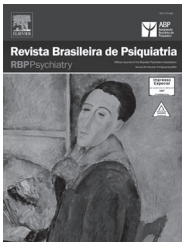
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UPDATE ARTICLE

Temperament and character dimensions and their relationship to major depression and panic disorder

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Abstract
Introduction: Since the first publication of Cloninger´s psychobiological model of personality, the relationship between temperament and character dimensions and psychiatric disorders has been widely studied. The exact nature of this interaction, however, is still unclear. Different models have been proposed (state-dependency, vulnerability, continuous spectrum etc). *Objective:* To analyze the relationship between temperament and character dimensions with depression and panic disorder. *Method:* Systematic review on interventional studies published up until December 2011 on MEDLINE and ISI databases. Also, a brief review on genetic studies is hereby undertaken, aiming to discuss the gene-environment interaction in relation to this topic. *Results:* Thirteen studies were included: 10 related to depression and 3 to panic disorder (or unspecific anxiety symptoms). All of them showed association between high harm avoidance (HA) and low self-directedness (SD) with depression and anxiety symptoms. Longitudinal studies demonstrated that these traits may not be just state-dependent. *Conclusions:* HA and SD dimensions are associated with both the occurrence of depressive and anxiety symptoms. There is also some evidence to suggest that high HA and low SD indicates susceptibility to depression. Longitudinal studies are not sufficient to affirm the same about panic disorder up to the present moment.

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DESCRITORES:
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Dimensões de temperamento e caráter e sua relação com depressão maior e transtorno do pânico

Resumo
Introdução: Desde a primeira publicação do modelo psicobiológico de personalidade de Robert Cloninger, a relação entre as dimensões de temperamento e caráter e transtornos psiquiátricos tem sido amplamente estudada. A natureza exata dessa interação, no entanto, ainda não está totalmente esclarecida. Diferentes modelos foram propostos (estado-dependência, vulnerabilidade, espectro contínuo). *Objetivo:* Analisar a associação entre as dimensões de temperamento e caráter e os diagnósticos de depressão maior e transtorno do pânico. *Método:* Revisão sistemática de estudos de intervenção publicados até dezembro de 2011 nos bancos de dados MEDLINE e ISI. Além disso, foi realizada uma breve revisão de estudos genéticos, visando discutir a interação gene-ambiente em relação a este tópico. *Resultados:* Treze estudos foram incluídos, 10 deles relacionados à depressão e 3 ao transtorno de pânico (ou sintomas inespecíficos de ansiedade). Alta pontuação para a dimensão "evitação de danos" e baixa para "autodiretividade" foram associadas em todos os estudos com sintomas de depressão e ansiedade. Estudos longitudinais demonstraram que estas dimensões de personalidade podem não ser apenas dependentes do estado de humor (estado-dependentes). *Conclusões:* Há evidências consistentes de que "evitação de danos" e "autodiretividade" são dimensões associadas à depressão e ao transtorno do pânico. Existem também evidências que sugerem que a presença destas dimensões de personalidade indicam suscetibilidade à depressão. No entanto, estudos longitudinais ainda não são suficientes para afirmar o mesmo em relação ao transtorno do pânico.

Introduction

According to Cloninger and collaborator's model, personality can be defined as individual differences with respect to the adaptive systems of receiving, processing and storing information and experiences. This psychobiological theory of personality was first formulated in two stages during the late '80s and early '90s (1987 and 1993), when major definitions were proposed. Temperament is understood as the automatic responses to ambient stimuli, which relate to an individual's implicit memory and are associated with neurobiological predispositions. In other words, temperament is related to prelogical emotional processes of associative conditioning. Character, however, represents a more complex cognitive process that is associated with semantics or explicit memory. It is defined as the rational reorganization of perceptions and experiences, which transforms them into concepts, giving them significance.[1]

Four dimensions have been defined for temperament: *harm avoidance, novelty seeking, reward dependence* and *persistence*. Three dimensions of character have also been defined, which include *self-directedness, cooperativeness* and *self-transcendence*. The dimension of temperament called *harm avoidance* (HA) is characterized by anticipated pessimistic concerns with future events, fear of the unknown and shyness with strangers, which leads to avoidance behavior, whereby the individual seeks to stay clear of challenges or involvement in new situations. The dimension of *novelty seeking* (NS), in contrast, is characterized by impulsive behavior, an exploratory search for novelty and pleasure and low tolerance for frustration. In these situations, these individuals may show an explosive attitude with frequent emotional disinhibition. The third dimension of temperament is *reward dependence* (RD), which is characterized by a great fondness for social relationships and the placement of great value by the individual on external approval. These individuals are, in general, more sentimental and more sensitive to offense.[1] For the last dimension of temperament, *persistence* (P), perseverance is the main characteristic and can be described as the tendency not to give up easily on one's objectives. Initially, it was considered a subitem of the previous dimension (*reward dependence*) but was later shown to be a fourth hereditary dimension of temperament to be considered separately.[1,2]

Self-directedness (SD) is the first dimension of character described in Cloninger's classification and is defined as the individual capacity to adapt to different situations that need to be addressed to obtain personal objectives. It also encompasses the potential of committing oneself to these objectives and taking responsibility for one's own actions. The second dimension of character is *cooperativeness* (C), which is the capacity to understand and accept others, in contrast to self-centeredness and hostility. The last one is *self-transcendence* (ST), which is associated with the presence of spirituality, that is, the sentiment of belonging to a unified whole. This involves a state of "unified consciousness" in which everything is part of one totality, leading to acceptance, identification, or spiritual union with nature and its source.[1]

The temperament and character inventory (TCI) was created as an instrument of research with the aim of grouping aspects of personality into a dimensional form by evaluating both temperament and character factors.[1,2]

In 2004, Cloninger revised the psychobiological theory of temperament and character taking into consideration empirical findings and more recent studies, such as functional brain

imaging.[3,4] This current model still considers the temperament and character dimensions described above and adds to these definitions a nonlinear dynamical perspective, where personality is represented as a spiral structure with five layers. These layers were called "planes of being" and are related to a hierarchy of steps over time to allow the survival of progressively more flexible, aware, and creative organisms.[4] They are: sexual plane, material plane, emotional plane, intellectual plane and spiritual plane. These five layers can be decomposed to define 25 "subplanes of being", as each plane deals with one another. The resulting model is a 5x5 matrix where each subplane corresponds to one temperament subscale (Table 1).

As said before, temperament subscales are related to prelogical emotional drives, while character traits are hypothesized to measure the rational cognitive processes and each character subscale also correspond to one of the five layers of personality[4] (Table 2).

At this stage, Cloninger et al. developed a new version of the TCI, the Temperament and Character Inventory-Revised (TCI-R), which has a five-point Likert scale that enables a better evaluation of each dimension subgroup. It also provides subscales for Persistence, which was absent in the scale's first version.[4] The equivalence structure between the two scale versions has already been demonstrated.[5]

Personality traits and psychiatric disorders

Understanding the associations between personality and depression may have important implications for clinical practice. Personality may be useful in identifying more homogeneous subgroups of depressive disorders that differ in developmental trajectories and etiological influences. Temperament and character dimensions may also provide means to identify at-risk individuals who could benefit from prevention and early intervention efforts, as well as be useful in tailoring treatment and predicting treatment response. Finally, personality could help explain patterns of comorbidity and point toward more etiologically relevant classification systems.[6]

There are several models who propose to explain the relationship between personality traits and major psychiatric disorders, such as depression and panic disorder.[6-9] These proposed relations include:

(a) The continuous spectrum model, which considers that personality traits and major psychiatric disorders are epiphenomena of the same process, and the relationship between them is not hierarchical;
(b) The predisposition or vulnerability model in which personality could facilitate the emergence of mental disorders and is, in fact, part of its etiopathogenesis;
(c) The plasticity model that suggests that personality characteristics influence the course and intensity of larger symptoms without any causation;
(d) The concomitants model holds that personality features are state-dependent concomitants of depressive episodes;
(e) The "scar" hypothesis, in which the occurrence of mental disorders, such as PD and depression, could provoke permanent personality alterations.

Table 1 Resulting model: 5x5 matrix with each subplane corresponding to one temperament subscale

Subplane	Sexual plane	Material plane	Emotional plane	Intellectual plane	Spiritual plane
Spiritual plane	shy vs. beguiling (HA3)	exploratory vs. unexcitable (NS1)	attached vs. detached (RD3)	perfectionistic vs. pragmatic (PS4)	Peaceful
Intellectual plane	pessimistic vs. optimistic (HA1)	impulsive vs. rigid (NS2)	sentimental vs. indifferent (RD1)	determined vs. ambivalent (PS2)	Patient
Emotional plane	inhibited vs. uninhibited (HA total)	irritable vs. soic (NS total)	sociable vs. distant (RD total)	persistent vs. impersistent (PS total)	Charitable
Material plane	fearful vs. risk-taking (HA2)	extravagant vs. frugal (NS3)	warm vs. aloof (RD2)	eager effort vs. lazy (PS1)	Respectful
Sexual plane	fatigable vs. vigorous (HA4)	disorderly vs. regimented (NS4)	dependent vs. independent (RD4)	ambitious vs. underachieving (PS3)	Hopeful

HA: harm avoidance; NS: novelty seeking; RD: reward dependence; PS: persistence. Adapted from Cloninger.[4]

Table 2 Maturation in each of the three character dimensions and layers of personality

Character dimension	Characteristics of the sexual layer	Characteristics of the material layer	Characteristics of the emotional layer	Characteristics of the intellectual layer	Characteristics of the spiritual layer
Self-directedness (SD)	responsible vs. irresponsible (SD1)	purposeful vs. aimless (SD2)	exuberant vs. insecure (SD4)	resourceful vs. inadequate (SD3)	spontaneous vs. predetermined (SD5)
Cooperativeness (C)	tolerant vs. prejudiced (C1)	forgiving vs. revengeful (C4)	empathic vs. inconsiderate (C2)	helpful vs. unhelpful (C3)	principled vs. opportunistic (C5)
Self-transcendence (ST)	self-forgetful vs. alienated (pre-logical inaction - categorizing) (ST1)	patient vs. impatient (concrete - abstract logic)	transpersonal vs. avoiding (non-verbal emotive imagery) (ST2)	creative vs. imitative (vocal-archetypal symbols)	spiritual vs. conventional (preverbal holistic schemas) (ST3)

Within each layer of personality, maturation involves increasing each of the three character dimensions. The temperament and character inventory (TCI) subscales predicted to measure these processes are indicated in parentheses. Adapted from Cloninger.[4]

Klein et al,[6] in a recent review on this theme, divided the existing models of the relation between personality and mood disorders into three groups. The first includes the common cause, the continuum/spectrum and the precursor models and view personality and depression as having similar causal influences, but do not see one as having a causal influence on the other. The second group is formed by the predisposition and pathoplasticity models and hold that personality has causal effects on the onset or maintenance of depression. Finally, the third one consists in the concomitants and consequence models affirming that depression may have a causal influence on personality.[6]

In this review study, an evaluation of the relation between depression, panic disorder and Cloninger´s temperament and character dimensions are presented. Based on these results, the models described above are discussed.

Methods

In this article, a systematic review was conducted on PubMed/MEDLINE and ISI databases using the keywords: "temperament", "character", "depression", "panic disorder" and "temperament and character inventory". We found 258 articles related to the theme. Original interventional studies aiming to evaluate the relationship between temperament and character dimensions and depression or anxiety symptoms and panic disorder were included. Studies should use the TCI or TCI-R to measure temperament and character dimensions and had been published in English, up until December 2011. The exclusion criteria were: articles considering other psychiatric disorders as well (such as bipolar disorder), samples consisting of specific populations or patients with a specific subtype of depression (as psychotic depression), studies that were not interventional or not written in English. Studies that used the Tridimensional Personality Questionnaire - the first version of the TCI, created before the integration of the fourth temperament dimension (persistence) - were also excluded.

The dimensions of temperament and character and depressive disorder

The relationship between depressive disorder and temperament and character aspects has been studied since the '90s, initially using the Tridimensional Personality Questionnaire.[10-16] Later, the TCI came to be used, whereby the fourth dimension of temperament - *persistence* - was included. It is important to separate the following studies between those based on clinical[17-20] or student samples[21] from the population-based studies.[22-25] One differs from the others, since it has evaluated a specific teacher sample.[26]

Sectional Studies

In the study by Jylhä et al.,[22] a sample of 900 individuals from the general population were given the Beck Depression Inventory (BDI), the Beck Anxiety Inventory (BAI) and the Temperament and Character Inventory-Revised (TCI-R). Of the 441 respondents, 77.8% did not show signs of depression, 15.2% showed minor depression, 5.3% had moderate depression, and 1.8% had severe depression. The BDI score was positively correlated with HA ($r = 0.555$; $p < 0.001$) and negatively correlated with SD ($r = -0.495$; $p < 0.001$). There were also negative correlations with the dimensions of NS, RD, P and C; however, they were weaker than the others cited above. Another interesting piece of data in this study was the correlation between a record of mental illness in the family with dimensions of temperament (principally HA), but not dimensions of character, such as SD. These data are compatible with Cloninger´s previous theory about the strongest heritability of temperament traits, when compared to character traits.[3] This theory however has been contested and reconsidered by the author, since genetic studies such as Gillespie´s study with twins[27] demonstrated that both temperament and character dimensions can be partially hereditary.

Prior to Jylhä's study, other cross-sectional studies had already been undertaken in student samples, such as the study by Peirson et al.,[21] who were the first authors to use TCI and BDI on a sample of psychology students ($N = 472$). In this study, depression, as assessed by the BDI, was associated with low scores for SD ($r = -0.54$; $p < 0.001$) and C. In this study, depression, as assessed by the BDI, was associated with low scores for SD ($r = -0.26$, $p < 0.001$), as well as with high scores for HA ($r = 0.44$; $p < 0.001$).

Jurado et al.[26] evaluated the presence of depression and TCI dimensions in a 498 sample of teachers in Spain. Symptoms were measured by the Center for Epidemiologic Studies Depression scale (CES-D). Depression was associated with high HA and low SD scores as well as female gender, age, low job satisfaction, high job stress, the wish to change jobs, working at a public school. High NS scores were also associated with depression in this study.

Another interesting cross-sectional study, which was also undertaken in a population-based sample, but which still used an earlier version of the TCI, was from Grucza et al.[23] This study undertook a multidimensional analysis of the personality aspects of patients with depression. The TCI and the CES-D were administered to a sample of 804 community-based individuals. The personality aspects were correlated not only with the total CES-D score but also with differentiated standards of replies in relation to items of this scale. High HA and low RD scores were correlated with the total CES-D score. High scores for the NS dimension were associated with the maintenance of positive affection, an inability to concentrate and previous suicide attempts.

Case-control studies

Three case-control studies were developed to compare temperament and character dimensions in patients with depression and healthy controls.[17-19]

Nery et al.[17] compared 60 patients with DSM-IV depression assessed using the Hamilton Depression Rating Scale to 60 healthy controls. The patients with depression were subdivided into two groups, one group with relevant symptoms at the time of assessment and the other group with depression in remission. TCI was administered to both groups. Significantly higher scores were found for the HA dimensions in patients with active depression than in patients in remission and controls. Patients with depression in remission obtained HA scores closer to healthy controls than patients with active symptoms. Surprisingly, there were greater scores for NS and lower scores for RD in depressed patients when compared

to controls, which was interpreted by the authors as a possible manifestation of bipolar tendencies in these patients. As for character dimensions, there was a lower score for SD in patients with depression. Indeed, the score was as low for patients with active symptoms as for patients who were in remission, with both groups differentiating themselves significantly from the controls. This data suggests that this character dimension was not dependent on the actual mood state.[17]

An interesting study by Smith et al.[18] compared 52 euthymic patients diagnosed with premature recurrent depression (with at least two episodes by the age of 22) with 89 healthy controls matched for age, gender and ethnicity. In this sample, patients were euthymic (i.e., they had already been treated with antidepressant medication) at the time of the exam. TCI was used to evaluate the temperament and character dimensions of both groups, and euthymia was evaluated as a score lower than 9 on the Hamilton depression rating scale. Significantly higher scores were found for HA in the group of euthymic patients when compared to the control group (14.5 versus 7.8, $p < 0.0001$), and significantly lower scores for SD were found in the first group than in the second group (14.1 versus 19.9, $p < 0.0001$). No other significant association was found for other aspects of personality when the two groups were compared; however, there was a tendency toward lower scores in C for the euthymic patients (20.6 versus 22.1, $p < 0.02$) than for controls. Thus, even euthymic patients may continue to have this exacerbated personality trait. The same can be said for low SD. Furthermore, an analysis of covariance showed that HA and SD could be independent risk factors for familial depression, since this sample included patients presenting depression with strong genetic component (premature recurrent depression).

The last case-control study analyzed in this review was from Celikel et al.[19] This study, published in 2009, compared 81 depressed patients with 51 healthy controls and confirmed the association of depression and high HA scores, as well as low SD scores. Furthermore, significantly higher scores on sub-items of the RD (sentimentality and dependency) and ST (spiritual acceptance) dimensions were found in depressed patients in comparison to the controls, while the score for the sub-item attachment (also of the RD dimension) was lower for the patient group than for the controls. The severity of the depressive condition was evaluated using the Hamilton Depression Rating Scale and the Beck Depression Inventory. The duration of depression and the age at which the condition first occurred did not influence the TCI results.

Cohort studies

Cohort studies seek to measure the risk of a specific factor on an outcome. Three studies sought to determine whether aspects of personality constitute risk factors for the development of depression.[20,24,25]

In the most recent study, Farmer et al.[20] obtained a community sample of 591 individuals and administered the TCI and CES-D (Center for Epidemiologic Studies Depression scale). This time point was defined by the authors as "TI". After four years, the CES-D was re-administered to assess the emergence of depression; this time point was defined as "T2". HA was the only aspect of personality that proved to be an independent and significant depression predictive factor. This aspect was associated with higher levels of depression at both TI and T2, indicating a probable phenotypic indicator of a greater frequency of depressive episodes or permanent alterations in mood.

Two other prospective studies found similar results.[24,25] The first was published in 2006 by Cloninger et al.[24] In this study, the authors followed 631 individuals from the general population for one year; they administered the TCI and the CES-D at baseline and at the end of the study. High scores for HA and low scores for SD, as well as high P scores, were aspects of personality considered predictive of the development of major depression. In Elovainio's study,[25] the TCI and BDI were administered to 1,593 subjects at the beginning of the study and after four years. After additional adjustment for all of the temperament dimensions (multivariate model), high HA subscales (shyness with strangers and fatigability), high RD subscale sentimentality, low scores of another RD subscale - attachment - and high persistence were associated with future depression and, thus, still predicted depressive symptoms. All subscales of HA dimension were associated with current depression (Table 3).

Temperament and character dimensions and anxiety disorders: Focus on panic disorder

The relationship between aspects of personality and anxiety disorders was not as widely studied when compared to the relationship of these personality aspects with depressive disorder. However, some studies have been developed aiming to clarify this association. Studies during the 90s show that patients with panic disorder and generalized anxiety disorder had higher HA than individuals without these disorders, even after being treated.[28,29,30]

Cross-sectional studies

Jylhä's[28] cross-sectional study, mentioned previously, evaluated the correlation of anxiety symptoms and temperament and character dimensions, in addition to the correlation between depression and personality aspects in the general population. Apart from the TCI and the BDI, the BAI (Beck Anxiety Inventory) was applied to 900 individuals. In this case, no diagnostic scale for any specific anxiety disorder was applied. The findings were similar to those for depressive symptoms. There was a correlation between anxiety symptoms and high scores for HA ($rs = 0{,}560$, $p < 0.001$) and low scores for SD ($rs = -0.458$; $p < 0.001$). The correlation among other aspects of temperament and character with anxiety symptoms were not as apparent because they were negative for RD, P, NS and C and positive for ST. It is interesting to note that there was a significant correlation between the BDI and BAI scores ($rs = 0.726$; $p < 0.001$).

Case-control studies

In their study, Ball et al.[31] evaluated 120 patients diagnosed with at least one anxiety disorder using DSM-IV criteria and 17 healthy controls. Several scales were administered, including the TCI. All of the patients, independent of a specific anxiety disorder, showed higher scores for HA when compared to the controls. There were no significant differences between the groups for any of the other aspects of temperament or

Table 3 Studies associating depression and temperament and character dimensions

Study	Study design	Sample from	Measure of depression	Current depressive symptoms associated with	Euthimic state (after depression episodes) associated with	Later depressive symptoms associated with
Jylhä et al.[22]	Sectional	General population (N = 900)	BDI	High HA Low SD	N/A	N/A
Peirson et al.[21]	Sectional	Students population (N = 472)	BDI	High HA Low SD Low C	N/A	N/A
Jurado et al.[26]	Sectional	Spanish teachers	CES-D	High HA Low NS Low SD	N/A	N/A
Grucza et al.[23]	Sectional	General population (N = 804)	CES-D	High HA Low RD	N/A	N/A
Nery et al.[17]	Case-control	Clinical sample (N = 120)	HDRS	High HA Low SD	Intermediate HA Low SD	N/A
Smith et al.[18]	Case-control	Clinical sample (N = 141)	HDRS	N/A	High HA Low SD Low C	N/A
Celikel et al.[19]	Case-control	Clinical sample (N = 132)	HDRS BDI	High HA Low SD	N/A	N/A
Farmer et al.[20]	Cohort	Community sample (N = 591)	CES-D	High HA (anticipatory worry, fatigability)	N/A	High HA
Cloninger et al.[24]	Cohort	General population (N = 631)	CES-D	High HA Low SD High P	N/A	High HA
Elovainio et al.[25]	Cohort	General population (N = 1,576)	BDI	High HA (all subscales)	N/A	High HA (shyness, fatigability) High RD (sentimentality) Low RD (attachment) High P

BDI: Beck depression inventory; CES-D: Center for Epidemiological Studies depression scale; HDRS: Hamilton depression rating scale; N/A: Not applicable.

character. While the mean HA score for controls was 0.29, patients with some anxiety disorder had much higher scores. The HA scores for panic disorder, generalized anxiety, social anxiety disorder, and obsessive-compulsive disorder were 0.64, 0.73, 0.64 and 0.65, respectively. The severity of the disorder and the presence of co-morbid depression led to an exacerbation in the differences in HA score, which made it even larger in relation to the controls.

Wachleski et al.[9] compared 135 patients with panic disorder, as assessed by the Mini International Neuropsychiatric Interview (MINI), with 135 controls matched by gender and age. The TCI was administered to both groups. The findings corroborated previous studies in that patients with panic disorder showed higher scores for HA (23.20 ± 5.41 vs. 15.21 ± 4.92; $p < 0.001$) and lower scores for SD (27.81 ± 7.25 vs. 35.16 ± 5.47; $p < 0.001$) (Table 4).

Genetic Aspects

Several studies have analyzed the influence of genetic polymorphisms on temperament and character dimensions in healthy subjects. Not so may, however, have analyzed the relationship of mood and anxiety disorders with temperament and character dimensions considering genetic polymorphisms.

Cloninger's psychobiological model was based on genetic studies and was demonstrated to be associated with hereditary factors.[3] One of the important studies for the development of this model was the twin study of Heath et al.,[32] which demonstrated a 50 to 65% hereditability for the four aspects of temperament.

Studies seeking to identify specific genes associated with these hereditary patterns have been published. In their study, Serretti et al.[33] analyzed 207 euthymic patients affected by unipolar depression (N = 73) and bipolar disorder (N = 134) using the TCI and genotyping via PCR technique. Focus was placed on genes of serotoninergic and dopaminergic systems, which were: dopamine receptor D4 gene (DRD4); serotonin transporter gene (promoter region SERTPR); tryptophan hydroxylase gene (TPH) and monoamine oxidase A gene (MAO-A). Homozygosis for the short SERTPR allele was associated with low novelty-seeking scores ($p = 0.006$) and genotypes containing the DRD4 long allele were associated

Table 4 Studies associating anxiety or panic disorder with temperament and character dimensions

Study	Study design	Sample from	Measure of anxiety / panic symptoms	Current anxiety / panic symptoms associated with
Jylhä et al.[22]	Sectional	General population (N = 900)	BAI	High HA Low SD
Ball et al.[31]	Case-control	Clinical population (N = 137)	Scid I	High HA
Wachleski et al.[9]	Case-control	Clinical population (N = 135)	MINI	High HA Low SD

BAI: Beck anxiety inventory; Scid I: Structured Clinical Interview for the DSM-IV axis I disorders; MINI: Mini International Neuropsychiatric Interview.

with low HA (p = 0.05). Finally, the long MAO-A allele was associated with decreased persistence scores among females (p = 0.006).

Considering healthy subjects, Sen et al.[34] published a meta-analysis reviewing the association of genetic polymorphisms and neurotic traits. The main finding of these studies was the association of the short allele of the 5-HTTLR promoter region, which is related to the transport of serotonin, with this personality aspect (neuroticism). Neuroticism could, in turn, lead to the development of anxiety disorders. However, when the TCI was used to analyze temperament and character dimensions, the association between the variation in the serotonin transporter promoter (5-HTTLPR) and high scores for HA were not statistically significant (p = 0.166). This finding could be due to the small number of studies that used TCI for this analysis or due to publication bias. Another later meta-analysis by Munafò et al.[35] indicated no evidence of significant association of 5-HTTLPR with HA and also suggested a large well-powered primary study to test this hypothesis directly and adequately.[35]

Findings have shown that interactions between allelic variants of the different genes may contribute to personality traits. Kim et al.[36] examined the effects of serotonin transporter-linked promoter region (5-HTTLPR) and dopamine transporter (DAT1) gene polymorphisms for associations with the TCI temperament subscales in 209 Koreans. Variants of 5-HTTLPR interacted with the DAT1 gene polymorphism to influence the HA and RD temperament subscales of TCI. Neither of these two genes affected any subscales of TCI alone. In the presence of the DAT1 10/10 genotype, subjects of group L of 5-HTTLPR had a significantly higher HA score and significantly lower RD score than those of group S (p = 0.03 and p = 0.004, respectively).[36]

Besides serotoninergic and dopaminergic systems, the brain-derived neurotrophic factor (BDNF) has already shown to play a crucial role in depression and anxiety. The 66Met allele has been discovered as a functional variant of the BDNF gene. In a sample of 610 Caucasian participants, subjects homozygous for the 66Met allele scored significantly higher than Val66 allele carriers on anxiety-related facets of harm avoidance ('anticipatory worry' and 'fear of uncertainty').[37]

A recent study tested the individual association of the serotonin transporter gene (SLC6A4), the brain-derived neurotrophic factor gene (BDNF) and the GABA(A) α(6) receptor subunit gene (GABRA6) with anxiety-related traits in 937 individuals from a Spanish healthy sample. Homozygous individuals for the T allele of the T1512C polymorphism presented higher scores for HA than C allele carriers (p = 0.019). In addition, there was a significant gene-gene interaction on HA between the 5-HTTLPR and Val66Met polymorphisms (p = 0.009). Thus, GABRA6 emerges as a candidate gene involved in the variability of HA. The effect of a significant gene-gene interaction between the SLC6A4 and BDNF genes on HA could also explain part of the genetic basis underlying anxiety-related traits.[38]

One mechanism by which genes may affect anxiety-proneness is through altering sensitivity to fear-related stimuli in limbic areas of the brain.[39] Studies of women with X-monosomy (Turner syndrome) have implicated x-linked genes in the mediation of fear recognition and threat detection.[40] One of them was the study by Weiss et al. that reported that variants in the X chromosome gene EF-hand domain containing 2 (*EFHC2)* were associated with differences in fear recognition among women with this condition.[41] *EFHC2* is a novel transcript predicted to contain a calcium-binding domain, which could have diverse neuronal functions related to normal social cognitive competence.[41] Blaya et al.[42] examined whether *EFHC2* variants are also associated with non-syndromic anxiety-related traits such as harm avoidance and panic disorder.[42] With a sample of 127 PD patients and 132 healthy controls, the authors observed evidence of association between a variant in *EFHC2* and HA and PD, but larger studies are still necessary to confirm it.[42]

Another interesting finding recently published by Suchankova et al.[43] is that genetic variability within the S100B gene influences the personality trait self-directedness. S100B is also a calcium binding protein expressed in glia cells. Variations in the S100B gene were recently associated with schizophrenia and bipolar affective disorder and this study shows its relation to this dimension of personality as well.[43]

At last, there is relevant evidence that the function of hypothalamic-pituitary-adrenal (HPA) axis is also involved in the characterization of personality traits. FK506-binding protein 51 (FKBP51 or FKBP5) is a co-chaperone of heat-shock protein 90, and plays an important role in the negative feedback regulation of HPA axis function. Shibuya et al.[44] have evaluated whether C/T single nucleotide polymorphism in the FKBP5 gene affected personality traits in 826 healthy Japanese subjects. In total subjects, the group with the T allele predictive of impaired negative feedback regulation of the HPA axis had higher scores of harm avoidance (HA) and lower scores of cooperativeness (CO) compared to that without the T allele. The T allele was associated with higher scores of HA in females and lower scores of CO in males, suggesting that FKBP5 polymorphism affects HA and CO in healthy subjects, with gender specificity.[44]

Discussion

In this review, great consistency was observed between the analyzed studies referring to the relationship between HA and SD dimensions and depressive disorders, as well as anxiety symptoms and panic disorder. These findings are in line with previous studies.

There is also great consistency in the association of these dimensions of temperament and character between each other. Quite often, HA is negatively associated with SD, which creates a personality standard defined by self-regard, difficulty determining and eventually following through with one's goals and defending one's own values.

It can be said that personality traits are associated with mood state (concomitant model); however, studies have shown that the relationship between personality traits and mood may extend itself beyond. In Smith's study, patients were euthymic and a strongly genetically depressed subgroup; there were higher HA and lower SD scores in depressed patients when compared to controls, even after effective treatment.[18] Thus, either the "scar" model or the continuous spectrum model could be considered here. The first is explained by the presumption that self-concept and self-esteem can be affected by the mood disorder. The last, on the other hand, defends that personality traits are an intermediary phenotype for mood disorders sharing the same biological basis.

The prospective cohort studies by Farmer et al.[20], Cloninger et al.[24] and Elovainio et al.[25] evaluated personality traits before the initiation of the depressive disorder (4 years and 1 year prior, respectively). Due to this particular methodology, it was possible to test and defend the vulnerability hypothesis for the association found. However, more longitudinal studies are needed to confirm this hypothesis.

Although fewer studies have been published concerning anxiety disorders, it shows that similar findings to those for depression could be evidenced. The similarity of temperament and character traits among patients with depression and anxiety, respectively, is in line with the high prevalence of comorbidity between these disorders, apart from the significant symptom overlap between them.

Other temperament and character dimensions also show associations with the development of depression and anxiety disorders; however, these findings were less consistent. Most studies indicated relation between low NS and C scores, as well as high ST scores and the onset of these disorders. However, these personality aspects do not seem to be as predictive as the HA and SD dimensions. The RD temperament dimension yielded contradictory results in different studies; however, the differentiation between this dimension's subscales may justify this contradiction. As described by Elovainio et al.,[25] the subscales *sentimentality* (RD1) and *persistence* (RD2) are positively associated with depression, while *attachment* (RD3) is a subscale that is negatively associated with depression.[25]

Cloninger's psychobiological model[3] has also been tested from a genetic standpoint. Despite the fact that family and twin studies[27,32] have already demonstrated the heritability of temperament and character traits, the genetic polymorphisms that correspond to such phenotypic characteristics have still not been totally clarified. Serotoninergic, dopaminergic and gabaergic systems seem to be associated, and important proteins involved in the regulation of a number of cellular processes such as BDNF and S100B have also been studied. For this reason, future genetic studies are necessary, aiming to better understand the gene-environment interaction in the development of human personality and its relationship with psychiatry disorders.

Recently, studies have been performed to analyze the effect of temperament and character dimensions in treatment response with antidepressants and also the effect of this treatment on the dimensions described above. A meta-analysis by Kampaman et al.[45] showed consistent decrease in HA during treatment and this change was even more clearly associated with treatment response. One important study by Abrams et al.[46] found that higher HA scores predicted less improvement in subjects with dysthymic disorder and major depressive disorder, as determined by less decrease in HDRS-17 scores. In addition, mean HA scores decreased significantly in all depressive-spectrum disorders after treatment, but still remained higher than harm avoidance scores in control subjects. Thus, HA seems to be a reliable predictor of antidepressant treatment in subjects with major depressive disorder and dysthymic disorder. This study also supports that harm avoidance is both trait- and state-dependent in depressive-spectrum disorders.

There are no studies up to this moment analyzing the relation of temperament and character dimensions and treatment response for anxiety disorders.

Conclusion

In conclusion, HA and SD dimension are associated with both the occurrence of depressive and anxiety symptoms. There is also some evidence to suggest that high HA and low SD indicate susceptibility to depression, but more longitudinal studies are needed to confirm this finding as well as to affirm the same about panic disorder.

The study of genetic polymorphisms associated with temperament and character dimensions have also been important in understanding its relationship with psychiatric disorders. Future studies remain necessary.

Further studies considering the influence of personality traits on therapeutic results for mood and anxiety disorders are also essential for the customization of treatment and, consequently, the achievement of better results.

Disclosures

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** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*

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