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Life-course Effects of the Early Life Adversity Exposure on Eating Behavior and Metabolism

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ABSTRACT

Environmental variations in early life influence brain development, making individuals more vulnerable to psychiatric and metabolic disorders. Early life stress (ELS) has a strong impact on the development of eating behavior. However, eating is a complex behavior, determined by an interaction between signals of energy homeostasis, neuronal circuits involved in its regulation, and circuits related to rewarding properties of the food. Although mechanisms underlying ELS-induced altered feeding behavior are not completely understood, evidence suggest that the effects of ELS on metabolic, mood, and emotional disorders, as well as reward system dysfunctions can contribute directly or indirectly to altered feeding behavior. The focus of this chapter is to discuss the effects of ELS on eating behavior and metabolism, considering different factors that control appetite such as energy homeostasis, hedonic properties of the food, emotional and cognitive status. After highlighting classic studies on the association between ELS and eating behavior alterations, we discuss how exposure to adversity can interact with genetics characteristics to predict variable outcomes.

Keywords: Early life adversity, feeding behavior, metabolism, appetite.

Introduction

The ability of the organism to modify its physiology or behavior as it develops, responding to changes in the environment, is called developmental plasticity (Bateson et al., 2004) and may be adaptive or maladaptive. Stressors in childhood, such as physical or sexual abuse, emotional neglect, family conflict, lack of maternal care, deprivation of food, among others, are associated with an increased risk of physiological and psychological disorders. In children and adolescents, early life stress (ELS) is associated with the vulnerability to developing behavioral problems that can remain until adulthood. One of the most studied outcomes of ELS is its effect on neuroendocrine signaling, with altered responses of the hypothalamus-pituitary-adrenal axis to stress throughout life (Levine, Huchton, Wiener, & Rosenfeld, 1991; Rosenfeld, Suchecki, & Levine, 1992). It also affects metabolic and behavioral parameters, markedly influencing eating behavior.

The feeding circuit involving the hypothalamus is directly associated with homeostatic control of body weight. The hypothalamus homeostasis involves the control of nutrient intake necessary for metabolic maintenance. The energy needs vary according to different states of the organism (e.g., growing up, recovery from diseases), distinct basal metabolic rate between individuals, activity-induced energy expenditure, etc. Peripheral circulating hormones, such as leptin and insulin, act by informing the hypothalamus about the body's energy stores. Leptin, one of the main hormones in this signaling, is produced by adipocytes (Friedman & Halaas, 1998). It crosses the blood-brain barrier and its effects are mediated by receptors located in the arcuate nucleus of the hypothalamus. The hypothalamus produces anorexigenic and orexigenic neuropeptides. The release of the anorexigenic neuropeptides pro-opiomelanocortin (POMC) and cocaine- and amphetamine- regulated transcript (CART) reduces food intake and increases energy expenditure (Balthasar et al., 2004; Bharne, Borkar, Subhedar, & Kokare, 2015). On the other hand, the orexigenic neuropeptide Y (NPY) and the agouti-related peptide (AgRP) are associated with an increased food intake (Asakawa et al., 2002; Ramos, Meguid, Campos, & Coelho, 2005). Leptin acts on ObRb receptors and induces an increase in the expression of POMC and CART, and antagonizes the activity of NPY and AgRP neurons, leading to a decrease in food intake (Berthoud, 2002). Eating is a complex behavior, determined by an interaction between signals of energy homeostasis and the neuronal circuits involved in its regulation (Grill, 2006). However, these neural circuits go beyond seeking food to satisfy the

demand for energy (Zhang, Hernandez-Sanchez, & Herzog, 2019). The regulation of food intake depends on the interaction between mechanisms of energy balance, reward circuits, food choices, and preferences, emotional state and cognitive decisions (figure 1).

<Insert figure 1 near here>

The mechanisms underlying ELS-induced altered eating behavior are not known; however, several factors could be related to this outcome. ELS disturbs the animal`s emotional state, which can be perceived by depressive/anxious behavior. Changes in the emotional state may induce palatable food consumption (fat and sucrose) (Kim, Shou, Abera, & Ziff, 2018; Lee, Kim, & Jahng, 2014; Maniam & Morris, 2010), and reduce stress effects (Aya-Ramos, Contreras-Vargas, Rico, & Duenas, 2017; Donahue, Muschamp, Russo, Nestler, & Carlezon, 2014; Maniam, Antoniadis, Le, & Morris, 2016). For a better understanding of the effects of stress in early human life on adult behavior and physiology, researchers have developed animal models that mimic ELS. Maternal separation (MS) or maternal deprivation (MD) protocols are a well-established model to study the effects of ELS in rodents. MS corresponds to a separation of the pup from the mother during the first weeks of life, from a few minutes to few hours of separation, while MD consists of a severe disruption of maternal care for 24 hours in the neonatal period. These studies using experimental models seek to understand the effects of stress on eating behavior. In this review we will discuss different factors that control appetite such as energy homeostasis, hedonic properties of the food, emotional and cognitive status.

Early life stress adversities and feeding-related behaviors

The effects of stress on food consumption are controversial, acute stress lead to reduced food intake, while chronic stress induces increased food intake and motivation for comfort foods (Adam & Epel, 2007; Gonzalez-Torres & Dos Santos, 2019; Tomiyama et al., 2012; Tryon, Carter, Decant, & Laugero, 2013). Interestingly, it is well-known that stress in critical periods of development, such as early childhood can modulate the response to stressors later in life (Weaver et al., 2004). Individuals that are stronger reactors to stress have higher emotional eating, suggesting a possible mechanism linking early life stress (ELS) to emotional eating (Adam & Epel, 2007). In this scenario, several studies have demonstrated that exposure to neonatal stress

and neonatal handling can lead to increased consumption of palatable food in adulthood, possibly due to effects on hedonic mechanisms of eating behavior (de Lima, Dos Santos Bento, et al., 2020; Portella et al., 2010; Silveira et al., 2006; Silveira, Portella, Assis, Nieto, Diehl, Crema, Peres, Costa, Scorza, Quillfeldt, et al., 2010; Silveira et al., 2008). It is also well known that mood can affect eating behavior, and there are several common pathways linking homeostatic food control, stress, reward, appetite, and anxiety behaviors (Berridge, 2009a).

These ELS effects on eating behavior have been studied in animal models and shown to be dependent on the of model of intervention applied, sex, age when the behavior is evaluated, and type of food offered. Maternal separation (MS) may promote lower intake of standard lab chow and higher intake of palatable food (de Souza, da Silva, de Matos, do Amaral Almeida, Beltrao, et al., 2018; de Souza et al., 2020), as well as a decline in circulating leptin, which has been associated with impaired hypothalamic development (Mela et al., 2016; Viveros, Diaz, Mateos, Rodriguez, & Chowen, 2010). Additionally, studies suggest that maternal deprivation (MD) leads to food intake alteration related to modifications in NPY and POMC expression in the hypothalamus (de Lima, Dos Santos Bento, et al., 2020; Wertheimer, Girardi, de Oliveira, Monteiro Longo, & Suchecki, 2016). Together these findings suggest that ELS substantially influence the food control network, both central and peripherally.

Animal studies have suggested that some ELS models such as MS and limited access to nesting material increases sucrose preference, palatable food consumption, as well as anxiolytic-like behavior (Aya-Ramos et al., 2017; Machado et al., 2013). Interestingly, these studies observed sex-specific differences in the vulnerability to ELS-induced changes in behavior. In humans, studies observed that emotional stimuli lead to emotional over or under eating in adolescent girls and young adult woman (van Strien et al., 2013; van Strien, van der Zwaluw, & Engels, 2010). Poor emotional maternal-child interactions predict emotional overeating in girls but not in boys (Escobar et al., 2014). ELS exposure in children induces eating in the absence of hunger and emotional overeating, predicting obesogenic behaviors (Miller et al., 2018). The hypothesis is that ELS can program the inappropriate use of food as a relief mechanism to anxiety status (Machado et al., 2013). Thus, ELS increases the preference for palatable food as a way to compensate anxiety status.

ELS is also a risk factor for major depressive disorders, which may affect eating behavior. Several studies have indicated a strong correlation between MS and increased

immobility in the forced swim test in male animals, which is indicative of depressive-like behavior (Lee et al., 2007; Ryu, Yoo, Kang, Lee, & Jahng, 2009). Disruption of mother-pups relationships during 3 or 24 h in sensitive periods of development leads to depressive-like behavior (Lee et al., 2007; Miragaia et al., 2018). Some authors suggest that ELS may result in the development of depression-like behavior due to the alterations in serotoninergic neurotransmission and reduction of NPY in brain regions linked to emotional behaviors (Aisa, Tordera, Lasheras, Del Rio, & Ramirez, 2008; Miragaia et al., 2018). MD also leads to reduced standard food intake compared to control animals, which could be associated with anhedonia, a symptom of major depression. Anhedonia is characterized by loss of interest or pleasure in activities, including eating (Stanton, Holmes, Chang, & Joormann, 2019). Indeed, individuals with depressive behavior experience reward-related deficits, observed in animals by a decrease in sucrose intake and behavioral response to food (Der-Avakian & Markou, 2012). However, despite the lower voluntary food intake, ELS seems to stimulate the intake of palatable sweet food as a way to ameliorate anxiety and depression (Maniam & Morris, 2010). These findings together help to explain, at least in part, that mechanisms underlying mood disorders may moderate the effects of ELS on food intake.

In addition to emotion and mood, eating behavior may also be influenced by memory deficits. Evidence suggests that the memory of the previous ingested meals influence the subsequent intake. For example, individuals distracted during a meal tend to show increased feeling of hunger and over-eating in the next eating episode (Hannapel et al., 2019; Hannapel, Henderson, Nalloor, Vazdarjanova, & Parent, 2017). Conversely, enhancing the memory of a meal decreases the amount of food consumed in the following meal (Robinson et al., 2013). In this scenario, several studies have demonstrated that ELS induces learning and memory deficits. For example, MS and early life malnutrition interfere with memory formation in a spatial memory task and affect aversive memory reconsolidation (Couto-Pereira et al., 2019; Maghami et al., 2018). Hill and colleagues (2014) observed that, in a “two hit” model of developmental stress, males are more susceptible to impairments in spatial memory, while females are more susceptible to anhedonic behavior (Hill et al., 2014). Some authors suggest that memory impairments caused by ELS in males are associated with reduced hippocampal long-term potentiation (Sousa et al., 2014). Interestingly, hippocampal neurons development occurs in the first three postnatal weeks, which corresponds to the MS period (Bayer, 1980). Although few

studies have evaluated the effects of neonatal stress on memory of females, male studies suggest that ELS impairs memory, what may indirectly result in problems related to appetite control and weight gain.

Several evidence suggest that ELS exposure affects other cognitive processes that could be implicated in the control of eating behavior, such as attention and hyperactivity (Colorado, Shumake, Conejo, Gonzalez-Pardo, & Gonzalez-Lima, 2006; de Lima, Barth, et al., 2020; Spivey et al., 2009). Recent studies reported that symptoms of Attention Deficit Hyperactivity Disorder (ADHD) are associated with disordered eating (Bleck & DeBate, 2013; Reinblatt et al., 2015). ADHD is positively associated with eating disorders, such as bulimia nervosa, binge eating disorder, and loss of control over-eating (Kaisari, Dourish, & Higgs, 2017). It is possible that ADHD patients may be relatively inattentive to signs of hunger and satiety or have compulsive eating as a compensatory mechanism to control the frustration associated with attention problems (Kaisari et al., 2017). Although few studies have evaluated the mechanisms behind this association, deficient inhibitory control and impulsivity traits could be a link between ADHD and eating disorders (Davis, Levitan, Smith, Tweed, & Curtis, 2006). Furthermore, impulsivity problems also influence unhealthy eating behavior. Studies have observed that impulsive children exhibit high scores of emotional overeating, and impulsive adolescents appear to be prone to the consumption of soft drinks (Farrow, 2012; Melbye et al., 2016). In this context, ELS have been associated with susceptibility to development of ADHD as well as impulsivity problems, both in animal models and in humans (Bock, Breuer, Poeggel, & Braun, 2017; Colorado et al., 2006; de Lima, Barth, et al., 2020; Gondre-Lewis et al., 2016; Miguel et al., 2019).

The findings reviewed above confirm that the postnatal environment affects the development of distinct aspects related to eating behavior. Besides affecting mood and emotion processes, exposure to stress in this period may also cause metabolic changes that may directly or indirectly lead to alterations on food behavior. In the next sections we will discuss these points.

Postnatal adversities programming of metabolism as another factor on early life stress-induced weight gain and appetite

Homeostatic control of feeding is concerned with regulation of energy balance, energy metabolism and storage signals related to the control of appetite and/or eating behavior (Zanchi et al., 2017). Exposure to adverse early environmental experiences is also associated with development of impaired glucose homeostasis, including decreased insulin sensitivity (Raff et al., 2018; Ruiz et al., 2018; Vargas, Junco, Gomez, & Lajud, 2016). These and other ELS outcomes related to energy metabolism could influence homeostatic control. In this section, we will focus on how early adversities may contribute to the increased vulnerability to metabolic disturbances in adulthood, which in turn could modify appetite.

In animal models, ELS has been shown to lead to increased fasting glucose (Vargas et al., 2016), impaired glucose tolerance (Ruiz et al., 2018), and altered indexes of insulin resistance, such as increased homeostatic model assessment (HOMA)-IR (Raff et al., 2018) and decreased quantitative insulin sensitivity check index (QUICKI) (Ruiz et al., 2018), as well as dyslipidemia (Baxi, Singh, Vachhrajani, & Ramachandran, 2012), in adult animals. Adult maternal separated males (but not females) also had augmented insulin and glucose responses to arginine administration, pointing to altered responsiveness of pancreatic beta cells and to lower responses by target tissues (Gehrand et al., 2016). Other studies have also shown sex-specific effects, with males being more susceptible to the effects of ELS on insulinemia (Jaimes-Hoy, Romero, Charli, & Joseph-Bravo, 2019), leptinemia (Raff et al., 2018), and cortisolemia (Jaimes-Hoy et al., 2019), that increased with early stress (Gehrand et al., 2016). These results suggest that ELS increases metabolic risk in adulthood, with increased insulin resistance, and that males are particularly susceptible.

ELS has also been suggested to affect microbiota homeostasis in adult rodents (Donoso et al., 2020), and fecal dysbiosis has been related to feeding choices (Alcock, Maley, & Aktipis, 2014). ELS-induced alterations in the gut-brain axis could influence life-long metabolic function: in a study using ageing mice, maternal separation led to microbiota dysfunction, increased fasted blood glycemia, glucose intolerance and decreased insulin sensitivity (Ilchmann-Diounou et al., 2019). Since glucose and insulin are reported to influence eating control (Zanchi et al., 2017), these ELS-induced changes could also influence feeding.

As we have already considered, the postnatal environment plays a critical role in the neuroendocrine programming. A proposed mechanism through which early stress can modulate hormonal effects, resulting in altered metabolism, is associated with altered expression of genes

related to glucocorticoid function. For example, the expression of the glucocorticoid receptor, and 11-beta hydroxysteroid dehydrogenase (11β-HSD1), that converts inactive to active glucocorticoids (Doig et al., 2017; Paterson et al., 2004) is altered in peripheral and central tissues (Maniam, Antoniadis, & Morris, 2014; Meaney et al., 2013; Poletto, Steibel, Siegford, & Zanella, 2006). In addition, some studies observed that MS could program brown adipose tissue (BAT) metabolism, for example, affecting deiodinase-2 activity, and decreasing the expression of β3-adrenergic receptor (Jaimes-Hoy et al., 2016; Miki et al., 2013); it may also influence the fate of adipose tissue proliferation (Miki et al., 2013). However, other authors found increased expression of uncoupling protein 1 in the inguinal white adipose tissue (WAT) at P9, and decreased WAT mass, plasma leptin and leptin expression in WAT in adulthood (Yam et al., 2017). Some of these results suggest that ELS may also influence basal metabolic activity.

Metabolic homeostasis is distinctly controlled in males and females, and evolutionary reasons have been proposed for these differences, suggesting that females are better able to maintain energy reserves (Mauvais-Jarvis, 2015). Therefore, it is not surprising that ELS causes sex-specific metabolic responses in adults. For example, in animal models of ELS, hypothalamus–pituitary–thyroid axis (HPT) activity is affected in adults, with males and females responding differently. This axis is a major regulator of energy homeostasis, and it is also regulated by stress (Joseph-Bravo, Jaimes-Hoy, & Charli, 2016). In adult male rats subjected to neonatal MS, TSH and T_3 serum concentrations are decreased, while thyrotropin releasing hormone degrading enzyme *(Trhde)* expression is increased in tanycytes (Jaimes-Hoy et al., 2019), suggesting increased inactivation of TRH before arriving at the pituitary, contributing to reduce TSH secretion. HPT axis response to fasting is also partially blunted in MS males (Jaimes-Hoy et al., 2016). In addition, MS abolished the fasting-induced increase in Trh expression in both sexes (Jaimes-Hoy et al., 2016). Another animal model of ELS, social isolation in the childhood (from PND 21 to PND 28), has also showed to affect HPT function: stress in the prepubertal period induced a reduction in the T3/T4 ratio in adult animals (Toniazzo et al., 2018), but only in males. All these conditions would suggest a lower HPT function and possibly an impairment of the adaptive response to negative energy balance.

Metabolism in females is also affected by MS. In an animal model of prepubertal stress using social isolation, stressed females showed reduced leptin signaling in the hypothalamus later on in life (Toniazzo et al., 2018). Some studies show that MS females gain more weight

(Gehrand et al., 2016; Jaimes-Hoy et al., 2016; Raff et al., 2018), while other studies show no effect on body weight (Ilchmann-Diounou et al., 2019). This discrepancy could be due to different protocols. For example, MD has been shown to reduce body weight gain in both males and females (de Lima, Dos Santos Bento, et al., 2020). Interestingly, in MS female rats, higher gain of weight and fat mass have been reported even without changes in rat chow consumption or even in the presence of a decreased consumption (Jaimes-Hoy et al., 2016), with increased caloric efficiency, that could be explained by distinct basal metabolism. Although thyrotropin releasing hormone *(Trh)* expression in the PVN has been shown to increase in adult MS females (Jaimes-Hoy et al., 2016), serum TSH or TH concentrations show no differences or a slight decrease (Jaimes-Hoy et al., 2016; Jaimes-Hoy et al., 2019).

Beneficial effects of early stress on some metabolic markers have also been reported, when an interaction between a high fat and sugar diet (HFS) and MS was observed in the expression of leptin in periovaric adipose tissue, as well as in the amount of this tissue, so that MS counteracts the diet-induced effects, suggesting that ELS affects the metabolic response to this diet later in life (Paternain et al., 2012). Besides, in that study, MS reduced insulin resistance markers in chow-fed rats, although not in animals receiving HFS diet (Paternain et al., 2012). One point to take into account, considering these studies on the effects of ELS, is that most of them used MS as a ELS model. However, different protocols are used and these protocols could involve, besides separation from the dam, altered maternal care and changes in the schedule of feeding and body temperature (Gehrand et al., 2016).

In humans, several studies have reported ELS effects similar to the ones observed in the animal studies considered above. Exposure to physical or emotional abuse during childhood increases the likelihood of obesity (Hollingsworth, Callaway, Duhig, Matheson, & Scott, 2012; van Reedt Dortland, Giltay, van Veen, Zitman, & Penninx, 2012; Wang, Wu, Yang, & Song, 2015), and leads to higher waist circumference (Midei, Matthews, Chang, & Bromberger, 2013; van Reedt Dortland et al., 2012), higher blood pressure (Misiak, Kiejna, & Frydecka, 2015), dyslipidemia (Misiak et al., 2015; van Reedt Dortland et al., 2012), with higher low-density lipoprotein (LDL) levels, decreased high-density lipoprotein (HDL) levels and HDL/LDL ratios, particularly in males (Spann et al., 2014). Besides, impaired tolerance to glucose and insulin sensitivity (Li, Garvey, & Gower, 2017), increased C-reactive protein and tumor necrosis factor-α levels (Li et al., 2017) have also been associated with early trauma in humans. Childhood

abuse leads to altered serum TSH and thyroid hormones levels. Early life trauma evaluated using CTQ is associated with reduced T3 levels, but not with altered peripheral T4 levels in adolescents (Machado et al., 2015), and increased TSH levels in women that experienced childhood trauma have also been found (Bunevicius, Leserman, & Girdler, 2012; Moog et al., 2017), suggesting enhanced risk of hypothyroidism. On the other hand, some distinct effects of childhood trauma have also been reported on HPT function in women with functional somatic syndrome (Fischer et al., 2018), and with post-traumatic stress disorder (Friedman, Wang, Jalowiec, McHugo, & McDonagh-Coyle, 2005), in which higher childhood trauma was associated with lower TSH. Increased risk of HPT dysfunction was also observed in post-partum depressed patients who experienced childhood trauma (Plaza et al., 2010). Although many of the effects above were observed in women, men appear to be more susceptible to the effects of early trauma on dyslipidemia (Spann et al., 2014), and the effects of emotional and physical abuse on the risk of developing metabolic syndrome are observed independently of sex, although sexual abuse was a predictor especially in women (Lee, Tsenkova, & Carr, 2014).

Taken together, these findings suggest that ELS increases vulnerability to metabolic disturbances later in life, affecting glucose homeostasis and causing dysfunctions of the HPT axis, effects that could modify appetite and eating behavior.

Influence of postnatal adversities on hedonic behavior and reward system

Reward is defined as a neural activation in response to an attractive and motivational property of a stimulus that facilitates behavioral reactions to pursue the rewarding stimulus (Berridge, 1996). Food is considered an important rewarding stimulus, especially palatable foods rich in sugar and/or fat (Kenny, 2011). The repeated ingestion of these foods with higher palatability can induce neurochemical changes in brain regions involved in the reward system, influencing the frequency, quantity, and quality of food ingested (Kenny, 2011). In this case, the homeostatic signaling can be overridden by the pleasure through the ingestion of palatable foods (Zheng, Lenard, Shin, & Berthoud, 2009). The stimulation of brain reward systems by palatable foods may contribute to the development of obesity and associated diseases.

A set of interconnected brain regions are implicated in the reward-driven mechanisms. These brain reward circuits include nucleus accumbens (NAc, a component of the ventral striatum), ventral tegmental area (VTA), frontal regions of the cerebral cortex, hippocampus,

hypothalamus, and amygdala (Berridge & Kringelbach, 2015; Kenny, 2011). The mesocortical and mesolimbic brain circuits, with projection from the VTA to the frontal cortex regions and nucleus accumbens (NAc), respectively, are considered the central pathways in the food reward regulation (Berridge & Kringelbach, 2015). These circuits receive rich dopaminergic innervation. Dopamine is an important reward neurotransmission compound in the brain (Berridge & Kringelbach, 2015). Exposure to early life adversities can affect the maturation of the dopaminergic system since the developing brain is characterized by high levels of neuroplasticity and reorganization, which may cause a dopaminergic dysfunction (Burke & Miczek, 2014; Rothmond, Weickert, & Webster, 2012), as we discuss below. In this sense, modifications caused by early environmental changes can affect the regulation of the reward system leading to an alteration in feeding behavior.

The reward system is usually related to an increased effort for obtaining food. The activation of the brain reward circuitry is associated with distinct responses; the incentive salience is related to the motivational value of the reward ("wanting"), while the hedonic reaction is associated with the pleasure of the reward ("liking") (Berridge, 2009b). These responses are mediated through distinct processes in the motivation and reward neurotransmission, however, both are necessary for the normal reward process. Dopaminergic neurons projections from VTA to NAc are more involved in the incentive salience associated to food ("wanting" responses). Animal studies showed an increase of dopamine release by VTA when the animal first accesses a palatable food, increasing the activity of dopaminergic neurons in NAc (Volkow, Wang, Tomasi, & Baler, 2013). On the other hand, "liking" responses to food appear to be more associated with the opioid and cannabinoid systems (Berridge, 2009b). A large number of studies have suggested that both opioid and cannabinoid activation stimulate appetite in part by enhancing the "liking" responses associated with the palatability of food (Jarrett, Limebeer, & Parker, 2005; Kelley et al., 2002; Niki, Jyotaki, Yoshida, & Ninomiya, 2011; Peciña & Smith, 2010). Despite the differences in the modulatory action of these neurotransmitter systems, it is suggested a functional interaction between them in the regulation of hedonic feeding behavior (Wenzel & Cheer, 2018).

The early life environment effects on reward responses are controversial in the literature. For example, rodent studies using MS protocol, indicate decreased preference for sweets/sucrose (Amiri et al., 2016; Bolton et al., 2018; Hui et al., 2011; Sadeghi, Peeri, & Hosseini, 2016), while

others have reported increased preference (Chocyk, Majcher-Maślanka, Przyborowska, Maćkowiak, & Wędzony, 2015a; Ferreira et al., 2013). In this sense, ELS is associated with both hypersensitive and hyposensitive mesolimbic dopaminergic functions associated with food reward. Romaní-Perez et al (Romaní-Pérez et al., 2017) showed that MS promotes exacerbated food-motivated behavior and blunted dopamine release in the NAc during palatable food consumption in adult male offspring. MS inhibits the expression of D2 receptors in VTA and fronto-parietal cortex (Ploj, Roman, & Nylander, 2003), increases the expression of tyrosine hydroxylase (TH) in the cerebral cortex (Braun, Lange, Metzger, & Poeggel, 2000), and decreases the density of nucleus accumbens-core and striatal dopamine transporter (DAT) sites (Brake, Zhang, Diorio, Meaney, & Gratton, 2004; Meaney, Brake, & Gratton, 2002). Also, maternally separated rats showed an adolescent peak in D1 expression and a blunted peak in D2 expression on projection neurons from PFC to NAc (Brenhouse, Lukkes, & Andersen, 2013). Neonatally handled rats, a model of briefly mother-pups separation, displayed less conditioned place preference and less hedonic reactions to sweet food, but higher incentive salience to a sweet reward in a runway test, in addition to lower dopamine metabolism in NAc (Silveira, Portella, Assis, Nieto, Diehl, Crema, Peres, Costa, Scorza, & Quillfeldt, 2010). Decreased in conditioned locomotor activity to food-related cues (Matthews, Hall, Wilkinson, & Robbins, 1996; Matthews, Wilkinson, & Robbins, 1996), and decreased conditioned place preference to chocolate (Sasagawa et al., 2017) were observed in maternally separated rats, suggesting an impairment in the reward valuation and decreased incentive salience in these animals. Although the studies considered above reported distinct processes related to the reward system, a scenario appears to emerge in which ELS consistently affects dopaminergic neurotransmission, especially in regions related to the reward system, such as NAc and frontal cortex. This could lead to altered motivation to eat palatable foods. It should be taken into account that distinct models may differently affect these circuits.

Maternally separated rats demonstrate increased opioid receptor expression in the dorsal striatum (Granholm et al., 2017) and modified response to opioid agonists (Kalinichev, Easterling, & Holtzman, 2001) and antagonists (Daoura & Nylander, 2011) in adult life. Exposure to MS also modulates the endocannabinoid signaling in neonates and causes a persistent downregulation of cannabinoid receptors (CB1) in adolescence and adulthood in the PFC and amygdala (Hill, Eiland, Lee, Hillard, & McEwen, 2019). CB1 downregulation was

observed in the NAc of adult rats exposed to neonatal handling (Vangopoulou et al., 2018), and might contribute to alterations in rewarding behaviors observed in these animals.

Another ELS model, post-weaning social isolation appears to have a significant impact on reward-associated behaviors. In general, animals subjected to social isolation during the juvenile period demonstrate increased hedonic behavior, increasing sucrose preference or "liking" responses (Brenes & Fornaguera, 2008, 2009; Van den Berg, Van Ree, & Spruijt, 2000), although in other studies no differences were found (Arcego et al., 2020; McCool & Chappell, 2009). These discrepancies can be explained by the differences in the period of isolation between these studies. Briefly, a short period of isolation after weaning is associated with a decrease of conditioned locomotor activity to sucrose (Van den Berg et al., 1999), opposite to longer periods of isolation (Jones, Marsden, & Robbins, 1990). An increase in the locomotor response to psychostimulants was observed in both short and long post-weaning social isolation (Fabricius et al., 2010; Lampert et al., 2017). Data from the literature showed that social isolation stress overall increased dopamine function in NAc by increasing firing of midbrain dopaminergic neurons (Fabricius et al., 2010), resulting in increased dopamine release in NAc and striatum (Heidbreder et al., 2000; Yorgason et al., 2016; Yorgason, Espana, Konstantopoulos, Weiner, & Jones, 2013) in response to psychostimulants. However, in basal conditions early social isolation decreased dopaminergic turnover in NAc, which means less dopamine being released in the synaptic cleft and more stored in vesicles, without differences in opioid and cannabinoid receptors (Arcego et al., 2020). A decreased dopamine activity in PFC is also observed (Baarendse, Limpens, & Vanderschuren, 2014; Heidbreder et al., 2000), which could be associated with decreased reward learning, as observed in socially isolated animals (Amitai et al., 2014; Schrijver & Würbel, 2001). From these findings we can assume that the link between social isolation early in life and changes in the reward system are consistent, despite the differences on effects according to the period in which the stress occurs. The dopaminergic system appears to be very susceptible to ELS, responding differently depending on the reward stimulus presented.

ELS may affect the reward system differently according to sex. Some studies have suggested that male MS rats have increased dopaminergic activity, observed by increased expression of brainstem D1 and D2 receptors in adulthood (de Souza, da Silva, de Matos, do Amaral Almeida, Beltrão, et al., 2018), as well as increased cannabinoid receptors (CB1 and

CB2) expression in the frontal cortex (Marco et al., 2014), and sucrose preference (Chocyk, Majcher-Maślanka, Przyborowska, Maćkowiak, & Wędzony, 2015b). In females, MS leads to increased density of tyrosine hydroxylase immunoreactive fibers in the prelimbic cortex and NAc, decreased D5 and increased D2 expression in the prelimbic cortex of adolescent animals (Majcher-Maślanka, Solarz, Wędzony, & Chocyk, 2017), while others have found decreased D2 receptors in the NAc of adults (Lampert et al., 2017; Majcher-Maślanka et al., 2017). As the information regarding the effects of ELS in females is very limited, it is not possible to establish similar comparisons between sexes. However, the sex differences in the effects induced by ELS on the above parameters may be related to the maturation and plasticity in dopaminergic brain regions according to the developmental periods, and appear to be more expressive during adolescence in females, while in males they are more evident in adulthood (Chocyk, Dudys, Przyborowska, Maćkowiak, & Wędzony, 2010). In summary, the effects of ELS on reward responses can be related to the sex, the type and duration of the stressor, the specific developmental period in which the stress occurs.

ELS can also have an impact on hedonic behavior and reward system in humans. ELS is associated with blunted subjective responses to reward-predicting cues and decreased activity in basal ganglia regions related to reward-related learning and motivation (Dillon et al., 2009; Hanson et al., 2016), suggesting reduced approach motivation in individuals exposed to early life adversity. ELS is also associated with NAc hypoactivation in adolescence that was correlated with depression scores (Goff et al., 2013). Early life maltreatment and deprivation were associated with reduced activation of ventral striatum during a rewarding task (Mehta et al., 2010; Takiguchi et al., 2015). These findings suggest that a reward system dysfunction occurs in individuals previously exposed to ELS. Despite the limitations in animal and human studies, it can be clearly observed that the sensitivity of reward-related brain functions is modulated by early adverse experiences, changing reward responsiveness and approach motivation that can influence eating behavior.

Interactions between early life adversities and palatable food consumption

Stress experienced in early life can profoundly change eating behavior, influencing the quantity and quality of calories ingested. Generally, there is a preference for consumption of palatable foods (food rich in carbohydrates, and fats) (Arcego et al., 2018; de Lima, Dos Santos

Bento, et al., 2020; Lee, Kim, et al., 2014; Maniam et al., 2016). Foods eaten in stressful situations are known as “comfort foods”. They act by damping the stress response, in a reward-based model (Adam & Epel, 2007; Cohen, Janicki-Deverts, & Miller, 2007; Dallman, 2010; Dallman, Pecoraro, & la Fleur, 2005; Foster et al., 2009; Ryu et al., 2009). Many of these effects are similar in humans and in studies using animal models, and various studies indicate that the consumption of comfort foods in stressful situations reduces cortisol (humans) and corticosterone (rodents) levels (Pecoraro, Reyes, Gomez, Bhargava, & Dallman, 2004; Tomiyama, Dallman, & Epel, 2011). The neurobiological mechanism by which the consumption of palatable foods reduces the stress response is complex and still needs to be better elucidated. However, strong evidence suggest that factors involved in the neurobiology of stress may interact with the homeostatic and hedonic signals that control eating behavior.

In studies considering the influence of ELS on consumption of distinct diets, both stress and diet may have different outcomes depending on sex, type of stressor/diet used, length of time for stress/diet application, the period of development when stress/diet are applied. Prolonged access to palatable food (chocolate cookies) during adolescence (PND21-59) partly improves anxiety-related, but not depressive symptoms, in male rats that experienced MS (Lee, Kim, et al., 2014). In the same study, palatable diet improved hypothalamic-pituitary-adrenal axis (HPA) function normalizing corticosterone plasma levels (Lee, Kim, et al., 2014). In female rats, cookie access during adolescence improved MS-induced anxiety-/depression-like behaviors; however, MS effects on corticosterone plasma levels were not changed (Kim et al., 2015). The authors suggest that the anxiolytic and/or antidepressant efficacy of this palatable diet during adolescence in female MS rats may not be related with the HPA axis function. In this same study, palatable diet increased ΔFosB (a transcription factor known to be related to addictive and compulsive behaviors (Nestler, Barrot, & Self, 2001)) and brain-derived neurotrophic factor (BDNF) expressions in the NAc in female MS rats. Another study showed that increased ΔFosB expression in striatum could be associated with a reduction in stress-induced depressive effects (Donahue et al., 2014). Early-life stress may also affect the consumption of sweeteners later in life. One study found an interaction between MS (6 h per day in two periods of 180 minutes) and sweetener intake on blood glucose levels; besides, both early MS and sweetener intake during adolescence resulted in increased blood glucose and hyperactivity in male rats, but not in female rats (Aya-Ramos et al., 2017).

Maniam et al. (2010) investigated the influence of palatable cafeteria high-fat diet (HFD) on behavioral responses in animals subjected to MS (180 min) or non-handled controls (NH), versus 15 min brief separation (S15). HFD offered from weaning (PND 21 until adulthood) reversed anxiety-like behavior induced by MS (PND 1-10) in both sexes, increased hippocampal GR mRNA, and led to normalization of hypothalamic CRH mRNA in adult rats. The rats fed HFD and submitted to S15 showed increased body weight, epididymal white adipose tissue total mass and elevated plasma leptin and insulin levels (Maniam & Morris, 2010). In another study, the consumption of a cafeteria diet after weaning until adulthood also reversed the effects of an adverse environment induced by limited nesting (PND 2–9). The findings showed that this diet reversed anxious behavior and increased hippocampal GR mRNA in adulthood in male rats (Maniam et al., 2016). These studies indicate that the palatable diet is able to improve anxiety behavior and increase the efficiency of the negative feedback of the HPA axis, reducing the effects of stress and suggesting that the consumption of a palatable diet may induce positive emotional behavior.

The influence of MS and consumption of a palatable diet on dopamine receptors (Drd1a and Drd2a) in the brainstem has been studied, considering the circadian rhythm and sex of the animals (de Souza, da Silva, de Matos, do Amaral Almeida, Beltrão, et al., 2018). Regardless of the luminosity phase in which MS occurred, there was an increase in the consumption of palatable diet in both male and female rats. In addition, early stress applied during the dark phase of the cycle led to increased gene expression of the Drd1a and Drd2a in the brainstem in males only. The authors suggested that dopamine receptor expression changes are not necessary for the feeding changes in female rats (de Souza, da Silva, de Matos, do Amaral Almeida, Beltrão, et al., 2018).

Certain diets could also add to the effects of MS. When MS rats received a n-3 PUFAs deficient diet, this diet aggravated MS effects on glucose homeostasis, affecting plasma insulin and leptin, and HOMA index in adulthood (Bernardi et al., 2013). A western diet was also able to aggravate the effects of ELS on adiposity (Yam et al., 2017). A high fat diet increases prepubertal social isolation-induced reduction in T3/T4 ratio in adult male rats (Toniazzo et al., 2018).

Sex-differences are observed in ELS-induced outcomes on food consumption in adulthood (Bekker, Barnea, Brauner, & Weller, 2014; Krolow et al., 2013; Tomiyama et al.,

2011). Krolow et al. (2013) showed that during a stressful event in the prepubertal period (social isolation; PND21-28), female rats showed higher increase in palatable diet (rich in simple sugars) consumption and higher weight gain compared to male rats, suggesting that female rats in the prepubertal period are more susceptible to the use of palatable diet as comfort food during periods of stress (Krolow et al., 2013). However, studies concerned with sex differences on the effects of early stress on the consumption of palatable foods are scare and sometimes inconclusive. This is a topic of great interest, and why females exhibit higher vulnerability to eating changes related to palatable diets and which are the molecular explanations warrant investigation.

In summary, the findings in experimental models suggest that palatable diet consumption may be used by the organism to reverse the postnatal stress-induced anxious behavior of animals of both sexes. In male rats, improvement in anxious behavior can be attributed to diet-induced reduction in the activity of the HPA axis, due to increased hippocampal GR mRNA, and normalization of hypothalamic CRH mRNA. However, in females other mechanisms may be involved, and need to be investigated.

Similarly, human studies show that children who experienced negative emotions have increased preference for consumption of foods with high fat and sugar contents (Balantekin & Roemmich, 2012; Michels, Sioen, Ruige, & De Henauw, 2017; Roemmich, Lambiase, Lobarinas, & Balantekin, 2011). In addition, children in disharmonious families adopt eating habits where they regularly consume energy dense junk food for emotional and stress-related relief and pleasure (Balantekin & Roemmich, 2012). Systematic research review and meta-analysis suggests that stress is positively related with unhealthy eating in children aged 8 and18 years old (Hill, Moss, Sykes-Muskett, Conner, & O'Connor, 2018). The preference for an increased consumption of comforting foods induced by stress may increase prevalence of childhood obesity and the risk of developing metabolic syndrome in adulthood (Panagiota & Chrousos, 2016; Todd, Street, Ziviani, Byrne, & Hills, 2015; Wabitsch, Moss, & Kromeyer-Hauschild, 2014).

Collectively, the studies commented above show the increased consumption of comfort food when stress was experienced in early life as a way to reduce negative emotional behavior. Despite these positive effects of comfort foods, it is important to mention that the use of an unhealthy diet during development will possibly lead to harmful health outcomes.

Gene by environment interaction studies on the development of eating behavior and related phenotypes

As discussed on the previous sections, ELS has an impact on the development of eating behavior, being linked to metabolic, mood and emotion disorders as well as reward system dysfunction that can contribute direct or indirectly to altered eating behavior. However, the impact of exposure to stressful conditions is not homogeneous and a vast literature shows that some individuals may be at greater risk to suffer from the deleterious effect of this exposure in comparison to others (Belsky, 1997). Such pieces of evidence pose an intriguing question on what could shape these differential responses. A promising venue comes from gene by environment (GxE) interaction studies, that considers that biological conditions, represented by genetic variations, moderates the susceptibility to environmental variations (Belsky, 1997; Belsky et al., 2009). For this research field, the dichotomy of nurture versus nature is seen as an intricate interplay that cannot be dissociated. Such approach is suited to study the developmental basis of complex traits, such as eating behavior, that is known to have multiple contributing factors, that not only play a role independently but also through interaction (Wood, 2018).

Some theoretical paradigms guide the understanding of this relationship. The dominant view is based on the diathesis-stress hypothesis, stating that some individuals are more vulnerable than others to the negative effects of the environment (e.g., insensitive parenting, childhood maltreatment, poverty) (Zuckerman & Riskind, 2000). This vulnerability would come from innate features, such as being carrier of a specific genetic variant (Belsky et al., 2009) (e.g. 5-HTTLPR polymorphism) (Kenna et al., 2012). Alternatively, the differential susceptibility hypothesis (biological sensitivity to context) (Belsky, 1997; Boyce & Ellis, 2005), considers that some individuals are more susceptible to environmental variations, either positively or negatively. First observed in psychiatric-genetic research (Pluess & Belsky, 2013), this hypothesis suggests that an individual's response can vary in degree of how much they are negatively affected by environmental adversity (Caspi et al., 2002; Caspi et al., 2003) and also positively affected by a positive environment (Barth et al., 2020; Blair, 2002) or absence of adversity (Belsky et al., 2009).

Studies have used the GxE methodological approach to elucidate the joint role of specific genes (and associated polymorphisms) and early life conditions on eating behavior phenotypes.

Dopaminergic genes have been suggested as an important player in this regard (Barth et al., 2020; Silveira et al., 2016; van Strien, Levitan, Engels, & Homberg, 2015; van Strien, Snoek, van der Zwaluw, & Engels, 2010), due to the known role of the dopaminergic system on motivated behaviors and decision making process (known to be involved in eating behavior) (Silveira et al., 2016). Besides that, dopaminergic genes are considered plasticity genes that may have been set up as a form of preparation of the individual to vary its responses according to diverse environmental conditions, in corroboration with the differential susceptibility hypothesis (Belsky et al., 2009). Variants that are related to the hypo-function of dopaminergic genes, such as the 7-repeat allele variant (7R) of the D4 receptor (DRD4) gene and the Taq1A polymorphism of the D2 receptor (DRD2) gene, have been associated to non-adaptive eating behavior styles as a function of different negative environment exposures (Silveira et al., 2016; van Strien et al., 2015; van Strien, Snoek, et al., 2010). For example, girls carrying the 7-repeat allele of the DRD4 gene (DRD4 exon III 48bp VNTR polymorphism) and living under adverse socioeconomic conditions have higher fat intake, while those carrying the same genetic variant but living in a healthy environment have lower fat intake when compared to non-carriers (Silveira et al., 2016). Adolescents exposed to high parental psychological control and carriers of the hypo-functional variant of DRD2 gene, showed an increase in emotional eating (van Strien, Snoek, et al., 2010). It is interesting to point that a study evaluating the differential responsivity to positive scenarios on eating outcomes also found evidence of the role of the DRD4 gene (Barth et al., 2020). The genetically predicted gene expression of DRD4 in the prefrontal cortex was calculated by PrediXcan (Gamazon et al., 2015) using the entire genotype information of a Canadian cohort of children. A significant interaction between the exposure to positive environments and the predicted prefrontal DRD4 gene expression on emotional over-eating at 48 months was found. This interaction followed the differential susceptibility framework (Roisman et al., 2012), in which children with high predicted DRD4 gene expression show elevated emotional eating in a less positive environment, but show less emotional eating symptoms in more positive environments (Barth et al., 2020). This corroborates the idea of dopaminergic genes being plasticity genes (Bakermans-Kranenburg & Van Ijzendoorn, 2011; Belsky et al., 2009), while also showing the protective aspect of exposure to positive environments.

Dopaminergic genes have also been related to altered metabolic and behavioral outcomes that can contribute to the onset and maintenance of eating behavior disturbances. Results from

two independent birth cohorts showed a significant interaction between maternal sensitivity and the presence of the DRD4 7R variant on predicting higher body mass indices (BMI) and/or obesity risk in children. When exposed to poor maternal sensitivity, 7R carriers have a higher chance of being obese or overweight, especially in Canadian girls or in Dutch boys (Levitan et al., 2017). A study conducted in American found that children who carried the long DRD4 alleles were significant influenced by responsive–supportive parenting showing better self-regulation status when compared to non-carriers (Cho, Kogan, & Brody, 2016). Reward processing also seems to be influence by early life environment and dopaminergic genes as showed in a study using a monetary incentive delay task: carriers of the Met homozygotes COMT Val158Met polymorphism that were exposed to stress during childhood (as measured by family adversities up to 11 years of age) showed higher reward sensitivity and reduced efficiency in processing rewarding stimuli in comparison with Val/Met heterozygotes and Val homozygotes (Boecker-Schlier et al., 2016).

There is growing evidence that the serotonin system plays a role in the neurobiology of eating behavior disorders (Kaye, 2008). The serotonin transporter (encoded by the 5-HTT gene) mediates the sodium-dependent presynaptic re-uptake of serotonin, therefore dictating the serotonergic neurotransmission (Gelernter, Pakstis, & Kidd, 1995). For that reason, GxE studies have focused on elucidating the interaction effect of the 5-HTT gene and environment conditions on eating behavior disorders, specially the short allele in the 5-HTT gene-linked polymorphic region (5-HTTLPR) that has been associated with lower transcriptional activity of the serotonin promoter (Heils et al., 1996). For example, Estonian adolescents' carriers of the short allele of the 5-HTTLPR that reported an elevated history of adverse life events at 15 years of age (e.g parental death, poor parental care, poverty, poor health, sexual abuse) have elevated scores of bulimia at age 18. When considering past sexual abuse alone, the short allele carriers also showed more drive for thinness (Akkermann et al., 2012). Corroborating this evidence, it was found that women carrying lower expression alleles (LG or S) of the 5-HTTLPR who were exposed to high levels of childhood trauma, reported significantly higher number of eating problems (according to the eating attitudes test (Garner, Olmsted, Bohr, & Garfinkel, 1982)) in comparison to controls (Stoltenberg, Anderson, Nag, & Anagnopoulos, 2012).

Other genes have also been explored in GxE studies concerning other possible underlying mechanisms for the effect of early life adversities on eating behavior. The functioning of the

HPA axis is a candidate mechanism, since it is involved in stress response (McLaughlin et al., 2015). The Bcl1 polymorphism (associated with relatively low glucocorticoid receptors feedback) is thought to mediate inhibitory feedback within the HPA axis. A study found that bulimic women were significantly more likely to be carriers of the low-function Bcl1 C allele (CC or CG genotypes) and have history of childhood abuse. This suggests that individuals inclined to a lower glucocorticoid receptors' modulation, when exposed to childhood abuse have greater risk for developing eating disorders, in this case bulimia nervosa (Steiger et al., 2011). Another study focused on the FKBP5 gene, an important player in the HPA axis regulation (Binder et al., 2004). Carriers of minor allele FKBP5 polymorphisms in combination with being exposed to ELS predicted higher insulin and glucose values in midlife. This is interesting since insulin and glucose values have been shown to impact eating behavior, either inducing satiety (Gielkens, Verkijk, Lam, Lamers, & Masclee, 1998) or overeating (Brandes, 1977; Destefano, Stern, & Castonguay, 1991; Leggio et al., 2008; Rodin, Wack, Ferrannini, & DeFronzo, 1985).

The BDNF-Val66Met gene variant is associated with impaired brain-derived neurotrophic factor (BDNF) release and function, which is related to increased risk for several anxiety and altered eating behavior, including anorexia nervosa (Notaras, Hill, & van den Buuse, 2015; Ribasés et al., 2005). An animal model study found that the Val66Met genotype markedly increases the likelihood and severity of anorexic behavior in mice exposed to caloric restriction and social isolation models, but only when occurring in the peri-pubertal period (adolescence) in comparison to adulthood.

Taken together, evidence commented above shows that genetic and environment factors act together in modulating eating behavior and related phenotypes. Despite the fact that all the evidence reviewed above suggests an involvement of different genes interacting with the environment in modifying these outcomes, it is important to highlight that candidate polymorphism studies are not anymore considered state-of-the-art, and therefore more advanced genomic approaches should be employed to confirm or refute these associations. Moreover, it is known that complex traits have a complex genetic etiology and are likely influenced by multiple genes that do not operate in isolation, but rather in networks (Gaiteri, Ding, French, Tseng, & Sibille, 2014). Thus, future studies that analyze genomic data through gene sets defined by functional pathways (Tam et al., 2019) have the power to better elucidate the underlying biological pathways of the effects seen in these GxE studies.

Concluding remarks and future directions

ELS may influence eating behavior by affecting metabolic regulation and glucose homeostasis, or by causing reward system dysfunction, or even affecting emotion, which may lead to emotional eating (figure 2). In general, animal studies point to the fact that stress experienced in early life induces increased consumption of comfort food as a way to reduce negative emotional behavior. Several studies emphasize sex-specific differences in the effects of ELS on eating behavior, which highlights the importance of studies using both males and females. The genetic background may confer vulnerability to exposure to early life stress/adversities, making individuals more susceptible to unfavorable outcomes such as eating behavior disturbances, although these assumptions need to be confirmed using advanced genomic technologies. These types of studies are crucial for elucidating the joint role of two important layers (genetic and environment) of a complex phenomenon (eating behavior).

<Insert Figure 2 near here>

Early life adversity is extremely common, and takes many different forms. We have to consider the diverse types and intensities of stress that infants and children may be exposed to. Beyond the intense and more rare abuse and neglect, other situations like poverty, discrimination and poor social networks also affect the youth. Neonatal conditions, parental depression or disease also impose a stress burden in families and especially children. More recently, the COVID-19 pandemics inflicted restrictions leading to social isolation in most of the countries, and is certainly having its toll on childhood emotional state. Understanding early life stress and its consequences is important as a factor capable of modifying eating behavior and its impact on growth, adiposity and risk for later chronic diseases.

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Figure 1: Schematic representation of the interaction between signals of energy homeostasis and the hedonic circuits involved in the regulation of eating behavior. The interaction between gene and environmental exposure modulates circuits involved in feeding. Created with BioRender.com (2020).

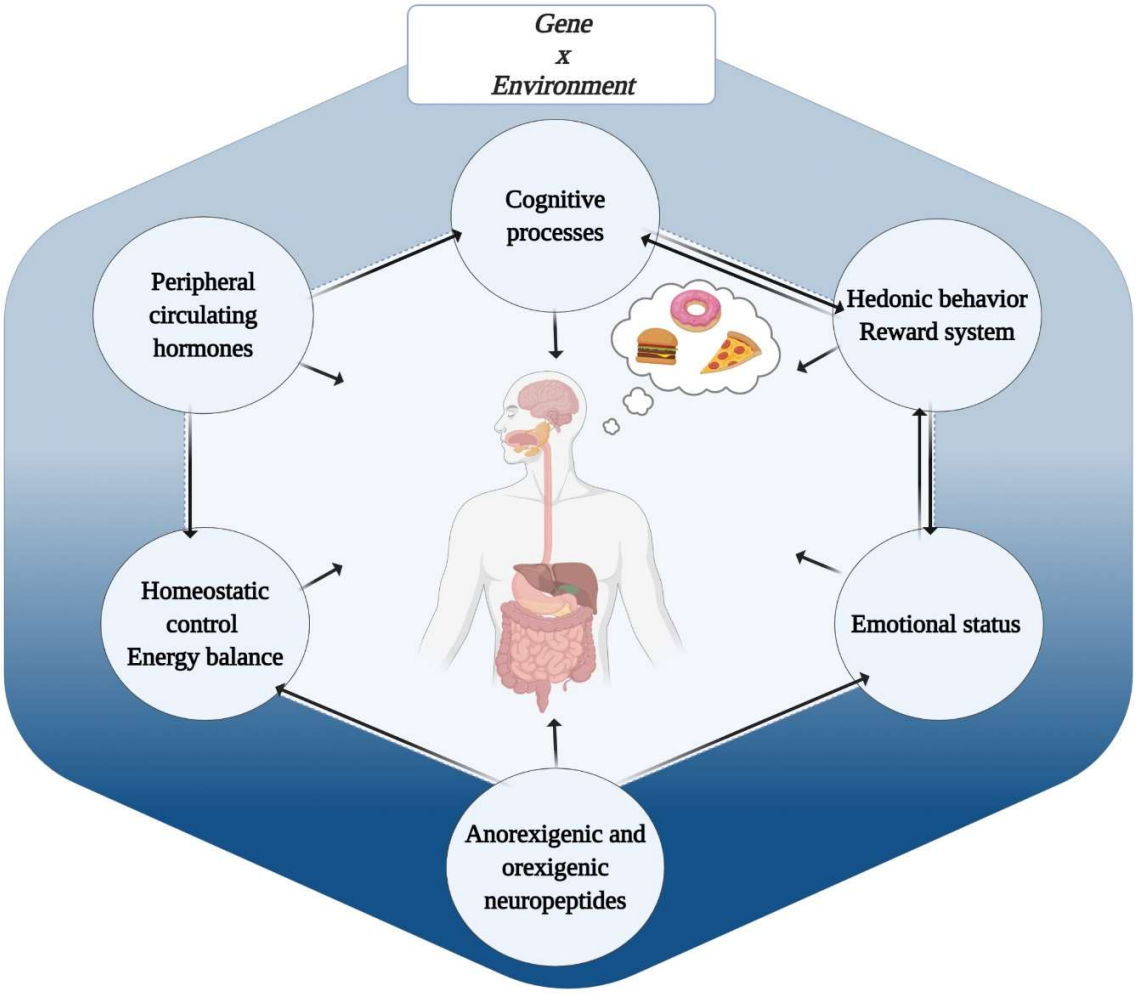

Figure 2: Summary diagram illustrating how postnatal adversities modulate eating behavior and metabolism throughout life. Exposure to early life adversity can affect individuals in a different manner. Some genetic variants may confer vulnerability to ELS, making individuals more reactive to stress exposure culminating in increasing of eating behavior. For these individuals, ELS can lead to metabolic alterations, resulting in induced weight gain and appetite changes; affecting the hedonic and homeostatic signaling; increasing risk for psychiatric and cognitive disorders. ELS can also potentially induce increased consumption of comfort food as a way to reduce stress response. Created with BioRender.com (2020).