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# Inverse relationship between numbers of 5-HT transporter binding sites and life history of aggression and intermittent explosive disorder

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ABSTRACT

The objective of this study was to determine if platelet 5-HT transporter (5-HTT) sites vary as a function of aggression, and/or impulsiveness, and differ as a function of Intermittent Explosive Disorder (IED). Accordingly, the number of platelet 5-HTT sites was assessed in 100 personality disordered (PD) individuals with varying degrees of aggressiveness. The number of platelet 5-HTT sites was assessed by examining the Bmax of $H^3$-Paroxetine Binding to the blood platelet. Life history of aggression was assessed by Life History of Aggression. Impulsivity was assessed by the Barratt Impulsiveness Scale. Diagnoses of IED were made by both DSM-IV and Research Criteria. Examination of the data revealed that Bmax, but not Kd, values of Platelet $H^3$-Paroxetine Binding correlated inversely with the LHA Aggression score ($r = -.42$ $n = 87$, $p < .001$) but not with the BIS-11 Impulsivity score ($r = .03$, $n = 77$, $p = .777$). PD subjects meeting Research Criteria for IED demonstrated a significant reduction in Bmax values for Platelet $H^3$-Paroxetine Binding. These results were similar after accounting for the effect of lifetime history of depressive mood disorder on Bmax values for Platelet $H^3$-Paroxetine Binding. These data indicate a significant inverse relationship between platelet 5-HTT and aggression, though not impulsivity, as a dimensional variable in personality disordered individuals. Results from the examination of IED as a categorical aggression variable suggest that Research, rather than DSM-IV, criteria better identify individuals with reduced numbers of platelet 5-HTT sites.



## 1. Introduction

More than two decades of research has supported the hypothesis that reductions in brain serotonin (5-HT) function is associated with aggressive behavior, particularly impulsive aggression (Coccaro and Siever, 2002). While most studies of various central measures of 5-HT support this hypothesis, studies using peripheral 5-HT receptor measures have been less consistent in their findings, specifically, in studies examining 5-HT transporter (5-HTT) binding sites on the platelet. Although the platelet constitutes a peripheral site, and does not share the same microenvironment as central 5-HT neurons (Murphy et al., 1990), platelet 5-HTT sites are structurally identical to corresponding sites on central 5-HT neurons (Lesch et al., 1993; Ramamoorthy et al., 1993) and are, thus, under the same genetic influence as those on 5-HT terminals in the brain. Note, also, that the 5-HTT promoter genotypes (e.g., ss genotype) associated with less production of transporter protein synthesized by 5-HT neurons, are also associated with less transporter protein on platelets in human subjects (Little et al., 2006).

The finding that the number of platelet 5-HTT binding sites correlated with aggressive behavior in humans was first noted by our laboratory (Coccaro et al., 1996). In our first study, we reported a significant inverse correlation between life history of aggression and the Bmax of $^3$H-Paroxetine on the platelet in twenty-four subjects with personality disorder. Since that report, six other studies have been published in different clinical populations with varying results. One study of 105 cocaine-dependent subjects reported an inverse correlation between aggression and Bmax of Platelet $^3$H-Paroxetine Binding (Patkar et al., 2003a) while another study of eleven currently aggressive schizophrenic subjects reported greater numbers of 5-HTT binding sites (Modai et al., 2000). Another study of forty schizophrenic subjects (Maguire et al., 1997), and a study of twenty-one Obsessive–Compulsive Disorder subjects (Marazziti et al., 2001) also reported no relationship between these two variables. Finally, two studies of twenty adolescents with ADHD, (Oades et al., 2002) or forty-three subjects with Conduct Disorder (Unis et al., 1997), also report no correlation between measures of aggression and Bmax of Platelet $^3$H-Paroxetine Binding. Differences in these results may be due to differences in the measures that were used and to differences in the brain-behavioral substrates underlying the pathology in the groups.

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In this study we report on a sample of personality disordered subjects that includes an additional seventy-six subjects from our original report of twenty-four subjects. In addition, we explore the potential differences in 5-HTT binding in subjects classified as aggressive by the diagnosis of Intermittent Explosive Disorder (IED). IED is a disorder of impulsive aggression not better accounted for by other psychiatric/medical conditions, or the influence of pharmacologically induced behavioral states.

## 2. Methods and materials

### 2.1. Subjects

This paper reports data from 100 consecutive physically healthy personality disordered individuals in whom platelet measures of $^{3}$H-Paroxetine Binding were assessed. All subjects were systematically evaluated as part of a larger program designed to study the biological correlates of personality traits in human subjects. Study subjects (83 male, 17 female) were recruited by newspaper and public service announcements seeking subjects with, and without, histories of anger and aggression, to take part in medically related studies. Written informed consent, using an IRB-approved consent document, was obtained from all subjects after all procedures were fully explained. Medical health of all subjects was documented by medical history, physical examination, and a variety of clinical laboratory studies including a urine screen for illicit drugs.

### 2.2. Diagnostic assessment

Axis I and Axis II Personality Disorder (PD) diagnoses were made according to DSM-IV criteria (American Psychiatric Association, 1994). Diagnosis of Alcoholism were made by modified Research Diagnostic Criteria as described in previous reports (Coccaro et al., 1996, 1989). Diagnosis of Intermittent Explosive Disorder (IED) were made by both DSM-IV (1994) and by Research Criteria using both the initially proposed Research Criteria (IED-R; (Coccaro et al., 1998), and the most recently proposed Integrated Research Criteria (IED-IR; (Coccaro et al., 2004) for IED. Research Criteria (Coccaro et al., 1998) differ from DSM-IV criteria in that they require: (a) one-month (or more) period of aggressive outbursts (including verbal outbursts only, or outbursts in which property is not destroyed) occurring twice a week on average, (b) aggressive outbursts to be, primarily, impulsive in nature, (c) aggressive outbursts to be associated with significant subjective distress or psychosocial impairment, and that they allow for comorbid diagnoses of Borderline, or Antisocial, Personality Disorder. Integrated Research Criteria for IED (Coccaro et al., 2004) are the same except that they allow an for an IED diagnosis if there are at least three episodes of serious assaultive or destructive behavior (even when there are not recurrent aggressive outbursts within the one-month time frame as required by the initially proposed Research Criteria); accordingly, this revision "integrates" the originally proposed Research Criteria with DSM-IV Criteria.

All diagnoses were made using information from: (a) semi-structured interviews conducted by trained masters, or doctoral, level clinicians using the Schedule for Affective Disorders and Schizophrenia (Spitzer and Endicott, 1978) modified to include modules for the diagnosis of DSM Axis I disorders not covered by the original SADS, or the Structured Clinical Interview for DSM Diagnoses (SCID-I; First MB et al., 1997) for Axis I disorders, and the Structured Interview for the Diagnosis of DSM Personality Disorder (SIDP: Pfohl et al., 1989, 1997) for Axis II disorders; (b) clinical interview by a research psychiatrist; and, (c) review of all other available clinical data. Final diagnoses were assigned by team best-estimate consensus procedures (Klein et al., 1994; Leckman et al., 1982) involving at least two research psychiatrists and three clinical psychologists as previously described (Coccaro et al., 1996). This methodology has previously been shown to enhance the accuracy of diagnosis over direct interview alone (Kosten and Rounsaville, 1992). Subjects with a life history of Bipolar disorder, Schizophrenia (or other psychotic disorder), or mental retardation were excluded from this study.

Fifty-four of the 100 PD subjects met DSM-IV criteria for a specific personality disorder as follows: (a) Cluster A ($n = 22$), i.e., Paranoid ($n = 16$), Schizoid ($n = 8$), Schizotypal ($n = 2$); (b) Cluster B ($n = 29$), i.e., Borderline ($n = 13$), Narcissistic ($n = 13$); Antisocial ($n = 12$); Histrionic ($n = 5$); (c) Cluster C ($n = 19$), i.e., Obsessive–Compulsive ($n = 16$), Avoidant ($n = 6$). The remaining 46 subjects were diagnosed as Personality Disorder-Not Otherwise Specified (PD-NOS). These subjects met DSM-IV general criteria for personality disorder, had pathological personality traits from a variety of personality disorder categories and had clear evidence of impaired psychosocial functioning (mean GAF score = 62.1 + 6.6). Most PD subjects had a life history of at least one Axis I disorder (79 of 100) and nearly half had a current history of at least one Axis I disorder (49 of 100). Current Axis I disorders were as follows: Any Mood Disorder ($n = 17$): major depression ($n = 2$), dythymia ($n = 7$), depressive disorder-nos ($n = 9$); Any Anxiety Disorder ($n = 9$), i.e., phobic ($n = 6$), and non-phobic ($n = 4$) anxiety disorder; Intermittent Explosive Disorder: IED by DSM-IV ($n = 18$), IED-R ($n = 32$, IED-IR ($n = 35$); Adjustment Disorder ($n = 1$); Somatoform Disorder ($n = 1$). Lifetime Axis I disorders were as follows: follows: Any Mood Disorder ($n = 44$): major depression ($n = 22$), dythymia ($n = 9$), depressive disorder-nos ($n = 17$); Any Anxiety Disorder ($n = 16$), i.e., phobic ($n = 8$), and non-phobic ($n = 10$) anxiety disorder; Substance Use Disorders ($n = 32$): Alcoholism ($n = 24$), Drug Dependence ($n = 18$); Intermittent Explosive Disorder: IED by DSM-IV ($n = 23$), IED-R ($n = 36$), IED-IR ($n = 44$); Non-IED Impulse Control Disorders ($n = 1$); Adjustment Disorder ($n = 8$); Eating Disorder ($n = 1$); Somatoform Disorder ($n = 1$).

### 2.3. General preparation for study

Only seventeen of the 100 subjects had any lifetime history of exposure to psychotropic agents. In order of frequency, these agents fell into the following classes: anxiolytics ($n = 14$), antidepressants ($n = 9$), neuroleptics ($n = 5$), stimulants ($n = 4$), and sedative-hypnotics ($n = 3$). Subjects were instructed to remain drug-free for at least two-weeks prior to study and no subject was taking any psychotropic agent for at least two-weeks at time of study. Subjects were also instructed to follow a low monoamine diet for at least three (3) days prior to study. At the time that samples for platelets were obtained, subjects had been fasting, without smoking, from midnight the night before. Subjects were informed that initial and follow-up urine toxicology would be performed randomly just prior to study; illicit drug use was not detected in any subject reported herein. Females were all studied within the first ten days of the follicular phase of the menstrual cycle.

### 2.4. Platelet study

All blood samples for platelet study were obtained between 9:00 and 9:30 am through a 20 gauge indwelling intravenous catheter that was in place for the purposes of other biological studies being performed in our unit. 20 cc of venous blood was collected in a plastic syringe and transferred to EDTA containing vacutainer collection tubes. Samples were processed and assayed for $H^{3}$-Paroxetine Binding parameters as previously described (Coccaro et al., 1996).

### 2.5. Dimensional assessment of aggression, impulsivity, and other behavioral variables

Aggression was assessed dimensionally (in most, though not all subjects) using the Aggression scales of the Life History of Aggression ($n = 87$; Coccaro et al., 1997) and the Buss-Durkee Hostility Inventory ($n = 90$; BDHI; (Buss and Durkee, 1957). Impulsivity was assessed using the total score of the Barratt Impulsiveness Scale ($n = 77$; BIS-11; (Patton et al., 1995). Secondary variables included general personality variables (i.e., neuroticism, psychoticism, extraversion) from the Eysenck Personality Questionnaire ($n = 78$; Eysenck and Eysenck, 1975).

### 2.6. Statistical analysis

The primary biological variable tested was Bmax for platelet $^3$H-Paroxetine Binding. Values for Bmax and Kd for $^3$H-Paroxetine Binding followed normal distributions and neither demonstrated a seasonal pattern. The primary dimensional behavioral variables under study included: (a) LHA "Aggression", (b) BDHI: "Aggression" and, (c) BIS-11: "Impulsivity". EPQ Neuroticism, Extraversion, and Psychoticism were examined as secondary variables representing general personality factors. The primary categorical variable for impulsive aggression was Intermittent Explosive Disorder as diagnosed by DSM-IV, IED-R, and IED-IR criteria. Primary analyses involved examination of the raw study variables without consideration of potential covariates. Secondary analyses included lifetime history of any depressive mood disorder (i.e., Major Depression, Dysthymic Disorder, Depressive Disorder-NOS) as a covariate. Correlational relationships were assessed by Pearson correlation, partial correlation, and multiple regression, where appropriate. Comparisons between groups were performed by *t*-test, with correction for unequal variances where necessary, or univariate/multivariate ANOVA/ANCOVA as appropriate. All reported *p*-values are two-tailed.

## 3. Results

### 3.1. Bmax: Platelet $^3$H-Paroxetine Binding as a function of aggression, impulsivity, and other personality variables

Bmax: Platelet $^3$H-Paroxetine Binding displayed a significant inverse correlation with LHA Aggression ($r = -.42$, $n = 87$, $p < .001$), (Fig. 1). Removal from analysis of the twenty-four subjects, reported in our first paper (Coccaro et al., 1996), did not alter these results ($r = -.46$, $p < .001$). The correlation with BDHI Aggression was similar, but smaller in magnitude and statistical significance ($r = -.20$, $n = 90$, $p = .056$). Kd values did not correlate with either LHA ($r = .04$, $n = 87$, $p = .691$) or BDHI ($r = .03$, $n = 90$, $p = .750$) Aggression variables. Despite a significant correlation between LHA Aggression and BIS-11 Impulsivity ($r = .31$, $n = 70$, $p = .009$), however, BIS-11 Impulsivity scores did not correlate with Bmax values ($r = .03$, $n = 77$, $p = .777$). General personality variables from the EPQ also did not correlate significantly with Bmax values (i.e., Neuroticism: $r = .02$, $n = 78$, $p = .890$; Extraversion: $r = .01$, $n = 78$, $p = .969$; Psychoticism: $r = -.04$, $n = 78$, $p = .738$).

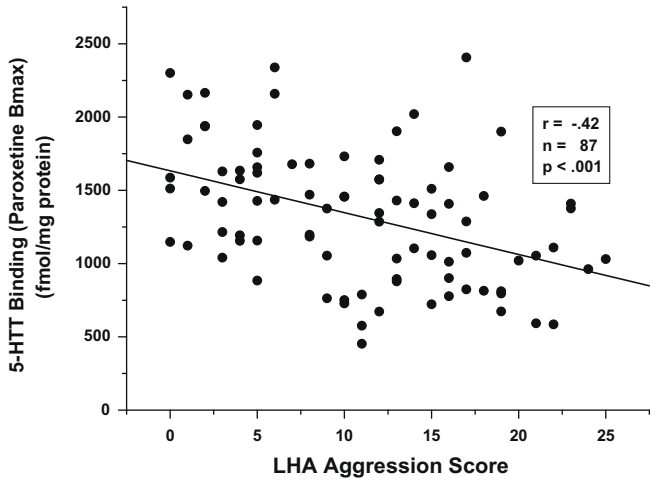


**Fig. 1.** Correlation of Bmax (Platelet $^3$H-Binding: fmol/mg protein) values with LHA Aggression scores (partial correlation, after accounting for effect of life history of depressive disorder on these variables: $r_{partial} = -.30$, df = 84, $p = .004$).

### 3.2. Bmax: Platelet $^3$H-Paroxetine Binding as a function of lifetime history of depressive disorder and aggression, impulsivity, and other personality variables

The Bmax value for Platelet $^3$H-Paroxetine binding displayed a significant correlation with lifetime history of depressive disorder (i.e., Major Depression, Dysthymic Disorder, Depressive Disorder-NOS: $r = -.40$, $n = 100$, $p < .001$) and with behavioral variables of interest (e.g., LHA Aggression: $r = .37$, $n = 87$, $p < .001$). Subsequent multiple regression analysis revealed that, among all other relevant non-aggression/non-impulsivity related variables (i.e., age, gender, race, socioeconomic status, global assessment of function, lifetime history of exposure to psychotropic medication), only lifetime history of mood disorder covaried significantly with the Bmax value for Platelet $^3$H-Paroxetine Binding. Controlling for lifetime history of depressive disorder did not affect the statistical significance of the relationship with LHA Aggression ($r_{partial} = -.30$, df = 84, $p = .004$). Removal from analysis of the subjects reported in our first paper (Coccaro et al., 1996), also, did not alter these results ($r_{partial} = -.36$, df = 61, $p = .004$). Controlling for lifetime history of depressive disorder, however, greatly diminished the statistical significance of the relationship with BDHI Aggression ($r_{partial} = -.07$, df = 87, $p = .501$).

### 3.3. Bmax: Platelet $^3$H-Paroxetine Binding as a function of intermittent explosive disorder

Demographic, global function, biological, behavioral, and diagnostic characteristics of the subjects as a function of IED-IR diagnosis are displayed in Table 1. This is done because: (a) results with IED-R subjects were similar and, (b) IED-IR represents all the subjects in this study given any IED diagnosis. Bmax Platelet $^3$H-Paroxetine Binding values were non-significantly lower in subjects as a function of a DSM-IV IED diagnosis (1190.6 + 369.1 fmol/mg protein vs. 1346.0 + 480.0 fmol/mg protein; $t_{98} = 1.43$, $p = .156$). In contrast, Bmax values were significantly lower as a function of an IED-R diagnosis (1134.0 + 369.0 vs. 1409.4 + 478.5 fmol/mg protein; $t_{98} = 2.99$, $p = .004$) or of an IED-IR diagnosis (1185.4 + 410.3 vs. 1408.3 + 476.2 fmol/mg protein; $t_{98} = 2.47$, $p = .015$), (Fig. 2). Repeat analysis, with lifetime history of depressive disorder as covariate demonstrated a significant effect of the IED-R diagnosis on Bmax values ($F[1,97] = 4.46$, $p = .037$) and a trend for a significant effect of IED-IR on Bmax values ($F[1,97] = 3.44$, $p = .067$). Despite a greater proportion of Cluster B (or of those with either BPD and/or AsPD) subjects among groups defined by IED Research Criteria, Bmax: Platelet H$^3$-Paraoxetine Binding values were not significantly reduced in subjects with a Cluster B Personality Disorder (e.g., raw data for IED-IR subjects: $F[1,98] = 1.29$, $p = .259$) or in subjects diagnoses either with Borderline and/or Antisocial Personality Disorder (e.g., raw data for IED-IR subjects: $F[1,98] = 1.77$, $p = .382$) Finally, Bmax values did not vary as a function of a history of suicide attempt ($F[1,97] = 1.00$, $p = .320$).

**Table 1**
Demographic, functional, biological, behavioral and diagnostic data: IED + vs. IED – By Integrated Research Criteria.

| Variable | IED-IR ($n$ = 44) | Non-IED-IR ($n$ = 66) | Statistic | $p$ |
|---|---|---|---|---|
| *Demographic Variables* | | | | |
| Age | 38.5 + 8.2 | 32.3 + 8.6 | $t(98) = 3.45$ | <.001 |
| Gender (M/F) | 37/7 | 46/56 | Fishers Exact Test | 1.000 |
| Race (White/Non-White) | 32/12 | 29/17 | Fishers Exact Test | .040 |
| SES (I/II/III/IV/V) | 1/6/16/15/6 | 0 / 6 / 19 / 13 / 18 | $X^2 = 6.05$, df = 4 | .196 |
| GAF | 55.1 + 8.2 | 61.9 + 7.9 | $t(98) = 4.16$ | <.001 |
| *Biological Variables* | | | | |
| Bmax | 1185.4 + 410.3 | 1408.3 + 476.2 | $t(98) = 2.47$ | .015 |
| Kd | 0.39 + 0.21 | 0.33 + 0.15 | $t(74.4) = 1.66$ | .106 |
| *Behavioral Variables* | | | | |
| LHA Aggression | 15.7 + 4.9 | 6.8 + 5.2 | $t(85) = 8.16$ | <.001 |
| BDHI Aggression | 29.8 + 8.5 | 18.3 + 7.9 | $t(88) = 6.65$ | <.001 |
| BIS-11 Impulsivity | 69.6 + 13.6 | 60.9 + 7.7 | $t(35.2) = 3.08$ | =.004 |
| Hx of Suicidal Behavior (±) | 8/36 | 2/54 | Fishers Exact Test | .020 |
| Hx of Self-Injurious Behavior (±) | 2/42 | 5/61 | Fishers Exact Test | .461 |
| EPQ Neuroticism | 13.5 + 6.3 | 8.2 + 4.9 | $t(48.1) = 3.93$ | <.000 |
| EPQ Psychoticism | 5.6 + 3.1 | 4.0 + 2.4 | $t(76) = 2.51$ | .014 |
| EPQ Extraversion | 12.6 + 4.8 | 14.1 + 4.5 | $t(76) = 1.44$ | .154 |

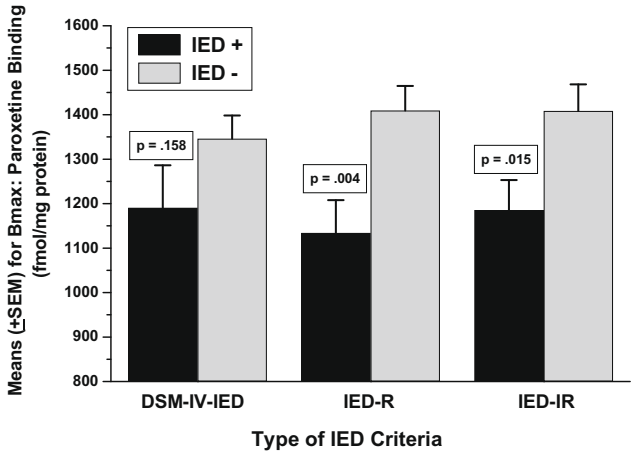


**Fig. 2.** Mean (±SEM) for Bmax values for Paroxetine Binding (fmol/mg protein) using DSM-IV, IED-R, and IED-IR Criteria for Intermittent Explosive Disorder (p-values for the marginal means for ANCOVA, with life history of depressive disorder as covariate, were: $p$ = .248 for DSM-IV, $p$ = .037 for IED-R, $p$ = .067 for IED-IR).

## 4. Discussion

The results of the present study demonstrate that platelet 5-HTT binding sites of physically healthy personality disordered subjects correlate inversely with a life history of aggressive behavior assessed both dimensionally and categorically. This relationship did not extend to generalized impulsivity as reflected by the BIS-11 scale, nor did it extend to assessments of general personality traits such as neuroticism, psychoticism, or extraversion. While a life history of depressive disorders was also inversely correlated with platelet 5-HTT binding sites, the inverse relationship with life history of aggression remained significant even after accounting for this covariate. This suggests that the inverse relationship between platelet 5-HTT binding sites and life history of aggression is relatively unique among personality traits and is independent of the lifetime presence of depressive disorders.

These data replicate and extend the finding we reported previously in a small group of personality disordered subjects. Specifically, these replicate the original finding in that the inverse correlation between numbers of platelet 5-HTT binding sites and life history of aggression in the new subjects ($r$ = –.46) is essentially the same as that in the previously reported subjects ($r$ = –.50; Coccaro et al., 1996). These data also replicate the finding that this relationship is specific to the Bmax (number of 5-HTT binding sites), and not the Kd (affinity of the 5-HTT binding site), parameter of the $^3$H-Paroxetine Binding assay. These data extend the previously reported findings in demonstrating a relationship with a clinically relevant form of aggression as assessed by the Research Diagnostic Criteria sets for Intermittent Explosive Disorder (IED).

IED is a disorder of aggression, typically impulsive in nature, not better accounted for by other psychiatric/medical conditions or by pharmacologically induced behavioral states (Coccaro, 2003). In recent epidemiologic studies, IED has a lifetime prevalence of about 3–5% depending on the study and the specific diagnostic criteria used (Coccaro et al., 2004; Kessler et al., 2006). In this study, we applied all three types of criteria for IED: DSM-IV, IED-R (Coccaro et al., 1998), and lastly, IED-IR (Coccaro et al., 2004) which integrates DSM-IV and IED-R Research Criteria. While subjects who met IED by any of the three criteria sets demonstrated a reduction in platelet 5-HTT binding sites, compared to Non-IED subjects, only the IED Research Criteria (IED-R and IED-IR) demonstrated a significant reduction in 5-HTT binding sites. When controlled for lifetime history of depressive mood disorder, IED-R Criteria remained statistically significant and IED-IR criteria remained statistically significant at a trend level. It is notable that IED-R criteria was associated with reduced 5-HTT binding sites, compared with DSM-IV criteria, because IED-R criteria allows for frequent, though low intensity, aggressive episodes. Such episodes are allowed in the diagnostic set only if they involve clinically significant verbal aggression and non-destructive aggression against objects (i.e., episodes that are associated with subjective distress and/or impairment of occupational or psychosocial function).

The observation that inclusion of verbal and non-assaultive aggressive episodes, as a diagnostic criteria for IED, is associated with a reduction in platelet 5-HTT binding sites appears to support the validity of including these kinds of aggressive episodes in the next iteration of the Diagnostic Criteria for IED in DSM-V. Data from other studies also support the validity of IED-R (and IED-IR) criteria in regard to the inclusion of verbal and non-assaultive aggressive episodes. First, IEDs with verbal aggression, alone, do not differ from other IEDs in a validated behavioral aggression task (McCloskey et al., 2008a). Second, neuroimaging studies using IED-R criteria have reported, compared with controls, abnormalities in 5-HT activation in the frontal cortex (Siever et al., 1999) and in the

anterior cingulate cortex (New et al., 2002) and have reported reduced numbers of neuronal 5-HTT binding sites in the anterior cingulate, and possibly other areas as well (Frankle et al., 2005). Additionally, an fMRI study of emotional information processing in IED-IR subjects reported enhanced amygdala activation, compared with controls, specifically, in response to exposure to angry faces (Coccaro et al., 2007). Third, treatment with fluoxetine (Coccaro et al., 2009), or with cognitive-behavioral therapy (McCloskey et al., 2008b), clearly reduces verbal and non-assaultive physical aggressive behavior in subjects with IED-IR.

The present findings are consistent with reduced platelet 5-HTT binding in a mixed population of aggressive, "mentally-handicapped", institutionalized residents compared with controls (Marazziti et al., 1993) and in conduct-disordered adolescents compared with controls (Birmaher et al., 1990; Stoff et al., 1987), and with an inverse correlation between platelet 5-HTT binding and measures of aggression in personality disordered (Coccaro et al., 1996; Simeon et al., 1992), and in cocaine-dependent (Patkar et al., 2003a), subjects. Despite these positive studies, several studies report other findings. One small study of eleven currently aggressive schizophrenic subjects reported greater numbers of 5-HTT binding sites compared to non-aggressive schizophrenics and controls (Modai et al., 2000), another study reported greater 5-HTT binding sites in schizophrenic and violent offenders compared to controls (Sarne et al., 1995), while another study reported no differences between schizophrenics and controls (Maguire et al., 1997). Finally, one study of Obsessive–Compulsive Disorder subjects (Marazziti et al., 2001) and three studies of adolescents with either ADHD (Oades et al., 2002) or Conduct Disorder (Stoff et al., 1991; Unis et al., 1997) reported no relationship between measures of aggression and platelet 5-HTT binding sites. Differences in these results may be due to differences in the measures that were used. For example, use of measures of the personality trait of aggression, rather than history of actual aggressive behavior, may not show this relationship as it failed to do in the present study. Differences in the brain-behavioral substrates underlying the specific psychopathologies may also account for the differences observed in the negative studies.

Limitations of this study include the fact that platelet 5-HT binding is a peripheral measure of 5-HT, the cross-sectional nature of this study, the fact that not all subjects completed all of the dimensional behavioral measures, the fact that drug-free status was not confirmed by blood or urine testing, and the ascertainment of the subjects. First, while the platelet is a peripheral blood element and does not share the same microenvironment as central 5-HT neurons, platelet 5-HTT sites are structurally identical to corresponding sites on central 5-HT neurons (Lesch et al., 1993; Ramamoorthy et al., 1993). In addition, aggressive subjects, similar to those in this study, have been shown to display reduced neuronal 5-HTT binding sites in many areas of the brain, including the brainstem (SPECT study: (Tiihonen et al., 1997) and the anterior cingulate cortex (PET study: Frankle et al., 2005). While some studies report a relationship between the numbers of 5-HTT transporters on brain neurons and 5-HTT promoter genotypes (In Vitro Study: Lesch et al., 1996; Post-Mortem Studies: Little et al., 1998; SPECT Studies: Heinz et al., 2000; Platelet Studies: Stoltenberg et al., 2002; Little et al., 2006), many studies do not report this relationship (Platelet Studies: Hanna et al., 1998; Mellerup et al., 2001; Anderson et al., 2002; Javors et al., 2005; Patkar et al., 2004; Post-Mortem Study: Naylor et al., 1998; Neuroimaging: Willeit et al., 2001). Second, the cross-sectional nature of this study does not allow to an examination of the developmental aspects of serotonin and aggression over time. In fact, the juxtaposition of studies in childhood, adolescence, and adulthood suggest meaningful differences in the 5-HT/Aggression relationship over development. However, there are no studies in humans to allow a fuller examination in this regard. The ease of collecting platelet 5-HTT binding site data does make possible the conduct of such developmental studies in large numbers of subjects. While we did not note any seasonal variation in platelet 5-HTT binding in this study, as others have (e.g., Patkar et al., 2003b), the cross-sectional nature of the study does not allow consideration of other factors that may affect platelet 5-HTT binding over time. Third, the fact that not all subjects completed all behavioral measures limits the power to reject the null hypothesis in the cases of the negative findings. Even so, this study had 80% power to detect statistically significant correlations of moderate effect size ($r = .30$) in the case of each of the behavioral measures. To detect correlations of small effect size ($r = .10$; which would have represented limited clinical significance) would have required 770 subjects; far more than could be, realistically, studied at our center. Fourth, while subjects were reportedly drug-free for more than two-weeks (often much more than two-weeks), there was no confirmation of this by blood or urine testing. Despite this, 83% of subjects were naive to psychotropics and the findings in these subjects did not differ from the findings observed in the entire group (e.g., LHA correlation: $r = -.39$, $n = 72$, $p = .001$; $r_{partial} = -.32$, df = 69, $p = .006$ after controlling for life history of depressive disorder). Finally, the ascertainment of subjects may limit the generalizability of these findings since in the subjects in this study represent those who volunteered for research studies. Accordingly, these data may not fully generalize to a population based sample or to individuals in current psychiatric treatment.

## Contributors

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## Conflict of interest statement

None declared.

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