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Associations among central nervous system serotonergic function and neuroticism are moderated by gender☆

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ABSTRACT

Serotonergic dysregulation is associated with negative affect. Plasma prolactin responses to a tryptophan enhancement challenge are used as a measure of central nervous system serotonergic activity. We examined prolactin responses to a tryptophan challenge as they relate to the personality domains of neuroticism, extraversion, openness, agreeableness, and conscientiousness. Participants were 67 volunteers. Regression models assessed peak prolactin response to intravenous tryptophan infusion as a predictor of neuroticism, extraversion, openness, agreeableness, and conscientiousness. Prolactin × gender product terms were included to examine moderation by gender. Models were adjusted for baseline levels of prolactin, age, and race. Gender moderated the association between N and prolactin level ($p < .03$). Higher levels of N were associated with decreased levels of prolactin responses in females, whereas the *opposite* was true for males. Remaining personality domains were not related to prolactin levels. Findings add to literature suggesting the serotonin system functions differently, in important ways, in males and females.

It is generally thought that individual differences in central nervous system (CNS) serotonergic function underlie differences in disposition, in particular for those traits associated with negative affectivity such as aggression, hostility, and depression. This hypothesis has been investigated using various neuroendocrine challenge protocols, e.g., intravenous infusion of L-tryptophan and oral fenfluramine. Although the specific mechanisms differ, all challenge protocols create an ultimate rise in the level of CNS serotonin resulting in a release of prolactin via the hypothalamic pituitary axis (Lesch et al., 1989). Thus, the increase in plasma prolactin following experimental enhancement of the 5-HT precursor L-tryptophan has been used as a measure of CNS serotonergic activity (Charney et al., 1982).

A large body of research has been conducted using the neuroendocrine challenge to assess associations between the tendency toward aggression or lack of impulse control and central serotonergic function in patients with antisocial personality disorder and/or those with criminal backgrounds (e.g., Coccaro et al., 1989; O'Keane et al., 1992). Results of these studies indicate that there is a significant association between decreased CNS serotonergic activity and violent behaviors. Fewer studies have used the neuroendocrine challenge to examine associations between normal variation in personality traits and CNS serotonergic function in non-clinical populations. The majority of studies that do exist in non-patient samples have focused primarily on the traits of aggression and impulsivity, with mixed results (e.g., Cleare and Bond, 1995, 1997; Coccaro, 1992; Marsh et al., 2002; Moeller et al., 1994).

Findings from existent challenge protocols conducted in non-clinical samples do, however, indicate that traits representing a broader range of behaviors and emotions than those accompanying aggression and impulse control may be associated with serotonergic activity. In a non-patient sample of 244 adults, Flory et al. (2004) found that higher peak prolactin response to a fenfluramine challenge was associated with ratings of positive mood averaged over a 7-day period. The personality traits of conscientiousness and neuroticism were associated, positively and negatively, respectively, with maximal prolactin response to a fenfluramine challenge for males, whereas, in females those relations were nonsignificant (Manuck et al., 1998). Another study

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(Wingrove et al., 1999) using oral tryptophan enhancement reported that trait assessments of hostility were negatively associated with change in prolactin in males, however, the within group sample size was small ($n = 14$).

Related work has shown that levels of free plasma tryptophan are positively associated with trait hostility, propensity for anger, and outward expression of anger, but only in women (Suarez and Krishnan, 2006). These findings, along with those of others that report differences between men and women (Cleare and Bond, 1997; Manuck et al., 1998), suggest the importance of considering gender when further assessing associations between CNS serotonin activity and variation in personality. Thus, in the present study we examined gender as a moderator of the association between prolactin response to a tryptophan enhancement challenge and the big five personality domains of neuroticism (N), extraversion (E), openness (O), agreeableness (A), and conscientiousness (C).

1. Methods

1.1. Participants

Participants were recruited to take part in a study designed to examine the moderating effects of genetic, behavioral, and environmental mechanisms on health disparities. The study was conducted at Duke University Medical Center, and all subjects gave informed consent prior to their participation in the study using a form approved by the Duke University Medical Center Institutional Review Board. Those enrolled in the study received $500 for their participation. The study protocol required that participants be in good current health because of the study procedures, see below and (Williams et al., 2001, 2003), therefore all participants underwent a comprehensive psychological examination, as well as medical history, physical exam, electrocardiogram, chest radiograph, hemoglobin, hematocrit, white cell count, and blood chemistries to rule out current medical and psychiatric disorders. Use of any prescription drugs as well as use of illegal drugs (as detected by a urine screen prior to entry into study) were grounds for exclusion (Burroughs et al., 2003). The full study sample consisted of 165 participants, 80 of which were randomized to a tryptophan enhancement condition. Of these 80 participants, 12 individuals did not have data for one or more of the prolactin values used in the present study, and one participant did not have data for the personality assessment, resulting in 67 participants (25 females and 42 males) who are the focus of the present study.

1.2. Procedure

Upon evening admission to the General Research Unit at Duke University Medical Center, sociodemographic and personality data were gathered, and blood was drawn for assessment of biological parameters. Test day 1 consisted of a sham tryptophan infusion, followed by a cardiovascular reactivity protocol (see Williams et al., 2001), and test day 2 consisted of an active tryptophan infusion, again followed by a cardiovascular reactivity protocol. With the exception of administration of either the active or sham tryptophan infusion, the protocol for days 1 and 2 were identical.

1.3. Tryptophan challenge protocol

On the day of the active tryptophan infusion, beginning at 6:30 a.m. participants were not allowed food or liquids, nor were they allowed to smoke, until the completion of all study procedures at approximately 1:30 p.m. At 7:00 a.m. an IV (d5w/.5n saline) was started and kept running at 50 cc per hour till 1:30. All participants were seated in a reclined position and activity was limited to watching nature videos provided by the investigator or playing cards. Bathroom visits were allowed up to the time of tryptophan infusion. At 11:00 participants received a full dose of tryptophan (100 mg/kg body weight) over a period lasting 25 min. A blood pressure cuff was placed around the infusion bag and inflated up to a maximum of 35 mm Hg if needed to complete the total dose within 25 min. At the end of the infusion, the IV was returned to normal saline.

1.4. Prolactin

Blood samples for assessment of plasma prolactin levels were drawn just prior to infusion and at 30, 45 min, and 1 h post-infusion. Blood samples were spun for 15 min in a refrigerated centrifuge and plasma was transferred into polypropylene tubes containing 0.050 ml glutathione and then frozen at −70°C. Blood samples were processed at the Clinical Research Unit at Duke University Medical Center under the supervision of Dr. Cynthia Kuhn. Levels of plasma prolactin were measured by radioimmune assay.

1.5. NEO personality inventory-revised (NEO-PI-R)

The NEO personality inventory (NEO-PI(-R) (Costa and McCrae, 1992) is a measure of the dimensions of the five-factor model (FFM) (Digman, 1990); with six facet level scales to assess specific aspects of each of the personality domains of neuroticism (N), extraversion (E), openness (O), agreeableness (A), and conscientiousness (C) (Costa et al., 2000; Costa and McCrae, 1992). NEO-PI-R items were summed and converted to T-scores, based on combined gender norms, for each domain. Higher scores reflect the greater presence of each specific personality construct.

1.6. Analytic plan

Values for plasma prolactin were log transformed for use in all analyses in order to achieve appropriate distributional properties. Values representing the peak rise in prolactin were determined by obtaining the maximum value across the three time points during which prolactin was measured. Separate linear regression models were used to assess associations among peak prolactin and the personality domains of N, E, O, A, and C. Initially, each model included a prolactin × gender interaction term to examine moderation by gender. Importantly, all models included pre-infusion (baseline) levels of prolactin, as well as age, race, and gender. Thus, the five initial regression models included the following terms: (1) a continuous term representing either N, E, O, A, or C, (2) a term representing the log transformed peak prolactin level across the three measurement points, (3) a term for the baseline level of prolactin, (4) terms for age, race and gender, and (5) a product term for the peak prolactin × gender interaction. Any non-significant interaction terms were then removed prior to final examination of main effects. SAS (Cary, NC) software was used to conduct all analyses.

2. Results

2.1. Background analyses

Demographic characteristics of the participants are presented in Table 1. Both males and females were 35 years of age on average. Pre-infusion levels of prolactin were somewhat higher for females, as compared to males ($p < .08$). In addition, there was a significant gender difference between males and females with respect to the peak level of prolactin observed during the infusion period ($p < .05$). However, levels of pre- to post-infusion *change* in prolactin did not differ significantly by gender, suggesting that the gender differences in peak prolactin levels were largely accounted for by females having higher baseline levels. The observed increase in pre- to post-infusion prolactin was significant ($p < .01$) for both males and females alike. Similar analyses were conducted for the sham day and as expected, prolactin levels did not change significantly (prolactin $p < .90$).

2.2. Primary analyses

With regard to the planned analyses of personality, the interaction of gender × peak prolactin was a statistically significant

Table 1
Sample characteristics

	Males, $n = 42$	Females, $n = 25$
Age (years)	34.8 (9.2)	35.2 (8.3)
Race n (%) caucasian	17 (40.5%)	14 (56.0%)
Neuroticism[b]	46.8 (9.2)	51.2 (8.0)
Extraversion	53.9 (8.4)	56.2 (9.1)
Openness	51.7 (9.7)	52.9 (7.8)
Agreeableness	47.4 (9.7)	51.3 (10.4)
Conscientiousness	47.9 (11.5)	48.4 (8.8)
Pre-infusion prolactin (nmol/l)[a]	9.4 (7.3)	12.4 (11.4)
Peak prolactin[b]	21.2 (11.0)	36.7 (27.4)
Change (post-infusion–pre-infusion) prolactin[c]	11.8 (9.0)	24.3 (28.0)

Note: Values are group means (S.D.) unless otherwise stated; it is important to note that values presented for prolactin are not log transformed, however, accompanying statistical tests were calculated appropriately using log transformed data.

[a] $p < .10$, for a between groups difference t-test for males and females.

[b] $p < .05$ for a between groups difference t-test for males and females.

[c] $p < .01$ for paired t-test assessing change in prolactin for both males and females.