skin Res Technol 25, 3–11 (2019). [PubMed: 30030941]

294. Lam J, Barr RG, Catherine N, et al. Electronic and paper diary recording of infant and caregiver behaviors. J Dev Behav Pediatr 31, 685–693 (2010). [PubMed: 20975577]

295. Acharjee A, Prentice P, Acerini C, et al. The translation of lipid profiles to nutritional biomarkers in the study of infant metabolism. Metabolomics 13, 25–9 (2017). [PubMed: 28190990]

296. Miller EM, Aiello MO, Fujita M, et al. Field and laboratory methods in human milk research. Am. J. Hum. Biol. 25, 1–11 (2013). [PubMed: 23109280]

297. Arslanoglu S, Moro GE, Ziegler EE & Nutrition TWWGO Optimization of human milk fortification for preterm infants: new concepts and recommendations. J Perinat Med 38, 233–238 (2010). [PubMed: 20184400]

298. Dewey KG, Nommsen-Rivers LA, Heinig MJ & Cohen RJ Risk factors for suboptimal infant breastfeeding behavior, delayed onset of lactation, and excess neonatal weight loss. Pediatrics 112, 607–619 (2003). [PubMed: 12949292]

299. Chow S, Chow R, Popovíc M, et al. The Use of Nipple Shields: A Review. Front Public Health 3, 236 (2015). [PubMed: 26528467]

300. Elad D, Kozlovsky P, Blum O, et al. Biomechanics of milk extraction during breast-feeding. Proc. Natl. Acad. Sci. U.S.A. 111, 5230–5235 (2014). [PubMed: 24706845]

301. Woolridge M The Biomechanics of breastfeeding: Bridging the gap between engineering-based studies and clinical practice. Nestle Nutr Inst Workshop Ser 90, 13–32 (2019). [PubMed: 30865973]

302. Jackson DA, Woolridge MW, Imong SM, et al. The automatic sampling shield: a device for sampling suckled breast milk. Early Human Development 15, 295–306 (1987). [PubMed: 3678121]

303. Lee C-Y, Chang C-L, Wang Y-N & Fu L-M Microfluidic mixing: a review. Int J Mol Sci 12, 3263–3287 (2011). [PubMed: 21686184]

304. Li R, Fein SB & Grummer-Strawn LM Association of breastfeeding intensity and bottle-emptying behaviors at early infancy with infants' risk for excess weight at late infancy. Pediatrics 122 Suppl 2, S77–84 (2008). [PubMed: 18829835]

305. Li R, Scanlon KS, May A, Rose C & Birch L Bottle-feeding practices during early infancy and eating behaviors at 6 years of age. PEDIATRICS 134 Suppl 1, S70–7 (2014). [PubMed: 25183759]

306. McCloskey K, Burgner D, Carlin JB, et al. Infant adiposity at birth and early postnatal weight gain predict increased aortic intima-media thickness at 6 weeks of age: a population-derived cohort study. Clinical Science 130, 443–450 (2016). [PubMed: 26666445]

307. Wells JCK, Hallal PC, Wright A, Singhal A & Victora CG Fetal, infant and childhood growth: relationships with body composition in Brazilian boys aged 9 years. International Journal of Obesity 29, 1192–1198 (2005). [PubMed: 16103893]

308. Koontz MB, Gunzler DD, Presley L & Catalano PM Longitudinal changes in infant body composition: association with childhood obesity. Pediatr Obes 9, e141–4 (2014). [PubMed: 25267097]

309. Baird J, Fisher D, Lucas P, Kleijnen J & Roberts H Being big or growing fast: systematic review of size and growth in infancy and later obesity. BMJ 331:929 (2005). [PubMed: 16227306]

310. Druet C, Stettler N, Sharp S, et al. Prediction of childhood obesity by infancy weight gain: an individual-level meta-analysis. Paediatr Perinat Epidemiol 26, 19–26 (2012). [PubMed: 22150704]

311. Stettler N, Kumanyika SK, Katz SH, Zemel BS & Stallings VA Rapid weight gain during infancy and obesity in young adulthood in a cohort of African Americans. Am. J. Clin. Nutr. 77, 1374–1378 (2003). [PubMed: 12791612]

312. Monteiro POA & Victora CG Rapid growth in infancy and childhood and obesity in later life--a systematic review. Obes Rev 6, 143–154 (2005). [PubMed: 15836465]

313. Ong KK, Emmett P & Northstone K Infancy weight gain predicts childhood body fat and age at menarche in girls. JCEM 5: 1527–1532 (2009).

314. Kruithof CJ, Gishti O, Hofman A, Gaillard R & Jaddoe VWV Infant weight growth velocity patterns and general and abdominal adiposity in school-age children. The Generation R Study. Eur J Clin Nutr (2016). doi:10.1038/ejcn.2016.60

315. Magnus MC, Olsen SF, Granström C, et al. Infant growth and risk of childhood-onset type 1 diabetes in children from 2 Scandinavian birth cohorts. JAMA Pediatr 169, e153759 (2015). [PubMed: 26642117]

316. Ekelund U, Ong KK, Linné Y et al. Association of weight gain in infancy and early childhood with metabolic risk in young adults. J. Clin. Endocrinol. Metab. 92, 98–103 (2007). [PubMed: 17032722]

317. Huxley RR, Shiell AW & Law CM The role of size at birth and postnatal catch-up growth in determining systolic blood pressure: a systematic review of the literature. Journal of hypertension (2000).

318. Sonnenschein-van der Voort AMM, Arends LR, de Jongste JC, et al. Preterm birth, infant weight gain, and childhood asthma risk: a meta-analysis of 147,000 European children. J. Allergy Clin. Immunol. 133, 1317–1329 (2014). [PubMed: 24529685]

319. Breij LM, Kerkhof GF, De Lucia Rolfe E, et al. Longitudinal fat mass and visceral fat during the first 6 months after birth in healthy infants: support for a critical window for adiposity in early life. Pediatr Obes 12, 286–294 (2017). [PubMed: 27072083]

320. Johnson W, Choh AC, Lee M, et al. Characterization of the infant BMI peak: sex differences, birth year cohort effects, association with concurrent adiposity, and heritability. Am. J. Hum. Biol. 25, 378–388 (2013). [PubMed: 23606227]

321. Silverwood RJ, De Stavola BL, Cole TJ & Leon DA BMI peak in infancy as a predictor for later BMI in the Uppsala Family Study. Int J Obes (Lond) 33, 929–937 (2009). [PubMed: 19564879]

322. Johnson L, van Jaarsveld CHM, Llewellyn CH, Cole TJ & Wardle J Associations between infant feeding and the size, tempo and velocity of infant weight gain: SITAR analysis of the Gemini twin birth cohort. Int J Obes (Lond) 38, 980–987 (2014). [PubMed: 24722545]

323. Conkle J, Ramakrishnan U, Flores-Ayala R, Suchdev PS & Martorell R Improving the quality of child anthropometry: Manual anthropometry in the Body Imaging for Nutritional Assessment Study (BINA). PLoS ONE 12, e0189332 (2017). [PubMed: 29240796]

324. Pedroli E, Digilia R, Tuena C, et al. The Use of 3D Body Scanner in Medicine and Psychology: A Narrative Review. Pervasive Computing for Mental Health 74–83 (2018).

325. Caprio S, Pierpont B & Kursawe R The 'adipose tissue expandability' hypothesis: a potential mechanism for insulin resistance in obese youth. Horm Mol Biol Clin Investig 33, 1201 (2018).

326. Stefan N Causes, consequences, and treatment of metabolically unhealthy fat distribution. Lancet Diabetes Endocrinol 8, 616–627 (2020). [PubMed: 32559477]

327. Armstrong T, Dregely I, Stemmer A, et al. Free-breathing liver fat quantification using a multiecho 3D stack-of-radial technique. Magn. Reson. Med. 79, 370–382 (2018). [PubMed: 28419582]

328. Benkert T, Feng L, Sodickson DK, Chandarana H & Block KT Free-breathing volumetric fat/water separation by combining radial sampling, compressed sensing, and parallel imaging. Magn. Reson. Med. 78, 565–576 (2017). [PubMed: 27612300]

329. Rasmussen JM, Entringer S, Nguyen A, et al. Brown adipose tissue quantification in human neonates using water-fat separated MRI. PLoS ONE 8, e77907 (2013). [PubMed: 24205024]

330. Harms M & Seale P Brown and beige fat: development, function and therapeutic potential. Nature Medicine 19, 1252–1263 (2013).

331. Björkroth S, Vaarno J, Junttila N, et al A. Initiation and exclusivity of breastfeeding: association with mothers' and fathers' prenatal and postnatal depression and marital distress. Acta Obstetricia et Gynecologica Scandinavica 95, 396–404 (2016). [PubMed: 26826608]

332. Arifunhera JH, Srinivasaraghavan R, Sarkar S, et al. Is maternal anxiety a barrier to exclusive breastfeeding? The Journal of Maternal-Fetal & Neonatal Medicine 2798–2801 (2015). doi:10.3109/14767058.2015.1104662 [PubMed: 26526568]

333. Wojcicki JM Maternal prepregnancy Body Mass Index and initiation and duration of breastfeeding: A Review of the Literature. Journal of Women's Health (2011). doi:10.1089/jwh.2010.2248

334. Codagnone MG, Stanton C, O'Mahony SM, Dinan TG & Cryan JF Microbiota and neurodevelopmental trajectories: Role of maternal and early-Life nutrition. Ann Nutr Metab 74 Suppl 2, 16–27 (2019). [PubMed: 31234188]

335. Lu J & Claud EC Connection between gut microbiome and brain development in preterm infants. Dev. Psychobiol. 61, 739–751 (2019). [PubMed: 30460694]

336. Kozyrskyj AL, Kalu R, Koleva PT & Bridgman SL Fetal programming of overweight through the microbiome: boys are disproportionately affected. J Dev Orig Health Dis 7, 25–34 (2016). [PubMed: 26118444]

337. Guru A, Post RJ, Ho Y-Y & Warden MR Making Sense of Optogenetics. Int J Neuropsychopharmacol 18, pyv079 (2015). [PubMed: 26209858]

338. Lin P, Fang Z, Liu J & Lee JH Optogenetic Functional MRI. J Vis Exp (2016). doi:10.3791/53346

339. Leong ATL et al. Optogenetic fMRI interrogation of brain-wide central vestibular pathways. Proc. Natl. Acad. Sci. U.S.A. 116, 10122–10129 (2019). [PubMed: 31028140]

340. Chen Y, Pais-Roldan P, Chen X, Frosz MH & Yu X MRI-guided robotic arm drives optogenetic fMRI with concurrent Ca2+ recording. Nat Commun 10, 2536–11 (2019). [PubMed: 31182714]

341. Sperry MM, Kandel BM, Wehrli S, et al. Mapping of pain circuitry in early post-natal development using manganese-enhanced MRI in rats. Neuroscience 352, 180–189 (2017). [PubMed: 28391012]

342. Szulc KU, Lerch JP, Nieman BJ, et al. 4D MEMRI atlas of neonatal FVB/N mouse brain development. NeuroImage 118, 49–62 (2015). [PubMed: 26037053]

343. Chan KC, Cheng JS, Fan S, et al. In vivo evaluation of retinal and callosal projections in early postnatal development and plasticity using manganese-enhanced MRI and diffusion tensor imaging. NeuroImage 59, 2274–2283 (2012). [PubMed: 21985904]

344. Qiu LR, Fernandes DJ, Szulc-Lerch KU, et al. Mouse MRI shows brain areas relatively larger in males emerge before those larger in females. Nat Commun 9, 2615–15 (2018). [PubMed: 29976930]

345. Lizarbe B, Benitez A, Sánchez-Montañés M, et al. Imaging hypothalamic activity using diffusion weighted magnetic resonance imaging in the mouse and human brain. NeuroImage 64, 448–457 (2013). [PubMed: 23000787]

346. Thuen M, Olsen Ø, Berry M, et al. Combination of Mn(2+)-enhanced and diffusion tensor MR imaging gives complementary information about injury and regeneration in the adult rat optic nerve. J Magn Reson Imaging 29, 39–51 (2009). [PubMed: 19097077]

347. Girardi G, Fraser J, Lennen R, et al. Imaging of activated complement using ultrasmall superparamagnetic iron oxide particles (USPIO)--conjugated vectors: an in vivo in utero non-invasive method to predict placental insufficiency and abnormal fetal brain development. Mol. Psychiatry 20, 1017–1026 (2015). [PubMed: 25245499]

348. Girardi G MRI-based methods to detect placental and fetal brain abnormalities in utero. J Reprod Immunol 114, 86–91 (2016). [PubMed: 26187242]

349. Blundell C, Tess ER, Schanzer ASR, et al. A microphysiological model of the human placental barrier. Lab Chip 16, 3065–3073 (2016). [PubMed: 27229450]

350. Lancaster MA & Knoblich JA Organogenesis in a dish: modeling development and disease using organoid technologies. Science 345, 1247125–1247125 (2014). [PubMed: 25035496]

351. Kelava I & Lancaster MA Dishing out mini-brains: Current progress and future prospects in brain organoid research. Dev. Biol. 420, 199–209 (2016). [PubMed: 27402594]

352. Quadrato G, Nguyen T, Macosko EZ, et al. Cell diversity and network dynamics in photosensitive human brain organoids. Nature 545, 48–53 (2017). [PubMed: 28445462]

353. Bagley JA, Reumann D, Bian S, Lévi-Strauss J & Knoblich JA Fused cerebral organoids model interactions between brain regions. Nat Methods 14, 743–751 (2017). [PubMed: 28504681]

354. Birey F, Andersen J, Makinson CD, et al. Assembly of functionally integrated human forebrain spheroids. Nature 545, 54–59 (2017). [PubMed: 28445465]

355. Lancaster MA, Corsini NS, Wolfinger S, et al. Guided self-organization and cortical plate formation in human brain organoids. Nat Biotechnol 35, 659–666 (2017). [PubMed: 28562594]

356. Lowe CJ, Reichelt AC & Hall PA The prefrontal cortex and obesity: A health neuroscience perspective. Trends in Cognitive Sciences 23, 349–361 (2019). [PubMed: 30824229]

357. Lo Y-T, Chang Y-H, Lee M-S & Wahlqvist ML Health and nutrition economics: diet costs are associated with diet quality. Asia Pac J Clin Nutr 18, 598–604 (2009). [PubMed: 19965354]

358. Masterson TD, Stein WM, Beidler E, et al. Brain response to food brands correlates with increased intake from branded meals in children: an fMRI study. Brain Imaging Behav 13, 1035–1048 (2019). [PubMed: 29971684]

359. O'Rahilly S & Farooqi IS Human obesity: a heritable neurobehavioral disorder that is highly sensitive to environmental conditions. Diabetes (2008).

360. Liu W-C, Wu CW, Hung PL, et al. Environmental stimulation counteracts the suppressive effects of maternal high-fructose diet on cell proliferation and neuronal differentiation in the dentate gyrus of adult female offspring via histone deacetylase 4. Int J Environ Res Public Health 17, 3919 (2020). [PubMed: 32492926]
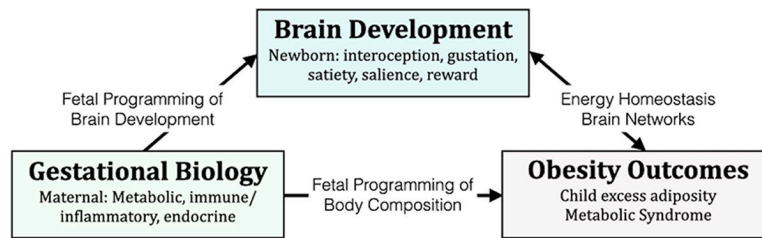
Figure 1. Conceptual Model.

The conceptual model incorporates the role of fetal programming of the setpoint of energy homeostasis-related brain circuitry at birth into the process of fetal programming of offspring body composition.
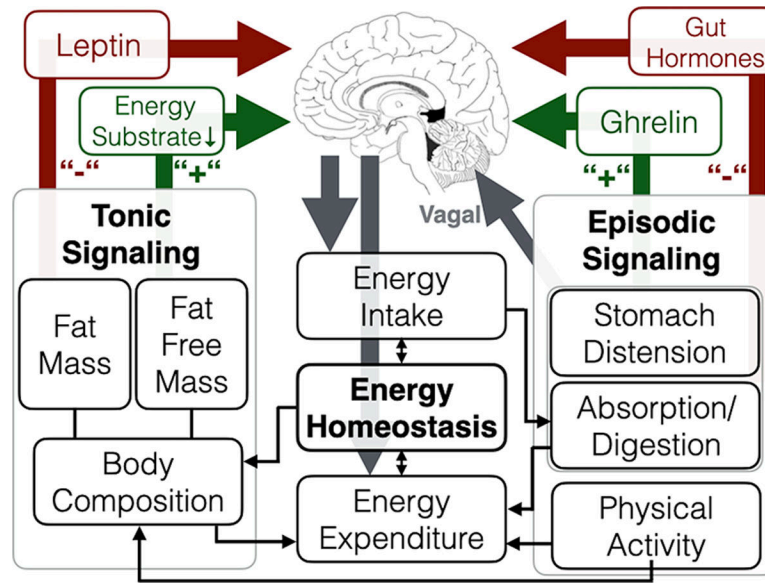
Figure 2. Hormonal Inputs to the Central Regulation of Energy Homeostasis.
Hormonal orexegenic input to the CNS originates from stomach contraction, specific nutrient sensing in the gut, and peripheral energy substrate sensing. Anorexigenic signaling arises from stomach distension, nutrient sensing in the gut, and adipocytes. The CNS integrates these signals in order to regulate energy homeostasis through modulation of energy intake and expenditure.
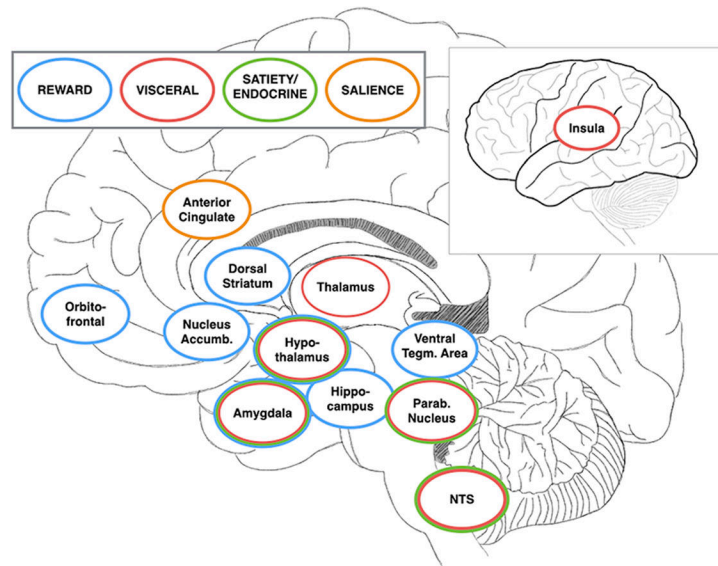
Figure 3. Energy Homeostasis Relevant Brain Regions.
Highlighted brain regions are organized based on their network membership (color outline).

Table 1.

Summary of Evidence Supporting Structural and Functional Inter-individual Variation in Newborn Energy Homeostasis Brain Circuitry.

Energy Homeostasis Relevant Brain Networks and Structures	Model species	Evidence supporting notion that function is present by the time of birth?	Evidence supporting notion that variation at birth is prospectively associated with obesity risk?
Satiety: Hypothalamus	Rodents, non-human primates	Yes See: Baquero 2014; Bouret 2012; Caron 2010; Gali Ramamoorthy 2015; Greyson 2006; Steculorum 2011	Yes See: Barrand 2017; Gali Ramamoorthy 2015; Plagemann 2017
Reward: VTA, NA, Amygdala, Hippocampus, Insula, Prefrontal/ Orbitofrontal Cortex, Caudate, Putamen, Thalamus, Pituitary Gland	Rodents, humans	Yes See: Antonopoulos 2002; Van den Heuvel 2008; Meng 1999; Contreras 2013; Loos 2019	Yes See: Ayres 2012; Dalle Molle 2015; Dalle Molle 2016; Laureano 2016; Silveira 2018
Visceral: Insula, Olfactory and Gustatory Cortices, NTS, VPMpc	Rodents, humans	Yes See: Rinaman 1999; Swithers 1989	Yes See: Rasmussen 2017
Salience: ACC, anterior Insula	Humans	Yes See: Gao 2016; Li 2016; Rudolph 2018;	Unknown

Table 2.

Summary of Evidence supporting the presence of developmental plasticity in Newborn Brain Energy Homeostasis Regulating Structures and Networks.

The presented evidence relates to human studies unless otherwise indicated by an asterisk (*) in which the evidence predominantly exists in rodent models.

Maternal Risk Factors that are prospectively associated with Obesity Risk	Brain Networks/Structures/Regions that exhibit Developmental Plasticity
Sociodemographic (e.g., SES)	Executive function (e.g., Insula, Frontal Cortex)[148], Amygdala[151]
Maternal Biophysical (e.g., Obesity, Gestational Weight Gain)	Prefrontal Cortex, Anterior Cingulate Cortex[134, 169], Hypothalamus[248]
Maternal Nutrition*	*Indirect* evidence for appetite regulating networks (e.g., satiety[170, 172], limbic/reward circuitry [171, 174–179]), hypothalamus[173]
Maternal Metabolic State	Non-specific to date. Literature suggests insulin sensitivity-dependent brain function
Maternal Endocrine Stress Biology	Amygdala[213, 217]*, Hippocampus[217], Insula[214], Frontal Cortex[215], Anterior Cingulate[216]
Maternal Inflammation	Limbic (Hippocampus, Amygdala)/Frontal Cortex[135,245,246]