Deriving behavioural phenotypes in an international, multi-centre study of eating disorders

THE PRICE FOUNDATION COLLABORATIVE GROUP

ABSTRACT

Background. An international, multi-site study funded by the Price Foundation has collected 237 affected relative pairs to identify potential genetic factors that may contribute to the pathogenesis of anorexia nervosa (AN). The current report utilized this sample to derive phenotypes from the personality and behavioural traits assessed in a large number of individuals with eating disorders.

Methods. Multivariate analytical techniques were used to characterize the relationships among personality (e.g. trait anxiety, perfectionism, harm avoidance, novelty seeking) and behavioural traits (obsessions and compulsions) in individuals with eating disorders (primarily AN; N = 348) and assess the effectiveness of these traits in classifying subjects into diagnostic subtypes.

Results. Factor analysis revealed that the most influential factor was one of trait anxiety, harm avoidance, perfectionism, obsessive–compulsive behaviours, and diminished self-directedness, although the precise nature of this factor differed slightly across sites. Discriminant analysis was used to evaluate the utility of these personality/behavioural factors in predicting subdiagnosis. Overall, the misclassification rate was 34%; however, there was an 80% rate of accurate classification of those individuals with a diagnosis of restricting-type AN.

Conclusions. Trait anxiety, harm avoidance, perfectionism, obsessive–compulsive behaviours and diminished self-directedness may best be conceptualized as parts of the same underlying construct among individuals with eating disorders, particularly AN. These personality and behavioural traits were also found to be of some utility in classifying eating disordered individuals into diagnostic subgroups, particularly those with restricting-type AN. We expect these phenotypic findings to benefit our ongoing search for genetic loci underlying the liability to eating disorders.

INTRODUCTION

Psychometric studies have consistently linked anorexia nervosa (AN) to a cluster of moderately heritable (Heath et al. 1994) personality and temperamental traits, specifically, obsessionality, perfectionism and harm avoidance (Strober, 1980; Brewerton et al. 1993; Kleifield et al. 1993; Waller et al. 1993; Sohlberg & Strober, 1994; Vitousek & Manke, 1994; Bulik et al. 1995a; Srinivasagam et al. 1995; O’Dwyer et al. 1996; Lilenfeld et al. 1998; Ranson et al. 1999; Kaye & Strober, 2000), as have earlier writings (e.g. Palmer & Jones, 1939; DuBois, 1949). In this regard, it has been speculated that phenotype similarities between these traits and the rigidly persevering, obsessive and anxiety-
reducing character of the anorexic’s dietary restraint may be based upon shared genetic and environmental factors (Strober, 1991, 1995; Vitousek & Manke, 1994). These findings are remarkably consistent across studies (Lilenfeld & Kaye, 1998) and continue to characterize individuals with AN even after recovery (Casper, 1990; Kaye et al. 1993; Srinivasagam et al. 1995). While such traits may be exaggerated by starvation (Keys et al. 1950; Pollice et al. 1997), their persistence after recovery supports the speculation that such traits may be vulnerability factors for AN, rather than merely consequences of the disorder.

Personality traits associated with bulimia nervosa (BN) have been less well-studied and appear more heterogeneous; however, certain consistencies are evident. While impulsivity and emotional instability are more common in BN than AN (Casper et al. 1980; Garfinkel et al. 1980; Strober, 1981), traits such as harm avoidance, compulsivity, perfectionism and obsessionality are prominent (Vitousek & Manke, 1994; Bulik et al. 1995a; Joiner et al. 1997) and often persist after clinical recovery (Kaye et al. 1998). The common occurrence of particular personality traits in AN and BN, especially those associated with anxiety and restraint, converges with evidence of significant co-morbidity between AN and BN (Kendler et al. 1991; Walters & Kendler, 1995), the frequency in both of antecedent anxiety disorders (Deep et al. 1995; Bulik et al. 1996, 1997a) and evidence of serotonergic hyperactivity in both disorders after long-term clinical recovery (Kaye et al. 1991, 1998).

Research using twin and adoption study methodology suggests that a broad range of personality traits are heritable, with perhaps 50% of measured personality variation attributed to genetic diversity (Tellegen et al. 1988). A heuristic model proposed by Cloninger (1986) hypothesizes the existence of three core dimensions underlying most personality variation. Importantly, four independent studies (Brewerton et al. 1993; Kleifield et al. 1993; Waller et al. 1993; Bulik et al. 1995b) converge in showing that one particular dimension on the Temperament and Personality Questionnaire (TPQ) (Cloninger, 1986), namely harm avoidance, is significantly elevated in both AN and BN subjects compared to normal controls. This commonality is consistent with aetiological models positing the role of phobic anxiety as a predisposing factor in these conditions (Vitousek & Manke, 1994).

The overarching goal of these collaborative studies (Kaye et al. 2000) is to identify genes that may influence susceptibility to AN. Belmaker & Biederman (1994) suggest that it may be more prudent to search for genetic markers of personality traits (e.g. behavioural inhibition) as expressions of genetic vulnerability to psychopathology than to look for markers of specific illness, as defined solely by psychiatric diagnosis. This may be particularly applicable to restricting-type AN, which may have the most homogeneous personality presentation of any psychiatric illness (Vitousek & Manke, 1994; Strober, 1995). Thus, our collaborative studies (Kaye et al. 2000) will correlate personality and behavioural traits, as well as psychiatric diagnosis, with genotypes. The goal of the current report was to utilize a multivariate analytical approach to improve the characterization of behavioural phenotypes of our subjects. This was accomplished by examining the inter-relationships among personality and behavioural traits and evaluating the utility of these traits in classifying subjects in our sample. The concise characterization of these personality and behavioural traits will aid in the search for liability loci.

METHOD
Study design and collaborative arrangements
In an effort to map genetic susceptibility loci involved in AN, and international, multi-site study, funded by the Price Foundation, was designed (Kaye et al. 2000). This study utilized affected relative pairs to identify genetic factors that might contribute to the pathogenesis of AN. In the Kaye et al. (2000) study, all probands met modified DSM-IV (American Psychiatric Association, 1994) criteria for AN, whereas all affected first-, second- and third-degree relatives met modified DSM-IV criteria for AN, DSM-IV BN, or eating disorder not otherwise specified (NOS) (refer to ‘Participants’ section).

The investigators, using a collaborative consensus, selected a battery to assess psychological
and personality features that have been shown to be associated with, and may underlie vulnerability to, eating disorders. In general, we attempted to evaluate persistent traits rather than personality features confined to the acute phase of the illness (Brewerton et al. 1993, Kleifeld et al. 1993, Bulik et al. 1995a, Srinivasagam et al. 1995; O’Dwyer et al. 1996; Kaye et al. 1998; Von Ranson et al. 1999). These traits included harm avoidance, perfectionism, and anxiety.

Six sites in North America and Europe were identified that had well-established programmes for the treatment of AN. The sites included University of Pittsburgh (W. H. K.), Cornell University (K. A. H.), University of California at Los Angeles (M. S.), University of Toronto (A. K. and D. B. W.), University of Munich (M. M. F.) and University of London (J. T.). An additional site, Thomas Jefferson University in Philadelphia (W. H. B.), was included for its expertise in molecular genetic research on psychiatric illness. See Kaye et al. (2000) for a complete description of the overall study design.

Participants
The subjects reported in this manuscript (N = 348) are a subset of the sample from the multisite project (Kaye et al. 2000). This manuscript reports on all AN probands (N = 196) and their siblings who had a lifetime diagnosis of modified DSM-IV AN (N = 116) or DSM-IV BN (N = 36). All other relatives from the original sample (e.g. half-siblings, cousins, aunts, uncles), as well as siblings with a diagnosis of NOS, were excluded in the current report. Our reasoning for this sampling approach is as follows. Both genetic and environmental effects on the correlation of personality/behavioural traits should be consistent within full siblings and greater than these effects on more distant relative pairs, such as aunt–niece pairs. Thus, in statistical terms, observations of sibling-pairs are exchangeable across pairs (i.e. the identity of the pairs is irrelevant), but a sibling-pair and aunt–niece pair are not exchangeable. By analysing only full siblings we maintain the majority of the sample while also meeting this important statistical criterion of exchangeability.

Probands were required to meet the following criteria for acceptance into the study: (a) an unequivocal lifetime ‘core’ diagnosis of AN by DSM-IV criteria, waiving the single criterion of amenorrhoea for 3 consecutive months, since some subjects were menstruating due to treatment with exogenous hormone replacement and some were male; (b) age between 13 and 65; and (c) fulfilment of AN diagnostic criteria for not less than 3 years prior to ascertainment. Exclusion criteria included a lifetime history of any of the following: organic brain syndrome; IQ < 70; dementia, schizophrenia; bipolar illness; obesity; medical illness that could affect appetite, eating behaviour, or body weight (e.g. diabetes); DSM-IV binge eating disorder, and any ‘regular’ binge eating. The latter was defined as bingeing at least once weekly for ≥ 3 or more consecutive months. All siblings had similar exclusion criteria, with the exception of binge eating, as some of these subjects had bingeing symptomatology in the context of an AN diagnosis and some had a BN diagnosis. BN diagnoses were made according to DSM-IV criteria.

Assessment instruments
The assessment battery was selected, based on existing literature, to include those personality and behavioural features most consistently associated with eating disorders and not confined to the acute phase of the illness (Brewerton et al. 1993; Kleifeld et al. 1993; Waller et al. 1993; Bulik et al. 1995a; Srinivasagam et al. 1995; O’Dwyer et al. 1996; Kaye et al. 1998; Von Ranson et al. 1999). However, we did ask subjects to report some behaviours (e.g. obsessions and compulsions) at the time when their eating disorder was at its worst in order to access the maximum lifetime severity of the behaviour. Methods for interviewer training and reliability are described elsewhere (Kaye et al. 2000).

Eating disorder diagnostic assessment

Structured Interview of Anorexia Nervosa and Bulimic Syndromes (SIAB)

This instrument was used to assess lifetime history of eating disorders among probands and affected relatives. The SIAB (Fichter et al. 1998) is a detailed structured interview schedule that derives eating disorder diagnostic information, as well as additional psychopathological factors
related to eating disorders. The internal consistency of the six SIAB subscales on the lifetime version of the instrument is moderate to high, with Cronbach’s alpha ranging from 0.64 to 0.89 (Fichter et al. 1998), and their inter-rater reliability for these same subscales is excellent, ranging between 0.80 and 0.90 (Fichter et al. 1998). No psychometric information has yet been published on the English translation of the SIAB. Subjects were asked to report ‘worst lifetime’ symptoms.

**Behavioural assessments**

**Yale–Brown Obsessive–Compulsive Scale (Y-BOCS)**

The Y-BOCS (Goodman et al. 1989) is a semi-structured interview designed to rate the presence and severity of obsessive thoughts and compulsive behaviours typically found among individuals with obsessive–compulsive disorder (OCD). It has excellent inter-rater reliability (Goodman et al. 1989) and is considered to be the ‘gold standard’ for measuring obsessive–compulsive symptom severity (Pato et al. 1994). There is a published German translation of this instrument as well (Goodman et al. 1991). Subjects were asked to report ‘worst lifetime’ symptoms.

**Yale–Brown–Cornell Eating Disorder Scale (YBC-EDS)**

The YBC-EDS (Sunday et al. 1995) is similar to the Y-BOCS; however, it assesses core obsessions and compulsions specific to eating disorders (e.g. those related to food, eating, weight and exercise). Excellent inter-rater reliability, internal consistency and convergent validity have been demonstrated for the YBC-EDS (Mazure et al. 1994). No psychometric information has yet been published on the German translation of the YBC-EDS. The YBC-EDS was modified with the authors of the instrument to assess ‘worst lifetime’ symptoms, as well as current symptoms.

**Self-report psychological symptom and personality assessments**

**State-Trait Anxiety Inventory (STAI)**

The STAI (Spielberger et al. 1970) is a widely used instrument for the assessment of anxiety. The state anxiety assessment asks subjects to report how they feel ‘at this moment’ and the trait anxiety assessment asks subjects to report how they ‘generally feel’. There is also a published German translation of this instrument (Laux et al. 1981).

**Multidimensional Perfectionism Scale (MPS)**

The MPS (Frost et al. 1990) is a 35-item, factor-analytically developed self-rating instrument that consists of an overall assessment of perfectionism, as well as six specific dimensions of perfectionism. The coefficients of internal consistency for the factor scales range from 0.77 to 0.93 and the reliability of the overall scale is 0.90 (Frost et al. 1990). The MPS successfully discriminates between subjects with and without eating disorders (Srinivasagam et al. 1995). No psychometric information has yet been published on the German translation of the MPS. To assess worst lifetime symptom expression, subjects were instructed to respond to the questions according to how they felt at the time when their concerns about eating and weight were strongest.

**Temperament and Character Inventory (TCI)**

The TCI (Cloninger et al. 1993) is a 226-item factor-analytically developed self-rating instrument that measures seven dimensions of personality. The TCI is an extension of the Tridimensional Personality Questionnaire (TPQ) (Cloninger et al. 1991), which assesses the temperament dimensions of novelty seeking, harm avoidance and reward dependence (Cloninger et al. 1991). The authors’ original model has been extended to measure the additional temperament factor of persistence and the three character dimensions of self-directedness, cooperativeness, and self-transcendence. The internal consistency of all seven scales is high, ranging from 0.76–0.89 (Cloninger et al. 1993). There is a published German translation of the TCI as well (Cloninger et al. 2000).

**Procedure**

Subjects were recruited through several sources, including: (1) identification of potential subjects through clinic databases; (2) referrals from clinicians with knowledge of the study; (3) advertisement in a variety of different media at local and national levels. Potential subjects were first screened to determine study suitability. If a
likely proband denied a family history of eating disorders, or refused permission to contact possibly ill relatives, the screening was terminated. Otherwise, a preliminary verification of the diagnosis of AN was undertaken and eating disorder histories on possibly affected relatives were obtained. If probands met all inclusion and no exclusion criteria, and gave a history suggestive of eating disorder in a non-parent, non-child, and a non-MZ twin blood relative, the proband was asked to discuss the study with the affected relative and obtain permission for study personnel to contact the relative for informed consent. Study personnel then contacted the relative who was screened for eligibility. If the relative fulfilled entrance criteria, both the proband and affected relative were scheduled for the complete battery of evaluative procedures. At the time that the interviews were scheduled, the proband and affected relative were told that they would be mailed a packet of self-rating assessments. They were asked to complete the assessments and bring the packet to the interview. For those probands and relatives who were not able to come to a satellite centre for an in-person interview, the interview was conducted by telephone and the self-rating assessments were returned by mail. Only AN probands and siblings with AN and BN diagnoses are reported in the current study due to reasons described in the ‘Participants’ section.

Data analysis
Data analysis was conducted in several stages. An initial principal components factor analysis applying a varimax rotation was performed on individual TCI scales to evaluate whether the factor structure would be replicated with our eating disorder sample.

Next, to characterize the personality and behavioural attributes of individuals with eating disorders, we performed an exploratory factor analysis with varimax rotation using the responses of our study participants to the following personality and behavioural assessments: the seven TCI scales, two measures of obsessive–compulsive symptoms (Y-BOCS and YBC-EDS), a multidimensional measure of perfectionism (MPS), and a measure of trait anxiety (STAI).

The initial factor analysis grouped data for all sites (or populations). To determine whether there was heterogeneity among populations, a delete-one jackknife procedure was done. This evaluated the results of the factor analysis after deleting one population at a time. Any population that was an ‘outsider’, as determined by the jackknife analysis, was deleted from the sample and the initial factor analysis was repeated. To explore further potential differences among populations, a factor analysis was performed on data from the three populations with the largest sample sizes (excluding any ‘outsiders’).

To evaluate whether the personality/behavioural constructs extracted from the factor analysis were useful for predicting eating disorder subdiagnoses, a discriminant analysis was performed using the factors and the four diagnostic subclassifications: anorexia nervosa-restricting type (AN-R), anorexia nervosa-purging type (AN-P), anorexia nervosa-bingeing or bingeing and purging type (AN-B), and BN. Discriminant analysis is a statistical method that utilizes trait attributes to discriminate members of two or more groups from one another. That is, this analytical approach allows one to predict the group membership status of subjects based upon their scores on quantitative trait attributes. Our methods follow classic discriminant analysis procedures as implemented in S-Plus (Venables & Ripley, 1994). First, using a random selection of 80% of the data (the training set), a classification tree was built based on factors 1–4 from the factor analysis. The tree itself is based on bifurcating factor splits that yield optimal separation of populations into diagnostic categories. Using the remaining 20% of the data as the test set, the tree built with the training set is pruned to provide a more accurate classification tree. The accuracy is improved by avoiding overfitting the training data. All data analyses were performed using the SAS statistical package (version 6.12)

RESULTS
Factor analysis of the TCI with an eating disordered sample
Factor loadings for each individual scale were similar and positive, confirming the TCI factor structure for our eating disorder sample. In addition, the fraction of variance explained by the first factor was substantial for all scales.
Thus, we had confidence in using the seven temperament and character scales for the remaining analyses.

Factor analysis of personality and behavioural measures

The jackknife analysis revealed one highly-influential population, Munich, which differed from other sites with regard to the personality and behavioural traits of their subjects. In viewing Table 1, it is clear that the primary discrepancy between Munich and the other sites is substantially lower Y-BOCS scores, as well as lower YBC-EDS and MPS scores compared to all other sites. Due to the undetermined reason for this significant site difference, we excluded Munich from the remaining factor analyses.

The results of the factor analysis are presented in Table 2. The first four factors explained 51% of the variance in the personality and behavioural traits, with factors 1–4 accounting for 14, 13, 13 and 11% of the variance respectively. The weightings for factor 1 reflect a classic profile of eating disordered individuals, which includes moderate to strong positive loadings on trait anxiety (STAI-T), harm avoidance (HA), perfectionism (MPS), general and eating-specific obsessive–compulsive symptoms (YBOCS; YBC-EDS). An additional strong negative loading on this factor was found for self-directedness (SD). Factor 2 reveals ties between reward dependence (RD) and cooperativeness (C), with weaker links to SD and lack of anxiety (STAI-T). Factor 3 reveals a connection between perfectionism (MPS), persistence (PS), and self-transcendence (ST), with some weaker associations with general (Y-BOCS) and eating-specific obsessive–compulsive behaviours (YBC-EDS). Factor 4’s weightings are dominated by novelty-seeking (NS).

To explore differences among populations, a factor analysis was performed on data from the three North American sites with the largest sample sizes. Because a 5:1 ratio of subjects to variables is recommended for factor analysis (Bryant & Yarnold, 1998), data from the Los Angeles, London and Philadelphia sites were not factor analysed individually due to their

### Table 1. Raw scores on the personality and behavioural measures across all sites

<table>
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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>YBC-EDS</td>
<td>21.55 (6.53)</td>
<td>25.23 (5.59)</td>
<td>25.07 (4.66)</td>
<td>26.51 (7.53)</td>
<td>23.54 (5.52)</td>
<td>25.46 (5.74)</td>
<td>25.78 (5.64)</td>
</tr>
<tr>
<td>Y-BOCS</td>
<td>8.57 (10.70)</td>
<td>15.88 (11.84)</td>
<td>17.88 (10.89)</td>
<td>18.78 (13.50)</td>
<td>17.69 (10.46)</td>
<td>12.38 (12.31)</td>
<td>17.25 (11.02)</td>
</tr>
<tr>
<td>MPS</td>
<td>84.71 (23.97)</td>
<td>95.86 (21.06)</td>
<td>101.63 (21.68)</td>
<td>104.94 (23.61)</td>
<td>102.74 (20.44)</td>
<td>101.86 (18.50)</td>
<td>106.27 (27.15)</td>
</tr>
<tr>
<td>STAI-T</td>
<td>50.32 (12.35)</td>
<td>52.63 (14.10)</td>
<td>50.50 (14.24)</td>
<td>55.61 (15.92)</td>
<td>53.95 (13.25)</td>
<td>53.59 (13.01)</td>
<td>49.75 (16.60)</td>
</tr>
<tr>
<td>NS</td>
<td>18.88 (7.20)</td>
<td>19.53 (7.60)</td>
<td>15.55 (7.97)</td>
<td>16.37 (7.74)</td>
<td>18.04 (7.57)</td>
<td>14.53 (7.80)</td>
<td>19.79 (7.30)</td>
</tr>
<tr>
<td>RD</td>
<td>15.72 (3.86)</td>
<td>16.90 (3.84)</td>
<td>17.33 (3.97)</td>
<td>16.37 (3.96)</td>
<td>15.89 (4.50)</td>
<td>16.49 (5.50)</td>
<td>18.21 (3.50)</td>
</tr>
<tr>
<td>PS</td>
<td>4.76 (2.11)</td>
<td>5.80 (2.28)</td>
<td>6.76 (1.71)</td>
<td>6.11 (1.96)</td>
<td>5.72 (2.22)</td>
<td>6.38 (1.99)</td>
<td>6.22 (1.32)</td>
</tr>
<tr>
<td>SD</td>
<td>22.13 (8.96)</td>
<td>24.50 (9.40)</td>
<td>28.48 (9.75)</td>
<td>25.74 (9.59)</td>
<td>25.81 (9.54)</td>
<td>24.23 (7.60)</td>
<td>24.36 (9.44)</td>
</tr>
<tr>
<td>C</td>
<td>29.45 (5.57)</td>
<td>32.85 (6.51)</td>
<td>35.24 (6.30)</td>
<td>34.08 (7.24)</td>
<td>31.66 (6.93)</td>
<td>33.89 (5.98)</td>
<td>30.04 (5.46)</td>
</tr>
<tr>
<td>ST</td>
<td>13.62 (6.41)</td>
<td>13.74 (6.32)</td>
<td>16.01 (7.00)</td>
<td>15.87 (7.61)</td>
<td>14.04 (6.41)</td>
<td>13.09 (6.46)</td>
<td>18.00 (9.27)</td>
</tr>
</tbody>
</table>

*Values are means (standard deviations).*

YBC-EDS: Lifetime worst total score from the Yale–Brown–Cornell-Eating Disorder Scale.
Y-BOCS: Lifetime worst total score from the Yale–Brown–Obsessive–Compulsive Scale.
MPS: Lifetime worst total score from the Multidimensional Perfectionism Scale.
STAI-T: Trait Anxiety from the State-Trait Anxiety Inventory.
Temperament and Character Inventory (TCI) scales: NS, Novelty Seeking; HA, Harm Avoidance; RD, Reward Dependence; PS, Persistence; SD, Self-Directedness; C, Cooperativeness; ST, Self-Transcendence.
Deriving behavioural phenotypes of eating disorders

...relatively small individual sample sizes. Data from the Munich site were not factor analysed individually due to the undetermined reason for substantial differences on several assessment measures compared to all other sites. Only the weightings for the first factor are reported (Table 3), although four factors were extracted from the data. The first factor explains 23, 26 and 29% of the variance for the data from the New York (N = 65), Pittsburgh (N = 59), and Toronto (N = 52) populations respectively. For individuals from New York, the construct is specifically characterized by high loadings on STAI-T and HA. For individuals from Pittsburgh and Toronto, the construct encompasses a wider range of characteristics, including HA, STAI-T, MPS and obsessive–compulsive symptoms (general and eating-related) (Y-BOCS and YBC-EDS). Diminished SD is also strongly tied to this anxious–obsessional construct for each of these three sites.

**Discriminant analysis**

Discriminant analysis was used to evaluate the extent to which we can accurately classify subjects into diagnostic subgroups using only the extracted personality/behavioural factors. The degree to which these factors can accurately ‘sort’ our subjects has direct implications for using these traits to define a useful behavioural phenotype. To evaluate whether the factors were indeed useful for predicting subdiagnosis, discriminant analysis was performed using the factors and the four diagnostic subclassifications: AN-R, AN-P, AN-B and BN.

**Table 2. Factor analysis of personality and behavioural measures for individuals diagnosed with eating disorders (N = 270) (excluding the sample from Munich)**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Factor 1</th>
<th>Factor 2</th>
<th>Factor 3</th>
<th>Factor 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>YBC-EDS</td>
<td>0.454</td>
<td>*</td>
<td>0.294</td>
<td>*</td>
</tr>
<tr>
<td>Y-BOCS</td>
<td>0.486</td>
<td>*</td>
<td>0.274</td>
<td>*</td>
</tr>
<tr>
<td>MPS</td>
<td>0.531</td>
<td>*</td>
<td>0.508</td>
<td>*</td>
</tr>
<tr>
<td>STAI-T</td>
<td>0.806</td>
<td>-0.197</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>NS</td>
<td>-0.187</td>
<td>*</td>
<td>-0.201</td>
<td>0.722</td>
</tr>
<tr>
<td>HA</td>
<td>0.780</td>
<td>*</td>
<td>-0.187</td>
<td>-0.383</td>
</tr>
<tr>
<td>RD</td>
<td>*</td>
<td>0.692</td>
<td>*</td>
<td>0.152</td>
</tr>
<tr>
<td>PS</td>
<td>*</td>
<td>*</td>
<td>0.594</td>
<td>-0.204</td>
</tr>
<tr>
<td>SD</td>
<td>-0.773</td>
<td>0.325</td>
<td>0.212</td>
<td>*</td>
</tr>
<tr>
<td>C</td>
<td>-0.210</td>
<td>0.607</td>
<td>0.186</td>
<td>-0.149</td>
</tr>
<tr>
<td>ST</td>
<td>*</td>
<td>0.155</td>
<td>0.434</td>
<td>0.356</td>
</tr>
</tbody>
</table>

* YBC-EDS, Lifetime worst total score from the Yale-Brown-Cornell-Eating Disorder Scale.
* Y-BOCS, Lifetime worst total score from the Yale-Brown-Obsessive–Compulsive Scale.
* MPS, Lifetime worst total score from the Multidimensional Perfectionism Scale.
* STAI-T, Trait Anxiety from the State-Trait Anxiety Inventory.
* Temperament and Character Inventory (TCI) scales: NS, Novelty Seeking; HA, Harm Avoidance; RD, Reward Dependence; PS, Persistence; SD, Self-Directedness; C, Cooperativeness; ST, Self-Transcendence.

**Table 3. Factor analyses for the three North American recruitment sites with the largest sample sizes. Only the first factor loadings are presented**

<table>
<thead>
<tr>
<th>Sites</th>
<th>YBC-EDS</th>
<th>Y-BOCS</th>
<th>MPS</th>
<th>STAI-T</th>
<th>NS</th>
<th>HA</th>
<th>RD</th>
<th>PS</th>
<th>SD</th>
<th>C</th>
<th>ST</th>
<th>% Variance explained</th>
</tr>
</thead>
<tbody>
<tr>
<td>New York (N = 65)</td>
<td>0.277</td>
<td>0.395</td>
<td>0.368</td>
<td>0.830</td>
<td>-0.146</td>
<td>0.827</td>
<td>0.830</td>
<td>-0.213</td>
<td>-0.771</td>
<td>-0.227</td>
<td>0.168</td>
<td>23%</td>
</tr>
<tr>
<td>Pittsburgh (N = 59)</td>
<td>0.558</td>
<td>0.471</td>
<td>0.659</td>
<td>0.728</td>
<td>0.236</td>
<td>0.758</td>
<td>0.844</td>
<td>*</td>
<td>-0.844</td>
<td>-0.326</td>
<td>0.141</td>
<td>26%</td>
</tr>
<tr>
<td>Toronto (N = 52)</td>
<td>0.541</td>
<td>0.645</td>
<td>0.660</td>
<td>0.830</td>
<td>*</td>
<td>-0.119</td>
<td>*</td>
<td>-0.259</td>
<td>*</td>
<td>-0.907</td>
<td>0.163</td>
<td>29%</td>
</tr>
</tbody>
</table>

* Factor loading was 0.
Table 4. Discriminant analysis into four diagnostic subcategories using the personality/behavioural trait factors from Table 2

A Percentage of subjects with a given subdiagnosis who were correctly labelled as having that subdiagnosis

<table>
<thead>
<tr>
<th>Actual subdiagnosis</th>
<th>Correctly classified (true positive)</th>
<th>Incorrectly classified (false negative)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restricting anorexia nervosa</td>
<td>80.0%</td>
<td>20.0%*</td>
</tr>
<tr>
<td>Purging anorexia nervosa</td>
<td>52.0%</td>
<td>48.0%</td>
</tr>
<tr>
<td>Bingeing anorexia nervosa</td>
<td>49.0%</td>
<td>51.0%</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>57.6%</td>
<td>42.8%</td>
</tr>
</tbody>
</table>

* These subjects were incorrectly labelled with some subdiagnosis other than their true subdiagnosis of restricting anorexia nervosa when classified using the personality/behavioural factors.

B Percentage of subjects labelled as having a given subdiagnosis who actually have that subdiagnosis

<table>
<thead>
<tr>
<th>'Subdiagnosis’ based upon personality/behavioural factors</th>
<th>Correctly classified (true positive)</th>
<th>Incorrectly classified (false positive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Restricting anorexia nervosa</td>
<td>68.9%</td>
<td>31.1%†</td>
</tr>
<tr>
<td>Purging anorexia nervosa</td>
<td>64.6%</td>
<td>35.4%</td>
</tr>
<tr>
<td>Bingeing anorexia nervosa</td>
<td>60.0%</td>
<td>40.0%</td>
</tr>
<tr>
<td>Bulimia nervosa</td>
<td>47.5%</td>
<td>52.5%</td>
</tr>
</tbody>
</table>

† The actual subdiagnosis of these subjects is something other than restricting anorexia nervosa.

Bingeing anorexia nervosa' includes those anorexic subjects with bingeing only and those with bingeing and purging symptomatology; 'Purging anorexia nervosa’ includes those anorexic subjects with purging, but no history of bingeing.

the assigned ‘subdiagnosis’ based upon the personality/behavioural factors, what fraction of individuals actually have that subdiagnosis?’. By this view, the discriminant analysis was successful approximately two-thirds of the time for all AN subdiagnoses, but slightly less than half the time for a BN diagnosis (Table 4B).

DISCUSSION

Phenotypic characterization

Factor analysis revealed that the strongest factor underlying the cluster of personality and behavioural traits in this sample is a combination of trait anxiety, harm avoidance, perfectionism, obsessive– compulsive behaviour, and diminished self-directedness. Importantly, the current study raises the possibility that these five traits may be best conceptualized as parts of the same underlying construct among individuals with AN and related eating disorders. This primary factor supports past research (Casper, 1990; Brewerton et al. 1993; Kleifield et al. 1993; Kaye et al. 1993; Waller et al. 1993; Bulik et al. 1995a, b; 1997 a; Srinivasagam et al. 1995; Joiner et al. 1997; Fairbumb et al. 1997; Pollice et al. 1997; Kaye et al. 1998; Lilenfeld et al. 1998, 2000) demonstrating anxiety, harm avoidance, perfectionism and obsessive– compulsive behaviour to be potential vulnerability factors for the development of eating disorders, AN in particular.

Of all five traits, self-directedness has been the least studied. The central elements of self-directedness are the acceptance of responsibility for one’s own choices, identification of individually valued goals and purposes, development of skills and confidence in solving problems, and self-acceptance (Cloninger et al. 1993). Therefore, low levels of self-directedness may be conceptualized as immaturity, ineffectiveness, and lacking an integrated view of oneself. Low self-directedness has recently been demonstrated to be a reasonably good predictor of personality disorder (Bulik et al. 1995b) and high self-directedness has been found to predict rapid and sustained treatment response (Bulik et al. 1999) in a bulimic sample.
Several differences emerged across subjects from different parts of the world when sites were compared. For those individuals from New York, the primary personality factor was best characterized by trait anxiety, harm avoidance and diminished self-directedness. In addition to these three traits, for those from Pittsburgh and Toronto, the factor also encompassed perfectionism and obsessive–compulsive behaviour. Notably, the Munich sample differed from the other sites. There are at least two possible explanations for this difference. There could be cultural differences in the personality/behavioural constructs that characterize individuals with eating disorders from Munich compared with those from other parts of the world. Such differences may suggest the importance of cultural influences in the development of eating disorders and related personality characteristics. Alternatively, the differences could be due to translation of the assessment instruments, as Munich was the only non-English speaking site. Overall however, there were more similarities than differences across sites.

**Classification**

Our first question was: ‘How often are subjects assigned the correct subdiagnostic label, based solely upon the personality/behavioural factors?’ Results of the discriminant analysis revealed that on average, subjects were accurately classified into the proper diagnostic subtype category based solely upon the extracted personality/behavioural factors approximately two-thirds of the time. However, we were much more accurate (i.e. 80% accuracy) in classifying subjects with restricting-type anorexia nervosa into the appropriate category than any other eating disorder subtype.

Our second question was: ‘Of all those subjects “labelled” as belonging to a particular diagnostic subgroup based solely upon the personality/behavioural factors, how many actually have that diagnosis?’ Comparable diagnostic accuracy was demonstrated across all anorexic subgroups, whereas there was substantially less accuracy in classifying subjects as having bulimia nervosa. That is, more than half of subjects who were classified as bulimic based upon the personality/behavioural factors, were actually anorexic.

One possible reason that there was more accuracy in classifying subjects with restricting-type AN is because they have a more homogeneous phenotype. Our findings support the frequent observation that these individuals have a remarkably consistent personality and behavioural presentation (Sohlberg & Strober, 1994). If the restricting anorexic subtype indeed has the clearest phenotypic characterization, this subset of individuals may be the most promising focus for future genetic work.

Subtype misclassification may be partly explained by the fact that a significant minority of individuals with AN later develop BN (e.g. Eckert et al. 1995; Bulik et al. 1997b; Strober et al. 1997). However, if this ‘conversion’ is to take place, it most often occurs within 3 to 5 years after the onset of AN. This is precisely why we required restricting-type AN probands to have a ‘pure’ diagnosis; that is, the onset of their illness must have been at least 3 years prior to ascertainment, with no prior or subsequent history of bulimic behaviour. However, a similar ‘purity’ criterion was not applied to affected relatives; that is, they simply needed to meet DSM-IV criteria in order to receive a diagnosis of restricting-type AN. Therefore, some subtype misclassification may be explained by ‘impure’ diagnostic categories, consisting partially of relatives classified as AN-R who may later go on to develop BN.

**Caveats**

Inference for this study is restricted to a population of individuals with eating disorders. This population is commonly characterized by extreme values on personality and behavioural measures. Therefore, the relationships among these measures cannot be taken as representative of the general population. In addition, the nature of the current sample is very selective (i.e. anorexic probands and their eating disordered siblings). Therefore, we also may not be able to generalize our findings to all individuals with eating disorders. Next, the current study lacks a comparison group, such as a random sample from the population. A comparison sample would undoubtedly magnify the similarities among individuals with eating disorders, who tend to score more extremely on these personality and behavioural measures than would randomly-chosen individuals from the popu-
lation. Finally, our findings should be replicated on an independent sample.

Conclusions

The current findings suggest that the phenotypic characterization of eating disorders may be enriched for genetic studies by the inclusion of empirically derived personality and behavioural constructs. An important implication of the current findings is that trait anxiety, harm avoidance, perfectionism, obsessive–compulsive behaviour, and diminished self-directedness may constitute a single underlying construct among individuals with AN and related eating disorders. These data are consistent with a substantial literature showing that anorexic individuals have extreme levels of behavioural rigidity, emotional restraint and perfectionism.

The phenotypic variables assessed in this cohort may prove useful in elucidating the genetic susceptibility to disease in several ways. For example, analysis of genotypic data on pairs of affected relatives by allele-sharing methods can include quantitative covariates, such that pairs of relatives characterized by high trait anxiety, harm avoidance, perfectionism, obsessive–compulsive behaviour, and diminished self-directedness scores are given greater weight than pairs without this profile. This may allow for the definition of more genetically homogeneous subgroups among the cohort, facilitating the detection of loci whose action to increase risk for AN is more pronounced on the background of these personality/behavioural traits. We are hopeful that this effort to identify quantitative traits will offer enhanced power to search for accompanying genotypes that contribute to the pathophysiology of eating disorders.

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REFERENCES


