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Original article

A real world study on the genetic, cognitive and psychopathological differences of obese patients clustered according to eating behaviours

Mariarita Caroleo[a,b], Amedeo Primerano[a], Marianna Rania[a,b], Matteo Aloi[a,b], Valentina Pugliese[a], Fabio Magliocco[a], Gilda Fazia[a], Andrea Filippo[a], Flora Sinopoli[b,c], Marco Ricchio[d], Franco Arturi[d], Susana Jimenez-Murcia[e,f,g], Fernando Fernandez-Aranda[e,f,g], Pasquale De Fazio[a], Cristina Segura-Garcia[a,b,*]

[a] Department of Health Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy
[b] Outpatient Unit for Clinical Research and the Treatment of Eating Disorders, Mater Domini University Hospital, Catanzaro, Italy
[c] Dietetic Service, University Hospital Mater Domini, Catanzaro, Italy
[d] Department of Medical and Surgical Sciences, University Magna Graecia of Catanzaro, Catanzaro, Italy
[e] Department of Psychiatry, University Hospital Bellvitge-IDIBELL, Barcelona, Spain
[f] CIBER Fisiopatología Obesidad y Nutrición (CIBEROBN), ISCIII, Barcelona, Spain
[g] Department of Clinical Sciences, School of Medicine and Health Sciences, Campus Bellvitge, Barcelona, Spain

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ABSTRACT

Background: Considering that specific genetic profiles, psychopathological conditions and neurobiological systems underlie human behaviours, the phenotypic differentiation of obese patients according to eating behaviours should be investigated. The aim of this study was to classify obese patients according to their eating behaviours and to compare these clusters in regard to psychopathology, personality traits, neurocognitive patterns and genetic profiles.
Methods: A total of 201 obese outpatients seeking weight reduction treatment underwent a dietetic visit, psychological and psychiatric assessment and genotyping for SCL6A2 polymorphisms. Eating behaviours were clustered through two-step cluster analysis, and these clusters were subsequently compared.
Results: Two groups emerged: cluster 1 contained patients with predominantly prandial hyperphagia, social eating, an increased frequency of the long allele of the 5-HTTLPR and low scores in all tests; and cluster 2 included patients with more emotionally related eating behaviours (emotional eating, grazing, binge eating, night eating, post-dinner eating, craving for carbohydrates), dysfunctional personality traits, neurocognitive impairment, affective disorders and increased frequencies of the short (S) allele and the S/S genotype.
Conclusions: Aside from binge eating, dysfunctional eating behaviours were useful symptoms to identify two different phenotypes of obese patients from a comprehensive set of parameters (genetic, clinical, personality and neuropsychology) in this sample. Grazing and emotional eating were the most important predictors for classifying obese patients, followed by binge eating. This clustering overcomes the idea that 'binging' is the predominant altered eating behaviour, and could help physicians other than psychiatrists to identify whether an obese patient has an eating disorder. Finally, recognising different types of obesity may not only allow a more comprehensive understanding of this illness, but also make it possible to tailor patient-specific treatment pathways.

1. Introduction

Obesity is a multi-factorial and heterogeneous illness [1] that presents a complex and bidirectional relationship with several psychiatric disorders [2,3]. Eating behaviours are important features that can help to better define obesity and its comorbidities, and can also be associated with psychological domains [4]. However, there have been only few investigations to date

* Corresponding author at: Department of Health Sciences, University Magna Graecia of Catanzaro, Viale Europa, 88100–Catanzaro, Italy.
E-mail addresses: segura@unicz.it, ambulatoriodca.psichiatriaumg@gmail.com (C. Segura-Garcia).

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concerning the psychopathological importance of most pathological eating behaviours other than binge eating [5]. Considering that specific genetic profiles, psychopathological conditions and neurobiological systems underlie human behaviours, the identification of different phenotypes of obese patients according to eating behaviours is important.

Eating disorders (EDs) show trait-related alterations in serotonin function, which might be linked to the gene encoding the serotonin transporter (SERT) [6]. The two functional polymorphisms of the *SERT* gene, STin2 and 5-HTTLPR, have also been associated with affective disorders, suicidal behaviour [7], response to antidepressants [8], substance dependence and abuse [9]. The *SERT* gene may also be associated with the pathophysiology of "binge eating", but it is not clear how changes in 5-HT function could influence eating behaviours in obese patients [10].

On the other hand, personality and psychopathological traits seem to play an important role as risk factors in the development and maintenance of overweight and obesity [3,11–12], and recent studies have also described a pattern of impairment in the cognitive flexibility and decision-making domains [13,14] of obese patients with and without EDs.

Previous cluster-analysis studies of EDs have yielded clinical subtypes for dietary restraint and negative affect dimensions; however, to our knowledge no studies have clarified the relationship between neurobiological and behavioural variables in obese patients [15,16]. This could be useful for identifying recurrent eating patterns that could differentiate subjects and characterise different behavioural phenotypes, which have clear implications from both nosological and therapeutic/management perspectives.

Based on the above, our aim was to identify different behavioural phenotypes of obese patients by classifying obese patients according to their eating behaviours and comparing the resulting clusters for psychopathological features, personality traits, neurocognitive patterns and genetic profiles (i.e., 5-HTTLPR and STin2 serotonin polymorphism). Our hypothesis was that eating behaviours could be related to different phenotypes of obese patients and that these phenotypes have specific psychological and neurobiological associations.

2. Methods

2.1. Participants

From March 2014 to July 2016, all obese patients (n = 250; 82 males and 168 females) admitted to a department of Internal Medicine in Southern Italy for weight loss treatment were given the opportunity to participate in this cross-sectional investigation. Patients were selected according to the following eligibility criteria: body mass index (BMI) $\geq 30\,kg/m^2$, aged 18–65 years, and the capacity to answer a self-reporting questionnaire and to understand the process in which they were involved. The exclusion criteria were: aged under 18 or over 65 years, neurological or other medical conditions that might affect cognitive functioning, pharmacological treatment with the potential to induce cognitive impairment, and pregnancy or childbirth over the previous 12 months. All participants were informed of the aim of the study, the research procedures and their complete anonymity in the processing of all data. Those who accepted signed an informed consent form before any procedure took place. The Ethical Committee of the Hospital (Azienda Ospedaliera Universitaria Mater Domini) approved the protocol in September 2013. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

2.2. Measures

This study consisted of three parts: (1) a visit with a dietician, (2) psychological assessment, and (3) blood sampling.

An experienced dietician initially conducted an in-depth assessment of participants' abnormal eating behaviours (namely grazing, emotional eating, craving for carbohydrates, sweet eating, post-dinner eating, night eating, binge eating, hyperphagia and social eating) during the previous 6 months with the aid of a checklist (Supplementary Table 1). Behaviours were considered to be present when all the related items were answered "yes" and if the behaviour had caused clinically significant impairment or distress. The dietician also performed an anthropometrical evaluation (waist circumference, height and weight) with the patients wearing light indoor clothing and no shoes, after which their BMI (kg/m^2) was calculated. Body composition was estimated by bioelectrical impedance.

A trained psychiatrist subsequently administered the Structured Clinical Interview for the DSM-IV (SCID-I) [17] to make a diagnosis of psychiatric comorbidity. During the psychological assessment, patients also completed the following psychometrical batteries, the results of which were used to compare the clusters:

2.2.1. Eating psychopathology

- *Eating Disorder Inventory-2 (EDI-2)* [18,19]. The EDI-2 is a self-report questionnaire that assesses the psychopathology of EDs. Cronbach's alpha was 0.91.
- *Binge Eating Scale (BES)* [20]. This self-administered test is widely used in research to measure binge eating severity in the non-purge binge-eating population or to determine whether potential research participants meet the inclusion criteria for binge eating. Total BES scores < 17, 17–27 and > 27 respectively indicate that the risk of an individual having Binge Eating Disorder (BED) is unlikely, possible and probable. Participants who scored > 27 were considered positive to the test in this study. Cronbach's alpha was 0.89.

2.2.2. Measurement of personality traits

- *Temperament and Character Inventory-revised (TCI-R)* [21]. This 240-item questionnaire is based on Cloninger's neurobiological personality theory, which assesses personality through four temperamental and three character dimensions. Cronbach's alpha in this study was 0.646.

2.2.3. Psychopathology measures

- *Barratt Impulsiveness Scale (BIS) version 11* [22]. The BIS is a 30-item self-report questionnaire that measures impulsivity through three subscales: attentional (cognitive instability and inattention), non-planning (intolerance of cognitive complexity and lack of self-control), and motor (lack of perseverance and motor impulsiveness). The BIS also yields a total score. Cronbach's alpha was 0.858.
- *Mood Disorder Questionnaire (MDQ)* [23]. The MDQ is used to determine the lifetime presence of bipolar features and consists of three questions. The first question evaluates bipolar symptoms through 13 dichotomous ("yes"/"no") items and the last two assess family history, past diagnoses and disease severity. Participants are considered positive if they simultaneously answer "yes" to at least 7 of the first 13 items in question

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1 and indicate that the symptoms clustered within the same time period ("yes" to question 2) caused moderate or serious problems ("moderate" or "serious" on question 3). In this study, those patients who scored ≥ 7 for question 1, but did not answer affirmatively to question 2 and/or did not answer "moderate" or "serious" to question 3 were considered under the MDQ threshold. Those who scored < 7 for question 1 were directly considered negative. Cronbach's alpha was 0.702.

- *Beck Depression Inventory-21 (BDI)* [24]. This self-report questionnaire assesses the severity of depressive symptoms. Scores of < 10, 10–16, 17–29 and ≥ 30 respectively indicate minimum, mild, moderate and severe depression. A total score >16 is considered the clinical cut-off. Cronbach's alpha was 0.91.
- *State-Trait Anxiety Disorder (STAI)* [25]. This self-administered questionnaire is made up of 40 items that assess state (STAI-St) and trait (STAI-Tr) anxiety. Cronbach's alpha for the data in this study was 0.845.

2.2.4. Neuropsychological testing

- *Iowa Gambling Test (IGT)* [26]. The computerised version of the original IGT is used to assess decision-making. Decision-making ability is determined by examining IGT performance over time by dividing the 100 card choices into five blocks of 20 trials. Performance is measured by calculating a net score for each block; this is obtained by counting card picks from the advantageous decks (C + D) minus the number from the disadvantageous decks (A + B) in each block, i.e., (C + D)–(A + B). Higher results indicate better performance, while negative results indicate a preference for the disadvantageous decks.
- *Wisconsin Card Sorting Test (WCST)* [27]. This task requires participants to match stimulus cards that vary in term of colour, number of items and geometric shape. The global score (number of trials – [number of achieved categories × 10]), perseverative errors, non-perseverative errors and failure to maintain sets are evaluated.

2.3. Genetics

A venous blood sample (5 ml) was drawn for genetic testing. Genomic DNA was extracted and genotyped for SCL6A2 polymorphisms. We designed an optimised highly specific sequencing primer set (Table 1) for 5-HTTLPR and sTin2 using the NCBI platform, (Ampli FX bioinformatics software and Repeat Masker web application from the Institute for Systems Biology) [28]. Specific primers for the region of interest were designed and optimised. A 15 μl aliquot of PCR product was resolved on a 2.5% agarose gel, and the genotype was determined by fragment analysis.

2.4. Statistical analysis

The data were analysed using the Statistical Package for Social Sciences version 21 (SPSS, Chicago, Illinois, USA). Continuous data were expressed as mean ± standard deviation (SD) and categorical variables as frequencies and percentages. A two-step cluster analysis was used to identify clusters based on eating behaviours (emotional eating, binging, grazing, social eating, hyperphagia, night eating, craving for carbohydrates, post-dinner eating; considering yes = 1, no = 0). Two-step cluster analysis was chosen as it is appropriate for both continuous and categorical data. The log-likelihood criterion was used for distance measure and cluster solutions were compared using Schwarz's Bayesian criterion (BIC) and the silhouette coefficient. Silhouette measure of less than 0.2 were classified as poor, between 0.2 and 0.5 as fair, and greater than 0.5 as good solution quality [29], with fair or higher considered acceptable clustering. Differences between clusters (psychiatric diagnosis, results of tests and genetics) were then explored through chi-squared (χ^2) and analysis of variance (ANOVA) tests as appropriate. Cohen's d effect sizes (ES) were calculated for all significant findings considering that values of 0.00–0.20, 0.21–0.50, 0.51–0.80, 0.81–1.20, 1.21–2.0 and > 2.0 respectively indicate very small, small, medium, large, very large and huge effect sizes. A p-value of <0.05 was considered statistically significant.

Table 1
Specific primers and annealing temperature.

Polymorphism	Primers	Annealing T°
5HTTLPR	F 5′ GGCGTTGCCGCTCTGAATGC 3′ R 5′ GAGGGACTGAGCTGG3′	62 °C
Stin2	F 5′ GGTCAGTATCACAGGCTGCGAGTAG 3′ R 5′ TGTTCCTAGTCTTACGCCAGTGAAG3′	69 °C

3. Results

Overall, 201 out of 250 participants (80.4%) met the inclusion criteria and agreed to participate in the study. The sample consisted of 63 males (31.3%) and 138 females (68.7%) with an average age of 45.27 ± 1.86 years. Table 2 shows the results of the two-step cluster analysis. In our study, the best solution was obtained with two clusters, as this solution gave the highest value for the ratio of distance measure (2.773) and the lowest BIC value (1583.473). The silhouette coefficient was 0.4. Two distinct groups (Fig. 1) emerged, with 47.8% patients in cluster 1 and 52.2% in cluster 2. The importance of the predictors in decreasing order was: grazing, 1.0; emotional eating, 0.98; binge eating, 0.6; sweet eating, 0.49; craving for carbohydrates, 0.47; social eating, 0.22; and hyperphagia, 0.08.

Clusters differed significantly in gender distribution, anthropometric features and eating behaviours, as expected. Hyperphagia and social eating were predominant in cluster 1, whereas the remaining eating behaviours were significantly overrepresented in cluster 2. Significantly higher percentages of BED, affective disorders and anxiety disorders, according to DSM-5, were evident in cluster 2.

As shown in Table 3, comparison of the questionnaire data produced highly significant differences with large to hugh effect sizes in the BES, BDI, STAI, EDI-2 and TCI-R scores between the two clusters. In particular, we observed significantly higher mean values for depression, trait and state anxiety and eating psychopathology in cluster 2. The percentages of participants that scored above the cut-off for BES (7% vs. 76%; $\chi^2 = 92.416$; $p < 0.001$), BDI (20% vs. 66%; $\chi^2 = 26.888$; $p < 0.001$), STAI-St (41% vs. 74%; $\chi^2 = 12.309$; $p < 0.001$) and STAI-Tr (55% vs. 78%; $\chi^2 = 7.068$; $p = 0.008$) were significantly higher in cluster 2. Significantly higher average scores on all BIS-11 subscales were evident in cluster 2, revealing increased levels of total, motor and unplanned impulsivity. Increased harm avoidance and lower self-directedness in TCI-R also characterised this cluster. In terms of neurocognitive function, worse results for IGT and more perseverative errors in WCST were found in cluster 2.

The distribution of alleles and genotypes in relation to serotonin transporter polymorphisms also differed between clusters. The short (S) variant 5-HTTLPR and the STin2.12 allele were much more frequent in cluster 2, both in the homo- and heterozygous variants (Table 4). Conversely, the long (L) variant allele in homo- and heterozygous variants were more frequent in cluster 1. The distribution of alleles and genotypes in the groups of obese

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Table 2
Clusters description.

		Cluster 1 (N = 96)		Cluster 2 (N = 105)		F/χ^2	*df*	p	*d*[c]
Age[a]		46.7	12.2	44.0	11.4	F = 2.525	1	NS	
Gender[b]	F	52	54	86	82	$\chi^2 = 17.93$	1	<0.001	
	M	44	46	19	18				
Body Mass Index[a]		37.5	6.6	39.8	6.5	F = 4.561	1	<0.05	0.351
Waist/Hip Ratio[a]		0.96	0.07	0.95	0.10	F = 0.870	1	NS	
Fat mass percentage[a]		37.8	11.1	43.7	8.3	F = 11.038	1	0.001	0.606
Lean mass percentage[a]		63.0	9.1	57.4	7.8	F = 31.851	1	<0.001	−0.663
Basal metabolism[a]		1846.2	301.8	1752.1	280.3	F = 3.167	1	NS	
Hyperphagia[b]		60	62.5	52	49.5	$\chi^2 = 3.422$	1	0.06	
Binge[b]		23	24.0	89	84.8	$\chi^2 = 75.146$	1	< 0.001	
Grazing[b]		33	34.4	89	84.8	$\chi^2 = 53.371$	1	< 0.001	
Emotional eating[b]		20	20.8	103	98.1	$\chi^2 = 126.063$	1	<0.001	
Post-dinner eating[b]		25	26.0	50	48.1	$\chi^2 = 10.342$	1	0.001	
Night eating[b]		5	5.2	27	26	$\chi^2 = 15.997$	1	<0.001	
Sweet eating[b]		35	36.5	81	77.1	$\chi^2 = 34.012$	1	< 0.001	
Craving for carbohydrates[b]		35	36.5	90	85.7	$\chi^2 = 51.743$	1	<0.001	
Social eating[b]		75	78.1	32	30.5	$\chi^2 = 45.735$	1	<0.001	
Binge Eating Disorder[b]		6	6.3	57	54.3	$\chi^2 = 53.773$	1	<0.001	
Anxiety Disorder[b]		18	18.8	51	48.6	$\chi^2 = 19.783$	1	<0.001	
Bipolar Disorder Type 1[b]		8	8.3	16	15.2	$\chi^2 = 43.964$	6	<0.001	
Bipolar Disorder Type 2[b]		13	13.6	34	32.4				
Cyclothymic Disorder[b]		10	10.4	16	15.2				
Major Depressive Disorder[b]		12	12.5	23	21.9				
Dysthymia[b]		16	16.7	14	13.3				

[a] Data are presented as means and standard deviations.
[b] Data are presented as frequencies and percentages.
[c] Cohen's d is only calculated for significant results.

patients were consistent with the Hardy–Weinberg equilibrium and were comparable to other European populations, confirming a normal distribution.

4. Discussion

This study aimed to firstly cluster obese patients according to their eating behaviours, and secondly to compare these clusters in terms of psychopathology, personality traits, cognitive functioning and serotonin transporter polymorphisms. The two-step cluster analysis identified two groups that differed in all variables considered. Cluster 1 contained mainly obese patients with prandial hyperphagia and social eating along with increased frequencies of the long (L) allelic variant of 5-HTTLPR, while cluster 2 included obese patients with elevated emotional eating, grazing, binge eating, craving for carbohydrates and night eating scores, impaired scores on every psychopathological scale, frequent psychiatric comorbidities and increased frequencies of the S

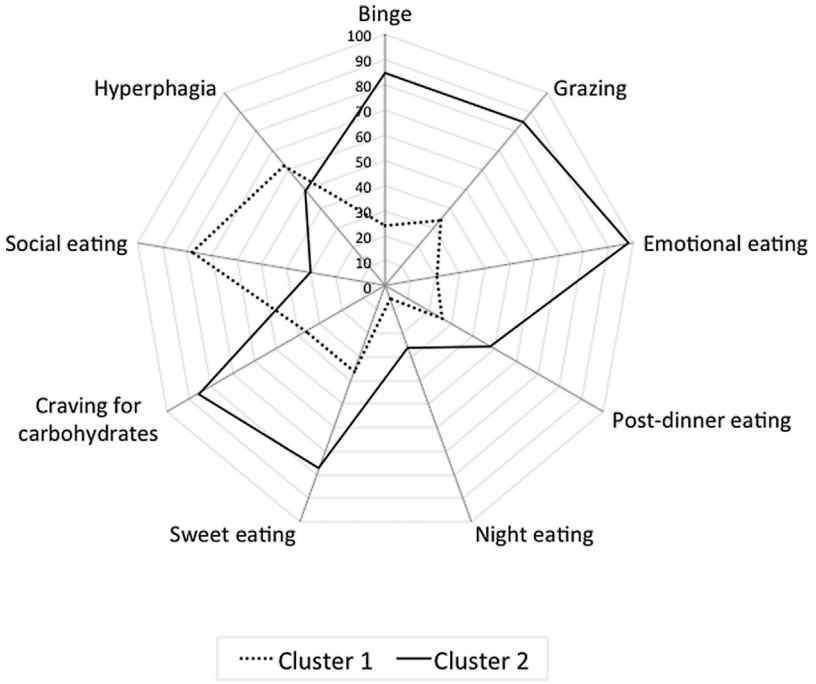

Fig. 1. Distribution of eating behaviours in each cluster (%).

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Table 3
Comparison of tests between clusters.

		Cluster 1 (N = 96)		Cluster 2 (N = 105)					
		Mean	SD	Mean	SD	F/χ^2	*df*	Sig.	*d*[a]
BES		6.8	5.6	23.1	9.0	206.476	1	<0.001	1.806
BDI		9.8	7.7	22.1	11.3	48.576	1	<0.001	1.159
STAI	State	39.5	10.8	48.9	13.4	15.381	1	<0.001	0.769
	Trait	42.2	10.6	50.8	12.9	13.650	1	<0.001	0.725
MDQ[b]	Negative	28	68.3	26	36.6	χ^2=10.470	3	0.005	
	Under-threshold	8	19.5	29	40.8				
	Positive	5	12.2	16	22.5				
EDI-2	Drive for thinness	5.0	4.8	11.8	5.9	54.324	1	<0.001	1.259
	Bulimia	1.5	3.7	6.8	5.8	39.409	1	<0.001	1.079
	Body dissatisfaction	11.5	6.7	17.2	7.1	23.543	1	<0.001	0.825
	Ineffectiveness	3.0	3.1	8.0	7.6	23.285	1	<0.001	0.848
	Perfectionism	3.9	3.0	4.4	3.9	0.675	1	0.413	
	Interpersonal distrust	3.5	3.0	5.1	3.5	8.063	1	0.005	0.489
	Interoceptive awareness	4.2	5.0	8.7	6.7	19.905	1	<0.001	0.756
	Maturity fears	6.4	4.4	7.3	4.5	1.600	1	0.208	
	Ascetism	4.9	3.7	6.6	4.1	6.329	1	0.013	0.434
	Impulse regulation	3.2	5.3	5.6	6.0	6.184	1	0.014	0.423
	Social insecurity	3.9	3.4	6.6	4.6	14.884	1	<0.001	0.663
	Total score	50.9	27.5	87.2	39.3	37.973	1	<0.001	1.062
TCI-R	Novelty Seeking	98.8	17.7	100.0	16.8	0.173	1	0.678	
	Harm Avoidance	91.3	16.7	107.5	19.3	25.033	1	<0.001	0.895
	Reward Dependence	100.1	17.6	99.3	16.3	0.059	1	0.809	
	Persistence	120.7	22.4	112.2	26.6	3.752	1	0.055	
	Self Directedness	142.8	22.9	127.6	24.3	13.059	1	<0.001	−0.643
	Cooperativeness	135.0	20.6	130.7	19.9	1.415	1	0.236	
	Self Transcendence	68.2	18.1	70.4	17.9	0.484	1	0.488	
BIS-11	Total Attentional impulsivity	14.5	2.4	17.5	3.9	16.427	1	<0.001	0.917
	Total Motor impulsivity	18.6	4.0	21.7	4.6	10.676	1	0.001	0.717
	Total Non-planning impulsivity	26.7	5.6	31.6	5.8	17.081	1	<0.001	0.859
	Total BIS	59.6	7.3	70.8	11.1	28.250	1	<0.001	1.182
IGT	IGT net score	2.0	35.7	−14.0	24.9	5.093	1	0.027	−0.524
	IGT-1	0.2	6.8	−3.4	5.1	6.715	1	0.012	−0.603
	IGT-2	2.3	9.6	−3.6	9.3	6.874	1	0.011	−0.625
	IGT-3	0.2	9.5	−3.3	6.9	3.250	1	0.076	
	IGT-4	−0.2	9.2	−2.3	7.6	1.157	1	0.286	
	IGT-5	−0.5	10.7	−1.4	7.6	0.210	1	0.648	
WCST	Global score	35.4	26.5	38.0	32.2	0.115	1	NS	
	Perseverative errors	5.3	3.3	4.0	2.0	4.432	1	< 0.05	−0.482
	Non perseverative errors	17.6	16.7	18.9	19.0	0.082	1	NS	

BES: Binge eating scale; BDI: Beck Depression Inventory; STAI: State-Trait Anxiety Inventory; MDQ: Mood Disorder Questionnaire; EDI-2: Eating Disorder Inventory-2; TCI-R: Temperament Character Inventory Revised; BIS-11: Barratt Impulsivity Scale; IGT: Iowa Gambling Task; WCST: Wisconsin Card Sorting Test.
[a] Cohen's d is only calculated for significant results.
[b] Data are presented as frequencies and percentages.

allelic variant of 5-HTTLPR. Accordingly, our results identified two phenotypes of obese patients in terms of eating behaviours. The first phenotype characterised obese patients with no evidence of relevant psychopathology, and the second characterised obese patients with a more pathological eating pattern and relevant psychopathology. These phenotypes gained further support from the different frequencies of serotonin transporter polymorphisms, anthropometric measures (i.e., higher BMI and fat mass percentage in cluster 2 and higher lean mass percentage in cluster 1) and gender distribution.

Our results confirm that it is not only important to address eating behaviours in detail, but also to address behaviours other than binge eating (emotional eating and grazing, among others), which were demonstrated to have higher weight in the clustering analysis.

Cluster 2 contained the largest proportion of BED-obese patients and a higher prevalence of affective symptoms and dysfunctional personality traits, such as higher harm avoidance and lower self-directedness, which confirms previous results [3,30].

Data regarding the cognitive profiles of patients with BED are controversial. Obese females with BED seem to perform poorly on the IGT in comparison with normal-weight women [31]. In contrast, another study found that individuals with binge eating behaviour performed significantly poorer on problem-solving tasks and inhibitory control and displayed higher prioritisation of immediate versus delayed rewards, although they did not differ in set-shifting, working memory or risk-taking compared to non-BED overweight females [32]. More recently, our group found a pattern of impairment in cognitive flexibility, lack of attention and difficulty in adapting to changes among those with BED [13], and other researchers have described higher cognitive impairment in obese patients when compared with healthy weight/eating controls [14]. In the present study, obese patients in cluster 2, in which BED was over-represented, exhibited poorer decision-making and impaired cognitive flexibility, thus confirming our previous results.

Regarding the two functional polymorphisms of the *SERT* gene, STin2 and 5-HTTLPR, we found that the L allelic variant and the L/L genotype of SERT 5-HTTLPR were more frequent in cluster 1, and more subjects with at least one S allele were present in cluster 2, although no differences were found in the 10 and 12 alleles of STin2 VNTR between clusters.

To our knowledge, studies conducted thus far have focused on the effect of only one SLC6A4 polymorphism (STin2 or 5-HTTLPR) in regard to EDs. It has been proposed that 5-HTTLPR may

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Table 4
Comparison of 5-HTTLPR and sTin2 distribution between clusters.

	Cluster 1 (N = 96)		Cluster 2 (N = 105)				
	Fr	%	Fr	%	χ^2	*df*	p
5HTTLPR-S	52	54.2	77	73.3	8.014	1	0.005
5HTTLPR-L	90	93.8	61	58.0	34.115	1	<0.001
5HTTLPR-LL	44	45.8	28	26.6	35.560	3	<0.001
5HTTLPR-SL	46	47.9	32	30.5			
5HTTLPR-SS	6	6.2	45	42.9			
sTIN2-10	57	59.3	51	48.6	2.354	1	0.125
sTIN2-12	74	77.1	85	80.9	0.454	1	0.500

modulate gene expression through a combined effect with the STin2 polymorphism [15]. Instead, we investigated the effects of eating behaviours on STin2 and 5-HTTLPR. Few studies have analysed the relationship between the functional polymorphism of the serotonin 5-HTTLPR transporter and BED [15,16,33], and none have assessed the association between STin2 and BED.

One study found the L/L genotype and the L allele of 5-HTTLPR to be significantly more frequent in women with BED than in those without [34]. In this case-controlled study (BED vs. non-BED, independent of BMI), only a minority of the sample was made up of obese subjects. As noted by the authors, because the sample did not include a control group of obese participants, they could not exclude the possibility that their findings were related to the occurrence of obesity in BED patients. Instead, our study compared a homogeneous and wider sample of obese subjects of both genders with and without BED. Calati et al. [15] confirmed that being a carrier of the 5-HTTLPR S allele seems to represent a risk factor for all EDs, especially anorexia nervosa. In their meta-analysis, the only study focussed on BED was the above-mentioned study by Monteleone et al. [34]. In contrast, another recent meta-analysis [35] concluded that "neither low- nor high-functioning genotype frequencies in ED patients, with both bi- and tri-allelic models, differed from controls" and that "neither low- nor high-functioning allele frequencies in ED or in BN, in both bi- and tri-allelic models, differed from control groups". The authors recommended exploring the role of psychiatric comorbidity as a possible source of bias. In this context, the high frequency of low-functioning alleles and genotypes in our results could be explained by the high frequency of affective disorders in cluster 2.

Our results are in line with those of Akkermann et al. [33], who found that women prone to binge eating who were carriers of the 5-HTTLPR S allele showed significantly higher bulimia scores on the EDI-2 together with higher levels of state anxiety and higher impulsivity when compared to the homozygous L allele carriers and the control group. In addition, higher levels of state anxiety and impulsivity were evident in the binge eating group of women with the S/S genotype. The authors also highlighted that the S allele, and especially the S/S genotype, increased the risk for affective instability and symptom severity in the general population.

Functional studies suggest that the S allele of 5-HTTLPR leads to a less efficient and less flexible 5-HT system, as well as different forms of psychopathology. The S form, in particular, is associated with lower transcriptional activity and reduced 5HT re-uptake efficiency [36], which may explain the presence of other psychiatric disorders [37]. Previous studies have associated SLC6A4 with affective disorders [38], and carriers of the 5-HTTLPR S allele are more likely to experience major depressive episodes following stressful life events [7], as well as exhibiting higher levels of harm avoidance [34].

Our results confirm these findings. Patients were carefully screened for comorbid psychiatric symptoms such as depression, anxiety and specific personality traits, but cluster analysis was performed only on the basis of eating behaviours in order to avoid the eventual bias of the psychiatric symptoms. Subjects in cluster 2 not only exhibited the typical behavioural patterns of BED, but also displayed more frequent psychiatric comorbid disorders and higher pathological scores, obtaining higher BES, BDI, STAI and BIS scores together with an increased frequency of the S allele, both in the S/L and S/S genotypes. They also showed higher harm avoidance and lower self-directedness personality traits. Conversely, obese patients in cluster 1 had a higher prevalence of the L allele or L/L genotype, lower scores in all tests, were less prone to present the typical dysfunctional eating behaviours related to BED and showed less frequent comorbid affective disorders.

Partially in agreement with our results, Borkowska et al. [10] found that the S/S genotype was associated with a depressive temperament and L/L with a cyclothymic temperament. They also found that the S allele was associated with the development of a depressive temperament, whereas the L allele was associated with higher BMI and more frequent depressive episodes.

Akkerman et al. [39] described that the effect of adverse life events on binge eating and a drive for thinness was even more pronounced when adolescents girls were carriers of the S allele. Indeed, subjects with the S allele who at the age of 15 reported a history of frequent adverse life events had elevated scores on the subscale of bulimia in the EDI-2 at the age of 18. Interestingly, the effect of the S allele on binge eating was even more pronounced. Thus, possible synergistic effects of the serotonin system following exposure to environmental adversities may heighten affective instability and affect regulation difficulties in carriers of the S allele, which in turn may manifest in increased binge eating. A possible explanation for these findings is that the S allele moderates the relationship between depressive feelings and an increase in emotional eating.

Some methodological issues need to be addressed prior to proceeding with the conclusions of this study. Firstly, as this is a cross-sectional study, we are unable to confirm if the present results will remain stable over time or whether current psychopathology is precedent, concomitant or related to the development of obesity. Secondly, the sample size was not large, but this cross-sectional research included all consecutive patients admitted to an internal medicine service for weight reduction treatment, therefore, data are representative on the catchment area. Finally, we did not apply the GWAS approach, known to be superior to SNP genotyping, as this approach requires a larger homogeneous sample and is more expensive in terms of both money and time. Nevertheless, these preliminary results highlight that eating behaviours deserve in-depth analysis in a larger samples of obese patients.

Based on the results of our sample, dysfunctional eating behaviours were useful features for the identification two different phenotypes of obese patients, which could be applied for the early recognition of patients more likely to develop a psychiatric disorder or require a more complex therapeutic approach. These phenotypes may be able to distinguish obese patients seeking weight reduction from a genetic and psychopathological point of view. This separation could facilitate more accurate patient-specific treatment pathways, and may help overcome the idea that "binging" is the most significant altered eating behaviour when identifying obese patients with and without EDs. Our findings gain further importance in light of our previous study which demonstrated that obese patients with pathological eating behaviours such as grazing, emotional eating, sweet eating, craving for carbohydrates and night eating had a worse metabolic and inflammatory profile [4]. Larger samples that are not cross-sectional in design would allow the involvement of other genetic

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mechanisms to be studied, and to further characterise the association between eating behaviours and obesity.

In conclusion, physicians (not only psychiatrists) who treat obesity could tailor patient-specific interventions for obese patients beginning with their eating habits. Future longitudinal observational studies that measure the results of different types of treatments according to these phenotypes could be useful to test the clinical validity of behavioural distinction of obese patients.

Declaration of Interest

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eurpsy.2017.11.009.

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