Original Research

Association of COMT, BDNF and 5-HTT functional polymorphisms with personality characteristics

Marco Tommasi[1], Maria Rita Sergi[1], Fani Konstantinidou[2,3], Marica Franzago[1,3], Mirko Pesce[4], Irene La Fratta[4], Alfredo Grilli[4], Liborio Stuppia[2,3], Laura Picconi[1], Aristide Saggino[1,†], Valentina Gatta[2,3,∗,†]

[1]Department of Medicine and Aging Sciences, "G. d'Annunzio" University of Chieti-Pescara, 66100 Chieti, Italy, [2]Department of Psychological, Health and Territorial Sciences, School of Medicine and Health Sciences, "G. d'Annunzio" University of Chieti-Pescara, 66100 Chieti, Italy, [3]Center for Advanced Studies and Technology (CAST), "G. d'Annunzio" University of Chieti-Pescara, 66100 Chieti, Italy, [4]Department of Medical and Oral Sciences and Biotechnologies, "G. d'Annunzio" University of Chieti-Pescara, 66100 Chieti, Italy

TABLE OF CONTENTS

1. Abstract

Background: The real impact of genetic factors on personality is still unknown, even if in literature about 50% of variance in personality traits are considered genetically determined. The determination of the genetic variance in personality traits could promote psychological well-being and the prevention of psychopathologies, because there are many experimental evidences showing that mental illness is associated to personality. Numerous studies have showed that Catechol-O-methyltransferase (*COMT*), brain derived neurotrophic factor (*BDNF*) and serotonin transporter (*5-HTT*) are genes whose variants are associated with personality traits. This aim of this study is the investigation of the association between personality traits and *5-HTTLPR*/rs255315-*HTT* promoter variant, *COMT* Val158Met and *BDNF* Val66Met gene polymorphisms. **Methods**: The sample was composed by 132 healthy female students. Genomic DNA was extracted from buccal swab, while personality was assessed with Cloninger's Temperament and Character Inventory-Revised (TCI-R). Linear discriminant analysis was used to analyze how personality characteristics can differentiate individuals in re-

lation to their genetic polymorphisms. **Results**: Data showed that the temperament trait Reward Dependence discriminated individuals with different *BDNF* variants; Novelty Seeking and Harm Avoidance discriminated individuals with different *5HTTLPR* variants; Persistence discriminated individuals with different *COMT* variants. **Conclusions**: Since these traits are connected to psychological diseases as depression, social anxiety, anorexia and obsessive-compulsive disorders of personality, the study of their genetic component can be used as intermediary issue to better define the connection between genes and predisposition toward maladaptive behavior and mental illness.

2. Introduction

The latest epidemiological world data show an increment of mental illness, together with a parallel increment of health care costs. For example, in Italy about 6% of adults (18–69 years) report depressive symptoms and reduction of perceived well-being. Moreover, in Iceland, Norway and Switzerland, 27% of adults (18–65 years) experienced at least one episode of mental disorder in the past year (including eating disorders or anxiety) [1]. In literature, genetic factors are considered capable to predict about 50% of the variance in personality traits, but the real impact of genetic factors on personality is still unknown [2]. Because there is an association between personality and probability of suffering from mental diseases, the relation between personality and genetic factors is an important topic to analyze the influence of genetic factors on mental diseases [3, 4]. The determination of the genetic variance in personality traits could promote psychological well-being and the prevention of psychopathologies through the definition of possible associations between specific gene variants and personality traits [5]. The most important and known models of personality based on biological factors are Eysenck's three-factors model [6, 7] and Cloninger's model of personality [8]. The three personality factors of Eysenck's model are: Neuroticism (anxious and depressed mood and low self-esteem), Extraversion (characterized by high assertiveness, sociability and dominance), Psychoticism (characterized by aggressive, antisocial and impulsive behavior). Eysenck assumed that Neuroticism was based on low activation thresholds in the sympathetic nervous system, or visceral brain; that Extraversion was associated to higher arousal thresholds in react to the varying stimulations; that Psychoticism was related to the increased testosterone levels. Cloninger's model, instead, defined four basic personality dimensions: Harm Avoidance, Novelty Seeking, Reward Dependence and Persistence. These dimensions are linked to tendency to feel emotions of fear, anger, love and tenacity, respectively. These factors are genetically determined and produce automatic behavioral reactions to emotive stimuli. In addition, Cloninger defined other three personality dimensions, Self-Directed behavior, Cooperativeness and Self-Transcendence, considered as specific character traits that are mostly affected by environment influence [9]. Behavior genetic research (e.g., Genomic-wide association and genetic linkage studies) is an ever increasingly growing area of analysis of the relation between genes and personality, but this relation is far from being clarified [10]. The most studied personality trait in association with genetic characteristics of individuals is Neuroticism, that is the trait with the strongest association with depression and anxiety [1]. Extraversion is the trait which showed to be strongly associated with agoraphobia, social phobia and dysthymia [11]. Cloninger's High Reward Dependence, Persistence and Cooperativeness are personality dimensions that seemed to be involved as causes of several of psychopathologies, but, nowadays, it is necessary to clarify their real impact on psychiatric disorders [12–15]. The major psychological diseases associated to Cloninger's personality dimensions are depression, social anxiety, anorexia and obsessive-compulsive disorders of personality. In particular, depression is associated to the stress during the performance, the higher attention for negative details during the performance and the constant presence of ruminative thoughts [16–24]. Social anxiety is characterized by a fear of social situations in which the person is exposed to unfamiliar people and the possibility to be judged or criticized [25–28]. Some personality theories showed a connection between the serotonergic, noradrenergic and dopaminergic neurotransmitter and personality traits [29–31]. Novelty Seeking and Extraversion are the personality factors prevalently studied in the association with the neurotransmitter circuit. Indeed, some studies showed a positive correlation between Extraversion and the density of the volume of the medial orbitofrontal brain's area. This area is innervated by dopamine fibers, that play an important role in elaborating emotive contents of stimuli [32]. Several neuroimaging studies [33–36] established that the orbital region of prefrontal cortex is implicated in motivational and emotive states (e.g., to give an emotive value to a stimulus) [37–41]. The Behavioral Activation System theory asserts that dopamine is associated to a motivational system, sensible to the reward signals and responsible for escape from punishments [42]. According to this neuropsychological theory, an increase of dopamine causes a growth of neural activity, that leads to seek positive and negative reinforcements. This mechanism is maintained, through Persistence and Cooperativeness, to successfully achieve a target. Persistence and Cooperativeness allow elevated levels of resilience and emotional intelligence which favors social approval [43–45].

There is growing evidence that particular cognitive-affective phenomena could be influenced by key gene variants altering the activity within specific neuronal circuits. One example is the catechol-O-methyltransferase (*COMT*) gene that codes for the COMT enzyme, which breaks down dopamine in the brain's prefrontal cortex [46].

In the exon three of the gene is mapped the Val158Met (rs4680) common coding Single-Nucleotide Polymorphism (SNP) including the substitution of guanine (G) with adenosin (A) that results in a change in the amino acid located at position 158 of the codon [47]. This changes the structure of the resultant enzyme with an activity modulation. Specifically, the Val/Val version of the COMT enzyme breaks down dopamine with a degradation rate 40% faster than the Met/Met version [46]. An allele carriers (Met158) have more dopamine in their prefrontal cortex, which may be responsible for many of the neuropsychological associations as well as lower pain threshold, enhanced vulnerability to stress, anxiety yet also more efficient at processing information under most conditions [48–50].

Some studies suggest that Val158 alleles are associated with schizophrenia, higher pain threshold, better stress resiliency, albeit with a modest reduction in executive cognition performance under most conditions [51, 52]. In conclusion Val158 alleles may be associated with an advantage in the processing of aversive stimuli (warrior strategy), while Met158 alleles may be associated with an advantage in memory and attention tasks (worrier strategy) [53, 54].

Several lines of evidence suggest that another high priority candidate gene related to behaviour phenotype is represented by *BDNF* gene. Neurobiological studies showed the implication of *BDNF* gene in fear memory, sensitivity to stress, and stress-related disorders [55]. *BDNF* encodes the protein brain-derived neurotrophic factor a regulator of synaptic transmission and plasticity at adult synapses and in response to injury. Different genetic polymorphisms have been shown to affect the availability and activity of *BDNF* [56, 57]. The most investigated single-nucleotide polymorphism in the *BDNF* gene is Val66Met (rs6265 A>G). This substitution, in exon 11, from valine (Val) to methionine (Met) at codon 66 has functional consequences with impairments in intracellular trafficking and activity. However, the substitution is not transferred to the final form of BDNF and the BDNF protein precursor can significantly decrease the secretion of BDNF extracellularly and subsequently reduce its availability to the Central Nervous System (CNS) neurons [58]. Studies also report associations between SNP and brain volume alterations in people with schizophrenia. Met allele carriers showed lower total brain volume, greater reductions in frontal, temporal, and occipital regions and greater reductions in hippocampal volume respect to Val/Val homozygotes [59]. Val66Me variant has also been implicated in modulating the clinical features of Bipolar Disorder, including impulsive aggression [60]. and susceptibility to environmental stress [61]. Other studies showed the implication of *BDNF* gene in modulation of negative emotion processing [62, 63].

Numerous studies have showed that several psychological processes, including individual differences in personality traits could be affected by serotonin [5-hydroxytryptamine (5-HT)] which plays a central role in regulating activity of the central nervous system [64, 65].

The promoter region of the serotonin transporter gene (*5-HTT*) includes the variable number tandem repeats (VNTR) polymorphism (*5-HTTLPR*). It is characterized by short and long functional variants which are associated with different levels of transporter expression. The short variant draws less serotonin back to the presynaptic neuron. When it is set again to the long (L) version, there is an overload of serotonin in the synaptic cleft that keeps stimulating, in this way, the serotonin receptors [66]. Afterwards a single nucleotide polymorphism (SNP) A → G (rs25531) has been disclosed inside the sixth repeat of the S- and L-variants. LG allele has a lower expression level compared to the LA allele.

In this view, S/S homozygosity is associated with the lowest 5-HTT mRNA expression while LA/LA homozygotes have the highest expression with inside the rs25531 (A/G) SNP [67].

Individuals with at least one short allele of the *5-HTTLPR*, have more depressive symptoms in response to early life or recent stress, and was associated with anxiety and schizophrenia [68].

The purpose of the present study is to examine the possible role of the combined *5-HTTLPR*/rs255315-*HTT* promoter variant and *COMT* Val158Met, *BDNF* Val66Met gene polymorphisms with specific personality factors that resulted associated to psychological well-being according to literature, to find a genetic mechanism of personality which can guarantee the prevention of mental illnesses associated to personality.

3. Materials and methods

3.1 Subjects

Participants were 132 healthy female students attending courses at the University of Chieti-Pescara. Their ages ranged from 18 to 24 years, with an average value of 19.76 (SD = 0.99).

3.2 Genotyping

Genomic DNA was extracted from buccal swab samples using NucleoSpin Tissue kit (Macherey-Nagel, Düren, Germany). The identification of the *BDNF* Val66Met (rs6265 G>A) and *COMT* VAL158Met (rs4680) was assayed by polymerase chain reaction (PCR) followed by PCR-based restriction fragment length polymorphism (RFLP)–PCR. Primers for detection of the SNPs were: for Val158Met: 5′-GGAGCTGGGGGCCTACTGTG-3′ (forward) and 5′-GGCCCTTTTTCCAGGTCTGACA-3′ (reverse) and for Val66Met were: 5′-CCCCATGAAAGAAGCAAACA-

3′ (forward) and 5′-TTTGTCTGCTGCCGTTACC-3′ (reverse). The PCR was performed using 10 pmol of each constructed primer and 20ng gDNA as template in 25 μL final volume, containing 1× Kapa Taq buffer, 0.2 mM dNTPs, 1.5 mM MgCl$_2$, 1U Kapa Taq (Kapa biosystems, Wilmington, MA, USA). PCR cycling conditions were: an initial denaturation at 94 °C for 10 min, 35 cycles of 94 °C for 1 min, 59 °C for 30 s and 63 °C, and 72 °C for 1 min with a final extension at 72 °C for 10 min. The resulting PCR products were subjected to restriction digestion for 2 h at 37 °C using 5 U Nla III (New England Biolabs, Ipswich, MA, USA) in a 12 μL volume. Following digestion, the fragments were resolved by 3% agarose gel stained with ethidium bromide. The *COMT*-Val/Val genotype was represented by 114-bp, 36-bp, and 35-bp fragments, *COMT*-Met/Met by 96-bp, 35-bp, 36-bp, and 18-bp fragments, and *COMT*-Val/Met by 114-bp, 96-bp, 36-bp, 35-bp, and 18-bp fragments. *BDNF*-Val homozygote samples produced a visible band of 245 bp. *BDNF*-Met homozygote samples produced a visible band of 168 bp and heterozygosity resulted in two visible products of 245 and 168 bp.

The 5-*HTTLPR* was amplified by PCR using Kapa Taq (Kapa biosystems,Wilmington, MA, USA) and the primer pairs were 5′-GGCGTTGCCGCTCTGAAT-3′ (forward) and 5′-GAGGGACTGAGCTGGACAACCCAC-3′ (reverse). PCR conditions were as follows: initial denaturation at 94 °C for 10 min, followed by 35 cycles of 94 °C for 30 s, 61 °C for 30 s, 72 °C for 30 s, and a final extension at 72 °C for 10 min. The observed alleles yield either a 486 bp (short) or 529 bp (long) product. To distinguish among the SA, LA, and LG fragments, the PCR fragment was digested with MspI (New England Biolabs, Ipswich, MA, USA) and the digested products were separated by 3% agarose gel (LA: 340, 127, and 62 bp, LG: 174, 166, 127, and 62 bp, SA: 297, 127, 62 bp).

3.3 Personality assessment

Temperament and Character Inventory-Revised [69]. It is a 240-item self-administered questionnaire, rated on a 5-point Likert scale format (from 1 = "Definitively False" to 5 = "Definitively True"). The TCI-R is composed by 7 scales, which measure four temperament traits, mostly affected by genetic factors, and three personality factors, mostly affected by environmental factors according to Cloninger's theory. The temperament traits are: Novelty Seeking (NS), Harm Avoidance (HA), Reward Dependence (RD) and Persistence (P). These dimensions reflect the different response to novelty, to avoiding aversive stimuli, to reactions to reward and the time invested in staying on the task. These traits are stable throughout life and they are moderately heritable. Each temperament scale is composed by several facet scales: NS includes Exploratory excitability (NS1), Impulsiveness (NS2), Extravagance (NS3) and Disorderliness (NS4); HA consists

of Anticipatory worry (HA1), Fear of uncertainty (HA2), Shyness (HA3) and Fatigability (HA4); RD comprises Sentimentality (RD1), Openness to warm communication (RD2), Attachment (RD3) and Dependence (RD4); P contains Eagerness of effort (P1), Work hardened (P2), Ambitious (P3) and Perfectionist (P4). Self-Directedness (SD), Cooperativeness (C), and Self-Transcendence (ST) are the three personality factors, that reflect the self-determination, the ability to establish positive relationships and the experiencing spiritual ideas. These factors are composed by different subscales: SD includes Responsibility (SD1), Purposeful (SD2), Resourcefulness (SD3), Self- acceptance (SD4) and Enlightened second nature (SD5); Comprises Social acceptance (C1), Empathy (C2), Helpfulness (C3), Compassion (C4) and Pure-hearted conscience (C5); ST is composed by Self-forgetful (ST1), Transpersonal identification (ST2) and Spiritual acceptance (ST3).

3.4 Statistical analysis

Genotype distributions was analyzed through Hardy-Weinberg equilibrium. We performed a linear discriminant analysis to investigate the differences between groups in relation to personality characteristics of individuals. The groups were composed by individuals with different gene polymorphism (*COMT*, *BDNF* and *5HTTLPR*). On the basis of genetic variants, we created two groups for *COMT* and *BDNF*. The *COMT* groups were targeted with 0 (VAL/VAL) and 1 (VAL/MET and MET/MET) genomic variants. The *BDNF* groups were targeted with 0 (VAL/VAL) and 1 (VAL/MET and MET/MET) genomic variants. The *5HTTLPR* groups were targeted with 1 (LA/LA), 2 (LA/LG = LA/S) and 3 (S/S = LG/LG = LG/S) genetic variants. The aim of the statistical analysis in discriminant analysis is to combine (weight) the variable scores in some way so that a single new composite variable, the discriminant score, is produced. The discriminant score is defined by a discriminate function which maximizes the differences between groups. In our case, the independent variables of the discriminate functions are the personality characteristics measured by the 29 TCI–R facet scales. We compared the results between the three genetic groupings to find which grouping has the highest difference. The level of difference indicates that the psychological characteristics have an important contribution in determining grouping separation and, therefore, that there is, probably, a connection between genetic variants and personality characteristics. We reported the eigenvalues, the explained variance, the Wilks' test, the standardized discriminant function coefficients, the classification tables and the histograms or groups plots for each genetic grouping [70]. All analyses were carried on using IBM-SPSS 26.0 (IBM Corp., Chicago, IL, USA).
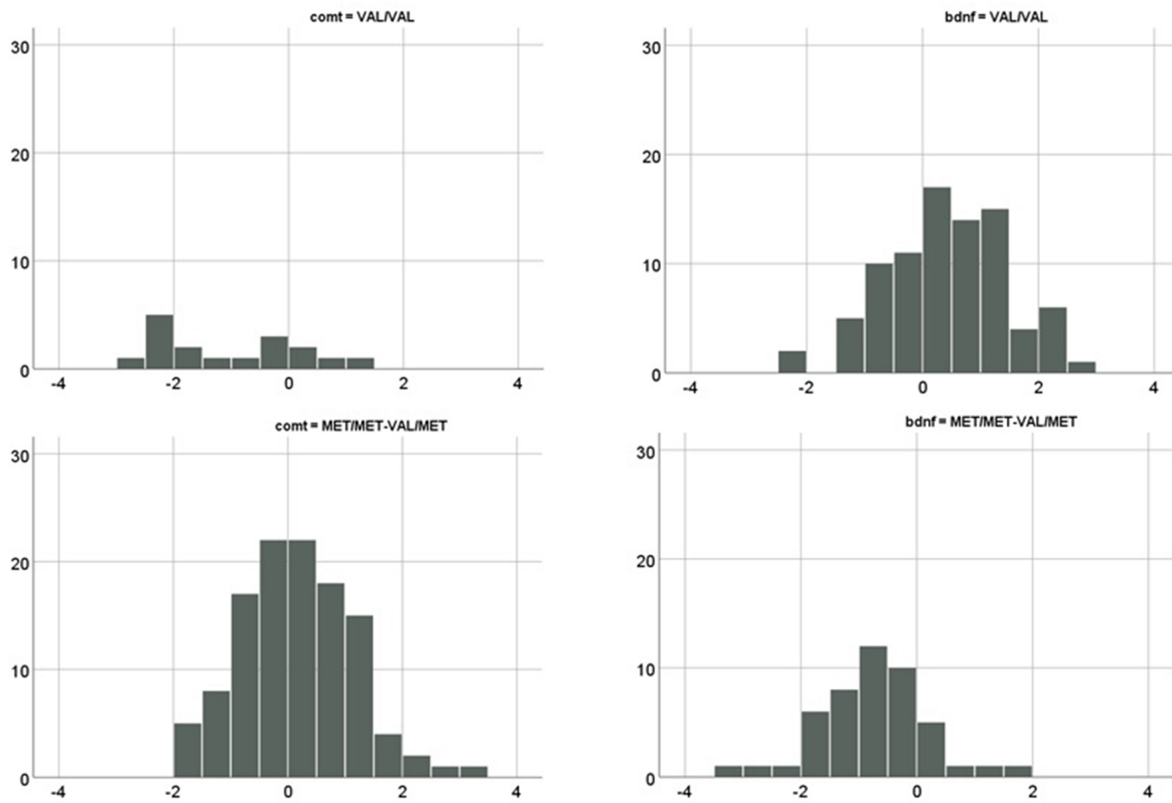
Fig. 1. Histograms of discrimination function for *COMT* (left plots) and *BDNF* (right plots) grouping.

3.5 Procedure

All respondents were asked to participate on a voluntary basis, and were provided written informed consent before administering the questionnaire and extracting buccal swab. Anonymity was guaranteed to all participants. Anonymity and privacy of the participants were guaranteed according the Italian and the European laws about privacy (Italian law n. 196/2003 and EU GDPR 679/2016, respectively). The study was approved by the Department of Psychological Science, Health and Territory. The Genetics Laboratory of University of Chieti-Pescara/CAST is in accordance with the DL 81/08 for Biological Safety and has issued an IQNet recognized certificate number 51897 (Registration number: IT-134045).

4. Results

Supplementary Table 1 was provided with descriptive statistics (mean, standard deviation and standard error) for each variant of *COMT*, *BDNF* and *5HTTLPR*.

4.1 Hardy-Weinberg equilibrium

Genotype distributions is reported in Table 1. They were consistent with what is typically observed in the general population and did not deviate from Hardy-Weinberg equilibrium.

Table 1. Genotype frequency distribution.

Gene/SNP	Genotype	Frequency	N%
BDNF	VAL/VAL	85	64.4
Val66Met (rs6265 A>G)	VAL/MET	40	30.3
	MET/MET	7	5.3
COMT	VAL/VAL	72	54.6
Val158Met (rs4680)	VAL/MET	43	32.6
	MET/MET	17	12.8
5-HTT	La/La	58	44
5HTTLPR/rs255315-*HTT*	La/Lg	39	29.5
	La/S	19	14.4
	Lg/S	3	2.3
	Lg/Lg	8	6
	S/S	5	3.8

Note. Genotype frequencies were in Hardy-Weinberg equilibrium (χ^2 test p value > 0.05).

4.2 Eigenvalues, Wilks' lambda and Chi-squared test

Table 2 shows the eigenvalue, percentage of explained variance, Wilks' lambda and Chi-squared test for each genetic grouping (*COMT*, *BDNF* and *5HTTLPR*). *BDNF* and *5HTTLPR* grouping had the lowest lambda values. Lambda values indicate the proportion of total unexplained variance. *BDNF* and *5HTTLPR* had 75.6% and 62.6% of unexplained variance, respectively, while *COMT* had 84.9%, conversely.

Table 2. Eigenvalues Wilks' lambda ($\triangle$) test and percentage of variance for *COMT*, *BDNF* and *5HTTLPR* gene polymorphisms.

Genetic grouping	Discriminant function	Eigenvalue	Variance (%)	Wilks' D	chi squared	df	p ($\triangle$)
COMT	function 1	0.177	100	0.849	18.870	29	0.925
BDNF	function 1	0.323	100	0.756	32.299	29	0.307
5HTTLPR	function 1	0.302	57.0	0.626	53.949	58	0.627
	function 2	0.228	43.0	0.814	23.616	28	0.702

Table 3. Standardized coefficients of discriminant functions for *COMT*, *BDNF* and *5HTTLPR* grouping.

Predictors	COMT	BDNF	5HTTLPR function 1	5HTTLPR function 2
NS1	−0.01	−0.08	−0.58	0.04
NS2	−0.22	−0.18	0.18	0.29
NS3	0.13	0.16	0.75	0.07
NS4	0.23	0.33	0.53	−0.04
HA1	−0.23	−0.62	−0.28	−0.72
HA2	0.06	0.04	0.31	0.08
HA3	−0.45	0.25	−0.51	0.63
HA4	0.17	0.34	−0.13	0.67
RD1	0.25	0.20	0.46	0.24
RD2	0.05	0.45	−0.90	0.16
RD3	−0.13	−0.56	0.34	0.18
RD4	0.17	0.78	0.38	−0.38
PS1	−0.06	0.30	−0.32	−0.30
PS2	0.18	0.51	0.54	0.12
PS3	0.24	−0.31	0.02	0.56
PS4	0.16	−0.29	0.07	−0.36
SD1	0.33	0.31	0.14	0.17
SD2	0.44	−0.22	0.23	−1.07
SD3	−0.56	−0.14	−0.34	0.48
SD4	−0.37	0.21	0.29	0.36
SD5	0.04	0.44	0.35	−0.33
C1	−0.10	−0.19	0.14	0.65
C2	−0.84	−0.52	−0.22	−0.22
C3	−0.69	−0.14	−0.25	0.29
C4	0.27	−0.21	−0.15	−0.24
C5	0.49	0.22	0.09	0.61
ST1	0.47	0.36	0.08	0.01
ST2	0.33	−0.44	0.32	−0.66
ST3	−0.10	0.15	0.22	0.11

4.3 Discriminant function coefficients

Table 3 reports the standardized discriminant function coefficients for *COMT*, *BDNF* and *5HTTLPR* grouping. The standardized coefficients indicate the importance of each variable in differencing groups.

Discriminant loadings were estimated for each variable to determine the correlation of each variable with the determinant function. The variables with the largest discriminant loadings are those that best characterize the discriminant function. The logic applied to discriminant loadings is similar to that applied to factor analysis, in which variables with loadings $<$0.30 are excluded [71]. Therefore, the predictors with loadings $>$0.30 were PS3 and PS4

for COMT, RD4 for BDNF grouping and NS3 and HA4 for 5HTTLPR grouping. Therefore, different combinations of personality characteristics characterize the discriminant functions for each genomic variant. In particular, Persistence is related to COMT grouping, Reward Dependence is related to BDNF grouping and Novelty Seeking and Harm Avoidance to 5HTTLPR grouping.

4.4 Classification tables

Table 4 reports the classification table for each genomic grouping. The rows are the observed categories of the dependent and the columns are the predicted categories. When prediction is perfect all cases will lie on the diagonal. The percentage of cases on the diagonal is the percentage of correct classifications. The classification results reveal that 91.7%, 77.3% and 65.9% of individuals were correctly classified into the different genomic variants for COMT, BDNF and 5HTTLPR, respectively. In particular, individuals of group 1 were identified with higher accuracy (100%) than those of group 0 (35.3%) for COMT; individuals of group 0 were identified with higher accuracy (88.2%) than those of group 1 (57.4%) for BDNF; individuals of group 1 were identified with higher accuracy (67.2%) than those of group 2 and 3 (69% and 50%, respectively) for 5HTTLPR.

Fig. 1 shows the histograms illustrating the distribution of the discriminant function scores for each group for *COMT* and *BDNF*, respectively. It is possible to see that for *BDNF* the overlap of group distributions is lower that for *COMT*.

Fig. 2 shows the group distributions for *5HTTLPR*. All the three groups had different barycenters. Therefore, the personality factors can discriminate the *5HTTLPR* groups.

5. Discussions

The aim of the present study was to analyze the undefined association among the *COMT*, *BDNF* and *5HTTLPR* gene polymorphisms with personality traits. Results showed that temperaments measured with TCI-R can discriminate individuals with different genomic polymorphisms. In particular, the temperament trait Persistence discriminates individuals with different *COMT* variants, Reward Dependence discriminates individuals with different *BDNF* variants, while Novelty Seeking and Harm Avoidance discriminate individuals with different *5HTTLPR* variants. Our results confirm the association among *COMT*,

Table 4. Classification tables (frequencies and percentages %) for *COMT*, *BDNF* and *5HTTLPR* grouping.

Observed membership	*COMT*	VAL/VAL	MET/MET-VAL/MET	Total	
		Predicted group membership		
Frequencies %	VAL/VAL	6	11	17	
	MET/MET-VAL/MET	0	115	115	
	VAL/VAL	35.3	64.7	100	
	MET/MET-VAL/MET	0	100	100	
	BDNF	VAL/VAL	MET/MET-VAL/MET	total	
Frequencies %	VAL/VAL	75	10	85	
	MET/MET-VAL/MET	20	27	47	
	VAL/VAL	88.2	11.8	100	
	MET/MET-VAL/MET	42.6	57.4	100	
	5HTTLPR	LA/LA	LA/LG = LA/S	S/S = LG/LG = LG/S	Total
Frequencies %	LA/LA	39	17	2	58
	LA/LG = LA/S	16	40	2	58
	S/S = LG/LG = LG/S	6	2	8	16
	LA/LA	67.2	29.3	3.4	100
	LA/LG = LA/S	27.6	69	3.4	100
	S/S = LG/LG = LG/S	37.5	12.5	50	100
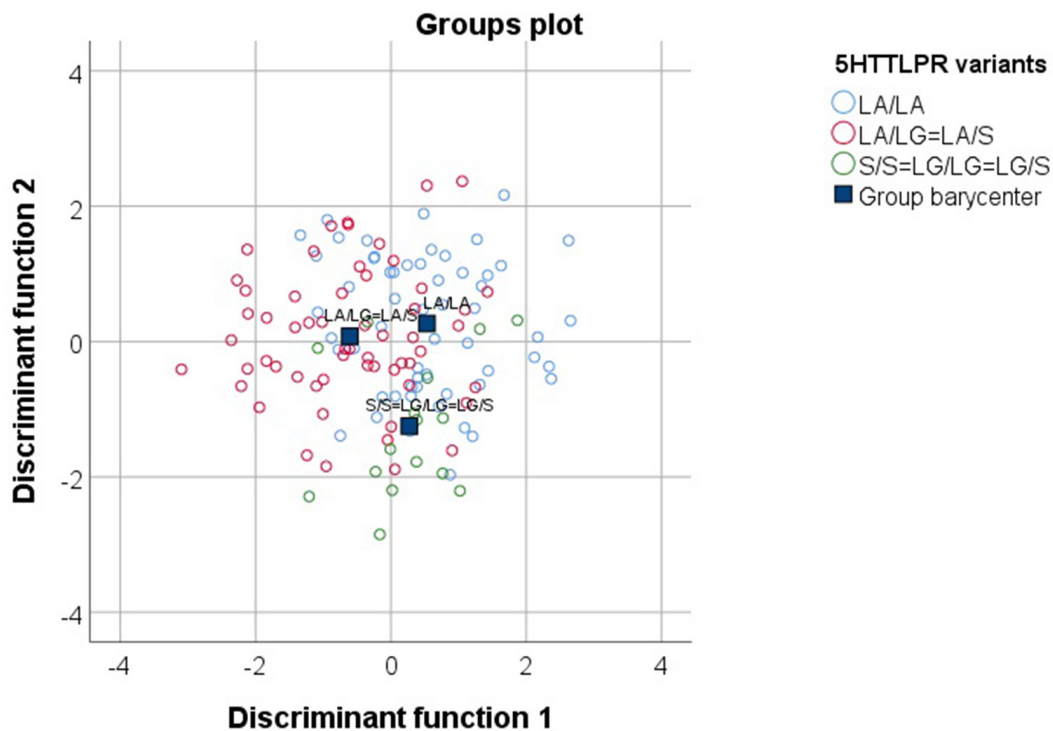
Fig. 2. Groups plot for *5HTTLPR*.

BDNF, *5HTTLPR* and specific personality traits (Reward Dependence, Novelty Seeking, Harm Avoidance and Persistence) due to neurotransmitter circuit [29, 30]. The neuropsychological theory proposes a probable path that associates genes, environment and behaviour. In particular, genes and environment affect brain physiology, through the specific neurotransmitter function of dopamine, serotonin and noradrenalin. The brain activity affects directly behaviour (such as arousal in specific tasks) and indirectly through behavioral tendencies (e.g., avoidance). These behavior tendencies have complex social consequences and modulate the vulnerability to mental illnesses [29]. For example, Cloninger *et al*. [9] associated HA to variation of *5HTTLPR*, NS to low activity of dopamine, P to low activity of noradrenaline. This neurochemical activity is genetically determined, but the link between polymorphisms and behavioral traits was not clearly defined [31].

Our study demonstrates that *COMT*, *BDNF* and *5HTTLPR* are associated to specific personality factors, by using personality characteristics to show how much individuals with different gene variants can be discriminated. Personality characteristics can discriminate groups with different genetic variants, and this result could be purposeful to use the personality profile of each individual to assess mental diseases and personality disorders [3–5]. For example, High scores in Persistence are associated to Obsessive-Compulsive Disorder [72, 73] and anorexia nervosa [74, 75]. Both disorders are associated to tendency toward perfectionism, that allows individuals to be prone to sacrifice to obtain a particular target. Specifically, Obsessive-Compulsive Disorder is characterized by meticulousness, abnormal preoccupation for orderliness and by an excessively commitment to work [76, 77]. Anorexia nervosa is determined by body dismomorphism and a strong fear to increase in weight [78–80]. High levels of Concientiosuness (one of the five-factors of personality) are related to positive emotionality and social well-being [8, 9, 13]. This personality trait allows individuals to persist and to successfully achieve a target. Reward Dependence and Persistence are associated to persistence, resilience to stress and perfectionism and, thus, they are characteristic strongly related to Conscientiousness [17, 73]. If personality factors are connected to mental and psychological diseases, it is possible to define the genetic aspects of psychological diseases through the study of the association between genetic factors and personality traits or tendencies. The personality traits could allow researchers to select and define more precisely the genetic variants that have the greatest weight in determining psychological disorders. In other words, personality traits associated to mental illness can be used as intermediary elements to define the connection between genes and mental illness.

6. Conclusions

In conclusion, this study is part of the research area that analyzes the association between genes and personality. In particular, reactions to reward are associated to *BDNF* variants; response to novelty and avoidance of aversive stimuli are associated to *5HTTLPR*; finally, tenancy to achieve targets is associated to *COMT* gene polymorphisms.

The major limitations of this work concern the small sample size and the absence of comparison with a sample consisting of male subjects. In addition, future perspectives, are addressed to replicate the study for other ages, making the sample more heterogeneous. Further researches are necessary to study the association between genetic factors of individuals and their personality to reduce the still present undefined association between genes, behavior and psychological well-being [81].

7. Author contributions

MT, AS, VG designed the study; MRS, LP, ILF performed testing and data collection; MF, MP, FK performed the genetic data analysis and interpretation; MT, VG, AS, MRS, interpreted data and prepared the manuscript for publication; AS, VG, AG, LS reviewed the draft of the manuscript and provided critical revisions; All authors have read and approved the manuscript.

8. Ethics approval and consent to participate

All respondents were asked to participate on a voluntary basis, and were provided written informed consent before administering the questionnaire and extracting buccal swab. Anonymity was guaranteed to all participants. Anonymity and privacy of the participants were guaranteed according the Italian and the European laws about privacy (Italian law n. 196/2003 and EU GDPR 679/2016, respectively). The study was approved by the Department of Psychological Science, Health and Territory, University of Studies "G. d'Annunzio" Chieti-Pescara, code 21012.

9. Acknowledgment

10. Funding

11. Conflict of interest

The authors declare no conflict of interest. VG is serving as one of the Editorial Board members of this journal. We declare that VG had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to AGG.

12. Informed consent statement

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

13. References

[1] National Institute of Statistics. Epidemiological aspects. Mental Health. 2021. Available at: https://www.epicentro.iss.it (Accessed: 12 October 2021).

[2] Edwards HA, Hajduk GK, Durieux G, Burke T, Dugdale HL. No Association between Personality and Candidate Gene Polymorphisms in a Wild Bird Population. PLoS ONE. 2015; 10: e0138439.

[3] Røysamb E, Nes RB, Czajkowski NO, Vassend O. Genetics, personality and wellbeing. a twin study of traits, facets and life satisfaction. Scientific Reports. 2018; 8: 12298.

[4] Sanchez-Roige S, Gray JC, MacKillop J, Chen C-, Palmer AA. The genetics of human personality. Genes, Brain and Behavior. 2018; 17: e12439.

[5] Kandler C, Bratko D, Butković A, Hlupić TV, Tybur JM, Wesseldijk LW, et al. How genetic and environmental variance in personality traits shift across the life span: Evidence from a cross-national twin study. Journal of Personality and Social Psychology. 2020. (in press)

[6] Eysenck HJ. The biological basis of personality. Piscataway, NJ: Transaction. 1967; 689.

[7] Eysenck HJ. Personality and experimental psychology: the unification of psychology and the possibility of a paradigm. Journal of Personality and Social Psychology. 1997; 73: 1224–1237.

[8] Cloninger CR. A Systematic Method for Clinical Description and Classification of Personality Variants. Archives of General Psychiatry. 1987; 44: 573.

[9] Cloninger CR, Svrakic DM, Przybeck TR. A psychobiological model of temperament and character. Archives of General Psychiatry. 1993; 50: 975–990.

[10] Penke L, Jokela M. The evolutionary genetics of personality revisited. Current Opinion in Psychology. 2016; 7: 104–109.

[11] Vinkhuyzen AAE, Pedersen NL, Yang J, Lee SH, Magnusson PKE, Iacono WG, et al. Common SNPs explain some of the variation in the personality dimensions of neuroticism and extraversion. Translational Psychiatry. 2012; 2: e102.

[12] Balsamo M. Personality and depression: evidence of a possible mediating role for anger trait in the relationship between cooperativeness and depression. Comprehensive Psychiatry. 2013; 54: 46–52.

[13] Cloninger CR, Zohar AH, Cloninger KM. Promotion of well-being in Person-Centered Mental Health Care. Focus. 2010; 8: 165–179.

[14] Cloninger CR, Zohar AH, Hirschmann S, Dahan D. The psychological costs and benefits of being highly persistent: Personality profiles distinguish mood disorders from anxiety disorders. Journal of Affective Disorders. 2012; 136: 758–766.

[15] Martinotti G, Mandelli L, Di Nicola M, Serretti A, Fossati A, Borroni S, et al. Psychometric characteristic of the Italian version of the Temperament and Character Inventory–revised, personality, psychopathology, and attachment styles. Comprehensive Psychiatry. 2008; 49: 514–522.

[16] Cloninger CR, Svrakic DM, Przybeck TR. Can personality assessment predict future depression? A twelve-month follow-up of 631 subjects. Journal of Affective Disorders. 2006; 92: 35–44.

[17] de Simoni E. The role of maladaptive perfectionism in depressive disorders. Cognitivismo Clinico. 2014; 11: 3–26.

[18] Elovainio M, Kivimäki M, Puttonen S, Heponiemi T, Pulkki L, Keltikangas-Järvinen L. Temperament and depressive symptoms: a population-based longitudinal study on Cloninger's psychobiological temperament model. Journal of Affective Disorders. 2004; 83: 227–232.

[19] Hansenne M, Reggers J, Pinto E, Kjiri K, Ajamier A, Ansseau M. Temperament and character inventory (TCI) and depression. Journal of Psychiatric Research. 1999; 33: 31–36.

[20] Josefsson K, Merjonen P, Jokela M, Pulkki-Råback L, Keltikangas-Järvinen L. Personality Profiles Identify Depressive Symptoms over Ten Years? A Population-Based Study. Depression Research and Treatment. 2011; 2011: 431314.

[21] Nelson EC, Cloninger CR. The tridimensional personality questionnaire as a predictor of response to nefazodone treatment of depression. Journal of Affective Disorders. 1995; 35: 51–57.

[22] Richter J, Eisemann M, Richter G. Temperament and character during the course of unipolar depression among inpatients. European Archives of Psychiatry and Clinical Neuroscience. 2000; 250: 40–47.

[23] Santos DDM, Lage LV, Jabur EK, Kaziyama HHS, Iosifescu DV, Lucia MCSD, et al. The association of major depressive episode and personality traits in patients with fibromyalgia. Clinics. 2011; 66: 973–978.

[24] Smith DJ, Duffy L, Stewart ME, Muir WJ, Blackwood DHR. High harm avoidance and low self-directedness in euthymic young adults with recurrent, early-onset depression. Journal of Affective Disorders. 2005; 87: 83–89.

[25] Clark LA, Watson D, Mineka S. Temperament, personality, and the mood and anxiety disorders. Journal of Abnormal Psychology. 1994; 103: 103–116.

[26] Hofmann SG, Bitran S. Sensory-processing sensitivity in social anxiety disorder: relationship to harm avoidance and diagnostic subtypes. Journal of Anxiety Disorders. 2007; 21: 944–954.

[27] Jylhä P, Isometsä E. Temperament, character and symptoms of anxiety and depression in the general population. European Psychiatry. 2006; 21: 389–395.

[28] Matsudaira T, Kitamura T. Personality traits as risk factors of depression and anxiety among Japanese students. Journal of Clinical Psychology. 2006; 62: 97–109.

[29] Matthews G, Deary IJ, Whiteman MC. Personality Traits. Cambridge University Press: Cambridge, UK. 2003.

[30] Munafò MR, Flint J. Dissecting the genetic architecture of human personality. Trends in Cognitive Sciences. 2011; 15: 395–400.

[31] Robbins TW. Opinion on monoaminergic contributions to traits and temperament. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2018; 373: 20170153.

[32] Wacker J, Smillie LD. Trait Extraversion and Dopamine Function. Social and Personality Psychology Compass. 2015; 9: 225–238.

[33] Coan JA, Allen JJB. Frontal EEG asymmetry and the behavioral activation and inhibition systems. Psychophysiology. 2003; 40: 106–114.

[34] Davidson RJ, Jackson DC, Kalin NH. Emotion, Plasticity, Context, and Regulation: Perspectives From Affective Neuroscience. Psychological Bulletin. 2000; 126: 890–909.

[35] Davidson RJ. Anxiety and affective style: role of prefrontal cortex and amygdala. Biological Psychiatry. 2002; 51: 68–80.

[36] Davidson RJ. What does the prefrontal cortex "do" in affect: perspectives on frontal EEG asymmetry research. Biological Psychology. 2004; 67: 219–234.

[37] Díaz-Mataix L, Scorza MC, Bortolozzi A, Toth M, Celada P, Artigas F. Involvement of 5-HT1a receptors in prefrontal cortex in the modulation of dopaminergic activity: role in atypical antipsychotic action. The Journal of Neuroscience. 2005; 25: 10831–10843.

[38] Dixon ML. Cognitive control, emotional value, and the lateral prefrontal cortex. Frontiers in Psychology. 2015; 6: 758.

[39] Ebisch SJ, Perrucci MG, Mercuri P, Romanelli R, Mantini D, Romani GL, et al. Common and unique neuro-functional basis of induction, visualization, and spatial relationships as cognitive components of fluid intelligence. NeuroImage. 2012; 62: 331–342.

[40] Ebisch SJH, Mantini D, Romanelli R, Tommasi M, Perrucci MG, Romani GL, et al. Long-range functional interactions of anterior insula and medial frontal cortex are differently modulated by visuospatial and inductive reasoning tasks. NeuroImage. 2013; 78: 426–438.

[41] Perfetti B, Saggino A, Ferretti A, Caulo M, Romani GL, Onofrj M. Differential patterns of cortical activation as a function of fluid reasoning complexity. Human Brain Mapping. 2007; 30: 497–510.

[42] Harmon-Jones E, Allen JJ. Behavioral activation sensitivity and resting frontal EEG asymmetry: covariation of putative indicators related to risk for mood disorders. Journal of Abnormal Psychology. 1997; 106: 159–163.

[43] Amodio DM, Master SL, Yee CM, Taylor SE. Neurocognitive components of the behavioral inhibition and activation systems: implications for theories of self-regulation. Psychophysiology. 2008; 45: 11–19.

[44] Wacker J, Chavanon M, Stemmler G. Resting EEG signatures of agentic extraversion: New results and meta-analytic integration. Journal of Research in Personality. 2010; 44: 167–179.

[45] Wacker J, Mueller EM, Pizzagalli DA, Hennig J, Stemmler G. Dopamine-d2-receptor blockade reverses the association between trait approach motivation and frontal asymmetry in an approach-motivation context. Psychological Science. 2013; 24: 489–497.

[46] Chen J, Lipska BK, Halim N, Ma QD, Matsumoto M, Melhem S, et al. Functional analysis of genetic variation in catechol-O-methyltransferase (COMT): effects on mRNA, protein, and enzyme activity in postmortem human brain. American Journal of Human Genetics. 2004; 75: 807–821.

[47] Bishop SJ, Fossella J, Croucher CJ, Duncan J. COMT val158met genotype affects recruitment of neural mechanisms supporting fluid intelligence. Cerebral Cortex. 2008; 18: 2132–2140.

[48] Bonetti L, Bruzzone SEP, Sedghi NA, Haumann NT, Paunio T, Kantojärvi K, et al. Brain predictive coding processes are associated to COMT gene Val158Met polymorphism. NeuroImage. 2021; 233: 117954.

[49] He Q, Shen Z, Ren L, Wang X, Qian M, Zhu J, et al. The association of catechol-O-methyltransferase (COMT) rs4680 polymorphisms and generalized anxiety disorder in the Chinese Han population. International Journal of Clinical and Experimental Pathology. 2020; 13: 1712.

[50] Serrano JM, Banks JB, Fagan TJ, Tartar JL. The influence of Val158Met COMT on physiological stress responsivity. Stress. 2019; 22: 276–279.

[51] Nogueira NGDHM, Bacelar MFB, Ferreira BDP, Parma JO, Lage GM. Association between the catechol-O-methyltransferase (COMT) Val158Met polymorphism and motor behavior in healthy adults: a study review. Brain Research Bulletin. 2019; 144: 223–232.

[52] Wang J, Xu H, Wang D, Wei G, Zhou H, Wang L, et al. The interactive effect of genetic polymorphisms of IL-10 and COMT on cognitive function in schizophrenia. Journal of Psychiatric Research. 2021; 136: 501–507.

[53] Schacht JP. COMT val158met moderation of dopaminergic drug effects on cognitive function: a critical review. The Pharmacogenomics Journal. 2016; 16: 430–438.

[54] Stein DJ, Newman TK, Savitz J, Ramesar R. Warriors versus worriers: the role of COMT gene variants. CNS Spectrums. 2006; 11: 745–748.

[55] Notaras M, van den Buuse M. Neurobiology of BDNF in fear memory, sensitivity to stress, and stress-related disorders. Molecular Psychiatry. 2020; 25: 2251–2274.

[56] Binch ALA, Cole AA, Breakwell LM, Michael ALR, Chiverton N, Cross AK, et al. Expression and regulation of neurotrophic and angiogenic factors during human intervertebral disc degeneration. Arthritis Research & Therapy. 2014; 16: 416.

[57] Williams FMK, Bansal AT, van Meurs JB, Bell JT, Meulenbelt I, Suri P, et al. Novel genetic variants associated with lumbar disc degeneration in northern Europeans: a meta-analysis of 4600 subjects. Annals of the Rheumatic Diseases. 2013; 72: 1141–1148.

[58] Hempstead BL. Brain-Derived Neurotrophic Factor: Three Ligands, many Actions. Transactions of the American Clinical and Climatological Association. 2015; 126: 9–19.

[59] Ahmed AO, Kramer S, Hofman N, Flynn J, Hansen M, Martin V, et al. Meta-Analysis of Brain-Derived Neurotrophic Factor Effects on Brain Volume in Schizophrenia: Genotype and Serum Levels. Neuropsychobiology. 2021; 80: 411–424.

[60] Wagner S, Baskaya O, Dahmen N, Lieb K, Tadić A. Modulatory role of the brain-derived neurotrophic factor Val66Met polymorphism on the effects of serious life events on impulsive aggression in borderline personality disorder. Genes, Brain and Behavior. 2010; 9: 97–102.

[61] Bresin K, Sima Finy M, Verona E. Childhood emotional environment and self-injurious behaviors: the moderating role of the BDNF Val66Met polymorphism. Journal of Affective Disorders. 2013; 150: 594–600.

[62] Kourmouli N, Samakouri M, Mamatsiou A, Trypsianis G, Livaditis M, Veletza S. Effect of BDNF Val66Met and serotonin transporter 5-HTTLPR polymorphisms on psychopathological characteristics in a sample of university students. Psychiatric Genetics. 2013; 23: 188–197.

[63] Perez-Rodriguez MM, New AS, Goldstein KE, Rosell D, Yuan Q, Zhou Z, et al. Brain-derived neurotrophic factor Val66Met genotype modulates amygdala habituation. Psychiatry Research: Neuroimaging. 2017; 263: 85–92.

[64] Delvecchio G, Bellani M, Altamura AC, Brambilla P. The association between the serotonin and dopamine neurotransmitters and personality traits. Epidemiology and Psychiatric Sciences. 2016; 25: 109–112.

[65] Licht CL, Mortensen EL, Hjordt LV, Stenbaek DS, Arentzen TE, Nørremølle A, et al. Knudsen GM. Serotonin transporter gene (SLC6A4) variation and sensory processing sensitivity-Comparison with other anxiety-related temperamental dimensions. Molecular Genetics & Genomic Medicine. 2020; 8: e1352.

[66] Martínez RM, Chen CY, Liao TT, Cheng Y, Fan YT, Chou SH, et al. The Multifaceted Effects of Serotonin Transporter Polymorphism (5-HTTLPR) on Anxiety, Implicit Moral Attitudes, and Harmful Behaviors. Frontiers in Psychology. 2020; 10: 1521.

[67] Goldman N, Glei DA, Lin Y, Weinstein M. The serotonin transporter polymorphism (5-HTTLPR): allelic variation and links with depressive symptoms. Depression and Anxiety. 2010; 27: 260–269.

[68] Soga T, Teo CH, Parhar I. Genetic and Epigenetic Consequence of Early-Life Social Stress on Depression: Role of Serotonin-Associated Genes. Frontiers in Genetics. 2021; 22: 601868.

[69] Cloninger CR. A New Conceptual Paradigm from Genetics and Psychobiology for the Science of Mental Health. Australian & New Zealand Journal of Psychiatry. 1999; 33: 174–186.

[70] George D, Mallery P. IBM SPSS statistics 26 step by step: A simple guide and reference. Routledge. 2019.

[71] Samuels P. Advice on exploratory factor analysis. Centre for Academic Success. Birmingham City University. 2017.

[72] Fassino S, Abbate-Daga G, Amianto F, Leombruni P, Boggio S, Rovera GG. Temperament and character profile of eating disorders: a controlled study with the Temperament and Character Inventory. International Journal of Eating Disorders. 2002; 32: 412–425.

[73] Miettunen J, Raevuori A. A meta-analysis of temperament in axis i psychiatric disorders. Comprehensive Psychiatry. 2012; 53: 152–166.

[74] Battaglia M, Przybeck TR, Bellodi L, Cloninger CR. Temperament dimensions explain the comorbidity of psychiatric disorders. Comprehensive Psychiatry. 1996; 37: 292–298.

[75] Kim SW, Grant JE. Personality dimensions in pathological gambling disorder and obsessive-compulsive disorder. Psychiatry Research. 2001; 104: 205–212.

[76] Lázaro L, Font E, Moreno E, Calvo R, Vila M, Andrés-Perpiñá S, et al. Effectiveness of self-esteem and social skills group therapy in adolescent eating disorder patients attending a day hospital treatment programme. European Eating Disorders Review. 2011; 19: 398–406.

[77] Samuel DB, Widiger TA. Conscientiousness and obsessive-compulsive personality disorder. Personality Disorders. 2011; 2: 161–174.

[78] Bachner-Melman R, Zohar AH, Ebstein RP. An examination of cognitive versus behavioral components of recovery from anorexia nervosa. The Journal of Nervous and Mental Disease. 2006; 194: 697–703.

[79] Bulik CM, Tozzi F, Anderson C, Mazzeo SE, Aggen S, Sullivan PF. The relation between eating disorders and components of perfectionism. The American Journal of Psychiatry. 2003; 160: 366–368.

[80] Halmi KA, Sunday SR, Strober M, Kaplan A, Woodside DB, Fichter M, *et al*. Perfectionism in anorexia nervosa: variation by clinical subtype, obsessionality, and pathological eating behavior. The American Journal of Psychiatry. 2000; 157: 1799–1805.

[81] Keyes CL, Myers JM, Kendler KS. The structure of the genetic and environmental influences on mental well-being. American Journal of Public Health. 2010; 100: 2379–2384.

Abbreviations: *COMT*, Catechol-O-Methyltransferase; *BDNF*, Brain derived Neurotrophic Factor; *5-HTT*, Serotonin transporter gene; RD, High Reward Dependence; P, Persistence; C, Cooperativeness; CNS, Central Nervous System; OCD, Obsessive-compulsive disorders of personality; PFC, Region of prefrontal cortex; BAS, Behavioral Activation System's theory; SNP, single-nucleotide polymorphism; G, Guanine; A, Adenosine; Val, Valine; Met, Methionine; 5-HT, serotonin 5-hydroxytryptamine; VNTR, Variable Number Tandem Repeats; L, Long; PCR, Polymerase Chain Reaction; RFLP–PCR, PCR-based restriction fragment length polymorphism; TCI-R, Temperament and Character Inventory-Revised; NS, Novelty Seeking; NS1, Exploratory excitability; NS2, Impulsiveness; NS3, Extravagance; NS4, Disorderliness; HA, Harm Avoidance; HA1, Anticipatory worry; HA2, Fear of uncertainty; HA3, Shyness; HA4, Fatigability; RD, Reward Dependence; RD1, Sentimentality; RD2, Openness to warm communication; RD3, Attachment; RD4, Dependence; P, Persistence; P1, Eagerness of effort; P2, Work hardened; P3, Ambitious; P4, Perfectionist; SD, Self-Directedness; SD1, Responsibility; SD2, Purposeful; SD3, Resourcefulness; SD4, Self- acceptance; SD5, Enlightened second nature; C, Cooperativeness; C1, Social acceptance; C2, Empathy; C3, Helpfulness; C4, Compassion; C5, Pure-hearted conscience; ST, Self-Transcendence; ST1, Self-forgetful; ST2, Transpersonal identification; ST3, Spiritual acceptance; AN, anorexia nervosa.

Send correspondence to: Valentina Gatta, Department of Psychological, Health and Territorial Sciences, School of Medicine and Health Sciences, "G. d'Annunzio" University of Chieti-Pescara, 66100 Chieti, Italy, Center for Advanced Studies and Technology (CAST), "G. d'Annunzio" University of Chieti-Pescara, 66100 Chieti, Italy, E-mail: v.gatta@unich.it

† These authors contributed equally.