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ORIGINAL ARTICLE

Genetic variants in dopamine pathways affect personality dimensions displayed by patients with eating disorders

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Abstract

Purpose We aimed to analyze the association between common polymorphisms in dopamine pathways with personality dimensions frequently present in patients with eating disorders (ED).

Methods A total of 324 patients [210 with anorexia nervosa (AN), 80 with bulimia nervosa (BN) and 34 with binge-eating disorder (BED)] were diagnosed according to DSM-5 criteria and interviewed using the EDI 2 and SCL-90R questionnaires at the eating disorders unit. Blood samples were drawn and the DNA screened for polymorphisms in dopamine receptor genes (*DRD2* A2/A1 and *DRD3* Ser9Gly) and in the dopamine transporter *DAT1* 10R/9R.

Results AN patients who carried the *DRD3* Gly9Gly genotype displayed significantly higher EDI-2 total scores than patients with the Ser9 allele (118.09 ± 8.75 vs. 97.23 ± 2.73, $p = 0.010$). In these patients, Gly9Gly carriers also showed higher scores in all the individuals' EDI-2 scales. Differences were especially relevant for bulimia ($p = 0.004$), ineffectiveness ($p = 0.044$), interpersonal distrust ($p = 0.037$), interoceptive awareness ($p = 0.006$) and maturity fears ($p = 0.038$). Epistasis analyses showed a strong effect of the interaction between *DRD3* Ser9Gly and *DRD2* A2A1 on the bulimia ($p < 0.05$), ineffectiveness ($p < 0.05$) and asceticism ($p < 0.01$) scales, as well as on the EDI-2 total score ($p < 0.05$). The scores of the SCL-90R inventory were largely unaffected by the presence of the polymorphisms.

Conclusion Whilst no associations were found for the BN and BED groups, our results suggest that women with AN carrying the homozygous variant Gly9Gly genotype in the dopamine D3 receptor have significantly worse ED-related symptomatology.

Level of evidence Level III (evidence obtained from well-designed cohort or case–control analytic studies).

Keywords Eating disorder · Anorexia nervosa · Bulimia nervosa · Binge-eating disorder · Dopamine · Polymorphism

Introduction

Twin and family studies have established high heritability estimates for disordered eating behavior; therefore, a significant genetic influence can be assumed for these pathologies [1]. As a result, numerous candidate gene studies have been carried out to assess the implication of neurotransmitters, hormones and proteins in the etiology of eating disorders (ED) and/or in personality dimensions that are often coupled with ED. Amongst these compounds, dopamine, given its participation in the regulation of feeding behavior, motor activity, the distortion of body image and reward and reinforcement processes [2], has been suggested to play a relevant role in anorexia nervosa (AN) [3], bulimia nervosa (BN) [4] and binge-eating disorder (BED) [5]. In consequence, genes involved in dopaminergic routes are

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considered suitable candidates for association studies in patients with ED.

Most of the initial studies in this setting, including some carried out by our group, focused on the genes coding for catechol-ortho-methyltransferase (COMT) [6, 7], which is responsible for the metabolism of dopamine in the brain, or for the highly polymorphic dopamine D4 receptor [8, 9]. However, there seems to be less available information for the dopamine DAT1 (SLC6A3) transporter and for the D2 or D3 receptors. In this regard, a variable number of tandem repeats in the promoter region of the *DAT1* gene (VNTR, rs28363170) has been found, with the 9-repeat (R) variant apparently decreasing the reuptake of this neurotransmitter compared with the 10R allele [10]. With regard to dopamine receptors 2 and 3 (DRD2-3), the *TaqIA* restriction endonuclease site in the *DRD2* gene (A2/A1, rs1800497) has been shown to reduce the density of D2 autoreceptors in the striatum [11]. Finally, a substitution of Serine for Glycine in aminoacid 9 of the DRD3 protein (rs6280) increases the affinity for endogenous dopamine [12].

The available information on the putative clinical implications of these three polymorphisms in patients with ED is scarce, especially from the point of view of their influence on associated personality dimensions. Indeed, psychological traits and comorbid personality disorders are often overlooked in genetic association studies on ED; however, we have previously shown that certain traits in these patients can be influenced by variability in the loci of central genes [13–18]. In the present study, we have aimed to analyze the association between the aforementioned three common polymorphisms in the dopaminergic pathways (*DAT1* VNTR 10R/9R, *DRD2* A2/A1 and *DRD3* Ser9Gly) with personality dimensions that are frequently present in patients with AN, BN or BED.

Patients and methods

The study group included 324 consecutive female patients with ED (210 with AN, 80 with BN and 34 with BED). Patients visited the Eating Disorder Unit of the Institute of Mental Disorders (Badajoz, Spain) and were interviewed and diagnosed by one psychiatrist and one psychologist using the ED section of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Diagnosis was blind to genotype and was later re-evaluated to comply with the new DSM-5 guidelines. The patients were referred to the Unit by their general practitioners due to the indications of a possible ED (significant alterations in weight, presence of suggestive psychological characteristics, etc.). Exclusion criteria for the study, determined after screening, included neurological disorders (such as mental retardation, dementia or Turner syndrome) and underlying endocrine pathologies. All the participants were Spanish Caucasian females living in the Health District of Badajoz (Southwest Spain).

The study protocol was approved by the Bioethics Committee of the University of Extremadura and was conducted in accordance with the Declaration of Helsinki and its subsequent revisions. Written informed consent was obtained from all patients for their inclusion in the study.

Psychometric evaluation

The evaluation of the general psychopathological parameters in patients with ED was carried out with the Eating Disorders Inventory Test-2 (EDI-2) and the revised Symptom Checklist 90 (SCL-90R) questionnaire. EDI-2 was designed to evaluate ED-related cognitive and behavioral characteristics by initially measuring eight main subscales: drive for thinness, bulimia, body dissatisfaction, inefficacy, perfectionism, interpersonal distrust, interoceptive awareness and maturity fears [19]. In a second version of the test, three more subscales were added: asceticism, impulse regulation and social insecurity. The EDI-2 test has been validated in the Spanish population showing high consistency between the different subscales [20]. The second inventory utilized, SCL-90R, is composed of three global indices [global severity index (GSI), designed to measure general psychological distress; Positive Symptoms Distress Index (PSDI), designed to measure the intensity of symptoms and total positive symptoms (PST)], which shows the number of self-reported symptoms, in addition to the nine main dimensions of the symptoms (somatization, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism) [21]. This test has shown a sufficient invariance in the measurement of the items, validated in the Spanish population [22], which is why it is considered a good tool to evaluate the general psychological state in adolescent psychiatric patients [23].

Genotype analysis

Genomic DNA was isolated from whole blood samples using a standard phenol–chloroform extraction method. Standard real-time PCR methods were used for the identification of the polymorphisms considered. Reactions were performed using Taqman probes purchased from Thermofisher (Waltham, Massachusetts, USA). These three polymorphisms, namely *DRD2* A2/A1 (rs1800497), *DRD3* Ser9Gly (rs6280) and *DAT1* 10R/9R (rs28363170), were selected based on their reported impact on gene function/expression and/or their involvement in psychiatric conditions [24].

Statistical analysis

Scores obtained for the EDI-2 and SCL-90R questionnaires are presented as mean ± standard deviation (SD) values. Chi-square or Fisher tests were performed to compare the frequencies of alleles and genotypes. Differences of quantitative variables between ED subgroups were assessed with Student's *t*/Mann–Whitney or ANOVA/Kruskal–Wallis tests, depending on the normality of the data and the number of groups involved. Logistic regression models adjusted by age were used to analyze the association of single marker using the *SNPassoc* R package [25]. This software is available at https://cran.r-project.org/web/packages/SNPassoc/index.html and it is used to obtain descriptive statistics, exploratory analyses of missing values, calculation of Hardy–Weinberg equilibrium and analysis of associations based on generalized linear models (either for quantitative or binary traits).

Gene–gene interaction (epistasis) analyses were performed using log-likelihood ratio tests adjusted by age (*SNPassoc* package) in a codominant model. In the resulting plots, the diagonal line contains the *p* values from likelihood ratio test for the crude effect of each SNP, which are sorted by their genomic position. The upper triangle in the matrix contains the *p* values for the interaction (epistasis) log-likelihood ratio test. Finally, the lower triangle contains the *p* values from likelihood ratio test comparing the two-SNP additive likelihood to the best of the single-SNP models.

Results

Mean weights for AN, BN and BED patients were, respectively, 45.47 ± 6.85, 66.47 ± 21.67 and 94.78 ± 33.51 kg, whilst BMI values were 17.60 ± 2.24, 25.61 ± 8.99 and 35.42 ± 11.52 kg/m^2 for the same three groups. As expected, age at onset showed differences between the AN, BN and BED groups, with AN patients being significantly younger than women with BN and BED (Table 1). In addition, the global scores in the inventories that evaluated personality dimensions were found to be consistently higher in BN patients than in patients with AN or BED, with marked differences in the case of the EDI-2 questionnaire (123.2 ± 40.5, 90.1 ± 46.2 and 96.2 ± 40.0 for the three groups; $p < 10e{-}6$, Table 1). In this inventory, post hoc tests showed that differences were statistically significant when comparing the BN vs. AN groups ($p < 10e{-}7$) and the BN vs. BED groups ($p = 0.003$), but not when AN and BED patients were compared ($p = 0.255$).

Table 2 shows the observed genotype distribution for the three polymorphisms assayed, namely *DAT1* VNTR, *DRD2 A2/A1* and *DRD3* Ser9Gly, in the three different diagnosis groups. Obtained frequencies showed no deviations from Hardy–Weinberg equilibrium. There were no differences between AN, BN and BED with regard to the distribution of the different genotypes ($p > 0.05$ in all cases).

With regard to the psychometric evaluation, we observed that while the three indices of the SCL-90R inventory were largely unaffected by the presence of the SNPs (Supplementary Table 1), women with ED who carried the *DRD3* Gly9Gly genotype displayed significantly higher EDI-2 total scores than the rest of patients did (118.09 ± 8.75 vs. 97.23 ± 2.73, $p = 0.010$, Table 3). Furthermore, when the population was stratified by diagnosis, AN patients followed the same pattern, with recessive Gly9Gly genotypes correlating with far higher EDI-2 scores after Bonferroni correction of the data (114.32 ± 12.00 vs. 87.43 ± 3.25 in Ser9 carriers, $p = 0.010$). The only other significant association was observed in the BED group, as patients with the 9Gly variant also showed higher scores than Ser9Ser carriers (110.18 ± 36.21 vs. 76.42 ± 38.02, $p = 0.018$). Only two individuals in the BED group harbored the homozygous variant genotype and hence the recessive model could not be formally applied as it was for the other ED. Table 3 shows

Table 1 Demographic and clinical characteristics of the study population

	AN	BN	BED
Age at onset	16.93 ± 4.21*	18.51 ± 5.87	21.41 ± 8.72
GSI	1.6 ± 0.8*	1.9 ± 0.8	1.4 ± 0.6
PST	61.1 ± 21.8*	69.8 ± 16.5	59.5 ± 17.9
PSDI	2.2 ± 0.6*	2.4 ± 0.6	2.0 ± 0.5
EDI-2	90.1 ± 46.2**	123.2 ± 40.5	96.2 ± 40.0

p values refer to differences between the three diagnosis groups: *$p < 0.005$; **$p < 10^{-6}$

ED eating disorder, *AN* anorexia nervosa, *BN* bulimia nervosa, *BED* binge-eating disorder, *GSI* Global Severity Index, *PSDI* Positive Symptom Distress Index, *PST* positive symptom total

Table 2 Genotype frequencies for the three polymorphism assayed in the population of study

Polymorphism	AN, *n* (%)	BN, *n* (%)	BED, *n* (%)	HWE
DAT1 10R/10R	95 (45.2)	39 (48.7)	14 (41.2)	0.799
DAT1 10R/9R	94 (44.8)	34 (42.5)	16 (47.0)	
DAT1 9R/9R	21 (10.0)	7 (8.7)	4 (11.8)	
DRD2 A2/A2	140 (66.7)	51 (63.7)	23 (67.6)	0.853
DRD2 A2/A1	62 (29.5)	27 (33.7)	11 (32.3)	
DRD2 A1/A1	8 (3.8)	2 (2.5)	0 (0)	
DRD3 Ser9Ser	100 (47.6)	39 (48.7)	16 (47.0)	0.698
DRD3 Ser9Gly	88 (41.9)	32 (40.0)	16 (47.0)	
DRD3 Gly9Gly	22 (10.5)	9 (11.2)	2 (5.9)	

ED eating disorder, *AN* anorexia nervosa, *BN* bulimia nervosa, *BED* binge-eating disorder, *n* number of subjects, *HWE* Hardy–Weinberg equilibrium

Table 3 EDI-2 global scores according to the three SNPs analyzed in all diagnosis groups

	AN	*p*	BN	*p*	BED	*p*
DAT1 10R/10R-10R/9R	88.4 ± 3.3	ns	124.6 ± 4.8	ns	100.1 ± 7.8	ns
DAT1 9R/9R	107.1 ± 11.6		135.8 ± 9.5		70.0 ± 25.8	
DRD2 A2/A2-A2/A1	89.4 ± 3.2	ns	125.1 ± 4.6	ns	96.2 ± 40.0	–
DRD2 A1/A1	114.6 ± 23.9		139.0 ± 33.0		–	
DRD3 Ser/Ser-Ser/Gly	87.4 ± 3.2	0.011	125.2 ± 4.8	ns	94.6 ± 41.1	–[a]
DRD3 Gly9Gly	114.3 ± 12.0		127.3 ± 13.6		118.0 ± 5.6	

ED eating disorder, *AN* anorexia nervosa, *BN* bulimia nervosa, *BED* binge-eating disorder, *ns* not significant

[a]Only two BED patients carried the Gly9Gly recessive genotype

EDI-2 global scores according to the three SNPs analyzed in all diagnosis groups.

Next, to further investigate the association observed between the Ser9Gly SNP and the psychometric evaluation in AN patients, we assessed the effect of the Gly9Gly genotype on each individual dimension evaluated by the EDI-2 questionnaire. Figure 1 shows that in all 11 scales, Gly9Gly carriers always displayed higher scores than carriers of the Ser9 wild-type allele. These differences were significant for bulimia, ineffectiveness, interpersonal distrust, interoceptive awareness and maturity fears (Fig. 1). After correction for the three SNPs assayed, the associations with bulimia and interoceptive awareness retained significance.

The analysis of how the other two SNPs affected EDI-2 individual scales showed that, in the AN group, *DAT1* 9R/9R carriers had higher scores for both bulimia and asceticism compared with 10R/10R-10R/9R carriers (6.03 ± 6.12 vs, 5.18 ± 6.20, $p = 0.046$ and 8.90 ± 5.20, $p = 0.004$, respectively). Finally, *DRD2* A1/A1 carriers displayed elevated scores for perfectionism (7.70 ± 4.45 vs. 5.99 ± 4.10, $p = 0.014$) and ineffectiveness (14.60 ± 9.74 vs. 11.02 ± 7.95, $p = 0.042$). Only the associations with asceticism and perfectionism retained significance after Bonferroni correction of the analysis.

Gene–Gene interactions

Figure 2 shows interactions between genetic variability in the three assayed genes with regard to their effect on personality dimensions in the AN patients measured by the EDI-2 questionnaire. Bulimia was the scale mostly affected by these interactions, with significant associations for the *DRD3* Ser9Gly–*DRD2* A2A1 ($p < 0.05$) and *DRD3* Ser9Gly–*DAT1* 10R/9R ($p < 0.05$) SNP pairs. In general, the effect of epistasis was more profound for the interaction between *DRD3* Ser9Gly and *DRD2* A2A1, as seen in the bulimia ($p < 0.05$), ineffectiveness ($p < 0.05$) and asceticism ($p < 0.01$) scales as well as in the EDI-2 total score ($p < 0.05$) (Fig. 2).

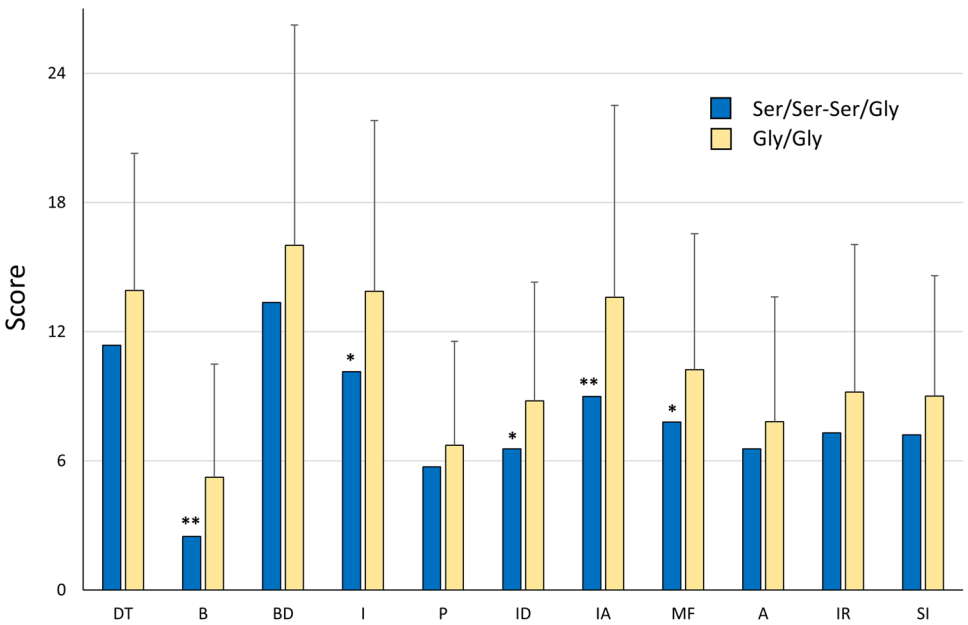

Fig. 1 Mean and standard deviation values of EDI-2 test scores in anorexia nervosa patients according to the DRD3 Ser9Gly genotype. *DT* drive for thinness, *B* bulimia, *BD* body dissatisfaction, *I* inefficacy, *P* perfectionism, *ID* interpersonal distrust, *IA* interoceptive awareness, *MF* maturity fears, *A* asceticism, *IR* impulse regulation, *SI* social insecurity. *$p < 0.05$, **$p < 0.01$

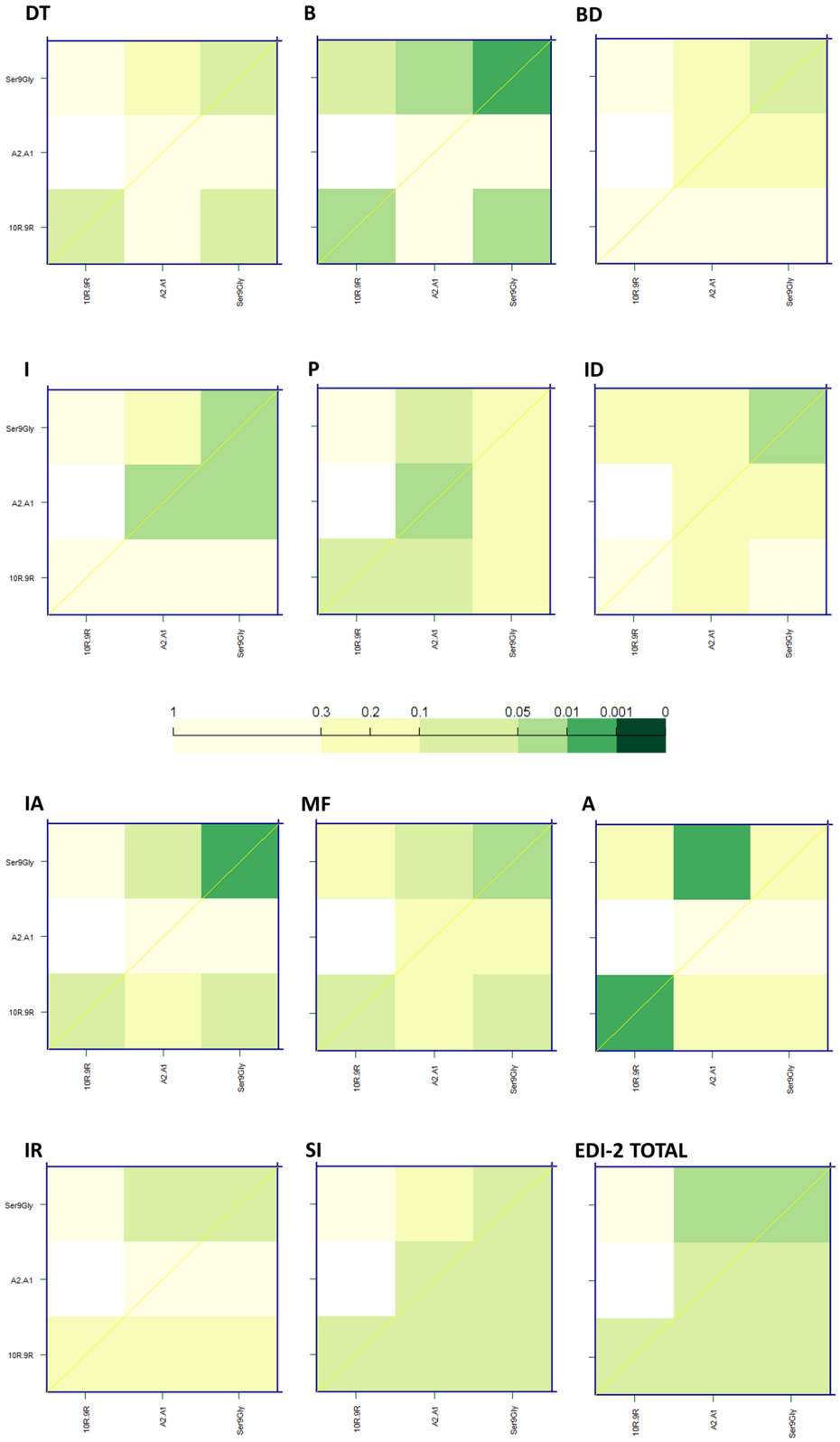

Fig. 2 Effect of interactions between the *DAT1* 10R/9R, *DRD2* A2/A1 and *DRD3* Ser9Gly polymorphisms on the personality dimensions measured by the EDI-2 inventory in anorexia nervosa patients. The diagonal line contains the *p* values from likelihood ratio test for the crude effect of each polymorphism. The upper triangle in the matrix contains the *p* values for the interaction (epistasis) log-likelihood ratio test. Finally, the lower triangle contains the *p* values from likelihood ratio test comparing the two-polymorphism additive likelihood to the best of the single-polymorphism models. *DT* drive for thinness, *B* bulimia, *BD* body dissatisfaction, *I* inefficacy, *P* perfectionism, *ID* interpersonal distrust, *IA* interoceptive awareness, *MF* maturity fears, *A* asceticism, *IR* impulse regulation, *SI* social insecurity

Discussion

Serotonin was the first neurotransmitter that attracted the researchers' attention with regard to genetic association studies in ED. However, dopaminergic genes are gradually gaining interest in this field, both because dopamine plays a key function in reward and reinforcement processes [2, 5], and because dopaminergic signaling is pivotal to many of

the ED-associated comorbidities. These comorbid disorders are frequently as protracted and impairing as the ED itself is [26–29]; therefore, the study of how genetic variability can make patients more prone to develop certain psychopathological traits and personality dimensions is of great interest in the ED setting.

Our results show that AN patients carrying the *DRD3* Gly9Gly genotype had not only significantly elevated scores for the EDI-2 global results, but also displayed higher scores in all the personality dimensions evaluated with this inventory. To our knowledge, there are no studies that have addressed the effect of this SNP on the psychological features of AN patients. However, in other pathologies, the 9Gly variant has also been related to traits such as impulsive behavior [30] or depression [31] in patients with Parkinson's disease, suicide behavior in schizophrenics [32], substance dependence [33, 34], novelty seeking [35] or obsessive–compulsive personality trait [36].

Dopamine is involved in the reward system at several levels, being the "wanting" aspect of it, meaning the pursuit of reward through attribution of incentive motivation to reward-related stimuli, where this neurotransmitter seems to be primarily involved [37]. A hypothesis has been formulated in which the stress induced by food deprivation in AN may stimulate dopamine-dependent reward systems. This could in turn sensitize the mesolimbic reward system and amplify cues previously experienced as rewarding (e.g., food restriction or exercise). This would result in a dopamine-mediated pathological drive for illness-related reward eventually leading to anorectic psychopathology [3, 38]. According to this theory, it is food deprivation what triggers this cascade of events; however, the same authors also acknowledge that AN patients could also display elevated dopamine levels before developing the ED [3]. Our findings, pointing to a genetic background that translates into higher dopamine activity in individuals with more marked pathological traits, seem to support this last hypothesis. This higher dopamine activity would be a consequence of the presence of the Gly9 variant, which is a gain-of-function allele with almost fivefold more affinity for endogenous dopamine than the Ser9 allele [12]. This enhanced affinity could, therefore, impair reward-risk assessment in the mesolimbic system and contribute to development of pathological traits in carriers of the homozygous genotype [30]. Also interestingly, D3 receptors have been shown to be widely expressed in these mesolimbic brain areas, which are central to the reward process of addictive behaviors [39].

As we mentioned before, there are no other studies evaluating the association of *DRD3* Ser9Gly with personality dimensions in ED patients. However, other authors have also reported how allelic variants also increasing dopamine signaling can be related to these psychopathological features. For instance, Frieling et al. observed the *COMT* 158Met variant (significantly decreasing dopamine degradation) was associated with higher scores in practically the same EDI-2 scales for which we have observed significant results, including bulimia, ineffectiveness, interoceptive awareness and maturity fears [40]. In the same manner, the scores on ineffectiveness, which assesses feelings of inadequacy, insecurity and worthlessness, have been shown to correlate with a polymorphism in the *DRD2* gene. The authors of this study argued, in line with the aforementioned hypothesis, that this association may represent the initial stimulus to take up dieting behavior, which could progress to an ED should other psychopathological characteristics be present [41]. With regard to the bulimia dimension, heavily affected by the Gly9Gly genotype in our study, several lines of evidence support the importance of dopamine in bulimic symptomatology [4]; indeed, polymorphisms in dopaminergic genes have also been shown to contribute to variations in the presentation of these bulimic symptoms [42]. Finally, there are also studies reporting how interoceptive awareness, which measures the ability to discriminate between sensations and feelings, e.g. hunger vs. satiety, and that we also observed to be altered by the same genotype, is related to impairments in dopaminergic pathways [43]. However, we would like to remark that sometimes the link between genetic variability and behaviors or personality traits in psychiatric disorders is based on results of genome-wide association studies (GWAS) [44]. These associations need to be formalized into hypotheses and these tested in ad hoc patients' cohorts. Moreover, GWAS and genetic association studies, in general, focus on diseases and adverse behaviors, while omitting the study of associations with beneficial behaviors [45], which could also be important to understand the mechanisms underlying psychiatric disorders.

With regard to the other two polymorphisms studied, the *DAT1 9R/9R*, genotype showed a marginal effect on the psychometric evaluation of the ED patients, mainly affecting the asceticism scale, a finding we had reported previously in a very limited AN population ($n = 78$). However, in that initial study [46], a significant effect on maturity fears and body dissatisfaction was also observed that could not be confirmed herein. Our gene–gene interaction results also show that the impact of the *DAT1* 10R/9R SNP seems to be more relevant when in combination with the *DRD3* Ser9Gly polymorphism. Interestingly, Hersrud et al. have also shown a significant interaction of the *DAT1* 10R/9R SNP with the *COMT* Val158Met SNP to aggravate eating-related psychopathology, again pointing to an increase of dopaminergic activity as the mechanism underlying the association [47]. Finally, the *DRD2* A1/A1 genotype was found to significantly affect perfectionism. In the same line, Nisoli et al. [41] reported that the A1 allele correlated with scales of the EDI-2 inventory (although not perfectionism). It should be remarked, however, that this study included obese subjects

along with AN and BN patients. Moreover, the number of women with AN was comparatively very low ($n=28$), which makes their results hard to compare with those of the present work.

With regard to the epistasis analyses, we showed that the Ser9Gly SNP had a more profound effect on some of the scales when combined with the *DAT1* 10R/9R or *DRD2* A2/A1 polymorphism, as revealed by the p values obtained from likelihood ratio test comparing the two-SNP additive likelihood to the best of the single-SNP models. This finding is not unprecedented, for instance, Loch et al. reported that the Ser9Gly SNP could interact with the widely studied *COMT* Val158Met to modify cognitive performance on schizophrenia patients [48]. Moreover, there are also reports of clinically significant interactions of the Ser9Gly SNP with a Val66Met mutation in the *BDNF* gene in relation to suicidal behavior in schizophrenia patients [32] or in association with bipolar and anxiety disorders [49, 50]. Both the *DRD3* Ser9Gly and *DAT1* 10R/9R SNPs are believed to lead to increased dopamine signaling (because of increased affinity for the receptor and decreased reuptake, respectively), which would explain why their interaction is able to aggravate the bulimia symptomatology more than either of the SNPs separately. The rationale for the findings regarding the other significant interaction observed (*DRD3* Ser9Gly–*DRD2* A2/A1) is similar. The *DRD2* A1 variant has been associated with increased activity of a decarboxylase enzyme that is key for dopamine synthesis, as well as decreased autoreceptor function, i.e. less inhibition of dopamine release [11]. Therefore, carriers of the A1 allele would presumably have an elevated dopaminergic activity that, together with the increased affinity conferred by the Gly9 variant, would result in elevated dopaminergic signaling, able to impair the reward systems in these AN patients.

A limitation of the study was its relatively low sample size in the case of the BN or, especially, BED populations. No relevant genetic associations were found for these groups, but we should not underestimate the influence of dopamine genetics on these disorders until larger cohorts are analyzed. On the other hand, all the patients were from the same geographical area and were diagnosed and followed-up at the same facility by the same clinicians, which reduced the chance that the findings may be due to population structure. Finally, we did not consider the different psychopathological scales to correct for multiple testing, as we did with the 3 SNPs assayed, as this procedure has been suggested to be too stringent to detect a moderate correlation with different endophenotypes in similar studies [51].

Our results, taken together, indicate that, while there were no differences between AN, BN and BED patients with regard to the distribution of the different genotypes, women with AN who carried the Gly9Gly genotype in the dopamine D3 receptor had significantly worse symptomatology than those with other genotypes. The fact that this is a gain-of-function variant suggests that increased mesolimbic dopamine activity, an area where the D3 receptor is extensively expressed, impairs the dopamine-mediated reward system, thus precipitating psychopathological features of this disorder. Notwithstanding, further studies evaluating larger cohorts and possibly more genes involved in these pathways are warranted to confirm the results presented herein.

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Authors' contribution Author GG designed and carried out the study conception. Material preparation was performed by EL-N, data collection was performed by SM-Z and AG-H, data analysis was performed by LMG. The first draft of the manuscript was written by LMG. All authors read and approved the final manuscript.

Data availability The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee (include name of committee + reference number) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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