Title: Allostatic load and executive functions in overweight adults

Authors: Ottino-González, J.[a,b,c], Jurado, M.A.[a,b,c], García-García, I.[d], Caldú, X.[a,b,c], Prats-Soteras, X.[a,b,c], Tor, E.[e], Sender-Palacios, M.J.[e], Garolera, M.[f,g].

Affiliations:

(a) Departament de Psicologia Clínica i Psicobiologia, Universitat de Barcelona (Spain)
(b) Institut de Neurociències, Universitat de Barcelona (Spain)
(c) Institut de Recerca Sant Joan de Déu, Hospital Sant Joan de Déu (Spain)
(d) Montreal Neurological Institute, McGill University (Canada)
(e) CAP Terrassa Nord, Consorci Sanitari de Terrassa (Spain)
(f) Hospital de Terrassa, Consorci Sanitari de Terrassa (Spain)
(g) Brain, cognition and behaviour research group, Consorci Sanitari de Terrassa (Spain)

Corresponding author:

Dr. María Ángeles Jurado

majurado@ub.edu

Facultat de Psicologia, Passeig de la Vall d’Hebron, 171 (08035, Barcelona).

Tel: + 34 93 312 50 55.

Background/Objective: 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. **Method:** Forty-seven healthy-weight and 56 overweight volunteers aged from 21-40 underwent medical and neuropsychological examination. **Results:** 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. **Conclusions:** 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 sustain rigid-like behaviours and attitudes towards food.

Keywords: allostatic load; stress; inflammation; executive functions; overweight; BMI

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). According to 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, poor quality of life, and accelerated brain ageing (Cole et al., 2017; Juster et al., 2010). We have previously demonstrated that an overweight 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 performance 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 accordance 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 and conducting analyses using 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) right 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, with greater scores indicating better performance. 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 ($\pm$ 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 an 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 & 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 (mean and standard deviation, range, and frequency)

	Overweight (N = 56)		**Healthy-weight (N = 47)**	
Age	31.52 (5.99)	21 – 40	30.15 (6.14)	21 – 40
Education	13.20 (2.60)	9 – 20	14.15 (2.47)	9 – 18
Males	19		19	
Females	37		28	
Contraceptives	5		5	
Medication	6		4	
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	-0.06 (1.08)	-2.44 – 3.16	0.07 (0.90)	-1.43 – 2.66
Inhibitory control	-0.06 (0.95)	-2.46 – 2.78	0.08 (1.07)	-2.74 – 2.22
Working memory	-0.17 (1.11)	-2.64 – 2.32	0.20 (0.81)	-1.28 – 1.87

BMI = body mass index (kg/m²), WHTR = waist-to-height ratio (cms), AL = Allostatic Load (sex-adjusted)

Table 2. Family income in euros per month and professional level (frequency, %)

	Overweight (N = 56)	**Healthy-weight (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

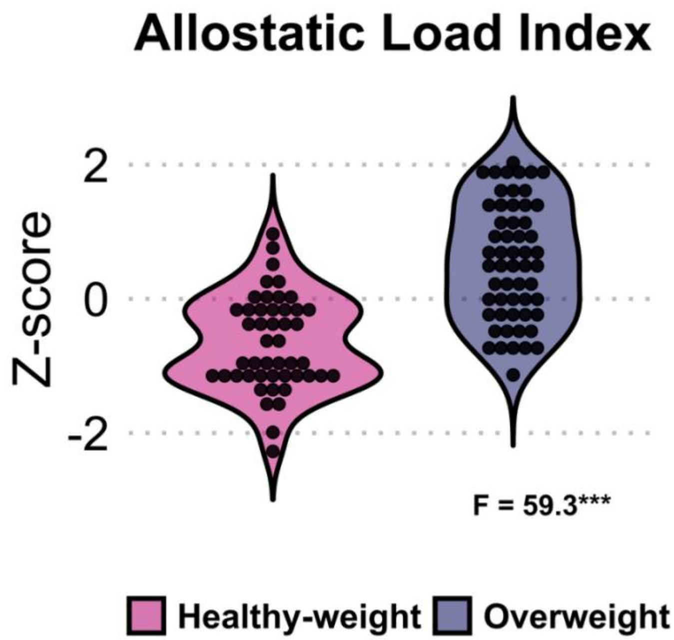

Figure 1. Comparison between groups for the AL index. The overweight group (density map in purple) exhibited a greater AL index score than the healthy-weight group (density map in pink). ***$p < 0.001$

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.

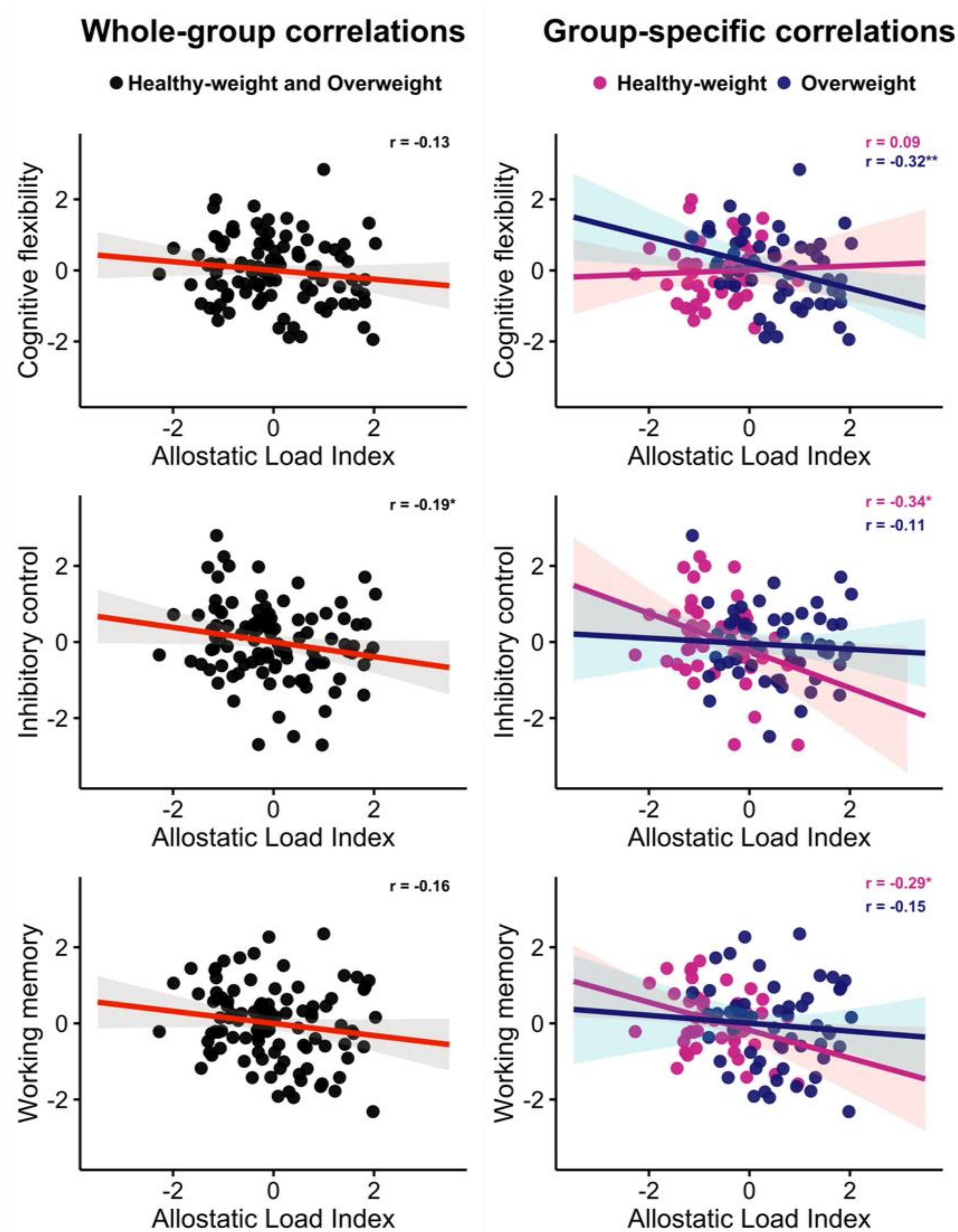

Figure 2. Correlations between the AL index and core EF in the entire group (on the right, black = all participants), and accounting for groups (on the left, pink = healthy-weight, purple = overweight). * $p < 0.05$, ** $p < 0.01$

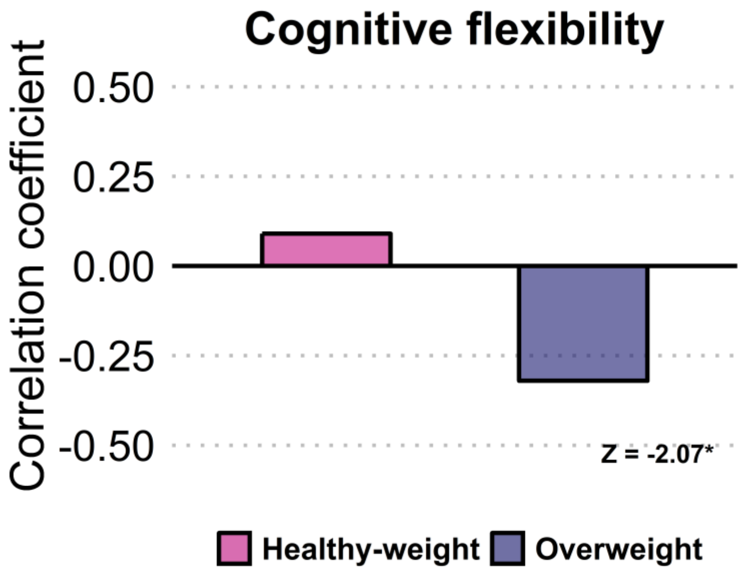

Figure 3. Group-specific correlation comparison for AL Index and core EF (pink = healthy-weight, purple = overweight). * $p < 0.05$

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 the 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 disturb 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 disturb 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 were not different between groups. 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 differences between groups, we have additionally repeated this analysis comparing individuals with obesity (N= 34) to normal-weight subjects (N = 47). Groups did not differ 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 kind 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

María Ángeles Jurado and Maite Garolera received funding from the Spanish Ministry of Economy, Industry and Competitiveness (PS2013-48045 and PSI2017-86536). Jonatan Ottino González was awarded a PhD fellowship from the University of Barcelona (ADR2015-2016).

7. References

Bianchi, V.E., 2019. The Anti-Inflammatory Effects of Testosterone. J. Endocr. Soc. 3, 91–107. https://doi.org/10.1210/js.2018-00186

Bischof, G.N., Park, D.C., 2015. Obesity and Aging. Psychosom. Med. 77, 697–709. https://doi.org/10.1097/PSY.0000000000000212

Booth, T., Royle, N.A., Corley, J., Gow, A.J., Valdés Hernández, M. del C., Muñoz Maniega, S., Ritchie, S.J., Bastin, M.E., Starr, J.M., Wardlaw, J.M., Deary, I.J., 2015. Association of allostatic load with brain structure and cognitive ability in later life. Neurobiol. Aging 36, 1390–9. https://doi.org/10.1016/j.neurobiolaging.2014.12.020

Bourassa, K., Sbarra, D.A., 2017. Body mass and cognitive decline are indirectly associated via inflammation among aging adults. Brain. Behav. Immun. 60, 63–70. https://doi.org/10.1016/j.bbi.2016.09.023

Caleyachetty, R., Thomas, G.N., Toulis, K.A., Mohammed, N., Gokhale, K.M., Balachandran, K., Nirantharakumar, K., 2017. Metabolically Healthy Obese and Incident Cardiovascular Disease Events Among 3.5 Million Men and Women. J. Am. Coll. Cardiol. 70, 1429–1437. https://doi.org/10.1016/j.jacc.2017.07.763

Calvo, D., Galioto, R., Gunstad, J., Spitznagel, M.B., 2014. Uncontrolled eating is associated with reduced executive functioning. Clin. Obes. 4, 172–179. https://doi.org/10.1111/cob.12058

Cole, J.H., Ritchie, S.J., Bastin, M.E., Valdés Hernández, M.C., Muñoz Maniega, S., Royle, N., Corley, J., Pattie, A., Harris, S.E., Zhang, Q., Wray, N.R., Redmond, P., Marioni, R.E., Starr, J.M., Cox, S.R., Wardlaw, J.M., Sharp, D.J., Deary, I.J., 2017. Brain age predicts mortality. Mol. Psychiatry 00, 1–8. https://doi.org/10.1038/mp.2017.62

Coppin, G., Nolan-Poupart, S., Jones-Gotman, M., Small, D.M., 2014. Working memory and reward association learning impairments in obesity. Neuropsychologia 65, 146–55. https://doi.org/10.1016/j.neuropsychologia.2014.10.004

Diamond, A., 2014. Executive Functions. Annu. Rev. Clin. Psychol. 64, 135–168. https://doi.org/10.1146/annurev-psych-113011-143750.Executive

Diedenhofen, B., Musch, J., 2015. cocor: A Comprehensive Solution for the Statistical Comparison of Correlations. PLoS One 10, e0121945. https://doi.org/10.1371/journal.pone.0121945

Dohle, S., Diel, K., Hofmann, W., 2018. Executive functions and the self-regulation of eating behavior: A review. Appetite 124, 4–9. https://doi.org/10.1016/j.appet.2017.05.041

Elias, M.F., Goodell, A.L., Waldstein, S.R., 2012. Obesity, cognitive functioning and dementia: back to the future. J. Alzheimers. Dis. 30 Suppl 2, S113-25. https://doi.org/10.3233/JAD-2011-111175

First, M.B., Spitzer, R.L., Gibbon, M., Williams, J.B.W., 1999. Structured Clinical Interview for DSM-IV Axis I Disorders-Clinician. Masson, Barcelona.

Fitzpatrick, S., Gilbert, S., Serpell, L., 2013. Systematic Review: Are Overweight and Obese Individuals Impaired on Behavioural Tasks of Executive Functioning? Neuropsychol. Rev. 23, 138–156. https://doi.org/10.1007/s11065-013-9224-7

Golden, C.J., 1995. STROOP, test de colores y palabras, TEA Ediciones. TEA Ediciones.

Goodale, T., Sadhu, A., Petak, S., Robbins, R., 2017. Testosterone and the Heart. Methodist Debakey Cardiovasc. J. 13, 68–72. https://doi.org/10.14797/mdcj-13-2-68

Guillemot-Legris, O., Muccioli, G.G., 2017. Obesity-Induced Neuroinflammation: Beyond the Hypothalamus. Trends Neurosci. https://doi.org/10.1016/j.tins.2017.02.005

Heaton, R.K., 1999. Wisconsin Card Sorting Test: Computer Version 4-Research Edition. Psychol. Assess. Resour. 4.

Henderson, M., Freeman, C.P., 1987. A self-rating scale for bulimia. The “BITE.” Br. J. Psychiatry J. Ment. Sci. 150, 18–24.

Herrero, M.J., Blanch, J., Peri, J.M., De Pablo, J., Pintor, L., Bulbena, A., 2003. A validation study of the hospital anxiety and depression scale (HADS) in a Spanish population. Gen. Hosp. Psychiatry 25, 277–283.

Juster, R.P., McEwen, B.S., Lupien, S.J., 2010. Allostatic load biomarkers of chronic stress and impact on health and cognition. Neurosci. Biobehav. Rev. 35, 2–16. https://doi.org/10.1016/j.neubiorev.2009.10.002

Karlamangla, A.S., Miller-Martinez, D., Lachman, M.E., Tun, P.A., Koretz, B.K., Seeman, T.E., 2014.

Biological correlates of adult cognition: Midlife in the United States (MIDUS). Neurobiol. Aging 35, 387–394. https://doi.org/10.1016/j.neurobiolaging.2013.07.028

Kim, S., 2015. ppcor: An R Package for a Fast Calculation to Semi-partial Correlation Coefficients. Commun. Stat. Appl. Methods 22, 665–674. https://doi.org/10.5351/CSAM.2015.22.6.665

Lasselin, J., Magne, E., Beau, C., Aubert, A., Dexpert, S., Carrez, J., Layé, S., Forestier, D., Ledaguenel, P., Capuron, L., 2016. Low-grade inflammation is a major contributor of impaired attentional set shifting in obese subjects. Brain. Behav. Immun. 58, 63–68. https://doi.org/10.1016/j.bbi.2016.05.013

Lavagnino, L., Arnone, D., Cao, B., Soares, J.C., Selvaraj, S., 2016. Inhibitory control in obesity and binge eating disorder: A systematic review and meta-analysis of neurocognitive and neuroimaging studies. Neurosci. Biobehav. Rev. 68, 714–726. https://doi.org/10.1016/j.neubiorev.2016.06.041

Luine, V.N., 2014. Estradiol and cognitive function: Past, present and future. Horm. Behav. 66, 602–618. https://doi.org/10.1016/j.yhbeh.2014.08.011

McEwen, B.S., Nasca, C., Gray, J.D., 2016. Stress Effects on Neuronal Structure: Hippocampus, Amygdala, and Prefrontal Cortex. Neuropsychopharmacology 41, 3–23. https://doi.org/10.1038/npp.2015.171

Mucci, N., Giorgi, G., De Pasquale Ceratti, S., Fiz-Pérez, J., Mucci, F., Arcangeli, G., 2016. Anxiety, Stress-Related Factors, and Blood Pressure in Young Adults. Front. Psychol. 7. https://doi.org/10.3389/fpsyg.2016.01682

Ottino-González, J., Jurado, M.A., García-García, I., Segura, B., Marqués-Iturria, I., Sender-Palacios, M.J., Tor, E., Prats-Soteras, X., Caldú, X., Junqué, C., Garolera, M., 2017. Allostatic Load Is Linked to Cortical Thickness Changes Depending on Body-Weight Status. Front. Hum. Neurosci. 11, 1–11. https://doi.org/10.3389/fnhum.2017.00639

Ottino-González, J., Jurado, M.A., García-García, I., Segura, B., Marqués-Iturria, I., Sender-Palacios, M.J., Tor, E., Prats-Soteras, X., Caldú, X., Junqué, C., Pasternak, O., Garolera, M., 2018. Allostatic load and disordered white matter microstructure in overweight adults. Sci. Rep. 8, 15898. https://doi.org/10.1038/s41598-018-34219-8

Perpiñá, C., Segura, M., Sánchez-Reales, S., 2017. Cognitive flexibility and decision-making in eating disorders and obesity. Eat. Weight Disord. - Stud. Anorexia, Bulim. Obes. 22, 435–444. https://doi.org/10.1007/s40519-016-0331-3

R Core Team, 2018. R: A Language and Environment for Statistical Computing.

Reilly, S.M., Saltiel, A.R., 2017. Adapting to obesity with adipose tissue inflammation. Nat. Rev. Endocrinol. 13, 633–643. https://doi.org/10.1038/nrendo.2017.90

Reitan, R.M., 1958. Validity of the Trail Making Test as an indicator of organic brain damage. Percept Mot Ski. 8, 271–276.

Restivo, M.R., McKinnon, M.C., Frey, B.N., Hall, G.B., Syed, W., Taylor, V.H., 2017. The impact of obesity on neuropsychological functioning in adults with and without major depressive disorder. PLoS One 12, e0176898. https://doi.org/10.1371/journal.pone.0176898

Shields, G.S., Moons, W.G., Slavich, G.M., 2017. Inflammation, Self-Regulation, and Health: An Immunologic Model of Self-Regulatory Failure. Perspect. Psychol. Sci. 12, 588–612. https://doi.org/10.1177/1745691616689091

Smith, E., Hay, P., Campbell, L., Trollor, J.N., 2011. A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. Obes. Rev. 12, 740–755. https://doi.org/10.1111/j.1467-789X.2011.00920.x

Spitoni, G.F., Ottaviani, C., Petta, A.M., Zingaretti, P., Aragona, M., Sarnicola, A., Antonucci, G., 2017. Obesity is associated with lack of inhibitory control and impaired heart rate variability reactivity and recovery in response to food stimuli. Int. J. Psychophysiol. 116, 77–84. https://doi.org/10.1016/j.ijpsycho.2017.04.001

Spyridaki, E.C., Avgoustinaki, P.D., Margioris, A.N., 2016. Obesity, inflammation and cognition. Curr. Opin. Behav. Sci. 9, 169–175. https://doi.org/10.1016/j.cobeha.2016.05.004

Vallis, M., 2016. Quality of life and psychological well-being in obesity management: improving the odds of success by managing distress. Int. J. Clin. Pract. 70, 196–205. https://doi.org/10.1111/ijcp.12765

Wechsler, D., 1999. WAIS III. Escala de Inteligencia de Wechsler para adultos III (adaptación española ed.). TEA Editores S.A., Madrid.

Whitelock, V., Nouwen, A., van den Akker, O., Higgs, S., 2018. The role of working memory subcomponents in food choice and dieting success. Appetite 124, 24–32. https://doi.org/10.1016/j.appet.2017.05.043

World Health Organization, 2016. Obesity and overweight [WWW Document]. WHO. URL http://www.who.int/mediacentre/factsheets/fs311/en/ (accessed 12.16.16).

Yang, Y., Shields, G.S., Guo, C., Liu, Y., 2018. Executive function performance in obesity and overweight individuals: A meta-analysis and review. Neurosci. Biobehav. Rev. 84, 225–244. https://doi.org/10.1016/j.neubiorev.2017.11.020

Zigmond, A.S., Snaith, R.P., 1983. The Hospital Anxiety and Depression Scale. Acta Psychiatr. Scand. 67, 361–370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x

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).

A. 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.

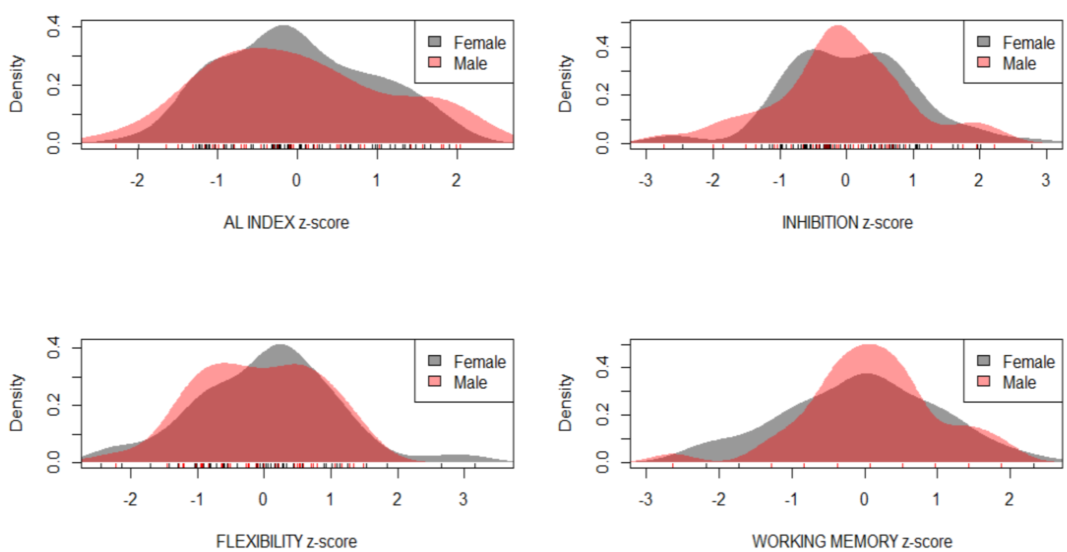

Figure 1 – Density distribution on variables of interest between males and females (z-scores)

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.

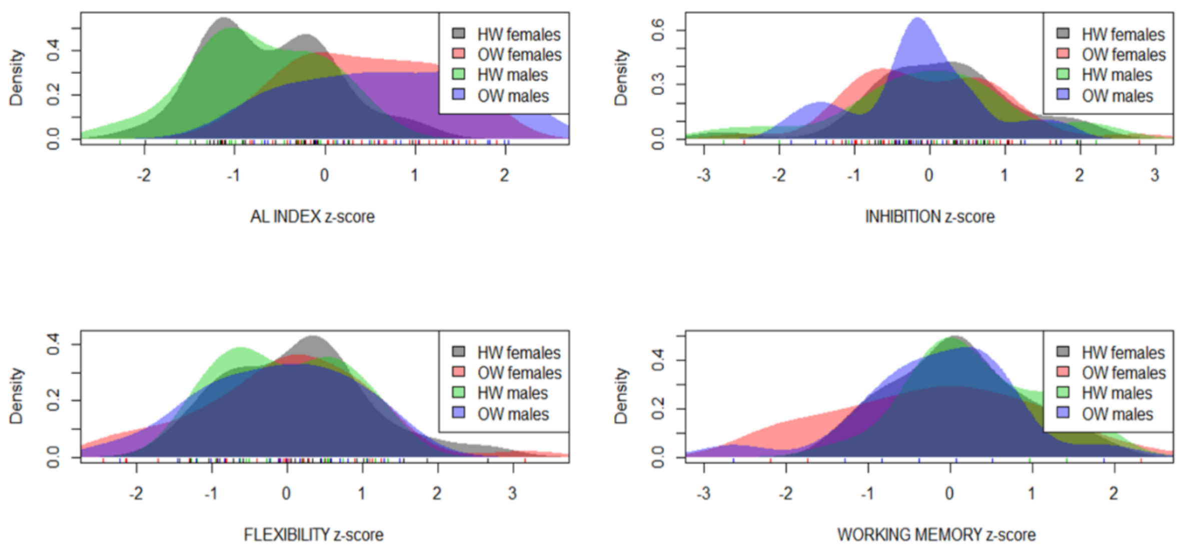

Figure 2 – Density plots accounting for sex and BMI group for variables of interest (z-scores)

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.

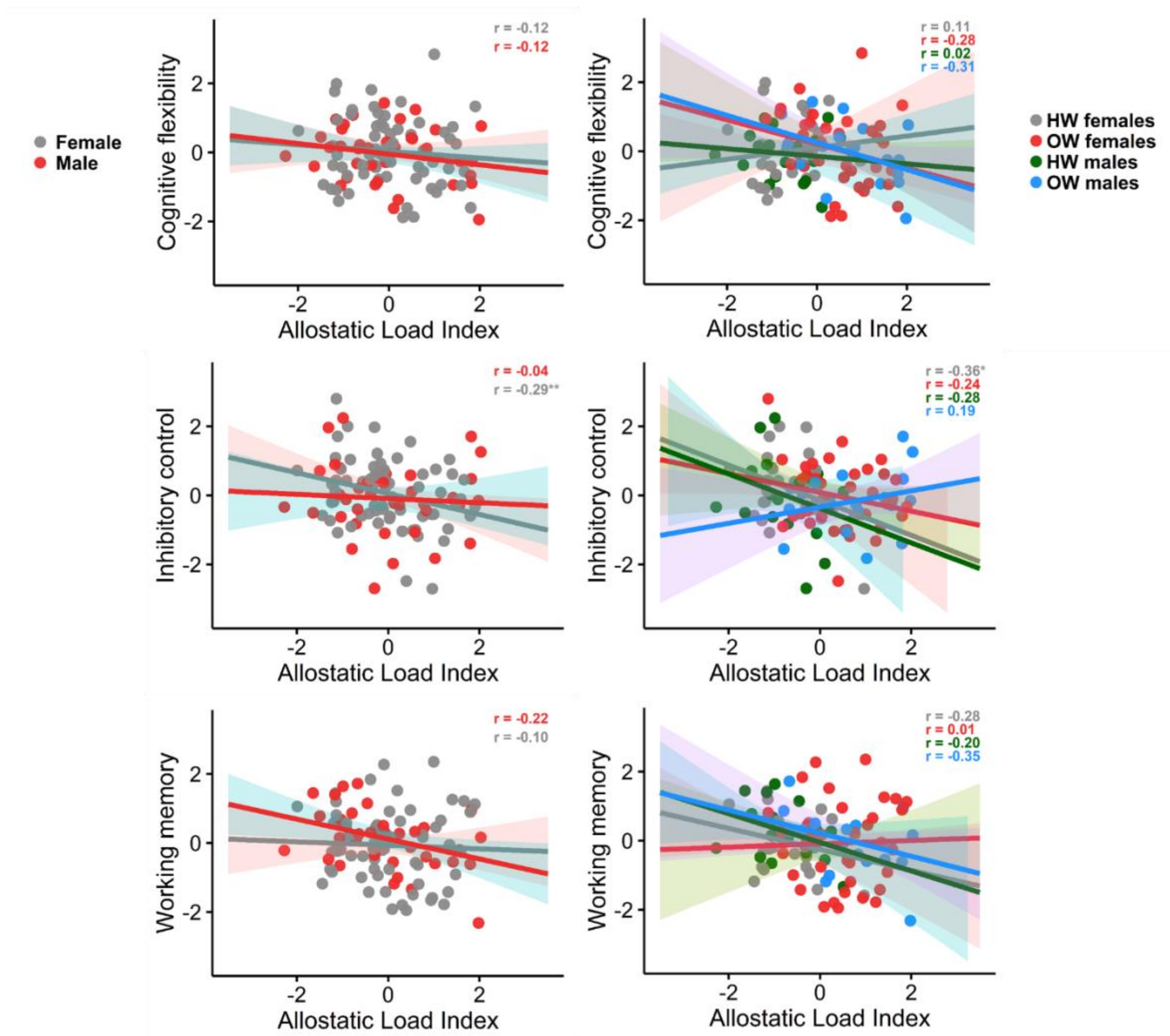

Figure 3 – On the left, correlations between the AL index and core EF accounting for males and females. On the right, correlations between the AL index and core EF separating for males and females regarding BMI group (healthy-weight or overweight). HW = healthy-weight, OW = overweight. **p* < 0.05, **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

B. 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.