Review

Neuropsychobiology

Neuropsychobiology 2014;69:175–186
DOI: 10.1159/000360738

Received: July 1, 2013
Accepted after revision: February 19, 2014
Published online: May 16, 2014

Meta-Analysis of Anxiety Disorders and Temperament

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Key Words
Temperament · Temperament and Character Inventory · Harm avoidance · Novelty seeking · Anxiety disorders · Meta-analysis

Abstract
Background: The aims of the present study were to explore whether symptoms in different anxiety disorders are associated with Cloninger's model temperament dimensions novelty seeking (NS), harm avoidance (HA), reward dependence and persistence compared with control subjects in clinical samples of adults or late adolescents. ***Method:*** Literature search in the following databases: Cochrane Library, PubMed (Medline), Web of Science, Psycinfo and PsycArticles. Systematic review, grading the level of evidence and meta-analysis for each disorder by comparing the temperament dimension scores between patient and control samples in single studies. ***Results:*** A total of 40 papers fulfilled the inclusion criteria. Meta-analyses were conducted on a total of 24 studies focusing on panic disorder (PD), social anxiety disorder (SAD) and obsessive-compulsive disorder (OCD). The primary finding was a constant and clinically marked positive association between the HA temperament dimension and symptoms of PD, SAD and OCD, with a most marked effect in SAD, and a moderate effect in OCD and PD. Second, less marked and clinically marginal associations between NS score and SAD and OCD (negative associations), but no associations with PD were observed. The meta-analyses revealed heterogeneity between the results of individual studies, especially in the analyses including SAD and OCD. ***Conclusions:*** PD, SAD and OCD share a marked and state-dependent avoidant behavioral pattern, which is common for all anxiety disorders. However, PD showed a different pattern of arousal to novel stimuli from that of SAD and OCD. The findings are state dependent and based on cross-sectional studies.

Introduction

Anxiety disorders are characterized by fear or anxious distress, or both, and often by avoidant behavior secondary to emotional symptoms [1]. On the other hand, long-lasting fearful or avoidant behavioral patterns may predispose to anxiety disorders [2, 3]. In the current international classification of diseases, separate anxiety disorders have marked overlapping criteria resulting in low specificity and high comorbidity rates [4]. On the other hand,

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genetic endophenotypes [5] with high vulnerability to different anxiety disorders cannot be detected in clinical practice or health screenings, although this early detection could have a preventive function and influence the outcome of these disorders. The dimensional models of personality have added knowledge about the stability and genetic and other neurobiological factors of anxiety-related behavior. In the psychobiological model by Cloninger et al. [6], the personality is divided into temperament and character dimensions. The most commonly used questionnaires within this model are the Tridimensional Personality Questionnaire (TPQ) and its later version, the Temperament and Character Inventory (TCI or revised TCI) [6]. The TCI includes 4 facets of temperament, namely novelty seeking (NS), harm avoidance (HA), reward dependence (RD) and persistence, and 3 facets of character, namely self-directedness, cooperativeness and self-transcendence [6]. HA is the temperament dimension that corresponds to behavioral inhibition in the TCI. In the TPQ, there are 3 temperament dimensions, NS, HA and RD, and the later developed persistence is included in the RD.

There are also some other validated dimensional models of personality. Costa and McCrae [7] developed a 5-factor model (FFM) of personality using the Neuroticism-Extraversion-Openness Inventory (NEO-PI, NEO-PI-R or NEO-FFI) in the assessment of the dimensions. This model includes the dimensions extraversion, agreeableness, conscientiousness, neuroticism and openness to experience, of which the dimensions neuroticism and extraversion are the most extensively studied in relation to genetic variability. A meta-analysis by Kotov et al. [8] showed several types of relationships between symptoms of anxiety disorders and personality traits according to the FFM. Neuroticism was associated with anxiety disorders in general, and more specifically low extraversion was associated with social phobia. In specific phobias, weaker associations were detected with all traits. In Eysenck's model of personality [9], the corresponding dimensions are neuroticism, psychoticism and extraversion. The questionnaire based on this model is the Eysenck Personality Questionnaire (or its revised version). The Temperament Evaluation of the Memphis, Pisa, Paris and San Diego questionnaire model divides temperament into depressive, hyperthymic, cyclothymic and irritable dimensions [10], of which depressive and cyclothymic dimensions are related to high HA, and hyperthymic and cyclothymic dimensions to high NS [11].

The construct within each of these models that corresponds most closely to an anxiety-related trait differs, with Costa and McCrae's FFM and Eysenck's model reflecting a neuroticism construct, and Cloninger's tridimensional theory reflecting an HA construct. The neuroticism construct reflects a tendency to experience negative emotions and interpret situations as threatening [7], whereas the HA construct is defined as avoidance of aversive stimuli, anxiety proneness and an aversion to risk-taking [12]. In his paper on the theoretical background of chronic anxiety, Cloninger postulated that long-term anxiety can be divided into cognitive anxiety with 'obsessional' information-processing type (responding high HA), somatic anxiety with 'histrionic' information-processing type (responding high NS) and social detachment or stability of behavior (responding RD and persistence) dimensions. This classification of anxiety was different from the clinical features identified and the criteria determined for separate anxiety disorders in the DSM-III [12].

Panic disorder (PD) or specific phobias can be more clearly separated from an anxious temperament trait according to the specific symptoms, as well as the typical onset age and stability in the course, whereas social anxiety disorder (SAD) or generalized anxiety disorders (GAD) are much more difficult to distinguish from this trait [13]. Also, a tendency to misinterpret physical sensations as danger signals, which has been determined as anxiety sensitivity trait, has been associated most specifically with PD in a meta-analytic study [14].

According to twin studies, TCI temperament dimensions have shown moderate (RD and persistence) to strong heritability (HA and NS) [15], with RD also sharing some environmental effects [16]. In neurobiological studies trait anxiety, which is characterized by hypervigilance and hyperarousal, can be differentiated from fear, but these two are also overlapping phenomena [17]. High HA has been found to be associated with decreased white matter tract density measures in the areas responsible for emotional processing and reappraisal (corticolimbic pathways) [18]. Studied with functional magnetic resonance imaging (fMRI), the inhibited temperament feature in adulthood has been connected with higher amygdala reactivity to expected fearful faces, which clinically corresponds to anticipatory anxiety and hypervigilance [19]. Also, inhibited behavior in early childhood predicts later bilateral amygdalar hyperreactivity to novel stimuli studied by fMRI [20]. The circuit between amygdala and ventrolateral prefrontal cortex is engaged when threats capture attention [21]. The nucleus accumbens, which is involved in modulating behavioral responses to both re-

warding and aversive events, is activated in an active avoidance pattern rather than with passive avoidance [22]. The connectivity between dorsal and rostral anterior cingulate cortex and anterior insula studied by fMRI without external stimuli also correlates with HA in healthy individuals [23]. Anxiety-related traits in adulthood have also been associated with serotonin transporter gene polymorphism [24] and abnormal cortisol response during stress [25].

Aims of the Study

To systematically examine and expand the current knowledge on underlying temperament-based endophenotypes representing the vulnerability for different anxiety disorders, the study focused on the following question: are symptoms of different anxiety disorders or symptoms occurring at a later stage (during follow-up) associated with the different levels and patterns of temperament dimension (HA, NS, RD or persistence) scores according to the psychobiological model by Cloninger et al. [6]?

Methods

Systematic Literature Review

A literature search was conducted in the databases below on November 5, 2013, using the terms ('temperament' or 'harm avoidance' or 'TCI' or 'TPQ') and ('anxiety disorders' or 'obsessive-compulsive disorder' or 'generalized anxiety disorder' or 'social anxiety disorder' or 'panic disorder' or 'post-traumatic stress disorder' or 'phobic disorders') and limiting the search to peer-reviewed journal articles published in English. The databases were the Cochrane Library, PubMed (Medline), Web of Science, Psycinfo and PsycArticles. The initial search resulted in a total of 1,668 articles.

The inclusion criteria for the papers selected were: using a TPQ/TCI as a temperament measure and focusing on (1) the severity, symptom quality or diagnostic criteria of anxiety disorders classified in the DSM-IV and temperament profiles in adult or late adolescent samples (ages 15 and over). The exclusion criteria were: (1) duplicates and (2) papers reporting other clinical features than those related to classified anxiety disorders despite the assessment of temperament profiles, or studies assessing solely personality profiles in relation to anxiety disorders. Reports on studies using identical samples were considered as single studies in the analyses. However, as all the results reported in different papers using the same samples were explored, the final number of papers included was greater than the number of studies. Publications with a similar focus according to reference lists of selected papers were also searched. During the selection phase, in cases of initial disagreement a final consensus was reached after discussion between at least 2 researchers. The quality of the evidence in individual studies was graded according to the GRADE workgroup recommendation by 2 or more researchers [26].

Statistical Methods

The selected 40 papers were analyzed according to the results reported in each paper. The levels of temperament dimension scores (NS, HA, RD and persistence) were compared in each anxiety disorder – PD, GAD, SAD, obsessive-compulsive disorder (OCD) and posttraumatic stress disorder (PTSD) – with the corresponding scores in control groups in each study. We conducted meta-analyses for each temperament dimension (NS, HA, RD and persistence) in PD, SAD and OCD studies, which comprised at least 5 studies with a control group and including the available TCI or TPQ data (tables 1–5). The TPQ dimensional scores were converted into TCI scores according to the results from Finnish normative data [27, 28] and the reported persistence subscale scores were used in analyses with TPQ studies. The meta-analyses were calculated with MIX Pro software (version 2.0 [29]) using the fixed effects model and inverse variance as a weighting method, and using age as a covariate. The analyses using age as a covariate yielded results similar to those without this covariate. Due to heterogeneity in gender distributions between patient and control groups in studies on SAD, gender was also used as a covariate, but the results were similar to those without this covariate. Therefore, only the latter analyses (without age or gender correction) are reported. The gender distributions had only minor differences in PD and OCD studies, and therefore no analyses with gender correction were conducted on these disorders. The random effects model was also tested in samples with heterogeneity levels >80% (HA in PD and OCD, NS in SAD, RD in OCD and persistence in SAD and OCD), but this model produced results similar to those yielded by the fixed effects model. The results of the meta-analyses are presented as mean differences between patient and control sample scores for each temperament dimension (positive values indicate higher patient scores than scores of controls) with 95% confidence intervals. Heterogeneity testing between individual studies in each analysis was calculated by I^2 statistics with confidence intervals (table 6). The magnitude of clinical significance (effect size) in individual findings was estimated as Cohen's d (mean difference between patient and control groups divided by the standard deviation of the data), and the level of clinical significance was set at d >0.4.

Results

A hundred and forty-one papers were further selected for thorough reading on the basis of the information in the article title and/or abstract. The final selection agreed on by 2 or more investigators comprised 40 papers reporting 38 different studies (in 2 cases different results from the same sample were reported in 2 different papers). Of these papers, the temperament dimension scores for patient and control groups had been reported as mean and standard deviation values in 24 papers, and these were included in the meta-analyses (fig. 1). All papers included concerned prospective studies. Twelve of the 40 papers selected focused on PD (table 1), with 2 of the studies including 2 different reports, 4 on GAD (table 2), with 1 of the studies including both PD and GAD groups,

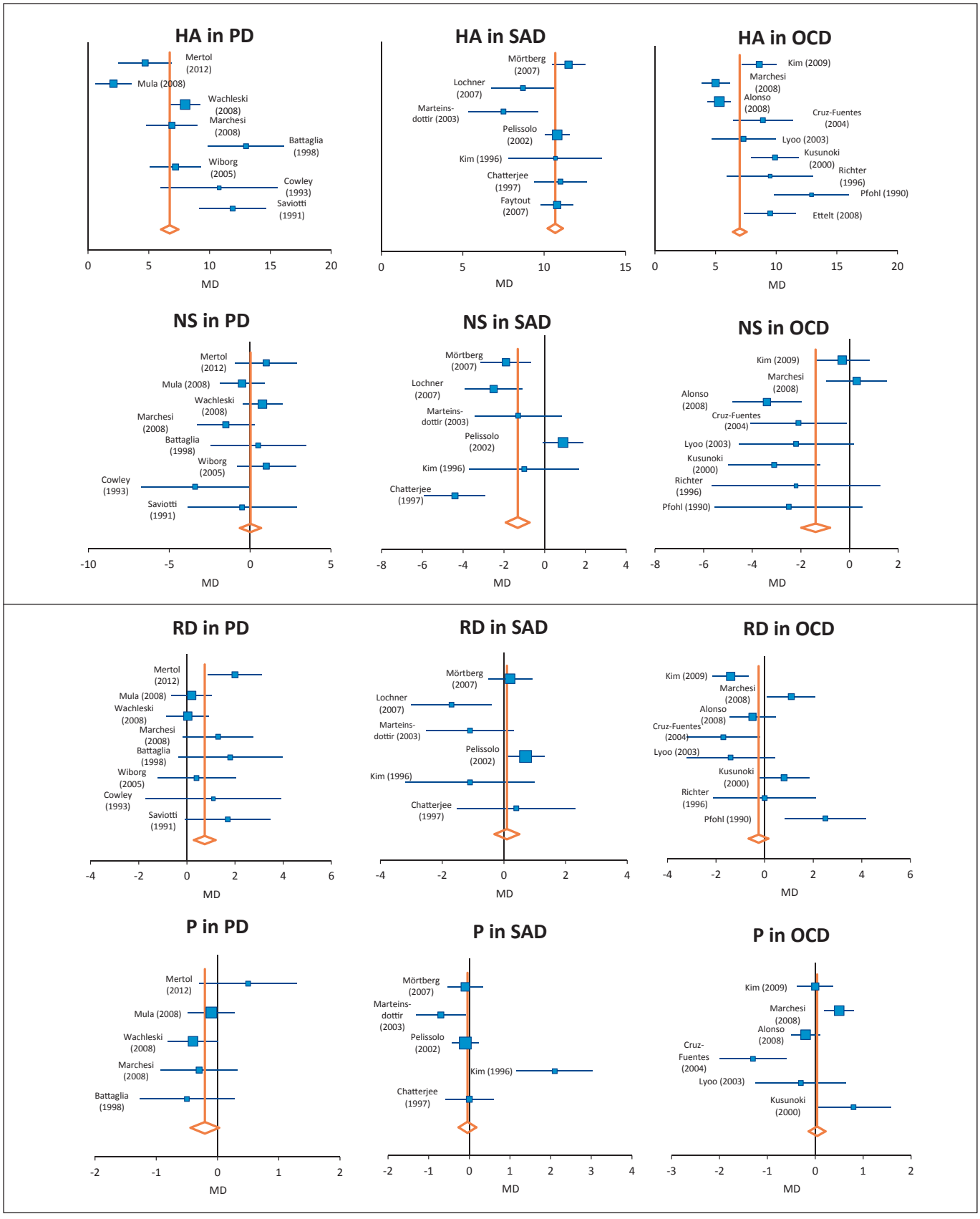

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Table 1. Studies focusing on the relationship between temperament and PD

Study	Sample	Mean age, years	n	Measure of anxiety disorder and symptoms	Measure of temperament	Follow-up	Level of evidence and study limitations	Current symptoms of PD associated with	Later symptoms of PD associated with
Mertol and Alkin [30], 2012	Turkish outpatients	NR	44	SCID	TCI	CS	Low; small sample	High HA, high RD	
Mula et al. [31], 2008	Italian euthymic patients with BD or UD	46.2	50	SCID-I	TCI-R	CS	Low; small sample, selected population	High HA	
Wachleski et al. [32], 2008	Brasilian outpatients	38.1	135	MINI; CGI; PI; HAM-A	TCI	CS	Low; selected controls	High HA	
Marchesi et al. [33], 2008	Italian outpatients	35.4	65	DSM-IV; SCL-90; HAM-D; HAM-A	TCI	1 year (treatment with paroxetine or citalopram)	Low; high number of dropouts, small sample, short follow-up	High HA, low P	High HA
Marchesi et al. [34], 2006	Italian outpatients	35.4	71	DSM-IV; SCL-90; HAM-D; HAM-A	TCI	1 year (treatment with paroxetine or citalopram)	Low; high number of dropouts, small sample, short follow-up	High HA, low P	
Wiborg et al. [35], 2005	Norwegian outpatients	31.6	43	DSM-III-R, SCID-I	TPQ	CS	Low; small sample	High HA	
Ampollini et al. [36], 1999	Italian outpatients	31.4	42	DSM-III-R	TPQ	CS	Low; small sample	High HA, high RD	
Battaglia et al. [37], 1998	Italian female outpatients	34.5	41	DSM-III-R, AA of PASS	TPQ	CS	Low; small sample	High HA, low RD	
Starcevic et al. [38], 1996	Outpatients who were recruited for drug studies in the USA	36.56	32	DSM-III-R	TPQ	CS	Low; selected sample	High HA, high NS, high RD (men), low RD (women)	
Starcevic and Uhlenhuth [39], 1996	Outpatients who were recruited for drug studies in the USA	40.73	42	DSM-III-R	TPQ	8 weeks of alprazolam treatment	Low; selected sample, no control group	High HA	High HA
Cowley et al. [40], 1993	North American patients	30.8	18	DSM-III-R	TPQ	CS	Low; small sample	High HA	
Saviotti et al. [41], 1991	Italian outpatients recovered from PD	30.7	33	DSM-III-R	TPQ	CS	Low; small sample	High HA	

NR = Not reported; BD = bipolar depression; UD = unipolar depression; SCID = Structured Clinical Interview for DSM-IV (or DSM-III-R); MINI = Mini International Neuropsychiatric Interview; CGI = Clinical Global Impression; PI = Panic Inventory; HAM-A = Hamilton Anxiety Scale; SCL-90 = Symptoms Check List-90; HAM-D = Hamilton Depression Scale; AA of PASS = Anticipatory Anxiety subscale of the Panic-Associated Symptoms Score; CS = cross-sectional study; P = persistence.

Fig. 1. Forest plots of HA, NS, RD and persistence (P) scores in PD, SAD and OCD. The results are presented as mean differences (md) between the corresponding patient and control groups. Square dots and horizontal lines represent the weight and 95% confidence intervals of individual studies. The vertical lines represent the overall result of meta-analysis. Names of first authors refer to the following references: Mertol [30], Mula [31], Wachleski [32], Marchesi [33], Battaglia [37], Wiborg [35], Cowley [40], Saviotti [41], Mörtberg [45], Lochner [46], Marteinsdottir [49], Pelissolo [50], Kim (1996) [51], Chatterjee [52], Faytout [47], Kim (2009) [53], Alonso [57], Cruz-Fuentes [58], Lyoo [59], Kusunoki [61], Richter [62], Pfohl [63], Ettelt [56].

Table 2. Studies focusing on the relationship between temperament and GAD

Study	Sample	Mean age, years	n	Measure of anxiety disorder and symptoms	Measure of temperament	Follow-up	Level of evidence and study limitations	Current symptoms of GAD associated with	Later symptoms of GAD associated with
Piero [42], 2010	Italian outpatients	37.4	79	DSM-IV-TR, CGI, BIS-11	TCI	CS	Low; no control group	High NS, low RD (impulsiveness in GAD)	
Rettew et al. [43], 2006	North American parents of children with behavior problems	40.5	231	VSDI	TCI	CS	Moderate; selected sample	High HA	
Allgulander et al. [44], 1998	Swedish symptomatic volunteers	NR	29	DSM-IV	TCI	6 months	Low; no control group	NR	High HA
Starcevic et al. [38], 1996	American outpatients	43.7	49	DSM-III-R	TPQ	CS	Low; selected sample	High HA, low RD	

NR = Not reported; CGI = Clinical Global Impression; BIS-11 = Barratt Impulsiveness Scale, version 11; VSDI = Vermont Structured Diagnostic Interview; CS = cross-sectional study.

Table 3. Studies focusing on the relationship between temperament and SAD

Study	Sample	Mean age, years	n	Measure of anxiety disorder and symptoms	Measure of temperament	Follow-up	Level of evidence and study limitations	Current symptoms of social phobia associated with	Later symptoms of social phobia associated with
Mörtberg et al. [45], 2007	Swedish outpatients	34.9	100	SCID	TCI	1 year	High	High HA, low NS	Treatment response associated with lower HA
Lochner et al. [46], 2007	South African outpatients	35.2	63	SCID; SPIN	TCI	CS	Low	High HA, low NS	
Faytout et al. [47], 2007	French outpatients	34	157	CIDI; MINI; LSAS	TCI	24 months	Moderate; no control group	High HA	High baseline HA
Hofmann and Loh [48], 2006	American outpatients	31.3	47	ADIS; SPAI	TPQ	12 weeks	Very low; no control group		Positive correlation between pre-post change in HA and social anxiety
Marteinsdottir et al. [49], 2003	Swedish outpatients	33.5	31	SCID; SPSQ; SPS; SIAS	TCI	CS	Very low; historical controls	High HA, low P	
Pelissolo et al. [50], 2002	French outpatients	34.3	178	M-CIDI	TCI	CS	Moderate; historical controls	High HA	
Kim and Hoover [51], 1996	American outpatients	42	47	SCID; DBSPS	TPQ	CS	Low	High HA	
Chatterjee et al. [52], 1997	Indian outpatients	26.8	20	FNE; SAD	TCI	CS	Very low; small sample	High HA, low NS	

SCID = Structured Clinical Interview for DSM-IV (or DSM-III-R); SPIN = Social Phobia Inventory; (M)-CIDI = (social phobia module of) Composite International Diagnostic Interview; MINI = Mini International Neuropsychiatric Interview; LSAS = Liebowitz Social Anxiety Scale; ADIS = Anxiety Disorders Interview Schedule; SPAI = Social Phobia and Anxiety Inventory; SPSQ = Social Screening Phobia Questionnaire; SPS = Social Phobia Scale; SIAS = Social Anxiety Interaction Scale; DBSPS = Duke Brief Social Phobia Scale; FNE = Fear of Negative Evaluation Scale; SAD = Social Avoidance and Distress Scale; CS = cross-sectional study; P = persistence.

Table 4. Studies focusing on the relationship between temperament and OCD

Study	Sample	Mean age, years	n	Measure of anxiety disorder and symptoms	Measure of temperament	Follow-up	Level of evidence and study limitations	Current symptoms of OCD associated with	Later symptoms of OCD associated with
Kim et al. [53], 2009	South Korean OCD hospital patients	35.0	130	Y-BOCS	TCI	CS	Moderate	High HA, low RD	
Marchesi et al. [54], 2008	Italian high school students	17.4	119	LOI-CV	TPQ	CS	High	NS, HA and P (egodystonic symptoms)	
Corchs et al. [55], 2008	Brazilian OCD patients	39.6	99	SCID-I/P, Y-BOCS	TCI	CS	Low; no control group	High HA	
Ettelt et al. [56], 2008	German OCD patients	37.7	75	SADS-LA-IV	TPQ	CS	Moderate	High HA	
Alonso et al. [57], 2008	Spanish OCD patients	31.8	60	SCID–CV, Y-BOCS	TCI	CS	Low	High HA and low NS	
Cruz-Fuentes et al. [58], 2004	Mexican OCD patients	33.0	54	DIS, Y-BOCS	TCI	CS	Low	High HA and low P	
Lyoo et al. [59], 2001	South Korean OCD patients	28.9	40	SCID, DIPD, Y-BOCS	TCI	CS	Low; small sample	High HA	
Lyoo et al. [60], 2003	South Korean OCD patients	28.9	35	SCID, DIPD, Y-BOCS	TCI	4 months	Low; small sample	High HA	Posttreatment HA higher in patient group
Kusunoki et al. [61], 2000	Japanese OCD patients	35.3	43	Y-BOCS	TCI	CS	Very low; small sample	High HA and low NS	
Richter et al. [62], 1996	Canadian OCD patients	33.6	32	SADS-LA, Y-BOCS	TPQ	CS	Very low; small sample	High HA	
Pfohl et al. [63], 1990	American OCD patients	37.9	25		TPQ	CS	Very low; small sample	High HA, high RD	

Y-BOCS = Yale-Brown Obsessive Compulsive Scale; LOI-CV = Leyton Obsessive Inventory, child version; SCID = Structured Clinical Interview for DSM disorders; SADS-LA = Schedule for Affective Disorders and Schizophrenia lifetime version; DIS = Diagnostic Interview Schedule; DIPD = Diagnostic Interview for Personality Disorders; CS = cross-sectional study; P = persistence.

8 on SAD (table 3), 11 on OCD (table 4), with 1 of the studies including 2 different reports, and 6 on PTSD (table 5). No papers on simple phobia with a selected focus were found.

The findings of the meta-analyses were (1) a definite and clear positive association between HA temperament dimension and the occurrence of PD, SAD and OCD, with a most marked effect in SAD, and a moderate effect in OCD and PD, (2) less remarkable and clinically marginal negative associations between NS score, SAD and OCD, (3) a positive, but clinically insignificant association between RD score in PD, and (4) no associations between RD score and other anxiety disorders studied or between persistence scores in any of the disorders studied.

The results of the meta-analyses of the PD, SAD and OCD studies with each temperament dimension are presented in table 6 and forest plots for each temperament dimension in these disorders in figure 1. Three out of 4 GAD studies reported a positive association between HA and current or subsequent GAD symptoms (table 2). All 6 PTSD studies reported a positive association between symptoms and HA, 3 studies reported a positive association with NS, and the same 3 studies also reported a negative association with RD (table 5).

Discussion

The purpose of this meta-analysis was to test for differences in self-rating scores on the temperament dimensions of the Cloninger test in different anxiety disorders. The method of analyzing the differences in temperament dimensions between patients and control subjects aimed

Table 5. Studies focusing on the relationship between temperament and PTSD

Study	Sample	Mean age, years	n	Measure of anxiety disorder and symptoms	Measure of temperament	Follow-up	Level of evidence and study limitations	Current symptoms of PTSD associated with
North et al. [64], 2012	American PTSD patients	43	151	DIS/DS	TCI	CS	Moderate	High HA
Yoon et al. [65], 2009	Korean psychiatric outpatients	29	65	IES-R, HARS	TCI	CS	Low	High HA
Gil and Caspi [66], 2006	Israeli undergraduate students with PTSD	23	31	SCID	TPQ	1 month	Low; small sample	High HA and low NS
Richman and Frueh [67], 1997	American war veterans with PTSD	45	53	CAPS, M-PTSD, MMPI-2-PK	TPQ	CS	Very low	High HA, high NS, low RD
Wang et al. [68], 1997	American war veterans with PTSD	42	27	SCID, CAPS, M-PTSD, CES	TPQ	CS	Very low; small sample	High HA, high NS, low RD
Kotler et al. [69], 1996	Israeli outpatients	41	46	CGI	TPQ	CS	Very low	High HA, high NS, low RD

DIS/DS = Diagnostic Interview Schedule/Disaster Supplement; IES-R = Impact of Events Scale-Revised; HARS = Hamilton Anxiety Rating Scale; CAPS = Clinician-Administered PTSD Scale; M-PTSD = Mississippi Scale for Combat-Related PTSD; CES = Combat Exposure Scale; MMPI-2-PK = Keane PTSD scale of the Minnesota Multiphasic Personality Inventory-2; CGI = Clinical Global Impression; CS = cross-sectional study.

Table 6. Meta-analysis (Z scores and p values for mean differences between patient and control groups, and corresponding Cohen's d for analyses with $p < 0.05$) and heterogeneity (I^2 with confidence intervals CI– and CI+) between individual studies in meta-analyses in different diagnostic groups and temperament dimensions

	PD						SAD						OCD					
	Z	p	d	I^2, %	CI–	CI+	Z	p	d	I^2, %	CI–	CI+	Z	p	d	I^2, %	CI–	CI+
HA	18.8	0	1.26	90.76	84.21	94.60	45.16	0	1.79	60.64	9.85	82.82	24.72	0	1.32	86.60	76.58	92.34
NS	0.070	0.94		36.54	0	71.96	–4.46	8.0×10^{-6}	0.27	87.18	74.43	93.57	–4.62	3.8×10^{-6}	0.30	70.00	37.64	85.56
RD	3.26	0.001	0.17	39.96	0	73.49	0.48	0.63		67.29	22.24	86.24	–1.22	0.22		80.59	62.53	89.94
P	–1.74	0.08		16.68	0	82.67	–0.17	0.87		83.74	63.28	92.80	0.44	0.66		82.73	63.56	91.82

P = Persistence

at investigating the possible genetic influence of each disorder studied. This may both help to differentiate the vulnerability factors between and within the disorders studied and also to generate further hypotheses and to determine more suitable phenotype markers for future genetic studies. Also, the high comorbidity rates between anxiety disorders [4] imply that the present classification of these disorders is still far from specific, but rather represents a historical paradigm of recognizing and clustering the different symptoms of anxiety. The temperament dimensions determined in the psychobiological model of Cloninger et al. [6] reflect the various immediate and long-term forms of individuals' automatic reactions forming the basis for human behavior, including sensitivity to anxious reactions regarded as the vulnerability factor for the subsequent development of clinical anxiety disorders.

When analyzing the quality of individual studies, we focused on the criteria of sample selection, follow-up time and rates of missing data [26]. The level of evidence remained moderate to low in many of the studies selected. This was most commonly due to small sample size, cross-sectional designs and in 6 studies to an absence of control groups. Four of the studies with no control group addressed the three disorders (PD, SAD or OCD) and on these there were indeed sufficient eligible studies to permit meta-analysis. In the cases of GAD and PTSD, the number of eligible studies was too low for meta-analysis, and only descriptive analyses were feasible for these dis-

orders. No studies on simple phobias were found for this review.

There was heterogeneity in the results on all temperament dimensions, and this was especially common in the analyses of SAD and OCD. This may be due to variation in sample selection, the small number of subjects in many of the studies, and other issues related to study design. Many of the studies included also used TPQ as the assessment instrument, and although the conversion into TCI scores was based on Finnish normative data [27, 28], the different structures of the two scales as regards RD may explain some of the heterogeneity found, especially between SAD and OCD, but not between PD studies. The finding is even more likely due to the wide individual variation in the assessment of temperament regarding separate dimensions and their subscales, as well as the wide individual variation in anxiety disorder symptomatology. The fixed effects method was preferred in the meta-analysis assuming that the same outcome measure (TCI) in all studies included and similar inclusion criteria for the patient samples within each diagnosis would yield a reliable analysis with this particular method. To ensure this, the alternative random effects method was tested with the groups of studies showing the most marked heterogeneity, and the results were comparable with the fixed effects method analyses. There was also some heterogeneity between studies in the age and sex distributions. Age was not found to be a markedly confounding factor in an earlier meta-analysis of temperament and gender differences [70]. The present meta-analyses yielded similar results regardless of the covariation of sample age or without this variable, which supports the earlier result. Likewise, the covariance of gender was not significant even in the studies of SAD, where the variation in gender distributions between patient and control groups was more marked in contrast to PD and OCD studies, which had only little variation in gender ratios between patient and control groups. Also, most of the selected studies in the meta-analyses had age- and gender-matched control groups or, if not, the control groups represented epidemiological samples. It is, however, possible that some of the heterogeneity in the results is attributed to the differences in age or sex distributions in patient and control samples in individual studies.

When considering the overall level of evidence and the clinical effects of findings on each temperament dimension and in distinct disorders (PD, SAD and OCD), the differences between the patient samples and controls were found to be most marked in HA scores in all these disorders. The clinical effect in HA was large in SAD and moderate in PD and OCD. In all three disorders the association between HA score and the disorder was positive. With NS scores there was no association in PD, and a negative association in SAD and OCD. However, the mean differences in NS between patients and controls even in SAD and OCD were not clinically significant. With RD scores, only PD was positively associated, but this difference likewise yielded no clinical effect. In SAD and OCD no associations were found. The persistence scores revealed no differences in any of the disorders between patients and controls. Although most of the studies selected were of limited samples, and there was some heterogeneity in the results, almost all studies included (except 2/8 PD studies) showed significant differences in HA between patients and controls, and the level of evidence with increase in the HA scores can be considered high in all three disorders. When evaluating the temperament profiles including HA, NS and RD temperament dimensions in each disorder analyzed, PD showed a pattern of high HA/moderate NS/high RD, SAD a very high HA/low NS/moderate RD, and OCD a high HA/low NS/moderate RD.

The finding of increased HA in anxiety disorders corresponds to a finding observed earlier in major depression and with depressive symptoms in general samples [71]. There are several possible explanations for the relationship in these two categories, namely the common genetic background related to the neurobiological regulation of emotions and stress, overlapping in the clinical picture, which may explain the high comorbidity rates, and similar stress-induced changes in automatic behavioral reaction patterns associated with the clinical state in both disorder groups. With NS the distinct anxiety disorders resulted in varying profiles, with an unchanged score in PD compared to controls, but a lower score in SAD and OCD. Although the effect size of these changes was below clinical significance, it may be interpreted to corroborate the earlier conclusion on classifying different profiles of anxiety disorders as regards the axis fear versus distress [72]. The unchanged NS in relation to the high HA score, as represented solely in PD, could reflect the positive association found earlier between both NS and HA, and extraversion of NEO-PI on sympaticotonic bodily symptoms [73], which are the core feature in PD. Conversely, as Wu et al. [74] confirmed among some earlier studies, the extraversion dimension of the NEO-PI scale was found to be lower in OCD patients than in controls, which may reflect the affective nature being of the distress type more than of the fear type in this disorder. In clinical practice this disorder is characterized by ruminating

thoughts that in many cases have a very limited thematic content, but it often leads to poor functioning and social isolation. The descriptive analysis of the results of GAD revealed an inconclusive association with the HA trait only. As GAD is a chronic disorder with a potentially stronger association with trait aspects, the relationship of this disorder with temperament is undoubtedly an important topic for future studies. In comparison to the present findings regarding HA and NS, Jylhä et al. [75] recently reported high NS to be associated with cluster B and high HA levels with cluster C personality disorders, which concurs with the earlier reported specificity of personality clusters and temperament, that also includes the association with low RD and cluster A personality disorders [76]. In patients with bipolar disorder, high HA and low persistence dimensional scores have been found in several studies, whereas the findings for NS and RD have been contradictory [77]. All in all, when considering the findings both in affective disorders and in the present study, these disorders can also be seen as dimensions on which scores in the normal populations represent, perhaps, milder forms of psychopathological symptoms.

The possible genetic, neurobiological and associative learning-related mechanisms predisposing to different forms of anxiety disorders involve (1) the genetic risk factors related to functions of the hippocampus and prefrontal cortex, (2) hyperreactivity in the amygdala and learned avoidant behavioral pattern in childhood leading to negative emotionally biased episodic memory functioning, (3) alertness towards threat-associated stimuli, and (4) continued learned avoidant behavior in adulthood. The present findings on temperament dimensions reflect the anxiety-state-dependent signs, symptoms, attitudes and beliefs as only a small minority of the studies involving a longitudinal perspective. This prevents reliable causal interpretations. Thus, according to these results, no assumptions on trait-dependent changes in temperament can be made. The low consistence and relationship of the disorders with RD are probably also due to the lack of true comparability between the RD scale in the TPQ and TCI. Moreover, the meta-analytic procedure has several limitations [78]. Due to the low to moderate level of evidence in the majority of individual studies, the results of this analysis should be interpreted with caution.

This review was focused solely on TPQ and TCI assessments. A comparison with the FFM has shown moderate correlations between the corresponding dimensions in the two models, but mainly a marked inconsistency [79]. Kotov et al. [8] conducted a meta-analysis of the FFM and anxiety disorders. Their results corroborated the present HA findings, suggesting heightened neuroticism scores with very high effect sizes in PD, SAD and OCD. With extraversion scores, the finding was somewhat different from the present study, showing lowered extraversion scores in all 3 disorders with high effect sizes. The inconsistent results are likely to reflect the diverging concepts between FFM and Cloninger's models [79].

In conclusion, PD, SAD and OCD share a marked and state-dependent avoidant behavioral pattern. However, PD showed a slightly different pattern of arousal to novel stimuli from SAD and OCD, which may partly explain the different course and clinical picture of these disorders.

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