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

Elsmarieke van de Giessen [a, b], Daniel R. Rosell [c, d], Judy L. Thompson [a, b], Xiaoyan Xu [a, b], Ragy R. Girgis [a, b], Yosefa Ehrlich [c, d], Mark Slifstein [a, b], Anissa Abi-Dargham [a, b], Larry J. Siever [c, d, *]

[a] Department of Psychiatry, Columbia University College of Physicians and Surgeons, New York, USA
[b] New York State Psychiatric Institute, New York, USA
[c] James J. Peters Department of Veterans Affairs Medical Center, Bronx, New York, USA
[d] Department of Psychiatry, Mount Sinai School of Medicine, New York, USA

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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.

* Corresponding author. James J. Peters Department of Veterans Affairs Medical Center, 130 West Kingsbridge Road, Room 6A–44, Bronx, New York 10468. Tel.: +1 718 584 9000x5227/5225; fax: +1 718 364 3576.
E-mail addresses: larry.siever@va.gov, larry.siever@mssm.edu (L.J. Siever).

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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