Associations between Dimensional Personality Measures and Preclinical Atherosclerosis: The Cardiovascular Risk in Young Finns Study

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Keywords: Atherosclerosis, Behavioral medicine, Carotid Intima-media thickness, Multivariate analysis, Personality, Temperament and character

Acronyms: IMT = carotid Intima-media thickness, TCI = Temperament and Character Inventory, NEO-FFI = a version of the five factor personality inventory, NS=Novelty seeking, HA=Harm avoidance, RD=Reward dependence, P=Persistence, SD=Self-directedness, C=Cooperativeness, and ST=Self-transcendence.

Abstract

Objective: To assess how multidimensional personality-trait theories, such as the Psychobiological Model of Temperament and Character, and the Five-factor Model of Personality, are associated with subclinical atherosclerosis as indicated by carotid Intima-media thickness (IMT). The analysis was designed to tolerate non-linear development in which the same personality profiles can have multiple final outcomes and different antecedent profiles can have the same final outcome.

Methods: 605 men and 844 women (average age 31.6 yr, s.d.=5.0, range=24-39) provided data on IMT and traits of the Psychobiological Model, 725 men and 1011 women were assessed for IMT and the Five-factor Model (age 37.7 yr, s.d.=5.0, range=30-45). Robust multidimensional Hotelling's T^2 statistic was used to detect personality differences between participants with high IMT and others. Model-based clustering method further explored the effect.

Results: Those with a high level of subclinical atherosclerosis within the sample (highest IMT-decile) had a combined higher persistence (i.e., were perseverative or perfectionistic), more disorganized (schizotypal) character, and more antisocial temperamental configuration than others ($p=0.019$). No effect was found for the Five-factor model ($p=0.978$). Traditional methods that did not account for multidimensionality and nonlinearity did not detect an association.

Conclusion: Psychological well-being may have positive effects on health that reduce atherosclerosis in the population as a whole. Increased subclinical atherosclerosis was associated with a profile that combines known risk factors, such as cynical distrust and hostile tendencies. More frequent use of statistical procedures that can cope with non-linear interactions in complex psychobiological systems may facilitate scientific advances in health promotion.

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Introduction

Surgeon and scientist John Hunter, “known for his anxious and argumentative nature (personality)” [1], noticed the association between stress and heart disease already in the 18th century by observing his patients and his own state [1]. The role of stress, and personality traits exposing individuals to stress, has been a topic of considerable interest in health psychology and behavioral medicine. A recent study found that Type D (distressed) personality [2] predicts clinical events after myocardial infarction, above and beyond disease severity and depression [3]. Type D is defined as a joint tendency towards negative affectivity and social inhibition. Several other studies have also found associations between different personality traits and cardiac risk factors [4-6]. In particular, extensive research has shown that personality components of hostility, including anger-proneness, cynical distrust, and paranoia, increased the risk of heart disease [7-15]. Likewise, components of personality related to anxiety-proneness, such as perfectionism, may be significant but are weaker and less consistent when their average effects are considered using linear regression analysis [16-19].

Following Gordon Allport’s early definition of personality as “the dynamic organization within the individual of those psychophysical systems that determine his unique adjustments to his environment” [20], most theories of personality have embraced the idea of personality as a complex system of interactions [21, 22]. Yet, most empirical research on personality divides this holistic concept into sub-traits and examines associations between the average effects of single traits and other variables of interest. For example, in regression analyses of population-based

data, psychosomatic researchers seek to establish a dose-response relation between single traits and atherosclerosis [5], thereby supporting the hypothesis of causation [23].

Linear regression analyses, with independent predictors, may be ill-suited for assessing the way the personalities of people influence their health and other important life outcomes if personality functions as a complex adaptive system rather than as a collection of separate components. First, personality traits may not follow dose-response patterns. For example, both high- and low-end deviations from the population average may be maladaptive. Second, the independent risk-trait approach ignores the clustering of multiple adverse traits that may act synergistically [24]. Third, personality is thought to induce predispositions rather than deterministic consequences, showing multi- and equi-finality [25]: the same initial value may occasionally lead to various outcomes ("multi-finality"), and different initial values may nonetheless result in the same outcome ("equi-finality"). Such behavior can result from randomness, chaotic dynamics, or from observations influenced by unmeasured variables in an incompletely specified dynamical system. Long-term emotional states and unhealthy behavior (personality) can spread dynamically through time and social networks, which is suggestive of rich underlying non-linear dynamics [26-30]. What kinds of approaches then might supersede the logic of linear analysis? First, instead of the dose-responses, it may be more natural and more informative to think in terms of the consequences of being in a certain location of the multidimensional personality space; that is, to seek the consequences of having a given personality profile that combines multiple dimensions of personality. Second, and related to the first point, careful re-examination of existing data sets using statistical strategies that assess multiple additive and interactive influences has been called for [24]. Third, in terms of statistical modeling, multi-finality and equi-finality imply that

"outliers" must be expected. Fortunately, robust statistics are available that can cope with the expected outliers [31].

In this study, we examine with a robust statistic whether there are specific personality configurations (profiles) associated with carotid intima-media thickness (IMT), a widely used indicator of subclinical atherosclerosis and its consequences [32-34]. The methodological approach is applied in a large population-based sample of Finnish men and women using two widely-used personality inventories defined by 1) the Psychobiological Model of temperament and character [35], and 2) the Five-factor Model of personality [36]. The 7 personality traits (4 temperament traits and 3 character traits) of the psychobiological model are assessed by the Temperament and Character Inventory (TCI) [37], while the five factors are assessed by the NEO-FFI personality inventory [38].

Methods

Participants

The participants were drawn from the ongoing prospective Young Finns study beginning in 1980. The subjects for the original sample (n = 3596) were selected randomly from 6 different birth cohorts, aged 3, 6, 9, 12, 15, and 18 years at baseline, as comprehensively detailed elsewhere [39]. All participants gave written informed consent, and the study was approved by the local ethics committees.

The Young Finns study currently contains two IMT measurements, one from the year 2001 and another from 2007. Data for full TCI together with IMT are only available from the 2001 follow-up, and data for NEO-FFI data have only been collected in 2007. Thus, the association between TCI and IMT was examined with 2001 data, and the association between NEO-FFI and IMT was examined with the 2007 data. Requiring a complete data-set for the measures in question, we are left with 605 men and 844 women in 2001 (for the TCI comparison), and 725 men and 1011 women in 2007 (for the NEO-FFI comparison). Altogether, 437 men and 658 women are the same in both comparisons. Table 1 summarizes the basic characteristics of the sample.

Measures

To assess carotid IMT, ultrasound studies were performed using Sequoia 512 ultrasound mainframes (Acuson, CA) with 13.0-MHz linear array transducers. The left carotid artery was scanned following a standardized protocol [40]. At least 4 measurements of the common carotid far wall were taken approximately 10 mm proximal to the bifurcation in order to derive mean carotid IMT. IMT measurements from the years 2001 and 2007 correlated with the coefficient 0.64. A shorter time-interval correlation of the IMT measurement over three months, assessed from 57 participants during 2001, was 0.7.

The Temperament and Character Inventory (TCI) [37], is based on the Psychobiological Model of Temperament and Character [35, 41]. Instead of the original true–false response format, the TCI items were rated on a five-point scale, ranging from 1 (not true for me at all) to 5 (true for me). Traits were calculated as means of the items comprising the trait. The four temperament traits of the TCI are Novelty seeking (NS), Harm avoidance (HA), Reward dependence (RD) [41] and Persistence (P) [35]. Novelty seeking is a tendency toward excitement in response to novel stimuli or signals of potential rewards or potential relief of punishment. Harm avoidance is a tendency to respond intensely to signals of aversive stimuli, thereby learning to inhibit behavior. Reward dependence is a tendency to respond intensely to signals of reward (especially to verbal signals of social approval). Persistence describes the ability to maintain or resist extinction of behavior previously associated with intermittent rewards or relief from punishment. The number of items in the questionnaire was 40 for Novelty seeking (Cronbach's $\alpha = 0.85$), 35 for Harm avoidance ($\alpha = 0.92$), 24 for Reward dependence ($\alpha = 0.81$), and 8 for Persistence ($\alpha = 0.64$).

The TCI also includes three character traits that measure the ability to regulate emotional conflicts in order to achieve mature goals and values [35]: Self-directedness (SD) is related to the individual's locus of control, Cooperativeness (C) to his or her ability to co-operate with other people, and Self-transcendence (ST) to the awareness of connections with what is beyond the individual self, such as spirituality and universal values. There were 44 items per scale for the Self-directedness (Cronbach's $\alpha = 0.90$), 42 Cooperativeness ($\alpha = 0.91$), and 33 Self-transcendence ($\alpha = 0.91$) dimensions.

The NEO-FFI test of the Five-factor theory was based on a 60-item English FFI-test developed by Costa and McCrae [38] and on a previous Finnish standardization of the 181-item NEO-PI-test by Costa and McCrae [42]. Some items were altered in the standardization process [43]. Altogether, there were 13 items for trait Extraversion ($\alpha = 0.82$), 12 for Neuroticism ($\alpha = 0.89$), 11 for Agreeableness ($\alpha = 0.77$), 12 for Conscientiousness ($\alpha = 0.84$), and 12 items for trait Openness ($\alpha = 0.74$).

Statistical Approach

Since we are mainly interested in how participants with the *high* (age and sex adjusted) IMT values behave, we first divide the sample to a high IMT and low/average IMT groups using a percentile cut-point. All participants with an IMT-value above 90^{th} sample percentile were assigned to a high IMT group, whereas the rest belong to the low IMT group. Then, we ask whether the multidimensional mean vectors of these two groups are the same (null hypothesis). If not, such a separation would indicate that IMT and personality are not independent, and

differences in means would then yield information about the behavioral patterns that are associated with the vascular health risk. Hypotheses regarding multidimensional means are classically evaluated using Hotelling's T^2 test that differs from its unidimensional counterpart, Student's t-test [44]. See supplementary online material for in-depth explanation.

The 90^{th} percentile cut-off was chosen because it implies a relatively high level of atherosclerosis in a given sample, but preserves sufficient group sizes for statistical comparisons. With this approach we seek the configuration of personality traits that is associated with the high IMT. Whereas logistic regression predicting the high IMT group-membership would ask what a linear trend in a given trait adds over the linear trends in other traits, the present approach asks where (in coordinates of the personality dimensions) the center of mass for observations lies for the high IMT group, and does this differ from the center of mass for other participants. This approach avoids some known measurement error problems [45], the multiple comparisons problem [46], and does not assume that group membership is predicted by a linear trend over the population, thereby allowing for nonlinearity.

In cross-sectional data, unless multi-finality is simply taken to mean randomness or low effect sizes, it actually implies either *several* models (as in mixture modeling [47]) or *outliers* from some core model (as modeled in robust statistics [31]): Although certain personality configurations (i.e. profiles of multiple personality dimensions) may predispose to adverse outcomes, a small proportion of participants with such configurations may be far-off in another direction, and vice versa (i.e. protective configurations give no guarantee of health). Therefore a robust statistic should perform better than the ones relying on strong distributional assumptions

[31]. For example, estimates of the mean can change markedly as a result of a large perturbation in just a single observation, whereas the median estimate can handle nearly 50% of 'incorrect' observations before it starts to yield arbitrary values (i.e., there is a break-down point 0.5 using the median as a measure of central tendency). Hence, we use the fast and robust bootstrap version [48] of the Hotelling's two sample T^2 test with MM-estimator (as implemented in FRB package, http://cran.r-project.org/web/packages/FRB/FRB.pdf version 1.6, by Roelant, E.; Van Aelst, S.; and Willems, G.; of the r-project in statistical computing http://cran.r-project.org/). For comparison, the S-estimator [31, 48] version and the ordinary version of the Hotelling's two sample T^2 test are applied in single occasion. The latter was an implementation by Klaus Nordhausen from the ICSNP package (http://cran.r-project.org/web/packages/ICSNP/ICSNP.pdf) version 1.0-7. For a different robustness procedure, an approach based on the Minimum Covariance Determinant is available for the one sample T^2 test [49]. An implementation from the Rrcov package (http://cran.r-project.org/web/packages/rrcov/rrcov.pdf) was used (version 1.3-01 by Valentin Todorov). Computations were carried out in cran-version R-2.31.1 for Windows.

In the case that a detectable difference exists between those high in IMT and others, model-based clustering (a mixture model) is also applied in order to explore how individual participants cluster in the personality-IMT-space [50]. Mbclust-function from EDA (exploratory data analysis) Matlab-toolbox by Wendy and Angel Martinez (http://lib.stat.cmu.edu/matlab/) was used. The procedure automatically selected the best-fitting model out of 9 x 4 models (varying cluster form flexibility x number of clusters), "best" being defined according to Bayesian

information criterion [50, 51]. Graphs were also plotted with Matlab® software-version 7.10.0 by Mathworks company (Natick, Massachusetts, USA).

Prior to actual analyses, age and sex were linearly regressed out from all variables, and the residuals were substituted for the original variables with the same naming convention. Then, standardization (mean to zero and standard deviation to one) was applied to all variables prior to further analysis. The observations about the unmodified original variables are summarized in Table 1 for convenience in comparison to other results.

Results

[TABLE 1]

Table 1 summarizes sample attrition and the basic characteristics of the sample. We defined the high IMT group as the highest sample decile in IMT. With this definition, there is a statistically significant difference between the high IMT groups' multidimensional TCI-mean vector and that of the other participants ($p = 0.019$), as indicated by the fast and robust version of the Hotelling's T^2 test. However, there was no detectable difference ($p = 0.978$) for the NEO-FFI measurement scale. As a sensitivity analysis, Figure 1 shows how the p-value changes as a function of the cut-off percentile, both in the immediate vicinity of 90^{th} percentile (left column) and for the wider set of possible cut-points (right column). It is clear that the cut-point does matter, but the p-value behaves smoothly around the set where significant values are seen: Arbitrarily small perturbations in the cut-point do not produce large jumps from significance to non-significance. Notice also that it is precisely the high cut-points (i.e., near to 90^{th} percentile or higher) that have an interesting health interpretation.

[FIGURE 1]

By showing the likelihood of a non-arbitrary mean difference in TCI profiles as stratified by the IMT, the preceding result also indicates that the multidimensional structure of the TCI traits is not independent of the IMT. Figure 2 shows the fast and robust bootstrap estimate for the

difference between the high IMT and low/average IMT group means in TCI traits that is one component determining the Hotelling's two sample statistic (for comparison, the non-robust ordinary estimate is shown with the dotted line). A weighted sum of group covariance matrices is another important ingredient of the statistic, thereby taking the covariance between the traits into account. Thus, Figure 2 does not contain all relevant information (cf. ellipses of supplementary Fig. S1), and single confidence intervals overlapping zero do not necessarily mean that the corresponding trait would not contribute to the overall T^2 statistic. The robustness of the estimate did matter, as shown by our finding that the ordinary Hotelling's two sample T^2 test did not achieve the usual threshold significance of 0.05 for the TCI (although it did show a trend with $p = 0.067$). The specific implementation of the robustness procedure did not matter: in addition to the MM-type robust estimator, the S-type robust estimator yielded a comparable result with $p = 0.018$ (breakdown point was 0.5 for both estimators). Ordinary one sample T^2 test did not find a difference between the zero vector and high IMT group mean ($p = 0.987$), but the Minimum Covariance Determinant-based robust version of the same test did find a difference with $p = 0.030$ (break-down point 0.75).

[FIGURE 2]

A similar pattern emerges using the unidimensional medians of the TCI traits (Figure 3). Because there the outlier control (robustness) works in one dimension at time, comparisons with existing literature may be facilitated. For each trait, the 95% confidence interval of the difference in high and low IMT group medians is derived from the permutation distribution, and it is thus (in the lower panel) comparable to a robust unidimensional level 0.05 test for the group

difference [52]. Since the single statistically significant effect would not withstand a correction for multiple comparisons, traits are unlikely to represent independent effects in the Hotelling's tests.

[FIGURE 3]

Model-based clustering further describes the dependencies among different TCI-traits and IMT. Figure 4 shows results for the best fitting model, for three different sets of variables. When all seven TCI-traits were used together with IMT, a clear high-IMT cluster was not found; when temperament and character traits were separately analyzed, high-IMT cluster covered approximately 10% of the sample with similar pattern as in Figures 2 and 3. At first sight, it seems that participants might differ in temperament- vs. character-analysis. However, in the former case 5.6% of participants were from high-IMT cluster with higher likelihood than from other clusters [50], in latter case 9.7% of participants were labeled to high-IMT cluster, and intersection of these labels constituted 3.5% of the sample. Therefore, it appears that some do have both temperament- and character-related high IMT; only, the seven-dimensional clustering model is too large (too many free parameters) to detect this, because larger models require larger data sets for successful estimation [53]. The intersection group had the largest effect-size in IMT (Cohen's d = 2.53 [54]), with absolute TCI effect sizes ranging from 0.09 to 0.41.

[Figure 4]

In order to show that the above methodological steps were needed, supplementary on-line material presents results for other frequently used statistical methods including linear and logistic regression analyses, trait-wise group comparisons, and effect size analyses. Due to space restrictions, the subsection below only briefly summarizes these results.

Methodological Comparison with Other Basic Approaches (Summary of Supplementary Results)

When using TCI-traits as independent variables, the linear IMT-trend in the total population differed from the linear trend in predicting the probability of having a high IMT (Tables S1 and S2). The linear trend predicting high IMT was still weaker than simple group-mean comparisons against the high IMT group. Stronger linear effects were demonstrated by boosting TCI stability via averaging with earlier sequential data [5]. In that earlier study, high Reward dependence was associated with a high IMT [5], which differs from the present findings. There is no contradiction between these observations within the same population, but the differences point out that it may be sometimes risky to draw conclusions from linear analyses in health psychology and behavioral medicine, which typically involve time-evolving non-linear systems [20, 22, 26-30].

Individual traits alone did not produce significant associations in this data (albeit a single one that did not withstand the correction for multiple comparisons). In general, it may be unwise to neglect borderline significant effects in a holistic theory without considering the synergistic effects of component variables within the complex system (cf. Figure S1) [24]. Robust Hotelling's T^2 statistic detected information that would not be readily seen using some of the

most traditional regression approaches (linear and logistic regression). It is likely that it also avoided a known bias that complicates the interpretation of regression results [45]: while in single linear model it seems that NEO-FFI traits Extraversion and Neuroticism had statistically significant effects (see Table S1), using them in a separate linear model suggests that these effects are an artifact resulting from bias due to the combination of their correlation ($r = -0.523$) and measurement errors (Cronbach's α of 0.82 and 0.89, respectively).

Discussion

The results presented here indicate that IMT is significantly dependent on personality variables as measured by the TCI, but not on those measured by the Five-factor model. A robust statistic was needed to detect the difference, possibly due to the multi- and equi-finality of personality outcomes [25]. High IMT values (indicating elevated subclinical atherosclerosis) were associated with a disorganized character configuration (a schizotypal profile with low self-directedness, low cooperativeness, and high self-transcendence [35]) in combination with an antisocial temperament configuration (an adventurous profile with high Novelty seeking, low Harm avoidance, Low Reward dependence [41]). Furthermore, the tendency to be persistent despite intermittent reinforcement (high Persistence) was the third component of the personality configuration associated with the high IMT (see Figures 3 and 4). Highly persistent people are typically described as determined, ambitious, and perseverative or perfectionistic [35]. Highly persistent people are usually described as perfectionistic when they persist in behaviors that lead to high achievement, whereas they are usually describe as “perseverative” when they persist in the self-defeating behaviors that are typical of people who are also antisocial and disorganized. However, notice that these results pertain to tendencies in continuous traits, not necessarily to clinically significant personality disorders.

The pattern that we observed has some similarity with the Type D personality (negative affectivity combined with social inhibition), which is associated with coronary heart disease and hypertension [2], and predicts clinical events after myocardial infarction [3]. Type D is

associated significantly with low Reward Dependence (Cohen's d = 0.63 [54]), low Self-directedness (d = 1.03), and low Cooperativeness (d = 0.66) [55], as in our results for the predictors of atherosclerosis. However, Type D is also associated with significantly lower scores on Novelty Seeking (d = 0.18) and Persistence (d = 0.20), higher scores in Harm Avoidance (d = 1.25), and has no significant association with Self-transcendence [55]. Thus some of the effects identified by the TCI are represented within the Type D construct, but other contributors are not recognized. Harm Avoidance, in particular, seems to play an important role in cardiovascular susceptibility that is nonetheless difficult to understand in isolation; for example, low values are associated with IMT both independently (see Supplementary Table 2 and ref. [5]) and within the presently identified trait-configuration (e.g., Figure 3), but high values are associated with lower vagal control and higher resting heart rate [4], and with high blood pressure in non-persistent men [56].

The disorganized (schizotypal) character configuration is the strongest predictor for the presence of psychopathology in TCI [35, 57, 58]. People with the disorganized profile are expected to exhibit cynical distrust and paranoia, which are typical of schizotypal people [59] and also two of the most consistent psychological predictors of heart disease [7-9, 11, 12]. In psychiatric patients, the antisocial temperament configuration is associated with impulsive-aggressive, oppositional, and opportunistic behavior [37], so it is characterized by a distinct component of hostility that is usually described as anger-proneness and argumentativeness [11, 13-15]. Likewise, high Persistence is characterized by a person's being striving, ambitious, and perseverative or perfectionistic, which leads to an intense mixture of positive (i.e., active, enthusiastic) and negative (i.e., anxious, frustrated) emotions [60]. Hence, the TCI profiles we

identified capture the full range of personality features that have been identified in prior work. This result illustrates the advantages of working with a comprehensive personality inventory rather than deriving specialized scales. Indeed, it has been suggested that a general disposition toward negative affectivity and maladjustment may be more important for disease risk than any specific negative affect [24]. We found that the people with high IMT were more prone to anger and cynical distrust and were perseverative, which suggests that they are likely to persist in self-defeating behaviors that reinforce their negative feelings and expectations.

Healthy psychological functioning protects against the heart disease [61], which is in line with Figure 3 where maturely organized and flexible characteristics are associated with low or average IMT. Such well-organized personality profiles are strongly predictive of perceived health and happiness [62, 63]. Instead, simultaneous persistent, antisocial, and disorganized behavioral tendencies may result in discontent, maladjustment, and psychological stress. Discontent, anxiety, and depression have predicted the future progression of IMT in previous studies [12, 64, 65], although depression was only cross-sectionally associated with IMT in the Young Finns data [66].

Psychogenic stress is likely to result from maladaptive behavior and has been repeatedly linked to cardiac risk [1, 67, 68] and inflammation [69]. Atherosclerosis is a complex inflammatory disease whose exact etiology is still unclear [70]; stressor responsiveness interacts with immune function [71]. Chronic stress and continuously elevated blood cortisol-level can damage the hippocampal formation of the brain that is involved in the shutting-down of the stress response; therefore, a vicious circle may form [72]. Another pathway from antecedent personality traits to

IMT is through unhealthy habits (e.g., smoking and fast food diets) that are well-known correlates of personality disorders, especially antisocial personality disorder [37, 41, 57, 58]. However, putative stress and habit formation pathways to atherosclerosis are likely to be intertwined, as both the hypothalamus and the hippocampus have been linked to disturbances of food intake and body-weight regulation [72], and emotional stress can lead to fatigue and physical inactivity [71]. In contrast, physical activity can increase neurotrophin expression in cortex and hippocampal regions, and positive affect and good self-esteem can lower cortisol-levels [72].

A crude estimate for the effect size of the combined disorganized character, antisocial temperament, and high persistence on IMT, versus the effect of opposite configuration (organized, cautious, and non-persistent) exceeded over twice that of any individual component, being statistically between small and moderate (Cohen's $d = 0.38$, supplementary results). IMT-difference between these two overall-typologies was 42.13 μm. Clinically such IMT-difference is meaningful. For the individual temperament traits averaged over two assessments, the difference between the lowest and highest *tertile* varies from 4 μm to 22 μm [5]. For a smoking habit, an age-adjusted IMT effect size of 11-13 μm was observed in the same population study as here [40]. In a study for males (age 40-59) with previous coronary artery bypass surgery, each 30 μm increase per year in carotid IMT translated to 3.1-fold relative risk of coronary event [73]. A meta-analysis of the general population estimated that a 100 μm increase in age- and sex-adjusted IMT implies a 10-15% increase in the future risk of myocardial infarction, and 13-18% increase in stroke risk [33].

There are good reasons to believe that multidimensional, nonlinear interactions exist between personality and IMT, because classical (minimum-variance unbiased) estimators had less statistical power than the applied robust procedures, and existing literature supports the view [20, 22, 25-30]. Taking the potential multi- and equi-finality [25] directly into account would require a dense longitudinal sampling, or intimate understanding of a (possibly very high-dimensional) system of personality-health interactions; an understanding that does not yet seem to exist. However, if we assume that a degree of multi-finality exists, some proportion of participants end-up having very different IMT-values or personality traits despite similar pattern of other traits (reasons may include differing background conditions, long-tailed random deviations, and dynamical development that is sensitive to small deviations in initial values, i.e. chaotic [74]). These conditions should interfere more with non-robust/classical analyses using a constrained set of informative variables (background conditions) than with robust analyses that allow some outliers and more potential interactions. Indeed, taking multi- and equi-finality into account via the robust, multidimensional statistic, allowed the detection of an effect that would have otherwise remained merely a suggestive finding. Therefore, the present results lend further indirect support for the hypothesis of multi-/equi-finality and nonlinear development.

Limitations

We have observed differing results for IMT measured in 2001 compared to that measured in the 2007 with respect to some other variables, work stress for example [75]. The results shown in Table 1 also suggest that attrition may have had a greater influence on the IMT sample in the 2007 measurement than it did in 2001. Although there is substantial overlap between the subjects

studied at the two times of measurement, a direct comparison between different theories of personality may be questioned because they were not both measured at the same time. Nevertheless, psychopathological tendencies are expected to be greater in the attrition sample than in the active study participants according to both theories (see Table 1 and ref. [35, 36]). While differential attrition may have consequences on the direct generalizability of the present results, it does not invalidate comparisons that were made within each sample here. It is very likely that similar trends exist in the total study population as well. Regarding interpretation of the results in general, a population-level effect was observed using a robust statistic. This means that one must be cautious when extrapolating results from groups to particular individuals because outliers exist.

Summary

When assessed with a robust and multidimensional statistic, persistent people with disorganized (schizotypal) character and antisocial temperamental configurations had higher intima-media thickness than others, and thus have a comparatively high atherosclerosis progression [32-34]. Lower IMT was linked with well-organized character traits that are known to be associated also with perceived well-being [62, 63]. Psychological well-being may thus have health-promoting effects to reduce the burden of physical disease on the population level. Methods that do not take multidimensionality, multi-finality and non-linearity into account did not detect an association between personality and IMT. Therefore, robust statistical procedures that can cope with non-linear interactions offer promise in advancing a rigorous understanding of the complex psychobiological systems that are crucial for health promotion in behavioral medicine.

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Figure captions

Figure 1. The achieved significance level (p-value) for the fast and robust bootstrap Hotelling's two sample T^2 test between the high IMT group and others as a function of the IMT percentile cut-point. The upper panels show this for the TCI measurement scale and the middle panels for the NEO-FFI, while the solid line indicates where p = 0.05. Lower panels plot the high IMT group size per cut-point.

Figure 2. Fast and robust bootstrap estimate for the difference between the high IMT and low/average IMT group mean-vectors of TCI traits (the non-robust ordinary estimate is shown with the dotted line), along with 95% confidence intervals. 'High' is defined as exceeding the 90^{th} percentile of the IMT sample distribution. Abbreviations are NS=Novelty seeking, HA=Harm avoidance, RD=Reward dependence, P=Persistence, SD=Self-directedness, C=Cooperativeness, and ST=Self-transcendence.

Figure 3. Differences between high and low/average IMT group medians in all TCI traits. 'High' is defined as exceeding the 90^{th} percentile of the IMT sample distribution, 'low' as the rest of sample. Ninety five percent confidence intervals are derived from the permutation distribution. If they do not overlap zero in the lower panel, then the unidimensional permutation test for the given trait would reject the null hypothesis with a significance level of 0.05. Abbreviations are NS=Novelty seeking, HA=Harm avoidance, RD=Reward dependence, P=Persistence, SD=Self-directedness, C=Cooperativeness, and ST=Self-transcendence.

Figure 4. Results from Model-based cluster analyses. Each panel in the figure corresponds to an analysis using the variables that are indicated below the panel (abbreviations are IMT=Carotid intima-media thickness, NS=Novelty seeking, HA=Harm avoidance, RD=Reward dependence, P=Persistence, SD=Self-directedness, C=Cooperativeness, and ST=Self-transcendence). Bars show the means for the clusters indicated by respective coloring; the number of clusters was chosen using Bayesian Information Criterion. Legends show what proportion of participants is estimated as belonging to each of the clusters (size), and how large high-dimensional volume that cluster spans (det, the value of the determinant of covariance-matrix associated with the cluster; the choice between equal vs. differing cluster volumes was also contingent on Bayesian Information Criterion).

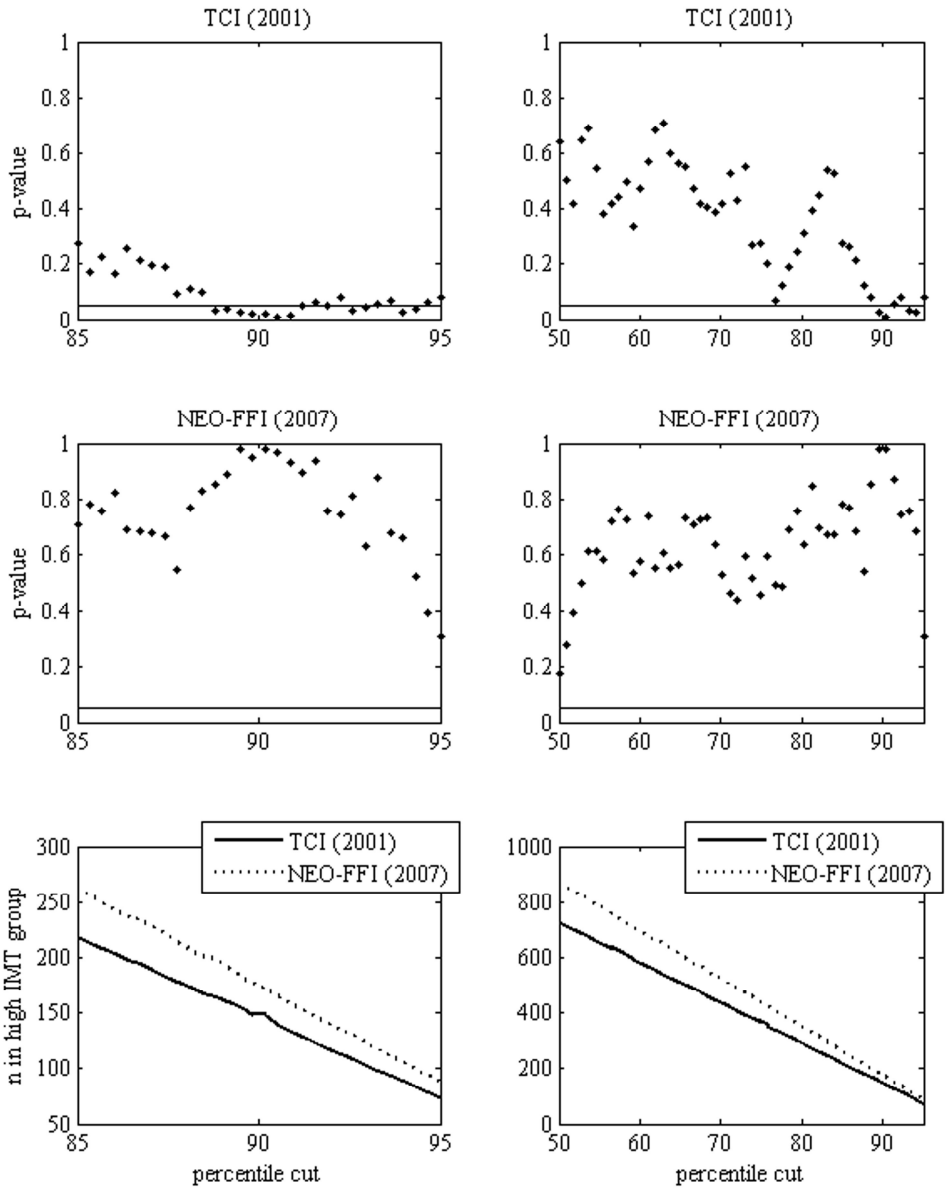
Table 1. Sample Characteristics and Attrition

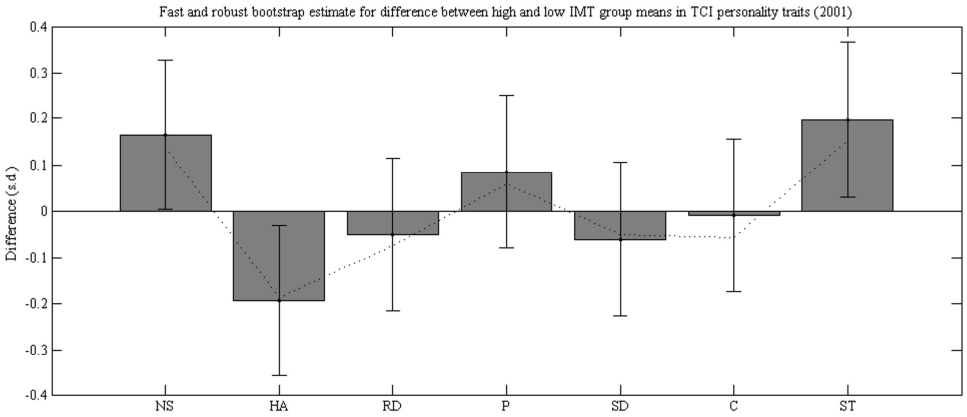
Comparison between TCI and IMT using data collected during the year 2001					
Measure	**Study sample**		**Attrition sample**		**p-value**
Number of participants	1449		2147		
Percentage of males	41%		54%		< .001
	mean	**s.d.**	**mean**	**s.d.**	
Age of participants (years)	31.59	5.03	31.35	4.96	.157
Intima-media thickness (μm)	580.84	92.62	581.00 (n=816)	91.77	.969
Novelty seeking	2.99	0.40	3.02 (n=304)	0.42	.213
Harm avoidance	2.62	0.53	2.70 (n=304)	0.58	.021
Reward dependence	3.37	0.43	3.32 (n=304)	0.51	.069
Persistence	3.21	0.56	3.18 (n=304)	0.53	.353
Self-directedness	3.72	0.44	3.65 (n=304)	0.50	.011
Cooperativeness	3.76	0.41	3.71 (n=304)	0.45	.046
Self-transcendence	2.47	0.56	2.53 (n=304)	0.58	.056

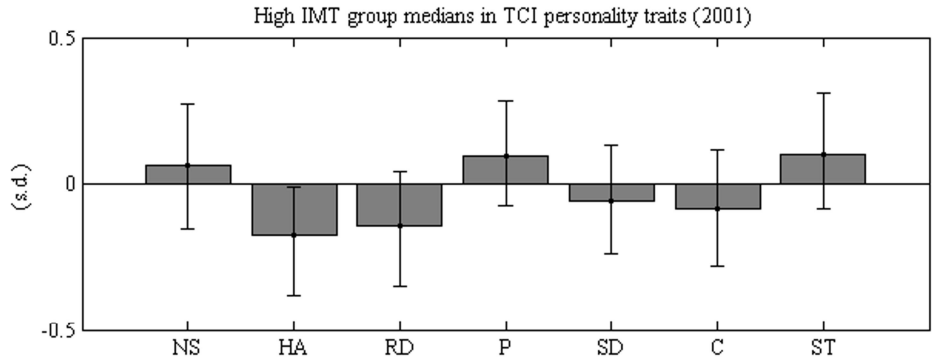
Comparison between NEO-FFI and IMT using data collected during the year 2007					
Measure	**Study sample**		**Attrition sample**		**p-value**
Number of participants	1736		1860		
Percentage of males	42%		56%		< .001
	mean	**s.d.**	**mean**	**s.d.**	
Age of participants (years)	37.72	4.99	37.18	4.98	.001
Intima-media thickness (μm)	623.48	95.55	637.69 (n=461)	99.67	.005
Extraversion	2.21	0.34	2.20 (n=318)	0.37	.520
Neuroticism	2.38	0.67	2.53 (n=318)	0.74	< .001
Agreeableness	3.66	0.49	3.60 (n=318)	0.50	.031
Conscientiousness	3.70	0.55	3.67 (n=318)	0.59	.475
Openness	3.18	0.53	3.21 (n=318)	0.59	.261

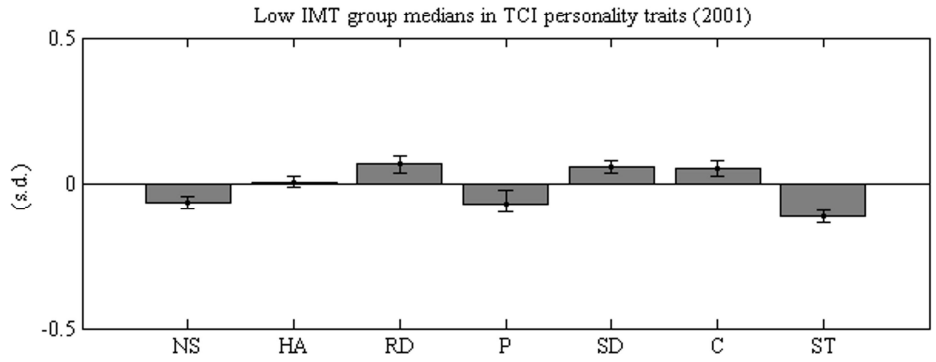
Note: the p-values are from two-tailed t- or chi-squared tests for the difference between the study and attrition samples, and s.d. denotes the standard deviation. The attrition sample consists of participants who lacked information either regarding personality or regarding IMT. Some had one but not other, allowing comparison against those with both. For such cases, n in parentheses denotes the sample size for this sub-sample.

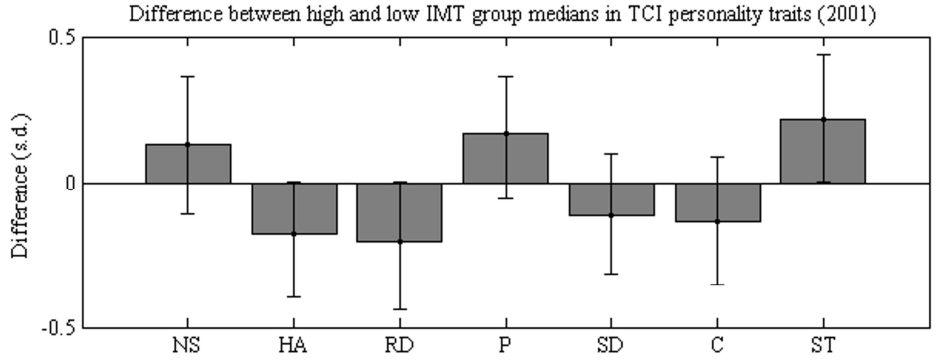
Figures


TCI (2001)
p-value
TCI (2001)
NEO-FFI (2007)
p-value
NEO-FFI (2007)
TCI (2001)
NEO-FFI (2007)
n in high IMT group
percentile cut
TCI (2001)
NEO-FFI (2007)
percentile cut

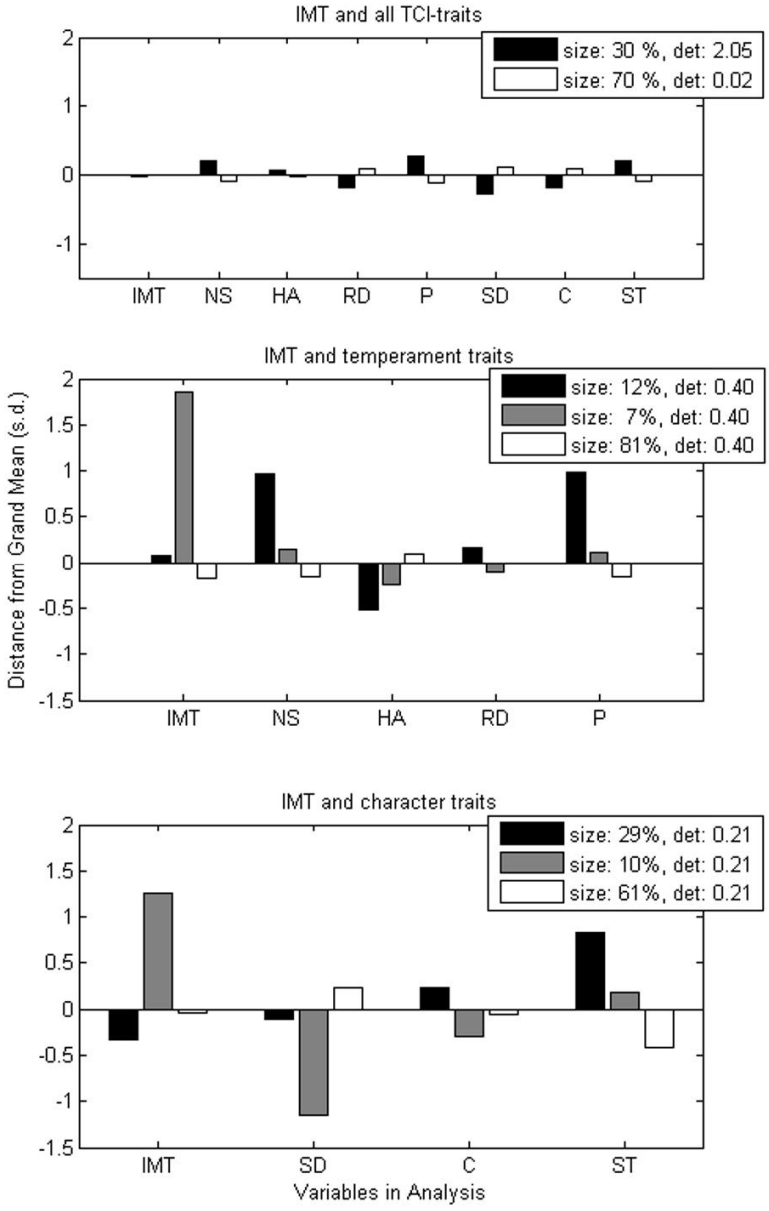

Fast and robust bootstrap estimate for difference between high and low IMT group means in TCI personality traits (2001)
Difference (s.d.)
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
NS
HA
RD
P
SD
C
ST


High IMT group medians in TCI personality traits (2001)
0.5
0
-0.5
(s.d.)
NS
HA
RD
P
SD
C
ST


Low IMT group medians in TCI personality traits (2001)
0.5
0
-0.5
(s.d.)
NS
HA
RD
P
SD
C
ST


Difference between high and low IMT group medians in TCI personality traits (2001)
0.5
0
-0.5
Difference (s.d.)
NS
HA
RD
P
SD
C
ST

Model-based Cluster Means for Standardized Variables



Associations between Dimensional Personality Measures and Preclinical Atherosclerosis: Supplementary On-line Material

Intuitive Examples of Hotelling's statistic and Model-based clustering

Simple statistical t-tests may not detect a synergistic multidimensional difference, and in the context of inherently multidimensional systems, they lead to the multiple comparisons problem. The Hotelling's T^2 statistic corrects these problems: Figure 1S visualizes this argument in order to provide geometric intuition for the reader. In addition, as discussed in the main article, a robust version of the method is needed. Robustness indicates that a minor proportion of observations are allowed to divert from the pattern of the majority (e.g., of the Figure 1), possibly greatly. Robust statistical procedures implement this by preventing outliers from disproportionally affecting the estimation procedure of the core model.

[Figure 1S]

Model-based clustering can automatically accommodate for outliers with an additional 'cluster' that has a large variance but small weight (i.e., only a small proportion of observations is modeled as being 'generated' from that cluster). This method needs more care in its interpretation, because almost any data density can be approximated with a mixture (i.e., weighted sum) of sufficiently many normal distributions [1]; model flexibility can be controlled with Bayesian information criterion [1, 2]. In addition to outliers, hidden variables can be modeled with a mixture model. Figure 2S provides an intuitive example of how a cluster-model

can automatically accommodate the presence of an unobserved bivariate latent variable that serves to confound many classical statistical methods.

[Figure 2S]

Other Statistical Analyses for Comparison

Demonstrating that the methodological steps in the associated manuscript were indeed needed, we now present results from other frequently used statistical methods. An ordinary linear regression model predicting IMT with all TCI traits ($p = 0.234$), or with all NEO-FFI traits ($p = 0.071$), does not significantly differ from the null model (IMT mean). The individual linear regression coefficients are shown in Table S1, both when all the traits of the respective theory are included in the model and when separate traits are used alone.

[TABLE S1]

Table S2 shows results from the logistic regression model predicting who will belong to the highest decile in IMT using TCI or NEO-FFI traits. Logistic regression models did not predict a single participant to belong to the high IMT group, thus they have an error rate equal to the null model with just a single constant predictor. The same holds for a model using only the statistically significant Harm avoidance dimension of the TCI.The single significant effect would also be drowned out by the usual multiple comparison corrections. Linear models do not readily recognize the effect of Harm avoidance (Table S1), suggesting a non-linear interaction between

Harm avoidance and other personality variables on IMT. Very similar results were obtained for robust counterparts of linear and logistic regression models (not shown, available from authors upon request).

[TABLE S2]

Finally, we wish to show that the present multidimensional result of interest is not simply due to a single trait. An unidimensional Welch's test, assessing mean difference in IMT between the group above 90th IMT-percentile versus others, yielded p-value 0.093 for the trait Novelty seeking, 0.017 for Harm avoidance, 0.414 for Reward dependence, 0.485 for Persistence, 0.569 for Self-directedness, 0.524 for Cooperativeness, and 0.073 for Self-transcendence (a two sample t-test yielded 0.109, 0.029, 0.383, 0.505, 0.559, 0.503, and 0.075). The achieved significance level of 0.05 with both a Bonferroni- and a Šidàk-correction for multiple comparisons [3] implies that p-values should be lower than 0.007. None achieve this strict limit (the same holds for the robust counterparts in Figure 4). Clearly, several individual p-values are suggestive (i.e. < 0.1), and hence it is probably unwise to exclude the multidimensional information (cf. Fig. S1). For the individual NEO-FFI traits, the lowest p-value for a two-sample test between the high IMT group and others was 0.577 (t-test) or 0.648 (Welch's test).

The ninety percentile cut-off naturally induced a large (Cohen's) effect size [4] between the high IMT and low IMT groups ($d = 2.76$, and 183.64 μm age- and sex-adjusted IMT-difference with pooled standard deviation 66.37 μm). The *d*-values for TCI-traits were small: Novelty seeking (0.14), Harm avoidance (-0.19), Reward dependence (-0.08), Persistence (0.06), Self-

directedness (-0.05), Cooperativeness (-0.06), and Self-transcendence (0.15). Medians are often used to divide the TCI-traits into high versus low configurations, which are then combined to form typologies [5, 6]. The IMT-effect size for the antisocial topology (high Novelty seeking, low Harm avoidance, low Reward dependence, as in Figure 4, n = 186, 12.8% of the sample) versus its opposite configuration (low Novelty seeking, high Harm avoidance, high Reward dependence, n = 179, 12.3%) was 0.16, corresponding to 14.21 μm in IMT. For disorganized typology (low Self-directedness, low Cooperativeness, high Self-transcendence, n = 290, 20.0%) and its' opposite (n = 285, 19.6%), the effect size was 0.10 (8.55 μm IMT-difference). For high versus low Persistence, the effect size was 0.05 (4.52 μm). For the intersection of antisocial, disorganized, and persistent typologies (n = 25, 1.7%) versus the opposite typology (n = 12, 0.8%), effect size was 0.38, corresponding to a 42.13 μm (s.d. 109.84 μm, p = .282 for a non-robust t-test).

Supplementary References

[1] Fraley C, Raftery AE. Model-based clustering, discriminant analysis, and density estimation. J Am Stat Assoc. 2002;97:611-32.

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Supplementary Figure Captions

Figure 1. Illustration of the Hotelling's two sample T^2 test: Two samples (circles and stars) were simulated from two different two-dimensional normal distributions whose level sets are shown with the solid and the dotted ellipse. Horizontal thick line shows the mean difference in the canonical x *variable, whereas the vertical thick line shows the same for the* y *variable. The third and slanted thick line is the multidimensional distance between mean vectors. Hotelling's test is more sensitive than the two Student's tests because 1) the multidimensional distance between two groups is larger than the unidimensional ones, 2) the multidimensional overlap of distributions is small due to their elliptic form (correlation) in contrast to the large overlap in their unidimensional projections (density functions shown in the bottom and in the left corner of the figure), and 3) if one wishes to be conservative the unidimensional p-values need to be adjusted upwards in order to avoid making a type I error in at least one test.*

Figure 2. Artificial data set for illustration of Model-based clustering. Stars correspond to observations with unobserved factor A and circles to observations without it. In panel a, contours correspond to contours of simple normal distribution fitted to the data points, while in panel b, they correspond to weighted sum (mixture) of two normal distributions. Many classical statistics, like correlation and regression coefficients, treat the data according to the first model (panel a). Model-based clustering, however, can accommodate to data being divided by an unobserved factor A, yielding a more realistic interpretation of the data (in panel b): Instead of positive correlation between x *and* y *(panel a), a small group (those with factor* A*) exists that have a negative association between* x *and* y *but higher overall-values in both variables.*

Supplementary Tables

Table S1. Ordinary Least Squares Regression Analyses Predicting IMT with TCI or NEO-FFI

TCI	**Single linear model**			**Separate linear models**		
Predictor variable	**β**	**s.e.**	**p**	**β**	**s.e.**	**p**
Novelty seeking	0.008	0.030	0.790	0.033	0.026	0.217
Harm avoidance	-0.063	0.039	0.106	-0.027	0.026	0.301
Reward dependence	-0.006	0.033	0.863	0.018	0.026	0.503
Persistence	-0.027	0.028	0.326	-0.017	0.026	0.507
Self-directedness	-0.090	0.041	0.028	-0.021	0.026	0.427
Cooperativeness	0.061	0.039	0.118	0.028	0.026	0.285
Self-transcendence	0.014	0.029	0.618	0.032	0.026	0.218
NEO						
Predictor variable	**β**	**s.e.**	**p**	**β**	**s.e.**	**p**
Extraversion	0.082	0.030	0.007	0.032	0.024	0.179
Neuroticism	0.066	0.030	0.025	0.033	0.024	0.176
Agreeableness	-0.023	0.026	0.361	-0.027	0.024	0.260
Conscientiousness	-0.003	0.026	0.914	-0.002	0.024	0.933
Openness	-0.030	0.025	0.236	-0.014	0.024	0.573

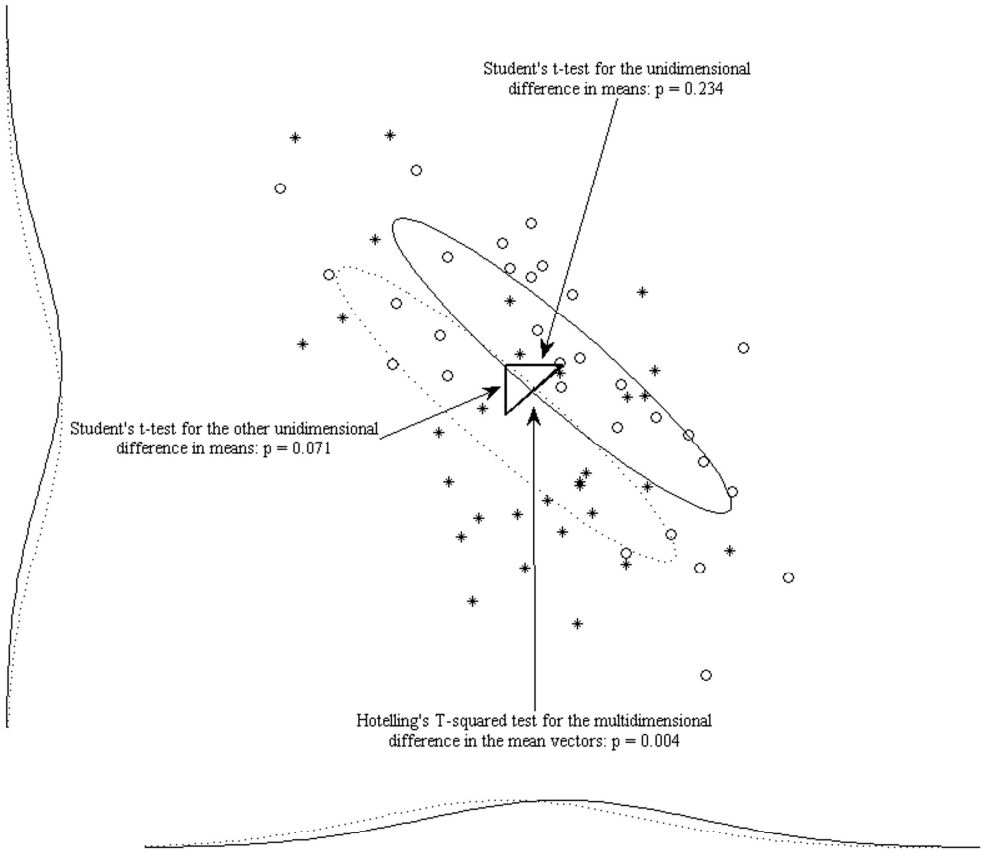
Note: TCI and NEO-FFI traits were always modeled separately. Under the title ‘Single linear model’, all traits of the respective theory were included in a single linear regression model. The columns corresponding to title ‘Separate linear models’ show the results when only the given trait was used in ordinary least squares regression model. All variables were adjusted for age and sex and standardized prior to analyses.

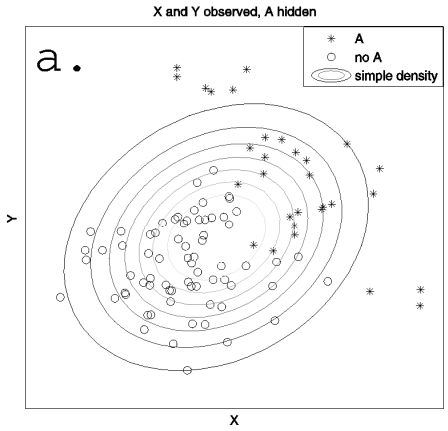
Table S2. Logistic Regression Analyses Predicting who is above 90th Percentile of IMT Using TCI Traits, and then, Using NEO-FFI Traits

TCI	**Single logistic model**			**Separate logistic models**		
Predictor variable	**β**	**s.e.**	**p**	**β**	**s.e.**	**p**
Novelty seeking	0.019	0.100	0.852	0.138	0.086	0.109
Harm avoidance	-0.321	0.131	0.014	-0.194	0.089	0.030
Reward dependence	-0.069	0.107	0.519	-0.075	0.086	0.383
Persistence	0.005	0.093	0.959	0.058	0.087	0.504
Self-directedness	-0.199	0.136	0.143	-0.050	0.086	0.559
Cooperativeness	-0.040	0.127	0.759	-0.058	0.086	0.503
Self-transcendence	0.113	0.093	0.225	0.151	0.085	0.076
NEO-FFI						
Predictor variable	**β**	**s.e.**	**p**	**β**	**s.e.**	**p**
Extraversion	0.062	0.101	0.541	0.036	0.080	0.648
Neuroticism	0.049	0.098	0.618	0.017	0.079	0.828
Agreeableness	-0.042	0.084	0.619	-0.036	0.080	0.653
Conscientiousness	0.034	0.087	0.696	0.031	0.080	0.696
Openness	-0.003	0.084	0.970	0.006	0.080	0.936

Note: TCI and NEO-FFI traits were always modeled separately. Under the title ‘Single logistic model’, all traits of the respective theory were included in a single logistic regression model. The columns corresponding to title ‘Separate logistic models’ show the results when only the given trait was used in a logistic regression model. All variables were adjusted for age and sex and standardized prior to analyses.

Supplementary Figures

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A
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Y
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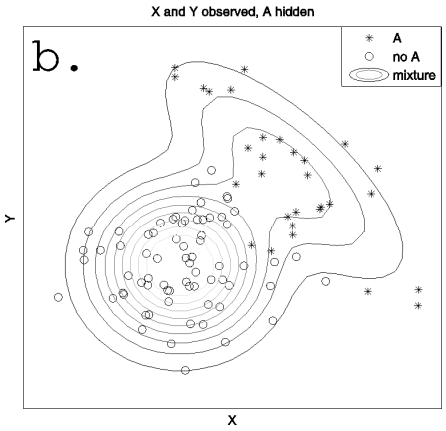
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