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ORIGINAL INVESTIGATION

Acute tryptophan depletion and self-injurious behavior in aggressive patients and healthy volunteers

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Abstract
Rationale An association between serotonin (5-HT) activity and self-injurious (i.e., self-aggressive) behavior across the spectrum of lethality (from self-mutilation through completed suicide) is a well-replicated finding. Studies to date, however, have relied on nonexperimental designs to examine this relationship, limiting the causal inferences that can be drawn about the role of 5-HT in self-aggressive behavior.
Objective Examine the effect of experimentally altered 5-HT activity (via dietary tryptophan depletion) on self-aggressive behavior among adults with and without intermittent explosive disorder (IED). Individuals with a marked history of aggression, such as those with IED, are characterized by compromised 5-HT and heightened risk for self-aggression, making this a population of interest for examining the proposed relations.
Materials and methods IED patients ($n=16$) and healthy controls ($n=16$) received a tryptophan depletion and a placebo drink on separate days at least 1 week apart. Self-aggressive behavior was assessed on both study days using a well-validated laboratory-based behavioral assessment with self-aggression defined as the intensity of shock self-administered.
Results Tryptophan depletion facilitated selection of more intense shocks, on average, in both groups. Patients with IED were also more self-aggressive overall than healthy volunteers. No IED by drink condition interactions were found.
Conclusion Experimentally lowered 5-HT bioavailability enhances overall self-injurious behavior irrespective of aggression history.

Keywords Self-aggression · Serotonin · Tryptophan depletion · Intermittent explosive disorder

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Introduction

Self-aggression (i.e., suicidal and self-injurious behavior) is a growing public health concern (Favazza 1998; Gunnell et al. 2000). Nonfatal deliberate acts of self-harm have been shown to be a reliable predictor for later suicide (Comtois 2002), which is one of the leading causes of death among 15- to 34-year-olds (CDC 2005). Estimates of lifetime self-injurious behavior are as high as 35% (Gratz 2001) with repeated acts of self-injury occurring in approximately 4% of nonclinical samples (Briere and Gil 1998). Within clinical populations, the incidence of self-aggressive behavior is often much greater, particularly among psychiatric populations characterized by affective dysregulation and other-directed aggressive behavior (Kidd and Carroll 2007; Kisiel and Lyons 2001; Zlotnick et al. 1999).

Self- and other-directed aggression are considered separate but overlapping constructs. History of lifetime aggression and impulsivity are known risk factors for self-aggression and suicidal behavior (Favazza 1998; Mann et al. 1999), and clinically aggressive psychiatric populations, such as individuals with borderline personality disorder or

intermittent explosive disorder (IED), are more likely to engage in self-aggressive behavior (that is, intentional self-injurious behavior) across the spectrum of lethality (Linehan et al. 1991; McCloskey et al. 2008a; Yen et al. 2004). Both self-and other-directed aggression may be, in part, mediated by serotonergic dysfunction, which may be responsible for a general tendency to engage in impulsive behaviors that have the potential for harm to self or others.

Reduced central serotonin (5-HT) functioning has been associated both with a self-reported history of aggression (Coccaro and Kavoussi 1997; Goveas et al. 2004) and aggressive responding on laboratory measures of aggression (Moeller et al. 1996; Pihl et al. 1995). Experimentally, agents that putatively increase 5-HT levels, such as selective serotonin reuptake inhibitors and manipulation of dietary precursors via tryptophan enhancement, have been found to decrease aggression on both retrospective self-report and behavioral measures in clinically aggressive groups (Coccaro and Kavoussi 1997; Fava et al. 1993; Salzman et al. 1995). Reduction of 5-HT levels via acute tryptophan depletion (ATD) has been shown to produce the opposite effect with increased aggressive behavior observed, especially in individuals predisposed to aggression (Bjork et al. 2000; Bond et al. 2001; Cleare and Bond 1995; Marsh et al. 2002).

Nonexperimental research has also supported an inverse association between 5-HT functioning and intentional self-injurious behavior. For example, results of autopsy studies indicate that suicide victims to have significantly lower 5-HT levels and increased numbers of prefrontal 5-HT receptors compared to controls (Gross-Isseroff et al. 1998; Stockmeier 2003). This association is also supported by genetic studies which link suicide attempts, particularly violent ones, to theoretically meaningful 5-HT transporter gene alleles and genotypes (Joiner et al. 2002; Mann et al. 2000). Furthermore, reduced levels of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) in cerebral spinal fluid are associated with suicidal (Lester 1995) and self-injurious (Lopez-Ibor et al. 1985) behaviors, and patients with a history of self-aggression have a blunted hormonal responses to the 5-HT agonist D,L-fenfluramine (New et al. 1997).

These data suggest that, similar to other-directed aggression, self-aggression is associated with reduced 5-HT functioning. However, to date, no published study has tested the hypothesis that 5-HT is causally related to self-aggression via experimental manipulation of 5-HT activity. One reason for this is that, unlike the other-directed aggression research, which has used behavioral analogs to experimentally examine causal associations between risk factors and aggression, until recently, there has been no laboratory analog of self-aggressive behavior. With the advent of the self-aggression paradigm (SAP) (Berman and Walley 2003; McCloskey and Berman 2003), a laboratory analog of self-aggression, the causal hypothesis that reduced 5-HT increases self-aggression can now be tested.

The current study experimentally examined the effects of ATD on the self-aggressive behavior of two groups: one at a lower risk for self-aggression (healthy volunteers) and one at a heightened risk for self-aggression (patients with IED). ATD is accomplished by consuming a drink that contains a large number of neutral amino acids but lacks L-tryptophan, the substance which serves as the main precursor for 5-HT synthesis in the brain. As a result, 5-HT synthesis and, consequently, central nervous system 5-HT levels are reduced (Carpenter et al. 1998; Nishizawa et al. 1997). All participants received both an ATD drink and a pharmacologically inert balanced amino acid placebo drink which included tryptophan on separate days spaced at least 1 week apart. The order of the drink ingestion was counterbalanced and administered using double-blind procedures. Approximately 5 h after drink administration, self-aggressive behavior was assessed using the SAP. It was hypothesized that ATD would be associated with higher self-aggression compared to the placebo balanced amino acid drink in both groups with a greater effect of 5-HT depletion on self-aggression in the IED participants. It was also hypothesized that the IED participants would be more self-aggressive across drink conditions compared to healthy controls.

Materials and methods

Participants

Participants were 16 men and 16 women (age M=35.16; SD=10.19) recruited as part of ongoing research studies of personality psychopathology in the Clinical Neuroscience and Psychopharmacology Research Unit (CNPRU) at the University of Chicago. Informed consent was obtained for all participants. Participants were excluded from the present study if they reported: (a) current drug or alcohol dependence, (b) current psychotherapy or psychopharmacotherapy, (c) a history of bipolar or psychotic disorder, (d) traumatic head injury with a loss of consciousness greater than 60 min, or (e) a history of suicidal or self-injurious behavior assessed using the *Suicidal Behavior History Form* (Spitzer et al. 1978) and the *Self-Injurious Behavior History Form* (Coccaro 2008, unpublished instrument).

The participants in the sample were predominately unmarried (71.9%) and Caucasian (68.8%) or African-American (18.8%) and were relatively well-educated (87.5% had some college experience). Median family income range was $35,000–49,999. Participants were grouped based on DSM-IV diagnoses (American Psychiat-

ric Association 2000) assigned via semistructured clinical interviews: Structured Clinical Interview for DSM-IV, the Structured Interview for DSM-IV Personality, and the IED Interview (see below). The two diagnostic groups used for this study had either (a) no history of any axis I or axis II disorders (healthy volunteer [HV]) or (b) DSM-IV IED.

Measures

Structured Clinical Interview for the DSM-IV The Structured Clinical Interview for the DSM-IV (SCID; First et al. 1996) is a semistructured clinical interview used to assign diagnoses for axis I disorders. In the current study, the SCID was used to diagnose both current and past major depression (including age of onset of first depressive episode and number of lifetime episodes) as well as the other exclusionary DSM-IV axis I disorders, including schizophrenia, bipolar disorder, and substance dependence. The SCID has adequate interrater reliability with kappa values for modules ranging from 0.70 to 1.00 (First et al. 1996).

Intermittent Explosive Disorder Interview The Intermittent Explosive Disorder Interview (IED Interview; McCloskey and Coccaro 2003) is a semistructured clinical interview used to diagnose IED that obtains quantitative (e.g., frequency) and qualitative (e.g., description of most severe events) information for verbal aggression, aggression against property, and aggression against others, as well as aggression-related distress and psychosocial impairment and potential exclusionary information (i.e., aggressive acts occurring solely within the context of another axis I disorder, substance use, or a medical condition). Preliminary data by the authors show the IED Interview to be a valid and reliable instrument (McCloskey and Coccaro 2003). In the current study, all healthy control subjects reported two or less total acts of lifetime physical aggression and/or property damage.

Structured Interview for DSM-IV Personality The Structured Interview for DSM-IV Personality (SID-P; Pfohl et al. 1995) was used to assign DSM-IV axis II personality disorder diagnoses. Estimates of interrater reliability for the SID-P are reported to be adequate (Pfohl et al. 1995).

Visual analog scales The visual analog scales (VAS) is a series of 100 mm horizontal lines with anchors at each end (i.e., “not at all” and “most ever”) with one of five affect descriptors (i.e., energetic, happy, sad, anxious, irritable) over each line. The participant places a mark along the continuum that describe the extent to which they have that affect at the time of completing the form. The VAS is a commonly used, reliable, and valid measure of subjective affect (Miller and Ferris 1993).

Self-aggression paradigm The SAP (Berman and Walley 2003; McCloskey and Berman 2003) is a laboratory measure of self-aggressive behavior disguised as a competitive reaction–time task with another (fictitious) subject. During the SAP, the participant selects from a range of electric shocks (low to high) for self-administration with self-aggression defined as the level of shock chosen. Validity for the inferences that can be drawn from SAP behavior are supported by positive associations between shock intensity and self-ratings of self-aggressive disposition, along with other variables related to extralaboratory self-injurious behaviors (see (Berman et al. 2005; Berman and Walley 2003; McCloskey and Berman 2003).

Posttask questionnaire A brief posttask questionnaire was given after participants completed the SAP to assess if they accepted the social conditions of the task. This included whether participants believed the SAP was a psychomotor task rather than a self-aggression task and to what extent the drink had an effect on them (from 1=“not at all” to 8=“very much”).

Tryptophan depletion ATD and placebo drinks were administered in a randomized order across participants. The participants ingested a liquid beverage and accompanying capsules containing neutral amino acids. The liquid beverage included alanine, glycine, histidine, isoleucine, leucine, lysine, phenylalanine, proline, serine, threonine, tyrosine, valine, ±tryptophan (91.9 g total in males, 73.5 g total in females) as a chilled, 300-cc blended chocolate flavored drink. Capsules containing the remainder of neutral amino acids were swallowed in a 30-min period (methionine, cysteine, and arginine; 102.2 g in males, 82 g in females). Placebo and ATD drinks differed only in that tryptophan was included in the liquid beverage for participants in the placebo (but not ATD) condition.

Procedure

The protocol was approved by the Institutional Review Board at the University of Chicago and is in accordance with the 1964 Declaration of Helsinki ethical standards. Participants completed the clinical interview on their first visit and the SAP on the two subsequent visits (visit 2 and 3) scheduled approximately 1–2 weeks apart from each other. On visit 1, participants were interviewed using the SCID and SID-P. All diagnoses were made according to DSM-IV criteria using a best estimate procedure in which both the written diagnostic report and raw interview data were reviewed by a multidisciplinary committee of at least six research professionals, including psychiatrists and psychologists (Klein et al. 1994).

Participants were asked to abstain from using alcohol or nonprescription medication from 2 weeks prior to visit 2 until after visit 3. Participants were also given instructions to follow a low monoamine diet the day prior to these visits and not to eat or smoke after midnight on the study days. On visits 2 and 3, participants completed a urine drug test and an alcohol breathalyzer test. All participants were negative for both tests. They then completed the VAS. Participants underwent a baseline blood sample (10 cc) for plasma tryptophan level between 8:30 A.M. and 9:00 A.M. At 9:00 A.M., either a tryptophan-free (T−) or placebo drink was consumed. At 1:00 P.M., a second blood sample was obtained. At 2:00 P.M., participants completed another set of VAS scales immediately followed by the SAP and then a posttask questionnaire. A final blood sample for plasma tryptophan was drawn at 3:00 P.M. Participants who ingested the T− mixture during visit 2 received the placebo drink on visit 3, and vice versa.

Participants were prepared for the SAP by attaching fingertip electrodes to the index and middle fingers of the nondominant hand. The experimenter informed the participant that he or she would be competing in a task against another (fictitious) participant who was in an adjacent room. The experimenter then excused him or herself "to prepare the other subject" for the experiment.

After a short delay, an upper shock pain threshold was determined by administering increasingly intense shocks until the participant reported that the shock was "extremely unpleasant." To increase the credibility of the experimental situation, this procedure was repeated with the other "subject" (an audiotape of a same-sex confederate) and overheard by the participant. Mean (SD) milliampere threshold current for the entire sample was 0.93 (0.65).

After the threshold determination, task instructions were provided via intercom to both "subjects," indicating that the purpose of the task was to see which subject could lift a finger off a reaction–time key fastest. Before each reaction–time trial, each subject selected a shock from *0* through *10* or *20* by pressing one of 12 buttons on the bottom of the console. The slower person on each trial received the shock level they chose for herself or himself before that trial. The *10* shock was equivalent to the shock level judged extremely unpleasant. The *9* shock was set at 95% of this maximum, *8* at 90%, and so forth. A *20* shock would administer a "severe" shock, twice the intensity of the *10* shock (in actuality, a *20* delivered a shock the intensity of *10*). Participants were also told that if they selected a *0*, no shock would be administered, reflecting a nonself-aggressive response option.

The participant then completed a series of 28 reaction–time trials. The participant lost (received his or her chosen shock) on half the trials with the frequency of wins and losses preprogrammed by the experimenter. After each trial, the participant received feedback as to what the fictitious subject set for themselves on that trial via 12 LED lights labeled, from left to right, *0* to *10* and *20*, respectively, at the top of the panel. The 28 trials consist of an initial trial, followed by four blocks of six trials with a single transition trial following each block, except the last. The blocks varied as to the average level of shock the fictitious subject selected, averaging 2.5, 5.5, and 8.5 for blocks 1 through 3, respectively. Block 4 was identical to that of block 3, except the other "subject" chose a "severe" shock (*20*) before (trial 21) and during (trial 24) block 4. The change in shock settings is to facilitate self-aggressive responding via self-aggressive cues (self-aggressive modeling), consistent with research on the effect of behavioral modeling on self-aggression (Berman and Walley 2003; McCloskey and Berman 2003). The lights following trials 7 and 14 were of intermediate intensity (*4* and *7*, respectively) to smooth the transitions between blocks. Immediately after completing the SAP, the participant completed the VAS a second time.

Results

Preliminary analyses

Serum tryptophan A 2 (drink: ATD vs. placebo)×3 (time) repeated-measures analysis of variance (ANOVA) revealed a significant effect of drink [$F(1, 29)=370.33$, $p<0.001$, $\eta^2=0.92$] and time [$F(2, 58)=298.40$, $p<0.001$, $\eta^2=0.91$] that was limited by a drink×time interaction [$F(2, 58)=372.06$, $p<0.001$, $\eta^2=0.93$]. Simple effects analyses revealed that tryptophan levels did not differ at baseline (predrink) between ATD and placebo days [$F(1, 58)=2.06$, $p=0.16$]. However, participants consuming ATD had lower levels of plasma tryptophan at 4 h [$F(1, 58)=1{,}016.38$, $p<0.001$] and 6 h [$F(1, 58)=1{,}028.17$, $p<0.001$] postdrink (see Table 1). Tryptophan levels dropped 88% postdrink in the ATD condition compared to only 18% postdrink tryptophan reduction in the placebo condition. Visual inspection of the data showed that one subject was not tryptophan-depleted after consuming the ATD drink (ATD levels at time 1:00 P.M. and 3:00 P.M. were 44 and 43, respectively; all other subjects on ATD visit were ≤23). This participant was excluded from further data analysis.

Table 1 Mean (SD) tryptophan levels as a function of drug and time

Visit	Time		
	Baseline (9:00 a.m.)	1:00 P.M.	3:00 P.M.
ATD	55.36 (11.77)	8.28 (4.44)	10.80 (4.88)
Placebo	53.26 (10.76)	43.72 (8.30)	46.20 (7.89)

ATD acute tryptophan depletion

In terms of side effects, eight participants reported some nausea after consuming the placebo drink, while five subjects reported nausea after consuming the ATD drink. Four subjects in both drink conditions reported getting a headache. However, participants reported that both the ATD (M=2.11 SD=2.06) and placebo drinks (M=2.52 SD=2.13) had an equally modest effect on them t<1. Thus, the participants were not able to distinguish the drug and placebo drinks.

Cover task Three (two IED and one HV) of the remaining 31 participants reported not believing the cover task, that is, they reported on the posttask questionnaire that the SAP involved self-aggression. These cases were removed from subsequent analyses, leaving a sample of 28 subjects (15 HV, 13 IED).

Psychopathology Amongst the 13 subjects in the IED group, 11 (85%) of the subjects had a personality disorder with PD NOS as the most frequent PD diagnosis (n=7).

Demographic variables IED and HV groups did not differ in age, $t(26)<1$; gender composition, $\chi^2(1)<1$; ethnicity, $\chi^2(1)<1$; education level, $\chi^2(2)=2.15$, $p=0.15$; or marital status, $\chi^2(2)=1.25$, $p=0.26$, (see Table 2 for means and percentages).

Shock threshold Across the sample, the upper shock threshold was 1.05 mA (SD=0.59 mA). Upper shock threshold did not vary as a function of drink [$F(1, 26)<1$], group [$F(1, 26)=2.61$, $p=0.12$], or their interaction [$F(1, 26)<1$].

Table 2 Demographic variables as a function of diagnostic group

Variable	Condition		
	HV (n=15)	IED (n=13)	Total
Age (SD)	36.07 (9.99)	33.92 (10.53)	35.07 (10.11)
Gender, *n* (%)			
Male	8 (53.3)	7 (53.8)	15 (53.6)
Female	7 (46.7)	6 (46.2)	13 (46.4)
Race, *n* (%)			
Caucasian	11 (73.3)	8 (61.5)	19 (67.8)
AA/other	4 (26.7)	5 (38.5)	9 (32.2)
Education, *n* (%)			
−College grad	4 (26.6)	7 (53.8)	11 (60.7)
+College grad	11(73.4)	6 (46.2)	17 (39.3)
Married, *n* (%)			
Single/divorced	13 (86.6)	9 (69.2)	22 (78.5)
Married	2 (23.4)	4 (30.8)	6 (21.5)

HV healthy volunteer, *IED* intermittent explosive disorder, *AA* African-American

Self-aggression: SAP shock selections

To control for the number of statistical comparisons associated with the primary ANOVAs, the Benjamini-Hochberg false discovery correction (FD) was used for the analyses of mean and extreme self-shock. Self-aggressive behavior was defined as the intensity of shock self-administered. Two indices of self-aggression were examined: (a) average shock and (b) use of the extreme shock (i.e., "20"). To calculate average shock, 20 shocks were first recoded as 11. This ensures that group means are not unduly influenced by data outliers or skew (McCloskey and Berman 2003).

Mean shock selection A 2 (diagnostic group: IED vs. HV)×2 (drink: ATD vs. placebo)×4 (self-aggressive model) mixed-model ANCOVA was conducted on mean self-selected shock with drink order (ATD first vs. placebo first) as the covariate. Order was a significant covariate, $F(1, 25)=4.51$, $p_{FD}<0.05$ with participants becoming more self-aggressive with repeated exposure to the SAP. Therefore, the means presented in Figs. 1 and 2 were adjusted for order. Results showed a significant effect of drink, $F(1, 25)=8.84$, $p_{FD}<0.01$, $\eta^2=0.26$ with participants selecting a higher mean self-shock after consuming the ATD drink compared to the placebo drink (Fig. 1). There was also a significant effect for diagnostic group, $F(1, 25)=5.57$, $p_{FD}=0.05$, $\eta^2=0.19$ with IED subjects selecting higher self-shocks than healthy volunteers (Fig. 2). The drink by group interaction was not significant ($F<1$). There was no main effect of model ($F<1$), nor were there any significant self-aggressive model interactions (all Fs<1).

Extreme (20) shock selection A 2 (diagnostic group: IED vs. HV)×2 (drink: ATD vs. placebo)×2×4 (self-aggressive

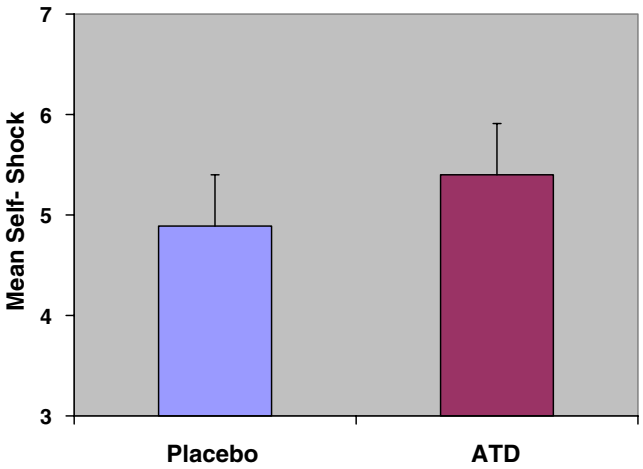

Fig. 1 Mean (SEM) self-shock a function of ATD

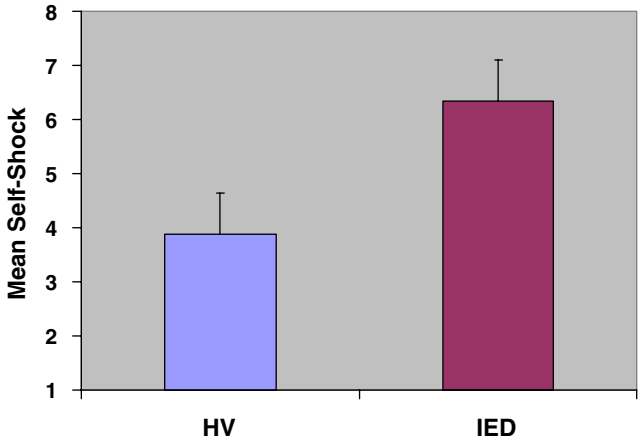

Fig. 2 Mean (SEM) self-shock for healthy volunteers (*HV*) and patients with IED

model) mixed-model ANCOVA for the number of extreme (20) self-shocks revealed no significant main effects or interactions (all *p*s>0.25). There was also no effect of order ($F<1$). Subjects did not select significantly more extreme self-shocks after consuming the ATD drink ($M=2.50$, SD=6.50) than after consuming the placebo drink ($M=2.21$, SD=2.24), nor did IED subjects ($M=3.31$, SD=7.46) select more extreme self-shocks than healthy volunteers ($M=1.00$, SD=3.41).

Mood

To assess the effects of tryptophan depletion and diagnostic group on mood during the SAP, 2 (drink)×2 (time: baseline vs. pre-SAP)×2 (group) multivariate analysis of variance was performed for the five VAS items.[1] There was a multivariate trend for time [Wilks $F(5, 20)=2.36$, $p<0.08$]. No other multivariate main effects or interaction approached significance (all *p*s>0.10).Follow-up ANOVAs revealed a significant effect of time for feeling energetic [$F(1, 24)=7.05$, $p<0.05$, $\eta^2=0.23$]. Participants were more energetic at baseline ($M=35.57$, SD=21.98) than they were 5 h later when they completed the SAP ($M=28.33$, SD=21.09). No other univariate time effects were significant (all *p*s>0.10).

Discussion

The purpose of this study was to experimentally examine the effects of ATD on self-aggressive behavior using a sample of participants at high risk (IED subjects) and low risk (healthy volunteers) of self-aggression. We hypothesized that ATD and IED status would each be associated with greater self-aggression. We further posited that the effect of ATD on self-aggression would be greatest for IED participants. Our findings provided partial support for the hypotheses that ATD would facilitate self-aggression and that IED subjects would be more self-aggressive overall. However, ATD did not exert a greater effect on self-aggression in IED subjects.

We found that, after consuming the ATD drink, participants self-administered higher mean shocks on the SAP compared to the placebo drink. This is consistent with previous correlational studies linking suicidal and self-injurious behavior with indices of decreased serotonergic bioavailability such as increased 5-HT_{2A} receptor binding in the prefrontal cortex (Arango et al. 1990; Arora and Meltzer 1989) and dorsal raphe (Boldrini et al. 2005) and decreased levels of 5-HIAA in the cerebrospinal fluid (Brown et al. 1982; Roy-Byrne et al. 1983; Traskman et al. 1981). Our study extends these findings by showing that acute decreases in 5-HT can facilitate self-aggression, even among individuals without any history of self-aggression. There are multiple mechanisms through which this may occur. Decreased 5-HT is associated with increased negative emotions, most notably sadness and anger, which in turn are associated with self-aggressive acts (Brown et al. 2002; Nock and Prinstein 2004). However, in the present study, subjects reported no significant increases in negative affect (e.g., sadness, anger, anxiety). ATD has also been shown to increase impulsivity (LeMarquand et al. 1999; Walderhaug et al. 2002). Increased self-aggression in the current study may be a function of increased impulsivity in a task combined with the explicit opportunity to self-aggress. Impulsivity was not directly assessed in the current study, but pilot research by the authors found self-aggression on the SAP to be positively correlated with behavioral measures of impulsivity. Future research will need to test the potential mediating role of impulsivity in the relationship between ATD and self-aggression.

Individuals with IED selected a higher mean self-shock than control subjects independent of ATD. This occurred despite neither group reporting any history of previous self-aggression. Previous research has shown aggression (Keilp et al. 2006) and specifically IED (McCloskey et al. 2008a) is associated with self-aggression. Our results extend these findings by suggesting that, even among patients without a demonstrated history of self-aggression, IED may be associated with higher baseline propensity for self-aggression. This may be related to a biological predisposition, environmental factors, or an interaction between the two. As stated, individuals with IED have 5-HT dysregulation which may increase the diatheses for self-

[1] Complete VAS data was available from 26 (15 control and 11 IED) of the 28 subjects who completed the SAP. The two remaining subjects failed to complete the VAS for at least one time point.

aggression (Coccaro 2003). Individuals with IED also have increased exposure to pain, which may make self-aggression a more viable response (Joiner 2005). Finally, IED is often comorbid with disorders that increase their risk of self-aggression (e.g., depressive disorders, borderline personality disorders).

Despite their effect on mean self-shock, neither ATD nor presence of IED had a significant impact on extreme self-aggression (i.e., 20 shock). Furthermore, the large majority of both groups (>75%) did not self-select a 20 shock in either drink condition. Remember, a 20 shock was a level believed to be twice the pain threshold and thus the closest proxy to self-injurious behavior. The finding that IED subjects did not select more extreme shocks supports the validity of the SAP as a measure of self-directed aggression separate from behavioral measures of other-directed aggression on which IED subjects consistently select far more extreme shocks for their opponent than subjects in comparison groups (McCloskey et al. 2006, 2008b). The lack of an ATD effect on extreme self-shock suggests that acute 5-HT depletion is not sufficient to lead to actual self-injurious behavior among individuals who are not otherwise predisposed to engage in the behavior. Studies of other-directed aggression have found that ATD has a mild effect on aggression across subjects, but exerts its greatest effect among who are already hostile and aggressive (Cleare and Bond 1995). Similarly, ATD appears to have a mild facilitatory effect on self-aggression, but may only elicit behavior that approximate self-injury among individuals who actually engage in intentional self-harm. An obvious extension of the current study is to examine the effect of ATD on self-aggression among self-injurers.

Contrary to our hypothesis, ATD did not have a differential effect on self-aggression across groups, facilitating mean, but not extreme self-shock in both IED and control subjects. Thus, the relationship between acute 5-HT depletion and SAP responding among individuals who are not otherwise predisposed to self-harm was not moderated by IED. However, this should not be interpreted as suggesting that IED or aggression itself is not associated with increased vulnerability to self-aggression in the context of ATD. Furthermore, it is possible that, by including only IED subjects with no history of self-aggression, we selected an atypically "mild" IED sample with less severe preexisting 5-HT deficits.

Replication of this finding using a larger sample, including individuals with and without a life history of self-injurious behaviors, are needed confirm or modify the observed relation between IED, tryptophan depletion, and self-aggression. With this caveat, the current findings support a limited causal regulatory role of 5-HT in self-aggression. Specifically, acute experimental depletion of the main serotonin precursor (tryptophan) is inversely related to self-aggressive behavior in healthy adults and individuals diagnosed with IED using a validated laboratory measure of self-aggression. It seems unlikely that increases in negative affect were a moderating factor in the facilitative effect of ATD on self-injurious behavior. Additional studies are required to reveal the specific conditions and boundaries of ATD and decreased central 5-HT functioning's relationship to self-aggression. Future research should, therefore, consider examining tryptophan loading procedures to evaluate whether increased availability of serotonin in the central nervous system also has an effect on participant SAP responses.

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