Gene and environment interaction: is the differential susceptibility hypothesis relevant for obesity?

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Abstract

The differential susceptibility model states that a given genetic variant is associated with an increased risk of pathology in negative environments but greater than average resilience in enriched ones. While this theory was first implemented in psychiatric-genetic research, it may also help us to unravel the complex ways that genes and environments interact to influence feeding behavior and obesity. We reviewed evidence on gene vs. environment interactions that influence obesity development, aiming to support the applicability of the differential susceptibility model for this condition, and propose that various environmental "layers" relevant for human development should be considered when bearing the differential susceptibility model in mind. Mother-child relationship, socioeconomic status and individual's response are important modifiers of BMI and food intake when interacting with gene variants, "for better and for worse". While only a few studies to date have investigated obesity outcomes using this approach, we propose that the differential susceptibility hypothesis is in fact highly applicable to the study of genetic and environmental influences on feeding behavior and obesity risk.

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Keywords

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1. Introduction

Changes in lifestyle overtime have led to an increased availability/consumption of energy-dense food, and to a decrease in physical activity, predisposing many more individuals to obesity and its complications. It is known that genetic heritage also contributes to obesity risk, and both linkage analysis and candidate gene association studies identified numerous genetic variants underlying body-weight regulation (Apalasamy and Mohamed, 2015; Locke *et al.*, 2015). However, as is the case with other complex phenotypes, the total variance in BMI explained using these approaches is only in the 2-5% range. There are clear limitations when explaining obesity risk based on environment or genetics alone, and thus an urgent need to implement new strategies to unravel the complex mechanisms and pathways leading to pathological weight gain over time.

Different types of genetic variants, their frequency in the population, and the effect of the variant on phenotype can mediate the genetic effects on body weight. Variants include: a) single-nucleotide variations in which only one nucleotide is changed; b) copy number variations in which a stretch of DNA is repeated or deleted (often containing many genes); or c) small insertions and deletions of a few base pairs. Generally, the effect size of common obesity associated variants on body weight is modest (Van Der Klaauw and Farooqi, 2015).

Genome-wide Association Studies (GWAS) have made significant headway in identifying genetic variants underlying obesity (Cotsapas *et al.*, 2009; Meyre *et al.*, 2009; Jiao *et al.*, 2011; Paternoster *et al.*, 2011; Wang *et al.*, 2011; Melka *et al.*, 2012; Pei *et al.*, 2014; Locke *et al.*, 2015). However, most of these studies focused on body mass index as the main outcome, failing to take into consideration behavioral differences that can precede the development of obesity. A better understanding of individual behaviors, specially eating behavior, is very important to explain BMI variability and also BMI increases (Vainik *et al.*, 2013). Therefore, not only metabolic variables but also behavioral variables should be the focus of studies involving genetic variants. We propose that a better understanding of individual behaviors is helpful in terms of identifying vulnerability and proposing interventions to prevent or reverse weight gain. Also, genes may work by modulating the way individuals respond to environmental variation, and these discrete and differential genes vs. environment interactions may not be readily captured in simple association studies.

Therefore, many studies are trying to elucidate how genes interact with environmental exposures to shape human health. The dominant paradigm in most of the gene X environment (GxE) work is based on the diathesis-stress hypothesis, in which some individuals are more vulnerable than others to the negative effects of environmental adversity (e.g., insensitive parenting, childhood maltreatment, poverty), saying nothing about different genetic predispositions for responsiveness to positive environmental experiences (Zuckerman, 1999; Cameron *et al.*, 2005).

The differential susceptibility hypothesis (Belsky, 1997; Boyce and Ellis, 2005; Belsky and Hartman, 2014), firstly observed in psychiatric-genetic research (Belsky and Pluess, 2013), suggests an alternative approach to genetic association studies that may have particular utility for other common, complex diseases such as obesity. The differential susceptibility hypothesis proposes that, as a form of bet-hedging against an uncertain future, natural selection has maintained genes for both "conditional" (shaped by the environment) and "alternative" (fixed) health strategies (Rowe *et al.*, 1997). In other words, individual variations in the magnitude of biological responses regulate openness or susceptibility to environmental influences, ranging from harmful to protective (Boyce and Ellis, 2005).

In recent years, evidence is clarifying that individuals vary both in relation to how much they are negatively affected by environmental adverse events (Caspi *et al.*, 2002; Caspi *et al.*, 2003) and how much they are positively influenced by the provision of resources and supports (Blair, 2002; Quas *et al.*, 2004). Interestingly, it seems that the same characteristics that make individuals vulnerable to adversity could also make them more likely to benefit from environmental support (Boyce *et al.*, 1995; Belsky, 1997; Boyce and Ellis, 2005; Belsky *et al.*, 2007).

Belsky et al. (2009) suggests that individuals vary for genetic reasons in their susceptibility to context. According to Belsky's theory, vulnerability genes may function like developmental plasticity genes, resulting in certain individuals being more responsive than others to both positive (e.g healthy fetal environment, warm/sensitive care, high socioeconomic status) and negative (e.g. altered fetal environment, low maternal sensitivity, low socioeconomic status) environmental experiences, including the simple absence of contextual adversity (Belsky et al., 2009). There are two genes, the serotonin transporter gene (5-HTT) and the dopamine receptor gene (DRD4), that have been extensively studied as "vulnerability genes" predisposing carriers of particular alleles to psychiatric disorders in the face of adversity. However, recent evidence indicates that these genes might behave as "plasticity genes", making carriers of the putative risk alleles especially susceptible to environmental influences (Belsky and Hartman, 2014). Interestingly, these two genes known to have supported the differential susceptibility hypothesis have also been explored as potential genes associated to obesity (Fuemmeler *et al.*, 2008). Many studies explore the relationship between overweight and the genetic variations in DRD2 and DRD4 receptors (Levitan, Masellis, Basile, *et al.*, 2004; Levitan, Masellis, Lam, *et al.*, 2004; Levitan *et al.*, 2006; Epstein, Temple, *et al.*, 2007; Kaplan *et al.*, 2008; Levitan *et al.*, 2010; Silveira *et al.*, 2014). It is well established that dopamine system genes modulate experiential and behavioral responses to the environment on the one hand, while promoting phenotypic vulnerability to overeating and obesity on the other, though limited work to date has attempted to link these two effects. In addition, it is known that serotonin signaling modulates the reward value in humans (Seymour *et al.*, 2012), expanding its classic role on mood regulation (Haddjeri *et al.*, 1998) and emotional development (Pluess *et al.*, 2011). These studies provide a basis to propose that dopamine and serotonin systems genes can promote overeating and obesity through the developmental plasticity effects.

According to this theory we can propose that individuals with genetic variants related to obesity could have a chance of not developing the disease if they could engage in an

enriched/healthier environment. Therefore, combining the advance in genetic technology with theoretical hypotheses promotes the development of new studies handling both the genetic and environmental factors that contribute to obesity, promising to point to more effective interventions for prevention and treatment.

In this report we propose a brief review of the "plasticity genes" theory and the main genes involved (serotonin and dopamine systems' genes); and a more deep review and discussion regarding the interaction between gene and environment when having in mind feeding behavior and obesity as outcomes.

2. Which Genes Confer a Differential Susceptibility ("Plasticity Genes")?

Plasticity is being used in the field of developmental research to refer to experience-based changes in cognitive, emotional and/or behavioral phenotypes. The theoretical and empirical development of the differential susceptibility hypothesis has occurred when the interaction between some specific polymorphisms and the human development regarding these phenotypes was observed, prompting the concept of "plasticity" genes rather than "vulnerability" genes (Belsky *et al.*, 2007; Belsky and Pluess, 2009; Belsky and Hartman, 2014). Research on the differential susceptibility hypothesis has thus far focused on socio-emotional and cognitive/developmental outcomes, showing that "plasticity genes" vary both in relation to how much carriers (compared to non-carriers) are negatively affected by environmental adverse events (Caspi *et al.*, 2002; Caspi *et al.*, 2003) and how much they benefit from support (Boyce *et al.*, 1995; Belsky, 1997; Blair, 2002; Quas *et al.*, 2004; Boyce and Ellis, 2005; Bakermans-Kranenburg and Van Ijzendoorn, 2007). Studies have documented both "for-better-and-for-worse" rearing effects in the case of susceptible infants, with extent research identifying "susceptibility" alleles on DAT1 (10R allele) (Belsky and Beaver, 2011; Beaver and Belsky, 2012), DRD2 (A1 allele) (Beaver and Belsky, 2012), 5HTTLPR (short allele) (Pluess *et al.*, 2011; Simons *et al.*, 2012), MAOA (2R/3R alleles) (Simons *et al.*, 2012), and DRD4 (7R allele) (Van Ijzendoorn *et al.*, 2008; Kaitz *et al.*, 2010; Simons *et al.*, 2012). For instance, Bakermans-Kranenburg and van Ijzendoorn (2006) observed that 10 month children with the 7-repeat DRD4 allele displayed the most externalizing behavior two years later when mothers were judged insensitive. However, they also manifested the least externalizing behavior when mothers were highly sensitive. In the case of 5HTTPLR, Taylor *et al.* (2006) reported that young adults carrying the short alleles (s/s) were more depressive than individuals with other allelic variants when exposed to early adversity, as well as recent negative life events. On the other hand, fewest depressive symptoms where observed in those who experienced a supportive early environment or recent positive experiences. To date, much of the evidence from "for-better-and-for-worse" rearing effects comes from studies involving polymorphisms of the serotonin and dopamine systems' genes.

Serotonin (5-HT) is a neurotransmitter involved in behavioral inhibition, aversion and response to punishment (Cools *et al.*, 2008). Low levels of 5-HT are associated with diminished inhibitory control, which can be observed in impulse control disorders such as mania and aggression resulting from drug abuse. Serotonin could be seen as acting as a 'brake' to inhibit behavior (Evenden, 1999; Pattij and Vanderschuren, 2008). Dopamine is a

neurotransmitter that serves as a gateway between biology and environment in guiding behavior, and has long been associated with reward, motivation, reinforcement and associative learning (Wise, 2004), neurobehavioral process relevant to eating behavior. Mesolimbic dopaminergic system manipulations modify the motivation for food measured by voluntary intake, preference tests or instrumental behavior for food (reviewed by (Berridge and Robinson, 1998).

The notion of differential susceptibility has been stated in a way that could be formally operationalized using two adolescents' samples of the American Add Health project (Resnick *et al.*, 1997; Harris *et al.*, 2006) that were scored on a "cumulative-genetic-plasticity" index, measured by coding the presence of putative plasticity alleles from four genes: the 10R allele of DAT1, the A1 allele of DRD2, the 7R allele of DRD4, and the short allele of 5HTTLPR, and classifying individuals in terms of how many "plasticity genes" they carried (0 to 4). Belsky and Beaver (2011) described that in individuals with high plasticity index exposed to unsupportive parenting conditions there was decreased levels of adolescent self-regulation. On the other hand, when individuals classified with a high plasticity index were raised by supportive parents, they manifested increased levels of self-regulation in adolescence.

It is noteworthy that the main plasticity genes documented so far in the developmental literature are involved in the functioning of the dopaminergic and/or serotonergic systems. As proposed by Belsky and Beaver (2011), this raises the possibility that these genes may collectively make some individuals more "opened" to both positive and negative environmental influences because they modulate sensitivity to reward and punishment. Interestingly, the main brain systems known to have "susceptibility" alleles also underlie motivated behaviors and decision-making processes, which are involved in eating choices (Wise, 2004; Rogers, 2011).

2.1 Plasticity genes were initially seen as risk alleles

In the past years, many studies have been trying to elucidate the relation between the presence of certain genes and the development of diseases by investigating the association between gene and disease or the interaction between gene and environment in promoting disease. In GxE studies the diathesis-stress hypothesis was the dominant paradigm. This hypothesis proposes that some individuals are more vulnerable than others to the negative effects of environmental adversity (e.g., insensitive parenting, childhood maltreatment, poverty) (Monroe and Simons, 1991). For example, individuals carrying certain risk alleles (dopamine and serotonin system's genes are the most studied) were found to be more likely to develop psychopathology when exposed to adversity (Caspi *et al.*, 2003), saying nothing about the outcomes when the individuals are exposed to a positive environment.

Studies interested in obesity as outcome showed an association between the presence of certain polymorphisms in dopamine and serotonin system's genes and weight gain. For example, in the dopamine receptor 4 (DRD4) gene, a functional variable number of tandem repeats (VNTR) polymorphism was identified in the third exon, specifically at the region coding for the third intracellular loop of the receptor (Van Tol *et al.*, 1992). Functional studies suggest that the 7-repeat allele (7R) has decreased affinity for dopamine, generating

weaker intracellular signals when compared to other exon III alleles (Asghari *et al.*, 1995). As early as 1998, Poston *et al.* (1998) assessed the association between the long alleles of the DRD4 and obesity. Studying 115 obese subjects, they found a significant increase in the frequency of the DRD4 long alleles in individuals defined as high risk using the combination of novelty-seeking-related personality traits, severe obesity (i.e., BMI > 40), and any other traditional risk factor (i.e., long-term history of obesity, parental obesity, a body mass index > 40) suggesting a role for the DRD4 gene variation in increasing obesity susceptibility (Poston *et al.*, 1998). Afterwards, other studies have associated the presence of the DRD4 polymorphism with obesity, eating disorders or altered feeding behavior (Gervasini *et al.*, 2013; Sikora *et al.*, 2013; Silveira *et al.*, 2014).

In the case of the serotonin transporter gene (5-HTT), the presence of a short (S) allele polymorphism in the promoter region (5-HTTLPR) confers lower transcriptional efficiency, reducing the magnitude and duration of serotonin function (Heils *et al.*, 1996; Lesch *et al.*, 1996; Hariri and Holmes, 2006). The presence of the S allele was associated with overweight in children and adolescents independently of sex, age, and hypertension (Sookoian *et al.*, 2007). The same authors also demonstrate a 1.36 odds ratio (OR) (95% CI 1.01–1.85) for obesity in SS carriers in comparison with LL carriers among 1,329 unrelated adult men of European ancestry (Sookoian *et al.*, 2008). A series of studies investigated the association between the 5-HTTLPR gene polymorphic variation and the risk for eating disorders. They were reviewed in two meta-analysis (Lee and Lin, 2010; Calati *et al.*, 2011), demonstrating that to be carrier of the 5-HTTLPR S allele seems to represent a risk factor for eating disorders, in particular for anorexia nervosa. Therefore, the studies cited in this section observed that there are risk alleles for obesity, but they did not investigate the interaction between the presence of these risk alleles and different environmental exposures.

3. Is the "Differential Susceptibility" Model Relevant for Obesity?

There are only a few studies exploring the differential susceptibility hypothesis when it comes to obesity. However, the first studies pointed out to relevant results. Carr *et al.* (2013) examined, in a sample of 245 individuals, the relationship among 44 candidate-gene polymorphisms (dopamine, serotonin and opioid systems), food reinforcement and BMI. They were able to find that the polymorphism *rs6314* from the serotonin 2A receptor gene seems to confer both increased and decreased risk of high BMI for individuals with high and low food reinforcement, respectively. According to them, the A allele may be associated with a blunted response to serotonin stimulation, perhaps related to decreased sensitivity to feelings of satiety. In combination with a high motivation to eat, this mutation is associated with increased BMI.

Silveira et al. (2016), evaluated the food diaries and social environment of 199 children who were genotyped for the 7 repeat allele of the DRD4 gene and found that girls carrying the DRD4 7-repeat allele consume more calories derived from fat when living under adverse social and economic conditions, when compared to non-carriers, On the other hand, when living in a priviledged economic and social strata, they eat less calories derived from fat when compared to non-carriers (Silveira *et al.*, 2016).

Recently, Levitan *et al.* evaluated the association between maternal sensitivity and overweight/obesity risk in preschoolers who carry or not the 7-repeat allele of the dopamine-4 receptor gene (DRD4). They found that 7R allele carriers were more strongly influenced by maternal sensitivity regarding overweight/obesity risk, with a particular evidence of the differential susceptibility effect in Canadian girls. Those carrying the 7R allele exposed to high maternal sensitivity have a very low chance of being at a higher BMI, and vice-versa (Levitan *et al.*, 2016).

According to these studies, we can see that different environmental stimuli (internal reinforcement value of food, socioeconomic status or maternal sensitivity) can interact with the genetic background and influence health outcomes related to obesity), in a differential susceptibility manner. Then an important exercise is to identify which different environmental "layers" can potentially interact with genes and modulate eating behaviors and obesity according to what has already been published.

3.1. Which are the "environmental layers"?

When it comes to obesity, beyond the immediate food environment, several other environmental "layers" have been already described to impact developmental trajectories predisposing the individuals to later life diseases. It is important to mention that the environmental "layers" are by no means independent, in other words, they do not have isolated effects throughout development. The developmental trajectory is impacted by interactive effects from diverse environmental exposures, and the effects of one "layer" likely interfere with others. Below we describe some of these environmental factors and evidence of their interaction with serotonin and dopamine genes in modulating behaviors related to obesity, including studies that describe the differential susceptibility hypothesis in the context of obesity when results are available. Despite of the interdependence between the environmental "layers", they will be considered separately for the sake of clarity.

3.1.1 Intrauterine environment—Fetal life has been recognized as a crucial developmental period, in which intrinsic and extrinsic factors can play an important role in programming metabolism and behavior throughout postnatal life. In the perspective of life history, the context during fetal life informs the developing organism about the nature of the postnatal environment (Gluckman and Hanson, 2004).

According to Pluess and Blesky (2011), prenatal environment may shape physiological (e.g. children's salivary cortisol) and behavioral (e.g. irregularity of eating and sleeping behaviors) child characteristics; and genetic markers can make some fetuses more susceptible to prenatal-stress effects. For instance, a GxE study observed that maternal anxiety during pregnancy significantly predicts negative emotionality at 6 months in infants carrying one or more copies of the 5-HTTLPR short allele, but not in those homozygous for the long allele. The results suggest that the 5-HTTLPR short allele might increase vulnerability to adverse environmental influences as early as the fetal period, supporting the diathesis-stress model (Pluess *et al.*, 2011). The first evidence of genetic susceptibility to prenatal environment was demonstrated by Pluess et al (2009) when they reanalyzed data from Neuman *et al.* (2007) and observed that children carrying the DRD4 7-repeat allele

were not only those most likely to be diagnosed with ADHD when exposed to prenatal smoking, as the diathesis-stress model proposes, but also were least likely to show ADHD symptoms when exposed to a 'better' intrauterine environment (i.e., no prenatal smoking). Following the same theory, a recent study proposes that the 5-HTTLPR genotype interacts with prenatal depression in predicting childhood dysregulation (failures in regulating or controlling thoughts, emotions and behaviors) in a for better-and-for-worse manner. Children carrying the S or L_G alleles have higher levels of dysregulation when exposed to prenatal depression, whereas higher capacity for regulation when exposed to lower or little prenatal depression (Babineau *et al.*, 2015).

Pluess and Belsky (2011) proposes that the prenatal programming of postnatal plasticity is an adaptation rather than disease-oriented process, which is in according to the "predictive adaptive" hypothesis proposed by Gluckman *et al.* (2007). From this perspective, "as a forecast of the postnatal environment, prenatal stress promotes developmental plasticity, perhaps particularly in individuals carrying "plasticity genes," and thereby leads to "negative" behavioral outcomes when the postnatal environment proves harsh, unpredictable, uncaring, or otherwise adverse. If prenatally programmed plastic individuals encounter a positive environment instead of the predicted negative one, these children would develop dramatically differentially, but in the service of the same ultimate fitness goals" (Pluess and Belsky, 2011).

3.1.2 Mother-child interaction (or bonding)—It is well established that the emerging social, psychological and biological capacities of a child depend on the child-mother interaction, therefore the quality of this interaction can affect the child neurodevelopment, stress response and emotional regulation (Schore, 2001). Studies have reported an association between low parental bonding, particularly low maternal care (cold and distant mother-child relationship), with increased risk of depression and anxiety later in life (Parker, 1981; Canetti *et al.*, 1997; Hill *et al.*, 2001; Kendler *et al.*, 2002; 2006). However, this association is not only with mental health outcomes, a study found that the participants who rated their relationship with parents as cold and detached during college have a fourfold greater risk of chronic illness thirty-five years later, including coronary artery disease and hypertension (Russak and Schuwartz, 1997). Also children exposed to poor maternal care quality, characterized as low maternal sensitivity and insecure attachment, have increased risk for adolescent obesity (Anderson *et al.*, 2012b) and increased high-caloric food consumption in adulthood (Faber and Dube, 2015). On the other hand, warm and nurturing families can diminish the offspring's vulnerability to stress-induced illness (Smith and Prior, 1995; Schor, 2003).

In humans, there are some ways of assessing mother-child interaction, through questionnaires (e.g. parental bonding index) (Parker, 1979) or based on direct observation using standardized coding to score the interaction (Tarabulsy *et al.*, 2009). The direct observation method can give us measures of maternal-infant attachment and maternal sensitivity. The latter refers to how the mother responds to the cues of her infant, if the response is timely and appropriate (Ainsworth and Marvin, 1995). As cited before, some studies have shown that maternal sensitivity and insecure attachment in preschoolers are related to increased risk of obesity later in life (Wu *et al.*, 2011; Anderson *et al.*, 2012a) and

also that maternal sensitivity impacts girls' BMI more intensively than boys' (Wendland *et al.*, 2014). There is also evidence showing that insecure parental attachment in infancy is associated with increased high-caloric food consumption in children and adults, even after controlling for confounding variables (Faber and Dube, 2015). In addition to maternal sensitivity and attachment, nourishment is another important environmental factor during the first years of life, as there are many studies showing that breastfeeding is a factor that can contribute to prevent the development of obesity (Dietz, 2001; Gillman *et al.*, 2001; Poulton and Williams, 2001; Dewey, 2003; Frye and Heinrich, 2003; Parsons *et al.*, 2003; Owen *et al.*, 2005).

Nevertheless, children with certain genotypes have greater sensitivity to the environment, particularly care giving. For example, studies developed with children from institutional settings found that those with the 5-HTTLPR s/s genotype have lower levels of emotional problems when they were early adopted and spent less time of their first years in institutions (Kumsta *et al.*, 2010), but increased externalizing scores when they remained in the institution receiving the usual group care (Brett *et al.*, 2015; Humphreys *et al.*, 2015). In addition, offsprings' 5-HTTLPR S or L_G alleles moderate the transgenerational effect of maternal childhood adversity on child's cognitive/emotional function in a for better-and-for-worse manner (Bouvette-Turcot *et al.*, 2015). Therefore, evidence support the theory that certain genotypes interact with the care giving quality in shaping mental health, but what about shaping eating behavior/obesity? Specific findings suggest that the differential susceptibility can impact eating behavior/obesity when investigating maternal sensitivity as the environmental factor. A four-year follow-up study with an adolescent's sample observed increased emotional eating associated with adverse rearing experiences (high parental psychological (manipulative) control) in combination with carrying at least one DRD2 A1 allele, demonstrating a gene vs. adverse parenting interaction on the emergence of emotional eating in adolescents. Interestingly, although the authors do not mention it, it appears that when exposed to an environment with low parental psychological control (as a proxy of better parenting) adolescents carrying the A1 allele seem to be at a lower risk for emotional eating (Van Strien, Tatjana *et al.*, 2010). Also, Levitan *et al.* (2016) found a particular evidence of the differential susceptibility effect in Canadian girls carrying the 7-repeat allele of the DRD4. The carriers exposed to low maternal sensitivity as infants had the highest risk of a higher BMI at age 48 months, while the ones exposed to high maternal sensitivity had a very low chance of developing increased BMIs.

3.1.3 Parents/family feeding-related behavior—Parental feeding styles and practices can influence child's eating behavior. The former is the result of behaviors and attitudes of interplay with the child (authoritative, authoritarian, indulgent, or neglectful). The parental feeding practice is based on the strategy of control that parents use, e.g. pressure to eat healthy food, restrict access to sweet and fatty food, and use food as reward. Then, parents may create environments that promote healthy eating behavior or promote overweight and disordered eating (see the reviews (Scaglioni *et al.*, 2008; Scaglioni *et al.*, 2011). A restrictive environment, i.e. when parents restrain children's dietary intake or specific snack food intake, is associated with increased dietary intake and/or child weight gain (Clark *et al.*, 2007; Scaglioni *et al.*, 2008). Some studies provide evidence for a causal relationship

between parental restriction and childhood overweight (Lee *et al.*, 2001; Fisher and Birch, 2002; Faith *et al.*, 2004; Francis and Birch, 2005). Also a "high-pressure" environment, which involves pressuring children to eat more in general as well as healthy foods, has negative consequences in children's eating behavior since it is related to children's inability to regulate energy intake ans their reduced consumption of fruit and vegetables (Scaglioni *et al.*, 2008). The use of food as a reward for good behavior (e.g. to eat main meal) is also a common practice that has a negative impact, because it is associated to greater intake of unhealthy foods and beverages (Spurrier *et al.*, 2008). Considering the parenting style, authoritative parents (who are both responsive and demanding) have children that eat more healthy foods, are more active and have lower BMI, when compared to children raised in an environment with other parenting style (authoritarian, permissive/indulgent, uninvolved/neglectful) (Sleddens *et al.*, 2011; Lu *et al.*, 2015).

Therefore, there is evidence of an association between the immediate family environment (parental feeding-related behavior) and child eating behavior. In addition, studies show that genetic factors influence appetitive traits (Kral and Faith, 2009; Faith *et al.*, 2013). However, it is not clear how genetic and some specific environmental factors (e.g. parents feeding style and practices) interact at a behavioral level to influence child's eating and weight gain.

3.1.4 Food/community environment and social capital—The food environment can be divided in two main domains: the types of food sources that an individual can have access (e.g. supermarkets, corner stores, restaurants, etc.), and what the individual is exposed to in these environments (e.g. availability of healthy and unhealthy foods, food prices, promotions/marketing, etc.). These can be measured from simple to complex data collection involving perceived, observed and geographic data (Eyler *et al.*, 2015).

The modernization of food production and marketing practices, linked to lifestyle, media, and culture modifications, have made food and food cues ubiquitous, increasing the reinforcing intensity of the environment, turning it potentially obesogenic. Cross-country studies have associated the increase in ultra-processed food (typically energy-dense foods, rich in fat and sugars) with obesity prevalence (Popkin, 2006; Monteiro *et al.*, 2010; Monteiro *et al.*, 2011; Moubarac, J.-C. *et al.*, 2013; Moubarac, J. C. *et al.*, 2013). Reviews suggest an association between food environments and dietary outcomes. Obesity is linked to increased access to convenience stores, corner stores, and fast-food outlets, whereas reduced levels of obesity are related to increased access to supermarkets/grocery stores (Larson *et al.*, 2009; Ni Mhurchu *et al.*, 2013). There are also studies showing that food advertising and various facets of product formulation, packaging, pricing and retailing are related to alterations in the consumption pattern consistent with an obesogenic behavior (Buijzen *et al.*, 2008; Scott *et al.*, 2008; Dhar and Baylis, 2013).

There is a growing body of evidence in the neuroscience field suggesting that the repeated exposure to highly reinforcing foods and marketing cues linked to this type of food may activate brain reward regions. Specifically, individuals who usually eat foods highly reinforcing and heavily marketed undergo a conditioning process in which cues associated to these foods (e.g. the brand logos, food images, restaurant settings, as well as other material viewed in commercials) become associated with the pleasure of consuming them (activation

of the reward system), which can induce cravings for and increased consumption (Bruce *et al.*, 2013; Burger and Stice, 2014; Gearhardt *et al.*, 2014). Interestingly, prospective fMRI studies found a positive correlation between activity in reward-related brain regions in response to food cues with change in BMI (Stice *et al.*, 2010; Yokum *et al.*, 2011; Demos *et al.*, 2012).

Above the food environment there is also the community built environment that includes the physical activity environment (e.g. neighborhood walkability and access to recreational facilities). Therefore, the community built environment characteristics can influence the quality of the food consumed and energy intake, as well as energy expenditure (Valera *et al.*, 2015), promoting healthy or unhealthy behaviors. Studies suggest that neighborhoods with lower income and minority populations have fewer stores selling healthy foods but greater fast food restaurants, in other words are more likely to have abundant sources of foods that promote unhealthy eating (Cubbin *et al.*, 2001; Beaulac *et al.*, 2009; Hilmers *et al.*, 2012). It was also observed that residents of these areas have increased probability of having an adverse CVD risk profile, independent of an individual's SES (Cubbin *et al.*, 2001).

Besides the food/community environment, social capital also seems to influence health outcomes. Social capital refers to the material, informational and affective resources to which individuals have access through social connections (Moore *et al.*, 2009). According to Moore et al. (2009), individuals with higher levels of network social capital were less likely to have elevated waist circumference and BMI than those with lower levels of social capital. Regardless of the residential place, individuals with more diverse ties and greater access to resources tend to have less excess adiposity and overweight/obesity risk.

The evidence summarized in this section (Which are the "environmental layers"?) shows that studies investigating the differential susceptibility hypothesis having eating behavior and/or obesity as outcomes are still scarce. However, the review leads us to state that there are many environmental "layers" that can shape human health (including eating behavior and body weight) by their own impact or by interacting with genes. According to the differential susceptibility theory, we propose that individuals who carry certain dopamine and serotonin polymorphisms are more susceptible to changes in these environmental "layers", therefore the exposure to an adequate environment may prevent obesity in these individuals. Considering the prevalence of the most studied polymorphisms [7-repeat allele of the DRD4: global mean = 20.6%, Americas mean = 48.3% (Chang *et al.*, 1996); and 5-HTTLPR short allele: S/S = 19%, S/L = 48% in Caucasian samples (Goldman *et al.*, 2010)] we may significantly decrease obesity rates in adult life by exposing the carriers to an enriched/healthier environment during their developmental trajectory.

Besides the environmental "layers" discussed until here, there are other variables such as individual traits, gender and socioeconomic status that can have effect on obesity rates. These other variables are discussed below.

3.2. Individual traits

People have to make many choices every day. There are several alternatives to choose and the pleasurable ones can exert considerable influence to highlight certain behaviors rather

than others, finally influencing eating and body weight (Epstein, Leddy, *et al.*, 2007). Therefore, reinforcement is a fundamental determinant of choice; people choose to engage in behaviors that are reinforcing. However, what is reinforcing for one individual may not be to another, because our life repertoire of reinforcers shapes many aspects of our behavioral choices. Thus, reinforcers are fundamental to learning and motivation, having impact in adaptive and also maladaptive behaviors such as drug self-administration and overconsumption of unhealthy foods (Epstein *et al.*, 2010), and vary from one person to another.

Individual differences in the reinforcing value of food may contribute to excess energy intake and to the difficulty in losing weight and partially explain why some people become and remain obese (Epstein, Leddy, *et al.*, 2007). Food is more reinforcing for obese than lean individuals (Epstein, Leddy, *et al.*, 2007; Temple *et al.*, 2008) and adolescent sibling pairs with greater differences in food reinforcement and delay discounting have greater differences in zBMI (Feda *et al.*, 2015). Interestingly, Lin *et al.* (2013) observed that the food reinforcement can mediate the association between lower household income and greater BMI, which suggests that deprivation and restricted food choice associated with low SES enhance food reinforcement, increasing the risk for obesity.

When it comes to food consumption, individuals' characteristics, e.g. food reinforcement, interact with food/community environment. For instance, studies have observed that food consumption can be affected by the interaction of food retail environment and food advertisement with the individual sensitivity to external food cues and general reward. Children (6-12 years old) with high sensitivity to food cues have a greater consumption of healthy food in environments with proportionally more 'healthy' food retailers. In the case of unhealthy food environment the interaction is not found. Also, girls with high reward sensitivity have lower diet quality when experiencing a greater exposure to junk food advertisements. Together these results suggest that sensitivity to food cues and reward sensitivity may explain individual variability in responsiveness to environmental and advertising food cues (Paquet *et al.*, submitted).

Another individual characteristic that can be related to food intake and obesity is mastery. Mastery represents the degree to which individuals feel in control of the circumstances of their lives. It refers to a global sense of control and not to a specific domain of life (Thompson and Spacapan, 1991). Paquet *et al.* (2010) showed that the sense of mastery interacts with fast-food exposure in relation to metabolic risk. The association between greater mastery and lower metabolic risk was most apparent for individuals in residential areas with higher fast-food restaurant exposure. The higher sense of mastery might result in greater self-regulation, which makes individuals resist to fast-food cues present in their environment.

The study from Carr *et al.* (2013), cited above, is an example of differential susceptibility findings having the individual trait (food reinforcement) as the environmental variable. They found that the presence of the polymorphism *rs6314* from the serotonin 2A receptor gene seems to confer both increased and decreased risk of high BMI, at high and low food reinforcement levels, respectively.

Markus and Capello also investigated the effects of the interaction between the polymorphism in the promoter region of the 5-HTT and the individual's trait (e.g neuroticism) on feeding behavior and obesity risk, observing some plasticity evidence. In 2012, they investigated 857 students from a Dutch university and observed a robust interaction between the 5-HTTLPR genotype and neuroticism, in which the S-allele genotype was associated with weight gain only in individuals reporting high-trait neuroticism (Markus and Capello, 2012). Around the same time they investigated the effect of tryptophan on stress-induced emotional eating in S allele compared to long (L) allele 5-HTTLPR carriers. They showed that tryptophan intake significantly increased the plasma tryptophan in the L'/L' group (70%) compared to the S'/S' group (30%), but in both groups tryptophan intake reduced food consumption. However, tryptophan was able to reduce stress-induced negative mood and desire for sweet, high-fat foods only in the L'/L' group (Markus *et al.,* 2012). Results from a subsequent study suggested that 5-HTTLPR and neuroticism may influence stress-induced overeating depending on the type of food available (Capello and Markus, 2014a). Afterwards, they researched the influence of repeated tryptophan administration on stress responsiveness and emotional eating in homozygous 5-HTTLPR S-allele and L-allele carriers with high and low neuroticism in 118 university students. When including neuroticism in the analysis, unlike the study from 2012, they observed that tryptophan treatment reduced stress-induced cortisol levels, as well as stress-induced appetite only in S'/S'-allele carriers with high trait neuroticism (Capello and Markus, 2014b). Interestingly, tryptophan treatment benefited the more susceptible group (S $'/S'$ -allele carriers with high trait neuroticism), suggesting that susceptible individuals, who have higher risk to develop the disease, can be more benefited from a good intervention.

3.3. Socioeconomic status (SES)

Since food price can influence food choices, socioeconomic status may significantly affect feeding behavior. Higher socioeconomic status (SES) individuals have a more frequent consumption of fresh and better quality products such as fresh fruits, vegetables, and fish since these foods are charged higher in grocery and convenience stores (Dunn *et al.*, 2011). Whereas, the poorer segments of society normally opt for energy-dense diets rich in trans-fats and cheap vegetable oils (Mclaren, 2007).

Nonetheless, the literature describes that the association between socioeconomic status (SES) and nutritional patterns vary according to the country's social development (Sobal and Stunkard, 1989). SES appears to be negatively correlated to obesity in developed countries (despite differences in gender and age) (Costa-Font *et al.*, 2014), whereas the opposite trend is found in developing countries (Mclaren, 2007). However, this relationship is not so clear in emerging economies. A recent Mexican study showed that a new middle class, rising out of poverty, is the most exposed to adiposity risk; individuals from the upper class seem to be fatter than individuals from the upper middle class; and the influence of SES on central adiposity appears to be particularly strong for men. The results reveal that education and work status (positions with high levels of responsibility vs. precarious and informal activities) have important and independent effects on anthropometric health indicators (Levasseur, 2015). Educational disparities can impact dietary knowledge and, consequently,

how people classify foods as healthy or unhealthy as well as food purchasing behavior (Bhurosy and Jeewon, 2014).

In children, obesity is more prevalent among the wealthy groups in developing countries (Dinsa *et al.*, 2012), while in high-income countries there is generally an inverse association between SES (particularly education) and child obesity (Lamerz *et al.*, 2005). A recently study with Australian adolescents reflects a pattern commonly reported in the literature, with lower SES associated with increased weight status and poor diet quality. They classified adolescents in clusters according to their time use and diet and observed that boys' unhealthy cluster, characterized by screen time and extra food intake, was associated with low SES (parental income and education); and the girls' healthy academic cluster characterized by academic activities, breads/cereals, and vegetable intake, was associated with a higher frequency of high parental income. Interestingly they identified sex-specific multidimensional patterns of adolescent time use and dietary behavior being some of them related to the SES and overweight/obesity (Ferrar and Golley, 2015).

An interesting study accorded with the recently proposed developmental model of GxE interaction (differential susceptibility) when evaluating the association between SES, DRD4 genotype and delay discounting behavioral measures. They reported that relative preference for immediate, smaller rewards over larger rewards (delay discounting) varied according to the DRD4 genotype and childhood SES. Participants who were both raised in families of low SES (low parental education and occupational grade) and carried the DRD4 7-repeat allele discounted future rewards more steeply than those also raised in low SES families but with an alternate DRD4 genotype. In the absence of childhood socioeconomic disadvantage, however, participants carrying the 7-repeat allele discounted future rewards less steeply. These associations were independent of age, sex, adulthood SES and IQ (Sweitzer *et al.*, 2013). The delay discounting paradigm has been used to study obese vs. non-obese differences, and there are results showing that obese are more likely to choose smaller, immediate rewards (Epstein *et al.*, 2010). In addition, substance-dependent individuals, as well as individuals with other behavioral disorders such as pathological gambling, poor health behavior, and overeating tend to discount delayed reinforcers more rapidly than do healthy controls (Bickel *et al.*, 2012). It is worth citing again Silveira's study in which they observed a higher consumption of calories derived from fat in girls carrying the DRD4 7-repeat allele when living under adverse social and economic conditions, however when living in an opposite economic and social condition they eat less calories derived from fat (Silveira *et al.*, 2016).

3.4. Gender

It is commonly accepted that men and women normally differ both at the biological and neurological level. These differences result in sex specific metabolism and behaviors (food preferences and eating patterns), which can make men and women develop obesity in different ways and rates (Power and Schulkin, 2008; Loke *et al.*, 2015).

Some biological aspects can interact with neurological processes, generating sex-specific effects. For example, it appears that leptin and insulin have different effects on males and females. Typically, females have more subcutaneous fat, whereas males have more visceral

fat (Clegg *et al.*, 2003). Specifically, insulin is related mainly to visceral fat and leptin to subcutaneous fat. It is also known that these hormones interact with food intake control central systems. Within this context, Woods *et al.* (2003) suggest that female brains are more sensitive to the catabolic activity of leptin, while male brains are more sensitive to the catabolic activity of insulin.

In women, it was shown that the menstrual cycle influences neural mechanisms related to reward processing (Dreher *et al.*, 2007). It affects the dopamine function in the striatum and nucleus accumbens, structures that are involved in the mediation of motivation, pleasure and reward (Becker, 1999). In female rats, estrogen enhances the release of dopamine and dopamine-mediated behaviors. This effect is not observed in male rats and the presence or absence of testosterone does not have any effect on brain activation (Becker, 1999).

Therefore, evidence shows that the human brain exhibits gender specific responses to and processing of the feelings of hunger and satiation. Uher *et al.* (2006) observed that during fasting women have stronger responses to gustatory stimuli in the insula and to visual stimuli in the occipito-temporal cortex, which suggests a stronger response to external food stimuli compared to men. Men and women also differ in their abilities to voluntarily inhibit feelings of hunger following food stimulation (Wang *et al.*, 2009). Men, but not women, are able to significantly suppress the activation of brain regions involved in emotional regulation, conditioning, and motivation. Therefore, women's lower ability to inhibit the desire for food and drive for hunger may be an implication for the gender differences seen in obesity.

In addition, studies propose that response inhibition is a predictor of body mass index (BMI), but this association varies according to gender. Both boys and girls with longer Stop-Signal Reaction Time (SSRT) (poor response inhibition) consume more carbohydrates and sugars during a subsequent snack test. However, a correlation between long SSRT and higher BMI was observed only in girls (Levitan *et al.*, 2015).

Gender differences appear at the level of food preferences too. UK girls (4-16 y/o) prefer fruit and vegetables whereas boys prefer fatty and sugary foods, as well as animal protein products (Cooke and Wardle, 2005). The wanting for certain foods varies with gender, age, the motivational state (hunger/satiety), the nature of the food and the sensory cue used to represent it (visual vs. olfactory). Following visual stimuli, boys have higher wanting and liking scores than girls. No significant difference is noted following olfactory stimuli. In addition to having lower wanting and liking scores, girls express lower feelings of hunger compared to boys (Jiang *et al.*, 2013). Men and women also differ in their preference and motivation for 'comfort' foods. Men prefer meal related comfort foods (steak, casseroles, soups) whereas women prefer snack related comfort foods (ice cream, chocolate). Studies that explore the motivation behind the consumption of comfort food have found that positive emotions trigger men's consumption, whereas negative emotions trigger women's consumption (Dubé *et al.*, 2005).

The literature also shows that there are differences between the sexes when it comes to genetic background. For example, a study evaluated whether the presence of the 7R allele of

DRD4 is associated with total caloric intake and/or food choices in preschoolers and observed an influence of this gene variant on macronutrient intake and specific food choices. 7R carriers girls, but not boys, eat more fat and protein than do non-carriers; moreover, both sexes with the 7R allele demonstrate greater consumption of ice cream, and less consumption of vegetables, eggs, nuts, and whole bread according to maternal food diaries. Therefore, the 7R allele of DRD4 influences macronutrient intake and specific food choices as early as four years of age, suggesting that prior associations between the 7R allele and adult overeating/obesity may originate in food choices observable in the preschool years (Silveira *et al.*, 2014). Another study describes that adolescents carrying the short allele of the 5-HTTLPR polymorphism have increased emotional eating when reporting high depressive feelings. This moderator effect of 5-HTTLPR genotype was found in both sexes in young adolescents (13 years). However, in older adolescents (15 years), it is seen only in girls. Remarkably, in older boys carrying the 5-HTTLPR short allele, the relationship between depressive feelings and increase in emotional eating was negative (Van Strien, T. *et al.*, 2010). The above mentioned study from Silveira et al. (2016) describing genetic differential susceptibility to socio-economic status in carriers of the 7R allele of DRD4 had significant results only observed in girls. These findings points out to the importance of taking sex into account as moderator in G×E studies.

4. Discussion

The review shows that there are many environmental "layers" and other variables such as individual traits, gender and socioeconomic status which can impact eating behavior and weight gain by their own effect or by interacting with the genetic background. Interestingly, some of the studies reviewed have already found consistent results when taking into account the differential susceptibility hypothesis and having eating behavior and BMI as outcomes. For now the first results point out to mother-child interaction, SES and individual's traits as important modifiers of the outcomes related to obesity when considering the differential susceptibility hypothesis, i.e. individuals carrying certain dopamine or serotonin system's genetic variants are more susceptible to changes in their interaction with their caregivers, to the surroundings SES and in their own individual traits in response to the environment (e.g. food reinforcement) in a "for-better-and-for-worse" manner. Despite of the scarcity of studies investigating specifically outcomes related to obesity, the other research reviewed in the various environmental "layers" lead us to propose that the differential susceptibility model -thus far almost exclusively dedicated to the understanding of socio-emotional and neurodevelopmental phenomena - is also relevant to outcomes such as food intake and obesity risk (Figure 1).

Historical studies also support our hypothesis. An investigation performed in Ariaal pastoralists that live in northern Kenya, where the prevailing feeding challenge remains undernutrition, shows that BMI is higher in those with one or two DRD4/7R alleles that are nomadic, but lower among the settled. Further analysis demonstrates that the DRD4 differences in BMI were due primarily to differences in fat free body mass (Eisenberg *et al.*, 2008). As this population is chronically undernourished, the results suggest that the DRD4/7R allele seems to be more advantageous among nomadic than settled Ariaal men, and that a selective advantage mediated through behavior may be responsible for a higher

frequency of the 7R alleles found in the nomadic relative to sedentary populations around the world.

Ding *et al.* (2002) showed that the allele 7R has increased in frequency within the last few thousands to tens of thousands of years, although it has probably been present in our ancestors for hundreds of thousands or even millions of years. This suggests that the drastically changing environment during the past few thousand of years is involved in the 7R selection in populations. Evidence for a recent positive selection for 7R alleles could at first go against the idea of its association to diseases in any evolutionary sense. However, one has to understand that a higher BMI may be considered highly adaptive for the nutritionally modest environments that humans were shaped for. Increased body fat also accelerates puberty and consequently guarantees early reproduction, leaving healthy aging in a second plan in adaptive terms. This may be an important factor contributing to the positive selection of these dopamine-related alleles in populations, even if they are linked to a series of neuropsychological disturbances. The positive selection of these genes may even be seen as another evidence for the "differential susceptibility" hypothesis, as individuals carrying these alleles would be more prone to survival in nutritionally adequate environments.

Although of high interest, the exploration of the hypothesis that the differential susceptibility plays a role in modulating eating behavior and/or obesity risk in different environments is a very hard task. Any comparisons involving human behavior in diverse scenarios (e.g. different SES contexts, diverse geographical locations, clinical vs. non clinical populations, etc.) may be largely influenced by the environmental "layers" proposed in this review, as well as by genetic adaptations and epigenetics. However, the continuity in exploring if the differential susceptibility model is relevant to understand variations in eating behavior and/or obesity risk can be more promisingly done in two contexts. The first context bears on responsiveness to broad societal changes that are occurring worldwide over time, some increasing the adverse nature of environmental conditions by accelerated spreading of western obesogenic patterns to emerging economies (Webb and Block, 2012), others targeting improvement in western countries to broad societal prevention interventions (Berger *et al.*, 2011; Cheyne *et al.*, 2013). On the adverse condition side, increase in obesity in developing countries and emerging economy as the share of western-type high caloric food increases in the environment and in the population's diet is well documented (Finucane *et al.*, 2011; Webb and Block, 2012). However, research has also found decreases in childhood obesity prevalence in cities from USA, that have pioneered obesity-prevention and health-promoting school and community interventions and food systems transformation, reducing the progression of childhood obesity (Berger *et al.*, 2011). As both field (Paquet, Daniel, *et al.*, 2010) and laboratory (Dagher, 2012) studies have shown, the dopamine system moderates the responsiveness to the environmental intensity of food exposure and food cues. The differential susceptibility hypothesis would suggest that individuals with 7-repeat allele would be more vulnerable to change over time, being more "at risk" of developing obesity under increasingly adverse conditions (i.e., the context of developing countries) and more 'responsive" to improvement in the supporting health promoting quality of broad societal effort (i.e., the context of obesity prevention in western countries).

The second context where the differential susceptibility hypothesis could promisingly be tested is in terms of responsiveness to reinforcement-based behavioral intervention. It is widely accepted that intense and repeated exposure to marketing of high caloric food and beverages, which typically uses reinforcement-based persuasion, is one of the causal factor of obesity (Cheyne *et al.*, 2013). Lu *et al.* (2011) suggest that similar reinforcement can be tied to healthy food such as broccoli and other green vegetables that are somewhat biologically handicapped from a taste perspective, in comparison with their sweeter and fatter alternatives. The differential susceptibility hypothesis would suggest that individuals with 7-repeat allele would be more responsive to both types of reinforcement-based behavioral change intervention, making them more "at risk" when exposed to behavioral change effort that promote high caloric food and more "responsive" when target shifts to healthy food. In this line of thought, it is interesting to bring an important question, discussed before by Belsky and Van Ijzendoorn (2015), "*What works for whom?*". As reviewed by Van Ijzendoorn and Bakermans-Kranenburg (2015), there are some studies demonstrating that individuals' characteristics (e.g. presence of susceptibility polymorphism) are important to amplify the effects of some types of intervention. Therefore, this question turns out to be very important in a context of global obesity pandemic in which the differential susceptibility hypothesis suggests the possibility to improve the efficiency and maximize the impact of some interventions that might have different impacts according to the environmental "layer" selected as the intervention target (e.g. fetal environment, parental care, SES, etc.) and the individuals' genotype. However, as stated by Belsky and Van Ijzendoorn (2015), the implementation of interventions based on the susceptibility "*can raise ethical issues concerning stigma, discrimination, and equity of service provision*". Future intervention studies to treat or prevent obesity should be designed to help us to understand "*What works for whom?*". After proposing these two contexts where the plasticity genes influence on feeding behavior and obesity risk could be tested, we would like to remind that during their developmental trajectories individuals are exposed to a combination of different environmental "layers" reviewed here, which may be seen as a challenge in terms of data collection and data analysis. Longitudinal studies would better capture the environmental exposures, and the statistical analyses proposed by (Roisman *et al.*, 2012; Belsky *et al.*, 2015) could be applied to take into consideration these various environmental expositions throughout the development. Another important issue to address is the mechanism by which the exposure to different environmental "layers" quality may lead to better or worse outcomes in susceptible individuals. It is believed that the main mechanisms are via epigenetic processes, which are structural modifications in the DNA (e.g. methylation, acetylation) in response to environmental signals that do not change the DNA sequence but alter the DNA expression (Meaney, 2010). For example, Van der Doelen et al. (2015) observed in an animal model that early life stress (maternal separation) interacts with the 5-HTT genotype to promote DNA methylation of the promoter region of the Crf gene, influencing stress coping behavior. Therefore, exposure to positive or negative environments may quickly change DNA methylation/acethylation especially in individuals that are more opened to the environmental changes. In an enriched paradigm, DNA alterations due to positive interventions can improve the response to other environmental "layers" in a cascade effect (Bakermans-Kranenburg and Van, 2015). With the advancements in research techniques, future studies will be able to better explore these mechanisms in humans.

As the prevalence of obesity continues increasing especially among children and adolescents, who in most cases will carry the phenotype along to adulthood and transmit it to the next generations, investigation of these issues are of large importance and priority.

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Highlights

- Genes may work by modulating the way individuals respond to environmental variation.

- The differential susceptibility hypothesis was firstly observed in psychiatric-genetic research.

- Nowadays there is evidence of the applicability of this theory to obesity.

- Capturing the various environmental expositions during development is a challenge.
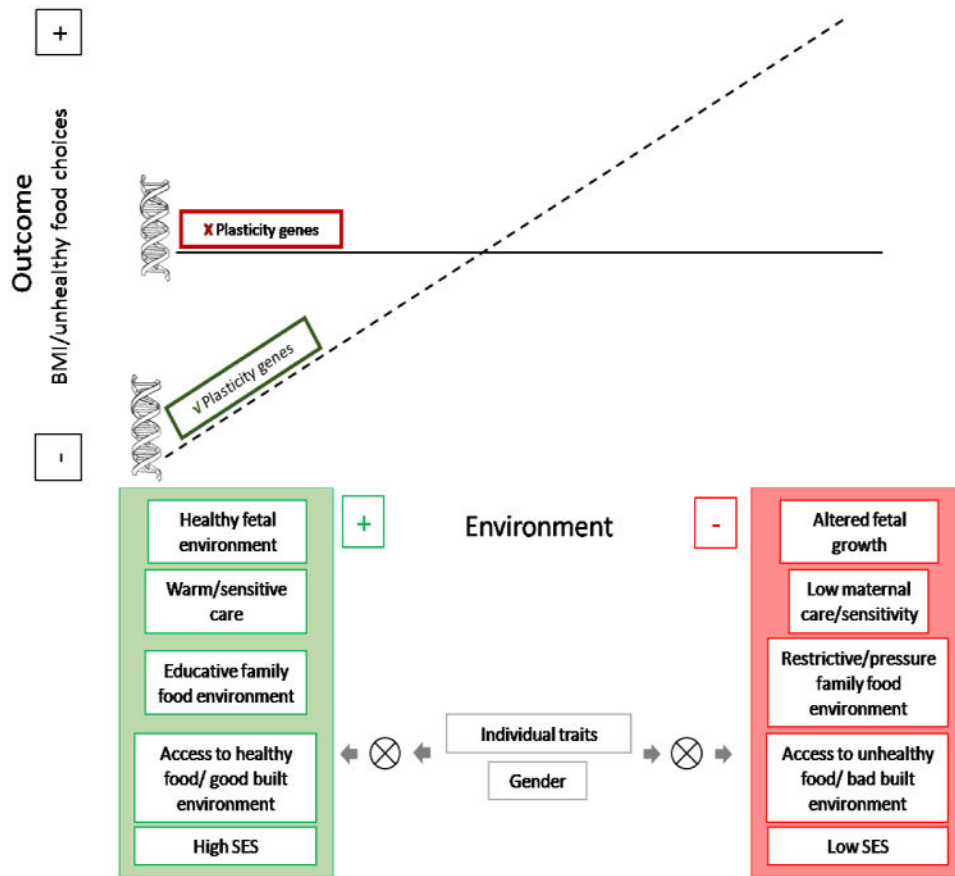
Figure 1.
Conceptual framework representing the differential susceptibility hypothesis to the various environmental "layers" on feeding behavior/choices and BMI. The positive or negative environment will impact more on individuals carrying "plasticity" genes, leading to healthier food choices and lower BMI in positive environments and the opposite in negative environments. Individual traits and gender interact with the various environments (circles with a cross inside represent interaction). Boxes with edges in dark red and dark green represent the absence or presence of the plasticity genes, respectively. The filled boxes in green and red represent positive and negative environmental influences, respectively.