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Relationship between body mass index and neuropsychiatric symptoms: Evidence and inflammatory correlates

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ABSTRACT

Objective: Neuropsychiatric symptoms are frequent in obese individuals. Mounting evidence suggests that adiposity-related inflammation contributes to this effect. This study assessed the relationship between adiposity, neuropsychiatric symptom dimensions and systemic inflammation in subjects stratified by body-mass-index (BMI).

Methods: The study included 165 subjects, of whom 70 were very severely obese (BMI $\geq$ 40 kg/m^2), 50 severely obese (BMI: 35–39.99 kg/m^2), 21 overweight or moderately obese (BMI: 25–34.9 kg/m^2), and 24 lean (BMI $<$ 25 kg/m^2). Depressive symptoms were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS) and the Mini-International Neuropsychiatric Interview (MINI). Fatigue and general neurobehavioral symptoms were assessed using the Multidimensional Fatigue Inventory (MFI) and Neurotoxicity Rating Scale (NRS) respectively. Serum levels of the inflammatory markers, high-sensitive (hs) CRP and hsIL-6, were determined by ELISA.

Results: Severely obese subjects exhibited higher MADRS, MFI and NRS scores and were more frequently afflicted with current diagnosis of major depression than lean participants. Scores on psychometric scales were also increased in very severely obese subjects, although to a lesser extent. Alterations in neuropsychiatric dimensions were highly inter-related. HsCRP was significantly increased in subjects with severe or very severe obesity, while hsIL-6 was augmented in all obese groups. Overall, increased neuropsychiatric comorbidity was associated with greater systemic inflammation, notably hsCRP.

Conclusion: Obesity is characterized by an increased prevalence of inter-related neuropsychiatric symptoms together with low-grade systemic inflammation augmenting with adiposity. The association between adiposity, systemic inflammation and neuropsychiatric alterations supports the contribution of adiposity-related inflammatory processes to neuropsychiatric comorbidities in obesity. These data suggest that consideration of adiposity characteristics may help identifying subjects at increased risk for neuropsychiatric comorbidity.

1. Introduction

Obesity is considered the pandemic of the 21st century, representing an important societal and economic burden associated with a greater risk of morbidity and mortality (Blüher, 2019). Its prevalence has dramatically increased during the last decades, with more than 650 million adults being obese worldwide in 2016 according to the last World Health Organization (WHO) estimates. The most commonly used measure of obesity is the Body Mass Index (BMI), calculated as the weight (kg) divided by the square of the height (m). Based on WHO criteria, individuals with a BMI $\geq$ 30 kg/m^2 are considered as being obese, and individuals with a BMI between 25 and 29.9 kg/m^2 are considered as being overweight or preobese. Obesity is further subdivided into severity degrees/classes, corresponding respectively to obesity class I (*moderate obesity*; 30 $\leq$ BMI $\leq$ 34.9 kg/m^2), obesity class II (*severe obesity*; 35 $\leq$ BMI $\leq$ 39.9 kg/m^2) and obesity class III (*very severe/*

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massive obesity; BMI $\geq$ 40 kg/m^2). Higher degrees of obesity are believed to be associated with an increased risk of comorbidities, including type-2 diabetes and cardiovascular diseases (Pantalone et al., 2017).

Neuropsychiatric complications are also frequent in obese subjects. Accordingly, the prevalence of depression is significantly increased in the obese and obesity represents by itself a potent risk factor for the development of depressive disorders in longitudinal cohort studies (Lasselin and Capuron, 2014; Onyike et al., 2003; Herva et al., 2006). The occurrence of depressive symptoms in obese subjects represents a major concern as it strongly impacts quality of life, compromises adherence to treatment and weight management programs and is associated with an increased risk of death by suicide (Mazzeschi et al., 2012; Mather et al., 2009). Data from epidemiological surveys indicate that the relationship between obesity and depression is particularly strong in higher degrees of obesity; with subjects afflicted with severe or very severe obesity exhibiting greater rates of depression than subjects with overweight or moderate obesity (Onyike et al., 2003; Zhao et al., 2009). In line with this, results from a meta-analysis show that being obese significantly increases the risk of depression, notably in women with severe obesity (Jung et al., 2017). Fatigue, sleep disturbances and cognitive alterations are also frequently reported in obese subjects (Zhao et al., 2009). Whether these alterations are connected in some ways to depressive symptoms or, in contrast, develop in distinct populations of obese subjects remains to be investigated.

The link between obesity and neuropsychiatric comorbidity likely relies on mechanisms that are shared by both conditions (Huet et al., 2019; Milaneschi et al., 2019). Among those mechanisms, adiposity-related inflammation appears critical as mounting evidence supports the role of inflammatory processes in neuropsychiatric symptoms in obese subjects (Capuron et al., 2017). Obesity is characterized by a chronic low-grade inflammatory state that originates primarily from the adipose tissue in which adipocytes and infiltrated immune cells secrete inflammatory factors (Hotamisligil, 2017; Lasselin et al., 2014). Accordingly, the inflammatory state of the visceral adipose tissue was found to correlate with circulating levels of inflammatory markers in subjects with obesity (Lasselin et al., 2014). Alterations in gut permeability and gut microbiota composition are also believed to contribute to the obesity-related inflammatory state, notably by sustaining inflammation in adipocytes (Cani et al., 2012; Hersoug et al., 2016). Increased blood concentrations of inflammatory markers, including C-reactive protein (CRP) and interleukin-6 (IL-6), have been repeatedly reported in obese subjects (Park et al., 2005; Capuron et al., 2011; Delgado et al., 2018). Interestingly, those markers significantly correlated with obesity and adiposity indices, such as BMI, waist circumference, and fat distribution (Park et al., 2005; Capuron et al., 2011).

A large database has been developed that substantiates the role of chronic inflammatory processes in the physiopathology of depression and neuropsychiatric symptoms (Capuron and Miller, 2011; Dantzer et al., 2008; Raison et al., 2006). Accordingly, it is likely that adiposity-related chronic inflammation contributes to neuropsychiatric comorbidities in obesity. Consistent with this scenario, we found that systemic inflammation significantly correlates with emotional distress and depressive symptoms in severely obese subjects (Capuron et al., 2011; Delgado et al., 2018). Interestingly, similar associations were reported with respect to obesity-related cognitive alterations (Lasselin et al., 2016). Supporting further the hypothesis that inflammation represents a key mediator of neuropsychiatric comorbidity in obesity, linear relationships were measured between obesity grades and levels of circulating inflammatory markers (Nguyen et al., 2009); in line with findings reporting greater neuropsychiatric symptoms in severe degrees of obesity (Lasselin and Capuron, 2014; Onyike et al., 2003; Herva et al., 2006; Zhao et al., 2009; Jung et al., 2017). Altogether, these data suggest a preferential association of neuropsychiatric comorbidities with higher degrees of obesity, probably due to an increased activation of adiposity-related inflammatory processes.

The aim of the present study was to provide a detailed characterization of neuropsychiatric symptom profiles and their relationship with adiposity-related inflammatory status in a sample of subjects stratified by BMI.

2. Methods

2.1. Study participants

A total of 165 participants were recruited. Since depressive symptoms were shown to be more prevalent in severe and very severe obesity in epidemiological studies (Onyike et al., 2003), recruitment of individuals from these obesity classes was privileged. Accordingly, fifty participants with severe obesity (BMI: 35–39.99 kg/m^2) and seventy participants with very severe obesity (BMI $\geq$ 40 kg/m^2) were included. Additionally, a group of twenty-one participants with overweight or moderate obesity (BMI: 25–34.9 kg/m^2) and a group of twenty-four healthy lean participants (BMI $<$ 25 kg/m^2) were included for comparative purposes. Obese subjects were recruited from the services of digestive and parietal surgery of two private clinics (Tivoli and Jean-Villar) in Bordeaux, France. Non-obese participants were either enrolled from the same clinics as obese subjects or through public advertisements.

For all study participants, exclusion criteria were: age $>$ 75 years old; acute or chronic inflammatory conditions (other than obesity or obesity-related comorbidities for the groups of obese subjects); current treatment with antidepressants or any other psychotropic drug; current treatment with anti-inflammatory agents; current diagnosis of psychiatric disease (except for major depression); and/or severe medical illness. The study was approved by the Institutional Ethics Committee for the Protection of Persons (CPP Bordeaux, France). All participants provided written informed consent after reading a complete description of the study.

2.2. Clinical and neuropsychiatric assessments

Socio-demographic (age, gender) and anthropometric variables (BMI, weight) were collected in all participants. Psychiatric antecedents, treatments, obesity history and obesity-related comorbidities, including type-2 diabetes, hypertension (HTA), dysthyroidism, obstructive sleep apnea (OSA) were also gathered.

Depressive symptoms were assessed using the Montgomery-Asberg Depression Rating Scale (MADRS), a clinician administered scale that includes 10 items scored 0 to 6 with higher scores indicating greater symptom severity (Montgomery and Åsberg, 1979). Diagnosis of current major depressive disorder (MDD) was determined during a semi-structured interview with a trained clinician using the MINI-International Neuropsychiatric Interview (MINI) according to DSM criteria (Sheehan et al., 1998).

Fatigue symptoms were assessed using the Multidimensional Fatigue Inventory (MFI), a 20-item self-report measuring five dimensions of fatigue including general fatigue, physical fatigue, mental fatigue, reduced activity and reduced motivation. Each dimension contains four items scored 1 to 5 with higher scores reflecting higher severity (Smets et al., 1995).

The Neurotoxicity Rating Scale (NRS), a 39-item self-report validated in inflammatory conditions, was used to assess general and neurobehavioral symptoms (Valentine et al., 1995). Items on the scale are scored 0 “not present” to 4 “extremely severe”. As previously described, NRS symptoms were grouped into four specific symptom dimensions for data analysis, including the dimensions of sickness (tiredness, fever, sick feeling, body aches, joint/muscle pain, headaches), cognitive symptoms (indecisiveness, distractibility, episodes of confusion, word-finding problems, memory impairment), anxiety symptoms (anxiety, tension, irritability, agitation, worries about health) and sleep problems (difficulty getting to sleep or staying asleep, sleeping too much) (Capuron et al., 2002, 2011). An average score was calculated per dimension to

homogenize scores across all dimensions.

2.3. Biological measurements

Fasting blood samples were collected the same day as neuropsychiatric assessments for the measurement of serum concentrations of high-sensitive (hs)CRP and hsIL-6. After 30–45 min at room temperature, samples were centrifuged (3200 rpm, 10 min at 4 °C) and sera were stored at −80 °C until the assays. Concentrations of inflammatory markers were determined by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's specifications (hsCRP: CYT298, Millipore, Billerica, Massachusetts; hsIL-6: R&D Systems, Minneapolis, Minnesota). Intra-/inter-assay variability was ±4.6/6.0% for hsCRP, and ±7.4/7.8% for hsIL-6. Sensitivities were 0.20 ng/mL for hsCRP and 0.039 pg/mL for hsIL-6.

2.4. Data analysis

Clinical and neuropsychiatric variables were assessed using the Chi-square test (χ^2) for categorical variables and analyses of covariance (ANCOVA), controlling for age, gender and comorbidities (type-2 diabetes, dysthyroidism, HTA, OSA) for continuous variables. Post-hoc comparisons were performed using the Tukey test of significance. Of note, data for self-reports (MFI and NRS) were missing in three participants who did not fully complete the questionnaires.

Raw values for hsCRP and hsIL-6 were log-transformed because of non-normality of the distribution, as determined by the Shapiro-Wilk test. Extreme values for hsCRP and/or hsIL-6 (>3 SD above the mean) were obtained in three participants. Accordingly, data from these subjects were considered as outliers and were excluded from data analyses performed on biological markers. Associations between obesity indices, scores on neuropsychiatric scales and biological variables were assessed using *Bravais-Pearson* correlations. Further, the relationship between neuropsychiatric variables was assessed using a principal component analysis (PCA) in the whole sample under study to assess the interconnection between neuropsychiatric symptoms and to potentially extract reduced and/or specific symptom dimensions. Statistical analyses were performed using XLStat software (StatSoft). Probabilities were two-tailed with the level of significance set at $p < 0.05$.

3. Results

3.1. Characteristics of study participants

Characteristics of study participants are shown in Table 1. There was no significant differences between groups in terms of age and gender ($F(3,161) = 1.11$, $p = 0.35$; $\chi^2 = 3.49$, $p = 0.32$). As expected, BMI and weight were different across groups ($F(3,161) = 438.1$, $p < 0.0001$ and $F(3,161) = 156.4$, $p < 0.0001$, respectively). Similarly, obesity-related comorbidities, in particular type-2 diabetes ($\chi^2 = 8.60$, $p = 0.04$) and OSA ($\chi^2 = 24.89$, $p < 0.0001$) were more frequent in subjects with very severe obesity and in subjects with severe and very severe obesity, respectively. Interestingly, the proportion of subjects with early onset obesity (obesity since childhood/adolescence) was greater in the group of very severe obesity.

Table 1
Characteristics of study participants.

	Lean Controls BMI < 25	Overweight or Moderate Obesity BMI: 25–34.9	Severe Obesity BMI: 35–39.9	Very Severe Obesity BMI ≥ 40	*p*
Sample size, n	24	21	50	70	
Age, years (SD)	44.1 (14.7)	45.7 (17.1)	40.9 (13.1)	41.1 (8.8)	0.35
Women, n (%)	21 (88)	16 (76)	38 (76)	61 (87)	0.32
BMI, kg/m^2, (SD)	21.6 (2.2)	30.0 (3.5)[a]	37.7 (1.2)[a,c]	44.0 (3.4)[a,c,e]	<0.001
Weight, kg, (SD)	58.2 (9.4)	84.2 (14.8)[a]	105.5 (10.4)[a,c]	118.4 (13.7)[a,c,e]	<0.001
Early onset obesity, n (%)*	n/a	6 (31.6)	22 (47.8)	46 (65.7)[d]	0.01
Comorbidities					
T2D, n (%)	0 (0)	0 (0)	1 (2)	8 (11)[b,d]	0.04
HTA, n (%)	2 (8)	4 (19)	7 (14)	13 (19)	0.64
Dyst, n (%)	3 (13)	2 (10)	4 (8)	6 (9)	0.93
OSA, n (%)	0 (0)	3 (17)	18 (41)[b]	35 (53)[b,d]	<0.001

Continuous variables are presented as mean and standard deviation and compared using one-way ANOVA, whereas categorical variables are presened as n (%) and compared by chi-square test. Post-hoc comparisons were performed using the Tukey test of significance. [a] $p < 0.001$ *vs* lean controls; [b] $p < 0.01$ *vs* lean controls; [c] $p < 0.001$ *vs* overweight or moderate obesity; [d] $p < 0.01$ *vs* overweight or moderate obesity; [e] $p < 0.001$ *vs* severe obesity. *Early onset obesity was considered when obesity was already present at childhood/adolescence (this information was missing in 2 subjects with overweight or moderate obesity and 4 subjects with severe obesity). *Abbreviations:* BMI: Body Mass Index; T2D: type-2 diabetes; HTA: Hypertension; Dyst: Dysthyroidism; OSA: Obstructive Sleep Apneas; SD: standard deviation.

3.2. Neuropsychiatric symptoms

3.2.1. Depressive symptoms

As shown in Fig. 1**A**, the prevalence of current MDD according to DSM criteria was significantly different across groups ($\chi^2 = 13.15$, $p < 0.01$), with subjects with severe and very severe obesity exhibiting higher prevalence rates than lean controls. Albeit severely obese subjects tended to show increased MDD rates compared to very severely obese participants, this difference did not reach significance level. Consistent with these data, ANCOVA controlling for age, gender and comorbidities revealed significant differences in MADRS total scores between groups ($F(3,158) = 4.67$, $p < 0.01$). In particular, subjects with severe obesity exhibited significantly higher MADRS scores than lean controls ($p < 0.01$) and participants with overweight or moderate obesity ($p < 0.05$) (Fig. 1**B**). Analysis performed on individual items of the MADRS scale indicated that this difference was primarily apparent for items of apparent sadness, inability to feel, pessimistic thoughts and suicidal thoughts where, overall, subjects with severe obesity exhibited higher scores (Table 2).

3.2.2. Fatigue symptoms

MFI total scores were significantly different across groups ($F(3,155) = 4.92$, $p < 0.01$), with subjects with severe and very severe obesity exhibiting overall higher MFI total scores than lean controls (Table 3). Analyses on fatigue symptom dimensions revealed that subjects with severe obesity exhibited greater scores in each dimension of fatigue when compared to lean controls. All obese groups (from overweight to very severe obesity) exhibited higher scores of physical fatigue compared to lean controls.

3.2.3. Other general and neurobehavioral symptoms

Overall, NRS total scores were significantly different across groups ($F(3,154) = 5.87$, $p < 0.001$), with subjects with severe obesity and very severe obesity exhibiting higher scores than lean controls and subjects with overweight or moderate obesity (Table 3). This difference was particularly apparent in the NRS dimensions of sickness.

In order to assess the relationship between neuropsychiatric symptom dimensions, a PCA was performed on neuropsychiatric scores (including MADRS total scores, MFI and NRS dimension scores) in the whole population under study. Results indicated that neuropsychiatric scores were highly interconnected as they all loaded in one single factor (eigenvalue = 5.86) explaining 58.6% of the variance and interpreted as

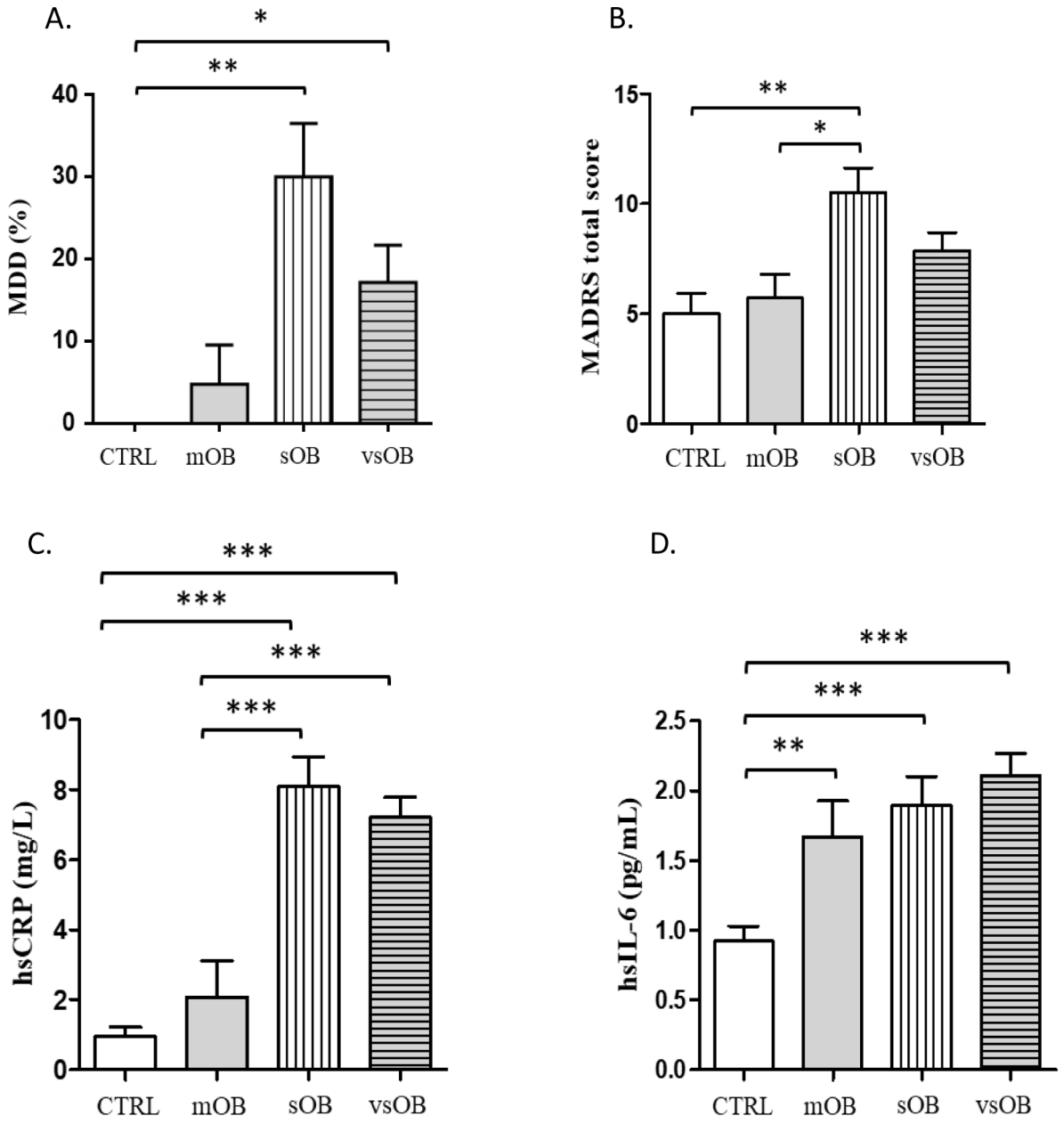

Fig. 1. Depressive symptoms and circulating concentrations of inflammatory markers in obese subjects and lean participants. *Panels A & B*. Prevalence of current MDD according to DSM criteria (*panel A*) and MADRS total scores (*panel B*) in the study population. Analyses were performed using chi-square test for MDD prevalence and ANCOVA controlling for age, gender and comorbidities for MADRS total scores. *Panels C & D*. HsCRP (*panel C*) and hsIL-6 (*panel D*) concentrations in the study population. Values were log-transformed for statistical analysis but displayed as raw value geometric means for information and readability purposes. Analyses were performed using ANCOVA controlling for age, gender and comorbidities. Post-hoc comparisons were performed using the Tukey test of significance. Data are shown as mean (+SEM). * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. *Abbreviations*: CTRL: lean participants; mOB: subjects with overweight or moderate obesity; sOB: subjects with severe obesity; vsOB: subjects with very severe obesity; MADRS: Montgomery-Asberg Depression Rating Scale; MDD: major depressive disorder; hsCRP: high-sensitive C-reactive protein; hsIL-6: high-sensitive interleukin-6; DSM: Diagnostic and Statistical Manual of Mental Disorders; SEM: standard error of the mean.

a *neuropsychiatric comorbidity factor*. Neuropsychiatric comorbidity, indicated by positive scores on this component, was observed in 17.4% of lean participants and in 36.8% of subjects with overweight or moderate obesity. This proportion was increased up to 56% and 44.3% in subjects with severe and very severe obesity respectively.

3.3. Obesity-related systemic inflammation and its relationship with neuropsychiatric symptoms

Circulating concentrations of inflammatory markers across BMI groups are depicted in Fig. 1**C-D**. ANCOVA controlling for age, gender and comorbidities indicated a significant difference in hsCRP levels across groups ($F(3,155) = 59.44$, $p < 0.001$). In particular, subjects with severe and very severe obesity were found to exhibit higher levels of hsCRP compared to lean controls and subjects with overweight or moderate obesity (all $p < 0.001$). No difference was found between subjects with severe and very severe obesity and between lean controls and subjects with overweight or moderate obesity with respect to hsCRP levels. Similarly, levels of hsIL-6 were significantly different across groups ($F(3,155) = 12.45$, $p < 0.001$), with obese subjects, whatever the degree of obesity, exhibiting higher concentrations of this marker than lean controls. In line with this, BMI was highly correlated with hsCRP (R

Table 2
MADRS item scores across BMI classes.

	Lean Controls BMI < 25	Overweight or Moderate Obesity BMI: 25–34.9	Severe Obesity BMI: 35–39.9	Very Severe Obesity BMI ≥ 40	*p*
MADRS items, mean (SD)					
1.Apparent sadness	0.3 (0.6)	0.5 (0.7)	0.9 (1.2)[b]	0.4 (0.8)[c]	0.005
2.Reported sadness	0.6 (0.9)	0.7 (1.0)	1.3 (1.3)	0.9 (1.1)	0.04
3.Inner tension	1.1 (1.1)	1.0 (1.0)	1.5 (1.1)	1.2 (1.0)	0.24
4.Reduced sleep	0.7 (1.2)	0.9 (1.3)	1.3 (1.4)	1.0 (1.3)	0.28
5.Reduced appetite	0.1 (0.3)	0.0 (0.0)	0.2 (0.6)	0.3 (0.8)	0.14
6.Concentration difficulties	0.5 (1.0)	0.3 (0.6)	0.8 (1.1)	0.6 (1.1)	0.31
7.Lassitude	0.5 (0.8)	0.5 (0.9)	1.1 (1.3)	1.0 (1.3)	0.18
8.Inability to feel	0.3 (0.6)	0.5 (1.0)	1.1 (1.3)[b]	0.5 (0.8)[c]	0.005
9.Pessimistic thoughts	0.8 (0.9)	1.1 (1.3)	1.7 (1.2)[a]	1.4 (1.3)	0.01
10.Suicidal thoughts	0.2 (0.4)	0.3 (0.5)	0.6 (0.8)[a]	0.5 (0.7)	0.009

Analyses were performed using ANCOVA controlling for age, gender and comorbidities. Post-hoc comparisons were performed using the Tukey test of significance. [a] $p < 0.01$ *vs* lean controls, [b] $p < 0.05$ *vs* lean controls, [c] $p < 0.05$ *vs* severe obesity. *Abbreviations:* BMI: Body Mass Index; MADRS: Montgomery-Asberg Depression Rating Scale; SD: standard deviation.

Table 3
MFI and NRS scores across BMI classes.

	Lean Controls BMI < 25	Overweight or Moderate Obesity BMI: 25–34.9	Severe Obesity BMI: 35–39.9	Very Severe Obesity BMI ≥ 40	*p*
MFI scores, mean (SD)*					
Total score	38.9 (11.6)	46.3 (12.6)	52.9 (17.2)[a]	48.1 (14.8)	0.003
General fatigue	9.8 (3.7)	11.6 (3.7)	12.3 (4.3) [b]	11.2 (3.9)	0.05
Physical fatigue	7.9 (3.2)	11.1 (4.0)[b]	12.8 (4.4) [a]	12.3 (4.1)[a]	<0.001
Mental fatigue	6.8 (2.3)	7.3 (2.8)	8.9 (3.6)[b]	7.7 (3.5)	0.03
Reduced activity	7.5 (3.3)	9.2 (3.4)	10.1 (4.2)[b]	9.1 (3.5)	0.05
Reduced motivation	6.9 (2.4)	7.1 (2.6)	8.8 (3.7) [b]	7.9 (3.2)	0.03
NRS scores, mean (SD)*					
Total score	17.5 (12.1)	25.0 (15.7)	39.4 (21.9)[a]	35.2 (22.2)[b]	<0.001
Cognitive alterations	0.5 (0.5)	0.6 (0.6)	0.8 (0.7)	0.7 (0.7)	0.22
Altered sleep	0.8 (0.9)	0.9 (0.6)	1.4 (1.1)	1.0 (0.9)	0.07
Sickness symptoms	0.7 (0.5)	1.1 (0.6)	1.6 (0.8)[a]	1.4 (0.8)[a]	<0.001
Anxiety	1.0 (0.8)	0.9 (0.6)	1.4 (0.8)	1.4 (0.7)	0.05

Analyses were performed using ANCOVA controlling for age, gender and comorbidities. Post-hoc comparisons were performed using the Tukey test of significance. [a] $p < 0.01$ *vs* lean controls, [b] $p < 0.05$ *vs* lean controls. *MFI and NRS scores were missing for 1 lean control and 2 subjects with overweight or moderate obesity. *Abbreviations:* BMI: Body Mass Index; MFI: Multidimensional Fatigue Inventory; NRS: Neurotoxicity rating Scale; SD: standard deviation.

$= 0.633$, $p < 0.001$) and hsIL-6 ($R = 0.428$, $p < 0.001$) in the whole population under study and in the obese groups only ($R = 0.443$, $p < 0.001$ and $R = 0.216$, $p < 0.05$ respectively). In the whole population under study, levels of hsCRP and hsIL-6 were highly correlated ($R = 0.493$, $p < 0.001$). The association remained significant when the analysis was restricted to subgroups of obese subjects ($R = 0.349$, $p < 0.001$).

As shown in Table 4, hsCRP and hsIL-6 were individually correlated with neuropsychiatric scores in the whole population under study. Correlations were more frequent with hsCRP that was significantly associated with MADRS total scores, MFI scores of physical fatigue, NRS total scores, and NRS scores of sickness and anxiety. Significant correlations were also measured between hsIL-6 and NRS total scores and scores on the MFI dimensions of physical fatigue and reduced activity. Similarly, scores on the *neuropsychiatric comorbidity factor* were significantly correlated with hsCRP. In line with these data, cross-sectional analyses comparing participants afflicted or not with neuropsychiatric comorbitidity (score either negative or positive on the *neuropsychiatric comorbidity factor*) indicated greater levels of hsCRP and hsIL-6 in subjects with neuropsychiatric comorbidity (Table 5). These results remained significant when comparisons were adjusted for age, gender and comorbidities.

Table 4
Relationship between systemic inflammation and neuropsychiatric symptoms.

	Log hsCRP	Log hsIL-6
Depressive Symptoms		
MADRS total score	0.242**	0.101
Fatigue		
MFI total score	0.124	0.151
General fatigue	0.048	0.055
Physical fatigue	0.228**	0.232**
Mental fatigue	0.132	0.107
Reduced activity	0.045	0.158*
Reduced motivation	0.035	0.048
General and Neurobehavioral Symptoms		
NRS total score	0.264***	0.165*
Cognitive alterations	0.137	0.150
Altered sleep	0.151	0.101
Sickness symptoms	0.290***	0.113
Anxiety	0.248**	0.086
Neuropsychiatric Comorbidity Factor score	0.202*	0.148

Neuropsychiatric comorbidity factor was extracted from a principal component analysis performed on neuropsychiatric scores. Results are showed as Bravais-Pearson correlations performed on the whole population under study. *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$. *Abbreviations:* MADRS: Montgomery-Asberg Depression Rating Scale; MFI: Multidimensional Fatigue Inventory; NRS: Neurotoxicity Rating Scale; hsCRP: high-sensitive C-reactive protein; hsIL-6: high-sensitive interleukin-6.

4. Discussion

To our knowledge, the present study is the first to examine the association between incrementing degrees of adiposity, markers of

Table 5
Association of neuropsychiatric comorbidity with adiposity-related systemic inflammation.

	Neuropsychiatric Comorbidity			
	Negative n = 91	Positive n = 69	*p1*	*p2*
Log hsCRP	0.41 (0.58)	0.64 (0.52)	0.009	0.025
Log hsIL-6	0.13 (0.31)	0.22 (0.22)	0.041	0.047

Participants were stratified on the basis of their scores on the neuropsychiatric comorbidity factor extracted from the principal component analysis performed on neuropsychiatric scores. Data are shown as mean (+ SEM) compared by Student t-test (*p1*) or ANCOVA controlling for age, gender and comorbidities (*p2*), performed on the whole population under study. *Abbreviations*: hsCRP: high-sensitive C-reactive protein; hsIL-6: high-sensitive interleukin-6; SEM: standard error of the mean.

systemic inflammation and neuropsychiatric symptom profiles in a sample of individuals stratified by BMI. Findings indicate an overall increased neuropsychiatric comorbidity, non-specific to symptom dimensions/profiles, related obesity degrees and systemic inflammation in subjects afflicted with obesity. Accordingly, MDD was found to be more prevalent in subjects with severe or very severe obesity compared to lean controls. Albeit there was no significant difference between severe and very severe obesity with regard to prevalence of MDD, severely obese subjects tended to exhibit higher rates. In line with this, MADRS scores were greater in subjects with severe obesity, notably in items assessing sadness, inability to feel, pessimistic and suicidal thoughts. Fatigue and sickness symptoms, assessed with the MFI and NRS respectively, were also found to be more severe in subjects with severe obesity compared to lean controls. Nevertheless, these symptoms were also apparent in subjects with overweight or moderate obesity (physical fatigue) and in subjects with very severe obesity (physical fatigue and sickness symptoms). Strong associations were found between obesity-related depressive symptoms, fatigue and general neurobehavioral symptoms, providing new insights on the phenomenology of neuropsychiatric symptoms developing in obese subjects. The subtle, but constant, exacerbation of neuropsychiatric symptoms in subjects with severe obesity compared to very severe obesity is also noteworthy. Whereas further investigations are needed to elucidate the reason for this finding, differences in the history/anteriority of obesity in the two groups may be involved. Indeed, and consistent with previous studies (Wrzosek et al., 2018), most of subjects with very severe obesity were obese since childhood/adolescence, whereas the proportions early-onset obesity *versus* late-onset obesity were equal in the group of severely obese subjects. Accordingly, it may be that long-term obesity is associated with the development, over time, of psychological compensatory or adjustment strategies that could moderate the impact of obesity on psychological wellbeing (Puhl and Brownell, 2006). This possibility merits to be assessed in future studies.

In line with previous reports (Park et al., 2005; Capuron et al., 2011; Delgado et al., 2018), we found strong associations between adiposity and systemic inflammation, reflected in higher hsCRP and hsIL-6 in the groups of obese subjects. While hsCRP levels were primarily increased in subjects with severe and very severe obesity relatively to subjects with overweight or moderate obesity and lean controls, hsIL-6 levels were steadily increased in all obese groups, regardless of obesity severity. Of note, no significant difference was found between subjects with severe and very severe obesity and between lean controls and subjects with overweight or moderate obesity with respect to hsCRP levels. Consistent with previous data and supporting the role of inflammation in obesity-related neuropsychiatric symptoms (Capuron et al., 2011; Delgado et al., 2018; Lasselin et al., 2016; Shelton et al., 2015), hsCRP and hsIL-6 were individually correlated with neuropsychiatric comorbidities in the whole population under study. Associations were stronger for hsCRP that correlated significantly with a large number of neuropsychiatric parameters including depression scores, physical fatigue, sickness and anxiety. HsIL-6 was primarily associated with symptoms of physical fatigue and reduced activity. In line with this, increased neuropsychiatric comorbidity was associated with higher levels of inflammation, in particular hsCRP, in both correlational and cross-sectional analyses. The specific associations found between hsCRP and hsIL6 with neuropsychiatric symptoms were consistent with the differential concentration profiles of these two markers per BMI categories. In particular, the fact that hsCRP was preferentially associated with neuropsychiatric symptoms was coherent with the similarity of distribution of both hsCRP levels and neuropsychiatric symptoms along obesity severity degrees. Similarly, hsIL6 concentrations, which were already increased in low grades of obesity, correlated preferentially with non-specific symptoms (e.g., physical fatigue) that were apparent in all obese subjects, regardless of obesity severity degrees. Altogether, these findings support the involvement of low-grade inflammation in obesity-related neuropsychiatric comorbidity. They suggest that strategies aiming at reducing systemic inflammation could be relevant to improve neuropsychiatric status and reduce the risk of depression in subjects with increased adiposity. Consistent with this notion, weight-loss interventions, including bariatric surgery, were found to simultaneously reduce systemic inflammation, emotional distress and depressive symptoms in severely obese subjects (Capuron et al., 2011; Emery et al., 2007).

The present study includes limitations that future investigations should overcome. Although BMI represents the most common measure of obesity, this index is not fully representative of body fat distribution, notably central adiposity. Compared to the subcutaneous adipose tissue, the visceral adipose tissue is considered as being a more reliable determinant of obesity-related comorbidities. Accordingly, it could be more relevant than BMI with respect to adiposity-related inflammation and its relationship with neuropsychiatric symptoms consistent with data showing associations between central/abdominal adiposity (e.g., waist circumference, waist-to-hip ratio), inflammation and depressive symptoms (Everson-Rose et al., 2009). Additional measures of fat distribution could help addressing this issue so as to ultimately improve the identification of obese individuals with greater risk of neuropsychiatric comorbidity. It may also be interesting to add assessments of markers involved in the promotion of inflammation, including gut microbiota, endotoxemia, and oxidative stress markers, whose implication in the pathophysiology of neuropsychiatric symptoms has raised significant interest over the last years. Moreover, albeit results were systematically controlled for gender, the high prevalence of women among participants from this study may represent another limitation given the known influence of gender on the association between inflammation and depression (Köhler-Forsberg et al., 2017; Vetter et al., 2013). In addition, the small and unequal size of study groups may have contributed to reduce the statistical power for detection of significant associations. Finally, the cross-sectional design of the present study does not allow the establishment of a temporal or causal relationship between adiposity-related inflammation and neuropsychiatric symptoms. Large longitudinal studies should be performed to specifically address this issue.

In conclusion, this study provides a detailed picture of the relationship between neuropsychiatric symptoms and inflammatory status, according to obesity severity grades. It shows that obesity is characterized by inter-related neuropsychiatric symptoms, including depression, fatigue and general behavioral symptoms, together with a chronic low-grade inflammatory state that augment with adiposity degrees. The significant linear association found between adiposity degrees, systemic inflammation and neuropsychiatric alterations strongly supports the involvement of adiposity-related inflammatory processes in neuropsychiatric comorbidities. These data provide new insight on the phenomenology of neuropsychiatric symptoms developing in contexts of obesity. They suggest that the consideration of adiposity characteristics may help to identify subjects with an increased risk of neuropsychiatric comorbidity and to improve the management/treatment of specific subgroups of patients afflicted with neuropsychiatric symptoms (Shelton et al., 2015). They point to hsCRP as a relevant biomarker of adiposity-

related neuropsychiatric symptoms that could help orienting clinical assessment/practice and guiding innovative and personalized treatment strategies targeting inflammatory processes in depressed patients with obesity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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