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# Cluster analysis in gambling disorder based on sociodemographic, neuropsychological, and neuroendocrine features regulating energy homeostasis

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ABSTRACT

*Background:* The heterogeneity of gambling disorder (GD) has led to the identification of different subtypes, mostly including phenotypic features, with distinctive implications on the GD severity and treatment outcome. However, clustering analyses based on potential endophenotypic features, such as neuropsychological and neuroendocrine factors, are scarce so far.

*Aims:* This study firstly aimed to identify empirical clusters in individuals with GD based on sociodemographic (i.e., age and sex), neuropsychological (i.e., cognitive flexibility, inhibitory control, decision making, working memory, attention, and set-shifting), and neuroendocrine factors regulating energy homeostasis (i.e., leptin, ghrelin, adiponectin, and liver-expressed antimicrobial peptide 2, LEAP-2). The second objective was to compare the profiles between clusters, considering the variables used for the clustering procedure and other different sociodemographic, clinical, and psychological features.

*Methods:* 297 seeking-treatment adult outpatients with GD (93.6% males, mean age of 39.58 years old) were evaluated through a semi-structured clinical interview, self-reported psychometric assessments, and a protocolized neuropsychological battery. Plasma concentrations of neuroendocrine factors were assessed in peripheral blood after an overnight fast. Agglomerative hierarchical clustering was applied using sociodemographic, neuropsychological, and neuroendocrine variables as indicators for the grouping procedure. Comparisons between the empirical groups were performed using Chi-square tests ($\chi^2$) for categorical variables, and analysis of variance (ANOVA) for quantitative measures.

*Results:* Three-mutually-exclusive groups were obtained, being neuropsychological features those with the greatest weight in differentiating groups. The largest cluster (Cluster 1, 65.3%) was composed by younger males with strategic and online gambling preferences, scoring higher on self-reported impulsivity traits, but with a lower cognitive impairment. Cluster 2 (18.2%) and 3 (16.5%) were characterized by a significantly higher proportion of females and older patients with non-strategic gambling preferences and a worse

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neuropsychological performance. Particularly, Cluster 3 had the poorest neuropsychological performance, especially in cognitive flexibility, while Cluster 2 reported the poorest inhibitory control. This latter cluster was also distinguished by a poorer self-reported emotion regulation, the highest prevalence of food addiction, as well as a metabolic profile characterized by the highest mean concentrations of leptin, adiponectin, and LEAP-2.
*Conclusions:* To the best of our knowledge, this is the first study to identify well-differentiated GD clusters using neuropsychological and neuroendocrine features. Our findings reinforce the heterogeneous nature of the disorder and emphasize a role of potential endophenotypic features in GD subtyping. This more comprehensive characterization of GD profiles could contribute to optimize therapeutic interventions based on a medicine of precision.

## 1. Introduction

Individuals with gambling disorder (GD) are characterized by recurrent gambling behavior with a loss of control that leads to negative consequences in several life areas [1]. GD is classified within the "substance-related and addiction disorders" category in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [1]. Similarly, the *International Classification of Diseases*, eleventh edition, includes GD as a diagnostic category within the section "disorders due to substance use or addictive behaviors" [2]. Considered as a growing burden health problem [3], the world's lifetime prevalence of GD varies from 0.2 to 10.6% [4,5]. From an etiological perspective, GD is a multicausal disorder, involving environmental and biological features [5]. Many of these factors are shared with other disorders related to impulsivity and compulsivity, such as substance use disorders (SUD) or eating disorders (ED) [6–9]. Based on its complex etiology and consideration as a highly heterogeneous disorder, several authors have defended the existence of GD subtypes [10–12], which could imply distinctive considerations regarding GD prognosis and treatment outcome [13–16]. So far, studies using cluster analysis are mostly based on phenotypic features [17,18], including gambling preferences [19–24], psychopathology and personality traits [25–28], or the presence of illegal acts [29], in addition to sex [15,30] and age [17,31].

To date, the well-known pathways model of Blaszczynski & Nower [28] represents a widely accepted theoretical typology of individuals with gambling behavior in the scientific community [28]. This model postulates the identification of three GD pathways, the "behaviorally conditioned gamblers", "emotionally vulnerable gamblers", and "antisocial impulsivist gamblers", by integrating biological, psychosocial, and environmental features [12,28]. This comprehensive classification has served as the basis for more recent subtyping proporsals in GD. In this line, it is worth mentioning the cluster analysis performed by Jiménez-Murcia et al., [18] in a large sample of 2570 seeking-treatment individuals with GD, including different sociodemographic, gambling, psychopathological, and personality characteristics. This exploratory work identified three-mutually-exclusive clusters, concluding that emotional distress was the most relevant variable for the clustering. Thus, Cluster 1 ("high emotional distress") was characterized by the oldest patients with the longest illness duration, the highest GD severity, and the most severe levels of psychopathology; Cluster 2 ("mild emotional distress") included the biggest part of the sample, with the lowest levels of GD severity and the lowest levels of psychopathology; and, Cluster 3 ("moderate emotional distress") was composed by the youngest patients with the shortest illness duration, the highest level of education, and moderate levels of psychopathology.

Considering specifically sex and age, previous research has reported their differential effect on sociodemographic and clinical variables, severity, and treatment outcome in GD [15,18,32–34]. Then, for example, some studies have described a latter onset of gambling behavior among women, but a faster evolution of gambling problems, a phenomenon known as "telescoping effect" [15,35]. On the other hand, younger age and earlier GD onset have been associated with each other, as well as with higher GD severity [36–38]. Moreover, men and younger individuals show preferences for strategic gambling, that refers to the type of gambling in which a person's knowledge and skills can influence the outcome derived from the gambling behavior beyond the involvement of chance (e.g., sport betting, cards) [23,32]. Likewise, both men and younger individuals also tend to engage in a high number of games [15,23,32,39]. Precisely, this factor seems to play a powerful discrimative role in GD severity among females [15]. Compared with men, severe subtypes of GD in women have also been associated with more dysfunctional mood-related behaviors, older age, and higher impulsive tendencies in terms of lower perseverance [15,18,40,41]. Moreover, men usually seek for treatment earlier in life, although reporting a higher illness duration [5]. Indeed, whereas male sex has been described as one predictor of successful treatment outcome in GD [42], female sex has been associated with a higher risk of poor treatment outcomes since the first stages of the disorder [33]. Similarly, older age has been define as a predictor of better treatment outcome [42].

Regarding neurobiological endophenotypes, neuropsychological deficits form one of the core features of behavioral addictions [43]. Specifically, some neurocognitive studies have proposed that diminished/impaired executive functions (EF), such as decision-making, planning, cognitive flexibility, inhibitory control, or working memory might underlie impulse control deficits in GD [8,16,44–46]. In fact, the impairment of some of these cognitive domains has been linked to a higher likelihood of developing the disorder [47], also contributing to its maintenance [48] and severity [16,49]. Cluster analysis regarding cognitive processes in GD has identified individuals with low and high impaired EF, with distinctive clinical implications [45]. Thus, the subtype with higher impairment in EF has been characterized by an older age, a later GD onset, higher unemployment rates, a worse psychopathological state, and a more dysfunctional personality profile (i.e., higher scores in harm-avoidance and lower in self-directedness). Nonetheless, this study did not find an association between a poorer cognitive status and greater GD severity [45]. Noticeably, there is a growing evidence about the influence of cognitive features on the treatment outcome [14,50]. In this line, cognitive flexibility has been specifically highlighted as a predictor of dropout and relapse [50]. Hence, some authors have proposed the development of specific approaches depending on the neuropsychological profile in order to provide individualized interventions that may improve treatment efficacy [51,52].

Moreover, several neuroendocrine systems have been involved in addiction [53–55]. However, there is still scarce research focused on indentifying potential endophenotypic profiles based on these factors in GD. Particularly, gut hormones (e.g., ghrelin) and adipocytokines (i.e., leptin, adiponectin) participate in reward processing, impulsivity, cognitive functions such as memory, and mood regulation, beyond being classically recognized for their role in feeding and energy homeostasis [54,56–62].

In the mesolimbic circuit, the interaction between ghrelin (a classical orexigenic signal) and other neuroendocrine factors related to impulsivity and reward processing (e.g., dopamine, serotonin, opioids) mediates rewards' reinforcement (e.g., food, substances) and impulsive-seeking behaviors towards natural and non-natural rewards [61,63–68]. Indeed, preclinical and clinical studies have linked ghrelin stimulation to motor disinhibition (i.e., motor impulsivity), impulsive decision-making (i.e., choice impulsivity), and novelty-seeking (i.e., trait impulsivity) [68–70]. In SUD, some genetic variants of the ghrelin

receptor and ghrelin up-regulation have been linked to higher impulsivity and reward sensitivity to drug exposure and discontinuation (craving) and then, to reward-seeking behaviors that perpetuate consumption and relapse [58,71–75]. Interestingly, ghrelin receptors have been suggested as potential therapeutic targets for the development of pharmacological treatment in SUD [76]. The recent case-control study by Etxandi et al., [47] described higher circulating fasting ghrelin concentrations in individuals with GD compared to healthy controls (HC), also hypothesizing the existence of ghrelin up-regulation in this disorder. A previous experimental study in females with GD and at risk individuals found that gambling cues significantly increased circulating ghrelin concentrations, which was enhanced after an overnight fast. Besides, the same study found that ghrelin concentrations predicted gambling persistence despite losses [77]. Hence, these findings indicate that ghrelin could be a common neuroendocrine factor involved in addiction-related disorders that may influence several relevant aspects of GD, such as reinforcing motivation toward gambling, craving-mediated seeking behaviors, loss of control, and relapse.

The liver-expressed antimicrobial peptide 2 (LEAP-2) is a recently described factor which antagonizes ghrelin actions in feeding [56,78]. In the study by Voigt et al., [79], a relationship between LEAP-2 concentrations and attentional control was reported in a non-clinical-population. Specifically, higher fasting circulating LEAP-2 concentrations were associated with faster reaction times, which suggests the notion that LEAP-2 could be involved in impulsive responses [79]. Compared with HC, individuals with GD have shown lower plasma LEAP-2 concentrations. Interestingly, lower LEAP-2 concentrations also predicted the presence of GD [47]. Despite further studies are needed, these results reinforce a potential involvemnent of the ghrelin system in the pathophysiology of the disorder. Noticeably, LEAP-2 seems to be a very attractive target in addiction-related disorders due to the antagonism of the ghrelin receptor has been linked to lower impulsive-seeking behavior, craving, and reward consumption [68,80–83].

Leptin has been mainly distinguished for its anorexigenic and pro-inflammatory functions, whereas the involvement of adiponectin in feeding regulation might be glucose-dependent and have insulin-sensitizing and antinflammatory properties [61]. Their peripheral concentrations have been closely related to adiposity and body mass index (BMI), as they are predominantly produced in the white adipose tissue [61]. At brain level, the presence of leptin receptors on dopaminergic neurons in the limbic system has led to suggest the implication of leptin in the modulation of reward-related behaviors (e.g., food, drugs) through mesolimbic pathways [66,84,85]. Likewise, the wide distribution of receptors for both adipocytokines in brain areas such as the hippocampus and neocortex may suggest a possible involvement in processes related to addiction, including cognitive performance and mood regulation [86]. In this line, their participation in inflammatory responses has been linked to their implications in psychopathological and cognitive aspects among different psychiatric disorders [86,87], as well as in metabolic disturbances such as obesity [66,88].

Interestingly, higher circulating leptin concentrations have been associated with higher scores in food addiction (FA, measured by the Yale Food Addiction Scale 2.0, YFAS 2.0) and trait impulsivity (measured by the Revised NEO Personality Inventory) in non-clinical population, even after adjusting for BMI. Nonetheless these associations were significantly influenced by sex and age [62,89]. Besides, leptin has been proposed as a mediating factor in the link between trait impulsivity, adiposity, and weight gain [62]. Particularly, higher circulating leptin concentrations, but lower adiponectin ones, have been related to loss of control over eating among individuals with overweight and obesity [66]. In SUD, some studies have described an association between circulating leptin concentrations and both craving for drugs and relapse, although the directionality of this association remain inconsistent [85,90–102]. Fewer studies have explored a link between plasma adiponectin concentrations and craving in SUD with mixed results [103,104]. Previous research in the field of GD is scarce and has not reported significant differences in circulating leptin concentrations between patients and HC [47,57]. The single observational case-control study that has explored adiponectin in this clinical population described lower plasma concentrations after adjusting for BMI [47]. In this line, some authors have hypothesized that descreased adiponectin could be related to a higher risk for metabolic diseases in patients with addiction-related disorders, such as SUD and GD [47,103]. Going one step further, fasting concentrations of leptin and adiponectin did not correlate with craving nor with neuropsychological and clinical features in patients with GD [47,57]. That said, a novel study has revealed that those patients with GD and FA had higher circulating leptin concentrations than those without FA after adjusting for sex, age, and BMI [105]. Interestingly, in the subgroup with FA, higher leptin concentrations positively correlated with self-reported impulsivity trait and a poorer neuropsychological performance regarding cognitive flexibility and inhibitory control [105].

In summary, previous research has defined consistent GD clusters based predominantly on phenotypic features that support the heterogeneity of the disorder, with few studies using neuropsychological variables [12,18,24,45]. On the other hand, neuroendocrine signals regulating energy homeostasis have been involved in different addiction-related processes and have shown some differences in their circulating concentrations between individuals with GD and HC [47,61,63–68,79,85]. To the best of our knowledge, the present study was the first one to include both neuropsychological and neuroendocrine variables for clustering in a large clinical sample of seeking-treatment adults with GD. Precisely, cluster analysis highlights intra-individual links between the different variables, favoring a more integrative characterization of individuals with GD according to between-group differences. In this regard, considering neuropsychological and neuroendocrine variables may provide insights into the biological underpinnings of GD and lead to a more refined understanding of the pathogenia of this disorder. Moreover, the use of other variables for external validation (e.g., psychological variables) can help determine whether the neuropsychological and neuroendocrine subtypes have meaningful implications for the manifestation and severity of psychopathological symptoms. Therefore, a cluster analysis based on neuropsychological and neuroendocrine variables could be relevant for a better understanding of severity profiles in GD and for enabling tailored preventive and therapeutic strategies.

The first aim of this study was to define empirical clusters in a seeking-treatment clinical sample with GD, based on neuropsychological and neuroendocrine features, as well as on age and sex. The second objective was to explore and compare the profiles between clusters, considering the variables used for the clustering procedure and other different sociodemographic, clinical, and psychological features. Hence, we hypothesized that not only sociodemographic and neuropsychological, but also these neuroendocrine features could have a relevant role in GD clustering. Accordingly, we expected to differentiate at least between two broad GD subtypes characterized by distinctive sociodemographic, clinical, and psychological features.

## 2. Methods

### 2.1. Participants

The sample consisted of $n$=297 treatment-seeking adult outpatients with GD, mostly males (93.6%), with a mean age of 39.58 years old ($SD$=14.16). They were recruited between April 2018 and September 2021 at the Behavioral Addictions Unit of the Bellvitge University Hospital (HUB)- Bellvitge Biomedical Research Institute (IDIBELL) (Barcelona, Spain). All the participants had a diagnosis of GD based on a semi-structured clinical interview [106] and a self-report psychometric assessment according to DSM-5 criteria [1]. Exclusion criteria, also screened through a semi-structured clinical interview at the first visit in the Unit, were the presence of an organic mental disorder, an intellectual

disability, a neurodegenerative disorder (such as Parkinson's disease), or an active psychotic disorder. All the participants included had completed assessments.

### 2.2. Assessments

#### 2.2.1. Sociodemographic, gambling-related, and anthropometric variables

Sociodemographic (i.e., sex, age, marital status, educational level, occupational status) and clinical variables related to GD (i.e., age of GD onset, illness duration, gambling preferences, modality, and activities, substance consumption) were collected in a semi-structured face-to-face clinical interview as described elsewhere [106,107]. The socioeconomic status was assessed with the Hollingshead coefficient, a measure of the positions in the status structure of the society based on the occupational status, the education level, and sex [108]. Self-reported anthropometric measures such as weight and height were used to calculate BMI.

#### 2.2.2. Neuropsychological variables

*Iowa Gambling Task (IGT)* [109,110]: this is a computerized task to evaluate decision-making. The participant must select 100 cards from four decks (i.e., A, B, C, and D) and, after each card selection, an output is given either a gain or a loss of money. The participant is instructed that the final aim of the task is to win as much money as possible. This test is scored by subtracting the number of cards selected from decks A and B from the number of cards selected from decks C and D. While decks A and B are not advantageous as the final loss is higher than the final gain, decks C and D are advantageous since the punishments are smaller. Higher scores point to better performance while negative scores point to persistently choosing disadvantageous decks. The test score for each block (IGT-1, 2, 3, 4, and 5) is calculated by subtracting the number of choices from disadvantageous decks to the number of choices from advantageous decks draws. The total task score (IGT-Total) is obatined by adding the scores of the five blocks. The learning score (IGT-Learning) measures differences between the two first blocks (where the participant has not learned which decks are advantageous and disadvantageous) and the two last blocks (where the participant could have already detected which decks involve a risky choice and then, the experience gained through the trial can produce changes in choice patterns). Additionally, the risk score (IGT-Risk) is measured considering the scores from the two last blocks.

*Wisconsin Card Sorting Test (WCST)* [111]: this is a task for assessing cognitive flexibility, composed of four stimulus cards and 128 response cards showing four different shapes, four different colors, and four different number of figures in each one. The participant must match response cards with the stimulus cards in a way that it seems justifiable before receiving the feedback (i.e., correct, or incorrect). After ten sequential correct answers the categorization criterion changes. Total trials, total errors, perseverative errors and non-perseverative errors, the number of complete categories, conceptual, and trials to complete first category are recorded.

*Trail Making Test (TMT, part A and B)* [112]: TMT part A consists of 25 circles on a piece of paper with the numbers 1 to 25 written randomly in each. The person is tasked with drawing a line from one circle to the next in ascending numerical order, from 1 to 25, as quickly as possible. The lines between the circles are referred to as the "trail." For part B, the dots go from 1 to 13 and include letters from A to L. As in the first part, the person must connect the dots in order while alternating letters and numbers, as in 1-A-2-B-3-C..., in the shortest time possible without lifting the pen from the paper. The task assesses visual conceptual and visual-motor tracking, entailing motor speed, attention, and the capacity to alternate between cognitive categories (set-shifting). Each part is scored according to the time spent to complete the task.

*Stroop Color and Word Test (SCWT)* [113]: it measures cognitive inhibition and consists of three different lists, beginning with a word list containing the names of colors printed in black ink, followed by a color list that comprises letter *"X"* printed in color and finally, by a color-word list constituted of names of colors in a color ink that does not match the written name. Three final scores are obtained based on the number of items that the participant can read on each of the three lists in a time of 45 seconds. Moreover, an interference score is calculated based on the scores of the three lists, which reflects the ability to inhibit cognitive interference.

*Digits task of the Wechsler Memory Scale-Third Edition (WMS-III)* [114]: it consists of two lists of digits presented verbally by the examiner. In the Digits Forward Task, the participant is asked to repeat the digits in the same order. It assesses short-term memory and attention skills. In the Digits Backward Task, the participant is asked to repeat the digits in reverse order. It evaluates verbal working memory due to internal manipulation of mnemonic representations of verbal information in the absence of external cues.

*Vocabulary task of the Wechsler Adult Intelligence Scale-Third Edition (WAIS-III)* [115]: requires defining words of increasing difficulty presented orally. It is used to assess the vocabulary expression and as a measure of estimated intelligence [116].

#### 2.2.3. Neuroendocrine variables

These variables were quantified from peripheral blood sample extraction by venous aspiration with ethylenediamine tetraacetic acid (EDTA) (25 mM final concentration) after an overnight fasting of at least 8 hours. The blood was centrifuged at 1700g in a refrigerated centrifuge (4°C) for 20 minutes. Plasma was immediately separated from serum and stored at -80°C until analysis. Parameter determinations were carried out using specific commercial kits according to the manufacturer's instructions. Plasma LEAP-2 (ng/ml) was quantitatively measured using a previously validated commercial enzyme-linked immunosorbent assay (ELISA) kit (Human LEAP-2 ELISA kit, Phoenix Pharmaceuticals, Inc) [117,118]. Intra-assay and inter-assay variation coefficients were <10% and <15%, respectively. The assay sensitivity limit was 0.15 ng/ml. Total ghrelin (pg/ml) was measured using an ELISA kit (Invitrogen-Thermofisher scientific) with a specificity of 100%. Intra-assay variation coefficient was <6% and inter-assay <8.5%. The assay sensitivity limit was 11.8 pg/ml [119]. Adiponectin (ng/ml) and leptin (ng/ml) plasma measurements were performed using a solid-phase sandwich ELISA kit (Invitrogen-Thermofisher scientific) with a specificity of 100%. Intra-assay and inter-assay variation coefficients were <4% and < 5%, respectively, and assay sensitivity limit was 100 pg/ml for adiponectin and <3.5 pg/ml for leptin. The absorbance from each sample was measured in duplicate using a spectrophotometric microplate reader at a wavelength of 450 nm (Epoch 2 microplate reader, Biotek Instruments, Inc).

#### 2.2.4. Psychometric assessment of gambling and psychological variables

*Diagnostic Questionnaire for Pathological Gambling According to DSM criteria* [120]; Spanish validation [121]: a self-report questionnaire with 19 items coded in a binary scale (yes-no), used for diagnosing GD according to the DSM-IV-TR [122] and DSM-5 criteria [1]. The cut-off score according to DSM-5 is represented by the achievement of at least four of the nine criteria for the diagnosis of GD in the last 12 months. A quantitative severity index is included (mild GD based on meeting 4 to 5 criteria; moderate GD based on meeting 6 to 7 criteria; and severe GD based on meeting 8 to 9 criteria). The internal consistency in this study was Cronbach's alpha ($\alpha$) = .80.

*South Oaks Gambling Screen (SOGS)* [123]; Spanish validation [124]: a 20-item instrument screening gambling problems and related negative consequences for the past-year. Total score obtained as the sum of the scored items measures problem-gambling severity, with a score of 5 or more suggestive of "probable pathological gambling". The internal consistency in this study was $\alpha$ = .77.

*Symptom Checklist-90-Revised (SCL-90-R)* [125]; Spanish validation [126]: a 90-item self-report questionnaire measured on an ordinal 3-point scale. It evaluates a broad range of psychological problems and psychopathology, based on nine primary symptom dimensions

(Somatization, Obsession-Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation, and Psychoticism). It includes three global indices (global severity index, GSI; positive symptom distress index, PSDI; and, total positive symptoms, PST). The internal consistency in this study was between $\alpha = .78$ (paranoid ideation) and $\alpha = .92$ (depressive dimension).

*Impulsive Behavior Scale (UPPS-P)* [127]; Spanish validation [128]: it measures five facets of impulsive behavior through self-report on 59 items: negative urgency; positive urgency; lack of premeditation; lack of perseverance; and sensation-seeking. The internal consistency in this study was between $\alpha = .80$ (lack of perseverance) and $\alpha = .93$ (positive urgency).

*Difficulties in Emotion Regulation Strategies (DERS)* [129]; Spanish validation [130]: a 36-item self-reported scale to assess emotion dysregulation, divided into six subscales (i.e., non-acceptance of emotional responses, difficulties engaging in goal-directed behavior when having strong emotions, impulse-control difficulties, lack of emotional awareness, limited access to emotion regulation (ER) strategies, and lack of emotional clarity). Participants are asked to respond to each item using a five-point Likert scale ranging from 1 (almost never) to 5 (almost always). Higher scores indicate greater problems in ER. The internal consistency in our sample was between $\alpha = .72$ (lack emotional awareness) and $\alpha = .89$ (non-acceptance emotions).

*Temperament and Character Inventory-Revised (TCI-R)* [131]; Spanish validation [132]: a questionnaire with 240-items scored on a 5-point Likert scale and measuring personality derived from three character dimensions (Self-Directedness, Cooperativeness, and Self-Transcendence) and four temperament dimensions (Harm-Avoidance, Novelty-Seeking, Reward-Dependence and Persistence). The internal consistency in this study was between $\alpha = .70$ (novelty-seeking) and $\alpha = .88$ (persistence).

*Yale Food Addiction Scale 2.0 (YFAS 2.0)* [133]; Spanish validation [134]: a self-reported scale to assess FA based on the 11-substance dependence-related symptoms adapted to the context of food consumption. The YFAS 2.0 consists of 35 items and produces two measurements: (1) a continuous symptom count score that reflects the number of fulfilled diagnostic criteria (ranging from 0 to 11), and (2) a binary measurement (present versus absent) based on the number of symptoms (at least 2) and the self-reported clinical impairment or distress. Additionally, it gives the severity cut-offs: mild (2–3 symptoms), moderate (4–5 symptoms), and severe (6–11 symptoms). The internal consistency in this study was $\alpha = .97$.

### 2.3. Procedure

All participants were evaluated at the Behavioral Addictions Unit of the HUB-IDIBELL institution. The data collection was carried out by a multidisciplinary team (psychology, psychiatry, nursing) with more than 25 years of experience in the field of GD and other behavioral addictions. In the first session, a comprehensive semi-structured clinical interview was conducted, in which sociodemographic, gambling-related, and anthropometric variables were assessed. During the second session, the psychometric assessment regarding gambling and psychological variables took placed, along with the extraction of blood samples. These biological samples were subsequently analyzed at the Singular Center for Research in Molecular Medicine and Chronic Diseases (CIMUS, Santiago de Compostela, Spain). Finally, in the third session, the neuropsychological assessment was performed by an experienced neuropsychologist for 50 - 60 minutes. All the measures used in this study were carried out prior to the beginning of specialized treatment in our Unit.

### 2.4. Statistical analysis

SPSS24 for windows was used for the statistical analysis [135]. Two-step cluster method identified differentiated empirical profiles of patients. This is an agglomerative hierarchical classification method useful to explore natural groupings within a dataset with both continuous and categorical variables, with the possibility of selecting the optimal number of empirical clusters. In this study, the log-likelihood distance, the Akaike's Information Criterion (AIC), and the Schwarz Bayesian Information Criterion (BIC) were used to determine the optimal model (based on choosing a solution with a reasonably large ratio of Schwarz Bayesian Information Criterion and a large ratio of distance measures). The dataset used to identify the clusters included the sociodemographic variables (i.e., sex and age), neuropsychological measures (i.e., IGT, WCST, TMT, SCWT), and neurendocrine variables (i.e., LEAP-2, leptin, adiponectin, and ghrelin). The calculation of the internal consistency for the cluster solution was based on the Silhouette-index, a measure of the cohesion/separation (how similar individuals are to their own cluster compared to other clusters) extending from -1 to +1 (values of 0.30 and 0.50 define the ranges of fair and good, interpreted as adequate matching in one's own cluster and of poor matching in other clusters) [136].

To value the discriminative capacity of the clusters, comparisons between the empirical groups were performed for all the variables of the study. Chi-square tests ($\chi^2$) compared categorical variables, and analysis of variance (ANOVA) was used for quantitative measures. The standardized coefficient Cohen's-h measured the effect sizes for the proportion differences and Cohen's-d measured the effect sizes for the mean differences (small effect size was considered for values lower than 0.20, medium for values higher than 0.5, and large for values higher than 0.80) [137].

The potential increase in the Type-I error due to the application of many null-hypothesis tests was controlled for with Finner's method (a stepwise familywise error rate procedure which provides a more powerful test than the classical Bonferroni correction) [138].

## 3. Results

### 3.1. Descriptives for the sample

Most patients in the study reported primary (52.9%) or secondary (37.7%) education level, were single (53.2%) or married (34.7%), and pertained to mean-low and low social index groups (82.8%). The mean age of GD onset was 29.1 years old (SD=12.4) and the GD duration was 5.2 years (SD= 6.0). The prevalence of patients who reported non-strategic gambling preference was 49.8%, strategic gambling 31.0%, and mixed gambling activities 19.2%. These results are shown in Table S1 (supplementary material).

### 3.2. Clustering procedure

The optimal solution automatically selected by the system was the three-cluster grouping, which achieved the highest measure of cohesion/separation (Silhouette=0.30). The Silhouette index was in the fair range, with evidence of an adequate cluster structure in this subsample. Cluster 1 (identified as "young reward-seeker") included $n$= 194 patients (65.3%), Cluster 2 (designated as "comorbid vulnerable coping-seeker") included $n$= 54 (18.2%), and Cluster 3 (denominated as "cognitive inflexible") included $n$= 49 (16.5%). Ratio of sizes (largest to smallest) was 3.96. Other candidate solutions with a higher number of clusters were rejected since they achieved poorer fitting indexes, included some low sample groups and did not facilitate better clinical interpretation. The complete results obtained in the auto-clustering procedure are displayed in Table S2 (supplementary material).

The upper panel of Fig. 1 displays the bar-chart with the relative relevance of each predictor in the clustering process (these weights are into the range 1 [assigned to the measure with the maximum relevance] and 0 [for variables with the minimum relevance]). The relative relevance weights are measures of the discriminative capacity of the variables within the clustering process: higher relevance suggests less likely

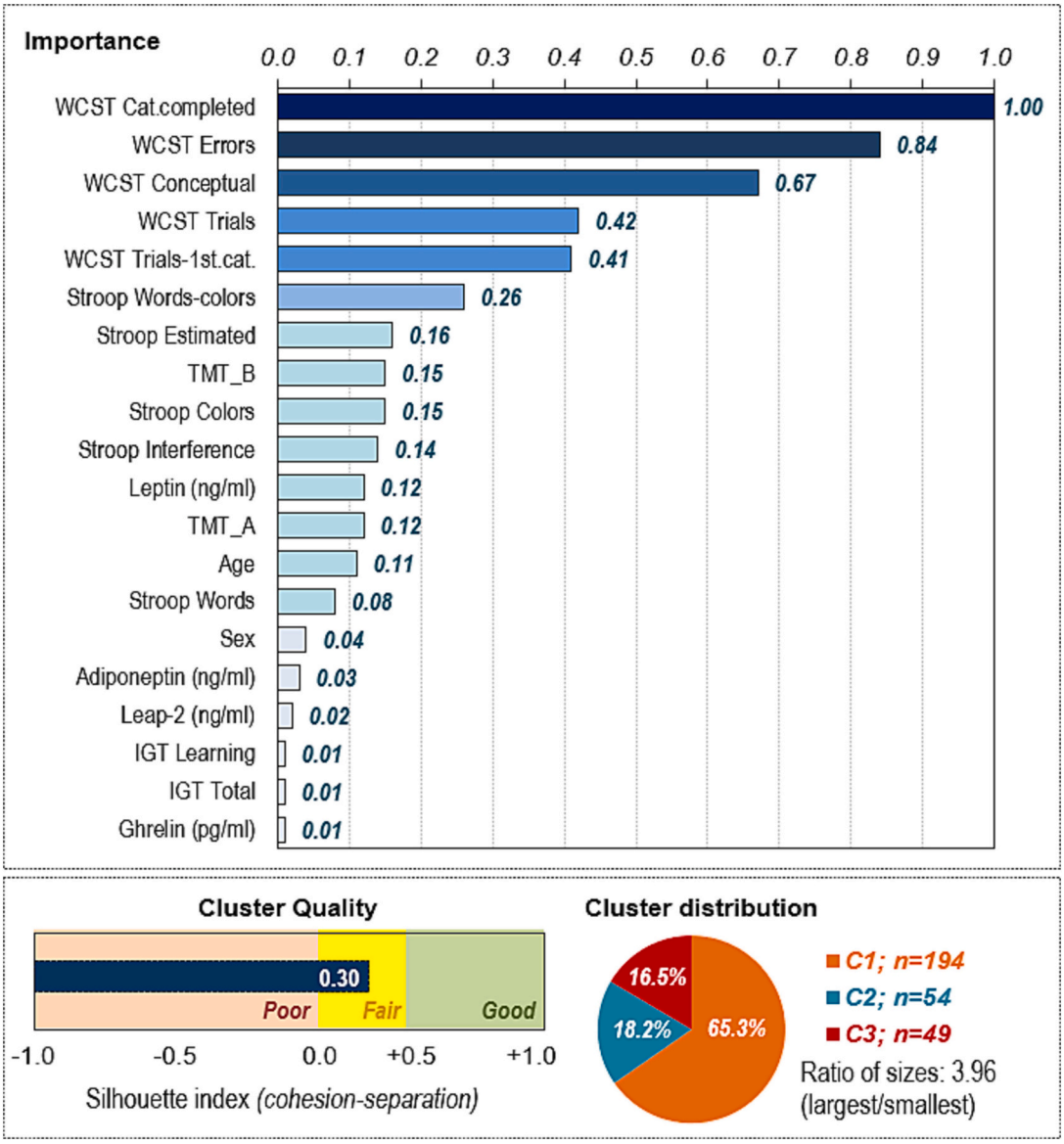


**Fig. 1.** Clustering procedure.

**Table 1**
Comparison of sociodemographic variables and body mass index.

| | | Cluster 1 *N=194* | | Cluster 2 *N=54* | | Cluster 3 *N=49* | | Cluster 1 *vs* Cluster 2 | | Cluster 1 *vs* Cluster 3 | | Cluster 2 *vs* Cluster 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | *n* | % | *n* | % | *n* | % | *p* | \|*h*\| | *p* | \|*h*\| | *p* | \|*h*\| |
| Sex | Women | 4 | 2.1% | 9 | 16.7% | 6 | 12.2% | **.001*** | **0.55**† | **.001*** | 0.43 | .525 | 0.13 |
| | Men | 190 | 97.9% | 45 | 83.3% | 43 | 87.8% | | | | | | |
| Education | Primary | 83 | 42.8% | 37 | 68.5% | 37 | 75.5% | **.004*** | **0.52**† | **.001*** | **0.68**† | .731 | 0.16 |
| | Secondary | 88 | 45.4% | 14 | 25.9% | 10 | 20.4% | | 0.41 | | **0.54**† | | 0.13 |
| | University | 23 | 11.9% | 3 | 5.6% | 2 | 4.1% | | 0.23 | | 0.30 | | 0.07 |
| Marital status | Single | 116 | 59.8% | 20 | 37.0% | 22 | 44.9% | **.005*** | **0.51**† | .135 | 0.30 | .254 | 0.16 |
| | Married | 59 | 30.4% | 22 | 40.7% | 22 | 44.9% | | 0.22 | | 0.30 | | 0.08 |
| | Divorced | 19 | 9.8% | 12 | 22.2% | 5 | 10.2% | | 0.35 | | 0.01 | | 0.33 |
| Social position | High | 8 | 4.1% | 0 | 0.0% | 0 | 0.0% | **.001*** | 0.41 | **.001*** | 0.41 | .135 | 0.00 |
| | Mean-high | 17 | 8.8% | 0 | 0.0% | 2 | 4.1% | | **0.60**† | | 0.19 | | 0.41 |
| | Mean | 20 | 10.3% | 1 | 1.9% | 3 | 6.1% | | 0.38 | | 0.15 | | 0.23 |
| | Mean-low | 84 | 43.3% | 19 | 35.2% | 10 | 20.4% | | 0.17 | | **0.50**† | | 0.33 |
| | Low | 65 | 33.5% | 34 | 63.0% | 34 | 69.4% | | **0.60**† | | **0.73**† | | 0.14 |
| | | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* | *p* | \|*d*\| | *p* | \|*d*\| | *p* | \|*d*\| |
| Age (years old) | | 35.50 | 11.26 | 48.13 | 15.31 | 46.31 | 16.47 | **.001*** | **0.94**† | **.001*** | **0.77**† | .479 | 0.11 |
| Body mass index (kg/m$^2$) | | 25.91 | 5.02 | 28.32 | 5.48 | 26.72 | 4.12 | **.002*** | 0.46 | .311 | 0.18 | .103 | 0.33 |

***Note.*** SD: standard deviation. *Bold: significant comparison. †Bold: effect size into the range mild-moderate to high-large.

to attribute to chance differences between clusters for the measure. Broadly, neuropsychological variables achieved the largest discriminative capacity between groups, particularly regarding cognitive flexibility (WCST). Among the neuroendocrine factors, leptin was the strongest indicator for clustering. Sociodemographic features (i.e., sex and age) had a mild-moderate effect in distinguishing subtypes, being age slightly more determinant than sex. The poorest discriminative capacity was achieved by some endocrine measures (i.e., adiponectin, LEAP-2, and ghrelin), as well as the IGT global measures.

### 3.3. Comparison between groups

Table 1 contains the comparison between the empirical clusters for the sociodemographic variables. Cluster 1 ("young reward-seeker") was the largest cluster, characterized by the lowest proportion of women, but the youngest patients, as well as the highest proportion of single ones, with high education levels and social position indexes. No differences between Cluster 2 ("comorbid vulnerable coping-seeker") and 3 ("cognitive inflexible") emerged for the sociodemographic profile. Although men still predominated, in these clusters a significantly higher proportion of females and older individuals were found. Besides, Cluster 2 showed the highest BMI.

Table 2 shows the comparison of the gambling profile and substance use between clusters. Cluster 1 included patients with the earliest age of GD onset, the highest proportion of individuals with preference for strategic gambling (i.e., sports-betting and cards), while the lowest for non-strategic gambling. Likewise, this cluster presented the highest rates of online and mixed mode. Cluster 2 showed a gambling profile statistically equal to Cluster 3, characterized by higher prevalence of non-strategic gambling (i.e., lotteries, bingo) and offline mode. No differences between the three empirical clusters were found regarding substance use, illness duration, and gambling severity levels (number of DSM-5 total criteria and SOGS total score).

The best neuropsychological performance was observed in Cluster 1 while the worst one (i.e., lower cognitive reserve, poorer learning curve, cognitive inflexibility) was described in Cluster 3 (upper part of Table 3, and Fig. S1). Cluster 2 had the poorest inhibitory control while Cluster 3 reported the highest cognitive inflexibility. Regarding the endocrine profile, Cluster 2 obtained the highest mean values in leptin, adiponectin, and LEAP-2 while no differences between the Cluster 1 and 3 were achieved (lower part of Table 3).

Table 4 shows the comparison for the psychological measures. Cluster 1 was defined by the best psychopathological state (the lowest means in the SCL-90-R scales), the lowest ER difficulties (DERS), the highest sensation seeking (UPPS-P), novelty-seeking, and self-directedness scores, and the lowest mean scores in harm-avoidance and self-transcendence personality traits (TCI-R). Compared to Cluster 3, Cluster 2 registered higher mean scores in the SCL-90-R positive symptom distress index (PSDI) and more difficulties engaging in goal-oriented behaviors (DERS). Cluster 2 reported higher rates of FA (measured with the YFAS 2.0) than the other two clusters.

Fig. 2 displays radar-charts showing the differences between clusters in the variables used for clustering, as well as other sociodemographic, clinical, and psychological features.

## 4. Discussion

The current study aimed to describe for the first time the existence of GD subtypes based on sociodemographic, neuropsychological, and neuroendocrine indicators. According to our initial hypothesis, three mutually-exclusive subtypes were detected (Cluster 1, 2, and 3). Broadly, neuropsychological features had the greatest weight in differentiating groups, especially cognitive flexibility and inhibitory control. Interestingly, leptin ranked in the middle among all indicators, being the strongest neuroendocrine feature for clustering. Sex and age showed a mild-moderate effect in distinguishing subtypes. Moreover, the use of these indicators also allowed to distinctively identify individuals regarding their sociodemographic, clinical, and psychological profile (Cluster 1-"young reward-seeker", Cluster 2-"comorbid vulnerable coping-seeker", and Cluster 3- "cognitive inflexible").

**Table 2**
Comparison of gambling profile and substance use.

| | Cluster 1 *N=194* | | Cluster 2 *N=54* | | Cluster 3 *N=49* | | Cluster 1 *vs* Cluster 2 | | Cluster 1 *vs* Cluster 3 | | Cluster 2 *vs* Cluster 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| *Gambling profile* | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* | *p* | \|*d*\| | *p* | \|*d*\| | *p* | \|*d*\| |
| Age of onset of GD | 25.82 | 9.49 | 35.52 | 15.31 | 35.05 | 14.28 | **.001*** | **0.76**† | **.001*** | **0.76**† | .838 | 0.03 |
| Duration of GD | 5.04 | 5.78 | 4.91 | 5.44 | 6.31 | 7.42 | .885 | 0.02 | .190 | 0.19 | .240 | 0.22 |
| DSM-5 total criteria | 7.14 | 1.80 | 7.04 | 1.79 | 7.20 | 1.81 | .699 | 0.06 | .836 | 0.03 | .639 | 0.09 |
| SOGS total score | 11.03 | 3.27 | 10.48 | 3.33 | 10.55 | 2.97 | .275 | 0.16 | .359 | 0.15 | .913 | 0.02 |
| *Gambling preference* | *n* | *%* | *n* | *%* | *n* | *%* | *p* | \|*h*\| | *p* | \|*h*\| | *p* | \|*h*\| |
| Non-strategic type | 84 | 43.3% | 33 | 61.1% | 31 | 63.3% | **.042*** | 0.36 | **.015*** | 0.40 | .714 | 0.04 |
| Strategic type | 72 | 37.1% | 12 | 22.2% | 8 | 16.3% | | 0.33 | | **0.52**† | | 0.15 |
| Mixed type | 38 | 19.6% | 9 | 16.7% | 10 | 20.4% | | 0.08 | | 0.02 | | 0.10 |
| *Gambling modality* | *n* | *%* | *n* | *%* | *n* | *%* | *p* | \|*h*\| | *p* | \|*h*\| | *p* | \|*h*\| |
| Offline mode | 152 | 78.4% | 50 | 92.6% | 49 | 100% | **.026*** | 0.42 | **.001*** | **0.97**† | .070 | **0.55**† |
| Online mode | 19 | 9.8% | 1 | 1.9% | 0 | 0% | | 0.36 | | **0.64**† | | 0.27 |
| Mixed mode | 23 | 11.9% | 3 | 5.6% | 0 | 0% | | 0.23 | | **0.70**† | | **0.51**† |
| *Gambling activities* | *n* | *%* | *n* | *%* | *n* | *%* | *p* | \|*h*\| | *p* | \|*h*\| | *p* | \|*h*\| |
| Slot-machines | 103 | 53.1% | 35 | 64.8% | 27 | 55.1% | .125 | 0.24 | .801 | 0.04 | .315 | 0.20 |
| Bingo | 11 | 5.7% | 7 | 13.0% | 6 | 12.2% | **.048*** | 0.26 | .107 | 0.23 | .913 | 0.02 |
| Lotteries | 5 | 2.6% | 7 | 13.0% | 8 | 16.3% | **.002*** | 0.41 | **.001*** | **0.51**† | .629 | 0.10 |
| Sports-betting | 65 | 33.5% | 9 | 16.7% | 7 | 14.3% | **.017*** | 0.39 | **.008*** | **0.50**† | .739 | 0.07 |
| Casinos | 36 | 18.6% | 9 | 16.7% | 6 | 12.2% | .750 | 0.05 | .296 | 0.18 | .525 | 0.13 |
| Gambling-saloons | 17 | 8.8% | 8 | 14.8% | 10 | 20.4% | .191 | 0.19 | **.020*** | 0.34 | .455 | 0.15 |
| Cards | 17 | 8.8% | 1 | 1.9% | 2 | 4.1% | **.049*** | 0.33 | .275 | 0.19 | .502 | 0.13 |
| Stock-market | 6 | 3.1% | 1 | 1.9% | 0 | 0.0% | .610 | 0.08 | .213 | 0.35 | .338 | 0.27 |
| *Substances use-abuse* | *n* | *%* | *n* | *%* | *n* | *%* | *p* | \|*h*\| | *p* | \|*h*\| | *p* | \|*h*\| |
| Tobacco | 92 | 47.4% | 24 | 44.4% | 22 | 44.9% | .698 | 0.06 | .752 | 0.05 | .963 | 0.01 |
| Alcohol | 29 | 14.9% | 7 | 13.0% | 7 | 14.3% | .882 | 0.06 | 1.000 | 0.02 | .845 | 0.04 |
| Other drugs | 23 | 11.9% | 5 | 9.3% | 6 | 12.2% | .772 | 0.08 | .940 | 0.01 | .624 | 0.10 |

***Note.*** SD: standard deviation. SOGS: South Oaks Gambling Screen. In *Gambling Preference*, "mixed type" refers to both non-strategic and strategic gambling". Likewise, in Gambling modality, "mixed mode" refers to both offline and online gambling". *Bold: significant comparison. †Bold: effect size into the range mild-moderate to high-large.

**Table 3**
Comparison between the clusters for endocrine and neuropsychological measures.

| | Cluster 1 *N=194* | | Cluster 2 *N=54* | | Cluster 3 *N=49* | | Cluster 1 *vs* Cluster 2 | | Cluster 1 *vs* Cluster 3 | | Cluster 2 *vs* Cluster 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* | *p* | \|*d*\| | *p* | \|*d*\| | *p* | \|*d*\| |
| IGT Block 1 | -2.12 | 5.30 | -1.33 | 4.27 | -1.80 | 5.48 | .321 | 0.16 | .692 | 0.06 | .650 | 0.09 |
| IGT Block 2 | -0.04 | 5.31 | 0.19 | 4.76 | 0.45 | 7.03 | .791 | 0.04 | .580 | 0.08 | .809 | 0.04 |
| IGT Block 3 | 1.51 | 7.02 | 1.44 | 6.42 | -1.12 | 7.07 | .951 | 0.01 | **.018*** | 0.37 | **.041*** | 0.38 |
| IGT Block 4 | 1.98 | 7.28 | -0.37 | 6.29 | -0.35 | 8.89 | **.040*** | 0.35 | **.050*** | 0.29 | .987 | 0.00 |
| IGT Block 5 | 1.40 | 8.88 | 1.20 | 7.07 | 0.92 | 8.89 | .920 | 0.01 | .837 | 0.05 | .807 | 0.05 |
| IGT Total | 2.85 | 22.80 | 1.52 | 19.03 | -1.84 | 21.46 | .695 | 0.06 | .183 | 0.21 | .439 | 0.17 |
| IGT Learning | 5.35 | 13.60 | 2.11 | 12.09 | 1.92 | 15.76 | .126 | 0.25 | .119 | 0.23 | .943 | 0.01 |
| IGT Risk | 3.19 | 14.08 | 0.96 | 10.93 | 0.57 | 14.53 | .290 | 0.18 | .232 | 0.18 | .884 | 0.03 |
| WCST Trials | 93.69 | 15.77 | 114.07 | 14.66 | 128.00 | 0.00 | **.001*** | **1.34**† | **.001*** | **3.08**† | **.001*** | **1.34**† |
| WCST Errors | 22.03 | 10.62 | 36.98 | 11.54 | 72.90 | 13.85 | **.001*** | **1.35**† | **.001*** | **4.12**† | **.001*** | **2.82**† |
| WCST Errors persever. | 10.59 | 4.82 | 17.93 | 6.87 | 29.84 | 12.86 | **.001*** | **1.24**† | **.001*** | **1.98**† | **.001*** | **1.16**† |
| WCST Errors non.pers. | 11.44 | 6.52 | 19.06 | 6.57 | 43.06 | 15.82 | **.001*** | **1.16**† | **.001*** | **2.61**† | **.001*** | **1.98**† |
| WCST Conceptual | 66.49 | 7.22 | 66.35 | 9.08 | 31.37 | 16.70 | .927 | 0.02 | **.001*** | **2.73**† | **.001*** | **2.60**† |
| WCST Cat.completed | 5.67 | 0.51 | 4.65 | 1.36 | 1.29 | 1.06 | **.001*** | **0.99**† | **.001*** | **5.26**† | **.001*** | **2.75**† |
| WCST Trials 1-categ. | 18.22 | 9.07 | 20.41 | 7.92 | 70.29 | 46.83 | .490 | 0.26 | **.001*** | **1.54**† | **.001*** | **1.49**† |
| TMT A | 28.60 | 7.52 | 37.63 | 9.74 | 37.57 | 15.35 | **.001*** | **1.04**† | **.001*** | **0.74**† | .976 | 0.00 |
| TMT B | 67.50 | 19.18 | 92.76 | 31.07 | 108.94 | 62.88 | **.001*** | **0.98**† | **.001*** | **0.89**† | **.012*** | 0.33 |
| TMT Diff | 39.07 | 16.59 | 57.78 | 27.33 | 74.43 | 58.12 | **.001*** | **0.83**† | **.001*** | **0.83**† | **.004*** | 0.37 |
| Stroop words | 101.49 | 11.72 | 89.85 | 14.30 | 93.33 | 16.40 | **.001*** | **0.89**† | **.001*** | **0.57**† | .179 | 0.23 |
| Stroop colors | 71.81 | 8.78 | 60.70 | 9.46 | 62.39 | 13.69 | **.001*** | **1.22**† | **.001*** | **0.82**† | .388 | 0.14 |
| Stroop words-colors | 47.32 | 8.07 | 33.24 | 9.07 | 36.61 | 10.46 | **.001*** | **1.64**† | **.001*** | **1.15**† | **.050*** | 0.34 |
| Stroop estimated | 41.95 | 4.18 | 36.05 | 5.21 | 37.08 | 6.85 | **.001*** | **1.25**† | **.001*** | **0.86**† | .289 | 0.17 |
| Stroop interference | 5.38 | 6.24 | -2.81 | 8.33 | -0.47 | 8.00 | **.001*** | **1.11**† | **.001*** | **0.81**† | **.049*** | 0.29 |
| Digits direct | 9.36 | 1.74 | 7.83 | 2.13 | 8.18 | 2.29 | **.001*** | **0.79**† | **.001*** | **0.58**† | .354 | 0.16 |
| Digits direct-span | 6.23 | 1.04 | 5.33 | 1.13 | 5.65 | 1.33 | **.001*** | **0.82**† | **.001*** | **0.48**† | .145 | 0.26 |
| Digits inverse | 6.69 | 1.81 | 5.22 | 1.99 | 4.94 | 1.78 | **.001*** | **0.77**† | **.001*** | **0.97**† | .436 | 0.15 |
| Digits inverse-span | 4.93 | 0.99 | 4.15 | 1.31 | 3.90 | 1.05 | **.001*** | **0.68**† | **.001*** | **1.02**† | .235 | 0.21 |
| Digits total | 16.05 | 3.16 | 13.06 | 3.76 | 13.12 | 3.53 | **.001*** | **0.86**† | **.001*** | **0.87**† | .919 | 0.02 |
| WAIS Vocabulary | 40.97 | 6.30 | 33.13 | 9.63 | 33.18 | 9.99 | **.001*** | **0.96**† | **.001*** | **0.93**† | .972 | 0.01 |
| Ghrelin (pg/ml) | 958.6 | 743.3 | 877.4 | 826.4 | 962.6 | 719.1 | .485 | 0.10 | .973 | 0.01 | .568 | 0.11 |
| LEAP-2 (ng/ml) | 5.05 | 2.84 | 6.39 | 2.97 | 5.13 | 2.74 | **.002*** | 0.46 | .852 | 0.03 | **.026*** | 0.44 |
| Leptin (ng/ml) | 6.48 | 4.74 | 15.13 | 13.04 | 7.44 | 5.97 | **.001*** | **0.88**† | .401 | 0.18 | **.001*** | **0.76**† |
| Adiponectin (ng/ml) | 8276.1 | 3738.2 | 10064.1 | 5544.2 | 7189.8 | 4816.5 | **.007*** | 0.38 | .115 | 0.25 | **.001*** | **0.55**† |

***Note.*** SD: standard deviation. IGT: Iowa Gambling Task. WCST: Wisconsin Card Sorting Test. WCST Trials: Wisconsin Card Sorting Test, total trials. WCST Errors: Wisconsin Card Sorting Test, total errors. WCST Errors persever.: Wisconsin Card Sorting Test, perseverative errors. WCST Errors non.pers.: Wisconsin Card Sorting Test, non-perseverative errors. WCST Cat.completed: Wisconsin Card Sorting Test, the number of complete categories. WCST Trials 1-categ.: Wisconsin Card Sorting Test, number of trials to complete first category. TMT: Trial Making Test. TMT A: Trial Making Test Part A. TMT B: Trial Making Test Part B. TMT Diff: TMT B- TMT A. WAIS: Wechsler Adult Intelligence Scale. LEAP2: liver enriched antimicrobial peptide 2. *Bold: significant comparison. †Bold: effect size into the range mild-moderate to high-large.

### *4.1. The prominent role of neuropsychological variables in cluster characterization*

Cluster 1 brings together different GD subtypes described in the literature, based on sociodemographic, clinical, or neuropsychological features [12,18,24,28,45,139]. It was the largest subgroup in this sample, with its sociodemographic characteristics forming the most typical profile among patients with GD [12,18]. Indeed, younger age, single civil status, and male sex have been widely recognized as vulnerability factors for GD, being a lower age of GD onset also linked to the youngest patients [37,38]. Aligned with their sociodemographic profile, Cluster 1 had significantly higher prevalence of skill-based games such as sport betting [39], resembling the "type I gambling" described by Navas et al., [24]. In this line, their higher scores in sensation and novelty-seeking could be in consonance with the higher reward sensitivity observed in "type I gamblers" [24]. Certainly, higher rates of excitement or arousal-seeking behavior have been associated with strategic gambling preferences [23] and could mainly drive motivation to gamble in this subgroup of individuals characterized by a more functional personality structure in terms of self-directedness and harm-avoidance, and without high self-reported general psychopathology or major neuropsychological impairments [18,25,28,140]. In fact, as strategic gambling is cognitively more demanding, a better cognitive performance may also underpin their gambling preferences [18,141]. The neuropsychological profile of these "young reward-seekers" mostly overlaps with the "low impaired EF" subtype identified by Mallorquí-Bagué, Tolosa-Sola, et al., [45], showing a better performance in cognitive flexibility, inhibitory control, decision-making, working memory, as well as cognitive reserve than the other clusters. Besides, the learning curve was poorer in Cluster 2 and 3 (IGT). Differences in factors such as age, estimated intelligence, and educational level between clusters could contribute to explain our findings.

Altogether, Cluster 1 might bear some resemblance to the "behaviorally conditioned gambler" described by Blaszczynski & Nower [28]. When analyzing other models, this cluster would also be closer to the "sensation-seeking impulsive" subtype [26,142], but without necessarily implying the identification with an "antisocial impulsivist gambler" [28,140]. Remarkably, the characteristics that defined Cluster 1 may also contribute to explain a predominant use of online and mixed gambling modes. Indeed, this subtype largely matches the "online gambler" prototype, putting the spotlight on younger individuals with higher educational levels and financially stable, who are mostly engaged in Internet-based gambling [139,143]. In Cluster 1, continuous gambling might constitute a crucial vulnerability factor for developing negative consequences associated with gambling behavior and its maintenance, being linked to a high addictive potential [139,143]. Likewise, their strategic gambling preferences influence the severity of the gambling behavior, being these individuals more prone to make higher bets and acquire higher debts in a smaller period of time [23]. Our results pointed to a close relationship between strategic and online gambling. The confluence of both modalities could confer a higher risk for a faster development of a severe GD [23]. This gambling pattern

**Table 4**
Comparison between the clusters for the psychological measures.

| | Cluster 1 *N=194* | | Cluster 2 *N=54* | | Cluster 3 *N=49* | | Cluster 1 *vs* Cluster 2 | | Cluster 1 *vs* Cluster 3 | | Cluster 2 *vs* Cluster 3 | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | *Mean* | *SD* | *Mean* | *SD* | *Mean* | *SD* | *p* | \|*d*\| | *p* | \|*d*\| | *p* | \|*d*\| |
| *SCL-90R* | | | | | | | | | | | | |
| Somatization | 0.90 | 0.73 | 1.21 | 0.87 | 1.08 | 0.86 | **.010*** | 0.39 | .141 | 0.23 | .415 | 0.14 |
| Obsession-compulsion | 1.11 | 0.76 | 1.43 | 0.93 | 1.27 | 0.95 | **.011*** | 0.38 | .217 | 0.19 | .316 | 0.17 |
| Interpersonal sensitivity | 0.89 | 0.74 | 1.25 | 0.89 | 1.09 | 0.87 | **.004*** | 0.43 | .116 | 0.25 | .324 | 0.18 |
| Depression | 1.44 | 0.90 | 1.82 | 0.98 | 1.56 | 0.93 | **.008*** | 0.40 | .442 | 0.12 | .143 | 0.28 |
| Anxiety | 0.91 | 0.72 | 1.25 | 0.89 | 1.06 | 0.92 | **.006*** | 0.41 | .253 | 0.18 | .221 | 0.21 |
| Hostility | 0.91 | 0.79 | 1.19 | 1.03 | 0.98 | 0.96 | **.031*** | 0.31 | .594 | 0.08 | .211 | 0.22 |
| Phobic anxiety | 0.33 | 0.50 | 0.63 | 0.85 | 0.45 | 0.64 | **.001*** | 0.43 | .189 | 0.22 | .150 | 0.23 |
| Paranoid Ideation | 0.85 | 0.70 | 1.14 | 0.95 | 1.13 | 0.84 | **.015*** | 0.35 | **.025*** | 0.36 | .934 | 0.01 |
| Psychoticism | 0.82 | 0.67 | 1.03 | 0.84 | 1.03 | 0.91 | **.043*** | 0.27 | **.047*** | 0.26 | .974 | 0.01 |
| GSI score | 0.99 | 0.63 | 1.30 | 0.78 | 1.15 | 0.79 | **.004*** | 0.44 | .151 | 0.22 | .264 | 0.19 |
| PST score | 45.64 | 20.38 | 52.13 | 20.76 | 49.49 | 21.73 | **.042*** | 0.32 | .245 | 0.18 | .518 | 0.12 |
| PSDI score | 1.80 | 0.56 | 2.08 | 0.59 | 1.88 | 0.67 | **.002*** | **0.50**† | .400 | 0.13 | **.041*** | 0.33 |
| *UPPS-P* | | | | | | | | | | | | |
| Lack premeditation | 24.51 | 5.79 | 23.81 | 4.65 | 24.35 | 5.27 | .413 | 0.13 | .853 | 0.03 | .625 | 0.11 |
| Lack perseverance | 22.01 | 5.14 | 22.07 | 4.25 | 21.71 | 4.20 | .932 | 0.01 | .703 | 0.06 | .707 | 0.09 |
| Sensation seeking | 29.39 | 8.32 | 26.30 | 6.99 | 28.49 | 6.62 | **.011*** | 0.40 | .475 | 0.12 | .157 | 0.32 |
| Positive urgency | 31.41 | 9.21 | 32.61 | 9.85 | 32.88 | 8.60 | .399 | 0.13 | .322 | 0.16 | .884 | 0.03 |
| Negative urgency | 31.84 | 6.39 | 33.13 | 7.07 | 33.04 | 5.89 | .192 | 0.19 | .242 | 0.20 | .944 | 0.01 |
| *DERS* | | | | | | | | | | | | |
| Non-acceptance emotions | 15.87 | 6.15 | 18.63 | 5.78 | 17.12 | 6.89 | **.004*** | 0.46 | .207 | 0.19 | .220 | 0.24 |
| Diff. goal-directed | 13.94 | 4.42 | 15.30 | 4.04 | 13.86 | 4.10 | **.042*** | 0.32 | .900 | 0.02 | **.041*** | 0.35 |
| Impulse-control difficulties | 12.71 | 4.60 | 14.59 | 5.71 | 13.98 | 4.67 | **.012*** | 0.36 | .100 | 0.27 | .520 | 0.12 |
| Lack emot. awareness | 16.59 | 4.14 | 16.57 | 4.71 | 16.98 | 4.39 | .984 | 0.00 | .568 | 0.09 | .632 | 0.09 |
| Limited access | 18.26 | 6.57 | 21.31 | 6.56 | 19.43 | 6.94 | **.003*** | 0.47 | .271 | 0.17 | .151 | 0.28 |
| Lack emotional clarity | 11.49 | 3.84 | 13.11 | 4.12 | 12.41 | 3.65 | **.007*** | 0.41 | .140 | 0.24 | .357 | 0.18 |
| Total score | 89.03 | 21.16 | 99.43 | 21.53 | 93.78 | 22.89 | **.002*** | **0.51**† | .168 | 0.22 | .184 | 0.25 |
| *TCI-R* | | | | | | | | | | | | |
| Novelty seeking | 112.85 | 13.18 | 106.41 | 12.43 | 108.90 | 12.37 | **.001*** | **0.50**† | .057 | 0.31 | .329 | 0.20 |
| Harm avoidance | 96.02 | 16.40 | 105.65 | 19.21 | 100.84 | 13.06 | **.001*** | **0.54**† | .068 | 0.32 | .139 | 0.29 |
| Reward dependence | 97.96 | 13.58 | 96.98 | 13.36 | 98.49 | 13.54 | .639 | 0.07 | .806 | 0.04 | .573 | 0.11 |
| Persistence | 109.71 | 18.82 | 107.11 | 20.24 | 109.16 | 17.87 | .373 | 0.13 | .856 | 0.03 | .583 | 0.11 |
| Self-directedness | 131.68 | 19.77 | 125.87 | 21.74 | 128.65 | 21.73 | **.046*** | 0.28 | .356 | 0.15 | .491 | 0.13 |
| Cooperativeness | 130.48 | 14.87 | 129.91 | 16.59 | 128.65 | 16.41 | .810 | 0.04 | .460 | 0.12 | .681 | 0.08 |
| Self-transcendence | 58.47 | 12.62 | 66.96 | 16.26 | 65.59 | 12.63 | **.001*** | **0.58**† | **.001*** | **0.56**† | .603 | 0.09 |
| *Food addiction* | *n* | *%* | *n* | *%* | *n* | *%* | *p* | \|*h*\| | *p* | \|*h*\| | *p* | \|*h*\| |
| YFAS-2 positive | 12 | 6.2% | 9 | 16.7% | 2 | 4.1% | **.014*** | 0.34 | .572 | 0.10 | **.039*** | 0.43 |

***Note.*** SD: standard deviation. SCL-90R Symptom Checklist-90-Revised. GSI score: global severity index. PST score: total positive symptoms. PSDI score: positive symptom distress index. UPPS-P: Impulsive Behavior Scale. DERS: Difficulties in Emotion Regulation Strategies. DERS Non-acceptance emotions: non-acceptance of emotional responses. DERS Diff. goal-directed: difficulties engaging in goal-directed behavior when having strong emotions. DERS Lack emot. awareness: lack of emotional awareness. DERS Limited access: limited access to emotion regulation strategies. TCI-R: Temperament and Character Inventory-Revised. YFAS-2: Yale Food addiction Scale 2.0. *Bold: significant comparison. †Bold: effect size into the range mild-moderate to high-large.

leads us to speculate whether the existence of a telescoping-like effect linked to the binomial strategic-online gambling with potential therapeutic implications, since the online mode could reinforce the likelihood of poorer treatment outcomes that has been already associated with strategic gambling from earlier stages of GD [33]. Furthermore, as younger patients usually show a lower motivation to discontinue their gambling behavior and to seek treatment, together these factors could imply a high risk of early relapse and treatment dropout [33,140,144].

Cluster 2 and 3 shared similarities in most of their sociodemographic and gambling-related characteristics. Particularly, factors such as lower socioeconomic and educational status would increase vulnerability for GD in these subgroups [145]. Although male still predominated, both clusters were conformed by a significantly higher proportion of females and older individuals. In this line, women tend to be more represented among older patients with GD, as they usually start gambling later in life [5]. Besides, an older age may contribute to explain higher scores in self-transcedence among these clusters [18,37]. Likewise, both older age and female sex have been associated wih non-strategic gambling preferences, such as lotteries and bingo [5,23], being these chance-based gambling evocative of the "type II gambling" defined by Navas et al., [24]. Interestingly, "type II gamblers" are characterized by greater difficulties for delaying gratification which, in turn, have been linked to poor decision-making [20,24,146]. In this line, we speculate whether a poorer performance in decision-making tasks (IGT) could also reveal underlying higher difficulties for delaying gratification among these patients. Certainly, their neuropsychological profile was more similar to the subtype with "high impaired EF" described by Mallorquí-Bagué, Tolosa-Sola, et al., [45], which could also contribute to explain non-strategic and offline gambling preferences in older individuals [18]. However, our findings allow us to suggest that Clusters 2 and 3 might be understood as a division of the aforementioned subtype [45]. Specifically, our results revealed interesting differences regarding inhibitory control (an impulsive measure) and cognitive flexibility (a compulsive measure), which were the two main indicators for clustering in our study.

Cluster 2 was characterized by the poorest inhibitory control (Stroop interference), a facet of impulsivity that may influence GD severity among these patients [147–149]. This cognitive trait could be related to worse scores in ER, especially regarding difficulties in goal-directed behaviors. In this line, neurocognitive research has suggested a connection between inhibitory control and ER, as both involve cognitive processes that help individuals modulate their behavior and responses to stimuli [150]. Indeed, it has been speculated that there are common underlying psychooneurobiological mechanisms between the two processes [151,152]. While a better inhibitory control has been associated with better ER and the use of adaptive ER strategies in daily life [153], a

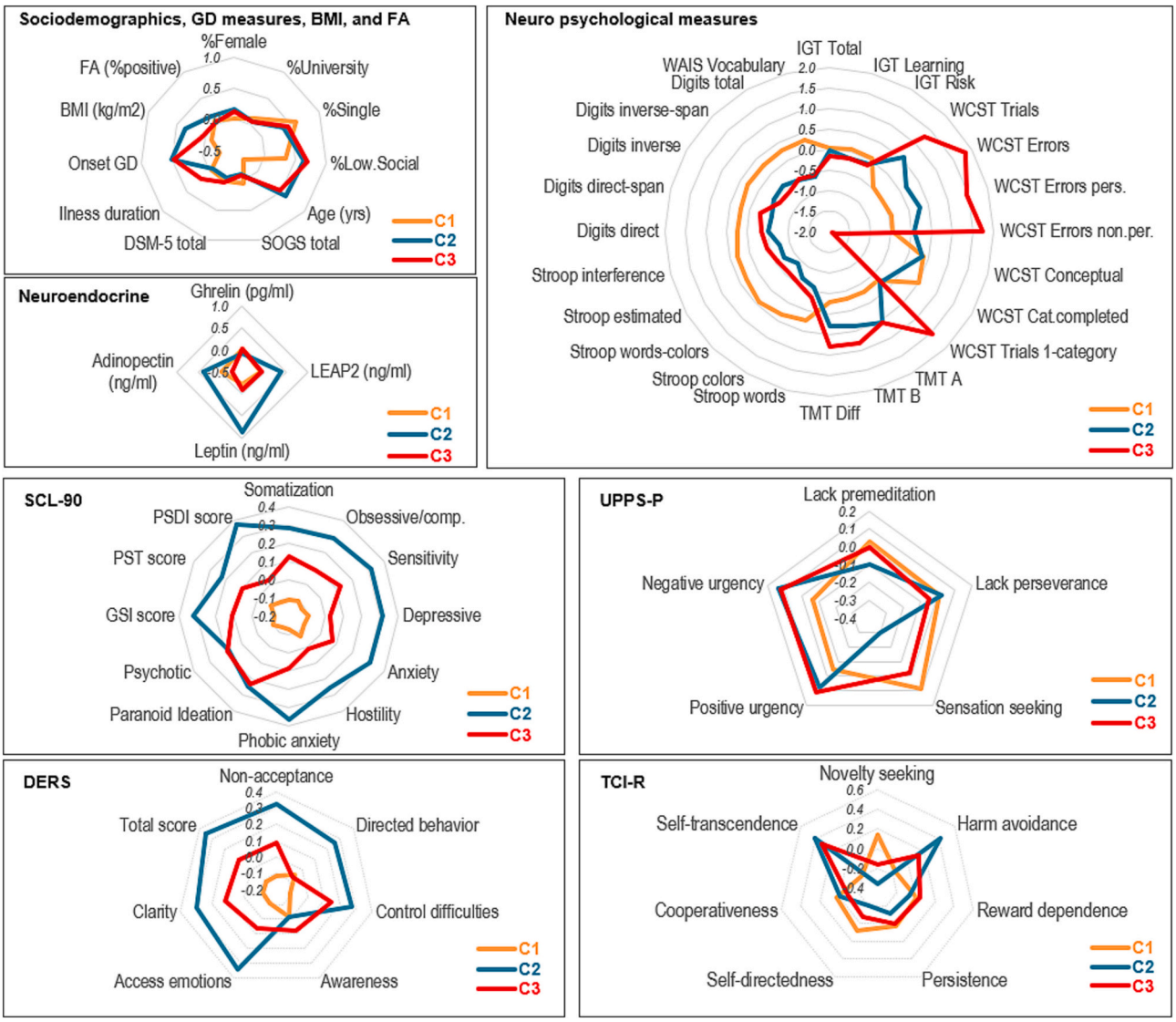


**Fig. 2.** Radar-charts.

poorer inhibitory control has been related to higher stress reactivity [150]. On the other hand, those psychiatric disorders typically linked to difficulties in ER, such as borderline personality disorder, postraumatic stress disorder, anxiety, and depression have also been linked to a poorer inhibitory control [154–156]. Besides, more difficulties in ER might contribute to greater emotional distress, being also described in GD, mainly among women and older individuals [18,157,158]. That said, poorer ER strategies along with a significantly poorer inhibitory control could favor using gambling as a maladaptive coping mechanism in this cluster, being acquired and maintained over time to deal with unpleasant emotions [12,140,159]. Furthermore, their lower ability to behavioral and negative affect regulation might be related to the presence of comorbidities that also contribute to emotional distress [12,13,37,160]. This fact may help to explain that addiction-related behaviors, such as substance use and FA, were prevalent in Cluster 2, with a gambling-like functionality or even, to counterbalance gambling seeking-behaviors [160–162]. Indeed, the "comorbid-vulnerable coping-seeker" resembles the GD subtype with FA described by Etxandi et al., [163], being FA a condition closely linked to higher BMI [163].

The whole context might confer higher emotional vulnerability to the "comorbid-vulnerable coping-seeker" subtype. Precisely, this profile shares some similarities with the "high emotional distress" type described in the study by Jiménez-Murcia et al., [18], in analogy with the "emotionally vulnerable gambler" of Blaszczynski & Nower [28] or the "evasion seeker" of Lesieur [26]. Precisely, these patients have also been characterized by a more dysfunctional personality structure in terms of high harm-avoidance and low self-directedness, which contrasts with the "young reward-seeker" type [18,26,37]. Remarkably, the gambling-to-cope pattern and its link to affective symptoms represent a crucial risk factor for relapse in this cluster [164].

Cluster 3 was characterized by the poorest neuropsychological performance and notably, by the poorest cognitive flexibility (WCST, TMT difference). That said, these patients could represent a vulnerable group with the highest difficulties in modifying their thinking and behavior, as well as in recognizing and adapting to changing stimuli-reward contingencies, finding alternative adaptive strategies to solve problems, and making optimal decisions [14,146,148,165,166]. This cognitive characterization has been associated with a less reward-driven, more repetitive, and obsessive gambling pattern [166–168]. Precisely, the impossibility of performing the gambling behavior could play a crucial role in modulating emotional distress in this "cognitive inflexible" subtype [166–168]. The higher cognitive inflexibility could strongly influence the severity of their gambling behavior, being linked to higher gambling frequency, finantial losses, and gambling urges, which may also impact on their emotional well-being [169]. Furthermore, the poorest performance in cognitive flexibility, and especially the higher

perseverative errors, could confer this cluster a particularly greater vulnerability to a poorer treatment response [50].

Bearing all this in mind, Cluster 3 could be distinguished mainly on the basis of neuropsychological aspects, although it seems to represent a subgroup less differentiated from Cluster 1 and 2 in other clinical features. Overall, Cluster 3 may be closer to the "antisocial impulsivist" type in some respects [28]. According to this third pathway of Blaszczynski & Nower [28], the significantly poorest neuropsychological performance found in Cluster 3 could represent a crucial factor strongly conditioning gambling behavior in interaction with processes such as impulsivity and emotional management. Nonetheless, the reviewed pathways model by Nower et al., [12] emphasized that this "antisocial impulsivist" type would constitute a separate subgroup rather than the second one (i.e., "emotionally vulnerable gambler") with additional contributing factors. The distinction between pathways 2 and 3 may also contribute to reinforce some hypothesized differences between Cluster 2 and 3, such as a distinctively relationship between their gambling behaviour and stress management. Particularly, enganing in gambling to search for meaning, together with the presence of antisocial personality traits or a tendency to adopt risky behaviors, have also been some of the factors associated with the "antisocial impulsivist" type [12]. These features could speculatively be shared by individuals in Cluster 3.

Taken together, our results support that neuropsychological features have a core role not only in the pathogenia and prognosis of GD [5], but also in cluster formation. Hence, their use has allowed to identify independent subgroups with distinctive phenotypic profiles that are clinically meaningful and consistent with previous studies of clusters based on clinical and psychological characteristics. Remarkably, this work supports findings from research using neuropsychological variables for GD subtyping [45] in a larger clinical sample with GD and, in particular, points to a valuable distinction between those subgroups with a higher impairment in EF. Consequently, potential diagnostic and therapeutic implications can be derived from these results [45,49].

### 4.2. Exploring neuroendocrine profiles among GD subtypes

Interestingly, findings regarding neuroendocrine variables delineated a metabolic profile among "comorbid-vulnerable coping-seekers" that differed significantly from the other subgroups. Certainly, some factors could partially explain higher leptin concentrations in Cluster 2, such as higher BMI, older age, and female sex [61,170,171]. Besides, higher leptin concentrations may also be related to a higher prevalence of FA in this subtype [89,105,172]. In this vein, the overproduction of leptin could even represent a state of hyperleptinemia [173] and leptin resistance over time [105], which promotes overeating by influencing homeostatic and hedonic regulation of food intake and subsequently, weight gain [61,174]. Indeed, leptin has been identified as a proinflammatory agent that stimulates the production of proinflammatory cytokines, being higher leptin concentrations associated with a higher metabolic risk [175,176]. This fact is remarkable since a poorer physical health and increased metabolic risk have been described in individuals with GD compared with the general population [177]. Moreover, a proinflammatory state has been mutually linked to a susbtained hyperactivation of the hypothalamus-pituitary-adrenal (HPA) axis, which could be another mechanism that potentially underlies higher leptin concentrations by stimulating the production of leptin and in a second step, favoring leptin resistence [66]. Although ansiolitic and antidepressant-like effects have been attributed to leptin throughout the attenuation of this axis, higher leptin concentrations have been described among individuals with a greater perceived stress [178]. In fact, the desensitization of brain leptin receptors has been linked to anxiogenic and depressive-like behaviors [179]. Apart from being proposed as a factor involved in mood regulation [86,180,181], the association of leptin with impulsivity and cognitive performance has also yielded promissing results [62]. Central leptin signaling is directly related to the dopaminergic reward circuit and higher leptin concentrations have been related to a poorer inhibitory control [182,183]. Altogether, neuroinflammation and oxidative stress secondary to leptin disturbances may contribute to changes in brain neuroplasticity which, in turn, have been associated with addiction by favoring impulse reward-seeking behaviors (e.g., gambling, food, drugs) [184,185].

Lower adiponectin concentrations have been linked to a higher BMI and metabolic risk due to its anti-inflammatory properties [61], which has also been suggested among patients with GD [47,66]. Then, one possible rationale to explain the higher fasting plasma adiponectin concentrations in Cluster 2 may be linked to the existence of metabolic compensatory mechanisms. Moreover, the between-group differences in LEAP-2 concentrations suggest that the involvement of the ghrelin system in differentiating clusters may be based on a substrate other than ghrelin itself. Interestingly, we observed a similar distribution of LEAP-2 and leptin among clusters. Since leptin and ghrelin act in opposing ways and LEAP-2 antagonizes ghrelin [56,66], the potential synergistic role of leptin and LEAP-2 in addiction-related processes needs to be further investigated. In this line, LEAP-2 concentrations seem to increase with BMI and glycemia [118]. Then, we wonder whether higher LEAP-2 concentrations could be related to a worse metabolic state. Moreover, as higher fasting LEAP-2 concentrations have been associated with more impulsive responses [79], we speculate whether LEAP-2 concentrations could be related to a worse inhibitory control in Cluster 2, which influences approaching behaviors towards rewards such as food and gambling.

Globally, these results should be cautiosly interpreted and further research is needed to get more insight into the complex neuroendocrine interplay in the pathogenesis of GD, as well as regarding their clinical correlates. So far, the role of these neuroendocrine substrates in GD clustering remains slightly modest in comparison with neuropsychological variables. That said, their inclusion as indicators for subtyping represents a novel contribution that opens the door for future studies to focus on neuroendocrine substrates in GD. In this line, promising results on leptin make it a potential target that warrants further research to consolidate preliminary evidence. Furthermore, the analysis of neuroendocrine variables puts the spotlight on biological candidates for designing useful psychopharmacological approaches in GD, that could selectively benefits patients according to their individual profile.

### 4.3. Potential implications of clustering in the severity, diagnosis, and treatment of GD

It is worth mentioning that we did not find significant differences in GD severity based on clinical criteria diagnosis (i.e., DSM and SOGS) between clusters, which might be explained due to some reasons. Certainly, one possible rationale could be related to the fact that individuals who seek for treatment often represent more severe cases [5]. Moreover, within each cluster, the confluence of different features that have been related to GD severity could confer a distinctive intragroup vulnerability [5,23,147–149,169,186]. In this regard, our results emphasized the complexity and heterogeneity of the disorder also when defining its severity, that could imply a broad number of features and processes, from neurobiology to environmental factors. Hence, a more comprehensive understanding of the pathogenia of the disorder and the identification of GD subtypes might contribute to a more individualized evaluation of GD severity, which could help to elucidate more personalized preventive and therapeutic approaches.

In this line, our results highlight the potential benefit of including neuropsychological tests in standard GD assessments. Considering the three identified clusters and their main differences, the recommended neuropsychological evaluations should include assessments of cognitive flexibility (e.g., WCST) and inhibitory control (e.g., SCWT). The occurence of impairments in these EF could serve as indicators of which group of patients may best fit into and thus help to tailor personalized interventions. On the other hand, the differences in neuroendocrine

variables observed in this study would need further evidence to consider these variables as a potential gold standard for GD assessment.

Findings related to the "young reward-seekers" point in particular to the need to focus on prevention in different areas of the individual's life (e.g., academic and working ambit, socio-familial context) since early stages of GD [5]. Psychoeducation and motivational interventions could represent crucial strategies to promote a healthy lifestyle and raise social awareness about the adaptive use of gambling and technologies, favoring an early detection of at-risk cases, insight acquisition, motivation to seek treatment and, especially, an earlier intervention in cases of gambling problems related to strategic preferences [5]. Adjuctive to traditional treatment based on cognitive-behavioral therapy, these interventions seem useful to enhance treatment adherence in underage and young population with GD [187,188]. Furthermore, future research aimed at further adapting the regulation of online gambling is warranted, especially given that Cluster 1 appears to represent the most frequent subtype and with the youngest individuals [49,143,189].

The "comorbid-vulnerable coping-seekers" could particularly benefit from psychological approaches oriented towards the development of adaptive skills to deal with relapse-risk situations [140]. For that purpose, ER and inhibitory control represent two cardinal processes to guide therapeutic approaches among these patients. In fact, some authors have suggested that training one process can improve performance in the other one [151,156]. In this line, mindfulness-based training seems to be helpful in addressing both emotional dysregulation and potentially linked neuropsychological features [190]. On the other hand, research evaluating cognitive enhancement interventions for impulsivity such as cognitive remediation, computerized cognitive training, or pharmacological cognitive enhancers (e.g., moldafinil) is scarce. While cognitive remediation based on goal management training seems promising for improving impulsive choice (IGT), inconclusive results have been yielded so far and future longitudinal studies are warranted [191,192]. Improving interventional strategies based on these targets should also be crucial due to its potential beneficial effect on other addiction-related behaviors such as FA and substance use and even, on the metabolic state of patients with GD [193,194]. Likewise, our findings also reinforce the idea of incorporating physical health into mental health by favoring a more integrative and multidisciplinary therapeutic approach that contemplates the promotion of healthy lifestyle habits as an additional interventional branch, as well as metabolic screening among individuals with GD.

Results from the "cognitive inflexible" subtype support the notion of considering cognitive flexibility as a crucial therapeutic target since early stages of GD, which could have a positive impact on the GD course and treatment outcome. Adjuntive to conventional treatment for GD, some biological strategies have been suggested to improve cognitive control, including cognitive flexibility. For example, brain stimulation therapies such as repetitive transcranial magnetic stimulation (rTMS) and transcranial direct current stimulation (tDCS) [195,196], although their efficacy in GD remains inconclusive [197]. Besides, psychopharmacological interventions with antidepressant, mood stabilizers such as lithium, and opiod antagonists seem promising due to the modulation of serotonin and dopamine neurotransmission [195]. Hence, it should be a "must" for govenors and the scientific community to promote these research lines that need a consolidated evidence for their suitability and approval in the treatment of GD.

### 4.4. Strengths and limitations

One strength of the current study is the use of clustering procedure to identify the latent empirical groups among patients with GD, based on a relatively large set of predictors, including sociodemographic, neuropsychological, and neuroendocrine features. Compared with usual analytical procedures, cluster analysis does not require *a priori* assumptions regarding the underlying profiles in the sample and therefore, it allows empirically identifying the systematic covariation of multiple features contributing to the inter-individual variance in the gambling habits. Likewise, it is worth noting the relatively large sample size for the three latent subgroups identified (194, 54 and 49, respectively), suggesting that the clusters adequately cover the variance of naturally occurring individual differences (likelihood of small extreme groups are minimized). Moreover, the characterization of the participants was multifaceted on several underlying endophenotypic characteristics, enabling to discern the relative importance of different endophenotypical indicators.

On the other hand, some limitations should be considered when interpreting the results of this study. As the cross-sectional nature of this study limits causality attributions and does not allow the prognosis and treatment response of the different clusters to be assessed, future longitudinal studies are needed to identify potential risk factors for the empirical clusters and obtain evidence of their predictive validity. Secondly, the sample was principally composed of treatment-seeking males referred to a specialized unit, which should be considered when results would be generalized. However, it should be noted that the frequency of women in the study is consistent with the prevalence estimates in clinical treatment-seeking samples in GD, and their inclusion in the study increases its ecological validity. Despite the use of previous validated methods for endocrine analysis and well-established psychometric and neuropsychological batteries, limitations related to self-reported data should also be highlighted. Certainly, our work constitutes a first approximation to the study of endophenotypic variables in the clustering of GD. That said, future research including additional variables (e.g., psychological features) as part of the cluster analysis could be an interesting approach, allowing for a comparison of the role of different variables in the discrimination of GD subtypes.

## 5. Conclusions

This study underpins empirical evidence for the effect of neuropsychological and neuroendocrine features on GD subtyping, leading to distinguish well-defined clinical profiles. Specifically, neuropsychological variables were the main indicators for clustering, mainly cognitive flexibility and inhibitory control. Within neuroendocrine features, leptin was the strongest indicator. Similar to sex and age, leptin showed a modest effect on differentiating subgroups. While our results should be carefully interpreted and future research is needed, they might contribute to a more comprehensive characterization of GD profiles based on potential endophenotypic features, which distinctively influence GD severity and therapeutic approaches.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.comppsych.2023.152435.

## Statement of ethics

The latest version of the Declaration of Helsinki was used to conduct the present study, which was approved by the Clinical Research Ethics Committee of the HUB-IDIBELL institution (ref. PR329/19 and PR338/17). Signed informed consent was obtained from all participants.

## CRediT authorship contribution statement

**Isabel Baenas:** Conceptualization, Data curation, Investigation, Writing - original draft. Bernat Mora-Maltas: Conceptualization, Data curation, Investigation, Writing - original draft. **Mikel Etxandi:** Conceptualization, Data curation, Investigation, Writing - original draft. **Ignacio Lucas:** Investigation, Writing - original draft. **Roser Granero:** Formal analysis, Methodology, Software. **Fernando Fernández-Aranda:** Funding acquisition, Supervision, Writing - review and editing. **Sulay Tovar:** Formal analysis, Investigation, Resources, Writing - review and editing. **Neus Solé-Morata:** Writing - review and editing. **Mónica Gómez-Peña:** Data curation, Resources, Writing - review and editing. **Laura Moragas:** Data curation, Resources, Writing - review and

editing. **Amparo del Pino-Gutiérrez:** Data curation, Resources, Writing - review and editing. **Javier Tapia:** Writing - review and editing. **Carlos Diéguez:** Formal analysis, Resources, Writing - review and editing. **Anna E. Goudriaan:** Supervision, Writing - review and editing. **Susana Jiménez-Murcia:** Funding acquisition, Project administration, Supervision, Writing - review and editing.

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## Declaration of Competing Interest

Fernando Fernández-Aranda and Susana Jiménez-Murcia received consultancy honoraria from Novo Nordisk.

## Data availability

The datasets generated for this study will not be made publicly available because the data used in this study is part of the hospital database, and it is restricted to protect patients' confidentiality.

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