Published in final edited form as:

Biol Psychol. 2008 May ; 78(2): 200–203.

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 X gender product terms 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.

Keywords

CNS serotonergic activity; Personality; Gender; Prolactin

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, Muller, Rupprecht, Kruse, & Schulte, 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, Heninger, Reinhard, Sternberg, & Hafstead, 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

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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 & Bond, 1997; Cleare & Bond, 1995; Coccaro, 1992; Marsh, Dougherty, Moeller, Swann, & Spiga, 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. (Flory, Manuck, Matthews, & Muldoon, 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 (Wingrove, Bond, Cleare, & Sherwood, 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 & Krishnan, 2006). These findings, along with those of others that report differences between men and women (Cleare & Bond, 1997; Manuck et al., 1998), suggest the importance of considering gender when further assessing associations between CSN 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).

Methods

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.

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 one consisted of a sham tryptophan infusion, followed by a cardiovascular reactivity protocol (see, (Williams et al., 2001), and test day two 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 one and two were identical.

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 minutes. A blood pressure cuff was placed around the infusion bag and inflated up to a maximum of 35mmHg if needed to complete the total dose within 25 minutes. At the end of the infusion, the IV was returned to normal saline.

Prolactin

Blood samples for assessment of plasma prolactin levels were drawn just prior to infusion and at 30-minutes, 45-minutes, and 1 hour post infusion. Blood samples were spun for 15 minutes in a refrigerated centrifuge and plasma was transferred into polypropylene tubes containing .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.

NEO Personality Inventory – Revised (NEO-PI-R)

The NEO Personality Inventory (NEO-PI(-R) (Costa & 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, Herbst, McCrae, & Siegler, 2000; Costa & 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.

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 3 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 X 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 3 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 personality domain X gender interaction. Any

nonsignificant interaction terms were then removed prior to final examination of main effects. SAS (Cary, NC) software was used to conduct all analyses.

Results

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 $p < .90$).

Primary Analyses

With regard to the planned analyses of personality, the interaction of gender X peak prolactin was a statistically significant predictor of Neuroticism ($p < .03$). For females higher neuroticism scores were associated with *smaller* prolactin responses to infusion; whereas, for males the *opposite* was true (see Table 2 and Figure 1). Remaining personality domains were not related to peak prolactin levels, nor was gender a significant moderator of these associations.

We repeated the above analyses using peak post-infusion prolactin levels (and gender X peak prolactin) as predictors of personality domains on the sham day. As expected, no significant associations for any of the gender X prolactin interaction terms, nor for the main effects of prolactin, were observed on the sham day.

In follow-up analyses we examined the gender X peak prolactin interaction term as a predictor of each of the 6 facets of neuroticism. The interaction of gender X peak prolactin was significantly associated with N1-Anxiety ($p < .01$), N3-Depression ($p < .02$), and N6-Vulnerability ($p < .03$). The form of the above interactions for each of the facets of N were such that higher ratings of N1, N3, and N6 were associated with lower peak prolactin levels for females; whereas, for males the opposite association was found (see Table 2).

Discussion

The present findings indicate that, in women, increased CNS serotonergic functioning, as assessed by prolactin response to tryptophan enhancement is associated with lower levels of neuroticism, in particular those aspects associated with depression, anxiety, and vulnerability. These results suggest that the larger body of literature linking more extreme manifestations of similar aspects of personality to serotonergic function in clinical populations may also apply to normal variation of these traits expressed in non-patient samples. The current findings also suggest that these associations may differ significantly by gender. Indeed, the strength of the association in males was not only weaker than that in females, but it was also in the *opposite* direction.

The present results add to a growing body of literature that shows the serotonin system in men and women may behave differently in many important ways. The following basic gender differences have been observed: in males the rates of CNS serotonin synthesis are approximately 50% higher than that in females (Nishizawa et al., 1997); studies (Jonsson et al., 2000; Williams et al., 2003) have shown that CSF 5 HIAA is higher in women than in men;

5-HT_{1A} and 5-HT₂ receptor density is lower in the brains of women than men (Biver et al., 1996; Costes et al., 2005); and selective serotonin re-uptake inhibitors (SSRI) have greater efficacy in females, as compared to males (Kornstein et al., 2000). It is possible that sex differences in serotonergic function may contribute to the enhanced risk for depression found in women (Piccinelli & Wilkinson, 2000). Interestingly, the mood deterioration seen during tryptophan depletion studies has been shown to be more pronounced in females, as compared to males (Booji, Van der Does, Haffmans, Spinhoven, & McNally, 2005; Booji et al., 2002; Moreno, McGahuey, Freeman, & Delgado, 2006). In addition, results of several studies suggest that the serotonin transporter gene promoter polymorphism (5-HTTLPR) genotype may have an opposite effect on behavioral characteristics in men and women. Specifically, in females experiencing chronic stress the presence of the s allele is positively associated with negative behavioral traits such as symptoms of depression, whereas, in stressed males the presence of the l allele has similar associations (Brummett et al., 2003; Eley et al., 2004; Flory et al., 1999; Gonda, Juhasz, Laszik, Rihmer, & Bagdy, 2005; Jacobs et al., 2006; Sjöberg et al., 2006). At present specific sex differences in serotonergic function are not thoroughly understood, and results such as those seen in the present study underscore the need for continued research in this area.

The most consistent relationships demonstrated between serotonergic functioning and emotional experience have been those related to negative traits, yet we might have expected additional personality domains to be related to the change in prolactin. Others have demonstrated an association between trait ratings of conscientiousness and peak prolactin response (Manuck et al., 1998). Daily ratings of positive mood, while conceptually different than trait measures, have also been associated with prolactin response to a fenfluramine challenge (Flory et al., 2004). Tryptophan has also been shown to alter positive mood when administered acutely and chronically, see (Sobczak, Honig, Schmitt, & Riedel, 2003; Young & Leyton, 2002). Currently less is understood regarding the relation between serotonergic activity and traits not related to negative affectivity.

Our findings in women are similar to related work that has shown that levels of free plasma tryptophan are associated with trait hostility and anger ratings in women, but not men (Suarez & Krishnan, 2006). However, the present gender findings conflict with results from some of the studies that assess associations among CNS serotonergic function and emotional experience. Manuck (Manuck et al., 1998) reported that peak prolactin response to fenfluramine was negatively associated with Neuroticism in men, but not women. Similarly, hostility and aggression ratings have been found to correlate inversely with cortisol responses to D-Fenfluramine in males, but not females (Cleare & Bond, 1997). Results from challenge studies may vary, in part, due to the differences in the nature of the enhancement challenge protocol used. In particular, fenfluramine stimulates prolactin release by causing increased release of serotonin from the presynaptic nerve ending and also inhibiting serotonin reuptake (Nestler, 2001). In contrast, tryptophan infusion causes prolactin release via increased synthesis of serotonin from tryptophan, a process more likely to differ in men and women due to effects of estrogen to increase tryptophan hydroxylase expression. Moreover, the prolactin response to fenfluramine is thought to be mediated by 5-HT₂ receptors (Newman, Shapira, & Lerer, 1998), whereas, response to tryptophan is believed to be mediated by 5-HT_{1A} and 5-HT₂ receptors (e.g., Coccaro, Kavoussi, Oakes, Cooper, & Hauger, 1996; Heninger, Charney, & Sternberg, 1984; Power & Cowen, 1992). Research also suggests that testosterone interacts with serotonin to influence psychological traits, such as aggression (Birger et al., 2003). Therefore, it is possible that testosterone may also play a broader role in modulating negative affect in general. Thus, specifics regarding the enhancement protocol may help account for sex differences in outcomes, and the continued use of protocols that differ in mode of enhancement may provide a more comprehensive understanding of the specific mechanisms.

Certain limitations should be noted with respect to the present findings. Because the sample consisted of only 67 participants, all results should be interpreted with proper caution and replication in additional samples will be required in order to determine their validity. The lack of a stronger relation in the opposite direction for males, as well as the inability to detect differences for other personality constructs may have been due to lack of adequate power, which is a particularly important issue to be considered when examining models that contain interactions. In addition, we were unable to examine ethnicity as a further moderator due to insufficient numbers of participants in certain cells. Finally, given the sample size we maximized power by not correcting for multiplicity, hence, the reported *p* values may be liberal.

In conclusion, the present findings suggest that CNS serotonergic activity is associated with negative affect in a non-clinical sample, with the relation differing by gender. It is hoped that converging results from related areas of research will provide insight into the increasing number of sex differences demonstrated in serotonergic functioning.

Acknowledgements

This research was supported by the by National Heart, Lung, and Blood Institutes grant 3P01 HL036587; the National Institutes of Mental Health grant R01MH57663; the National Institute on Aging grant R01AG19605, with co-funding by National Institute of Environmental Health Sciences; and by the Clinical Research Unit grant M01RR301.

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Figure 1. Association between Neuroticism (predicted values, residualized for baseline prolactin levels, age, and race) and peak prolactin response (log transformed): by gender.

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 (+ SD) unless otherwise stated

^a denotes (p < .10)

^b denotes (p < .05) for a between groups difference *t*-test for males and females

^c denotes (p < .01) for paired *t*-test assessing change in prolactin for both males and females. 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.

Table 2

Partial correlations among peak prolactin levels and related personality measures, by gender (adjusted for baseline prolactin, race, and age).

Personality Measure	Males, n=42	Females, n=25
Neuroticism	$r = + 0.19$	$r = - 0.30$
N1-Anxiety	$r = + 0.25$	$r = - 0.36$
N3-Depression	$r = + 0.31$	$r = - 0.25$
N6-Vulnerability	$r = + 0.26$	$r = - 0.18$