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Serotonin transporter availability in impulsive aggressive personality disordered patients: A PET study with [^{11}C]DASB

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ABSTRACT

Serotonin (5-HT) has consistently been implicated in the pathophysiology of impulsive aggression. In the current study, we tested the hypothesis that 5-HT transporter (5-HTT) binding is reduced in the anterior cingulate cortex (ACC) in impulsive aggressive patients. Additionally, we characterized pathological personality dimensions, with a specific focus on callousness (i.e. emotional indifference, a facet of psychopathy). Callousness is putatively *positively* correlated with presynaptic 5-HT, and thus could potentially confound the hypothesized *negative* relation between 5-HTT levels and trait aggression.

We determined 5-HTT binding with positron emission tomography and [^{11}C]DASB in 29 patients with intermittent explosive disorder (IED-IR) and 30 controls. We assessed group differences in 5-HTT binding in the pregenual ACC, amygdala and subcortical regions and examined correlations between 5-HTT binding and clinical measures.

There were no significant differences in 5-HTT binding between IED-IR patients and controls. Trait callousness exhibited a significant, positive correlation with ACC 5-HTT availability. Among IED-IR patients, a trend-level negative partial correlation was observed between trait aggression and ACC 5-HTT availability, while covarying for callousness and age. Exploratory analyses revealed a significant negative correlation between state aggression levels and 5-HTT availability in subcortical regions, namely striatum and thalamus.

We did not confirm our hypothesis of lower ACC 5-HTT availability in impulsive aggressive patients, however, the positive correlation between callousness and ACC 5-HTT availability likely played a confounding role. Subtypes of aggression (e.g., reactive vs. proactive aggression), which are differentially associated with pathological personality dimensions such as callousness, may contribute to variability between 5-HT functioning and aggression.

1. Objectives of the study and background

Impulsive aggression is a common symptomatic behavior that poses a significant clinical and public health problem. Although aggression can occur as a function of a number of major psychiatric conditions – e.g., attention-deficit/hyperactivity disorder (ADHD), post-traumatic stress disorder (PTSD), bipolar disorder, and substance abuse – recurrent, episodic assaultive behavior has been observed independently of other major psychiatric conditions. Such observations led to the delineation of intermittent explosive disorder (IED) as a distinct syndrome. More recently, integrated research criteria of IED have been developed (IED-IR) (McCloskey et al., 2006), which address in an evidence-based manner limitations of the original DSM-III and DSM-IV descriptions of this syndrome. In addition to its clinical utility, IED-IR serves as a particularly useful diagnostic construct to study neurobiological correlates of clinically significant pathological aggression.

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Multiple lines of evidence implicate pre-synaptic serotonin (5-HT) dysfunction, particularly in fronto-cortical regions, in the neurobiology of impulsive aggression (Siever, 2008). In rodents, lower cortical 5-HT is associated with increased aggressive behavior (for review see (Krakowski, 2003)). Studies in both non-human primates (Mehlman et al., 1994; Doudet et al., 1995) and humans (Brown et al., 1979; Virkkunen et al., 1994), have demonstrated an association between lower cerebrospinal fluid (CSF) 5-hydroxyindolacetic acid (5-HIAA), the major metabolite of 5-HT, and impulsive aggressive behavior. Imaging of alpha-[^{11}C]methyl-L-tryptophan trapping (Young et al., 1999) – a putative measure of 5-HT synthesis – suggests that presynaptic 5-HT functioning is attenuated in orbital and ventromedial frontal cortices in impulsive patients with borderline personality disorder (BPD) (Leyton et al., 2001), suicide attempters (Leyton et al., 2006), and adult males with a childhood history of physical aggression (Booij et al., 2010).

Examination of the 5-HT transporter (5-HTT) has also served as a functionally significant molecular index of presynaptic 5-HT integrity. Mice lacking the 5-HTT exhibit lower levels of aggression (Holmes et al., 2002). In humans, an inverse relationship between aggression and platelet 5-HTT has been described (Coccaro et al., 2010). Furthermore, S allele carriers for the 5-HTT promoter region polymorphism (5-HTTPLR) tend to be more aggressive (Aluja et al., 2009; Payer et al., 2012) and have lower 5-HTT availability in 5-HTT rich brain regions (Willeit and Praschak-Rieder, 2010). Serotonin-specific reuptake inhibitors (SSRIs) are effective for reduction of impulsive aggression (Coccaro et al., 2009), and this effect depends on genotype of the 5-HTT (L/L homozygotes respond better than S allele carriers) (Silva et al., 2010), highlighting the importance of individual differences.

Despite burgeoning evidence on the importance of the 5-HTT in impulsive aggression, few studies have investigated its in vivo distribution in the brains of patients with IED-IR. We previously demonstrated lower 5-HTT availability using [^{11}C]McN 5652 in the pregenual anterior cingulate cortex (pgACC) of personality disordered patients with IED (Frankle et al., 2005). Recently it was shown that in an all-male, healthy, non-clinical population specifically selected for the absence of callous-unemotional traits (a facet of psychopathy), those scoring high on a trait measure of impulsive aggression had higher 5-HTT availability in brainstem regions and modestly lower 5-HTT availability in cortical regions (including the pgACC) compared to those scoring low for impulsive aggression (Rylands et al., 2012). In abstinent methamphetamine users, [^{11}C]McN 5652 binding was lower in cortical and subcortical brain regions compared to healthy controls; and, greater levels of aggression in the methamphetamine users was correlated with lower 5-HTT availability in the pgACC, orbitofrontal and temporal cortices (Sekine et al., 2006). These studies support the view that attenuated functional integrity of the presynaptic cortical 5-HT system, reflected by lower cortical by 5-HTT availability, is involved in the pathophysiology of impulsive aggression.

The aim of this study was to replicate our previous finding of lower cortical 5-HTT, specifically in the pgACC, in patients with IED-IR using a larger cohort and a more selective radiotracer, [^{11}C]DASB. An additional aim was to determine whether among IED-IR patients, greater levels of trait aggression would be associated with lower pgACC 5-HTT availability. Therefore, we examined 5-HTT availability with positron emission tomography (PET) in a sample of medication-free IED-IR patients and healthy controls. We also characterized various pathological personality dimensions in IED-IR patients, in order to take into account traits that may moderate the relationship between aggression and 5-HTT availability. Stimulated by the work of Rylands et al. (Rylands et al., 2012), we were particularly interested in callousness (i.e. emotional indifference, a facet of psychopathy), which studies indicate is positively correlated with presynaptic 5-HT function (Dolan and Anderson, 2003), and is differentially associated with proactive and reactive subtypes of aggression (Raine et al., 2006). Therefore, callousness might be a factor moderating the hypothesized association between impulsive aggression and 5-HTT availability. Furthermore, we performed exploratory analyses of 5-HTT availability in other limbic and subcortical regions, and examined associations between 5-HTT availability and measures of aggression, impulsivity, affective lability and depressive symptoms.

2. Methods and materials

2.1. Human subjects

IED-IR patients met the diagnostic criteria for IED-IR (McCloskey et al., 2006) and at least one DSM-IV personality disorder. Patients were excluded if they met criteria for current major depressive episode, history of schizophrenia or other psychotic disorder, bipolar-I, or current/recent (within the past 6 months) alcohol or substance abuse/dependence. Patients were also excluded if they had a history of serious past alcohol/substance abuse/dependence, which might have led to long-standing neurochemical sequelae, namely: delirium tremens or medically complicated alcohol withdrawal, intravenous drug use, or chronic/persistent cocaine dependence. In order avoid the confounding role of prior methamphetamine or methylenedioxy-methylamphetamine (MDMA), patients were excluded for a lifetime history of abuse or dependence of these stimulants. Healthy controls were medically and neurologically healthy, had no current or past psychiatric disorder or first-degree relative with a history of psychotic disorders. All subjects were between 18 and 55 years old, had negative urine toxicology, were free of psychotropic medication for at least six weeks prior to the scan, and were not pregnant or nursing. Participants were recruited through advertisements in local newspapers and the Internet and clinical referral for IED-IR patients. All participants underwent a medical clearance, consisting of a medical history, physical examination, basic blood and urine tests, and electrocardiogram. The study was approved by the institutional review boards of the New York State Psychiatric Institute, Columbia University Medical Center, Mount Sinai Hospital, and the Bronx Veterans Affairs Medical Center. Written informed consent was obtained from each research participant after explanation of study procedures.

2.2. Clinical and behavioral measures

The Structured Clinical Interview for DSM-IV Axis I Disorder (SCID-IV) was used for Axis I diagnoses and the Structured Interview for DSM-IV Personality Disorders was used for Axis II diagnoses in patients. For controls, absence of psychiatric conditions was confirmed with either an abbreviated version of the SCID-IV or the Diagnostic Interview for Genetic Studies (DIGS) (Nurnberger et al., 1994).

For IED-IR patients, several self-report behavioral measures were obtained. The Buss-Perry Aggression Questionnaire (BPAQ) was used to assess trait verbal and physical aggression (Buss and Perry, 1992). The Overt Aggression Scale-Modified (OAS-M) is composed of three subscales: assaultiveness, global irritability, and suicidality (Coccaro et al., 1991). The subscales assaultiveness and global irritability were used as measures of state aggression. The Life History of Aggression (LHA) assessment was a measure for life history of aggressive behavior (Coccaro et al., 1997). The callousness subscale of the Dimensional Assessment of Personality Pathology (DAPP) (Pukrop et al., 2009) was used to assess emotional indifference, a facet of psychopathy. The Affective Lability Scale (ALS) measures the trait affective lability (Harvey et al., 1989). The Barratt Impulsiveness Scale, version 11 (BIS-11), was used to measure trait impulsivity (Patton et al., 1995) and the Beck Depression Inventory

(BDI) to assess depressive symptoms (Beck and Steer, 1984). Childhood trauma was assessed with the Childhood Trauma Questionnaire (CTQ) (Bernstein and Fink, 1998).

2.3. PET acquisition

[^{11}C]DASB was produced from the precursor desmethyl DASB and [^{11}C]methyl ioidide as previously described (Frankle et al., 2004). PET imaging was performed with the ECAT EXACT HR + scanner (Siemens/CTI, Knoxville, TN). A 10-min transmission scan for attenuation correction preceded [^{11}C]DASB administration, which was injected i.v. as a single bolus. Emission data were acquired for 100 min using frames of increasing duration (3*20 s, 3*1 min, 3*2 min, 2*5 min, 8*10 min). 8 controls and 1 IED-IR patient received a 120 min emission scan and 1 control and 2 IED-IR patients received a 110 min emission scan. For these subjects, only the data acquired for the first 100 min were used to ensure that the data were comparable for all subjects.

2.4. Input function measurement

Following radiotracer injection, arterial samples were collected to determine the input function for kinetic analysis. Samples were collected with an automated sampling system every 10 s for the first 2 min and every 20 s for the third and fourth minutes. Thereafter samples were drawn manually at longer intervals. A total of 29 samples were obtained. Following centrifugation, plasma was collected in 200 μL aliquots and activities were counted in a gamma counter (Wallac 1480 Wizard 3M Automatic Gamma Counter). Six samples (collected at 2, 16, 30, 50, 70, 90 min post-injection) were further processed by high-performance liquid chromatography to measure the fraction of plasma activity representing unmetabolized parent compound (Frankle et al., 2004).

The measured unmetabolized fraction of [^{11}C]DASB in arterial plasma was fitted to a bi-exponential function. This curve was multiplied by the (decay corrected) measured plasma activity to generate a sampled arterial plasma input function. The sampled input function was then fitted (from the time of peak activity) to a sum of three exponential functions and this fitted curve was used as the input function for kinetic modeling. Prior to radiotracer injection, a separate sample of arterial plasma was obtained and later spiked with radioligand to determine the free fraction (fraction not bound to plasma protein, f_P).

2.5. Image analysis

After attenuation correction, data were reconstructed by filtered backprojection with a Shepp filter (cutoff 0.5 cycles/projection ray). A high-resolution T1-weighted magnetic resonance image (MRI) was acquired for each subject and PET data were registered to the MRI using SPM2 software (Friston et al., 1995). Regions of interest (ROIs) were drawn on each subject's MRI and then transferred to the coregistered PET data. Time activity curves were formed for each ROI by measuring the mean activity in the ROI in each frame.

Limbic ROIs were the pgACC and amygdala and were drawn according to criteria based on brain atlases (Talairach and Tournoux, 1988; Duvernoy, 1991) and on published reports (Pani et al., 1990; Kates et al., 1997; Killiany et al., 1997) (for pgACC see also Fig. 1 in Frankle et al. (2005)). A gray/white tissue segmentation procedure (Abi-Dargham et al., 2002) was applied to the limbic regions so that only voxels classified as gray matter were included in these ROIs. Subcortical ROIs included the midbrain, thalamus, associative striatum (AST), including precommissural dorsal caudate, postcommissural caudate and pre-commissural dorsal putamen, the limbic striatum (LST) which comprises the ventral striatum (VST), and the sensorimotor striatum (SMST) which comprises the post-commissural putamen. Striatal subregions were defined as in Mawlawi et al. (2001). The cerebellum (CER) was included as a reference region for non-displaceable activity.

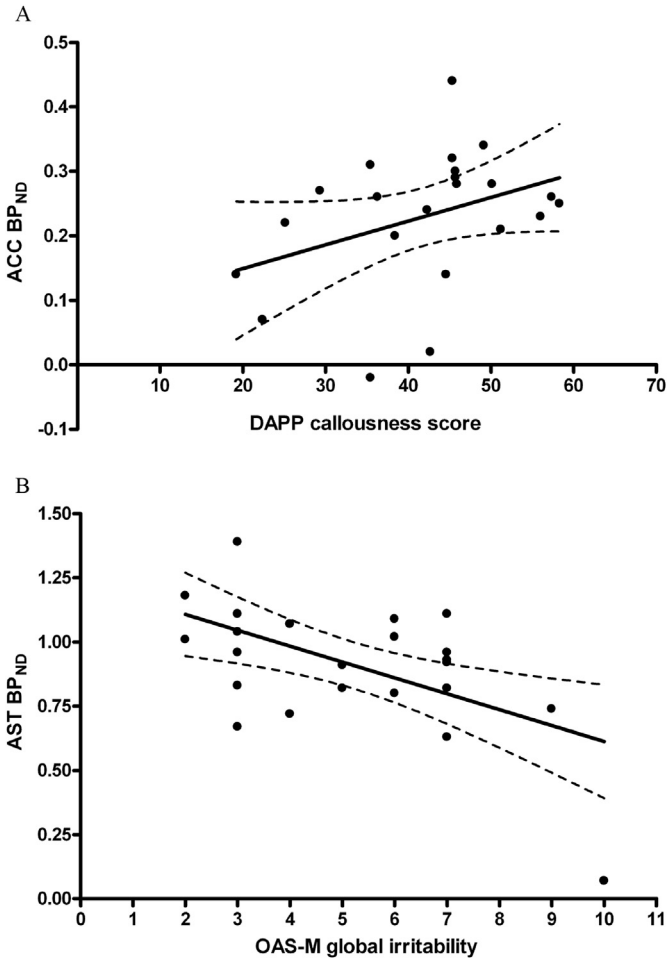

Fig. 1. Significant correlations between 5-HTT availablility and behavioral measures. (A) Correlation between BP_{ND} in the anterior cingulate cortex and DAPP callousness scores (beta = 0.366, p = 0.047, adjusted for age). (B) Correlation between BP_{ND} in the associative striatum and OAS-M global irritability scores (beta = −0.506, p = 0.012, adjusted for age). ACC = pregenual anterior cingulate cortex, AST = associative striatum, BP_{ND} = binding potential relative to the non-displaceable compartment, DAPP = Dimensional Assessment of Personality Pathology, OAS-M = Overt Aggression Scale-Modified.

Data were analyzed using 2-tissue compartment modeling (2 TC) with arterial plasma input. Total distribution volume (V_T) was estimated in each brain region. The outcome measure BP_{ND} was then determined from regional V_T values according to the formula:

$$BP_{ND} = (V_T(ROI) - V_T(CER))/V_T(CER) = f_{ND} * B_{avail}/K_D$$

where f_{ND} is the free fraction of free plus nonspecifically-bound radioligand in the brain. K_D is the equilibrium dissociation constant and B_{avail} is the concentration of 5-HTT available for binding to [^{11}C]DASB (Innis et al., 2007).

2.6. Statistical analyses

Demographics, scan parameters and regional volumes were compared between groups with independent samples t-tests or where appropriate with chi-square tests. We used one-way analysis of covariance (ANCOVA) to test for a group difference in pgACC and

amygdala BP_{ND}. For subcortical regions, mixed linear modeling was used to assess between-group differences in BP_{ND} with subcortical regions as repeated measures. Because the patient and control groups were not strictly age-matched and age has been associated with 5-HTT availability (Meyer et al., 2001; Frokjaer et al., 2009; Erritzoe et al., 2010), age was included as a covariate in the ANCOVA and linear mixed model analyses.

Furthermore, we performed exploratory analyses in the IED-IR patients to test for correlations between BP_{ND} and scores on the behavioral measures (BPAQ verbal/physical aggression, OAS-M assaultiveness, OAS-M global irritability, LHA, DAPP callousness, ALS, BIS-11, BDI). For the pgACC and amygdala, we used linear regression analysis with age as a covariate. For the subcortical regions, we used a linear mixed model with BP_{ND} in these regions as repeated measures and behavioral assessment score and age as covariates. In case of significant findings, we performed *post-hoc* tests, using linear regression with age as a covariate. Probability values below 0.05 were considered significant for hypothesis-based analyses and below 0.007 for exploratory analyses to correct for multiple testing.

3. Results

3.1. Demographics

We included 29 IED-IR patients and 30 healthy control subjects. There were no significant group differences in age, gender, or ethnicity (see Table 1). Axis I and Axis II diagnoses for the IED-IR patients are displayed in Supplementary Table S1.

Table 1
Demographics, scan parameters, and behavioral measures.

	IED-IR patients	Control subjects	*p*-Value
Number	29	30	
Age (years; mean ± SD)	39.7 ± 11.5	35.5 ± 6.8	0.095[a]
Gender			
M/F	22/7	21/9	0.613[b]
Ethnicity			
C/AA/H/A/Other	9/14/4/2/0	12/8/5/3/2	0.472[b,c]
Smoking status			
Yes/No	6/23	3/27	0.254[b]
Scan parameters (mean ± SD)			
Injected dose (mCi)	12.6 ± 1.9	13.6 ± 2.4	0.101[a]
Injected mass (μg)	3.8 ± 2.0	4.7 ± 2.4	0.124[a]
Specific activity	1292 ± 789	1077 ± 621	0.250[a]
Plasma free fraction (f_p)	0.103 ± 0.023	0.088 ± 0.017	0.007[a]
Non-specific distribution volume (ml/g)	10.6 ± 2.2	10.9 ± 2.1	0.574[a]
Behavioral measures (mean ± SD (N))			
BPAQ verbal/physical aggression	6.9 ± 1.6 (25)		
OAS-M			
Assaultiveness	44.9 ± 66.5 (25)		
Global irritability	5.3 ± 2.2 (25)		
LHA	30.3 ± 8.5 (19)		
DAPP callousness	43.2 ± 11.2 (24)		
ALS	82.4 ± 32.2 (29)		
BIS-11	69.9 ± 9.6 (23)		
BDI	14.7 ± 9.5 (28)		
CTQ	58.1 ± 14.4 (24)		

M = male, F = female, C = Caucasian, AA = African American, H = Hispanic, A = Asian, BPAQ = Buss-Perry Aggression Questionnaire, OAS-M = Overt Aggression Scale-Modified, LHA = Life History of Aggression, DAPP = Dimensional Assessment of Personality Pathology, ALS = Affective Lability Scale, BIS = Barratt Impulsiveness Scale, BDI = Beck Depression Inventory, CTQ = Childhood Trauma Questionnaire.
[a] Independent samples *t*-test.
[b] Chi-square test.
[c] Dichotomized to Caucasian vs. non-Caucasian.

3.2. Scan parameters

Groups did not differ significantly in injected dose, injected mass, specific activity or distribution volume in the reference region for non-displaceable binding (V_{ND}, cerebellum) (see Table 1). There was a significant difference in plasma free fraction (f_P) between groups ($p = 0.007$). However, our outcome measure BP_{ND} is not affected by this, as the f_P contributions to the numerator and denominator in the BP_{ND} formula cancel.

3.3. Regional volumes

There were no significant group differences for the pgACC, amygdala, or subcortical regions (see Table S2).

3.4. Group comparison of BP_{ND}

For the a priori region of interest pgACC, we found no group difference in BP_{ND} (see Table 2), whereas age had a significant effect on BP_{ND} in the pgACC ($p = 0.029$, $B = -0.003$).

BP_{ND} also did not differ significantly between groups in the amygdala or in the subcortical regions. There was an effect of age on BP_{ND} in the amygdala ($p = 0.003$, $B = -0.012$).

Furthermore, we compared a subgroup of IED-IR patients with current physical aggression ($n = 22$, see Supplementary Table S1) to the control subjects in exploratory analyses to test for BP_{ND} differences, as we have previously demonstrated that $5HT_{2A}$ receptor availability differs between IED-IR patients with *current* as opposed to *past* physical aggression (Rosell et al., 2010). These analyses showed qualitatively the same results as for the whole IED-IR patient group, i.e. there were no significant group differences in BP_{ND} between IED-IR patients with current physical aggression and control subjects.

3.5. Correlations between BP_{ND} and behavioral measures in IED-IR patients

The average scores on the behavioral measures are displayed in Table 1. There was no significant correlation between pgACC BP_{ND} and BPAQ verbal/physical aggression. However, there was a significant positive association between DAPP callousness and pgACC BP_{ND} (beta = 0.366, $p = 0.047$; Fig. 1A). In order to determine whether the hypothesized negative association between pgACC BP_{ND} and BPAQ verbal/physical may have been confounded by trait callousness, we subsequently examined whether BPAQ verbal/physical aggression was associated with pgACC BP_{ND}, when adjusting for both callousness and age. This revealed a trend-level

Table 2
Regional BP_{ND} for patients and controls.

	BP_{ND} IED-IR patients mean ± SD	BP_{ND} control subjects mean ± SD	*p*-Value
Limbic			
ACC	0.22 ± 0.10	0.25 ± 0.06	0.622[a]
Amygdala	1.05 ± 0.34	1.07 ± 0.22	0.686[a]
Subcortical			0.312[b]
Midbrain	1.84 ± 0.52	2.01 ± 0.34	
Thalamus	0.87 ± 0.24	0.91 ± 0.17	
AST	0.90 ± 0.25	0.97 ± 0.18	
LST	1.25 ± 0.33	1.28 ± 0.25	
SMST	0.95 ± 0.25	1.05 ± 0.19	

ACC = anterior cingulate cortex, AST = associative striatum, LST = limbic striatum, SMST = sensorimotor striatum.
[a] ANCOVA with age as a covariate.
[b] Linear mixed model with age as a covariate.

negative association between BPAQ verbal/physical aggression and pgACC BP_{ND} (beta = −0.323, $p = 0.097$).

Furthermore, there was a significant association between OAS-M global irritability and BP_{ND} in the subcortical regions ($F = 11.4$, $p = 0.001$). *Post-hoc* analyses revealed that this was based on negative correlations between OAS-M global irritability and BP_{ND} in the AST (beta = −0.506, $p = 0.012$, Fig. 1B), SMST (beta = −0.405, $p = 0.024$), and thalamus (beta = −0.343, $p = 0.033$) and a trend-level correlation in the LST (beta = −0.362, $p = 0.060$), although these correlations were not significant after correction for multiple comparisons (Bonferroni correction).

There were no significant correlations between BP_{ND} in the pgACC, limbic or subcortical regions and scores on OAS-M assaultiveness, LHA, ALS, BIS-11, or BDI. Additional exploratory analyses, which aimed to identify additional sources of variance, included personality disorder type (antisocial personality disorder or bipolar personality disorder), sex or childhood trauma (CTQ score) as covariates in the analyses described above (both group comparisons and correlational analysis with behavioral measures), but they did not show significant results.

4. Discussion

Unlike our previous report (Frankle et al., 2005), we did not observe lower pgACC 5-HTT availability in impulsive aggressive patients compared to healthy controls. However, we observed a significant positive association between the dissocial trait callousness and pgACC 5-HTT availability, which supports the notion of greater presynaptic 5-HT function in the affective psychopathy domain. When adjusting for the callousness – which studies suggest is associated with *increased* 5-HT function (Dolan and Anderson, 2003) – the hypothesized, negative correlation between trait aggression and pgACC 5-HTT availability was observed at the level of a statistical trend. These findings suggest that the relation between fronto-cortical 5-HTT availability and aggression is a complex one, and lower-order pathological personality dimensions as well as pathophysiologic aggression-subtypes (see below) need to be taken into account.

An unexpected finding from an exploratory analysis of subcortical regions was a significant, negative correlation between 5-HTT availability and state aggression (OAS-M global irritability) in striatal regions and the thalamus, but not in the midbrain. The literature regarding aggression in the striatum is fairly limited (Perez-Rodriguez et al., 2012), and even more so with respect to the thalamus. A recent study (Crockett et al., 2013) combined functional magnetic resonance imaging (fMRI) with a social-economic behavioral paradigm. They (Crockett et al., 2013) demonstrated that dietary depletion of the 5-HT precursor, tryptophan, led to increased delivery of costly, retaliatory responses in response to receiving an unfair financial offer as well as to increased dorsal caudate activity (which is part of the AST). Consistent with receiving cortical afferents from dorsolateral prefrontal regions, the AST has been implicated in higher-order cognitive and executive processes (Haber, 2003). Therefore, 5-HTergic modulation in the AST of these cognitive/executive processes could potentially influence state levels of impulsive aggression.

4.1. Comparison with related studies

Compared to our prior report (Frankle et al., 2005), the current study consisted of larger sample sizes (i.e., 29-30 subjects/group versus 10 subjects/group). The use of [^{11}C]DASB is preferred over [^{11}C]McN, the radiotracer used in our previous study, because it has higher specific-to-nonspecific binding ratios. However, there are important qualitative differences between the IED patients in these two studies: 1) the male-female ratio of patients with impulsive aggression in the present study is 3:1, as opposed to 1:1 in our prior report; and, 2) we mainly recruited patients with impulsive *physical* aggression in the current study, whereas the proportion of IED patients with verbal rather than physical aggression was greater in the patient sample of our prior study. Therefore, while the difference in group size and radioligand suggest the findings of the current study may be more valid than our previous report, the qualitative differences between IED groups, in terms of gender and aggression severity, may contribute to the disparity of the findings.

Rylands et al. (Rylands et al., 2012) used [^{11}C]DASB and PET in participants with low callous/unemotional traits that either scored at the high or low extreme of a trait measure of aggression (i.e., 1.5 standard deviations above/below normative scores). Participants were excluded for current/past Axis I disorders, alcohol/drug misuse within the preceding 6 months, and Cluster A personality disorders. Participants in the high-aggression group of the Rylands et al. study, however, were found to have either BPD or antisocial personality disorder (ASPD). Consistent with our hypothesis that lower pgACC 5-HTT availability may underlie trait impulsive aggression, Rylands et al. observed moderately decreased cortical 5-HTT availability in the high- compared to low-aggression group; they did not assess for a correlation between clinical measures (viz., aggression, impulsivity) and cortical 5-HTT availability, however. Controlling for the confounding effect of callous/unemotional traits may have allowed Rylands et al. to identify relatively lower cortical 5-HTT availability in their high-aggression group, which we expected to observe in our IED-IR compared to healthy group. In contrast to our study, Rylands et al. also reported significantly increased brainstem 5-HTT in the high- compared to low-aggression group; moreover, impulsivity, aggression, and childhood trauma were correlated with brainstem 5-HTT availability among all participants. These disparities, in terms of brainstem findings, between our study and that of Rylands et al., likely owe to important differences between the two 'aggression' groups: Our group likely represented a more clinically severe and complex population, as it consisted of patients with IED-IR, comorbid Axis I disorders, and personality disorders other than BPD and ASPD. One additional study used [^{11}C]DASB to examine the 5-HTT in aggressive and non-aggressive alcoholics (Brown et al., 2007). Like the current study, they did not observe significant differences in 5-HTT availability between the two groups. However, patients with current substance abuse/dependence were excluded from the current study, limiting the comparisons that can be made between these studies.

4.2. 5-HT, personality disorder dimensions, and pathophysiologic subtypes of aggression

As illustrated in the present study, there is an important relationship between aggression, 5-HT, and pathological personality dimensions. While the prevailing model has been that aggression is associated with low presynaptic 5-HT, generally speaking, results have been inconsistent. For example, while a number of studies have demonstrated an inverse correlation with cerebrospinal fluid 5-HIAA levels and trait aggression (Brown et al., 1979, 1982; Kruesi et al., 1990), there have been reports of either the absence of a relationship (Coccaro et al., 1998), or a positive correlation (Coccaro and Lee, 2010). There has also been variability with respect to post-synaptic 5-HT function, probably best illustrated by studies of the 5-HT2A receptor. We previously observed a positive relationship between orbitofrontal 5-HT2A receptor availability and state levels of impulsive aggression in (predominantly borderline) personality disordered patients (Rosell et al., 2010). Meyer et al. Meyer et al. (2008) on the other hand, demonstrated an inverse correlation

between 5-HT2A receptor availability in frontal and temporal cortical regions and trait measures of both impulsivity and aggression in patients with predominantly antisocial personality disorder. In a healthy, non-clinical sample, Da Cunha-Bang et al. da Cunha-Bang et al. (2013) observed no relationship between frontal 5-HT2A receptor availability and trait impulsivity or aggression. Additionally, Rylands et al. (2012) found that in a non-clinical sample, selected for low callous/unemotional traits, cortical 5-HT2A receptor availability was lower in the high-aggression compared to low-aggression participants; however, cortical 5-HT2A receptor availability was not significantly associated with either trait impulsivity or trait aggression.

We hypothesize that this variability in 5-HTergic abnormalities owes to pathophysiologic subtypes of aggression, as well as associated personality disorder dimensions. A valuable distinction to consider is that between *reactive* and *proactive* forms of aggression, with the former being an impulsive, angry reaction to frustration or threat, and the latter being unprovoked, calculated and goal-oriented (Lobbestael et al., 2013). Although the constructs of proactive and reactive forms of aggression have predominantly been characterized in child and adolescent populations, their existence in adults was confirmed (Murray-Close et al., 2010). Reactive aggression has been more closely associated with history of abuse and negative emotionality, whereas proactive aggression appears to be related to the interpersonal/affective dimensions of psychopathy (e.g., callous/unemotional traits) (Raine et al., 2006). These two forms of aggression are not mutually exclusive, but are frequently co-occurring. We speculate that it is the reactive form of aggression that accounts for the 'standard model' of low presynaptic 5-HT. Accordingly, proactive aggression, we suspect, is related to increased presynaptic 5-HT. As trait measures of aggression, such as the BPAQ, are not designed to differentiate between reactive and proactive aggression, it follows that despite covarying for trait callousness, the correlation between trait aggression and pgACC 5-HTT availability reached only the level of a statistical trend.

4.3. Study limitations

There are several methodological considerations of the current study. First, we did not include neocortical regions in our analyses. For these regions (frontal, temporal, parietal, and occipital cortex) the average BP_{ND} in our sample ranged between −0.02 and 0.11. When BP_{ND} is very low, statistical analysis of these regions leads to less reliable results.

In addition, we included IED-IR patients with axis I disorders such as past MDD and substance use disorders. MDD has previously been associated with lower 5-HTT availability (Malison et al., 1998; Newberg et al., 2005; Parsey et al., 2006), although not consistently (Meyer et al., 2004; Herold et al., 2006). The subjects in our sample that had been classified with MDD were in remission, and BDI scores were not significantly correlated with 5-HTT availability in this sample. Therefore the effect on our findings of past MDD in a subset of the patients should be limited.

Furthermore, 5-HTT genotype (5-HTTPLR polymorphism) of our subjects is not available, so we did not include this factor in the analyses. It has previously been shown that 5-HTT genotype influences 5-HTT availability, at least in subcortical regions (for review Willeit and Praschak-Rieder (2010)). Therefore, the potential contribution of 5-HTT genotype to our findings is unknown.

Finally, the healthy control sample was not as well characterized by measures of aggressive behavior as the IED-IR patients. However, score range would have been narrow on these measures for the control subjects and thus would most likely not have provided additional information on the relationship between 5-HTT availability and aggression.

5. Conclusion

The present study reflects the conflicting findings in the literature regarding the role of presynaptic 5-HT and the 5-HTT in impulsive aggression. Our findings also further demonstrates the importance of various confounds, most notably, the interpersonal/affective factor of psychopathy (e.g., callousness). We propose that at least two forms of aggression – reactive and proactive – may coexist to varying degrees among clinical populations; and, these two forms these two forms of aggression may differ in terms of the nature of their 5-HTergic system abnormalities, as well as their associated pathological personality dimensions. Therefore, future studies should account for the differential contribution of these two forms of aggression, in order to clarify the 5-HTergic abnormalities associated with each, and to determine to what extent there may be convergent elements to their underlying pathophysiology. The significant positive association between callousness and pgACC 5-HTT availability supports the notion of greater presynaptic 5-HT function in the interpersonal/affective psychopathy domain. Lastly, future studies that examine 5-HTT availability in striatal and thalamic regions may help to elucidate factors that affect state levels of aggression.

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Contributors

Authors Larry J. Siever, Daniel R. Rosell, Anissa Abi-Dargham and Mark Slifstein designed the study and wrote the protocol. Authors Daniel R. Rosell, Yosefa Ehrlich, Judy Thompson, Xiaoyan Xu and Ragy R. Girgis managed the data collection and performed data analysis. Authors Elsmarieke van de Giessen and Mark Slifstein undertook the statistical analysis, and authors Elsmarieke van de Giessen and Daniel R. Rosell wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Conflict of interest

Ragy R. Girgis receives research support from Otsuka. Mark Slifstein has consulted for Amgen. Anissa Abi-Dargham is on the scientific advisory boards for UCB Pharmaceuticals and Roche and has received research support from Pierre-Fabre, Takeda, Otsuka, and Forest. All other authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jpsychires.2014.07.025.

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