Universidad de Granada

PROGRAMA DE DOCTORADO EN PSICOLOGÍA (B.13.56.1)

TESIS DOCTORAL

Brain mechanisms underlying stress and eating behavior in adolescents with excess weight

[Mecanismos cerebrales asociados al estrés y al comportamiento alimentario en adolescentes con exceso de peso]

PhD candidate:

Cristina Martín Pérez

Supervisors:

Dra. Oren Contreras Rodríguez

Dra. Raquel Vilar López

Granada 2018

Editor: Universidad de Granada. Tesis Doctorales
Autor: Cristina Martín Pérez
ISBN: 978-84-1117-093-2
URI: http://hdl.handle.net/10481/71564

Agradecimientos

En primer lugar, quiero agradecer el papel fundamental que han desarrollado mis directoras, Raquel y Oren, durante todo el proceso. En este papel, no sólo incluyo vuestra increíble capacidad para motivarme, para hacerme ver que lo que hacemos tiene sentido, o para darme seguridad, también quiero agradeceros que siempre hayáis estado acompañándome emocionalmente, durante los "altibajos del doctorando". Gracias también por ser las primeras personas que creyeron en mí, y que me dieron la oportunidad de desarrollarme en esta profesión. Sois magníficas personas e investigadoras, no imagino mejores directoras, y soy muy feliz por haber podido trabajar con vosotras. Este agradecimiento siempre se quedará corto para todo lo que os tengo que agradecer.

Quiero extender este agradecimiento a cada una de las personas que forman el grupo de investigación al que, con tanto orgullo, pertenezco. A Miguel Pérez, por estar siempre pendiente, y disponible para lo que haya necesitado. Eres un apoyo incondicional para todo el grupo, y un ejemplo a seguir como persona y profesional. A Julia, Natalia, Sabina y a todos los demás. A los que ya se han ido y a las nuevas incorporaciones, porque todos han aportado (y siguen aportando) algo bueno a mi vida. Gracias por darme vuestro apoyo y por hacer mi vida más feliz dentro y fuera del trabajo.

Especialmente, quiero dar las gracias a Juan, una persona imprescindible, mi tutor "en la sombra". Gracias por todo lo que me has dado. Gracias por haber sido mi profesor y mi amigo, por estar siempre disponible, por ayudarme día a día, por aguantarme hiperactiva y de bajón (por esto te mereces dinero, más que un agradecimiento). Sin tu apoyo y ayuda, no habría llegado hasta aquí.

También quería aprovechar la oportunidad de agradecer a Antonio Verdejo por su gran contribución en esta tesis y durante el proceso de doctorado. Gracias por acogerme en Australia, y gracias por las oportunidades que me has dado. Gracias también a Carles Soriano-Mas y a todas las personas de su grupo de investigación, que me acogieron con los brazos abiertos en mi estancia. Gracias a todos ellos, por haberme ayudado desinteresadamente, incluso tras volver de Barcelona.

No puedo dejar de agradecer a las personas que me han aportado tanto en el ámbito personal. A Fran, mi apoyo incondicional y a todos mis amigos. A los que están fuera y siempre han estado apoyándome cuando lo he necesitado y a los que están aquí, y que han sabido comprender mis ausencias. Y por supuesto a mi familia. A mi hermana, por su apoyo y por su ayuda, y en especial, a mi madre. Muchas gracias por todos los esfuerzos que has tenido que hacer, durante toda tu vida, para que hoy esté aquí. Esto es gracias a ti. A Leo, que aun no siendo consciente, ha hecho mi vida mucho más feliz. A mis tíos y mis primos, que siempre me han apoyado. Gracias por mostrarme que estáis orgullosos de mí.

Finalmente, creo necesario agradecer a todos los participantes de los estudios que forman parte de esta tesis. Pero también a aquellos que pertenecen a otros estudios y que me han hecho crecer enormemente, tanto laboral como personalmente.

INDEX

Glossary……..…….……... 1

Summary……..…….. 3

I. INTRODUCTION…….... 11

Chapter 1. A global public health challenge…….. 13

1. The importance of excess weight research in adolescence…….. 13

1.1.Prevalence and definition of excess weight in adolescence…….….. 14

1.2.Health consequences: having excess weight is killing us younger…… 15

1.2.1. Metabolic/endocrine consequences and disease……... 16

1.2.2. Psychosocial and psychological consequences: the bottom of the iceberg……... 18

1.3.Economic and quality of life consequences: life-cost of excess weight…. 20

2. Predisposing and maintaining factors. Is excess weight a choice?…… 22

2.1.Obesogenic environment……. 22

2.2.Individual factors……. 24

2.2.1. Executive function…….. 25

2.2.2. Stress…….. 26

Chapter 2. Beyond homeostatic eating…….……... 30

1. Homeostatic and hedonic eating……. 32

1.1. Brain pathways responsible for homeostatic eating behavior……. 32

1.2. Overriding homeostasis: non-homeostatic brain network…….. 36

1.3. Affective and executive alterations of homeostasis and non-homeostasis brain regions…… 42

1.3.1. The role of stress……. 42

1.3.2. Executive function: the role of decision-making…… 45

II. RATIONALE AND AIMS…… 50

Chapter 3. Rationale and aims…….. 52

1. Rationale…….. 52
2. Aims……. 54

III. COMPILATION OF WORKS……... 59

Chapter 4. The role of stress in excess weight: overriding homeostatic brain……. 61

1. Introduction……. 63
2. Method and materials……. 65
3. Results…… 73
4. Discussion…….. 79

Chapter 5. Non-homeostatic brain and stress in excess weight…….…… 84

1. Introduction…… 86
2. Method and materials…… 89
3. Results…… 96
4. Discussion……. 102

Chapter 6. The executive brain and excess weight……. 107

1. Introduction……... 109
2. Method and materials…… 112
3. Results…… 117
4. Discussion……. 120
5. Appendix…… 124

IV. GENERAL DISCUSSION, CONCLUSIONS AND FUTURE PERSPECTIVES……..…… 127

Chapter 7. General discussion, conclusions and future perspectives..... 129

1. Discussion..... 129

2. Clinical implications and applications..... 133

3. Limitations and future perspectives..... 135

4. Conclusions..... 137

V. INTERNATIONAL DOCTORATE..... 140

1. Resumen..... 142

2. Conclusiones..... 147

VI. REFERENCES..... 150

GLOSSARY

Body fat: total accumulation of fat across the body. This measure includes "good fat", defined as the amount of fat necessary for maintaining life, and "bad fat", which is derived from storage.

Brain network (as large-scale brain networks): a set of structures organized due to their structural connectivity or functional interdependence.

Comfort food: normally, high-caloric foods whose consumption provides consolation or feeling of well-being. In obesity research, it has been considered as a way to cope with negative emotion.

Dopamine/Dopaminergic: neurotransmitter that helps control the brain´s reward and emotional response. The mesolimbic system is the one transporting dopamine from the ventral tegmental area to the nucleus accumbens, amygdala and hippocampus.

Emotional eating: (sometimes referred as stress eating) is defined as the coping strategy of overeating in order to relieve negative emotions. Normally, comfort food is the target of this maladapted eating behavior.

Energy homeostasis: biological process by which energy intake and expenditure are regulated. It is mainly driven by the hypothalamic-pituitary-adrenal axis.

Excess weight: defined as an excessive amount of body weight, this concept captures the term of both "obesity" and "overweight".

Executive function: a set of cognitive processes necessary for cognitive control of behavior. Inhibitory control, cognitive flexibility and working memory would be considered the main executive functions according to Miyake & Friedman (2012). Also, decision-making has been presented in numerous studies as the most important component of executive functions, as it requires the adequate functioning of the other components.

Food liking: the state of sensory "pleasure" derived from eating any given food. Related to consummatory reward.

Food wanting: the cognitive process of anticipating and desiring the rewarding effect of any food. Related to anticipatory reward. Includes a motivational component. Also referred as incentive salience in some papers/documents.

Independent Component Analysis: a method for separating a multivariate signal into additive subcomponents, statistically independent from each other. In fMRI, this technique is used to separate the functionally-related areas into distinct brain networks.

Insulin Resistance: a pathological condition in which cells fail to respond normally to insulin. In these cases, the high levels of insulin in obesity will provoke a pre-diabetes stage. More insulin resistance relates to more health problems.

Insulin sensitivity: the sensitivity of our body to the effects of insulin. Higher insulin sensitivity is related with better health outcomes.

Obesogenic environment: this concept refers to an environment that promotes gaining weight through the continuous exposition to food, and the high availability of unhealthy food products.

Palatable food: this is a term used for foods that are considered as tasty, and that normally contains high amounts of sugar, salt and/or fat.

Resting-State Functional Connectivity: a method for mapping the regional interactions that occurs at rest (namely, task-negative state). This technique allows observing the functional organization of the brain in a baseline condition.

Reward system/circuitry: a group of brain areas responsible for the aspects of "liking" and "wanting" to food. Several systems join in the reward neurocircuitry. Among them, the limbic, and its mesolimbic subsystem, would be the most important pathways in obesity.

SUMMARY/RESUMEN

Excess weight has become one of the greatest challenges for today´s society. The World Health Organization has described obesity as a slow-acting, but devastating global epidemic.

Regarding adolescence, more than 340 million of individuals between 12 and 19 years old currently have excess weight, although it is expected that, at the beginning of the following decade, the obesity rates in adolescents will surpass underweight rates around the world. Due to these overwhelming figures, many studies have emerged to explore the causes and consequences of weight issues.

While several studies propose that obesity has a lot to do with the obesogenic environment in which we live, others have proposed the importance of the psychological, metabolic and neurobiological factors that trigger obesity. Among those individual factors, stress and executive dysfunction, and its underlying hormonal/metabolic processes, stand out as the greatest drivers of high-fat food intake, and hence also the greatest disruptors in the regulation of energy balance. The heightened reactivity of the Hypothalamic-Pituitary-Adrenal (HPA) axis, main responsible of homeostatic energy balance, and the lower function of the executive brain (dorsal prefrontal areas) contribute to the higher engagement of non-homeostatic brain areas in regulating eating behavior. Recently, imaging studies have provided evidence supporting the idea that the dysregulation between the homeostatic (HPA axis, hypothalamus), executive and the hedonic/non-homeostatic brain centers, such as the limbic and mesolimbic systems, may be associated with excess weight, and that this dysregulation could be promoted by stress and executive factors.

Under this context, this doctoral thesis aims to characterize the brain functional connectivity of the main areas related to both stress and cognitive factors, and its impact overeating behavior beyond homeostatic needs in adolescents with excess weight, in comparison with those with normal weight. To this end, three studies shape the present thesis.

The first study, focused on the homeostatic brain center, stemmed from studies reporting alterations in the hypothalamic nuclei in adults with excess weight, and also from the theoretical model of Dallman (2010), suggesting that stress could lead to maladaptive eating behaviors, as emotional eating, through the dysregulation of hypothalamic and cortico-mesostriatal-limbic circuits. We explored whether such brain alterations already exist since adolescence in individuals with excess weight, by investigating differences in the functional connectivity of the two main regions of the hypothalamus, the medial and the lateral hypothalamus, when compared with adolescents with normal weight. Following the model of Dallman (2010), we also explored the hypothalamic stress-related connectivity and its association with emotional eating behavior. The results indicated that excess weight in adolescence is related to a greater functional connectivity between the lateral hypothalamus and areas related to reward, and that the strength connectivity in this network was positively associated with the stress response, and in turn, with emotional eating behavior. These results support Dallman´s model in adolescence, and also highlight the importance of stress-related eating since early stages of development.

The second study is focused on the limbic system, which is the ultimate non-homeostatic system implicated in the regulation of the HPA axis. One of the most important regions of the limbic system is the amygdala, which acts as an excitatory area that projects to the hypothalamus. This area has also been studied previously in adults with excess weight, due to its importance on feeding (Wijngaarden et al., 2014; Lips et al., 2014). Indeed, an alteration in the amygdala could modify the function of the HPA axis, and subsequently, worsen the adequate regulation of eating behavior and weight (Sun et al., 2015). In this context, we investigated the differences between both adolescent groups (excess versus normal weight) in the functional connectivity of the main nuclei of the amygdala (central and basolateral), and then explored associations with the accumulated stress and weight change over a three months'

diet in the adolescents with excess weight. Adolescents with excess weight showed higher functional connectivity between the central amygdala and the prefrontal areas related to the rewarding and emotional valuation of stimuli, and lower connectivity with the posterior cingulate cortex, an area related to interoception. Also the basolateral nucleus showed lower connectivity with a dorsal striatal area known to have hyper-functionality when facing food stimuli, but hypo-functionality under resting. The results of the amygdala´s functional-connectivity related to weight change showed that those who lose less weight, had higher connectivity between the central amygdala and the mesolimbic system, related to food wanting behaviors. Interestingly, this connectivity indirectly mediated the relationship between chronic stress and weight change in adolescents with excess weight. Thus, this study highlights the connection between emotional and rewarding areas. Importanty, the weight loss-related connectivity within the central amygdala-midbrain network, and its associations with chronic stress, support the proposed theory of Mietus-Snyder & Lustig (2008), which suggest that the stress processes in the amygdala networks may override the normal regulation of food intake in children, by its connections with the midbrain and the hypothalamus in children.

Finally, the third study places the attention in the relevance of metabolic, brain and cognitive factors over excess weight problems. Insulin and body fat accumulation are two of the major metabolic problems related to excess weight. Indeed, some studies have found that high levels of insulin and fat not only affect physiological comorbidities, but also relate to executive dysfunctions (Higgs et al., 2016). One of the leading executive dysfunction, which in turn is quite related to maladapted eating behaviors, is decision-making (He et al., 2014). In this context, we explored the insulin and body fat-related activity within the salience, central executive, and the default mode brain networks, and the relationship between the potential alterations in these networks and the dysfunction in the neuropsychological measures of decision-making and shifting, an important proxy of decision-making. Our results showed a

heightened insulin/body fat-related activity of the ventral striatum, and a lower activity of the dorsal ACC within the salience network. Also, we found that these areas were differently related to disadvantageous decision-making and shifting ability.

Overall, these studies highlight that adolescents with excess weight show brain functional connectivity alterations partially consistent with those previously found in excess weight adults. These brain alterations were characterized by the hyper-connectivity/activity of areas related to non-homeostatic eating (i.e., mesolimbic and cortico-limbic circuits) and the hypoactivity of cognitive and attentional control areas. It is worth noting that the strength functional connectivity of both the hypothalamus and the amygdala with the midbrain was associated with altered obesity-related behaviors, including an enhanced acute and maintained stress response, emotional eating, and weight status. Therefore, the midbrain may likely be an important signature for stress-induced excess weight in adolescence, which would guide motivational eating behavior in early obese conditions. Hence, stress, as proposed by several models of obesity, is a core concept to consider in the vicious cycle of chronic stress-eating and should be taken into account in the current treatments of excess weight.

On the other hand, executive function is another important aspect for eating behavior, mainly regulated by the action of the dorsal prefrontal areas and the abnormal high levels of insulin. The dysregulation of these cognitive-related brain areas may play an important role in the adequate performance in executive function tasks. Indeed, the enhancement of impulsive brain, such as the ventral striatum, areas and the decreased activity in inhibitory areas within the executive brain, lead to worse decision-making and shifting, which is highly related to overeating and unhealthy eating behaviors. Our results found a positive association between insulin/body fat, and the higher engagement of the ventral striatum, while the lower activity in dorsal anterior cingulate cortex. This "brain model" totally supports the dual-processing theory, and previous studies relating these brain dysregulations in eating behavior (He et al., 2014).

Besides, we found that in excess weight adolescents, the alteration in these brain areas predicted a lower performance in decision-making and shifting tasks. This third study emphasizes the importance of metabolic dysregulations (heightened levels of insulin and fat) on the regulation of the executive brain. Besides, this study tries to stress the function of the executive brain in the problems related to excess weight. The better understanding of this brain regions would be helpful for a better understanding of food choices.

Altogether, the three studies provide new knowledge on the neurobiological dysregulations promoting excess weight in adolescence, and on the influence of stress and executive functions over eating behavior in those individuals.

Current excess weight interventions are based in the promotion of exercise and calorie-restrictive diets, which although effective tend to fail because of difficulties in its following and implementation. According to our results, these difficulties could be heightened by cognitive and affective factors, and also by neuroadaptations fostering overeating. For this reason, this thesis is commited to the integration of multidisciplinary approaches that include psychological factors, as motivational enhancing and stress management programs, as well as cognitive training, to improve the actual attainment to weight loss interventions.

I. INTRODUCTION

Chapter 1. A global public health challenge

On this first chapter, we will state the importance of the study of obesity as a major global problem. The first section will comprise basic information to better understand the importance of the study of excess weight since earlier stages of maturation. Although this thesis is focused on the neuroscientist perspective of the excess weight condition, obesity and overweight raise as complex, multifactorial and multidimensional issues. Thus, it is important to briefly review the health, economic and psychosocial consequences of this global challenge.

The second section includes a description of the environmental and psychological factors that helps maintain or develop the excess weight problem. Mainly, this thesis will review, on one hand, the influence of the obesogenic context in today´s western societies, and on the other, the individual cognitive (executive function) and affective (stress) factors that lead to maladapted eating behaviors.

1. The importance of excess weight research in adolescence

Obesity is a global problem that continues to expand worldwide. Nowadays, more than 1.9 billion people (WHO, 2017) have excess weight and it has been estimated that approximately half of the world´s adult population will be overweight or obese by 2030. Most worrisome would be that obesity is responsible for a 5 percent of all death worldwide. Likewise, 340 million children and adolescents are already above their healthy weight (WHO, 2017).

Adolescence is a critical period for weight gain due to the stronger expression of inheritable predispositions (Stice, Presnell, Shaw & Rhode, 2005) and the start of the own decision-making process about food choices, previously controlled by family habits, which arises as a relevant aspect to determine future eating preferences and behaviors.

Besides, overweight and obesity in adolescence tend to persist into adulthood. In fact, adolescents with excess weight are five times more likely to be obese or overweight in the adult stage, and the 80% of adolescents with obesity keeps on having excess weight in adulthood (Simmonds, Llewellyn, Owen & Woolacott, 2015). This is concerning, as several studies have found a relationship between excess weight in adolescence and both an increased mortality risk in adulthood, and a much lower life expectancy (Engeland, Bjorge, Tverdal & Sogaard, 2004; Reilly & Kelly, 2010). Because of this, numerous studies have been launched on obesity field in adolescence, with the aim of determining the prevalence, the consequences of obesity in earlier stages of maturation and finally, its cost in public health services.

1.1. Prevalence and definition of excess weight in adolescence

The global prevalence of excess weight in children and adolescents has evolved from 4% in 1975, to 18% in 2016 (WHO, 2017). This uncontrolled expansion occurred similarly in boys and girls, and in developed and developing countries, so obesity is no longer a particular problem of the "rich world". In fact, the raise of excess weight rates in adolescence has accelerated astoundingly quickly in developing and low-income countries, especially in Asia (WHO, 2017). In 2016, the highest rates of obesity, regardless of sex, were reported in Polynesia (25.4%) and Micronesia (22.4%), followed by high-income countries, as the United States of America (20.6%), which has the greatest obesity rates within developed countries, Canada (13.1%) or Australia (10%) (Hales, Carroll, Fryar & Ogden, 2017; Rao, Kropac, Do, Roberts & Javaraman, 2017; AIHW, 2017). In Europe, the rates are also high. Surprisingly, the prevalence of adolescents with obesity has also rapidly increased in the Mediterranean countries such as Greece (11.3%), Malta (16.7%) or Spain (6.3%), which supposedly follow a healthy diet (WHO, 2017). Moreover, the percentage of children <5 years old with obesity have rocketed in these Mediterranean countries, being over 21% in the last study performed (Musaiger, 2011). Although these data are worrying per se, we should be even more concerned

as these official reports provide information only about obese population, albeit there is a greater proportion of adolescents around the world who are overweight, and are not taken into account in these surveys above.

To better understand the content of this thesis, it is worth noting that the term "excess weight" includes every individual who is overweight or obese. Indeed, they have different definitions and characteristics. Obesity has been defined as abnormal and excessive fat accumulation that may impair health (WHO, 2016), while overweight is defined as a pre-obesity stage where the fat exceeds the optimal value. In practice, and contrary to the definition, the fat is not so commonly measured, and obesity is normally diagnosed by the Body Mass Index (BMI). This index has been criticized because its lack of specificity for some individuals, for instance, those very muscled (Romero-Corral et al., 2008). However, BMI shows high positive correlations with body fat, and it is nowadays the most used measure to estimate the prevalence of excess weight worldwide (WHO, 2018; Cole et al., 2012).

In children and adolescents, the BMI-percentile is considered a more descriptive measure to diagnose excess weight. This measurement considers the age and sex of the individuals, so the maturation stage is considered in the equation, and the BMI is expressed in relation to other children/adolescents in the same phase of development (CDC, 2016; Cole, 2000). To consider a child/adolescent to be overweight, their BMI-percentile should be between $\geq 85^{th}$ and $<95^{th}$, and higher of 95^{th} for diagnosing obesity.

1.2.Health consequences: having excess weight is killing us younger

Excess weight impacts in all major organs of the body, and is highly comorbid with medical diseases such as those affecting the cardiovascular and metabolic systems, even in adolescents (Raj, 2012). In the latter years, the rapid escalation of prevalence and severity of excess weight problems in adolescence has increased the incidence of serious comorbidities in

this young population. Unfortunately, most of the adolescents with excess weight easily maintain or worsen these comorbidities along time (Kindblom et al., 2009), and thus, substantially decrease their life expectancy. For this reason, clinicians, researchers, and even government institutions are announcing that this generation of children will be the first in the history that will have shorter lives than their parents (Mathers, 2015; Olshansky et al., 2005).

1.2.1 Metabolic/endocrine consequences and disease

Although the medical consequences of obesity are not the target of this thesis, a brief description of the most relevant comorbidities in adolescents with obesity are reviewed hereunder. Also, the most common hormonal and metabolic dysregulations will be stressed, in order to better understand the theoretical and methodological development of the following chapters and studies within this thesis.

- Metabolic Syndrome. It is defined as a cluster of conditions comprising hyper-insulinaemia, obesity, hypertension and hyperlipidemia (Lee & Sanders 2012). The prevalence of this syndrome is high among adolescents with excess weight, and it increases as weight grows. A global study has provided an estimated prevalence of metabolic syndrome among children and adolescents with overweight and obesity up to 60% worldwide (Tailor, Peeters, Norat, Vineis & Romaguera, 2010).
- Inflammation. One of the most common inflammation in obesity is the non-alcoholic liver steatosis or fatty liver (Manton et al, 2000). The increase of reactants as C-reactive protein in the liver leads to the enhancement of inflammation and oxidative stress (Montero, Walthers, Perez-Martin, Roche & Vinet, 2011).
- Cardiovascular disease. Obesity in early ages impacts all major systems of the body and promotes atherosclerotic disease in important vascular bodies as the aorta, and

coronary arteries. This ends up in high risk for cardiovascular problems (Sinaiko et al., 2005).

- Type 1/2 Diabetes Mellitus (T1D/T2D). T1/2D´s complications include accelerated development of cardiovascular or renal problems (Reinehr, 2013). T1D is the least common variant of diabetes, although it has been increasing by 2-5% worldwide. Besides, more than 85% of the cases are reported in individuals younger than 20 years old (Maahs, West, Lawrence & Mayer-Davis, 2010), so it is an almost specific comorbidity to adolescents with obesity. T2D, on its part, is suffered by 1 in 11 people worldwide. However, the figures vary substantially between geographical situations, cultures and countries. This leaves an open door to the importance of the environmental factors such as the diet or sedentary habits in the development of these conditions. Some disturbed and early signs of T2D are increased levels of fasting plasma glucose, and fasting insulin levels, which lead to insulin resistance (Roth, Elfers & Hampe, 2017; Kahn, Hull & Utzschneider, 2006).
- Hormonal/metabolic dysregulations:
    - Leptin and insulin resistance (or insensitivity). Those peptides, are known to act as the metabolic regulators of feeding. Changes in these hormones, although are not enough to predict weight changes (Strohacker, McCaffery, MacLean & Wing, 2014), modulate rewarding properties of food, and promote overeating via dysregulation of fat and glucose metabolism, and also affecting cognitive and brain functions (Volkow, Wang & Baler, 2011; Higgs et al., 2017). Most obese individuals have heightened leptin and insulin levels, which indicate that obesity is a leptin and insulin resistance state (Kelesidis & Mantzoros, 2006; Kahn et al., 2006). Both peptides have a well-known relationship, although the directions of this association is not clearly known. Despite that, some studies

have proposed that insulin, together with cortisol, is the regulator of leptin production and secretion (Tan, Patel, Kaplan, Koenig & Hooi, 1998; Wabitsch et al., 1996). The alteration of both insulin and leptin leads to diabetes and metabolic syndrome (Huang, 2004).

- Hypercortisolemia. The cortisol is one of the hormonal mediators of obesity. Among the several alterations in obesity, heightened levels of cortisol would represent a problem of great relevance in the area of neuroscience, due to its implication in energy balance and affective disorders. Indeed, it exists a direct relationship between cortisol and weight, fat and feeding: as higher degrees of obesity, greater cortisol release (Mårin et al., 1992). The inverse direction of this association has also been studied from a neuroscientist perspective, as in the presence of insulin, cortisol is a critical contributor to visceral fat accumulation, and both hormones together are known to regulate energy balance in humans (Dallman, Akana, Strack, Hanson & Sebastian, 1995). Further information about the response of cortisol in excess weight individuals will be discussed later (details in the section 2.2.2. Stress).

1.2.2 Psychosocial and psychological consequences: the bottom of the iceberg

Whilst the well-known consequences of obesity are the biological problems commented above, excess weight in adolescence is accompanied by several psychosocial problems, which lead to increased susceptibility for psychological adverse consequences. However, those problems are usually not so evident and understood. A sentence extracted and adapted from "Confronting obesity in children" by Brownell and Wadden, (1984) is still valid today, and defines this problem:

"The professional community is concerned with the medical concomitants of obesity, but the psychological and social perils are at least as important to those afflicted by the problem. Society does not tolerate excess weight and the effects of this overt and covert pressure to be thin can be powerful and permanent."

That brings up one of the more prevalent psychosocial problems: the stigmatization (Latner & Stunkard 2003), which forces adolescents with overweight and obesity to shoulder the entire responsibility, and blame, for having that weight. Common and erroneous assumptions and stereotypes in society, as *"they are lazy"*, *"they just have to stop eating so much"*, or *"if they don´t lose weight is because they have not tried hard enough"*, only contribute to increase the problem. This stigma plays an important indirect role in social stress or higher weight gain among other consequences that have been extensively documented (Pont, Puhl, Cook & Slusser, 2017; Puhl & Latner, 2007; Strauss & Pollack, 2003).

Apart from stigmatization, although closely related, we find marginalization, whose consequences are even more troublesome in adolescence. As proposed by Strauss and Pollack, (2003): "*in adolescence, few problems have as significant impact on emotional development as being overweight*". Indeed, marginalization generally goes hand in hand with one devastating problem suffered by many adolescents with overweight: bullying (Janssen, Craing, Boyce & Pickett, 2004). Many adverse outcomes are related to the continuous exposure to such situations: low self-esteem, body dissatisfaction, unhealthy eating behaviors, maladaptive coping strategies, and anxiety or depression. Very likely, all those problems related to stigmatization and marginalization contribute to affective alterations such as the heightened stress reactivity that adolescents with excess weight present compared to their normal weight peers (see section 2.2.2. Stress).

Psychological studies have also stated that both being overweight or obese, and having weight concerns are related to mental health problems in adolescence (BeLue, Francis & Colaco, 2009; Jansen, van de Looji-Jansen, de Wilde & Brug, 2008). In this line, many studies find a higher prevalence of depressive symptoms in adolescents with excess weight in comparison with their normal-weight counterparts (Ozmen et al., 2007; Perrin, Boone-Heinonen, Field, Coyne-Beasley, & Gordon-Larsen, 2010). It is worth noting that depression and anxiety are the most frequent problems associated with excess weight. Indeed, there is a two-way relationship between these problems. While depressed and anxious adolescents are at risk for the persistence of obesity (Goodman & Whitaker, 2002), obese children, due to the presence heightened stress, are also at increased risk for developing depression and anxiety (Anderson, Cohen, Naumova, Jacques, & Must, 2007). This turns affective problems in consequences and predisposing factors for obesity (see section 2.2.2. Stress).

1.3 Economic and quality of life consequences: life-cost of excess weight

All these consequences previously seen have great costs in public health. Throughout their whole lives, the health expenditures in excess weight people are at least 25% higher than in those with normal weight (OECD, 2010). The most recent study examining the cost of excess weight in adolescence showed that the mean expenditure directly originated by obesity during the whole adolescence (between 12 and 19 ages years old) was of 17932.5 € per adolescent (Hamilton, Dee & Perry, 2017). In Spain, the country where our studies were performed, the 7% of the total annual expenditures in health were associated to treat excess weight problems in the last report of 2004 (Fundación Diabetes, 2004).

Apart from these direct costs in health systems over the world, several studies have proposed indirect costs related to obesity, much more abundant, but also more difficult to estimate. For instance, adolescents with excess weight miss more school days, which in turn

may lead to a poorer performance than their normal weight counterparts (Taras & Potts-Datema, 2005). Later in adulthood, absenteeism, productivity loses or activity restrictions due to their physical conditions produce the most important loses in the global economy (Cawley, 2004; Mitra, 2001; Morris, 2006; Sargent & Blanchflower, 1994). Besides, obese people are more discriminated in the workplaces and in the hiring process, and consequently, suffer from higher rates of unemployment (Bartels & Nordstrom, 2013). They are perceived as less successful, less competent and are often viewed as worse group leaders (Flint et al., 2016). The most important way in which this discrimination comes to light is the salary discrimination. Obese people earn approximately 3.3% less than people with normal weight (Baum & Ford, 2004; Brunello & D´Hombres, 2007).

In conclusion, adolescents with excess weight deal with many physical and metabolic consequences, traditionally attributed to adults, but also with intense psychological discomfort, that cost not only millions of dollars/euros worldwide, but many problems in the quality of life of these people. Thus, the exponential growth of obesity worldwide needs to be adequately addressed, since the current attempts trying to stop this increasing epidemic are failing. According to a quote extracted from Swinburn and colleagues (2011) in "The global obesity pandemic report": *"Governments have largely abdicated the responsibility for addressing obesity to individuals, the private sector, and non-governmental organisations, yet the obesity epidemic will not be reversed without government leadership, regulation, and investment in programmes, monitoring, and research"*

Given this statement, better policies have to be taken into account. Today´s obesity has changed what we knew about the physiological processes of gaining weight. Nowadays, obesity comprises physiological, metabolic, biochemical, anatomical, psychological and social alterations (Parízková & Hills 2001), and thus more research has to be done, leaving the

traditional simplistic view of obesity behind (mainly focused on energy intake and expenditure). Excess weight implies a multifactorial and complex definition.

In the next section, this thesis will review how the cutting-edge research in neuroscience has changed the traditional vision of obesity, moving the concept of excess weight to a phenomenon highly associated to both environmental and psychological factors.

2. Predisposing and maintaining factors. Is excess weight a choice?

At its simplest, excess weight is the result of eating more and exercising less, although the factors that predispose or maintain excess weight are much more complex than that. Hereafter, the most established factors are reviewed.

2.1. Obesogenic environment

This section should begin with a troubling question: Why developed and developing countries are increasingly getting fatter? The response is more complex than expected. Individuals do not have the full control over the food they eat, and even in some aspects or situations our control is minimal or nonexistent. In this sense, overeating and the increased consumption of high-dense food would be partially a consequence of this obesogenic world in which we live, and the control over our dietary behavior would be partially biased by this context.

In addition to the environment, genetics also has its piece of cake. The study of the contribution of environment and genetics in obesity has provided mixed results. Although it varies from study to study, the most recent research from Albuquerque, Nóbrega, Manco, and Padez (2017) indicated that approximately 47-80% of the variance of BMI relies on genetics. However, recent studies have shown that this inherit effect is modifiable by physical activity, alcohol consumption, and eating behavior habits (Van Vliet-

Ostaptchouk, Snieder & Lagou, 2012; Young, Wauthier & Donelly, 2010). This supports the idea that genetic susceptibility to obesity is not determinant, and that the environment plays a central role in shaping eating behaviors. The environment, unlike the genome, has strikingly changed during the last decades, turning to the so-called "obesogenic environment" where we live nowadays. As simplistically expressed in the "Homeostatic theory of obesity" by Marks (2015), *"Obesity is the result of people responding normally to the obesogenic environments they find themselves in".*

This brings to the fore the issue of the heightened availability of palatable food and the continuous exposition to food in our present society. Palatable foods with high-dense contents, and low prices, are readily available anywhere and anytime. This, together with the surge of fast-food restaurant chains and prepackaged foods, mixed with a low nutritional education, leads to a greater risk of having a poorer diet in developed and developing countries (Bowman & Vinyard, 2004; Satia & Galanko, 2007; Stamoulis, Pingali, & Shetty, 2004; Thorpe, Kestin, Riddell, Keast, & McNaughton, 2014). Along with the wider accessibility, the higher exposition to food is causing an excessive and continuous attention to food stimuli, altering the long-term preferences of food, more acutely in children and adolescents (Boyland, Harrold, Kirkham, & Halford, 2011; Brug, 2008; Dixon et al., 2007; EASO, 2018; Lake & Townshend, 2006; Reisch, Eberle & Lorek, 2013). This situation endorses those studies proposing an attentional bias, and an impairment in the executive processes related to the control food intake and choice, such as decision-making, inhibitory control and cognitive flexibility (Castellanos et al., 2009; Loeber et al., 2012; Verdejo-García et al., 2010). In order to address the problem, regulations over the aggressive marketing campaigns of high-fat foods are gaining attention, especially over those intended for children (Nestle, 2006).

Certain countries are taking actions in the restriction of fast-food exposition and availability in several ways. For instance, the USA, UK and other European countries are taking steps by following the proposals of scientific papers. These countries (i) have banned the fast-food stands near schools, (ii) have prohibited to the fast-food chains to give free toys to children with their meals, (iii) have labelled high fat food even in food chain restaurants, and (iv) have restricted fast-food advertising. Several institutions have warmly welcomed these efforts and the potential long-term benefits in the reduction of obesity rates. Despite that, we wonder: is this enough? Is the obesogenic environment the only thing that matters?

2.2. Individual factors

The notion of obesogenic environment has paradoxically placed the attention on individual factors. While some of the policies keep trying to indirectly reduce obesity rates by regulating junk food´s ads, or integrating the "fat tax" (Alkharfy, 2011; BØdker, Pisinger, Toft, & JØrgensen, 2015), these strategies did not provide major results (BØdker et al., 2015; Dubois, Griffith & O´Connell, 2017) and the obesity figures keep growing. This is indicating that the research in obesity must bear in mind the environment as a general factor, but also it must take into account the affective and cognitive factors that finally determine the individual choices in dietary behavior. Considering the research in psychology and neuroscience, we cannot leave everything to the context. Indeed, the environment is not almighty, and not everybody becomes obese, so the susceptibility to environment should be marked by other factors. In the next section, the most studied individual factors, which make an individual more prone to indulge with food than other, are reviewed.

2.2.1 Executive function

Overall, many studies have stressed the importance of an adequate performance in executive functions to promote healthy choices (He et al., 2014; Limbers, Egan, & Cohen, 2017; Riggs, Spruijt-Metz, Sakuma, Chou, & Pentz 2010). Several functions seem to be especially altered in excess weight, but most studies found inhibitory control, flexibility and decision-making as the most altered functions (Laureiro-Martínez & Brusoni, 2018; Mallorquí-Bagué et al., 2016; Smith, Hay, Campbell & Trollor, 2011). Indeed, different maladapted eating behaviors such as overeating, disinhibited eating or external eating, relate to an abnormal functioning of these specific executive markers (Dohle, Diel & Hofmann, 2018; Macchi, MacKew & Davis, 2017). Among them, decision-making would be the most important function to maintain a healthy eating behavior, and avoid excess weight-related eating patterns (He et al., 2014). An effective decision making requires the adequate functioning of the other executive components, such as the ability to update information (working memory), to shift our response and adapt it to a specific event (shifting) and to inhibit impulsive responses (inhibitory control), turning the performance on decision-making into a proxy of executive functioning (Laureiro-Martínez et al., 2018). Contrary to this, impulsivity has been named as the "antipode" of a good performance on executive functioning (Bickel, Jarmolowicz, Mueller, Gatchalian & McClure, 2012), and many studies stress the importance of this trait in overriding advantageous decision-making, and also in promoting overeating (Kakoschke, Kemps & Tiggemann, 2015).

According to previous studies, a lower control of impulses (Mobbs, Crépin, Thiéry, Golay & van der Linden, 2010) is related with obesity in different ways. For instance, the presence of higher cognitive impulsivity predicts difficulty in maintaining or losing weight through the maintenance of food addiction-related eating behaviors (Murphy, 2014). On the other side, under negative emotional situations, as stress, affective impulsivity makes

some individuals more prone to eat. Indeed, it stimulates eating under strong emotions, and "switch off" the cognitive control over feeding, leading to emotional eating behaviors (Guerrieri, Nederkoom, Schrooten, Martijn & Jansen, 2009).

Overall, these impulsivity dimensions help to the altered functioning of the executive components. This dysregulation plays a crucial role in obese conditions by fostering the automatic, and not mindful, responses to rewarding food (Hofmann, Friese & Roefs, 2009).

Besides these "cognitive" control of eating, a detrimental emotional control has also been proposed as one of the key factors that promotes obesity. In this sense, stress may increase impulsive or compulsive behaviors, depending on the chronicity of the stress. The contributions of stress to promote impulsive and compulsive eating behaviors are discussed below.

2.2.2 Stress

This section has been adapted from the book chapter **"Stress, reward and cognition in the obese brain"**. This chapter, now in press, will be published by ElSevier publications (Verdejo-García, Martín-Pérez & Kakoschke, in press).

Stress is defined as the state of real or perceived threat to homeostasis (Smith & Vale, 2006), but also as the response to this threat (Seyle, 1974). Stress produces negative emotions and individuals should be able to regulate these emotions in an adaptive way to cope with daily life. Adolescents with overweight or obesity are exposed to higher levels of threat and social stress (Hemmingsson, 2014; Agerstrom & Rooth, 2011; Strauss & Pollack, 2003) and they are also more reactive to stress, showing greater cortisol release than their normal weight counterparts under the same stressor (Verdejo-Garcia et al., 2015). The directionality of the associations between weight and stress is still unclear. Nevertheless, recent studies are

dilucidating the role of stress over weight gain, and the mediation of brain function and metabolic abnormalities (Brook, Zhang, Saar, & Brook, 2009; Cherbuin, Sargent-Cox, Fraser, Sachdev, & Anstey, 2015). Under stressful events, individuals with excess weight tend to increase the specific consumption of high-dense foods (Adam & Epel, 2007; Sinha & Jastreboff, 2013). This eating process could be interpreted as a way to cope with stress, as individuals alleviate stress by the so called comfort food eating (Dallman, 2003; Yau & Potenza, 2013). Therefore, stress is capable to override homeostatic eating and reduce cognitive control over feeding.

Recent studies have investigated how stress could lead to intense desires to consume high-dense foods, or the so-called food cravings (Potenza & Grilo, 2014; Sinha & Jastreboff, 2013; White, Wisenhunt, Williamson, Greenway & Netemeyer, 2002). Indeed, satiated individuals with excess weight present also higher self-reported food cravings under stressful tasks than their normal weight counterparts, which suggests the triggered salience of high-dense food under stressful conditions (Lemmens et al., 2011). Another study used the Trier Social Stress Task (TSST), consisting of a non-anticipated public speech, to explore the effects of stress on food cravings (Rosenberg et al., 2013). They found a correlation between higher sweet craving after the TSST, and perceived stress during the task (Lim, Norman, Clifton & Noakes, 2009).

To conclude, stress can be very harmful in adolescents with excess weight, because of the vicious cycle of stress and weight gain, and the involvement of stress-related neuroadaptations. Stress, as well as obesogenic environmental factors, are linked to neurobiological adaptations. Related to this, some authors have proposed that obesity could be considered as a brain disorder, as excess weight and fat accumulation lead to structural and functional changes (Volkow & O´Brien, 2007; Volkow et al., 2008). In this thesis, we provide further knowledge about the abnormal brain organization linked to eating behavior, executive

functions and stress in adolescents with excess weight to try to rise a neuroscientific comprehensive explanation of excess weight. In this line, the most important pathways regarding homeostatic and non-homeostatic brain regions will be discussed in the next chapter.

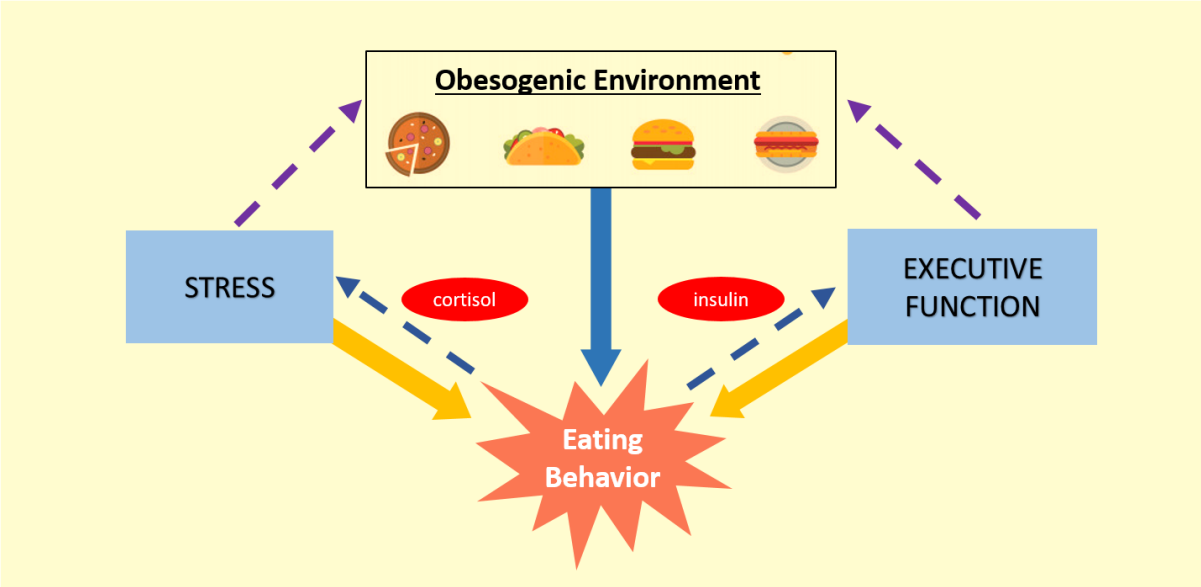

Figure 1. The exposition to the obesogenic environment in which we live leads to a maladapted eating behavior. However, individuals factors as stress and executive function mark the vulnerability of some individuals to this obesogenic environment (purple lines), and directly modulate eating behavior (yellow lines). Also, maladapted eating behavior is capable to enhance the detrimental influence of the individual factors via feedbac sigaling in the form of increased levels of hormones mediating stress (cortisol) and executive function (insulin).

Chapter 2. Beyond homeostatic eating

Approaching to the core of this thesis, this chapter places the attention in the brain mechanisms underlying eating behavior, and how both cognitive and affective factors modulate the activity of these brain networks to promote non-homeostatic eating.

In the first section, it will be discussed the neural pathways by which individuals regulate their energy balance. The relevance of the hypothalamic-pituitary-adrenal axis and its connections with the brainstem, another homeostatic area, will be stressed regarding their functions in energy homeostasis.

In the second section, the brain networks overriding homeostatic eating will be explained, according to previous studies in excess weight population. These networks are mainly composed of the limbic and mesolimbic systems, within the reward brain circuitry, responsible of the emotional and rewarding responses to food stimuli.

The last part of this chapter, divided in two sub-sections will be focused on the associations of stress, and executive function with the brain areas highlighted to be important for regulating homeostatic/hedonic eating. Specifically, it will be explained how stress affects the brain, and specifically how it interacts with the phenomena of overeating and eating under emotional circumstances, with special attention given to the concept of "comfort food". Also, the brain networks related to executive functioning will be exposed to understand the relationship between cognition and eating behavior.

In order to facilitate the understanding of the different areas involved in the regulation of eating behavior, a summary table is depicted hereafter describing the main functions and connections of each area (Table 1). This information will be explained in greater depth across the section.

Table 1

Areas involved in the regulation of eating behavior

Brain network	Brain Region	Association
Homeostatic	**Hypothalamus**	Direct connections with others areas involved on feeding as the OFC, amygdala, midbrain, ventral striatum (motivation and reward) and brainstem (homeostatic regulation). LH: "feeding center" and implicated in the reward system. MH: "satiety center", implicated in termination of intake.
	Brainstem (NTS)	Send the information of the visceral, peptides and homeostatic state to the hypothalamus.
Executive	**Dorsal PFC**	Dorsal prefrontal areas are known for their involvement in cognitive control and inhibition. These areas provide executive support to our behavior. The main areas altered in obesity are the dlPFC and the dACC.
Hedonic	**Ventral PFC**	Ventral areas of the prefrontal cortex are involved in reward and emotional valuation of the stimuli, and also in reward-related decision making and in emotional appraisal. The areas to take into account in obesity are the OFC, and the pgACC and sgACC.
	Insula	The anterior limbic portion provides feelings over the processing of external cues. Connected to amygdala, OFC and other areas in the salience network: dACC. Center of the "interoceptive system"
	Amygdala	The amygdala is the main emotional hub of the brain. Its subdivisions (central, CeA and basolateral, BLA) show different functions in food intake and emotion. CeA is the main output nucleus, and the regulator of the stress response and food intake. BLA is the main input nucleus which receive the emotional and sensory information. Area connected with the LH, cortical areas, midbrain and striatum.
	Ventral Striatum	The ventral striatum is known as the "impulsive system" of the brain. It is highly involved in the processing and response to rewarding stimuli. The main structures in the ventral striatum related to eating behavior are the VP, the putamen and the nucleus accumbens. Highly connected with midbrain, amygdala and cortical areas
	Midbrain	Finally, the midbrain regulates the hedonic response of the brain, together with the nucleus accumbens. These areas form the mesolimbic system, and interfere in the food wanting enhanced during emotional processes. Their preferential nucleus related to obesity are the VTA, SN and PG. Primarily connected with the striatum and hypothalamus.

Abbreviations: OFC, orbitofrontal cortex; LH/MH, lateral/medial hypothalamus; NTS, nucleus of the solitary tract; PFC, prefrontal cortex; dlPFC, dorsolateral PFC; dACC, dorsal anterior cingulate cortex; pg/sgACC, perigenual/subgenual ACC; VP, ventral pallidum; VTA, ventral tegmental area; SN, substantia nigra; PG, periaqueductal grey.

1. Homeostatic and hedonic eating

Feeding is a crucial process for survival that, optimally, arises from homeostatic energetic needs (Gao & Horvath, 2008). Homeostatic eating, in turn, would be defined as the consumption of food in response to a perceived energy need, unlike hedonic or non-homeostatic feeding, which is distinguished by eating under other circumstances beyond physiological needs (Faulconbridge & Hayes, 2011). Thus, excess weight may be triggered by an imbalance between energy intake and energy expenditure (Hill, Wyatt & Peters, 2012), and maintained by the altered affective and executive abilities to cope with the obesogenic environment (Singh, 2014; Davis, Strachan & Berkson, 2004).

In this context, the brain is a key organ in the homeostatic long-term regulation of energy balance (Dagher, Neseililer & Han, 2017). While the maintenance of an adequate brain regulation will facilitate an homeostatic energy balance, the higher functional overlap between the homeostatic and the non-homeostatic brain networks will promote unhealthy eating behaviors, and finally weight gain.

1.1. Brain pathways responsible for homeostatic eating behavior

According to Gao and Hovart (2008), the neural control of feeding is the main mechanism by which humans regulate the long term energy balance. The central system regulating homeostasis is the hypothalamic-pituitary-adrenal axis (HPA axis), which contains two brain regions, as the hypothalamus and the pituitary gland or hypophysis, and the adrenal gland in the kidneys´ tissue (Stephens & Wand, 2012). Likewise, the HPA axis is responsible of regulating important functions in excess weight: the hunger/satiety states and the emotional homeostasis due to the implication of the glucocorticoids function over this axis (Nieuwenhuizen & Rutters, 2008; Stephens & Wand, 2012). Therefore, a disruption in this axis may cause several alterations in our metabolic, emotional or immune system. According to

that, the brain has a central role in the homeostatic regulation of energy balance (Roh & Kim, 2016), and, in fact, we could say that essentially the whole brain is implicated in the control of feeding. Nevertheless, there are some regions whose functions are of paramount importance in excess weight condition (Dallman, 2010). Among them, several nuclei within the hypothalamus and the brainstem have emerged as the main areas responsible for eating regulation under homeostatic processes. Indeed, the hypothalamic-brainstem circuit has shown a great relevance in the studies of eating behavior since the very early studies in the 50s and 60s (Anand & Brobeck, 1951; Margules & Olds, 1962).

On one hand, the nucleus of the solitary tract of the brainstem (NTS) is one of the most relevant nucleus of this energy balance circuit, with a broad connection with hypothalamic and forebrain structures implicated in the control of feeding (Swanson, 2000). While eating, the brainstem captures the information from the circulating nutrients and peptide hormones, the visceral afferent information (i.e. gastric distension) and also, from the current homeostatic state (i.e. hunger vs satiety) (Blouet & Schwartz, 2012; Grill & Hayes, 2012; Rinaman, 2011). All this information is sent to the hypothalamus, which responds with negative-feedback signals to stop food intake under homeostatic situations (Blouet & Schwartz, 2012). Its dysregulation by high fat diets carries a bad signaling of hunger/satiety states from our body to the rest of the brain areas, and especially to the hypothalamus (Schneeberger, Gomis, & Claret, 2013).

Secondly, the hypothalamus would represent the main regulation center of energy balance. It controls "when" and "how much" we eat, and thus, adjusts the signal of hunger/satiety to our homeostatic needs. Regarding obesity research, some studies have shown that the hypothalamus has several nuclei with functional differentiation, but traditionally, it has been mainly divided between lateral and medial parts (Hoebel & Teitelbaum, 1962). The medial hypothalamus has been associated with the regulation of satiety, and lateral

hypothalamus with feeding behavior (Leibowitz, Weiss & Suh, 1990; Teitelbaum & Epstein, 1962). The respective functions of these hypothalamic subnuclei are possible thanks to the central actions of the insulin, secreted by the pancreas, the ghrelin, secreted by the gastrointestinal tract, and finally, the leptin, predominantly secreted by adipose cells (Klok, Jakobsdottir & Drent, 2007). Overall, under homeostatic conditions, leptin and insulin up-regulates anorexigenic peptides and down-regulates the orexogenic ones, contrary to the ghrelin function. Thus, hypothalamic nuclei and the regulatory peptides work together to promote a homeostatic feeding.

However, the lateral hypothalamus subnuclei, is not only centered in the homeostatic regulation, but plays a leading role in behavioral motivation due to its connections with the limbic and mesolimbic areas (amygdala, hippocampus, midbrain and nucleus accumbens), and the prefrontal cortex systems. Firstly, due to its projections to the mesolimbic areas, the lateral hypothalamus takes part in relevant processes in obesity such as enhanced incentive salience or "wanting" to food cues (Harris, Wimmer & Aston-Jones, 2005). Therefore, it is common to find the lateral hypothalamus as an important part of the reward brain system and a modulator of the dopamine system in numerous studies (Castro, Cole & Berridge, 2015; Stuber & Wise, 2016; Watabe-Uchida, Zhu, Ogawa, Vamanrao & Uchida, 2012). More recent studies have suggested the strengthening of the connections between the lateral hypothalamus and the mesolimbic system as a stimulating brain factor for non-homeostatic eating behaviors (Begriche, Sutton & Butler, 2011). On the other side, the hypothalamus receives projections from the limbic system. More specifically, the amygdala has excitatory connections to stimulate the activation of the HPA axis, while the hippocampus exerts an inhibitory control to stop the HPA response when necessary, thus, maintaining homeostasis (Herman et al., 2016). Conversely, several altered conditions, such as high-fat diets, lead to the hyperactivation of the amygdala, a powerful disruptor of eating behavior. This overstimulation results in the enhanced

motivational value of food and food craving behaviors (Avena, 2015), and consequently overeating, fat accumulation and weight gain.

To accurately determine the connections between these "homeostasis-regulating areas" and the rest of the brain, the use of resting-state functional magnetic resonance imaging (fMRI) has stood out as a handful tool in obesity research. Less studies have investigated the functioning of the NTS-brainstem due to its small size, but the little research performed until the moment has demonstrated changes in the BOLD signal of this area during the manipulation of the homeostatic state, and the glucose or ghrelin levels (Jones et al., 2012; Little et al., 2014; Rosenbaum, Sy, Pavlovich, Liebel & Hirsch, 2008). This demonstrates the relevance of this homeostatic area in regulating food intake. On the other hand, scientific evidence to date from neuroimaging studies, has provided results regarding several alterations in the functional connectivity of the hypothalamus in obesity. Wijngaarden et al., (2015) found a higher functional connectivity in obese people between the hypothalamus and the insula, but this study did not take into account the differential functioning of the medial and lateral hypothalamic subnuclei. Kullmann et al., (2014) were the first authors to investigate the differential functional connectivity of the medial and lateral parts of the hypothalamus in their study. This study found that obese, in comparison with people with normal weight, showed higher functional connectivity between the medial nuclei and the orbitofrontal cortex and nucleus accumbens, namely, rewarding areas, results that were partially supported by a posterior study using the same methodology (Contreras-Rodríguez et al., 2017). Notably, this last study also found a relationship between the lateral hypothalamus connectivity and weight change in adults with excess weight, suggesting the behavioral importance of a deregulated functional connectivity in this area.

1.2.Overriding homeostasis: non-homeostatic brain networks

Non-homeostatic eating arises from a mismatch between motivation to eat and the actual energy demand. When our brain is disturbed by an overfeeding episode, its functioning may momentarily disrupt, but eventually returns to the pre-disruption stage thanks to homeostatic regulation (Munzberg, Qualls-Creekmore, Yu, Morrison & Berridge, 2016). However, when overeating and diets based on high-fat foods become habitual, several neuroadaptations lead to a higher influence of hedonic over homeostatic and executive brain areas. It is worth noting that hedonic and homeostatic brain pathways are not separate entities (Munzberg et al., 2016), but several brain areas interacting with each other to promote feeding. However, in this section we are going to describe the different systems involved in homeostatic eating separately, for assuring a better understanding. Hence, among the brain circuits that this thesis is going to review, we focused on the limbic system, and its mesolimbic sub-system, rooted in the reward circuitry, and representing the most implicated pathways in the shifting from homeostatic to hedonic eating (Berthoud, 2007).

On one hand, the **limbic system** is implicated in the stress response, emotion, behavior and memory (Herman, Ostrander, Mueller & Figueiredo, 2005; Hyman, Malenka & Nestler, 2006; LeDoux, 1993; McDonald & White, 1993), and it is comprised of the amygdala, the hippocampus, the striatum, some midbrain nuclei, and the ventromedial areas within the prefrontal cortex, such as the orbitofrontal cortex (OFC) and the ventral perigenual and subgenual anterior cinculate cortex (pgACC and sgACC, respectively). Also, the anterior portion of the insula has been named as a limbic hub, due to its functions on emotion.

Firstly, the amygdala and the hippocampus play a critical role, as core limbic areas, in guiding the non-homeostatic circuitry to promote food intake (Dallman, 2010). The hippocampus itself has been suggested as the area by which the rewarding role of comfort food is learned under repetitive stimulation (Hyman, Malenka & Nestler, 2006), and the amygdala,

as the main region implicated in overeating, food cravings and even in weight gain. Because of that, its relevance on obesity research has rocketed in the last decades (Petrovich & Gallagher, 2005; Sharma, Fernandes & Fulton, 2013; Sun et al., 2015). However, most of the studies have not differed between amygdala nuclei, leading to unclear results. Although classical animal studies have stressed the different contribution of amygdala nuclei on emotion and eating behavior, it was not until a few years ago when this division gained momentum in fMRI human studies. The main divisions of the amygdala, in relation to eating behavior, are the centromedial (CeA) and the basolateral (BLA) nuclei, both highly connected with the hypothalamus. The CeA is the major output nucleus of the amygdala, and modulates homeostatic functions such as the control of the stress response via its connections to the HPA axis (Ulrich-Lai & Herman, 2009), and the dysregulation of homeostatic eating (Holland & Nsu, 2014). Thus, this nucleus has more connections with autonomic areas of the hypothalamus and the brainstem, and also with mesolimbic areas, as the nucleus accumbens and the midbrain nuclei. On the other side, the BLA is the sensory input nucleus, and it is associated with emotional processing. This nucleus has connections with striatal and cortical areas, and sends the input information to the CeA, for it to promote a response.

Secondly, the other areas that make up the limbic system, together with the amygdala, are the responsible of capturing the hedonic and emotional properties of food, and giving the rewarding value to these stimuli. In a more schematic manner, if someone eats a supposedly rewarding chocolate bar, the insula is the first responsible of orchestrating the integration of the sensorial characteristics of this meal. Later, this information will finally influence behavior by means of the emotional and rewarding effects that this high palatable meal triggers in the OFC, amygdala, the nucleus accumbens (nACC) and the ventral pallidum (VP) (Berridge, Robinson & Aldridge, 2009; Kringelbach, 2004; 2005; Dallman, 2010). The most interesting point is that the hedonic value of this chocolate bar lies not in its characteristics (tastes delicious

or has a good smell as collected by the amygdala), but in the rewarding/emotional value our brain gives to it (the reward perception), the so-called food liking. Unfortunately, our reward perception is fast-shifting under certain emotional conditions or metabolic states (Dallman et al., 2003; Higgs et al., 2016). The enhanced rewarding perception resulting from this "food liking" process, will enhance the motivation to eat this food in the future (food wanting), guided by a reward-related learning and not by homeostatic needs. This learning could lead to neuroadaptations, not only in brain areas, but in the neurotransmitters acting there. One of the well-known neurotransmitter adaptations in obesity is the down-regulation of dopamine D2 receptors (Michaelides, Thanos, Volkow & Wang, 2012; Stice & Yokum, 2016) and consequently, a decreased rewarding value of food, and an increased consumption to compensate (Blum, Thanos & Gold, 2014).

Recently, one model has tried to explain overeating from this perspective of blunted reward, and has proposed obesity as an addictive problem. This model (Volkow et al., 2013) is built around the bunch of studies showing similarities within the neurobiological mechanisms underlying drug addiction and overeating. The main idea of this model is that the disruption of energy homeostasis affect the reward circuitry, and that overconsumption of high palatable food leads to specific neural changes in the mesolimbic system, and to a downregulation of D2 receptors that result in compulsive food intake (Volkow et al., 2012). Thus, eating may become a compulsive response to cope with negative emotions (Havermans, 2011). In these situations, the activity in the midbrain, the nucleus accumbens and the hypothalamus, mesolimbic areas, increase as well (Nicola, 2016). This "brain trinity" forms the **mesolimbic dopamine system** or, in this case, **the food wanting system**, which has a lot to say in the explanatory hypothesis of non-homeostatic eating (Berridge, Robinson & Aldridge, 2009). This network entirely regulates the incentive salience of food and thus, increases the wanting for eating. Besides, this dopaminergic system contains strong projections to the hypothalamus, which have been

implicated in greater food intake by the modulation of the metabolic state signals for hunger and satiety (Naleid, Grace, Cummings & Levine, 2005).

Furthermore, functional studies have shown how these non-homeostatic networks are highly activated in obese people in response not only to consumption of food, but also in the anticipation of it (Stice, Spoor, Bohon, Veldhuizen & Small, 2008; Stice, Spoor, Ng & Zald, 2009; Stoeckel et al., 2008; 2009). Further, some other studies showed that the co-activation of several limbic areas in the attentional bias toward food (Siep et al., 2008), and also associated to weight gain in the future (Yokum, Ng & Stice, 2012). This alterations have been also shown in children, showing that this is not a specific alteration in adulthood (Bruce et al., 2010).

Regarding functional connectivity studies, ICA analysis showed that obese individuals in comparison with their normal weight counterparts, present less activity in the posterior default network in response to rewarding stimuli (García-García et al., 2013) and higher activity in the ventral prefrontal areas (Kullmann et al., 2011; García-García et al., 2013). These alterations have been suggested to lead to top-down deficiencies driving overeating. Another studies, based on the seed-based connectivity, showed higher connecitivty between the amygdala and the insula (Lips et al., 2014), and dorsal striatum and somatosensory areas (Nummenmaa et al., 2012; Contreras-Rodríguez et al., 2017). In adolescents, a recent study has also shown different functional connectivity between obese and normal weight individuals. Adolescents with excess weight showed higher connectivity between the insula, the middle frontal gyrus and the dorsolateral prefrontal cortex (Moreno-López, Contreras-Rodriguez, Soriano-Mas, Stamatakis & Verdejo-García, 2017). In this study, the authors concluded that adolescents with excess weight could have alterations related to emotion, interoception and cognitive control, as suggested in adults. These results showing alterations in the cognitive control of behavior are particularly relevant in obesity.

Despite the critical role of the homeostatic and hedonic brain networks in eating behavior,

the "executive brain" also helps to regulate feeding (Figure 2). This **executive network** is formed by dorsolateral regions, which are responsible to cognitive and attentional control (Ochsnet & Gross, 2005). A recent model comparing obesity and substance addiction has offered promising data, which support prefrontal dysfunction in excess weight (Volkow, Wang, Tomasi & Baler, 2013; Maayan, Hoogendoorn, Sweat & Convit, 2011). According to this hypothesis, the functioning of the dorsolateral areas related to cognitive control would be dampened, while the ventromedial limbic areas of the prefrontal cortex would grow stronger. This problem leads to a lower top-down control over the hedonic network via the alterations of executive functioning. The main brain areas and networks implicated in executive functioning will be discussed in the next section.

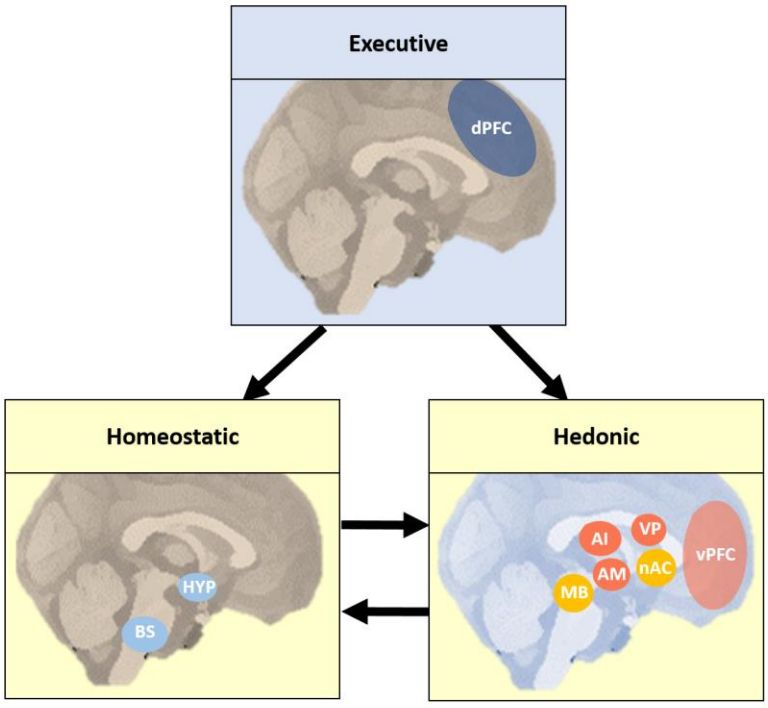

Figure 2. Simplistic model of the brain pathways regulating eating behavior. The homeostatic brain and the hedonic brain (comprised of limbic areas, pink, and specific mesolimbic areas, yellow) interact to regulate eating behavior. The adequate functioning of the executive brain help override/maintain eating under energy needs.

Abbreviations: dorsal prefrontal cortex (dlPFC); hypothalamus (HYP); brainstem (BS); anterior insula (AI); ventral palidum (VP); amygdala (AM); ventral prefrontal cortex (vPFC); nucleus accumbens (nAC); midbrain (MB).

In conclusion, high fat diets are capable to deregulate the HPA axis and drive hedonic eating, but this hedonic drives can be stimulated by other factors. Stress and executive alterations stand as the major factors leading to overeating and it is important to take them into account in obesity research. Despite these great advances in the knowledge of the "obese brain" in adults, less attention has been paid to adolescents. Thus, there is a lack of resting-state functional connectivity studies in this population, which could help to explain the brain organization in a central/important stage of maturation (Table 2). The present thesis aims to modestly fill that gap.

Table 2.
Summary of the previous studies exploring resting-state functional connectivity in adolescents with excess weight.

Study	Participants	Analysis	Results
Black et al., 2014	9 NW (mean age=12.3) 9 Obese (mean age=11.6)	Seed-based analysis (MFG)	**EW>NW** MFG-OFC/ACC
Krafft et al., 2014	22 EW (divided in 13 sedentary, Sed, and 9 exercise, ExcG)	Pre and post intervention ICA analysis (SN, DMN, CEN, MN)	**ExcG<Sed** DMN: PCC CEN: Cingulate extending to precuneus/culmen MN: Cuneus **ExcG>Sed:** MN: MFG
Moreno-López et al., 2016	55 NW (mean age=15.11) 60EW (mean age=14.67)	Seed-based analyses (Insula, MTC, dlPFC)	**EW>NW** Insula-cuneus MTC-OFC/IFG/MFG-Insula dlPFC-Occipital **EW<NW** Insula-dACC/SMA MTC-PCC/cuneus/precuneus
Sharkey et al., 2018	116 adolescents	Seed-based analyses (SN, STN, VTA, VS)	Striato-midbrain-limbic regions positively correlated with **BMI**

Abbreviations: NW, normal weight, EW, excess weight, MFG, middle frontal gyrus, OFC, orbitofrontal cortex, ACC, anterior cingulate cortex, SN, salience network, DMN, default mode network, CEN, central executive network, MN, motor network, PCC, posterior cingulate cortex, MTC, middle temporal cortex, dlPFC, dorsolateral prefrontal cortex, IFG, inferior frotal gyrus, SMA, supplementary motor area, dACC, dorsal ACC, SN, substantia nigra, STN, subthalamic nucleus, VTA, ventral tegmental area, VS, ventral striatum, BMI, body mass index.

1.3.Affective and executive alterations of homeostatic and non-homeostatic regions

Some of the predisposing factors explained above, as the worsened executive functions or the heightened stress, help maintain these long term disruptions of the homeostasis by increasing the consumption of high-fat food, and consequently hijack the homeostatic control of eating behavior. These adaptations produce a relative insensitivity to gut signals (hunger/satiety), and cede the drive of eating to hedonic, motivational or/and emotional states (Lutter & Nestler, 2009).

1.3.1. The role of stress

Stress and obesity share a neurobiological substrate due to its joint performance over unhealthy eating behavior. Indeed, stress promotes reward-dependent habits and this could be explained by the fact that high fat diets increase the sensitization of reward pathways to food stimuli (Sinha & Jastreboff, 2013). When chronic, stress is capable to enhance the incentive salience of food, thus, leading to the disruption of the HPA axis and the empowerment of non-homeostatic brain systems.

As in energy balance, the hypothalamus is the main regulator of the stress response. This area receives the information of the internal milieu (by the brainstem) and the external appetitive or aversive stimuli (by the amygdala). In consequence, two systems are activated in parallel by the hypothalamus: (i) the sympathetic nervous system, which is responsible of body response, and (ii) the adrenal-cortical system, which release the amount of cortisol needed to "survive". This co-activation is also known as the "fight or flight" response to environment (Figure 3).

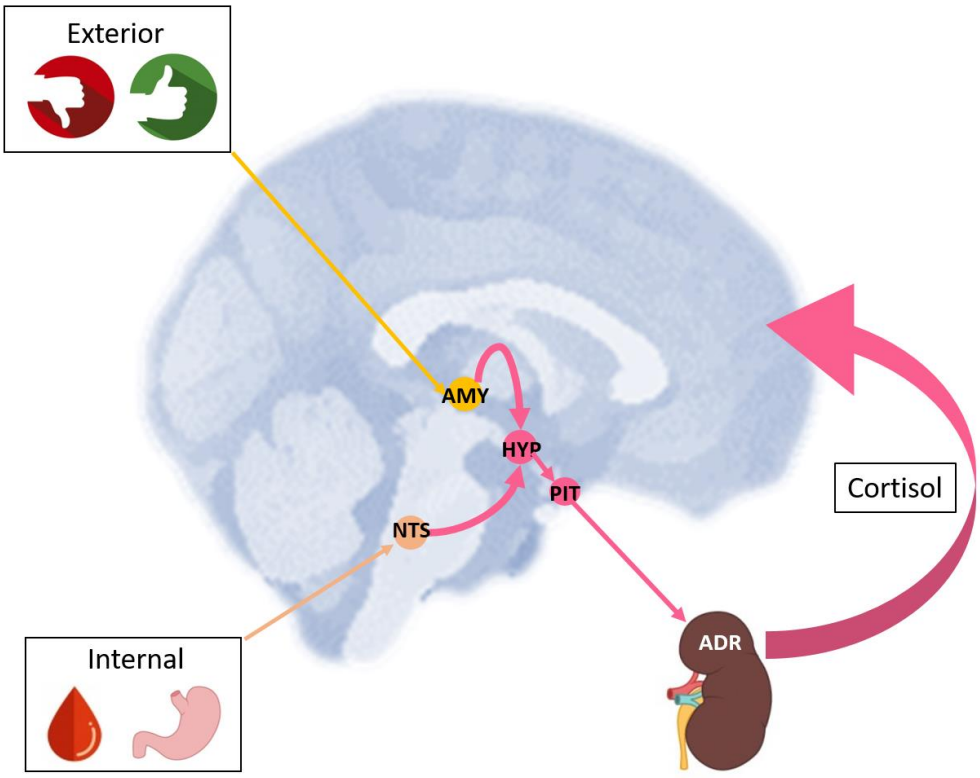

Figure 3. Simplistic graphic scheme showing the activation of the HPA. The hypothalamus (HYP) is the area where the appetitive/aversive external information (amygdala; AMY) and the signals of the internal states and gut hormones (brainstem; NTS) convey. The hypothalamus starts the stress response travelling to the pituitary (PIT) and finally arriving to the adrenal cortex (ADR), which is the responsible to release cortisol, and send it again to the brain.

To control this response, the limbic system works as a regulator of the HPA-axis function, via its connections with the hypothalamus (Herman et al., 2005). It is known that the amygdala acts like an excitatory hub, which activates the hypothalamus and, consequently, stimulates the release of cortisol (Tasker & Herman, 2011). Instead, the hippocampus and the prefrontal cortex are inhibitory areas that help to stop the stress response (Radley & Sawchenko, 2011). Thus, all these areas together, have an important role in the effects of an adequate cortisol release, in the behavioral response to stress, and also in the maintenance of homeostasis. However, under continuous stimulation, by chronic stress and/or high fat diets,

the regulating processes by which the limbic system acts over the HPA axis break. Under chronic stress, the inhibitory role of dorsal and ventral prefrontal areas, and hippocampus over the HPA axis partially "shuts-down", and both the regulation of behavioral and cognitive reappraisal are dampened (Jankord & Herman, 2008; Mcklveen et al., 2016). In contrast with these areas, the amygdala is thought to increase its size, and to raise its excitatory projections to the hypothalamus and to promote cortisol release when hyper-activated (McEwen, Nasca & Gray, 2016; Padival, Quinette & Rosenkranz, 2013; Rosenkranz, Venheim & Padival, 2010). These results are supported by several studies indicating a decrease of behavioral and emotional control as well as increased food wanting under stress (Lemmens et al., 2016; Sinha & Jastreboff, 2013). In excess weight, the malfunction of the executive brain and the hippocampus, and the hyper-function of the amygdala lead to detrimental decision-making and cognitive control. Consequently, the dysregulation of the amygdala-HPA pathway leads to emotional disruptions facing food, and to the promotion of stress by the stimulation of cortisol release (Roozendaal, McEwen & Chattarji, 2009).

In addition to the central limbic areas (amygdala and hippocampus), the **mesolimbic system** substantially participates in the homeostatic dysregulation under stress (Trainor, 2011). The mesolimbic regions, as a whole, increase their reactivity under stressful events leading to the override of homeostatic brain areas, as previously seen with high-fat diets.

On one side, the nucleus accumbens is the primary area that projects to the hypothalamus after receiving the information of other limbic/rewarding brain areas, stimulating the lateral area of hypothalamus and thus, enhancing the hedonic impact of food (Castro, Cole & Berridge, 2015). Also, several areas on the midbrain, such as the VTA or the substantia nigra, play important roles in stress-related pathologies, including addictive behaviors (Polter & Kauer, 2014), but they are also brain hubs of reward, highly connected with nucleus accumbens and hypothalamus (Castro, Cole & Berridge, 2015). In these regions,

a stressful situation would increase the mechanisms of incentive salience of food, leading to overeating (Berridge, 2009). Probably this "food wanting" issue is one of the biggest problems in people with excess weight suffering from chronic stress. Growing evidence indicates that neurobiological adaptations in the mesolimbic system related to non-homeostatic eating, could be modulated by the increased cortisol levels, by increasing the salience of food in obese individuals. The higher reactivity of these areas under stress, the greater wanting for some foods. This provokes an enhanced rewarding value of food in anticipation of it, and also promote this rewarding food intake as coping strategies to face stress, leading to the so-called non-homeostatic eating behavior or comfort food intake (Dallman et al., 2003; Lemmens, Rutters, Born, Westerterp-Platenga, 2011; Sinha & Jastreboff, 2013).

1.3.2. Executive alterations: the role of decision-making

Several alterations have been related to excess weight in adults and adolescents. The excess weight, indeed, is an important stressor, which compromise the executive function (Reinert, Po´e & Barkin, 2013). Besides, in comparison with other eating disorders, those related to overeating showed an especial vulnerability in shifting and decision-making (Aloi et al., 2015). Some studies have related the preferential alterations in executive function in obesity (shifting, and decision-making) with long-term maintaining factors such as higher vulnerability to high-fat food, and also long-term weight gain (Nederkoorn, Houben, Hofmann, Roefs & Jansen, 2010). It is important to note that decision-making would be a complex process that would need from the coordination of the other functions of shifting and inhibition. Likewise, higher scores on test of executive functions associates to better performance in decision-making (Gleichgerrcht, Ibañez, Roca, Torralva & Manes, 2010).

The traditional view in cognition, "places" the executive functions on the prefrontal cortex. Nowadays, this perspective has extended and well-known associations between many fronto-striatal regions, plus the correct functioning of some hormones (as insulin) regulating cognition, should act effectively for an adequate executive functioning (Miller, Jong & Lumeng, 2015; Morris et al., 2016).

Regarding brain areas, some of the frontal areas responsible of a good functioning of these executive factors include the dorsolateral PFC (dPFC), the dorsal anterior cingulate cortex (dACC), the orbital frontal cortex (OFC) and the medial prefrontal cortex (mPFC) (Miller et al., 2015), and would be included in the "reflective system". Indeed, underlying a good decision-making process, several dorsolateral areas of the prefrontal cortex, responsible to monitoring and shifting, together with the ACC, conflict resolution during decision-making, and posterior parietal cortices have been found to be activated (Labudda et al., 2008; Schiebener et al., 2014). On the other side, brain areas underlying impulsive and automatic behaviors such as the amygdala and the ventral striatum act as "impulsive areas", which are able to override the adequate cognitive and attentional control (He et al., 2014). An imbalance between the activity of reflective and impulsive areas lead to poorer executive function and indirectly, to numerous risky-behaviors and addictive problems (Van Leijenhorst et al., 2010; Wiers et al., 2013). Recently, new evidence is supporting the existence of another "system" related to neuro-cognition. This would be the "interoceptive" system, mainly comprised of the insular cortex and the posterior cingulate cortex, and involved in the translation of interoceptive signals into subjective experiences of desire or urge.

However, these "systems" are commonly studied across larger brain networks underlying cognition (Bressler & Vinod, 2010). In this line, several authors have recently proposed the interaction between three brain networks in the adequate executive functioning (Bressler & Menon, 2010; Goulden et al., 2014; Jilka et al., 2014; Putcha et al., 2016; Zhou et al., 2018).

Two of these networks, called salience network and central executive network, respond to executive tasks and mostly engage the dorsal prefrontal areas related to cognitive control ("the reflective system"). However the salience network also comprises subcortical areas related to motivation (striatum, "the impulsive system") and interoception (insula, "the interoceptive system"). The other network, the default mode network, comprises medial prefrontal areas and the posterior cingulate, and would be active during self-referential mental activity, unlike CEN that activates under a cognitive demand (Bressler & Menon, 2010). The SN, thanks to its sensory and limbic inputs, would be the network switching the attention between endogenous (DMN) or exogenous (CEN) processes.

For these reasons, a lot of attention is currently being applied to the SN, due to its relevance on the control of cognition and the resistance to tempting stimuli (Steimke et al., 2017), and to its dysfunction in many psychiatric conditions related to self-regulation and executive functions (Uddin, 2015), including obesity (García-García et al., 2012).

Putting all this information together, the neuro-cognitive triadic model, assuming three different systems regarding reflective, interoceptive and impulsive control of behavior, underlie over several large-scale brain networks including CEN, DMN and the SN. In this line, these three networks have become crucial candidates in the study of brain differences on executive functioning in adolescents and adults (Bressler & Menon, 2010; Goulden et al., 2014; Steimke et al., 2017; Turel & Bechara, 2016; Zhou et al., 2017).

To sum up this chapter, homeostatic eating is constantly challenged by hedonic and affective drives (stress), and also by cognitive abilities. Brain networks regulating homeostatic and non-homeostatic eating, partially overlap with those areas controlling affective and cognitive responses. These will lead to higher susceptibility to food stimuli under dysregulated conditions.

Diet-induced excess weight would lead to many alterations in several domains. On one side, acute and chronic stress could dampen emotional control of behavior, diminishing cognitive reappraisal and forcing the brain to display learned and automatic strategies to cope with that negative affect, enhancing the "impulsive system". These disruptions in eating behavior could be emotionally driven by the neuroadaptations of all these systems described above.

One of the important factors that also influence maladaptive eating behaviors would be the inability of making advantageous decision (as a marker of executive function), boosted by other functions such as mental rigidity or poor inhibitory control. These abilities are crucial for a healthier eating (He et al., 2014), and their altered associations with brain disruptions may lead to the development and maintenance of excess weight problems.

In summing, chronic stress could dampen emotional and cognitive control, diminishing cognitive reappraisal and forcing the brain to display learned and automatic strategies to cope with that negative affect. These disruptions in eating behavior could be emotion-driven by the neuroadaptations of all these systems described above. However, we should be cautious about the contribution of stress in maladaptive eating behavior, as many factors may influence the eating behavior in different individuals. Despite, this thesis is focused on stress and neuroadaptations over eating behavior, taking into account that adolescence is a stage of emotional maturation characterized by enhanced stress reactivity and lower capabilities of stress management. These factors turn stress in a relevant factor to explore in adolescents with excess weight.

II. RATIONALE AND AIMS

Chapter 3: Rationale and Aims

1. Rationale

The obesogenic environment is a recent concept proposed to explain how the great availability and continuous exposition to food have contributed to the increasing prevalence of the excess weight problems worldwide. Since this perspective, eating behavior is no longer guided by homeostatic needs of hunger and satiety, and several food-related cues could "switch" the drive to eat in vulnerable individuals such as adolescents.

The brain is one of the main organs involved in the control of food intake and two interconnected and overlapped brain systems are responsible of this regulation (Rossi & Stuber, 2017). One would act as "the homeostatic brain" driving feeding according to energetic bodily needs and the signals of hunger and satiety, while "the hedonic brain" would promote feeding under non-homeostatic conditions, namely, guided by external cues or emotional disruptions like stress (Lutter and Nestler, 2009). An alteration in the link between these two brain networks or/and the prevailing function of the "hedonic brain" promotes weight gain and increases the difficulties to weight loss (Sun et al., 2015).

Neuroimaging studies have been very useful to determine how the brain works under different conditions relevant in the regulation of eating behaviors. In adults, functional studies have demonstrated that the "obese brain" is related to altered connectivity patterns in the hypothalamic homeostatic center (Contreras-Rodriguez et al., 2017; Kullmann et al., 2014), as well as in hedonic hubs such as the amygdala or the striatum (Nummenmaa et al., 2012; Contreras-Rodríguez et al., 2017). Indeed, excess weight conditions have been associated with the dysfunction of large-scale brain networks, such as the salience network (García-García et al., 2013), the central executive network (Gupta et a, 2015), or the default mode network (Kullman et al., 2012), comprising several brain regions associated with the detection and

filtering of salient stimuli that would then be important in driving behaviors. It is nowadays clear how connectivity alterations between those brain elements may override homeostatic eating under certain emotional or rewarding challenges in adults with excess weight.

Stress per se is capable of changing eating behavior in most individuals. There is no consensus over whether excess weight people increase or decrease the general calorie intake, but most studies have found that people with excess weight present a stress-related increase in the consumption of high palatable food (rich in sugar, fat and/or salt). This specific increase in high-dense food, also known as "comfort food", is believed to be a coping strategy for soothing stress, which promotes emotional rather than homeostatic based eating behaviors. At the brain level, preliminary studies have shown that overeating share common neurobiological substrates with stress, which would interact in the development or maintenance of excess weight problems (Dallman, 2010), even since childhood (Mietus-Snyder & Lustig, 2008). Dallman (2010) proposed a structured model in which some brain areas, conforming the so-called "emotional brain system", modulate eating behavior through effects on the homeostatic and hedonic brain pathways. This study reflected the importance of several areas engaged in eating behavior such as the insula, the anterior cingulate cortex, the amygdala, the striatum, the hypothalamus and the mesolimbic dopaminergic system.

Until now, few studies have focused on the role of brain connectivity dysregulations in adolescents with excess weight problems, contrary to obese adults' research. Adolescence is a transitional stage of physical and psychological development that is generally characterized by the presence of several factors associated with a higher likelihood to acquire maladaptive eating behaviors. The physiological dysregulations, as high levels of insulin and LDL cholesterol or high accumulation of subcutaneous adipose tissue (McMorrow, Connaughton, Lithander & Roche, 2014), and psychological issues, as enhanced stress reactivity (Verdejo-García et al., 2015) or cognitive alterations (Yau, Kang, Javier & Convit, 2014) fuel excess weight problems

in this population, which may remain throughout adulthood (Wang et al., 2014). The use of "comfort food" behaviors to cope with the enhanced stress sensitivity in adolescents (Verdejo-García et al., 2015) may hinder the development of more adaptive coping strategies to manage stress, while perpetuating a higher presence of impulsive traits at a crucial moment when feeding gradually becomes independent from family diet. Mietus-Snyder and Lustig (2008) had suggested that the midbrain, the hypothalamus and the amygdala, known as the "limbic triangle", may promote food-seeking behaviors in children with obesity under stressful situations. This thesis wants to highlight the importance of deepening in the neural substrates regarding eating behavior and stress in adolescence.

2. Aims

2.1.General Aims

The general aim of the present thesis is to characterize, in adolescents with excess weight, the functional connectivity of the main brain areas and networks that have been associated to maladaptive eating behavior in adults with excess weight and, once determined, to investigate its significance in relation to stress and executive functions known to influence eating behaviors in adolescents with excess weight.

2.2.Specific aims and hypotheses

Study 1. **The homeostatic brain and stress.** The following **aims** were set out:

- To compare the functional connectivity of different nuclei of the hypothalamus (Lateral -LH- and Medial -MH-) between adolescents with excess and normal weight
- To explore whether such functional connectivity is associated with the cortisol released during a social stressful task and with the presence of emotional eating behaviors.

The following **hypotheses** were raised:

- Adolescents with excess weight compared to their normal weight counterparts will show higher functional connectivity between the LH/MH and regions of the "hedonic brain", especially limbic and reward systems, and lower connectivity between the LH/MH and areas related to control or awareness of hunger signals.
- Higher functional connectivity, mainly between the LH center and the key regions within the "emotional network system" (i.e., nucleus accumbens, amygdala and midbrain; Dallman, 2010) will be associated with both an increased stress response and emotional eating in the adolescents with excess weight.

This study is now accepted in the Journal of the American Academy for Child and Adolescent Psychiatry (Martín-Pérez, Cristina; Contreras-Rodríguez, Oren; Vilar-López, Raquel; Verdejo-García, Antonio, in press, 2018) and it is found in the Chapter 4.

Study 2. The hedonic brain and stress. The following **aims** were set out:

- To compare the functional connectivity of central and basolateral nuclei of the amygdala (BLA/CeA) between adolescents with excess and normal weight.
- To explore whether such functional connectivity is associated with weight change and cortisol release over a three month´s diet and exercise intervention in adolescents with excess weight.

The following **hypotheses** were raised:

- Adolescents with excess weight compared to those with normal weight will show higher functional connectivity between CeA and BLA seeds with brain areas related to emotion, motivation and reward processing, and lower connectivity with areas related to the consciousness of the internal milieu.

- Lower success in the three-month intervention (less weight loss) would be associated to higher functional connectivity mainly between the CeA center with the brain areas of the limbic triangle -hypothalamus, nucleus accumbens and midbrain-; Mietus-Snyder and Lustig, 2008) in the adolescents with excess weight.
- Higher connectivity in the above brain network will be related to accumulated cortisol over the three months´ intervention in the adolescents with excess weight.

This study has been submitted to International Journal of Obesity (Martín-Pérez, Cristina; Contreras-Rodríguez, Oren; Verdejo-Román, Juan; Vilar-López, Raquel; Verdejo-García, Antonio) and it is found in the Chapter 5.

Study 3. Brain networks, metabolism and executive function. The following **aims** were set out:

- To explore the insulin and fat-related activity of the salience network (SN) and the default mode network (DMN) in a group of adolescents with normal and excess weight.
- To assess the relationship between the altered areas within the SN and DMN functional connectivity with executive functioning in important areas to the control of food intake: shifting and decision-making.

The following **hypotheses** were raised:

- As high levels of insulin and body fat, we expected to find higher activity in the "impulsive" (ventral striatum and amygdala), and in the "interoceptive" (insula and posterior cingulate cortex) areas, and lower activity of the reflective prefrontal areas related to cognitive and attentional control.

- In adolescents with excess weight, higher activity of the impulsive and interoceptive, and lower activity of the reflective areas will be related with a poorer performance in the executive function measured in the study: shifting and decision-making.

This study has been submitted to Neuroimage: Clinical (Martín-Pérez, Cristina; Verdejo-Román, Juan; Contreras-Rodríguez, Oren; Navas, Juan F.; Vilar-López, Raquel; Verdejo-García, Antonio) and it is found in the Chapter 6.

III. COMPILATION OF WORKS

Chapter 4. The role of stress in excess weight: overriding homeostatic brain

The content of this chapter is an adaptation of the accepted manuscript in the Journal of the American Academy of Child and Adolescents Psychiatry as: Martín-Pérez, C., Contreras-Rodríguez, O., Vilar-López, R., and Verdejo-García, A. (2018). Hypothalamic networks in adolescents with excess weight: stress-related connectivity and associations with emotional eating. *Journal of the American Academy of Child and Adolescent Psychiatry*, (in press). IF=6.250; Q1 y D1 (2/124 Pediatrics; 12/124 Psychiatry).

Introduction

Over 23% of children and adolescents in developed countries are overweight or obese (Ng et al., 2014). In adolescents with excess weight, alterations in homeostatic regulation interact with higher emotional reactivity and stress sensitivity (Pervanidou & Chrousos, 2011). The hypothalamic-pituitary-adrenal axis (HPA), which regulates energy balance by increasing the motivation to eat in response to a depletion of energy stores (Lutter & Nestler, 2009), is also critically involved in stress response (Sominsky & Spencer, 2014). An important manifestation of the impact of stress on eating behavior is emotional eating, which is carried out to cope with negative affect. Stress can indeed increase food intake, specifically, a consumption of high calorie foods (Zellner et al., 2006). Adolescents with excess weight are particularly sensitive to stress (Verdejo-Garcia et al., 2015), and common stressors of adolescence that are more prevalent in those with excess weight (i.e., peer bullying, social exclusion) can sensitize emotional reactivity and promote overeating and obesity.

The hypothalamus constitutes a major integration area for studying stress and food intake due to its central role in the HPA axis (Tasker, 2006). Early studies of the hypothalamus involved the lateral hypothalamus (LH) in increasing feeding (Hoebel & Teitelbaum, 1962) and the medial hypothalamus (MH) in the inhibition of eating behaviors (Leibowitz, Weiss, & Suh, 1990). This knowledge is mainly derived from lesioning and excitatory preclinical experiments (Hoebel & Teitelbaum, 1962; Teitelbaum & Epstein, 1962), and the study of the influence that hunger and satiety-related peripheral signals (i.e., leptin, insulin, glucose) have on these hypothalamic nuclei (Volkow, Wang, & Baler, 2011). However, contemporary research on the neural substrates of feeding has highlighted the importance of hypothalamic connections with other neural regions that code the reward and affective properties of food (i.e. striatum, amygdala, hippocampus) and integrate internal and external sensory stimuli (i.e.

posterior insula and somatosensory cortices; Kringelbach, 2004). Affective and visceral information converge in the anterior cingulate cortex, which is involved in goal-directed attention and action selection (Val-Laillet et al., 2015). In this line, a recent study (Kullmann et al., 2014) showed a differential whole-brain map of functional connections for the LH and MH nuclei in adults with normal weight. Interestingly, this previous research and a recent study from our group (Contreras-Rodriguez et al., 2017) have shown that adults with obesity, versus lean adults, have differences in the functional connectivity of the MH and LH circuits. However, it is unknown if these findings are also present in adolescents with excess weight.

An influential theory has proposed that the "emotional nervous system", that overlaps with the neural networks involved in feeding behavior, is importantly implicated in the control of feeding under stress and other emotional threats (Dallman, 2010). This network comprises the hypothalamus, the midbrain, the striatum, the amygdala, and the insula (Dallman, 2010). According to this theory, stressful situations would increase the functioning of the amygdala-hippocampal complex -where emotions and "food-memories" arise-, and the mesostriatal network -involved in motivational and rewarding needs-, therefore overriding areas of homeostatic food intake and mindful eating. Existing research suggests that the key regions of this "emotional nervous system" are altered in obesity, whereby sensitization in this hypothalamic-mesostriatal-limbic system can enhance stress, the motivation to eat, and emotional eating behaviors (Dallman, 2010). The LH has been suggested to play a predominant role in the regulation of both feeding and stress, being particularly relevant in the preference for palatable food-cues (Harris, Wimmer, & Aston-Jones, 2005). Moreover, stressed humans show elevated ghrelin hormone levels (Lutter, et al., 2008), and the LH exclusively expresses the neuropeptide orexin, whose transmission to mesostriatal-limbic system has been associated with the enhancement of food reward during stress (Giardino & de Lecea, 2014).

This study aims to compare whole-brain LH and MH resting-state functional connectivity in adolescents with excess weight versus normal weight. A second aim is to examine the relationship between these hypothalamic circuits and stress response measured as the cortisol response to a stress challenge. A third aim is to establish if the hypothalamic circuits related to stress are associated with emotional eating. We hypothesized that EW compared to NW groups will show higher functional connectivity between the LH/MH and regions of the limbic and reward systems, and lower connectivity between the LH/MH and areas related to the inhibition of the signals of hunger or to consciousness of the internal millieu (Contreras-Rodríguez, Vilar-López, et al., 2017; Dallman, 2010; Stephanie Kullmann et al., 2014). In addition, we hypothesized that a higher functional connectivity [mainly in the excitatory LH center] with the key regions within the emotional network system (i.e., nucleus accumbens, amygdala and midbrain; Dallman, 2010; Stuber & Wise, 2016) will be associated with both an increased stress response and emotional eating in the EW-group (Dallman, 2010).

Method

Participants

Fifty-six adolescents with excess weight (EW) and 52 with normal weight (NW) were recruited via local press and social media. The main inclusion criteria were to be between 10 and 19 years old, according to the World Health Organization´s (WHO, 2011) definition of adolescence, and to have an age and sex specific Body Mass Index (BMI) percentile between 5^{th} and 85^{th} for NW and at or above 85^{th} for EW (Ogden & Flegal, 2010) (excluding underweight participants or those with morbid obesity). Exclusion criteria were: (i) self-reported history of traumatic brain injury, metabolic or systemic diseases impacting the central nervous system, (ii) clinical disorders (measured with Millon Adolescent Clinical Inventory)

or any eating disorder (assessed by the Eating Disorder Inventory) and (iii) self-reported use of any medication. The Human Research Ethics Committee of the University of Granada approved the study, and all participants provided an informed consent.

Adolescents completed two sessions separated by a week. In the first session, participants underwent a functional Magnetic Resonance Imaging (fMRI) scan. Four subjects (3.7% of the initial sample) were excluded from the imaging analysis because of motion during the imaging scan (see details below in the functional connectivity analyses section). In the second session, a subset of 54 participants (50% of the initial sample; 32 NW and 22 EW) performed a virtual reality version of the Trier Social Stress task (TSST), where cortisol levels were assessed, and they completed the Dutch Eating Behavior Questionnaire (DEBQ) to measure emotional-eating behavior.

Measures

Imaging data acquisition. All participants were scanned at the same time of the day, between 4 and 6 p.m., after the main meal of the day (between 2 and 3 pm). They performed a 6-min resting-state scan and were instructed to lie still with their eyes closed. We used a 3.0 Tesla clinical MRI scanner, equipped with an eight-channel phased-array head coil (Intera Achieva Philips Medical Systems, Eindhoven, The Netherlands). A T2*-weighted echo-planar imaging (EPI) was obtained (repetition time (TR)=2000ms, echo time (TE)=35ms, field of view (FOV)=230 x 230mm, 96x96 pixel matrix; flip angle=90º, 21 4-mm axial slices, 1-mm gap, 180 whole-brain volumes). The sequence included four initial dummy volumes to allow the magnetization to reach equilibrium. We also acquired a high-resolution T1-weighted anatomical image for each subject with 160 slices (TR= 8.3 ms; TE= 3.8 ms; flip angle = 8°; FOV= 240 x 240 mm^2; in-plane resolution= 0.94x0.94x1; slice thickness= 1 mm) to discard gross radiological alterations and for preprocessing purposes.

Trier Stress Social Task (TSST). The virtual reality TSST was used to induce stress in the participants. This task asked participants to deliver a 5-minutes speech and to perform an arithmetic task in front of an evaluating committee which was presented as a virtual audience on a 3D monitor. The speech should be about their qualities and defects. The participant must begin their speech when the curtain lifts and the virtual audience appears on the monitor. After two minutes, a change of attitude occurs in the audience, turning from an "interested audience" into a "restless audience". This will continue until the end of the speech, regardless of the performance of the participant. Once the speech is over, the arithmetic task starts, where the participant must serially subtract the number 13 from 1022 as quickly as possible during five minutes. In case of error, they will have to start again. The virtual version of the TSST has demonstrated to be useful to explore psycho-physiological stress in several studies (Jönsson et al., 2010; Kotlyar et al., 2008; Ruiz et al., 2010).

Cortisol measurements. For the salivary sampling, we used Salivette Cortisol (Sarstedt, Numbrecht, Germany), consisting of a small piece of cotton, which participants were told to chew during 60 seconds and two small tubes, where cotton were inserted. Saliva samples were stored at -20°C until required for assay. The samples were analyzed at the University Hospital of Granada by the electrochemiluminescence immunoassay (ECLIA) method, to be used in automatic analyzers Roche Elecsys 1010/2010 and the Elecsys MODULAR ANALYTICS E170 module.

Salivary cortisol levels were collected four times: before the onset of the TSST (T1), immediately after the TSST (T2) and T3 and T4 were measured 10 and 20 minutes after TSST termination. In this study, we used the area under the curve with respect to the ground (CortisolAUCg). CortisolAUCg, which is the estimation of one value comprising every measure of cortisol from zero, allows to transform a multivariate data into a univariate space, more convenient for SPM analysis. This variable was calculated with these four cortisol

measures above (Pruessner, Kirschbaum, Meinlschmid, & Hellhammer, 2003). Greater values reflect greater cortisol levels. This is a standard outcome measure used in several studies as an index of stress response (Dierolf et al., 2016; Hek et al., 2013). The physiological values of cortisol have been published, in a greater sample, elsewhere6 to demonstrate differences in cortisol levels between adolescents with excess weight and normal weight, and its relation to their neuropsychological performance. However, we use a different measure (CortisolAUCg), rather than the raw values of cortisol. Besides, this previous paper did not include any fMRI measure to explain the brain differences regarding stress in this population.

Eating Behavior. The Dutch eating behavior 33-items questionnaire (DEBQ; van Strien, Frijters, Bergers, & Defares, 1986) was used to measure three subscales: external (10 items), restrained (10 items) and emotional (13 items) eating behaviors. In alignment with our theoretical assumptions (Dallman, 2010), we used emotional eating. Higher scores represent greater emotional eating.

Subjective measures of hunger. We collected the ratings of hunger of those participants who underwent the TSST task both before this stress-inducing task (pre-TSST), and before the imaging session at the day of the scan (pre-scan). This was done by using a visual analogue scale (VAS) ranging from 0= 'not at all hungry' to 10 = 'very hungry'. The pre-TSST and the pre-scan ratings of hunger differed between-groups (see Table 1).

All behavioral data followed normal distribution as assessed with Kolmogorov-Smirnov tests (all $p>0.05$).

Analyses

Preprocessing and Analyses of Imaging data. The functional imaging data were processed and analyzed using MATLAB version R2008b (The MathWorks Inc, Natick, Mass) and Statistical Parametric Software (SPM12; The Welcome Department of Imaging

Neuroscience, London). Preprocessing steps involved motion correction, spatial normalization and smoothing using a Gaussian filter (FWHM 6 mm). The realigned functional sequences were coregistered to each participant's anatomical scan, which had been previously coregistered and normalized to the SPM-T1 template. Normalization parameters were then applied to the coregistered functional images, which were then resliced to a 2mm isotropic resolution in Montreal Neurological Institute (MNI) space. All images were inspected for potential acquisition and normalization artifacts. Additionally, we compared both study groups for potential differences in movement and found no significant differences [Mean Total (MT); (Standard Deviation; SD), NW= 0.038(0.026), EW= 0.042(0.029), p = 0.326; MT Translation (SD), NW= 0.042(0.034), EW= 0.046(0.030), p=0.499; MT Rotation (SD), NW= 0.033(0.023), EW= 0.039(0.031), p=0.233].

Hypothalamic seed-based functional connectivity analyses. Medial and lateral hypothalamic subregions were distinguished per hemisphere. Following prior work(Baroncini et al., 2012; Kullmann et al., 2014), respective seeds of interest were placed in the lateral (LH) (x= $\pm$6, y=-10, z=-10) and the medial hypothalamus (MH) (x= $\pm$4, y=-2, z=-12) using 2-mm-radius spheres. As in these previous studies, the MH included the arcuate nucleus, ventromedial and parts of the dorsomedial hypothalamus. The central voxel of the LH seed was in the most posterior part of this region to minimize overlap with the MH and obtain maximally specific functional connectivity maps. Importantly, these seeds were spatially separated by more than 6mm (>1 FWHM).

First-level t-test maps were estimated for each of LH and MH seeds by including its mean activity time-courses (extracted using marsbar toolbox; Brett et al., 2002) together with nuisance signals as predictors of interest and no interest in whole-brain SPM12 linear regression analyses. Nuisance signals included six head-motion parameters (3 translations and 3 rotations), the time-courses representing mean signal fluctuations in white matter,

cerebrospinal fluid, and the entire brain. Furthermore, to correct for subtle in-scanner movements from volume-to-volume, we identified the outliers scans present in the realigned functional imaging data using the CONN toolbox (Whitfield-Gabrieli & Nieto-Castanon, 2012). We excluded 1 adolescent with NW and 3 with EW that had <4 minutes of data (Satterthwaite et al., 2013). For the remaining sample, there were no significant differences in the percentage of outlier scans (mean 6.42% for NW, mean 5.39% for EW, t=0.643, p=0.522). For each participant, the actual removal of outliers scans (Power, Barnes, Snyder, Schlaggar & Petersen, 2012) was done by entering the subject-specific variables identifying the outliers scans (i.e., one regressor per outlier) in the first-level models as covariates of no interest. These outlier scans were removed from these and the subsequent analyses. Contrast images were generated for each subject by estimating the regression coefficient between all brain voxels and each seed's time series. Then they were included in separate second-level two-sample models to assess for between-group effects together with sex, age, and a variable containing the subject-specific number of outlier volumes, to control for the subject loss of temporal degrees of freedom.

Stress response analyses.

Behavioral. Repeated measures analyses were conducted in SPSS to assess Group x Time interaction on cortisol levels. To do that, in the analysis we entered the four samples across time of cortisol (T1 to T4) as different measures of the factors and group as within-group effect.

Neuroimaging. To test brain group-interactions in the association with stress response, the first-level contrast images representing the bilateral connectivity for each of the MH and LH seeds were entered in separate second-level two-sample models using the transformed into univariate variable "CortisolAUCg" (after regressing out the pre-TSST ratings of hunger) as a

covariate of interest in SPM. Sex, age, the variable containing the subject-specific number of outlier volumes, and the pre-scan rating of hunger were also included in the model as covariates of no interest.

Imaging thresholding criteria. Minimum threshold extents for the imaging analyses were calculated for all statistical comparisons by 1000 Monte Carlo simulations using the cluster-extent based AlphaSim thresholding approach (Song et al., 2011) as implemented in the SPM RESTplusV1.2 toolbox. For the within-group LH and MH functional connectivity maps, input parameters included an individual voxel threshold probability of 0.001, a cluster connection radius of 5 mm, and the respective actual smoothness of imaging data after model estimation, incorporating a whole-brain image mask volume (224406 voxels). The minimum cluster size extent (CS) was determined to be 1016 mm^3 for LH seed (127 voxels), and 976 mm^3 for MH seed (122 voxels). For the between-group effects in the functional connectivity of the LH and MH seeds, the required cluster extent was calculated using the same input parameters specified above, but entering as masks the joined positive and negative within-group maps of the functional connectivity of the adolescents with normal and excess weight for each of the seeds (38058 voxels for the LH seed, and 16001 voxels for the MH seed). The minimum cluster size was 456 mm^3 (57 voxels) for LH seed, and 288 mm^3 (36 voxels) for MH seed.

In the analyses testing for group-interactions in the association with stress response, we applied masks focused on our target subcortical regions: the nucleus accumbens, the amygdala, and the midbrain (Dallman, 2010; Sharma, Fernandes, & Fulton, 2013; see figure 1). In all cases, statistical significance was set at $p<0.05$, Family-Wise Error (FWE) corrected for multiple comparisons across all in-mask voxels (i.e., using small-volume correction procedures).

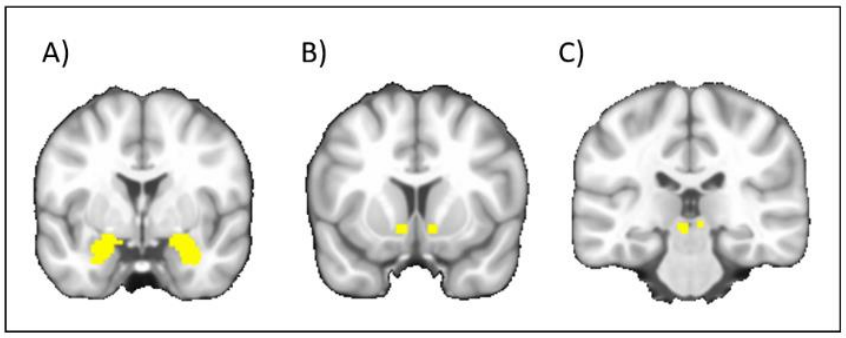

Figure 1. Bilateral masks used in small-volume correction procedures represented on anatomical images.

Note: A) Amygdala mask created using the Wake Forest University (WFU) toolbox (Maldjian, Laurienti, Kraft, & Burdette, 2003) (468 voxels). B) Nucleus accumbens 3-mm spherical mask centered in MNI coordinates, x=±9, y=9, z=-8 from Di Martino et al. 2008 (81 voxels). C) Midbrain 3-mm spherical mask centered in MNI coordinates, x=-4, y=-28, z=-8 for the left side and x=7, y=-28, z=-5 for the right side from Krebs et al., 2011(Krebs, Heipertz, Schuetze, & Duzel, 2011) (81 voxels). Spherical masks were created using Marsbar toolbox (Brett, Anton, Valabregue, & Poline, 2002b). The right hemisphere corresponds to the right side of coronal views.

Associations with emotional eating behavior. A two-tailed Pearson correlation analysis in SPSS was conducted to test for associations between the stress associated hypothalamic networks (LH/MH seeds) and emotional eating behavior. For that, we extracted the signal from the peak coordinate of the brain regions showing significant group-interactions in the association between hypothalamic networks and stress response. These analyses were carried out separately, due to our interest in the association within each of the participants' groups and controlled by the hunger pre-TSST. Correlations were considered significant at a threshold of $p<0.05$.

Results

Stress response and association with behavioral eating scores

Repeated measures analysis showed a significant change in the mean stress response along the TSST task [$F_{(3, 153)}=11.04$; $p<0.001$], as well as a significant Group x $Time_{(T1-T4)}$ interaction on

cortisol levels [$F_{(3, 153)}$=7.91; p<0.001], with greater stress response in EW-group. Conversely, the variable CortisolAUCg, used for the fMRI analyses, did not differ significantly between groups (p=0.066; Table 1), although the *d* of Cohen showed a medium effect size (*d*=0.53). The study groups showed similar emotional eating scores (p>0.05; Table 1).

Table 1

Demographics and clinical characteristics of the study groups

Whole Sample	**Normal weight (N=51)**	**Excess weight (N=53)**		
	Mean (SD)	Mean (SD)	Test statistics[a]	*p*
Age	15.29 (1.75)	14.64 (1.78)	1.888	0.062
BMI percentile	52.35 (24.35)	93.98 (3.98)	-12.053	0.000
Fat (kg)	13.13 (6.96)	32.17 (8.46)	-12.550	0.000
Sex (females)	31 (60.8%)	37 (69.8%)	0.936	0.333
TSST Sub-sample	**(n= 32)**	**(n= 22)**		
Age	15.75 (1.70)	15.27 (2.03)	-0.906	0.370
BMI percentile	51.28 (22.12)	95.09 (3.02)	-11.054	0.000
Fat (kg)	10.40 (3.98)	28.17 (8.11)	9.515	0.000
Sex (females)	19 (59.4%)	14 (63.6%)	0.100	0.752
CortisolAUCg	263.14 (117.7)	326.86 (122.7)	1.906	0.066
Emotional Eating [b]	24.03 (8.95)	22.23 (8.97)	-0.727	0.471
Hunger pre Scan	2.71 (2.06)	1.21 (1.57)	-3.148	0.003
Hunger pre TSST	1.82 (1.97)	0.92 (1.18)	-2.088	0.042

Note: [a]Independent samples t-tests for between-groups differences in all cases, except for sex where chi-square tests were employed. [b]Assessed by the Dutch Eating Behavior Questionnaire (DEBQ). *Abbreviations*: BMI, Body Mass Index; CortisolAUCg, Area under the curve (ground); TSST, Trier Stress Social Task.

Lateral and Medial Hypothalamic functional connectivity

The LH maps showed higher positive connectivity with and lateral frontal cortices (that were negatively connected with the MH seed), and the striatum. The MH maps showed higher positive connectivity with sensorimotor cortices and with a cluster comprising the nucleus accumbens and the bed nucleus of the stria terminalis at the subcortical level (Figure 2).

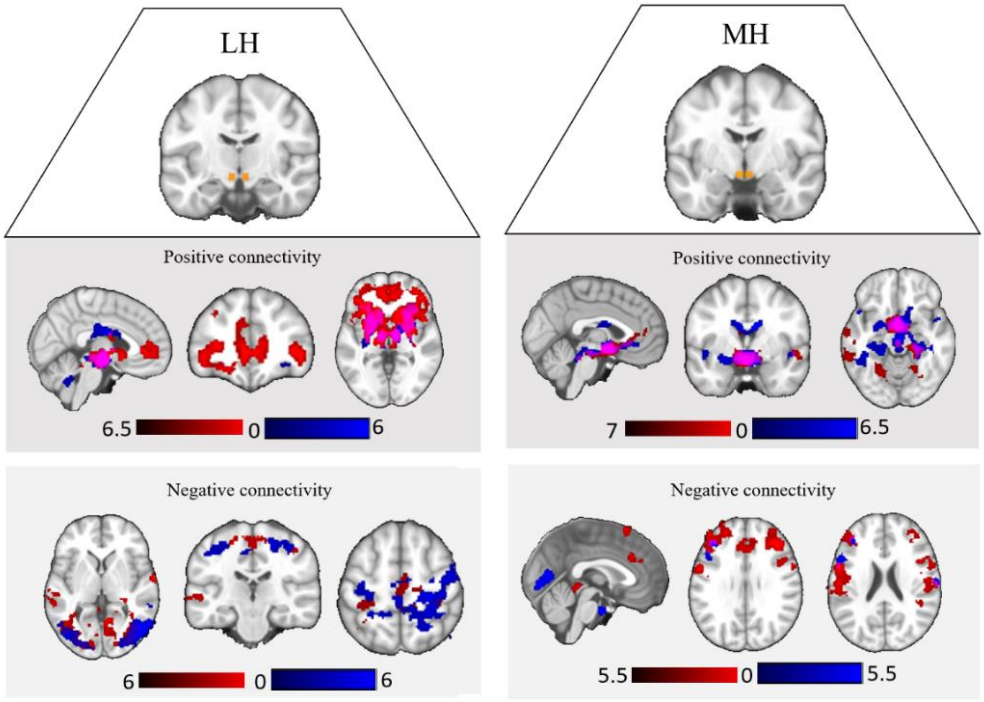

Figure 2. Positive and negative functional connectivity maps of the lateral and medial hypothalamus seeds in adolescents with excess (red) and normal weight (blue). Overlap between both groups is shown in violet.

Between-group differences.

Lateral Hypothalamus (LH). EW-group, compared to NW-group, showed higher functional connectivity between the LH seed and the lateral orbitofrontal cortex, the ventral striatum, the anterior insula extending to the operculum, and the hippocampal gyrus, and lower connectivity

with the cerebellum, and posterior cortices (i.e., the precuneus and the occipital cortex; Table 2, Figure 3).

Medial Hypothalamus (MH). EW-group, compared to NW-group, showed higher functional connectivity between the MH seed and the middle temporal gyrus, and lower connectivity with the middle frontal gyrus, pre- and postcentral gyri (Table 2, Figure 3).

Table 2

Between group differences in the functional connectivity of the medial (MH) and lateral (LH) hypothalamic seeds

Seed	Brain region	R/L	Coordinates	T	CS	Direction
LH						
	Orbitofrontal Cortex	L	-22, 32, -16	3.5	230[a]	EW>NW
	Anterior Insula	R	44, 18, 4	3.7	104[a]	EW>NW
		L	-40, 18, -12	4.5	243[a]	EW>NW
	Ventral Striatum	R	10, 10, -2	4.5	448[a]	EW>NW
		L	-6, 10, -10	4.3	230[a]	EW>NW
	Hippocampal Gyrus	L	-32, -16, -32	4.4	78[a]	EW>NW
	Precuneus	R	2, -58, 42	3.9	58	EW<NW
	Occipital Cortex	R	6, -80, -10	4.5	569[a]	EW<NW
	Cerebellum (IV)	R	20, -72, -24	4.3	94	EW<NW
MH						
	Middle Temporal Gyrus	L	-54, -24, -6	4.1	49	EW>NW
	Middle Frontal Gyrus	R	40, 36, 30	3.9	40	EW<NW
	Precentral Gyrus	L	-54, 2, 32	4.2	39	EW<NW
	Postcentral Gyrus	L	-58, -24, 22	3.9	68	EW<NW

Coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space. *Abbreviations*: EW, Excess weight; NW, Normal weight. [a] same cluster. All results surpassed P<0.001 and a cluster size (CS) of 456 mm^3 (57 voxels) for the LH, and 288 mm^3 (36 voxels) for the MH, inside the mask of within-group effects.

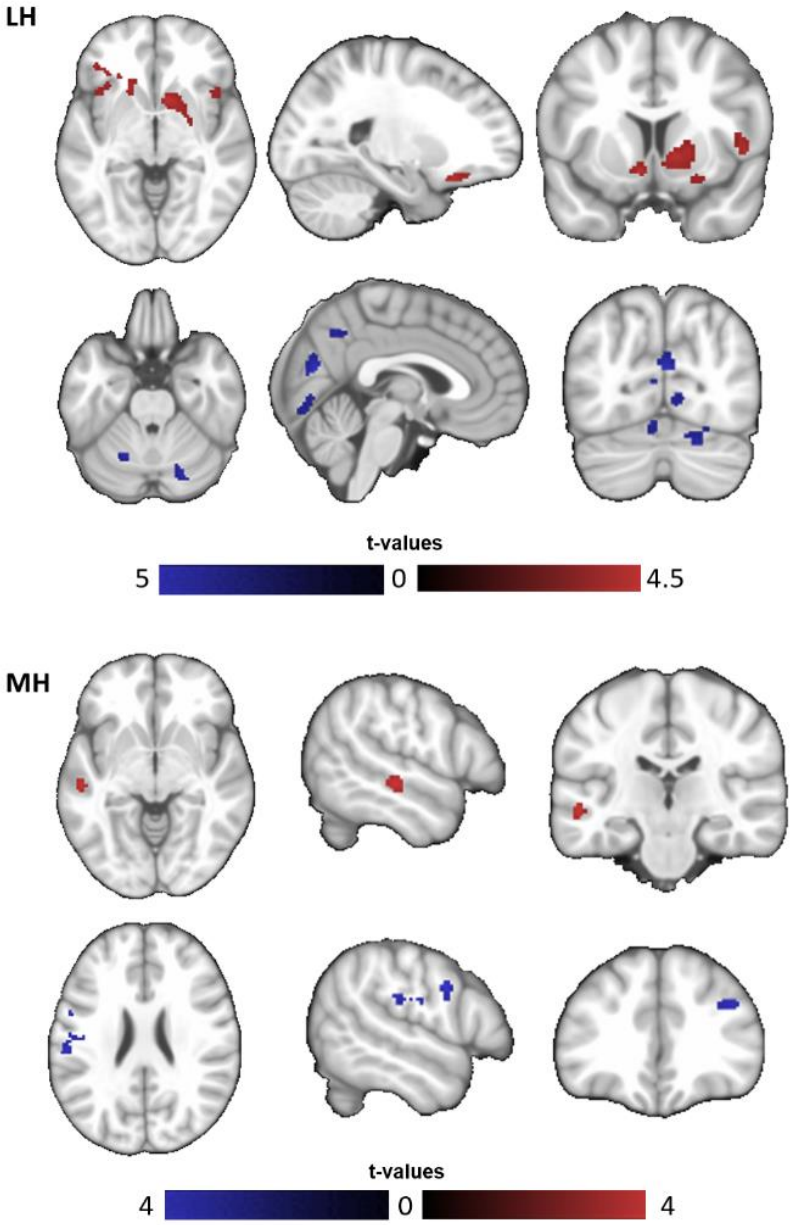

Figure 3. Between-group differences in the functional connectivity of the lateral and medial hypothalamus seeds.

Note: The regions in red indicate higher connectivity in excess versus healthy weight participants, whereas those in blue show lower connectivity. The right hemisphere corresponds to the right side of axial and coronal views. Coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space. *Abbreviations*: EW, Excess weight; NW, Normal weight. [a] same cluster. All results surpassed P<0.001 and a cluster size (CS) of 456 mm^3 (57 voxels) for the LH, and 288 mm^3 (36 voxels) for the MH, inside the mask of within-group effects.

Associations between hypothalamic functional connectivity and stress response

The within-group positive and negative maps of hypothalamic functional connectivity related to stress response, showed a significant positive association with the connectivity in the LH-amygdala and the LH-midbrain in the EW-group, only. MH results did not surpass the threshold for significance neither in EW-group, nor in the NW-group. Therefore, group interactions were explored only for the LH seed.

Group interactions of the lateral hypothalamic networks with stress response were found for the connectivity of the LH-right accumbens and the LH-midbrain. These survived corrections for multiple comparisons, which considered the number of masks used in small-volume correction procedures ($P_{FWE\text{-}SVC}$<0.05, 0.05/3 masks= 0.017; Table 3, Figure 4).

Table 3

Group-interactions between stress response and the functional connectivity of the lateral hypothalamus seed (LH).

LH- Brain region	R/L	Coordinates	T	CS	$P_{FWE\text{-}SVC}$
Nucleus Accumbens	R	8, 10, -6	3.4	11	0.010
Midbrain	R	8, -28, -4	3.3	12	0.010

Coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space. These results surpassed a P_{FWE}< 0.05 following small-volume correction procedures and after Bonferroni ($P_{FWE\text{-}SVC}$<0.05, 0.05/3 masks= 0.017).

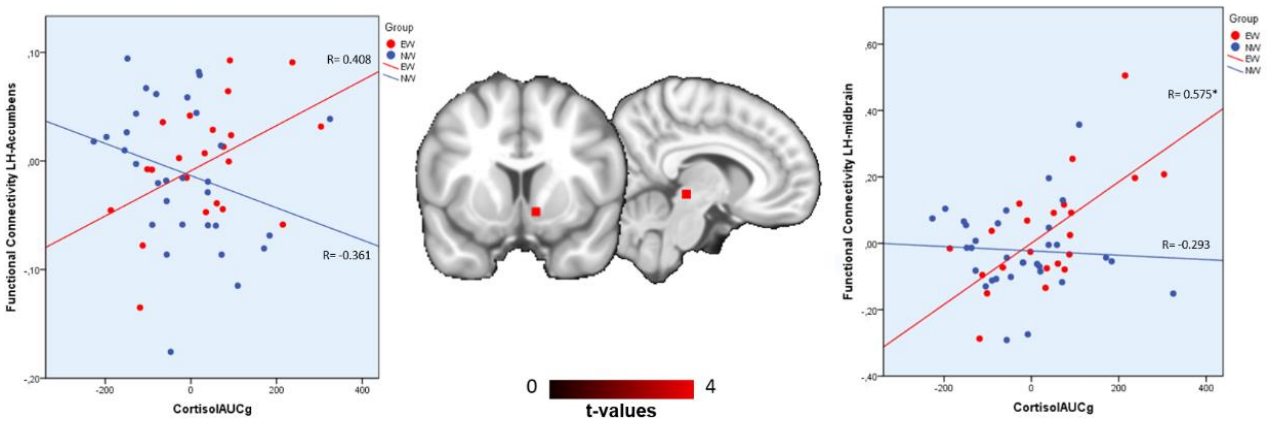

Figure 4. Brain regions displaying a significant between-group interaction in the relationship between the lateral hypothalamus (LH) functional connectivity and stress response.

Note: The right hemisphere corresponds to the right side of axial and coronal views. Scatter plots represent the within-group correlations between the stress response (x-axis= CortisolAUCg) and the functional connectivity of the lateral hypothalamus networks in adolescents with excess weight. Positive values in CortisolAUCg indicate higher stress response, whereas negative values indicate lower stress response. * corresponds to a significant correlation.

Associations with emotional eating behavior

After extracting the signal of the LH networks related to stress response, EW-group showed a positive association between the functional connectivity in the LH-midbrain network and emotional eating scores (r=0.440; p= 0.040; Figure 5). No significant associations with the LH-nucleus accumbens network were observed in this group, and no significant associations emerged in the NW-group.

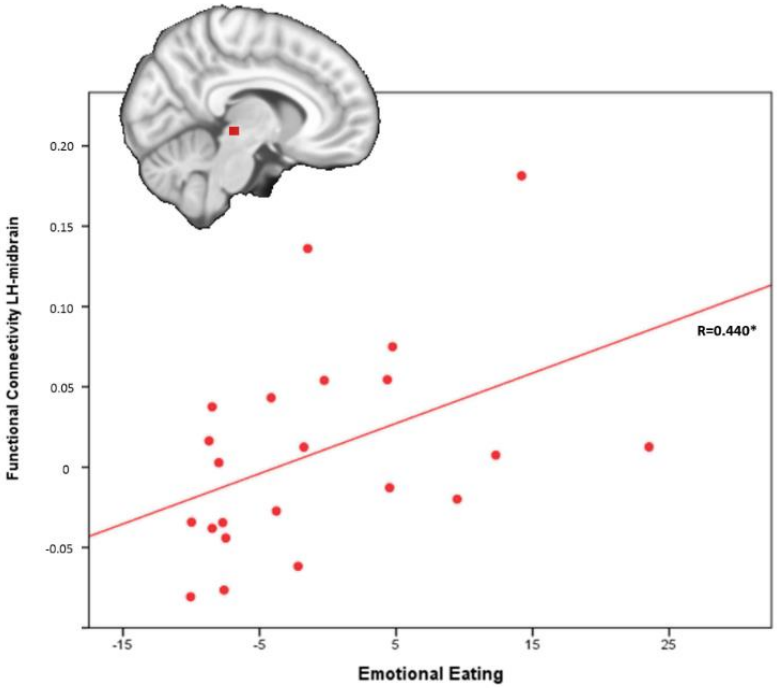

Figure 5. Plot showing the correlation between Emotional Eating and higher functional connectivity related to stress response in the Lateral Hypothalamus (LH)-Midbrain network in adolescents with excess weight.

Discussion

Adolescents with excess weight (EW) had higher functional connectivity between LH and orbitofrontal cortex, ventral striatum, and anterior insula, and between MH and middle temporal gyrus. Furthermore, EW-group also had lower functional connectivity between LH and cerebellum and posterior cortical areas (precuneus, occipital), and between MH and middle and precentral frontal gyri, and postcentral gyrus. Higher connectivity in LH-nucleus accumbens and LH-midbrain networks was positively associated with the stress response, with the connectivity in LH-midbrain network also showing a positive association with emotional eating in EW-group.

The differences between EW-group and adolescents with normal weight (NW) on LH connectivity fit with our hypothesis and thus, with the existing literature, which implicate the

LH, not only in homeostatic feeding behavior, but also in reward and motivation (Harris et al., 2005). The LH, the ventral striatum, the anterior insula, and the OFC are highly connected and commonly implicated in the processing of the rewarding, motivational and hedonic properties of food, whereas the hippocampus codes memory for foods (Berthoud & Münzberg, 2011; Kringelbach, 2004; Wijngaarden et al., 2015). Overall, higher connectivity in these networks might contribute to increase eating beyond homeostatic needs in EW. Additionally, EW-group also showed higher connectivity between the MH, which contributes to inhibit eating behaviors (Leibowitz et al., 1990), and the middle temporal gyrus, which has been reported to be positively associated with the cognitive restrain on eating, and BMI (Zhao et al., 2017). Congruently, MH-middle temporal cortex network may underlie restrained eating behaviors in EW (Rosenbaum, Sy, Pavlovich, Leibel, & Hirsch, 2008). However, this study cannot deduce whether this brain mechanism would positively or negatively affect long-term weight-loss outcomes.

The finding of lower functional connectivity in the LH-cerebellum in EW-group is congruent with altered hypothalamic resting-state connectivity in adults with excess weight (Contreras-Rodríguez et al., 2017), and may indicate alterations in the integration of somatic and visceral information (Zhu, Yung, Kwok-Chong Chow, Chan, & Wang, 2006). Also consistent with our previous study (Contreras-Rodríguez et al., 2017), and the literature (Wijngaarden et al., 2015) in adults with excess weight under fasting and satiation, EW-group also showed lower functional connectivity between the MH and the middle frontal gyrus and the precentral frontal gyri. These frontal areas are implicated in cognitive control, and particularly in the inhibition of hypothalamic input to induce internal signals of satiety, and promote the termination of a meal (Tataranni et al., 1999). However, the lower connectivity between the MH and the postcentral gyrus in the EW-group, does not fit with the increased connectivity found in this same brain network in adults with excess weight (Contreras-

Rodríguez et al., 2017). Taste processing and the representations of laryngeal and supralaryngeal movements are located in the postcentral gyrus (Grabski et al., 2012), and hyperactivation in this cortical area has been widely reported in research on food-cues in children and adolescents with excess weight (Bohon, 2017; Bruce et al., 2013; Rapuano, Huckins, Sargent, Heatherton, & Kelley, 2016; Stice, Yokum, Burger, Epstein, & Small, 2011). This may lead to an increased resting-state functional connectivity at adult ages if elevated BMI levels are maintained (Contreras-Rodríguez, Martín-Pérez, Vilar-López, & Verdejo-Garcia, 2017; Wang et al., 2002). This assumption should be tested by future longitudinal studies.

The specific association between the LH network and stress response suggests that adolescents with EW who are more sensitive to stressful situations, demonstrate more mesolimbic connectivity. These mesolimbic network is part of the reward system and feedback information about the rewarding nature of environmental stimuli. Indeed, the mesolimbic areas, through their dopaminergic connections with the hypothalamus, produce a paradoxical effect of greater motivation to reward under stress (Pool, Brosch, Delplanque, & Sander, 2015). Also, due to their connections with the amygdala, regulates the hedonic impact of emotionally salient stimuli (e.g., foods; Oliveira-Maia, Roberts, Simon, & Nicolelis, 2011; Sharma et al., 2013). An increased cortisol release, has been strongly suggested to impair the responsivity of this dopaminergic hubs, enhancing the food-associated drives and motivation (Rui, 2013; Volkow, Wise, & Baler, 2017).

This previous result is complemented by the association found between the stress-induced higher functional connectivity in the LH-midbrain network and the greater presence of emotional eating behaviors in EW (Dallman, 2010). This finding is interesting as several hormones and peptides have been highlighted as candidates for stress-induced palatable feeding within this specific brain network (Kullmann, Heni, Fritsche, & Preissl, 2015; Meye &

Adan, 2014). For instance, stress hormones may act on the midbrain dopamine segregation indirectly -by altering glucose metabolism-, and directly -by enhancing the glutamatergic drive to dopaminergic neurons (Birn, 2012; Hensleigh & Pritchard, 2013). Future studies are needed to formally evaluate the specific underlying neurobiological mechanism.

These results should be interpreted in the context of some limitations. The cross-sectional design of the present study prevents us from determining if the hypothalamic network´s alterations cause or are a consequence of overeating or, eventually, obesity. An fMRI version of the TSST may help to determine the direct impact of stress in hypothalamic networks. Further studies should define the potential implications of ghrelin and leptin peptides in the hypothalamic function, as well as direct measures of homeostatic status (i.e., the body's nutritional needs) versus perception of hunger (as assessed in this study). The self-reported measure of hunger was only measured in the subset of participants who completed the TSST session. Nevertheless, this is the first study to investigate hypothalamic connectivity network in adolescents with NW and EW, and the first to explore associations with stress and emotional eating. The several psychophysiological measures (i.e., resting-state brain connectivity, virtual reality stressful task with cortisol measures and psychological questionnaires) make up a comprehensive set of data.

In conclusion, functional connectivity alterations within the hypothalamic networks are present at early ages during adolescence in EW. These findings complement previous studies with samples of adults with excess weight (Contreras-Rodríguez, et al., 2017; Kullmann et al., 2014). Our study supports the hypothesis of functional connectivity disturbances between the hypothalamus and the "emotional nervous system" in EW (Dallman, 2010), specifically showing that an increased connectivity in the LH-midbrain network is associated with a greater stress response to stressful challenges, and non-homeostatic eating under emotional states in agreement with the comfort food model (Dallman et al., 2003).

Chapter 5. Non-homeostatic brain networks and stress in excess weight

Martín-Pérez, C., Contreras-Rodríguez, O., Verdejo-Roman, J., Vilar-López, R., and Verdejo-García, A. (submitted). Non-homeostatic amygdala networks in adolescents with excess weight: associations with accumulated stress and weight change during a three months´ intervention. *International Journal of Obesity.*

Introduction

Obesity in adolescents has expanded exponentially the last decades (NCD-RisC, 2017). Risk factors such as the greater intake of high palatable food, and the heightened stress responsivity in this stage, make adolescence an especially vulnerable period for developing obesity. The early presence of excess weight may lead to neurobiological adaptations, including not only the blunted functioning of homeostatic brain regulation, but the promotion of hedonic and stress-related pathways in guiding food intake (Adam & Epel, 2007; Martin-Pérez, Contreras-Rodríguez, Vilar-López, Verdejo-García, in press).

Recent studies have observed associations between the amygdala functioning and stress processing, and its effects on eating behavior and weight control (Siep et al., 2009; Tryon, Carter, DeCand & Laugero, 2013; Zhang, Li & Guo, 2011). The amygdala suffers from several structural and functional changes in excess weight individuals, and under the effects of chronic stress, due to the heightened cortisol release (Scott, Melhorn and Sakai, 2013; Sinha and Jastreboff, 2013; Sominsky and Spencer, 2014; Tryon et al., 2013; Yau and Potenza, 2013). Indeed, the high amount of glucocorticoid receptors and its connections with the hypothalamus turn the amygdala in one of the main regulators of the hypothalamic-pituitary-adrenal (HPA) axis (De Kloet et al., 2005; Hölzel et al., 2010; van Marle 2009). Thus, external cues may override homeostatic control of the hypothalamus via the amygdala (Sun et al., 2015). Furthermore, the amygdala is a key region in stress processing, being implicated in stress-related eating behaviors and the shift from nutritional to motivational value of food (Avena, 2015). These problems are exacerbated during adolescence, since adolescents compared to adults show hyperactivity of the amygdala to negatively valenced information (Hare et al., 2008).

Further studies in adults with excess weight have explored the functional connectivity of the amygdala as an important area regulating food intake. Several studies have suggested a disruption in the information flow between the amygdala and the hypothalamus, which may disturb homeostatic food intake and weight regulation, including efforts to lose weight in adult individuals with obesity (Lee et al. 2016; Petrovich et al., 2002; Sun et al., 2015). Lips et al. (2014) and Wijngaarden et al. (2015) found a higher functional connectivity between the amygdala and the insula and the OFC, areas related to motivation for food, under an overnight fasting in obese and lean individuals respectively. Nummenmaa et al., (2012), found a heightened functional connectivity between the amygdala and the dorsal striatum during the view of high palatable food. Conversely, other study in adults with excess and normal weight found this same relationship between dorsal striatum and amygdala only in lean individuals in a task-free fMRI scan (Contreras-Rodríguez et al., 2017). Beyond striatum, other studies found the amygdala to be connected with prefrontal areas of the salience and default mode networks under stress (Veer et al., 2011) and emotion appraisal (Etkin, Egner & Kalisch, 2011) in healthy adults, and related to higher anxiety trait in healthy adolescents (Hare et al., 2008).

Despite the study of the amygdala as a critical area in feeding and several emotional processes known to influence weight stability (Sun et al., 2015), no studies have explored the connectivity of the amygdala in adolescents with excess weight, and no studies have done so by focusing on subregions of the amygdala and its association with longitudinal assessments of stress and weight change in this sample. Two main interconnected networks have been defined within the amygdala (Bzdok, Laird, Zilles, Fox & Eickhoff, 2013; Fernando, Murray & Milton, 2013; Pico-Pérez et al., 2018). The Basolateral Amygdala (BLA), involved in processing high-level sensory input and stimuli-value associations, have predominant connections with cortical association areas and areas ascribed to reward valuation system, such as the ventral striatum and the lateral hypothalamus (Campbell-Smith, Holmes, Lingawi,

Panayi & Watbrook, 2015). Interestingly, the BLA has been implicated in the elicitation of eating in the absence of homeostatic need in humans (Weingarten, 1983) and further studies suggest that this circuit could be involved in weight gain susceptibility (Sun et al. 2015). On the other hand, the Centromedial Amygdala (CeA), is implicated in stress and negative affect, and in rewarding motivation (Kim et al., 2017), but also in generating attentional, vegetative and motor responses (Bzdok et al., 2013), by its principal connections with brainstem, midbrain and the lateral hypothalamus (Zseli et al., 2018). Preclinical studies have stressed CeA as the main subcortical area disrupting the HPA axis due to its role in stress reactivity (Herman & Cullinan, 1997), and stress coping (Roozendaal et al., 1997). More recent studies support these ideas and also suggest the importance of the CeA in the "comfort food eating" phenomenon, stimulating the eating behavior during chronic stressors (Dallman et al., 2003).

In view of the strong associations between the functions of the CeA and BLA amygdala pathways and eating behavior and weight regulation, we aimed to compare the functional connectivity of the CeA and BLA networks between adolescents with excess and normal weight. We hypothesized that CeA and BLA seeds will show higher functional connectivity with areas related to motivational drives to eat and emotional value of food (Petrovich & Gallagher, 2007; Petrovich, Ross, Mody, Holland & Gallacher, 2009), and lower functional connectivity between these seeds and areas related to internal awareness and attention. In addition, we sought to examine the longitudinal associations between CeA and BLA connectivity metrics and 3-month weight change among participants with excess weight. In line with other studies (Sun et al., 2015; Mietus-Snyder and Lustig, 2008; Dallman, 2010), we expected associations between weight change and mesolimbic areas controlling food intake (i.e. hypothalamus, midbrain, nucleus accumbens). Finally, a complementary aim was to investigate whether there is a relationship between chronic stress and weight change (Torres &

Nowson, 2007), and if so, to investigate whether the amygdala connectivity mediates such an association (Sinha & Jastreboff, 2013; Tryon et al., 2013).

Method

Participants

Seventy adolescents were recruited and classified in two groups according to their age-adjusted BMI-percentile: 36 adolescents with normal weight (NW) and 34 with excess weight (EW). Participants were recruited via local newspapers, social media and ads in schools. The inclusion criteria were (i) aged 14 to 19 years, in alignment with the WHO definition of adolescence, including individuals aged from 10 to 19 (WHO, 2011), (ii) BMI-percentile between 5^{th} and 85^{th} for NW, and at or above 85^{th} for EW according to their age (Ogden and Flegal, 2010). The exclusion criteria were to have (i) comorbid metabolic or systemic diseases associated with obesity (e.g., diabetes, hypertension), (ii) current eating (e.g., binge eating, bulimia) or depressive disorders, and (iii) presence of structural abnormalities on the Magnetic Resonance Imaging or any contraindications to MRI scanning (e.g., claustrophobia, implanted ferromagnetic objects).

All the adolescents completed two sessions. In the first session, participants underwent an fMRI scan. In addition, their current weight was measured with a digital scale (Tanita DC-430U). In a second session, participants with EW received a personal diet and exercise plan for losing weight made by an experienced nutritionist. Participants with NW were only given general exercise and eating guidelines for a healthy lifestyle.

Three follow-ups, where adolescents with EW were measured in their attainment to the nutritional and exercise recommendations, were done at 1, 2 and 3 months after receiving the weight loss plan. In the last session, all the participants were weighted again to measure their

weight change. Thirty of the initial 34 participants with EW completed all the sessions. Therefore, 34 participants were included in baseline analyses, and 30 in longitudinal analyses.

Finally, in the last follow-up a sample of hair cortisol was collected in a subset of 21 participants with excess weight. Nine participants were excluded due to the following reasons: (i) they did not want to have their hair cut or (ii) did not have enough hair to collect three centimeters, which was the length needed to assess cortisol during the three months of the diet intervention (see details in the Hair cortisol section).

Overall, participants could receive between 50 and 60 Euros in gift vouchers as reimbursement, depending on their performance in a neuroeconomic task not related to the present study. The Human Research Ethics Committee of the University of Granada approved the study, and all participants, and their parents if they were minors, were informed about the aim of the study and signed an informed consent.

Measures

Imaging data acquisition. All participants were scanned after the main meal of the day, approximately between 4 and 6 p.m., and performed a 6-min resting-state scan. They were instructed to lie still with eyes closed. A 3.0 Tesla clinical MRI scanner was used. It was equipped with an eight-channel phased-array head coil (Intera Achieva Philips Medical Systems, Eindhoven, The Netherlands). A T2*-weighted echo-planar imaging (EPI) was obtained (TR=2000ms, TE=35ms, FOV=230 x 230mm, 96x96 pixel matrix; flip angle=90º, 21 4-mm axial slices, 1-mm gap, 180 whole-brain volumes). The sequence included four initial dummy volumes to allow the magnetization to reach equilibrium.

Also, a high resolution T1-weighted anatomical image was acquired for each participant. This image, of 160 slices (TR= 8.3 ms; TE= 3.8 ms; flip angle = 8°; FOV= 240 x 240 mm; in-

plane resolution= 0.94x0.94x1; slice thickness= 1 mm) was used to discard structural alterations and for the co-registration step in the preprocessing stage.

Hair cortisol. We used the gold standard method to assess cortisol in hair, which has been validated and provides a test-retest reliability as a biomarker of chronic cortisol exposure (Russell, Koren, Rieder & Van Uum, 2012), which has been validated in children (Vanaelst, Huybrechts, Bammann, Michels & Vriendt, 2012). Hair samples consisting of approximately 150 strands of hair were collected from the posterior vertex with a length no greater than 3 cm (assuming an average growth rate of 1 cm/month; Russell et al., 2012; Short et al., 2016). A 3 cm segment contains cortisol that has been deposited over approximately the last 3 months. The hair was cut with scissors as close to the scalp as possible. The hair was then wrapped in a piece of aluminum foil to protect it from light and humidity, and was stored in an envelope in room temperature. Later, the hair samples were sent for analysis to the Faculty of Pharmacy of the University of Granada.

The sample was weighed and ground to a fine powder to break up the hair's protein matrix and increase the surface area for extraction using a ball mill (Bullet Blender Storm, Swedesboro NJ, USA). Cortisol from the interior of the hair shaft was extracted into HPLC-grade methanol by incubation of the sample for 72 hours at room temperature in the dark with constant inversion using a rotator. After incubation, the supernatant was evaporated until completely dry using a vacuum evaporator (Centrivac, Heraeus, Hanau, Germany) and the extract was reconstituted in 150 ul of phosphate buffered saline (PBS) at pH 8.0. The reconstituted sample was immediately frozen at -20ºC for later analysis (Sauve, Koren, Walsh, Tokmakejian & Van Uum, 2007; Chen et al., 2013; Meyer, Novak, Hamel & Rosenberg, 2014).

This measure has been recently validated in adult Spanish population (García-León et al., 2018).

Diet and exercising. After the scanner, participants with NW were given the standard recommendations for a healthier life in adolescents, based in the guidelines for adolescents' healthy life proposed by the World Health Organization (WHO, 2004). More specifically, some guidelines would be to accumulate at least 60 minutes of moderate-to-vigorous physical activity per day or the reduction of high-energy foods. However, they were not encouraged to lose weight as those with EW.

Besides that, some nutritional measures were collected the same day with the KrecePlus questionnaire (Serra, Aranceta, Ribas, Sangil & Perez, 2003). This test comprises 14 statements regarding healthy (+1) and unhealthy (-1) nutritional habits. The higher the score, the better nutritional status. Besides that, the Short Test for Physical Activity included in the KrecePlus (Viñas, Serra, Ribas, Pérez & Aranceta, 2003) was used to assess the physical activity with questions regarding the hours that participants spend exercising or in sedentary activities (e.g. watching TV, playing videogames).

Final weight and fat change. We calculated change in weight by subtracting the third follow-up weight of the initial weight, divided by the initial weight and multiplied by 100. This change index takes into account the initial weight in order to estimate the change (Contreras-Rodríguez et al., 2017). Greater positive values reflect higher weight loss.

Diet and exercise post-intervention measures. At the 3-month follow-up, we re-administered the KrecePlus tests and collected self-report information on attainment of diet/exercise plans using the questions: "Have you followed the proposed recommendations related to diet?", and "Have you followed the proposed recommendations related to physical activity?" These questions were answered with one of these options: "Never (0%)", "Sometimes (25%)", "Many times (50%)", "Most of the times (75%)" or "Always (100%)". In

addition, we collected a self-reported measure of motivation to follow the nutritional and exercise plan rated on a scale from zero (no motivation) to 10 (very motivated).

Analyses

Preprocessing of imaging data. Functional data was preprocessed using CONN functional connectivity toolbox v17 (Whitefield-Gabrielli & Nieto-Castanon, 2012), implemented in Matlab version R2017a. Firstly, functional images were realigned to the first scan, segmented, coregistered to the MNI anatomical template image and slice-time corrected. Secondly, the images of each subject were assessed in motion artifacts and head motion using the ART toolbox implemented in CONN. This toolbox allows to create motion confound regressors (3 translation and 3 rotation parameters) plus another six 1st order temporal derivates to detect and remove outlier images for subsequent analyses (Power et al., 2012). Next, the BOLD time-series within the white matter and cerebrospinal fluid (another ten PCA parameters in total) were regressed out using the CompCor strategy of CONN to remove potential confounds and improve the impact of the physiological noise and head motion in the fMRI data. The CompCor extracts the time series of the principal components of the previous nuisances (white matter and cerebrospinal fluid) and segment the anatomical images. These components, together with head motion parameters are entered in the denoising step as confounds. Detrending step was added.

Structural images were resliced to 2mm resolution in MNI anatomical space and then coregistered with each participant´s functional scan. Finally, functional images were spatially smoothed using a Gaussian kernel of FWHM 6 mm and denoised with a band-pass temporal filter (0.008-0.09 Hz).

Seed definition. Bilateral spheres with a radium of 3.5 mm were extracted around the original MNI coordinates of the basolateral (BLA; x=+29, y=-3, z=-23 for the right seed and x=-26, y=-5, z=-23 for the left seed) and the central amygdala (CeA; x=23, y=-5, z=-13 for the right seed and x=-19, y=-5, z=-15 for the left seed with the Marsbar toolbox for SPM12. These seeds were used according to the methodology of the functional connectivity study of the amygdala from Baur et al., 2013. It is worth noting that all these seeds were spatially separated by more than 6mm (>1 FWHM) to prevent overlap between signals.

Functional connectivity analyses. First-level t-test maps were estimated by using the seeds as regression parameters, together with nuisance signals (WM, CSF, motion parameters). Contrast images were generated for each subject by estimating the regression coefficient between all brain voxels and each seed's time series. None of the participants was excluded by a large amount of outlier scans as the percentage of these volumes was very low across both groups of the sample [mean for NW= 1% (SD=2.203), mean for EW= 1.09% (SD=2.404), t=-0.160, p=0.874]. The first level contrast images were then included in two separate second-level two-sample models to assess for between-group effects in each seed connectivity (BLA and CeA) together with sex and age as covariates of no-interest.

Functional connectivity associated to weight change in EW. To test the association between the amygdala functional connectivity and weight change only in adolescents with excess weight (who followed the weight loss intervention), the first-level contrast images representing the connectivity for each BLA and CeA seeds were entered in four separate second-level multiple regression models (left/right CeA and left/right BLA) using the variable "weight change" as a covariate of interest. Sex and age were included in the model as covariates of no interest.

Imaging thresholding criteria. The minimum threshold extents for the functional connectivity analyses were estimated by 1000 Monte Carlo simulations using the cluster-extent

based AlphaSim thresholding approach (Song et al., 2011), implemented in the SPM RESTplusV1.2 toolbox. For the within-group connectivity maps, we included as input parameters an individual voxel threshold probability of 0.001, a cluster connection radius of 5mm and the actual smoothness of imaging data after model estimation, incorporating a whole-brain image mask (240405 voxels). The minimum cluster size for each seed was 178 voxels (1424 mm^3) for left CeA, 181 voxels (1448 mm^3) for right CeA, 187 voxels (1496 mm^3) for left BLA and finally, 192 voxels (1536 mm^3) for right BLA. For the between-group effects in the functional connectivity of the amygdalae seeds (i.e., left and right CeA and BLA) and their association with weight change in the adolescents with EW, the required cluster extent was calculated including the same parameters except for the mask, which was created by joining positive and negative within-group maps of the functional connectivity of the adolescents with NW and EW for each seed (masks: 11486 voxels for the left CeA , 15537 voxels for the right CeA, 37802 voxels for the left BLA and 47933 voxels for the right BLA). The minimum cluster size was 42 voxels (336 mm^3) for left CeA seed, 54 voxels (432 mm^3) for right CeA seed, 89 voxels (712 mm^3) for left BLA seed and 107 voxels (856 mm^3) for right BLA seed.

Behavioral measures and mediation analysis. To better understand the attainment to the intervention and its relationship with the success in losing weight, we performed Pearson correlations between the relative weight loss and several variables measured the final day of the weight intervention. These measures were the following of the diet, the following of the exercise and the motivation to follow with the intervention.

To perform the mediation analysis between our variables of interest, we performed Pearson two-tailed correlations in SPSS between hair cortisol and the beta values from the peak coordinate of those regions showing a significant association with weight change in the adolescents with EW in the preceding analyses. Likewise, correlations between hair cortisol and the weight change in the adolescents with EW were also performed.

To complement the above analyses, we tested whether the relationship between hair cortisol (X) and weight change (Y) was mediated by the functional connectivity of the amygdala networks (M) using PROCESS macro (v.2.16; Hayes, 2013) as implemented in SPSS. These mediation analyses first tested: whether hair cortisol predicted the connectivity of the amygdala (path a); whether the connectivity of the amygdala predicted weight change, controlling for hair cortisol (path b); and whether hair cortisol predicted weight change (path c). Next, this model assessed whether the connectivity of the amygdala explained a significant proportion of the covariation between the hair cortisol and weight change (path c').

To test the significance of the mediation, we used a bootstrapping approach (5000 iterations). The mediation analysis was significant if the 95% confidence intervals (CI) did not include zero.

Results

Behavioral results

The EW and HW groups did not differ in age, sex or hunger before scanning (Table 1). After dividing the excess weight group into those who lose weight and those who gain or not change their weight after the intervention, our results showed significant between-group differences in hair cortisol and diet attainment during the weight loss intervention.

Table 1

Demographic and clinical characteristics of the groups

	Normal weight (N=36) Mean (SD)	**Excess weight (N=34)** Mean (SD)	Test statistics [a]	*p* value
Age	16.50 (1.40)	16.44 (1.66)	0.160	0.873
BMI percentile	50.33 (19.31)	93.74 (4.27)	-13.150	0.000
Fat (%)	21.28 (8.95)	30.49 (5.68)	-5.172	0.000
Sex (females)	19 (52.8%)	19 (55.9%)	0.068	0.794
Hunger pre-Scan	18.50 (18.99)	18.91 (20.41)	-0.087	0.931
	EW weight lost (n=21)	**EX weight gain (n=9)**		
Weight change (%)	-5.64 (3.07)	4.24 (2.83)	8.543	0.000
Diet Attainment	2.38 (1.07)	1.44 (0.73)	-2.782	0.011
Hair cortisol	**(n= 15)** 251.13 (111.34)	**(n= 6)** 395.47 (59.58)	3.833	0.001

Note: Independent samples t-tests were used to asses for between-groups differences in all cases, except for sex where chi-square tests were employed.

CeA and BLA functional connectivity in the whole sample

The left and right CeA maps showed positive functional connectivity with prefrontal cortices and subcortical areas, including regions such as the contralateral amygdala, the hypothalamus, and the ventral striatum. Negative functional connectivity maps involved parietal and occipital cortices, the cerebellum, and a prominent connectivity between the right CeA and the posterior cingulate cortex (PCC) extending to the precuneus (Figure S1, Table S1).

The left and right BLA maps showed positive functional connectivity with the insulae extending to adjacent temporal (i.e. temporal pole, fusiform gyri), bilateral dorsal caudate, and pre and postcentral cortices. Negative functional connectivity maps involved parietal (i.e. the PCC-precuneus, and superior areas), the medial prefrontal cortices, and the cerebellum (Figure S1, Table S1).

Between-group differences

CeA. Adolescents with EW, compared with those with HW, showed higher functional connectivity between left CeA and perigenual ACC, extending to the medial prefrontal cortex; and lowe connectivity between the right CeA and the PCC (Table 2; Figure 1).

BLA. Adolescents with EW, compared with those with HW, showed lower functional connectivity between left BLA and the right angular gyrus and both dorsal caudate nuclei (Table 2; Figure 1).

Table 2

Between group differences in the functional connectivity of the central (CeA) and basolateral (BLA) amygdala seeds.

Seed	Brain región		x, y, z	t	CS	Direction
CeA						
	Right Seed					
	Posterior Cingulate Cortex	R	10, -40, 22	4.8	312	EW<NW
	Left Seed					
	Perigenual ACC extending to OFC	R	8, 46, 2	5.2	823*	EW>NW
	Medial Prefrontal Cortex	R	2, 46, 24	4.5	823*	EW>NW
BLA						
	Left Seed					
	Dorsal Caudate	R	10, 20, 6	4.7	175	EW<NW
		L	-10, 22, 4	4.4	125	EW<NW
	Angular gyrus	R	48, -70, 22	4.2	150	EW<NW

Note: Coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space. *Abbreviations*: CeA, Central Amygdala, BLA, Basolateral Amygdala, EW, Excess weight; NW, Normal weight. * indicates part of the large cluster. All results herein surpassed a height threshold of P<0.001 and a cluster of 336 and 432 mm^3 (42 and 54 voxels) for the left and right CeA seeds respectively, and 712 and 856 mm^3 (89 and 107 voxels) for the left and right BLA seeds respectively, explored inside the mask of within-group effects.

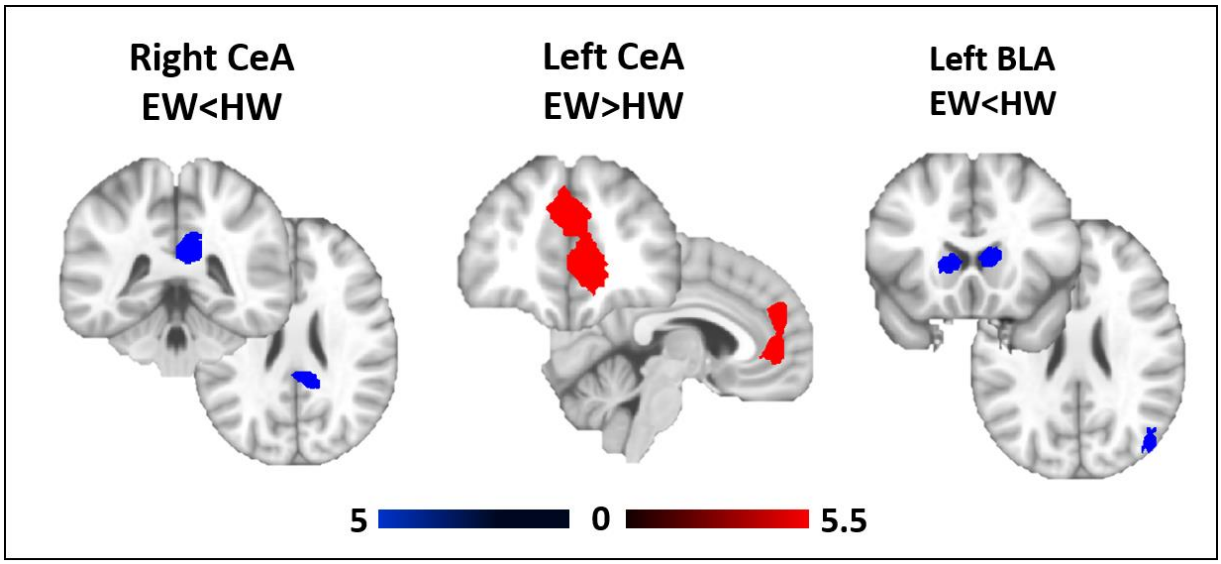

Figure 1. Between-Group differences in the functional connectivity of the different seeds of the amygdala (Right/Left CeA and Left BLA).

Note: Regions in red indicate higher connectivity in excess versus healthy weight participants, whereas those in blue show lower connectivity. The right hemisphere corresponds to the right side of axial and coronal views.

Correlation between the amygdala functional connectivity and weight change

In the adolescents with EW, weight loss was negatively associated with the functional connectivity between the left CeA and the midbrain (Coordinates=14, -14, -12; t= 5.6; CS=76; $p<0.001$), that is, lower functional connectivity was associated with more weight loss, and contrary, stronger connectivity correlated to more weight gain (see Figure 2). No other association between amygdala functional connectivity and weight loss surpassed the significance threshold.

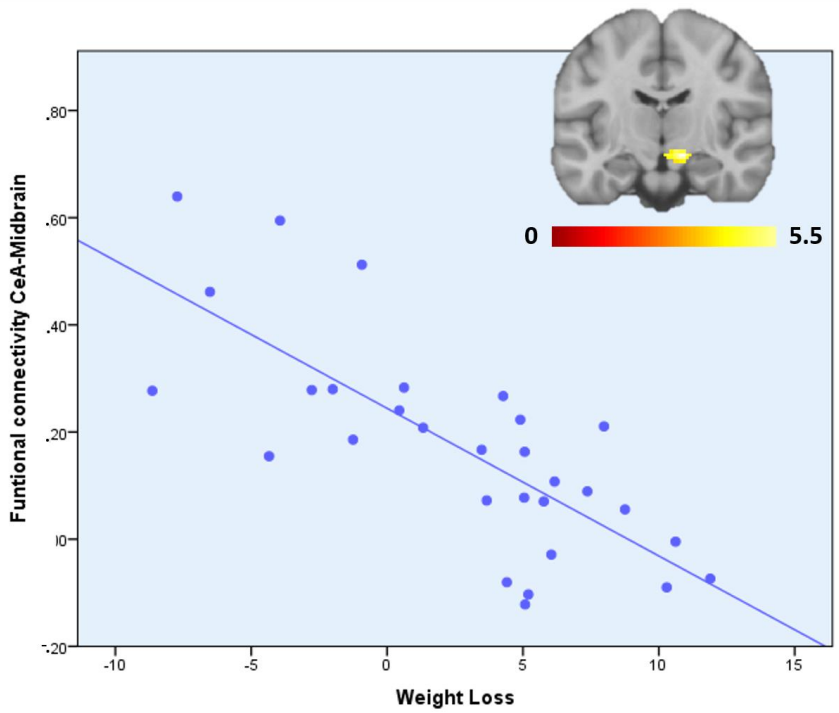

Figure 2. Plot showing the significant correlation between the functional connectivity of the CeA–midbrain network (MNI coordinates x,y,z: 14, -14, -12) and the weight loss (x-axis) after a three months´ intervention.

Note: Positive values in "Weight Loss" indicate greater weight loss, while negative values represent lower weight loss.

Mediation analysis

A mediation analysis was carried out to assess if the relationship between heightened stress (by means of heightened accumulation of cortisol) and less weight loss could be mediated by the functional connectivity between CeA and the midbrain. The potential mediational effect would support another data suggesting a role in the limbic and mesolimbic systems in children and adolescents (Mietus-Snyder & Lusting, 2008; Martín-Pérez et al., 2018). Thus, the relationship between all variables entered in the mediation analysis was assessed in a correlation matrix using Pearson´s correlations, as all the variables follow a normal distribution. There was a positive significant relationship between the three variables: between weight change and the connectivity in the left CeA-midbrain network (path b), between hair cortisol and weight

change (path c), and between hair cortisol and the connectivity in the left CeA-midbrain network (path a). The mediation analysis showed that the positive association between hair cortisol and weight change (path c), became non-significant when the connectivity in the left CeA-midbrain network is included in the model (path c'). These results suggest that no significant direct effects were found (CI= -0.1378, 0.5423). However, an indirect effect of mediation was found (CI= 0.1185, 0.7094) (see Figure 3). Specifically, the percentage of total effects explained by the indirect effects was of 62.5%.

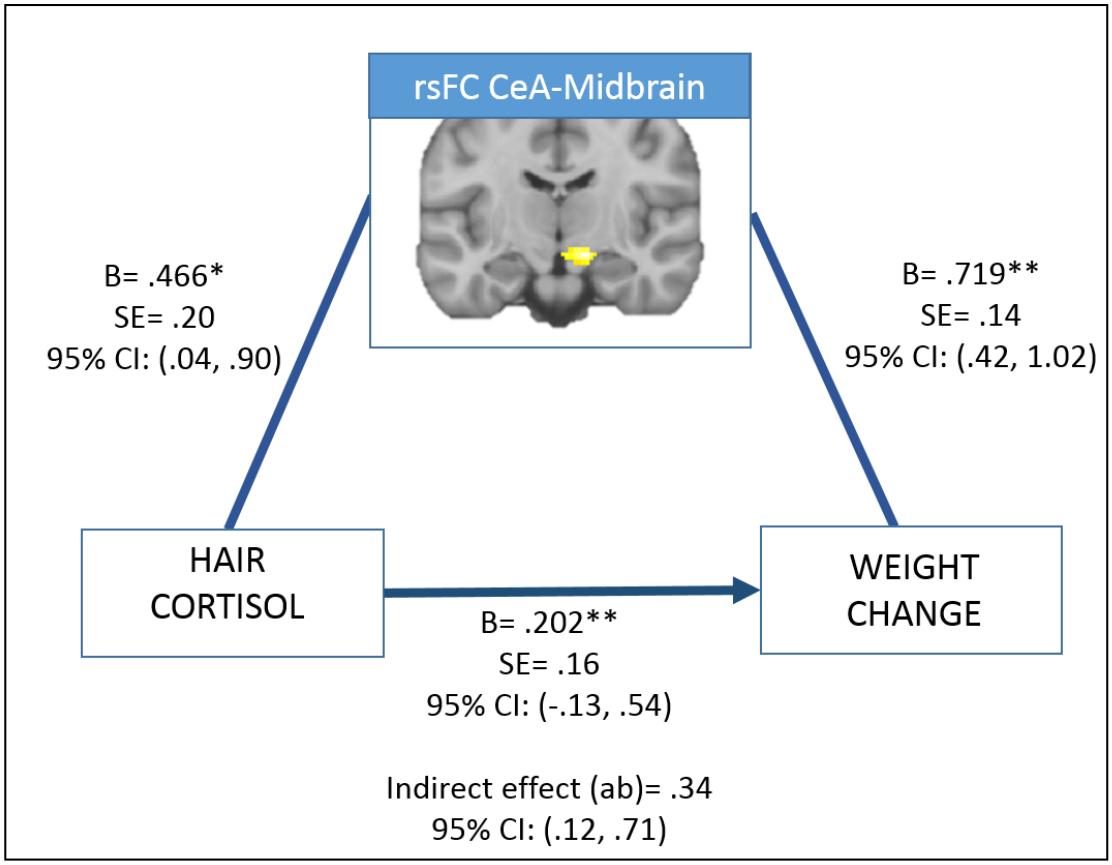

Figure 3. Mediation analysis between the functional connectivity of the CeA-midbrain network, accumulated hair cortisol and weight loss.

Discussion

The aim of the present study was twofold. Firstly, we wanted to characterize the resting-state functional connectivity of the amygdala in adolescents with excess weight (EW) in comparison with their normal weight (NW) counterparts. The adolescents with EW showed alterations in the functional connectivity between the central amygdala (CeA) and different parts of the default mode network (DMN), while the basolateral amygdala (BLA) seed showed a lower resting-state functional connectivity (rsFC) with the bilateral dorsal caudate.

The lower rsFC in the right CeA-PCC network suggest a lower interoceptive consciousness of the own emotional state, according to its role in emotional processing beyond the amygdala (Gentili et al., 2009). Some studies with excess weight samples have suggested a joint altered activation of the PCC and amygdala in obesity (Carnell, Gibson, Benson, Ochner & Geliebter, 2011) and stress (Veer et al., 2011), and also, others have proposed that after exercise and substantial weight loss PCC alterations may reverse (Legget et al., 2016, Wijngaarden et al., 2015). The heightened rsFC in the left CeA-ACC and mPFC networks has been more investigated and is one of the most replicated association of the amygdala related to emotion processes (Roy et al., 2009). These two prefrontal regions, in coordination with the amygdala, are known to automatically react to biologically relevant stimuli (Kim et al., 2011). Indeed, the specific area of the ACC found in our study, the pgACC, regulates autonomic and affective responses, which turns this area in a relevant region for emotional processing and regulation. It evaluates the emotional valence of complex stimuli and finally, facilitates the emotional response (Davey, Allen, Harrison & Yucel, 2011). When altered, this circuit is responsible of the memory formation of emotionally salient events, with the amygdala (Veer et al., 2011) being hyper-activated under heightened limbic reactivity, for example, in emotion regulation paradigms when the subject is asked to appraise (Etkin et al., 2011), as the ACC together with the amygdala are implicated in producing affective states (Roy et al., 2009).

Besides, and also in conjunction with the amygdala, the ACC is implicated in the reward-motivation circuit (Volkow et al., 2011), and specifically in food motivation (Martin et al., 2010), and has been related to higher food addiction scores, binge eating and emotional and external eating (Gearhardt, Yokum & Orr, 2011; Shienle, Schafer, Hermann & Vaiti, 2009). The distinct connections between the left and right amygdala seeds with areas of the DMN has demonstrated significant associations before (Marusak et al., 2016) and has been reported by a fMRI study in healthy adults that the normal functional connectivity of these prefrontal and posterior cingulate cortex seeds (Roy et al., 2009) may have different implications in excess weight conditions. Indeed, this distinctive connectivity between areas within the DMN has been observed in individuals with anxiety (Zhao et al., 2007) or major depression (Sambataro, Wolf, Pennuto, Vasic & Wolf, 2013), and has been related to maturation, with younger individuals showing lower anterior to posterior correlation (Washington & VanMeter, 2013).

The lower rsFC between the left BLA and both dorsal caudate nuclei in EW differs from the increased task-related functional connectivity in this same network in morbid obese adults to the sight of appetizing versus bland foods (Numenmma et al., 2012) and the enhanced activation of the dorsal caudate in excess weight adults (Verdejo-Román, Vilar-López, Navas, Soriano-Mas & Verdejo-García, 2017; Rothemund et al., 2007), and adolescents (Moreno-Padilla et al., 2018). However, other neuroimaging studies showed that the caudate activity was inversely related to BMI (Wang et al., 2011; Stice et al., 2008) and weight gain (Stice et al., 2010). All these findings together might support the idea of a hypofunctioning of reward circuitry while resting, which hyperactivates under the exposition to food cues (Stice et al., 2008), although longitudinal studies may help to clarify whether the connectivity the left BLA-dorsal caudate nuclei changes from adolescent to adulthood and whether interaction effects with food addiction traits exist, as the strength rsFC in this brain network has been associated

with food craving in lean individuals, but not in those with excess weight (Contreras-Rodriguez et al., 2017).

Finally, we found a negative relationship between the strenght rsFC in the left CeA-midbrain network and weight loss in the adolescents with excess weight. Importantly, higher connectivity in this brain network mediated the negative association between the accumulated cortisol over the 3-month intervention and weight loss. That implies that, as expected, those adolescents with excess weight who did not lose weight during the intervention, engage more of the amygdala-midbrain network. Stressful events, such as weight loss interventions, are known to stimulate the function of the mesolimbic reward system, comprising the midbrain and the CeA, which is known to be especially sensitive to these highly arousing negative events (Hrybouski et al., 2016). Besides the association with the amygdala and chronic stress, the rsFC connectivity of the midbrain has been recently associated to the hypothalamus and to stress-related eating in adolescents with excess weight (Martín-Pérez et al., 2018). Together with the midbrain, the amygdala and the hypothalamus form the "limbic triangle" proposed by Mietus-Snyder and Lustig (2008). According to this study, the hypothalamus and the midbrain are responsible to mediate satiety during homeostasis stages, but this connection can be easily overridden by the amygdala during stress (Mietus-Snyder & Lustig, 2008). The higher accumulation of cortisol might lead to the lower follow-up of the dieting and exercise intervention, in addition to the lower motivation to follow the intervention that we found in those who do not success in losing weight.

The present study has a number of limitations to be acknowledged. First of all, this study cannot determine if the alterations shown in the amygdala networks are a previous vulnerability or a consequence of excess weight, due to our cross-sectional design in the imaging variables. Besides, the small sample size for the mediation analysis with the cortisol measurement precludes from strong conclusions until results are replicated with bigger samples.

On the other side, this study is the first to explore the functional connectivity of the different seeds of the main non-homeostatic hub (the amygdala) in adolescents, and its association with the accumulated cortisol and weight change over a three months' intervention. Moreover, our study comprises hormonal, neural and behavioral measures, and contains longitudinal follow-ups in several measures. This study highlights the importance of the brain non-homeostatic pathways for the success of a weight change intervention, and how the accumulated cortisol during the dieting process could dampen the weight loss.

In conclusion, the alterations found in the functional connectivity of the amygdala seeds supports previous studies regarding the implication of several brain areas in a non-homeostatic eating network related to stress (Dallman, 2010; Mietus-Snyder & Lustig, 2008). Our result associating the higher functional connectivity between the central amygdala, heightened accumulation of cortisol and the less weight loss are in line with the previous studies above, and those relating this brain network with overeating and emotional eating behavior, and extend this knowledge to the adolescence stage.

Chapter 6. The executive brain and excess weight

Martín-Pérez, C., Verdejo-Roman, J., Contreras-Rodríguez, O., Navas, J.F., Vilar-López, R., and Verdejo-García, A. (submitted). Salience network alterations associated with insulin and body fat, and their neuropsychological correlates in adolescents with excess weight. *NeuroImage: Clinical.*

Introduction

Excess weight is a fast-spreading condition in the adolescent population worldwide. It is a slow devastating medical condition that leads to early mortality and many physical, metabolic and neural comorbidities (Raj & Kumar, 2010). Recently, several authors have offered a view of obesity beyond energy balance regarding the notion of obesogenic environment. The great availability and exposition to high fat food every day, stimulate reward-based decision-making and dampen cognitive control of overeating. Since this perspective, the homeostatic and the cognitive regulation of energy balance would be constantly challenged by hedonic drives (Neseliler, Han & Dagher et al., 2017), and this continuous struggle lead to alterations in brain, metabolic and executive domains regulating eating behavior.

The Salience, the Central Executive and the Default Mode networks have been pointed out to be responsible of self-regulation (Bressler & Menon, 2010; Goulden et al., 2014), and to integrate the activity of several brain areas important for the combination of internal and external signals to regulate executive function (Sridharan et al., 2008; McFadden et al., 2013). Thus, it is not surprising that some studies have found alterations in these networks in obese population (Doucet, Rasgon, McEwen, Micali & Frangou, 2018; Zhang et al., 2015; Lips et al., 2014; García-García et al., 2013; Kullmann et al., 2012), also found in children and adolescents with excess weight (Chodowski, 2016). The Salience Network (SN) is mainly comprised of the amygdala, the anterior insulae and operculum, extending to the striatum, and the anterior cingulate cortex (ACC); the Central Executive Network (CEN) involves the dorsolateral prefrontal, and the posterior parietal cortex, while the Default Mode Network (DMN) comprises the medial and ventral areas of the prefrontal cortex, the angular gyri and the posterior cingulate cortex (Zhou et al., 2018).

Beyond brain networks, the neuropsychological alterations in executive functions in adolescents with excess weight are well-known (Verdejo-García et al., 2012), especially in two core cognitive functions: disadvantageous decision making (Mallorquí-Bagué et al., 2016; Smith, Hay, Campbell & Trollor, 2011) and its related component of shifting, or cognitive flexibility, which is fundamental for effective decision-making (Laureiro-Martínez et al., 2018). The Iowa Gambling Task and the tasks of probabilistic reversal learning have become widely-used measures to evaluate these executive components. To measure real-life decision making, Bechara et al. (1994) developed the Iowa Gambling Task (IGT), which is capable to explore aspects related to affect in decision-making (Turnbull et al., 2014). Obese individuals show worsened performance in this task in many studies in adulthood (Fagundo et al., 2012; Pignatti et al., 2006), and adolescence (Moreno-Padilla et al., 2018). It is well-established that a poorer decision-making is associated with unhealthy eating behavior (He et al., 2014), less self-control and higher food cue sensitivity (van Meer et al., 2016)

Importantly, adaptive decision-making requires the ability to shift choices, and thus adapt the response to each specific event. High perseveration in choosing detrimental choices has been related to obesity, and linked to compulsive behaviors toward food, as measured with probabilistic reversal learning tasks (Contreras-Rodríguez et al., 2017). These alterations in reward-related decision making and shifting appear as salient neuropsychological factors in excess weight, leading to non-homeostatic eating behaviors, and to difficulties to lose weight, thus maintaining weight problems (Wu et al., 2016). This could be due to recent findings showing a lower engagement of executive areas on unhealthy food choices (He et al., 2014).

Interestingly, the insulin has an important role in the disruption of these executive areas. Insulin is one of the main hormones regulating the adequate energy balance and cognition. It acts in the brain networks important for higher cognition, such as SN, DMN and CEN, and when its levels are very high lead to cognitive impairment and poorer executive function

(Devoto et al., 2018; Kullman et al., 2012; Figlewitz et al., 2003; Timper & Brüning, 2017; Yau et al., 2014). High fat diets lead to chronic increases in insulin levels, and consequently greater fat accumulation that is linked to insulin resistance in adults and adolescents (Lustig et al., 2004; Oliva Gobato et al., 2014). In this line, individuals with excess weight show alterations related to the long-term regulation of these appetitive neuropeptides (Hussain & Bloom, 2013) which promote brain alterations, the reduction of the cognitive inhibitory control (Kullmann et al., 2016), and in turn, maladaptive eating behavior and a poorer weight control (Cheke et al., 2017), even since adolescence (Jastreboff et al., 2014; 2016; Martín-Pérez et al., 2018).

Despite that, as far as we know, no study has explored the associations between these related factors: adipose hormones (insulin), brain and executive function in adolescents with excess weight. Our study aims at characterizing the alterations in the most altered brain networks in obesity, SN, CEN and DMN (Kullmann et al., 2012; García-García et al., 2013; Gupta et al., 2015), in relation to common disruptions related to weight, as greater levels of insulin and body fat, in adolescents. Besides, in adolescents with excess weight, we wanted to explore the potential associations between the reflective/impulsive/interoceptive brain areas in excess weight and the performance in two crucial executive functions related to overeating and unhealthy eating behaviors: shifting and decision-making. We hypothesized that both networks (SN, CEN and DMN) will show higher activity among the impulsive (i.e. ventral striatum and amygdala) and interoceptive regions (i.e. insula), and lower activity in the reflective or executive areas (i.e. dorsal prefrontal areas; He et al., 2014), in relation with greater levels of insulin and body fat (Su et al., 2017). Besides, we also hypothesized a positive relationship between better performance in executive function tasks and reflective areas, while a negative association with impulsive and interoceptive areas (He at al., 2014).

Method

Participants

One hundred and twenty-two adolescents were recruited and classified in two groups according to their age-corrected BMI-percentile; 62 with normal weight and 60 with excess weight. Participants were recruited via advertisements in local newspapers and social media and information sessions in schools in the context of three separate projects (BRAINOBE, INTEROBE, NEUROECOBE). The inclusion criteria for all the projects were (1) age between 12 and 19 years old following the WHO criteria, (2) BMI-percentile between 5^{th} and 85^{th} for NW and at or above 85^{th} for EW according to their age. The exclusion criteria were: (1) comorbid metabolic or systemic diseases associated with obesity, (2) current eating or depressive disorders, (3) absence of structural abnormalities on the Magnetic Resonance Imaging. The Human Research Ethics Committee of the University of Granada approved both studies, and all participants, and their parents if they were minors, were informed about the aims of the study and provided an informed consent.

Adolescents in the first project (21 participants, 17.21% of the sample) completed two sessions. In the first one, participants underwent an MRI scanner and a measure of weight was collected with a digital scale (Tanita BC-420). Three subjects were excluded from imaging analysis due to their high motion during the scanning (see details in the preprocessing section). In a second session, a blood test was collected from all the participants in the Hospital Las Nieves in Granada. Participants in the second and third project (101 participants, 82.79%) completed these sessions above, and in addition they performed an assessment in neuropsychological tasks.

Measures

Imaging data acquisition. All participants were scanned at the same time of the day, approximately between the first and third our after lunch, and performed a 6-min resting-state scan. They were instructed to lie still with eyes closed and not to think about anything in particular. We used a 3.0 Tesla clinical MRI scanner, equipped with an eight-channel phased-array head coil (Intera Achieva Philips Medical Systems, Eindhoven, The Netherlands). A T2*-weighted echo-planar imaging (EPI) was obtained (TR=2000ms, TE=35ms, FOV=230 x 230mm, 96x96 pixel matrix; flip angle=90º, 21 4-mm axial slices, 1-mm gap, 180 whole-brain volumes). The sequence included four initial dummy volumes to allow the magnetization to reach equilibrium.

For the structural used in following preprocessing steps, a 3D volume was acquired using a T1-weighted turbo-gradient-echo sequence in the sagital plane. A resolution of 0.94×0.94×1.0 mm (160 slices, FOV=240×240 mm^2, matrix 256×256), TR=8.3 ms, a TE=3.8 ms, a TI=1022.6264 ms, and a flip angle=8° were obtained.

Metabolic variables.

Body Fat (subcutaneous adipose tissue). Body fat was collected using the Tanita BC-420 Segmental Body Composition Analyzer (Tanita Corporation, Tokyo, Japan) with correction for indoor clothing. Adolescents stood in the analyzer in bare feet. Regarding the measures, only the whole-body percentage fat was used in this study. This measure has been well-validated in several studies (Erdogan et al., 2013; Browning et al., 2011).

Fasting plasma insulin levels. Blood extraction was performed after a 12-hour night fasting, in the Hospital Virgen de las Nieves in Granada. Collected samples were stored in EDTA tubes and sent to the Instituto de la Grasa, Sevilla, to be analyzed. The plasma was separated through refrigerated centrifugation at 2500-3000 rpm during 10 minutes. Samples

were processed immediately or during the first week after their conservation at -20°C. Fasting insulin levels were collected for all the participants in order to perform subsequent analyses.

Neuropsychological tasks.

Shifting: an index of maladapted decision-making. The Probabilistic Reversal Learning Task we used is based on Swainson et al., (2000). This is a computer task of 160 trials (four phases), in which the participant has to choose between two different colored-pattern stimuli. They were instructed that one stimulus would be correct most of the times (the 80% of times the correct stimulus will give a reward) and the other would be incorrect the most of the times on each trial. After 40 trials (the first phase), the rule deciding the correct stimulus, change (second phase). The third and fourth phase were identical to the phases 1 and 2, but with a different probability given to each stimulus (70% of times the correct stimulus will give a reward). The outcome score from this task was the "flexibility index", calculated as the substraction between the trials of the first and third phase (original stimuli) and the second and fourth phase (reversed stimuli). The lower flexibility index, the worse performance in the task. A lower performance has been related with unhealthy eating patterns, and excess-weight related indexes (Contreras-Rodríguez et al., 2017) and has been identified as a proxy of compulsive behaviors.

Decision-making. The Iowa Gambling Task (with decks ABCD) has been widely used in previous studies to simulate real decision-making (Bechara et al., 2000). The participant´s task consist of choosing each of the 100 trials a card selected from one of the four decks, with the goal of earning as much virtual game money as possible. Some of these cards can either reward or penalize them and the decks differ among them in the reward-penalty balance. Likewise, some decks are described as "bad decks" and other like "good decks". The greater score at the final of the task implies the greater election of "good decks" and thus, the better

decision-making. This task is divided in five blocks and a net score below zero has been recently used as a "cut-off" for implying a disadvantageously decision-making (Verdejo-García et al., 2010; He et al., 2016).

Analyses

Preprocessing of imaging data. Functional data was preprocessed using the CONN functional connectivity toolbox v17, implemented in Matlab version R2017a, and in the Statistical Parametric Mapping (SPM12). This toolbox has been recently used in many psychological and clinical researches.

Respecting to the functional images, firstly they were realigned to the first scan, coregistered to the MNI anatomical template image and slice-time corrected. Secondly, the images of each subject were assessed in motion artifacts and head motion using the ART toolbox implemented in CONN. This toolbox allows to create motion confound regressors (3 translation and 3 rotation parameters) and remove outlier images for subsequent analyses (Power, 2012). Time series extracted from the white matter and the cerebrospinal fluid, as well as the head motion parameters were identified as nuisance signals. Those signals were regressed out using the CompCor strategy of CONN to remove potential confounds to the BOLD signal and reduce the impact of the physiological noise and head motion in the fMRI data. Resulting images were also registered according to the MNI anatomical coordinates and then coregistered with each participant´s functional scan. Finally, images were spatial smoothed using a Gaussian kernel of FWHM 6 mm. Three participants were removed from posterior analyses due to the high number of outlier scans in the realignment step. The criterion for eliminating participants with high motion is having less than 4 minutes of data after outliers' removal (Satterthwaite et al., 2013). Three participants met this criterion and were excluded

for the following analyses.

Independent component analysis (ICA). GIFT toolbox (Version 3.0b) was used to perform the group ICA analysis with the Infomax algorithm. Previous steps after ICA analysis included the estimation of the number of independent components (IC) via the minimum length criteria (Li et al., 2007) and the two step reduction approach using PCA. The process by which the ICs were determined was data-driven. Each spatial map (IC) was formed by a group of voxels showing a similar pattern of activity. In this line, thirty-seven IC were extracted with our data, and 20 iterations were performed by ICASSO, running the algorithm with different initial values each time (Himberg & Hyvarinen, 2003) to obtain the averaged maps across runs and to ensure the stability of the ICs. Finally, the spatial and temporal maps were estimated with a back reconstruction approach.

As some ICs may represent motion or physiological noise signals, some artifact ICs were eliminated after a visual inspection, following the recommendations of Griffanti et al., (2017). Besides, from the remaining ICs, we extracted those networks which overlap with the templates of the salience network (SN), central executive network (CEN) and default mode network (DMN), as they were the networks of our study´s interest.

Finally, SPM12 was used to perform multiple regression at the second level of analyses for the SN and the DMN, separately. In each model, insulin and fat were entered as variables of interest, while sex and age were inserted into both models as covariates of no interest.

Second level analyses and imaging thresholding criteria. SPM12 was used to perform multiple regressions at the second level of analyses for the SN, CEN and the DMN, separately. In each model, insulin and fat were entered as variables of interest, while sex and age were inserted into both models as covariates of no interest.

For the second level analyses in association with body fat and fasting insulin levels, we

applied the masks of the brain networks selected in this study (SN, CEN and DMN), extracted from the BrainMap database of 20 maps created on the basis of many functional imaging studies involving nearly 30000 human subjects (Smith et al., 2009; Laird et al., 2011). In all cases, statistical significance was set at $p<0.05$, Family-Wise Error (FWE) corrected for multiple comparisons across all in-mask voxels (i.e. using small-volume correction procedures).

Statistical analyses of the demographic and neuropsychological measures. These analyses were performed using the SPSS statistical package version 18. All data were tested for normality using the Kolmogorov-Smirnov test, and those which were not normally distributed were log-transformed. For illustrative purposes, t-test and chi-squared were used, to explore the differences in the demographic and neuropsychological tasks performance.

Finally, we extracted the peak value of the resulting cluster within the SN, CEN and DMN networks. Multiple regression analyses were used to explore if these brain variables could predict the performance over the PRLT/shifting and IGT/decision-making in the sub-sample of adolescents with excess weight, controlled by the variables of no interest, sex and age, in both regression analyses. A $p<0.05$ was considered to be significant.

Results

Demographic and neuropsychological tasks performance

The EW and HW groups did not differ in age or sex, but as expected participants with EW had higher BMI, body fat and insulin levels (Table 1).

Table 1

Demographics and clinical characteristics of the study groups

	Normal weight (N=62)	**Excess weight (N=57)**		
	Mean (SD)	Mean (SD)	Test statistics [a]	*p* value
Age (years)	15.74 (1.58)	15.18 (1.76)	1.840	0.068
BMI percentile	47.65 (20.91)	94.51 (3.689)	-17.352	0.000
Fat (%)	18.05 (6.68)	32.14 (9.10)	-9.560	0.000
Sex (females)	37 (59.7%)	32 (56.1%)	0.153	0.696
Fasting Insulin (µU/ml)	8.84 (4.14)	13.36 (6.67)	-4.610	0.000
	NW (N=53) Mean (SD)	EW (N=44) Mean (SD)	Test statistics [a]	*p* value
IGT total score	3.06 (25.75)	-0.07 (21.80)	0.647	0.519
RLT total score (log)	14.40 (11.96)	13.40 (11.83)	0.407	0.685

Note: [a] Independent samples t-tests were used to asses for between-groups differences in all cases, except for sex where chi-square tests were employed. *Abbreviations*: NW, normal weight; EW, excess weight, SD, standard deviation

Associations between brain networks and metabolic variables

Salience Network. Increased body fat and insulin levels were positively associated with a cluster containing ventral striatum extending to the subgenual anterior cingulate cortex (sgACC), and negatively associated with the dorsal anterior cingulate cortex within the salience network (Table 2; Figure 2).

Default Mode Network and Central Executive Network. No association with insulin and fat was found within these networks.

Table 2

Positive and negative associations between the salience networks activity and the targeted adiposity signals (insulin/fat) related to excess weight.

Brain Network	Brain Region		x, y, z	T	CS	Association	$P_{FWE-SVC}$
Salience							
	Ventral Striatum	R	16, 24, -14	5.2	53	Positive	0.008
	Dorsal ACC	L	-4, 30, 22	5.0	205	Negative	0.015

Note: Coordinates (x, y, z) are given in Montreal Neurological Institute (MNI) Atlas space. *Abbreviations*: CS, cluster size, ACC, anterior cingulate cortex. All results herein surpassed a PFWE<0.05 following small-volume correction procedures within the mask of each network.

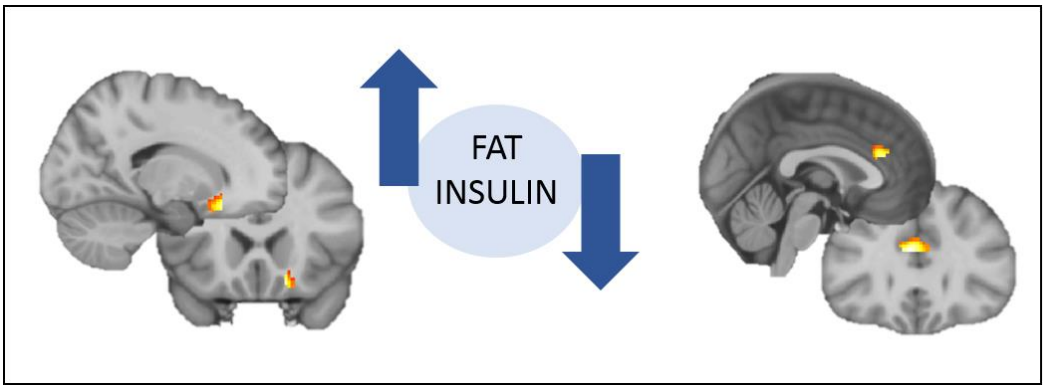

Figure 1. Brain regions within the salience networks displaying positive and negative significant associations with body fat and fasting insulin levels.

Note: The right hemisphere corresponds to the right side of axial and coronal views.

Associations between metabolic-related brain networks and neuropsychological tasks performance

Introducing sex and age in a stepwise multiple regression model, results showed that shifting, in the best fit model, was positively related to dACC, while negatively associated with VS within the salience network [$F_{(2, 43)}$=8.328; R=0.537; p=0.001]. Regarding decision-making, higher activity of the VS cluster associated with disadvantageous decision making [$F_{(2,}$

43)=3.863; R=0.398; p=0.029] (see in detail in Figure 2).

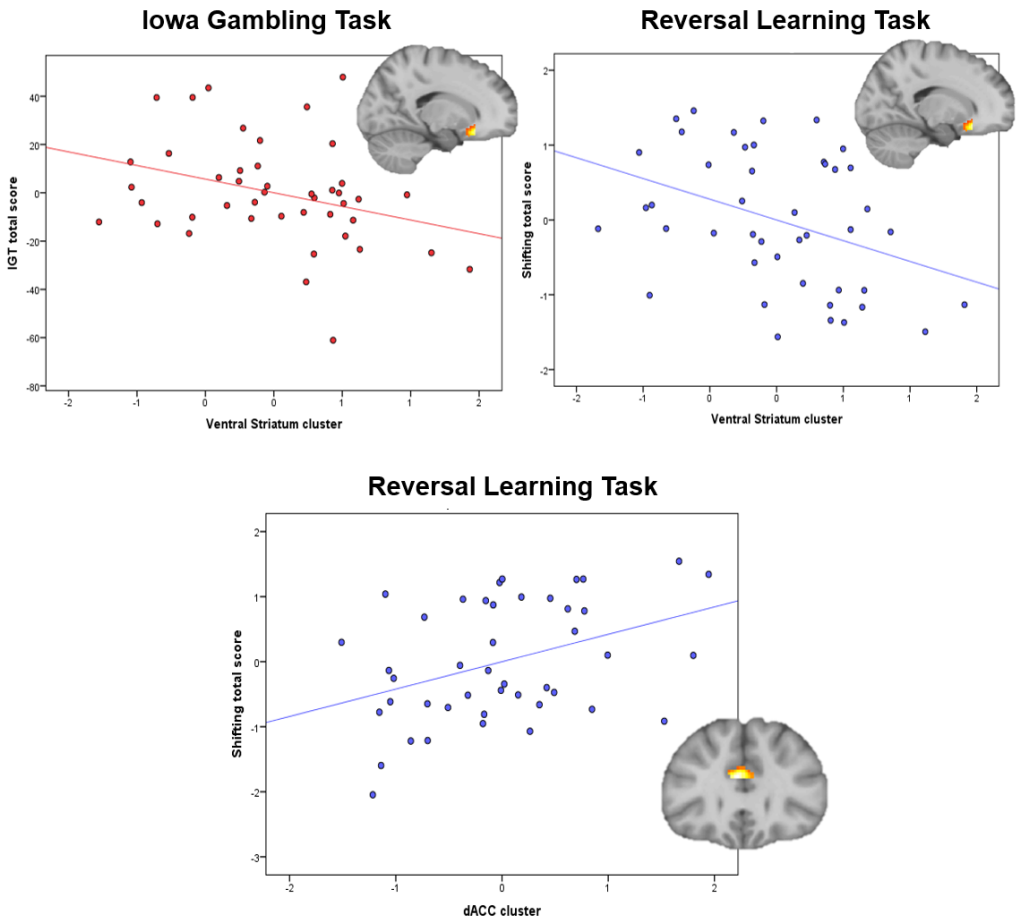

Figure 2. Plot showing significant associations between brain alterations within the Salience Network and neuropsychological executive functions in excess weight individuals.

Discussion

This study was focused on two main aims. First, we wanted to characterize the associations between high insulin and body fat levels -common metabolic dysregulations in obesity-, and the main brain networks involved in maladaptive eating behavior and worsened cognitive abilities (salience, SN, central executive, CEN, and default mode, DMN, networks)

in the whole sample of adolescents. At this regard, two areas within the SN showed a significant association with insulin and body fat. Greater insulin levels and body fat were positively related to greater activation of the ventral striatum extending to the subgenual anterior cingulate cortex (sgACC), related to the impulsive system, and negatively associated to greater activation of the dorsal anterior cingulate cortex (dACC), associated with the reflective system. Secondly, we aimed at studying the association between the brain alterations within the networks and the performance on shifting and decision making only in adolescents with excess weight. According to our second hypothesis, we found that both areas related to insulin and body fat levels within the SN were predictors of adequate shifting, while only the ventral striatum negatively predict advantageous decision-making.

Our brain results are in line with previous studies finding alterations in the salience network of obese individuals (García-García et al., 2013). In our study, abnormally high insulin and body fat levels were related to increased activity in the ventral striatum, which is congruent with other studies finding an alteration in the striatum within the salience network in obesity (García-García et al., 2013). Furthermore, our results are in line with recent studies implicating ventral striatum in the "impulsive system", associated with a lack of inhibitory control (He et al., 2014). More specifically, Jastreboff et al. (2013) showed a positive relationship between striatal areas related to reward and motivation and increased levels of insulin, and also an association of these alterations with food craving. Likewise Zhang et al. (2017) found a relationship between the increased signaling of insulin in the striatum and lower inhibitory control. Thus, the metabolic and brain disruptions could be very deleterious to control over eating behavior. These previous studies also support the role of heightened insulin levels in the promotion of hedonic or pleasurable response to food (Isganaitis & Lustig, 2005) via the alteration of the "impulsive" brain areas. Besides, this result is complemented with the lower activity of the dACC related to high insulin and body fat. The association dACC-insulin was

also found in healthy adults in a recent study (Ryan et al., 2018), in which it was suggested that altered insulin hinders the shift between reward areas to cognitive control regions to regulate eating. This area, comprised in the "reflective system" is necessary to balance the cited above "impulsive system", and when its activity is blunted, cognitive skills to inhibit food intake and overeating are dampened (Pignati et al., 2006; Frank & Kaye, 2012; He et al., 2014).

Overall, our results are in agreement with previous studies, which relate the imbalance of both VS and dACC with unhealthy eating habits due to their associations with urge and self-control, respectively (He et al., 2014; Zhang et al., 2015). Besides, our data support the implication of these brain areas in cognition, as found in previous studies (Bressler & Menon, 2010; Goulden et al., 2014). The fact that both areas significantly predict the performance in shifting, and that VS predict IGT performance might confirm that, also in adolescents with excess weight, metabolic and brain factors may alter decision-making and possibly lead to worse eating behaviors, as those regarding obesity, although this is merely speculative as our study did not measure eating behavior variables. However, our data did support that high insulin levels alter the homeostatic and hedonic brain, and also has an indirect relationship with executive dysfunction in some cognitive domains such as decision-making and shifting. According to Higgs et al. (2017), metabolic, cognitive and brain factors collaborate to regulate eating control, and they proposed a model integrating all these factors. Our results partially support this model, pointing to the importance of the associations between insulin, homeostatic and hedonic areas, and cognition.

Finally, this study was performed in the context of some limitations. First of all, this is a cross-sectional study, so our data did not allow us to know if these brain and neuropsychological problems are a cause or a consequence of obesity. Secondly, our study lacks from specific food behavior measures to ensure that this poor performance in neuropsychological tasks is really predicting obesity behaviors, or it is just an indirect

association. Besides, collecting measures of the affective states of the participants during the different sessions could have provided an interesting complement to know if mood could influence decision-making in excess weight individuals. Finally, the sample size to analyze neuropsychological tasks was smaller than the total sample introduced in the neuroimaging analyses, so future studies with bigger samples are needed to replicate our findings on flexibility and decision-making.

Further studies should take these flaws into account. The development in our knowledge about neuropsychological and neuro-metabolic alterations in adolescents with excess weight would contribute to improve current treatments for obesity, giving more importance to the cognitive components of current weight-loss interventions.

Appendix

Supplemental Results

Although the total scores in the Iowa Gambling Task (IGT) did not differ between normal weight and excess weight groups. Therefore, we explored these results dividing the excess weight group in those individuals who has overweight and those with obesity. According to this distinction, total scores result significantly lower in obese individuals in comparison to those in the control and overweight groups [$F_{(2,94)}=3.312; p=0.041$]. This was also explored by means of a repeated measures ANOVA with the different blocks of the IGT task. The results shown in the Figure S2, show how the learning curves in the obese group is lower compared with both non-obese groups, resulting in a significant Group X Block interaction [$F_{(4,92)}=3.560; p=0.031$]. On the other hand, individuals with overweight and those with healthy weight (control group), did not show differences.

Due to power issues, we used a unique group comprising overweight and obese individuals in an "excess weight group". However, our further analyses support the disadvantageous decision-making in obese individuals, as reported in other studies (Moreno-Padilla et al., 2018).

Supplemental Figures

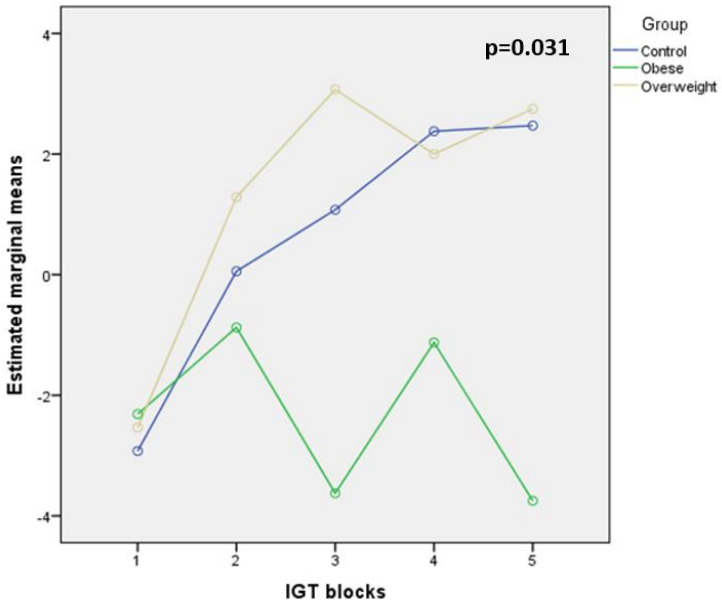

Figure S2. Figure showing a repeated Measures ANOVA analysis showing the different learning curves along the five blocks of the IGT.

Note: The excess weight group has been divided in overweight and obese to perform this analysis. Data show that overweight adolescents perform the task similarly to control group, while obese adolescents make the most disadvantageous decision and do show poor learning results along the task.

IV. GENERAL DISCUSSION, CONCLUSIONS AND FUTURE PERSPECTIVES

Chapter 7. General Discussion

1. Discussion

The present thesis aims at identifying functional connectivity alterations between the brain networks implicated in driving eating behaviors following "homeostatic" and "non-homeostatic" cues in adolescents with excess weight. The knowledge derived from the present thesis fulfills the lack of studies in this vulnerable population, prone to develop maladaptive eating habits because of the presence of enhanced stress sensitivity and impulsive behaviors at this stage of development (Verdejo-García et al., 2015). Adolescence is a critical period for weight gain due to the start of the own decision-making process about food choices, which is a relevant factor that determines future food behaviors, and therefore the persistence of excess weight into adulthood (Simmonds, Llewellyn, Owen & Woolacott, 2015).

We departed from those studies in adults with excess weight showing a neurobiological overlap between stress and "homeostatic" and "non-homeostatic" circuits that drive eating behaviors, and how alterations among these brain networks increase the presence of "comfort food" behaviors. From this point, the studies that make up this thesis were specifically designed to comprehensively explore for resting-state functional connectivity changes in relevant brain regions within the targeted brain circuits involved in driving eating behaviors in adolescents with excess weight. Furthermore, this thesis aimed to explore the relationship between the detected brain alterations and several psychological and behavioral variables that have been frequently associated to excess weight, such as stress, emotional eating, executive function, and the capacity to lose weight following a three months' diet.

These aims took the form of three studies which included the specific study of the functional connectivity of the hypothalamus, center of the homeostasis (Tasker, 2006); the amygdala, the main area receiving stressful inputs (Tasker & Herman, 2011) and more

associated to food craving (Petrovich & Gallagher, 2006); and the brain networks found to be altered in adults with excess weight: the salience, the central executive and the default mode networks (García-García et al., 2013; Kullmann et al. 2012).

The first study provided relevant new data on adolescents with excess weight. Previous functional connectivity studies in adults with excess weight showed greater connectivity between the medial hypothalamus (MH) and rewarding brain areas (Contreras-Rodríguez et al., 2017; Kullmann et al., 2014). Nevertheless, our results in adolescents with excess weight showed a strengthened functional connectivity between the lateral part of the hypothalamus (LH), more related to reward (Castro, Cole & Berridge, 2015) and brain regions associated to the emotional, salient and rewarding value of foods (i.e., OFC and ventral striatum) (Berridge, 2009). Yet the most interesting finding was that higher connectivity between the LH and brain regions that confer motivation for food (i.e., nucleus accumbens and the midbrain) was positively correlated with the stress response during a social stress task (TSST). The connectivity with the midbrain also showed a positive association with emotional eating behaviors, or the tendency to eat in an attempt to soothing negative emotional experiences, such as stress.

The existence of a relationship between stress-driven eating behavior and the LH-midbrain network supports the Dallman´s model (2010), and it extends its implications to adolescence. The relevance of the midbrain-hypothalamic circuit in adolescence had been previously emphasized (Mietus-Snyder & Lustig, 2008) in regulating food intake, according to energy strores in homeostatic conditions. However, this association seems to be easily overriden by emotional and regarding cues, when the limbic areas would gain relevance in regulating such processes.

Therefore, in our second study, we decided to specifically investigate the functional connectivity of the amygdala, attending to its different subnuclei, the central (CeA) and the basolateral amygdala (BLA), and the association of their altered functional connectivity with chronic stress and weight loss in a larger sample of adolescents with excess weight that underwent a three-months diet and physical exercise intervention, compared with a group of normal weight adolescents. The approach to the different amygdala subnuclei was useful to capture the abnormalities within the amygdala circuits in the adolescents with excess weight. Our results showed an altered functional connectivity between the central amygdala and the default mode network, specifically a lower connectivity with posterior regions, and a higher connectivity with anterior portions in the adolescents with excess weight. Furthermore, this group also showed a lower functional connectivity between the BLA and the dorsal caudate bilaterally. Interestingly, in the adolescents with excess weight, higher functional connectivity in the CeA-midbrain circuit was associated with less weight loss, and higher accumulation of hair cortisol during the three months´ intervention.

The finding involving the association between the CeA-midbrain connectivity and weight change, and chronic stress complements the findings of our first study. According to the theoretical model proposed by Mietus-Snyder & Lustig (2008), the amygdala would be the area overriding the homeostatic control of food regulated by the midbrain and the hypothalamus. Therefore, the results obtained in our first and second studies, point the midbrain as a key region in stress-related unhealthy eating behaviors. The midbrain stands in a central position for energy balance regulation and rewarding-related processes. Its projections to the hypothalamus and the amygdala are well-known since classical animal studies (Box et al., 1979; Rizvi et al., 1991). Despite, the CeA-midbrain circuit has been previously implicated in stress and eating behaviors in adults (Abizaid & Andrews, 2015) our work is the first showing its dysfunction and implications in adolescents with excess weight. Unlike BLA, it

exists great direct connections between the CeA and different nuclei of the midbrain (Rizvi et al., 1991; Lee et al., 2011; Tovote et al., 2016). Such connections, that also encompass the nucleus accumbens, are highly involved in modulating behaviors such as appetite, incentive salience, motivation and reward, and the willingness to work to access highly palatable foods (Mahler & Berridge, 2009; Abizaid, 2009; Ross et al., 2016), maybe due to the central role of these areas in the dopaminergic pathways. Moreover, the CeA is the most reactive nuclei to stressful events (Arnett et al., 2015). Therefore, a higher functional connectivity areas among the CeA, the midbrain and the nucleus accumbens may involve a heightened desire to food and food-seeking behaviors, altering eating behavior, through affective and rewarding dysregulations, since childhood (Mietus-Snyder & Lustig, 2008). This study, for the first time, found that the central amygdala-midbrain network would be one of the greatest disruptors of the homeostatic eating, as well as an important network to enhance the stress-related eating in adolescents with excess weight.

However, a proper regulation of both affect and food choices also rely upon adequate executive function, crucial for inhibiting maladaptive responses to food cues and making better decisions, especially under affective conditions (Higgs et al., 2016). In this line, our third study highlights the important association between brain alterations related to obesity and disadvantageous executive functioning in adolescents with excess weight. Our results showed a worse performance on decision-making in adolescents with excess weight, however we did not find such difference in shifting. Previous studies had already found differences between obese and normal weight individuals in the performance of several executive functions (Fagundo et al., 2012; Verdejo-García et al., 2010; Moreno-Padilla et al., 2018). However, no study to our knowledge has related these alterations in executive functions with the metabolic-related activity of the Salience Network, the Central Executive Network and the Default Mode Network in adolescents with obesity. The findings of our study support the role of "impulsive"

and "reflective" brain areas over executive function, not so with the interoceptive implication over cognition, as contrary to our hypothesis, the insula was not found to be significantly related to disrupted indexes of obesity (insulin and fat). The fact that our results finds alterations in the SN, but not in DMN and CEN is quite interesting. While DMN and CEN are responsible for endogenous and exogenous attention, the SN is the network shifting the attention between one process and the other. The SN has a crucial role in cognition, and according to our results, in obesity. The disruptions in these networks related to enhanced activity in impulsive areas and decreased activity in areas regarding cognitive control, could drive the SN to preferably focus attention on rewarding stimuli and, behaviorally, to have more difficulties to resist temptation (Steimke et al., 2017).

Overall, our findings support other previous results in the literature, which indicated a dysregulation in the homeostatic brain areas, an enhanced relevance of non-homeostatic areas in obesity and overweight, and a decreased activity in the executive brain. However, these previous studies have been carried out in adult population or in non-obese populations, and no study to our knowledge has studied previously if these areas were already dysregulated in adolescents with excess weight.

Our results also state specific brain connections by which the appetite and stress overlap. This overlap, when dysfunctional, allows adolescents with excess weight to use foods as an emotional comforting factor to relieve negative affective situations, such as stress.

2. Clinical implications and applications

Being overweight or obese may result from an imbalance of the increased intake of ubiquitous and inexpensive high palatable food (high in sugar and fat), and the decreased physical activity (WHO, 2016). Our results highlight the involvement of several brain networks in excess weight

problems, and also their relationship with stress and executive alterations. However, treating these affective and cognitive components on their own do not guarantee the restoration of brain abnormalities. It is important to understand the pathophysiology of excess weight in adolescence to develop more specific psychological interventions with localized brain targets.

On the basis of the above-mentioned affective and cognitive alterations, in relation to brain, this thesis suggests the implementation of treatment components guided to modify the attentional and approach bias, which would allow individuals to regulate the activation of the "impulsive brain" (amygdala, midbrain and ventral striatum) when exposing to rewarding food stimuli. Also, another important example of successful training in high-cognitive executive components is the goal-management training, which has shown good results in similar populations, as those with addictive problems (Valls-Serrano, Caracuel & Verdejo, 2016), and also in those with frontal lobe brain damage (Levine et al., 2011), supporting an improvement in the "reflective" brain (dorsal PFC). The optimization of decision-making must be specifically considered within a larger problem-solving program to make it more effective (Nezu, Nezu & Zurilla, 2013). In this kind of programs, might be interesting to develop other components related to improve the reflective path of decision-making in people with excess weight, such as mindful eating behaviors.

On the other side, according to the results of this thesis, stress and affective factors has a great importance over eating behavior. Learning how to cope with stress and also, as signaled above, to make better decisions could improve detrimental behaviors to health, such as emotional, external or disinhibited eating behaviors, or at worst, binge eating. For this purpose, cognitive-behavioral stress management or mindfulness-based stress reduction programs should be used to teach people how to cope with stress in a healthier way. These kind of programs are effective both for decreasing the amygdala volume (brain), augmented under

chronic stress, and for reducing weight (behavior/outcome) (Christaki et al., 2013; Holzel et al., 2010)

From governmental to society levels, much can be done to restrict the "obesogenic environment" by means of promoting the availability of healthy choices and social changes supporting those who feel marginalization and psychological distress only by their body shape. However, current interventions based in the promotion of exercise and calorie-restrictive diets are insufficiently effective (Langeveld and DeVries, 2015; Papies, Stroebe & Aarts, 2008). These difficulties are heightened in those with problems in cognitive and affective factors, and also because of brain functioning fostering overeating. In this sense, this thesis has tried to provide an insight into the neurobiological factors promoting excess weight in adolescence and how stress and personality influence food choices in those individuals.

This thesis also advocates for the need of multidisciplinary approaches to this problem, which cannot be solved with the current interventions, mostly based in limiting calorie intake. Psychological factors above must be considered in obesity interventions as a crucial part of the intervention.

Beyond cognitive/behavioral components suggested above, all these psychological interventions should be accompanied by motivational enhancing components to increased attainment to psychological, nutritional and exercise recommendations, as they have shown good results in enhancing the own´s inner motivation, especially in young people (Jensen et al., 2011), and also as an effective component of weight loss interventions.

3. **Limitations and future perspectives**

This thesis has been developed in the context of several limitations. Although we are aware of the specific limitations of each study, which are explained in the discussion section of each

chapter, in this section we have focused on general limitations of the thesis. First of all, two of the three studies used a cross-sectional design, which does not allow us to draw practical conclusions over the long-term effects of the measured variables and behaviors. Also, our longitudinal study regarding a weight loss intervention of three months, was not followed after the intervention was finished, so we only know the short-medium term consequences in weight loss, but we have not data about the weight status' maintenance. Also, the cross-sectional design in the brain measures collected does not let us know if these brain and neuropsychological problems are a cause or a consequence of obesity. Moreover, another important flaw was the loss of sample along the studies, provoking a loss in the statistical power of our results. Further studies should use higher samples and collect long-term measures to improve our results, and get stronger evidence.

Regarding method, the first study slightly differs from the second and third studies in the neuroimaging preprocessing steps. Due to the great improvement and the new evidence sheding light on functional neuroimaging´s motion correction, the first study is less updated than the other two. Thus, the method is not exactly the same, despite using resting-state functional connectivity measures across all the studies.

Besides that, our third study lacks of eating behavior measures, not being possible to determine if the brain alterations related to executive function actually are able to predict a maladaptive behavior or not. Based on this limitation, this thesis has given more importance to stress, as both studies regarding this affective factor, have taken into account physiological, brain and behavioral measures to provide a more comprehensive explanation of eating behavior. However, in the two studies comprising stress measures, we only collected physiological measures related to stress. Although these measures of hormonal concentration of stress, as measured by cortisol, are maybe a better index of actual activation of the HPA

axis, the subjective feeling of stress in every individual could have provided complementary information about the affective state of the individuals across the different sessions.

On other side, the lack of direct associations between stress and executive measures is one of the main flaws of this thesis. These measures were separated in the three studies, and no study was performed exploring the potential altered cross-talk between cognitive and affective measures. It would be interesting that future studies will analyze their relationship, and their conjoint influence over eating behavior in adolescents with excess weight.

Other important variable that was not directly measure was impulsivity. As it is the "antipode" of executive function, and it is quite related to stress-related eating, we can grossly guess that obese individuals would show higher impulsivity in relation to the affective and executive variables measured in this thesis. However, this is a naïve approach to a multidimensional measure, as it is impulsivity. Several domains of cognitive and affective impulsivity should be taking into account in future research regarding brain functioning in obesity. Also, the association of these impulsivity domains and different eating behavior would be a quite interesting way to distinguish different groups among obese individuals in the research and clinical practice (i.e. distinguish those with high affective impulsivity and emotional eating behaviors from those with cognitive impulsivity and restrained eating/external in treatment components). In this connection, it is important to highlight future perspectives in research and clinic applications. Further studies should investigate if different sub-groups in obese individuals respond differently to specific components in psychological interventions to better adjust treatment to "patients".

Looking ahead, new techniques such as neuromodulation, neurofeedback, and transcranial magnetic stimulation approaches have shown efficacy to reduce unhealthy eating behavior in the short and medium-term (Forcano et al., 2018; Kim et al., 2018). The

implementation of these techniques in the treatment protocol, together with psychological interventions, could enhance the improvement in brain function, and the efficacy of the weight lose interventions in the foreseeable future. Further research should provide more evidence regarding these new areas of knowledge to explore their potential benefits.

4. Conclusions

- Homeostatic and non-homeostatic pathways are dysregulated in adolescents with excess weight
- Stress may drive to emotional eating behaviors by means of a dysfunctional connectivity of the lateral hypothalamus with the midbrain
- The central amygdala functional connectivity with the midbrain is negatively related to weight loss.
- Accumulated cortisol during a three months intervention may lead to lower following of the interventions and less weight loss in adolescents with excess weight.
- Specific functional connectivity dysregulations in the homeostatic center, the hypothalamus, and the emotional hub, the amygdala, are related to the midbrain. Besides, the midbrain stands as a key region for stress-related eating in adolescents with excess weight.
- There is an imbalance between "impulsive" and "reflective" structures, which is directly related to high body fat and insulin levels, common disruptors in excess weight problems.
- This imbalance is related to poorer performance in crucial executive functions for controlling eating behavior: decision-making and shifting.

- There is an imbalance between homeostatic, hedonic and executive areas in excess weight adolescents. Affective and cognitive malfunction dampen the control of eating behavior and promote overeating and difficulties to lose weight.
- Brain alterations shown in this thesis go beyond specific brain problems. Our results have demonstrated that these brain disruptions represent the neural substrates of executive alterations and of maladapted eating behavior, highly related to the maintenance of excess weight problems.
- Our results show the necessity of adding both the management of stress and cognitive components to the current weight loss interventions. A complete therapeutic program regarding affective and executive alterations, could help to improve the brain function in specific areas related to affective and cognitive components and, in turn, it will improve intervention outcomes.

V. INTERNATIONAL DOCTORATE

1. Resumen

El exceso de peso se ha convertido en uno de los grandes problemas de la sociedad actual. La Organización Mundial de la Salud ha descrito la obesidad como una epidemia cuyas consecuencias son devastadoras e insidiosas.

Con respecto a la adolescencia, más de 340 millones de individuos de entre 12 y 19 años tienen exceso de peso, y se espera que, en 2022, el mundo cuente con más adolescentes con sobrepeso que con peso insuficiente. Debido a estas cifras abrumadoras, ha surgido un campo de investigación dedicado a explorar las causas y consecuencias de este problema y, a su vez, a intentar desarrollar estrategias de éxito para mejorar este problema que no deja de aumentar.

Mientras diferentes estudios proponen que el entorno "obesógeno" en el que vivimos, explica una gran parte del incremento del sobrepeso, otros resaltan la importancia que tienen los factores individuales psicológicos, metabólicos y neurobiológicos para desencadenar la obesidad. Entre estos factores individuales, el estrés y un mal funcionamiento ejecutivo, son dos grandes disruptores del consumo homeostático de alimentos, lo que a largo plazo, adaptaciones en el funcionamiento de las áreas cerebrales y alteraciones metabólicas que promueven la desregulación del balance energético. La reactividad aumentada del eje hipotalámico-hipofisario-adrenal (HHA), responsable de la homeostasis energética y emocional entre otros procesos, van más allá de los objetivos de esta tesis, contribuye a su vez a la reactividad de las áreas cerebrales no homeostáticas, y a la sobreingesta. Recientemente, estudios de neuroimagen han proporcionado suficiente evidencia sobre la desregulación entre los centros cerebrales homeostáticos (hipotálamo), y aquellos no-homeostáticos o hedónicos, como el sistema límbico y las áreas de recompensa. Este desequilibrio se ha asociado con exceso de peso, y puede estimularse por desequilibrios afectivos, como periodos de estrés, por

alteraciones en dimensiones cognitivas, como el funcionamiento ejecutivo, y por alteraciones metabólicas.

Bajo este contexto, la tesis doctoral tiene como objetivo caracterizar la conectividad funcional cerebral de las principales regiones relacionadas con el estrés, el funcionamiento ejecutivo y el comportamiento alimentario, y su impacto en el consumo de alimentos más allá de las necesidades energéticas en adolescentes con exceso de peso, en comparación con aquellos con peso normal. Para ello, tres estudios forman parte de esta tesis.

El **primer estudio**, centrado en el centro cerebral de la homeostasis, se ha derivado de estudios anteriores, que reportan alteraciones en los núcleos hipotalámicos de regulación homeostática en adultos con exceso de peso, y también del modelo de Dallman (2010), que sugiere que el estrés podría llevar a comportamientos alimentarios desadaptativos, como la ingesta emocional, mediante la desregulación de los circuitos hipotalámicos y cortico-estriatales y límbicos. Nuestro estudio explora si tales alteraciones existen ya en los adolescentes con exceso de peso, en comparación de aquellos adolescentes con un peso normal, mediante la investigación de las diferencias en conectividad funcional de los dos principales núcleos que conforman el hipotálamo, el medial y el lateral. Siguiendo el modelo teórico de Dallman, también exploramos la conectividad hipotalámica relacionada con el estrés y su asociación con el comportamiento de ingesta emocional.

Los resultados indicaron que los adolescentes con exceso de peso tenían una mayor conectividad funcional entre el hipotálamo lateral y áreas relacionadas con el sistema de recompensa cerebral, y que la conectividad más fuerte en esta red cerebral, específicamente con las principales áreas del sistema mesolímbico dopaminérgico (núcleo accumbens y mesencéfalo), se relacionó positivamente con la respuesta de estrés y, a su vez, con la ingesta emocional. Estos resultados extienden el modelo de Dallman a la adolescencia y destacan la

importancia de la ingesta de comida relacionada con el estrés desde etapas tempranas del desarrollo.

El **segundo estudio** se centró en el sistema límbico, ampliamente implicado en la regulación del eje HHA. Una de las regiones más importantes dentro del sistema límbico es la amígdala, que actúa como un área excitadora que proyecta hacia el hipotálamo. Una alteración en la amígdala podría modificar la función del eje HHA, y como consecuencia, empeorar la regulación adecuada del comportamiento alimentario. En este contexto, nosotros investigamos las diferencias entre dos grupos de adolescentes (exceso de peso versus peso normal) en la conectividad funcional de los diferentes núcleos de la amígdala (central y basolateral), para después explorar las asociaciones entre estos, y el cortisol acumulado y el cambio de peso, tras una intervención de pérdida de peso de tres meses de duración. Los adolescentes con exceso de peso mostraron una mayor conectividad funcional entre la amígdala central (CeA) y áreas prefrontales ventrales relacionadas con la valoración emocional y recompensante de los estímulos, y una menor conectividad funcional con la corteza cingulada posterior. Además, la amígdala basolateral (BLA) mostró una menor conectividad con el giro angular y con ambos caudados dorsales, un área hiperactiva ante estímulos recompensantes, pero hipofuncional en reposo. Además, encontramos que aquellos que no cambiaban el peso inicial o que ganaban peso tras la intervención de tres meses, mostraron una mayor conectividad funcional entre la CeA y el mesencéfalo. Es interesante resaltar que esta conectividad CeA-Mesencéfalo medió significativamente la relación negativa existente entre el estrés acumulado y la pérdida de peso en adolescentes con exceso de peso.

El **tercer y último estudio** pone la atención en la relevancia de los factores metabólicos, cerebrales y cognitivos comunes en obesidad, pero que no habíamos tratado en los estudios anteriores. Para ello, exploramos la actividad de las redes cerebrales de saliencia (RS), central ejecutivo (CEN) y de estado por defecto (RED) que se relacionaba con los altos niveles de

grasa corporal e insulina, como desajustes metabólicos comunes en los problemas de peso. Además, también quisimos explorar las relaciones entre la actividad alterada dentro de las redes RS, CEN y RED, y el funcionamiento ejecutivo en tareas de toma de decisiones y flexibilidad cognitiva o "shifting". Nuestros resultados mostraron un aumento de la actividad del estriado ventral, y un descenso de actividad en el cíngulo anterior dorsal, en relación con los niveles de insulina y grasa corporal. También, los resultados mostraron que las alteraciones en estas áreas se relacionaron significativamente con la ejecución en toma de decisiones y flexibilidad cognitiva. Es importante remarcar, que las asociaciones entre las áreas cerebrales y el funcionamiento ejecutivo fueron positivas con la activación del cíngulo anterior dorsal (zonas de control atencional y cognitivo, "sistema reflexivo"), y negativas con la actividad del estriado ventral (área de recompensa, "sistema impulsivo").

En general, estos estudios destacan que los adolescentes con exceso de peso muestran alteraciones en la conectividad funcional cerebral de áreas homeostáticas y hedónicas, lo cual es consistente con resultados previos en adultos bajo las mismas condiciones. Más específicamente, las alteraciones cerebrales se caracterizaron por la hiperactividad e hiperconectividad de regiones asociadas a la ingesta no-homeostática (ej., circuitos mesoestriatales y cortico-límbicos) y la hipoactividad de regiones de control atencional y cognitivo. Es importante remarcar que la fuerza de conectividad del hipotálamo y la amígdala con el mesencéfalo fue asociada a altos niveles de estrés, tanto crónico como agudo, además de a comportamientos relacionados con el exceso de peso, como la ingesta guiada por la emoción o "emotional eating" y cambios en el peso. Por consiguiente, el mesencéfalo podría ser un distintivo importante del exceso de peso inducido por condiciones emocionales adversas, al menos en adolescentes, donde esta área funcionaría motivando el comportamiento alimentario. Por lo tanto, el estrés, ya propuesto por varios modelos en obesidad, es un concepto

central a ser considerado en el círculo vicioso entre emociones e ingesta alimentaria, y debería ser tomado en cuenta en los actuales tratamientos para el exceso de peso.

Por otro lado, los resultados del tercer estudio, muestran que la desregulación de la insulina en las áreas cerebrales relacionadas con la cognición puede jugar un papel muy importante en la adecuada ejecución en tareas de función ejecutiva. Así, la relación entre la insulina y la actividad en áreas como el estriado ventral, implicada en el sistema mesolímbico dopaminérgico, y a su vez, en comportamientos motivados, se relaciona con una peor toma de decisiones y flexibilidad cognitiva. El estriado ventral, debido a su relación con el "sistema impulsivo" cerebral, sería muy sensible a la recompensa, y su hiperactividad, junto con una peor toma de decisiones, podría guiar los comportamientos alimentarios hacia opciones poco saludables y hacia la sobreingesta.

En conclusión, estos resultados ponen la atención en el especial papel que jugaría el sistema mesolímbico dopaminérgico en el mantenimiento del exceso de peso en adolescentes por dos vías. La primera, con una mayor implicación del mesencéfalo, estaría relacionada con alteraciones afectivas, específicamente con el estrés, y el uso de la ingesta de alimentos como forma de aliviar el malestar causado por los estados afectivos negativos. Por otro lado, la segunda vía, más guiada por el estriado ventral, se relacionaría con alteraciones cognitivas, específicamente en toma de decisiones y flexibilidad cognitiva.

Estas alteraciones afectivas y cognitivas afectarían de manera que ayudarían a mantener los problemas de peso, y a su vez, dificultarían la pérdida de peso y el éxito en las intervenciones dedicadas a esta población.

Estos cambios en el funcionamiento afectivo, metabólico, cognitivo y cerebral ponen de manifiesto la simplicidad de las intervenciones actuales. Estas intervenciones, basadas principalmente en el aumento de ejercicio y las dietas de restricción calórica, aunque efectivas,

son difíciles de mantener y están implementadas de manera poco eficiente. En este sentido, esta tesis ha intentado proporcionar una perspectiva de los factores neurobiológicos que fomentan el exceso de peso en la adolescencia, y como el estrés y las alteraciones ejecutivas influencian el comportamiento alimentario en estos individuos. Asimismo, esta tesis se rinde a la necesidad de aproximaciones multidisciplinares a este problema, que aborden los factores psicológicos tratados en este trabajo, y en numerosos trabajos de investigación sobre obesidad en adultos. Los factores psicológicos deben tomarse en cuenta en los tratamientos para la obesidad y deben desarrollarse intervenciones que incluyan técnicas de aumento de la motivación al cambio, y programas de manejo del estrés para mejorar el cumplimiento real de las intervenciones de pérdida de peso.

2. Conclusiones

- Las vías cerebrales homeostáticas y no homeostáticas están alteradas en adolescents con exceso de peso
- El estrés podría llevar a comportamientos de ingesta emocional por medio de las alteraciones en la conectividad funcional entre el hipotálamo lateral y el mesencéfalo
- La conectividad funcional de la amígdala central con el mesencéfalo se relaciona negativamente con la pérdida de peso.
- El cortisol acumulado durante una intervención de tres meses de duración se asocia a un menor seguimiento de la intervención y una menor pérdida de peso en los adolescentes con exceso de peso.
- Las alteraciones en la conectividad funcional en el centro homeostático, el hipotálamo, y el centro cerebral de la emoción, la amígdala, se relacionan con el mesencéfalo. Además, el mesencéfalo destaca como una region crucial en el comportamiento alimentario relacionado con el estrés en adolescentes con exceso de peso.

- Hay un desequilibrio entre las estructuras cerebrales que subyacen la impulsividad y el funcionamiento ejecutivo. Este desequilibrio se relaciona directamente con altos niveles de insulin y grasa subcutanea, alteraciones communes en problemas de exceso de peso.
- Esta alteración además, está relacionada con peor ejecución en funciones ejecutivas esenciales en el control de la ingesta: toma de decisiones y flexibilidad cognitiva.
- Existe un desequilibrio entre las áreas cerebrales homeostáticas y hedónicas en adolescentes con exceso de peso. Alteraciones afectivas o ejecutivas empeoran el control de la ingesta y promocionan la sobreingesta y las dificultades para perder peso.
- Las alteraciones cerebrales mostradas en esta tesis van más allá de problemas cerebrales específicos. Nuestros resultados han demostrado que estas alteraciones son los sustratos de peor funcionamiento ejecutivo, y de un comportamiento alimentario nocivo, relacionado a su vez con dificultades para perder peso y más importante, con el mantenimiento de los problemas asociados al exceso de peso.
- Nuestros resultados muestran la necesidad de añadir componentes cognitivos y afectivos a las intervenciones actuales de pérdida de peso. Un programa completo que comprenda las alteraciones en estos componentes, ayudará a mejorar el functionamiento cerebral en áreas específicamente relacionadas con el comportamiento alimentario, y a su vez, mejorará los resultados de la intervención.

V. REFERENCES

Abizaid, A., Andrews, Z. (2015). Neuroendocrine mechanisms that connect feeding behavior and stress. Lausanne: Frontiers Media.

Adam, T.C., and Epel, E.S. (2007). Stress, eating and the reward system. Physiology & Behavior, 91(4), 449-58.

Agerström, J., & Rooth, D. O. (2011). The role of automatic obesity stereotypes in real hiring discrimination. *Journal of Applied Psychology*, *96*(4), 790-805.

Alkharfy, K. (2011). Food Advertisements: To Ban or Not to Ban? Annals of Saudi Medicine, 31(6), 567.

Anand, B.K., Brobeck, J.R. (1951). Hypothalamic control of food intake in rats and cats. Yale J Bio Med., 24(2), 123-140.

Anderson, S. E., Cohen, P., Naumova, E. N., Jacques, P. F., & Must, A. (2007). Adolescent Obesity and Risk for Subsequent Major Depressive Disorder and Anxiety Disorder: Prospective Evidence. Psychosomatic Medicine, 69(8), 740–747.

Arnett, M. G., Pan, M. S., Doak, W., Cyr, P. E. P., Muglia, L. M., & Muglia, L. J. (2015). The role of glucocorticoid receptor-dependent activity in the amygdala central nucleus and reversibility of early-life stress programmed behavior. Translational Psychiatry, 5(4), e542–e542.

Australian Institute of Health and Welfare. (2017). *Australia´s Welfare 2017*. Retrieved https://www.aihw.gov.au/getmedia/088848dc-906d-4a8b-aa09-79df0f943984/aihw-aus-214-aw17.pdf

Avena, N.M. (Ed.). (2015). Hedonic Eating: How the Pleasure of Food Affects Our Brains and Behavior. New York: Oxford University Press

Baroncini, M., Jissendi, P., Balland, E., Besson, P., Pruvo, J. P., Francke, J. P., … Prevot, V. (2012). MRI atlas of the human hypothalamus. NeuroImage, 59(1), 168–180.

Bartels, L. K., & Nordstrom, C. R. (2013). Too big to hire: factors impacting weight discrimination. Management Research Review, 36(9), 868–881

Baum, C. L., & Ford, W. F. (2004). The wage effects of obesity: a longitudinal study. Health Economics, 13(9), 885–899.

Bechara, A. (2005). Decision making, impulse control and loss of willpower to resist drugs: a neurocognitive perspective. Nature Neuroscience, 8(11), 1458–1463

Bechara, A., Damasio, A. R., Damasio, H., & Anderson, S. W. (1994). Insensitivity to future consequences following damage to human prefrontal cortex. Cognition, 50(1-3), 7–15.

Begriche, K., Sutton, G. M., & Butler, A. A. (2011). Homeostastic and non-homeostatic functions of melanocortin-3 receptors in the control of energy balance and metabolism. Physiology & Behavior, 104(4), 546–554.

BeLue, R., Francis, L. A., & Colaco, B. (2009). Mental Health Problems and Overweight in a Nationally Representative Sample of Adolescents: Effects of Race and Ethnicity. PEDIATRICS, 123(2), 697–702.

Berridge, K. C. (2009). "Liking" and "wanting" food rewards: Brain substrates and roles in eating disorders. Physiology & Behavior, 97(5), 537–550.

Berridge, K. C., & Kringelbach, M. L. (2015). Pleasure Systems in the Brain. Neuron, 86(3), 646–664.

Berridge, K. C., Robinson, T. E., & Aldridge, J. W. (2009). Dissecting components of reward: "liking", "wanting", and learning. Current Opinion in Pharmacology, 9(1), 65–73.

Berthoud, H. R., & Münzberg, H. (2011). The lateral hypothalamus as integrator of metabolic and environmental needs: From electrical self-stimulation to opto-genetics. Physiology and Behavior, 104(1), 29–39.

Bickel, W. K., Jarmolowicz, D. P., Mueller, E. T., Gatchalian, K. M., & McClure, S. M. (2012). Are executive function and impulsivity antipodes? A conceptual reconstruction with special reference to addiction. Psychopharmacology, 221(3), 361–387.

Birn, R. M. (2012). The role of physiological noise in resting-state functional connectivity. NeuroImage, 62(2), 864-70.

Blouet, C., & Schwartz, G. J. (2012). Brainstem Nutrient Sensing in the Nucleus of the Solitary Tract Inhibits Feeding. Cell Metabolism, 16(5), 579–587

Blum, K., Thanos, P. K., & Gold, M. S. (2014). Dopamine and glucose, obesity, and reward deficiency syndrome. Frontiers in Psychology, 5, 919, doi:10.3389/fpsyg.2014.00919.

Bødker, M., Pisinger, C., Toft, U., & Jørgensen, T. (2015). The Danish fat tax—Effects on consumption patterns and risk of ischaemic heart disease. Preventive Medicine, 77, 200–203.

Bohon, C. (2017). Brain response to taste in overweight children: A pilot feasibility study. PLoS ONE, 12(2), e0172604.

Bonnelle, V., Ham, T. E., Leech, R., Kinnunen, K. M., Mehta, M. A., Greenwood, R. J., & Sharp, D. J. (2012). Salience network integrity predicts default mode network function after traumatic brain injury. Proceedings of the National Academy of Sciences, 109(12), 4690–4695.

Bowman, S. A., & Vinyard, B. T. (2004). Fast Food Consumption of U.S. Adults: Impact on Energy and Nutrient Intakes and Overweight Status. Journal of the American College of Nutrition, 23(2), 163–168.

Boyland, E. J., Harrold, J. A., Kirkham, T. C., & Halford, J. C. G. (2011). The extent of food advertising to children on UK television in 2008. International Journal of Pediatric Obesity, 6(5-6), 455–461.

Box, B. M., Bascom, R., & Mogenson, G. J. (1979). Hyperphagia and obesity produced by midbrain lesions in the rat: A comparison with hypothalamic hyperphagia and obesity. Behavioral and Neural Biology, 26(3), 330–341.

Bressler, S. L., & Menon, V. (2010). Large-scale brain networks in cognition: emerging methods and principles. Trends in Cognitive Sciences, 14(6), 277–290.

Brett, M., Anton, J.-L., Valabregue, R., & Poline, J.-B. (2002a). Region of interest analysis using the MarsBar toolbox for SPM 99. Neuroimage, 16(2), S497.

Brett, M., Anton, J.-L., Valabregue, R., & Poline, J.-B. (2002b). Region of interest analysis using the MarsBar toolbox for SPM 99. Neuroimage, 16, S497.

Brook, J. S., Zhang, C., Saar, N. S., & Brook, D. W. (2009). Psychosocial predictors, higher body mass index, and aspects of neurocognitive dysfunction. *Perceptual and Motor Skills*, *108*(1), 181-195.

Brownell, K.D., Wadden, T.A. (1984). Confronting obesity in children: behavioral and psychological factors, Pediatr Ann., 13(6), 473- 478, 480.

Bruce, A. S., Lepping, R. J., Bruce, J. M., Cherry, J. B. C., Martin, L. E., Davis, A. M., … Savage, C. R. (2013). Brain responses to food logos in obese and healthy weight children. The Journal of Pediatrics, 162(4), 759–764.e2.

Brug, J. (2008). Determinants of healthy eating: motivation, abilities and environmental opportunities. Family Practice, 25(Supplement 1), i50–i55.

Brunello, G., & D'Hombres, B. (2007). Does body weight affect wages? Economics & Human Biology, 5(1), 1–19.

Bzdok, D., Laird, A.R., Zilles, K., Fox, P.T., Eickhoff, S.B. (2013). An investigation of the structural, connectional, and functional subspecialization in the human amygdala. Human Brain Mapping, 34(12), 3247-66.

Campbell-Smith, E.J., Holmes et al., Lingawi, N.W., Panayi, M.C., Westbrook, R.F. (2015). Oxytocin signaling in basolateral and central amygdala nuclei differentially regulates the acquisition, expression, and extinction of context-conditioned fear in rats. Learning & Memory, 22(5), 247-257.

Carnell, S., Gibson, C., Benson, L., Ochner, C.N., Geliebter, A. (2011). Neuroimaging and obesity: current knowledge and future directions. Obesity Reviews, 13(1), 43-56.

Castellanos, E. H., Charboneau, E., Dietrich, M. S., Park, S., Bradley, B. P., Mogg, K., & Cowan, R. L. (2009). Obese adults have visual attention bias for food cue images: evidence for altered reward system function. International Journal of Obesity, 33(9), 1063–1073.

Castro, D. C., Cole, S. L., & Berridge, K. C. (2015). Lateral hypothalamus, nucleus accumbens, and ventral pallidum roles in eating and hunger: interactions between homeostatic and reward circuitry. Frontiers in Systems Neuroscience, 9, 90, doi: 10.3389/fnsys.2015.00090

Cawley, J., Rizzo, J. A., & Haas, K. (2007). Occupation-Specific Absenteeism Costs Associated With Obesity and Morbid Obesity. Journal of Occupational and Environmental Medicine, 49(12), 1317–1324.

Centers for disease control and prevention. (2016, October 20). Defining childhood obesity. Retrieved October 20, 2016, from https://www.cdc.gov/obesity/childhood/defining.html

Cheke, L. G., Bonnici, H. M., Clayton, N. S., & Simons, J. S. (2017). Obesity and insulin resistance are associated with reduced activity in core memory regions of the brain. Neuropsychologia, 96, 137–149.

Chen, Z., Li, J., Zhang, J., Xing, X., Gao, W., Lu, Z., Deng, H. (2013). Simultaneous determination of hair cortisol, cortisone and DHEAS with liquid chromatography–electrospray ionization-tandem mass spectrometry in negative mode. Journal of chromatography B, 929(15), 187-194.

Cherbuin, N., Sargent-Cox, K., Fraser, M., Sachdev, P., & Anstey, K. J. (2015). Being overweight is associated with hippocampal atrophy: The PATH Through Life Study. International Journal of Obesity, 39(10), 1509-1514.

Chodkowski, B. A., Cowan, R. L., & Niswender, K. D. (2016). Imbalance in resting state functional connectivity is associated with eating behaviors and adiposity in children. Heliyon, 2(1), e00058. doi:10.1016/j.heliyon.2015.e00058

Christaki, E., Kokkinos, A., Costarelli, V., Alexopoulos, E. C., Chrousos, G. P., & Darviri, C. (2013). Stress management can facilitate weight loss in Greek overweight and obese women: a pilot study. Journal of Human Nutrition and Dietetics, 26, 132–139.

Cohen, J. I., Yates, K. F., Duong, M., & Convit, A. (2011). Obesity, orbitofrontal structure and function are associated with food choice: a cross-sectional study. BMJ Open, 1(2), e000175–e000175.

Cole, T. J. (2000). Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ, 320(7244), 1240–1240.

Cole, T. J., & Lobstein, T. (2012). Extended international (IOTF) body mass index cut-offs for thinness, overweight and obesity. Pediatric Obesity, 7(4), 284–294.

Contreras-Rodríguez, O., Martín-Pérez, C., Vilar-López, R., & Verdejo-Garcia, A. (2017). Ventral and Dorsal Striatum Networks in Obesity: Link to Food Craving and Weight Gain. Biological Psychiatry, 81(9), 789–796.

Contreras-Rodríguez, O., Vilar-López, R., Andrews, Z. B., Navas, J. F., Soriano-Mas, C., & Verdejo-García, A. (2017). Altered cross-talk between the hypothalamus and non-homeostatic regions linked to obesity and difficulty to lose weight. Scientific Reports, 7(1), 9951.

Dagher, A., Neseliler, S., Han, J.E. (2017). Chapter 32 - Appetite as Motivated Choice: Hormonal and Environmental Influences. Decision Neuroscience, 397-409. Academic Press. El sevier inc

Dallman, M. F. (2010). Stress-induced obesity and the emotional nervous system. Trends in Endocrinology and Metabolism.

Dallman, M. F., Akana, S. F., Strack, A. M., Hanson, E. S., & Sebastian R. J. (1995). The Neural Network that Regulates Energy Balance Is Responsive to Glucocorticoids and Insulin and Also Regulates HPA Axis Responsivity at a Site Proximal to CRF Neurons. Annals of the New York Academy of Sciences, 771(1 Stress), 730–742.

Dallman, M. F., Pecoraro, N., Akana, S. F., La Fleur, S. E., Gomez, F., Houshyar, H., … Manalo, S. (2003). Chronic stress and obesity: a new view of “comfort food”. Proceedings of the National Academy of Sciences of the United States of America, 100(20), 11696–11701.

Davey, C.G., Allen, N.B., Harrison, B.J., Yucel, M. (2011). Increased Amygdala Response to Positive Social Feedback in Young People with Major Depressive Disorder. Biological Psychiatry, 69, 734-41.

De Kloet, E.R., Joëls, M., Holsboer, F. (2005). Stress and the brain: from adaptation to disease. Nature reviews neuroscience, 6, 463-475.

Devoto, F., Ferrulli, A., Zapparoli, L., Bonandrini, R., Sconfienza, L.M., Banfi, G., Luzi, L., Paulesu, E. (2018). Altered Brain Resting-State Functional Connectivity in Obese Patients Is Associated with Plasma Levels of Leptin. Diabetes, 67(S1). doi: https://doi.org/10.2337/db18-2077-P

Dierolf, A. M., Arlt, L. E., Roelofs, K., Kölsch, M., Hülsemann, M. J., Schächinger, H., & Naumann, E. (2016). Effects of basal and acute cortisol on cognitive flexibility in an emotional task switching paradigm in men. Hormones and Behavior, 81, 12–19.

Dixon, H. G., Scully, M. L., Wakefield, M. A., White, V. M., & Crawford, D. A. (2007). The effects of television advertisements for junk food versus nutritious food on children's food attitudes and preferences. Social Science & Medicine, 65(7), 1311–1323.

Dohle, S., Diel, K., & Hofmann, W. (2018). Executive functions and the self-regulation of eating behavior: A review. Appetite, 124, 4–9.

Doucet, G. E., Rasgon, N., McEwen, B. S., Micali, N., & Frangou, S. (2017). Elevated Body Mass Index is Associated with Increased Integration and Reduced Cohesion of Sensory-Driven and Internally Guided Resting-State Functional Brain Networks. Cerebral Cortex, 28(3), 988-97.

Dubois, P., Griffith, R., & O'Connell, M. (2017). The Effects of Banning Advertising in Junk Food Markets. The Review of Economic Studies, 85(1), 396–436.

EASO. (2018). Familiarity with junk-food ads linked with obesity in young people. Retrieved on 2018, May 22nd from https://www.eurekalert.org/pub_releases/2018-05/eaft-fwj052118.php

Engeland, A., Bjørge, T., Tverdal, A., & Søgaard, A. J. (2004). Obesity in Adolescence and Adulthood and the Risk of Adult Mortality. Epidemiology, 15(1), 79–85.

Etkin, A., Egner, T., Kalisch, R. (2010). Emotional processing in anterior cingulate and medial prefrontal cortex. Trends in Cognitive Sciences, 15(2), 85-93.

Fagundo, A. B., de la Torre, R., Jiménez-Murcia, S., Agüera, Z., Granero, R., Tárrega, S., … Fernández-Aranda, F. (2012). Executive Functions Profile in Extreme Eating/Weight Conditions: From Anorexia Nervosa to Obesity. PLoS ONE, 7(8), e43382. doi:10.1371/journal.pone.0043382

Faulconbridge, L. F., & Hayes, M. R. (2011). Regulation of Energy Balance and Body Weight by the Brain: A Distributed System Prone to Disruption. Psychiatric Clinics of North America, 34(4), 733–745.

Fernando, A.B.P., Murray, J.E., Milton, A.L. (2013). The amygdala: securing pleasure and avoiding pain. Frontiers in Behavioral Neuroscience, 7, 190. doi:0.3389/fnbeh.2013.00190.

Figlewicz, D. P. (2003). Adiposity signals and food reward: expanding the CNS roles of insulin and leptin. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 284(4), R882–R892. doi:10.1152/ajpregu.00602.2002

Figley, C. R., Asem, J. S. A., Levenbaum, E. L., & Courtney, S. M. (2016). Effects of Body Mass Index and Body Fat Percent on Default Mode, Executive Control, and Salience

Network Structure and Function. Frontiers in Neuroscience, 10. doi:10.3389/fnins.2016.00234

Flint, S. W., Čadek, M., Codreanu, S. C., Ivić, V., Zomer, C., & Gomoiu, A. (2016). Obesity Discrimination in the Recruitment Process: "You're Not Hired!" Frontiers in Psychology, 7. doi:10.3389/fpsyg.2016.00647

Forcano, L., Mata, F., de la Torre, R., & Verdejo-Garcia, A. (2018). Cognitive and neuromodulation strategies for unhealthy eating and obesity: Systematic review and discussion of neurocognitive mechanisms. Neuroscience & Biobehavioral Reviews, 87, 161–191.

Frank, G. K. W., & Kaye, W. H. (2012). Current status of functional imaging in eating disorders. International Journal of Eating Disorders, 45(6), 723–736.

Fundación Diabetes. (2004). La obesidad representa el 7% del gasto sanitario anual en España, unos 2.500 millones de euros. Retrieved 2004, May 18th from https://www.fundaciondiabetes.org/upload/noticias/3491/157.pdf

García-García, I., Jurado, M. Á., Garolera, M., Segura, B., Sala-Llonch, R., Marqués-Iturria, I., … Junqué, C. (2012). Alterations of the salience network in obesity: A resting-state fMRI study. Human Brain Mapping, 34(11), 2786–2797.

García-García, I., Jurado, M. A., Garolera, M., Segura, B., Marqués-Iturria, I., Pueyo, R., … Junqué, C. (2013). Functional connectivity in obesity during reward processing. NeuroImage, 66, 232–239.

Gao, Q., & Horvath, T. L. (2007). Neuronal control of energy homeostasis. FEBS Letters, 582(1), 132–141.

Giardino, W. J., & de Lecea, L. (2014). Hypocretin (orexin) neuromodulation of stress and reward pathways. Current Opinion in Neurobiology, 29, 103-8

Goodman, E., Whitaker, R.C. (2002). A prospective study of the role of depression in the development and persistence of adolescent obesity. Pediatrics, 110(3), 497-504.

Goulden, N., Khusnulina, A., Davis, N. J., Bracewell, R. M., Bokde, A. L., McNulty, J. P., & Mullins, P. G. (2014). The salience network is responsible for switching between the default mode network and the central executive network: Replication from DCM. NeuroImage, 99, 180–190.

Grabski, K., Lamalle, L., Vilain, C., Schwartz, J. L., Vallée, N., Tropres, I., … Sato, M. (2012). Functional MRI assessment of orofacial articulators: Neural correlates of lip, jaw, larynx, and tongue movements. Human Brain Mapping, 33(10), 2306–2321.

Gleichgerrcht, E., Ibáñez, A., Roca, M., Torralva, T., & Manes, F. (2010). Decision-making cognition in neurodegenerative diseases. Nature Reviews Neurology, 6(11), 611–623.

Grill, H. J., & Hayes, M. R. (2012). Hindbrain Neurons as an Essential Hub in the Neuroanatomically Distributed Control of Energy Balance. Cell Metabolism, 16(3), 296–309.

Gearhardt, A. N, Yokum, S., Orr, P.T. (2011). Neural Correlates of Food Addiction. Archives of General Psychiatry, 68(8), 808.

Gentili, C., Ricciardi, E., Gobbini, M.I., Santarelli, M.F., Haxby, J.V., Pietrini, P., Guazzelli, M. (2009). Beyond amygdala: Default Mode Network activity differs between patients with social phobia and healthy controls.

Guerrieri, R., Nederkoorn, C., Schrooten, M., Martijn, C., & Jansen, A. (2009). Inducing impulsivity leads high and low restrained eaters into overeating, whereas current dieters stick to their diet. Appetite, 53(1), 93–100.

Gupta, A., Mayer, E. A., Sanmiguel, C. P., Van Horn, J. D., Woodworth, D., Ellingson, B. M., … Labus, J. S. (2015). Patterns of brain structural connectivity differentiate normal weight from overweight subjects. NeuroImage: Clinical, 7, 506–517.

Hales, C. M., Carroll, M.D., Fryar, C.D., Ogden, C.L. (2017). Prevalence of Obesity Among Adults and Youth: United States, 2015-2016. NCHS Data Brief, 288:1-8.

Ham, T., Leff, A., de Boissezon, X., Joffe, A., & Sharp, D. J. (2013). Cognitive Control and the Salience Network: An Investigation of Error Processing and Effective Connectivity. Journal of Neuroscience, 33(16), 7091–7098.

Hamilton, D., Dee, A., & Perry, I. J. (2017). The lifetime costs of overweight and obesity in childhood and adolescence: a systematic review. Obesity Reviews, 19(4), 452–463. doi:10.1111/obr.12649

Hare T.A., Tottenham, N., Galvan, A., Voss, H.U., Glover G.H., Casey, B.J. (2008). Biological substrates of emotional reactivity and regulation in adolescence during an emotional go-nogo task. Biological Psychiatry, 63(10), 927-34.

Harris, G. C., Wimmer, M., & Aston-Jones, G. (2005). A role for lateral hypothalamic orexin neurons in reward seeking. Nature, 437(7058), 556–559.

Hassenstab, J. J., Sweet, L. H., Del Parigi, A., McCaffery, J. M., Haley, A. P., Demos, K. E., … Wing, R. R. (2012). Cortical thickness of the cognitive control network in obesity and successful weight loss maintenance: A preliminary MRI study. Psychiatry Research: Neuroimaging, 202(1), 77–79.

Havermans, R. C. (2011). “You Say it’s Liking, I Say it’s Wanting …”. On the difficulty of disentangling food reward in man. Appetite, 57(1), 286–294.

He, Q., Xiao, L., Xue, G., Wong, S., Ames, S. L., Xie, B., & Bechara, A. (2014). Altered dynamics between neural systems sub-serving decisions for unhealthy food. Frontiers in Neuroscience, 8. doi:10.3389/fnins.2014.00350

Hek, K., Direk, N., Newson, R. S., Hofman, A., Hoogendijk, W. J. G., Mulder, C. L., & Tiemeier, H. (2013). Anxiety disorders and salivary cortisol levels in older adults: A population-based study. Psychoneuroendocrinology, 38(2), 300–305.

Hemmingsson, E. (2014). A new model of the role of psychological and emotional distress in promoting obesity: Conceptual review with implications for treatment and prevention. Obesity Reviews, 15(9), 769-779.

Hensleigh, E., & Pritchard, L. M. (2013). Glucocorticoid receptor expression and sub-cellular localization in dopamine neurons of the rat midbrain. Neuroscience Letters, 556, 191–195.

Herman, J.P., Cullinan, W.E. (1997). Neurocircuitry of stress: central control of the hypothalamo-pituitary-adrenocortical axis. Trends in Neurosciences, 20(2):78-84.

Herman, J. P., McKlveen, J. M., Ghosal, S., Kopp, B., Wulsin, A., Makinson, R., … Myers, B. (2016). Regulation of the Hypothalamic-Pituitary-Adrenocortical Stress Response. Comprehensive Physiology, 603–621.

Herman, J. P., Ostrander, M. M., Mueller, N. K., & Figueiredo, H. (2005). Limbic system mechanisms of stress regulation: Hypothalamo-pituitary-adrenocortical axis. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 29(8), 1201–1213.

Higgs, S. (2016). Cognitive processing of food rewards. Appetite, 104, 10–17.

Higgs, S., Spetter, M. S., Thomas, J. M., Rotshtein, P., Lee, M., Hallschmid, M., & Dourish, C. T. (2017). Interactions between metabolic, reward and cognitive processes in appetite control: Implications for novel weight management therapies. Journal of Psychopharmacology, 31(11), 1460–1474.

Hill, J. O., Wyatt, H. R., & Peters, J. C. (2012). Energy Balance and Obesity. Circulation, 126(1), 126–132.

Hoebel, B. G., & Teitelbaum, P. (1962). Hypothalamic Control of Feeding and Self-Stimulation. Science, 135(3501), 375–377.

Hofmann, W., Friese, M., & Strack, F. (2009). Impulse and Self-Control From a Dual-Systems Perspective. Perspectives on Psychological Science, 4(2), 162–176.

Holland, P. C., & Hsu, M. (2014). Role of amygdala central nucleus in the potentiation of consuming and instrumental lever-pressing for sucrose by cues for the presentation or interruption of sucrose delivery in rats. Behavioral Neuroscience, 128(1), 71–82.

Hölzel, B.K., Carmody, J., Evans, K.C., Hoge, E.A., Dusek. J.A., Morgan, L., Pitman, R.K., Lazar, S.W. (2010). Stress reduction correlates with structural changes in the amygdala. Social Cognitive and Affective Neuroscience, 5(1), 11-17.

Houben, K., Nederkoorn, C., & Jansen, A. (2013). Eating on impulse: The relation between overweight and food-specific inhibitory control. Obesity, 22(5), E6–E8. doi:10.1002/oby.20670

Hrybouski, S., Aghamohammadi-Sereshki, A., Madan, C. R., Shafer, A. T., Baron, C. A., Seres, P., … Malykhin, N. V. (2016). Amygdala subnuclei response and connectivity during emotional processing. NeuroImage, 133, 98–110.

Huang, T. T.-K., Kempf, A. M., Strother, M. L., Li, C., Lee, R. E., Harris, K. J., & Kaur, H. (2004). Overweight and Components of the Metabolic Syndrome in College Students. Diabetes Care, 27(12), 3000–3001.

Hussain, S. S., & Bloom, S. R. (2012). The regulation of food intake by the gut-brain axis: implications for obesity. International Journal of Obesity, 37(5), 625–633.

Hyman, S. E., Malenka, R. C., & Nestler, E. J. (2006). NEURAL MECHANISMS OF ADDICTION: The Role of Reward-Related Learning and Memory. Annual Review of Neuroscience, 29(1), 565–598.

Isganaitis, E. (2005). Fast Food, Central Nervous System Insulin Resistance, and Obesity. Arteriosclerosis, Thrombosis, and Vascular Biology, 25(12), 2451–2462.

Janssen, I., Craing, W.M., Boyce, W.F., Pickett, W. (2004). Associations between overweight and obesity with bullying behaviors in school-aged children. Pediatrics, 113(5), 1887-94.

Jansen, W., van de Looij-Jansen, P. M., de Wilde, E. J., & Brug, J. (2008). Feeling Fat Rather than Being Fat May Be Associated with Psychological Well-Being in Young Dutch Adolescents. Journal of Adolescent Health, 42(2), 128–136.

Jasik, C.B., and Lustig, R.H. (2008). Adolescent Obesity and Puberty: The "Perfect Storm". Annals of the New York Academy of Sciences, 1135(1), 265-79.

Jastreboff, A. M., Lacadie, C., Seo, D., Kubat, J., Van Name, M. A., Giannini, C., … Sinha, R. (2014). Leptin Is Associated With Exaggerated Brain Reward and Emotion Responses to Food Images in Adolescent Obesity. Diabetes Care, 37(11), 3061–3068.

Jastreboff, A. M., Sinha, R., Arora, J., Giannini, C., Kubat, J., Malik, S., … Caprio, S. (2016). Altered Brain Response to Drinking Glucose and Fructose in Obese Adolescents. Diabetes, 65(7), 1929–1939.

Jensen, C. D., Cushing, C. C., Aylward, B. S., Craig, J. T., Sorell, D. M., & Steele, R. G. (2011). Effectiveness of motivational interviewing interventions for adolescent substance use behavior change: A meta-analytic review. Journal of Consulting and Clinical Psychology, 79(4), 433–440.

Jilka, S. R., Scott, G., Ham, T., Pickering, A., Bonnelle, V., Braga, R. M., … Sharp, D. J. (2014). Damage to the Salience Network and Interactions with the Default Mode Network. Journal of Neuroscience, 34(33), 10798–10807

Jones, R. B., McKie, S., Astbury, N., Little, T. J., Tivey, S., Lassman, D. J., … Thompson, D. G. (2012). Functional neuroimaging demonstrates that ghrelin inhibits the central nervous system response to ingested lipid. Gut, 61(11), 1543–1551

Jönsson, P., Wallergård, M., Österberg, K., Hansen, Å. M., Johansson, G., & Karlson, B. (2010). Cardiovascular and cortisol reactivity and habituation to a virtual reality version of the Trier Social Stress Test: A pilot study. Psychoneuroendocrinology, 35(9), 1397–1403.

Jankord, R., & Herman, J. P. (2008). Limbic Regulation of Hypothalamo-Pituitary-Adrenocortical Function during Acute and Chronic Stress. Annals of the New York Academy of Sciences, 1148(1), 64–73.

Kahn, S. E., Hull, R. L., & Utzschneider, K. M. (2006). Mechanisms linking obesity to insulin resistance and type 2 diabetes. Nature, 444(7121), 840–846.

Kakoschke, N., Kemps, E., & Tiggemann, M. (2015). External eating mediates the relationship between impulsivity and unhealthy food intake. Physiology & Behavior, 147, 117–121.

Kelesidis, T., Mantzoros, C.S. (2006). The emerging role of leptin in humans. Pediatr Endocrinol Rev., 3(3), 239-48.

Kim, J., Loucks, R.A., Palmer, A.L., Brown, A.C., Solomon, K.M., Marchante, A.N., Whalen, P.J. (2011). The structural and functional connectivity of the amygdala: from normal emotion to pathological anxiety. Behavioral Brain Research, 223(2), 403-410.

Kim, J., Zhang, X., Muralidhar, S., LeBlanc, S.A., Tonegawa, S. (2017). Basolateral to Central Amygdala Neural Circuits for Appetitive Behaviors. Neuron, 93(6), 1464-79.

Kim, S.-H., Chung, J.-H., Kim, T.-H., Lim, S. H., Kim, Y., Lee, Y.-A., & Song, S.-W. (2018). The effects of repetitive transcranial magnetic stimulation on eating behaviors and body weight in obesity: A randomized controlled study. Brain Stimulation, 11(3), 528–535.

Kindblom, J. M., Lorentzon, M., Hellqvist, A., Lonn, L., Brandberg, J., Nilsson, S., … Ohlsson, C. (2009). BMI Changes During Childhood and Adolescence as Predictors of Amount of Adult Subcutaneous and Visceral Adipose Tissue in Men: The GOOD Study. Diabetes, 58(4), 867–874.

Klok, M. D., Jakobsdottir, S., & Drent, M. L. (2007). The role of leptin and ghrelin in the regulation of food intake and body weight in humans: a review. Obesity Reviews, 8(1), 21–34.

Kotlyar, M., Donahue, C., Thuras, P., Kushner, M. G., O'Gorman, N., Smith, E. A., & Adson, D. E. (2008). Physiological response to a speech stressor presented in a virtual reality environment. Psychophysiology, 45(6), 1034–1037.

Krebs, R. M., Heipertz, D., Schuetze, H., & Duzel, E. (2011). Novelty increases the mesolimbic functional connectivity of the substantia nigra/ventral tegmental area (SN/VTA) during reward anticipation: Evidence from high-resolution fMRI. NeuroImage, 58(2), 647–655.

Kringelbach, M. L. (2004). Food for thought: Hedonic experience beyond homeostasis in the human brain. Neuroscience.

Kringelbach, M. (2004). The functional neuroanatomy of the human orbitofrontal cortex: evidence from neuroimaging and neuropsychology. Progress in Neurobiology, 72(5), 341–372.

Kringelbach, M. L. (2005). The human orbitofrontal cortex: linking reward to hedonic experience. Nature Reviews Neuroscience, 6(9), 691–702.

Kullmann, S., Heni, M., Fritsche, A., & Preissl, H. (2015). Insulin Action in the Human Brain: Evidence from Neuroimaging Studies. Journal of Neuroendocrinology.

Kullmann, S., Heni, M., Hallschmid, M., Fritsche, A., Preissl, H., & Häring, H.-U. (2016). Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. Physiological Reviews, 96(4), 1169–1209.

Kullmann, S., Heni, M., Linder, K., Zipfel, S., Häring, H. U., Veit, R., … Preissl, H. (2014). Resting-state functional connectivity of the human hypothalamus. Human Brain Mapping, 35(12), 6088–6096.

Kullmann, S., Heni, M., Veit, R., Ketterer, C., Schick, F., Häring, H.-U., … Preissl, H. (2011). The obese brain: Association of body mass index and insulin sensitivity with resting state network functional connectivity. Human Brain Mapping, 33(5), 1052–1061.

Labudda, K., Woermann, F. G., Mertens, M., Pohlmann-Eden, B., Markowitsch, H. J., & Brand, M. (2008). Neural correlates of decision making with explicit information about probabilities and incentives in elderly healthy subjects. Experimental Brain Research, 187(4), 641–650.

Lake, A., Townshend, T. (2006). Obesogenic environments: exploring the built and food environments. J R Soc Promot Health, 126(6): 262-7.

Langeveld, M., & DeVries, J. H. (2015). The long-term effect of energy restricted diets for treating obesity. Obesity, 23(8), 1529–1538.

Laureiro-Martínez, D., & Brusoni, S. (2018). Cognitive flexibility and adaptive decision-making: Evidence from a laboratory study of expert decision makers. Strategic Management Journal, 39(4), 1031–1058. doi:10.1002/smj.2774

Latner, J. D., & Stunkard, A. J. (2003). Getting Worse: The Stigmatization of Obese Children. Obesity Research, 11(3), 452–456.

LeDoux, J.E. (1993). Emotional memory systems in the brain. Behav Brain Res, 58(1-2),69-79.

Lee, S.C., Amir, A., Headley, D.B., Haufler, D., Pare, D. (2016). Basolateral amygdala nucleus responses to appetitive conditioned stimuli correlate with variations in conditioned behavior. Nature Communications, 7, 12275. doi: 10.1038/ncomms12275.

Lee, L., & Sanders, R. A. (2012). Metabolic Syndrome. Pediatrics in Review, 33(10), 459–468.

Legget, K.T., Wylie, K.P., Cornier, M.A, Melanson, E.L., Paschall, C.J., Tregellas, J.R. (2016). Exercise-related changes in between-network connectivity in overweight/obese adults, 158, 60-67.

Leibowitz, S. F., Weiss, G. F., & Suh, J. S. (1990). Medial hypothalamic nuclei mediate serotonin's inhibitory effect on feeding behavior. Pharmacology, Biochemistry and Behavior, 37(4), 735–742.

Lemmens, S. G., Rutters, F., Born, J. M., & Westerterp-Plantenga, M. S. (2011). Stress augments food "wanting" and energy intake in visceral overweight subjects in the absence of hunger. Physiology & Behavior, 103(2), 157–163.

Levine, B., Schweizer, T. A., O'Connor, C., Turner, G., Gillingham, S., Stuss, D. T., … Robertson, I. H. (2011). Rehabilitation of Executive Functioning in Patients with Frontal

Lobe Brain Damage with Goal Management Training. Frontiers Human Neuroscience, 5, 9, doi: 10.3389/fnhum.2011.00009.

Li, X., Lu, Z.-L., D'Argembeau, A., Ng, M., & Bechara, A. (2009). The Iowa Gambling Task in fMRI images. Human Brain Mapping, 31(3).

Lim, S. S., Norman, R. J., Clifton, P. M., & Noakes, M. (2009). Psychological Effects of Prescriptive vs General Lifestyle Advice for Weight Loss in Young Women. Journal of the American Dietetic Association, 109(11), 1917–1921.

Limbers, C.A., Egan, K., Cohen, L.A. (2018). Executive Functions and Dietary Behaviors in School-Aged Children. Int J School Health, 5(1), e61194. doi: 10.5812/intjsh.61194.

Lips, M.A., Wijngaarden, M.A., Van der Grond, J., Van Buchem, M. A., De Groot, G.H., Rombouts, S.A., Pijl, H., Veer, I.M. (2014). Resting-state functional connectivity of brain regions involved is enhanced in obese females. The American Journal of Clinical Nutrition, 100(2), 524-31

Little, T. J., McKie, S., Jones, R. B., D'Amato, M., Smith, C., Kiss, O., … McLaughlin, J. T. (2014). Mapping glucose-mediated gut-to-brain signalling pathways in humans. NeuroImage, 96, 1–11.

Loeber, S., Grosshans, M., Korucuoglu, O., Vollmert, C., Vollstädt-Klein, S., Schneider, S., … Kiefer, F. (2011). Impairment of inhibitory control in response to food-associated cues and attentional bias of obese participants and normal-weight controls. International Journal of Obesity, 36(10), 1334–1339.

Lustig, R. H., Sen, S., Soberman, J. E., & Velasquez-Mieyer, P. A. (2004). Obesity, leptin resistance and the effects of insulin reduction. International Journal of Obesity, 28(10), 1344–1348.

Lutter, M., & Nestler, E. J. (2009). Homeostatic and Hedonic Signals Interact in the Regulation of Food Intake. Journal of Nutrition, 139(3), 629–632.

Maahs, D. M., West, N. A., Lawrence, J. M., & Mayer-Davis, E. J. (2010). Epidemiology of Type 1 Diabetes. Endocrinology and Metabolism Clinics of North America, 39(3), 481–497.

Maayan, L., Hoogendoorn, C., Sweat, V., & Convit, A. (2011). Disinhibited Eating in Obese Adolescents Is Associated With Orbitofrontal Volume Reductions and Executive Dysfunction. Obesity, 19(7), 1382–1387.

Macchi, R., MacKew, L., & Davis, C. (2017). Is decision-making ability related to food choice and facets of eating behaviour in adolescents? Appetite, 116, 442–455.

Maldjian, J. A., Laurienti, P. J., Kraft, R. A., & Burdette, J. H. (2003). An automated method for neuroanatomic and cytoarchitectonic atlas-based interrogation of fMRI data sets. NeuroImage, 19(3), 1233–1239. https://doi.org/10.1016/S1053-8119(03)00169-1

Mallorquí-Bagué, N., Fagundo, A. B., Jimenez-Murcia, S., de la Torre, R., Baños, R. M., Botella, C., … Fernández-Aranda, F. (2016). Decision Making Impairment: A Shared Vulnerability in Obesity, Gambling Disorder and Substance Use Disorders? PLOS ONE, 11(9), e0163901.

Manton, N.D., Lipsett, J., Moore, D.J., Davidson, G.P., Bourne, A.J., Couper, R.T. (2000). N-on-alcoholic steatohepatitis in children and adolescents. Med J Aust, 173(9), 476-9.

Mårin, P., Darin, N., Amemiya, T., Andersson, B., Jern, S., & Björntorp, P. (1992). Cortisol secretion in relation to body fat distribution in obese premenopausal women. Metabolism, 41(8), 882–886.

Marks, D. F. (2015). Homeostatic theory of obesity. Health Psychology Open, 2(1), 205510291559069. doi:10.1177/2055102915590692

Margules, D.L., Olds, J. (1962). Identical "feeding" and "rewarding" systems in the lateral hypothalamus of rats. Science, 135(3501), 374-5.

Martin, L. E., Holsen, L. M., Chambers, R. J., Bruce, A. S., Brooks, W. M., Zarcone, J. R., … Savage, C. R. (2009). Neural Mechanisms Associated With Food Motivation in Obese and Healthy Weight Adults. Obesity, 18(2), 254–260.

Martín-Pérez, C., Contreras-Rodríguez, O., Vilar-López, R., and Verdejo-García, A. (2018). Hypothalamic networks in adolescents with excess weight: stress-related connectivity and associations with emotional eating. Journal of the American Academy of Child and Adolescent Psychiatry, (in press).

Marusak, H. A., Thomason, M. E., Peters, C., Zundel, C., Elrahal, F., & Rabinak, C. A. (2016). You say "prefrontal cortex" and I say "anterior cingulate": meta-analysis of spatial overlap in amygdala-to-prefrontal connectivity and internalizing symptomology. Translational Psychiatry, 6(11), e944–e944.

Mathers, J. C. (2015). Obesity and mortality: Is childhood obesity shortening life expectancy? Maturitas, 81(1), 1–2.

Matthews, D.R., Hosker, J.P., Rudenski, A.S., Naylor, B.A., Treacher, D.F., Turner, R.C. (1985). Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia, 28(7), 412-9.

McDonald, R.J., White, N.M. (1993). A triple dissociation of memory systems: hippocampus, amygdala, and dorsal striatum. Behav Neurosci, 107(1), 3-22.

McFadden, K. L., Cornier, M.-A., Melanson, E. L., Bechtell, J. L., & Tregellas, J. R. (2013). Effects of exercise on resting-state default mode and salience network activity in overweight/obese adults. NeuroReport, 24(15), 866–871.

McKlveen, J. M., Morano, R. L., Fitzgerald, M., Zoubovsky, S., Cassella, S. N., Scheimann, J. R., … Herman, J. P. (2016). Chronic Stress Increases Prefrontal Inhibition: A Mechanism for Stress-Induced Prefrontal Dysfunction. Biological Psychiatry, 80(10), 754–764.

McMorrow, A. M., Connaughton, R. M., Lithander, F. E., & Roche, H. M. (2014). Adipose tissue dysregulation and metabolic consequences in childhood and adolescent obesity: potential impact of dietary fat quality. Proceedings of the Nutrition Society, 74(01), 67–82.

Meye, F. J., & Adan, R. A. H. (2014). Feelings about food: the ventral tegmental area in food reward and emotional eating. Trends in Pharmacological Sciences, 35(1), 31–40.

Meyer, J., Novak, M., Hamel, A., Rosenberg, K. (2014). Extraction and Analysis of Cortisol from Human and Monkey Hair. Journal of Visualized Experiments, (83), e50882. doi: 10.3791/50882.

Michaelides, M., Thanos, P. K., Volkow, N. D., & Wang, G.-J. (2012). Dopamine-related frontostriatal abnormalities in obesity and binge-eating disorder: Emerging evidence for developmental psychopathology. International Review of Psychiatry, 24(3), 211–218.

Mietus-Snyder, M.L., Lustig, R.H. (2008). Childhood Obesity: Adrift in the “limbic triangle”. Annual review of medicine, 59, 147-162.

Miller, A. L., Lee, H. J., & Lumeng, J. C. (2014). Obesity-associated biomarkers and executive function in children. Pediatric Research, 77(1-2), 143–147.

Mitra, A. (2001). Effects of physical attributes on the wages of males and females. Applied Economics Letters, 8(11), 731–735.

Miyake, A., & Friedman, N. P. (2012). The Nature and Organization of Individual Differences in Executive Functions. Current Directions in Psychological Science, 21(1), 8–14.

Mobbs, O., Crépin, C., Thiéry, C., Golay, A., & Van der Linden, M. (2010). Obesity and the four facets of impulsivity. Patient Education and Counseling, 79(3), 372–377.

Montero, D., Walther, G., Perez-Martin, A., Roche, E., & Vinet, A. (2011). Endothelial dysfunction, inflammation, and oxidative stress in obese children and adolescents: markers and effect of lifestyle intervention. Obesity Reviews, 13(5), 441–455.

Moreno-Lopez, L., Contreras-Rodriguez, O., Soriano-Mas, C., Stamatakis, E. A., & Verdejo-Garcia, A. (2016). Disrupted functional connectivity in adolescent obesity. NeuroImage: Clinical, 12, 262–268.

Moreno-Padilla, M., Fernández-Serrano, M. J., & Reyes del Paso, G. A. (2018). Risky decision-making after exposure to a food-choice task in excess weight adolescents: Relationships with reward-related impulsivity and hunger. PLOS ONE, 13(8), e0202994.

Moreno-Padilla, M., Verdejo Román, J., Fernández-Serrano, M. J., Reyes del Paso, G. A., & Verdejo García, A. (2018). Increased food choice-evoked brain activation in adolescents with excess weight: Relationship with subjective craving and behavior. Appetite, 131, 7-13.

Morris, S. (2006). Body mass index and occupational attainment. Journal of Health Economics, 25(2), 347–364.

Morris, L. S., Kundu, P., Dowell, N., Mechelmans, D. J., Favre, P., Irvine, M. A., … Voon, V. (2016). Fronto-striatal organization: Defining functional and microstructural substrates of behavioural flexibility. Cortex, 74, 118–133.

Murphy, C. M., Stojek, M. K., & MacKillop, J. (2014). Interrelationships among impulsive personality traits, food addiction, and Body Mass Index. Appetite, 73, 45–50.

Musaiger, A. O. (2011). Overweight and Obesity in Eastern Mediterranean Region: Prevalence and Possible Causes. Journal of Obesity, 2011, 1–17.

Naleid, A. M., Grace, M. K., Cummings, D. E., & Levine, A. S. (2005). Ghrelin induces feeding in the mesolimbic reward pathway between the ventral tegmental area and the nucleus accumbens. Peptides, 26(11), 2274–2279.

Naqvi, N. H., Rudrauf, D., Damasio, H., & Bechara, A. (2007). Damage to the Insula Disrupts Addiction to Cigarette Smoking. Science, 315(5811), 531–534. doi:10.1126/science.1135926

Naqvi, N. H., & Bechara, A. (2010). The insula and drug addiction: an interoceptive view of pleasure, urges, and decision-making. Brain Structure and Function, 214(5-6), 435–450.

NCD-Risc: Abarca-Gómez, L., Abdeen, Z. A., Hamid, Z. A., Abu-Rmeileh, N. M., Acosta-Cazares, B., Acuin, C., … Aguilar-Salinas, C. A. (2017). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128•9 million children, adolescents, and adults. The Lancet, 390(10113), 2627–2642.

Nederkoorn, C., Houben, K., Hofmann, W., Roefs, A., & Jansen, A. (2010). Control yourself or just eat what you like? Weight gain over a year is predicted by an interactive effect of

response inhibition and implicit preference for snack foods. Health Psychology, 29(4), 389–393.

Nestle, M. (2006). Food Marketing and Childhood Obesity — A Matter of Policy. New England Journal of Medicine, 354(24), 2527–2529.

Nezu, A.M., Nezu, C.M., Zurilla T.J. (2013). Problem Solving Therapy. A treatment manual. New York, United States of America: Springer Publishing Company.

Ng, M., Fleming, T., Robinson, M., Thomson, B., Graetz, N., Margono, C., … Gakidou, E. (2014). Global, regional, and national prevalence of overweight and obesity in children and adults during 1980-2013: A systematic analysis for the Global Burden of Disease Study 2013. The Lancet, 384(9945), 766–781.

Nicola, S. M. (2016). Reassessing wanting and liking in the study of mesolimbic influence on food intake. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 311(5), R811–R840.

Nieuwenhuizen, A. G., & Rutters, F. (2008). The hypothalamic-pituitary-adrenal-axis in the regulation of energy balance. Physiology & Behavior, 94(2), 169–177.

Nummenmaa, L., Hirvonen, J., Hannukainen, J.C., Immonen, H., Lindroos, M.M., Salminen, P., Nuutila, P. (2012). Dorsal and its limbic connectivity mediate abnormal anticipatory reward processing in obesity. PLoS One, 7(2), e31089.

Ochsner, K., Gross, J. (2005). The cognitive control of emotion. Trends in Cognitive Sciences, 9(5), 242-49.

OECD. (2010). Obesity and the Economics of Prevention: Fit not Fat. OECD Publishing, Paris. Retrieved from https://doi.org/10.1787/9789264084865-en.

Ogden, C. L., & Flegal, K. M. (2010). Changes in terminology for childhood overweight and obesity. National Health Statistics Reports, (25), 1–5.

Oliveira-Maia, A. J., Roberts, C. D., Simon, S. A., & Nicolelis, M. A. L. (2011). Gustatory and reward brain circuits in the control of food intake. Advances and Technical Standards in Neurosurgery, 36, 31–59.

Olshansky, S. J., Passaro, D. J., Hershow, R. C., Layden, J., Carnes, B. A., Brody, J., … Ludwig, D. S. (2005). A Potential Decline in Life Expectancy in the United States in the 21st Century. New England Journal of Medicine, 352(11), 1138–1145.

Ozmen, D., Ozmen, E., Ergin, D., Cetinkaya, A. C., Sen, N., Dundar, P. E., & Taskin, E. O. (2007). The association of self-esteem, depression and body satisfaction with obesity among Turkish adolescents. BMC Public Health, 7(1). doi:10.1186/1471-2458-7-80.

Padival, M., Quinette, D., & Rosenkranz, J. A. (2013). Effects of Repeated Stress on Excitatory Drive of Basal Amygdala Neurons In Vivo. Neuropsychopharmacology, 38(9), 1748–1762.

Pannacciulli, N., Del Parigi, A., Chen, K., Le, D. S. N. T., Reiman, E. M., & Tataranni, P. A. (2006). Brain abnormalities in human obesity: A voxel-based morphometric study. NeuroImage, 31(4), 1419–1425.

Papies, E. K., Stroebe, W., & Aarts, H. (2008). Healthy Cognition: Processes of Self-Regulatory Success in Restrained Eating. Personality and Social Psychology Bulletin, 34(9), 1290–1300.

Parízková, J., Hills, A. (2001). Childhood obesity prevention and treatment, Florida, United States of America: CRC Press.

Peciña, S., Berridge, K. (2015). Food "liking" and "wanting". A neurobiological perspective. En N. Avena (Ed.), Hedonic Eating: How the Pleasure of Food Affects Our Brains and Behavior (pg. 125-147). New York, United States of America: Oxford University Press.

Perrin, E. M., Boone-Heinonen, J., Field, A. E., Coyne-Beasley, T., & Gordon-Larsen, P. (2009). Perception of overweight and self-esteem during adolescence. International Journal of Eating Disorders, 43(5), 447-54.

Pervanidou, P., & Chrousos, G. P. (2011). Stress and obesity/metabolic syndrome in childhood and adolescence. In International Journal of Pediatric Obesity (Vol. 6, pp. 21–28).

Petrovich, G.D., Gallagher, M. (2007). Control of food consumption by learned cues: A forebrain-hypothalamic network. Physiology & Behavior, 91(4), 397-403.

Petrovich, G. D., Holland, P.C., Gallagher, M. (2005). Amygdalar and Prefrontal Pathways to the Lateral Hypothalamus Are Activated by a Learned Cue That Stimulates Eating. Journal of Neuroscience, 25(36), 8295–8302.

Petrovich, G.A., Ross, C.A., Mody, P., Holland, P.C., Gallacher, M. (2009). Central, but not basolateral, amygdala is critical for control of feeding by aversive learned cues. Journal of Neuroscience, 29(48), 15205-15212.

Petrovich, G.D., Setlow, B, Holland, P.C., Gallagher, M. (2002). Amygdalo-Hypothalamic Circuit Allows Learned Cues to Override Satiety and Promote Eating. Journal of Neuroscience, 22(19), 8748-53.

Picó-Pérez, M., Alonso, P., Contreras-Rodríguez, O., Martínez-Zalacaín, I., López-Solà, C., Jiménez-Murcia, S., … Soriano-Mas, C. (2017). Dispositional use of emotion regulation strategies and resting-state cortico-limbic functional connectivity. Brain Imaging and Behavior, p. doi:10.1007/s11682-017-9762-3.

Pignatti, R., Bertella, L., Albani, G., Mauro, A., Molinari, E., & Semenza, C. (2006). Decision-making in obesity: A study using the Gambling Task. Eating and Weight Disorders - Studies on Anorexia, Bulimia and Obesity, 11(3), 126–132.

Polter, A. M., & Kauer, J. A. (2014). Stress and VTA synapses: implications for addiction and depression. European Journal of Neuroscience, 39(7), 1179–1188.

Pont, S. J., Puhl, R., Cook, S. R., & Slusser, W. (2017). Stigma Experienced by Children and Adolescents With Obesity. Pediatrics, 140(6), e20173034.

Pool, E., Brosch, T., Delplanque, S., & Sander, D. (2015). Stress Increases Cue-Triggered " Wanting " for Sweet Reward in Humans. Journal of Experimental Psychology, 41(2), 128–136.

Potenza, M. N., & Grilo, C. M. (2014). How Relevant is Food Craving to Obesity and Its Treatment? Frontiers in Psychiatry, 5. doi:10.3389/fpsyt.2014.00164

Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. NeuroImage, 59(3), 2142–2154.

Pruessner, J. C., Kirschbaum, C., Meinlschmid, G., & Hellhammer, D. H. (2003). Two formulas for computation of the area under the curve represent measures of total hormone concentration versus time-dependent change. Psychoneuroendocrinology, 28(7), 916–931.

Puhl, R. M., & Latner, J. D. (2007). Stigma, obesity, and the health of the nation's children. Psychological Bulletin, 133(4), 557–580.

Putcha, D., Ross, R. S., Cronin-Golomb, A., Janes, A. C., & Stern, C. E. (2016). Salience and Default Mode Network Coupling Predicts Cognition in Aging and Parkinson's Disease. Journal of the International Neuropsychological Society, 22(02), 205–215.

Radley, J. J., & Sawchenko, P. E. (2011). A Common Substrate for Prefrontal and Hippocampal Inhibition of the Neuroendocrine Stress Response. Journal of Neuroscience, 31(26), 9683–9695.

Raj, M. (2012). Obesity and cardiovascular risk in children and adolescents. Indian Journal of Endocrinology and Metabolism, 16(1), 13.

Rao, D.P., Kropac, E., Do, M.T., Roberts, K.C., Jayaraman, G.C. (2017). Status report-Childhood overweight and obesity in Canada: an integrative assessment. Health Promot Chronic Dis Prev Can, 37(3), 87-93.

Rapuano, K. M., Huckins, J. F., Sargent, J. D., Heatherton, T. F., & Kelley, W. M. (2016). Individual Differences in Reward and Somatosensory-Motor Brain Regions Correlate with Adiposity in Adolescents. Cerebral Cortex, 26(6), 2602–2611.

Reinehr, T. (2013). Type 2 diabetes mellitus in children and adolescents. World Journal of Diabetes, 4(6), 270. doi:10.4239/wjd.v4.i6.270

Reinert, K. R. S., Po'e, E. K., & Barkin, S. L. (2013). The Relationship between Executive Function and Obesity in Children and Adolescents: A Systematic Literature Review. Journal of Obesity, 2013, 1–10.

Reisch, L., Eberle, U., & Lorek, S. (2013). Sustainable food consumption: an overview of contemporary issues and policies. Sustainability: Science, Practice and Policy, 9(2), 7–25

Riggs, N. R., Spruijt-Metz, D., Sakuma, K.-L., Chou, C.-P., & Pentz, M. A. (2010). Executive Cognitive Function and Food Intake in Children. Journal of Nutrition Education and Behavior, 42(6), 398–403.

Rinaman, L. (2011). Hindbrain noradrenergic A2 neurons: diverse roles in autonomic, endocrine, cognitive, and behavioral functions. American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, 300(2), R222–R235.

Rizvi, T. A., Ennis, M., Behbehani, M. M., & Shipley, M. T. (1991). Connections between the central nucleus of the amygdala and the midbrain periaqueductal gray: Topography and reciprocity. The Journal of Comparative Neurology, 303(1), 121–131.

Roh, E., Kim, M-S. (2016). Brain Regulation of Energy Metabolism. Endocrinology and metabolism, 31(4), 519-24.

Romero-Corral, A., Somers, V. K., Sierra-Johnson, J., Thomas, R. J., Collazo-Clavell, M. L., Korinek, J., … Lopez-Jimenez, F. (2008). Accuracy of body mass index in diagnosing obesity in the adult general population. International Journal of Obesity, 32(6), 959–966.

Roozendaal, B., Koolhaas, J.M., Bohus, B. (1997). The role of the central amygdala in stress and adaption. Acta Physiologica Scandinavica, Supplementum, 640:51-54.

Roozendaal, B., McEwen, B. S., & Chattarji, S. (2009). Stress, memory and the amygdala. Nature Reviews Neuroscience, 10(6), 423–433.

Rosenbaum, M., Sy, M., Pavlovich, K., Leibel, R. L., & Hirsch, J. (2008). Leptin reverses weight loss-induced changes in regional neural activity responses to visual food stimuli. Journal of Clinical Investigation, 118(7), 2583–2591.

Rosenberg, N., Bloch, M., Ben Avi, I., Rouach, V., Schreiber, S., Stern, N., & Greenman, Y. (2013). Cortisol response and desire to binge following psychological stress: Comparison

between obese subjects with and without binge eating disorder. Psychiatry Research, 208(2), 156–161

Rosenkranz, J. A., Venheim, E. R., & Padival, M. (2010). Chronic Stress Causes Amygdala Hyperexcitability in Rodents. Biological Psychiatry, 67(12), 1128–1136.

Ross, S. E., Lehmann Levin, E., Itoga, C. A., Schoen, C. B., Selmane, R., & Aldridge, J. W. (2016). Deep brain stimulation in the central nucleus of the amygdala decreases "wanting" and "liking" of food rewards. European Journal of Neuroscience, 44(7), 2431–2445.

Rossi, M. A., & Stuber, G. D. (2018). Overlapping Brain Circuits for Homeostatic and Hedonic Feeding. Cell Metabolism, 27(1), 42–56.

Roth, C. L., Elfers, C., & Hampe, C. S. (2017). Assessment of disturbed glucose metabolism and surrogate measures of insulin sensitivity in obese children and adolescents. Nutrition & Diabetes, 7(12). doi:10.1038/s41387-017-0004-y

Rothemund, Y., Preuschhof, C., Bohner, G., Bauknecht, H.-C., Klingebiel, R., Flor, H., & Klapp, B. F. (2007). Differential activation of the dorsal striatum by high-calorie visual food stimuli in obese individuals. NeuroImage, 37(2), 410–421.

Roy, A. K., Shehzad, Z., Margulies, D. S., Kelly, A. M. C., Uddin, L. Q., Gotimer, K., … Milham, M. P. (2009). Functional connectivity of the human amygdala using resting state fMRI. NeuroImage, 45(2), 614–626.

Rui, L. (2013). Brain regulation of energy balance and body weight. Reviews in Endocrine & Metabolic Disorders, 14(4), 387–407.

Ruiz, A. S., Peralta-Ramirez, M. I., Garcia-Rios, M. C., Muñoz, M. A., Navarrete-Navarrete, N., & Blazquez-Ortiz, A. (2010). Adaptation of the trier social stress test to virtual reality:

Psycho-phsyiological and neuroendocrine modulation. Journal of Cyber Therapy and Rehabilitation, 3(4), 405–415.

Russell, E., Koren, G., Rieder, M., Van Uum, S. (2012). Hair cortisol as a biological marker of chronic stress: current status, future directions and unanswered questions. Psychoneuroendocrinology, 37(5), 589-601.

Ryan, J. P., Karim, H. T., Aizenstein, H. J., Helbling, N. L., & Toledo, F. G. S. (2018). Insulin sensitivity predicts brain network connectivity following a meal. NeuroImage, 171, 268–276.

Saad, Z. S., Gotts, S. J., Murphy, K., Chen, G., Jo, H. J., Martin, A., & Cox, R. W. (2012). Trouble at Rest: How Correlation Patterns and Group Differences Become Distorted After Global Signal Regression. Brain Connectivity, 2(1), 25–32.

Sambataro, F., Wolf, N. D., Pennuto, M., Vasic, N., & Wolf, R. C. (2013). Revisiting default mode network function in major depression: evidence for disrupted subsystem connectivity. Psychological Medicine, 44(10), 2041–2051.

Sargent; J.D., Blanchflower, D.G. (1994). Obesity and stature in adolescence and earnings in young adulthood. Analysis of a British birth cohort. Arch Pediatr Adolesc Med, 148(7), 681-7.

Satia, J. A., & Galanko, J. A. (2007). Comparison of Three Methods of Measuring Dietary Fat Consumption by African-American Adults. Journal of the American Dietetic Association, 107(5), 782–791.

Satterthwaite, T. D., Elliott, M. A., Gerraty, R. T., Ruparel, K., Loughead, J., Calkins, M. E., … Wolf, D. H. (2013). An improved framework for confound regression and filtering for

control of motion artifact in the preprocessing of resting-state functional connectivity data. NeuroImage, 64(1), 240–256.

Sauve, B., Koren, G., Walsh, G., Tokmakejian, S., Van Uum, S. (2007). Measurement of cortisol in human Hair as a biomarker of systemic exposure. Clinical and Investigative Medicine, 30(5), 183-91.

Schiebener, J., Wegmann, E., Gathmann, B., Laier, C., Pawlikowski, M., & Brand, M. (2014). Among three different executive functions, general executive control ability is a key predictor of decision making under objective risk. Frontiers in Psychology, 5, 1386, doi: 10.3389/fpsyg.2014.01386.

Schienle, A., Schafer, A., Hermann, A., Vaiti, D. (2009). Binge-Eating Disorder: Reward Sensitivity and Brain Activation to Images of Food. Biological Psychiatry, 65(8), 654-61.

Schneeberger, M., Gomis, R., & Claret, M. (2013). Hypothalamic and brainstem neuronal circuits controlling homeostatic energy balance. Journal of Endocrinology, 220(2), T25–T46.

Scott, K.A., Melhorn, S.J., Sakai, R.R. (2012). Effects of chronic social stress on obesity. Curr Obes Rep, 1(1), 16-25.

Sharma, S., Fernandes, M. F., & Fulton, S. (2013). Adaptations in brain reward circuitry underlie palatable food cravings and anxiety induced by high-fat diet withdrawal. International Journal of Obesity, 37(9), 1183–1191.

Serra, L.L., Aranceta, J., Ribas, L., Sangil, M., Pérez, C. (2003). Crecimiento y desarrollo: Dimensión alimentaria y nutricional. El cribado de riesgo nutricional en Pediatría.

Valoración del test rápido KRECE PLUS y resultados en la población española. In: LL Serra, J Aranceta, eds, (pp. 45-55). Barcelona: Masson.

Selye, H. (1974). Stress without Distress. Philadelphia, United States: Lippincott.

Sharma, S., Fernandes, M. F., & Fulton, S. (2012). Adaptations in brain reward circuitry underlie palatable food cravings and anxiety induced by high-fat diet withdrawal. International Journal of Obesity, 37(9), 1183–1191.

Short, S.J., Stalder, T., Marceau, K., Entringer, S., Moog, N.K., Shirtcliff, E.A., Wadhwa, P.D., Buss, C. (2016). Correspondence between hair cortisol concentrations and 30-day integrated daily salivary and weekly urinary cortisol measures. Psychoneuroendocrinology, 71, 12-18.

Siep, N., Roefs, A., Roebroeck, A., Havermans, R., Bonte, M.L., Jansen, A. (2008). Hunger is the best spice: An fMRI study of the effects of attention, hunger and calorie content on food reward processing in the amygdala and orbitofrontal cortex. Behavioural Brain Research, 198(1), 149-58.

Simmonds, M., Llewellyn, A., Owen, C. G., & Woolacott, N. (2015). Predicting adult obesity from childhood obesity: a systematic review and meta-analysis. Obesity Reviews, 17(2), 95–107.

Sinaiko, A. R Steinberger, J., Moran, A., Prineas, R.J., Vessby, B., Basu, S., Tracy, R., Jacobs, D.R. (2005). Relation of Body Mass Index and Insulin Resistance to Cardiovascular Risk Factors, Inflammatory Factors, and Oxidative Stress during Adolescence. Circulation, 111(15), 1985–1991.

Sinha, R., Jastreboff, A.M. (2013). Stress as a common risk factor for obesity and addiction. Biological Psychiatry, 73(9), 827-35.

Singh, M. (2014). Mood, food, and obesity. Frontiers in Psychology, 5. doi:10.3389/fpsyg.2014.00925

Sixty-fourth world health assembly. Resolution WHA 64.28: Youth and health risks. Geneva, World Health Organization. (2011).

Smith, E., Hay, P., Campbell, L., & Trollor, J. N. (2011). A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. Obesity Reviews, 12(9), 740–755.

Smith, S. M., Vale, W. W. (2006). The role of the hypothalamic-pituitary-adrenal axis in neuroendocrine responses to stress. Dialogues Clin Neurosci, 8(4), 383-95.

Sominsky, L., & Spencer, S. J. (2014). Eating behavior and stress: A pathway to obesity. Frontiers in Psychology.

Sridharan, D., Levitin, D. J., & Menon, V. (2008). A critical role for the right fronto-insular cortex in switching between central-executive and default-mode networks. Proceedings of the National Academy of Sciences, 105(34), 12569–12574.

Song, X. W., Dong, Z. Y., Long, X. Y., Li, S. F., Zuo, X. N., Zhu, C. Z., … Zang, Y. F. (2011). REST: A Toolkit for resting-state functional magnetic resonance imaging data processing. PLoS ONE, 6(9), e25031.

Stamoulis, K.G., Pingali, P. L., Shetty, P. (2004). Emerging Challenges for Food and Nutrition Policy in Developing Countries. eJADE, 1(2), 154-167.

Steimke, R., Nomi, J. S., Calhoun, V. D., Stelzel, C., Paschke, L. M., Gaschler, R., … Uddin, L. Q. (2017). Salience network dynamics underlying successful resistance of temptation. Social Cognitive and Affective Neuroscience, 12(12), 1928–1939.

Stephens M.A., Wand, G. (2012). Stress and the HPA axis: role of glucocorticoids in alcohol dependence. Alcohol Res, 34(4), 468-83.

Stice, E., Presnell, K., Shaw, H., & Rohde, P. (2005). Psychological and Behavioral Risk Factors for Obesity Onset in Adolescent Girls: A Prospective Study. Journal of Consulting and Clinical Psychology, 73(2), 195–202.

Stice, E., Spoor, S., Bohon, C., Veldhuizen, M. G., & Small, D. M. (2008). Relation of reward from food intake and anticipated food intake to obesity: A functional magnetic resonance imaging study. Journal of Abnormal Psychology, 117(4), 924–935.

Stice, E., Spoor, S., Ng, J., & Zald, D. H. (2009). Relation of obesity to consummatory and anticipatory food reward. Physiology & Behavior, 97(5), 551–560.

Stice, E., Yokum, S., Burger, K. S., Epstein, L. H., & Small, D. M. (2011). Youth at Risk for Obesity Show Greater Activation of Striatal and Somatosensory Regions to Food. Journal of Neuroscience, 31(12), 4360–4366.

Stice, E., Yokum, S., Zald, D., & Dagher, A. (2010). Dopamine-Based Reward Circuitry Responsivity, Genetics, and Overeating. Current Topics in Behavioral Neurosciences, 81–93.

Stoeckel, L. E., Kim, J., Weller, R. E., Cox, J. E., Cook, E. W., & Horwitz, B. (2009). Effective connectivity of a reward network in obese women. Brain Research Bulletin, 79(6), 388–395.

Stoeckel, L. E., Weller, R. E., Cook, E. W., Twieg, D. B., Knowlton, R. C., & Cox, J. E. (2008). Widespread reward-system activation in obese women in response to pictures of high-calorie foods. NeuroImage, 41(2), 636–647.

Stuber, G. D., & Wise, R. A. (2016). Lateral hypothalamic circuits for feeding and reward. Nature Neuroscience.

Strack, F., & Deutsch, R. (2004). Reflective and Impulsive Determinants of Social Behavior. Personality and Social Psychology Review, 8(3), 220–247.

Strauss, R. S., & Pollack, H. A. (2003). Social Marginalization of Overweight Children. Archives of Pediatrics & Adolescent Medicine, 157(8), 746.

Strohacker, K., McCaffery, J. M., MacLean, P. S., & Wing, R. R. (2013). Adaptations of leptin, ghrelin or insulin during weight loss as predictors of weight regain: a review of current literature. International Journal of Obesity, 38(3), 388–396.

Su, F., Shu, H., Ye, Q., Wang, Z., Xie, C., Yuan, B., … Bai, F. (2017). Brain insulin resistance deteriorates cognition by altering the topological features of brain networks. NeuroImage: Clinical, 13, 280–287. doi:10.1016/j.nicl.2016.12.009

Sun, X., Kroemer, N.B., Veldhuizen, M.G., Babbs, A.E., Araujo, I.E., Gitelman, D.R., Sherwin, R.S., Sinha, R., Small, D.M. (2015). Basolateral Amygdala Response to Food Cues in the Absence of Hunger Is Associated with Weight Gain Susceptibility. Journal of Neuroscience, 35(20), 7964-76.

Swainson, R., Rogers, R. D., Sahakian, B. J., Summers, B. A., Polkey, C. E., & Robbins, T. W. (2000). Probabilistic learning and reversal deficits in patients with Parkinson's disease or frontal or temporal lobe lesions: Possible adverse effects of dopaminergic medication. Neuropsychologia, 38, 596–612.

Swanson, L.W. (2000). Cerebral hemisphere regulation of motivated behavior. Brain Res, 886, 113–164.

Swinburn, B. A., Sacks, G., Hall, K. D., McPherson, K., Finegood, D. T., Moodie, M. L., & Gortmaker, S. L. (2011). The global obesity pandemic: shaped by global drivers and local environments. The Lancet, 378(9793), 804–814.

Tailor, A. M., Peeters, P. H. M., Norat, T., Vineis, P., & Romaguera, D. (2010). An update on the prevalence of the metabolic syndrome in children and adolescents. International Journal of Pediatric Obesity, 5(3), 202–213.

Tan, J. T. T., Patel, B. K., Kaplan, L. M., Koenig, J. I., & Hooi, S. C. (1998). Regulation of Leptin Expression and Secretion by Corticosteroids and Insulin: Implications for Body Weight. Endocrine, 8(1), 85–92.

Taras, H., & Potts-Datema, W. (2005). Obesity and Student Performance at School. Journal of School Health, 75(8), 291–295.

Tasker, J. G. (2006). Rapid Glucocorticoid Actions in the Hypothalamus as a Mechanism of Homeostatic Integration. Obesity, 14(S8), 259S–265S.

Tasker, J. G., & Herman, J. P. (2011). Mechanisms of rapid glucocorticoid feedback inhibition of the hypothalamic–pituitary–adrenal axis. Stress, 14(4), 398–406.

Tataranni, P. A., Gautier, J. F., Chen, K., Uecker, A., Bandy, D., Salbe, A. D., … Ravussin, E. (1999). Neuroanatomical correlates of hunger and satiation in humans using positron emission tomography. Proceedings of the National Academy of Sciences of the United States of America, 96(8), 4569–4574.

Teitelbaum, P., & Epstein, A. N. (1962). The lateral hypothalamic syndrome: Recovery of feeding and drinking after lateral hypothalamic lesions. Psychological Review, 69(2), 74–90.

Thorpe, M. G., Kestin, M., Riddell, L. J., Keast, R. S., & McNaughton, S. A. (2013). Diet quality in young adults and its association with food-related behaviours. Public Health Nutrition, 17(08), 1767–1775.

Timper, K., & Brüning, J. C. (2017). Hypothalamic circuits regulating appetite and energy homeostasis: pathways to obesity. Disease Models & Mechanisms, 10(6), 679–689.

Torres, S.J., Nowson, C.A. (2007). Relationship between stress, eating behavior, and obesity. Nutrition, 23(11-12), 887-94.

Trainor, B. C. (2011). Stress responses and the mesolimbic dopamine system: Social contexts and sex differences. Hormones and Behavior, 60(5), 457–469.

Tryon, M.S., Carter, C.S., DeCand, R., Laugero, K.D. (2013). Chronic stress exposure may affect the brain's response to high calorie food cues and predispose to obesogenic eating habits. Physiology & Behavior, 120(15), 233-242.

Turel, O., & Bechara, A. (2016). A Triadic Reflective-Impulsive-Interoceptive Awareness Model of General and Impulsive Information System Use: Behavioral Tests of Neuro-Cognitive Theory. Frontiers in Psychology, 7. doi:10.3389/fpsyg.2016.00601

Turnbull, O. H., Bowman, C. H., Shanker, S., & Davies, J. L. (2014). Emotion-based learning: insights from the Iowa Gambling Task. Frontiers in Psychology, 5. doi:10.3389/fpsyg.2014.00162

Uddin, L. Q. (2014). Salience processing and insular cortical function and dysfunction. Nature Reviews Neuroscience, 16(1), 55–61.

Ulrich-Lai, Y. M., & Herman, J. P. (2009). Neural regulation of endocrine and autonomic stress responses. Nature Reviews Neuroscience, 10(6), 397–409.

Val-Laillet, D., Aarts, E., Weber, B., Ferrari, M., Quaresima, V., Stoeckel, L. E., … Stice, E. (2015). Neuroimaging and neuromodulation approaches to study eating behavior and prevent and treat eating disorders and obesity. NeuroImage: Clinical, 8, 1–31.

Valls-Serrano, C., Caracuel, A., & Verdejo-Garcia, A. (2016). Goal Management Training and Mindfulness Meditation improve executive functions and transfer to ecological tasks of daily life in polysubstance users enrolled in therapeutic community treatment. Drug and Alcohol Dependence, 165, 9–14.

Van Leijenhorst, L., Moor, B. G., Op de Macks, Z. A., Rombouts, S. A. R. B., Westenberg, P. M., & Crone, E. A. (2010). Adolescent risky decision-making: Neurocognitive development of reward and control regions. NeuroImage, 51(1), 345–355.

Van Marle, H.J.F., Hermans, E.J., Qin, S., Fernández, G. (2009). From specificity to sensitivity: how acute stress affects amygdala processing of biologically salient stimuli. Biological Psychiatry, 66(7), 649-655.

van Strien, T., Frijters, J. E. R., Bergers, G. P. A., & Defares, P. B. (1986). The Dutch Eating Behavior Questionnaire (DEBQ) for assessment of restrained, emotional, and external eating behavior. International Journal of Eating Disorders, 5(2), 295–315.

Van Vliet-Ostaptchouk, J. V., Snieder, H., & Lagou, V. (2012). Gene–Lifestyle Interactions in Obesity. Current Nutrition Reports, 1(3), 184–196.

Vanaelst, B., Huybrechts, I., Bammann, K., Michels, N., Vriendt, T, et al. (2012). Intercorrelations between serum, salivary, and hair cortisol and child-reported estimates of stress in elementary school girls. Psychophysiology, 49(8), 1072-81.

Veer, I.M., Oei, N.Y.L., Spinhoven, P., Van Buchem, M.A., Elzinga, B.M., Rombouts, S.A.R.B. (2011). Beyond acute social stress: Increased functional connectivity between amygdala and cortical midline structures. Neuroimage, 57(4), 1534-41.

Verdejo-Garcia, A., Moreno-Padilla, M., Garcia-Rios, M. C., Lopez-Torrecillas, F., Delgado-Rico, E., Schmidt-Rio-Valle, J., & Fernandez-Serrano, M. J. (2015). Social stress increases cortisol and hampers attention in adolescents with excess weight. PLoS ONE, 10(4).

Verdejo-García, A., Pérez-Expósito, M., Schmidt-Río-Valle, J., Fernández-Serrano, M. J., Cruz, F., Pérez-García, M., … Campoy, C. (2010). Selective Alterations Within Executive Functions in Adolescents with Excess Weight. Obesity, 18(8), 1572–1578.

Verdejo-Román, J., Vilar-López, R., Navas, J. F., Soriano-Mas, C., & Verdejo-García, A. (2016). Brain reward system's alterations in response to food and monetary stimuli in overweight and obese individuals. Human Brain Mapping, 38(2), 666–677.

Viñas, B., Serra, L.L., Ribas, L., Pérez, C., Aranceta, J. (2003). Crecimiento y desarrollo: Actividad física. Estimación del nivel de actividad física, mediante el test corto KRECE PLUS. Resultados en la población española. In: LL Serra, J Aranceta, eds, (pp. 57-74). Barcelona: Masson.

Volkow, N. D., & O'Brien, C. P. (2007). Issues for DSM-V: Should Obesity Be Included as a Brain Disorder? American Journal of Psychiatry, 164(5), 708–710.

Volkow, N. D., Wang, G.-J., & Baler, R. D. (2011). Reward, dopamine and the control of food intake: implications for obesity. Trends in Cognitive Sciences, 15(1), 37–46.

Volkow, N. D., Wang, G.-J., Fowler, J. S., & Telang, F. (2008). Overlapping neuronal circuits in addiction and obesity: evidence of systems pathology. Philosophical Transactions of the Royal Society B: Biological Sciences, 363(1507), 3191–3200.

Volkow, N. D., Wang, G.-J., Tomasi, D., & Baler, R. D. (2013). The Addictive Dimensionality of Obesity. Biological Psychiatry, 73(9), 811–818.

Volkow, N. D., Wise, R. A., & Baler, R. (2017). The dopamine motive system: Implications for drug and food addiction. Nature Reviews Neuroscience.

Wabitsch, M., Bo Jensen, P., Blum, W. F., Christoffersen, C. T., Englaro, P., Heinze, E., … Hauner, H. (1996). Insulin and Cortisol Promote Leptin Production in Cultured Human Fat Cells. Diabetes, 45(10), 1435–1438. doi:10.2337/diab.45.10.1435

Wang, J., Freire, D., Knable, L., Zhao, W., Gong, B., Mazzola, P., … Pasinetti, G. M. (2014). Childhood and adolescent obesity and long-term cognitive consequences during aging. Journal of Comparative Neurology, 523(5), 757–768.

Wang, G.-J., Geliebter, A., Volkow, N. D., Telang, F. W., Logan, J., Jayne, M. C., … Fowler, J. S. (2011). Enhanced Striatal Dopamine Release During Food Stimulation in Binge Eating Disorder. Obesity, 19(8), 1601–1608.

Wang, G. J., Volkow, N. D., Felder, C., Fowler, J. S., Levy, A. V., Pappas, N. R., … Netusil, N. (2002). Enhanced resting activity of the oral somatosensory cortex in obese subjects. NeuroReport, 13(9), 1151–1155.

Washington, S. D., Gordon, E. M., Brar, J., Warburton, S., Sawyer, A. T., Wolfe, A., … VanMeter, J. W. (2013). Dysmaturation of the default mode network in autism. Human Brain Mapping, 35(4), 1284–1296.

Watabe-Uchida, M., Zhu, L., Ogawa, S. K., Vamanrao, A., & Uchida, N. (2012). Whole-Brain Mapping of Direct Inputs to Midbrain Dopamine Neurons. Neuron, 74(5), 858–873.

Weingarten, H.P. (1983). Conditioned cues elicit feeding in sated rats: a role for learning in meal initiation. Science, 220(4595), 431-33.

White, M. A., Whisenhunt, B. L., Williamson, D. A., Greenway, F. L., & Netemeyer, R. G. (2002). Development and validation of the food-craving inventory. *Obesity*, *10*(2), 107-114.

Wiers, R. W., Gladwin, T. E., Hofmann, W., Salemink, E., & Ridderinkhof, K. R. (2013). Cognitive Bias Modification and Cognitive Control Training in Addiction and Related Psychopathology. Clinical Psychological Science, 1(2), 192–212.

Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn : A Functional Connectivity Toolbox for Correlated and Anticorrelated Brain Networks. Brain Connectivity, 2(3), 125–141.

Wijngaarden, M. A., Veer, I. M., Rombouts, S. A. R. B., van Buchem, M. A., Willems van Dijk, K., Pijl, H., & van der Grond, J. (2015). Obesity is marked by distinct functional connectivity in brain networks involved in food reward and salience. Behavioural Brain Research, 287, 127–134.

World Health Organization. (2016, June). Obesity and overweight. Retrieved June, 2016, from http://www.who.int/mediacentre/factssheets/fs311/en.

World Health Organization. (2018, February 16). Obesity and overweight. Retrieved October 17, 2017, from http://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

Wu, M., Brockmeyer, T., Hartmann, M., Skunde, M., Herzog, W., & Friederich, H.-C. (2016). Reward-related decision making in eating and weight disorders: A systematic review and

meta-analysis of the evidence from neuropsychological studies. Neuroscience & Biobehavioral Reviews, 61, 177–196.

Yau, P. L., Kang, E. H., Javier, D. C., & Convit, A. (2014). Preliminary evidence of cognitive and brain abnormalities in uncomplicated adolescent obesity. Obesity, 22(8), 1865–1871.

Yau, Y.H., Potenza, M.N. (2013). Stress and eating behaviors. Minerva Endocrinol, 38(3), 255-67.

Yokum, S., Ng, J., & Stice, E. (2011). Relation of regional gray and white matter volumes to current BMI and future increases in BMI: a prospective MRI study. International Journal of Obesity, 36(5), 656–664.

Young, A. I., Wauthier, F., & Donnelly, P. (2016). Multiple novel gene-by-environment interactions modify the effect of FTO variants on body mass index. Nature Communications, 7, 12724. doi:10.1038/ncomms12724

Zellner, D. A., Loaiza, S., Gonzalez, Z., Pita, J., Morales, J., Pecora, D., & Wolf, A. (2006). Food selection changes under stress. Physiology and Behavior, 87(4), 789–793.

Zhang, Q., Li, H., and Guo, F. (2011). Amygdala, an important regulator for food intake. Frontiers in Biology, 6(1), 82-5.

Zhang, B., Tian, D., Yu, C., Zhang, J., Tian, X., von Deneen, K. M., … Liu, Y. (2015). Altered baseline brain activities before food intake in obese men: A resting state fMRI study. Neuroscience Letters, 584, 156–161

Zhang, B., Tian, X., Tian, D., Wang, J., Wang, Q., Yu, C., … Wang, J. (2017). Altered Regional Gray Matter Volume in Obese Men: A Structural MRI Study. Frontiers in Psychology, 8. doi:10.3389/fpsyg.2017.00125

Zhao, J., Li, M., Zhang, Y., Song, H., von Deneen, K. M., Shi, Y., … He, D. (2017). Intrinsic brain subsystem associated with dietary restraint, disinhibition and hunger: an fMRI study. Brain Imaging and Behavior, 11(1), 264–277.

Zhao, X.-H., Wang, P.-J., Li, C.-B., Hu, Z.-H., Xi, Q., Wu, W.-Y., & Tang, X.-W. (2007). Altered default mode network activity in patient with anxiety disorders: An fMRI study. European Journal of Radiology, 63(3), 373–378.

Zhou, Y., Friston, K. J., Zeidman, P., Chen, J., Li, S., & Razi, A. (2017). The Hierarchical Organization of the Default, Dorsal Attention and Salience Networks in Adolescents and Young Adults. Cerebral Cortex, 28(2), 726–737.

Zhu, J. N., Yung, W. H., Kwok-Chong Chow, B., Chan, Y. S., & Wang, J. J. (2006). The cerebellar-hypothalamic circuits: Potential pathways underlying cerebellar involvement in somatic-visceral integration. Brain Research Reviews.

Zseli, G., Vida, B., Szilvásy-Szabó, A., Tóth, M., Lechan, R.M., Fekete, C. (2018). Neuronal connections of the central amygdalar nucleus with refeeding-activated brain areas in rats. Brain Structure and Function, 223(1), 391-414.