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Association between endocrine and neuropsychological endophenotypes and gambling disorder severity

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ABSTRACT

Background: Neurobiological characteristics have been identified regarding the severity of gambling disorder (GD). The aims of this study were: (1) to examine, through a path analysis, whether there was a relationship between neuroendocrine features, potentially mediational GD variables, and GD severity, and (2) to associate neuroendocrine variables, with GD severity-related variables according to gambling preferences. **Methods:** The sample included 297 outpatients with GD. We analyzed endocrine concentrations of different appetite-related hormones (ghrelin, liver antimicrobial peptide 2 [LEAP-2], leptin, adiponectin), and neuropsychological performance (working memory, cognitive flexibility, inhibition, decision making, premorbid intelligence). Path analysis assessed mechanisms between neuroendocrine features and GD severity, including mediational GD variables (impulsivity traits and gambling-related cognitive distortions). Partial correlations evaluated the associations between neuroendocrine variables, including impulsivity traits, and variables related to GD severity (DSM-5, South Oaks Gambling Screen, illness duration, and gambling-related cognitive distortions). **Results:** Lower adiponectin concentrations predicted greater GD severity, while higher LEAP-2 concentrations predicted more gambling-related cognitive distortions. Likewise, better neuropsychological performance directly predicted GD severity, but worse neuropsychological performance was associated with GD severity through the mediational variables of impulsivity traits and gambling-related cognitive distortions. Also, in non-strategic individuals with GD, poor working memory was associated with gambling expectancies and predictive control. In strategic individuals with GD, poor cognitive flexibility was associated with illusion of control, predictive control, and inability to stop gambling. **Conclusions:** These results provide updated information about the comprehension of the interaction between neuroendocrine features, clinical variables, and severity of GD. Thus, neurobiological functions seem to be strongly related to GD severity.

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1. Introduction

Gambling disorder (GD) is a behavioral addiction characterized by an uncontrolled impulse to gamble despite its social and financial consequences, resulting in clinically significant impairment or distress (American Psychiatric Association [APA], 2013). Similar to substance use disorder (SUD), several studies have identified multiple features related to the development and maintenance of gambling behavior and its severity (Potenza et al., 2019). Beyond the Diagnostic and Statistical Manual of Mental Disorders (DSM-5; APA, 2013) which established GD severity based on the number of fulfilled clinical criteria, other alternative indicators of GD severity have been described. For instance, the South Oaks Gambling Screen (SOGS) questionnaire (Holtgraves, 2009; Lesieur & Blume, 1987; Stinchfield, 2002) has been considered to operationalize clinical severity, showing high correlations with DSM-IV (APA, 1994; Stinchfield, 2002) and DSM-5 (Goodie et al., 2013). The presence of gambling-related cognitive distortions (i.e., beliefs about gambling settings, behaviors, and outcomes) is another important predictor of the development of the disorder (Barrault & Varescon, 2013; Chrétien et al., 2017; Emond & Marmurek, 2010; Mathieu et al., 2018), and a severity indicator of GD (Cunningham et al., 2014; Tang & Oei, 2011). Regarding illness duration, some studies have reported a positive relationship with gambling severity (Ledgerwood et al., 2020; Medeiros et al., 2017), relapse, and dropout risk (Lucas et al., 2023; Roberts et al., 2020).

Neurobiological variables such as endocrine factors and neuropsychological performance have also been related to GD severity. Some studies uphold that endocrine factors classically linked to feeding regulation could be involved in addiction-related disorders. For instance, in the mesolimbic circuit, ghrelin has proved to be a neural reinforcer for both natural (e.g., food) and non-natural (e.g., money) rewards, interacting with other neuroendocrine factors related to impulsivity and reward processing (e.g., dopamine, serotonin, opioids) (Anderberg et al., 2016; Farokhnia et al., 2018; Vengeliene, 2013). Thus, an up-regulation of ghrelin has been observed to positively correlate with craving, abstinence, and relapse risk in SUD (Addolorato et al., 2006; Akkişi Kumsar & Dilbaz, 2015; Leggio et al., 2012), and it has also been linked with novelty-seeking (i.e., trait impulsivity), motor disinhibition (i.e., motor impulsivity), and impulsive decision-making (i.e., choice impulsivity) (Anderberg et al., 2016; Skibicka & Dickson, 2011). Until now, only one study investigated the relation between ghrelin and GD, hypothesizing a similar association in individuals with GD (Etxandi et al., 2022), and higher fasting ghrelin plasma level was reported. Moreover, lower concentrations of a ghrelin antagonist called liver antimicrobial peptide 2 (LEAP-2) was found and it predicted the presence of GD-(Etxandi et al., 2022). Similarly, LEAP-2 have been linked to impulsivity and cognitive functions (Ge et al., 2018; Lugilde et al., 2022; Voigt et al., 2021) showing a possible role in the addiction process due to its interaction with ghrelin. Also, adipocytokines (i.e., leptin, adiponectin) have been studied in relation to impulsivity (Sutin et al., 2013) and addiction (Bach et al., 2021; Novelle & Diéguez, 2018; Peters et al., 2018) due to the presence of adipocytokine receptors widely distributed in brain regions including the neocortex and hippocampal regions (Cao et al., 2018). As in the case of food intake regulation, leptin concentrations have been inversely correlated with the severity of consumption (Escobar et al., 2018), being proposed as a possible biomarker in SUD (i.e., alcohol, cocaine) (Martinotti et al., 2017; Mehta et al., 2020). The presence of leptin receptors on dopaminergic neurons within the limbic system has prompted speculation about their involvement in the regulation of reward-related behaviors (e.g. food, gambling, drugs) (Micioni Di Bonaventura et al., 2021; von der Goltz et al., 2010), contributing to neuroinflammation, oxidative stress, and motivating changes in brain plasticity (Heber & Carpenter, 2011; Montalvo-Martínez et al., 2018). Adiponectin has been proposed as a biomarker of craving in alcohol use disorder (Hillemacher et al., 2009), similar to ghrelin. However, decreased serum concentrations have been shown in GD (Etxandi et al., 2022), in individuals with obesity with and without eating disorders (Baenas et al., 2023), and in opioid use disorder (Shahouzehi et al., 2013; Yu et al., 2021). While some endocrine markers have been linked to SUD and GD, studies on endocrine factors remain scarce and their association with GD severity has not been evaluated.

Regarding neuropsychological variables, impaired cognitive flexibility, decision-making, and response inhibition have been linked to GD severity (Brevers et al., 2012; Cosenza et al., 2019; Leppink et al., 2016; Odlaug et al., 2011) and may predict relapse (Goudriaan et al., 2008). Interestingly, some gambling activities involve more executive function than others, considering the level of chance between gambling modalities (Jiménez-Murcia et al., 2020; Odlaug et al., 2011). In this sense, several studies have observed a specific subtype of individuals with GD who use strategic games (e.g., poker, sports betting, stock market). The majority of these individuals were young men, with high levels of education, well-paid employment and high levels of impulsivity (Jiménez-Murcia et al., 2019; Navas et al., 2017; Vintró-Alcaraz et al., 2022), as well as better neuropsychological performance (Lorains et al., 2014; Mallorquí-Bagué et al., 2018). This gambling profile also showed greater gambling severity (Gainsbury et al., 2012; Gainsbury, Russell, Blaszczynski, et al., 2015; Jiménez-Murcia et al., 2020; Mallorquí-Bagué et al., 2017; Wood & Williams, 2011). Regarding non-strategic games (e.g., slot-machines, bingo, lotteries), some studies demonstrated that this form was commonly correlated with women and older individuals (Assanangkornchai et al., 2016; Potenza, 2014) who showed poorer neuropsychological performance (Boggio et al., 2010; Di Rosa et al., 2017). Likewise, impulsivity traits have also been associated with GD severity (Billieux et al., 2012; Savvidou et al., 2017; Vintró-Alcaraz et al., 2022) and with cognitive distortions (Del Prete et al., 2017; Mallorquí-Bagué et al., 2018). Finally, although several studies have related cognitive distortions to brain areas (Clark et al., 2009; Dymond et al., 2014; Lu et al., 2019; Ruiz de Lara et al., 2018), as far as authors know, there are no studies linking extended neuropsychological functions to different types of cognitive distortions.

The primary aim of this study was to analyze the link between endocrine (ghrelin, LEAP-2, leptin and adiponectin) and neuropsychological (working memory, cognitive flexibility, decision making, inhibition, and premorbid intelligence) variables, potentially mediational GD measures (gambling-related cognitive distortions, and impulsivity), and the severity of GD (measured by SOGS), through a path analysis. The second aim was to identify whether, according to gambling preferences (strategic *vs* non-strategic), endocrine and neuropsychological features, including impulsivity traits, were associated with GD severity-related variables (DSM-5, SOGS, duration of illness, and gambling-related cognitive distortions). The authors hypothesized: 1) Endocrine markers would be associated to reward related executive functions (e.g., impulsivity, decision making), showing a targeted pathway to the GD severity. 2) Neuropsychological performance could have a different influence on GD severity considering gambling preferences.

2. Methods

2.1. Participants

The sample was made up of 297 treatment-seeking adult outpatients with GD (diagnosed according DSM-5 criteria) attending at the Behavioral Addictions Unit within the Clinical Psychology Department of Bellvitge University Hospital for treatment of GD. They were voluntarily recruited between April-2018 and September-2021. A structured interview was carried out to check for the existence of an organic mental disorder, an intellectual disability, a neurodegenerative disorder (e.g., Parkinson's disease), or an active psychotic disorder, all of which were considered exclusion criteria.

2.2. Assessments

Neuroendocrine and clinical variables were collected using standardized instruments, which are properly described in the supplementary material. Briefly, blood samples (25 mM final concentration) were collected using a venous aspiration method with ethylenediamine tetraacetic acid (EDTA). A minimum fasting period of eight hours was conserved prior to blood collection. The blood was centrifuged at 1700g for 20 min at 4 °C in a refrigerated centrifuge. Clinical variables were measured using the Spanish adaptation of the following questionnaires: SOGS-(Echeburúa et al., 1994; Lesieur & Blume, 1987); Diagnostic Questionnaire for Pathological Gambling According to DSM criteria (Jiménez-Murcia et al., 2009; Stinchfield, 2003); Impulsive Behavior Scale (UPPS-P) (Verdejo-García et al., 2010; Whiteside et al., 2005); Gambling-related cognitions scale (GRCS) (Del Prete et al., 2017; Raylu & Oei, 2004). Neuropsychological data has been collected by the following instruments: Iowa Gambling Task (IGT) (Bechara et al., 1994, 2000); Wisconsin Card Sorting Test (WCST) (Grant & Berg, 1948); Stroop Color and Word Test (SCWT) (Golden, 1978); Trail Making Test (TMT) (Reitan, 1958); Digits task of the Wechsler-Memory-Scale, Third Edition (WMS-III) (Wechsler, 1997); Vocabulary task of the Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) (Wechsler, 1999).

Socio-demographic, anthropometric, and clinical variables related to GD were collected in a semi-structured face-to-face clinical interview, as described elsewhere (Jiménez-Murcia et al., 2006).

2.3. Procedure

All participants were evaluated at the Behavioral Addictions Unit of the HUB-IDIBELL institution. A multidisciplinary team (psychology, psychiatry, and nursing), with an extensive experience (more than 25 years) in the study of GD and other behavioral addictions, collected the data. A completed semi-structured clinical interview was conducted in the first session (45–60 min) in which sociodemographic, gambling-related, and anthropometric variables were assessed. In the first part of the second visit (10 min), the collection of blood samples occurred between 8 and 10 am in the morning, before food intake. After that, participants underwent a 90-minute session (approximately) to complete psychometric assessments related to gambling and psychological variables. Endocrine variables were analyzed at the Singular Center for Research in Molecular Medicine and Chronic Diseases (CIMUS), University of Santiago de Compostela (Spain). The neuropsychological assessment was completed by experienced neuropsychologists in the third session, which lasted 50–60 min. The three sessions took place on three different days over the course of a week. All the measures used in this study correspond to the assessment carried out prior to the beginning of specialized treatment at the Unit.

2.4. Statistical analysis

Data analysis was done with Stata17 for Windows (Stata Press Publication, 2021). Path analysis tested the underlying associations (direct and indirect links) between endocrine, neuropsychological, and gambling measures. In this work, all parameters were free-estimated, and with the aim to achieve a parsimonious model with easier interpretation, statistically non-significant parameters were excluded. The maximum-likelihood estimation was used and goodness-of-fit was evaluated using standard statistical measures: chi-square test (χ^2), the root mean square error of approximation (RMSEA), Bentler's Comparative Fit Index (CFI), the Tucker-Lewis Index (TLI), and the standardized root mean square residual (SRMR). It was considered an adequate model fit for non-significant χ^2 tests, RMSEA < 0.08, TLI > 0.90, CFI > 0.90 and SRMR < 0.10 (Barrett, 2007). The global predictive capacity for the final model was measured by the coefficient of determination (CD).

Partial correlations adjusted by the patients' sex and age assessed the relationships between GD severity-related variables (DSM-5 criteria, SOGS total, duration of illness, and gambling-related cognitive distortions) with the endocrine and neuropsychological variables. The correlation estimates were interpreted considering the effect size measures (due the strong association between statistical significant for the R-coefficients and the sample size): mild-moderate effect for $|R|>0.24$ and large-high for $|R|>0.37$ (Rosnow & Rosenthal, 1996).

2.5. Ethics

The latest version of the Declaration of Helsinki was used to conduct the present study. The Clinical Research Ethics Committee of Bellvitge University Hospital approved this study (ref. PR329/19 and PR338/17). Signed informed consent was obtained from all participants.

3. Results

3.1. Descriptive for the sample

Table 1 displays the descriptives for the sociodemographic and the GD profile in the total sample (descriptive for the remaining variables of the study are shown in Table S1, supplementary material). Most patients in the study were men, with primary education level, single, and pertained to mean-low to low social position indexes. Mean age was 39.58 years (*SD* = 14.16), mean age of onset of the problematic gambling 29.1 years (*SD* = 12.42) and duration of the GD related problems 5.23 years (*SD* = 6.02). Most participants reported non-strategic games as the preferred gambling activity.

Table 1
Descriptive for the sociodemographic and the GD profile (total sample, n = 297).

	n	%		*Mean*	*SD*
SexWomen	19	6.4 %	Age (yrs-old)	39.58	14.16
Men	278	93.6 %	Age of onset of GD (yrs)	29.10	12.42
EducationPrimary	157	52.9 %	Duration of GD (yrs)	5.23	6.02
Secondary	112	37.7 %	DSM-5 criteria	7.13	1.80
University	28	9.4 %	SOGS total	10.85	3.23
MaritalSingle	158	53.2 %		*n*	*%*
Married	103	34.7 %	PreferenceNon-strategic	166	55.9 %
Divorced	36	12.1 %	Strategic	131	44.1 %
Social indexHigh	8	2.7 %			
Mean-high	19	6.4 %			
Mean	24	8.1 %			
Mean-low	113	38.0 %			
Low	133	44.8 %			

Note. SD: standard deviation. GD: gambling disorder. DSM: diagnostic and statistical manual of mental disorders. SOGS: South Oaks Gambling Screen.

3.2. Path analysis

Fig. 1 contains the standardized coefficients of the path diagram obtained in the study. With the aim of easier interpretation, only significant coefficients retained in this final model. Adequate goodness of fit was achieved ($\chi^2 = 127.61$ ($p = .278$); RMSEA = 0.016 (95 %CI: 0.001 to 0.034); CFI = 0.987; TLI = 0.984; SRMR = 0.049), and the global predictive capacity was around 42 % (CD = 0.422). The neuropsychological measures used to define the latent variable (labeled as "cognition" in the path diagram) achieved statistical significance, the higher scores (except TMT that score is reversed) in the latent variable were associated with better performance in the IGT, WCST, Stroop, Digits and WAIS vocabulary tasks.

Results of the SEM indicated that higher GD severity (SOGS total) was directly associated with lower adiponectin concentrations, more gambling-related cognitive distortions, higher impulsivity traits, and better performance in the neuropsychological tasks. Some indirect links explaining the GD severity were also identified: a) being a woman and higher LEAP2 concentrations predicted higher gambling-related cognitive distortions, which increased the likelihood of GD severity; b) younger age was related to higher impulsivity traits, which contributed to higher GD severity; and c) younger age also contributed to better performance in the neuropsychological tasks, which was related to higher GD severity. The path diagram also evidenced a positive correlation between ghrelin and adiponectin concentrations, a positive correlation between gambling-related cognitive distortions with impulsivity, and negative correlations between scores in the latent class cognition with impulsivity and gambling-related cognitive distortions. Finally, younger age was also a variable associated with the higher probability of strategic gambling activity.

3.3. Correlation analysis

Table 2 contains the partial correlations (adjusted by the patients' sex and age) between GD severity-related variables (DSM-5, SOGS, duration of illness and GRCS scores) with the neuroendocrine variables. This correlation matrix was obtained for the total sample (N = 297). Only relevant correlation coefficients were found for the impulsivity traits: a) lack of perseverance correlated with gambling-related expectancies; b) positive urgency, negative urgency, and UPPS total score

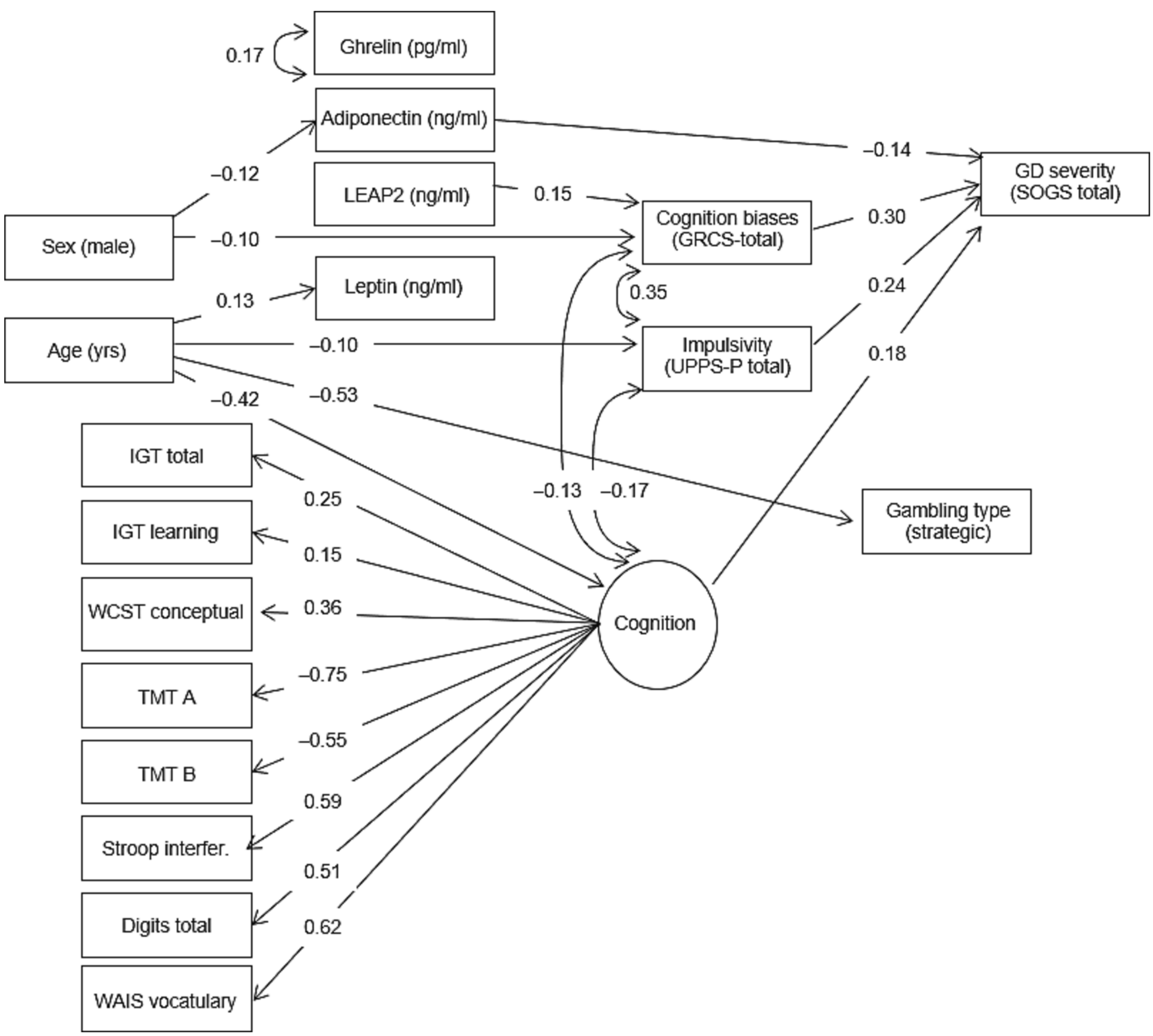

Fig. 1. Path-diagram: standardized coefficients (total sample, n = 297) Note. Only significant coefficients retained in the model. GD: gambling disorder. GRCS: Gambling Related Cognition Scale. UPPS-P: Impulsive Behavior Scale. LEAP2: liver enriched antimicrobial peptide 2. IGT: Iowa Gambling Test. WCST: Wisconsin Card Sorting Test. TMT: Trail Making Test. WAIS: Wechsler Adult Intelligence Scale.

Table 2
Association between the GD severity measures with the clinical profile: partial correlations adjusted by the patients' sex and age (total sample, n = 297).

	DSM-5 criteria	SOGS total	Duration of GD	GRCS GE	GRCS IC	GRCS PC	GRCS IS	GRCS IB	GRCS total
Ghrelin (pg/ml)	0.03	0.07	0.04	0.07	−0.01	−0.03	0.05	0.04	0.03
LEAP2 (ng/ml)	0.01	0.02	0.05	0.04	0.13	0.13	0.05	0.07	0.10
Leptin (ng/ml)	0.08	0.02	−0.05	0.05	0.04	0.09	0.12	0.08	0.10
Adiponectin (ng/ml)	−0.04	−0.14	0.03	−0.03	0.01	0.04	−0.02	0.04	0.01
UPPS-P Lack premeditation	0.14	0.13	0.08	0.10	0.04	0.02	0.12	0.10	0.10
UPPS-P Lack perseverance	0.19	0.16	0.15	**0.26**†	0.11	0.11	0.15	0.13	0.19
UPPS-P Sensation seeking	0.10	0.07	0.02	0.10	0.12	0.13	0.06	0.15	0.14
UPPS-P Positive urgency	**0.31**†	**0.29**†	0.15	**0.37**†	**0.27**†	**0.27**†	**0.31**†	**0.27**†	**0.37**†
UPPS-P Negative urgency	**0.41**†	**0.33**†	0.19	**0.43**†	0.19	**0.24**†	**0.40**†	**0.28**†	**0.39**†
UPPS-P Total	**0.36**†	**0.31**†	0.18	**0.37**†	0.21	**0.24**†	**0.32**†	**0.28**†	**0.36**†
IGT Block 1	0.07	−0.02	−0.06	−0.03	−0.06	0.03	−0.01	−0.08	−0.03
IGT Block 2	0.04	−0.06	−0.08	−0.08	0.01	−0.02	0.01	0.03	−0.01
IGT Block 3	−0.01	0.01	0.01	−0.04	−0.03	−0.01	0.03	0.02	0.00
IGT Block 4	−0.05	−0.10	−0.05	−0.13	−0.11	−0.03	−0.09	0.00	−0.09
IGT Block 5	−0.05	−0.13	−0.08	−0.13	−0.07	−0.04	−0.13	−0.06	−0.11
IGT Total	−0.02	−0.10	−0.08	−0.13	−0.08	−0.02	−0.07	−0.02	−0.08
IGT Learning	−0.10	−0.11	−0.02	−0.11	−0.08	−0.04	−0.13	−0.02	−0.10
IGT Risk	−0.06	−0.14	−0.08	−0.15	−0.10	−0.04	−0.13	−0.04	−0.11
WCST Trials	0.04	0.01	−0.14	0.11	0.06	0.05	0.13	0.08	0.11
WCST Errors perseverative	0.06	0.03	−0.04	0.13	0.08	0.07	0.10	0.10	0.12
WCST Conceptual	−0.03	0.04	−0.02	0.06	0.02	0.10	0.08	0.01	0.07
WCST Categories completed	0.00	0.07	0.06	0.02	0.00	0.07	0.02	−0.01	0.03
TMT A	−0.01	−0.04	−0.07	0.05	0.07	0.04	0.05	0.07	0.07
TMT B	−0.04	−0.08	−0.04	0.02	0.15	0.11	0.05	0.04	0.09
TMT Diff	−0.03	−0.08	−0.02	0.03	0.16	0.12	0.05	0.04	0.10
Stroop words	−0.02	−0.02	−0.02	0.02	−0.13	−0.07	−0.06	−0.08	−0.08
Stroop colors	0.03	0.07	0.02	−0.03	−0.10	−0.15	−0.03	−0.09	−0.10
Stroop words-colors	0.02	0.02	0.06	−0.07	−0.14	−0.17	−0.03	−0.09	−0.12
Stroop interference	0.02	−0.01	0.07	−0.09	−0.11	−0.12	−0.02	−0.05	−0.10
Digits direct	−0.05	0.07	−0.01	−0.09	−0.18	−0.15	−0.06	−0.02	−0.12
Digits direct-span	−0.04	0.05	−0.04	−0.08	−0.16	−0.15	−0.04	0.00	−0.11
Digits inverse	−0.03	0.06	0.02	−0.14	−0.13	−0.14	−0.02	0.00	−0.11
Digits inverse-span	−0.05	0.06	0.02	−0.13	−0.13	−0.14	−0.02	−0.02	−0.11
Digits total	−0.04	0.07	0.01	−0.13	−0.17	−0.16	−0.05	−0.01	−0.13
WAIS Vocabulary	0.02	0.04	0.12	−0.14	−0.13	−0.10	−0.07	−0.07	−0.12

Note. †Bold: effect size into the ranges mild-moderate to high-large. GD: gambling disorder. DSM: diagnostic and statistical manual of mental disorders. SOGS: South Oaks Gambling Screen. GRCS: Gambling Related Cognition Scale. GRCS-GE: gambling related expectancies. GRCS-IC: illusion of control. GRCS-PC: predictive control GRCS-IS: perceived inability to stop gambling. GRCS-IB: interpretative bias. UPPS-P: Impulsive Behavior Scale. LEAP2: liver enriched antimicrobial peptide 2. IGT: Iowa Gambling Test. WCST: Wisconsin Card Sorting Test. TMT: Trail Making Test. WAIS: Wechsler Adult Intelligence Scale.

correlated with all GRCS scales (except for illusion of control, which only correlated with positive urgency).

The partial correlation obtained within the group of patients who reported non-strategic gambling preference (Table 3) informed that: a) lack of perseverance correlated with gambling- related expectancies and the inability to stop gambling; b) positive urgency, negative urgency and UPPS total score correlated with GRCS total score, DSM-5 criteria and SOGS total; additionally, negative urgency was associated with longer duration of the illness; and c) worse performance in the Digits Inverse was associated with gambling-related expectancies and predictive control, and Digits total was associated with illusion of control and predictive control.

Within the group of patients with strategic gambling preference (Table 4), higher scores in positive urgency, negative urgency and UPPS total score correlated with DSM-5 criteria, SOGS total, and all GRCS scales (except illusion of control). Regarding the neuropsychological measures: a) worse performance in the IGT total was related to more gambling-related expectancies; b) worse performance in the WCST (number of trials) correlated with the inability to stop gambling; and c) more difficulties in the TMT (TMT-B and difference scales) were associated with more gambling-related illusion of control, predictive control and total GRCS score.

4. Discussion

The present study analyzed whether neuroendocrine variables predict the severity of GD, as well as its relationship with other potentially mediational GD variables. This study also evaluated whether these neuroendocrine factors were associated with GD severity-related variables according to gambling preferences. Although the results are not in agreement with our first hypothesis (endocrine markers could be related to reward-related executive function, showing a targeted pathway to the GD severity), we found that lower concentrations of adiponectin predicted more GD severity, while higher LEAP-2 concentrations predicted more gambling-related cognitive distortions. Likewise, we found that better neuropsychological performance, higher impulsivity traits, and a higher number of gambling-related cognitive distortions predicted GD severity. However, a worse neuropsychological performance predicted more gambling-related cognitive distortions and impulsivity traits, leading to greater GD severity. These results are consistent with our second hypothesis. Although we did not find other associations between endocrine variables and GD severity-related variables, we identified associations between poorer neuropsychological functions, specific gambling-related cognitive distortions and DSM-5 criteria.

Results regarding adiponectin and GD severity are in line with Etxandi et al. (2022), who found lower adiponectin concentrations in a GD sample. Low adiponectin concentrations have also been associated with greater severity in other addictive disorders (Hillemacher et al., 2009; Yu et al., 2021). This hormone has been associated with anti-inflammatory, anti-diabetic and anti-atherogenic properties (Benchebra et al., 2019). Therefore, the results could suggest that lower concentrations of adiponectin are related to the severity of gambling along with a worse metabolic state and a higher cardiometabolic risk associated with addiction-related disorders, which are usually linked to

Table 3
Association between the GD severity measures with the clinical profile: partial correlations adjusted by sex and age (non-strategic gambling, n = 166).

	DSM-5 criteria	SOGS total	Duration of GD	GRCS GE	GRCS IC	GRCS PC	GRCS IS	GRCS IB	GRCS total
Ghrelin (pg/ml)	0.05	0.10	0.04	0.10	0.01	0.06	0.04	0.08	0.08
LEAP2 (ng/ml)	0.02	−0.02	0.02	0.06	0.14	0.11	0.07	0.07	0.11
Leptin (ng/ml)	0.04	−0.02	−0.06	0.02	0.01	0.07	0.14	0.06	0.08
Adiponectin (ng/ml)	0.06	−0.11	0.12	0.01	0.09	0.08	0.06	0.07	0.07
UPPS-P Lack premeditation	0.06	0.09	0.07	0.02	0.06	−0.04	0.05	0.09	0.04
UPPS-P Lack perseverance	0.19	0.15	0.17	**0.36**†	0.15	0.07	**0.24**†	0.10	0.22
UPPS-P Sensation seeking	0.20	0.08	0.02	0.13	0.11	0.15	0.06	0.19	0.16
UPPS-P Positive urgency	**0.27**†	0.19	0.14	**0.42**†	**0.33**†	**0.31**†	**0.33**†	**0.25**†	**0.40**†
UPPS-P Negative urgency	**0.33**†	**0.27**†	**0.25**†	**0.40**†	0.22	0.22	**0.39**†	0.21	**0.36**†
UPPS-P Total	**0.34**†	**0.25**†	0.20	**0.39**†	**0.24**†	0.22	**0.32**†	**0.25**†	**0.35**†
IGT Block 1	0.13	−0.03	−0.02	−0.01	0.01	0.06	−0.02	−0.03	0.00
IGT Block 2	0.09	−0.05	−0.05	−0.01	0.10	0.09	0.03	0.10	0.08
IGT Block 3	0.07	0.06	0.02	0.10	0.04	0.08	0.10	0.10	0.11
IGT Block 4	−0.03	−0.12	−0.01	−0.05	−0.07	0.04	−0.05	0.05	−0.02
IGT Block 5	−0.01	−0.05	−0.07	−0.13	−0.06	−0.03	−0.11	−0.08	−0.10
IGT Total	0.06	−0.06	−0.05	−0.04	0.00	0.06	−0.03	0.04	0.01
IGT Learning	−0.11	−0.07	−0.03	−0.11	−0.12	−0.06	−0.10	−0.05	−0.11
IGT Risk	−0.02	−0.10	−0.05	−0.11	−0.07	0.00	−0.09	−0.02	−0.07
WCST Trials	0.00	−0.05	−0.18	0.03	−0.01	0.04	0.04	0.02	0.03
WCST Errors perseverative	0.04	0.03	−0.02	0.09	0.09	0.13	0.03	0.13	0.11
WCST Conceptual	−0.11	−0.01	−0.07	0.04	−0.03	0.05	0.09	−0.08	0.03
WCST Categories completed	−0.05	0.03	0.03	0.07	0.01	0.06	0.09	−0.03	0.06
TMT A	0.02	−0.02	−0.10	0.07	0.12	0.07	0.09	0.10	0.11
TMT B	−0.08	−0.12	−0.06	−0.02	0.04	0.02	−0.02	−0.03	0.00
TMT Diff	−0.09	−0.13	−0.04	−0.02	0.02	0.02	−0.03	−0.04	−0.02
Stroop words	−0.05	0.00	−0.02	−0.05	−0.20	−0.12	−0.13	−0.15	−0.16
Stroop colors	0.01	0.13	0.03	−0.08	−0.12	−0.20	0.00	−0.19	−0.14
Stroop words-colors	0.03	0.09	0.08	−0.09	−0.17	−0.23	−0.01	−0.12	−0.15
Stroop interference	0.05	0.06	0.09	−0.07	−0.13	−0.16	0.01	−0.03	−0.09
Digits direct	−0.08	0.08	0.03	−0.14	−0.22	−0.20	−0.08	−0.07	−0.17
Digits direct-span	−0.07	0.08	−0.03	−0.14	−0.19	−0.19	−0.08	−0.05	−0.16
Digits inverse	−0.09	0.08	0.04	**−0.25**†	−0.20	**−0.24**†	−0.06	−0.09	−0.20
Digits inverse-span	−0.08	0.10	0.05	**−0.24**†	−0.16	−0.20	−0.05	−0.11	−0.18
Digits total	−0.09	0.09	0.04	−0.21	**−0.23**†	**−0.24**†	−0.08	−0.09	−0.21
WAIS Vocabulary	0.04	0.05	0.19	−0.14	−0.18	−0.16	−0.07	−0.11	−0.16

Note. †Bold: effect size into the ranges mild-moderate to high-large. GD: gambling disorder. DSM: diagnostic and statistical manual of mental disorders. SOGS: South Oaks Gambling Screen. GRCS: Gambling Related Cognition Scale. GRCS-GE: gambling related expectancies. GRCS-IC: illusion of control. GRCS-PC: predictive control GRCS-IS: perceived inability to stop gambling. GRCS-IB: interpretative bias. UPPS-P: Impulsive Behavior Scale. LEAP2: liver enriched antimicrobial peptide 2. IGT: Iowa Gambling Test. WCST: Wisconsin Card Sorting Test. TMT: Trail Making Test. WAIS: Wechsler Adult Intelligence Scale.

weight disturbances in terms of higher BMI and other medical comorbidities (Baenas et al., 2024; Benchebra et al., 2019). Curiously, LEAP-2 concentrations predicted high GRCS scores. Similarly, in non-clinical population, higher LEAP-2 concentrations have been related to impulsivity (Voigt et al., 2021). Particularly in GD, lower concentrations of LEAP-2 predicted the presence of GD (Etxandi et al., 2022). Although LEAP-2 has been recently described, with a lack of extensive and consistent data in the literature, we hypothesized that LEAP-2 concentrations could be a neurobiological factor underlying cognitive distortions, which have not only been associated with the presence of GD, but also with the severity of GD. Altogether, our results reinforce the potential involvement of endocrine factors well-known for its role in food intake regulation in the pathophysiology of addiction-related disorders, including GD. Although preliminary, these findings contribute deeper understand the neurobiology of GD and its severity turning the focus of future research into biological targets as potential treatment strategies.

On the other hand, the association between a better neuropsychological performance and GD severity could suggest that those individuals with GD with preserved cognitive skills tend to gamble with greater amounts of money and greater complexity therefore, showing high GD severity scores. This profile usually occurs in young strategic individuals with GD (Gainsbury, Russell, Blaszczynski, et al., 2015; Gainsbury, Russell, Hing, et al., 2015; Jiménez-Murcia et al., 2019; Moragas et al., 2015) that could be very accurate at capturing statistical information from gambling devices, and together with preserved executive functioning, may contribute to false mastery (Navas et al., 2019). False mastery is a false sense of confidence and control over gambling activities due to the knowledge that one perceives to have. It is important to note that false mastery has not been assessed in the present study, since the GRCS measures other types of gambling-related cognitive distortions with a superstition component. The literature has reported a large heterogeneity among individuals with GD regarding not only socio-demographic, personality traits, and clinical variables (Bonnaire et al., 2013; Grant et al., 2012; Moragas et al., 2015), but also cognitive style (Mouneyrac et al., 2018; Navas et al., 2019). In this vein, some authors have stated that those individuals who exhibit a greater need to engage in demanding cognitive tasks, require more time and recruit working memory and attentional resources (De Neys & Bonnefon, 2013), particularly gambling for intellectual stimulation (Binde, 2013; Jiménez-Murcia et al., 2019; Mestre-Bach et al., 2019). This could explain why these individuals get involved and present serious gambling problems. Still, the literature has suggested that poorer neuropsychological performance is associated with greater severity of GD (Brevers et al., 2012; Leppink et al., 2016). Although this link was not directly observed in our path analysis, the results have shown an indirect alternative way. Specifically, poorer neuropsychological performance would affect GD severity by a positive association with impulsivity and gambling-related cognitive distortions. These two variables have been extensively studied in the field of GD and broadly connected to GD severity (Buen & Flack, 2022; Cunningham et al., 2014; Devos et al., 2020; Savvidou et al., 2017). These results would highlight the double role that neuropsychological performance may have in GD severity. In strategic individuals with GD, better neuropsychological performance would be related to GD severity because it may contribute to false

Table 4
Association between the GD severity measures with the clinical profile: partial correlations adjusted by sex and age (strategic gambling, n = 131).

	DSM-5 criteria	SOGS total	Duration of GD	GRCS GE	GRCS IC	GRCS PC	GRCS IS	GRCS IB	GRCS total
Ghrelin (pg/ml)	−0.02	0.04	0.03	0.01	−0.07	−0.17	0.05	0.00	−0.05
LEAP2 (ng/ml)	−0.02	0.01	0.09	0.01	0.13	0.13	0.04	0.04	0.09
Leptin (ng/ml)	0.09	0.02	−0.02	0.05	0.09	0.09	0.07	0.05	0.09
Adiponectin (ng/ml)	−0.10	−0.13	−0.13	−0.06	−0.10	0.00	−0.08	−0.01	−0.06
UPPS-P Lack premeditation	0.23	0.17	0.09	0.21	0.00	0.11	0.22	0.14	0.18
UPPS-P Lack perseverance	0.17	0.16	0.12	0.12	0.07	0.16	0.00	0.19	0.14
UPPS-P Sensation seeking	0.01	0.09	0.04	0.05	0.13	0.10	0.07	0.10	0.11
UPPS-P Positive urgency	**0.42**[†]	**0.45**[†]	0.17	**0.33**[†]	0.17	**0.24**[†]	**0.30**[†]	**0.33**[†]	**0.35**[†]
UPPS-P Negative urgency	**0.52**[†]	**0.38**[†]	0.08	**0.46**[†]	0.15	**0.27**[†]	**0.41**[†]	**0.41**[†]	**0.44**[†]
UPPS-P Total	**0.41**[†]	**0.40**[†]	0.15	**0.36**[†]	0.18	**0.27**[†]	**0.32**[†]	**0.36**[†]	**0.38**[†]
IGT Block 1	−0.05	−0.03	−0.14	−0.07	−0.16	−0.02	0.01	−0.17	−0.09
IGT Block 2	−0.09	−0.13	−0.17	−0.18	−0.14	−0.18	−0.04	−0.07	−0.15
IGT Block 3	−0.15	−0.08	−0.02	−0.22	−0.13	−0.14	−0.08	−0.12	−0.17
IGT Block 4	−0.10	−0.10	−0.13	−0.22	−0.20	−0.13	−0.14	−0.06	−0.19
IGT Block 5	−0.07	−0.21	−0.12	−0.10	−0.09	−0.03	−0.13	−0.01	−0.09
IGT Total	−0.14	−0.18	−0.17	**−0.25**[†]	−0.23	−0.15	−0.13	−0.12	−0.22
IGT Learning	−0.04	−0.11	−0.02	−0.08	−0.04	−0.01	−0.13	0.05	−0.06
IGT Risk	−0.10	−0.19	−0.15	−0.19	−0.17	−0.09	−0.16	−0.04	−0.16
WCST Trials	0.17	0.13	−0.06	0.21	0.18	0.08	**0.27**[†]	0.17	0.23
WCST Errors perseverative	0.16	0.09	−0.06	0.19	0.08	−0.03	0.23	0.04	0.13
WCST Conceptual	−0.01	0.03	0.07	0.07	0.10	0.17	0.02	0.19	0.14
WCST Categories completed	−0.03	0.02	0.09	−0.06	−0.04	0.08	−0.12	0.03	−0.03
TMT A	0.02	0.00	0.04	0.03	−0.01	−0.01	0.02	0.00	0.01
TMT B	0.13	0.06	0.02	0.12	**0.35**[†]	**0.28**[†]	0.21	0.17	**0.28**[†]
TMT Diff	0.14	0.07	0.03	0.13	**0.38**[†]	**0.29**[†]	0.22	0.19	**0.30**[†]
Stroop words	−0.05	−0.13	−0.04	0.11	−0.01	−0.01	0.03	0.03	0.04
Stroop colors	−0.06	−0.10	−0.01	0.01	−0.10	−0.13	−0.13	0.04	−0.08
Stroop words-colors	−0.08	−0.16	0.00	−0.05	−0.11	−0.09	−0.09	−0.04	−0.09
Stroop interference	−0.05	−0.13	0.02	−0.11	−0.09	−0.04	−0.07	−0.08	−0.10
Digits direct	−0.03	0.03	−0.08	−0.04	−0.11	−0.09	−0.06	0.06	−0.06
Digits direct-span	−0.02	0.01	−0.06	0.01	−0.11	−0.09	0.00	0.07	−0.03
Digits inverse	0.02	−0.02	−0.05	0.03	0.00	0.03	0.03	0.17	0.06
Digits inverse-span	−0.01	−0.03	−0.07	0.03	−0.09	−0.04	0.02	0.13	0.02
Digits total	−0.01	0.01	−0.08	0.00	−0.07	−0.04	−0.02	0.13	0.00
WAIS Vocabulary	−0.20	−0.14	−0.06	−0.19	−0.03	−0.04	−0.15	−0.04	−0.12

Note. [†]Bold: effect size into the ranges mild-moderate to high-large. GD: gambling disorder. DSM: diagnostic and statistical manual of mental disorders. SOGS: South Oaks Gambling Screen. GRCS: Gambling Related Cognition Scale. GRCS-GE: gambling related expectancies. GRCS-IC: illusion of control. GRCS-PC: predictive control GRCS-IS: perceived inability to stop gambling. GRCS-IB: interpretative bias. UPPS-P: Impulsive Behavior Scale. LEAP2: liver enriched antimicrobial peptide 2. IGT: Iowa Gambling Test. WCST: Wisconsin Card Sorting Test. TMT: Trail Making Test. WAIS: Wechsler Adult Intelligence Scale.

mastery and to use gambling as a form of intellectual stimulation. In non-strategic individuals with GD, worse neuropsychological performance could be related to higher severity, as higher impulsivity and gambling-related cognitive distortions may exert more effect when neuropsychological functioning is poorer. Indeed, impulsivity could be seen as the lack of executive functioning.

Based on the interesting and unexplored association between poorer neuropsychological performance and gambling-related cognitive distortions, we observed that impulsive traits (positive and negative urgencies) are associated with most of the gambling-related cognitive distortions (gambling expectancies, predictive control, inability to stop gambling, and interpretative bias). In addition, lack of perseverance (another impulsive trait) was associated with gambling expectancies. In our study, urgencies were also associated with DSM-5 criteria. An amount of literature supports that positive and negative urgencies are linked with gambling-related cognitive distortions (Del Prete et al., 2017; Michalczuk et al., 2011) and with DSM-5 criteria (Vintró-Alcaraz et al., 2022). Moreover, in non-strategic individuals with GD, our results suggested that working memory -meaning scores in Digits invers- could be negatively associated with gambling expectancies. Specifically, we hypothesize that worse capacity to manipulate information, planning and monitoring the task -which is reported in non-strategic individuals with GD-, would support a more intuitive reasoning, tending to process information in a more automatic way and favoring unconscious gambling (Navas et al., 2019). In this sense, positive rewards may be highly valued and risk undervalued as an emotional regulation strategy (Navas et al., 2019), resulting in maintaining positive expectations and remaining motivated to gamble after negative results (Gibson & Sanbonmatsu, 2004). In addition, predictive control, is also negatively associated with working memory. In fact, working memory has a key role in the ability to fully integrate gains and losses experienced during the task, as continuously updating relevant information and predicting future results is the essence of working memory (Dretsch & Tipples, 2008). In strategic individuals with GD, due to more analytical thinking, cognitive inflexibility (measured by TMT-B score) seems to have an association with gambling-related cognitive distortions. Specifically, we found a negative association between cognitive flexibility and illusion of control, that characterize strategic subjects with GD (Mallorquí-Bagué et al., 2019). We hypothesize that strategic individuals with GD would tend to show a certain reluctance to change their way of thinking because they believe that their skills or superstitions can influence the game, contributing to exacerbate this distortion, and therefore, maintain gambling behavior (Langer, 1975; Toneatto et al., 1997). Relatedly, the association between cognitive inflexibility and predictive control could be explained because strategic persons with GD show a greater perception of control (Navas et al., 2017). Hence, the skill element could create a false sense of higher control over the game (Myrseth et al., 2010). In the same line, lower cognitive flexibility (more trials in WCST), were associated with the inability to stop gambling. These results support the idea that GD, and particularly in strategic subjects with GD, are characterized by compulsivity-related neuropsychological impairments, as exemplified in perseveration and cognitive inflexibility (van Timmeren et al., 2018). Lastly, the association between worse decision-making on the IGT and gambling expectations could be interpreted due to a decreased sensitivity to rewards, leading to excessive responses to immediate and large gains observed in GD samples (Goudriaan et al., 2006). However, we could not explain why the association has only been observed in strategic gambling. It is worth noting that the negative association between IGT and cognitive distortions has also been reported in previous studies (Ciccarelli et al., 2016, 2017).

4.1. Limitations

This study must be interpreted considering its limitations. For instance, the cross-sectional nature of this study restricts causal attributions. Further longitudinal studies are required to better understand the implication of neuroendocrine factors and their functions in GD. Additionally, endocrine measurements were analyzed from peripheral blood samples, which could limit the inference of their functioning at a neural level. Our study also did not investigate the effect of some factors such as circadian rhythms that might influence variations in plasma concentrations of neuroendocrine substrates. Moreover, as the sample was only composed of treatment-seeking individuals, this fact could limit the generalization of the results. Nonetheless, it should be emphasized that the frequency of women in the study is in agreement with prevalence estimates in samples of GD patients who seek therapeutic treatment (Blanco et al., 2006), and their involvement in the research supports its ecological validity. The results may also be limited in their interpretation due to the absence of variables related to emotional regulation and psychiatric comorbidity (e.g., major depression or anxiety disorders) that could influence cognitive functioning (Thoma et al., 2011). Conversely, some of the strengths of this work are the use of a path analysis procedure to gain a broad comprehensive understanding of how neuroendocrine variables could determine the severity of GD and the well-characterized neuroendocrine profile.

4.2. Conclusions

These results offer new insights to understand the role of neuroendocrine factors in GD severity. Better and worse performance in cognitive tasks seems to influence the severity of GD through different pathways (in strategic individuals with GD would be a direct pathway between better neuropsychological performance and GD severity); in non-strategic individuals with GD, worse neuropsychological performance is associated with more impulsivity traits and gambling-related cognitive distortions, leading to greater GD severity), suggesting the importance of cognitive skills regarding GD severity. These results also provide updated information about the comprehension of the interaction between neuropsychological features and core GD variables, like cognitive distortions. In this sense, this work may open a new route to modify cognitive distortions through neuropsychological rehabilitation. Intervening in executive functions is likely to benefit not only those individuals who gamble and present greater difficulties in executive functions, but also could help to decrease cognitive distortions and impulsivity. Even though studies on neuromodulation and neuropsychological training in GD are largely insufficient, they have been observed in addictive disorders with promising results (Anderson et al., 2023; Verdejo-García et al., 2019), and may provide a way to improve neuropsychological functions.

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CRediT authorship contribution statement

Bernat Mora-Maltas: Conceptualization, Investigation, Writing – original draft. **Isabel Baenas:** Conceptualization, Investigation, Writing – original draft. **Mikel Etxandi:** Conceptualization, Investigation, Writing – original draft. **Ignacio Lucas:** Investigation. **Roser Granero:** Methodology, Formal analysis. **Fernando Fernández-Aranda:** Funding acquisition, Writing – review & editing. **Sulay Tovar:** Investigation. **Neus Solé-Morata:** Investigation. **Mónica Gómez-Peña:** Investigation. **Laura Moragas:** Investigation. **Amparo del Pino-Gutiérrez:** Investigation. **Javier Tapia:** Investigation. **Carlos Diéguez:** Investigation. **Anna E. Goudriaan:** Supervision. **Susana Jiménez-Murcia:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

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

Data availability

The datasets analyzed during the study are not publicly available due to patient confidentiality and other ethical reasons but are available from the corresponding author on reasonable request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.addbeh.2024.107968.

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