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Neurobiological Functioning and the Personality-Trait Hierarchy: Central Serotonergic Responsivity and the Stability Metatrait

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Abstract

Trait domains of the five-factor model are not orthogonal, and two metatraits have often been estimated from their covariation. Here, we focus on the stability metatrait, which reflects shared variance in conscientiousness, agreeableness, and (inversely) neuroticism. It has been hypothesized that stability manifests, in part, because of individual differences in central serotonergic functioning. We explored this possibility in a community sample ($N = 441$) using a multiverse analysis of (a) multi-informant five-factor-model traits and (b) stability as a predictor of individual differences in central serotonergic functioning. Differences in serotonergic functioning were assessed by indexing change in serum prolactin concentration following intravenous infusion of citalopram, a selective serotonin reuptake inhibitor. Results were mixed, showing that trait neuroticism, agreeableness, and conscientiousness, as well as the stability metatrait, were significantly associated with prolactin response but that these findings were contingent on a number of modeling decisions. Specifically, these effects were nonlinear, emerging most strongly for participants with the highest levels (or lowest, for neuroticism) of the component traits.

Keywords

personality traits, serotonin, stability, psychopharmacological challenge, structural equation modeling, open data

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Personality traits of the five-factor model (FFM) are not independent but rather correlated and hierarchically structured. Digman (1997) first showed that conscientiousness, agreeableness, and (inversely) neuroticism cohere as a single higher-order trait, which he labeled *alpha*; a second such metatrait, *beta*, was defined by convergence of extraversion and openness. Subsequently, DeYoung and colleagues confirmed this structure using multiple trait inventories and informant sources and relabeled the metatraits *stability* and *plasticity*, respectively (DeYoung, 2006; DeYoung, Peterson, & Higgins, 2002). Stability, the focus of the present research, is said to reflect a general tendency to regulate or restrain potentially disruptive emotions, motivations, and social relationships. DeYoung and colleagues further posited a neurobiologic substrate of stability rooted in individual differences in central-nervous-system (CNS) serotonergic function.

Serotonin-releasing neurons originate in the raphe nuclei of the brain stem and project to diverse areas of the forebrain, including subcortical structures such as the thalamus, basal ganglia, hypothalamus, hippocampus, amygdala, and septum, as well as most of the cerebral cortex. Primarily a monoamine neuromodulator, serotonin has largely inhibitory (i.e., stabilizing) effects

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on canonical circuitries of behavioral control (e.g., emotion and reward processing). Accordingly, diminished serotonergic neurotransmission may weaken restraints on goal-directed activity and impair the regulation of behavioral and affective responses (Soubrie, 1986; Spoont, 1992). Prominent inverse correlates of stability, such as aggression, impulsivity, and liability to depression, have been linked to low central serotonergic activity, as indexed by cerebral-spinal-fluid concentrations of the serotonin metabolite 5-hydroxyindoleacetic acid or inferred from neuroendocrine reactions to drugs that act on serotonin-releasing neurons or neurons expressing serotonin receptors (Cherek & Lane, 1999; Flory, Mann, Manuck, & Muldoon, 1998; Manuck et al., 1998; Manuck, Kaplan, & Lotrich, 2006). Whether CNS serotonergic activity is related to the correlated variance of conscientiousness, agreeableness, and neuroticism—that is, to the stability metatrait, as hypothesized by DeYoung et al. (2002)—has not previously been tested, and investigating that question was the objective of the current study.

A further consideration is that the literature linking serotonergic functioning to complex behaviors such as aggression, impulsivity, and affective disorders in humans is based on samples of modest size, typically numbering only several dozen participants, and few direct replications have been published. Given increasing appreciation of the effect of sampling variability when samples are small and of publication biases (e.g., Ioannidis, 2005), DeYoung's hypothesis at present might best be regarded as suggestive and lacking direct confirmation. Thus, research is needed that targets the posited stability–serotonin association specifically and that uses robust samples with a thorough and transparent reporting of results.

In the current study, using a large sample ($N = 441$) of midlife volunteers, we explored the relationship between multi-informant FFM traits and central serotonergic responsivity. Responsivity was measured by indexing the acute serum prolactin response to intravenous administration of citalopram, a serotonin reuptake inhibitor. Nonspecific neuropharmacologic challenges designed to assess central serotonergic responsivity enhance serotonergic neurotransmission by increasing the availability of serotonin in synapses, typically by promoting neuronal release of serotonin stores or inhibiting reuptake into presynaptic neurons. Serotonin (5-hydroxytryptamine , or 5-HT) receptors are thereby activated throughout the brain and, in the hypothalamus, stimulate the pituitary release of prolactin (among other hormones) into the peripheral circulation. The resulting rise in prolactin concentration therefore provides an index of relative serotonergic responsivity (Yatham & Steiner, 1993).

Our primary aim was to explore whether the stability metatrait and serotonergic responsivity are associated. We further examined whether serotonergic responsivity is associated with each of stability's component traits: conscientiousness, agreeableness, and neuroticism. Additional analyses explored whether extraversion and openness exhibited divergent patterns of associations. Although the motivating question of this work was straightforward, estimating the models required making several decisions that could have affected the inferences drawn. Therefore, we subjected these principal questions to a multiverse analysis (Steegen, Tuerlinckx, Gelman, & Vanpaemel, 2016), the goal of which was not to present the results of a single set of modeling choices, but instead to use "a large set of reasonable scenarios" (Steegen et al., p. 702). In the current study, models were estimated using both latent and observed variables, the stability trait was specified as a higher-order factor and as a general factor in a bifactor model, and both linear and nonlinear associations were explored. Models were estimated without covariates, with a standard set of covariates, and with outliers excluded.

Method

Participants

Data for the current study were derived from a subset of participants in the University of Pittsburgh Adult Health and Behavior (AHAB) project, a registry of behavioral and biological measurements of non-Hispanic Caucasian and African American individuals (30–54 years old). They were recruited between 2001 and 2005 via mass mailings from communities of southwestern Pennsylvania (principally Allegheny County; Manuck, Phillips, Gianaros, Flory, & Muldoon, 2010). General exclusion criteria for AHAB were history of atherosclerotic-cardiovascular disease, chronic kidney disease, or liver disease; cancer treatment in the past year; neurologic disorders; psychotic illness; pregnancy; and use of insulin, nitrates, and glucocorticoids, or antiarrhythmic, psychotropic, or prescription weight-loss medications. Additional exclusions for the present analyses included use of antihypertensive or lipid-lowering medications. Further, women were excluded if they were not using reliable birth control, were lactating, or were currently experiencing age-related menstrual-period irregularities. Informed consent was obtained in accordance with approved protocol guidelines of the University of Pittsburgh Institutional Review Board.

The pharmacological protocol was administered to 466 AHAB participants (see the description below of the citalopram challenge test). Of these, 441 were included in analyses. Twenty-five participants were excluded

because they experienced adverse reactions during the citalopram challenge that confounded interpretation of hormonal responses (vomiting, vasovagal syncope, or both), they had baseline prolactin levels greater than 40 ng/ml, or measurements of plasma citalopram concentrations were missing. This sample size provides sufficient power (.80 with $\alpha = .05$) to detect even small effects ($f^2 = .014$) in regression paths, which were the focus of our main hypotheses.

Measures

Citalopram challenge test. Historically, the most frequently reported challenge entailed administration of fenfluramine, which elicits a strong prolactin response by acting both as a releasing agent and a reuptake inhibitor. When use of fenfluramine was restricted several years ago because of toxicities of chronic administration and loss of commercial availability, alternative pharmacologic agents (or probes) that act presynaptically available at that time included the 5-HT precursor tryptophan and several selective serotonin reuptake inhibitors (SSRIs; e.g., citalopram, clomipramine; Manuck et al., 2006). Although SSRIs provoke a less potent prolactin response than fenfluramine does, we have shown that individual differences in citalopram-induced prolactin responses moderately correlate with responses to fenfluramine ($r = .50$), even though the two protocols were administered an average of 4.5 years apart; both have similar predicted physical health outcomes (e.g., aggregated cardiometabolic risk; Flory, Manuck, Perel, & Muldoon, 2004; Muldoon et al., 2006; Muldoon et al., 2007; Muldoon et al., 2004). In these studies, central serotonergic responsivity was measured as the change in serum prolactin concentration after the administration of citalopram.

Participants reported to the University of Pittsburgh's General Clinical Research Center between 1:00 p.m. and 3:00 p.m. after a 2-hr fast. Testing was conducted in the afternoon to minimize the influence of circadian variation on prolactin levels. Premenopausal women were scheduled during the early follicular phase (i.e., between 3 and 9 days after the onset of menses). An intravenous catheter was inserted into each forearm, one for blood sampling and one for drug infusion. After a 30-min adaptation period, blood samples for baseline prolactin were drawn at 5 and 1 min before citalopram infusion. Participants then received citalopram by infusion pump over 30 min at a dose of 0.33 mg per kilogram of lean body mass. Subsequent blood samples for prolactin determinations were obtained at 30, 45, 60, 75, 90, 105, 120, and 150 min after initiation of the drug infusion. Samples for citalopram concentration were obtained at 30, 45, 90, and 150 min after initiation of the drug infusion. All samples were centrifuged, separated, and stored at –70° C until analysis. Methods for determining serum prolactin and plasma citalopram concentrations have been described previously (Lotrich et al., 2005). Prolactin concentrations from the two baseline blood samples were averaged.

The citalopram-induced prolactin-response area under the curve (AUC), expressed as nanograms per milliliter per hour, was calculated by trapezoidal integration, using prolactin concentrations measured from 0 min to 150 min after infusion.

Personality assessments. Each participant completed the 240-item Revised NEO Personality Inventory (NEO PI-R), which includes five subscales assessing the FFM personality domains: neuroticism, agreeableness, openness to experience, extraversion, and conscientiousness (Costa & McCrae, 1992). One or two informants also rated the participant using the 60-item abbreviated form (the NEO Five-Factor Inventory, or NEO-FFI); the majority of participants (89%) had ratings from two informants. Informants were chosen by the participant, and they included spouses or partners (30%), parents (9%), siblings (12%), other close relatives (12%), close friends (31%), or other individuals (6%). To be consistent across self- and informant reports, we used the subset of 60 items from the NEO PI-R that overlapped with the NEO-FFI to create the five self-reported FFM traits. Thus, most participants had three subscale scores (i.e., ratings by the participant himself or herself and two other informants) for each 12-item personality trait.

Data analysis

All study models were estimated using Mplus (Version 8.2; Muthén & Muthén, 2018). For all models, prolactin response (i.e., baseline-adjusted prolactin AUC) was regressed on personality traits, adjusting for individual differences in baseline prolactin levels. In a first set of models, each first-order trait dimension was used as the predictor of prolactin response. Second, higher-order stability was used as the predictor. The stability model tested whether the shared variance in neuroticism, agreeableness, and conscientiousness predicted prolactin response but not whether any of the three lower-order factors had unique effects. Therefore, in a follow-up analysis, we also tested a model with neuroticism, agreeableness, and conscientiousness as simultaneous predictors. Only modest effects were anticipated because we used a reuptake inhibitor alone as the challenge agent, as opposed to fenfluramine, the previously common and stronger (but now restricted) releasing agent plus reuptake inhibitor.

We subjected this basic structure (i.e., of examining the association between personality trait and serotonergic

response) to a multiverse analysis (Steegen et al., 2016). The multiverse analysis was not designed to be exhaustive, but we estimated models in several key variations to determine whether, and under what conditions, a significant association between personality and serotonergic functioning emerged. Models varied in three ways. First, traits were estimated as both latent variables and observed variables. Because stability is a second-order trait, latent stability models were estimated as a higher-order model in a structural equation modeling framework, in which the stability trait was estimated from the shared variance in latent neuroticism, conscientiousness, and agreeableness, as well as in a bifactor model, with all observed variables loading on a general factor. Second, the functional form of the models was evaluated, and both linear and nonlinear (quadratic) models were estimated. Third, all models were estimated (a) as a baseline without covariates; (b) with standard covariates of sex, age, and mental-disorder diagnosis; and (c) with outliers excluded. In sum, this resulted in 78 separate models across the five lower-order traits (60 models) and the stability metatrait (18 models).

Trait estimation. Following the approach described by DeYoung (2006), estimates of trait scores were based on multi-informant ratings (self, Informant 1, and Informant 2). In the case of the latent-variable models, we first estimated measurement models for each Big Five domain, such that each reporter's rating served as an indicator for a latent trait. Three-indicator confirmatory factor analyses have perfect fit to the data (i.e., they are saturated models); therefore, these initial models were evaluated for reasonable parameter estimates. Latent stability factors were estimated in two distinct ways: first, as a higher-order factor (which accounts for the shared variance of multi-informant neuroticism, agreeableness, and conscientiousness) and second, as a general factor in a bifactor model (which directly accounts for the shared variance in all observed indicators—all nine observed scores of each trait across three informants). In the bifactor model, three specific factors were estimated, one for each first-order trait, as indicated by each informant's report of a given trait. In both variations of the stability latent variable, residual variances for each informant's scales were allowed to correlate, to account for nonsubstantive sources of shared variance (e.g., residuals for self-reported neuroticism, conscientiousness, and agreeableness freely covaried). As is common in other samples (DeYoung, 2006; DeYoung et al., 2002), extraversion and openness did not correlate substantially in this sample, precluding the estimation of a latent plasticity factor (Dermody et al., 2016). We also estimated models using only observed scores. Observed multi-informant first-order trait scores were calculated by standardizing the estimates of each informant's score and averaging the resulting z scores. Observed stability was calculated in the same fashion, by averaging across all the z scores for neuroticism (multiplied by −1), conscientiousness, and agreeableness.

Functional form. All models were initially estimated with a linear relationship between personality traits and serotonergic responsivity. Following this, we also explored nonlinear (i.e., quadratic) effects of personality traits on prolactin response. Quadratic effects for latent traits were estimated using latent moderated structural equation modeling (LMS; Kelava et al., 2011; Klein & Moosbrugger, 2000). LMS does not require the calculation of squared indicator variables but rather uses the expectation-maximization algorithm to directly estimate the coefficients for the first-order and polynomial effects. LMS relies on numerical integration in calculating these effects and therefore is computationally intensive. All models were estimated with 30 integration points and using maximum-likelihood estimation with first-order derivative-based standard errors (i.e., MLF estimator in Mplus) because lower numbers of estimation points and alternative estimators resulted in errors in estimation. Quadratic models were compared with their linear counterparts using the Akaike information criterion (AIC) and Bayesian information criterion (BIC) because Mplus does not provide traditional fit statistics for LMS models. The covariates were age (in years), sex (male = 0, female = 1), and current psychiatric syndrome, substance abuse, or dependence as diagnosed by a structured interview (no diagnosis = 0, diagnosis = 1; n = 86). Outliers were defined as participants with scores more than 3 standard deviations from the mean on the prolactin-response variable or any measure of neuroticism, conscientiousness, or agreeableness (n = 11).

In the latent models, missing data (i.e., missing informant reports) were handled using full-information maximum-likelihood estimation. For the models using observed trait scores, mean imputation was used when an informant report was missing. Model fit for models including latent variables and linear effects was evaluated using the χ^2 test, for which nonsignificant values indicate good fit. Because the χ^2 statistic tests a very stringent hypothesis (perfect fit of the data to the model), we followed convention and supplemented our evaluation of fit with multiple alternative indices as a less stringent but nevertheless conservative approach to evaluating model fit. If the χ^2 statistic was significant, a model was determined to have good fit when three or more of the following four criteria were met: The root-mean-square error of approximation (RMSEA) had a value less than .06, the comparative-fit index (CFI) was close to or greater than .95, the Tucker-Lewis index (TLI) was close to or greater than .95, and the standardized root-mean residual (SRMR) was less than .08 (Hu

Table 1. Descriptive Statistics for Prolactin and Personality Variables

Variable	*M*	*SD*	Skew	Kurtosis	Minimum	Maximum
Baseline prolactin (ng/ml)	2.22	0.49	−0.06	0.23	0.53	3.68
Prolactin-response AUC	3.28	0.45	0.14	0.75	1.82	5.28
Neuroticism (self)	16.55	7.56	0.53	−0.22	0	39
Neuroticism (Informant 1)	17.34	9.10	0.49	−0.34	0	44
Neuroticism (Informant 2)	16.03	7.64	0.52	0.13	0	39
Agreeableness (self)	33.38	5.74	−0.33	−0.09	15	48
Agreeableness (Informant 1)	32.48	7.69	−0.69	0.19	4	47
Agreeableness (Informant 2)	33.43	7.34	−0.68	0.68	0	48
Conscientiousness (self)	33.42	6.28	−0.26	−0.06	13	48
Conscientiousness (Informant 1)	34.53	8.90	0.43	−0.93	3	48
Conscientiousness (Informant 2)	36.19	8.16	−0.93	1.03	0	48
Extraversion (self)	28.76	6.68	−0.51	0.69	2	43
Extraversion (Informant 1)	29.74	7.57	−0.40	−0.34	8	47
Extraversion (Informant 2)	31.05	7.26	−0.44	−0.04	7	48
Openness (self)	28.30	6.50	−0.14	−0.19	8	44
Openness (Informant 1)	26.88	6.32	0.13	0.37	3	48
Openness (Informant 2)	27.10	5.59	0.08	0.18	10	43

Note: The sample size for prolactin and the self-reported personality variables was 441, the sample size for the Informant 1 variables was 417, and the sample size for the Informant 2 variables was 370. AUC = area under the curve.

& Bentler, 1999). Quadratic models do not provide traditional fit indices, including the χ^2, because the LMS approach requires numerical integration. Nevertheless, the AIC and BIC are provided and can be used to compare the linear and quadratic models that otherwise could not be compared using the likelihood-ratio test. The model with lower AIC and BIC scores would be interpreted as having better fit.

Results

Descriptive statistics for the main study variables can be found in Table 1. Baseline prolactin and prolactin response were transformed by taking their natural log, resulting in normally distributed variables. All other variables were normally distributed.

Each of the multi-informant factor models resulted in reasonable solutions, with significant loadings from each of the indicators. The higher-order stability meta-trait model was an acceptable fit to the data, $\chi^2(15) = 27.73$, $p = .023$, RMSEA = 0.044, CFI = .99, TLI = .97, SRMR = .04, whereas the bifactor stability model resulted in good fit, $\chi^2(9) = 14.07$, $p = .120$, RMSEA = 0.036, CFI = 1.00, TLI = .98, SRMR = .03.

Multiverse analysis

The *p* values for the effects of prolactin response, regressed on personality traits from each of the models in the multiverse analysis, are listed in Table 2 (significant values are boldfaced). With one exception (latent conscientiousness without covariates), no linear model generated a significant effect. Similarly, with few exceptions (models involving conscientiousness and extraversion), models using nonlatent traits (i.e., means of observed variables) were nonsignificant. In contrast, the nonlinear latent models returned significant linear and quadratic effects of stability, neuroticism, conscientiousness, and agreeableness on prolactin response. This was true for stability regardless of its specification (i.e., both higher-order and general factors). We also found only a significant quadratic effect for extraversion and no significant effects for openness. Thus, we found significant associations of prolactin response with the expected traits of neuroticism, conscientiousness, agreeableness, and stability that were nonlinear and emerged only in latent-variable models.

Nonlinear models

The latent quadratic models were significant and supported the effects of interest, and therefore we expand the reported results here. Point estimates, standard errors, and standardized effects for the baseline nonlinear structural equation models can be found in Table 3. All models with the exception of openness improved in fit relative to their respective linear models, as indicated by both the AIC and BIC (i.e., both were lower for the quadratic models). For readers interested in these comparisons, output for all models can be found at the Open Science Framework (https://osf.io/h5nbu/). Figure 1 diagrams the quadratic higher-order stability

Table 2. Summary of *p* Values From Multiverse Analyses Predicting Prolactin Response From Personality Traits

	Linear models			Nonlinear models					
	Latent		Observed	Latent				Observed	
Trait and model	Bifactor	Higher order	Mean of *z*s	Bifactor linear	Bifactor quadratic	Higher-order linear	Higher-order quadratic	Mean of *z*s linear	Mean of *z*s quadratic
Stability									
Baseline	.138	.214	.168	**< .001**	**< .001**	**< .001**	**< .001**	.089	.328
Covariate	.218	.311	.230	**< .001**	**< .001**	**< .001**	**< .001**	.128	.331
Outlier	.270	.645	.223	**.001**	**< .001**	**< .001**	**< .001**	.136	.316
Agreeableness									
Baseline		.200	.279			**< .001**	**< .001**	.094	.103
Covariate		.345	.550			**< .001**	**< .001**	.232	.136
Outlier		.261	.315			**< .001**	**< .001**	.129	.086
Conscientiousness									
Baseline		**< .001**	.053			**< .001**	**< .001**	**.013**	.234
Covariate		.141	.103			**< .001**	**< .001**	**.032**	.250
Outlier		.150	.129			**.018**	**< .001**	.073	.389
Neuroticism									
Baseline		.662	.697			**.018**	**< .001**	.553	.603
Covariate		.483	.508			**.009**	**< .001**	.369	.481
Outlier		.632	.665			**.019**	**< .001**	.495	.465
Extraversion									
Baseline		.553	.570			.766	**< .001**	.820	**.004**
Covariate		.341	.377			.972	**< .001**	.917	**.006**
Outlier		.426	.524			.581	**< .001**	.894	**.004**
Openness									
Baseline		.716	.807			.718	.734	.826	.683
Covariate		.735	.815			.734	.865	.825	.848
Outlier		.547	.620			.541	.973	.619	.963

Note: Boldface indicates significant effects. The effect of stability was estimated as a second-order factor in the higher-order model and as a general factor in the bifactor model.

model. Given that stability was indicated positively by agreeableness and conscientiousness and negatively by neuroticism, the pattern of effects was such that individuals with the highest level of stability had the strongest predicted prolactin response. Neuroticism, conscientiousness, and agreeableness each had significant linear and quadratic associations (in the predicted directions) with prolactin response. For agreeableness and conscientiousness, these effects were both positive, and the predicted prolactin response was highest among individuals with the highest levels of these traits. Conversely, the linear effect for neuroticism was negative, the quadratic effect was positive, and the predicted prolactin response was strongest for individuals with

Table 3. Results From the Structural Equation Models Predicting Prolactin Response to Citalopram From Multi-Informant Traits

	Linear models				Quadratic models			
Trait	*b*	*SE*	*p*	β	*b*	*SE*	*p*	β
Neuroticism	−0.04	0.02	.018	−0.09	0.09	0.01	< .001	0.20
Agreeableness	0.08	0.02	< .001	0.17	0.09	0.01	< .001	0.20
Conscientiousness	0.08	0.02	< .001	0.17	0.08	0.01	< .001	0.18
Extraversion	0.01	0.01	.766	0.01	0.09	0.01	< .001	0.20
Openness	−0.01	0.02	.718	−0.01	0.00	0.01	.734	−0.01
Stability	0.09	0.02	< .001	0.19	0.09	0.01	< .001	0.20

Note: $N = 441$.

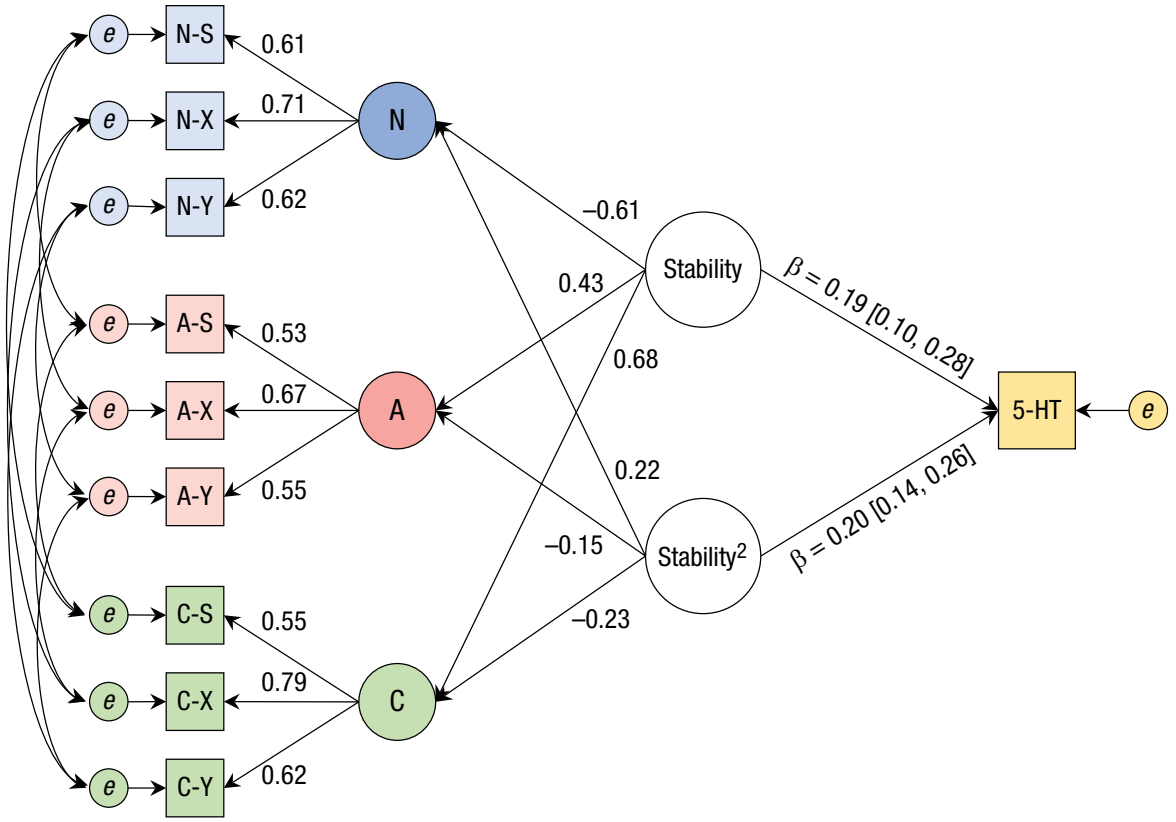

Fig. 1. Diagram of model showing baseline linear and quadratic multi-informant higher-order stability predicting 5-hydroxytryptamine (5-HT) prolactin response. Circles represent latent variables; squares represent observed variables. Single-headed arrows between latent stability and stability^2 and observed 5-HT response are regression paths. Single-headed arrows between latent constructs and between latent neuroticism (N), agreeableness (A), and conscientiousness (C) and observed variables reflect factor loadings. Double-headed arrows represent correlations. The residual variance in the prolactin response is represented by *e*. Standardized path estimates are shown. Values in brackets are 95% confidence intervals. S = self-report, X = Informant 1, Y = Informant 2.

the lowest level of the trait. In Figure 2, we plot the means of the highest tertile relative to the lower two tertiles to illustrate the nonlinear effect.

To follow up on these analyses and explore whether all associations among neuroticism, conscientiousness, and agreeableness and prolactin response would be shared, as opposed to unique, we examined neuroticism, agreeableness, and conscientiousness as simultaneous quadratic predictors of prolactin response. In contrast to expectations, we found that agreeableness had significant unique effects (linear: $b = 0.07$, $SE = 0.02$, $p < .001$, $\beta = 0.16$; quadratic: $b = 0.08$, $SE = 0.01$, $p < .001$, $\beta = 0.19$).

In terms of the anticipated divergent effects of associations with openness and extraversion, we found that openness had no significant effects predicting prolactin response regardless of whether it was latent or nonlinear in form, whereas extraversion had no significant linear effect but a significant quadratic effect. The quadratic effect showed that individuals with high or low levels of extraversion had the strongest prolactin responses to the citalopram challenge. This pattern differed from that of the stability traits, suggesting that both poles of extraversion may reflect enhanced serotonergic responsivity.

Discussion

We explored the hypothesis that the covariation of neuroticism, agreeableness, and conscientiousness, as manifested in the stability metatrait, reflects CNS serotonergic functioning. Multi-informant trait models were used to predict levels of prolactin response to an intravenous citalopram challenge. Because modeling decisions can have substantial consequences for the obtained results, we adopted a multiverse analytic approach and varied model specifications by whether the traits were estimated as latent or observed, whether the effect was linear or nonlinear, whether there were covariates absent or present, and whether outliers were excluded. Results of the multiverse analysis indicated that the effects of interest were significant only under

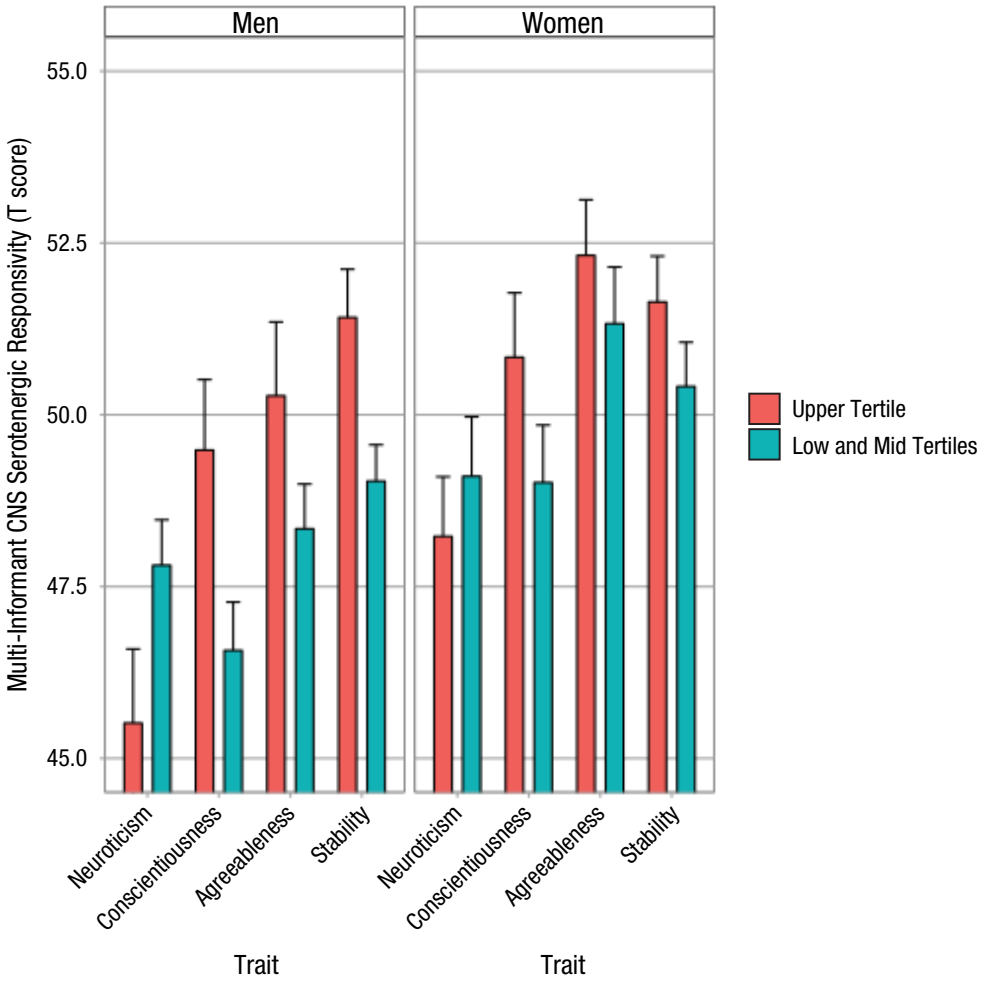

Fig. 2. Multi-informant-reported mean central-nervous-system (CNS) serotonergic responsivity as a function of personality trait, separately for men and women in the upper tertile and the lower two tertiles of prolactin response. Error bars show standard errors.

certain modeling conditions. Specifically, results for the main effects of interest were nonsignificant in almost all cases in which models were estimated using observed (as opposed to latent) variables and in almost all cases where models were estimated using only a linear association. In contrast, when traits were modeled as latent and the effect modeled as nonlinear, all effects predicted to be significant emerged as significant, regardless of the presence of covariates and outliers. Thus, the anticipated significant associations between certain personality traits and CNS serotonergic functioning were contingent on several modeling decisions.

The two main modeling decisions that affected the significance of the results merit closer examination. First, using observed, as opposed to latent, variables yielded nonsignificant effects. That the predicted associations emerged when using latent variables, but not observed variables, should not be surprising. First, the observed effects in latent-variable models are small to begin with, as one might expect when examining associations between two highly different methodologies. Furthermore, whereas averaging observed variables combines all sources of variance into one scale score, latent variables isolate the shared variance among the observed indicators, excluding nonshared variance from the predictor that might otherwise cloud associations. Although it is often discussed in terms of measurement unreliability or error, the effect of multiple sources of variance in the calculation of a predictor variable has the notable effect of attenuating the regression coefficient reflecting association with the outcome, biasing it toward zero. This is what we observed here: The effect of using an observed variable that combines all sources of variance in neuroticism, conscientiousness, and agreeableness scales attenuated a small association further toward zero, to the point of nonsignificance. However, it is precisely the shared variance in neuroticism,

conscientiousness, and agreeableness that defines stability, not all sources of variance contributing to their scores. In the first-order traits, we similarly found that latent variables resulted in small but significant effects, whereas observed variables did not. Although in the lower-order traits each contributing scale ostensibly measured the same trait, the shared variance across multiple observers presumably provided the most reliable estimate of the true trait score, excluding source-specific biases. The differing results across observed and latent variables are informative for what might be expected for other investigators who wish to perform similar analyses, and at the same time, they also reinforce the well-known advantages of latent-variable models for isolating shared variance and excluding nonsubstantive sources of variance.

Second, we found that the predicted associations between personality and prolactin response were nonlinear. The first-order traits and the higher-order stability factor were associated in the expected direction with the magnitude of prolactin response (positively for agreeableness, conscientiousness, and stability, but inversely for neuroticism). In these nonlinear relationships, trait associations with serotonergic responsivity emerged only at higher (or, for neuroticism, lower) trait levels, relative to persons at intermediate or low levels of these traits. On the one hand, this pattern of results comports with DeYoung's (2006) hypothesis that differences in serotonergic functioning contribute to trait variation in the stability domain. On the other hand, the nonlinear effects were not specified a priori and therefore represent these associations in an unanticipated form. Moreover, nonlinear effects are known to be more fragile and less reproducible than linear effects, so they should be interpreted with greater caution (e.g., McClelland & Judd, 1993). Thus, one could conclude that the form of these associations is anomalous and should not inspire confidence.

Nonetheless, we believe that at least two points argue for a more positive interpretation of our findings. The challenge agent used here, citalopram, augments serotonergic neurotransmission by blocking the reuptake of synaptic serotonin, but much prior research indexed central serotonergic responsivity using fenfluramine—a more potent pharmacologic probe that both stimulates the neuronal release of serotonin stores and inhibits reuptake. As noted earlier, the withdrawal of fenfluramine from commercial availability several years ago obliged researchers to turn to weaker agents, such as the reuptake inhibitors or serotonin precursors (e.g., tryptophan, 5-hydroxytryptophan). An overall weaker prolactin response to a reuptake inhibitor such as citalopram might, in turn, yield more limited discriminability because of floor effects or score compression at the lower end of a response distribution. Unlike studies using fenfluramine, a previous validation study, for instance, showed that only about a third of participants exhibited a robust prolactin response to citalopram, whereas in the remainder of participants, prolactin concentrations over the same sampling interval rose above baseline values barely or not at all (Flory et al., 2004). This nonlinearity in response to the agonist may occasion similarly nonlinear associations with external variables. Perhaps more persuasive is the fact that the pattern of results here was highly consistent across all of the individual traits, as well as the metatrait, and was thus consistent with DeYoung's hypothesis. Stated otherwise, the pattern replicated internally (i.e., within this sample) across three traits and a trait capturing their shared variance. We do not believe that this would be the observed pattern were these findings entirely anomalous or spurious.

In addition to examining the predicted associations, we also explored the association of openness and extraversion with the prolactin response. Openness was not significantly related, and extraversion had only a significant quadratic effect. The unpredicted extraversion finding is intriguing, and it is perhaps conceivable that heightened serotonergic activity is conducive to greater positive affect (high extraversion) and, conversely, to greater restraint (perhaps reflecting diminished sensation seeking, related to low extraversion). In either case, these two traits, which were not expected to show an association with serotonergic responsivity, demonstrate divergent associations from those predicted for neuroticism, agreeableness, conscientiousness, and stability.

One limitation of the current work is that these associations remain relatively nonspecific. Although the prolactin response to citalopram directly reflects serotonergic influences in the hypothalamic-pituitary-adrenal axis, it is nonetheless presumed to index responsivity at targets of serotonergic neurotransmission throughout the brain. Like other presynaptic probes, however, it cannot isolate effects related to specific brain regions, circuitries, or serotonin receptors. In future studies, postsynaptic mechanisms might be studied using direct agonists of differing specificity for particular receptor subtypes (Yatham & Steiner, 1993) or in conjunction with positron emission tomography to assess variation in region-specific metabolic activity under serotonergic stimulation (e.g., Manuck et al., 2006). Additionally, without use of analogous challenges for other monoamine neuromodulators (e.g., dopamine), we cannot conclude that stability and its component traits relate only to variation in central serotonergic function. Given our pattern of results, researchers interested in pursuing future work of this type should plan to enlist large

samples that would provide adequate power and support the use of nonlinear latent-variable modeling approaches.

In sum, we used a multiverse analysis to investigate the possibility that central serotonergic functioning may provide a neurobiological substrate for stability and its constituent traits. We found support for this hypothesis, but only under certain conditions—namely, using latent-variable models and examining nonlinear effects. This pattern, coupled with the small effect size even in models with significant effects, suggests that that these results may be tentative and potentially contingent on circumscribed model specifications. Nevertheless, we believe that there are reasonable explanations for the pattern of results, which are suggestive of the theoretical proposition that we examined and therefore warrant further investigation—for example, by extension to other metrics of brain serotonergic activity.

Action Editor

Brent W. Roberts served as action editor for this article.

Author Contributions

S. B. Manuck and M. F. Muldoon developed the basic idea for this research. S. B. Manuck, M. F. Muldoon, and J. D. Flory were involved in collecting the data. A. G. C. Wright and S. B. Manuck designed the analytic plan. A. G. C. Wright conducted all analyses. A. G. C. Wright, K. G. Creswell, and S. B. Manuck drafted the manuscript. All authors provided critical revisions and approved the final manuscript for submission.

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Open Practices

The design and analysis plan for this study were not formally preregistered. The data and a portion of the materials have been made publicly available on the Open Science Framework (https://osf.io/h5nbu/). Posted materials include the syntax and output for all statistical models but exclude the questionnaires because they are copyrighted. The complete Open Practices Disclosure for this article can be found at http://journals.sagepub.com/doi/suppl/10.1177/0956797619864530. This article has received the badge for Open Data. More information about the Open Practices badges can be found at http://www.psychologicalscience.org/publications/badges.

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