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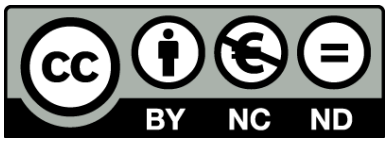
Overweight, Allostatic Load and Neuroimaging

Jonatan Ottino González



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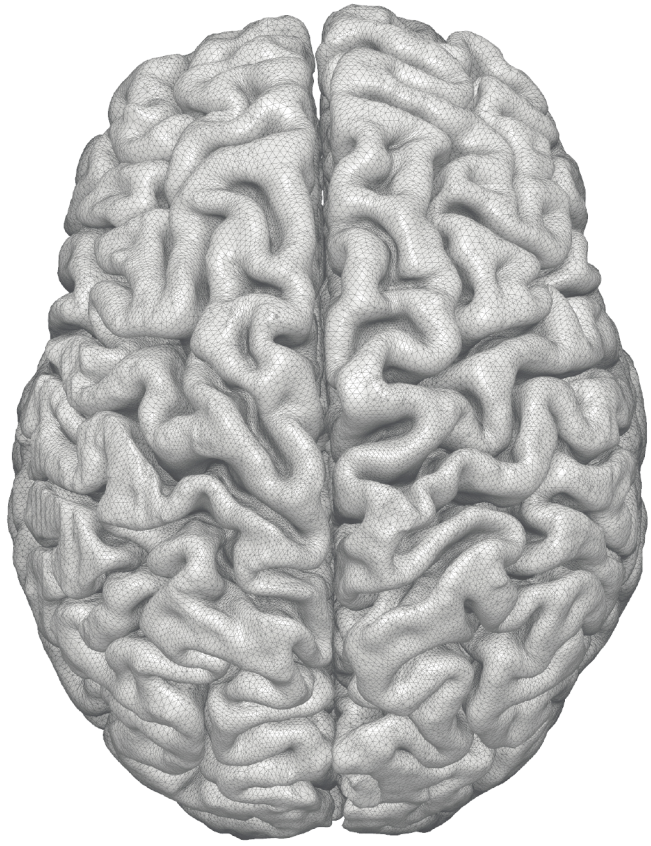

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Dr. MAITE GAROLERA

CLINICAL AND HEALTH PSYCHOLOGY DOCTORAL PROGRAM
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OVERWEIGHT, ALLOSTATIC LOAD AND NEUROIMAGING

Thesis presented by

JONATAN OTTINO GONZÁLEZ

to obtain the degree of doctor from the University of Barcelona with the requirements of the international PhD diploma

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A mi madre, Mónica
Y a mis abuelos, Rosa y Agustín

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Barcelona, February 28th 2019

Dr. María Ángeles Jurado – University of Barcelona

Dr. Maite Garolera – Consorci Sanitari de Terrassa

Certify that they have guided and supervised the doctoral thesis entitled *Overweight, Allostatic Load and Neuroimaging* presented by Jonatan Ottino González. They hereby assert this thesis fulfils the requirements to present his defence to be awarded the title of doctor.

Signature,

Dr. María Ángeles Jurado

Dr. Maite Garolera

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CONTENTS

SUMMARY

ABSTRACT

Overweight and stress interact in complex ways. Excess weight promotes chronic low-grade inflammatory states that can mobilise the hypothalamic-pituitary-adrenal (HPA) axis. HPA axis activation resulting from frequent stress situations can modify energy uptake and expenditure. Separately, both conditions have been linked to changes in brain integrity and executive performance. The organism adapts to situations of caloric surplus through boosting immune, neuroendocrine and cardiometabolic systems to restore energy homeostasis. The allostatic load model establishes that the cumulative effects of adapting to challenging scenarios may result in adverse health situations in the future. There is sufficient evidence to consider that a state of overweight is inherently linked to a higher chronic physiological stress, or allostatic load. Our hypothesis was that, independently of the effects of visceral adiposity, the aggregated effects of the biological alterations related to overweight would be enough detrimental to brain structure and executive functioning. Lean-to-obese volunteers aged 21 to 40 years were recruited from primary health care centres belonging to the *Consorci Sanitari de Terrassa*. Subjects underwent a medical and neuropsychological examination, as well as a magnetic resonance imaging acquisition at the *Hospital Clínic de Barcelona*. The allostatic load index consisted of the sum of several biomarkers representing physiological stress. Overweight subjects had a greater allostatic load than healthy weight participants. The allostatic load escalation was negatively correlated with the morphology of cortical areas and tracts known to be ascribed to circuits involved in cognitive control, reward-processing and the integration of visceral-sensory signalling. Finally, the intensification in this index correlated with worse cognitive flexibility.

RESUM

El sobrepès i l'estrès interactuen de formes complexes. L'excés de pes promou estats inflamatoris crònics de baix grau que poden mobilitzar l'eix hipotalàmic-pituitari-adrenal (HPA). L'activació de l'eix HPA resultant de situacions d'estrès freqüents pot modificar la captació i la despesa d'energia. Les dues condicions s'han vinculat per separat a canvis en la integritat cerebral i l'acompliment executiu. L'organisme s'adapta a situacions de superàvit calòric a través de impulsar sistemes immunes, neuroendocrins i cardiometabòlics per restaurar l'homeòstasi energètica. El model de càrrega alostàtica estableix que els efectes acumulatius de l'adaptació a escenaris desafiadors poden resultar en situacions adverses per a la salut en el futur. Hi ha evidència suficient per a considerar que un estat de sobrepès està inherentment vinculat a un major estrès fisiològic crònic, o càrrega alostàtica. La nostra hipòtesi va ser que, independentment dels efectes de l'adiposita visceral, els efectes agregats de les alteracions biològiques relacionades amb l'excés de pes resultarien suficientment perjudicials per a la estructura cerebral i el funcionament executiu. Es van reclutar voluntaris amb normopès i sobrepès amb edats compreses entre els 21 i els 40 anys de centres d'atenció primària de salut pertanyents al *Consorci Sanitari de Terrassa*. Els subjectes es van sotmetre a un examen mèdic i neuropsicològic, així com a l'adquisició d'imatges per ressonància magnètica a *l'Hospital Clínic de Barcelona*. L'índex de càrrega alostàtica va consistir en la suma de diversos biomarcadors representant estrès fisiològic. Els subjectes amb sobrepès van presentar major càrrega alostàtica que els participants de pes saludable. L'escalada de càrrega alostàtica es va correlacionar negativament amb la morfologia d'àrees corticals i tractes coneguts per estar adscrits a circuits implicats en el control cognitiu, el processament de recompenses i la integració de la senyalització visceral-sensorial. Finalment, la intensificació en l'esmentat índex va correlacionar amb una pitjor flexibilitat cognitiva.

RESUMEN

El sobrepeso y el estrés interactúan de formas complejas. El exceso de peso promueve estados inflamatorios crónicos de bajo grado que pueden movilizar el eje hipotalámico-pituitario-adrenal (HPA). La activación del eje HPA resultante de situaciones de estrés frecuentes puede modificar la captación y el gasto de energía. Ambas condiciones se han vinculado por separado a cambios en la integridad cerebral y el desempeño ejecutivo. El organismo se adapta a situaciones de superávit calórico a través de varias modificaciones fisiológicas. Esto incluye impulsar sistemas inmunes, neuroendocrinos y cardiometabólicos para restaurar la homeostasis energética. El modelo de carga alostática establece que los efectos acumulativos de la adaptación a escenarios desafiantes pueden resultar en situaciones adversas para la salud en el futuro. Existe evidencia suficiente para considerar que un estado de sobrepeso está inherentemente vinculado a un mayor estrés fisiológico crónico, o carga alostática. Nuestra hipótesis fue que, independientemente de los efectos de la adiposidad visceral, los efectos agregados de las alteraciones biológicas relacionadas con el sobrepeso resultarían suficientemente perjudiciales para la estructura cerebral y el funcionamiento ejecutivo. Se reclutaron voluntarios con normopeso y sobrepeso con edades comprendidas entre los 21 y los 40 años de centros de atención primaria de salud pertenecientes al *Consorci Sanitari de Terrassa*. Los sujetos se sometieron a un examen médico y neuropsicológico, así como a la adquisición de imágenes por resonancia magnética en el *Hospital Clínic de Barcelona*. El índice de carga alostática consistió en la suma de varios biomarcadores que representan estrés fisiológico. Los sujetos con sobrepeso presentaron mayor carga alostática que los participantes de peso saludable. La escalada de carga alostática se correlacionó negativamente con la morfología de áreas corticales y tractos conocidos por estar adscritos a circuitos implicados en el control cognitivo, el procesamiento de recompensas y la integración de la señalización visceral-sensorial. Finalmente, la intensificación en dicho índice correlacionó con una peor flexibilidad cognitiva.

GLOSSARY OF ABBREVIATIONS

BBB	Blood-brain barrier
BMI	Body Mass Index
CSF	Cerebrospinal fluid
CNS	Central nervous system
DTI	Diffusion tensor imaging
DWI	Diffusion weighted imaging
EPI	Echo-planar imaging
FA	Fractional anisotropy
GM	Grey matter
HPA	Hypothalamic-Pituitary-Adrenal
MRI	Magnetic Resonance Imaging
PFC	Prefrontal cortex
SBM	Surface-based morphometry
TBSS	Tract-based spatial statistics
VBM	Voxel-based morphometry
WC	Waist-circumference
WHR	Waist-to-hip ratio
WM	White matter
WTHR	Waist-to-height ratio

LIST OF FIGURES

FOREWORD

This thesis is presented to obtain the degree of International Doctor by the University of Barcelona and is the result of the research carried out at the Department of Clinical Psychology and Psychobiology (University of Barcelona, Spain) and the collaboration with the Montreal Neurological Institute (McGill University, Canada). This work consists of three studies published in international journals with a global impact factor (IF) of 11.724 (ISI Web of Knowledge, Journal Citation Reports). All figures and tables throughout this thesis were originally made by the author.

Study 1:

Ottino-González, J., Jurado, M. A., García-García, I., Segura, B., Marqués-Iturria, I., Sender-Palacios, M. J., … Garolera, M. (2017). Allostatic Load Is Linked to Cortical Thickness Changes Depending on Body-Weight Status. *Frontiers in Human Neuroscience*, *11*. DOI: 10.3389/fnhum.2017.00639. IF: 2.871, Q2 in Psychology.

Study 2:

Ottino-González, J., Jurado, M. A., García-García, I., Segura, B., Marqués-Iturria, I., Sender-Palacios, M. J., … Garolera, M. (2018). Allostatic load and disordered white matter microstructure in overweight adults. *Scientific Reports*, *8*(1). DOI: 10.1038/s41598-018-34219-8. IF: 4.122, Q1 in Multidisciplinary Sciences.

Study 3:

Ottino-González, J., Jurado, M. A., García-García, I., Sender-Palacios, M., Tor, E., Prats-Soteras, X., … Garolera, M. (in press). Allostatic load and executive functions in overweight adults. *Psychoneuroendocrinology*. DOI: 10.1016/j.psyneuen.2019.04.009 IF: 4.731, Q1 in Neurosciences.

CHAPTER 1 – INTRODUCTION

1.1. Overweight and obesity

Overweight is defined as the excessive accumulation of fat tissue resulting from the imbalance between consumed and expended calories (Berthoud & Morrison, 2008). In accordance with the World Health Organization (WHO), a body mass index (BMI) equal to or greater than 25 kg/m^2 defines an overweight status, while a BMI greater than 30 kg/m^2 describes obesity instead (World Health Organization, 2016). The BMI results from dividing the weight in kilograms by the square of the height in meters (kg/m^2). Overweight and obesity cases have three folded in the last thirty years becoming a major worldwide health problem. In 2016, more than 1.9 billion adults were overweight, and 650 million were obese. Despite obesity originally affected developed regions, nowadays it touches both low and high-income countries indistinctly. In Spain, it is estimated that more than 60% of the adult population suffer either from overweight (39.3%) or obesity (21.6%) (Aranceta-Bartrina, Pérez-Rodrigo, Alberdi-Aresti, Ramos-Carrera, & Lázaro-Masedo, 2016). Moreover, childhood obesity has increased ten times its prevalence in the last four decades (Tardón, 2017).

Larger meal portions and the rapid rise of energy-dense foods, as well as physical inactivity, have mutually helped in the development of the so-called obesogenic environment. Since the mid-1940s, food went from being scarce to widely available because of transportation improvements and chemical preservatives usage. Besides, the use of flavour enhancers and the increasing of sugar and salt content made processed foods more palatable to the public. This, irremediably, led to an increase in the caloric content on daily meals. On the other hand, work automation substantially reduced the level of everyday physical activity. Altogether, both situations facilitated the settlement of the current epidemic. For this reason, weight-loss has become a long-sought priority in modern civilisation. Governments have

dedicated near two-billion dollars, or 2.8% of the worldwide gross domestic product, in tackling this issue (Tremmel, Gerdtham, Nilsson, & Saha, 2017). In Spain, 7% of the annual health budget of 2016 was destined to overcome this problematic. In that very same year, overweight and obesity generated greater sanitary costs than those caused by smoking (Redacción, 2018). Because of its pandemic proportions, the WHO formulated a global strategy called DPAS (Diet, Physical Activity, and Health) to minimise the incidence of the condition by the year 2030 (World Health Organization, 2018). To do so, promoting physical activity, making healthy food choices more accessible to the general population, and increasing unhealthy food taxes are among the strategies to follow.

The excess weight is a preventable risk factor for cardiovascular diseases (Van Gaal, Mertens, & De Block, 2006), type II diabetes (Browning, Hsieh, & Ashwell, 2010), and some types of cancer (i.e., endometrial, breast, and colon) (Renehan, Tyson, Egger, Heller, & Zwahlen, 2008). The far-reaching consequences of being overweight reduce both life quality and expectancy (Ogden, Yanovski, Carroll, & Flegal, 2007). Moreover, this condition has been linked to cognitive decline (Bischof & Park, 2015; Dahl et al., 2010; Elias, Goodell, & Waldstein, 2012) and pathological ageing (Driscoll et al., 2012; Ronan et al., 2016; Whitmer et al., 2008). All things considered, being overweight is the result of the combination of several factors. In the last years, this condition has benefited from the different disciplines altogether co-existing under the neuroscience umbrella. Neuroscience has emerged as a promising field in the research of the cognitive and neural basis of normal and abnormal feeding behaviour. During the last decade, a good deal of studies have shed some light concerning this topic. Even though significant progress has been made, some unknowns persist. For instance, it is still not clear why the human body is unable to readjust to positive-energy balance situations. Besides, the contribution of the biological deregulations over the neuroanatomical changes observed in overweight subjects are still overlooked to date.

1.2. Neural basis of eating behaviour and body-weight control

Eating behaviour and body-weight control depend on complex meal-to-meal interactions between homeostatic and hedonic systems. Specific groups of neurons in the hypothalamus and brainstem areas are involved in regulating hunger-satiety cycles and monitoring energy storage and expenditure. The arcuate hypothalamic nucleus senses both central and peripheral signals to keep optimal energy homeostasis. This nucleus innerves other regions such as the dorsomedial, ventromedial, paraventricular, and lateral hypothalamus, each one of them ascribed to particular aspects of feeding and body-weight regulation (Berthoud, 2004; Morton, Meek, & Schwartz, 2014).

Orexigenic neurons are brain cells subpopulations located in the dorsomedial and lateral hypothalamus co-expressing neuropeptide Y, agouti-related protein, and GABA neurotransmitter. During fasting or negative energy balance, a decrease in insulin and leptin levels prompts ghrelin release, a hunger-inducing gut-hormone. This hormone stimulates the lateral hypothalamus lastly engaging the ventral tegmental area (VTA) and the striatum. These reward-related mesolimbic nuclei enhance motivation towards food consumption. Conversely, when roused, anorexigenic neurons in the ventromedial and paraventricular nucleus discontinue feeding. Withdrawal of hunger sensations occur in two stages after consumption. First, abdominal distention stimulates gastric mechanoreceptors rapidly signalling satiation via nervus vagus. Second, the increase in the circulating levels of glucose and free fatty acids indicates satiety, which occurs when nutritional requirements are met. This sensation takes longer to be perceived as emerges from the firing of neurons located in the arcuate nucleus as a result of exposing the gastrointestinal tract to food-derived nutrients (i.e., cholecystokinin, glucagon-like peptide 1, peptide YY, 5-HT) (Janssen et al., 2011).

Eating behaviour is also highly susceptible to the reinforcing value of food, especially those with highly palatable properties. Naturally, the taste for energy-dense meals has been fostered ontogenetically throughout evolution to ensure survival. High-calorie meals can hijack mesolimbic structures and precipitate pleasure-based feeding without a real need (Dagher, 2009). Both homeostatic and hedonic feeding comportments are also known as "reflexive eating" (Alonso-Alonso & Pascual-Leone, 2007). Reflexive eating mirrors the idea that unmotivated feeding can occur as a way to forestall a possible lack of food in the future. Oppositely, "reflective eating" integrates high-order cognitive activity, such as long-term health goals and social-related body image expectations. This type of ingestion ponders the further consequences of engaging in bad dietary choices and may assist in blocking hedonic-based ingestion. While the former is dependent on reward-processing and homeostatic-controlling structures, the latter mainly relies upon superior cortical areas such as the prefrontal cortex (PFC). The PFC is the most evolved brain structure in humans, integrating information from other superior regions mediating in self-recognition and socially acceptable responses. Specifically, the dorsolateral portion of the PFC is critical in exercising control over automatic responses (Gluck, Viswanath, & Stinson, 2017). Neurological evidence revealed the importance of this region in feeding conduct. Damage, atrophy or hypoperfusion within this area correlates positively with compulsive eating (Le et al., 2006; Volkow et al., 2010). Hence, an imbalance between reflexive and reflective systems could explain the unnecessary feeding occurring within overweight subjects. Figure 1 sums the interaction between systems.

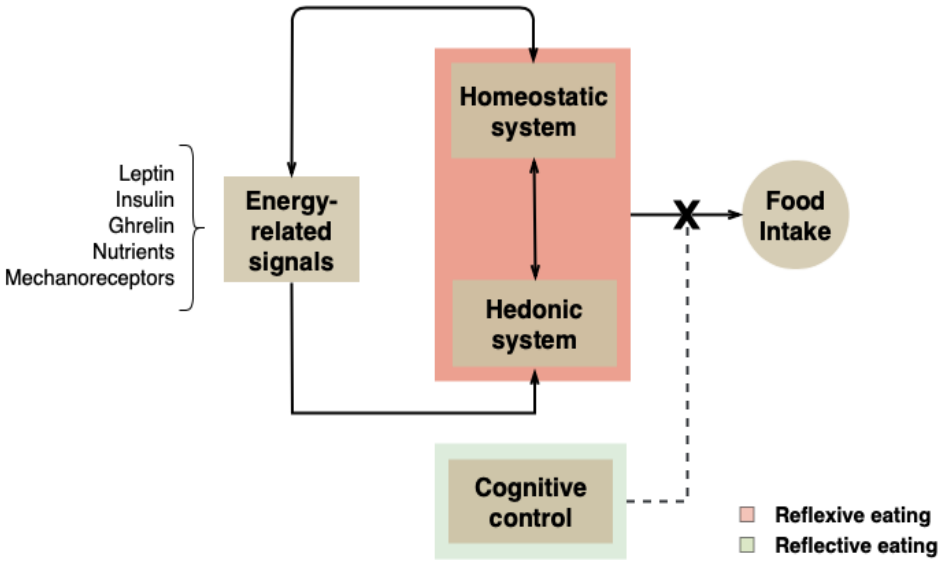

FIGURE 1 | Hunger and satiety responses depend on the correct communication between homeostatic and hedonic systems. Ultimately, cognitive control may obstruct feeding if considered unnecessary.

Regarding body-weight control, insulin and leptin circulate proportionally to body fat stores returning an approximate measure of energy reserve status. Consequently, both regulate changes in energy expenditure in the long-term (Morton et al., 2014). Altogether, when present, these metabolic-related signals block appetite and reduce energy expenditure. Noticeably, this proofs that the homeostatic system is intrinsically wired to be more sensitive to under rather than overnutrition. In the same way that insulin-resistance is considered as a logical consequence of energy-dense diets, some authors argue that adiposity and bad dietary habits can also promote leptin-resistance. In this vein, peripheral resistance could take place when leptin transportation across the blood-brain barrier (BBB) is disrupted due to an increase in circulating free fatty acids (Banks, 2012). Conversely, increased leptin levels could naturally downregulate hypothalamic receptors, therefore evoking central resistance (de Git & Adan, 2015; Dorfman & Thaler, 2015). Apart from this, mesolimbic regions are overly boosted when leptin fails to bind to its receptors in the hypothalamus, stirring unnecessary feeding in the end (Hommel et al., 2006). Humans with congenital leptin deficiency proved

hyperactivation of the striatum when visually exposed to food (Farooqi et al., 2007). Differences aside, leptin-signalling is noticeably affected in overweight as well. Leptin resistance in subjects with excess of weight could wrongly point to a negative-energy balance, induce gratuitous hunger responses, or trigger motivation for food consumption.

1.3. Physiological adaptations to weight-gain

Inflammatory and neuroendocrine responses have been proposed as underlying mechanisms to explain how inefficient weight management occurs in subjects who eat beyond their caloric needs on a daily basis. Accordingly, when favourable energy balance situations occur, the organism initiates intense responses to return to its former state while storing energy surplus. As aforesaid, we are naturally wired to prioritise energy storage for survival purposes. While expanding, fat cells, or adipocytes, start inflammatory responses to both accommodate energy excess and prevent growing fat-tissue hypoxia. Likewise, anabolic (i.e., insulin) and catabolic (i.e., leptin, catecholamines) responses are engaged to co-ordinately build or break molecules to host (i.e., lipogenesis) or make energy available (i.e., lipolysis) if needed. Despite initially adaptive, these reactions hinder weight control when prolonged over time. As previously pointed out, when energy-balance is regularly positive the organism is likely to desensitise to metabolic-related signals (Banks, 2012; de Git & Adan, 2015; Pan et al., 2014). Lastly, tailoring a new homeostatic set point turns the organism inefficient for accurately regulate body-weight. Besides, situations of caloric shortage likely resulting in weight-loss can cause a slowdown of basal metabolism as a way to prevent energy waste. As said before, the homeostatic system is prone to favour weight-gain rather than weight loss. Unsurprisingly, this situation of metabolic inflexibility facilitates weight re-gain if energy reserves decrease as in successfully dieting. In consequence, metabolic inflexibility is linked to the famous "yo-yo-dieting" effect, which is widely described in the literature (Fothergill et al., 2017; Müller & Bosy-Westphal, 2013). A graphical representation of short and long-term adipocyte-induced physiological adaptations to energy surplus are depicted in Figure 2.

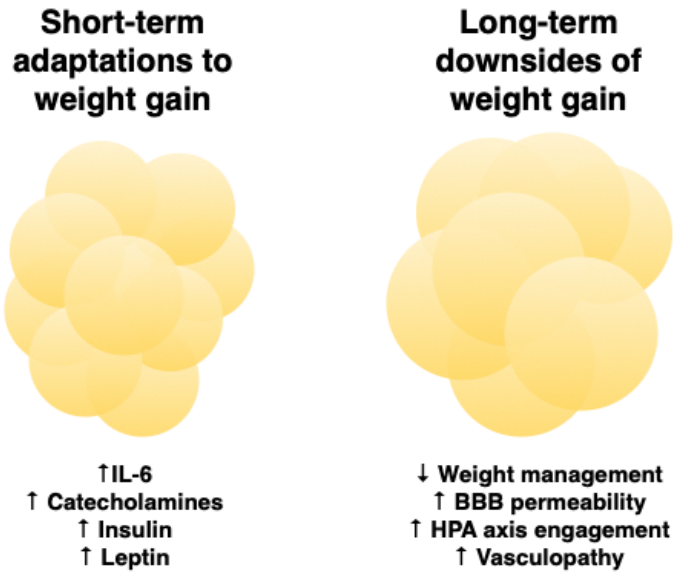

FIGURE 2 | Outcomes from short and long-term adaptations to weight-gain.

Apart from immune and neuroendocrine deregulations, an overweight status generates cascades of supplemental biological reactions that may harm the brain. The adipose-induced inflammation precedes the increase on the permeability of the BBB, exposing brain parenchyma to harmful by-products that could potentially initiate a second-wave of inflammatory replies (Hsuchou, Kastin, Mishra, & Pan, 2012; Ryu & McLarnon, 2009). Furthermore, excess weight and poor dietary choices are associated to higher levels of nitric oxide, oxidative stress, and neural death (Gzielo, Kielbinski, Ploszaj, Janeczko, Gazdzinski & Setwociz, 2017). Furthermore, the typical western-like diet rich in fats and sugars is linked to gut-bacteria disproportion, as well as the presence of strains likely to prompt thinning and leaking of the epithelium, endotoxinemia and inflammation (Agustí et al., 2018; Beaumont et al., 2016; Conterno, Fava, Viola, & Tuohy, 2011). Immune responses instinctively recruit the hypothalamic-pituitary-adrenal (HPA) axis to promote cortisol release due to its anti-inflammatory properties. However, unrelenting cortisol discharges decrease neurogenesis, tempt dendritic retraction, and shape brain immune responses useless (Arnsten, 2009), especially among PFC and limbic regions. Paradoxically, these areas play a major role in

cortisol regulation (McEwen, Nasca, & Gray, 2016). Moreover, other well-known downsides of cortisol secretion are overeating and weight-gain (Jackson, Kirschbaum, & Steptoe, 2017), as fight-or-flight responses are highly energy-consuming. In the same form, sympathetic activation and disruption of metabolism can augment blood pressure and atheromatous plaques presence, weakening vascular integrity, and provoking adverse cardiovascular outcomes occurrence. Vascular alterations can disturb correct brain oxygenation, precipitate small vessel disease, or even prompt severe neurovascular diseases (Kivipelto et al., 2005; Winter et al., 2008; Yamashiro et al., 2014).

In sum, a favourable balance in energy reserves initially yields adaptive neuroendocrine and inflammatory responses that, if regularly required, may obstruct weight-control and foster overeating. Moreover, these mechanisms are potentially injurious to the brain when frequently evoked. Consequently, energy-surplus and excess of weight would likely precipitate a significant number of damaging scenarios to the brain structure.

1.4. Overweight and brain morphology changes

A great number of studies in adults have found a relationship between body-weight and changes in the morphology and composition of both grey (GM) and white matter (WM). The nature of this link is typically negative, meaning by this that there is a decrease in the integrity of such tissues in relation to overweight or adiposity increases.

GM structure can be investigated with voxel or surface-based approaches. Voxel-based morphometry (VBM) is the most widely used technique to assess GM structure nowadays. VBM uses a probabilistic tissue segmentation approach, classifying each voxel of the brain correspondingly to the proportion of the contained tissue (i.e., GM, WM, and cerebrospinal fluid, or CSF). VBM, therefore, returns an indirect measure of tissue volume or density. In contrast, surface-based morphometry (SBM) reconstructs the cortical surface using the boundaries of GM and WM layers in a convoluted triangulated mesh. SBM principally informs about the thickness of the cortical

mantle in terms of millimetres between GM and WM limits. Generally, SBM is considered more accurate for assessing the cortical integrity as it better reflects the complex topography of the cortex, which is notoriously folded in humans. For this reason, SBM is progressively displacing the use of VBM in the analysis of GM integrity.

On the other hand, diffusion tensor imaging (DTI) is a non-invasive neuroimaging technique that traces *in vivo* the movement of water molecules in WM territory (Basser, Mattiello, & Lebihan, 1994). The diffusion of water indirectly echoes tract integrity. Tract-based spatial statistics (TBSS) is the method of choice for assessing WM composition, and fractional anisotropy (FA) is the most reported DTI metric (Bach et al., 2014). FA indicates how parallel and fast the movement of the water is along the fibre. Hence, high FA values are typical of well-myelinated undamaged tracts. Parallel diffusion, however, could decrease because of non-pathological reasons as with axonal pruning or particular traits in WM morphology (Bach et al., 2014; Jones, Knösche, & Turner, 2013). Even if pathological, a decrease in FA is still unspecific to the underlying source. In this vein, the mean, axial or radial diffusivities (MD, AD, and RD) aim FA interpretation. The MD is the average of all eigenvalues with higher values meaning exacerbated cell permeability due to oedema or necrosis. The AD and RD reflect parallel and perpendicular diffusion, proxies of axonal damage or poor myelination respectively. In recent years, it has been argued that the effect of interstitial water content might lead to underestimate DTI metrics. Inflammatory responses are likely to favour osmosis-inducing chemicals presence. The increase of extracellular water subsequently affects water movement in adjacent functional tissue, which could erroneously reveal lower FA values. What is more, adjusting for extracellular water content may also help in discriminating inflammatory from non-inflammatory processes underlying FA decreases.

VBM and cortical thickness studies have principally reported GM decreases in areas archetypally ascribed to the so-called cognitive-control network (García-García et al., 2018; Janowitz et al., 2015; Karlsson et al., 2013; Kharabian Masouleh et al., 2016; Kurth et al., 2012; Marqués-Iturria et al., 2013; Mathar, Horstmann, Pleger, Villringer, & Neumann, 2015; Opel et

al., 2017; Pannacciulli et al., 2006; Shott et al., 2015; Taki et al., 2008; Tuulari et al., 2015; Veit et al., 2014; Walther, Birdsill, Glisky, & Ryan, 2010; Weise et al., 2017; Weise, Thiyyagura, Reiman, Chen, & Krakoff, 2013; Yao, Li, Dai, & Dong, 2016; Zhang et al., 2017). This circuit principally harbours frontal and parietal regions involved in top-down regulation and executive functions, such as the dorsolateral PFC or the inferior and superior parietal cortex. Equally, changes in the FA of WM tracts structurally linking these cortical regions were reported in the literature (He et al., 2013; Karlsson et al., 2013; Papageorgiou et al., 2017; Shott et al., 2015; Verstynen et al., 2012). Both superior and inferior longitudinal fasciculi ipsilaterally link together posterior and anterior executive-related cortical areas (Kamali, Flanders, Brody, Hunter, & Hasan, 2014).

An excess of weight has also been linked to GM changes within reward-related regions such as the medial prefrontal, anterior cingulate, and the orbitofrontal cortex, as well as diverse subcortical nuclei (i.e., striatum) (Figley, Asem, Levenbaum, & Courtney, 2016; Horstmann et al., 2011; Janowitz et al., 2015; Karlsson et al., 2013; Kharabian Masouleh et al., 2016; Kim et al., 2015; Kurth et al., 2012; Marqués-Iturria et al., 2013; Mathar, Horstmann, Pleger, Villringer, & Neumann, 2015; Medic et al., 2016; Opel et al., 2017; Pannacciulli et al., 2006; Shott et al., 2015; Tuulari et al., 2015; Veit et al., 2014; Walther, Birdsill, Glisky, & Ryan, 2010; Weise, Thiyyagura, Reiman, Chen, & Krakoff, 2013; Yao, Li, Dai, & Dong, 2016). Moreover, an excessive body-weight has been related to decreases in the WM composition of fibres interconnecting these regions, such as the cingulum bundle, the fornix, and the inferior fronto-occipital fasciculi (Karlsson et al., 2013; Papageorgiou et al., 2017; Repple et al., 2018; Shott et al., 2015; Stanek et al., 2011; Verstynen et al., 2012). Surprisingly, there are works that have found greater GM density and increased FA in similar regions in obesity as well (Horstmann et al., 2011; Kaur et al., 2015; Kim et al., 2015; Pannacciulli et al., 2006; Weise et al., 2013; Widya et al., 2011; Yao et al., 2016; Zhang et al., 2017).

Although limited, neuroanatomical variations in areas involved in homeostatic regulation have also been reported. Marqués-Iturria et

al. (2013) described GM reductions in the ventral diencephalon (i.e., hypothalamus) and the brainstem in obese adults. Traditionally, the study of the hypothalamus has been challenging due to its reduced size and structural complexity. Moreover, studies have also found alterations in other visceral and self-referential processing areas such as the postcentral gyri, the insula, and the superior temporal lobe (Kharabian Masouleh et al., 2016; Kurth et al., 2012; Veit et al., 2014). Likewise, studies in TBSS have generally portrayed inverse associations between FA and adiposity in projecting tracts tying together the aforesaid areas, such as the corticospinal tract or the corona radiata (Karlsson et al., 2013; Papageorgiou et al., 2017; Repple et al., 2018; Ryan & Walther, 2014; Shott et al., 2015; Verstynen et al., 2012; Verstynen et al., 2013).

Hence, an increase in body-weight is negatively correlated to the GM and WM integrity of cognitive-control regions critical in assisting executive functions. These cognitive abilities are crucial for suppressing urgent drives and keeping health goals up-to-date. Optimal performance of these capacities can obstruct pleasure-based feeding, which is a central feature of the so-called reflective eating style. There is a plethora of works describing alterations of executive functions in overweight and obese subjects relative to healthy weight controls (Ariza et al., 2012; Bauer et al., 2015; Calvo, Galioto, Gunstad, & Spitznagel, 2014; Cserjesi, Luminet, Poncelet, & Lenard, 2009; Fagundo et al., 2012; Graham, Gluck, Votruba, Krakoff, & Thearle, 2014; Lokken, Boeka, Austin, Gunstad, & Harmon, 2009; Marqués-Iturria et al., 2014; Miller, Lee, & Lumeng, 2015; Monica et al., 2010; Navas et al., 2016; Reinert, Po'e, & Barkin, 2013; Wyckoff, Evans, Manasse, Butryn, & Forman, 2017; Xu et al., 2017).

Similarly, GM and WM alterations in reward-processing areas have also been described in prior works. Changes in these regions may relate to an extreme motivation towards food consumption, this pattern was earlier defined as reflexive eating. Analogous to executive dysfunctions, reward sensitivity in overweight and obese subjects has been extensively addressed (Davis & Fox, 2008; Dietrich, Hollmann, Mathar, Villringer, & Horstmann, 2016; Dietrich, Federbusch, Grellmann, Villringer, & Horstmann, 2014;

García-García et al., 2014; Horstmann et al., 2015; Scharmuller, Ubel, Ebner, & Schienle, 2012).

Lastly, and to a lesser extent, an excessive weight is related to changes in regions and tracts of circuits monitoring energy homeostasis. This can lead to a poor estimation of energy reserves, which would likely lead to engage in unnecessary food ingestion and wrongly reduce energy expenditure. Disruptions in energy-related signalling have been targeted in obesity studies as well (Morrison, 2009; Pan & Myers, 2018; Rosenbaum & Leibel, 2014; Warren, Hynan, & Weiner, 2012).

In sum, the excess of weight is associated to changes in brain regions and tracts important for regulating behaviour, seeking and processing reward stimuli, and managing visceral and self-referential information.

1.5. Overweight and executive functions

Along with the previously mentioned neuronal correlates of eating behaviour and energy homeostasis, cognitive activity plays a key role in translating brain activity into observable features. Eating behaviour is complex and relays in the rapid combination of essential and superior cognitive functions to initiate, supervise, and finish food consumption (Dohle, Diel, & Hofmann, 2018). Moreover, cognition is also behind food choices, for which it is necessary to conjugate information about past caloric ingestion and knowledge of food nutritional properties, as well as attitudes towards health-related behaviours and body-image expectations (Higgs, 2015).

The ability to incorporate different cognitive features to achieve an objective is known as executive functions (Diamond, 2014). Typically, this high-order cognitive activity could be broken down into core and superior executive domains. In this vein, while inhibitory control, flexibility, and working memory are classified as core executive functions, others like decision-making, planning, and problem-solving are considered on a higher scale. Inhibitory control is usually defined as the ability to override automatic

responses and control interference. Inhibitory control requires resisting oneself urges and avoid acting impulsively by exerting control over cognitive and motor responses. On the other hand, cognitive flexibility involves the ability to think out of the box and to alternate between responses whenever necessary. Indirectly, set shifting is influenced by self-monitoring and the capacity of learning from negative feedback. Finally, working memory refers to the ability to maintain available information when no longer perceptible and perform mental operations on it.

Core executive functions profoundly influence eating behaviour (Dohle et al., 2018). For instance, unnecessary feeding could be linked to the inability to suppress or not thinking about eating when confronted with food (i.e., inhibitory control). Hedonic feeding could also be prompted by the incapacity of considering the healthier-fare meal (i.e., cognitive flexibility). Finally, being incapable of maintaining health goals available when necessary could influence food choices. (i.e., working memory) Consequently, several studies have assessed these transversal executive domains in overweight and obesity (Dohle et al., 2018; Fitzpatrick, Gilbert, & Serpell, 2013; Smith, Hay, Campbell, & Trollor, 2011; Yang, Shields, Guo, & Liu, 2018). Recent works have demonstrated that, in general, overweight subjects tend to perform worse than normal-weight participants in tasks measuring inhibitory control (Chamberlain, Derbyshire, Leppink, & Grant, 2015; Lavagnino, Arnone, Cao, Soares, & Selvaraj, 2016; Spitoni et al., 2017), cognitive flexibility (Fagundo et al., 2012; Perpiñá, Segura, & Sánchez-Reales, 2017; Restivo et al., 2017), and working memory (Calvo et al., 2014; Coppin, Nolan-Poupart, Jones-Gotman, & Small, 2014; Gunstad et al., 2007). Altogether, executive impairments are broadly pointed to as potential mechanisms underlying lousy food choices and overeating.

1.6. Allostatic load model

McEwen and Stellar (1993) stressed in their model that the cumulative effects of chronic stress, or allostatic load (AL), lead to medical and psychological disorders in the end. The AL has been related to lower

quality of life, cardiovascular diseases (e.g., type II diabetes, dyslipidaemia, hypertension) and all-cause mortality, dementia and cognitive decline, and psychosomatic symptoms (Juster, McEwen, & Lupien, 2010). Non-pathological stress responses are likely to consume psychological and physiological resources to anticipate and overcome threatening situations (Kemeny, 2003). This preparation, known as allostasis, requires a good deal of energy to push biological systems to their maximum capacity allowing the energy boost needed when challenged. However, when flight-or-fight responses are regularly required, balancing and keeping biological systems working at their highest would eventually precipitate adverse outcomes. The AL can lead to mitochondrial dysfunction and telomere shortening, both related to oxidative stress and accelerated ageing (Epel, 2009; McEwen & Gianaros, 2011). On the other hand, cortisol has proved to be detrimental to the brain as disrupts neurogenesis and yields to neuronal loss (Arnsten, 2009; McEwen et al., 2016). Moreover, central pro-inflammatory cytokines recruit microglia to remove waste and aim in neuronal repair which may actually turn against healthy cells if prolonged enough (Porter, Leckie & Verstynen, 2018; Allan & Rothwell, 2003; Calcia et al., 2016; Haroon, Miller, & Sanacora, 2016). Moreover, misbalance within cardiovascular and metabolic systems may also play a key role in injuring the brain through vasculopathy (Kwon et al., 2006). In this model, once a challenge is perceived, primary outcomes occur in the form of neuroendocrine and short-term immune adaptations to support the organism in its first attempt to overcome the issue. However, if the situation escalates, metabolic, cardiovascular, and immunological adaptations are mobilised. This "domino effect" would finally evoke tertiary outcomes, or diseases, to appear in the future.

In line with the abovementioned, the weight-gain itself may represent a difficult position to the organism as well. Primary outcomes of this model involve neuroendocrine (i.e. anabolic and catabolic signals) and immune adaptations (i.e., inflammatory responses) to handle energy surplus and restore homeostasis. Secondary metabolic (i.e., glucose and lipid dysregulation), neuroendocrine (i.e., augment of blood pressure, catecholamine release), and inflammatory responses (i.e., increase in fibrinogen, C-reactive protein, or IL-6 concentrations) would take place if caloric consumption exceed

expenditure on a regular basis. Eventually, as body-weight regulation is hampered, tertiary outcomes will appear in the shape of diseases (e.g., type II diabetes, hypertension, pathological ageing, and so on). This model is summarised below in Figure 3.

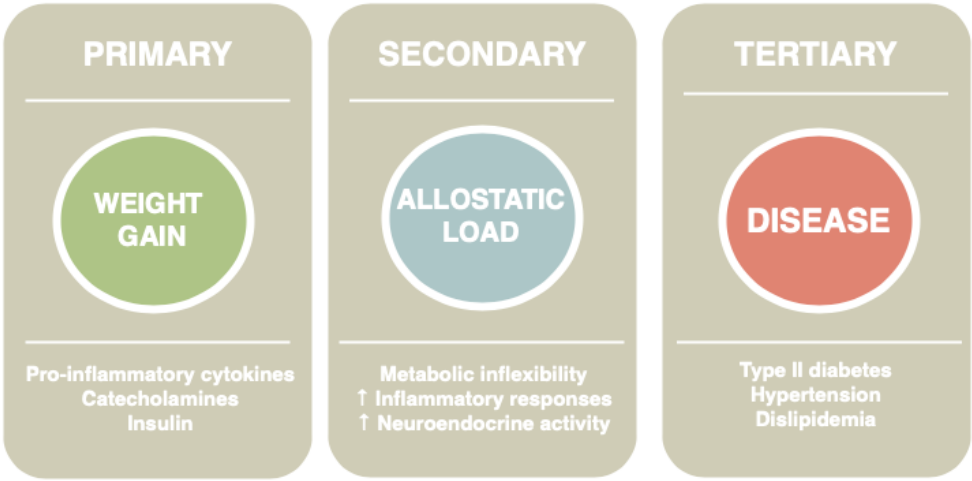

FIGURE 3 | Allostatic Load model in weight-gain scenarios. First, immune and neuroendocrine responses are triggered to adapt to energy surplus. Later, a new homeostatic set-point is achieved, and the organism prompts supplemental responses leading to a status of allostatic overload. Third, if not reverted, the situation would gradually escalate until the occurrence of several diseases.

1.7. Allostatic load and brain morphology changes

To date, the relationship between AL and neuroanatomical structure remains, at the very least, elusive. The closest approach to this topic has been done through the study of the impact of chronic stress, and specifically, those precipitated by the sustained cortisol release, which is the most popular surrogate of an overactive HPA axis. A recent work has summarised the harmful outcomes of cortisol on the brain (Lupien, Juster, Raymond, & Marin, 2018). The AL has been inversely associated in older adults with whole-brain and WM volume (Booth et al., 2015). The increase of AL in another sample of elderly participants was linked to GM volume reductions in the right insula, the right precentral gyrus, the left and right postcentral gyri, the right supramarginal gyrus, the left central operculum,

and the left frontal operculum (Zsoldos et al., 2018). Moreover, an increase in AL in patients with schizophrenia and healthy controls was related to whole-brain cortical thinning indistinctly (Chiappelli et al., 2017). Post-hoc analysis revealed that an increase in C-reactive protein (CRP) concentrations, a peripheral inflammatory biomarker, partially drove such alterations. In another work, these authors also proved that an escalation in AL was associated with lower FA in the fornix exclusively in the patient's group (Savransky et al., 2017). Regardless of the gross differences described in the total brain volume relative to the AL increase, regional changes emerging as statistically significant suggest indeed an affectation of structures involved in supervising cognitive performance (i.e., supramarginal gyrus), regulating affective responses (i.e., fornix), and processing self-referential information (i.e., pre and postcentral gyri, insula, and operculum).

1.8. Allostatic load and changes in executive functions

As with brain imaging studies, the relationship between AL and executive functions has not been enough covered to date. Chronic stress studies, which conceptually is the closest term to AL, proved deleteriously impact cognitive flexibility, inhibitory control, and working memory (Ajilchi & Nejati, 2017; Cerqueira, Mailliet, Almeida, Jay, & Sousa, 2007; Mika et al., 2012; Orem, Petrac, & Bedwell, 2008). In Booth et al. (2015) the escalation in AL in elders was inversely related to general cognitive function, processing speed, and knowledge. This measure of global cognitive function included tests quantifying speed processing and attention, verbal memory, verbal fluency, visual and spatial functions, and executive functions. However, when addressed separately, executive functions did not surface as statistically meaningful. In this study, executive functioning was accounted by means of non-verbal reasoning tasks, leaving other core executive functions unexplored. In other work conducted by Karlamangla and cols. (2014), an increase in AL inversely related to worsening in executive performance and episodic memory in senior citizens. What it is more, when addressing

different biological systems comprising the AL index, cardiovascular and glucose metabolism appeared to independently maintain a link with executive dysfunction (Karlamangla, Miller-Martínez, Lachman, Tun, Koretz, & Seeman, 2014). In short, an increase in either AL, chronic stress or stress-related variables did relate to worse performance in core executive domains.

CHAPTER 2 – OBJECTIVES AND HYPOTHESES

As discussed earlier, an overweight status may entail a challenging scenario to the organism. Evidence of strong immune, neuroendocrine, and cardiometabolic adaptations to weight-gain supports this premise (Guillemot-Legris & Muccioli, 2017; Reilly & Saltiel, 2017; Spyridaki, Avgoustinaki, & Margioris, 2016). Altogether, this cluster of physiological alterations may lead to adverse neurological outcomes such as oxidative stress, dendritic retraction, or vasculopathy (Calcia et al., 2016; Jauregui-Huerta et al., 2010; McEwen et al., 2016). That said, the PFC is particularly vulnerable to such insults, and therefore executive functions may resent. In the light of these events, the objective of this thesis is to address the relationship between long-term physiological stress, neuroanatomical changes and executive performance in otherwise healthy overweight volunteers. We hypothesise that subjects with excessive weight will present higher AL indexes than normal-weight participants. We state that they also will exhibit greater declines in brain integrity and executive functioning relative to such increase, regardless of the effects of adiposity itself. A detailed list of objectives and expected findings is depicted below.

1. Compare AL levels between healthy weight and overweight adults. We expect to find greater AL indexes in overweight adults.

2. Test the relationship between AL and whole-brain cortical thickness. We will find thinning in both groups relative to an AL increase. The overweight sample will show greater GM loss.

3. Study the link among AL and whole-brain FA. We expect lower FA in both groups concerning an AL escalation. The overweight group will exhibit larger FA decreases.

4. Address the association between AL and executive functions. We assume a worse executive performance with greater AL indexes. The overweight group will show greater impairments in such domain.

CHAPTER 3 – METHODS

The current thesis included two studies exploring the morphological brain characteristics in overweight relative to an increase in AL. Neuroimaging techniques and statistical analyses were performed according to the aim of each study. Additionally, a third experiment is presented as a working paper testing for the link between AL and executive performance.

3.1. Participants

All three studies shared a common recruitment process. Volunteers were randomly selected from Primary Health Care Centres belonging to the *Consorci Sanitari de Terrassa* (Terrassa, Spain) during a period comprised between September 2009 and November 2017. The study procedure consisted of three separated appointments. In the first visit, participants gave a blood-sample in fasting-state and passed an exhaustive medical examination. The second appointment comprised an extensive cognitive evaluation performed by an expert neuropsychologist in a 3-hour single session. For the third citation, participants underwent an MRI acquisition at the *Hospital Clinic* de Barcelona.

Inclusion criteria for all three studies entailed having an age between 21 and 40 years old and present a BMI greater than 18.5 kg/m^2. Exclusion criteria ruled out participants with (1) history of any past or present neurological, psychiatric or cardiometabolic comorbidity explored through a clinical interview; (2) suspicion of acute-infection by means of C-reactive protein levels serum concentrations greater than 10 mg/L; (3) an estimated intelligence quotient (IQ) below 85 addressed by the Vocabulary subtest of the Wechsler Adult Intelligence Scale 3rd version (Wechsler, 1999); (4) presence of anxiety and depression acute symptoms explored by the Hospital Anxiety and Depression Scale with a score of 11 as a cut-off point (Herrero et al., 2003; Zigmond & Snaith, 1983); (5) suggestion of binge-eating disorder according to the Bulimia Investigatory Test of Edinburgh cut-off score of 20 (Henderson & Freeman, 1987); and finally (6) a pathological use of drugs assessed by the Structured Clinical Interview for DSM-IV (First, Spitzer, Gibbon, & Williams, 1999).

The studies varied in sample size because of ongoing recruitment process that led to a different number of participants over time as well as for each study-specific requirements. A diagram explaining the participants' flow is depicted in Figure 4 in the next page. The sociodemographic characteristics of the different samples used in the three studies included in this thesis are available in Table 1 below. The institutional ethics committee approved both studies (Comissió de Bioètica de la Universitat de Barcelona; IRB 00003039; FWA00004225), which were performed following the Helsinki Declaration. Each participant signed informed written consent before taking part in the study.

TABLE 1 | Variables of interest

	Normative (N = 43)	OW Study 1 (N = 34)	HW Study 1 (N = 29)	OW Study 2 (N = 31)	HW Study 2 (N = 21)	OW Study 3 (N = 56)	HW Study 3 (N = 47)
Age	30.44 (6.03)	31.79 (6.10)	30.07 (6.21)	31.12 (5.88)	29.95 (6.02)	31.52 (5.99)	30.15 (6.14)
Sex	26 females	21 females	15 females	19 females	11 females	37 females	28 females
Education	14.12 (2.41)	13.76 (2.69)	14.62 (2.21)	13.58 (2.94)	14.48 (2.18)	13.20 (2.60)	14.15 (2.47)
IQ	11.50 (1.95)	12.00 (2.16)	11.93 (1.83)	11.90 (2.21)	12.05 (1.86)	11.86 (1.96)	11.62 (2.00)
Family income in euros per month (frequency, %)							
300 – 899	1 (2.3%)	-	-	-	-	3 (5.36%)	1 (2.13%)
900 – 1499	7 (16.3%)	4 (11.8%)	5 (17.2%)	5 (16.1%)	4 (19%)	11 (19.64%)	7 (14.89%)
1500 – 2099	13 (30.2%)	15 (44.1%)	9 (31.03%)	14 (45.2%)	6 (28.6%)	20 (35.71%)	16 (34.04%)
2100 –2699	7 (16.3%)	8 (23.5%)	4 (13.8%)	6 (19.4%)	3 (14.3%)	12 (21.43%)	8 (17.02%)
> 2700	13 (30.2%)	6 (17.6%)	10 (34.5%)	5 (16.1%)	7 (33.3%)	9 (16.07%)	13 (27.66%)
N.A.	2 (4.7%)	1 (2.9%)	1 (3.5%)	1 (3.2%)	1 (4.8%)	1 (1.78%)	2 (4.26%)
Professional level (frequency, %)							
Non-skilled	4 (9.3%)	3 (8.8%)	1 (3.5%)	4 (12.9%)	1 (4.8%)	10 (17.86%)	6 (12.77%)
Skilled	5 (11.6%)	10 (29.4%)	5 (17.2%)	9 (29%)	4 (19%)	13 (23.21%)	5 (10.64%)
Admin.	8 (18.6%)	8 (23.5%)	5 (17.2%)	6 (19.4%)	5 (23.8%)	14 (25.0 %)	8 (17.02%)
Intermediate	7 (16.3%)	5 (14.7%)	6 (20.7%)	4 (12.9%)	5 (23.8%)	11 (19.64%)	8 (17.02%)
Professional	9 (20.9%)	5 (14.7%)	6 (20.7%)	5 (16.1%)	3 (14.3%)	5 (8.93%)	9 (19.15%)
N.A.	10 (23.3%)	3 (8.8%)	6 (20.7%)	3 (9.7%)	3 (14.3%)	3 (5.36%)	11 (23.40%)

IQ, Intelligence Quotient (WAIS-III vocabulary scalar score), OW, Overweight, HW, Healthy-weight, N.A., t-available

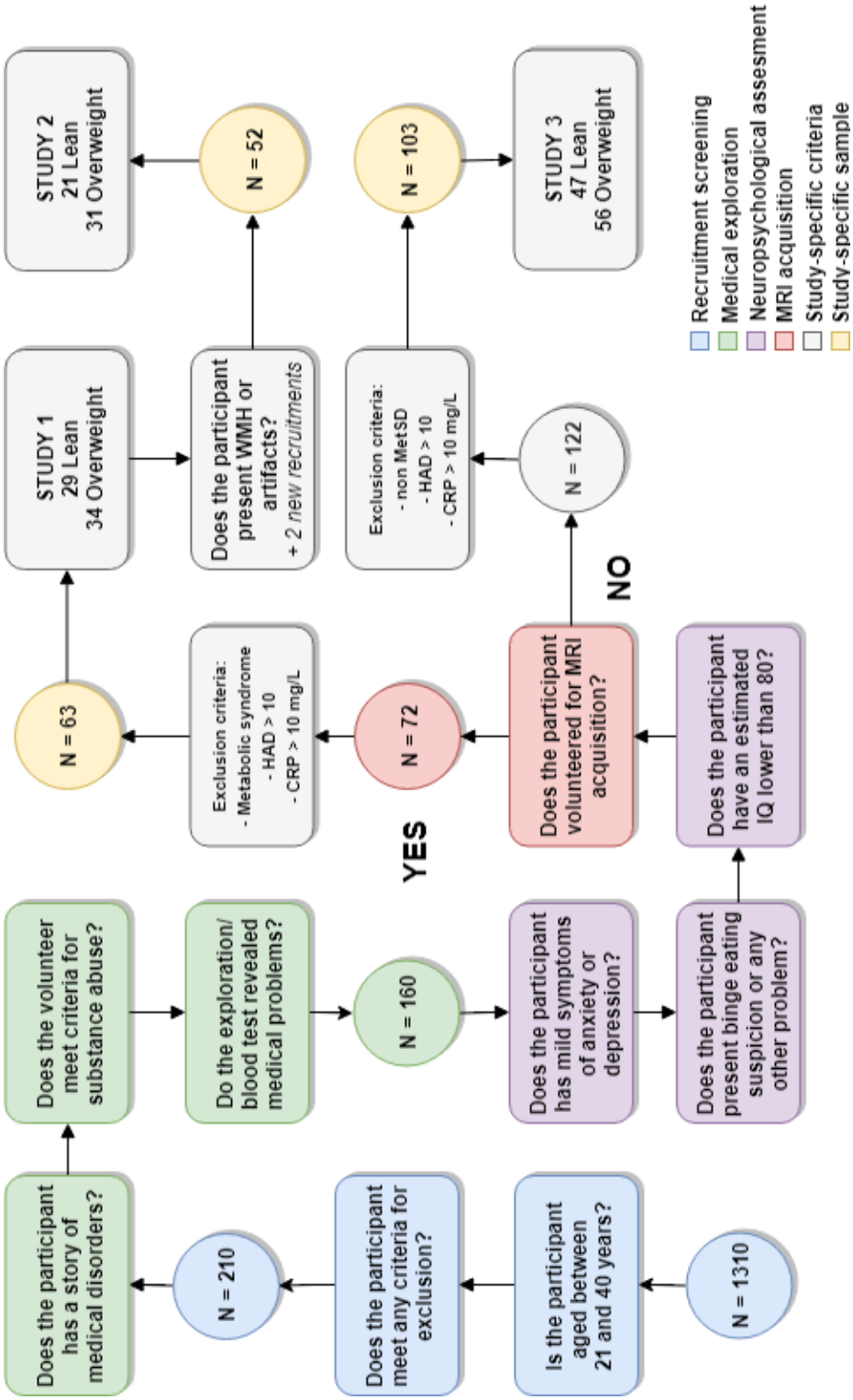

FIGURE 4 | Participant's flow through the different phases of the study.

3.2. Procedure

3.2.1. Allostatic Load Index

Study 1 and 2 served an AL index calculated with the high-risk percentiles of fifteen stress biomarkers, which is a standard procedure described in the literature (Juster, McEwen, & Lupien, 2010). The cut-off scores were based on a larger control group (N = 43), including sex-specific thresholds for those biomarkers presenting differences between males and females. The AL cut-off scores are available in the Method section in Study 1 and 2. Moreover, in Study 3, the AL index was configured by selecting and combining biomarkers into a z-score composite after adjusted for sex.

3.2.2. Neuroimaging

3.2.2.1. MRI acquisition

MRI data was acquired on a 3T MAGNETOM Trio (Siemens, Germany) at the *August Pi I Sunyer Biomedical Research Institute* (IDIBAPS) belonging to the *Hospital Clínic de Barcelona*. A high-resolution T1-weighted 3D scans were obtained for all participants with the following parameters: repetition time 2,300 ms, echo time 2.98 ms, inversion time 900 ms, 240 slices, field of view 256 x 256 mm, 1 mm isotropic voxel, T1w-sequence scan time = 7:48 minutes. The diffusion-weighted images (DWI) were collected with the following parameters: repetition time = 7,700 ms, echo time = 89 ms, acquisition matrix = 122 x 122, 2 mm isotropic voxel, field of view = 244 x 244 mm, diffusion directions = 30, slice thickness = 2 mm, gap distance = 0.6 mm, number of slices = 60, b-values = 0 and 1,000 s/mm^2, IPAT factor = 2, DWI-sequence scan time = 4:23 minutes.

3.2.2.2. Cortical thickness and volume analyses

Cortical thickness and volume analyses were performed in Study 1 and 2 with FreeSurfer software version 5.3 and version 6.0, respectively (FreeSurfer, RRID: nif-0000-00304). This procedure included skull-stripping (Ségonne et

al., 2004), motion correction and T1 averaging (Reuter et al., 2010), bias-field correction (Sled et al., 1998), and tessellation of GM and WM tissue. Representations of cortical thickness have been calculated as the closest distance from the grey to the white tissue boundary, and to the grey tissue to the CSF boundary at each vertex on the surface (Fischl and Dale, 2000). The surface was smoothed using a circularly symmetric Gaussian kernel with a full-width at half maximum of 15 mm. The post-processing outputs for each subject were visually checked and edited when required.

3.2.2.3. Tract-based spatial statistics analyses

Tract-based spatial statistics were performed with the Functional Magnetic Resonance Imaging of the Brain Software Library (FSL) version 5.0.10, and the BrainSuite software version 16a1. Briefly, DWI volumes were corrected for eddy distortions by rigidly registering (FLIRT) each slice to the non-diffusion volume (i.e., b_0). EPI distortions were unwrapped by non-rigidly registering each participant's DWI volumes to their T1-weighted image, as depicted below in Figure 5.

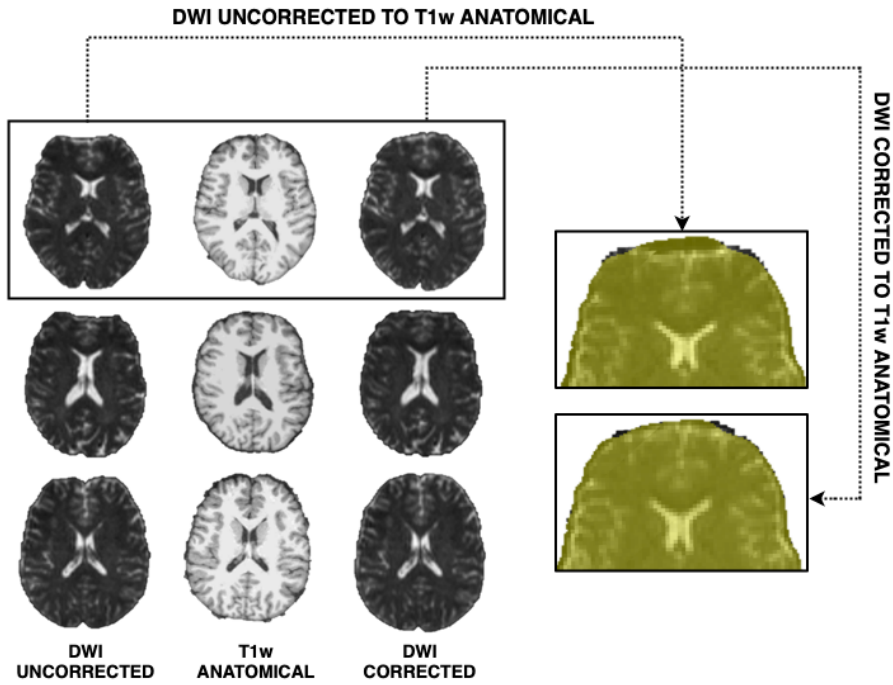

FIGURE 5 | Example of pre-processing pipeline to overcome EPI distortions.

The diffusion tensor was fitted to each voxel with a linear weighted least squares approach. The subject requiring the least distortions to fit the MNI template was selected. Each participant was registered to this target, and all volumes were averaged to build a study-specific template. The mean skeleton was based on the point of highest FA value across participants. Thereby, the centre of the tract constituted the most parallel fibre presenting FA values greater than 0.2. Supplemental DTI metrics were also calculated (i.e., MD, AD and RD). Moreover, a bi-tensor model was fitted by the following algorithm developed by Pasternak et al. (2009) to run *post-hoc* analyses.

$$A_q(D, f) = f exp(-bq^T Dq) + (1 - f)\exp(-bd_{water})$$

A_q is the normalised attenuated signal for the applied diffusion gradient (*q*) and the b-value (*b*). The first term reflects the tissue compartment, comprised by the diffusion tensor (*D*) and the fractional volume (*f*). The second term exposes an isotropic free-water compartment, with a fractional volume of *1- f* and d_{water} is the diffusion coefficient, set to the diffusivity of water in body temperature (3×10^{-3} mm^2/s). The model was fitted using an updated algorithm to use a Euclidean metric for tensor distances (Pasternak et al., 2010; 2012). The regularisation incorporates a tensor-based operator (Gur et al., 2009) indispensable to stabilise the model fit in single-shell data. The free-water fractional volume is consequently relative to the extracellular volume (Wang et al., 2011). Fitting tensors to the tissue compartment offer an accurate estimation of underlying pathological processes (Metzler-Baddeley et al., 2011).

3.2.3. Neuropsychological Assessment

An exhaustive exploration of executive functions was performed for Study 3. Concretely, cognitive flexibility was evaluated using the perseverative errors from the computerised-version of the Wisconsin Card-Sorting Test (WCST) (Heaton, 1999), and through the Trail Making Test (TMT) part B minus part A (Reitan, 1958). The interference score in the Stroop test (Golden, 1995) informed about inhibitory control. Total score in the Letter-Number subtest (WAIS-III) (Wechsler, 1999) equalled to working memory functioning.

3.3. Statistical analyses

The objective of the principal analysis in all three studies was comparing correlations between the independent (i.e., AL index) and the dependent variable (i.e., cortical thickness, FA, or executive functioning) accounting for body-weight status (i.e., overweight and normal-weight). All brain imaging analyses were performed with the FreeSurfer's Query, Design, Estimate, Contrast (Qdec) feature and the FSL's General Linear Model (Glm) tool.

In Study 1, sociodemographic variables such as age, sex, and years of education were treated as nuisance variables. In Study 2, age and sex were controlled as well. Sociodemographic variables, especially age and sex, may have a potential influence on brain morphology (Deary & Johnson, 2010; Hedman, van Haren, Schnack, Kahn, & Hulshoff Pol, 2012; Sacher, Neumann, Okon-Singer, Gotowiec, & Villringer, 2013). In addition, to test for the isolated effects of chronic physiological stress on the brain, measures of adiposity such as waist circumference (WC) and waist-to-height ratio (WTHR) were also controlled. All neuroimaging results were corrected for multiple comparisons with Monte-Carlo Null-Z simulation (10,000 permutations) in FreeSurfer, and with family-wise error (FWE) correction in FSL. Finally, in Study 3 the potentially biasing influence of years of education and visceral adiposity (i.e., WTHR) were controlled in the analyses.

The IBM Statistical Package for Social Sciences version 21 (SPSS, RRID: rid_000042) was used for sociodemographic data analysis, such as group comparisons. The freely distributed R statistical package version 3.4.4 also served for statistical purposes in Study 3. Detailed methodological specifications for each study are presented in their respective methods section. The bibliography of these three studies is presented along with the thesis' references in the References Section (pp. 169) to ease lecture.

CHAPTER 4 – RESULTS

STUDY 1

ALLOSTATIC LOAD IS LINKED TO CORTICAL THICKNESS CHANGES DEPENDING ON BODY-WEIGHT STATUS

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Abstract

Overweight (body mass index or BMI ≥ 25 kg/m^2) and stress interact with each other in complex ways. Overweight promotes chronic low-inflammation states, while stress is known to mediate caloric intake. Both conditions are linked to several avoidable health problems and to cognitive decline, brain atrophy, and dementia. Since it was proposed as a framework for the onset of mental illness, the allostatic load model has received increasing attention. Although changes in health and cognition related to overweight and stress are well-documented separately, the association between allostatic load and brain integrity has not been addressed in depth, especially among overweight subjects. Thirty-four healthy overweight-to-obese and 29 lean adults underwent blood testing, neuropsychological examination, and magnetic resonance imaging to assess the relationship between cortical thickness and allostatic load, represented as an index of 15 biomarkers (this is, systolic and diastolic arterial tension, glycated hemoglobin, glucose, creatinine, total cholesterol, HDL and LDL cholesterol, triglycerides, c-reactive protein, interleukin-6, insulin, cortisol, fibrinogen, and leptin). Allostatic load indexes showed widespread positive and negative significant correlations ($p < 0.01$) with cortical thickness values depending on body-weight status. The increase of allostatic load is linked to changes in the grey matter composition of regions monitoring behaviour, sensory-reward-processing, and general cognitive function.

1. Introduction

Overweight (BMI ≥ 25 kg/m^2) has become a major health problem worldwide; it affects up to 50% of the adult population in Western societies and it is a preventable risk factor for several medical conditions (World Health Organization, 2016). Caloric intake is mainly regulated by the homeostatic system (that is, the hypothalamus and brainstem structures) which promotes hunger or satiety responses via gut hormones and peptides (Dagher, 2009). However, the rewarding properties of food such as its odor and palatability can trigger approaching behaviours mediated by the hedonic or reward system (i.e., midbrain areas, striatum, and orbitofrontal cortex) even in the absence of hunger. This situation can be especially worrisome if top-down regulating systems (that is, cognitive-control areas such as the dorsolateral prefrontal cortex) fail frequently in regulating these urgent drives toward high-caloric food ingestion. Alterations within reward- processing and cognitive-control regions have been proposed as one of the possible mechanisms underlying pathological eating, or eating beyond caloric needs (Leigh and Morris, 2016). In addition, excess of weight and high-fat diets can be important sources of physiological stress as they promote chronic low- inflammation states detrimental for both physical and mental health (Castanon et al., 2014; Nguyen et al., 2014; Guillemot- Legris and Muccioli, 2017). Metabolic by-products characteristic of obesity augments the permeability of the blood-brain barrier and induce a sustained liberation of pro-inflammatory cytokines (e.g., interleukin-6, or IL-6), which ultimately increase the activity of the hypothalamic-pituitary-adrenal (HPA-) axis (Foss and Dyrstad, 2011).

Stress is a complex process resulting from an imbalance between one's resources and the demands of a given situation. It requires psychological, behavioural and physiological adaptations in order to overcome a defiant or threatening situation. This physiological modification, a process known as allostasis, includes significant and necessary changes in numerous biological systems (e.g., cardiovascular, metabolic, endocrine, and immune) to guarantee the energy boost needed during challenging scenarios (Kemeny,

2003). According to the allostatic load (AL) model (McEwen et al., 2015), the constant pushing of biological systems beyond their maximum capacity have a harmful cumulative effect that can lead to illness, or the so- called tertiary outcomes (e.g., hypercortisolemia, type II diabetes, psychiatric illness, and so on). Additionally, a recent study suggested that higher levels of circulating cortisol are related to an enhanced motivation for highly palatable food, greater abdominal fat accumulation and to an altered insulin metabolism (Jackson et al., 2017). As fight-or-flight responses consume a lot of energy, such changes in eating behaviour and metabolism occur as a compensatory mechanism to restore energy reserves (Kemeny, 2003). Consequently, both hypercaloric ingestion and fat mass increasing might trigger inflammatory responses as well (Jastreboff et al., 2013; Leigh and Morris, 2016).

Neuroimaging findings from structural studies have evidenced grey matter reductions (Bobb et al., 2014) and cortical thinning (Marqués-Iturria et al., 2013; Veit et al., 2014) in regions of the prefrontal cortex associated with reward-processing and self-regulation (among other functions) in overweight subjects. According to stress-related neuroanatomical studies, the prefrontal cortex has numerous adrenergic receptors, which made this region a target for chronic stress (Arnsten, 2009; Kremen et al., 2010; Leritz et al., 2011; Taki et al., 2013; Savic, 2015). As occurs in obesity and pathological eating, the settlement of abnormal stress responses also depends on blunted top-down regulating cortical areas (e.g., dorsolateral prefrontal cortex) on overly reactive limbic and subcortical structures (Leigh and Morris, 2016). In addition, posterior brain areas in temporal, parietal, and occipital lobes also show morphological alterations related to both overweight (Bobb et al., 2014; Veit et al., 2014; Kharabian Masouleh et al., 2016) and stress (Leritz et al., 2011; Taki et al., 2013). Some of these regions are ascribed to networks such as the dorsal-ventral attention, default mode, or cognitive-control networks. Although alterations in general health status, brain integrity, and cognition linked to both stress and overweight are well-documented separately, the relationship between the concept of AL and brain integrity has not been addressed to date, especially among overweight subjects. In fact, only two studies have assessed the detrimental effects related to an increase of AL in the cerebral cortex: the first showed total brain volume

reductions in relation to AL increase in later life (Booth et al., 2015), and the second showed cortical thinning in both patients with schizophrenia and healthy controls (Chiappelli et al., 2017).

Along with the growing concern about excess weight as a body stressor, scientific interest in the concept of AL has increased in recent years. Current literature revolves around the hypothetical role of chronic physiological stress and inflammation during the onset of mental disorders, cognitive decline and dementia (Juster et al., 2010; Beckie, 2012; McEwen et al., 2015). An overactive HPA-axis can induce lifelong damaging consequences for the central nervous system (CNS) through the incremented flow of excitatory aminoacids (e.g., excitotoxicity), glucocorticoids (e.g., decreased neurogenesis), and/or by triggering inflammatory processes (e.g., gliosis). Cell signaling proteins secreted by the adipose tissue (e.g., leptin) could also activate the HPA-axis (Foss and Dyrstad, 2011; Abella et al., 2017; Guillemot-Legris and Muccioli, 2017). According to the AL frame, overweight subjects could be at an advanced stage of such model and endure large amounts of physiological stress, even in the absence of other cardiometabolic comorbidities as occur within our overweight-to-obese sample. For this reason, disentangling the relationship between stress and brain structure in overweight individuals is of considerable clinical value. The aim of this study is, therefore, to explore if there is a relationship between the whole-brain cortical thickness and the AL in a group of healthy overweight and lean adults. We expect to find a pattern of cortical thinning related to an increase in AL in both groups, and especially a pattern of greater severity among the overweight group.

2. Materials and methods

2.1. Participants

The original sample consisted of one hundred and twenty-two adults recruited from public primary care centers belonging to the Consorci Sanitari de Terrassa. Eighty-four of them (43 obese individuals and 41 healthy controls) were already included in previous works (Ariza et al., 2012; García-García et al., 2013a, b, c, 2015; Marqués-Iturria et al., 2013, 2014, 2015). Since then, 38 new participants (29 overweight-to-obese and 9 lean subjects) have been recruited following the same procedure. Inclusion criteria were (1) being older than 20 years to guarantee a fully developed CNS, and (2) had a BMI higher than 18.5 kg/m^2, which is the limit for underweight. The overweight group (N = 72) was formed based on a BMI higher than 25 kg/m^2, following the World Health Organization's classification (World Health Organization, 2016). From the one- hundred and twenty-two included subjects, 25 of them (18 overweight-to-obese and 7 lean participants) met some of the exclusion criteria described below: (1) presence of past or present psychiatric illness (including addictive and/or eating disorders) or (2) any developmental, (3) neurological, or (4) systemic disorder (e.g., hyper or hypothyroidism, diabetes, cardiovascular disease). Participants were also ruled out because of (5) possible acute infection (C-reactive protein levels higher than 10 mg/L) or (6) meeting metabolic syndrome (MS) criteria (Alberti et al., 2009) (MS criteria are fully described in Supplementary Material section, Appendix A.1). Moreover, participants (7) with an estimated IQ below 85 (i.e., a scalar score lower than 7 in the WAIS-III vocabulary subtest) (Wechsler, 1999) were also excluded. Finally, the Bulimia Investigatory Test of Edinburgh (BITE) (Henderson and Freeman, 1987) and the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983; Herrero et al., 2003) were used as exclusion criteria because high scores in these tests could suggest the presence of either an eating disorder (i.e., BITE score higher than 20) or anxiety-depression symptoms (i.e., HADS score higher than 11). The flow of included and excluded participants is detailed in depth in the subsequent SM section (Appendix A.2). Briefly,

from this potential sample of 97 subjects, 20 overweight (of 54) and 14 lean subjects (of 43) declined to undergo a magnetic resonance imaging (MRI) acquisition of the head. Among the reasons for declining this phase of the study were the presence of claustrophobia, schedule incompatibilities, and/or being bearer of non-removable metallic objects (e.g., orthodontics). The final sample was composed by 34 overweight-to-obese subjects and 29 lean participants. This study has been approved by the University of Barcelona's (CBUB) Institutional Ethics Committee, Institutional Review Board (IRB 00003099, assurance number: FWA00004225; http:// www.ub.edu/recerca/comissiobioetica.htm). The research has been conducted in accordance with the Helsinki Declaration. Written informed consent was obtained from each participant prior to entry in the study.

2.2. Allostatic Load Index

We calculated the AL index by selecting 15 stress biomarkers using the high-risk percentile procedure described in previous reviews (Juster et al., 2010; Beckie, 2012) and original articles (Chiappelli et al., 2017; Savransky et al., 2017) as a well- established way of measuring the concept. Additionally, leptin has been selected as a metabolic biomarker because its presence is directly proportional to the amount of adipose tissue, has modulating effects over blood pressure (Simonds et al., 2014) and induces the production of pro-inflammatory cytokines (e.g., IL-6) (Abella et al., 2017). Moreover, C-reactive protein (CRP), which is an unspecific indicator of an ongoing inflammatory process, served both as a biomarker and as exclusion criteria. High levels of CRP (>10 mg/L) may suggest acute infection, which may alter the values of other immunologic biomarkers (e.g., IL-6 or fibrinogen). Despite overweight subjects did not meet diagnostic criteria for cardiometabolic diseases by the time they entered the study, they were more likely to score higher in almost all biomarkers when compared to controls. Similarly to current studies in AL (Chiappelli et al., 2017; Savransky et al., 2017), the high-risk percentiles were based on the control group (N = 43) to avoid an overweight-driven floor effect. This sample presented similar characteristics to the overweight group (see Appendix B.1 in the SM section). Additionally, different cut-off

points were set for each gender in those biomarkers (e.g., systolic arterial tension) that presented statistical differences ($p < 0.05$). Subjects in the high-risk percentile (i.e., greater than 75th, or below 25th in the case of HDL-cholesterol) obtained a binary score of "1" in that variable (or "0" if they did not exceed this cut-off point).

The list of biomarkers and their cut-off points are shown below in Table 1. The AL index was the sum of all 15 biomarker dichotomous scores, with higher scores meaning higher allostatic overload (range 0–15). A prorated AL index has been conducted in participants with missing values. Additionally, we calculated an alternative index because reducing a variable to a bi-dimentional trait (i.e., 1 or 0) could result in a loss of information (see Appendix B.2 in the SM for more details).

TABLE 1 | Allostatic load cut-off scores for individual biomarkers.

Biomarker	Male	Female	Both
Systolic arterial tension (mm Hg)	124.50	116.50	–
Diastolic arterial tension (mm Hg)	–	–	73
Glycated hemoglobin (%)	–	–	5.40
Glucose (mmol/L)	5.06	4.69	–
Creatinine (μmol/L)	90	70.25	–
Cholesterol (mmol/L)	4.21	4.88	–
HDL (mmol/L)	–	–	1.34
LDL (mmol/L)	–	–	3
Triglycerides (mmol/L)	–	–	0.86
C-reactive protein (mg/L)	–	–	0.93
Interleukin-6 (pg/mL)	–	–	1.65
Insulin (pmol/L)	–	–	52.02
Cortisol (nmol/L)	–	–	659.90
Fibrinogen (g/L)	3.07	3.32	–
Leptin (ng/mL)	4.80	20.30	–

mm Hg, millimeters of mercury; cm, centimeters; mmol/L, millimoles per liter; μmol/L, micromoles per liter; mg/L, milligrams per liter; pg/mL, picograms per milliliter; nmol/l, nanomoles per liter; g/L, grams per liter; ng/mL, nanograms per milliliter.

2.3. Image acquisition

Overweight (N = 34) and lean (N = 29) participants underwent MRI on a 3T MAGNETOM Trio (Siemens, Germany), performed at the Institut d'Investigacions Biomèdiques August Pi I Sunyer (IDIBAPS) from the Hospital Clínic de Barcelona with the following parameters: repetition time 2,300 ms; echo time 2.98 ms; inversion time 900 ms; 240 slices, field of view 256 × 256 mm, 1 mm isotropic voxel in order to obtain high resolution T1-weighted MPRAGE 3D scans.

2.4. Data pre-processing

T1-weighted images has been processed using FreeSurfer (v.5.3) pipeline by default (i.e., recon-all). Briefly this step includes skull stripping (Ségonne et al., 2004), motion correction and T1 averaging (Reuter et al., 2010), bias-field correction (Sled et al., 1998), and tessellation of grey/white matter tissue. Representations of cortical thickness has been calculated as the closest distance from the grey/white boundary to the grey/CSF boundary at each vertex on the surface (Fischl and Dale, 2000). The surface was smoothed using a circularly symmetric Gaussian kernel with a full-width at half maximum of 15 mm. The post- processing outputs for each subject were examined visually to ensure processing accuracy. Manual editing was performed when required to improve pial surface reconstruction.

2.5. Statistical analysis

Age, gender, IQ estimation (i.e., WAIS-III), and other sociodemographic (i.e., years of education, family income, professional level), psychological (i.e., HADS) and behavioural variables (i.e., smoking, drinking) were analyzed using Student's t-test and chi-square test (bootstrap 1,000 iterations) with IBM SPSS Statistics (v.23) to ensure that there were no significant differences ($p \geq 0.05$) between groups. Regarding the imaging analyses, global thickness (in mm) brain measures (i.e., left and right hemisphere mean cortical thickness) were extracted to conduct group comparisons (i.e., ANOVA, t-test) in SPSS. Whole-brain analyses has been performed using the general

linear modeling (GLM) implemented in the FreeSurfer's Qdec tool. The age, years of education, and gender were set by default as nuisance factors to avoid their potential biasing influence over brain morphology. We tested for group differences at the vertex-wise level in whole-brain cortical thickness in each hemisphere. The relationship between AL and cortical thickness was explored with linear regression analysis. This model included cortical thickness as the dependent factor and the AL index as the independent factor. The waist circumference (WC) was also included as nuisance factor in this model to assess this association independently of the effects of body weight by itself (Sahakyan et al., 2015). We first explored for associations in the entire sample (N = 63), and then we addressed the possibility of a group effect over this relationship (i.e., comparing the correlations coefficients of overweight and leans). All results were corrected for multiple comparisons using a precached Monte-Carlo null-Z Simulation (10,000 repetitions) with a cluster-wise corrected *p*-value (CWP) of <0.01 for statistical significance. The clusters that remained significant were reported according to the Desikan's atlas (Desikan et al., 2006) in MNI305 coordinates. Mean thickness (mm) of significant clusters were extracted for plotting results.

3. Results

We found no significant differences between groups in sociodemographic, cognitive (i.e., IQ estimation), psychological (i.e., HADS), or behavioural data (i.e., smoking, drinking). As expected, groups statistically differed in BMI [$T_{(61)} = -9.774$, $p < 0.001$, BCa 95% −11.09 ~ −7.30], WC [$T_{(61)} = -8.212$, $p < 0.001$, BCa 95% −26.18 ~ −16.64], and AL index [$T_{(61)} = -5.117$, $p < 0.001$]. The results of these variables are available below in Table 2. There were no significant differences for global thickness measures as shown in the SM section (Appendix C.1.).

TABLE 2 | Variables of interest of overweight and lean participants.

	Overweight (N = 34)		Lean (N = 29)	
	Mean (SD)	Range	Mean (SD)	Range
Age	31.79 (6.10)	21–40	30.07 (6.21)	21–40
Years education	13.76 (2.69)	10–20	14.62 (2.21)	10–18
IQ estimation	12.00 (2.16)	8–17	11.93 (1.83)	7–15
Gender (F/M)	21/13		15/14	
Smoker (yes/no)	10/24		6/23	
Drinker (yes/no)	17/17		18/11	
HADS anxiety	4.12 (2.41)	0–9	4.55 (2.97)	0–10
HADS depression	1.97 (2.17)	0–7	1.41 (1.57)	0–5
BMI (kg/m^2)*	31.39 (5.02)	25.20–49.69	22.35 (1.82)	19.00–24.99
WC (cm)*	99.52 (13.26)	82–137	77.96 (6.70)	67–92
AL Index*	6.78 (2.64)	2–12	3.56 (2.29)	0–9
FAMILY INCOME IN EUROS PER MONTH (FREQUENCY)				
300–899	0		0	
900–1,499	4		5	
1,500–2,099	15		9	
2,100–2,699	8		4	
>2,700	6		10	
Don’t know / Don’t answer	1		1	
PROFESSIONAL LEVEL (FREQUENCY)				
Non-skilled	3		1	
Skilled manual	10		5	
Administrative	8		5	
Intermediate	5		6	
Professional	5		6	
Don’t know / Don’t answer	3		6	

*$p < 0.05$, IQ estimation, Intelligence Quotient estimation (WAIS-III); F, female; M, male; BMI, body mass index (kg/m^2); WC, waist circumference (cm); HADS, Hospital Anxiety and Depression Scale; SD, Standard deviation.

The whole-brain vertex-wise comparisons between groups revealed a significant difference in cortical thickness in the left superior frontal gyrus (X = −18.1, Y = 17.3, Z = 52.8; size = 1920.55 mm^2, mean thickness in leans = 2.70 mm ± 0.13 and mean thickness in overweight = 2.53 mm ± 0.13, *Z* = 4.349, *CWP* < 0.001) and in the right superior frontal gyrus (X = 8.1, Y = 46.0, Z = 22.6, size = 2072.66 mm^2, mean thickness in leans = 3.02 mm ± 0.14, mean thickness in overweight = 2.87 mm ± 0.16, *Z* = 4.132, *CWP* < 0.001). When tested for linear regressions in FreeSurfer's GLM within the whole sample (N = 63), there were no significant relationship between the AL index increase and the thickness of the cortical mantle.

However, the results showed a significant interaction when this association was compared between groups. Overweight subjects showed lower cortical thickness as the AL index increase (i.e., thinning), while lean participants demonstrated greater thickness (i.e., thickening) as this AL score increased. This interaction was found in five clusters in the left hemisphere, with their maximum peak of intensity in the pars triangularis (*CWP* < 0.001), superior frontal gyrus (*CWP* < 0.001), supramarginal gyrus (*CWP* < 0.001), inferior parietal cortex (*CWP* < 0.001), and the precuneus *(CWP* = 0.001). An interaction was also significant on the right hemisphere and followed the same trend in clusters located in the precentral gyrus (*CWP* < 0.001), the precuneus (*CWP* < 0.001), the transversal temporal gyrus (*CWP* = 0.002), the inferior parietal cortex (*CWP* = 0.004), and the lateral orbitofrontal cortex (*CWP* = 0.005). Location, size, and coordinates of these interactions are shown in the SM section (Appendix C.2). Visual maps of cortical thickness patterns and the mean thickness standardised residuals (i.e., regressing out the effects of age, years of education) of each cluster are depicted in Figures 1 and 2.

Additionally, the results of the analysis conducted with the alternative AL index (i.e., factor reduction) and the visual representations of the overlapping results for both group comparisons and group interactions, are available in the SM section (Appendices D.1, D.2, respectively).

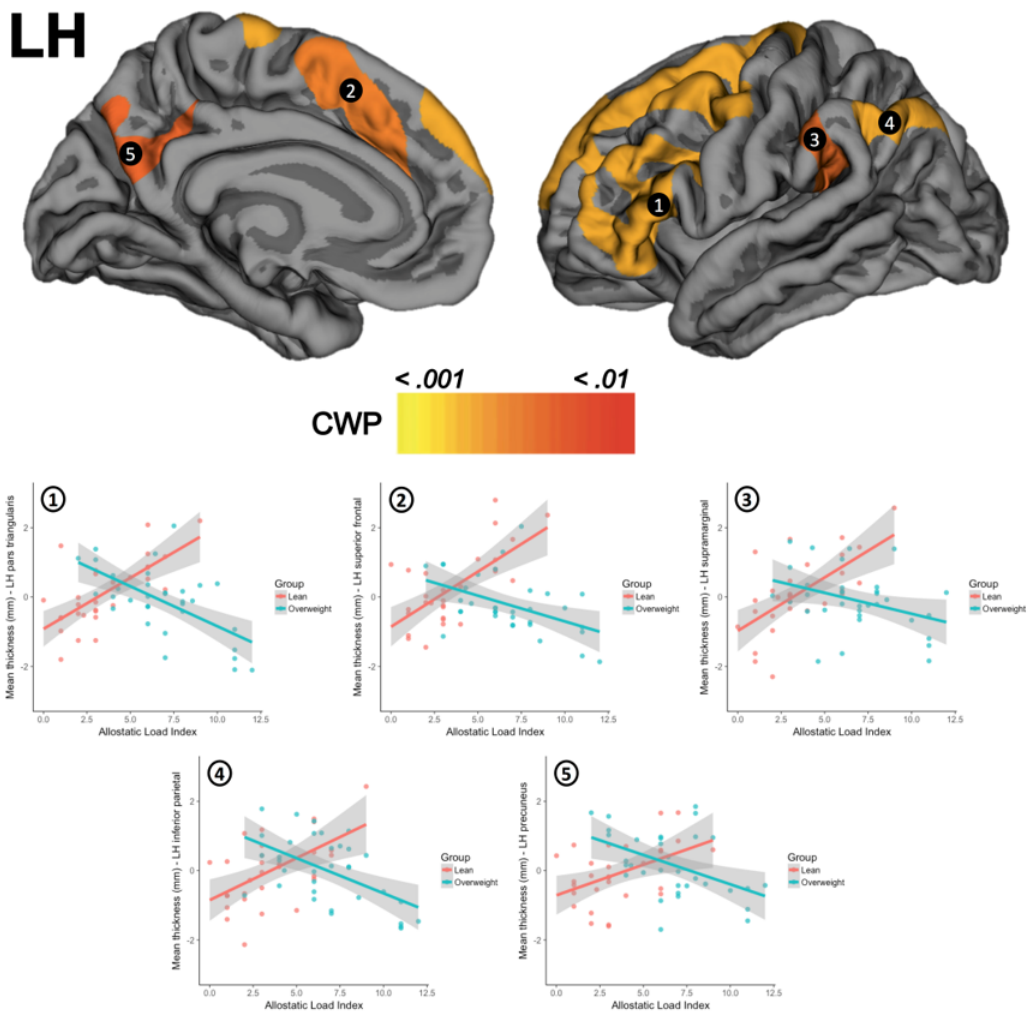

FIGURE 1 | The upper row shows the interactions between groups for clusters in the left hemisphere (LH) in (1) pars triangularis, (2) superior frontal gyrus, (3) supramarginal gyrus, (4) inferior parietal cortex, and (5) precuneus. The second row presents scatterplots of the interaction between groups (overweight/blue, lean/red) for the standardised residuals of mean cortical thickness (Y-axis) and AL index (X-axis). CWP, cluster-wise corrected *p*-value.

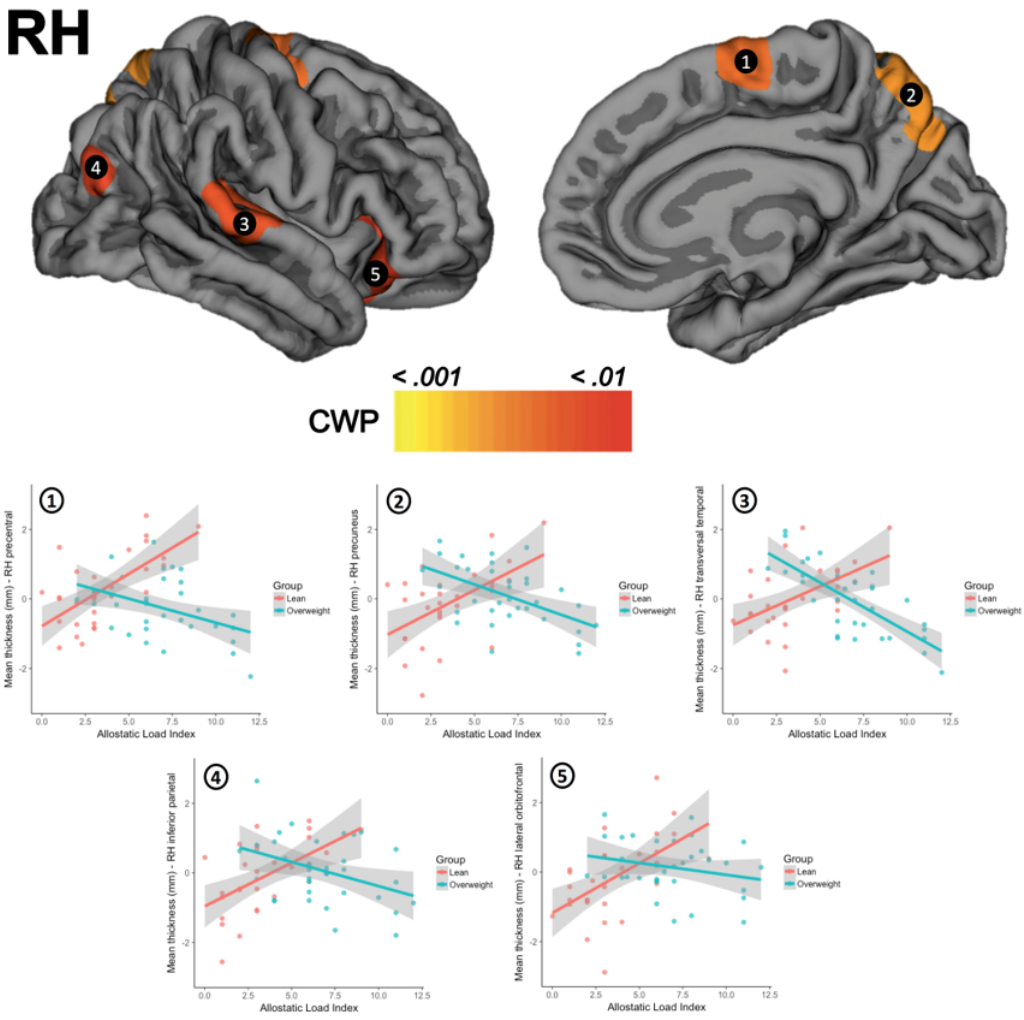

FIGURE 2 | The upper row shows the visual interactions between groups for clusters in the right hemisphere (RH) in (1) precentral gyrus, (2) precuneus, (3) transversal temporal gyrus, (4) inferior parietal cortex, and (5) lateral orbitofrontal cortex. The second row presents scatterplots of the interaction between groups (overweight/blue, lean/red) for the standardised residuals mean cortical thickness (Y-axis) and AL index (X-axis). CWP, cluster-wise corrected *p*-value.

4. Discussion

We addressed the relationship between AL and cortical thickness in a sample of healthy overweight-to-obese adults and lean controls with similar characteristics. Few studies to date have focused on linking the AL and the brain integrity beyond psychiatric (Chiappelli et al., 2017; Savransky et al., 2017) or elderly samples (Booth et al., 2015). Given the association between overweight and physiological stress/inflammation (Foss and Dyrstad, 2011; Castanon et al., 2014; Nguyen et al., 2014; Guillemot-Legris and Muccioli, 2017; Jackson et al., 2017), assessing the relationship between the stress and brain integrity is relevant with a view on prevention and early medical interventions (e.g., mental health wellness, healthy aging, and successful weight loss). First, in the present study overweight participants showed lower cortical thickness compared to controls in two clusters located in left and right superior frontal gyrus, as previously described in Marqués-Iturria et al. (2013). Second, and regarding to the main objective of this study, overweight subjects proved have higher AL indexes than lean controls. The AL index increase did not show a relationship with the cortical thickness when included the entire group in the analyses. However, when we examined the presence of possible group interactions, we observed a pattern of cortical thinning in overweight and cortical thickening in leans in relation to AL increase. This interaction occurred in several bilateral anterior (frontal and prefrontal cortex) and posterior cortical regions (temporal and parietal cortex). Some of these areas are part of networks involved in monitoring behaviour (including eating behaviour), sensory-reward-processing and support basic cognitive abilities (e.g., memory, attention, etc.).

The lack of significant results in the entire sample suggests in first place that the relationship between AL and cortical thickness may not follow a linear trend. Rather, our results suggest that this relationship may be modulated by body-weight status in a complex way. Moreover, although we expected that the AL increase would be linked to negative neurological outcomes (e.g., cortical thinning) independently of the group, the relationship between AL and cortical thickness did not behave as expected for lean subjects. A cortical thickening pattern has also been

described in very early stages at the onset of major depressive disorder (Qiu et al., 2014) and schizophrenia (van Haren et al., 2011), during presumably an ongoing inflammatory process. According to Qiu et al. (2014), while cortical thinning may suggest dendritic retraction, cortical thickening may be a sign of glial activity promoted by pro-inflammatory cytokines in order to prevent neuronal degeneration by increasing neurotrophic factor release (e.g., brain-derived neurotrophic factor, or BDNF). This is, in lean subjects, an engaged HPA-axis and the liberation of pro-inflammatory cytokines induced by a challenging situation could be linked to cortical thickening (e.g., gliosis, neurotrophin-signalling). Then, if this response does not revert and escalates (i.e., as it likely does in overweight subjects), it could be related to negative outcomes in the brain (e.g., dendritic retraction, neuronal degeneration, etc.). Our findings may represent the transition from allostasis (i.e., a natural response to a challenge) to allostatic load (i.e., a failed response to a repeated threat). Moreover, chronic-stress and/or adiposity (and its metabolic by- products, such as leptin, LDL cholesterol or triglycerides) could affect the functionality (e.g., hypertension) and structure of blood vessels (e.g., atherosclerosis). This, beyond being an important risk factor for cerebrovascular disease by itself, it can impair the glucose and oxygen transportation into the brain (Kemeny, 2003), which it might be as well another potential insult for neuronal integrity. The nature of the challenging situation (i.e., internal or external) and the causality between chronic-stress and overweight cannot be tackled with this design and statistical analysis. Nevertheless, our results showed that the increasing of AL index is linked to cortical changes whose pattern (i.e., thinning or thickening) depends on body-weight status.

We found a pattern of cortical thinning in overweight subjects and cortical thickening in controls related to an AL index increase in bilateral frontal and prefrontal cortex. Specifically, we observed changes in bilateral insula, precentral, lateral orbitofrontal and superior frontal gyrus, and in the left middle (rostral and caudal middle frontal) and inferior (pars orbitalis, pars opercularis, and pars triangularis) frontal gyrus. A similar pattern of results (especially with regards to middle

and inferior frontal gyrus) have also been reported by Chiappelli et al. (2017) in their study of AL and schizophrenia. Moreover, volume reductions of these areas have been described in obese subjects when compared to leans, or when assessing the relationship between BMI and/or WC increase and grey matter integrity (Bobb et al., 2014; Kharabian Masouleh et al., 2016; Janssen et al., 2017) or cortical thickness (Marqués-Iturria et al., 2013). Some of these regions have also been reported to be affected during stress situations (Savic, 2015), or in relation to stress biomarkers (Kremen et al., 2010; Leritz et al., 2011; Zhang et al., 2016). The pars opercularis is a key region for the integration of sensory-hedonic properties of food (e.g., taste, texture, palatability) given its involvement along with the anterior portions of the insula in the primary gustatory cortex (Kumar et al., 2016). Orbitofrontal regions are known as a second gustatory cortex and for their role in reward-processing, a function affected in overweight (García-García et al., 2013a,c, 2014, 2015; Marqués-Iturria et al., 2015) and stress (Porcelli et al., 2012). Dorsolateral (i.e., middle and superior frontal gyrus) and ventrolateral portions (i.e., inferior frontal gyrus) of the prefrontal cortex are involved in regulating behaviour through executive functions such as inhibitory control. The ability to suppress automatic responses and replace them with more appropriate ones seems to be altered in both overweight (Smith et al., 2011) and stress (Sandi, 2013). Finally, medial portions of the prefrontal cortex (i.e., medial superior frontal gyrus) are involved in decision-making and motivation, which also appear to be affected in overweight (Smith et al., 2011) and stress (Sandi, 2013). In coherence with Marqués- Iturria et al. (2013), dorsal and medial portions of both left and right superior frontal gyrus showed cortical thickness reductions in the overweight participants when compared to lean controls. Obesity status (overweight vs. lean) and AL seemed to share variance in the left superior frontal gyrus. However, this region remained significant after controlling for the effects of body weight in the linear regression analysis.

Our results showed dimorphic associations between cortical thickness and higher AL indexes in overweight and controls in bilateral superior temporal gyrus. Besides auditory and language processing, superior

temporal gyri have also been associated along with the insula with satiation signal processing (Kroemer et al., 2013) and the ventral-attention network (Vossel et al., 2014). The temporal lobe also has been related to learning and memory processes. Alterations of memory performance are usually reported in both obesity (Higgs, 2015) and stress (Sandi, 2013). The vulnerability of this structure has been linked to adiposity (Veit et al., 2014; Kharabian Masouleh et al., 2016), stress exposure (Leritz et al., 2011; Taki et al., 2013), and AL increase (Chiappelli et al., 2017) as well.

We also observed a group-dependent pattern of cortical changes linked to higher levels of AL index in bilateral precuneus, inferior and superior parietal cortex, and paracentral and supramarginal gyrus. Some of these dorsal regions (i.e., supramarginal gyrus, inferior, and superior parietal cortex, etc.) exhibit a high degree of connectivity with dorsolateral prefrontal areas, together forming what is known as the cognitive- control or frontoparietal network. Along with inhibitory control, working memory is an executive function usually associated with this network (Darki and Klingberg, 2014), and it is involved in keeping information available when it is no longer perceptible. Working memory impairments have been linked to both stress (Sandi, 2013) and overweight (Higgs, 2015). It is believed that lack of access to our long-term goals (e.g., having an online record of caloric intake during the day, maintaining a daily healthy food consumption or not eating beyond caloric need) when required may contribute to bad dietary choices and overeating (Higgs, 2015). Other works have also associated grey matter reductions in dorsal parietal regions with adiposity (Bobb et al., 2014; Kharabian Masouleh et al., 2016) and stress (Leritz et al., 2011). Finally, a ventral region such as the precuneus is considered an important hub in the default mode network (DMN). The DMN (precuneus, posterior and anterior cingulate cortex, middle temporal gyri, and inferior parietal and medial prefrontal cortex) is related to self-referential information processing, and is engaged during "wakeful rest" when we think about others or ourselves. Structural modifications in this region have been consistently reported in several mental disorders (Anticevic et al., 2012) and stress (Leritz et al., 2011), but not in obesity (García- García et al., 2013b). However, the precuneus overlaps with reward-salience processing regions, a network which is affected

in obesity (García-García et al., 2013a,b; Horstmann et al., 2015; Marqués-Iturria et al., 2015). In the study of Chiappelli et al. (2017), the increase of AL was related to decreases in the cortical thickness of parietal regions as the paracentral and postcentral gyrus, the inferior and superior parietal cortex, and the precuneus, similar to the results that we observed with overweight participants.

Some limitations emerge when it comes to the methodology under the AL measurement. Theorists have suggested that the AL model can provide an interesting and holistic perspective to explain the onset of several mental illnesses. In the present study, we assessed the AL following the most used method in the literature, which is based on high-risk percentiles and the sum of dichotomous scores. With this, we facilitate the replication of our results. However, it would help further research the fact of determining the normal (i.e., in absence of developed comorbidities) distribution of stress biomarkers based on large population studies accounting for age, gender, and socio-economic status. Since we excluded participants with medical pathologies, the use of clinical cut-off scores was not feasible. At least 9 out of 15 of the stress biomarkers used for this study referred to metabolic parameters. Because of this, it could be also reasonable to state that our results might be partially driven by the effect of metabolic variables. The AL concept may be confounded with MS, especially with the number of metabolic biomarkers we used in our work. However, the cortical thinning attributed to MS are mostly explained by the increase of the WC (Schwarz et al., 2017), which we controlled for its effects in all of our analyses. In this vein, and as the MS is usually referred to as a pre-stage for type II diabetes, the allostatic overload could be interpreted as a previous step for MS. Although more research is needed, the AL proved be useful for early detection of structural changes in young adults with a non-clinical status. As aforementioned, the exploratory nature, the cross-sectional design and the type of analysis performed in this study unfortunately do not allow concluding upon causality. Chronic stress may be a risk factor for weight-gain; just as overweight may be an important source of chronic stress (Foss and Dyrstad, 2011). Chronic-stress increases the appetite for high-caloric food to restore energy reserves, yet modern stressors do not usually threat physical integrity nor require physical

performances (i.e., fight-or-flight responses) as they once did. On the other hand, the fat tissue is capable of induce inflammation responses (in fact, early stress responses are originally intended to facilitate the vascularization of the increasing fat mass), which stresses the organism. Further works should focus on disentangling this issue, especially since not all chronically stressed people crave for highly palatable food and/or eat uncontrollably and gain weight. It is possible that when stressed, some people may involuntary increase their physical activity (e.g., augmented leg shaking and/or wandering around home/workplace), or change their habits in an overcompensating fashion (e.g., eating healthier, engaging in sport activities, etc.). Hence, psychological (e.g., personality traits, resilience, coping strategies), genetic (e.g., 5-HTT, BDNF, FTO), behavioural (e.g., diet, smoking, exercise, sleep quality), socioeconomic and environmental (e.g., family income, education, neighbourhood, exposure to contaminants) factors should be explored in order to identify phenotypes in which chronic stress predisposes to obesity development and vice versa. The sample size is another important limitation that makes difficult to generalise the results obtained. Our exclusion criteria are very strict in order to ensure that the observed results are not due to the presence of confounding variables (e.g., psychological distress, metabolic syndrome, or acute infection). On a similar note, the focus on overweight participants has a special clinical relevance, since this population does not necessarily show cardiometabolic comorbidities that are frequent in severe stages of obesity. This could facilitate the isolation of the effect of excess of weight. We encourage future works with bigger samples to replicate our findings. On the contrary, a strength that we would like to highlight is the use of samples with similar characteristics: the allostatic load cut-off points may vary according to gender, age and the socioeconomic and personal situation of each individual. Having matched groups ease the extrapolation of cut-off points for further investigations with similar groups. Additionally, and to the best of our knowledge, this is the first study approaching the AL concept in healthy overweight adults. Overweight is an increasingly prevalent condition that requires new therapeutic approaches to stop its progression and its associated complications.

In conclusion, our study suggests the existence of a dimorphic (i.e., thinning and thickening) and detrimental relationship between AL increase and the morphology of brain structures that supervise behaviour (e.g., inhibitory control, working memory), process the satiating signals and reward-hedonic properties of food (e.g., motivation/craving, satiety) and enable correct cognitive functioning (e.g., attention, memory). These brain regions are necessary to participate in healthy habits crucial for psychological and physical well-being. Early interventions in the general population may prevent the effects of chronic stress on the brain that can lead to serious potential comorbidities.

5. Author contributions

JO-G, MJ, IG-G, BS, IM-I, CJ, and MG: all provided substantial contributions either to the conception and design of the study, analysis, and/or interpretation of the results; JO-G, IG-G, IM-I, XP-S, MS-P, and XC: also participated in data acquisition (subject recruitment, medical, and neuropsychological evaluation, MRI acquisition); Additionally, all authors critically revisited the work, approved its final version for publishing, and agreed to be accountable for all aspects of such work.

6. Acknowledgments

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7. References

(See thesis references)

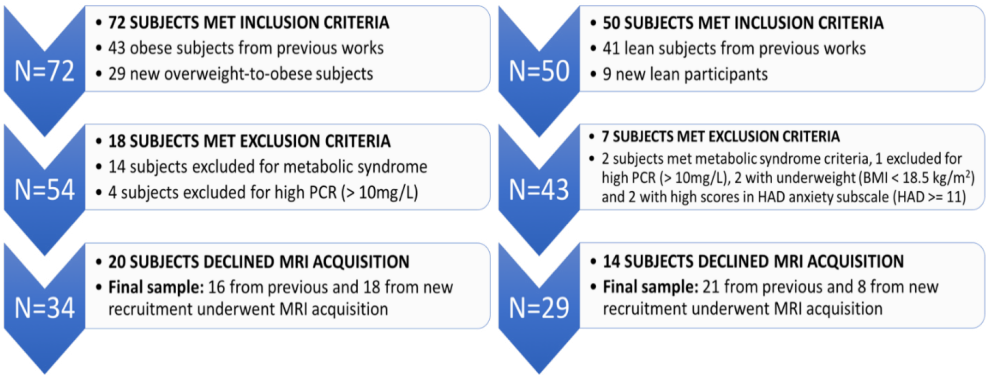
8. Supplementary material

APPENDIX A.1 | Metabolic syndrome criteria. At least three (3) of the presented above.

Measure	Cut-off point
Waist circumference	Male: 94 cm Female: 80 cm
Triglycerides	150 mg/dL (1.7 mmol/L)
High density lipoprotein (HDL-C)	Male: < 40 mg/dL (1.0 mmol/L) Female: < 50 mg/dL (1.3 mmol/L)
Arterial pressure	Systolic: 130 mm Hg Diastolic: 85 mm Hg
Fasting glucose	100 mg/dL

cm, centimeters, mg/dL, milligrams per deciliter, mmol/L, micromoles per liter, mm Hg, millimetres of mercury

APPENDIX A.2 | Flow of included and excluded participants.



APPENDIX B.1 | Characteristics of the normative group served for the cut-off calculation.

	Lean (N=43)	
	Mean (SD)	**Range**
Age	30.44 (6.03)	21 – 40
Years education	14.12 (2.41)	9 – 18
IQ estimation	11.50 (1.95)	7 – 15
Gender (F/M)	26 (60.5%)	
Smoker (yes/no)	9 (20.9%)	
Drinker (yes/no)	24 (55.8%)	
HADS anxiety	4.47 (2.80)	0 – 10
HADS depression	1.26 (1.60)	0 - 6
BMI (kg/m²)	21.99 (1.76)	18.59 – 24.99
WC (cm)	76.05 (6.95)	61 – 92
Family income in euros per month (frequency, %)		
300-899	1 (2.3%)	
900-1499	7 (16.3%)	
1500-2099	13 (30.2%)	
2100-2699	7 (16.3%)	
>2700	13 (30.2%)	
Do not know / do not answer	2 (4.7%)	
Professional level (frequency, %)		
Non-skilled	4 (9.30%)	
Skilled manual	5 (11.6%)	
Administrative	8 (18.6%)	
Intermediate	7 (16.3%)	
Professional	9 (20.9%)	
Do not know / do not answer	10 (23.3%)	

IQ estimation, Intelligence Quotient estimation, F, female, M, male, BMI, body mass index (kg/m^2), WC, waist circumference (centimeters), HADS, Hospital Anxiety and Depression Scale, SD, standard deviation

APPENDIX B.2 | Alternative index method calculation.

This alternative index has been constructed based on a factor reduction with a principal component analysis using IBM SPSS Statistics (v.23). Missing scores were substituted by the mean. Final scores were transformed following a square-root procedure.

APPENDIX C.1 | Global brain thickness (mm) ANOVA and t-test for groups.

	Overweight	Range	Lean	Range	F	T	p-value
Left	2.56 (0.11)	2.33 – 2.74	2.57 (0.08)	2.41 – 2.81	0.56	0.25	0.814
Right	2.54 (0.10)	2.34 – 2.72	2.55 (0.09)	2.38 – 2.77	0.01	-0.03	0.980
Global	2.55 (0.10)	2.33 – 2.73	2.56 (0.09)	2.40 – 2.79	0.01	0.11	0.911

APPENDIX C.2 | Cluster-level interactions between overweight and lean participants.

	Principal location	Extension	Size	MNI305 coordinates			Z	CWP
				X	Y	Z		
LH	**Pars triangularis**	Pars opercularis, pars triangularis, pars orbitalis, lateral orbitofrontal, insula, precentral, postcentral, paracentral, caudal and rostral middle frontal and superior frontal	8694.6	-51.7	25.3	7.2	5.52	0.0001
	Superior frontal	Superior frontal, caudal and rostral anterior cingulate	1198.8	-9.6	26.4	30.6	5.85	0.0004
	Supra marginal	Supramarginal and superior temporal	1173.2	-50.9	-29.8	34.8	4.83	0.0007
	Inferior parietal	Inferior parietal and supramarginal	1288.6	-47.0	-59.6	39.4	4.28	0.0001
	Precuneus	Precuneus and isthmus cingulate	1042.4	-4.8	-59.4	26.5	3.76	0.0010

APPENDIX C.2 | Cluster-level interactions between overweight and lean participants (cont.)

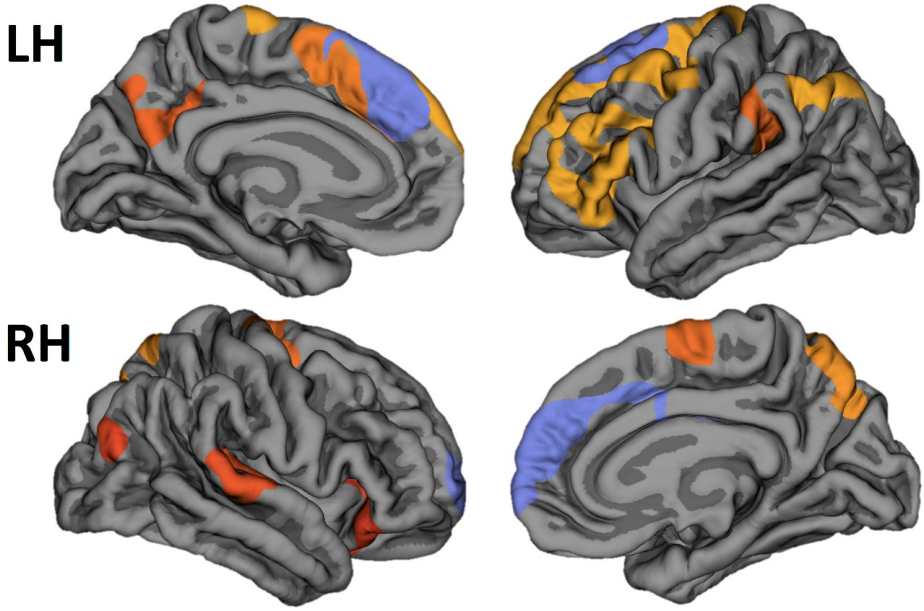
	Principal location	Extension	Size	MNI305 coordinates			Z	CWP
				X	Y	Z		
RH	**Precentral**	Precentral, paracentral and superior frontal	1084.2	20.7	-12.2	61.4	4.95	0.0007
	Precuneus	Precuneus and superior parietal	1280.4	6.8	-57.7	55.7	3.95	0.0002
	Transversal temporal	Transversal temporal, superior temporal and supramarginal	1009.3	50.7	-17.6	5.5	3.78	0.0019
	Inferior parietal	Inferior and superior parietal	936.8	33.1	-67.6	23.2	3.51	0.0037
	Lateral Orbitofrontal	Lateral orbitofrontal, insula and pars triangularis	936.8	28.3	29.9	-9.3	3.51	0.0054

Principal location based on the peak of maximum intensity. Size is reported in millimetres. CWP, cluster-wise corrected p-value, LH, left hemisphere, RH, right hemisphere.

APPENDIX D.1 | Alternative index results.

There were no significant interactions between groups with a cluster-wise correction (i.e., Monte-Carlo Simulation) set at $p < 0.01$. With a less restrictive threshold (i.e., $p < 0.05$) the left precuneus (X= -12.6, Y= -59.9, Z= 25.5, size in mm^2= 2916.80, Z-value= 3.843, CWP= 0.0001) and the right inferior parietal cortex (X= 37.2, Y= -77.7, Z= 17.2, size in mm^2= 3001.26, Z-value= 3.837, CWP = 0.001), the right lateral orbitofrontal cortex (X= 13.7, Y= 24.2, Z= -22.1, size in mm^2= 1871.99, Z-value= 4.443, CWP= 0.004) and the right inferior temporal gyrus (X= 49.1, Y= -9.9, Z= -31.3, size in mm^2= 1692.14, Z-value= 2.852, CWP= 0.009) showed significant results. The followed trend was the same as in prior results (i.e., overweight/thinning and lean/thickening).

APPENDIX D.2 | Overlapping results of group comparisons and interactions with AL.



Appendix D.2 | In cold colors (blue), group differences in thickness (lean > overweight) for the left and right frontal superior gyrus (corrected p-value < 0.01). In hot colors, group interactions for the AL index and cortical thickness relationship (corrected p-value < 0.01). LH, left hemisphere, RH, right hemisphere.

STUDY 2

ALLOSTATIC LOAD AND DISORDERED WHITE MATTER MICROSTRUCTURE IN OVERWEIGHT ADULTS

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Abstract

Overweight and stress are both related to brain structural abnormalities. The allostatic load model states that frequent disruption of homeostasis is inherently linked to oxidative stress and inflammatory responses that in turn can damage the brain. However, the effects of the allostatic load on the central nervous system remain largely unknown. The current study aimed to assess the relationship between the allostatic load and the composition of whole-brain white matter tracts in overweight subjects. Additionally, we have also tested for grey matter changes regarding allostatic load increase. Thirty-one overweight-to-obese adults and 21 lean controls participated in the study. Our results showed that overweight participants presented higher allostatic load indexes. Such increases correlated with lower fractional anisotropy in the inferior fronto-occipital fasciculi and the right anterior corona radiata, as well as with grey matter reductions in the left precentral gyrus, the left lateral occipital gyrus, and the right pars opercularis. These results suggest that an otherwise healthy overweight status is linked to long-term biological changes potentially harmful to the brain.

1. Introduction

Overweight (body mass index [BMI] ≥ 25 kg/m^2) is the result of sustained caloric surplus (Berthoud & Morrison, 2008). Anabolic (i.e., insulin) and catabolic signals (i.e., catecholamines, cortisol, and leptin) regulate energy reserves storage and expenditure via thermogenesis and lipolysis (Reilly & Saltiel, 2017). The abnormal accumulation of adipocytes during weight-gain promotes the release of pro-inflammatory cytokines and increases the permeability of the blood-brain barrier (BBB) and the gastrointestinal tract, exposing the brain to harmful bacterial endotoxins and another inflammatory by products (Guillemot-Legris & Muccioli, 2017). Ultimately, this can trigger physiological stress responses and disturb homeostasis through engaging the hypothalamic-pituitary-adrenal (HPA) axis (Foss & Dyrstad, 2011). Hence, overweight can precipitate long-term modifications in neuroendocrine and metabolic systems that subsequently hinder weight loss and may damage the brain. Cortical and subcortical structures are vulnerable to the effects of chronic stress (Arnsten, 2009; Bruce S McEwen, Nasca, & Gray, 2016). Alterations in cortical top-down regulating areas (e.g., prefrontal cortex) and subcortical bottom-up processing regions (e.g., hypothalamus, basal ganglia, and amygdala) have been proposed as an underlying mechanism in both stress (Arnsten, 2009) and overeating (Groppe & Elsner, 2015).

Stress is necessary for survival as it mobilises energy reserves (i.e., catabolic responses) to prepare us to overcome a threatening situation. Allostasis is the natural process whereby biological systems are pushed to their maximum capacity to guarantee fight-or-flight responses. However, frequent disruption of homeostasis can lead to a situation of allostatic load (AL). The AL is the 'wear and tear' of the body, and it has been associated with numerous comorbidities such as hypertension, type II diabetes, and dyslipidaemia (Juster, McEwen, & Lupien, 2010; B.S. McEwen & Stellar, 1993). Like chronic stress, the AL might jeopardise the integrity of the brain tissue by up-regulating cortisol and inflammatory cytokines release (Calcia

et al., 2016; Jauregui-Huerta et al., 2010; Bruce S McEwen et al., 2016). Nevertheless, only a few studies to date have assessed the relationship between AL and brain integrity (Booth et al., 2015; Chiappelli et al., 2017; Cole et al., 2017; Ottino-González et al., 2017; Savransky et al., 2017). Along with these works, this issue is similarly covered in chronic psychological stress or single stress biomarkers studies (e.g., cortisol, systolic arterial pressure). Likewise, chronic stress has also been proposed as a risk factor for obesity, as it plays an important role in feeding behaviour and body weight regulation. Cortisol enhances the desire for highly palatable food as a mechanism to restore the energy reserves consumed in surviving challenging contexts (Jackson, Kirschbaum, & Steptoe, 2017). Likewise, sustained discharge of stress hormones can also hinder weight control by affecting metabolic-related signalling (i.e., insulin and leptin resistance) responsible for thermogenesis and lipolysis processes (Sinha & Jastreboff, 2013; Sominsky & Spencer, 2014).

Diffusion tensor imaging (DTI) is a non-invasive neuroimaging technique that measures, in vivo, the displacement of water molecules in the brain (Basser, Mattiello, & Lebihan, 1994). Tract-based spatial statistics (TBSS) is the method of choice for assessing the microstructure of white matter (WM) tracts (Bach et al., 2014). The most widely used WM scalar in TBSS is fractional anisotropy (FA), which measures the orientation dependence (from 0 to 1) the water movement. If the tract is undamaged and well myelinated, motion along the fibre is faster than perpendicular to the fibre, returning higher FA values. However, decreased FA values are not specific to underlying pathological processes. In this vein, recent advances in DTI eliminate the effect of extracellular water content from surrounding brain tissue. This correction helps in discriminating processes that affect tissue, such as axonal degeneration, of processes that disturb the extracellular space, such as neuroinflammation (Pasternak et al., 2012).

Obesity and TBSS studies have generally described inverse associations between waist circumference (WC) or BMI and FA in tracts involved in reward-seeking (e.g., inferior fronto-occipital fasciculus, corpus callosum, and corticospinal tract) and cognitive control (e.g., inferior and superior

longitudinal fasciculus) (Kullmann, Schweizer, Veit, Fritsche, & Preissl, 2015; Kullmann et al., 2016; Papageorgiou et al., 2017). Although contradictory findings do exist (Birdsill et al., 2017), most indicate that the higher the BMI or WC, the lower the FA (Ou, Andres, Pivik, Cleves, & Badger, 2015; Repple et al., 2018; Ryan & Walther, 2014; Stanek et al., 2010; R. Zhang et al., 2018). In addition, studies on physiological markers of stress have found reductions in global and regional FA values (Nugent et al., 2015; Sheikh et al., 2014; Van Der Werff et al., 2014) linked to higher cortisol levels. Two other studies have reported negative associations between FA and cholesterol (Cohen, Cazettes, & Convit, 2011) or high blood pressure (Maillard et al., 2012). Gianaros et al. (2013) found that the relationship between low FA values and low socioeconomic status was exacerbated not only by high levels of C-reactive protein but also by augmented adiposity. A decrease in this peripheral inflammatory was associated with higher FA values in a community-dwelling sample of older adults (Bettcher et al., 2015). Aerobic fitness improves oxygen delivery to the brain, which promotes the expression of neurotrophic factors crucial in helping astrocytes to deal with the damaging outcomes of sustained stress and inflammatory responses. Overweight children (Schaeffer et al., 2014) and older adults (Voss et al., 2013) presented higher FA values after participating in a physical exercise routine. Thus, these findings suggest that the cerebral WM has plastic properties: WM exhibits variations after recovering from chronic inflammatory states or engaging in healthy activities.

As mentioned above, an increase in AL (or chronic physiological stress) is related to an excessive engagement of the HPA axis, which can induce changes in food intake and fat storage (Jackson et al., 2017; Sinha & Jastreboff, 2013; Sominsky & Spencer, 2014). Similarly, adipose-induced inflammation can activate the HPA axis by liberating pro-inflammatory cytokines (Guillemot-Legris & Muccioli, 2017; Reilly & Saltiel, 2017). Ultimately, an overly activated HPA axis may lead to adverse neurological outcomes, such as oxidative stress, decreased neurogenesis, or gliosis (Calcia et al., 2016; Jauregui-Huerta et al., 2010; Bruce S McEwen et al., 2016). According to the AL model, overweight subjects could be enduring higher levels of stress compared to healthy weight participants. This could be detrimental

to the brain as overweight is intrinsically linked to an excessively stimulated HPA axis and inflammatory responses. We explored this relationship in a previous study by conducting a cortical thickness analysis (Ottino-González et al., 2017). Overweight subjects presented higher AL indexes than lean participants did. Moreover, the increase in AL in both groups was correlated with cortical changes of regions involved in regulating behaviour, reward-processing, and controlling general cognitive function. Here we extend these findings on neuroanatomical differences and focus on microstructural white matter changes. Specifically, the present study is aimed at examining the relationship between AL and the composition of white matter tracts in participants with overweight and obesity. Several studies have correlated adiposity and physiological stress to changes in the microstructure of tracts involved in reward-processing and cognitive performance. Additionally, we have complemented this principal analysis testing for variations in cortical grey matter (GM) morphology (i.e., volume). We expect to find augmented levels of AL in overweight subjects, as well as changes in the WM/GM composition regarding such increase.

2. Methods

2.1. Subjects

One hundred and twenty-four participants were recruited from public primary care centres belonging to the Consorci Sanitari de Terrassa. Inclusion criteria were (1) being older than 20 years old and (2) having a BMI higher than 18.5 kg/m^2. Following the World's Health Organization criteria (World Health Organization, 2016), the overweight group was formed based on a BMI equal to or higher than 25 kg/m^2. All volunteers underwent a blood extraction in fasting condition (between 8:00 and 8:30 AM), a medical examination, a comprehensive neuropsychological evaluation, and a magnetic resonance imaging (MRI) acquisition of the head. None of the participants presented comorbidities such as neurological, psychiatric (including addictive or eating disorders), cardiometabolic (including metabolic syndrome, criteria fully described in Appendix A1), developmental or motor-sensorial disorders. The

presence of addictive disorders was evaluated by means of the Structured Clinical Interview for DSM-IV (SCID-I). Eating disorders were assessed using the Bulimia Inventory Test of Edinburgh (BITE, exclusion criteria were set for scores > 20) (Henderson & Freeman, 1987). Anxiety or depression symptoms were explored using the Hospital Anxiety and Depression Scale (HADS, exclusion cut-off score set at ≥ 11) (Herrero et al., 2003; Zigmond & Snaith, 1983). Additionally, we ruled out participants because of acute-infection suspicion (i.e., C-reactive protein levels > 10mg/L). Moreover, we estimated the intelligence quotient (IQ) using the WAIS-III (Wechsler, 1999) vocabulary subtest, excluding participants with scores lower than 7 (i.e., IQ estimated below 85). Finally, we also excluded participants whose MRI report (done by an expert neuroradiologist) indicated the presence of WM hyperintensities. Thirty-four subjects (20 overweight and 14 lean participants) declined to undergo the MRI acquisition by pleading claustrophobia or incompatibilities with the magnetic field. Besides, thirty-eight participants met exclusion criteria (19 overweight and 8 lean subjects), presented artefacts during the diffusion-weighted sequence (3 overweight and 7 lean participants), and/or WM hyperintensities (2 overweight participants and 1 lean subject). Thirty-one overweight and 21 lean controls formed the final sample. Fifty participants (29 overweight-to-obese and 21 healthy weight controls) of this final sample were included from a previous study (Ottino-González et al., 2017).

The study has been conducted following the Helsinki Declaration and has been approved by the University of Barcelona's Institutional Ethics Committee (CBUB) and the Institutional Review Board (IRB 00003099, assurance No.: FWA00004225; http://www.ub.edu/recerca/comissiobioetica.htm). All methods were performed in accordance with the relevant guidelines and regulations. All participants signed written informed consent before entering the study.

2.2. Allostatic Load Index

Fifteen stress biomarkers were used as in previous studies (Booth et al., 2015; Chiappelli et al., 2017; Cole et al., 2017; Ottino-González et al., 2017;

Savransky et al., 2017). Leptin was additionally selected as a biomarker since it can induce the release of pro-inflammatory cytokines (Abella et al., 2017). Cut-off scores were based on a larger healthy lean population (N=43) from previous studies (see characteristics in Appendix A2). Different cut-off scores were set in those biomarkers that presented differences ($p < 0.05$) regarding sex (e.g., systolic arterial pressure). Participants who fell into the high-risk biomarker percentile (i.e., 75th or 25th, in the case of HDL-cholesterol) were coded with a score of "1". The AL index was the sum of all 15 dichotomous scores (range 0-15). Higher values on this index indicate a greater AL. Participants with missing values had their AL indexes prorated by the number of available biomarkers. The list of biomarkers and their cut-off scores are presented in Table 3.

TABLE 3 | Allostatic load cut-off scores for individual biomarkers.

Biomarker	Male	Female	Both
Systolic arterial tension (mm Hg)	124.50	116.50	–
Diastolic arterial tension (mm Hg)	–	–	73
Glycated hemoglobin (%)	–	–	5.40
Glucose (mmol/L)	5.06	4.69	–
Creatinine (µmol/L)	90	70.25	–
Cholesterol (mmol/L)	4.21	4.88	–
HDL (mmol/L)	–	–	1.34
LDL (mmol/L)	–	–	3
Triglycerides (mmol/L)	–	–	0.86
C-reactive protein (mg/L)	–	–	0.93
Interleukin-6 (pg/mL)	–	–	1.65
Insulin (pmol/L)	–	–	52.02
Cortisol (nmol/L)	–	–	659.90
Fibrinogen (g/L)	3.07	3.32	–
Leptin (ng/mL)	4.80	20.30	–

mm Hg, millimeters of mercury; cm, centimeters; mmol/L, millimoles per liter; µmol/L, micromoles per liter; mg/L, milligrams per liter; pg/mL, picograms per milliliter; nmol/l, nanomoles per liter; g/L, grams per liter; ng/mL, nanograms per milliliter.

2.3. Other variables of interest

Sociodemographic (i.e., age, years of education, sex, professional level, and total income), psychological (i.e., IQ estimation, subjective anxiety, and depressive symptoms), and other behavioural variables (i.e., tobacco

smoking or non-pathological alcohol drinking) were analysed using IBM SPSS Statistics (v.23.0).

2.4. Magnetic-resonance imaging acquisition

Overweight (N=31) and lean (N=21) participants underwent MRI on a 3T MAGNETOM Trio (Siemens, Germany), performed at the Institut d'Investigacions Biomédiques August Pi I Sunyer (IDIBAPS) at the Hospital Clínic in Barcelona. The diffusion-weighted images (DWI) were acquired with the following parameters: repetition time (TR) = 7,700 ms, echo time (TE) = 89 ms, acquisition matrix = 122 x 122, 2 mm isotropic voxel, field of view (FOV) = 244 x 244 mm^2, diffusion directions = 30, slice thickness = 2 mm, gap distance = 0.6 mm, number of slices = 60, b-values = 0 and 1,000 s/mm^2, IPAT factor = 2, total scan time = 4:23 minutes. A T1-weighted MPRAGE 3D sequence was acquired as well for registration, EPI distortion correction, and cortical GM morphometry analysis using the following parameters: TR = 2300 ms, TE = 2.98 ms, inversion time = 900 ms, 240 slices, FOV = 256 mm x 256 mm^2, 1 mm isotropic voxel.

2.5. Diffusion-tensor imaging processing

All image processing was carried out using the FMRIB Software Library (FSL) v.5.0.10 (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FSL) and the BrainSuite (BS) software v.16a1 (http://brainsuite.org/). First, we visually inspected all DWI sequences to exclude subjects presenting artefacts (N=10). Second, images were skull-stripped and corrected for head motion and eddy currents. Parallel skull stripping and bias-field correction (FAST) were applied to the T1-weighted images. Geometrical distortions (i.e., EPI distortions) of DWI sequences were solved by using a constrained non-rigid registration to each participants' T1-weighted image (Bhushan et al., 2012), which is a default step from the BS Diffusion Pipeline. BS also rotates the gradients after this registration to optimise tensor fitting in subsequent steps. The diffusion tensor was fitted to each voxel to generate the FA maps with a linear weighted least squares model to appropriate scale data variances (Jones et

al., 2013). The most representative FA map was selected, and each subject was projected onto this study-specific template to overcome anatomical misalignments (Bach et al., 2014). The mean FA skeleton has been generated based on each participants' FA values with a threshold of > 0.2. Since FA is very unspecific to the source driving the changes in microstructure, we tested other complementary diffusivity scalars. The MD is the average of all eigenvalues with higher values meaning exacerbated cell permeability, presumably due to oedema or necrosis. The AD and RD reflect parallel and perpendicular diffusion, respectively. Lower AD values tend to be present in contexts of axonal damage, while higher RD values could indicate poor myelination (Alexander et al., 2011). MD, AD, and RD were also projected onto the mean FA skeleton for complementary analysis. Additionally, FW may alter DTI metrics, and its elimination showed an improvement in tract-reconstruction, tissue segmentation, and characterisation of underlying pathological disturbances (Pasternak et al., 2012; Pasternak, Sochen, Gur, Intrator, & Assaf, 2009). Hence, a bi-tensor model was fitted with the algorithm developed by Pasternak et al. (2009). Corrected FA maps were projected into the normalised FA skeleton for further post-hoc analysis.

2.6. Tract-based spatial statistics

Statistical analyses were performed with non-parametric permutation-based tests (10,000 iterations) correcting all results for multiple comparisons using an FWE procedure and a threshold-free cluster enhancement. Statistical significance was set at FWE corrected p-value < 0.05. Age and sex were selected as nuisance factors in all analyses. Moreover, as we aimed to explore the relationship between AL and WM composition isolated from abdominal obesity, we have regressed out its effects as in previous works. The WtHR was included in the principal model as an additional nuisance factor. This measure has proved to reflect better than BMI and WC the amount of visceral adipose tissue and its adverse outcomes (i.e., cardiovascular risk) (Ashwell & Gibson, 2016; Swainson et al., 2017). First, we extracted the average diffusivity values for the skeletonised maps and test for differences between groups controlling for age, sex, and AL. Second, we conducted a whole-brain voxel-

wise analysis to test for regional differences in diffusivity metrics between groups (nuisance factors: age, sex, and AL). Third, whole-brain correlation analysis with the AL index as the independent variable was conducted, first in the entire group (N=52) and then between groups (nuisance factors: age, sex, and WtHR). Fourth, clusters showing a significant relationship with the AL index were fed into a post-hoc analysis in FSL randomise (family-wise error corrected at $p < 0.05$, 10,000 permutations) with the FW corrected maps. We extracted the average diffusivity scores within each significant cluster to plot them against the AL index. We calculated the magnitude (i.e., Pearson's coefficient) of this relationship for visual purposes only using the FA standardised residual to control the effects of age, sex and WtHR. Note that we did not report the *p*-values of this correlation as its statistical significance has been already covered in the principal analysis. Since the skeletonised maps are a one-voxel-thick image, significant results were thickened 3 mm to ease their visualisation. The White-Matter Tractography Atlas and the ICBM DTI-81 White-Matter Labels, both from the John Hopkins University, were used to label each cluster according to their peak and extension. We additionally controlled the effects of tobacco smoking and non-pathological alcohol drinking, considering this as a complementary analysis due to the high risk of overfitting given our small sample size. Moreover, as the AL and the abdominal obesity increase are intrinsically related, we ran the same analysis only regressing out the effects of age and sex. The results of these two analyses are available with more detail in the SI section.

2.7. Grey matter morphometry analysis

Parallel to the principal analysis on TBSS, we have also tested for cortical GM volume (mm^3) changes in FreeSurfer v.6.0 (https://surfer.nmr.mgh.harvard.edu) with a surface-based approach. Surface-based morphometry (SBM) allows a better characterisation of the GM tissue as it considers the complicated topology of the cortical surface (i.e., gyri, sulci). Traditional voxel-based morphometry (VBM) approaches are limited in considering the intricate composition of a highly folded structure such as the human brain cortex is. VBM uses a probabilistic tissue segmentation approach where each

voxel is classified correspondingly to the proportion of contained tissue (i.e., GM, WM, and CSF). In contrast, SBM reconstructs the cortical surface using the boundaries of GM and WM layers in a convoluted triangulated mesh. Thus, T1-weighted images have been processed following this approach using the cortical reconstruction pipeline in FreeSurfer. Briefly, this process includes motion and intensity correction, removal of the skull and soft tissue, normalisation, segmentation, parcellation, and smoothing (Reuter, Rosas, & Fischl, 2010; Ségonne et al., 2004; Sled, Zijdenbos, & Evans, 1998). We have followed the same model as in the principal analysis in TBSS, where the AL index was the variable of interest and sex, age, and WtHR were selected as nuisance factors. The SBM analysis was performed with the Query, Design, Estimate, Contrast (Qdec) tool implemented in FreeSurfer. The surface was smoothed using a circularly symmetric Gaussian kernel with a full-width at half-maximum smoothing of 15mm. We have also controlled for multiple comparisons using a Monte-Carlo null-Z Simulation (10,000 repetitions) with a cluster-wise correction. Cortical structures were named after the Desikan's atlas (Desikan et al., 2006), and cluster coordinates were reported accordingly to MNI space. We calculated the mean GM volume (mm^3) of significant clusters and controlled the effects of age, sex, and WtHR to plot them against the AL index. Again, the reported Pearson's coefficients were only to facilitate visual interpretation.

3. Results

Overweight and healthy-weight controls differed ($p < 0.001$) for all anthropometric measures (i.e., BMI, WC, and waist-to-height ratio [WtHR]) and the AL index. There were no statistical differences in the remaining sociodemographic, psychological and behavioural variables (Table 1).

TABLE 1 | Overweight and I lean participant's variables of interest.

	Overweight (N = 31)		Lean (N = 21)	
	Mean (SD)	Range	Mean (SD)	Range
Age	31.12 (5.88)	21–40	29.95 (6.02)	21–39
Years education	13.58 (2.94)	9–20	14.48 (2.18)	10–18
IQ estimation	11.90 (2.21)	8–17	12.05 (1.86)	7–15
Gender (F/M)	19/12		11/10	
Smoker (yes/no)	8/23		5/16	
Drinker (yes/no)	14/17		13/8	
HADS anxiety	4.45 (2.78)	0–10	4.43 (2.52)	0–10
HADS depression	2.16 (2.19)	0–7	1.48 (1.60)	0–5
BMI (kg/m^2)*	30.75 (4.86)	25.20–49.69	22.35 (2.01)	19.00–24.99
WC (cm)*	96.97 (12.61)	82–137	78.56 (6.86)	68–92
WTHR*	0.58 (0.07)	0.46–0.80	0.46 (0.03)	0.40–0.50
AL Index*	6.64 (2.51)	3–11	3.38 (2.01)	0–7
FAMILY INCOME IN EUROS PER MONTH (FREQUENCY)				
300–899	0		0	
900–1,499	5		4	
1,500–2,099	14		6	
2,100–2,699	6		3	
>2,700	5		7	
Don't know / Don't answer	1		1	
PROFESSIONAL LEVEL (FREQUENCY)				
Non-skilled	4		1	
Skilled manual	9		4	
Administrative	6		5	
Intermediate	4		5	
Professional	5		3	
Don't know / Don't answer	3		3	

*$p < 0.05$, IQ estimation, Intelligence Quotient estimation (WAIS-III); F, female; M, male; BMI, body mass index (kg/m^2); WC, waist circumference (cm); WTHR, waist-to-height ratio (WC/height in centimetres), HADS, Hospital Anxiety and Depression Scale; SD, Standard deviation.

The whole-brain comparisons between groups did not show differences between groups in any diffusivity scalar. Groups did not differ for the skeletonised maps either (see Appendix B1 in the Supplementary Information section). The overweight group showed negative correlations (family-wise error corrected $p < 0.05$) between FA values and the AL index in three clusters with their maximum intensity peaks located in the left inferior fronto-occipital fasciculus (IFOF) (X = -21, Y = -85, Z = 5, size = 473 voxels, *p*-corrected = 0.041), the right IFOF (X = 29, Y = -66, Z = 15, size = 349 voxels, *p*-corrected = 0.043), and the right anterior corona radiata (ACR) (X = 18, Y = 21, Z = 34, size = 342 voxels, *p*-corrected = 0.045). This group also showed a trend towards positive correlations ($p = 0.09$) between the AL index and the radial diffusivity (RD) and the mean diffusivity (MD) in clusters located in the right superior corona radiata and the body of the corpus callosum, respectively. There were no associations between the AL index and axial diffusivity (AD). Conversely, the lean group did not show either positive or negative correlations with any DTI metric. Cluster size, MNI coordinates, and extension of the FA results are available in Table 2.

TABLE 2 | Whole-brain correlations results in the overweight group.

Peak	Voxels	MNI coordinates			Cluster extension	FWE peak p-value
		X	Y	Z		
L IFOF	473	-21	-85	5	L anterior thalamic radiation, L cingulum (hippocampus), forceps major, L inferior fronto-occipital fasciculus, L inferior longitudinal fasciculus, L superior longitudinal fasciculus, L superior longitudinal fasciculus (temporal part)	0.041
R IFOF	349	29	-66	15	R anterior thalamic radiation, R cingulum (hippocampus) forceps major, R inferior fronto-occipital fasciculus, R inferior longitudinal fasciculus and R superior longitudinal fasciculus	0.043
R ACR	342	18	21	34	R anterior thalamic radiation, R cingulum (cingulate gyrus), forceps minor, R inferior fronto-occipital fasciculus, R superior longitudinal fasciculus and R superior longitudinal fasciculus (temporal part).	0.045

MNI, Montreal Neurological Institute, FWE, family-wise error, FA, fractional anisotropy, L IFOF, left inferior fronto-occipital fasciculus, R IFOF, right inferior fronto-occipital fasciculus, R ACR, right anterior corona radiata.

Figure 1 shows the cluster extension and the magnitude of the relationship between FA and AL index in the overweight group, depicted in a T1-weighted MNI template.

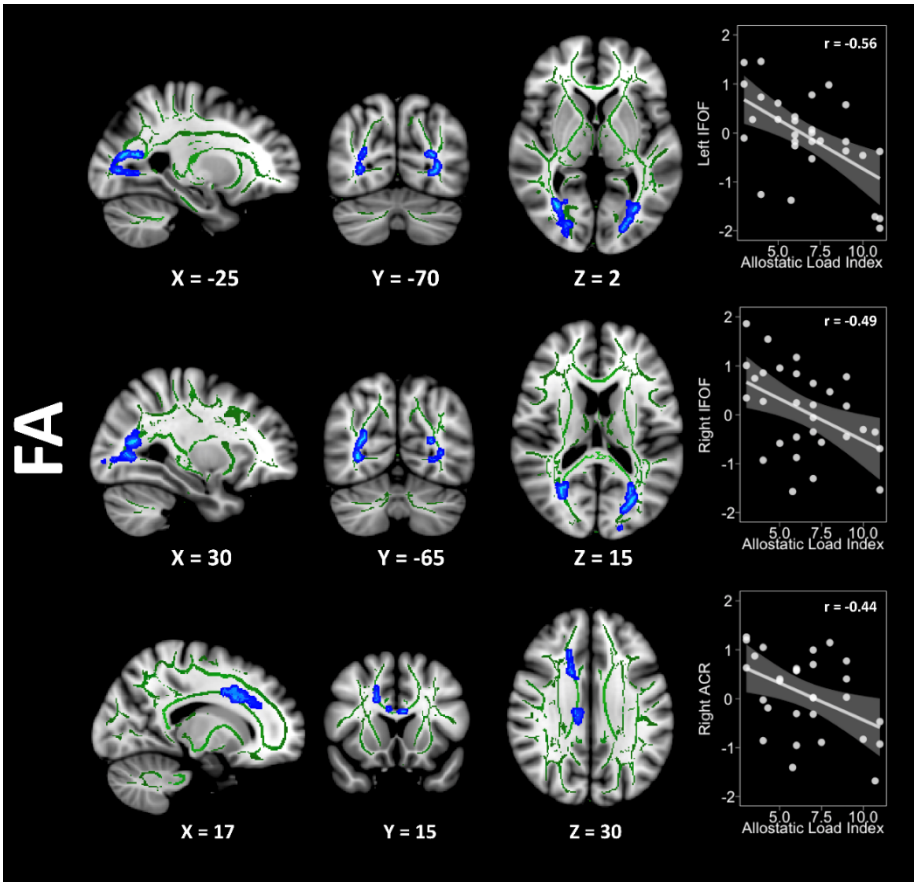


FIGURE 1 | Decreasing FA values regarding the AL index increase are represented in blue. The Y-axis in the scatterplots depicts the standardised residual (regressors: age, sex, and WtHR) of the FA average score within the cluster. The X-axis represents the AL index scores. Please note that correlation coefficients only intend to complement scatterplots visualisation. FA, fractional anisotropy, WtHR, waist-to-height ratio, IFOF, inferior fronto-occipital fasciculus, ACR, anterior corona radiata.

In an attempt to better characterise the pathological source behind this FA decrease, we conducted a *post-hoc* analysis with free-water (FW) corrected FA images in these clusters. Although significant, the results were less extended than the original ones (left IFOF size = 331 voxels, right IFOF size = 80 voxels, and right ACR size = 192 voxels). The comparison between uncorrected and corrected results is presented in Figure 2.

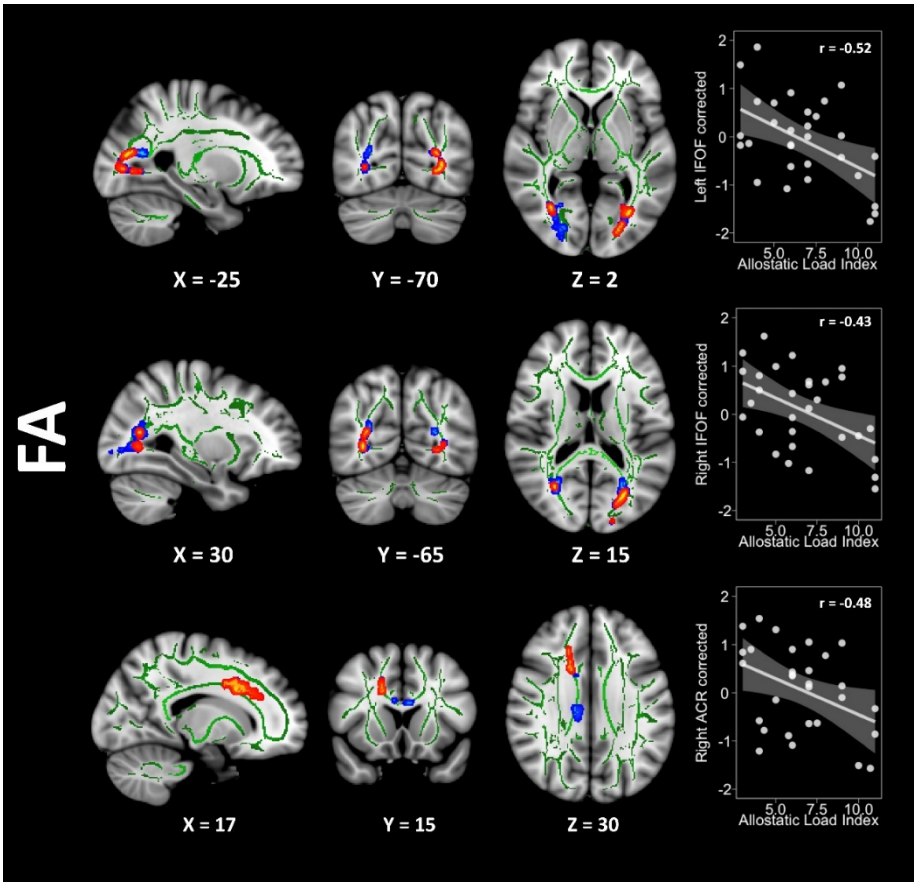


FIGURE 2 | Overlapping results derived from the uncorrected (blue) and corrected (red) FA maps. The Y-axis in the scatterplots depicts the standardised residual (regressors: age, sex, and WtHR) of the FA average score within the cluster. The X-axis represents the AL index scores. Please note that correlation coefficients only intend to complement scatterplots visualisation. FA, fractional anisotropy, WtHR, waist-to-height ratio, IFOF, inferior fronto-occipital fasciculus, ACR, anterior corona radiata.

On another note, the FA results from the principal analysis vaguely extended to the corpus callosum after additionally controlling for tobacco smoking and non-pathological alcohol usage. In addition, FA results (as well as RD) were substantially more extensive when only controlling for age and sex, presumably because overweight subjects with low AL but high WtHR may not have driven the principal analysis results. However, since the aim of the study was to address the isolated relationship between AL and WM composition, we only discuss in depth the results of the principal analysis, leaving these available in the SI section (Appendix B2, C1, C2, D1). Moreover,

overweight subjects showed volume reductions (cluster-wise corrected $p < 0.05$) regarding AL index increase in three clusters with their peak of maximum intensity in the left precentral gyrus (X= -60, Y= 2, Z= 14, size= 1756.31 mm^2 , Z = -2.20, p-corrected= 0.028), the left lateral occipital gyrus (X= -29, Y= -92, Z= -4, size= 1909.3 mm^2, Z = -3.03, p-corrected= 0.015), and the right pars opercularis (X= 53, Y= 14, Z= 5, size= 2057.64 mm^2, Z = -2.58, p-corrected= 0.010). Lean subjects did not show relationships between volume and AL index. Results of this analysis are shown in Figure 3.

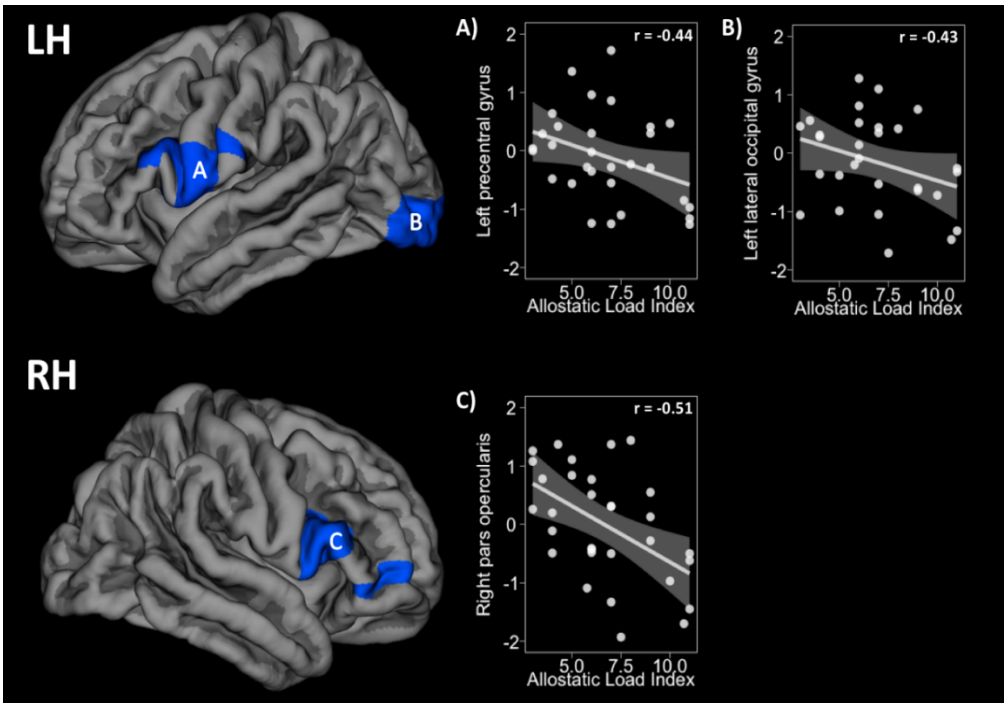


FIGURE 3 | The first row shows the density reductions in the left hemisphere regarding AL increase in (A) the left precentral gyrus and (B) the left lateral occipital pole. The second row shows reductions in the (C) right pars opercularis. The Y-axis in the scatterplots depicts the standardised residual (regressors: age, sex, and WtHR) of the FA average score within the cluster. The X-axis represents the AL index scores. Please note that correlation coefficients only intend to complement scatterplots visualisation. LH, left hemisphere, RH, right hemisphere, WtHR, waist-to-height ratio.

4. Discussion

In the present study, we examined the harmful effects that the relationship between chronic physiological stress (i.e., AL) and excess of weight might have on the brain. Here, we compared the microstructure of whole-brain WM tracts in relation to an AL index increase in two matched groups who only differed in anthropometric measures (i.e., BMI, WC, and WtHR) and did not present any cardiometabolic diagnosis (e.g., metabolic syndrome, type II diabetes). We found that overweight subjects presented higher AL indexes than lean controls. Our findings also showed that, regardless of the confounding effects of abdominal obesity (i.e., WtHR), the AL increase among the overweight participants was linked to an altered WM microstructure, as well as to changes in GM morphology.

We showed alterations in the WM composition regarding higher AL indexes in overweight subjects in the bilateral IFOF and the right ACR. Although the maximum peak of intensity was slightly asymmetrical between the right (Y= -66) and left (Y= -85) IFOF, the extension of both clusters comprised the same tracts. All three clusters extended to several projecting (i.e., corticospinal tract, anterior thalamic radiation, and corona radiata), commissural (i.e., forceps minor/major and corpus callosum), and associative tracts (i.e., cingulum and inferior/superior longitudinal fasciculi). Some of these tracts have also been described to be affected in overweight-to-obese subjects (Koch et al., 2014; Stephanie Kullmann et al., 2016; Ou et al., 2015; Papageorgiou et al., 2017; Ryan & Walther, 2014; Stanek et al., 2010) and chronic stress studies (Cohen et al., 2011; Gianaros et al., 2013; Maillard et al., 2012; Nugent et al., 2015; Sheikh et al., 2014; Van Der Werff et al., 2014). Even though a probabilistic tractography analysis would shed more light about this, these fibres anatomically connect mid-brain and superior cortical regions related to reward-seeking and supervising goal-directed behaviours (Kullmann et al., 2015; Stephanie Kullmann et al., 2016; Papageorgiou et al., 2017). Alterations in reward-seeking have been described in overweight (Papageorgiou et al., 2017) and stress (Starcke & Brand, 2016) studies. A study from our group has also described an abnormal configuration of the reward-processing network (Marqués-Iturria et al., 2015). In this study,

obese participants also showed a disturbed composition (i.e., low FA) in tracts ascribed to such network (i.e., striatum, accumbens, and orbitofrontal cortex). Similarly, impairments in executive functions, such as inhibitory control and working memory, have previously been found in pathological caloric intake (Higgs, 2015) and stress (Sandi, 2013). Hypothetically, not being able of suppressing urgent drives (i.e., inhibitory control) or failing in predicting short-term consequences correctly (i.e., working memory) could lead to poor dietary choices and eating beyond caloric needs. Alarcón and colleagues (2016) have recently demonstrated that both left inferior-longitudinal fasciculus and left superior longitudinal fasciculus were inversely correlated to BMI, a relationship that mediated working memory performance (Alarcón, Ray, & Nagel, 2016).

The less anisotropic diffusivity found in overweight volunteers linked to the AL increase may suggest underlying pathologies such as neuroinflammation, axonal degeneration, and/or structural remodelling (Calcia et al., 2016; Jauregui-Huerta et al., 2010; Kim, Kim, & Won, 2017; Lundgaard, Osório, Kress, Sanggaard, & Nedergaard, 2014; Qiu et al., 2014; Zatorre, Fields, & Johansen-Berg, 2012). To clarify this issue, we controlled for the contribution of FW within the clusters that emerged as statistically significant from the principal analysis. Microglia and astrocytes initiate inflammatory responses by prompting osmosis-inducing chemicals. This augments extracellular water content and subsequently affect water movement in adjacent functional tissue (Streit, 2006). Yet axonal degeneration can be a process independent of extracellular water contamination, chronic inflammation can also affect oligodendrocytes and myelin sheaths, and therefore, escalate to long-term axonal degeneration (Jauregui-Huerta et al., 2010; Streit, 2006). In accordance with our hypothesis, the augmented levels of AL in overweight subjects may be linked to low-grade chronic inflammation states as well. When compared to the original results, the extension of the clusters substantially decreased (i.e., 30% in the left IFOF, 77% in the right IFOF, and 44% in the right ACR). It is immediately obvious that the right IFOF diffusivity was very influenced by the presence of interstitial water content, as 269 voxels vanished from this cluster after correction. Thereby, in the light of these results, and relative to normal-weight participants, overweight subjects endure higher amounts of

physiological stress and sustained inflammatory responses that could have prompted axonal degeneration on a regional level, especially in the left IFOF and right ACR.

None of the participants included in our study presented WM hyperintensities that could suggest neurological pathologies, which is often a missed factor in TBSS studies. Despite showing some advantages, this technique also presents limitations (Bach et al., 2014; Jones, Knösche, & Turner, 2013). As an example of this, misalignments in registration are a common issue in TBSS. We dealt with this by registering our subjects onto a study-specific template. Moreover, signal dropouts and geometrical, or EPI distortions, are prone to occur along the phase-encoding direction at air-tissue interfaces such as the sinus, anatomically deforming the brain and worsening subject registration and alignment (Bhushan, Haldar, Joshi, & Leahy, 2012). We overcame this by non-rigidly registering each DWI image to its corresponding T1-weighted sequence. This issue is something that the majority of TBSS studies with a single encoding-direction do not usually address, as additional sequences (e.g., field map, two-opposite acquiring directions) are mandatory. Additionally, ventricular CSF-contamination and extracellular water content may lead to underestimating DTI metrics, raising fair concerns about the nature of the results in WM studies. Though TBSS has demonstrated not been as much sensitive to ventricular CSF-contamination as other techniques (i.e., WM with voxel-based morphometry) (Bergamino, Kuplicki, Victor, Cha, & Paulus, 2017), the elimination of FW in interstitial spaces allows discriminating inflammation-related neuropathy from axonal degeneration (Bergamino, Pasternak, Farmer, Shenton, & Paul Hamilton, 2016). Thus, this correction should be well-considered as it is gaining in presence in recent TBSS studies (Guttuso et al., 2018; Kaufmann et al., 2017). We have submitted our results to this correction, which revealed a substantial contribution of extracellular water content, a surrogate of sustained inflammatory responses potentially prompting axonal degeneration.

On another note, studies tend to explore the effects of stress biomarkers separately. This kind of focus might be not accurate because when stressed, the organism works synergistically. Something similar often occurs when

testing the effects that an increase in BMI or WC has on the brain aside from any other physiological variables. In one study, the significant negative relationship between BMI and FA in the fornix and corpus callosum was lost after controlling for cardiovascular and inflammatory factors (Bettcher et al., 2013). This could suggest that the brain abnormalities described in the literature are perhaps associated not to the weight-gain as such, but rather to the joint effects of different physiological alterations (e.g., neuroendocrine, immunological, metabolic, and cardiovascular deregulations). In a recent work, we did show that normal-weight and overweight participants respectively exhibited a pattern of cortical thickening and thinning as the AL index increased, regardless of the effects of abdominal obesity (Ottino-González et al., 2017). In the current study, normal-weight and overweight subjects showed correlations in the same direction, but only overweight showed a significant relationship between the AL and WM microstructure. According to our hypothesis, overweight participants endure a more significant amount of stress and present greater body fat mass than normal-weight adults, which could explain such outcomes (e.g., obesity-induced low-grade chronic inflammation states). Likewise, the WM could also be more vulnerable to the cardiometabolic comorbidities (i.e., hypertension, hyperlipidaemia, hyperinsulinemia) linked to chronic stress and obesity (Kullmann et al., 2015; Lundgaard et al., 2014; Maillard et al., 2012).

In another vein, the overweight group showed regional cortical volume reductions in the presence of higher AL index. Concretely, changes in GM density were found in the left precentral gyrus extended to the left postcentral gyrus and the left pars opercularis. Symmetrically, a cluster in the right hemisphere involving the precentral gyrus, the pars opercularis/triangularis, the lateral orbitofrontal gyrus, and the rostral middle frontal gyrus showed a volume decrement as well. Finally, GM alterations in the left lateral occipital gyrus were also found. Frontal and dorsolateral prefrontal areas are mainly known for their role in supervising goal-directed behaviours. Alterations in prefrontal regions and impairments in executive functions have been both described in overweight (Marqués-Iturria et al., 2013; Smith, Hay, Campbell, & Trollor, 2011; Veit et al., 2014) and stress (Sandi, 2013; Savic, 2015; Zhang et al., 2016). Additionally, some of these areas (i.e., pars

opercularis and lateral orbitofrontal gyrus) are also typically known for being involved in the sensorial and hedonic integration of food properties (Kumar et al., 2016; Small et al., 2007). Although scarce or controversial, findings in occipital regions, naturally involved in visual processing and integration, are described in the literature as well (Veit et al., 2014; Willette & Kapogiannis, 2015).

These results are in line with our previous study in which overweight subjects showed a widespread pattern of cortical thinning, especially in frontal and prefrontal regions, regarding the AL index increase (Ottino-González et al., 2017). High levels of AL could induce dendritic retraction or neuronal degeneration via oxidative stress and inflammatory responses ultimately affecting the GM morphology. Conversely, lean subjects did not present positive correlations between the AL index and GM concentrations as in our prior work. Loss of participants (N = 7) in this group due to artefacts during DWI acquisition may have reduced our power to capture any statistically meaningful association. Moreover, volume is three-dimensional measure including length, height, and depth, whilst cortical thickness only considers the latter. Volume is also strongly influenced by width (i.e., surface area), being possible that normal-weight participants presenting greater cortical thickness were showing a pattern of increased cortical folding instead. On another note, there is a partial anatomical overlap between TBSS and SBM results. The IFOF structurally connect occipital areas with dorsolateral prefrontal regions such as the inferior frontal gyri. Some of these areas (i.e., left lateral occipital and pars opercularis/triangularis) volumetrically shrunk relative to higher AL indexes in overweight participants. Likewise, the ACR project fibres from mid-brain regions to superior cortical areas, in which volume reductions were also observed (i.e., precentral and postcentral gyri). Hence, though more research is needed, our results could prompt that physiological stress in otherwise healthy overweight adults is related to GM/WM alterations in anatomically interconnected areas.

The main limitation of the current study was our small sample size. DWI artefacts were present in 16% of the eligible sample, which restricted the number of participants included (e.g., twenty-one lean controls instead of

28). We also refer to the cross-sectional design as another limitation. Because of this, inferences upon causality are not feasible with this methodological approach. To this date, it is still unclear whether the increase in body fat mass is a cause or a consequence of chronic-stress (Foss & Dyrstad, 2011; Sinha & Jastreboff, 2013; Sominsky & Spencer, 2014). We encourage further works to disentangle this issue with longitudinal designs. Another limitation is that we did not include measures of early stressful life events or health behaviours like physical exercise, both known for their ability to modify WM composition (Schaeffer et al., 2014; Sheikh et al., 2014; Voss et al., 2013). Moreover, this work could benefit from multimodal neuroimaging approaches fully covering the brain changes related to physiological stress increase. Since our results are limited to skeleton-based WM microstructure, we advise cautiously considering our conclusions. Tractography could inform about whole-tract density or morphology. Moreover, either structural or functional connectivity analyses could help in drawing better assumptions relative to how the brain wired under these circumstances. We hope to cover these technique-related limitations in further works. Our study also presents methodological strengths, such as the strict criteria employed to ensure that the excess of weight was considered independently of psychiatric (e.g., binge-eating disorder), neurological (e.g., WM lesions), or medical comorbidities (e.g., metabolic syndrome). Thus, we would like to highlight that, even in a non-clinical state, a 'metabolically healthy overweight' (MHO) status is associated with alterations in neuroendocrine, immunological, metabolic, and cardiovascular systems. In a recent work, MHO subjects proved to be more at risk for cardiovascular disease than normal-weight metabolically healthy individuals (age range 18-71) (Caleyachetty et al., 2017). Hence, overweight is related to a 'wear and tear' on biological systems that can be harmful to brain structure (e.g., cortical GM volume reductions, disordered WM composition). In addition, the AL concept requires further in-depth study to facilitate its use by the scientific and medical community. Future works should test for individual effects of each altered biological system in larger samples with a scope on prevention. In the same way, identifying the most important protective factors for stress-related comorbidities would help render public healthcare more efficiently.

In conclusion, our study showed that overweight subjects presented a higher AL index when compared to healthy weight controls. Overweight participants showed an altered WM microstructure regarding AL index increase in the bilateral inferior fronto-occipital fasciculus and the right anterior corona radiata. Some of these changes suggested inflammatory-induced neuropathy. Additionally, this group also presented cortical GM volume reductions concerning AL index increment in the left precentral gyrus, the left lateral occipital gyrus, and the right pars opercularis. Our results indicate that, even in the absence of cardiometabolic comorbidities, an overweight status was related to long-term biological changes potentially harmful to the brain.

5. Acknowledgements

The authors would like to thank all the participants and collaborators who made this study possible. This work was supported by the Spanish Ministry of Economy, Industry, and Competitiveness (MINECO) grants PSI2013-48045-C2-1-P and PSI2013-48045-C2-2-P to María Angeles Jurado and Maite Garolera, respectively, and the University of Barcelona's grant ADR2015-2016 to Jonatan Ottino-González. None of the authors had any biomedical or financial interests that might potentially bias their work.

6. Author contribution

JOG, MAJ, IGG, BS, IMI, XC, CJ, OP, and MG all provided substantial contributions either to the conception and design of the study, analysis, and/or interpretation of the results. JOG, IGG, IMI, XPS, ET, and MSP participated in data acquisition (subject recruitment, medical, neuropsychological evaluation, and MRI acquisition). Additionally, all authors critically revisited the work, approved its final version for publishing, and agreed to be accountable for all aspects of such work.

7. Competing interests

The authors of this manuscript have no financial or non-financial competing interest to declare.

8. Data availability

The datasets analysed during the current study are available from the corresponding author on reasonable re-quest.

9. References

(See thesis' references)

10. Supplementary material

APPENDIX A1 | Metabolic syndrome criteria (Alberti et al., 2009). At least 3:

1. Elevated waist circumference (≥ 94 cms. for males, ≥ 80 cms. for females)
2. Elevated triglycerides (≥ 150 mg/dL)
3. Low high-density lipoprotein (HDL) (≤ 40 mg/dL in males, ≤ 50 mg/dL in females)
4. High arterial pressure (≥ 130 mm Hg systolic and/or ≥ 85 mm Hg diastolic)
5. Elevated fasting glucose (≥ 100 mg/dL)

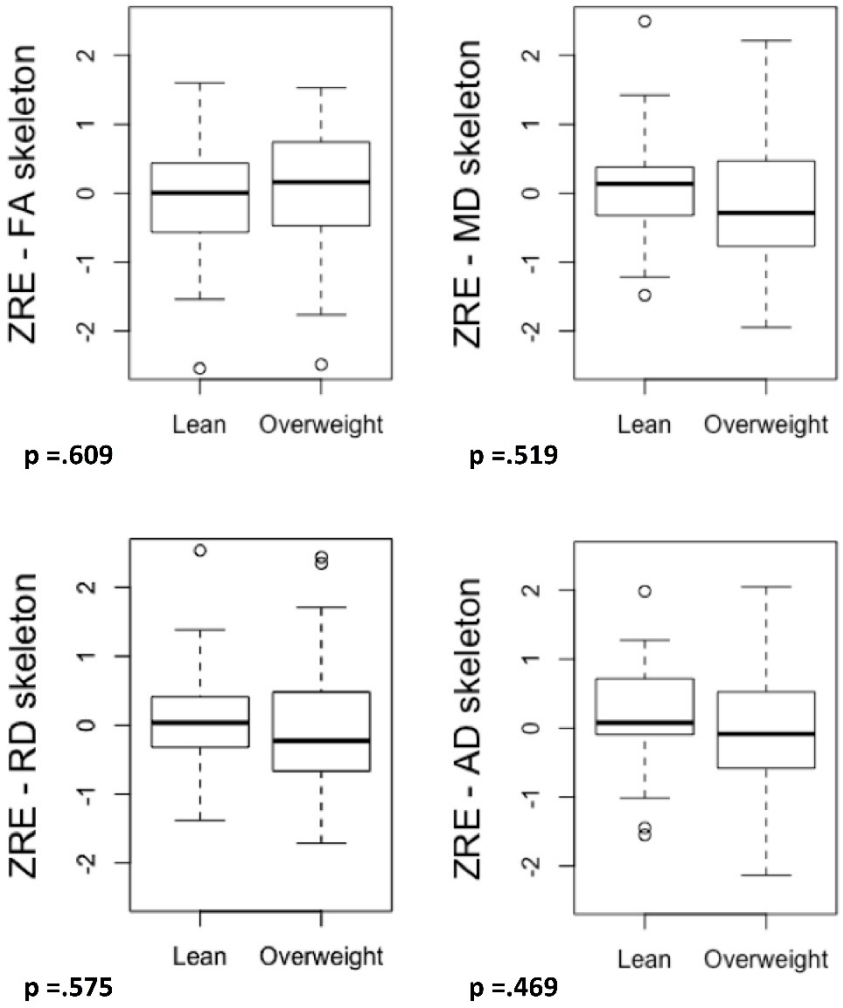
mg, milligrams, dL, decilitres, mm, millimetres, Hg, mercury

APPENDIX A2 | Characteristics of the normative group (cut-off calculation).

	Lean (N=43)	
	Mean (SD)	**Range**
Age	30.44 (6.03)	21 – 40
Years education	14.12 (2.41)	9 – 18
IQ estimation	11.50 (1.95)	7 – 15
Gender (F/M)	26 (60.5%)	
Smoker (yes/no)	9 (20.9%)	
Drinker (yes/no)	24 (55.8%)	
HADS anxiety	4.47 (2.80)	0 – 10
HADS depression	1.26 (1.60)	0 - 6
BMI (kg/m²)	21.99 (1.76)	18.59 – 24.99
WC (cm)	76.05 (6.95)	61 – 92
Family income in euros per month (frequency, %)		
300-899	1 (2.3%)	
900-1499	7 (16.3%)	
1500-2099	13 (30.2%)	
2100-2699	7 (16.3%)	
>2700	13 (30.2%)	
Do not know / do not answer	2 (4.7%)	
Professional level (frequency, %)		
Non-skilled	4 (9.30%)	
Skilled manual	5 (11.6%)	
Administrative	8 (18.6%)	
Intermediate	7 (16.3%)	
Professional	9 (20.9%)	
Do not know / do not answer	10 (23.3%)	

IQ estimation, Intelligence Quotient estimation, F, female, M, male, BMI, body mass index (kg/m²), WC, waist circumference (centimeters), HADS, Hospital Anxiety and Depression Scale, SD, standard deviation

APPENDIX B1 | ANOVA for global FA, MD, AD and RD skeleton maps.



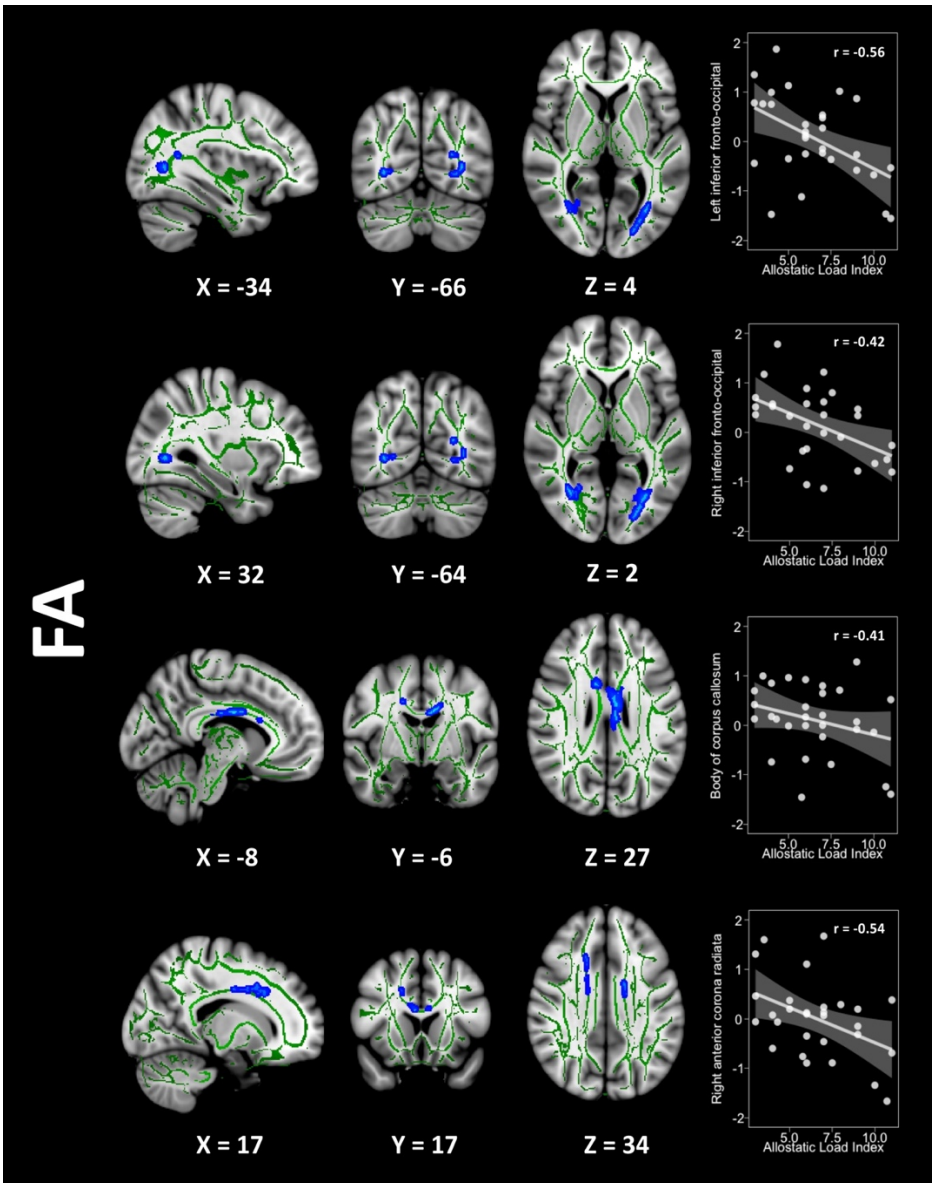
ZRE, standardised residuals (regressors: age, sex, and AL)

APPENDIX B2 | Whole-brain FA correlations in the overweight group (additionally controlling for tobacco/alcohol usage).

Peak	Voxels	MNI Coordinates			Cluster extension	FWE p-value
		X	Y	Z		
L IFOF	845	-32	-55	15	L anterior/posterior thalamic radiation, L cingulum (hippocampus), forceps major, splenium of corpus callosum, L inferior fronto-occipital fasciculus, L inferior longitudinal fasciculus, L superior longitudinal fasciculus (regular and temporal part).	0.035
R IFOF	78	31	-65	1	R anterior/posterior thalamic radiation, R cingulum (hippocampus), forceps major, R inferior fronto-occipital fasciculus, R inferior longitudinal fasciculus.	0.047
Body of CC	481	-2	11	22	R anterior thalamic radiation, R cingulum (cingulate gyrus), forceps minor, genu and body of corpus callosum, R superior longitudinal fasciculus (regular and temporal part).	0.038
R ACR	88	18	21	34	R anterior thalamic radiation, body of corpus callosum, R anterior/ superior corona radiata, R cingulum (cingulate gyrus), R superior longitudinal fasciculus (regular and temporal part).	0.048

MNI, Montreal Neurological Institute, FWE, family-wise error, L IFOF, left inferior fronto-occipital fasciculus, R IFOF, right inferior fronto-occipital fasciculus, CC, corpus callosum, R ACR, right anterior corona radiata, L, left, R, right.

APPENDIX C1 | The first four rows show in blue the location and extension of the decreasing FA values regarding the AL index increase. The Y-axis in the scatterplots depicts the average diffusivity standardised FA score within the cluster after controlling for age, sex, WtHR, tobacco, and alcohol usage. The X-axis represents the AL index scores. Please note that correlation coefficients (r) only intend to complement scatterplots visualization. FA, fractional anisotropy, WtHR, waist-to-height ratio.

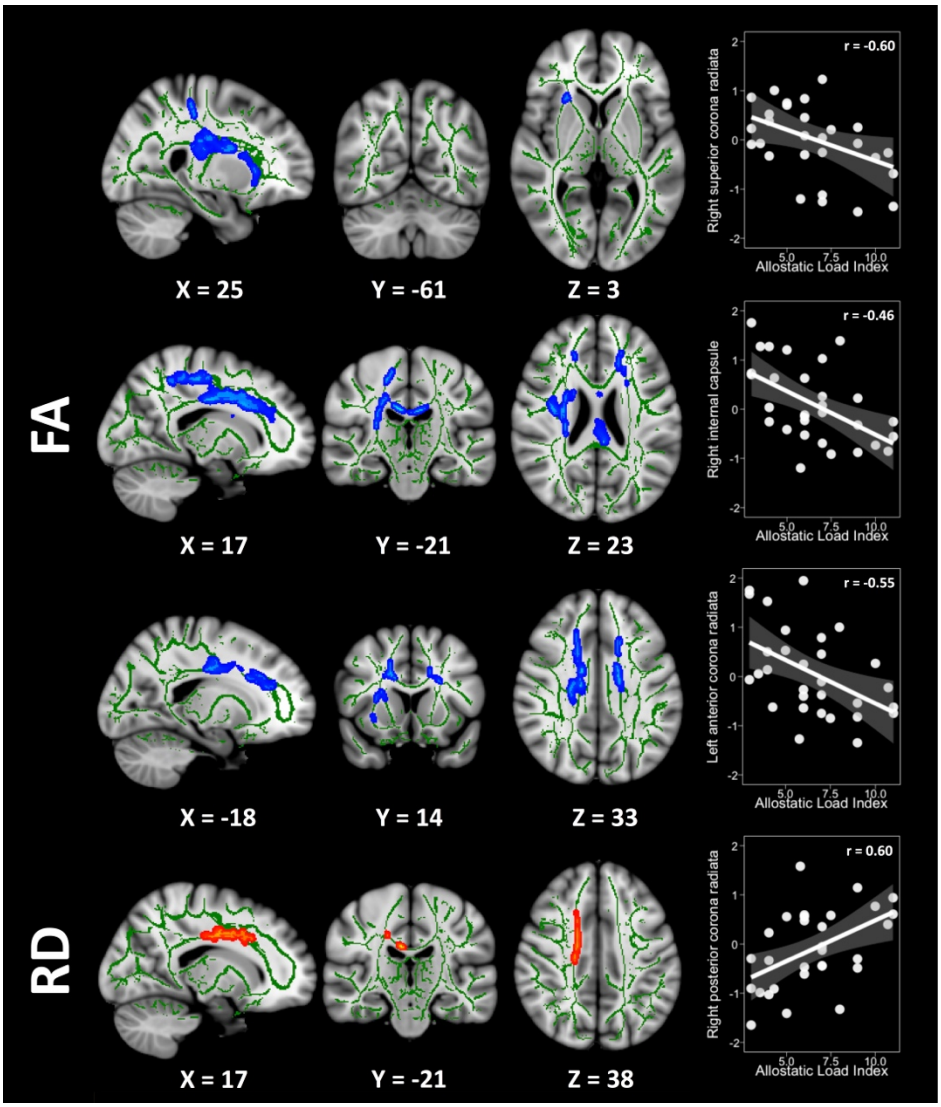


APPENDIX C2 | Whole-brain correlations in the overweight group (not controlling for WtHR).

	Peak	Voxels	MNI Coordinates			Cluster extension	FWE p-value
			X	Y	Z		
FA	**R ACR**	2812	17	15	35	Body and splenium of corpus callosum, R uncinate, R superior and inferior fronto-occipital fasciculus, R external and posterior limb of the internal capsule, R anterior, superior and posterior corona radiata, R corticospinal tract, R anterior thalamic radiation and L superior corona radiata.	0.025
FA	**R internal capsule**	55	21	12	121	R anterior limb of the internal capsule, R anterior thalamic radiation, R forceps minor, R anterior corona radiata and R inferior fronto-occipital fasciculus	0.043
FA	**L ACR**	273	-16	20	30	L anterior and superior corona radiata, L anterior thalamic radiation, L superior longitudinal fasciculus, L cingulum and L forceps minor	0.039
RD	**R ACR**	79	17	0	36	R superior and anterior corona radiata and body of corpus callosum	0.048

MNI, Montreal Neurological Institute, FWE, family-wise error, FA, fractional anisotropy, RD, radial diffusivity, R ACR, right anterior corona radiata, L ACR, left anterior corona radiata, R PCR, right posterior corona radiata, L, left, R, right

APPENDIX D1 | The first three rows show in blue the location and extension of the decreasing FA values regarding the AL index increase. The fourth row shows in red the relationship between RD and AL index. The Y-axis in the scatterplots depicts the average diffusivity standardised FA score within the cluster after controlling for age and sex. The X-axis represents the AL index scores. Please note that correlation coefficients (r) only intend to complement scatterplots visualization. FA, fractional anisotropy, RD, radial diffusivity.



STUDY 3

ALLOSTATIC LOAD AND EXECUTIVE FUNCTIONS IN OVERWEIGHT ADULTS

Psychoneuroendocrinology 2019 (in press)

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Abstract

Overweight is linked to inflammatory and neuroendocrine responses potentially prompting deregulations in biological systems harmful to the brain, particularly to the prefrontal cortex. This structure is crucial for executive performance, ultimately supervising behaviour. Thus, in the present work, we aimed to test the relationship between allostatic load increase, a surrogate of chronic physiological stress, and core executive functions, such as cognitive flexibility, inhibitory control, and working memory. Forty-seven healthy-weight and 56 overweight volunteers aged from 21 to 40 underwent medical and neuropsychological examination. Overweight subjects exhibited a greater allostatic load index than healthy-weight individuals. Moreover, the allostatic load index was negatively related to inhibitory control. When separated, the link between allostatic load index and cognitive flexibility was more marked in the overweight group. An overweight status was linked to chronic physiological stress. The inverse relationship between the allostatic load index and cognitive flexibility proved stronger in this group. Set-shifting alterations could sus-tain rigid-like behaviours and attitudes towards food.

1. Introduction

Overweight and obesity prevalence has tripled in the last three decades, affecting near 2 billion adults in 2016 according to World Health Organization reports (WHO; World Health Organization, 2016). The excess of weight is linked to a poorer quality of life, all-cause mortality, and pathological ageing (Bischof and Park, 2015; Vallis, 2016). Cognitive alterations could be mediated by adiposity-induced low-grade chronic inflammatory states (Bourassa and Sbarra, 2017; Lasselin et al., 2016; Spyridaki et al., 2016). A growing body of research stresses the fact that the organism adapts to energy surplus situations via immune and neuroendocrine adaptations that, in turn, can negatively impact the brain in the long-run (Guillemot-Legris and Muccioli, 2017; Reilly and Saltiel, 2017).

Executive functions (EF) encompass cognitive processes allowing goals achievement. Accordingly to Diamond (2014), core EF such as cognitive flexibility, inhibitory control and working memory allow the performance of superior abilities (i.e., reasoning, problem-solving and planning). These functions are mandatory for blocking hedonic-based feeding and stick to long-term health-related objectives. Consequently, core EF are likely to influence body-weight control and eating behaviour (Dohle et al., 2018). There is a plethora of works addressing that subjects with excess of weight tend to perform worse in tests measuring cognitive flexibility (Perpiñá et al., 2017; Restivo et al., 2017), inhibitory control (Lavagnino et al., 2016; Spitoni et al., 2017), and working memory (Coppin et al., 2014). A recent and extended review of this topic is available in the following work (Yang et al., 2018).

The allostatic load (AL) model states that pushing of biological systems to restore homeostasis during defiant circumstances may, if sustained, derive in severe further health outcomes (Juster et al., 2010). As defined in this model, when a stressful situation is identified, primary mediators in the shape of neuroendocrine responses are engaged to mobilise energy reserves. Additional outcomes involve immune, metabolic, and cardiovascular reactions (i.e., secondary outcomes). In this sense, the organism strives to keep the rest of

the systems working well-balanced while exhausts resources to guarantee the boost necessary to overcome the stressful situation. Nevertheless, maintaining the organism working at its maximum capacity would eventually lead to the appearance of tertiary outcomes (e.g., type II diabetes, hypertension, etc.). Similar to overweight, the AL has been linked to cardiovascular diseases, poorer quality of life, and accelerated brain ageing (Cole et al., 2017; Juster et al., 2010). We have previously demonstrated that an overweight status represents a challenge to the brain. Concretely, the escalation in AL was linked to structural changes in regions supporting EF (Ottino-González et al., 2018, 2017), such as the prefrontal cortex (PFC). The PFC is particularly vulnerable to the adverse effects of stress given its many receptors for glucocorticoids (McEwen et al., 2016). To the best of our knowledge, there are only two works exploring the association between AL and EF: one did not find a relationship between AL and working memory (Booth et al., 2015) and the other described a negative link among AL, cognitive flexibility, inhibitory control, and working memory (Karlamangla et al., 2014). Both works, however, were conducted in middle-aged adults. Hence, the association between AL and EF has been not enough covered to date in young adults.

In the current study, we aimed to supplement our previous results by comparing executive performance relative to an AL increase in individuals with and without an excess of weight. Thus, we expect to find an inverse relationship between AL index and core EF. Additionally, since overweight previously exhibited higher AL indexes relative to healthy-weight subjects (Ottino-González et al., 2018, 2017), we would presume to observe a stronger negative coupling between chronic stress and executive functioning in this group.

2. Method

a. Participants

One hundred and three young adults from the city of *Terrassa* (Barcelona, Spain) were recruited from public health centres belonging to the *Consorci Sanitari de Terrassa*. Inclusion criteria involved being from 21 to 40 years old and having a BMI ranging from normal-weight (18.5 to 24.9 kg/m^2) to

excessive weight (≥25 kg/m^2). Each participant signed informed consent before entering the study following the Helsinki declaration. In line with the WHO classification, forty-seven volunteers classified as healthy-weight (18.59 to 24.99 kg/m^2), while 56 were considered as overweight. Twenty-one individuals from this group qualified as overweight (25.2 to 29.82 kg/m^2), and 34 of them presented obesity (30.25 to 42.56 kg/m^2). The Institutional Ethics Committee (CBUB) and the Institutional Review Board of the University of Barcelona approved the current study (IRB 00003099, assurance No.: FWA00004225; http://www.ub.edu/recerca/comissiobioetica.htm).

b. Allostatic Load Index

The difference between the average of two different readings of systolic and diastolic blood pressure, or pulse pressure, served as an extent of cardiovascular functioning, and concretely, of arterial stiffness (Mucci et al., 2016). Serum concentrations of high-sensitive C-reactive protein and fibrinogen worked as surrogates of immune status. The ratio between low and high-density lipoprotein cholesterol, as well as levels of triglycerides, and the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) index were all considered as proxies of metabolic capacity. Finally, serum cortisol levels were used as a marker of neuroendocrine system functioning. Variables not following a normal distribution were log-transformed. All scores were z-scaled and added into a composite with greater scores meaning higher AL. Additionally, the latent influence of sex over AL was adjusted by regressing out its effects. Analyses were conducted with the AL standardised residual.

c. Neuropsychological assessment

Cognitive flexibility was evaluated using the perseverative errors from the computerised-version of the Wisconsin Card Sorting Test (WCST) (Heaton, 1999) and the Trail Making Test (TMT) part B minus part A (Reitan, 1958). In the WCST, participants were asked to match a series of cards following a specific rule (i.e., colour, shape or number of elements) not explained to them. The subjects had feedback (i.e., right or wrong) after every response.

For every ten consecutive hits, this rule changed without announcement. Then, responses under the last assumption were computed as perseverative errors. This type of errors mirrored cognitive rigidity, or the inability to switch from the original mindset to an alternative one. The TMT consists of twenty-five circles distributed over a paper sheet. The circles in part A are numbered from 1 to 25, while in part B this sheet included both numbers (i.e., 1 to 13) and letters (i.e., A to L). In part A, the subject had to connect all the circles in order (i.e., 1, 2, 3, …) as quickly as possible without lifting the pencil from the paper. In part B, the subject had to do the same but alternating between numbers and letters (i.e., 1-A, 2-B, …). If the volunteer committed a mistake was immediately told to amend it. The completion time (in seconds) from part A was subtracted from part B. This correction (i.e., B minus A) sought to control for the speed processing effects on flexibility. Greater scores meant greater cognitive rigidity. WCST and TMT scores were log-transformed, z-scaled, and reversed before adding them into a composite wherein lower values suggested worse set-shifting performance.

The interference score in the Stroop's test (Golden, 1995) informed about inhibitory control. The Stroop's test consists of three sheets with 20 words distributed in five columns each. Participants had forty-five seconds to read aloud and as fast as possible each condition. Individuals were instructed not to follow the reading with their finger, and if mistaken, they were told to correct their response immediately. In the word-sheet, the volunteer had to read the following black-inked words: red, green, and blue. In the colour-sheet, the subject had to name the colour (i.e., red, green or blue) of non-readable stimuli (i.e., "XXXX"). In the last condition or the incongruent-sheet, the participant had to name the colour of the word, which differed from the written name (i.e., "green" in red-ink). The interference score (i.e., [incongruent sheet – ((word sheet * colour sheet) / (word sheet + colour sheet))]) accounts for reading speed and accuracy effects, as they could exert as confounders. Lower interference values denoted less ability to suppress automatic responses.

Total score in the Letter-Number subtest (Wechsler Adult Intelligence Scale, or WAIS-III) (Wechsler, 1999) equalled to working memory functioning.

In this task, participants were read aloud a sequence of numbers and letters that they had to repeat ordering numbers first, from 1 to 10, and then letters, in alphabetical order. The number of series completed represented the total score, in which greater signified better performance in working memory. Within-group potential outliers (± 3.29 SD) had their scores winsorised and re-tested for normality assumption purposes. These outliers were found in the healthy-weight group: one subject had an extremely low interference score, and another participant scored very high in the working memory test.

d. Procedure

Participants were randomly contacted through a telephone call. Subjects with expressed intention to participate were briefly interviewed on general health aspects such as medical ("Have you ever been diagnosed with any severe medical condition and/or received treatment for any chronic disease?"), psychiatric ("Have you ever required psychological counselling, psychiatric treatment or received any formal diagnose?") developmental problems ("Did you had any problems during your school years, such as learning disabilities or ADHD?"), or substance usage ("Do or did you take any recreational drug?"). Potential candidates were cited within the following days to undergo a medical examination and blood sample extraction. Participants were told to fast overnight before the blood-draw and reminded to do so the day before such visit. In this first visit, physicians both took anthropometric measures (i.e., height, weight, and waist circumference) and explored the presence of either past or current disorders considered as exclusion criteria. In addition, volunteers presenting abnormal blood test results (e.g., elevated triglyceride or cholesterol levels) underwent a second draw to confirm exclusion. Exclusion criteria involved either diagnose of or treatment for systemic diseases (i.e., hypothyroidism, hypertension, hypercholesterolemia, type II diabetes, or metabolic syndrome), as well as neurological and psychiatric comorbidities of any kind. As in our previous works, participants with high levels of C-reactive protein (10 mg/l) were excluded because of suspicion of acute infection. Moreover, symptoms that could have suggested the acute presence of pathological eating patterns,

mood or anxiety disorders, or substance abuse were also explored. Mild anxiety or depressive symptoms were explored with the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), ruling out participants presenting scores equal or greater than 11 (Herrero et al., 2003). Moreover, suspicion of eating disorders was addressed by means of the Bulimic Investigatory Test Edinburgh (BITE) (Henderson and Freeman, 1987), excluding volunteers exhibiting scores greater than 20. Finally, substance abuse was assessed with the Structured Clinical Interview for DSM-IV-TR (SCID-I) (First et al., 1999). Subjects not presenting any medical, neurological nor psychiatric comorbidity were included in the neuropsychological visit. In this second appointment, participants presenting an estimated IQ below 85, or a WAIS-III vocabulary subtest score (Wechsler, 1999) lower than 7, were excluded from the study.

e. Statistical analysis

Data were analysed with the freely distributed R statistical package v.3.4.4 (https://www.r-project.org) and RStudio v.1.1.447 (https:// www.rstudio.com). Group differences in continuous sociodemographic and neuropsychological variables were tested with one-way ANOVA tests (F). Equality in sex distribution, professional level and income among groups was confirmed with Pearson's chi-square tests (X^2). All these tests were performed with the stats package v.3.5.0 (R Core Team, 2018). Semi-partial Pearson's bivariate correlations (*r*) were conducted with the sex-adjusted AL index and EF core functions. Being as years of education correlated to executive performance, the effects of this variable were removed from EF performance. Other variables such as age, sex and total income were also included as nuisance factors in additional analyses. Moreover, and to exclusively test for the association between executive functioning and AL, the waist-to-height ratio (WTHR) was also controlled along with years of education. Here, the WTHR served as an extent of visceral adiposity. Abdominal obesity, rather than excess weight itself, is strongly linked to adverse health outcomes (Caleyachetty et al., 2017) and cognitive alterations (Elias et al., 2012). Analyses were first performed in the entire sample, and

then in groups separately (*ppcor* package v.1.1, Kim, 2015). Then, group-specific correlation coefficients were compared as detailed in Diedenhofen and Musch (*cocor* package v.1.1.3, 2015).

3. Results

Groups did not differ for age ($F_{(1,101)}$ = 1.30, p = 0.256) nor education ($F_{(1,101)}$ = 3.59, p = 0.061). Groups were equally distributed in sex (X^2 = 0.46, p = 0.496), professional level (X^2 = 11.04, p = 0.051), and total income (X^2 = 3.43, p = 0.633). There were no differences in chronic medication uptake (i.e., bronchodilators, gastric protectors) (X^2 = 0.14, p = 0.707) nor oral contraceptive usage (X^2 = 0.08, p = 0.776). As expected, groups diverged for BMI ($F_{(1,76.79)}$ = 224.47, p < 0.001) and WTHR ($F_{(1,92.27)}$ = 227.5, p < 0.001). Similarly, groups differed for the AL index ($F_{(1,101)}$ = 59.3, p < 0.001). Groups performed equally in cognitive flexibility ($F_{(1,101)}$ = 0.005, p = 0.940), inhibitory control ($F_{(1,101)}$ = 0.66, p = 0.418), and working memory ($F_{(1,101)}$ = 2.56, p = 0.113). Variables of interest are shown below in Table 1 and Table 2. Differences in the AL index between groups are depicted in Figure 1.

TABLE 1 | Statistics of variables of interest

	Overweight (N = 56)		Lean (N = 47)	
Age	31.52 (5.99)	21 – 40	30.15 (6.14)	21 – 40
Sex	37 females and 19 males		28 females and 19 males	
Education	13.20 (2.60)	9 – 20	14.15 (2.47)	9 – 18
BMI (kg/m²)	31.38 (4.21)	25.20 – 42.56	22.10 (1.78)	18.59 – 24.99
WTHR	0.60 (0.07)	0.46 – 0.75	0.46 (0.03)	0.40 – 0.56
AL index	0.52 (0.90)	-1.17 – 2.24	-0.62 (0.71)	-2.22 – 1.01
Flexibility	0.02 (1.06)	-2.09 – 2.73	-0.03 (0.91)	-1.75 – 2.16
Inhibitory control	-0.08 (0.92)	-2.41 – 2.73	0.09 (1.07)	-3.27 – 2.19
Working memory	-0.06 (1.11)	-2.31 – 2.35	0.07 (0.84)	-1.62 – 2.31

BMI, body mass index (kg/m²), WHTR, waist-to-height ratio (centimetres), AL index, Allostatic Load index. Flexibility, inhibitory control, and working memory scores are standardised residuals.

TABLE 2 | Family income in euros per month and professional level (frequency, %)

	Overweight (N = 56)	Lean (N = 47)
300 – 899€	3 (5.36%)	1 (2.13%)
900 – 1499€	11 (19.64%)	7 (14.89%)
1500 – 2099€	20 (35.71%)	16 (34.04%)
2100 – 2699€	12 (21.43%)	8 (17.02%)
> 2700€	9 (16.07%)	13 (27.66%)
N.A.	1 (1.78%)	2 (4.26%)
Non-skilled	10 (17.86%)	6 (12.77%)
Skilled manual	13 (23.21%)	5 (10.64%)
Administrative	14 (25.00 %)	8 (17.02%)
Intermediate	11 (19.64%)	8 (17.02%)
Professional	5 (8.93%)	9 (19.15%)
N.A.	3 (5.36%)	11 (23.40%)

N.A., Not available

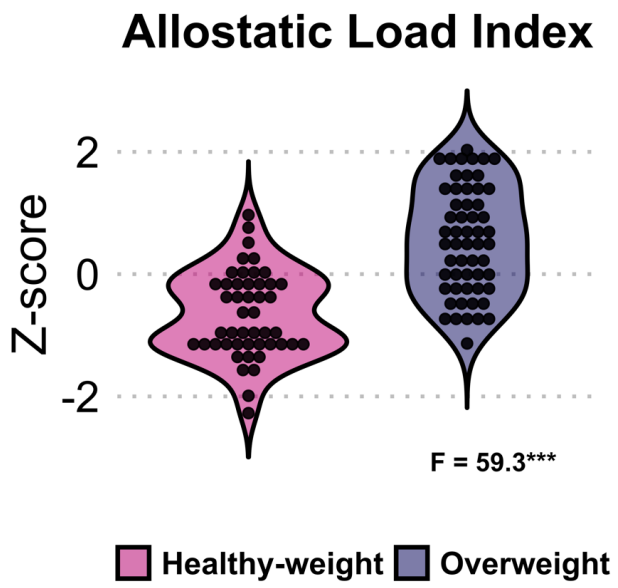

FIGURE 1 | Comparison between groups for the Allostatic Load Index. *** p < 0.001

Whole-group correlation analyses revealed a negative relationship between AL index and inhibitory control ($r_{(99)}$ = -0.19, p = 0.027). Trend-level correlations were observed for cognitive flexibility ($r_{(99)}$ = -0.13, p = 0.093) and working memory ($r_{(99)}$ = -0.16, p = 0.051). Group-specific correlations showed that AL index and cognitive flexibility were statistically negatively associated in overweight participants ($r_{(52)}$ = -0.32, p = 0.008), but not in healthy-weight subjects ($r_{(43)}$ = 0.09, p = 0.289). Correlation coefficients differed between groups (Z = -2.07, p = 0.019). AL index and inhibitory control were exclusively related among healthy-weight subjects ($r_{(43)}$ = -0.34, p = 0.011), but not in overweight participants ($r_{(52)}$ = -0.11, p = 0.204). However, group-specific correlations did not diverge (Z = 1.19, p = 0.116). Furthermore, AL index and working memory were linked only within healthy-weight subjects ($r_{(43)}$ = -0.29, p = 0.024), but not in overweight participants ($r_{(52)}$ = -0.15, p = 0.144). Groups were not different for such association (Z = 0.78, p = 0.219). Whole-group and group-specific associations are presented in Figure 2. The interaction between AL index and cognitive flexibility depending on the BMI group is available in Figure 3. The analyses including age, sex, and income as additional covariates remained unchanged and therefore will not be further discussed.

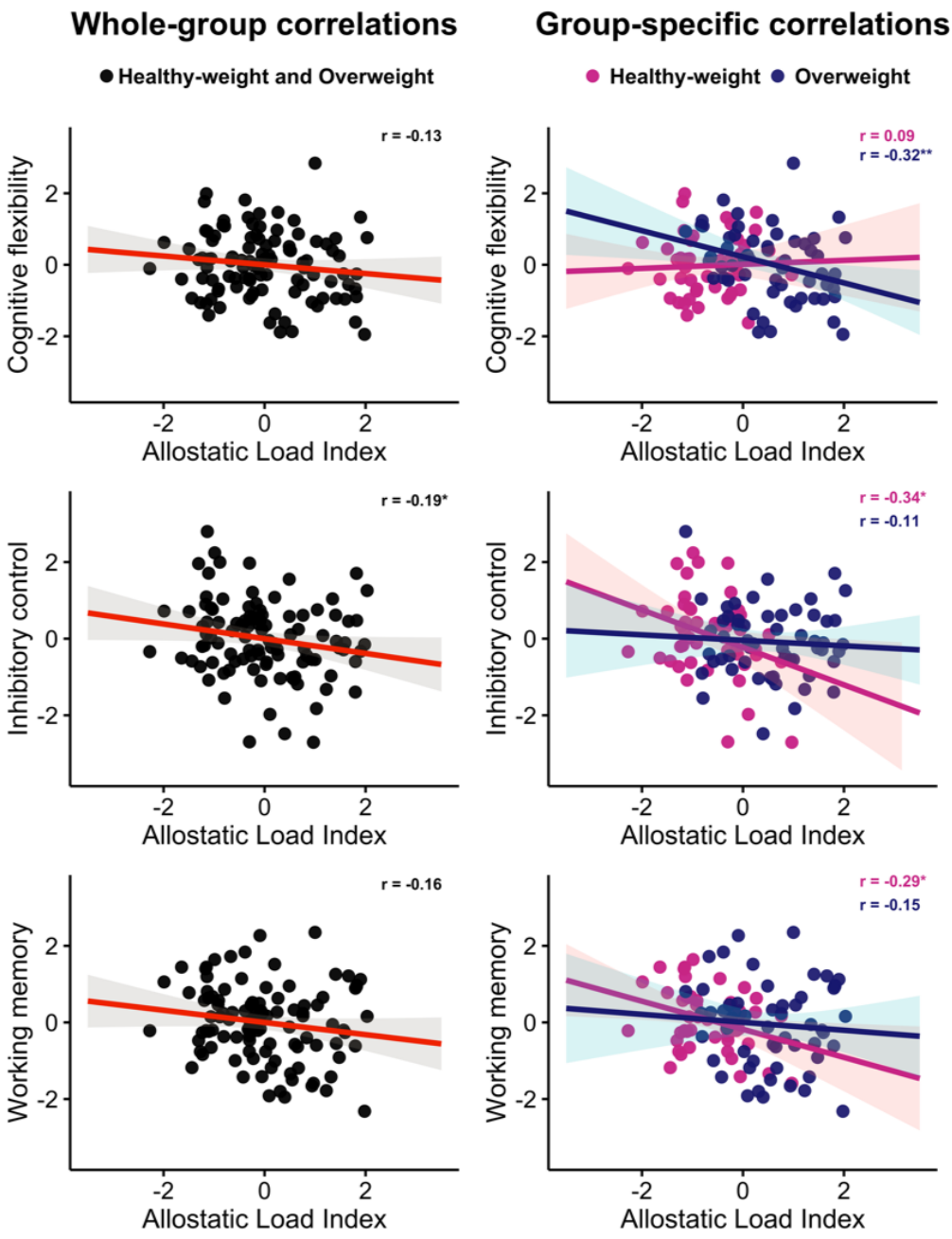

FIGURE 2 | Correlations between the AL index and core EF in the entire group (on the right, black = all participants), and accounting for groups (on the left, pink = healthy-weight, purple = overweight). * $p < 0.05$, ** $p < 0.01$

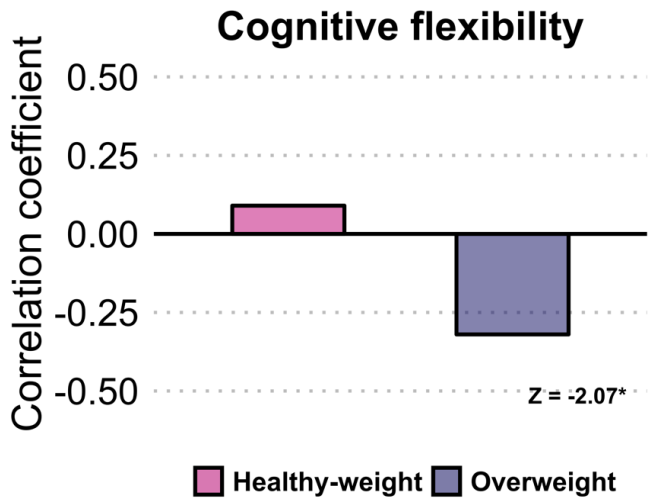

FIGURE 3 | Group-specific correlation comparison for Allostatic Load Index and flexibility.
* $p < 0.05$

4. Discussion

In the current work, we have addressed the relationship between AL and executive performance. As expected, the overweight group exhibited greater levels of AL index when compared to their healthy-weight peers. Furthermore, the AL inversely correlated with inhibitory control. Moreover, groups exhibited differences in their relationship between the AL index and core EF, and particularly, with cognitive flexibility ability. This association emerged as significant exclusively in the overweight sample. This correlation proved different among groups, being more markedly for individuals with an excess of weight. What is more, normal-weight volunteers exhibited a negative relationship between AL, inhibitory control, and working memory. Such associations, however, were not different among groups.

The AL model states that frequent homeostasis disruption could lead to severe health and psychological comorbidities in the future (Juster et al., 2010). Accordingly, the excess of weight itself represents a challenging scenario to the organism. Briefly, we adapt to energy surplus situations by prompting intense immune and neuroendocrine responses ultimately insulting the PFC and the functions it supports (Guillemot-Legris and Muccioli,

2017; Reilly and Saltiel, 2017). Similar to the AL model, the immunologic model of self-regulatory failure (Shields et al., 2017) states that inflammation insults the PFC and disturbs the cognitive resources required to stick to health-fostering behaviours. Likewise, problems within self-regulation could increase people's risk to engage in further inflammatory-inducing habits such as drinking, smoking or overeating. Although it is strongly discouraged to draw any statement upon causality with the present design and type of analysis, an escalation in AL could induce failures in core EF central for self-discipline. Hypothetically, a person who daily eats beyond their caloric need will challenge their organism and increase the likelihood to influence (or exacerbate premorbid) failures in self-regulation. This would naturally pave the way for further unhealthy behaviours to take place encouraging this long-lasting physiological imbalance. Hence, an increase in AL could be interpreted as a risk factor for disturbing self-discipline. Following this thought, and without targeting either of the two groups, failures in inhibitory control could yield to problems in suppressing hedonic-driven behaviours, such as unnecessary food consumption (Calvo et al., 2014; Lavagnino et al., 2016; Spitoni et al., 2017). Equally, working memory alterations could provoke not being able to keep health-related long-term objectives available when required, impacting negatively on eating behaviour and body-weight control (Whitelock et al., 2018). Lastly, the inability to switch from one mindset to another could translate in problems in abandoning disadvantageous food choices (Lasselin et al., 2016; Perpiñá et al., 2017; Restivo et al., 2017). Overall, and despite some correlations were present at a trend-level, chronic physiological stress and EF negatively interact with each other and can affect eating behaviour.

To date, the only works exploring the relationship between AL and EF were conducted in aged populations (Booth et al., 2015; Karlamangla et al., 2014). In Booth et al. (2015), the AL did inversely relate to general cognition, but not to executive performance (i.e., non-verbal reasoning and working memory). By contrast, in Karlamangla and cols. (2014), inhibitory control, set-shifting, and working memory proved a negative relationship with AL. Here, we have also found a negative association between AL and inhibitory control, and with cognitive flexibility and working memory

in a trend-level. However, when addressing separately, groups exhibited differences for such links. Concretely, the correlation between the AL index and set-shifting only emerged as negative and statistically meaningful in the overweight group. Contrariwise, this association in the healthy-weight group was weak, non-significant, and positive. When compared, these slopes emerged as different. Such conflicting results could put the spotlight on how body-weight status differently shapes the interaction between AL and cognitive flexibility. The increase in AL among overweight could be more hurtful for this ability. Furthermore, inhibitory control and working memory correlated to AL index solely within healthy-weight subjects. Even though they did not arise as statistically significant, the nature of the link between the AL index, inhibitory control, and working memory among participants with an excess of weight was negative as well. Each group's slopes for these relationships did not differ. It might be possible that compensatory mechanisms are being mobilised in overweight to dilute the damaging effects of chronic stress exposure. In this vein, the two groups included non-clinical, young, and well-educated subjects. Altogether, these factors might have behaved as protective in the face of the adverse outcomes of being overweight, at the very least, until comorbidities aggregate over time. These circumstances may have also explained why groups, when compared, did not display differences for core EF performance, which is a statement broadly pronounced in the literature (Fitzpatrick et al., 2013; Smith et al., 2011; Yang et al., 2018). Since overweight participants (BMI from 25 to 29.9 kg/m^2) could have watered-down potential group differences, we have additionally repeated this analysis comparing individuals with obesity (N = 34) to normal-weight subjects (N = 47). Groups did not diverge in their performance in core EF. As abovementioned, it is not possible ruling out the possibility of compensatory or protective mechanisms operating on the side. What is more, it is likely that the current sample size would have limited our statistical power to find subtle differences among groups, as we further discuss in the next paragraph.

The current results are an extension of prior works (Ottino-González et al., 2017, 2018) where we exposed the link between AL and the integrity of brain regions supportive of high-order cognitive activity. The sample

used in all three studies shared the same socio-demographic characteristics. Consequently, these findings add some robustness to the already published studies. Nevertheless, the current work has some limitations that worth the commentary. First, the cross-sectional nature and the type of analysis performed (i.e., bivariate correlations) made it difficult to draw any conclusion on causality. As with the circularity limitations pointed out in Karlamangla et al. (2014), the AL and the performance in EF can influence each other ultimately affecting behaviour. Equally, behaviour can influence these former two. Either longitudinal or experimental approaches would shed a broader light on this matter. As early noted, our limited sample size might have restricted our ability to catch, if any, subtle differences or relationships. Given the characteristics of the two groups, these effects would have potentially emerged as such with more appropriate sample sizes. Concretely, three hundred and ten individuals per group would be required to find small discrepancies in one-sided T-tests with 80% of chances of not incurring in type II errors. Because of the design, the type of analysis, and the sample size, we advise taking these results with caution. Furthermore, the study of sexual dimorphism in stress vulnerability could be an interesting line of research that we have not had the opportunity to conduct in the current work. The ups-and-downs of testosterone are well known because, by one hand, it presents anti-inflammatory properties as it exerts an inhibitory effect on adipocyte maturation (Bianchi, 2019). However, testosterone also shows a strong link with cardiovascular diseases in ageing men (Goodale et al., 2017). In the same way, it has been pointed out that estradiol might have protective effects on cognition (Luine, 2014). Although our sample size (i.e., 19 males per group) did not allow us to test for this appropriately, we have included the results and a brief discussion of this preliminary analysis in the supplementary material. Nevertheless, we encourage other researchers to explore this issue in samples with sufficient statistical power.

In conclusion, when compared to healthy-weight individuals, overweight subjects exhibited higher AL indexes. Regardless of the group, the AL index was negatively related to inhibitory control, and with other core executive abilities to a trend-level. Optimal functioning within primary executive domains is necessary for enabling self-discipline and health-fostering

behaviours. The inverse correlation between the AL index and cognitive flexibility proved stronger in the overweight group when compared to healthy-weight individuals. Set-shifting alterations could sustain rigid-like behaviours, obstructing not only the healthiest-fare choice but also self-regulation in general.

5. Collate acknowledgements

JOG, MAJ, IGG, XC, and MG contributed to study design and conception, analyses and results interpretation. JOG, IGG, XPS, ET, and MSP participated in data acquisition. Additionally, all authors critically revisited the work, approved its final version for publishing, and agreed to be accountable for all aspects of such work.

6. Funding

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7. References

(See thesis references)

8. Supplementary Material

This supplementary analysis is motivated due to the potential differences in how females and males could react to chronic stress exposure. Briefly, and despite testosterone naturally has anti-inflammatory properties as it exerts an inhibitory effect on adipose tissue formation and maturation (Bianchi, 2019), testosterone is also linked to greater incidence of cardiovascular diseases among ageing males (Goodale et al., 2017). Equally, it has also been broadly discussed whether estradiol might exert as a protective factor over cognition (Luine, 2014).

- Whole-group comparison between males and females

Males and females were not different in age ($T_{(101)}$ = 0.74, p = 0.463), years of education ($T_{(101)}$ = 0.55, p = 0.582), income (X^2 = 6.33, p = 0.276), professional level (X^2 = 1.23, p = 0.942) nor chronic medication usage (X^2 = 0.22, p = 0.942). Likewise, males and females did not differ for BMI (W = 1226.5, p = 0.956), WTHR (W = 1302, p = 0.649), or AL index ($T_{(101)}$ = -0.19, p = 0.851). Normality distribution for variables of interests (i.e., AL index, cognitive flexibility, inhibitory control and working memory) were confirmed across males and females, as shown below in Figure 1.

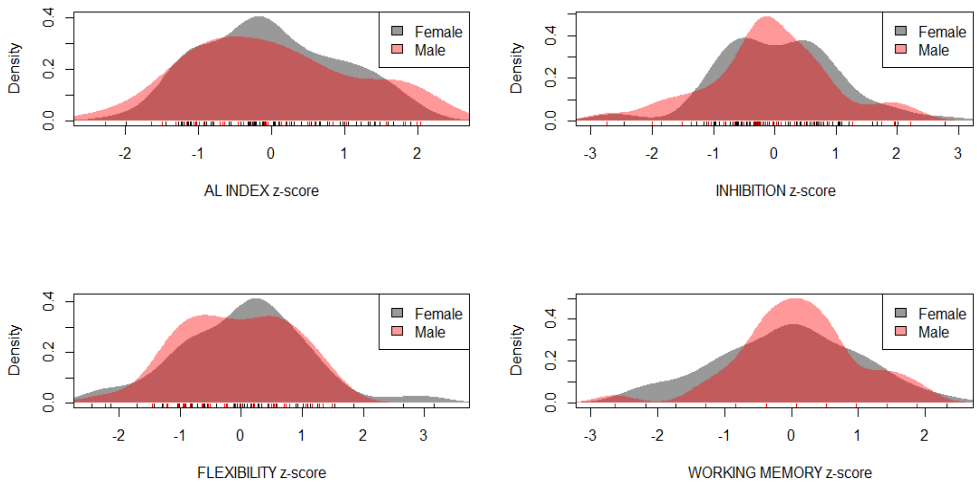

FIGURE 1 | Density distribution on variables of interest between males and females (z-scores).

Females with overweight and normal weight did not diverge in age ($T_{(63)}$ = -0.35, p = 0.729), years of education ($T_{(63)}$ = 1.91, p = 0.061), income (X^2 = 10.61, p = 0.060), professional level (X^2 = 4.80, p = 0.441), chronic medication (X^2 < 0.001, p = 0.990) or oral contraceptive consumption (X^2 = 0.08, p = 0.776).

Males with and without excessive weight were not different in age ($T_{(36)}$ = -1.33, p = 0.191), years of education ($T_{(36)}$ = 0.69, p = 0.496), income (X^2 = 2.22, p = 0.818), professional level (X^2 = 10, p = 0.075) or chronic medication usage (X^2 = 0.36, p = 0.548). Variables of interest followed a normal distribution as displayed below in Figure 2.

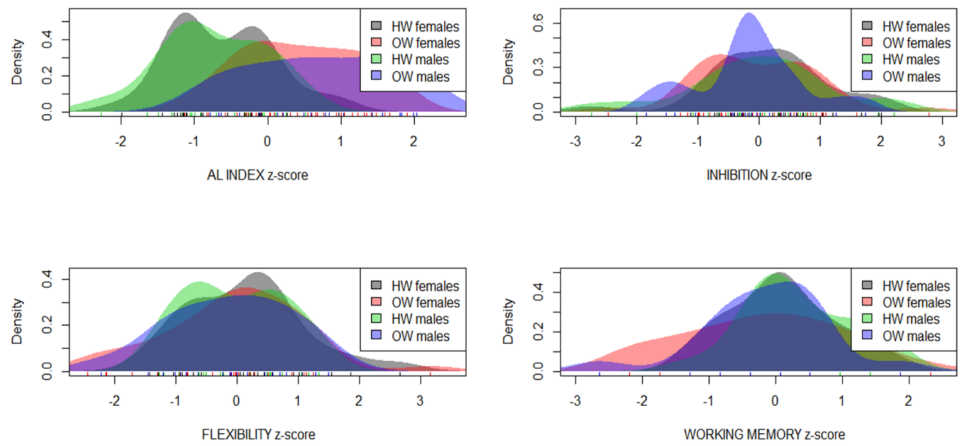

FIGURE 2 | Density plots accounting for sex and BMI group for variables of interest (z-scores).

Significant correlations only emerged for inhibitory control among females ($r_{(61)}$ = -0.29, p = 0.009). When accounting for BMI group, this correlation arose as meaningful within healthy-weight females ($r_{(24)}$ = -0.36, p = 0.034). In line with the original results, trend-level correlations were observed between healthy-weight females with working memory (p = 0.084), as well as with cognitive flexibility in women with an excess of weight (p = 0.050). Correlations between females and males, as well as correlations within females and males accounting for BMI group, are depicted below in Figure 3.

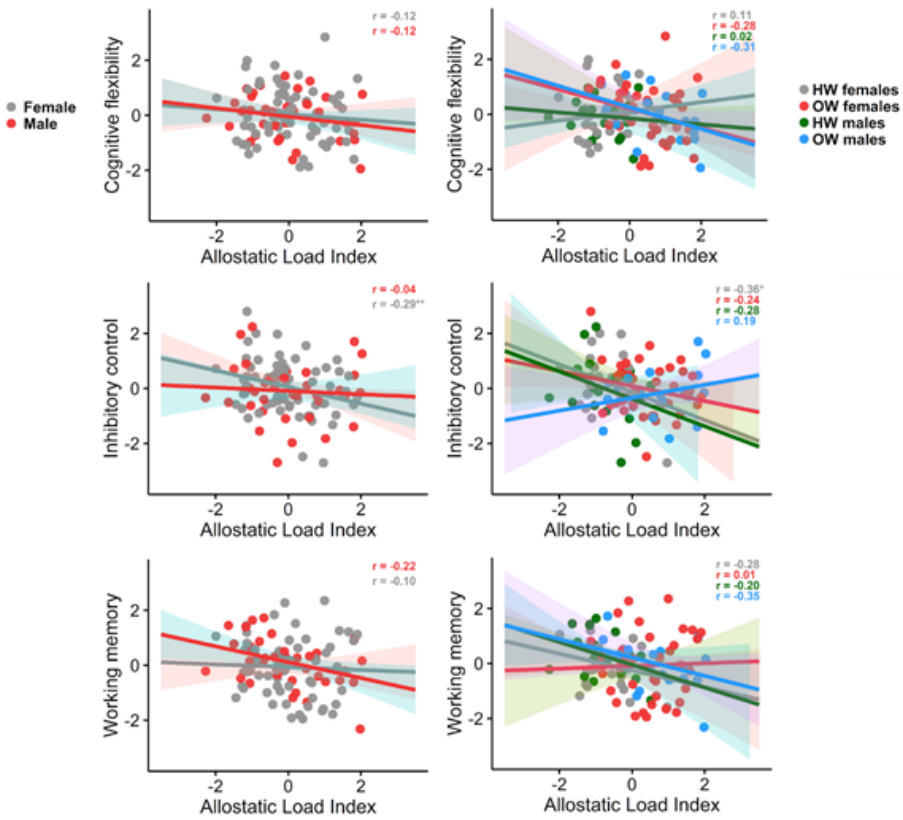

FIGURE 3 | On the left, correlations between the AL index and core EF accounting for males and females. On the right, correlations between the AL index and core EF separating for males and females regarding BMI group (healthy-weight or overweight). HW = healthy-weight, OW = overweight. *p < 0.05, ** p < 0.01

Discussion

In consonance with our findings, when comparing females and males, the formers presented a significant link with inhibitory control. Likewise, only the group of healthy-weight females presented a negative correlation with this domain. Although the relationship between cognitive flexibility and the AL index was negative and strong among males (-0.31) and females (-0.28) with excessive weight, such associations did not emerge as significant. What is more, women with excessive weight exhibited a trend-like negative association with inhibitory control (-0.24), while males exposed the opposite (0.19). In turn, overweight men showed a robust and negative link with

working memory performance (-0.35), whereas females did not (0.01). Furthermore, the directionality of all the three possible correlations among females and males with normal weight were all in the same direction (i.e., null or slightly positive for cognitive flexibility, and negative for inhibitory control and working memory). Altogether, the positive relationship in overweight males for inhibitory control, as well as the negative link in working memory among overweight females should be both further explored to disentangle whether this is due to hormone-related compensatory mechanisms or not. Similar to testosterone behaving as protective because of its anti-inflammatory properties, the shielding effects of estradiol on cognition have also been largely discussed (Luine, 2014). The lack of results, particularly among males who have exhibited very strong correlations, is perhaps because of the limited statistical power inherited from limited sample sizes. It is noteworthy to remark that there were only nineteen males per BMI group. For instance, to qualify as statistically meaningful, the correlation of -0.38 observed among overweight males would have required at least 48 subjects to do so with an 80% of chances of not committing type II error (this is, not finding as statistically meaningful a true effect). In sum, more research is needed in disentangle how sex-dimorphism may shock-absorb or boost the far-reaching consequences of sustained biological deregulation linked to an excess of weight.

CHAPTER 5 – DISCUSSION

5.1. Summary of findings

The three studies conducted for this doctoral thesis sought to address the relationship between AL, brain structure, and executive functioning in otherwise healthy overweight-to-obese young adults. To date, literature linking the AL to neuroanatomical changes revealed negative associations with global (Booth et al., 2015; Chiappelli et al., 2017) and regional alterations in GM volume (Zsoldos et al., 2018) and FA in WM tracts (Savransky et al., 2017). Equally, only two works tackled the relationship between AL and cognition (Booth et al., 2015; Karlamangla et al., 2014). Nevertheless, these studies focused on either ageing or psychiatric samples, leaving the general adult population uncovered. Our results have shown that the excess of weight is associated with higher chronic physiological stress when compared to healthy weight volunteers. Moreover, and independently from the effects of adiposity itself, this status of 'wear and tear' of the body was adversely related to the composition of GM/WM tissues and executive performance.

In Study 1, variations in cortical thickness relative to an AL increase were group-dependent. Respectively, normal weight and overweight participants exhibited patterns of widespread cortical thickening and thinning among frontal, temporal, parietal, and occipital lobes further detailed.

In Study 2, overweight subjects exclusively featured decreases in FA concerning an AL intensification in the inferior fronto-occipital fasciculi and the right anterior corona radiata. Furthermore, overweight participants presented GM volume reductions in relation to an AL escalation in the left lateral occipital gyrus, the left precentral gyrus, and the right pars opercularis.

In Study 3, the AL index augmentation was concomitant to decreases in overall executive functioning. Also, and oppositely to normal-weight volunteers, overweight participants exposed worsening in set shifting in the presence of higher AL.

5.2. Overweight, allostatic load and brain morphology changes

5.2.1. Structural alterations in cognitive-control areas

Results from Study 1 and 2 illustrated the presence of whole-brain GM morphological alterations relative to an AL increase. Namely, lean participants showed cortical thickening and overweight exhibited cortical thinning in the left pars triangularis, the left superior frontal gyrus, the right lateral orbitofrontal cortex, the right precentral gyrus, the left supramarginal gyrus, the left precuneus, the bilateral inferior parietal cortex, and the right transversal temporal gyrus. This unexpected pattern of cortical thickening among leans is later discussed in the General discussion section. Additionally, the overweight group also showed volume reductions in the left lateral occipital cortex, the left precentral gyrus, and the right pars opercularis.

Cortical thinning and shrinking within dorsolateral PFC areas, such as the inferior (i.e., pars orbitalis, pars triangularis) (Janowitz et al., 2015; Karlsson et al., 2013; Kurth et al., 2012; Mathar et al., 2015; Opel et al., 2017; Yao et al., 2016), the middle (i.e., rostral and caudal frontal gyrus) (Pannacciulli et al., 2006; Yao et al., 2016), and the superior frontal gyrus (Kurth et al., 2012; Weise et al., 2017; Yao et al., 2016) have been extensively reported relative to BMI status or adiposity increase. Although the right inferior frontal gyrus has been selectively targeted because of its crucial role in inhibitory control (Alonso-Alonso & Pascual-Leone, 2007; Aron, Robbins, & Poldrack, 2014), other prefrontal regions were also linked to weaker self-control along with increases in BMI (Krämer et al., 2013; Lavagnino, Mwangi, et al., 2016; Swick, Ashley, & Turken, 2008; Yokum, Ng, & Stice, 2012). Inhibitory control has been linked to maladaptive eating patterns (Bartholdy, Dalton, O'Daly, Campbell, & Schmidt, 2016). Nonetheless, the PFC harbours other core executive functions besides inhibitory control. For instance, the left inferior frontal gyrus mediated cognitive flexibility in healthy elders (Zamroziewicz, Zwilling, & Barbey, 2016) and neurological patients (Aron, Monsell, Sahakian, & Robbins, 2004). Other motor-related areas, like the precentral gyrus, has proved decrease with BMI increases (García-García et al., 2018; Kharabian

Masouleh et al., 2016; Kurth et al., 2012; Opel et al., 2017; Pannacciulli et al., 2006; Veit et al., 2014; Walther et al., 2010; Weise et al., 2017). Alterations in GM structure in the parietal lobes have also been outlined in numerous works. Cortical variations were mainly found in the inferior (Taki et al., 2008; Veit et al., 2014) and superior parietal gyri (Taki et al., 2008; Tuulari et al., 2015; Yao et al., 2016). Furthermore, changes in the supramarginal (Janowitz et al., 2015; Kurth et al., 2012; Opel et al., 2017; Yao et al., 2016), and the postcentral gyri (Janowitz et al., 2015; Kurth et al., 2012) have also been portrayed. These parietal regions, together with dorsolateral PFC areas, support executive performance (Zanto & Gazzaley, 2013).

Concerning the WM results in Study 2, less coherent diffusion relative to AL was present in tracts with their peaks located in the inferior fronto-occipital fasciculi, which extended but not limited to, the inferior and superior longitudinal fasciculi. Congruently, FA reductions in overweight subjects were also found in the inferior fronto-occipital fasciculi (Karlsson et al., 2013; Mazza et al., 2017; Papageorgiou et al., 2017; Repple et al., 2018), the inferior longitudinal fasciculi (Repple et al., 2018), and the superior longitudinal fasciculi (Papageorgiou et al., 2017). On top of this, recent works have demonstrated that the differences between lean and overweight subjects in the superior longitudinal fasciculi microstructure were mediated by obesity-induced inflammation (Moreno-Navarrete et al., 2017; Verstynen et al., 2013). On another note, prefrontal and parietal cortices are structurally and functionally wired in what is known as the cognitive-control, or the fronto-parietal network (Darki & Klingberg, 2015). The superior and inferior longitudinal fasciculi anatomically connect such network together. Although the discussion of the relationship between AL escalation and executive performance is later discussed in depth, structural alterations in cognitive-control areas could yield to impairments within these functions. Executive functions play a key part in supporting the so-called reflective eating, or the ability to supervise feeding and blocking unnecessary caloric uptake (i.e., reflexive eating).

5.2.2. Structural changes in reward-related territories

Overweight subjects also displayed GM reductions with higher AL indexes in reward-related areas in Study 1 and 2. Concretely, the lateral orbitofrontal cortex showed decreases in both thickness and volume. There is a plethora of works detailing reductions in participants with an overweight status (Shott et al., 2015; Tuulari et al., 2015). Likewise, increases in body mass (He; Xiao; Xue; Wong; Ames; Schembre; Bechara, 2014; Kharabian Masouleh et al., 2016; Medic et al., 2016; Opel et al., 2017; Yao et al., 2016), central obesity (Janowitz et al., 2015; Kurth et al., 2012), or fat mass (Weise et al., 2013) have also been linked to GM reductions in this area. The orbitofrontal cortex is part of the reward-processing circuit, playing a crucial role in wanting, liking, and learning from the gratifying properties of certain types of foods (Kringelbach, Stein, & van Hartevelt, 2012). In Study 2, overweight volunteers demonstrated GM reductions in occipital areas, concretely in the lateral occipital cortex. Although scarce, findings in these regions, naturally involved in visual processing and integration, are also described in the literature (Janowitz et al., 2015; Kurth et al., 2012; Medic et al., 2016; Opel et al., 2017; Tuulari et al., 2015; Veit et al., 2014; Weise et al., 2013). Logically, occipital areas are engaged when looking for reinforces in the environment. Phylogenetically, the visual cortex is highly evolved in humans as food-seeking relies almost entirely on visual detection (Linné, Barkeling, Rössner, & Rooth, 2002). A recent work conducted by DiFeliceantonio et al. (2018) exhibited that the accurate estimation of food caloric content rests on the correct coupling between visual and prefrontal regions (DiFeliceantonio, Coppin, Rigoux, Thanarajah, Dagher, Tittgemeyer & Small, 2018). Overweight volunteers usually showed altered activity to visual food-cues within these structures (García-García et al., 2013; Gearhardt, Yokum, Stice, Harris, & Brownell, 2013). Therefore, structural and functional alterations within this area may entail changes in both detection, valuation and processing of food rewards.

Results from Study 2 similarly revealed FA reductions concerning an escalation in AL in tracts innervating reinforce-processing areas. Specifically, decreases in FA locally emerged in the inferior fronto-occipital fasciculi

and in the right anterior corona radiata, and extended to other fibres such as the cingulum. Anatomically, these WM bundles link areas involved in either tracking or processing reinforces (Bracht, Linden, & Keedwell, 2015). The processing of the food pleasure-related properties in this circuit is fundamental for reward learning and anticipation (Gottfried, 2003; Knutson & Cooper, 2005; Kringelbach et al., 2012). Reward-processing is one of the most studied topics in obesity research. Several works have described alterations relative to body weight status (García-García et al., 2013; Martens et al., 2013; Nummenmaa et al., 2012; Opel et al., 2015; Eric Stice, Spoor, Bohon, Veldhuizen, & Small, 2008; Wijngaarden et al., 2015). BMI increases and changes in WM composition in the inferior fronto-occipital fasciculi and the cingulum have been widely reported in the literature (Bettcher et al., 2013; He; Xiao; Xue; Wong,; Ames; Schembre; Bechara, 2014; Kullmann et al., 2015; Papageorgiou et al., 2017; Verstynen et al., 2012). In addition, less parallel diffusivity has also been described in the anterior corona radiata (Kullmann et al., 2015; Mazza et al., 2017; Shott et al., 2015; Verstynen et al., 2012). In sum, structural changes in reward-seeking and processing areas could led to a status of hyper-alertness towards food detection and to an extreme motivation to pleasure-based feeding.

5.2.3. Structural alterations in homeostasis-related regions

Regions involved in sensing visceral and internal state information showed either cortical thinning or volume reductions in overweight subjects relative to the escalation of AL. Mainly, GM loss was found in the bilateral insula, the postcentral gyri, and the right superior temporal gyrus. Similarly, alterations in the insula and postcentral gyri were described regarding body mass (Kharabian Masouleh et al., 2016; Kurth et al., 2012; Yao et al., 2016) or visceral adiposity increase (Veit et al., 2014). Together with the opercular and orbitofrontal cortex, the insula is part of gustatory circuits (Avery et al., 2017; Kumar et al., 2016; Oliveira-Maia, Roberts, Simon, & Nicolelis, 2011; Small et al., 2007). Not surprisingly, this region and the somatosensory cortex increase their activity during the processing of food-related gratifying bodily sensations (Sescousse, Caldú, Segura, & Dreher, 2013). The insular cortex also

participates in higher cognitive functions (Florian Kurth, Zilles, Fox, Laird, & Eickhoff, 2010). For instance, patients with mild cognitive impairment shown abnormal insular volumes compared to controls (Xie et al., 2012). Obesity status (Tuulari et al., 2015), as well as increases in body mass (Opel et al., 2017; Yao et al., 2016), central obesity (Janowitz et al., 2015; Kurth et al., 2012) or visceral fat mass (Kaur et al., 2015) were all linked to GM reductions in the superior temporal gyrus. Traditionally, the temporal lobe is principally known for its role in auditory and speech processing, as well as with memory performance and visual integration. Comparably to the PFC, this structure is highly vulnerable to the effects of stress and pathological ageing (McEwen, 2017). The superior temporal gyrus has also been linked to satiation signal processing (Kroemer et al., 2013).

In another vein, WM composition adjacent to these cortical structures were found affected in overweight subjects. Specifically, relative to an AL increase, FA reductions were observed in the right anterior corona radiata. Similarly, there is an important body of publications portraying changes in this tract either in overweight participants (Karlsson et al., 2013; Kullmann, Schweizer, Veit, Fritsche, & Preissl, 2015; Ryan & Walther, 2014; Shott et al., 2015). Overall, variations in cortical structures and tracts involved in integrating visceral information could relate to erroneously sensing peripheral signals regulating feeding, which could precipitate craving responses and biasing attention towards food consumption.

5.2.4. Structural changes in the precuneus

Study 1 showed GM changes not typically ascribed to the aforesaid networks. AL index intensification proved to correlate with bilateral thinning of the precuneus in overweight subjects. Literature has reported volume reductions in this area linked to obesity status (Pannacciulli et al., 2006). The precuneus has also presented lower GM density relative to BMI (Figley et al., 2016; Taki et al., 2008) or WC increase (Janowitz et al., 2015) in other studies. Along with the posterior cingulate cortex, this posterior medial structure is part of the so-called Default Mode Network (DMN), which is usually defined

as a task-negative circuit. The DMN is classically implicated during internally oriented processing. Though it is mainly functional in wakeful rest and daydreaming, this network also participates in high-demanding cognitive tasks (Spreng, 2012). The DMN is recruited when the cognitive load of the task is either heavy or domain-specific information is required, such as picturing future scenarios or remembering situations taking place in the past (Shine & Breakspear, 2018). Additionally, optimal cognitive performance supported by task-positive circuits, such as the cognitive-control network, relies on the correct deactivation of the DMN. The DMN is also considered as a biomarker for major psychiatric disorders (Anticevic et al., 2012) and pathological ageing (Buckner, Andrews-Hanna, & Schacter, 2008; Palmqvist et al., 2017). This complex is also favourably vascularised, as it consumes a great deal of the total brain energy (i.e., 60~80%). Consequently, it is also extremely vulnerable to the obesity-related vascular and metabolic comorbidities such as hypertension (Haight et al., 2015), type II diabetes (Wang, Ji, Lu, & Zhang, 2016), and dyslipidaemia (Spielberg et al., 2017).

5.3. Overweight, allostatic load and executive functions

The most popular core executive functions are cognitive flexibility, inhibitory control, and working memory (Strauss, Sherman, & Spreen, 2006). As abovementioned in the introduction, impairments among these functions could lead to overeating and weight-gain as they inherently support a reflective eating style (Dohle et al., 2018). In the same way, lifestyles potentially prompting inflammation can lead to flaws among these abilities ultimately sabotaging self-discipline in the long-run (Shields et al., 2017). What is more, other functions could resent from failures in these core executive domains. For instance, poorer cognitive flexibility and inhibitory control could affect voluntary attention, which is commonly defined as the ability to willingly maintain, avert or re-direct the attentional focus to or away from a particular stimulus (Strauss et al., 2006). That said, the inability to ignore food stimuli when confronted has been broadly reported in the literature (Castellanos, Charboneau, Dietrich, Park, Bradley, Mogg, & Cowan, 2009; di Pellegrino, Magarelli, & Mengarelli, 2011; Graham et al., 2014; Hou

et al., 2011; Janssen et al., 2017; Piech, Pastorino, & Zald, 2009; Siep et al., 2009; Yokum & Stice, 2011). In like manner, working memory is necessary for keeping health goals up-to-date, and could influence the learning and retrieval of fare-related information (Whitelock, Nouwen, van den Akker, & Higgs, 2018). Memory impairments have been broadly mentioned in overweight and obesity studies (Fitzpatrick et al., 2013; Smith et al., 2011). What is more, not being able of recalling past meals to estimate the overall caloric consumption through the day or week could negatively influence eating and food choices (Higgs, Robinson, & Lee, 2012; Whitelock et al., 2018).

Eating also depends on higher executive functions such as decision-making. The ability to select an option out of several alternatives requires the coordinated intervention of the previous core functions. Decision-making involves rapidly coupling information from past, present, and future situations to work out the best possible choice. Overweight subjects tend to perform worse in making decisions under circumstances involving either monetary or food-related rewards (Davis, Patte, Curtis, & Reid, 2010; Fagundo et al., 2012; Mathar et al., 2015; Navas et al., 2016; Sutin et al., 2013). In 1999, Metcalfe and Mischel proposed two competing systems explaining the dynamics of willpower and gratification delay (Metcalfe & Mischel, 1999). The "cold" or cognitive-based system enables self-control, while the "hot" system underpins motivation. An imbalance in the development of cold and hot systems during childhood has been hypothesised to lead to obesity-predisposing eating styles later in adult life (Groppe & Elsner, 2015).

Results in Study 3 evidenced that an escalation in AL correlated with lower performance in core executive domains. Increases in chronic physiological stress linked to poorer inhibitory control, and with cognitive flexibility and working memory at a trend-level. These functions have been largely described disturbed in both overweight (Alonso-Alonso et al., 2015; Calvo et al., 2014; Coppin et al., 2014; Fagundo et al., 2012; Fitzpatrick et al., 2013; Gunstad et al., 2007; Lasselin et al., 2016; Lavagnino, Arnone, et al., 2016; Perpiñá et al., 2017; Restivo et al., 2017; Smith et al., 2011; Spitoni et al., 2017; Yang et al., 2018) and stress studies (Ajilchi & Nejati, 2017; Bulzacka

et al., 2016; Cerqueira et al., 2007; Karlamangla et al., 2014; Kesse-Guyot et al., 2015; Lasselin et al., 2016; Levandowski et al., 2016; Mika et al., 2012; Moreno-Navarrete et al., 2017; Orem et al., 2008; Segura et al., 2009; Solas, Milagro, Ramírez, & Martínez, 2017). Furthermore, when we addressed groups separately, such alterations proved to be dependent on the BMI group. Thus, only overweight subjects presented an inverse and statistically significant association between cognitive flexibility and AL increase. Normal-weight subjects showed a weak and positive relationship for set-shifting ability. Relatedly, inhibitory control and working memory originally emerged exclusively as meaningful among lean participants, though overweight participants showed decreases in their core EF performance as well. However, only the relationship between cognitive flexibility and AL proved different across groups. In the light of these results, pushing biological systems to preserve homeostasis revealed being disadvantageous to the ability to alternate between responses among volunteers with excessive weight. Aforesaid, greater inflexibility could prompt rigid-like behaviours potentially translating into uncontrollable food consumption or choosing more frequently the unhealthiest-fare.

5.4. General discussion

The escalation in AL proved unfavourable to GM and WM tissue depending on body-weight status. Surprisingly, and in terms of cortical thinning as an indicator of GM morphological disturbance, the escalation of AL did not behave as such for normal-weight subjects in Study 1, who instead exhibited thickening in their cortical mantle. In a longitudinal study, patients with schizophrenia presented thicker posterior cortices at baseline but not at follow-up (van Haren et al., 2011), although the potential mechanism were not discussed by the authors. What is more, a work conducted by Qiu and cols. (2014) showed that major depressive disorder *de novo* patients exhibited thicker cortices than controls as well. Here, the authors stated that cortical thickening could in turn reflect CNS glial activation. Astrocytes constitute about 90% of the cortical tissue volume, and when roused, extracellular water content increases and neurotrophic

factors are secreted to promote CNS recovery. That said, an increase in GM might erroneously suggest a greater presence of neuronal cells, negligently ruling out the possibility of considering inflammatory sources instead. In this sense, the cortical thickening exhibited by lean participants could imply the activity of neuroprotective factors. Distinctively, overweight subjects showed decreases in cortical thickness. In this vein, results could have revealed how groups differently reacted to the immunosuppressive effects of chronic stress. This underlying premise is analogous to the AL model. Both models underpin that, despite stress is formerly adaptive, it can harm the brain if sustained over time.

Regardless of its initial anti-inflammatory properties, when repeatedly secreted, cortisol can increase pro-inflammatory cytokines production and augment free radicals liberation (Jauregui-Huerta et al., 2010). This hormone also obstructs the proliferation of glial cells in cortisol-regulating areas (i.e., hippocampus, PFC), turning immune responses useless. Apart from neuronal regeneration, astrocytes are responsible of clearing the synaptic cleft of glutamate. Glucocorticoids also inhibit glutamine synthetase production, an enzyme relevant in breaking down glutamate allowing its recapture afterwards. A more significant presence of glutamate consequently increases intracellular calcium levels, which could precipitate apoptosis. Similarly, cortisol hinders glucose uptake in the brain resulting in reduced energy availability. This may compromise the capacity of neurons and astrocytes concerning glutamate regulation. Additionally, astrocytes are essential in preserving the integrity of endothelial cells supporting the BBB architecture. Biological insults to glial cells could induce leaking of such barrier. For obvious reasons, this barrier is more permeable in gland-neighbouring areas, such as the orbitofrontal, medial temporal, and occipital lobes. Metabolic and vascular deregulations occurring in type II diabetes have proved to augment its porosity, fittingly, at frontal and occipital lobes (Abuhaiba et al., 2018). Fibrinogen presence exacerbates inflammatory responses in animal models of Alzheimer's Disease (Ryu & McLarnon, 2009). Hence, an overly stimulated HPA axis can either insult the brain directly or hamper its natural immune responses.

In the light of the results in Study 1, the immunosuppressive hypothesis may explain the inconsistencies between groups. First, physiological stress responses activate glial cells to prevent neuronal loss, returning an apparent GM hypertrophy. Second, when stress responses are regularly demanded, the immune system becomes less efficient in preserving neuronal integrity. The first and second scenarios represent the pattern of cortical thickening and thinning that lean and overweight participants exhibited in Study 1. Our findings, which somehow mirrored a quadratic relationship, might have symbolised the transition from allostasis, a formerly adaptive reply to a challenging scenario, to allostatic load, a no longer beneficial status. Overweight subjects may lack resources to fight-back long-term stress outcomes as they likely have exhausted them when adapting to an energy surplus situation.

Oppositely, lean participants proved null associations between FA and AL index in Study 2. Presumably, grey and WM tissues could react in a different way to chronic stress. Typically, WM is more susceptible to the stress-related long-term comorbidities rather than to its short-term effects (Lundgaard, Osório, Kress, Sanggaard, & Nedergaard, 2014; Maillard et al., 2012). In accordance with our hypothesis, lean subjects would have probably fit best at the early stages of the AL model in which stress is acute rather than chronic. Another plausible explanation to the lack of results in this group could obey to the exclusion of participants presenting DWI artefacts. This particular setback occurred during a phase of the study in which the inclusion of lean participants was substantially more considerable, and therefore, the size of this group accused a higher loss (N = 7). Because of this, the statistical power to capture any significant effect could have been compromised, especially if such effect ranged from small to moderate. Also, and due to a combination of coincidences, it is also possible that the subjects that could have helped to find a meaningful result, if any, were precisely those that were excluded because of the DWI artefacts.

The biological source of the FA reductions, exclusively observed in the overweight group, could also be easily mistakable. As noted earlier, the extracellular free-water content may represent another confounder in the

DTI metrics estimation in TBSS analysis (Pasternak et al., 2009). During inflammation, microglia is activated to remove foreign molecules, waste or damaged cells. This inherently entails the increase in the content of interstitial water. The extracellular space lacks membranes restricting water movement. Hence, diffusivity in WM tracts spatially close to swollen tissue could derive in underestimate FA (Bergamino et al., 2016). This situation is, however, more problematic in VBM rather than in TBSS studies (Bergamino, Kuplicki, Victor, Cha, & Paulus, 2017). Nevertheless, accounting for FW content could assist in discriminating axonal degeneration from inflammation-induced neuropathy. We have performed post-hoc analysis with this correction to discern between those two pathological sources. Results showed a considerably reduction in the extension of the clusters. This suggested that there was a great contribution of the extracellular water content, and so inflammatory responses, in the original FA results. In consonance to the immunosuppressive hypothesis earlier introduced, long-term adaptations to overweight could have exhausted immunological resources to shield WM integrity.

Overall, our results demonstrated that overweight-related deregulations across several biological systems were detrimentally linked to brain structure and executive functioning. Although most of the works revisited for this thesis were performed in metabolically healthy overweight adults or have controlled for cardiovascular risk factors (Bettcher et al., 2013; Papageorgiou et al., 2017; Repple et al., 2018; Taki et al., 2008; Widya et al., 2011), very few have tested the joint effects of immune, neuroendocrine, or cardiometabolic deregulations. In their work, Bettcher et al. (2013) found that the negative relationship between BMI and FA diminished after adjusting for vascular and inflammatory markers. Oppositely, another work reported that the FA decreases in the genu of the corpus callosum and the cingulum bundle were only present after controlling for metabolic biomarkers (Birdsill et al., 2017). In Verstynen et al. (2013), adiposity, inflammation, and cardiometabolic deregulations showed competing each other to insult WM composition. A recent work exhibited that the increased circulating levels of lipopolysaccharide binding protein, an inflammatory biomarker, were negatively associated with FA after controlling for BMI influence (Moreno-Navarrete et al., 2017). These pieces of evidence support the notion that

physiological stress in overweight, rather than the excessive weight itself, may be central in inducing brain structural changes (Bettcher et al., 2013; Birdsill et al., 2017).

Still, no study has taken into account the confounding effects of inflammation over an apparent increase in GM density. Results from van Haren et al. (2011) and Qiu et al. (2014) open the debate that an increase in cortical thickness might not always mean positive. In this vein, augmentation in GM volume or thickness may precede later declines. Cytokines signal and mediate macrophage activity during acute inflammatory phases further leading to shrinking or losing of dendritic spines (Juster, McEwen, & Lupien, 2010). To date, the MRI scanners that most research groups have access to do not return images with enough resolution to allow the study of the different layers that make up the cortical mantle. In the face of an increase in GM volume, it is troublesome to discriminate inflammatory responses from compensatory mechanisms. Removing extracellular water content from T1-weighted images could offer a fair solution to this limitation (Montal et al., 2018).

All things considered, the escalation of an AL status among overweight participants was deleteriously correlated to the structure of brain regions involved in cognitive-control, reward-processing and integration of visceral information. Hypothetically, changes among these regions could prompt failures in blocking unnecessary caloric intake, boost motivation towards hedonic-based feeding, and obstruct correctly sensing of satiety-related signals. Additionally, increases in the AL index also negatively linked with cognitive flexibility, which is necessary for pondering the consequences of engaging in bad-dietary habits.

5.5. Strengths and limitations

This thesis has some strengths to remark. As far as we know, the three works included in this thesis were the first in assessing the relationship between AL, brain structure, and executive performance in overweight adults. Literature discrepancy perhaps obey to the fact that the concomitant biological deregulations to such condition are, somehow, ignored. Furthermore, our

strict exclusion criteria left out the potential confounding effects of ageing or cardiometabolic diseases. Thus, our results shown that, even in the absence of medical comorbidities, physiological adaptations to overweight negatively influenced the brain neuroanatomical characteristics and the executive functioning. This thesis could have helped to point out the need to intervene over concrete targets, such as tackling overweight-related chronic inflammation. Concerning the MRI analyses, the complexity of the cortical mantle is better characterised with surface-based approaches rather than traditional voxel-based techniques. Cortical thickness is more sensitive to GM atrophy than VBM. By the same token, geometrical distortions occurring in single-encoding EPI sequences likely compromise subject alignment and normalisation. We have overcome this issue by employing novel software in our regular pre-processing pipeline. Having done this, and along with the usage of a study-specific template, the analyses were performed on images anatomically more accurate. Finally, removing extracellular water content eased shedding a broader light on the nature of the observed FA decreases.

In the same way, this thesis has also some limitations that worth the commentary. The novelty of the AL topic results in a lack of consensus relative to its measurement. Authors characterise the AL with different biomarkers and approaches (i.e., high-risk percentiles, z-scores composites, canonical correlations). Additionally, and specific to the works hereby presented, the neuroendocrine system may be poorly represented as cortisol was the only measure available. Equally, the AL index might feel little revealing in some way as deregulations in biological systems may differently influence the dependent variable (i.e., cortical thickness, FA, or executive performance). Following this thought, some systems may even behave as protective factors by shock absorbing others' adverse effects. Given the exploratory nature of the study, and with the aim on establishing a first contact on the topic, the previous question should be explored in the future. On the other hand, the sample size was, unfortunately, the most significant limitation in all three studies. The limited number of volunteers could have both limited the power to find subtle differences between groups or curbed findings extrapolation. On another note, the cross-sectional nature of the study did

not allow draw reliable conclusions upon causality. Chronic physiological stress may be a risk factor for overweight just as overweight may be a risk factor for chronic physiological stress. As earlier noted in the introduction, stress increases the appetite for hyper-caloric food to restore energy reserves, while overweight may trigger unnecessary stress responses.

Minor limitations explicit to each study were also present. In relation to the interaction depicted in Study 1, the fact that groups exhibited different slopes do not imply that, if addressed separately, these correlations differed from zero. For instance, and although the relationship was inverse and still in line with the general discussion, the post-hoc correlation between AL and the right orbitofrontal cluster in the overweight was not statistically significant (r = -0.23, p = 0.184). Furthermore, non-parallel diffusion could occur in the absence of biological challenges because of axonal pruning during development or idiosyncrasies in WM topography. Water molecules are prone to aimlessly diffuse in long or light-packed tracts (Bach et al., 2014; Jones et al., 2013; Radua et al., 2014). Moreover, and depending on the author, crossing-fibres may ascend to 60% of the total WM tissue. By default, the diffusion-tensor model averages the water movement inside a voxel to shape a single-predominant diffusion direction. It is not an overstatement to think that, at least, two opposite-directed axons could pass through the same voxel. Consequently, crossing-fibres territories will return low anisotropy metrics, which would wrongly suggest the presence of an underlying pathological origin. Hence, findings in Study 2 and other works serving TBSS as a method to analyse the WM microstructure may require further replication with state-of-the-art models in diffusion imaging to override this particular pitfall (e.g., q-ball imaging, ball-n-stick models, or funk-radon transformation).

5.6. Further research proposals

On a general note, future works should start pivoting in the direction of exploring which biological deregulation explains most of the variance relative to the brain and cognitive changes associated to an overweight

status. Similarly, evidence has broadly shown that stress can negatively bias eating behaviour and body weight control (Adam & Epel, 2007; Born et al., 2009; Chao, Grilo, White, & Sinha, 2015; Laugero Kevin D, Tryon, Carter, & DeCant, 2013; Razzoli, Pearson, Crow, & Bartolomucci, 2017; Sinha & Jastreboff, 2013; Sominsky & Spencer, 2014). However, since not all chronically stressed people eat uncontrollably or put on weight, other socioeconomic, psychological, and genetic factors should not be ruled out. In this sense, the AL has been linked to low socioeconomic status (Seeman, Stein Merkin, Karlamangla, Koretz, & Seeman, 2014), which may predispose to lesser academic and professional success. A well-rounded personality is not only better equipped to deal with the negative effects of stress alone, but it also favours the support from social networks critical when stressful circumstances happen. Greater AL relates to increased neuroticism and decreased extraversion. The cumulative effects of stress are particularly corrosive to the wellness of supporting networks, as the desire to establish relationships with others tend to decline when the AL exceeds a specific burden (Stephan, Sutin, Luchetti, & Terracciano, 2016). Additionally, the effects of the genetic BDNF val ^{66}met variant could be essential as neurotrophic factors are central in fighting back the unfavourable impact of sustained immune responses (Xu et al., 2017). Last but not least, a critical issue to target in the short-term should be to inquire how reversible these changes are. Some works have tested the effects of medical or behavioural interventions in subjects with mild or severe obesity. After treatment, participants with an excessive weight have recovered from brain abnormalities (Faulconbridge et al., 2016; Yuan, 2016), physiological deregulations (Illan-Gomez et al., 2012), and cognitive impairments (Veronese et al., 2017).

Special mention to the focus that the study of the gut-microbiota composition and gut-brain communications have recently attracted. Today these topics stand as both refreshing and promising in overweight and other medical conditions research. It has been shown that, when compared to normal-weight subjects, overweight participants tend to hold a less diverse bacterial population with increases in pro-inflammatory strains.

Inoculating obesity-like strains in mice cause rodents to be metabolically less efficient, maintain a state of chronic inflammation, and exhibit more cardiometabolic diseases (Jiao et al., 2018; Rosenbaum, Knight, & Leibel, 2015; Zou et al., 2018). Pro-inflammatory bacteria augment the porosity of the intestinal epithelium, which settles a status of chronic inflammation. Ultimately, beneficial bacteria not only ward potentially pathological strains to colonise the host but also makes the most of consumed meals, which could result in more accurate satiety responses. Likewise, a by-product from fibre-fermenting bacteria reduces insulin-resistance and inflammation by decreasing the production of TNF-alpha. Therefore, the interaction between the diet and the gut-brain axis should be addressed for mediating in overweight-related adverse outcomes (Cani & Jordan, 2018).

CHAPTER 6 – CONCLUSIONS

- When compared to healthy-weight controls, overweight subjects showed higher AL indexes suggesting a greater state of chronic physiological stress.
- The relationship between the AL increase and the cortical GM integrity proved to be dependent on body-weight status. Conversely, lean participants presented cortical thickening in relation to the AL increase. As expected, overweight exhibited reductions in GM structure along with an AL escalation.
- Similarly, the relationship between the AL index intensification and the FA demonstrated being group-dependent. Lean participants did not present either negative or positive correlations in FA with the AL index increments. Again, only overweight subjects revealed an inverse correlation between AL and FA values.
- The escalation in the AL index was, regardless of the group, related to worse inhibitory control. When addressed separately, overweight individuals presented reductions in cognitive flexibility performance relative to an AL increase. This correlation was weak and positive in the healthy-weight group.
- In sum, our results showed that an overweight status was related to long-term biological changes. These changes, in turn, and independently from the direct effects that adiposity may have, were negatively linked to brain structure and executive functioning. The structures presenting neuroanatomical changes are known for being involved in supervising eating behaviour, processing the food-related rewarding properties, and sensing homeostasis-related signalling. Executive functions, and particularly cognitive flexibility, are necessary in goal-oriented behaviours such as regulating caloric intake.

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SUPPLEMENTARY MATERIAL

SUPPLEMENTARY TABLE 1 | FINDINGS IN GREY MATTER CHANGES (1/5)

Author	Sample	Nuisance	Pattern	Findings
Bobb et al. 2014	N = 347 Visit 1 Age = 60.1 Visit 2 Age = 65.1 Females N.R.	Race, APOE, age, smoking & ICV	↑ BMI ↓ GM	Temporal and occipital lobes
Figley et al. 2016	N = 32 Age = 29.8 16 females	Age & Sex	↑ BMI ↓ GM ↑ BF% ↓ GM	Subcallosal cortex L, Precuneus R, Accumbens L, Lingual L
García-García et al. 2018	N = 378 Age = 28.67 216 females	Age & Sex	↑ BMI ↓ GM	Medial frontal R, Crus II L/R, VIIIb L/R, temporal pole L, inferior parietal L, precentral L
Hassenstab et al. 2012	19 Lean (43.6 yrs.) 17 Obese (47.8 yrs.) 47 females	Age, Sex & anti-HTA medication	HW > OB	Anterior cingulate L/R, insula L/R, superior parietal L/R
He et al. 2015	N = 335 Age = 20.38 195 females	None	↑ BMI ↓ GM	Cingulate L, orbitofrontal L, frontal medial L
Horstmann et al. 2011	N = 122 Age = 25.35 61 females	Age	↑ BMI ↑ GM	Subcallosal cortex L/R, orbitofrontal R, putamen L
Jagust et al. 2005	N = 112 Age = 69.7 Females N.R.	Age	↑ BMI ↑ GM	Amygdala L/R, hippocampus L
Janowitz et al. 2015 (I)	N = 758 Age = 49.8 408 females	Age & Sex	↑ WC ↓ GM	Planum temporale L, superior temporal L/R, frontal medial R, orbitofrontal L, VIIb R, Crus I-II L, parahippocampal L, inferior frontal L/R, supramarginal R, thalamus L/R, postcentral L, cingulate L/R, temporal pole L, lingual R, precuneus R, lateral occipital L, fusiform L
Janowitz et al. 2015 (II)	N = 1586 Age = 46.3 849 females	Age & Sex	↑ WC ↓ GM	Frontal pole R, VIIb L/R, inferior temporal L, postcentral L

SUPPLEMENTARY TABLE 1 | CONTINUATION (2/5)

Author	Sample	Nuisance	Pattern	Findings
Karlsson et al. 2013	22 Lean (46.4 yrs.) 23 Obese (47.3 yrs.) 33 females	None	HW > OB	Occipital pole L/R, inferior frontal L/R, angular R, temporal pole R, planum temporale R, inferior temporal L, middle temporal R
Kaur et al. 2015	N = 103 Age = 49.63 54 females	Age, SBP, total cholesterol & glucose	↑ VFM ↑ GM ↑ VFI ↑GM	Superior temporal L
Kim et al. 2015	N = 1777 Age = 63.75 890 females	N.R.	↑ BF % ↑ GM ↑ WHR ↓ GM	All lobes (men) Total and frontal GM (men)
Kurth et al. 2013	N = 115 Age = 47.17 61 females	Age &Sex	↑ WC/BMI ↓ GM	Thalamus L/R, caudate L, superior frontal L, frontal pole L/R, middle temporal L/R, temporal pole L/R, VI R, VI vermis L, crus I L, inferior temporal L/R, inferior frontal L, angular gyrus L/R, parietal operculum L, planum temporale L, fusiform L, supramarginal R, postcentral R, parahippocampal L, orbitofrontal L, insula L, anterior cingulate R, sup. motor cortex R, posterior cingulate R, temporal pole L/R, precentral L, supramarginal L, central opercular L, cuneus L/R, occipital pole R, angular gyrus L, lateral occipital L, preuneus R, intracalcarine R
Marqués-Iturria et al. 2013	19 Obese (33.7 yrs.) 18 Lean (32.3 yrs.) 24 females	Age, Sex & Education	HW > OB	Frontal superior L, frontal medial R
Masouleh et al. 2016	N = 617 Age = 68.7 258 females	Age & Sex	↑ BMI ↓ GM	Frontal medial R, frontal pole L/R, subcallosal cortex R, orbitofrontal R, paracingulate L, precentral L, planum temporale L/R, insula L/R, parahippocampal L/R, fusiform L, occipital fusiform L/R, middle temporal L, intracalcarine R, thalamus R, Crus I L/R

SUPPLEMENTARY TABLE 1 | CONTINUATION (3/5)

Author	Sample	Nuisance	Pattern	Findings
Mathar et al. 2015	23 Lean (25.2 yrs.) 19 Obese (27 yrs.) 20 females	Age & Sex	HW > OB	Frontal pole R, inferior frontal L
Medic et al. 2016	N = 203 Age = 32.3 79 females	Age, Sex, Scan-time, Surface & Hemisphere	↑ BMI ↓ GM	Lateral occipital L, orbitofrontal R
Opel et al. 2017 (I)	N = 330 Age = 39.2 172 females	Age & Sex	↑ BMI ↓ GM	Frontal pole L/R, thalamus R, precentral L/R, superior temporal L, planum temporale L
Opel et al. 2017 (II)	N = 347 Age = 51.6 155 females	Age & Sex	↑ BMI ↓ GM	Supramarginal L/R, frontal pole L/R, subcallosal cortex R, superior temporal L, inferior frontal L/R, orbitofrontal L, lateral occipital L, posterior cingulate L, thalamus L, middle temporal L
Pannacciulli et al. 2006	36 Lean (33 yrs.) 24 Obese (32 yrs.) 24 females	Age & Sex	HW > OB HW < OB	Lateral occipital R, precentral L/R, putamen L/R, frontal pole R, middle frontal L Precuneus L, lateral occipital L, lingual L, frontal pole L/R, occipital pole R
Shott et al. 2015	42 Lean (24.42 yrs.) 18 Obese (28.67 yrs.) Age = 26.55	None	HW > OB	Temporal pole L, accumbens R, frontal pole R, orbitofrontal R, subcallosal R, hippocampus L/R
Taki et al. 2008(*)	N = 1428 Age = 45.45 738 females	Age, Alcohol, HTA & T2D	↑ BMI ↑ GM ↑ BMI ↓ GM	Inferior frontal L/R, cerebellum L/R, superior frontal R, superior temporal R, middle temporal L, thalamus L/R, cingulate R, caudate L/R, inferior temporal R, precentral L Uncus L/R, cerebellum L/R, fusiform L, superior parietal R, precentral R, inferior frontal R, precuneus L/R, superior frontal L, midbrain R

SUPPLEMENTARY TABLE 1 | CONTINUATION (4/5)

Author	Sample	Nuisance	Pattern	Findings
Tuulari et al. 2016	47 Obese (44.9 yrs.) 29 Lean (45.9 yrs.) 65 females	Age	HW > OB	Superior temporal L, frontal medial R, orbitofrontal R, thalamus R, caudate L, occipital pole L/R, angular gyrus R, lateral occipital L, inferior temporal L/R, fusiform L/R, middle temporal R, fusiform R, VI R, Crus I L/R, superior parietal R, parahippocampal R, amygdala R
Vainik et al. 2018	N = 895 Age = 28.83 482 females	Age, Sex, Race, Ethnicity, Handedness & Drug	↑ BMI ↑ GM	Superior frontal L, inferior frontal L, parietal L/R
			↑ BMI ↓ GM	Inferior frontal R, entorhinal L/R, parahippocampal L/R
Veit et al. 2014	N = 72 Age = 29.65 30 females	Age, Sex, Surface & Education	↑ BMI ↓ GM	Lateral occipital L, inferior temporal L, precentral L, inferior parietal L
			↑ VAT ↓ GM	Lateral occipital L, inferior temporal L, precentral L, inferior parietal L, insula R, fusiform L, inferior temporal R
Walther et al. 2010	N = 95 Age = 69.26 95 females	Age	↑ BMI ↓ GM	Frontal pole L/R, precentral R, fusiform L, crus I R
Weise et al. 2013	N = 76 Age = 32.1 24 females	Age & Sex	↑ FMI ↓ GM	Inferior temporal L, middle temporal L, inferior frontal R, orbitofrontal L
			↑ BF% ↓ GM	Crus II L, inferior temporal L, lateral occipital R
Weise et al. 2017	N = 875 Age = 28.8 489 females	Age & Sex	↑ BMI ↑ GM	Subcallosal cortex R, orbitofrontal R, VIIIa L
			↑ BMI ↓ GM	Frontal pole L/R, VI R, VIIb L/R, crus I R, crus II L/R, fusiform L/R, middle temporal R, VIIIa L, interior temporal R, lingual R, precentral L/R, lateral occipital L, superior frontal L/R, anterior cingulate L/R, posterior cingulate R, paracingulate L

SUPPLEMENTARY TABLE 1 | CONTINUATION (5/5)

Author	Sample	Nuisance	Pattern	Findings
Wydia et al. 2011	140 Lean (74.8 yrs.) 256 Overweight (74.3 yrs.) 75 Obese (73.8 yrs.) 208 females	Age, Sex, Smoking, HTA & Prevastatin	HW < OB ↑ BMI ↑ GM	Amygdala L/ R, hippocampus L
Yao et al. 2016	N = 109 Age = 35.15 62 females	Age & Sex	↑ BMI ↓ GM ↑ BMI ↑ GM	Posteriro cingulate L, X R, crus I R, putamen R Fusiform L/R, VIIb L, crus II R, angular R, inferior temporal L, thalamus L, paracingulate R, anterior cingulate L, middle temporal L/R, superior frontal L, fusiform L/R, lateral occipital L, inferior temporal R, superior parietal R, VIIIa L, orbitofrontal L, temporal pole R, postcentral L/R, temporal pole L, VIIIb R, frontal operculum R, hippocampus L, frontal pole R
Zhang et al. 2017	20 Lean (20-28 range) 20 Obese (20-28 range) 0 females	Age	HW < OB	Frontal pole L

HW, healthy weight, OW, overweight, OB, obesity, BMI, body-mass index, GM, grey matter, WC, waist-circumference, WHR, waist-to-hip ratio, FMI, fat-mass index, BF%, body fat percentage, VAT, visceral adipose tissue, VFM, visceral fat mass, VFI, visceral fat index, SBP, systolic blood pressure, HT, hypertension, ICV, intracranial volume. L, left, R, right. (*) Results only in men.

SUPPLEMENTARY TABLE 2 | FINDINGS IN WHITE MATTER CHANGES (1/2)

Author	Sample	Nuisance	Results	Findings
Birdsill et al. 2017	N = 168 49.5 years 96 females	Age, Sex, Glucose, Triglycerides, SBP & HDL	↑ WC ↑ FA	Superior corona radiata L/R, superior longitudinal fasciculus L/R, body of the corpus callosum, cingulum L/R, posterior limb of the internal capsule L/R, splenium of the corpus callosum, posterior thalamic radiation L/R, anterior limb of the internal capsule L/R, external capsule L/R
He et al. 2013	N = 336 Age = 20.38 195 females	None	↑ BMI ↓ FA	Cingulum L/R
Karlsson et al. 2013	22 Lean (46.5 yrs.) 23 Obese (47.3 yrs.) 33 females	None	HW > OB	Corticospinal tract L/R, optid radiation L/R, corpus callosum, inferior fronto-occipital fasciculus R
Kullmann et al. 2016	24 Lean (26.68 yrs.) 24 Overweight (26.50 yrs.) 14 females	Age, Sex & ICV	↑ BMI ↓ FA	Middle cerebellar peduncle
Mueller et al. 2011(*)	N = 49 Age = 26.4 23 females	Age	↑ BMI ↓ FA	Splenium of the corpus callosum
Papageourgiou et al. 2017	120 Lean (39.8 yrs.) 96 Overweight (51.5 yrs.) 52 Obese (52.0 yrs.) 153 females	Age & Sex	HW > OW	Posterior thalamic radiation R, inferior fronto-occipital fasciculus R, inferior longitudinal fasciculus R, anterior thalamic radiation R, optic radiation R, body of corpus callosum, uncinated fasciculus R, forceps minor, corticospinal tract R, retrolenticular part of internal capsule R
Repple et al. 2018 (I)	N = 369 Age = 39.39 186 females	Age & Sex	↑ BMI ↓ FA	Posterior thalamic radiation L, corticospinal tract R, cerebellar peduncle L

SUPPLEMENTARY TABLE 2 | FINDINGS IN WM CHANGES (2/2)

Author	Sample	Nuisance	Results	Findings
Repple et al. 2018 (II)	N = 1064 Age =28.75 574 females	Age, Sex, Hb1Ac & SBP	↑ BMI ↓ FA	Cerebellar peduncle L
Ryan et al. 2014	N = 94 Age = 69.33 years 94 females	Age, HTA & Diabetes	↑ BMI ↓ FA	Corticospinal tract R
Shott et al. 2015(*)	42 Lean (24.42 yrs.) 18 Obese (28.67 yrs.) 60 females	None	HW > OB	Anterior corona radiata R, superior corona radiata L/R, sagittal stratum L/R, external capsule L, uncinated fasciculus L, inferior fronto-occipital fasciculus L/R, inferior longitudinal fasciculus L/R
Stanek et al. 2011	N = 103 Age = 46.80 46 females	Age & Depression	↑ BMI ↓ FA	Genu, splenium and body of corpus callosum, fornix
Verstynen et al. 2012	N = 28 Age = 30 17 females	Age & Sex	↑ BMI ↓ FA	Pontine crossing tract, body of corpus callosum, corticospinal tract, medial leminiscus, inferior/ middle/superior cerebellar peduncle, cerebellar peduncle, internal capsule, superior corona radiata, cingulum, superior fronto-occipital fasciculus
Verstynen et al. 2013	N = 155 Age = 40.7 77 females	Age, Sex & Education	↑ BMI ↓ FA	Anterior corona radiata L/R
Xu et al. 2013	N = 51 Age = 27.4 21 females	Age & Sex	↑ BMI ↓ FA	Body of the corpus callosum
Zhang et al. 2018	N = 1255 Age = 55.43 636 females	Age, Sex & WMHV	↑ BMI ↓ FA ↑ WHR ↓ FA	Multiple WM tracts

HW, healthy weight, OW, overweight, OB, obese, BMI, body-mass index, FA, fractional anisotropy, WC, waist-circumference, WHR, waist-to-hip ratio, HDL, high-density cholesterol, Hb1Ac, glycated haemoglobin, SBP, systolic blood pressure, HTA, hypertension, ICV, intracranial volume, WMHV, white-matter hyperintensity volume, L, left, R, right. (*) Results only in women.


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