Psychopharmacology (2023) 240:361–371
https://doi.org/10.1007/s00213-022-06306-2

ORIGINAL INVESTIGATION

Serotonin transporter availability in physically aggressive personality disordered patients: associations with trait and state aggression, and response to fluoxetine

Daniel R. Rosell[1] · Mark Slifstein[2] · Judy Thompson[3] · Xiaoyan Xu[4] · M. Mercedes Perez-Rodriguez[1] · Margaret M. McClure[1,5] · Erin A. Hazlett[1,6] · Antonia S. New[1] · Nabeel Nabulsi[7] · Yiyun Huang[7] · Richard E. Carson[7] · Larry S. Siever[1,6,8] · Anissa Abi-Dargham[2] · Harold W. Koenigsberg[1,8]

Received: 18 October 2021 / Accepted: 27 December 2022 / Published online: 14 January 2023

Abstract

Rationale Characterizing the neuroanatomical basis of serotonergic abnormalities in severe, chronic, impulsive aggression will allow for rational treatment selection, development of novel therapeutics, and biomarkers to identify at-risk individuals.

Objectives The aim of this study is to identify associations between regional serotonin transporter (5-HTT) availability and trait and state aggression, as well as response to the anti-aggressive effects of fluoxetine.

Methods We examined 5-HTT availability using positron emission tomography (PET) imaging with [^{11}C]DASB in personality disordered patients with current physical intermittent explosive disorder (IED; $n=18$), and healthy comparison participants (HC; $n=11$), in the anterior cingulate cortex (ACC), amygdala (AMY), ventral striatum (VST), and midbrain (MID). After PET imaging, IED patients were treated with fluoxetine 20 mg daily ($n=9$) or placebo ($n=6$) for 12 weeks. Trait and state aggression, trait callousness, and childhood trauma were assessed.

Results In IED patients, trait aggression was positively associated with [^{11}C]DASB binding in the ACC and VST; covarying for trait callousness and childhood trauma enhanced these correlations. Baseline state aggression was positively correlated with ACC [^{11}C]DASB in IED patients. Greater baseline VST [^{11}C]DASB binding predicted greater decreases in state aggression with fluoxetine treatment.

Conclusions Consistent with prior reports, ACC 5-HTT is related to trait aggression, and adjusting for factors related to proactive (callousness) and reactive (childhood trauma) aggression subtypes further resolves this relationship. Novel findings of the study include a better understanding of the association between regional 5-HTT availability and state aggression, and the involvement of VST 5-HTT with trait aggression, and with the anti-aggressive effects of fluoxetine.

Keywords Aggression · Intermittent explosive disorder · Callousness · Childhood trauma · Fluoxetine · Positron emission tomography · DASB · Serotonin transporter · Anterior cingulate cortex · Ventral striatum

✉ Harold W. Koenigsberg
harold.koenigsberg@mssm.edu

[1] Department of Psychiatry, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA

[2] Department of Psychiatry, Stony Brook University, Stony Brook, NY 11794, USA

[3] Department of Psychiatry, University of Rochester Medical Center, Rochester, NY 14642, USA

[4] Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, NY 10032, USA

[5] Department of Psychology, Fairfield University, Fairfield, CT 06824, USA

[6] Mental Illness Research, Education, and Clinical Center (VISN 2), James J. Peters Veterans Affairs Medical Center, Bronx, NY 10468, USA

[7] Department of Radiology and Biomedical Imaging, Yale University, New Haven, CT 06520, USA

[8] Outpatient Psychiatry, James J. Peters Veterans Affairs Medical Center, Bronx, NY 10468, USA

Abbreviations

5-HT	5-Hydroxytryptamine or serotonin
5-HTT	Serotonin transporter
ACC	Anterior cingulate cortex
AMY	Amygdala
ASPD	Antisocial personality disorder
AvPD	Avoidant personality disorder
BPAQ	Buss-Perry aggression questionnaire
BPD	Borderline personality disorder
CTQ	Childhood trauma questionnaire
CU	Callous-unemotional
DAPP	Dimensional assessment of pathological personality
HC	Healthy comparison
IED	Intermittent explosive disorder
MAO-A	Monoamine oxidase-A
MRI	Magnetic resonance imaging
MID	Midbrain
NPD	Narcissistic personality disorder
OAS-M	Overt aggression scale-modified
OCPD	Obsessive-compulsive personality disorder
PDNOS	Personality disorder not otherwise specified
PET	Positron emission tomography
PPD	Paranoid personality disorder
ROI	Region of interest
SPD	Schizotypal personality disorder
SSRI	Serotonin specific reuptake inhibitor
Verb/Phys	Verbal and physical
VST	Ventral striatum

Introduction

Chronic, severe, impulsive aggression is common and associated with significant subjective distress, functional impairment (Rynar and Coccaro 2018), and public health burden (Cerda et al. 2018). Although the two do not exist in clear-cut isolation from one another, impulsive aggression is distinguished from instrumental forms of aggression in that the former is not planned or premeditated, typically associated with an angry affect, and the aim is immediate or proximal, rather than goal-directed or in pursuit of something of value (Fanning et al. 2019). Moreover, severe aggression can exist as a separate pathological entity, rather than solely as an associated feature of other major psychiatric conditions or on a continuum with aggression in healthy populations (Fanning et al. 2021). An improved neurobiological understanding of impulsive aggression may allow for enhanced diagnosis, treatment, and early intervention of vulnerable populations.

A critical role of the serotonin (5-hydroxytryptamine or 5-HT) system in impulsive aggression has been consistently suggested by genetic, developmental, pharmacological, and brain imaging studies (Coccaro et al. 2015). Presynaptic elements of the 5-HTergic system have received a great deal of focus, including enzymes mediating 5-HT synthesis (Perez-Rodriguez et al. 2010) and degradation (Godar et al. 2016); autoreceptor regulation of synaptic 5-HT release, e.g., 5-HT1A (Audero et al. 2013) and 5-HT1B receptors (Olivier and van Oorschot 2005); and synaptic reuptake by the 5-HT transporter (5-HTT) (Hallikainen et al. 1999).

Characterizing 5-HTT in impulsive aggression offers a number of advantages. First, it regulates 5-HT specifically, as opposed to monoamine oxidase-A (MAO-A), of which norepinephrine and dopamine are also substrates. Second, it is localized to presynaptic 5-HTergic neurons, as opposed to 5-HT autoreceptors, which can also be expressed post-synaptically and by non-5-HTergic neurons (Aggarwal and Mortensen 2017). Finally, 5-HTT is the substrate for fluoxetine, which has been examined as an anti-aggression treatment in patients with intermittent explosive disorder (IED) (Coccaro et al. 2009), personality disorders (Coccaro and Kavoussi 1997; Silva et al. 2007), and intimate partner abusers (Lee et al. 2008). Therefore, examining the 5-HTT and its association with treatment response to fluoxetine should advance our understanding of the neurobiology of impulsive aggression, and may aid in identifying biomarkers of treatment responsivity.

In the present study, we used PET imaging with [^{11}C] DASB to examine 5-HTT availability in personality disordered patients with current physical IED. Our primary goals were to replicate our previous finding of an association between 5-HTT availability in the anterior cingulate cortex (ACC) and trait levels of impulsive aggression (van de Giessen et al. 2014); to examine the association between 5-HTT regional availability and state aggression; and to identify neural targets of fluoxetine in mitigating state aggression. To accomplish this, we recruited a sample of actively, physically aggressive IED patients. Further, we used correlates of reactive and proactive aggression, as these two subtypes may have contrasting relations with the 5-HT system (Montoya et al. 2012). Three comparison regions that have been extensively implicated in impulsive aggression were also examined: the amygdala (AMY) (New et al. 2009), ventral striatum (VST) (Chester et al. 2018; Perez-Rodriguez et al. 2012), and midbrain (MID) (Rylands et al. 2012).

Materials and methods

Human subjects

The study was approved by the Institutional Review Boards of the New York State Psychiatric Institute, Columbia University Medical Center, Mount Sinai Hospital, the Bronx Veterans Affairs Medical Center, and Yale University

Medical Center. Written informed consent was obtained from each research participant after explanation of study procedures. Participants were recruited through advertisements in local newspapers and the internet. All participants underwent a medical clearance, consisting of a medical history, physical exam, basic blood and urine tests, and electrocardiogram. Study exclusion criteria for all participants included significant medical/neurological problems, psychotropic medication, or other medications with significant central nervous system effects, and pregnant or nursing.

Eighteen participants (15 males, 3 females, mean age = 40.54 [SD = 11.37, range = 18–53]) met criteria for at least one DSM-IV personality disorder and current DSM-IV IED with current physical aggression. Current physical aggression was designated if patients met IED criterion A2: three episodes of physical assault against other people or destruction of property over the past year. The Structured Clinical Interview for DSM-IV Axis I Disorders (First et al. 2002) and the Structured Interview for DSM-IV Personality Disorders (Pfohl and Zimmerman 1997) were used to assess syndromal ("Axis I") and personality disorder ("Axis II") diagnoses, respectively. Inclusion in the study also required patients with physical IED to have two consecutive 1-week scores of at least 15 on the assaultiveness subscale of the Overt Aggression Scale-Modified (OAS-M) (Coccaro 2020), in order to identify "actively aggressive" patients.

Exclusion criteria for IED patients included the following: a current major depressive episode; a history of psychotic disorder or bipolar I disorder; or current/recent (within the past 3 months) alcohol or substance abuse/dependence. Patients were also excluded for histories of serious past alcohol/substance abuse/dependence which may have led to long-standing neurochemical sequelae, namely delirium tremens or medically complicated alcohol withdrawal, significant methylene dioxymethamphetamine use, intravenous drug use, or chronic/persistent cocaine dependence.

Psychiatric diagnoses of IED patients are summarized in Table S4. Just over two-thirds of IED patients (13 of 18) met full criteria for either borderline (BPD), paranoid (PPD), or antisocial personality disorder (ASPD). Comorbidity among BPD, PPD, and ASPD was highly common, with six patients meeting criteria for all three.

Four other personality disorders—avoidant (AvPD), schizotypal (SPD), narcissistic (NPD), and obsessive–compulsive (OCPD)—were also common in our IED sample, but they were predominantly comorbid with BPD, ASPD, or PPD, except for one patient who met criteria only for AvPD. Four IED patients met criteria for DSM-IV personality disorder not otherwise specified (PDNOS); however, two of these patients also had subdiagnostic-threshold levels of BPD, ASPD, or PPD traits. Three patients had a history of past major depressive disorder; and seven had past alcohol/substance abuse.

Patients with IED completed self-report measures of trait aggression (Buss-Perry Aggression Questionnaire or BPAQ) (Buss and Perry 1992); childhood trauma (Childhood Trauma Questionnaire or CTQ) (Bernstein et al. 1994), pathological personality trait dimensions (Dimensional Assessment of Pathological Personality or DAPP) (Pukrop et al. 2009). There was no statistical difference between scores on these clinical measures among IED patients who received a PET scan at Columbia compared to Yale (Table S1).

Healthy comparison participants ($n = 11$, 6 males, 5 females, mean age = 34.40 [SD = 8.50, range = 24–56]) had no current DSM-IV Axis I or II psychiatric disorder, no past DSM-IV psychotic, mood, substance use, or personality disorder, and no first-degree relative with a history of schizophrenia, bipolar disorder, major depression, or Axis II disorder.

The difference in mean age between the HC group (M = 34.4, SD = 8.50, $n = 11$) and IED patients (M = 40.5, SD = 11.4, $n = 18$) did not reach statistical significance ($p = 0.135$). Nevertheless, we examined group differences with and without age as a covariate. The difference in the male:female ratio between the control (6:5) and IED (15:3) groups reached the level of a statistical trend ($X^2 = 2.83$, $p = 0.09$); thus, we examined group differences with and without gender as a covariate. Location of PET imaging was well balanced between groups, with no statistically significant difference ($X^2 = 0.03$, $p = 0.87$).

Fluoxetine trial

The 18 IED patients in the present study represent a subgroup from a larger cohort that participated in a placebo-controlled trial of fluoxetine 20 mg daily. This subgroup received a [^{11}C]DASB PET scan in order to identify predictors of response to fluoxetine. Of these 18 IED patients, 3 did not enter the clinical trial after PET scan, and the 15 that did complete the trial. Of these 15 IED patients, 9 received fluoxetine and 6 received placebo. Our study took place between 8/1/2008–12/1/2015, which is before the National Institutes of Health's policy requirement (January 18, 2017) for the registering of clinical trials. Therefore, this study does not have a clinical trial registration number.

Patients with physical IED were randomized in a double-blind manner to receive daily placebo or 20 mg of fluoxetine. A 4-to-1 fluoxetine-placebo ratio was used. Of note, all patients, regardless of condition assignment, initially received placebo in a single-blind manner for three weeks in order to rule out placebo-responders. After the placebo lead-in, patients either continued on placebo or were switched to fluoxetine 20 mg (according to randomization by the study pharmacy) and treated for 12 weeks. Patients were evaluated weekly by a study psychiatrist, and by a study psychologist or trained staff member

supervised by our study psychologist; weekly evaluations included the OAS-M, which was used to assess impulsive aggression that occurred over the preceding week.

In a previous study, we found the Global Anger/Aggression subscale of the OAS-M, which assesses weekly aggressive behavior using a Likert-scale, exhibited a significant correlation with our 5-HTergic radioligand, whereas the Overt Aggression subscale, which tallies specific aggressive acts in a severity-weighted manner, did not (Rosell et al. 2010). Therefore, we used the Global Anger/Aggression OAS-M subscale as our primary measure of state aggression when examining correlations with [^{11}C]DASB BP_{ND}. Baseline state aggression did not differ significantly between IED patients who received a PET scan at Columbia compared to Yale (Table S1). The change in OAS-M score was calculated using the difference between the mean of the first 3 weeks during the placebo lead in, and the mean of the last 4 weeks of the trial.

PET methods

All PET data were acquired on HR + scanners (Siemens, Knoxville TN) at Columbia University and Yale University medical centers. A venous catheter was placed in an antecubital vein for tracer injection. Following a 10-min transmission scan for attenuation correction, [^{11}C]DASB was administered as a slow bolus (2 min at Columbia and 1 min at Yale). Emission data were collected for 100 min, binned into a sequence of frames of increasing duration from 20 s to 10 min. A high-resolution T1-weighted anatomical magnetic resonance image (MRI) was also collected for each subject on a GE scanner. Regions of interest (ROIs) were drawn manually on each subject's structural MRI according to our previous criteria (Abi-Dargham et al. 2000; Mawlawi et al. 2001). The ROIs consisted of the ACC, VST, amygdala, and midbrain. PET data were corrected for individual frame motion and coregistered to the MRIs using a maximization of mutual information algorithm, implemented in SPM8 software (Friston et al. 1995). ROIs were transferred to the coregistered PET to generate time activity curves. The simplified reference tissue model (SRTM) (Lammertsma and Hume 1996) with cerebellum as reference tissue (excluding the vermis) was applied to obtain the outcome measure BP_{ND}, the binding potential relative to the non-displaceable compartment (Innis et al. 2007) in each ROI. For group comparisons, we also verified results with a graphical analysis (Logan et al. 1996). Data from both PET sites were analyzed through a common analysis pipeline.

Data analysis and statistics

One-way ANOVAs, adjusting for covariates, were used to examine between-group differences. Pearson product-moment correlations, or Spearman rank coefficients for non-normally distributed variables, were employed to examine bivariate correlations; and partial correlation was used in order to adjust for the influence of a third variable. When there was concern for confounding and/or suppressor variables, multiple linear regression was used to examine relationships between clinical variables and binding potential measures. Bonferroni corrections for the four ROIs were performed for each test.

Results

Group differences in 5-HTT availability

As seen in Table 1, injected mass of radiotracer was significantly greater in the HC group. All mass doses were within the tracer dose range, however, and would have had a non-detectably small effect on measured BP_{ND}. Although [^{11}C]DASB BP_{ND} was numerically greater in the four ROIs (ACC, MID, AMY, VST) in IED patients compared to the HC group, none of these differences reached statistical significance (Table 2). Covarying for age or gender did not change the findings. No group differences in BP_{ND} were observed with graphical analysis (data not shown).

Associations between 5-HTT availability and trait aggression

Trait aggression

As we have previously done, we used the sum of the verbal and physical aggression subscales of the Buss-Perry Aggression Questionnaire (BPAQ-Verb/Phys) as our measure of trait aggression (van de Giessen et al. 2014). The

Table 1 Study participant characteristics: age, sex, PET scan location, and scan parameters

	HC ($n = 11$) Mean (SD)	IED ($n = 18$) Mean (SD)	p value
Age	34.4 (8.50)	40.5 (11.4)	0.14
Sex (M:F)	6:5	15:3	0.09
Scan location (C:Y)	4:7	6:12	0.87
Injected dose (MBq)	492.43 (93.81)	440.98 (132.09)	0.27
Injected mass (μg)	5.28 (3.47)	2.23 (2.19)	0.007

C Columbia, *F* female, *HC* healthy comparison group, *IED* intermittent explosive disorder group, *M* male, *Y* Yale

Table 2 Group comparisons of regional [^{11}C]DASB BP_{ND}

Region	**HC (*n* = 11)** Mean (SD)	**IED (*n* = 18)** Mean (SD)	*p* value*	% Difference	Cohen's *d*
ACC	0.43 (0.29)	0.68 (0.46)	0.08	58	0.65
AMY	0.97 (0.24)	1.34 (0.83)	0.16	38	0.61
VST	1.25 (0.18)	1.34 (0.36)	0.47	7.2	0.32
MID	1.82 (0.32)	2.26 (1.14)	0.23	24	0.53

ACC anterior cingulate cortex, *AMY* amygdala, *HC* healthy comparison group, *IED* intermittent explosive disorder group, *MID* midbrain, *VST* ventral striatum

*p values shown are for comparisons without any covariates, and are not corrected for multiple comparisons. Group differences were also not significant when covarying for age or PET scan location

rationale was to specifically measure aggressive behaviors, as opposed to hostile/paranoid interpretive biases and angry affect, which are assessed by the other two subscales of the BPAQ. There were no significant differences in regional BP_{ND} between IED patients scanned at the two different PET sites (Table S2).

We performed bivariate correlations between BPAQ-Verb/Phys and [^{11}C]DASB BP_{ND} in the ACC and our three comparison ROIs (MID, AMY, VST). As [^{11}C]DASB values for the ACC, MID, and AMY were not normally distributed, Spearman's rho (r_s) was used. Three IED patients did not complete clinical assessments, and could not be included in the correlation analyses.

We found significant correlations between BPAQ-Verb/Phys and [^{11}C]DASB BP_{ND} in the ACC ($r_s = 0.64$, $p = 0.01$, uncorrected) and VST ($r = 0.68$, $p = 0.005$, uncorrected) (Fig. 1). These correlations survived Bonferroni correction for multiple comparisons ($p < 0.0125$). Correlations between BPAQ-Verb/Phys scores and [^{11}C]DASB BP_{ND} in the MID and AMY reached the level of a statistical trend prior to correcting for multiple comparisons.

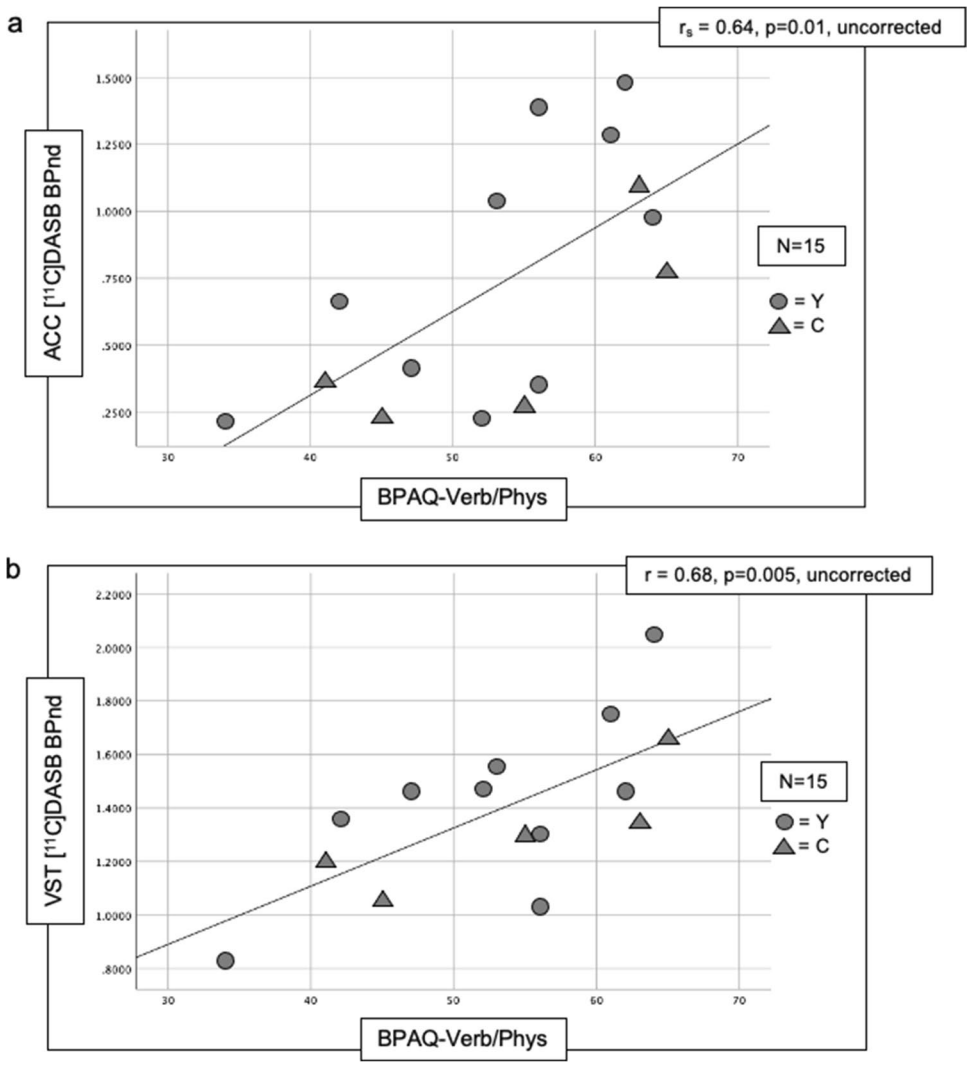

Fig. 1 Significant associations of ACC and VST 5-HTT availability with Trait Aggression in IED patients [^{11}C]DASB BP_{ND} in the ACC (**a**) and VST (**b**) were significantly correlated with trait aggression as measured with the BPAQ-Verb/Phys. Both correlations survived Bonferroni correction ($p < 0.0125$). No covariates were included. Circles and triangles represent IED patients scanned at Yale (Y) and Columbia (C), respectively

Similar to what has been previously reported (James et al. 2017), there were significant positive inter-regional correlations of [^{11}C]DASB BP_{ND} in our cohort of IED patients and HC participants (data not shown). These inter-regional correlations could potentially confound or suppress relationships between [^{11}C]DASB BP_{ND} in a particular ROI and the BPAQ-Verb/Phys. Therefore, in order to clarify the independent contributions of these four brain regions to trait aggression, we performed a multiple linear regression with BPAQ-Verb/Phys as the dependent variable, and [^{11}C]DASB BP_{ND} in the ACC, MID, AMY, and VST as the predictor variables.

The overall model for the linear regression was significant [$F(4,10) = 4.55$, $p = 0.024$]. Similar to the results of the bivariate correlations reported above, only ACC ($\beta = 0.472$, $p = 0.049$) and VST ($\beta = 0.560$, $p = 0.034$) [^{11}C]DASB BP_{ND} were significant predictors of BPAQ-Verb/Phys. Neither MID nor AMY [^{11}C]DASB BP_{ND} were significant predictors of BPAQ-Verb/Phys scores.

Trait aggression: resolving reactive and proactive variants

While the BPAQ does not differentiate between reactive and proactive aggression subtypes, we have previously found that covarying for clinical dimensions specifically related to either reactive or proactive aggression can help resolve the relationship between 5-HTT availability and BPAQ-Verb/Phys (van de Giessen et al. 2014). Therefore, we compared multiple linear regression models of BPAQ-Verb/Phys predicting ACC [^{11}C]DASB BP_{ND} with and without measures related to reactive and proactive aggression subtypes, viz., childhood trauma and callous traits, respectively (Kolla et al. 2013).

Since four IED participants were missing DAPP-callousness and CTQ scores, we repeated the previously described linear regression with the smaller ($n = 11$) sample to confirm the result before introducing the callousness and CTQ variables. Similar to what we described above with the bivariate correlation between trait aggression and ACC [^{11}C]DASB BP_{ND} in the full cohort, BPAQ-Verb/Phys, alone, was a significant predictor of ACC [^{11}C]DASB BP_{ND} ($\beta = 0.707$, $p = 0.015$) in the smaller cohort. After adding DAPP-callousness and CTQ as covariates, the regression model remained statistically significant [$F(3,7) = 5.29$, $p = 0.032$]. The variance explained by the model including DAPP-callousness and CTQ (adjusted R square = 0.563) was greater than the model with only BPAQ-Verb/Phys (adjusted R square = 0.444).

The predictive value of BPAQ-Verb/Phys on ACC [^{11}C]DASB BP_{ND}, in the first model ($\beta = 0.707$, $p = 0.015$), was enhanced ($\beta = 0.987$, $p = 0.005$) in the model that included DAPP-callousness and CTQ. In contrast to BPAQ-Verb/Phys, DAPP-callousness appeared to be a negative predictor of ACC [^{11}C]DASB BP_{ND}, albeit, at the level of a statistical trend ($\beta = -0.891$, $p = 0.083$). Total CTQ scores appeared to positively predict ACC [^{11}C]DASB BP_{ND}; however, this beta coefficient did not reach statistical significance ($\beta = 0.590$, $p = 0.194$). Finally, a model including only DAPP-callousness and CTQ, but not BPAQ-Verb/Phys, was not statistically significant. These findings highlight potential contrasting 5-HTergic abnormalities between subtypes of impulsive aggression, as well as collinear clinical dimensions. Similar results were found when predicting [^{11}C]DASB BP_{ND} in the VST.

Associations between 5-HTT availability and state aggression

Next, we evaluated whether 5-HTT availability in our ROIs was related to state levels of impulsive aggression in patients with IED. Bivariate correlations between [^{11}C]DASB BP_{ND} in our four ROIs with the baseline OAS-M Global Anger/Aggression scale revealed a significant positive correlation in the ACC ($r_s = 0.724$, $p = 0.002$, uncorrected) (Fig. 2). A similar correlation was found between the Assaultiveness subscale of the baseline OAS-M and ACC [^{11}C]DASB BP_{ND} ($r_s = 0.514$, $p = 0.05$, uncorrected). As we described in the "Methods" section, the Global Anger/Aggression subscale is our primary measure of state aggression.

In order to account for possible statistical suppressor effects between the ROIs, we performed a multiple linear regression with baseline OAS-M Global Anger/Aggression as the dependent variable, and [^{11}C]DASB binding in our four ROIs as predictor variables. The overall model for the linear regression was significant [$F(4,10) = 7.02$, $p = 0.006$]. Consistent with the bivariate correlations, ACC [^{11}C]DASB BP_{ND} was a significant predictor of state

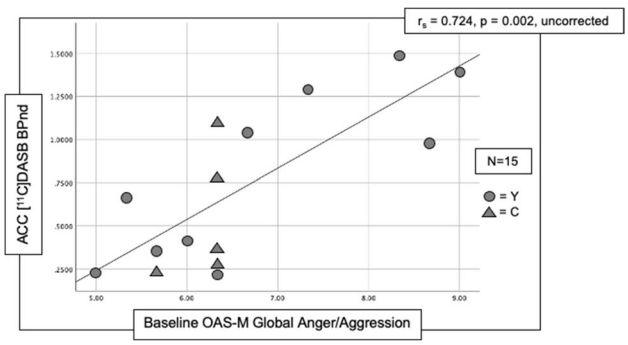

Fig. 2 Significant association of ACC 5-HTT availability with baseline state aggression in IED patients [^{11}C]DASB BPnd in the ACC was significantly correlated with baseline state aggression as measured with the Global Anger/Aggression subscale of the OAS-M. The correlation survived Bonferroni correction ($p < 0.0125$). Circles and triangles represent IED patients scanned at Yale (Y) and Columbia (C), respectively

aggression (β = 0.823, $p = 0.001$). Notably, amygdala [^{11}C]DASB BP_{ND} was a significant *negative* predictor of OAS-M Global Anger/Aggression (β = −0.828, $p = 0.047$), which was an effect not detected using bivariate correlations. This likely was due to a statistical suppressor effect, as amygdala [^{11}C]DASB BP_{ND} was positively correlated with ACC [^{11}C]DASB (data not shown).

As ACC [^{11}C]DASB binding was positively associated with measures of both trait and state aggression, we sought to determine whether these represented two independent effects. Bivariate correlations between BPAQ-Verb/Phys and baseline OAS-M Global Anger/Aggression scores suggested that these two variables were not completely independent ($r_s = 0.509$, $p = 0.053$). Therefore, we performed partial correlations of ACC BP_{ND} and BPAQ-Verb/Phys, while covarying for baseline OAS-M Global Anger/Aggression; and conversely, ACC BP_{ND} and OAS-M Global Anger/Aggression, while covarying for BPAQ-Verb/Phys.

Covarying for BPAQ-Verb/Phys did not abrogate the correlation between ACC BP_{ND} and baseline OAS-M Global Anger/Aggression ($r = 0.690$, $p = 0.006$). Likewise, when covarying for baseline OAS-M Global Anger/Aggression, the correlation between ACC BP_{ND} and BPAQ-Verb/Phys persisted, albeit at the level of a statistical trend ($r = 0.489$, $p = 0.076$). Therefore, ACC [^{11}C]DASB BP_{ND} was independently, positively associated with our measures of trait and state aggression.

Associations between baseline 5-HTT availability and change in state aggression with fluoxetine treatment

We were interested in determining whether baseline 5-HTT availability in any of our four ROIs predicted the change in state aggression in IED patients after 12 weeks of treatment with fluoxetine. Therefore, we performed bivariate correlations between [^{11}C]DASB binding in our four ROIs and the difference in OAS-M Global Anger/Aggression scores before and after fluoxetine treatment.

We observed a significant negative correlation between baseline VST [^{11}C]DASB BP_{ND} and the difference in OAS-M Global Anger/Aggression in IED patients ($n = 9$) before and after treatment with fluoxetine ($r = -0.815$, $p = 0.007$, uncorrected) (Fig. 3). That is, greater VST 5-HTT availability at baseline was associated with greater improvement (i.e., decrease) in state aggression with fluoxetine treatment.

Including aggressive patients treated with placebo ($n = 6$) weakened the bivariate correlation between VST [^{11}C]DASB BP_{ND} and the change in OAS-M Global Anger/Aggression ($r = -0.40$, $p = 0.15$), consistent with the relationship between baseline VST 5-HTT availability and change in state aggression after 12 weeks being dependent on fluoxetine treatment. However, studies with a larger placebo group will ultimately be necessary to confirm this. The fluoxetine- and placebo-treated IED groups were similarly matched in terms of demographics, scan location, and scanning parameters (Table S3).

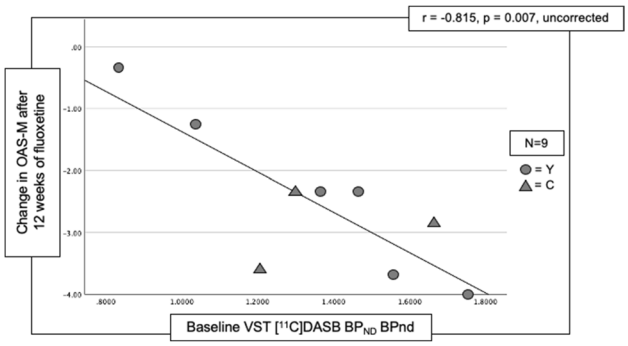

Fig. 3 Baseline VST 5-HTT availability in IED patients predicts decrease in state aggression with fluoxetine treatment [^{11}C]DASB BPnd in the VST was significantly correlated with the change in state aggression, as measured with the Global Anger/Aggression subscale of the OAS-M, after 12 weeks of fluoxetine 20 mg daily in IED participants. The correlation survived Bonferroni correction ($p < 0.0125$). Circles and triangles represent IED patients scanned at Yale (Y) and Columbia (C), respectively

Discussion

The findings of the present study are consistent with reports from our group and others that implicate the ACC as a critical region within which the 5-HTergic system is involved in severe impulsive aggression (Frankle et al. 2005; Sekine et al. 2006; van de Giessen et al. 2014). Nevertheless, there are important areas of divergence between studies that need to be addressed.

Similar to the present findings, our prior study found no group differences between patients with physical IED and healthy controls in 5-HTT binding in the ACC (van de Giessen et al. 2014). However, the first study from our group (Frankle et al. 2005) demonstrated reduced ACC 5-HTT availability (using [^{11}C]McN 5652) in a group of IED patients compared to healthy controls. Along similar lines, Rylands et al. reported lower 5-HTT availability (using [^{11}C]DASB) in the cerebral cortex as a whole in participants with high- compared to low-trait aggression (Rylands et al. 2012). However, their cortical subregion analysis did not demonstrate 5-HTT availability group differences, possibly due to lack of statistical power; further, they did not examine the ACC, specifically.

We believe that these inconsistencies between studies may be related to differential levels of reactive and proactive aggression subtypes among the aggressive patients across

these studies. Reactive and proactive forms of impulsive aggression are highly collinear (Brugman et al. 2017; Lobbestael et al. 2013; Smeets et al. 2017) but exhibit divergent characteristics: the former is associated with an aversive affect (e.g., anger), in response to a (real or perceived) provocation, and the rudimentary motive of retaliation. On the other hand, the proactive subtype is typically self-initiated, with a positive or appetitive affect, and a goal of obtaining social dominance, status or something of value (Runions et al. 2018). Further, reactive aggression is associated with impulsivity, emotional reactivity, and childhood trauma; whereas psychopathy and callousness are uniquely related to proactive aggression (Kolla et al. 2013; Raine et al. 2006).

There is growing evidence that these two impulsive aggression subtypes (and their associated dimensions) manifest contrasting relationships with the 5-HTergic system (Dolan and Anderson 2003; Montoya et al. 2012) and other functional parameters (Lozier et al. 2014). It has been hypothesized that susceptibility to impulsive aggression in general (i.e., total trait impulsive aggression) may be due to disturbances in testosterone and cortisol levels; and hypo- and hyper-serotonergic states may be responsible for the degree to which impulsive aggression manifests as reactive and proactive forms, respectively (Montoya et al. 2012).

Thus, the co-occurrence of reactive and proactive subtypes could have statistical suppressor effects on indices of the 5-HT system if the two forms are not disaggregated. This is consistent with our observation that including callousness and childhood trauma as covariates enhances the relationship between ACC 5-HTT availability and trait aggression.

We suspect that the samples of impulsive aggressive patients in our current study and the one by Van Giessen et al. may have had a greater ratio of proactive-to-reactive aggression than the studies by Frankle et al. and Rylands et al. The former two required the presence of physical IED, and physical aggression is specifically predictive of proactive aggression (Cima et al. 2013). A diagnosis of verbal IED was sufficient in Frankle et al., and in Rylands et al. participants with high levels of callous-unemotional (CU) traits were excluded from both the low- and high-aggression groups, owing to concerns that CU traits may have a contrasting relation with 5-HTT than impulsive aggression. Therefore, cohorts with predominantly reactive forms of aggression may evince group differences in ACC/cortical 5-HTT binding compared to healthy control groups; but aggressive cohorts with high levels of both proactive and reactive aggression may not.

An important difference between the current study and Van Giessen et al. should be noted with respect to the relationship between ACC 5-HTT binding, trait aggression, and trait callousness. In the current study, a significant positive bivariate correlation between trait aggression and ACC 5-HTT binding was observed, and it was enhanced when covarying for callousness. When added to the model, callousness negatively predicted ACC 5-HTT (at the level of a statistical trend).

In van de Giessen et al., on the other hand, trait aggression was negatively correlated with ACC 5-HTT binding (at the level of a statistical trend) only while covarying for trait callousness, and callousness was positively correlated with ACC 5-HTT binding without the need for covariates (van de Giessen et al. 2014). Of note, we did not examine childhood trauma in our previous study. Thus, in both studies, a complex relationship between trait aggression, trait callousness, and ACC 5-HTT binding was identified, but the directionality of these relationships and the suppressed variable were contrasting.

We believe these differences reflect the varying types of 5-HTergic disturbances that contribute to impulsive aggression (Rosell and Siever 2015). There are numerous examples in the literature suggesting that there is not a simple, linear relationship between risk for impulsive aggression and presynaptic 5-HT synthesis and turnover: both low- and high-expressing 5-HTT polymorphisms that confer a risk for impulsive aggression have been described (Aluja et al. 2009; Davidge et al. 2004; Fiskerstrand et al. 1999; Hallikainen et al. 1999; Hemmings et al. 2018; MacKenzie and Quinn 1999). Complicating matters further, studies have found that the combination of the short 5-HTTLPR (low expression) and the 12-repeat VNTR intron 2 (high expression) allele confers aggression risk (Aluja et al. 2009; Cherepkova et al. 2018; Garcia et al. 2010). Absent/inhibited 5-HT reuptake during mouse development can either lead to attenuated aggression, such as in 5-HTT "knock-out" mice (Holmes et al. 2002), or elevated aggression, as in mice treated postnatally with fluoxetine (Kiryanova and Dyck 2014).

From the positive association between VST 5-HTT and trait aggression, alone, it is difficult to interpret whether 5-HTT is acting as a direct, pathogenic contributor to trait aggression, or rather, if it reflects a compensatory mechanism. However, the fact that elevated VST 5-HTT also predicts response to fluoxetine suggests that greater VST 5-HTT may directly promote trait aggression, as blocking a compensatory process, presumably, would not mitigate aggression.

Therefore, we suspect that elevated VST 5-HTT may contribute to trait aggression in patients with IED by reducing synaptic 5-HT. A hypo-serotonergic state in the VST may promote a lower threshold for experiencing provocation in social/interpersonal contexts (Crockett et al. 2013) and favor selecting immediately rewarding (Tanaka et al. 2007), retaliatory responses, as opposed to more delayed, adaptive ones.

The VST is involved in reward processing and motivation (Daniel and Pollmann 2014; Haber and McFarland 1999). Therefore, it is functionally poised to be involved in the provocation of aggressive behavior owing to absence of social rewards (e.g., social rejection or frustrative

nonreward), as well as the hedonic or rewarding aspects of aggression (Chester and DeWall 2016; Chester et al. 2018). The 5-HTergic system in the striatum functions in part by presynaptic modulation of dopaminergic activity; however, the precise effects differ depending on 5-HT receptor subtype (Navailles and De Deurwaerdere 2011).

Few studies have examined 5-HTergic abnormalities in the striatum in relation to aggression. In a study of violent offenders, 5-HT1B receptor availability was positively correlated with trait anger and psychopathy (namely, self-centered impulsivity) in the caudate (e.g., dorsal striatum), but not the nucleus accumbens (e.g., ventral striatum). No correlations between 5-HT1B receptors and anger or psychopathy were observed in healthy controls, however, suggesting this relationship reflects a pathophysiologic process (da Cunha-Bang et al. 2017).

In addition to differences in molecular target (5-HTT vs 5-HT1B receptor), our study differs from da Cunha-Bang et al. with respect to population and clinical measures: our study consisted of patients from the community whose acts of physical aggression against others typically were not more severe than a simple assault. In contrast, the violent cohort in the da Cunha-Bang study were recruited from a forensic population and had been convicted of serious crimes such as murder and rape. We also focused on aggression, which is related to but distinct from the anger and psychopathy constructs.

There are important limitations of this study. The sample size was relatively small; two PET imaging sites were used; and the study would have benefited from a more substantial placebo group. Assessing trait aggression in the HC group would have allowed us to address whether these relationships were specific to IED or common across groups. Further, we did not take into account past medication exposure (particularly agents that act on the 5-HTergic system). Future studies would benefit from controlling for 5-HTT polymorphisms, which may resolve inconsistencies across studies.

Conclusion

Our study provides further evidence for the role of the ACC as a region within which the 5-HTergic system may contribute to trait levels of severe impulsive aggression in patients. This study also calls attention to the role of the VST in trait aggression, as well as a role for ACC 5-HTT availability in state levels of aggression. Preliminary evidence suggests that responsivity to the anti-aggressive effects of fluoxetine may be directly related to 5-HTT availability in the VST. The importance of considering factors associated with reactive and proactive aggression to refine associations between ACC 5-HTT and trait aggression was also further supported. Strengths of this study consist of examining severe, pathological impulsive aggression in a sample of individuals selected for current physical aggression, using a standard, diagnostic clinical construct. This is the first study to examine a biomarker of anti-aggressive treatment responsivity to fluoxetine.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00213-022-06306-2.

Acknowledgements The authors declare no financial conflict of interest. This research was supported by Grant RO1MH063875 from the National Institute of Mental Health to Larry J. Siever and subsequently to Harold W. Koenigsberg. This publication was made possible by Grant Number MO1-RR-00071 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH).

The authors would like to thank Lauren Brickman, Cameryn Cooley, Samuel Fels, Hayley Galitzer, Nabila Hoque, Maria Martin Lopez, Jacqueline Trumbull, and Lauren Zaluda for their technical assistance on this project.

Declarations

Conflict of interest Research reported in this publication was supported by the National Institute of Mental Health of the National Institutes of Health under Award Number R01 MH063875. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors declare no financial conflict of interest. Dr Rosell receives a royalty from UpToDate. Dr Slifstein has consulted for Curasen Therapeutics and Neurocrine Inc., and has stock options in Storm Bioscience. Dr. Thompson has received research support from diaMentis for a project unrelated to this work. Dr. Perez-Rodriguez has received research grant funding from Neurocrine Biosciences (Inc.), Millennium Pharmaceuticals, Takeda, Merck, and AI Cure for projects unrelated to this work. She is an Advisory Board member for Neurocrine Biosciences, Inc., and a consultant on an American Foundation for Suicide Prevention (AFSP) grant (LSRG-1–005-16, PI: Baca-Garcia). She is part of the research networks "CIBERSAM" (https://www.cibersam.es/en), "WORECA" (World Research Consortium forSuicide), MEMind Working Group, and the Borderline Personality Disorder International Genetics Consortium. Dr. Hazlett is supported by a VA CSR&D Research Career Scientist Award (1 IK6 CX001738). Dr. Abi-Dargham received consulting fees and/or honoraria from Sunovion, Otsuka, Merck, Neurocrine and Intracellular Therapies. She holds stock options in Systems 1 Bio and in Terran Biosciences. Dr. Koenigsberg has received research grant funding from NIMH grants R01 MH 109730, R61 MH125130 and R01 MH123069. He receives salary support from James J Peters Veterans Affairs Medical Center.

References

Abi-Dargham A, Martinez D, Mawlawi O, Simpson N, Hwang DR, Slifstein M, Anjilvel S, Pidcock J, Guo NN, Lombardo I, Mann JJ, Van Heertum R, Foged C, Halldin C, Laruelle M (2000) Measurement of striatal and extrastriatal dopamine D-1 receptor binding potential with [C-11]NNC 112 in humans: validation and reproducibility. J Cerebr Blood F Met 20:225–243

Aggarwal S, Mortensen OV (2017) Overview of monoamine transporters. Curr Protoc Pharmacol 79:12 16 1-12 16 17

Aluja A, Garcia LF, Blanch A, De Lorenzo D, Fibla J (2009) Impulsive-disinhibited personality and serotonin transporter gene

polymorphisms: association study in an inmate's sample. J Psychiatr Res 43:906–914
Audero E, Mlinar B, Baccini G, Skachokova ZK, Corradetti R, Gross C (2013) Suppression of serotonin neuron firing increases aggression in mice. J Neurosci 33:8678–8688
Bernstein DP, Fink L, Handelsman L, Foote J, Lovejoy M, Wenzel K, Sapareto E, Ruggiero J (1994) Initial reliability and validity of a new retrospective measure of child abuse and neglect. Am J Psychiatry 151:1132–1136
Brugman S, Cornet LJ, Smeijers D, Smeets K, Oostermeijer S, Buitelaar JK, Verkes RJ, Lobbestael J, de Kogel CH, Jansen LM (2017) Examining the reactive proactive questionnaire in adults in forensic and non-forensic settings: A variable- and person-based approach. Aggress Behav 43:155–162
Buss AH, Perry M (1992) The aggression questionnaire. J Pers Soc Psychol 63:452–459
Cerda M, Tracy M, Keyes KM (2018) Reducing urban violence: a contrast of public health and criminal justice approaches. Epidemiology 29:142–150
Cherepkova EV, Maksimov VV, Aftanas LI (2018) Polymorphism of serotonin transporter gene in male subjects with antisocial behavior and MMA fighters. Transl Psychiatry 8:248
Chester DS, DeWall CN (2016) The pleasure of revenge: retaliatory aggression arises from a neural imbalance toward reward. Soc Cogn Affect Neurosci 11:1173–1182
Chester DS, Lynam DR, Milich R, DeWall CN (2018) Neural mechanisms of the rejection-aggression link. Soc Cogn Affect Neurosci 13:501–512
Cima M, Raine A, Meesters C, Popma A (2013) Validation of the Dutch Reactive Proactive Questionnaire (RPQ): differential correlates of reactive and proactive aggression from childhood to adulthood. Aggress Behav 39:99–113
Coccaro EF (2020) The Overt Aggression Scale Modified (OAS-M) for clinical trials targeting impulsive aggression and intermittent explosive disorder: validity, reliability, and correlates. J Psychiatr Res 124:50–57
Coccaro EF, Kavoussi RJ (1997) Fluoxetine and impulsive aggressive behavior in personality-disordered subjects. Arch Gen Psychiatry 54:1081–1088
Coccaro EF, Lee RJ, Kavoussi RJ (2009) A double-blind, randomized, placebo-controlled trial of fluoxetine in patients with intermittent explosive disorder. J Clin Psychiatry 70:653–662
Coccaro EF, Fanning JR, Phan KL, Lee R (2015) Serotonin and impulsive aggression. CNS Spectr 20:295–302
Crockett MJ, Apergis-Schoute A, Herrmann B, Lieberman MD, Muller U, Robbins TW, Clark L (2013) Serotonin modulates striatal responses to fairness and retaliation in humans. J Neurosci 33:3505–3513
da Cunha-Bang S, Hjordt LV, Perfalk E, Beliveau V, Bock C, Lehel S, Thomsen C, Sestoft D, Svarer C, Knudsen GM (2017) Serotonin 1B receptor binding is associated with trait anger and level of psychopathy in violent offenders. Biol Psychiatry 82:267–274
Daniel R, Pollmann S (2014) A universal role of the ventral striatum in reward-based learning: evidence from human studies. Neurobiol Learn Mem 114:90–100
Davidge KM, Atkinson L, Douglas L, Lee V, Shapiro S, Kennedy JL, Beitchman JH (2004) Association of the serotonin transporter and 5HT1Dbeta receptor genes with extreme, persistent and pervasive aggressive behaviour in children. Psychiatr Genet 14:143–146
Dolan MC, Anderson IM (2003) The relationship between serotonergic function and the Psychopathy Checklist: Screening Version. J Psychopharmacol 17:216–222
Fanning JR, Coleman M, Lee R, Coccaro EF (2019) Subtypes of aggression in intermittent explosive disorder. J Psychiatr Res 109:164–172
Fanning JR, Marcus DK, Preszler JR, Coccaro EF (2021) Evidence for the taxonic latent structure for DSM-5 intermittent explosive disorder in adults. Psychol Med 51:54–61
First MB, Spitzer RL, Gibbon M, Williams JBW (2002) Structured clinical interview for DSM-IV-TR axis I disorders, research version, patient edition. (SCID-I/P) Biometrics Research. New York State Psychiatric Institute, New York
Fiskerstrand CE, Lovejoy EA, Quinn JP (1999) An intronic polymorphic domain often associated with susceptibility to affective disorders has allele dependent differential enhancer activity in embryonic stem cells. FEBS Lett 458:171–174
Frankle WG, Lombardo I, New AS, Goodman M, Talbot PS, Huang Y, Hwang DR, Slifstein M, Curry S, Abi-Dargham A, Laruelle M, Siever LJ (2005) Brain serotonin transporter distribution in subjects with impulsive aggressivity: a positron emission study with [11C]McN 5652. Am J Psychiatry 162:915–923
Friston KJ, Holmes AP, Worsley KJ, Poline J-P, Frith CD, Frakowiak RSJ (1995) Statistical parametric maps in functional imaging: a general linear approach. Hum Brain Mapping 2:189–210
Garcia LF, Aluja A, Fibla J, Cuevas L, Garcia O (2010) Incremental effect for antisocial personality disorder genetic risk combining 5-HTTLPR and 5-HTTVNTR polymorphisms. Psychiatry Res 177:161–166
Godar SC, Fite PJ, McFarlin KM, Bortolato M (2016) The role of monoamine oxidase A in aggression: current translational developments and future challenges. Prog Neuropsychopharmacol Biol Psychiatry 69:90–100
Haber SN, McFarland NR (1999) The concept of the ventral striatum in nonhuman primates. Ann N Y Acad Sci 877:33–48
Hallikainen T, Saito T, Lachman HM, Volavka J, Pohjalainen T, Ryynanen OP, Kauhanen J, Syvalahti E, Hietala J, Tiihonen J (1999) Association between low activity serotonin transporter promoter genotype and early onset alcoholism with habitual impulsive violent behavior. Mol Psychiatry 4:385–388
Hemmings SMJ, Xulu K, Sommer J, Hinsberger M, Malan-Muller S, Tromp G, Elbert T, Weierstall R, Seedat S (2018) Appetitive and reactive aggression are differentially associated with the STin2 genetic variant in the serotonin transporter gene. Sci Rep 8:6714
Holmes A, Murphy DL, Crawley JN (2002) Reduced aggression in mice lacking the serotonin transporter. Psychopharmacology 161:160–167
Innis RB, Cunningham VJ, Delforge J, Fujita M, Gjedde A, Gunn RN, Holden J, Houle S, Huang SC, Ichise M, Iida H, Ito H, Kimura Y, Koeppe RA, Knudsen GM, Knuuti J, Lammertsma AA, Laruelle M, Logan J, Maguire RP, Mintun MA, Morris ED, Parsey R, Price JC, Slifstein M, Sossi V, Suhara T, Votaw JR, Wong DF, Carson RE (2007) Consensus nomenclature for in vivo imaging of reversibly binding radioligands. J Cereb Blood Flow Metab 27:1533–1539
James GM, Baldinger-Melich P, Philippe C, Kranz GS, Vanicek T, Hahn A, Gryglewski G, Hienert M, Spies M, Traub-Weidinger T, Mitterhauser M, Wadsak W, Hacker M, Kasper S, Lanzenberger R (2017) Effects of selective serotonin reuptake inhibitors on interregional relation of serotonin transporter availability in major depression. Front Hum Neurosci 11:48
Kiryanova V, Dyck RH (2014) Increased aggression, improved spatial memory, and reduced anxiety-like behaviour in adult male mice exposed to fluoxetine early in life. Dev Neurosci 36:396–408
Kolla NJ, Malcolm C, Attard S, Arenovich T, Blackwood N, Hodgins S (2013) Childhood maltreatment and aggressive behaviour in violent offenders with psychopathy. Can J Psychiatry 58:487–494
Lammertsma AA, Hume SP (1996) Simplified reference tissue model for PET receptor studies. Neuroimage 4:153–158
Lee R, Kavoussi RJ, Coccaro EF (2008) Placebo-controlled, randomized trial of fluoxetine in the treatment of aggression in male intimate partner abusers. Int Clin Psychopharmacol 23:337–341

Lobbestael J, Cima M, Arntz A (2013) The relationship between adult reactive and proactive aggression, hostile interpretation bias, and antisocial personality disorder. J Pers Disord 27:53–66

Logan J, Fowler JS, Volkow ND, Wang GJ, Ding YS, Alexoff DL (1996) Distribution volume ratios without blood sampling from graphical analysis of PET data. J Cereb Blood Flow Metab 16:834–840

Lozier LM, Cardinale EM, VanMeter JW, Marsh AA (2014) Mediation of the relationship between callous-unemotional traits and proactive aggression by amygdala response to fear among children with conduct problems. JAMA Psychiat 71:627–636

MacKenzie A, Quinn J (1999) A serotonin transporter gene intron 2 polymorphic region, correlated with affective disorders, has allele-dependent differential enhancer-like properties in the mouse embryo. Proc Natl Acad Sci U S A 96:15251–15255

Mawlawi O, Martinez D, Slifstein M, Broft A, Chatterjee R, Hwang DR, Huang YY, Simpson N, Ngo K, Van Heertum R, Laruelle M (2001) Imaging human mesolimbic dopamine transmission with positron emission tomography: I. Accuracy and precision of D-2 receptor parameter measurements in ventral striatum. J Cerebr Blood F Met 21:1034–1057

Montoya ER, Terburg D, Bos PA, van Honk J (2012) Testosterone, cortisol, and serotonin as key regulators of social aggression: a review and theoretical perspective. Motiv Emot 36:65–73

Navailles S, De Deurwaerdere P (2011) Presynaptic control of serotonin on striatal dopamine function. Psychopharmacology 213:213–242

New AS, Hazlett EA, Newmark RE, Zhang J, Triebwasser J, Meyerson D, Lazarus S, Trisdorfer R, Goldstein KE, Goodman M, Koenigsberg HW, Flory JD, Siever LJ, Buchsbaum MS (2009) Laboratory induced aggression: a positron emission tomography study of aggressive individuals with borderline personality disorder. Biol Psychiatry 66:1107–1114

Olivier B, van Oorschot R (2005) 5-HT1B receptors and aggression: a review. Eur J Pharmacol 526:207–217

Perez-Rodriguez MM, Weinstein S, New AS, Bevilacqua L, Yuan Q, Zhou Z, Hodgkinson C, Goodman M, Koenigsberg HW, Goldman D, Siever LJ (2010) Tryptophan-hydroxylase 2 haplotype association with borderline personality disorder and aggression in a sample of patients with personality disorders and healthy controls. J Psychiatr Res 44:1075–1081

Perez-Rodriguez MM, Hazlett EA, Rich EL, Ripoll LH, Weiner DM, Spence N, Goodman M, Koenigsberg HW, Siever LJ, New AS (2012) Striatal activity in borderline personality disorder with comorbid intermittent explosive disorder: sex differences. J Psychiatr Res 46:797–804

Pfohl BB, N; Zimmerman, M. (1997) Structured Interview for DSM-IV Personality (SIDP-IV). American Psychiatric Association

Pukrop R, Steinbring I, Gentil I, Schulte C, Larstone R, Livesley JW (2009) Clinical validity of the "Dimensional Assessment of Personality Pathology (DAPP)" for psychiatric patients with and without a personality disorder diagnosis. J Pers Disord 23:572–586

Raine A, Dodge K, Loeber R, Gatzke-Kopp L, Lynam D, Reynolds C, Stouthamer-Loeber M, Liu J (2006) The reactive-proactive aggression questionnaire: differential correlates of reactive and proactive aggression in adolescent boys. Aggress Behav 32:159–171

Rosell DR, Siever LJ (2015) The neurobiology of aggression and violence. CNS Spectr 20:254–279

Rosell DR, Thompson JL, Slifstein M, Xu X, Frankle WG, New AS, Goodman M, Weinstein SR, Laruelle M, Abi-Dargham A, Siever LJ (2010) Increased serotonin 2A receptor availability in the orbitofrontal cortex of physically aggressive personality disordered patients. Biol Psychiatry 67:1154–1162

Runions KC, Salmivalli C, Shaw T, Burns S, Cross D (2018) Beyond the reactive-proactive dichotomy: rage, revenge, reward, and recreational aggression predict early high school bully and bully/victim status. Aggress Behav 44:501–511

Rylands AJ, Hinz R, Jones M, Holmes SE, Feldmann M, Brown G, McMahon AW, Talbot PS (2012) Pre- and postsynaptic serotonergic differences in males with extreme levels of impulsive aggression without callous unemotional traits: a positron emission tomography study using (11)C-DASB and (11)C-MDL100907. Biol Psychiatry 72:1004–1011

Rynar L, Coccaro EF (2018) Psychosocial impairment in DSM-5 intermittent explosive disorder. Psychiatry Res 264:91–95

Sekine Y, Ouchi Y, Takei N, Yoshikawa E, Nakamura K, Futatsubashi M, Okada H, Minabe Y, Suzuki K, Iwata Y, Tsuchiya KJ, Tsukada H, Iyo M, Mori N (2006) Brain serotonin transporter density and aggression in abstinent methamphetamine abusers. Arch Gen Psychiatry 63:90–100

Silva H, Iturra P, Solari A, Villarroel J, Jerez S, Vielma W, Montes C, Pumarino L, Roa N (2007) Serotonin transporter polymorphism and fluoxetine effect on impulsiveness and aggression in borderline personality disorder. Actas Esp Psiquiatr 35:387–392

Smeets KC, Oostermeijer S, Lappenschaar M, Cohn M, van der Meer JM, Popma A, Jansen LM, Rommelse NN, Scheepers FE, Buitelaar JK (2017) Are proactive and reactive aggression meaningful distinctions in adolescents? A variable- and person-based approach. J Abnorm Child Psychol 45:1–14

Tanaka SC, Schweighofer N, Asahi S, Shishida K, Okamoto Y, Yamawaki S, Doya K (2007) Serotonin differentially regulates short- and long-term prediction of rewards in the ventral and dorsal striatum. PLoS ONE 2:e1333

van de Giessen E, Rosell DR, Thompson JL, Xu X, Girgis RR, Ehrlich Y, Slifstein M, Abi-Dargham A, Siever LJ (2014) Serotonin transporter availability in impulsive aggressive personality disordered patients: a PET study with [11C]DASB. J Psychiatr Res 58:147–154

Terms and Conditions

Springer Nature journal content, brought to you courtesy of Springer Nature Customer Service Center GmbH (“Springer Nature”).
Springer Nature supports a reasonable amount of sharing of research papers by authors, subscribers and authorised users (“Users”), for small-scale personal, non-commercial use provided that all copyright, trade and service marks and other proprietary notices are maintained. By accessing, sharing, receiving or otherwise using the Springer Nature journal content you agree to these terms of use (“Terms”). For these purposes, Springer Nature considers academic use (by researchers and students) to be non-commercial.
These Terms are supplementary and will apply in addition to any applicable website terms and conditions, a relevant site licence or a personal subscription. These Terms will prevail over any conflict or ambiguity with regards to the relevant terms, a site licence or a personal subscription (to the extent of the conflict or ambiguity only). For Creative Commons-licensed articles, the terms of the Creative Commons license used will apply.
We collect and use personal data to provide access to the Springer Nature journal content. We may also use these personal data internally within ResearchGate and Springer Nature and as agreed share it, in an anonymised way, for purposes of tracking, analysis and reporting. We will not otherwise disclose your personal data outside the ResearchGate or the Springer Nature group of companies unless we have your permission as detailed in the Privacy Policy.
While Users may use the Springer Nature journal content for small scale, personal non-commercial use, it is important to note that Users may not:

1. use such content for the purpose of providing other users with access on a regular or large scale basis or as a means to circumvent access control;
2. use such content where to do so would be considered a criminal or statutory offence in any jurisdiction, or gives rise to civil liability, or is otherwise unlawful;
3. falsely or misleadingly imply or suggest endorsement, approval , sponsorship, or association unless explicitly agreed to by Springer Nature in writing;
4. use bots or other automated methods to access the content or redirect messages
5. override any security feature or exclusionary protocol; or
6. share the content in order to create substitute for Springer Nature products or services or a systematic database of Springer Nature journal content.

In line with the restriction against commercial use, Springer Nature does not permit the creation of a product or service that creates revenue, royalties, rent or income from our content or its inclusion as part of a paid for service or for other commercial gain. Springer Nature journal content cannot be used for inter-library loans and librarians may not upload Springer Nature journal content on a large scale into their, or any other, institutional repository.
These terms of use are reviewed regularly and may be amended at any time. Springer Nature is not obligated to publish any information or content on this website and may remove it or features or functionality at our sole discretion, at any time with or without notice. Springer Nature may revoke this licence to you at any time and remove access to any copies of the Springer Nature journal content which have been saved.
To the fullest extent permitted by law, Springer Nature makes no warranties, representations or guarantees to Users, either express or implied with respect to the Springer nature journal content and all parties disclaim and waive any implied warranties or warranties imposed by law, including merchantability or fitness for any particular purpose.
Please note that these rights do not automatically extend to content, data or other material published by Springer Nature that may be licensed from third parties.
If you would like to use or distribute our Springer Nature journal content to a wider audience or on a regular basis or in any other manner not expressly permitted by these Terms, please contact Springer Nature at

onlineservice@springernature.com