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# Aggression, Impulsivity, and Central Nervous System Serotonergic Responsivity in a Nonpatient Sample

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*To test the hypothesis that traits of aggression and impulsivity correlate negatively with central serotonergic system function in a nonpatient population, a standard fenfluramine challenge (for assessment of serotonergic responsivity) and behavioral measurements germane to aggression/impulsivity were administered to a community-derived sample of 119 men and women. In men, peak prolactin responses to fenfluramine correlated significantly with an interview-assessed life history of aggression ($r = -.40$, $p < .002$), the Barratt Impulsiveness Scale ($r = -.30$, $p < .03$), and traits of Conscientiousness ($r = +.30$, $p < .03$), Neuroticism ($r = -.31$, $p < .02$) and Angry Hostility ($r = -.35$, $p < .01$) on the NEO-Personality Inventory. No significant relationships were observed across all women, although subanalyses restricted to postmenopausal subjects (in whom ovarian influences on prolactin secretion may be mitigated because of diminished estrogen) showed a pattern of behavioral associations somewhat similar to that seen in men. By extending documented relationships between an index of central serotonergic system function and traits of aggression and impulsivity to a more normative range of population variability than is represented in prior literature, this study supports speculation that these associations reflect a basic neurobehavioral dimension of individual differences.*
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Individual differences in expressed aggression and impulse control are associated with variability in central nervous system (CNS) serotonergic function, as seen in a variety of clinical and forensic populations. Cerebrospinal fluid (CSF) concentrations of the serotonin metabolite, 5-hydroxyindoleacetic acid (5-HIAA), have been shown to correlate inversely with (1) lifetime histories of aggression and antisocial behavior among personality disordered (PD) patients and alcoholics (Brown et al. 1979; Brown et al. 1982; Limson et al. 1991); (2) parent reports of physical aggression in children and adolescents having disruptive behavior disorders (Kruesi et al. 1990; Kruesi et al. 1992); and (3) a history of impulsive fire setting and unpremeditated homicide among incarcerated, adult offenders (Linnoila et al. 1983; Virkkunen et al. 1987; Virkkunen et al. 1994). In other studies, neuroendocrine responses to agents that exert a variety of pre- and/or postsynaptic effects on serotonin (5-HT) neurotransmission have been used to assess central serotonergic function. Prolactin responses

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to fenfluramine hydrochloride (which promotes serotonin release and inhibits reuptake) were found to be attenuated in antisocial PD and mixed PD patients, relative to normal controls (Coccaro 1992; Coccaro et al. 1989; O'Keane et al. 1992); moreover, prolactin responses among PD patients correlated negatively with histories of aggression and psychometric indices of assaultiveness, irritability, and impulsivity (Coccaro et al. 1989; Coccaro et al. 1997). Similar findings have been reported with respect to other central serotonergic probes, including: (1) prolactin responses to m-chlorophenylpiperazine in patients having both antisocial PD and substance abuse diagnoses (Moss et al. 1990); (2) prolactin responses to buspirone hydrochloride in PD patients (Coccaro et al. 1990); (3) growth hormone responses to buspirone among cocaine-dependent subjects (Moeller et al. 1994); and (4) cortisol and temperature responses to ipsapirone, again in a mixed PD patient group (Coccaro et al. 1995). Most recently, self-report and interview-derived measures of aggression were found to correlate negatively, in PD patients, with tritiated paroxetine binding to platelet serotonin transporter sites, a model for transporter activity in the CNS serotonergic neuron (Coccaro et al. 1996b).

Some failures of replication have also been reported (Fishbein et al. 1989; Stoff et al. 1992; Wetzler et al. 1991), however, and even where similar outcomes are recorded, specific serotonin-related behavioral indices do not always replicate or reflect the same magnitude of association across studies (Brown et al. 1979; Coccaro et al. 1989; Coccaro et al. 1995; Coccaro et al. 1997; Limson et al. 1991; Tuinier et al. 1995). Nonetheless, the preponderance of existing literature indicates that aspects of aggression and impulsivity are associated with diminished central serotonergic function. Consistent, too, are recent studies in nonhuman primates. Among adolescent male rhesus monkeys (*Macaca mullata*) observed in a natural environment, for instance, animals that had low CSF 5-HIAA concentrations expressed more severe aggression and less affiliative behavior than those with higher 5-HIAA levels (Higley et al. 1992); CSF 5-HIAA was also associated inversely with certain forms of high-risk behavior (long leaps in the forest canopy, early emigration from natal groups) and premature mortality, often the result of wounds sustained in fights (Higley et al. 1996b; Kaplan et al. 1995; Mehlman et al. 1994; Mehlman et al. 1995). In adult females of the same species, interindividual variability of CSF 5-HIAA concentrations was stable over time and correlated negatively with spontaneous aggression and positively with social rank (Higley et al. 1996a). Finally, behavioral observations on male cynomolgus monkeys (*Macaca fascicularis*) housed in small social groups showed a high frequency of overt aggression and relative social withdrawal to be associated with blunted responses to a standard fenfluramine challenge (Botchin et al. 1993).

It is now widely hypothesized that population variability in central serotonergic function reflects a trait-like attribute of individuals that may partly underlie temperamental differences in impulse control—variously described as dimensions of constraint (Depue and Spoont 1986), behavioral inhibition (Gray 1987; Soubrie 1986; Zuckerman 1995) and harm avoidance (Cloninger 1987). Most consistent with such speculation are the findings in nonhuman primates, where study samples exhibit distributions of behavior and serotonergic activity existing in natural populations (Botchin et al. 1993; Higley et al. 1992; Higley et al. 1996a; Higley et al. 1996b; Kaplan et al. 1995; Mehlman et al. 1994; Mehlman et al. 1995). In contrast, human studies have entailed selection primarily for deviance, as reflected in a variety of diagnostic entities or history of criminal activity (Brown et al. 1979; Brown et al. 1982; Coccaro 1992; Coccaro et al. 1989; Coccaro et al. 1990; Coccaro et al. 1996b; Coccaro et al. 1997; Fishbein et al. 1989; Kruesi et al. 1990; Kruesi et al. 1992; Limson et al. 1991; Linnoila et al. 1983; Moeller et al. 1994; Moss et al. 1990; O'Keane et al. 1992; Stoff et al. 1992; Virkkunen et al. 1987; Virkkunen et al. 1994). In the few studies evaluating "normal" subjects as well, measures of central serotonergic function showed either no relationship to indices of aggression and implusivity (Limson et al. 1991; Moeller et al. 1994), or more commonly, nonsignificant trends to inverse association (Coccaro 1992; Coccaro et al. 1996b; Moeller et al. 1994) or relationships reduced to nonsignificance after statistical adjustment for appropriate covariates (Roy et al. 1988). In one recent study of a small nonpatient sample, a psychometric index of aggression was found to correlate inversely with cortisol, but not with prolactin, responses to fenfluramine, and in men, but not women (Cleare and Bond, 1997). These mixed outcomes, together with the absence of a consistent association between serotonergic activity and impulsivity or outwardly expressed aggression in patients with mood or panic disorders (Coccaro et al. 1989; Rydin et al. 1982; Tuinier et al. 1995; vanPraag. 1986; Wetzler et al. 1991), leave the normative dimensionality of CNS serotonin–behavior covariation unresolved. On the other hand, because most study samples in this literature are quite small (e.g., with *N*s typically less than 20 per group), any modest-to-moderate relationship between serotonergic activity, aggression, and impulsivity in a nonclinical population may have eluded detection previously for lack of statistical power (Coccaro et al. 1996b).

At present, therefore, it remains unclear whether impulsivity and expressed aggression covary inversely with indices of central serotonergic function as a broad dimension of interindividual variability, or do so only within certain clinical and forensic populations (Wetzler et al. 1991). In the current study, we extend prior observations by further evaluating the generality of serotonin–behavior associations in a community-derived,

nonpatient sample. Subjects were participants in a separate investigation concerning correlates of cardiovascular disease risk and risk factor modification, the protocol for which included administration of a fenfluramine challenge and many of the behavioral indices previously associated with central serotonergic function. Analyses were conducted on individuals having neither current nor past histories of DSM-III-R Axis I disorders, including alcohol or other drug abuse or dependence. Although diagnostic information regarding Axis II psychopathology was unavailable, the low population prevalence of PDs and their significant comorbidity with substance abuse (excluded here) suggests minimal confounding in the present sample (Kessler et al. 1994; Lenzenweger et al. 1997; Reich et al. 1989; Samuels et al. 1994; Weissman 1993; Zimmerman and Coryell 1989). Results indicated that, in men, heightened aggression and impulsivity were associated with low prolactin responses to fenfluramine (i.e., reduced serotonergic activity). Fenfluramine-induced prolactin changes did not correlate significantly with indices of aggression, hostility, or impulsivity among all women tested, although subanalyses restricted to postmenopausal subjects (in whom ovarian influences on prolactin secretion may be mitigated by diminished estrogen) revealed a pattern of behavioral associations somewhat similar to that seen in men.

## METHOD

### Subjects

All subjects were enrolled in the University of Pittsburgh Cholesterol and Risk Evaluation (CARE) project, a study of neurobehavioral correlates of population variability in plasma lipids. Participants were recruited through media advertisements and local distribution of brochures and posters. Exclusion criteria included medical diagnoses of schizophrenia or delusional disorder, cancer, stroke, insulin-dependent diabetes, chronic kidney or liver disease, and use of psychotropic, glucocorticoid, or hypolipidemic medication. Pregnant or lactating women were also excluded. The study protocol was approved by the University of Pittsburgh Institutional Review Board for Biomedical Research and subjects gave informed consent to participate.

Subjects attended three laboratory appointments for the measurement of fasting plasma lipids, blood pressure, and other cardiovascular disease risk factors; demographic characteristics; aspects of mood, personality, and health-related quality of life; neuropsychological (cognitive) functioning; and plasma prolactin responses to an orally administered fenfluramine challenge. A diagnostic interview for evaluation of DSM-III-R Axis I disorders (Structured Clinical Interview for DSM-III-R: Nonpatient edition [SCID-NP]) (Spitzer et al. 1990) was administered by a trained interviewer and clinical psychologist, with psychiatric consultation and review. The present analyses are based on 125 consecutively enrolled CARE participants who: (1) completed all components of the assessment protocol; and (2) were free of any Axis I disorder, both current and past. Of these subjects, six were subsequently excluded because of hyperprolactinemia (Elin 1992) at baseline (>20 ng/ml) or missing prolactin values due to technical difficulties. The remaining 119 subjects included 59 men and 60 women ranging in age from 30 to 60 years (mean age = 46.4 years). Mean length of education was 15.6 years; 86% of subjects were Caucasian, 69% were married, and 77% were employed full- or part-time. Thirty-nine women were premenopausal (two were on oral contraceptives), and of the 21 postmenopausal women, eight were prescribed hormone replacement therapy at the time of testing.

### Behavioral Assessments

To constrain experiment-wise error, only a subset of behavioral measurements obtained in the parent project were selected for analysis. Except for the inclusion of one broad measure of personality (the Revised NEO Personality Inventory) (Costa and McCrae 1992), all instruments evaluated here were selected based on prior evidence that total scores or scores on certain subscales correlated inversely with indices of central serotonergic function in clinical samples. These measures include an interview-derived Life History of Aggression (LHA) (Brown et al. 1979; Brown et al. 1982; Coccaro 1992; Coccaro et al. 1989; Coccaro et al. 1996b; Limson et al. 1991; Moeller et al. 1994), the Buss–Durkee Hostility Inventory (Buss and Durkee 1957; Coccaro 1992; Coccaro et al. 1989; Coccaro et al. 1990; Coccaro et al. 1995; Coccaro et al. 1996b; Moss et al. 1990), and the Barratt Impulsiveness Scale (Barratt 1985; Coccaro 1992; Coccaro et al. 1989).

First reported by Brown et al. (1979, 1982), the aggression history interview was revised by Coccaro et al. (1996b) to assess diverse aspects of aggressive behavior, as reflected in three item clusters or subscales; *aggression* expressed toward others (by verbal and physical assault) or toward inanimate objects (destruction of property), and temper tantrums; *antisocial* behaviors involving disciplinary action (in school and workplace) and illicit acts committed with and without police contact; and *injury to self* (with both suicidal and nonsuicidal intent). The 11-item LHA used in the current study differed from Coccaro et al. (1996b) by the exclusion of an item on attempted suicide and inclusion of one additional question concerning conflict with authority figures. This semistructured instrument was administered by one of two experienced interviewers, who recorded subjects' responses to each question and queried for corroborating detail by a common protocol. Items were scored for frequency of occurrence on a 1 to

4 scale (never, rarely, occasionally, often), referenced separately to subjects' experiences in childhood, adolescence, and adulthood. Excellent interrater reliability was observed between the two interviewers (kappa coefficients = 1.0, 0.92, and 0.86 for the childhood, adolescent, and adult codes, respectively). For present purposes, a total LHA score and scores on the "aggression" and "antisocial" subscales described by Coccaro et al. (1996b) were calculated by summing the highest code assigned in the adolescent or adult age periods across all applicable items. The subscale for self-injurious behavior was not computed here because of the absence of reported acts in this category.

The Buss–Durkee Hostility Inventory (BDHI) is a well-established, 75-item questionnaire structured in a true–false format (Buss and Durkee 1957). The BDHI contains eight scales, six of which cohere psychometrically within two factors, "motor aggression" and "attitudinal hostility." This inventory has good internal consistency (Bendig 1962) and test–retest reliability (Biaggio et al. 1981). The current analyses were restricted to the two major factors and their component scales (Buss and Durkee 1957). Motor aggression subsumes four scales, labeled assault, irritability, indirect hostility ("undirected aggression"), and verbal hostility. The attitudinal hostility factor includes two scales, resentment and suspiciousness.

The Barratt Impulsiveness Scale (BIS-11) contains 30 questions regarding subjects' control of thoughts and behavior (e.g., acts without thinking, decides "on the spur of the moment," does not plan ahead), each scored on a 4-point Likert scale (Barratt 1985; Barratt 1994). The Barratt Scale has high internal consistency (alpha coefficients = 0.79 to 0.83) (Patton et al. 1995) and, although retest reliability of the BIS-11 has not been reported, we found interindividual variability on this scale to be highly reproducible over 6-months (reliability coefficient = 0.88) in a sample of 64 CARE participants. Several subscales derived by factor analysis of the Barratt Scale have been described previously (e.g., "motor," "cognitive," and "nonplanning" impulsiveness), but because of variability of factor structures across study populations we have employed only the total score in the present analyses (Barratt 1985, 1994; Luengo et al. 1994; Patton et al. 1995).

The NEO Personality Inventory is the most prominent self-report instrument for measuring the five broad domains of personality variability commonly observed in factor-analytic studies of lexically derived trait ratings (Costa and McCrae 1992). Respondents indicate on a four-point scale the degree to which each of 240 items is descriptive of their own behavior, attitudes, and feelings. The five personality domains are labeled neuroticism (emotionality, emotional stability), extraversion, openness to experience (e.g., imaginativeness, "intellectual curiosity and independence of judgment"), agreeableness (vs. interpersonal antagonism), and conscientiousness. The five domain scales have high internal consistency and acceptable retest reliability ($r$s = .75–.83, over 3 months) (Costa and McCrae). Insofar as low scores on agreeableness may imply variability in some aspects of hostility (e.g., rudeness, suspiciousness) and the dimensions of neuroticism and conscientiousness (e.g., purposefulness, reliability and self-discipline, planfulness) imply variability in impulse control, these scales might also be predicted to covary with indices of central serotonergic function. Openness to experience and extraversion, on the other hand, are less related to the putative behavioral correlates of CNS serotonin and were included to help establish discriminant validity. Finally, each of the five domains assessed by the NEO personality inventory subsumes six "facet" scales that tap diverse features, or attributes, of the corresponding personality dimension. We selected two facet scales for inclusion in the present analyses; these are labeled "Angry Hostility" and "Excitement Seeking."

### Fenfluramine Challenge

Fenfluramine, in both its d,l- and d- stereoisomers, induces presynaptic release of serotonin stores, inhibits the reuptake of synaptic serotonin, and by possible direct activation of postsynaptic serotonergic receptors, enhances serotonin neurotransmission (Borroni et al. 1983; Coccaro et al. 1989; Quattrone et al. 1983). Stimulation of serotonergic receptors in the hypothalamus promotes pituitary release of prolactin into the circulation. The resulting change in plasma prolactin (PRL) concentration provides an index of overall serotonergic responsivity in the hypothalamic–pituitary axis, an interpretation that is supported by the inhibition of PRL responses by central 5-HT (in particular, 5-$HT_2$) receptor blockade (DiRenzo et al. 1989; Goodall et al. 1993; Lewis and Sherman 1985; Quattrone et al. 1983).

Subjects were administered fenfluramine orally as a single dose, and their PRL levels were determined on five occasions over a period of 3.5 hours. Our prior experience using a 60 mg, fixed-dose d,l-fenfluramine challenge in a nonclinical sample revealed a high incidence of adverse side effects, particularly in persons of lighter weight, and a substantial inverse correlation between body weight and the peak PRL response (Muldoon et al. 1996). As a result, we modified our protocol here to administer d,l-fenfluramine hydrochloride over a dose range of 30, 40, 50, and 60 mg to achieve a weight-relative dose of approximately 0.55 to 0.65 mg/kg of body weight. As anticipated, we observed no significant association between body weight and the peak PRL response to fenfluramine on this dosing schedule, in either women or men ($r$s $< -.02$, NS).

On reporting to the laboratory between 8 and 10 A.M. after a 12-hour fast, participants were seated in a com-

fortable chair and a 20-gauge, heparin-locked catheter was inserted aseptically into a vein in the antecubital fossa. Following a 30-minute adaptation period, a blood sample for determination of baseline PRL concentration was obtained, and the drug was administered; subsequent blood samples were drawn 60, 120, 150, 180, and 210 minutes later. Additional samples were taken at 150 and 210 minutes for measurement of fenfluramine and norfenfluramine concentrations. All blood samples were centrifuged immediately, separated, and frozen at −70°C until analysis.

Plasma PRL levels were determined in duplicate using Immunocorp's (Montreal, Canada) solid phase, two-site immunoradiometric method. The lower limit of sensitivity of the PRL assay is 0.5 ng/ml and the inter-assay coefficient of variation is 6 to 9%. Plasma levels of fenfluramine and norfenfluramine (the principal active metabolite) were measured to examine individual differences in bioavailability. These samples were collected in borosiliate acid-washed glass tubes with balanced ammonium–potassium oxylate crystals. A gas chromatograph fitted with a nitrogen detection system was used, and the internal standard was isopropyl fenfluramine. The lower detection limit is 2 ng/ml, and the coefficient of variation is 5.2% at 5 ng/ml.

The current protocol is shorter than the standard 5-hour fenfluramine test because of practical constraints on participation and scheduling in our sample of nonpatient volunteers. The period of 3.5 hours was selected, because previously published data indicated that the peak PRL response typically occurs 3 to 4 hours after oral fenfluramine administration in normal controls (McBride et al. 1990). In addition, we have compared peak PRL concentrations over 3.5, 4, and 5 hours in a nonpatient sample of 42 individuals (21 men, 21 women; mean age = 42.8 years). The highest PRL value over 3.5 hours correlated 0.95 and 0.91, respectively, with peak concentrations observed across intervals of 4 and 5 hours, thus indicating a high concordance between assessments based on the abbreviated and standard sampling intervals.

### Statistical Analysis

The data of men and women were subjected to separate, but parallel, analyses. To index the PRL response to fenfluramine [fen], a peak PRL change (Δ) was calculated for each subject as the arithmetic difference between the highest PRL value obtained following drug administration and PRL concentration at baseline. The resulting distributions of ΔPRL[fen] scores were skewed positively in both men and women and, therefore, were normalized by logarithmic transformation ($\log_{10}(\Delta\text{PRL[fen]}+c)$, where $c$ is the smallest constant yielding a minimum score greater than 1) (Kirk 1968). Because preliminary analyses showed baseline PRL concentrations in men to correlate inversely with log-transformed, ΔPRL[fen] scores ($r = -.40$, $p < .001$), the latter were adjusted for covariation with initial values, yielding a baseline-free index of PRL response to fenfluramine. For consistency, the same adjustment was made in women, although the correlation between baseline and PRL change was not statistically significant ($r = -.09$, NS). Spearman rank order correlations ($r_s$) between the baseline-adjusted, log-ΔPRL[fen] values and raw ΔPRL[fen] scores, uncorrected for baseline PRL, were 0.92 in men and 0.99 in women. Although normalization of ΔPRL[fen] distributions and correction for baseline covariation were performed to allow parametric analyses and to unconfound measures of baseline PRL and PRL response, all significant bivariate correlations with behavioral measurements reported below retained significance when recalculated as Spearman coefficients using the unadjusted baseline-to-peak PRL change as an index of serotonergic responsivity.

For descriptive purposes, men and women were first compared on demographic characteristics, weight and height; fenfluramine dose, plasma fenfluramine and norfenfluramine concentrations, baseline PRL and uncorrected ΔPRL[fen] scores; and the various measures of behavior and personality. These analyses were conducted by *t*-test, chi-square analysis, and the Mann–Whitney test for rank differences, as appropriate to the scale of measurement. Within sexes, Pearson correlations were calculated between the PRL response to fenfluramine (baseline-corrected, log-ΔPRL[fen] scores) and measures of aggression, hostility, impulsivity, and NEO personality traits. When several significant correlations were observed (and sample size permitted), a principal components analysis was performed to determine whether the pattern of covariation among these measures reflected one or more underlying dimensions of behavioral variability. Factors extracted with eigenvalues greater than 1.0 were subjected to oblique rotation, and factor scores were computed by unit-weighting scales having factor loadings above 0.50.

Ovarian status varied appreciably among women in this study. In addition to including both pre- and postmenopausal participants, menstrual phase at the time of fenfluramine testing was not controlled in premenopausal subjects and exposure to sex hormone replacement therapy differed among postmenopausal women. Estrogens are known to modulate PRL synthesis and release (Ben-Jonathan 1985; Liebenluft et al. 1994), and it has been reported that PRL responses to d-fenfluramine exhibit threefold variability across the menstrual cycle (O'Keane et al. 1991). Because ovarian influences on PRL changes might mask relationships between serotonergic responsivity and behavior, analyses were also conducted on a subset of women ($n = 13$) who were hypoestrogenic because of either natural (11) or surgical (2) menopause, without hormone replacement. Because of the small number of subjects, these correlations are reported as Spearman coefficients.

**Table 1.** Demographic and Subject Characteristics, Fenfluramine Dose, Baseline Prolactin (PRL), and Peak PRL Response to Fenfluramine (ΔPRL[fenfluramine]), and Plasma Fenfluramine and Norfenfluramine Concentrations During Challenge, in Male and Female Subjects. Unless indicated otherwise, values listed are group means (± SEM)

| | Men ($n$ = 59) | | Women ($n$ = 60) | | Statistic | $p$ |
|---|---|---|---|---|---|---|
| Age (Years) | 46.5 | (1.07) | 46.2 | (1.07) | $t_{117} = 0.22$ | ns |
| Marital status (% Married) | 73 | | 65 | | $\chi^2_1 = 0.86$ | ns |
| Education (Years) | 16.4 | (0.37) | 14.9 | (0.36) | $t_{117} = 2.95$ | <.004 |
| Employment status (% Employed) | 74.6 | | 78.3 | | $\chi^2_1 = 0.23$ | ns |
| Race (% Caucasian) | 89.8 | | 81.7 | | $\chi^2_1 = 1.02$ | ns |
| Weight (Kg) | 83.3 | (1.38) | 71.0 | (0.32) | $t_{117} = 5.77$ | <.0001 |
| Height (cm) | 175.01 | (6.68) | 162.56 | (6.30) | $t_{117} = 10.51$ | <.0001 |
| Season (Fall, Winter, Spring, Summer) | 13/15/22/9 | | 20/10/16/14 | | $\chi^2_3 = 4.51$ | ns |
| Fenfluramine dose (mg) | 53.4 | (0.96) | 44.2 | (1.12) | $t_{117} = 6.25$ | <.0001 |
| Baseline PRL (ng/ml) | 6.3 | (0.28) | 7.5 | (0.53) | $t_{117} = -2.00$ | <.05 |
| ΔPRL[fen] (ng/ml) | 2.7 | (0.45) | 5.3 | (0.32) | $Z = -2.90$[a] | <.004 |
| Plasma measurements (ng/ml) | | | | | | |
| Fenfluramine, 150 min | 40.7 | (2.01) | 39.7 | (2.15) | $t_{117} = 0.32$ | ns |
| Norfenfluramine, 150 min | 7.4 | (0.44) | 7.0 | (0.53) | $t_{117} = 0.64$ | ns |
| Fenfluramine, 210 min | 48.4 | (1.92) | 46.5 | (1.87) | $t_{117} = 0.71$ | ns |
| Norfenfluramine, 210 min | 10.6 | (0.53) | 9.9 | (0.53) | $t_{117} = 0.87$ | ns |

[a]Mann-Whitney test for rank differences.

## RESULTS

### Subject Characteristics

As indicated in Table 1, men and women were similar in age, seasonal distribution at testing, ethnic composition, and marital and employment status, although men reported more years of education. In consequence of their lighter weight, women were administered significantly less fenfluramine than men. However, the baseline PRL concentration was significantly higher in women, and although plasma fenfluramine/norfenfluramine concentrations did not differ by sex during challenge, the peak PRL response to fenfluramine (ΔPRL[fen]) was also significantly greater among women. To determine whether baseline PRL or PRL responses to fenfluramine varied by season of testing (fall, winter, spring, summer), baseline values and baseline-adjusted, log-ΔPRL[fen] scores were subjected to one-way analysis of variance

**Table 2.** Measures of Aggression, Hostility, Impulsivity and NEO-derived Personality Traits, in Male and Female Subjects. Values listed are group means (± SEM)

| | Men ($n$ = 59) | | Women ($n$ = 60) | | $t_{117}$ | $p$ |
|---|---|---|---|---|---|---|
| Life history of aggression (LHA) | | | | | | |
| Total score | 18.4 | (0.58) | 14.4 | (0.41) | 5.64 | <.0001 |
| Aggression | 9.0 | (0.33) | 8.1 | (0.30) | 2.06 | <.05 |
| Antisocial | 9.4 | (0.39) | 6.3 | (0.22) | 6.80 | <.0001 |
| Buss-Durkee Hostility Inventory (BDHI) | | | | | | |
| Motor hostility | 15.8 | (0.70) | 14.4 | (0.79) | 1.34 | ns |
| Assault | 2.9 | (0.23) | 2.4 | (0.25) | 1.57 | ns |
| Irritability | 3.1 | (0.25) | 3.2 | (0.30) | −0.43 | ns |
| Indirect hostility | 3.7 | (0.25) | 3.6 | (0.25) | 0.08 | ns |
| Verbal hostility | 6.2 | (0.33) | 5.1 | (0.30) | 2.30 | <.03 |
| Attitudinal hostility | 2.5 | (0.33) | 3.1 | (0.33) | −1.14 | ns |
| Resentment | 1.1 | (0.19) | 1.3 | (0.18) | −0.82 | ns |
| Suspiciousness | 1.4 | (0.19) | 1.7 | (0.22) | −1.09 | ns |
| Barratt Impulsiveness Scale (BIS-11) | | | | | | |
| Total score | 34.4 | (1.45) | 36.5 | (1.78) | −0.92 | ns |
| NEO-Personality Inventory | | | | | | |
| Conscientiousness | 126.0 | (2.55) | 121.9 | (2.49) | 1.14 | ns |
| Neuroticism | 68.2 | (2.38) | 77.5 | (2.81) | −2.55 | <.02 |
| Angry hostility | 11.8 | (0.48) | 11.3 | (0.59) | 0.70 | ns |
| Extraversion | 114.7 | (2.53) | 112.7 | (2.45) | 0.57 | ns |
| Excitement seeking | 17.9 | (0.52) | 14.7 | (0.58) | 4.07 | <.0001 |
| Openness to experience | 112.7 | (2.42) | 114.6 | (2.25) | −0.57 | ns |
| Agreeableness | 124.2 | (1.92) | 130.9 | (2.10) | −2.34 | <.03 |

(ANOVA); no seasonal effect was observed for either variable, in either men or women. With respect to behavioral measurements (Table 2), men scored higher than women on the LHA (total score, as well as the aggression and antisocial factors) and on the verbal hostility scale of the BDHI. Conversely, women scored higher than men on two of the five NEO domain scales, neuroticism and agreeableness.

### Behavioral Correlates of Serotonergic Responsivity in Men

Pearson correlations between baseline-adjusted, log-ΔPRL[fen] scores and measures of behavior and personality are presented in Table 3. In men, the LHA-Total score and LHA-aggression factor correlated inversely with PRL responses to fenfluramine, as did the Barratt Impulsiveness Scale and the NEO traits of neuroticism and angry hostility. A significant, positive correlation was also observed between subjects' PRL responses and scores on the NEO-conscientiousness scale. BDHI scores did not correlate significantly with PRL responses to fenfluramine, although the coefficient for the BDHI-assault scale approached significance. These relationships were unaffected by adjustment (by means of partial correlation) for variability in age, weight, fenfluramine dose, or plasma fenfluramine and norfenfluramine concentrations during challenge.

Four of the behavioral measures associated with subjects' fenfluramine-induced PRL responses were subjected to a principal components analysis. These variables included the LHA-aggression score, Barratt Impulsiveness Scale, and NEO measures of Conscientiousness and Angry Hostility; NEO-Neuroticism was excluded because of its item overlap with the Angry Hostility scale. This analysis yielded a single factor (for convenience, labeled Aggression/Impulsivity) on which all variables loaded highly: LHA-Aggression (0.64), Barratt Impulsiveness Scale (0.75), NEO Conscientiousness (−0.79) and Angry Hostility (0.66). As we would expect from the pattern of bivariate correlations, unit-weighted factor scores also correlated significantly with baseline-adjusted, log-ΔPRL[fen] values ($r = -.47$, $p < .0002$), accounting for 22% of the variance in subjects' PRL responses to fenfluramine ($r = -.54$, $p < .0001$, when adjusted by partial correlation for variability in age, education, weight, fenfluramine dose, and plasma concentrations of fenfluramine and norfenfluramine during challenge). See Figure 1. That this association is not attributable to the influence of statistical outliers is indicated by a similarly significant Spearman coefficient based on rank order relationships alone ($r_s = -.46$, $p < .0002$).

**Table 3.** Correlation of Fenfluramine-Induced PRL Responses (Baseline-Adjusted, Log-ΔPRL[fen] Scores) with Measures of Aggression, Hostility, Impulsivity and NEO Personality Traits, in Men ($n = 59$), all Women ($n = 60$), and Postmenopausal Women without Estrogen Replacement ($n = 13$)

| | Men | | Women | | Postmenopausal Women | |
|---|---|---|---|---|---|---|
| | r | *p* | r | *p* | $r_s$ | *p* |
| Life history of aggression (LHA) | | | | | | |
| Total score | −0.33 | =.01 | 0.08 | ns | −0.21 | ns |
| Aggression | −0.40 | <.002 | 0.09 | ns | 0.05 | ns |
| Antisocial | −0.15 | ns | 0.03 | ns | −0.35 | ns |
| Buss-Durkee Hostility Inventory (BDHI) | | | | | | |
| Motor hostility | −0.18 | ns | 0.17 | ns | 0.11 | ns |
| Assault | −0.22 | <.10 | 0.09 | ns | 0.09 | ns |
| Irritability | −0.03 | ns | 0.11 | ns | 0.04 | ns |
| Indirect hostility | −0.18 | ns | 0.07 | ns | 0.28 | ns |
| Verbal hostility | −0.09 | ns | 0.19 | ns | −0.04 | ns |
| Attitudinal hostility | −0.07 | ns | −0.08 | ns | −0.81 | <.001 |
| Resentment | −0.08 | ns | 0.06 | ns | −0.45 | ns |
| Suspiciousness | −0.04 | ns | −0.17 | ns | −0.82 | <.001 |
| Barratt Impulsiveness Scale (BIS-11) | | | | | | |
| Total score | −0.30 | <.025 | −0.09 | ns | −0.59 | <.035 |
| NEO-Personality Inventory | | | | | | |
| Conscientiousness | 0.30 | <.025 | 0.15 | ns | 0.69 | <.001 |
| Neuroticism | −0.31 | <.02 | −0.17 | ns | −0.24 | ns |
| Angry hostility | −0.35 | <.001 | −0.02 | ns | −0.32 | ns |
| Extraversion | −0.01 | ns | −0.05 | ns | 0.04 | ns |
| Excitement seeking | −0.02 | ns | 0.02 | ns | −0.23 | ns |
| Openness to experience | −0.07 | ns | 0.17 | ns | 0.04 | ns |
| Agreeableness | 0.01 | ns | −0.23 | ns | −0.21 | ns |

### Behavioral Correlates of Serotonergic Responsivity in Women

None of the behavioral measurements correlated significantly with fenfluramine-induced PRL changes among all women (Table 3). In the analyses restricted to hypoestrogenic subjects (i.e., postmenopausal women untreated by hormone replacement), however, variability of PRL responses was found to correlate inversely with several behavioral indices, including the BDHI-Attitudinal Hostility factor and BDHI Suspiciousness scale. As in men, moreover, subjects' PRL responses to fenfluramine also correlated positively with scores on the NEO scale for Conscientiousness and negatively with the Barratt Impulsiveness Scale. In contrast to comparisons involving all women, this subset of postmenopausal subjects had mean baseline PRL concentrations and **Δ**PRL[fen] scores similar to those of men (baseline PRL: $\overline{X}$ = 5.5 and 6.3 ng/ml, respectively: $t_{70}$ = 1.06, NS; ΔPRL[fen]: $\overline{X}$ = 3.5 and 2.7 ng/ml: Mann Whitney test for rank differences, $Z$ = 0.43, NS). Finally, because these subjects were postmenopausal, it is not surprising that they also exceeded the mean age of all women studied (55.8 vs. 46.2 years). Correlational analyses among these subjects do not seem to reflect a confounding of age and menopausal status, however, because neither adjusting for age in correlations involving all women nor reanalyzing associations between behavioral indices and PRL responses to fenfluramine in groups stratified by age (median division) alters the pattern of findings reported in Table 3.

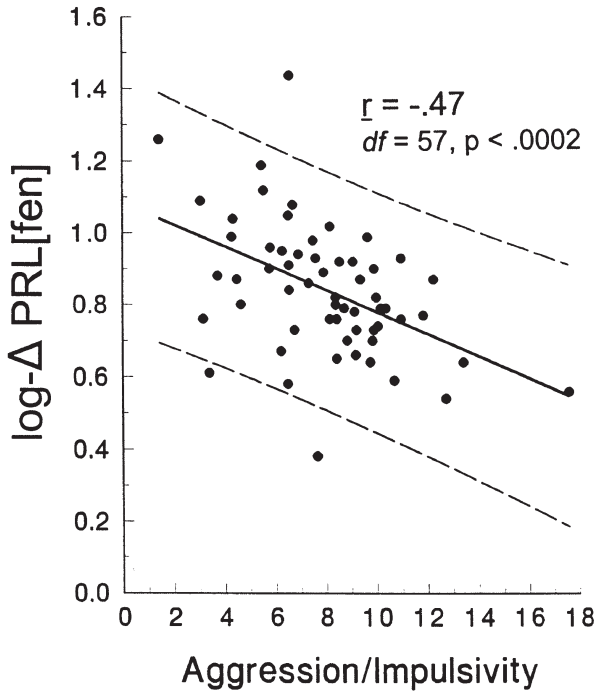


**Figure 1.** Mean peak prolactin (PRL) responses to fenfluramine (baseline-adjusted, log-ΔPRL[fen] values) among men, as a function of subjects' aggression/impulsivity factor scores (scaled to a score range of 0–18); dashed lines denote 95% confidence intervals; $n$ = 59, Pearson r = −.47, $p$ < .0002.

## DISCUSSION

In this study, interindividual variability in the PRL response to orally administered fenfluramine—an indirect assessment of central serotonergic function—covaried inversely with indices of aggression and impulse control in a community-derived, nonpatient sample of adult men. Although only moderate in magnitude, these associations are consistent with trends seen in prior studies involving smaller samples (Cleare and Bond, 1997; Coccaro 1992; Coccaro et al. 1996b; Moeller et al. 1994; Roy et al. 1988) and were observed on two of the same behavioral instruments previously reported to correlate negatively with measures of serotonergic activity (e.g., CSF 5-HIAA concentrations, fenfluramine and other neuroendocrine challenges) among PD patients and persons with substance abuse disorders (Brown et al. 1979; Brown et al. 1982; Coccaro 1992; Coccaro et al. 1989; Coccaro et al. 1997; Limson et al. 1991; Moeller et al. 1994). These measures included a life history of aggression (LHA) and the Barratt Impulsiveness Scale. NEO-Neuroticism and Angry Hostility also correlated inversely with PRL changes, and the NEO-Conscientiousness scale (tapping attributes such as resourcefulness, persistence, and self-discipline, and, by their absence, impatience, haste, and carelessness) (Costa and McCrae 1992) correlated positively. Finally, these conceptually related traits were found to load on a single factor when subjected to principal components analysis, indicating that a common axis of behavioral variability (aggression/impulsivity) may underlie men's PRL responses to fenfluramine. Additional studies will be needed, of course, to determine the replicability of these associations, as well as their factorial coherence as a unidimensional construct.

Nonetheless, these findings support speculation that inverse relationships between indices of central serotonergic activity and aspects of aggression and impulse control reflect a basic neurobehavioral dimension of individual differences in human subjects, at least as seen in men (Coccaro 1992). This dimensional interpretation is naturally strengthened to the extent that our data may be viewed as extending the spectrum of documented associations between central serotonergic activity and behavior from clinical samples (the principal focus of previous literature) to a more normative range of population variability. In this regard, it may be asked to what degree the present sample resembles a largely normal population, free of significant, or at least disproportionate, psychopathology. The study is not ideal in

this respect, because the parent investigation from which the sample was drawn was not designed to identify all individuals with a psychiatric history. Although persons on psychoactive medication were excluded from participation and both current and past Axis I psychopathology (including substance abuse and dependence) were exclusionary in these analyses, diagnostic information was unavailable with respect to Axis II disorders. However, inclusion of a significant number of individuals meeting DSM criteria for a PD diagnosis seems unlikely, because the population prevalence of all Axis II psychopathology is relatively low (Lenzenweger et al. 1997; Reich et al. 1989; Samuels et al. 1994; Weissman 1993). In addition, CNS serotonergic function has been found to correlate with indices of aggression and impulsivity most commonly in patient samples having borderline and antisocial PD. These two conditions are also highly comorbid with substance abuse, which again was exlusionary in the current study (Kessler et al. 1994; Lyons 1995; Zimmerman and Coryell 1989).

It may be noted, too, that subjects' scores on the five major dimensions of the NEO Personality Inventory, for which normative data are available (Costa and McCrae 1992), averaged within a quarter standard deviation of estimated population means; moreover, what small differences exist indicate somewhat less neuroticism among subjects here, as well as slightly higher scores on traits of agreeableness, extraversion, openness to experience, and conscientiousness. Subjects' PRL responses to fenfluramine were also unrelated to antisocial items on the LHA (Coccaro et al. 1996b), which by content (e.g., legal infractions, disciplinary sanctions) are pathognomonic of antisocial PD. Finally, we note the general linearity of behavioral association across the range of PRL responsivity (e.g., Figure 1). Indeed, the inverse correlation in men between fenfluramine-induced PRL responses and scores on our aggression/impulsivity factor retains statistical significance even after deleting subjects comprising either the lowest quartile of the distribution of PRL responses to fenfluramine ($r = -.48$, $df = 42$, $p < .0007$) or the highest quartile of aggression/impulsivity scores ($r = -.35$, $df = 42$, $p < .03$). These observations are similarly inconsistent with an interpretation of the results reported here as confounded by concurrent (unrecognized) Axis II psychopathology among a small subset of low fenfluramine-responsive men.

In contrast to men, we found no significant behavioral correlate of subjects' PRL responses to fenfluramine in analyses conducted across all women. It is at least conceivable that this null outcome is attributable less to a gender difference in the extent of serotonin-behavior covariation than to sex-specific influences on PRL responsivity in the fenfluramine challenge. Two-thirds of women in this sample were premenopausal and menstrual phase at the time of participation was not controlled. PRL synthesis, storage, and release are increased by estrogen (Ben-Jonathan 1985; Liebenluft et al. 1994) and, more specifically, PRL responsivity following oral administration of d-fenfluramine parallels plasma estradiol concentrations over the menstrual cycle (with a nadir early in the follicular phase and peak at midcycle) (O'Keane et al. 1991). Thus, it is possible that estrogenic effects associated with menstrual cyclicity accounted for a substantial portion of the variability in our PRL-dependent index of serotonergic activity. Moreover, estrogen can alter serotonin receptor number and responses, and thereby potentially modulate serotonin-associated behaviors as well (Biegon et al. 1982).

That such influences may have obscured serotonin-behavior relationships here is suggested by analyses conducted among postmenopausal (hypoestrogenic) women without hormone replacement. Baseline PRL concentrations and PRL responses to fenfluramine were similar to those seen in men, as was the pattern of behavioral association shown in correlational analyses. As in men, fenfluramine-induced PRL responses among these women correlated inversely with the Barratt Impulsiveness Scale and positively with NEO-Conscientiousness. Unlike men, however, the BDHI-Attitudinal Hostility factor covaried inversely with serotonergic activity in postmenopausal women, a relationship attributable to the component scale for Suspiciousness. These results suggest that whereas impulsivity is similarly associated with diminished central serotonergic function in both men and women, correlates in aggression may relate more to hostile attributions among women and to overt expressions of hostile intent in men. Finally, it must be cautioned that these results reflect analyses conducted on a small sample of postmenopausal subjects and that their extrapolation to the broader population of women remains to be demonstrated. In further studies using the fenfluramine challenge in premenopausal women, moreover, it may be prudent to study subjects at a time when estrogen concentrations are least variable, as occurs, for instance, early in the follicular phase of the normal menstrual cycle.

As noted earlier, it is widely speculated that variability in central serotonergic activity underlies, in part, individual differences in the constraint of impulse, with "deficiencies" of serotonergic function associated with disinhibition of behavior, as evidenced by a disregard for future consequences, actions committed in haste, and a propensity to aggressive expression (Cloninger 1987; Coccaro et al. 1989; Depue and Spoont 1986; Gray 1987; Soubrie 1986; Zuckerman 1995). When conceived as a dimension of temperament, such associations are thought to denote an enduring characteristic of individuals—one that appears early in life, has significant heritability, and for reasons of common origin, shows phylogenetic continuity (Buss and Plomin 1984). Experimental and comparative studies suggest that central serotoner-

gic activity can be influenced both environmentally (e.g., by conditions of rearing or social stress) and by genetic transmission (Fontenot et al. 1995; Higley et al. 1991; Higley et al. 1993; McKittrick et al. 1995). Among young rhesus monkeys, for example, studies of paternal half-siblings and of maternal offspring reared by unrelated mothers demonstrate substantial heritability of CSF 5-HIAA concentrations (Higley et al. 1993). In this same species, monkeys with low central serotonergic activity are those most likely to engage in high-risk behaviors and to escalate agonistic encounters to high levels of contact aggression (Higley et al. 1992; Higley et al. 1996a; Higley et al. 1996b; Kaplan et al. 1995; Mehlman et al. 1994; Mehlman et al. 1995).

In human subjects, Coccaro and colleagues have shown both significant heritability and nongenetic transmission of aggressiveness and irritable impulsivity among adult twins raised either together or apart (Coccaro et al. 1993). As in most behavioral genetic studies of personality development, nongenetic effects in this investigation were limited to "nonshared" environmental influences; that is, factors that promote differences rather than similarities among related individuals (e.g., idiosyncratic experiences) (Bouchard 1994; Plomin and Daniels 1987). Whereas the heritability of central serotonergic activity in humans has received little attention in biometric family studies (Meltzer and Arora 1988; Oxenstierna et al. 1976), Coccaro et al. (1994b) have also reported that personality traits indicative of impulsive PD are more prevalent in the first-degree relatives of PD patients who exhibit blunted PRL responses to fenfluramine than among relatives of probands showing a more pronounced PRL responsivity. These findings provide no direct evidence of genetic influence, but are at least consistent with this possibility. Most recently, self-report measures of anxiety-related traits were found associated with a 44-base pair polymorphism in the regulatory region of the serotonin transporter gene (Lesch et al. 1996). This finding is particularly interesting as two of the behavioral measurements that differentiated persons possessing long and short forms of the transporter polymorphism, NEO-Neuroticism and Angry Hostility, were also associated with fenfluramine-induced PRL responsivity in the current study (albeit, only in men). Because the functional effect of the short allele is presumably to increase serotonin neurotransmission and the presence of this allele was associated with *higher* scores on the two NEO scales however, it is unlikely that our findings (which also cohere more clearly on an axis of aggression/impulsivity than of anxiety) reflect an appreciable influence of this single polymorphism. In any case, elucidating the relative genetic and environmental determinants of these associated traits will ultimately require more comprehensive investigation incorporating both behavioral and neurobiological assessments, and in the ideal, applying both biometric and molecular approaches to genetic analysis.

Finally, in the absence of data pertinent to other transmitter systems, a serotonergic interpretation of these findings rests on the relative specificity of the fenfluramine challenge. It is well established that prolactin responses to fenfluramine may be blocked by serotonin antagonists (e.g., DiRenzo et al. 1989; Goodall et al. 1993; Lewis and Sherman 1985; Quattrone et al. 1983), and in rats, by lesioning of the raphe nuclei (Quattrone et al. 1979). However, the levo-rotary isomer of fenfluramine is also known to affect dopaminergic and noradrenergic activity in rodents (Garattini et al. 1988), and prolactin release may reflect nonserotonergic influences on the secretory capacity of the lactotroph. Prolactin responses to d,l-fenfluramine have been found to correlate highly, however, with responses to the more selective d-fenfluramine (Coccaro et al. 1993; Coccaro et al. 1996a). It has also been reported that prolactin changes provoked by d,l-fenfluramine are unrelated to the prolactin response to thyrotropin-releasing hormone, thus tending to exclude variability in pituitary lactotroph function (including dopaminergic inhibition of lactotroph cells) as an explanation for individual differences on the fenfluramine challenge test (Coccaro et al. 1994a). Additionally, the inverse association seen here between aggression/impulsivity and fenfluramine-induced prolactin responses has also been observed in clinical and forensic samples using a variety of other serotonergic probes, including m-chlorophenylpiperazine (Moss et al. 1990), buspirone (Coccaro et al. 1990), ipsapirone (Coccaro et al. 1995), and tritiated paroxetine binding to platelet serotonin transporter sites (Coccaro et al. 1996b). Nonetheless, replication of the present results using more specific neuroendocrine challenges in normal populations would substantially reinforce our tentative interpretation that these associations reflect behavioral correlates of interindividual variability in CNS serotonergic activity.

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