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Harm Avoidance as a possible mediator in the relationship between the 5-HTTLPR and Cognitive Anxiety in High Level Athletes

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Abstract

Background: The identification of relationship between genes and emotional distress mediated by personality traits among high level athletes may help to implement specific clinical psychology programs. Findings suggest that 5-HTTLPR genetic polymorphisms may be associated with Harm Avoidance (HA). The present research is aimed at evaluating the relationship between HA, the serotonin transporter's (5-HTTLPR) polymorphisms and cognitive anxiety (CA) in high level athletes during championship.

Methods: 133 athletes completed the Temperament and Character Inventory (TCI) test. Sport Performance Psychological Inventory (IPPS-48) was used to assess athlete's cognitive and emotional aspects. Genotypes at the 5-HTTLPR polymorphisms were identified through a polymerase chain reaction.

Results: An association has been found between the 5-HTTLPR s/s genotype and both cognitive anxiety ($p<0.05$) and HA ($p<0.05$). Significant correlations were proved between HA and CA ($p<0.01$), Emotional Arousal Control ($p<0.001$) and Concentration Disruption ($p<0.05$). HA has been proven to mediate the association between the 5-HTTLPR polymorphisms and CA symptoms ($p<0.05$).

Conclusions: Such findings clearly suggest, there is a substantial interaction between 5-HTTLPR polymorphisms, HA and competition-related stress that predicts adverse psychological outcomes in high level athletes. The interaction between the environment and genetics can lead directly to emotional disturbance and therefore to disturbances in cognitive and emotional processing.

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1. Introduction

Previous research suggests an increase of the prevalence of depressive and anxiety-related disorders in high level athletes (Broshek & Freeman, 2005). Affective and mood disorders, eating and addiction disorders have been increasingly reported among athletes (Fredericks et al., 2002; Iuso et al., 2019; Wolanin et al., 2015; Yang et al., 2007). Certain personality traits seem to have an influence on the development of depressive and anxiety symptoms. Competition-related stress (Puente-Diaz & Anshelm, 2005), overtraining (O'Connor et al., 1989), ineffective coping strategies (Altamura et al., 2018; Nixdorf et al., 2013; Proctor & Boan-Lenzo, 2010), negative group dynamics/peer interaction (Eccles & Barber, 1999; Mahoney, 2000) have been considered risk factors.

Particularly, athletes exposed to stressful competitive situations could perceive higher levels of psychosomatic syndromes, alarming cognitive symptoms and concentration disruption (Valenzano et al., 2020). McCarthy et al. (2013) highlighted a state of anxiety is very common in sports contexts. Trait anxiety refers to a predisposition to a state of high anxiety under adverse conditions. Martens defined competitive state anxiety as the "tendency to perceive competitive situations as threatening and to respond to them with feelings of apprehension and tension". These feelings include somatic and cognitive symptoms of anxiety (Martens et al., 1990; Smith et al., 1998). Worry and concentration disruption have to be considered cognitive anxiety components. Worry is defined as non-optimistic expectation regarding potential negative personal and social consequences of insufficient performance (Sarason, 1984). Concentration disruption is conceptualized as difficulties in focusing on task relevant cues and evaluating a competitive strategy (Nideffer & Sagal, 2006).

Anxiety-related personality traits can increase the onset of anxiety symptoms in high level athletes involved in competitive situations (Lahey, 2009). Environment and genetics contribute to structuring the personality. Twin and family studies, individual variation of the heritable component can account for 30–60% of variance in personality traits (Bouchard et al., 1990; Bouchard, 1994). Serotonin (5-HT) neurotransmission has a dominant role on regulating activities of the CNS and influences a wide array of physiological and psychological processes including individual variances in personality traits (Leonardo & Hen, 2006; Lieben et al., 2004). The serotonin transporter gene (SLC6A4) encodes the serotonin transporter protein (5HTT), which removes serotonin from the synaptic cleft, acting as a key regulator. The promoter region of the SLC6A4 gene contains a polymorphism with short (s) and long (l) repetitions in a region: 5HTT-linked polymorphic region (5-HTTLPR). Higher expression of gene product is related via the long form and the short form with lower (Lesch et al., 1994; Sessa et al., 2011). Studies

highlighted a relationship between anxiety-related personality traits (neuroticism for instance) and depressive and anxiety disorders (Caspi et al., 2003; Lahey, 2009). Also, our previous study established proof for correlation between a serotonin transporter promoter polymorphism (5-HTTLPR), personality trait of neuroticism and symptoms of depression and anxiety among high level athletes (Petito et al., 2016). Although there is proof that athletes are highly susceptible to developing mental health problems caused by level of stress they experience (Costa & McCrae, 1992), fewer information is available about the correlation between the 5-HTTLPR polymorphisms and the development of cognitive anxiety symptoms inside the athlete population (Gomes et al., 2017; Pons et al., 2018).

The instruments mostly used in biological studies of personality are the NEO-Personality Inventory (Cloninger et al., 1993) and the Temperament and Character Inventory (TCI) (Zuckerman & Cloninger, 1996). Although NEO and TCI have relevant differences, they appear similar evaluating anxiety traits just as well as Neuroticism (N) and Harm Avoidance (HA). Previous studies have highlighted that N is highly related to HA (Aluja et al., 2002; De Fruyt et al., 2006), however Munafò et al. (2003) excluded their equivalence. Moreover, in same study the authors reported an association between the 5-HTTLPR polymorphism and avoidance traits, but this effect was no longer being significant when into data from studies were not reported allele frequencies in Hardy-Weinberg equilibrium (HWE) and unpublished data were excluded. Meta-analyses (Schinka et al., 2004; Sen et al., 2004) showed only an association between N and 5-HTTLPR. More recently, the same authors (Munafò et al., 2009) analyzed a more complete meta-analysis, which showed no relationship between the 5-HTTLPR and HA but a significant relationship between the 5-HTTLPR and N. However, the relationship was lost due to high heterogeneity of the analyses elaborated in different studies and evaluated using the random effects model. Instead, studies of the molecular genetic basis of anxiety traits have used both measures of N and HA almost equally (Munafò et al., 2009). Notably, the importance of association between 5-HTTLPR and HA has been increasingly recognized but its relation remains unclear.

Therefore, the purpose of this study is to examine the correlation between personality, the presence of the polymorphism in the 5-HTTLPR and cognitive anxiety in a homogenous group of high-level athletes during championship season. We hypothesize that the 5-HTTLPR "s" genotype as well as HA could influence the cognitive anxiety in high level athletes engaged in competitive sports.

There is the possibility that HA personality trait is a mediator between 5-HTTLPR "s" genotype and cognitive anxiety. A mediation analysis was used to test this hypothesis.

2. Materials and Methods

2.1 Subjects

Consecutive 133 male high level athletes were recruited from national sporting centers in the Apulia Region (Italy). An initial letter of presentation the research was sent to head coaches as well as to directors of high-level sport organizations.

Eighteen sporting centers, within which the 73% (133/182) of male high-level athletes and the 63% of females (12/19) chose to participate, cause of women represent less than 10% of our sample, it was decided to exclude them. The athletes were evaluated at the beginning of the competitive championship. Participants were healthy men who competed, within the last 5 years, at a national or international level in their chosen sport. Specifically, were included 51 soccer players, 43 basketball players, 39 hockey players, certificated by CONI (Italian National Olympic Committee). All participants gave their written consent for taking part in the study, for collecting their blood, as well as storing and subjecting it to a genetic analysis. Exclusion criteria for the athletes were: a history of traumatic brain injury, epilepsy, developmental disorder, diagnosable current substance abuse dependence or other known neurological condition and the presence or previous presence of psychiatric disorders. The present study is in accordance with the Helsinki declaration and was approved by the local Institutional Review Board (Comitato Etico ASL-FG; prot. n. 09/CE/07).

2.2 DNA analysis

A blood sample was collected in ethylenediaminetetraacetic acid or sodium citrate from each participant and DNA was extracted from peripheral blood leukocytes according to standard protocols (Heils et al., 1996). DNA amplification was amplified using the 2 flanking primers suggested in 1996 by Heils et coll.: 5-HTTU:5'GGCGTTGCCGCTCTUAATGC3', nt-1416,-1397 5-HTTL:5'GAGGGACTGAGCTGGACAACCAC, nt-910,-889. This set of primers amplifies a 484/ 528 fragment corresponding to the SLC6A4_C short and long allele, respectively to each other. The PCR conditions were slightly modified from Heils et coll. (1996). The PCR reaction was carried out in a total volume of 20 μL consisting of 100 ng of genomic DNA, 0.1 μmol of primers per liter, 40-μmol/L deoxynucleotide triphosphates, 20-μmol/L 7-deaza-2'deoxyguanosine, and 1 unit of AmpliTaq with the appropriate buffer in a Mastercycler polymerase chain reaction thermal cycler (Miller et al., 1988). Cycling conditions were as follows: 1 denaturing cycle at 95°C for 5 minutes, 2 cycles with a touchdown annealing temperature of 63°C and 62°C, respectively for 30 seconds, and 38 cycles with an annealing temperature at 61°C. Final DNA elongation was at 72°C for 10 minutes. DNA bands were visualized in prestained (0.4-μg/mL ethidium bromide) 3% agarose gels that were run for 1 hour at 120 V.

2.3 Psychometric Evaluation

The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) and Structured Clinical Interview for DSM-IV Axis II Personality Disorders (SCID II), were performed to assess current and previous psychiatric diagnoses. SCID-I and II conducted by psychiatrists and/or licensed research psychologists who were trained to a minimum interclass correlation of 0.80 (First et al., 2000, 2003).

Personality traits were evaluated by the Italian version of Temperament and Character Inventory (TCI), a 240-item true-false self-report questionnaire (Martinotti et al., 2008). TCI is divided into seven independent dimensions four of which test temperament, novelty seeking (NS), harm avoidance (HA), reward dependence (RD), and persistence (P) and three evaluate character, self-directedness (SD), cooperativeness (C), and self-transcendence (ST) (Cloninger et al., 1993). Cloninger's tridimensional theory reflects a Harm Avoidance (HA) scale, construct that corresponds most closely to anxiety traits. HA is conceptualized as avoidance of conditions of threat, being prone to anxiety and an aversion to risk-taking (Dale, 1996; Zohar et al., 2003).

The Sport Performance Psychological Inventory (IPPS-48) and the Profile of Mood States (POMS) self-reporting questionnaires were used to assess anxiety and depressive symptoms. The IPPS-48 includes 48 items pertaining to eight factors. These factors are further included into two broader conceptual categories. The Cognitive aspects category encompasses race preparation (RP), goal setting (GS), mental practice (MP), and self-talk (ST) factors. The Emotional aspects category comprises self-confidence (SC), emotional arousal control (EAC), cognitive anxiety (CA) or worry and concentration disruption (CD). The IPPS-48 has good psychometric properties (which include alpha and test-retest reliability), and discriminant validity (Robazza et al., 2009).

The POMS is a standard validated psychological test formulated by McNair et al. (1971) consisting of 65 items that fit into 6 categories: tension-anxiety (T/A), depression-dejection (D/D), anger-hostility (A/H), vigor-activity (V/A), confusion-bewilderment (C/B) and fatigue-inertia (F/I). POMS, developed as a means of measuring the current mood of subjects, has often been employed in studies measuring athletes' emotional states. These unstructured interviews began with an open-ended prompt designed to guide the direction of the interview: "Tell me about your experience of stress as an athlete". All of the athletes were participating in competitive sport events while the study was conducted.

2.4 Statistical Analysis

Analyses were performed in STATA (V.15.1; StataCorp).

Means and SD have been calculated for each studied parameter, and an alpha level of 0.05 was selected throughout the study. The differences in psychometric dimensions across the three 5HTT-LPR genotypes were compared using nonparametric Kruskal Wallis test with Dunn's multiple Comparison post-hoc testing. The assessments of the relationship between dimensions of HA temperament (TCI) and mood states (POMS and IPPS-48) were performed using Pearson's correlation. Conformity of empirical genotype frequency distribution to theoretically expected Hardy–Weinberg equilibrium was verified using Pearson $\chi 2$ test.

2.5 Mediation analyses

A path method was applied to test the hypothesis that the association between 5-HTTLPR genotype and Cognitive Anxiety was mediated by HA. In particular, a series of linear regression models was run to assess the fourth criterion for mediation proposed by Baron and Kenny (1986). This approach involves testing three equations. First, the outcome variable is regressed on the predictor (Path c) (Fig 1). Second, the mediator is regressed on the predictor variable (Path a). In the third equation, the outcome variable is regressed on both the predictor and the mediator. This provides a test of whether the mediator is related to the outcome (Path b) as well as an estimate of the relation between the predictor and the outcome controlling for the mediator (Path c'). If the relation between the predictor and the outcome is significantly smaller when the mediator is in the equation (Path c') than when the mediator is not in the equation (Path c), the data suggest a mediation effect (Baron & Kenny, 1986; Frazier et al., 2004). Therefore, first, the IPPS-48, POMS scores (the outcome variables) were regressed on the 5-HTTLPR genotype (the predictor; coded as 0 for 'll', 1 for 'ls', and 2 for 'ss') to establish that there was an effect to mediate (Path c). Second, HA (TCI) score (the mediator) was regressed on the 5-HTTLPR genotype (the predictor variable) to show that the predictor was related to the mediator (Path a). Finally, the IPPS-48 and POMS scores (the outcome variables) were regressed on both the 5-HTTLPR genotype (the predictor) (Path b) and HA (TCI) score (the mediator) (Path c'). To assess the significance of the mediating variable effect we used a method proposed by Baron and Kenny. Specifically, the product of paths a and b is divided by a standard error term. The mediated effect divided by its standard error yields a z score of the mediated effect. If the z score is greater than 1.96, the effect is significant at the .05 level.

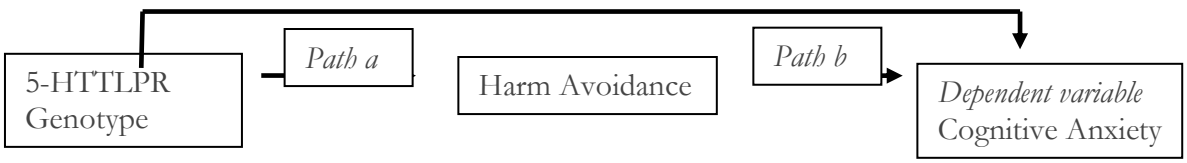

Figure 1. Paths in mediation model.

3. Results

Participants had no history of neurologic, psychiatric disorders or alcohol and other drug dependence disorders. The average age of the participants was 23.36 (SD = 8.48), ranged from 18–36 years. Mean educational level was 14.41 (SD = 2.42). The genotype subgroups did not differ significantly in age (s/s = 24.52 (SD = 4.56); s/l = 22.79 (SD = 3.86); l/l = 24.06 SD = 4.24) and education years (s/s = 14.75 (SD = 2.36); s/l = 14.05 (SD = 2.54); l/l = 14.44 (SD = 2.36) (all $p > .05$). All participants reported high levels of stress related to competition (e.g., pressure to perform well and pressure of meeting expectations). 5-HTTLPR genotype and allele frequencies are shown in Table 1.

Table 1. Frequencies of the genotypes and alleles of the 5-HTTLPR.

Genotypes			**Alleles**	
Alleles				
l/l	l/s	s/s	l	s
(N = 37)	(N = 74)	(N = 22)		
28%	56%	16%	56%	44%

The distribution of allele in the sample was in the Hardy-Weinberg equilibrium ($p>0.05$). The mean scores on the five personality sub-scales of the TCI for each genotype group are presented in Table 2.

Table 2. Association between 5-HTTLPR genotype and Temperament and Character Inventory (TCI). Mean ± SD. P = level of significance.

Genotype	**n**	**TCI NS**	**TCI HA**	**TCI RD**	**TCI P**	**TCI SD**	**TCI C**	**TCI ST**
l/l	37	8.64 ± 1.97	6.00 ± 2.40	7.60 ± 2.57	4.4 ± 2.60	17.56 ± 3.95	15.72 ± 2.95	6.2 ± 2.16
l/s	74	8.66 ± 2.67	7.19 ± 3.12	8.31 ± 2.25	3.63 ± 2.69	17.18 ± 4.42	17.06 ± 4.02	6.71 ± 3.65
s/s	22	8.16 ± 2.21	7.79 ± 2.84	8.26 ± 2.02	3.89 ± 0.93	15.95 ± 4.36	17.11 ± 2.59	6.89 ± 2.58
p		0.5540	0.0303	0.1597	0.0570	0.2012	0.0280	0.6465

NS = Novelty Seeking, HA = Harm Avoidance (HA), RD = Reward Dependence, P = Persistence (P), SD = Self-Directedness, C = Cooperativeness, ST = Self-Transcendence

The analyses across the 5-HTTLPR genotype groups (l/l; l/s; s/s) indicated a significant main effect of the s/s genotype on Harm Avoidance and Cooperativeness. Post-hoc analyses revealed a recessive effect of the short allele of the 5-HTTLPR gene with increased Harm Avoidance and Cooperativeness score in the s/s genotype group compared with l/l group (both, $p< 0.05$).

There was no association with the other major personality subscales of the TCI. The mean scores on sub-scales of the POMS and IPPS for each genotype group are presented in Tables 3 and 4.

Table 3. Association between 5-HTTLPR genotype and Profile of Mood States (POMS). Mean ± SD. P = level of significance.

Genotype	n	POMS T/A	POMS D/D	POMS A/H	POMS V/A	POMS C/B	POMS F/I
ll	37	5.32 ± 3.76	5.25 ± 5.50	7.18 ± 6.93	18.60 ± 6.93	7.25 ± 5.28	5.96 ± 3.82
l/s	74	7.880 ± 5.68	5.65 ± 6.77	7.10 ± 6.37	17.51± 6.747	8.18 ± 6.04	6.34 ± 4.66
s/s	22	9.052 ± 5.76	9.36 ± 10.87	11 ± 11.37	18.52 ± 3.791	7.84 ± 5.59	7.05 ± 6.39
p		0.0457	0.7630	0.7588	0.7556	0.7988	0.9745

T/A = Tension-Anxiety, D/D = Depression/Dejection, A/H = Anger/Hostility, V/A = Vigor/Activity, C/B = Confusion/Bewilderment, F/I = Fatigue/Inertia

Table 4. Association between 5-HTTLPR genotype and Sport Performance Psychological Inventory (IPPS-48). Mean ± SD. P = level of significance.

Genotype	n	RP	ST	CA	SC	GS	EAC	MP	CD
ll	37	24.62 ± 8.09	20.03 ± 8.08	15.00 ± 5.84	27.34 ± 8.65	21.44 ± 7.04	24.57 ± 4.37	21.46 ± 8.13	11.60 ± 4.43
l/s	74	24.06 ± 6.19	21.61 ± 7.97	18.47 ± 7.35	24.54 ± 8.87	22.09 ± 8.52	21.79 ± 6.13	20.5 ± 8.07	11.01 ± 5.34
s/s	22	25.37 ± 4.57	24.73 ± 7.22	22.0 ± 7.20	24.57 ± 8.64	17.47 ± 7.40	21.21 ± 2.46	19.42 ± 8.96	12.63 ± 3.32
P		0.7195	0.1970	0.0036	0.3875	0.0931	0.0156	0.5276	0.0491

RP = Race Preparation, ST = Self-Talk, CA = Cognitive Anxiety, SC = Self-Confidence, GS = Goal setting (GS), EAC = Emotional Arousal Control, MP = Mental Practice, CD = Concentration Disruption

There was a significant main effect of 5-HTTLPR genotype on anxiety symptoms according to the POMS. Post-hoc analyses revealed that participants with two copies of the "s" genotype had significantly higher POMS tension /anxiety (T/A) scores than those with the l/l genotype ($p< 0.05$). Furthermore, we found a main effect of 5-HTTLPR polymorphism on cognitive anxiety, emotional arousal control and concentration disruption, according the IPPS-48. Post-hoc analyses revealed that participants with two copies of "s" allele had higher IPPS cognitive anxiety, lower IPPS emotional arousal control and, higher IPPS concentration disruption scores than those with the l/l genotype (all, $p<0.05$). A significant correlation was observed between anxiety and depressive symptoms according to the POMS (tension/anxiety,

depression/dejection, anger/hostility, fatigue/inertia) and IPSS (race preparation, self-talk, cognitive anxiety, goal setting, emotional arousal control, concentration disruption) and Harm Avoidance according to the TCI (Table 5).

Table 5. Correlation (Pearson's r) between and Sport Performance Psychological Inventory (IPPS), Profile of Mood States (POMS) and Harm Avoidance.

	Correlation	
TCI HA	**Coefficent**	**p-value**
POMS Tension-Anxiety	0.3362	0.0000
POMS Depression-Dejection	0.2451	0.0005
POMS Anger-Hostility	0.2037	0.0038
POMS Vigor-Activity	0.0083	0.9066
POMS Fatigue-Inertia	0.2425	0.0005
POMS Confusion-Bewilderment	-0.0114	0.8728
IPPS Race Preparation	-0.1697	0.0145
IPPS Self-Talk	-0.2438	0.0004
IPPS Cognitive Anxiety	0.2867	0.0000
IPPS Self-Confidence	-0.1316	0.0587
IPPS Goal-Setting	-0.1895	0.0076
IPPS Emotional Arousal Control	-0.2350	0.0010
IPPS Mental Practice	-0.0652	0.3664
IPPS Concentration Disruption	0.1603	0.0256

The results of regression analyses are summarized in Table 6. These analyses indicated that the criteria proposed for mediation by Baron and Kenny were met for a mediating influence of Harm Avoidance on the association between 5-HTTLPR genotype, cognitive anxiety and emotional arousal control as measured with IPPS. To establish the statistical significance of the difference between paths c and c' we used the Baron and Kenny's test as described earlier. The application of this test yielded the following results: the drop of the unstandardized regression coefficient associated with cognitive anxiety in the models without (B = 3.52) and with Harm Avoidance (B = 2.95) (i.e., from c to c') was significant ($p < .05$). The drop of the unstandardized regression coefficient associated with tension/anxiety in the models without (B = 1.95) and with Harm Avoidance (B = 1.48) was not significant ($p > .05$). The drop of the unstandardized regression coefficient associated with emotional arousal control in the models without (B = -1.80) and with Harm Avoidance (B = -1.46) was not significant ($p > .05$).

Table 6. Mediator Effects Using Multiple Regression (Only the outcome variables entering the final model are shown. B = unstandardized regression coefficient; SE = Standard Error; CL: Confidence Limits; β = standardized regression coefficient).

Path c	Coefficient	SE	Beta	t	95% CI		p
Outcome: POMS Tension-Anxiety							
Predictor: 5HTT genotype	1.944855	0.7761444	0.2304045	2.51	0.4070244	3.482686	0.014
Outcome: Cognitive-Anxiety							
Predictor: 5HTT genotype	3.51941	1.013509	0.3068587	3.47	1.512028	5.526793	0.001
Outcome: Arousal-Control							
Predictor: 5HTT genotype	-1.803154	0.7753695	-0.2174181	-2.33	-3.339911	-0.2663971	0.022
Outcome: TCI HA							
Predictor: 5HTT genotype	0.9382362	0.3813286	0.2101683	2.46	0.1838772	1.692595	0.015
Outcome: TCI C							
Predictor: 5HTT genotype	0.7877355	0.4682368	0.1454245	1.68	-0.1385486	1.71402	0.095
Path a							
Outcome: Neuroticism							
Predictor: 5HTT genotype	3.727212	1.047964	0.2967464	3.56	1.654088	5.800336	0.001
Outcome: Extraversion							
Predictor: 5HTT genotype	-1.446591	0.595417	-0.2076437	-2.43	-2.624468	-0.2687145	0.016
Outcome: TCI HA							
Predictor: 5HTT genotype	0.9382362	0.3813286	0.2101683	2.46	0.1838772	1.692595	0.015
Paths b and c							
Outcome: POMS Tension-Anxiety							
Mediator: TCI HA	0.501829	0.1538067	0.2931245	3.26	0.1970507	0.8066073	0.001
Predictor: 5HTT genotype	1.478215	0.7583472	0.1751222	1.95	-.0245005	2.980931	0.054
Outcome: Cognitive-Anxiety							
Mediator: TCI HA	0.611813	0.2037486	0.2614059	3.00	0.2082263	1.0154	0.003
Predictor: 5HTT genotype	2.948995	0.9984416	0.257124	2.95	0.9712742	4.926716	0.004
Outcome: Arousal-Control							
Mediator: TCI HA	-0.4061564	0.160819	-0.2341208	-2.53	-0.7249275	-0.0873852	0.013
Predictor: 5HTT genotype	-1.462933	0.768814	-0.1763954	-1.90	-2.986856	0.0609896	0.060

4. Discussions

The main finding of this study has been proofed by relationship between the serotonin transporter promoter polymorphism (5-HTTLPR), the Harm Avoidance (HA) personality trait, and cognitive anxiety among high level athletes. Particularly, subjects with 5-HTTLPR s genotypes (s/s, s/l) had highest scores for anxiety as measured with POMS, increased scores for cognitive anxiety and concentration disruption, decreased scores for emotional arousal control as assessed with IPPS-48. Additionally, high level athletes with 5-HTTLPR "s" genotype had greater level of HA, as measured by the TCI, than their counterparts with two copies of l allele. Moreover, our findings demonstrated that the HA personality trait mediates the relationship between 5-HTTLPR Genotype and Cognitive Anxiety.

Previous research has suggested a relationship between anxiety personality traits such as neuroticism (N) and anxiety disorders (Caspi et al., 2003; Clarke et al., 2010). Furthermore, studies of the molecular genetic basis of anxiety traits have used both measures of personality traits N and HA with inconsistent results (Munafo et al., 2003, 2009; Schinka et al., 2004; Sen et al., 2004). Although several studies have shown that N is highly related to HA (Zuckerman et al., 1996), there is an evidence that N and HA may not be equivalent (De Fruyt et al., 2006). However, these contrasting results may be explained by inclusing studies in meta-analyses that recruited both healthy subjects and psychiatric patients (Schinka et al., 2004; Sen et al., 2004). Instead, others meta-analyses included studies which recruited only healthy adults (Munafo et al., 2003, 2009). Indeed, the personality traits of pathological people could be confounding factors. Minelli et al. (2011) in the whole sample of 287 volunteers with 5-HTTLPR s/s genotypes, found that were associated with higher scores on HA. In the same study Minelli et al. evidenced the presence of 55 volunteers affected by anxious-depressive syndromes, they evaluated patients and healthy adults separately and they found that significant effects of s/s genotype were lost in healthy adults. In contrast, our study high level athletes with 5-HTTLPR s genotypes had greater level of HA, as measured by the TCI, than their counterparts with two copies of l allele. Although the athletes participating in our study had no history of neurologic, psychiatric disorders, alcohol and other drug dependence disorders they showed differences instead of healthy adults in previous studies, this could be explained by the specificity of the sample consisting of "high level athletes" differentiable from adults healthy or patients.

Moreover, Harm Avoidance (HA), a core personality trait defined by Cloninger (Cloninger et al., 1993), reflects a tendency to the inhibition or cessation of behaviors, passive avoidance, shyness of strangers, and rapid fatigability and, like neuroticism, is related to traits such as pessimism, anxiousness, insecurity (Bey et al., 2017; Naylor et al., 2017). Several studies have

shown a link between personality and outcomes including performance, career success (Judge, 1998). In previous sports-based personality studies, Han et al. (2006) compared groups of winner athletes and loser athletes. The authors reported that losers' athletes scores were significantly higher than winners in HA.

HA is an interesting personality trait to be identified in the sports population as high scores can compromise sports performance and the quality of job satisfaction of high-level athletes with compromised emotional balance. High HA scores on temperamental and character inventory appear to be a risk factor for depressive and anxiety disorders (Saigo et al., 2018). Previous findings suggest that temperament and character may impact anxiety through dysfunctional cognition. Gaweda and Kokoszka (2014) suggest the mediating role of cognitive beliefs in the relationship between HA and symptom of anxiety. In their study HA was related to negative beliefs about uncontrollability of thoughts and to beliefs about cognitive confidence. Further, cognitive anxiety may mediate the relationship between HA and burnout. Gomes et al. (2017) demonstrated in 673 young athletes that cognitive appraisal mediates the relationship between anxiety and burnout. Clinical psychology can intervene about specific characteristics of stressful events, and the role of cognitive appraisal on adaptation to stress. According to prior reports stress seemed to be associated with psychological dysfunction. Cognitive anxiety in young athletes would be a risk factor for both sports performance and drop-outs (Ommundsen & Vaglum, 1992; Robinson & Carron, 1982). Therefore, clinical psychology could help in promoting strategies that can psychologically relieve stress during sports activities.

In the current study, 5-HTTLPR genotype was significantly related to HA and anxiety symptoms. HA was also significantly related to cognitive anxiety and concentration disruption. Finally, when relationship between HA and cognitive anxiety have been checked out, the strength of relationship between 5-HTTLPR genotype and cognitive anxiety has been notably reduced. Particularly our results suggest that the relationship between 5-HTTLPR and symptoms of cognitive anxiety could be partly mediated by HA in high-level athletes.

This is consistent with results of previous studies suggesting that personality trait mediate, at least in part, the relationship between 5-HTTLPR genotype and affective disorders (Petito et al., 2016).

Additionally, the relationship between the 5-HTTLPR "s" genotype to anxiety symptoms and concentration disruption in athletes is not unexpected. This affirmation is rationally given thanks to the findings of our previous studies that showed a significant association between the 5-HTTLPR polymorphism and anxiety and depression disorders (Petito et al., 2016).

5. Limitations

Firstly, our study did not consider a possible mediation of HA even in the healthy sedentary population. Also, the findings presented in this paper only concern subjects without a clinical diagnosis of anxiety disorder. Secondly, the studied sample is composed only of male athletes. Thirdly, from a statistical point of view we have used statistical tests that do not assume the same variance between the groups. Finally, the assessment of the stress level is based solely on the self-report rather than the clinical interview. Despite these limitations, the present study provides proof in regard to the relationship between the 5-HTTLPR s/s genotype and cognitive anxiety and concentration disruption in high-level athletes.

Furthermore, we found that the (HA) personality trait has a significant role in the etiology of anxiety and in particularly of cognitive anxiety. This is an innovative study presenting a new research area and suggesting the direction of further investigation.

6. Conclusions

In conclusion, we have determined a significant association between personality, the presence of the 5-HTTLPR polymorphisms, and the severity of cognitive anxiety among high level athletes. This is an observation that mirrors previous works indicating that same polymorphisms predispose to negative clinical psychological outcomes in presence of stressors. It would be desirable to investigate for future studies, the etiology both mental and physical health disorder by highlighting the combined interaction between genes and environments general risk, linked to genes and specific environments, both related to the disorder (Khan et al., 2005; Leonardo & Hen, 2006).

Clinical psychology could take advantage through the identification of specific genetic and environmental variables in order to prevent or contrast the impairment of sports performance, the manifestation of the athlete's emotional suffering and the risk of sport exhaustion or abandonment.

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any potential conflict of interest.

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