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Title	Affective temperaments in anorexia nervosa: the relevance of depressive and anxious traits
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Abstract

Background: Affective temperaments have been so far understudied in anorexia nervosa (AN) despite the relevance of personality and both affective and anxious comorbidity with regard to vulnerability, course, and outcome of this deadly disorder. Methods: Ninety-eight female inpatients diagnosed with AN and 131 healthy controls (HCs) were enrolled in this study and completed the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) in addition to assessments of eating psychopathology, depression, and anxiety. Results: AN patients and HCs differed in all affective temperaments. The diagnostic subtypes of AN differed as well with binge-purging individuals being more cyclothymic and anxious than those with restricting-type AN. TEMPS-A scores correlated with body mass index and eating psychopathology but not with duration of illness. Concerning comorbidity, grater scores on the depressive and lower scores on the hyperthymic temperaments were found in depressed patients. Those who had either an anxious or irritable temperament were significantly more diagnosed with an anxious disorder than those who did not show this temperament. When logistic regression was performed, high depressive/low hyperthymic and high irritable/anxious traits resulted to be associated with depressive and anxious comorbidity, respectively, independently of confounding factors. Limitations: Cross-sectional design, some patients on medications, few baseline clinical differences between diagnostic subtypes, no other personality assessments. Conclusions: An affective continuum strongly associated with mood and anxious comorbidity emerged in AN. Such an evaluation could have several research and clinical implications given the need of improving treatment individualization and early interventions for such a complex disorder.

Keywords	anorexia nervosa; affective temperaments; comorbidity; anxiety; depression
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Turin, 9th April 2017

Dear Professor Soares,

Please find attached the revised version of our manuscript “Affective temperaments in anorexia nervosa: the relevance of depressive and anxious traits”. We are grateful for your and the reviewer’s evaluation of our paper. Without a doubt the paper is now clearer and the reviewer’s suggestions have helped us to improve the quality of the manuscript.

We have highlighted with colored text how we addressed the points raised by the reviewer. A point-by-point letter is also provided.

Best regards,
Prof. Giovanni Abbate-Daga

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Authors' disclosure

Contributors

GAD and EM conceived and designed this study; EM and FA critically revised the literature; EM and GAD led the data acquisition and analysis; SF and FA have made substantial contributions to interpret the data; EM and FA drafted the manuscript and SF and GAD revised it critically. All authors read and approved the final manuscript.

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Conflicts of interest

All authors have no conflicts of interest to declare.

With the paper entitled “Affective temperaments in anorexia nervosa: the relevance of depressive and anxious traits” the Authors aimed to verify whether AN patients (and variants) and healthy controls differ with respect to affective temperaments, and to assess differences in affective temperaments among those patients with anxious or depressive comorbid disorders. This is an interesting topic as affective temperaments have been understudied in anorexia nervosa so far.

The state-of-the-art is well described, research methodology is sound, and clinical implications are widely discussed.

Thank you for your positive comments.

This paper can be further improved as follows:

- Please provide a more detailed characterization of those cases affected by anxiety disorders. The Authors mentioned “generalized anxiety disorder, panic disorder, and social phobia” but the proportions for each diagnosis are not reported.

Thank you for pointing this out. We added to the text the following sentence: “The latter diagnoses were distributed as follows: social phobia (n=21, 43%), specific phobia (n=8, 16.3%), agoraphobia (n=3, 6.1%), panic disorder (n=10, 20.4%), and generalized anxiety disorder, (n=7, 14.2%). Three patients were affected by obsessive compulsive disorder and none met criteria for bipolar disorders”.

- The presence/absence of bipolar patients should be pointed out .

Thank you for helping us clarify this issue: although this was not an exclusion criterion, none was affected by bipolar disorders. We have now specified this in our paper.

- The study by Ramacciotti et al (2004) should be considered and discussed in the light of these findings.

We touched upon that paper more in the current version of our work, thank you. “AN patients were found to markedly differ from HCs with regard to temperament traits and this is in line with previous literature on personality (Fassino et al., 2002; Wagner et al., 2006; Atiye et al., 2016) although in part differing from earlier research using the TEMPS-I (Ramacciotti et al., 2004). In particular, AN patients were reported to be more likely to have more depressed, cyclothymic, irritable, and anxious temperament traits than HCs and less marked hyperthymic traits. The larger sample size of this work, when compared to earlier investigations of AN (Ramacciotti et al., 2004) could account for the significant differences we found in the AN sample. With more detail, Ramacciotti and collaborators (2004) analyzed only 16 R-AN individuals and used a different instrument (i.e., TEMPS-I). The latter on one hand did not consider the anxious temperament and on the other hand adopted a categorical scoring thus hindering a coherent comparison of the findings. Notwithstanding, in line with that investigation (Ramacciotti et al., 2004) we also found differences between restricting and bulimic variants”.

- Some more detailed information about medications treatment should be provided. In order to clarify this issue we added the following: “The majority of patients were on medications (n=75, 76.5%), mostly selective serotonin reuptake inhibitors. Some patients (n=23, 23.5%) were on atypical antipsychotics as well as augmentation therapy as proposed by recent literature (Marzola et al., 2015)”.

- As a minor point: some repetitions can be found all throughout the paper (e.g., trait, existing literature, etc.), please amend them.

Done.

In conclusion, this is an interesting contribution adding new, useful information in the field for both researchers and clinicians.

Thank you for your encouraging overall comment.

Affective temperaments in anorexia nervosa: the relevance of depressive and anxious traits

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Abstract

Background: Affective temperaments have been so far understudied in anorexia nervosa (AN) despite the relevance of personality and both affective and anxious comorbidity with regard to vulnerability, course, and outcome of this deadly disorder.

Methods: Ninety-eight female inpatients diagnosed with AN and 131 healthy controls (HCs) were enrolled in this study and completed the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) in addition to assessments of eating psychopathology, depression, and anxiety.

Results: AN patients and HCs differed in all affective temperaments. The diagnostic subtypes of AN differed as well with binge-purging individuals being more cyclothymic and anxious than those with restricting-type AN. TEMPS-A scores correlated with body mass index and eating psychopathology but not with duration of illness. Concerning comorbidity, greater scores on the depressive and lower scores on the hyperthymic temperaments were found in depressed patients. Those who had either an anxious or irritable temperament were significantly more diagnosed with an anxious disorder than those who did not show this temperament. When logistic regression was performed, high depressive/low hyperthymic and high irritable/anxious traits resulted to be associated with depressive and anxious comorbidity, respectively, independently of confounding factors.

Limitations: Cross-sectional design, some patients on medications, few baseline clinical differences between diagnostic subtypes, no other personality assessments.

Conclusions: An affective continuum strongly associated with mood and anxious comorbidity emerged in AN. Such an evaluation could have several research and clinical implications given the need of improving treatment individualization and early interventions for such a complex disorder.

Keywords: anorexia nervosa, affective temperaments, comorbidity, anxiety, depression

Introduction

Temperament describes those emotional and behavioral characteristics of personality that are biologically driven, genetically determined, present in childhood, and stable across the lifespan (Atiye et al., 2016). Certain temperamental traits like inhibition, perfectionism, anxiety, and altered reward sensitivity and interoceptive awareness are common in individuals affected by anorexia nervosa (AN; Anderluh et al., 2003; Fassino et al., 2004; Lilenfeld, 2011) and new insights into the neurobiology of such traits have been recently proposed (Kaye et al., 2013).

Over the last decades, research on temperament in AN has been widely conducted in the framework of Cloninger's model of personality using the Temperament and Character Inventory (TCI, Cloninger, 1993) yielding important results. In fact, temperament dimensions like harm avoidance and novelty seeking (Cloninger, 1993) have been called into question in neurobiology (Kaye et al., 2013), treatment (Fassino et al., 2005), and outcome-related (Segura-Garcia et al., 2013) lines of research in the field of eating disorders (EDs) with personality characteristics being now acknowledged as important contributors to AN (Lilenfeld, 2011; Atiye et al., 2016). However, there is no doubt that a whole variety of models has been applied to the investigation of personality in AN, including the five-factor model (Costa and McCrae, 1992), the Minnesota Multiphasic Personality Inventory (Hathaway and McKinley, 1983), and the sensitivity to punishment/sensitivity to reward model (Gray, 1970; Keating, 2010).

Nevertheless, affective temperaments (Akiskal et al., 2005a) have been so far understudied in AN. According to this model, affective temperaments represent those sub-affective traits initially theorized by the Ancient Greek medicine and then developed in the Nineteenth Century by German psychiatrists (Kraepelin, 1921; Akiskal and Akiskal, 2007; Rihmer et al., 2010). In fact, this model was originally inspired by Kraepelin's conception of the inter-episode "fundamental states" ("Grundzustande") of manic-depressive patients (Kraepelin, 1921) and then broadened in order to capture five temperaments: depressive, cyclothymic, hyperthymic, irritable, and anxious. Such affective temperaments reflect clinically observable, biologically-based vulnerabilities toward certain patterns of emotions, cognitions and behaviors, similarly to the concept of endophenotypes (Panksepp, 2006; MacDonald et al., 2013). These traits have been found to be stable over time (Kawamura et al., 2010) and to have solid genetic underpinnings (Gonda et al., 2006; Vazquez et al., 2008). Affective temperaments are thought to delineate the

subclinical extreme of the continuum that encompasses the spectrum of affective disorders (Solmi et al., 2016). Nevertheless, they also apply to the affective core of different diagnostic categories, such as borderline personality disorder (Perugi et al., 2011) or attention-deficit/hyperactivity disorder, as recently proposed (Landaas et al., 2012; Ekinici et al., 2013).

Psychiatric comorbidities are hallmarks of AN; in fact, an anxiety disorder is also present in up to 65% of cases (Swinbourne et al., 2012) and major depressive disorder has a lifetime prevalence in patients with AN up to 75% (Abbate-Daga et al., 2011; Thornton et al., 2016). Still, anxiety tends to predate AN onset and has been found to persist after recovery (Kaye et al., 2004; Holtkamp et al., 2005). Notwithstanding, affective temperaments – including depressive and anxious ones - have been to date poorly applied to the AN field. A handful of papers focused mostly on the overlap between bipolar disorders and bulimia nervosa (BN) leading to accumulating evidence supporting an association between these diagnoses (Lunde et al., 2009; Nagata et al., 2013; McElroy et al., 2016). Ramacciotti and collaborators (2004) with a mixed sample of ED diagnoses found that those who binged showed greater scores on the cyclothymic temperament than the normal population. Perugi et al. (2006) investigated atypical depression in BN finding a 17.8% prevalence of BN in patients with atypical depression; moreover, higher scores of cyclothymic temperament emerged in those with BN. Recently, the relationship between BN and affective temperaments has been studied by Rybakowski and coworkers (2014) finding that cyclothymic and irritable temperaments may be significantly higher in comorbid bipolar disorder and BN compared with both pure diagnoses.

However, a characterization of affective temperaments in AN sufferers has been neglected so far in spite of the relevance of the aforementioned neurobiology and comorbidity issues. Therefore, the overarching aim of the current study is grounded on these gaps in literature and is three-fold: a) verify as to whether AN patients and healthy controls (HCs) differ with respect to affective temperaments; b) to ascertain if bulimic and restricting variants of AN show differences in this regard; and c) to assess differences in affective temperaments amongst those patients with anxious or depressive comorbid disorders also addressing the eventual association between temperament and clinical features. Our a priori hypothesis was that AN sufferers will show greater depressive and anxious affective traits than HCs and that those affected by the bulimic variant of AN will report more markedly altered affective features. Likewise, we expected to find that those patients with heightened scores on anxious and depressive temperaments would be more likely

affected by a psychiatric comorbid condition, independently of body mass index (BMI) and duration of illness.

Methods

Participants and procedures

We enrolled in this study 98 women diagnosed with AN according to DSM-5 criteria (APA, 2013) at the Eating Disorders Center for Treatment and Research of the University of Turin, Turin, Italy. Patients were clinically interviewed in person upon hospital admission in order to collect socio-demographic data, duration of illness, clinical and psychiatric history, medications in use. BMI was measured by a trained nurse. Psychiatric anxious and depressive comorbidity was evaluated by an experienced psychiatrist according to DSM-5 criteria (APA, 2013). Moreover, to be included in this study patients had to meet the following inclusion criteria: a) age > 18 and < 55 y.o.; b) no substance dependence; c) no history of head injuries; d) psychosis or psychotic symptoms according to DSM-5 criteria (APA, 2013).

One-hundred and thirty-one gender-matched HCs were also recruited through flyers and e-mails sent around to University of Turin students; they were then interviewed in person in order to measure their BMI and to ascertain the following inclusion criteria: a) no lifetime history of psychiatric disorders according to DSM-5 criteria (APA, 2013); b) no use of medications; c) no current or lifetime organic illness as assessed per clinical interview; d) no substance dependence; e) age > 18 and < 55 y.o.

All participants provided written informed consent for this ethical committee-approved study.

Measures

Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A)

In its first version, the TEMPS-A contained 84 items, assessing Dysthymic (items 1–22), Cyclothymic (items 23–42), Hyperthymic (items 43–63) and Irritable (items 64–84) temperaments (Akiskal et al., 2005b). Later, deep clinical and theoretical work that yielded 26 new items capturing the Anxious temperament which has been added resulting in the 110-item (109-item for

men) full-length version of the TEMPS-A. Such a version has been validated in 25 different languages including Italian (Pompili et al., 2008).

Eating Disorders Inventory-2 (EDI-2)

The EDI-2 (Garner, 1991) is a psychometrically robust (Thiel & Paul, 2006) self-report measure of disordered eating attitudes, behaviors and personality traits common to individuals who are diagnosed with an ED. Ninety-one items and eleven subscales evaluate the symptoms and psychological correlates of EDs. Each item can be rated on a 6-point response scale; the higher the score, the more elevated eating psychopathology. Drive for thinness (seven items), bulimia (seven items) and body dissatisfaction (nine items) represent the ‘symptom index’.

State Trait Anxiety Inventory (STAI)

The STAI (Spielberger et al., 1983) is a well-established 20-item instrument for the self-reporting of state and trait anxiety. All items are rated on a 4-point scale (e.g., from “Almost Never” to “Almost Always”). The STAI measures two types of anxiety: state anxiety, a temporary condition experienced in specific situations, and trait anxiety, a general tendency to perceive situations as threatening. Total scores for state and trait sections separately range from 20 to 80, with higher scores denoting higher levels of anxiety.

Beck Depression Inventory (BDI)

The BDI (Beck et al., 1961) is a 13-item self-report questionnaire used to evaluate depressive symptoms according to the following scoring system: scores from 0 to 4 represent minimal depressive symptoms, scores of 5 to 7 indicate mild depression, scores of 8 to 15 indicate moderate depression and scores of 16 to 39 indicate severe depression.

Statistical analysis

The Statistical Package for Social Sciences 23.0 (SPSS, SPSS Inc., Chicago, IL) was used for all analyses. A two-tailed alpha level of 0.05 was set.

Student's t-test and Fisher's exact test were used to evaluate continuous and categorical variables, respectively, between patients and HCs and between AN variants. A one-way analysis of variance (ANOVA) with Tukey post-hoc test was performed to analyze the differences in affective temperaments among AN variants and HCs.

Cohen's d effect sizes were calculated as well; differences are defined as negligible (≥ -0.15 and <0.15), small (≥ 0.15 and <0.40), medium (≥ 0.40 and <0.75), large (≥ 0.75 and <1.10), very large (≥ 1.10 and <1.45), and huge (>1.45).

Pearson's linear correlations have been run in order to ascertain the correlation profile between affective temperaments, BMI and duration of illness. Correlations have been run also with eating psychopathology as measured by the three core subscales of the EDI-2: drive for thinness, bulimia, and body dissatisfaction.

Binary logistic regression was performed in order to investigate the association between affective temperaments and depressive and anxious comorbidity. Presence versus absence of a comorbid depressive or anxious disorder was considered as dependent variable; the TEMPS-A scores were the independent variables and BMI and duration of illness were added to the model as potential confounders.

Results

Clinical characteristics of the sample

The total sample was composed by 229 individuals, 98 inpatients with AN and 131 HCs recruited at the Eating Disorders Center for Treatment and Research of the University of Turin, Turin, Italy.

Sixty-four patients (65.3%) were diagnosed with the restricting subtype of AN (R-AN) while 34 (34.7%) with the binge-purging subtype (BP-AN). According to DSM-5 criteria (APA, 2013), 63 patients (64.3%) resulted to be affected by major depressive disorder and 49 (50%) by anxiety disorders. The latter diagnoses were distributed as follows: social phobia (n=21, 43%), specific phobia (n=8, 16.3%), agoraphobia (n=3, 6.1%), panic disorder (n=10, 20.4%), and

generalized anxiety disorder, (n=7, 14.2%). Three patients were affected by obsessive compulsive disorder and none met criteria for bipolar disorders.

The majority of patients were on medications (n=75, 76.5%), mostly selective serotonin reuptake inhibitors. Some patients (n=23, 23.5%) were on atypical antipsychotics as well as augmentation therapy as proposed by recent literature (Marzola et al., 2015).

No statistically significant differences were found with respect to age between the HCs and AN individuals, but all other features were significantly different: BMI, marital status, and occupation (see Table 1). Moreover, HCs and AN patients differed on all measures of eating psychopathology, anxiety, and depression as measured by EDI-2, STAI, and BDI, respectively (see Table 1).

Table 1. Socio-demographic and clinical features of the sample.

	Total sample (n=229)				Test statistics	
	AN patients (n=98)		Healthy controls (n=131)		t	p
	Mean(SD)	N(%)	Mean(SD)	N(%)		
Age, years	25.06(9.55)		23.72(3.22)		-1.49	0.137
Body Mass Index	14.63(2.1)		20.49(2.01)		20.88	<0.001
Occupation						<0.001
Student		51(52)		101(77.1)		
Employed		14(14.3)		26(19.8)		
Unemployed		33(33.7)		4(3.1)		
EDI-2						
DT	13.57(7.57)		2.06(3.95)		-14.807	<0.001
B	3.08(4.98)		1(1.91)		-4.342	<0.001
BD	15.81(7.3)		6.02(5.8)		-11.198	<0.001
I	12.61(8.13)		2.93(3.73)		-11.973	<0.001

P	5.97(4.24)	2.91(4.67)	-5.048	<0.001
ID	7.39(4.65)	2.82(3.01)	-8.927	<0.001
IA	13.23(13.77)	2.04(3.05)	-9.00	<0.001
MF	7.92(5.88)	4.71(4.29)	-4.728	<0.001
A	8.56(5.5)	2.95(2.17)	-10.580	<0.001
IR	6.45(6.17)	1.58(2.55)	-8.135	<0.001
SI	9.28(5.2)	3.49(3.19)	-10.324	<0.001
STAI				
Trait	58.9(13.1)	40.63(9.7)	-12.105	<0.001
State	55.97(14.02)	37.46(10.43)	-11.403	<0.001
BDI				
	16.61(7.76)	3.32(3.2)	-17.658	<0.001

Legend: AN: anorexia nervosa; EDI-2: Eating Disorder Inventory-2; DT: drive for thinness; B: bulimia; BD: body dissatisfaction; I: ineffectiveness; P: perfectionism; ID: interpersonal distrust; IA: interoceptive awareness; MF: maturity fears; A: asceticism; IR: impulse regulation; SI: social insecurity; STAI: State Trait Anxiety Inventory; BDI: Beck Depression Inventory.

AN variants differed with regard to BMI (R-AN: 14.24±1.66, BP-AN: 15.37±2.62; $t = -2.606$; $p = 0.011$), age (R-AN: 23.5±9.3, BP-AN: 28±9.5; $t = -2.267$; $p = 0.026$), and duration of illness (R-AN: 5.4±7.4, BP-AN: 10.56±10.1; $t = -2.815$; $p = 0.006$).

Differences between AN patients and HCs with respect to affective temperaments

Concerning affective temperaments, AN patients and HCs differed in all temperaments with medium to huge effect sizes (see Table 2). In particular, statistically significant differences emerged with respect to both depressive and anxious temperaments with huge and very large effect sizes, respectively.

Table 2. Differences in affective temperaments between anorexia nervosa patients and healthy controls.

AN patients	Healthy controls	Test statistics	Effect size
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	(n=98)	(n=131)			
	Mean(SD)	Mean(SD)	t	p	
TEMPS-A					
Depressive	13.14(4.01)	6.9(3.18)	-13.127	<0.001	1.77 huge
Cyclothymic	9.59(4.92)	6.21(4.15)	-5.616	<0.001	0.76 large
Hyperthymic	6.64(4.24)	9.31(4.1)	4.802	<0.001	0.65 medium
Irritable	6.83(4.23)	4.54(3.54)	-4.441	<0.001	0.60 medium
Anxious	13.88(5.33)	7.82(4.84)	-8.975	<0.001	1.21 very large

Legend: Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto-questionnaire;
AN: anorexia nervosa.

Differences in affective temperaments between AN variants and HCs

HCs resulted to have significantly lower depressive, cyclothymic, irritable, and anxious traits when compared to both AN variants. On the contrary, HCs showed higher scores on the hyperthymic temperament when compared to both AN subtypes.

As showed in Table 3, BP-AN patients resulted to be more cyclothymic and anxious when compared to both HCs and R-AN. The two subtypes did not significantly differ on depressive, hyperthymic, and irritable affective temperaments.

Table 3. Differences in affective temperaments between anorexia nervosa variants and healthy controls.

	Restricting variant (R-AN, n=64)	Bulimic variant (BP-AN, n=34)	Healthy controls (HCs, n=131)	Test statistics	Tukey Post-hoc
	Mean(SD)	Mean(SD)	Mean(SD)	F	p
TEMPS-A					

Depressive	12.71(4.32)	13.94(3.23)	6.9(3.18)	88.092	<0.001	HC < R-AN, BP-AN R-AN = B
Cyclothymic	8.68(5.04)	11.29(4.26)	6.21(4.15)	20.063	<0.001	HC < R-AN, BP-AN BP-AN > R-AN
Hyperthymic	6.61(4.26)	6.71(4.27)	9.31(4.1)	11.485	<0.001	HC > R-AN, BP-AN R-AN = B
Irritable	6.43(4.16)	7.58(4.33)	4.54(3.54)	10.895	<0.001	HC < R-AN, BP-AN R-AN = B
Anxious	12.81(5.49)	15.91(4.41)	7.82(4.84)	45.930	<0.001	HC < R-AN, BP-AN BP-AN > R-AN

Legend: Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto-questionnaire.

Affective temperaments and AN clinical features

BMI resulted to positively correlate with depressive ($r = .278$; $p = 0.006$), cyclothymic ($r = .205$; $p = 0.043$), and anxious ($r = .372$; $p < 0.001$) traits while duration of illness was not correlated with any temperaments (data not shown).

All affective temperaments significantly correlated with drive for thinness and body dissatisfaction (data not shown), but only the depressive and anxious temperaments correlated also with the bulimia subscale ($r = .254$; $p = 0.014$ and $r = .209$; $p = 0.043$, respectively).

Affective temperaments and depressive comorbidity

Concerning the depressive comorbidity those who had greater scores on the depressive temperament and lower scores on the hyperthymic temperament were significantly more diagnosed with a depressive disorder with medium effect sizes (see Table 4).

Table 4. Differences in affective temperaments between patients affected by anorexia nervosa diagnosed or not with a comorbid depressive disorder.

	AN depressed sample (n=63)	AN non- depressed sample (n=35)	Test statistics	Effect size
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	Mean(SD)	Mean(SD)	t	p	Cohen's d
TEMPS-A					
Depressive	13.84(3.97)	11.88(3.80)	-2.367	0.020	0.51 medium
Cyclothymic	9.22(4.88)	10.25(5.01)	0.996	0.322	0.21 small
Hyperthymic	5.95(3.72)	7.88(4.86)	2.202	0.030	0.47 medium
Irritable	6.47(3.81)	7.48(4.90)	1.131	0.261	0.24 small
Anxious	13.95(5.39)	13.77(5.28)	-0.161	0.873	0.03 negligible

Legend: TEMPS-A: Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto-questionnaire.

Affective temperaments and anxious comorbidity

As shown in Table 5, those who had either an anxious or irritable temperament were significantly more diagnosed with an anxious disorder than those who did not show this temperament.

Table 5. Differences in affective temperaments between patients affected by anorexia nervosa diagnosed or not with a comorbid anxious disorder.

	AN anxious sample (n=49)	AN non-anxious sample (n=49)	Test statistics		Effect size
	Mean(SD)	Mean(SD)	t	p	Cohen's d
TEMPS-A					
Depressive	13.81(3.4)	12.46(4.47)	-1.678	0.097	0.34 small
Cyclothymic	10.53(4.81)	8.65(4.91)	-1.911	0.059	0.39 small
Hyperthymic	6.04(3.97)	7.24(4.46)	1.411	0.162	0.29 small
Irritable	7.77(4.42)	5.89(3.86)	-2.237	0.028	0.46 medium
Anxious	15.46(4.84)	12.31(5.37)	-3.062	0.003	0.62 medium

Legend: TEMPS-A: Temperament Evaluation of Memphis, Pisa, Paris and San Diego Auto-questionnaire.

Affective temperaments as associated to depressive and anxious comorbidity

Also, running binary logistic regression we found that both depressive and low hyperthymic temperaments were significantly associated to the depressive comorbidity. As shown in Table 6, when correcting for BMI such data held significance; the depressive temperament was still significant when correcting for both BMI and duration of illness.

Furthermore, running a model with binary logistic regression, we found that both anxious and irritable temperaments were significantly associated to the anxious comorbidity. With a multivariate analyses, when correcting for both BMI and duration of illness such data were still significant (see Table 6).

Table 6. Association of affective temperaments to psychiatric comorbidity in anorexia nervosa.

	Wald's test	p	OR	OR 95% CI
Depressed patients				
Depressive	5.143	.023 [§]	1.133	1.017, 1.261
Cyclothymic	.995	.319	.957	.879, 1.043
Hyperthymic	4.500	.034 *	.897	.810, .992
Irritable	1.276	.259	.945	.856, 1.043
Anxious	.026	.871	.871	.931, 1.088
Anxious patients				
Depressive	2.722	.099	1.091	.984, 1.209
Cyclothymic	3.503	.061	1.083	.996, 1.178
Hyperthymic	1.955	.162	.934	.848, 1.028
Irritable	4.676	.031 [§]	1.116	1.010, 1.232
Anxious	7.964	.005 [§]	1.132	1.038, 1.233

* p <0.05 when correcting for BMI

§ p <0.05 when correcting for BMI and duration of illness

Discussion

The investigation of affective temperaments in AN sufferers with the TEMPS-A (Akiskal et al., 2005b) demonstrated that not only AN patients differ in all five temperaments when compared to HCs but also that bulimic variants of AN show greater cyclothymic and anxious traits than those with restricting AN, overall confirming our a priori hypothesis. Interestingly, those patients clinically diagnosed with a depressive disorder were found to show greater depressive and lower hyperthymic temperaments. Still, those affected by an anxious disorder reported heightened anxious and irritable traits. Taken together, these findings show also in AN a continuum between affective temperaments and clinical conditions, paralleling the field of affective disorders (Solmi et al. 2016). On one hand these data are consistent with the available literature on the overlap between EDs and affective disorders (McElroy et al., 2016) but on the other hand are novel since the available studies in the ED field focused mainly on mixed samples (Ramacciotti et al., 2004) and BN patients (Perugi et al., 2006; Lunde et al., 2009; Nagata et al., 2013; Rybakowski et al., 2014). Moreover, earlier studies used a different instrument in order to assess affective temperament (i.e., Temperament Evaluation of the Memphis, Pisa, Paris, and San Diego-Interview version [(Akiskal et al., 1998; Placidi et al., 1998)]) making it difficult to capture the anxious temperament in a straightforward way (Ramacciotti et al., 2004).

AN patients were found to markedly differ from HCs with regard to temperament traits and this is in line with previous literature on personality (Fassino et al., 2002; Wagner et al., 2006; Atiye et al., 2016) although in part differing from earlier research using the TEMPS-I (Ramacciotti et al., 2004). In particular, AN patients were reported to be more likely to have more depressed, cyclothymic, irritable, and anxious temperament traits than HCs and less marked hyperthymic traits. The larger sample size of this work when compared to earlier investigations of AN (Ramacciotti et al., 2004) could account for the significant differences we found in the AN sample. With more detail, Ramacciotti and collaborators (2004) analyzed only 16 R-AN individuals and used a different instrument (i.e., TEMPS-I). The latter on one hand did not consider the anxious temperament and on the other hand adopted a categorical scoring thus hindering a coherent comparison of the findings. Notwithstanding, in line with that investigation (Ramacciotti et al., 2004) we also found differences between restricting and bulimic variants.

Depressive features are commonly found in those with AN (Abbate-Daga et al., 2011; Thornton et al., 2016) and in our paper the depressive temperament was characterized by a huge

effect size; however, the relationship between depressed mood and AN is multifaceted. In fact, response to antidepressants tends to be scarce (Walsh et al., 2006) and recovery from the eating disorder is associated with depressive relapse (Mischoulon et al., 2011). Cyclothymic traits are quite understudied in AN in spite of a clearer picture on the relationship between BN and bipolarity (McElroy et al., 2005, 2016; Perugi 2006; Lunde, 2009). In this light, bulimic variants of AN could be responsible for this result, because we found a significant difference on this trait between diagnostic subtypes, as discussed below. A greater irritable temperament is in line with every-day clinical practice also given the role of anger in EDs (Fassino et al., 2001) and individuals with AN, mostly when severely emaciated, tend to show greatly dysphoric mood (Kaye et al., 2009). In this light it would be of interest to assess if an overlap exists between such clinical condition and higher scores on the irritable temperament. Also, patients with AN are often plagued by heightened levels of anxiety and our temperament data seem to provide support to those lines of research suggesting anxiety as a trait thus predating the ED onset (Kaye et al., 2004; Holtkamp et al., 2005) although only longitudinal studies could clarify this intriguing possibility. It should be noted that the anxious temperament is characterized by a very large effect size thus providing support to the key-role of anxiety as predating AN and persisting after recovery (Kaye et al., 2004, 2009; Wagner et al., 2006; Pallister and Waller, 2008).

Still, it is noteworthy that AN variants did not show the same temperamental profile, in line with earlier investigations of personality using different instruments (Fassino et al., 2002). In fact, both R-AN and BP-AN significantly differed from HCs in all five dimensions but those with BP-AN resulted to be more cyclothymic and more anxious than the R-AN group. This is in line with studies on BN showing that such patients tend to be more cyclothymic than HCs (Ramacciotti et al., 2004; Perugi et al., 2006; Rybakowsky et al., 2014). However, R-AN resulted more cyclothymic than HCs as well. Longitudinal studies are needed to verify this finding: in fact, a weaker association between R-AN and bipolar spectrum may exist or higher scores on the cyclothymic traits may predict a diagnostic crossover between R-AN and BP-AN. This hypothesis relies on the fact that R-AN participants showed a shorter duration of illness than those with BP-AN and the diagnostic crossover is more likely during the first five years of illness (Krug et al., 2009) thus making the AN diagnosis less stable. Furthermore, earlier studies on the TCI showed how personality dimensions can predict crossover (Tozzi et al., 2005; Krug et al., 2009). Although

the datum on the anxious temperament is novel and not fully comparable with previous research, it could be raised the hypothesis that even the anxious affective vulnerability could contribute to the poorer outcome of those with binge-purging symptomatology (Vall et al., 2015). This finding is of interest from a clinical standpoint since a more specific characterization of patients (e.g., not relying only on the phenotypic presentation) could have implications in treatment for both psychotherapy and pharmacotherapy approaches in such treatment-resistant conditions (Abbate-Daga et al., 2013). Still, as already pointed out in the literature on affective disorders (Solmi et al., 2016), a continuum of affective temperaments could be hypothesized also in AN, with a sort of gradient of severity ranging from HCs to BP-AN. Further research is warranted to verify this hypothesis.

Anxiety and depression are commonly diagnosed as comorbid conditions in AN (Blinder et al., 2006; Abbate-Daga et al., 2011; Swinbourne et al., 2012; Thornton et al., 2016) and in this view our data are consistent with **earlier research** because the majority of patients had a depressive disorder and about a half of the sample was affected by an anxious disorder. When studying affective temperaments, we found that depressed patients had greater depressive and lower hyperthymic traits than non-depressed ones and that those with a comorbid anxious disorder had heightened irritable and anxious traits. This is of interest because according to our findings such an alteration seems to be specific. In other words, the depressive trait as well as a low hyperthymic traits were strictly associated with clinical depression; similarly, the anxious-irritable temperament resulted as strongly linked to anxiety disorders. In this view, the TEMPS-A turned out to be a helpful tool to reliably distinguish between temperaments in AN. Moreover, this potentially confirms a gradient/diathesis between temperament and comorbid psychiatric disorders in AN with an increased likelihood of developing a depressive or anxious disorder depending on TEMPS-A scores. This is a quite novel finding in the AN field but it is consistent instead with previous research showing affective temperaments as stable, running in families, and highly genetically-determined (Gonda et al., 2006; Vazquez et al., 2008; Kawamura et al., 2010). Additionally, our findings suggest that such associations are independent of both BMI and duration of illness. This is noteworthy because both these clinical elements may strongly impact patients' comorbidity; the effects of starvation are known since decades (Keys et al., 1950) and it is widely acknowledged how duration of illness can influence sufferers' quality of life and treatment response (Abbate-

Daga et al., 2013, 2014; Hay and Touyz, 2015). Additionally, our data on bivariate correlations are also in line with more specific earlier investigations demonstrating how early anxious vulnerability can lead to full-blown AN (Raney et al., 2008) and lower BMI during AN (Dellava et al., 2010).

Major depressive disorder is very common in AN (Kaye et al., 2008; Mischoulon et al., 2011) and depressive symptomatology persists after weight restoration or full recovery from the eating disorder (Pollice et al., 1997; Holtkamp et al., 2005; Wagner et al., 2006). In this light, our findings are overall in line with the existing literature and overall show that depressive temperament may be a factor indeed contributing to both high prevalence (i.e., 75% Mischoulon et al., 2011) and strong persistence of depressed symptomatology in AN. Of course only longitudinal studies could be able to disentangle the time relationship between temperament and clinical presentations and this is beyond the scope of this paper; nevertheless, these data could be of help in every-day clinical practice in order to individualize treatment plans. Longitudinal research is also needed to deepen the relationship between malnutrition and depression: it is well-known that in the acute phases of AN the depressive symptomatology is associated with lower BMI and severe eating symptoms (Bizeul et al. 2003; Abbate-Daga et al. 2011). Therefore, our correlations are in line with earlier findings; nevertheless, differently from the anxious temperament, it remains unclear as to whether depression exaggerates eating symptoms or predicts greater severity of the ED or both (Abbate-Daga et al., 2011). Importantly, future research may want to investigate whether patients respond differently to treatments on the basis of their temperament profiles, as it has been described for affective disorders (de Aguiar Ferreira et al., 2014).

In closing, this novel investigation provided support to the relevance of assessing temperament in AN but it also shed light on some interesting potential clinical and research implications. First and foremost, the assessment of affective temperaments could be successfully applied in real-world clinical practice in order to highly individualize treatments. In fact, clinicians may benefit from knowing what temperamental traits are mostly expressed by patients when planning both psychotherapies and pharmacotherapies. For example, in the field of affective disorders, antidepressants response was modulated by affective temperaments (de Aguiar Ferreira et al., 2014). Therefore, if on one hand it has been authoritatively stated that the AN field is

characterized by “unacceptable treatment outcomes” (Bulik et al., 2007), on the other hand a greater individualization of treatments has been advocated (Marzola et al., 2015; Dold et al., 2015). In this light, high scores on the BDI resulted as independent predictors of hospital admissions (Amettler et al., 2005) and the depressive temperament may be involved as well in this regard. Secondly, AN is characterized by high mortality (Arcelus et al., 2011) with a recent meta-analysis showing that AN sufferers have an 18.1 times higher risk of dying from suicide when compared to the general population of females aged 15–34 years (Keshaviah et al., 2014). Data in literature show that the cyclothymic temperament is a recognized risk factor for suicidal behavior, given its relationship with hopelessness (Solmi et al., 2016). Similarly, the anxious temperament is another well-known risk factor for suicide attempts in individual with or without mental disorders (Karam et al., 2015). Also, earlier literature has consistently found that the binge-purging subtype of AN is at higher risk than the restricting variant of committing suicide (Franko & Keel, 2006; Bulik et al., 2008). Taken together, on one hand our data are overall in line with these lines of research (i.e., binge-purging variants of AN as more cyclothymic and anxious) but on the other hand these results raise the hypothesis that even in the AN field a relationship between affective temperament and suicide may exist. Further research is warranted to clarify this interesting hypothesis. Thirdly, this line of research is consistent with emerging therapeutic approaches highlighting the need of taking neurobiology (and particularly temperament) into account in the treatment of AN (i.e., Temperament-Based Treatment; Kaye et al., 2015) in order to avoid “brainless” approaches (Schmidt and Campbell, 2013). In spite of these strengths, some limitations need to be acknowledged as well: this study adopted a cross-sectional design, some patients were on medications, there were a few baseline clinical differences between R-AN and BP-AN individuals, and no other personality assessments were used and compared. However, future studies may want to deepen the investigation of the affective temperaments in AN given their real-world clinical and research implications.

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Abstract

Background: Affective temperaments have been so far understudied in anorexia nervosa (AN) despite the relevance of personality and both affective and anxious comorbidity with regard to vulnerability, course, and outcome of this deadly disorder.

Methods: Ninety-eight female inpatients diagnosed with AN and 131 healthy controls (HCs) were enrolled in this study and completed the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) in addition to assessments of eating psychopathology, depression, and anxiety.

Results: AN patients and HCs differed in all affective temperaments. The diagnostic subtypes of AN differed as well with binge-purging individuals being more cyclothymic and anxious than those with restricting-type AN. TEMPS-A scores correlated with body mass index and eating psychopathology but not with duration of illness. Concerning comorbidity, grater scores on the depressive and lower scores on the hyperthymic temperaments were found in depressed patients. Those who had either an anxious or irritable temperament were significantly more diagnosed with an anxious disorder than those who did not show this temperament. When logistic regression was performed, high depressive/low hyperthymic and high irritable/anxious traits resulted to be associated with depressive and anxious comorbidity, respectively, independently of confounding factors.

Limitations: Cross-sectional design, some patients on medications, few baseline clinical differences between diagnostic subtypes, no other personality assessments.

Conclusions: An affective continuum strongly associated with mood and anxious comorbidity emerged in AN. Such an evaluation could have several research and clinical implications given the need of improving treatment individualization and early interventions for such a complex disorder.

Keywords: anorexia nervosa, affective temperaments, comorbidity, anxiety, depression

Highlights

- Affective temperaments have been so far understudied in anorexia nervosa (AN).
- AN patients and healthy controls differed in all affective temperaments.
- Binge-purging patients resulted more cyclothymic and anxious than restrictors.
- High depressive/low hyperthymic traits were associated with comorbid depression.
- High irritable/anxious traits were associated with comorbid anxiety disorders.