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Serotonergic functioning correlates with positive and negative affect in psychiatrically healthy males

David H. Zald [a,*], Richard A. Depue [b]

[a] *Division of Neuroscience Research, Department of Psychiatry, University of Minnesota and Cognitive Neuroimaging Unit, VA Medical Center, Minneapolis, MN, USA*

[b] *Laboratory of Neurobiology of Personality and Emotion, Department of Human Development, Cornell University, Ithaca, New York, USA*

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Abstract

A large animal literature implicates serotonin (5-HT) in the modulation of positive and negative affective behavior. In contrast, data from human studies almost exclusively emphasize 5-HT modulation of negative emotional processing. However, no previous studies have directly assessed the relation between 5-HT functioning and positive (PA) and negative (NA) affect. The present investigation tested whether individual differences in 5-HT functioning correlate with PA and NA ratings in a group of healthy subjects. Thirty-one psychiatrically healthy males completed separate assessments of affect and 5-HT functioning. Affect was examined with the Positive and Negative Affect Schedule rated three times a day for two work-weeks. 5-HT functioning was indexed by the maximum prolactin response to d,l-fenfluramine. The prolactin response to d,l-fenfluramine demonstrated a significant inverse correlation with mean ratings of both PA ($r = -0.49$; $p < 0.005$) and NA ($r = -0.42$; $p < 0.05$). These data provide evidence that 5-HT exerts an inhibitory influence over both PA and NA in humans, such that individual differences in 5-HT functioning inversely correlate with ratings of affect.

Keywords: Affect; Emotion; Lability; Personality; Serotonin; Temperament

1. Introduction

A large body of research with animals demonstrates that serotonin (5-HT) modulates the expression of multiple classes of behavior, including locomotor activity, reactivity to reward, sexual activity, affective and irritable aggression, active avoidance and escape latencies to aversive stimulation, and reactivity to sensory stimuli (Depue & Collins, 1999; Depue & Spoont, 1986;

* Corresponding author. Tel.: +1-612-725-2000; fax: +1-612-725-2249.
E-mail address: zald@james.psych.umn.edu (D.H. Zald).

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Depue & Zald, 1993; Lucki, 1992; Soubrie, 1986; Spoont, 1992). In most cases, 5-HT appears to exert an inhibitory influence on behavior, whereby reductions of 5-HT result in exaggerated behavioral responding (Depue & Collins, 1999; Depue & Spoont, 1986; Soubrie, 1986; Spoont, 1992). The broad range of functions modulated by 5-HT suggests that, in most cases, 5-HT does not mediate any specific behavioral, emotional, or motivational system. Accordingly, we and others have proposed that serotonergic functioning modulates both positive and negative affective processing, as well as other motor, and cognitive processes (Depue & Collins, 1999; Depue & Spoont, 1986; Depue & Zald, 1993; Panksepp, 1986; Soubrie, 1986; Spoont, 1992; Zuckerman, 1991).

Data from human studies of psychiatrically healthy and personality disordered subjects also indicate that 5-HT modulates many behavioral and motivational systems, including aggression, "violent" suicidal behavior, irritability, generalized impulsivity and risk-taking behavior (Cleare and Bond, 1997; Coccaro & Kavoussi, 1996; Coccaro, Kavoussi, Cooper & Hauger, 1997; Coccaro et al., 1989; Depue & Collins, 1999; Manuck et al., 1998; Spoont, 1992). However, the human literature has emphasized 5-HT's specific influence over negative emotions and aggression (Coccaro & Kavoussi, 1996; Coccaro et al., 1997; Coccaro et al., 1989; Knutson et al., 1998). This has led to a narrow view of 5-HT's influence on affective processing which conflicts with the animal literature indicating that 5-HT influences both negative and positive affective behavior.

Unfortunately, little research has directly assessed the relationship between 5-HT functioning and affect. Instead, researchers have tended to examine personality factors that are theoretically or empirically related to affect. To more directly address this issue, we examined the association between 5-HT functioning, indexed by fenfluramine activation of prolactin secretion, and positive affect (PA) and negative affect (NA) ratings taken three-times daily over a period of two weeks in 31 psychiatrically-healthy male subjects.

2. Method

2.1. Subjects

Subjects were recruited through the distribution of notices to graduate students and staff of several large academic departments and by advertisement in the university newspaper. Only males were included in this study due to the complex hormonal influences on prolactin levels in females (Josimovich et al., 1987; O'Keane, O'Hanlon, Webb & Dinan, 1991). Of the 45 male subjects who attended an initial group meeting, 41 (91%) agreed to participate in the study. These subjects were screened using the structured clinical interview for DSM-III-R (Nonpatient version 1.0) (Spitzer, Williams, Gibbon & First, 1990), and excluded if they had any current or past DSM-III-R Axis I diagnoses, or if they reported high levels of current life stressors which might affect emotional reactivity in a relatively ongoing manner. No subject manifested marked personality disorder. Subjects completed a medical screening questionnaire and a physical examination. Potential subjects who reported use of any prescribed medication during the past six months, any form of substance abuse, endocrinopathies or other relevant medical conditions were excluded from the study. This left 34 psychiatrically and medically healthy male subjects ranging in age from 19 to 37 years ($M = 25$; s.d. $= 3.1$). All subjects completed written informed consent as approved by the Institutional Review Board of the University of Minnesota.

2.2. Assessment of affect

PA and NA emerge as higher-order factors in almost every published study of self-rated mood (Watson, Clark & Tellegen, 1988; Watson & Tellegen, 1985). Taken together, they account for 50–75% of the common variance of emotional experience (Watson & Tellegen, 1985). PA reflects a person's level of pleasurable engagement with the environment. High states of PA are characterized by terms such as interested, excited and determined that denote behavioral engagement, while low states are marked by terms reflecting lethargy, fatigue, and disengagement. NA comprises a general factor of subjective distress, with high states of NA marked by descriptors such as distressed, nervous and hostile, and low NA states marked by terms such as calm and relaxed.

We utilized the Positive and Negative Affect Schedule (PANAS) (Watson et al., 1988) to assess affect over two work-weeks. The PANAS is an internally consistent, state measure of PA and NA (Watson et al., 1988) with a reliable factor structure that reflects the two-factor model of self-rated mood (Watson & Tellegen, 1985). The PANAS consists of 10 PA and 10 NA adjectives with high loadings on the PA and NA factors respectively (Watson et al., 1988). Each adjective is rated on a 5-point rating scale, with scale labels ranging from "very slight or not at all" to "extremely."

Subjects completed PANAS ratings at noon, 5.00 pm, and 10.00 pm each day for two consecutive weeks minus weekends, resulting in a total of 30 possible rating events in the two-week period. At each rating period, subjects rated their current mood state ("right now").

Subjects were instructed to leave a rating event blank if it was missed by more than 2 h. Subjects were also instructed to describe major emotional stressors (e.g., death in the family) that occurred during the rating period, but no subject reported stressors of this magnitude. Subjects who missed two or more days of ratings in a given week, or whose schedules prevented rating for two consecutive weeks, completed ratings during a third week ($n = 3$). To minimize potential seasonal influences on mood, all subjects were assessed during the late spring and summer. No ratings were performed within three days following administration of the fenfluramine challenge. Two subjects were excluded from analysis after failing to complete at least 25 of the 30 rating events. Of the remaining 32 subjects, the mean number of completed rating events was 28 (range = 25–30).

Several measures were derived from the current ratings of the PANAS. The primary measures consisted of mean rating of PA and NA (henceforth referred to as PA-mean and NA-mean). We additionally included measures of affective variability and perturbability. Current theories of 5-HT's influence over neural functioning emphasize its homeostatic influence (e.g., see Spoont, 1992). These theories posit that 5-HT limits fluctuations or perturbations in the output of neural systems and thus suggest that 5-HT should limit the variability, or the frequency and magnitude of perturbations in neural systems mediating affect. Unfortunately, there is virtually no data directly assessing this hypothesis in humans. We operationalized variability in the PA domain by calculating the standard deviation of each subject's 25–30 PA ratings (labeled PA-SD). This represents an index of how much each subject varies around their mean level of PA. Intraindividual variability in the NA domain was similarly assessed by calculating the standard deviation of each subject's 25–30 NA ratings. Because the modal level of NA is its absence, the reactivity or ease of perturbation of the NA system is reflected in the frequency with which any NA occurs. We operationalized this by calculating the percentage of rating periods in which any NA term received a rating greater than 1 (NA-frequency). We additionally calculated the magnitude of NA responses by determining the mean level of NA only for those rating periods in which at least one

NA term received a rating of greater than 1 (NA-intensity). Thus, NA-intensity reflects the magnitude of NA after correcting for the frequency of experienced NA. Similar frequency and intensity ratings could not be calculated in the PA domain since healthy subjects almost always report the presence of some PA.

In the hopes of deriving another index of affective variability, we additionally asked subjects to rate the highest and lowest degree to which they had experienced each adjective since their last rating period. However, ratings of highest retrospective mood, and the range of retrospective mood (i.e., highest minus lowest rating of each affective term during a rating period) failed to demonstrate complete independence across the NA and PA domains. For instance retrospective ratings of highest NA and PA were significantly correlated ($r = 0.43$; $p < 0.05$). Given the failure of these retrospective ratings to define independent PA and NA dimensions, we excluded them from further analysis.

2.3. Fenfluramine challenge

5-HT functioning was assessed by the prolactin (PRL) response to 60 mg oral administration of d,l-fenfluramine. The PRL response to d,l-fenfluramine has been widely utilized as a "net" index of 5-HT functioning (Coccaro et al., 1989). d,l-fenfluramine releases endogenous presynaptic stores of 5-HT, which, along with the metabolite norfenfluramine, stimulate postsynaptic 5-HT receptors in the hypothalamus leading to a robust, dose-dependent increase in PRL release (Quattrone et al., 1983; Rowland & Carlton, 1986). Peak changes in the PRL response to d,l-fenfluramine [MaxΔPRL(fen)] demonstrate high short-term test–retest reliability [1 week test–retest intraclass correlation coefficient = 0.80 (Stoff, Pasatiempo, Yeung, Bridger & Rabinovich, 1992)]. Long-term test–retest reliability has not been assessed in adults, but a recent study of children with attention deficit disorder revealed a reasonable level of stability over a two year period (Pick, Halperin, Schwartz & Newcorn, 1999).

Each protocol began at 11.00 am with the insertion into the forearm of a 22-gauge, indwelling, intravenous catheter kept open by use of a heparin lock. Identical d,l-fenfluramine (60 mg) or placebo (lactose) capsules were ingested orally at 12.00 noon in a randomized, crossover design under double-blind conditions. The two drug conditions were separated by no less than 3 days. The protocol ended at 8.00 pm. The period of noon to 8.00 pm was selected because pilot data showed that placebo PRL values during this time interval are relatively flat, thereby avoiding an increasing or decreasing placebo series that might interact with drug effects.

Subjects remained in an awake, reclining position, with head elevated, for the entire protocol. They stood only to go to the bathroom, but this did not require alteration of the catheter. Subjects were allowed to read nonemotional material or to do academic work during the protocol, except between 3.30–4.30 pm when cognitive tasks were administered as part of another study (Luciana, Collins & Depue, 1998). Subjects fasted from 10.00 pm the previous night until noon on the day of the study. Subjects fasted throughout the remainder of the protocol with the exception of water and an 8-oz glass of 2% milk taken at the time of medication (or placebo) to prevent excessive hunger. Subjects abstained from caffeine, nonprescription medications, and alcoholic beverages for no less than 24 h prior to test days. Additionally, subjects were instructed to follow a low monoamine diet for 48 h prior to study days. No subjects reported any significant transgressions from the restricted diet when interviewed upon arrival at the laboratory.

2.4. Prolactin assessment

Samples for baseline serum PRL were obtained at 11.45 and 11.55 am (i.e., approximately 40 min after venapuncture and after adopting a reclined position) and averaged. This provided enough time for any PRL changes induced by venapuncture to return to normal, and comparison of baseline and 1.00 pm samples on the placebo day confirmed that baseline samples of PRL were no higher than 1.00 pm samples (baseline = 6.0 ng/ml, 1.00 pm = 6.3 ng/ml: $t = 1.4$; $p > 0.10$). After receiving the noon medication, PRL samples were obtained every 30 min starting at 1.00 pm and ending at 7.30 pm. To minimize seasonal differences in PRL responsiveness and seasonal differences in 5-HT functioning (Brewerton, 1989), all subjects completed PRL assessments during the spring and summer.

Blood samples were spun down immediately, and assayed within 1–2 days by double-antibody radioimmunoassay with a sensitivity of 1.0 ng/ml. Previous studies using this technique produced an inter-assay coefficient of variation of 7.2% and an intra-assay coefficient of variation of 6.1% (Depue, Luciana, Arbisi, Collins & Leon, 1994).

One subject displayed an abnormally exaggerated response to d,l-fenfluramine, with the peak change in prolactin exceeding the mean peak prolactin response of the sample by 3.5 standard deviations and the next highest response by almost 2 standard deviations. Although, all the findings reported below remained significant when this subject was included in the analysis, we excluded his data to limit any undue influence of this outlier on the reported effect sizes. This left a total of 31 subjects.

3. Results

3.1. PANAS ratings

Table 1 displays descriptive ratings for all of the affective variables. Ratings of PA-mean and NA-mean were similar to those published in the literature for healthy, normal subjects (Watson et al., 1988). Moreover, the pattern of ratings in this sample conformed to the two factor model of affect (Watson et al., 1988; Watson & Tellegen, 1985), with high intercorrelations for terms within dimensions, and no significant correlations between terms in different dimensions. PA-mean and NA-mean demonstrated reasonable independence ($r = 0.21$; $p > 0.10$), as is typical in the state

Table 1
Descriptive statistics for affective variables

Affective variable	Mean (s.d.)
PA-mean	22.4 (5.7)
PA-SD	5.0 (1.7)
NA-mean	12.1 (1.9)
NA-SD	2.4 (1.4)
NA-intensity	13.3 (1.6)
NA-frequency	0.6 (0.3)

Table 2
Intercorrelations among NA variables

	NA-mean	NA-SD	NA-intensity	NA-frequency
NA-mean	1.0			
NA-SD	0.84*	1.0		
NA-intensity	0.95*	0.91*	1.0	
NA-frequency	0.89*	0.71*	0.77*	1.0

*$p < 0.0001$.

mood-rating literature. Mean ratings of affect showed high split-half reliability (week-one vs week-two) for ratings of both PA-mean ($r = 0.90$; $p < 0.0001$) and NA-mean ($r = 0.78$; $p < 0.0001$).

Measures of affective variability and perturbability were never completely independent of the mean level of affect. PA-SD showed a moderate correlation with PA-mean ($r = 0.38$; $p < 0.05$), and no significant correlations with NA-mean or any measures of NA variability (all $p > 0.10$). Table 2 displays the correlations among measures of NA variability and NA-mean. Measures of NA variability and reactivity were highly correlated with each other and with NA-mean. Even NA-frequency (which removed the influence of magnitude) and NA-intensity (which removed the influence of frequency) were highly correlated with each other. It thus appears that NA perturbability and variability are closely related to mean NA levels, which likely reflects the reactive nature of the NA dimension (Zevon & Tellegen, 1982).

3.2. Prolactin activation by fenfluramine

Fig. 1 displays average PRL levels at each sampling time point from predrug baseline until 8.00 pm for the fenfluramine and placebo conditions. All subjects showed robust increases in PRL (M = 16.4 ng/ml; s.d. = 6.4 ng/ml), with the modal time of peak response at 3 h following fenfluramine administration. A Time×Drug Condition (16×2) repeated measures ANOVA, with Time (16) and Drug Condition (placebo, fenfluramine) entered as within-subject repeated mea-

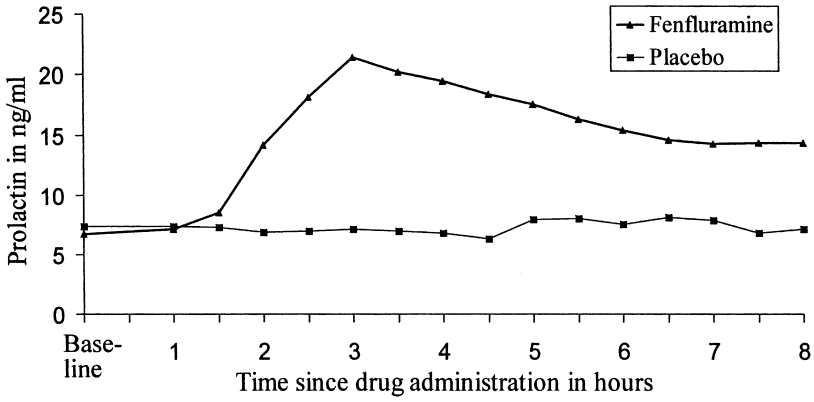

Fig. 1. Prolactin values as a function of time in the fenfluramine and placebo conditions.

sures, revealed that fenfluramine significantly increased PRL values (Drug Condition main effect: $F(1,29) = 159.1$; $p < 0.001$), and had a significant effect on PRL over time relative to placebo (Time main effect: $F(15,435) = 31.1$; $p < 0.001$; Drug Condition×Time interaction: $F(15,435) = 36.2$; $p < 0.001$). The correlation between placebo corrected and uncorrected MaxΔPRL(fen) values was substantial ($r = 0.90$; $p < 0.001$), indicating that neither diurnal variation nor laboratory procedures substantially influenced MaxΔPRL(fen).

The majority of studies involving fenfluramine challenges utilize a single fixed dose of d,l-fenfluramine without alterations for weight. However, a recent report observed an inverse correlation between MaxΔPRL(fen) and weight in a mixed sample of men and women (Muldoon et al., 1996). In the present study, the range of subject's weight was relatively small. This resulted in a narrow dose range (0.04–0.05 mg/kg) and no association between body weight and MaxΔPRL(-fen) ($r = -0.08$; $p > 0.10$). Hence, no correction for weight was applied in the analysis of the data.

3.3. Relation between affect and fenfluramine-induced prolactin secretion

MaxΔPRL(fen) inversely correlated with both PA-mean ($r = -0.49$; $p = 0.005$) and NA-mean ($r = -0.42$; $p < 0.05$) (see Figs. 2 and 3). Although adjectives within the PA and NA scales show high intercorrelations with other adjectives within the same scale, they may be differentially related to 5-HT functioning. As an exploratory analysis, we examined the correlations between MaxΔPRL(fen) and individual PA and NA adjectives. Table 3 displays correlations between MaxΔPRL(fen) and individual PA adjectives. MaxΔPRL(fen) showed significant inverse associations with eight of the 10 PA adjectives, including in ranked order *Interested, Active, Attentive, Enthusiastic, Excited, Alert, Inspired*, and *Determined*. Table 4 displays the correlation between MaxΔPRL(fen) and NA adjectives, where MaxΔPRL(fen) showed significant inverse associations with half of the adjectives, including *Jittery, Nervous, Distressed, Scared* and *Afraid*.

If 5-HT modulates affective magnitude in a nonspecific manner (as animal research and the above results suggest), then combined measures of PA-mean and NA-mean should maximally correlate with MaxΔPRL(fen). This conclusion appears particularly likely given the independence of PA-mean and NA-mean (Watson et al., 1988; Watson & Tellegen, 1985). Not surprisingly,

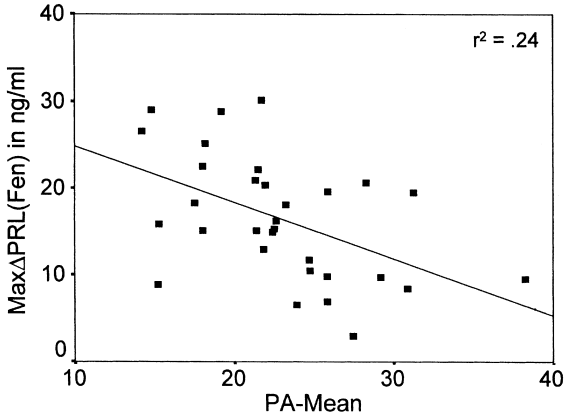

Fig. 2. Scatterplot of PA-mean and maximum fenfluramine-induced change in prolactin secretion [MaxΔPRL(fen)].

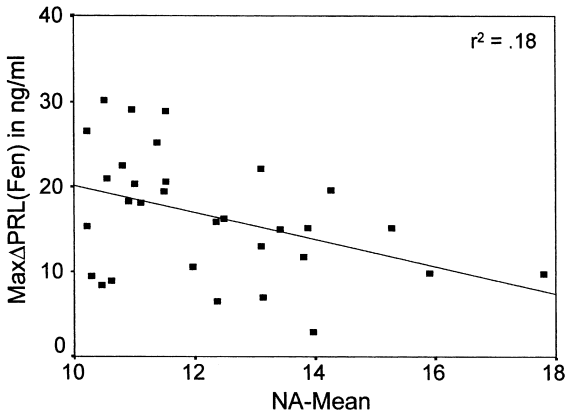

Fig. 3. Scatterplot of NA-mean and maximum fenfluramine-induced change in prolactin secretion [MaxΔPRL(fen)].

Table 3
Correlations of specific positive affect descriptors and MaxΔPRL(fen)

PA descriptor	MaxΔPRL(fen)
Interested	−0.61****
Active	−0.52***
Attentive	−0.49**
Enthusiastic	−0.44*
Excited	−0.43*
Alert	−0.42*
Inspired	−0.40*
Determined	−0.37*
Strong	−0.34
Proud	0.08

*$p < 0.05$; **$p < 0.01$; ***$p < 0.005$; ****$p < 0.0005$.

Table 4
Correlations of specific negative affect descriptors and MaxΔPRL(fen)

NA descriptor	MaxΔPRL(fen)
Jittery	−0.43*
Nervous	−0.39*
Distressed	−0.37*
Scared	−0.35*
Afraid	−0.35*
Guilty	−0.29
Ashamed	−0.27
Upset	−0.20
Irritable	−0.19
Hostile	−0.18

*$p < 0.05$.

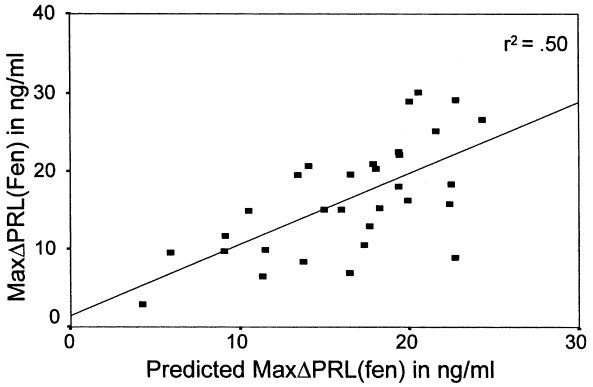

Fig. 4. Scatterplot of actual MaxΔPRL(fen) and predicted MaxΔPRL(fen) based on the linear regression of the terms *Interested* and *Jittery* on MaxΔPRL(fen).

when PA-mean and NA-mean were entered as independent variables into a multiple regression, they significantly predicted MaxΔPRL(fen) at a level that exceeded the predictive power of either measure on its own ($F(2,28) = 7.4$; $p < 0.005$; multiple $r = 0.59$). The predictive power of PA and NA further increased when the scales were limited to those terms showing significant correlations with MaxΔPRL(fen) ($F(2,28) = 9.5$; $p < 0.001$, multiple $r = 0.64$). As a final exploratory analysis, we performed a stepwise regression to determine which combination of PANAS adjectives best predicted MaxΔPRL(fen). This analysis resulted in a two-step model with *Interested* as the first variable and *Jittery* as the second variable ($F(2,28) = 14.8$, $p < 0.001$, multiple $r = 0.71$) (see Fig. 4). Inclusion of additional terms did not significantly increase the prediction of MaxΔPRL(fen).

Examination of the relation between 5-HT functioning and affective variability or perturbability is complicated by the lack of full independence between measures of variability and mean level of affect. Nevertheless, these measures show a differential pattern of relations with MaxΔPRL(fen). No correlation emerged between PA-SD and MaxΔPRL(fen) ($r = -0.12$; $p > 0.10$), indicating that individual differences in 5-HT functioning show little relation to intraindividual variability in PA. Within the NA domain, NA-frequency showed the highest correlation with MaxΔPRL(fen) ($r = -0.44$; $p < 0.05$). In contrast, the association of NA-intensity and NA-SD with MaxΔPRL(fen) failed to reach statistical significance ($r = -0.31$; $p = 0.09$, and $r = -0.24$; $p > 0.10$ respectively).

4. Discussion

The present results indicate that individual differences in 5-HT functioning are inversely associated with the magnitude of self-reported positive and negative affect. This represents the first study to report an association between 5-HT and individual variation in both positive and negative affective experience measured over time in a normal population. The magnitude of this association appears substantial. Individual differences in PA and NA ratings accounted for approximately 36% of the variance in MaxΔPRL(fen), and up to 50% of the variance when restricted to an optimal combination of NA and PA adjectives.

The observation of an inverse association between 5-HT functioning and NA converges with the ability of selective serotonin reuptake inhibitors (which increase the net functioning of the serotonin system) to decrease the magnitude of NA states in psychiatric patients (Salzman et al., 1995; Steiner et al., 1995; Van Vliet, Den Boer & Westenberg, 1994) and healthy controls (Knutson et al., 1998). It similarly converges with the ability of 5-HT depletions to enhance NA during yohimbine challenge (Goddard et al., 1995) and to accentuate feelings of dysphoria in individuals who are already dysphoric (Smith, Pihl, Young & Ervin, 1985; Young, Smith, Pihl & Ervin, 1985). It is also consistent with the inhibitory effect of 5-HT on fight/flight behaviors in animals (Graeff, 1984).

The observation that the magnitude of PA ratings also demonstrate an inverse association with MaxΔPRL(fen) represents a more novel finding. This association was broadly evident among the array of PA adjectives. PA may be viewed as the subjective, experiential component of a neurobehavioral incentive motivation system that facilitates approach behavior to rewarding goals (Depue & Collins, 1999; Depue & Zald, 1993). A large animal literature indicates that mesolimbic dopamine (DA) activity plays a critical role in facilitating incentive-motivational behavior within this system (Depue & Collins, 1999). 5-HT provides an inhibitory influence over a host of DA-facilitated behaviors associated with this system, including the reinforcing properties of psychostimulants, novelty-induced locomotor activity, and self-administration of cocaine and DA utilization in the nucleus accumbens (Depue & Collins, 1999; Depue & Spoont, 1986; Herve et al., 1981; Kelland & Chiodo, 1996; Loh & Roberts, 1990; Lucki, 1992; Spoont, 1992). Thus, the strong inverse association between 5-HT functioning and PA observed in the present study appears highly consistent with 5-HT's ability to reduce DA-facilitated, incentive-motivational behaviors in animals.

At a theoretical level, the current results support a model wherein 5-HT provides a constraining influence over neurobehavioral systems mediating affective processes (Depue & Collins, 1999; Depue & Spoont, 1986; Depue & Zald, 1993; Panksepp, 1986; Soubrie, 1986; Spoont, 1992; Zuckerman, 1991). This influence may act as a threshold variable that modulates stimulus elicitation of affective states, as well as providing a constraint on the magnitude of activated affective states (Spoont, 1992). The actual form of affect expressed at any particular point in time would depend on the affective system activated by the stimulus, whereas the qualitative features of that affective system (such as the frequency of elicitation or the amplitude of responses) would be a function of the level of 5-HT modulation (Depue & Spoont, 1986; Depue & Zald, 1993; Soubrie, 1986; Spoont, 1992).

Unfortunately, it remains difficult to determine the relationship between 5-HT functioning and the specific qualitative features (i.e., intensity, frequency) of affective processing. Although several studies demonstrate large and relatively stable inter-individual differences in affective variability (Cooper & McConville, 1990; Hepburn & Eysenck, 1989; McConville & Cooper, 1992), measures of intensity, frequency and variability typically fail to achieve complete statistical independence from each other (see Larsen, 1987 and Kardum, 1999 for a discussion of these issues). This appears particularly true in the NA domain, where measures of frequency, intensity, variability and mean affective level demonstrated high intercorrelations. Despite these limitations, several interesting features emerged from this data set. First, measures of affective variability (NA-SD and PA-SD) did not show a statistically significant relationship to 5-HT functioning. Thus, 5-HT's relation to affect does not appear to specifically relate to inter-individual differences in

affective variability. Second, within the NA domain, the frequency with which subjects experienced at least low levels of NA appeared closely related to 5-HT functioning. In other words, subjects with lower 5-HT functioning experience more frequent or chronic NA than subjects with higher 5-HT levels. This suggests that 5-HT may exert a particularly potent influence in determining the threshold at which a given stimulus or situation elicits NA. Alternatively, 5-HT may act to dampen a tonic low level engagement of NA systems. Lacking this dampening effect, subjects with lower 5-HT functioning may experience chronic low-level NA even in the absence of specific NA-inducing stimuli.

Although the present results are based on measures of state-wise affect, the findings are pertinent to studies examining personality traits. The NA adjectives showing the strongest inverse association with 5-HT functioning in the current study were *Jittery, Nervous, Scared* and *Distressed*, which together comprise a lower-order factor of NA related to anxiety (Watson & Clark, 1992). This appears consistent with a recent report of an inverse correlation between the PRL response to d,l-fenfluramine and the trait of neuroticism as measured by the NEO personality inventory (Manuck et al., 1998). Conversely, the present results provide no support for the opposing view that overall 5-HT functioning is positively associated with anxiety-related traits (Gray, 1982). The hypothesis that 5-HT possesses a positive relation to anxiety-related traits derives primarily from animal studies using punishment paradigms which for a number of reasons (including their motoric and positive motivational components) may not represent an appropriate model for assessing anxiety (Soubrie, 1986).

On the surface, the present results also appear discordant with the reported association of a 5-HT transporter polymorphism and increased anxiety-related personality traits of neuroticism and harm avoidance (Lesch et al., 1996). This association finds partial support from a recent study indicating the presence of higher self-reported anxiety in Japanese subjects with the short/short variant of the polymorphism (Murakami et al., 1999). Lesch et al. (1996) argue that the short allele of this polymorphism (which they observed to be associated with higher neuroticism scores) produces decreased uptake of 5-HT and enhanced 5-HT functioning. However, two comments are warranted regarding this polymorphism. First, the amount of the variance in neuroticism and harm avoidance that is explained by the polymorphism is extremely small and numerous attempts to replicate the finding have failed to observe the same association (Ball et al., 1997; Ebstein et al., 1997a; Gelernter, Kranzler, Coccaro, Siever & New, 1998; Jorm et al., 1998; Katsuragi et al., 1999; Kumakiri et al., 1999). Indeed, in one case, the direct opposite pattern of association was observed (Flory et al., 1999). Second, the actual effect of the transporter polymorphism on both "net" and post-synaptic 5-HT functioning remains unknown. Thus, even if there is a weak association between the polymorphism and anxiety-related traits, the difference between the present results and the data on the polymorphism may simply reflect the assessment of different aspects of the 5-HT system (see discussion below).

The present findings raise an obvious question. If 5-HT functioning inversely relates to both NA and PA, why do SSRI-induced 5-HT increases produce mood elevating effects in depressed patients? Unfortunately, the relationship between SSRI treatment and PA changes in depression remains unclear. Pharmacotherapy studies of depression rarely collect or report data in terms of independent measures of PA and NA. Thus, little information is actually available regarding the relative changes in NA and PA during SSRI treatment. At least three possibilities can be posited. First, perhaps SSRIs preferentially reduce NA without causing a similar decrease in PA levels.

Such a pattern could emerge due to the more reactive nature of NA (Watson & Clark, 1985), where SSRI-induced increases in 5-HT functioning may increase the threshold at which stimuli elicit negative affective responses. This could lead to more pleasant mood and a secondary increase in PA, even in the absence of a direct change in the 5-HT modulation of PA. Second, SSRI treatments may differentially impact areas mediating PA and NA due to the varying distributions of 5-HT receptor subtypes in limbic and paralimbic regions. Different receptor subtypes may respond differently to 5-HT enhancements due to variations in affinity, feedback and self-regulatory mechanisms. Thus, even if PA and NA show a similar inverse correlation with 5-HT functioning, they may respond differently to SSRIs. Third, it is also possible that SSRI-induced PA increases in depression result secondarily to a 5-HT-mediated stabilization of a dysregulated neurobehavioral system underlying PA functions (Depue 1995; Depue & Collins 1999; Depue & Iacono 1989).

Several issues warrant consideration in regards to the prolactin response to d,l-fenfluramine. In addition to acting on the 5-HT system, d,l-fenfluramine can increase DA metabolite levels in both animals and humans, particularly at higher doses (Mitchell & Smythe, 1991; Rowland & Carlton, 1986). This poses a potential problem because DA acts as a major inhibitor of PRL release in the hypothalamus (Ben-Jonathon, 1985). However, several factors make it unlikely that DA significantly contributed to the current results. First, the PRL response to d,l-fenfluramine largely derives from the d-isomer, which shows high specificity for the 5-HT system (Feeney, Goodall & Silverstone, 1993; Goodall, Cowen, Franklin & Silverstone, 1993). Second, the PRL response to d,l-fenfluramine and d-fenfluramine show an extremely high degree of correlation (Coccaro, Kavoussi, Cooper & Hauger, 1996a). Third, the results of studies conducted with the purer d-isomer are highly convergent with studies conducted with the d,l-racemic variant of fenfluramine (Coccaro et al. 1997; O'Keane et al., 1992; O'Keane et al., 1991). These data make evident that the PRL response to d,l-fenfluramine almost exclusively derives from 5-HT specific effects of the d-isomer. Furthermore, the PRL response to the D2 dopaminergic agents bromocriptine and haloperidol shows no correlation with MaxΔPRL(fen) (Zald, 1997). Thus, it appears highly unlikely that the present results could reflect a dopaminergic effect of d,l-fenfluramine.

The PRL response to d,l-fenfluramine has traditionally been interpreted to reflect "Net" 5-HT functioning, due to its effects on both pre- and post-synaptic targets (Coccaro et al., 1989). However, increasing evidence indicates that activation of post-synaptic 5-HT_{2c} receptors provides the critical route through which 5-HT agents, including fenfluramine, induce PRL release (Albinsson, Palazidou, Stephenson & Andersson, 1994; Coccaro, Kavoussi, Oakes, Cooper & Hauger, 1996b; Goodall et al., 1993; Lowy & Meltzer, 1988; Mueller, Sunderland & Murphy, 1985; Van De Kar, Lorens, Urban & Bethea, 1989). Because of the complex pre- and post-synaptic effects of fenfluramine, it appears premature to conclude that the observed correlations with affect specifically reflect individual differences in 5-HT_{2c} functioning. Nevertheless, the present results suggest that future studies should specifically examine the role of the 5-HT_{2c} receptor in the modulation of affect. It is notable in this regard that a recent genetic study of 5-HT_{2c} receptor polymorphisms in humans found an association between a 5-HT_{2c} polymorphism and reward dependence and persistence scores on the tridimensional personality questionnaire (Ebstein et al., 1997b). Thus, an interpretation of the current data as reflecting 5-HT_{2c} functioning would appear consistent with genetic data on the role of the 5-HT_{2c} receptor in modulating functioning within incentive-motivational systems.

The potent role of 5-HT_{2c} receptors in the mediation of PRL release also raises the possibility that fenfluramine induced PRL release may not represent an index of 5-HT functioning throughout the brain, but may more narrowly reflect 5-HT functioning in regions expressing the 5-HT_{2c} receptor. This would include many areas involved in affective processing: the ventral striatum/nucleus accumbens, substantia nigra, amygdala, medial thalamus, and portions of the hippocampus and hypothalamus all possess intermediate to high levels of 5-HT_{2c} receptors (Pazos, Probst & Palacios, 1987). Indeed, given the neurobehavioral systems meeting incentive motivation systems, it would appear reasonable to hypothesize that the relation between 5-HT functioning and PA reflects serotonergic influences in the nucleus accumbens/ventral striatal region (Depue & Collins, 1999; Depue & Spoont, 1986; Depue & Zald, 1993). However, the fenfluramine challenge clearly provides too general an index to provide direct evidence for such a regionally specific hypothesis. The development of receptor-specific ligands for use with positron emission tomographic (PET) imaging should in the future provide more direct measures of regionally specific 5-HT functioning.

In summary, the current study provides evidence that individual differences in 5-HT functioning inversely correlate with differences in subjective positive and negative affective experience in psychiatrically healthy individuals. These findings suggest that focussed examination of the relation between affect and neurotransmitter functioning may provide a useful avenue for examining 5-HT's relation to human temperament, personality, and psychopathology.

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