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The Neurocognitive Phenotype of Excess Weight in Adolescents and Young Adults: Biological, Genetic, and Psychosocial Factors

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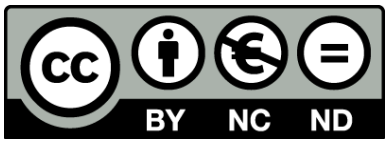

The Neurocognitive Phenotype of Excess Weight in Adolescents and Young Adults: Biological, Genetic, and Psychosocial Factors

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TABLE OF CONTENT

ABBREVIATIONS

ACEs	adverse childhood experiences
AL	allostatic load
AxD	axial diffusivity
BMI	body mass index
CPT-II	Conners' Continuous Performance Test II
CRP	C-reactive protein
DTI	diffusion tensor imaging
EF	executive functions
FA	fractional anisotropy
FTO	fat mass and obesity-related gene
GM	gray matter
GPS	genome-wide polygenic score
GWAS	genome-wide association studies
HDL	high-density lipoprotein cholesterol
HPA	hypothalamic-pituitary-adrenal
IL-6	interleukin 6
LDL	low-density lipoprotein cholesterol
MD	mean diffusivity
MRI	magnetic resonance imaging
NAcc	nucleus accumbens
NW	normal weight
OB	obesity
OFC	orbitofrontal cortex
OW	overweight
PFC	prefrontal cortex
RD	radial diffusivity
SES	socioeconomic status
TFEQ-R18	Three-Factor Eating Questionnaire R-18
TNFα	tumor necrosis factor alpha
WC	waist circumference
WCST	Wisconsin Card Sorting Test
WM	white matter

LIST OF FIGURES

LIST OF TABLES

FOREWORD

Thesis in compendium of publications format. The thesis consists of six objectives and three articles:

Prunell-Castañé A, Beyer F, Witte V, Sánchez Garre C, Hernán I, Caldú X, Jurado MÁ, Garolera M. From the reward network to whole-brain metrics: structural connectivity in adolescents and young adults according to body mass index and genetic risk of obesity. Int J Obes. 2024;48(4):567–74. IF (2022): 4.9, Q2 in Endocrinology and Metabolism.

Prunell-Castañé A, Jurado MÁ, Ottino-González J, Prats-Soteras X, Sánchez Garre C, Cano Marco N, Gómez-Pablos PS, García-García I, Garolera M. Beyond BMI: cardiometabolic measures as predictors of impulsivity and white matter changes in adolescents. Brain Struct Funct. 2023;228(3):751–60. IF (2022): 3.1, Q1 in Anatomy.

Prunell-Castañé A, Garolera M, Ottino-González J, Jurado MÁ. Allostatic load, adverse childhood experiences, executive functions, and BMI status in adolescents and young adults. Am J Hum Biol. 2024;e24089. IF (2022): 2.9, Q1 in Anthropology and Q2 in Biology.

RESUM

Títol: El fenotip neurocognitiu de l'excés de pes en adolescents i adults joves: factors biològics, genètics i psicosocials

Introducció: L'excés de pes és una condició de salut complexa que s'associa amb el desenvolupament de (multi)morbiditat. El fet que els adolescents amb excés de pes tinguin cinc vegades més risc de mantenir aquesta condició en l'edat adulta posa de manifest la necessitat d'estudiar quins factors afavoreixen la seva aparició i cronicitat. El fenotip neurocognitiu de l'excés de pes es podria referir a aquelles característiques psicològiques i cerebrals que representen una vulnerabilitat per adoptar comportaments que promouen l'excés de pes. Estudiar els correlats d'aquest fenotip neurocognitiu ajudaria a identificar individus amb risc de desenvolupar excés de pes i proposar intervencions específiques.

Hipòtesis: Aquesta tesi aborda l'excés de pes més enllà de l'adipositat i se centra en factors biològics, genètics i psicosocials per estudiar el fenotip neurocognitiu de l'excés de pes en adolescents i adults joves. Així, aquesta tesi presenta tres hipòtesis. En primer lloc, l'excés de pes i l'al·lel A del gen associat a la massa grassa i l'obesitat rs99396309 podrien estar associats amb una connectivitat estructural més baixa a la xarxa de recompensa. En segon lloc, els factors cardiometabòlics habitualment presents en l'excés de pes podrien estar associats a una major impulsivitat i alteracions en la microestructura de la substància blanca. En tercer lloc, l'estrès, ja sigui precedit per l'exposició a experiències adverses en la infància o subseguit per la càrrega alostàtica, podria estar associat a un pitjor funcionament executiu.

Objectius: En el primer estudi es va investigar els patrons de connectivitat estructural de la xarxa de recompensa segons l'índex de massa corporal i el risc genètic d'obesitat avaluat per l'al·lel A del gen associat a la massa grassa i l'obesitat rs99396309. En el segon estudi es va avaluar l'associació entre factors cardiometabòlics, la impulsivitat i els canvis microestructurals en els tractes de substància blanca normalment associats amb l'excés de pes i la impulsivitat. En el tercer estudi es va estudiar si les funcions executives eren vulnerables a l'estrès fisiològic (càrrega alostàtica) i psicològic (experiències adverses en la infància).

Mètodes: Al llarg de tres estudis originals, vam incloure adolescents i adults joves (de 10 a 21 anys) amb i sense excés de pes. Es van sotmetre a una avaluació mèdica (antropometria, pressió arterial, extracció de sang, genètica) i neuropsicològica (funcions executives,

impulsivitat, exposició a experiències adverses en la infància), i a l'adquisició d'una ressonància magnètica cerebral. L'índex de càrrega alostàtica es va estimar amb biomarcadors que representen l'estrès fisiològic. Les anàlisis de neuroimatge es van basar en imatges per tensor de difusió, tant per avaluar la microestructura de la substància blanca com la connectivitat estructural.

Resultats principals: En el primer estudi vam trobar una connectivitat estructural més baixa de la xarxa de recompensa en participants amb categories d'índex de massa corporal més altes, però no en aquells portadors de l'al·lel A del gen associat a la massa grassa i l'obesitat rs99396309. En una anàlisi exploratòria vam observar que la connectivitat estructural global estava positivament associada amb l'índex de massa corporal. En el segon estudi vam observar una relació inversa entre l'hemoglobina glicada i l'anisotropia fraccional al cíngol. A més, vam evidenciar que nivells més alts de triglicèrids estaven associats amb més errors de comissió al *Conners' Continuous Performance Test (CPT-II)* i que la glucosa i la pressió arterial diastòlica es van associar amb puntuacions més altes a la subescala d'ingesta emocional del *Three-Factor Eating Questionnaire R-18*. En el tercer estudi, vam trobar que una exposició més elevada a experiències adverses en la infància, però no la càrrega alostàtica, estava associada amb un pitjor funcionament executiu.

Conclusions: En adolescents i adults joves, els mecanismes pels quals l'excés de pes afecta la connectivitat estructural cerebral van més enllà del risc genètic d'obesitat. A més, factors cardiometabòlics de diferent naturalesa s'associen amb una impulsivitat més alta i una anisotropia fraccional més baixa en els tractes de substància blanca normalment relacionats amb l'excés de pes i la impulsivitat, cosa que suggereix que fins i tot a nivells preclínics, els factors cardiometabòlics són potencials biomarcadors del fenotip neurocognitiu de l'excés de pes. Finalment, l'estrès psicològic mesurat per l'exposició a experiències adverses en la infància, però no l'estrès fisiològic estimat per un índex de càrrega alostàtica, s'associa amb un pitjor funcionament executiu.

SUMMARY

Title: The neurocognitive phenotype of excess weight in adolescents and young adults: biological, genetic, and psychosocial factors

Introduction: Excess weight is a complex health condition that is associated with the development of (multi)morbidity. The fact that adolescents with excess weight have a five-fold increased risk of maintaining this condition as adults highlights the need to study which factors favor its emergence and chronicity. The neurocognitive phenotype of excess weight could be referred to as the psychological and brain characteristics that represent a vulnerability to engage in behaviors that promote excess weight. Studying the correlates of this neurocognitive phenotype would help identify individuals at risk of developing excess weight and to propose specific interventions.

Hypotheses: This thesis approaches excess weight beyond adiposity and targets biological, genetic, and psychosocial factors to study the neurocognitive phenotype of excess weight in adolescents and young adults. Consequently, the hypotheses of this thesis are threefold. First, excess weight and the A allele of the fat mass and obesity-related gene rs9939609 may be associated with lower structural connectivity in the reward network. Second, cardiometabolic factors usually present in excess weight may be associated with increased impulsivity and alterations in white matter microstructure. Third, stress, either led or followed by exposure to adverse childhood experiences or allostatic load, may be associated with poorer executive functioning.

Objectives: In the first study, we aimed to investigate the structural connectivity patterns in the reward network according to body mass index and the genetic risk of obesity assessed by the A allele of the fat mass and obesity-related gene rs99396309. In the second study, we evaluated the association between cardiometabolic factors and both impulsivity and microstructural changes in white matter tracts typically associated with excess weight and impulsivity. In the third study, we examined whether executive functioning was vulnerable to physiological (allostatic load) and psychological stress (adverse childhood experiences).

Methods: Along three original studies we included adolescents and young adults (aged 10-21) with and without excess weight. They underwent a medical (i.e., anthropometry, blood pressure, blood draw, genetics) and neuropsychological (i.e., executive functions, impulsivity, exposure to adverse childhood experiences) evaluation, and a brain magnetic resonance

acquisition. The allostatic load index was estimated using biomarkers representing physiological stress. Neuroimaging analyses were based on diffusion tensor imaging to evaluate white matter microstructure and structural connectivity.

Main results: In the first study, we found lower structural connectivity in the reward network in participants with higher body mass index categories, but not in those carriers of the A allele of the fat mass and obesity-related gene rs99396309. In an exploratory analysis we found that whole-brain structural connectivity was positively associated with body mass index. In our second study, we observed an inverse relationship between glycated hemoglobin and fractional anisotropy in the cingulum. We also reported that higher triglyceride levels were associated with higher commission errors in Conners' Continuous Performance Test (CPT-II), and that glucose and diastolic blood pressure were associated with higher scores on the emotional eating subscale of the Three-Factor Eating Questionnaire R-18 8 (TFEQ-R18). In the third study, we found that higher exposure to adverse childhood experiences, but not to allostatic load, was associated with worse executive functioning.

Conclusions: In adolescents and young adults, the mechanisms by which excess weight affects brain structural connectivity go beyond the genetic risk of obesity. Moreover, cardiometabolic factors of different nature are associated with higher impulsivity and lower fractional anisotropy in white matter tracts typically related to both excess weight and impulsivity, suggesting that even at preclinical levels, cardiometabolic factors are potential biomarkers for the neurocognitive phenotype of excess weight. Finally, psychological stress, measured by exposure to adverse childhood experiences but not physiological stress estimated by an allostatic load index, is associated with poorer executive functioning.

Chapter 1. Introduction

Excess Weight: Public Health, Determinants, and Pathophysiology

1.1. Excess weight as a public health concern

Excess weight is a health condition defined as the excessive accumulation of body fat. The most commonly used anthropometric measure to classify excess weight is the body mass index (BMI), calculated as the body weight in kilograms divided by the square of the body height in meters (kg/m2). Within this thesis, the term **excess weight** will be used to group both **overweight** (OW) **and obesity** (OB) conditions. A BMI of 25 kg/m^2 or higher would be indicative of OW, while a BMI of 30 kg/m^2 or higher would be indicative of OB. In children (aged less than 10 years) and adolescents (aged 10-19), excess weight status is determined by applying age and sex-specific centile curves equivalent to adults' BMI (2). Table 1 displays the excess weight cut-off points according to age. Although BMI is widely used, it is an indirect and limited measure of adiposity. BMI does not differentiate between body lean mass and body fat mass, nor does it capture the location of body fat accumulation. On the other hand, waist circumference (WC) measures abdominal adiposity and can thus detect higher-risk phenotypes of OB. However, there is no consensus on how WC should be measured (i.e., by using the midpoint between the lower border of the last rib and the iliac crest, or by using the superior border of the iliac crest), and absolute differences between these two measurements have been reported in females, even in samples including children and adolescents (3). Other sensitive but also subject to error methods to measure adiposity are bioelectric impedance and skinfold thickness, among others (4). Overall, the precise characterization of excess weight requires the use of multiple measurements.

Table 1. Excess weight definition by age.

	Excess weight	
	Overweight	**Obesity**
Children and adolescents	≥ 85th BMI Pc <95th for age and sex	BMI Pc ≥ 95^{h} for age and sex
Adults	BMI ≥ 25 kg/m^2 and < 30kg/m^2	BMI ≥ 30 kg/m^2

Adapted from Hampl (5). Abbreviations: BMI: body mass index; Pc: percentile.

Despite the World Health Organization targets, no country has reported a decline in OB prevalence. In 2020, 38% of the global population had excess weight, and current predictions suggest that the global prevalence of excess weight will increase to 51% by 2035. Obesity

alone is also expected to increase worldwide from 14% in 2020 to 24% by 2035. The prevalence of OB is particularly concerning in children and adolescents. Globally, although the prevalence in adults is higher in women, it is predicted that 18% of girls and 20% of boys will be living with OB by 2035. In Europe, these estimates are 14% for girls and 21% for boys. In Spain, projections indicate a 2.5% annual increase in childhood OB from 2020 to 2035 (6). Importantly, pediatric OB is not limited to the developmental period in which it occurs. Obesity throughout childhood and adolescence is associated with a 5-fold increased risk of OB in adulthood (7). Moreover, OB is not an isolated health condition. Its presence is a risk factor for other diseases and their co-occurrences. In children and adolescents, OB is linked to a higher risk of hypertension, dyslipidemia, fatty liver disease, impaired glucose tolerance, metabolic syndrome, and type 2 diabetes mellitus, among others (8). This morbidity also protracts into adulthood and, in adults, a large observational multicohort study reported that the OB condition was related to a 50% risk increase in developing 21 non-overlapping diseases compared to those with normal weight (NW). Moreover, the degree of OB was associated with complex multimorbidity (i.e., ≥4 co-occurring diseases) in a dose-response relationship (9).

Given the high prevalence of excess weight in our society, understanding the determinants of this health condition might help implement preventive strategies to diminish its current impact.

1.2. Excess weight determinants

Excess weight is usually the product of energy imbalance, where energy intake exceeds expenditure and the surplus of energy is stored (10). However, excess weight is not only the result of specific nutritional and lifestyle-related habits; it is a complex and multifactorial health condition that can also be modulated by genetic and environmental factors.

1.2.1. Genetic factors

From a genetic perspective, OB can be classified into two categories: monogenic and polygenic. Monogenic OB is an infrequent condition characterized by an early onset of severe OB and involves chromosomal deletions or single-gene defects. On the other hand, polygenic OB – otherwise known as common OB – is the product of the small effect of hundreds of polymorphisms and the environment. Gene discovery for both monogenic and

polygenic OB was initially restricted to candidate gene studies, based on their susceptibility to the phenotype of interest, and genome-wide linkage studies, which tested whether certain chromosomal regions co-segregate with a specific phenotype across individuals from the same pedigree (11).

Over time, gene discovery methods rapidly advanced, and the study of genetic variants across the whole genome became possible, although most were – and still are – performed in European populations, not accurately representing other ancestries. In 2007, the first genome-wide association study (GWAS) for OB identified a cluster of variants in the first intron of the fat mass and OB-related gene *(**FTO**)* locus that were associated with BMI. Multiple GWAS later, more than 750 loci have been associated with BMI, including variants in brain-derived neurotrophic factor and melanocortin 4 receptor (11), both of which are highly expressed in the hypothalamus and are associated with food intake and energy homeostasis (12,13). However, *FTO* is the locus with the largest effect (0.35 kg/m^2 per risk allele), which can start as early as 3 years old and increase progressively to reach its peak in the twenties. However, the underlying biological mechanisms by which *FTO* affects body weight have not been fully elucidated. In humans, the literature suggests that variations in *FTO* may modulate food intake by influencing the brain regions that affect appetite and reward processing. Still, the presence of the *FTO* risk allele is not deterministic. Even polygenic score studies that estimate susceptibility to OB by summarizing the effect of multiple variants observed in a GWAS report a discrete explained variance (11,14).

Thus, if genes only explain a small fraction of phenotypic variations, it is possible that OB-associated variants interact with the environment to modify OB risk. Concerning lifestyle habits, which are subject to socioeconomic status (SES), evidence suggests that moderate-to-vigorous physical activity may attenuate the effect of *FTO* on OB development. On the other hand, eating-related habits, such as the consumption of high-fat, high-sugar foods, may accentuate OB risk (15). Therefore, in common OB, although genetics may play an important role in OB development and maintenance, adherence to healthy habits may act as a protective factor.

1.2.2. Environmental factors and adverse childhood experiences

Given that no human exists out of a concrete context, environmental factors are crucial builders of an individual's reality.

The **obesogenic environment** can be defined as "the sum of influences that the surroundings, opportunities, or conditions of life have on promoting OB in individuals or populations" (16). These influences may be due to the increased availability of palatable foods, or from neuromarketing strategies that condition food intake in the absence of metabolic need or amplify hedonic hunger in the presence of metabolic depletion (17). One of the key neural substrates of incentive salience may be the mesolimbic dopamine system, including the ventral tegmental area, nucleus accumbens (NAcc), prefrontal cortex (PFC), and hippocampus (17). Beyond how modern times have changed access to certain types of food and implemented aggressive food marketing campaigns, **SES** also shapes adherence to healthy habits. SES is an increasing field of interest in neuroscience, and although there is no consensus on its definition, the most commonly used measures are parental education, income, occupational status, and neighborhood quality (18). Research on the importance of social inequalities in health is mostly based on high-income countries, underrepresenting impoverished countries and populations (19). With that in mind, a meta-analysis concluded that individuals with a lower life SES had a higher mean BMI than those with a more privileged SES and that there was an association between lower SES and OB among women, but not among men (20).

In children, multiple socioeconomic factors may interact to influence the development of excess weight, such as food insecurity, which leads to affordable high-energy dense foods with limited nutritional value, or neighborhoods with high crime rates that are not safe to engage in physical activity (19). Moreover, significant SES and brain system interactions have been reported, in which more deprivation imposes distinctive effects on brain health. Structurally, reductions in gray matter (GM) volumes in the prefrontal, insular, frontal opercular, lateral parietal, and lateral temporal regions, as well as subcortical areas including the cerebellum, striatum, and thalamus, have been described in lower SES, with a special stronger association in the striatum (21). Despite this, low SES should not be pathologized, categorizing it as a property of the brain rather than a situation that needs to be politically and socially addressed (22).

Adverse childhood experiences (ACEs), defined as potential traumatic events that destabilize children's lives, are a form of victimization – usually more prevalent in vulnerable SES (23) – that have long-lasting consequences on mental and physical health. Adolescents exposed to ACEs are more likely to develop mental health conditions such as depression, anxiety, behavioral problems, attention-deficit/hyperactivity disorder, or substance use disorder (24). On the physical dimension, ACEs have been associated with higher BMI

measures as early as 6 years of age (25). Consistently, ACEs increase the odds of adult OB, cardiovascular disease, and diabetes, among others (26). Possible factors that may mediate the relationship between ACEs and excess weight are lack of social support, engagement in unhealthy habits, changes in the stress response – including the possible disruption of the hypothalamic-pituitary-adrenal (HPA) axis and the chronic role of weight stigma –, and mental health issues (27)

Overall, excess weight development and maintenance are modulated by multiple factors – from genetic to environmental – that interact with each other and condition the adherence to health-related habits.

1.3. Excess weight pathophysiology

A sustained positive energy balance initiates pathophysiological changes that can ultimately lead to disease. Taking adipose tissue expansion as the starting point, other processes, such as inflammation, insulin resistance, dyslipidemia, and stress responses, are also involved.

1.3.1. Adipose tissue

The surplus energy is stored in adipocytes, which are known as adipose tissue cells. Although adipose tissue was initially considered as an energy reservoir depot, it was subsequently redefined as an endocrine organ (28). Adipose tissue can be classified into two types: brown adipose tissue and white adipose tissue, which exhibit functional differences. Brown adipose tissue is present in small proportions, mainly in the shoulders and ribs, and it has thermoregulatory properties. In contrast, white adipose tissue is present throughout the body at both the subcutaneous and visceral levels, and is the main source of energy storage and regulation (29).

When there is a positive energy balance, insulin drives lipid storage in white adipocytes by stimulating fatty acid uptake and converting the heightened levels of glucose, via de novo lipogenesis, into lipids, which are also stored in the adipose tissue (29). If this situation is sustained over time, white adipocytes will eventually expand to accommodate the need for increased lipid storage, either by number (i.e., hyperplasia) or size (i.e., hypertrophy) (30). However, white adipocyte expansion has a limit and, when reached, its vascular supply becomes insufficient, angiogenesis is inhibited, fibrosis is accelerated, macrophages infiltrate and polarize to an inflammatory profile, and inflammatory cytokines are locally produced

(e.g., tumor necrosis factor alpha (TNFα), interleukin 6 (IL-6)) (29), leading to subsequent chronic low-grade systemic inflammation (28). In addition, visceral adipose tissue is considered to be more active than subcutaneous tissue, displaying higher levels of lipolysis, macrophage infiltration, and cytokine production, and thus is associated with a less favorable metabolic profile (29). In addition, when the storage capacity of adipose tissue is exceeded, the remaining circulating lipids accumulate in other organs (i.e., the liver, muscle, heart, and pancreas), a phenomenon known as ectopic fat accumulation, which promotes systemic insulin resistance and inflammation (30).

1.3.2. Chronic low-grade systemic inflammation

Inflammation is an immune physiological reaction to harmful stimuli intended to restore homeostasis. When an acute insult occurs, inflammatory, cellular, and molecular mediators interact to heal the affected tissue. If successful, harmful stimuli are eliminated, inflammatory responses dissipate, and tissue repair is initiated (31). However, under excess weight conditions, an inflammatory response of a different nature is generated. The trigger is not an infection or trauma but metabolic in nature, leading to chronic low-grade systemic inflammation. It is hypothesized that the chronicity of the inflammatory state observed in excess weight might be related to the metabolic origin of inflammation. It is possible that a metabolic trigger does not initiate inflammatory responses that are strong enough to resolve noxious stimuli, or that there is an evolutionary defect in responding to such metabolic signals. Nevertheless, the presence of chronic low-grade systemic inflammation is one of the hallmarks of excess weight and has multiple implications (32). Table 2 summarizes the main biomarkers involved in the inflammatory process.

Table 2. Biomarkers involved in chronic low-grade systemic inflammation.

Cytokines	Adipokines	Acute-phase proteins
↑ TNFα	↑ Leptin	↑ Fibrinogen
↑ IL-6	↓ Adiponectin	↑ CRP

Abbreviations. CPR: C reactive protein, IL-6: interleukin 6, TNFα: tumor necrosis factor alpha.

Local inflammatory responses that are initiated within the dysregulated adipose tissue involve the presence of proinflammatory factors – at the expense of protective anti-inflammatory

adipokines, such as **adiponectin** – that not only contribute to local inflammation but also induce systemic inflammation (33). Proinflammatory cytokines, such as **TNFα** and **IL-6,** decrease insulin sensitivity and glucose uptake, and induce lipolysis (32). IL-6 also acts in the hypothalamus to regulate satiety and energy expenditure (34), influences the secretion of other cytokines from adipocytes (35), and stimulates hepatocytes to synthesize and secrete **fibrinogen** and C-reactive protein (**CRP**), which are markers of systemic inflammation (34). **Leptin**, an adipokine that also acts in the hypothalamus, promotes lipolysis by stimulating neuroadipose junctions and promotes an inflammatory state by directly interacting with immune cells. (29)

Systemic inflammation has been associated with metabolic and cardiovascular pathologies, as well as cognitive decline, possibly due to metabolic and endothelial dysfunction, and neuroinflammation, respectively (34). Regarding neuroinflammation, when the blood-brain barrier is persistently challenged, such as in low-grade chronic systemic inflammation, its permeability changes, and pro-inflammatory molecules can enter the brain and interact with microglia, the brain-resident macrophages. Microglia then induce the secretion of more inflammatory cytokines, particularly in brain regions with higher microglial density, such as the hypothalamus, hippocampus, cerebral cortex, and striatum (36).

1.3.3. Cardiometabolic and cardiovascular alterations

Although excess weight itself has been described as an independent predictor of cardiovascular risk, the initial consequences of adipose tissue dysregulation – such as alterations in lipid metabolism and insulin resistance – can act as intermediate risk factors that promote cardiovascular and metabolic events (37). Table 3 provides a list of biomarkers whose dysregulation may lead to cardiometabolic diseases.

Table 3. Biomarkers associated with cardiometabolic diseases.

Dyslipidemia	Hypertension	Diabetes
↑ Total cholesterol	↑ Systolic blood pressure	↑ Glucose
↓ HDL	↑ Diastolic blood pressure	↑ Glycated hemoglobin
↑ LDL		
↑ Triglycerides		

Abbreviations. HDL: high-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol.

Alterations in lipid metabolism can lead to dyslipidemia, characterized by increased levels of low-density lipoprotein cholesterol (**LDL**), **triglycerides** and **total cholesterol**, and decreased levels of high-density lipoprotein cholesterol (**HDL**). Dyslipidemia is one of the features of metabolic syndrome, and it is also related to atherosclerosis through the accumulation of LDL particles. Moreover, the presence of endothelial dysfunction – the inability of the endothelium to vasodilate correctly – is considered an early marker of atherosclerosis and one of the possible mechanisms leading to hypertension (i.e., high **systolic** and **diastolic blood pressure**) (38). On the other hand, peripheral insulin resistance can dysregulate hepatic and pancreatic mechanisms that support **glucose** homeostasis. In the liver, decreased insulin sensitivity prevents the regulation of glucose production, contributing to hyperglycemia. In the pancreas, the overproduction of insulin to remove excess circulating glucose levels results in the apoptosis of pancreatic β cells, a common feature of diabetes mellitus (32). Diabetes mellitus can be diagnosed using plasma glucose and **glycated hemoglobin** concentrations (39).

These intermediate risk factors lead to the development of metabolic and cardiovascular diseases such as diabetes, coronary heart disease, and ischemic stroke (37). However, engagement in healthy lifestyle habits can improve metabolic profiles. Specifically, physical activity has been associated with improvement in glucose tolerance and HDL-LDL ratio, as well as with decreases in triglyceride concentration and platelet aggregation (38).

1.3.4. Stress and allostatic load

Stress responses are adaptive and allow the organism to maintain stability through challenging contexts and to recover homeostasis. However, when facing long-term stress, the primary neuroendocrine responses (i.e., catecholamines from the sympathetic adrenal-medullary axis or glucocorticoids from the HPA axis) that prepare the organism for a fight-or-flight response become chronically over-activated. This over-activation, in conjunction with cytokine engagement (e.g., IL-6, TNFα), dysregulates other interconnected systems that, by trying to compensate for the chronic effects of neuroendocrine mediators (e.g., **cortisol**), initiate secondary preclinical variations. This preclinical state is known as allostatic load (**AL**) and affects the metabolic (e.g., glycated hemoglobin, HDL, LDL, and triglycerides), cardiovascular (e.g., systolic and diastolic blood pressure), and immune systems (e.g., fibrinogen and CRP). If sustained over time, what was initially a dysregulation eventually

becomes a disease, a final stage known as allostatic overload (40). Figure 1 illustrates the progression of AL.

When excess weight is added to this cascade of events, some mediators may become even more affected. Cardiometabolic and cardiovascular dysregulations already present in excess weight can increase the cumulative effects of AL (41). Moreover, low-grade inflammation can increase HPA axis activity and cortisol production (42). This increase in cortisol levels has different implications. First, cortisol also contributes to hepatic glucose production (43). Second, cortisol promotes eating by enhancing reward pathways (i.e., dopamine release) and leptin resistance in the brain, as well as promoting abdominal fat deposition, leading to a vicious cycle of excess weight and stress responses (44).

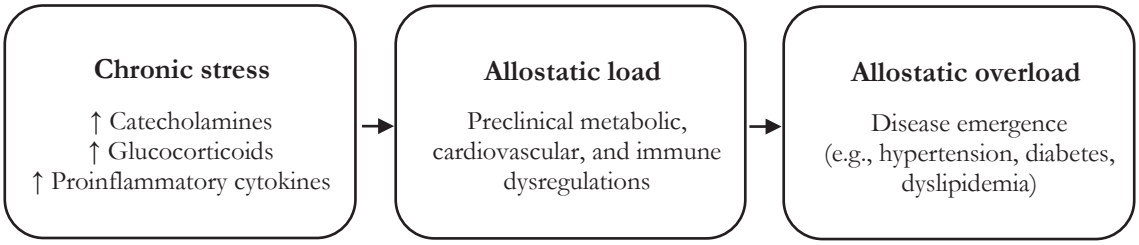

Figure 1. Allostatic load diagram. Original figure created specifically for this doctoral thesis.

Overall, the medical consequences of excess weight are not the result of a single physiological alteration but rather of the interconnected dysregulation of multiple systems, which confers a challenge for its correct management. Disentangling how these dysregulations may affect neurocognitive traits that ultimately favor excess weight development and maintenance requires the implementation of neuropsychological and neuroimaging protocols.

Brain Characterization Using Magnetic Resonance Neuroimaging

1.4. A brief history of human white matter

Throughout human history, the study of the brain has been an ongoing question. While the prevalent doctrine in antiquity was that the ventricular system acted as a recipient for mental functions, a scientific revolution started in 1543, when Andreas Vesalius differentiated human GM and white matter (WM) for the first time. The anatomical and functional

understanding of the brain advanced, and almost 100 years later, it was proved that WM was formed by fibers. Subsequently, numerous advances happened, such as the description of WM tracts, their classification (i.e., projection, association, or commissural fibers) and organization, and the acknowledgement of the communication between brain regions. However, the architecture of the WM fibers was still unknown. The discovery by Santiago Ramón y Cajal of neurons as an independent entity of the nervous system was crucial to enable a finer examination of fiber bundles. Studies focusing on myelination and the description of the pathological correlates of WM disturbance continued, and an *in vivo* study of the cerebral anatomy became a reality using magnetic resonance imaging (MRI) techniques (45). The first brain MRI of a living human being was performed in 1978 (46). In the 1990s, the possibility of using the diffusion tensor in MRI, known as diffusion tensor imaging (DTI), was introduced. This diffusion tensor model allowed the indirect measurement of the diffusion of water molecules in the brain and to infer the architecture of its surroundings (47).

1.5. Diffusion tensor imaging

MRI techniques allow the study of the brain from different perspectives. Structural MRI provides information on the macrostructural features of the brain, such as volume, area, surface, length, or thickness. The GM can be assessed using either voxel- or surface-based approaches. Voxel-based morphometry, using probabilistic segmentation, labels each brain voxel as GM, WM, or cerebrospinal fluid and returns an estimated measure of tissue volume (48). Surface-based morphometry, by identifying the borders between tissue types, has the ability to measure GM volume, cortical thickness, surface area, gyrification, and folding patterns (49). Microstructural features, which assess the properties of tissue components, are usually studied using DTI, a type of diffusion MRI.

DTI describes diffusion in each voxel by modeling it as a mathematical tensor that can be decomposed into eigenvectors representing the direction of diffusion and eigenvalues representing the magnitude of diffusion. Diffusion can be either isotropic, where water molecules disperse equally in all directions, or anisotropic, where molecules follow a certain direction owing to structural limits (i.e., WM axons). Tract-based spatial statistics is one of the most common methods for quantitatively assessing diffusion. This method produces different measures, including fractional anisotropy (**FA**), mean diffusivity (**MD**), axial diffusivity (AxD), and radial diffusivity (RD), which provide an indirect estimation of

microstructural status. FA is the most used metric to study WM microstructure. FA – ranging from 0 meaning isotropic to 1 meaning anisotropic – indicates how coherent the movement of the water is along the fiber with higher values suggesting well-myelinated and undamaged tracts. MD is the average of all eigenvalues ($\lambda_1, \lambda_2, \lambda_3$) and reflects the overall magnitude of diffusion, where lower values are indicative of heightened myelination (50). AxD is a measure of diffusivity along the primary axis (λ_1), which reflects axonal integrity, and RD is a measure of the amount of diffusivity perpendicular to the primary axis of diffusion, calculated by averaging λ_2 and λ_3, and reflects myelin integrity (47). Figure 2 provides a graphical representation of the diffusion tensor ellipsoid.

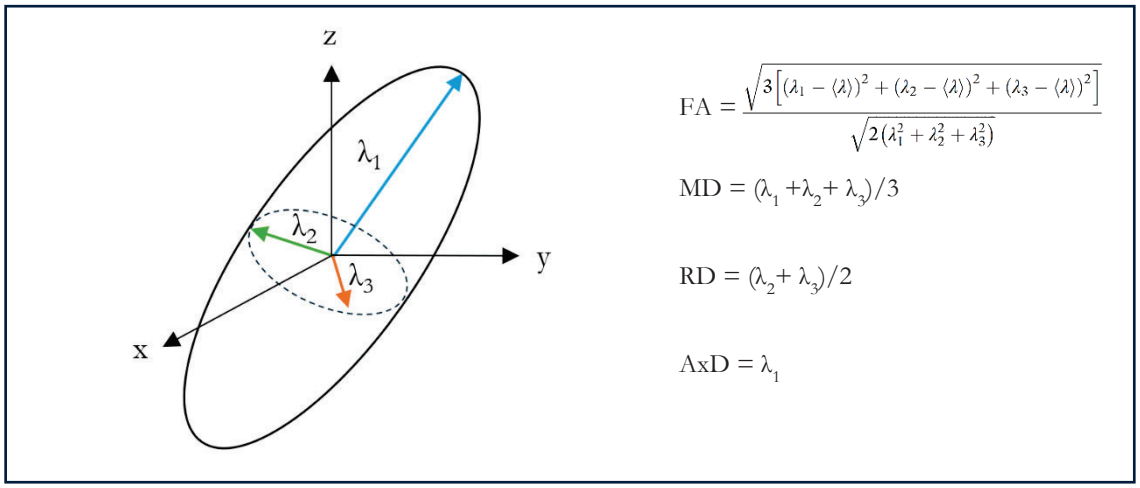

Figure 2. Diffusion tensor ellipsoid representing anisotropic diffusion. Adapted from García-Martín and López-Larrubia (51). Abbreviations. AxD: axial diffusivity, FA: fractional anisotropy, MD: mean diffusivity, RD: radial diffusivity.

Structural connectivity

The architecture of WM fibers and their connections with cortical and subcortical regions – the structural connectome – can be studied using tractography and graph metrics. Deterministic tractography reconstructs WM pathways by inferring the orientation of the principal eigenvector of the tensor model in each voxel, whereas probabilistic tractography models multiple diffusion orientations per voxel based on their probability distribution (47). Either way, tractography visually reconstructs the inferred WM fiber connections between GM areas using DTI (52). Graph theory suggests that structural brain networks can be represented as graphs composed of nodes (i.e., brain regions usually defined by brain parcellation methods) connected by edges (i.e., axonal projections). The connectivity of these

edges can be assessed quantitatively (e.g., number of streamlines between regions) or qualitatively (e.g., mean value of a diffusion metric across voxels included in the streamlines) (52). Moreover, the organization of a brain network can be analyzed globally by means of connectivity strength, which describes the overall strength of the connections between brain regions, or locally by means of a clustering coefficient, which measures the probability of neighboring nodes in the network being interconnected (53).

1.6. Normative brain development

Human brain development is a dynamic and adaptive process that begins in the third gestational week and extends at least through late adolescence, facilitating the emergence of new neural organizations (54). Brain development occurs at different rates across brain regions, and beyond the complexity of developing in a posterior-to-anterior fashion, the temporal sequence of maturation is mostly led by the function served rather than its location. Thus, GM maturation begins in brain regions that underlie basic sensory (i.e., primary visual, sensory, olfactory, and gustatory areas) and motor (i.e., precentral gyrus) functions, followed by the development of regions that assist complex processing, spatial orientation, and attention (i.e., inferior-posterior temporal and inferior parietal areas). Regions implicated in executive functioning (i.e., PFC) and multimodal integration (i.e., superior temporal areas) are the last to develop (55), with full maturation of the PFC in the mid-twenties indicating complete brain development (56). Consistently, WM somatosensory pathways mature first, whereas frontotemporal tracts show a protracted maturational trajectory (55).

Throughout development, the global GM volume strongly increases from mid-gestation onwards, peaking before the onset of puberty – at 5.9 years – and following a progressive reduction (57) that reflects synaptic pruning (54). Cortical thickness peaks early at 1.7 years, but its maximum velocity development peaks even earlier, during mid-gestation (57). Subcortically, GM volume is characterized by an intermediate growth pattern, peaking in adolescence and mid-puberty at 14.4 years (57). Concerning WM trajectories, WM volume increases quickly from mid-gestation to early childhood, peaking in adulthood at 28.7 years, with a subsequent rapid decline after the fifties (57). Microstructurally, FA exponentially increases in the first three years of life and continues to increase until age 25 in a more discrete

manner, while the reverse pattern is observed for MD (58). In addition, the increased structural connectivity present during development, which follows an inverted U-shaped trajectory and peaks approximately in the third decade, is supported by the parallel nonlinear trajectories of WM integrity. The most prominent changes in brain connections occur in the prefrontal and temporal cortices, facilitating higher-order cognitive functions during development (59). Figure 3 provides a visual representation of the age at peak of the different brain development trajectories.

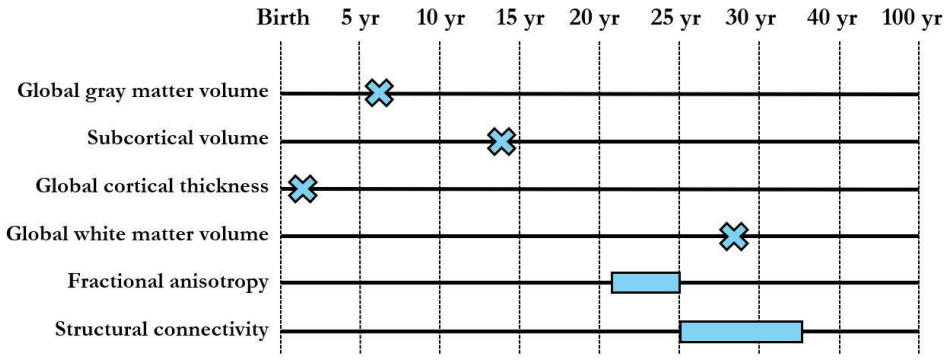

Figure 3. Age at peak of normative neurodevelopmental trajectories. Adapted from Bethlehem (57), Lebel (58), and Zaho (59). Crosses and rectangles represent the peak value (57) and peak range (58,59) of each brain category, respectively. Abbreviations. Yr: years.

Moreover, developmental brain trajectories might not only be a function of age, but also of sex and puberty. At the macrostructural level, more advanced pubertal stages and higher testosterone and estradiol levels are associated with GM volume reductions, even though their effects may differ depending on sex (60). WM maturation starts earlier in girls than in boys and is positively associated with more advanced pubertal maturation, either defined using physical measurements (i.e., Tanner scale) or hormonal markers (i.e., gonadal hormones). However, boys develop larger WM volumetric increments than girls do (61).

To summarize, while trajectories of brain development are variable between brain tissues, there is consistency between WM, GM, and structural connectivity patterns to first develop core sensory and motor regions, followed by more protract development in frontal and temporal areas. In addition, biological sex and hormonal changes during puberty may influence these trajectories. Determining how excess weight might uniquely impact the

developing brain can help elucidate the neural mechanisms that promote and maintain such condition in adolescent populations.

1.7. Normative development of executive functions

Normative brain developmental trajectories are synchronized with the development of neurocognitive skills. The protract maturation of the PFC parallels the continuous advances seen in **executive functions** (EF) throughout childhood and adolescence, although EF also rely on other interconnected brain areas (e.g., the anterior cingulate and parietal cortices, hippocampus, or amygdala) that support their correct functioning (62). EF can be defined as top-down mental processes that allow goal-oriented behavior. Therefore, EF are essential for maintaining one's health and cognitive, social, and psychological development, as well as academic and personal achievement (63). Within this set of skills, according to Diamond's framework (63), three core EF can be distinguished: inhibitory control, working memory, and cognitive flexibility. Table 4 provides a description of each domain. From these core EF, higher-order EF are built, including problem-solving, reasoning, and planning (63). EF can be further distinguished by using the hot and cold principle, where EF that are required in emotionally charged situations would be hot EF, whereas those required in more affectively neutral contexts would be cold EF (64).

Table 4. Description of core executive functions.

Inhibitory control	Ability to control one's attention, behavior, thoughts, or emotions to ignore a strong internal predisposition or external distractors, and instead do what's more appropriate.
Working memory	Involves holding information in mind, either verbal or visual-spatial, and mentally working with it.
Cognitive flexibility	Allows the adjustment to changing environments or demands by inhibiting previous perspectives and loading into working memory a new perspective.

Adapted from Diamond 2013 (63)

The development of EF is gradual. Even in the immaturity of a newborn, primitive reflexes are shown in their interaction with the environment. In the first months of life, early evidence of inhibitory control, working memory, and cognitive flexibility is shown in infants' looking

behavior, which extends to reaching behavior by the second half of the first year of life. From 3 to 5 years of age, children show dramatic improvements in inhibitory control and cognitive flexibility, as well as working memory by 5 years of age. Nevertheless, their executive skills are error-prone and require refinement (64,65).

During middle childhood, improvement in EF is more evident. Inhibitory control, which is disproportionately difficult for young children, shifts from reactive to proactive and becomes less sensitive to interference. Working memory boosts, and children can engage in complex span and spatial tasks that require the manipulation of multiple elements. Cognitive flexibility also improves, and the cost of switching declines progressively (64).

EF skills continue to mature and stabilize throughout adolescence, following nonlinear trajectories. Significant age-related changes in EF accuracy (i.e., increases in correct responses) and latency (i.e., decreases in response speed) are observed from 10 to 15 years of age. More discrete changes occur from age 15 to 18, and very little improvement is seen after age 18, suggesting a potential closure of adolescent EF development between 18 and 20 years of age, which some studies extend into the mid-twenties (66).

1.8. Adolescent behavior: impulsivity, reward, and stress responses

Adolescence is a vulnerable developmental period characterized by dramatic biological, behavioral, emotional, and social changes. The onset of puberty determines its beginning, and from an evolutionary perspective, the full acquisition of independence skills marks the transition to adulthood. Adolescence is characterized by suboptimal decisions that are generally the product of impulsive and reward-seeking behaviors (56). These tendencies seem to underlie the normative maturation of the adolescent brain, and do not necessarily represent psychopathology. Individual differences in neural responses to rewards may explain the predisposition of some adolescents to engage in risky behaviors (56).

Impulsive and reward-seeking behaviors follow distinct developmental trajectories. **Impulsivity**, which can be conceptualized as a multidimensional construct that involves urgency, lack of perseverance and premeditation, and sensation seeking (67), steadily diminishes with age across childhood and adolescence. The protracted and linear development of the PFC sustains the ongoing acquisition of inhibitory control competence, which is paired with progressive reduction of impulsivity. However, **reward**-seeking and risky behaviors appear to increase during adolescence. It has been proposed that this is due to a developmental mismatch between the early maturation of subcortical structures that

influence affect and reward, as opposed to the delayed maturation of the PFC, which is involved in cognitive control. The delayed functional connectivity between prefrontal and limbic subcortical regions observed in adolescents could explain the lack of top-down control of reward processing (56,68). In addition, puberty itself may intensify sensitivity to reward (69).

Adolescence is characterized by increased **stress** and heightened stress reactivity (70). Stress can be defined as a "negative emotional experience accompanied by predictable biochemical, physiological, and behavioral changes that are directed toward adaptation either by manipulating the situation to alter the stressor or by accommodating to its effects" (71). During this time of development, the HPA axis is remarkably sensitive to social challenges and the PFC is richer in cortisol receptors, making adolescents more susceptible to the consequences of stress. The nature of stressors varies among adolescents. Some are only subjected to adolescent-specific daily stressors, such as academic, peer, or romantic pressures, whereas others face additional exposure to adverse and victimizing experiences (70) that further dysregulate the HPA axis (72).

1.9. A neural, cognitive, and behavioral approach to adolescent eating behavior

Eating behavior is the product of the interaction between multiple homeostatic and non-homeostatic systems. **Homeostatic** regulation of eating behavior relies on information about the energy status provided by physiological signals (e.g., ghrelin, insulin, and leptin) to the hypothalamus. Under conditions of negative energy balance, neuropeptide Y, agouti-related protein, and gamma-aminobutyric acid neurons located in the arcuate nucleus of the hypothalamus are activated and stimulate food intake. Satiety perception is posteriorly determined by peptide secretion from the gastrointestinal tract (e.g., glucagon-like peptide 1 and cholecystokinin) and by neural signaling of gastric distension via the vagus nerve to the hindbrain. Moreover, leptin favors brain responsiveness to satiety signals and stimulates hypothalamic proopiomelanocortin neurons, which inhibit food intake (73).

These homeostatic processes do not operate alone. Eating behavior is also guided by **reward** and **cognitive control** systems, among others. Several brain regions are involved in reward processes. Although the anterior cingulate cortex, orbitofrontal cortex (OFC), ventral striatum, ventral pallidum, and midbrain dopamine neurons could be considered key structures, connections to and projections from these areas to others (e.g., hippocampus, hypothalamus, and amygdala) are also important (74). However, in this thesis, the reward

network is defined – following Marqués-Iturria et al. (75) approach – as lateral and medial OFC, NAcc, caudate nucleus, and putamen. The reward network is influenced by signals that inform about the energy status, which are used to adjust the rewarding value of food, defined as the momentary value of a specific food to a person. Thus, hunger states would increase food reward to facilitate meal initiation, and satiety states would decrease food reward to facilitate meal termination. However, the rewarding aspect of food can go beyond nutritional purposes (73). It is hypothesized that either hypo- or hyperactivation of the reward network can lead to food ingestion in the absence of an energy deficit, favoring excess weight states. Dopamine deficiency in the reward network may decrease the reward sensitivity to food consumption and induce overeating as a compensatory mechanism. Likewise, elevated reward responsivity to food cues may lead to overeating (76).

On the other hand, cognitive control, which mainly depends on the PFC, is central to successful regulation of eating behavior. Working memory supports long-term goal achievement (e.g., healthy eating) by maintaining goal-relevant information and redirecting attention away from the tempting stimuli. Inhibitory control limits impulsive responses that may impede goal accomplishment (e.g., eating highly palatable foods), and cognitive flexibility facilitates health-related goals by pursuing a more adaptive method to accomplish them (e.g., avoiding unrealistic or too restrictive dieting) (77). Although all EF are involved in eating behavior, it has been theorized that deficits in inhibitory control can increase sensitivity to food reward and impulsivity traits, leading to food overconsumption and excess weight (76).

Throughout adolescence, the interaction between multiple systems that regulate eating behavior is conditioned by ongoing developmental processes. Rapid physical growth and elevated metabolic activity increase food intake. Moreover, the conjunction of changes in caloric needs, increased reward sensitivity, and the development of PFC and cognitive control abilities (e.g., inhibitory and impulsivity control) can easily lead to overconsumption of highly palatable and nutritionally deprived foods. Simultaneously, repetitive exposure to unhealthy food increases the vulnerability of developing brain systems involved in self-regulation by inducing structural and functional changes in the PFC and altering the mesocorticolimbic system (78). Additionally, the increased exposure to stress seen in adolescents may promote dopamine release and thus food reward responsivity (44). Finally, environmental factors (e.g., food insecurity and food availability) also determine the quality of food choices.

1.10. Brain characteristics of the excess weight phenotype

Excess weight involves increases in adiposity, the onset of cardiometabolic changes, and higher AL states, among others. Research has suggested that these factors are associated with varying degrees of structural, microstructural, and connectivity changes in the brain. Different frameworks have been proposed to outline the directionality of this relationship; however, there is still no consensus. Brain changes have been described as predictors and outcomes of excess weight. Some studies suggest that individual differences in regions that support cognitive control, such as the PFC and particularly the dorsolateral PFC, may predict susceptibility to overeating. Others point to pathophysiological changes associated with excess weight as disruptors of brain health. Even some researchers have proposed a potential reciprocal relationship between the brain and excess weight (79). This thesis follows the premise that brain changes may be a consequence of the excess weight phenotype. A description of these brain outcomes across different age ranges (children younger than 10 years, adolescents: 10-19, young adults: 20-39, middle-aged adults: 40-64, and old adults aged 65 years or older) continues below.

1.10.1. Structural brain changes

Excess weight is associated with structural changes in the brain. This relationship has been primarily studied in adult populations, and there is less evidence in younger populations, particularly adolescents. Table 5 highlights how brain regions that undergo structural changes in excess weight states are also involved in impulsivity (e.g., basal ganglia, frontal gyri, insula, anterior cingulate cortex, OFC (80)), reward (e.g., lateral and medial OFC, NAcc, caudate nucleus, putamen (75)), and executive functioning (e.g., PFC including the OFC, anterior cingulate cortex, parietal cortex, cerebellum (81)).

1.10.2. Microstructural brain changes

Excess weight and its related physiological characteristics are also related to WM microstructural changes, which have been reported in association fibers connecting cortical areas within the same hemisphere, commissural fibers connecting the two hemispheres, and in projection and thalamic fibers connecting cortical and subcortical structures. Again, this relationship has been underexplored in youth, especially in adolescents. Table 6 provides

information about how WM tracts affected in excess weight states are intrinsically related to neuropsychological processes that could potentially maintain or increase the excess weight condition, such as impulsivity (e.g., superior longitudinal fasciculus, forceps major, corticospinal tract (82)), reward (e.g., corpus callosum, uncinate fasciculus, cingulum (83)), and executive functioning (e.g., superior longitudinal fasciculus, corpus callosum, forceps major, anterior corona radiata, fornix, cingulum (84)).

1.10.3. Structural connectivity changes

Excess weight can affect the structural connectome. Although multiple brain networks may support eating behaviors, the reward network is particularly relevant for the excess weight phenotype. Higher **adiposity** measures have been related to lower structural connectivity of the reward network in samples comprising adolescents, young adults, and middle-aged adults (75,85). Studies assessing brain signatures of the excess weight phenotype beyond the reward network found, in young adults with OW (compared to their NW peers), an increased structural connectivity between the reward network and regions of executive control, emotional arousal, and somatosensory networks. Moreover, decreased connectivity was found between the ventromedial PFC and anterior insula, and between the thalamus and executive control network regions (86). Another study of young adult females with OB reported lower connectivity in WM tracts connecting the insula, amygdala, PFC, OFC, and striatum, as well as higher connectivity between the amygdala and anterior cingulate cortex (87). Regarding eating patterns, in healthy adolescents and young adults aged 17-25, those with higher scores on a food addiction scale presented lower structural connectivity between brain regions related to reward, cognitive control, and interoceptive processes (i.e., the insula and anterior cingulate cortex, insula and caudate, and ventromedial PFC and putamen) than those with lower food addiction scores (88). In addition, in healthy adults aged 50 years or older, a higher adherence to the Mediterranean diet was associated with higher structural connectivity between the left amygdala, left lingual, olfactory, and middle occipital gyri, and left calcarine areas, suggesting their possible implication in the integration of sensory and tase stimuli, and thus in food intake (89).

The extent to which **cardiometabolic** factors and **AL** affect structural connectivity is underexplored. Adults aged 50-70 with type 2 diabetes showed lower structural connectivity in the bilateral lingual gyrus than healthy controls (90). In another study comprising young and middle-aged adults with schizophrenia and healthy controls, higher AL scores were

associated with lower structural connectivity between the hippocampus and hypothalamus, regardless of the diagnosis (91). Overall, despite initial efforts made to disentangle the impact of the excess weight phenotype on the structural connectome, evidence is limited and mainly focused on adults.