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Serotonin Augmentation Reduces Response to Attack in Aggressive Individuals

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Abstract

We tested the theory that central serotonin (5- hydroxytryptamine, or 5-HT) activity regulates aggression by modulating response to provocation. Eighty men and women (40 with and 40 without a history of aggression) were randomly assigned to receive either 40 mg of paroxetine (to acutely augment serotonergic activity) or a placebo, administered using double-blind procedures. Aggression was assessed during a competitive reaction time game with a fictitious opponent. Shocks were selected by the participant and opponent before each trial, with the loser on each trial receiving the shock set by the other player. Provocation was manipulated by having the opponent select increasingly intense shocks for the participant and eventually an ostensibly severe shock toward the end of the trials. Aggression was measured by the number of severe shocks set by the participant for the opponent. As predicted, aggressive responding after provocation was attenuated by augmentation of serotonin in individuals with a pronounced history of aggression.

A rich nonexperimental literature supports the notion that there is a modest but replicable inverse association between human aggressive behavior and central serotonin (5- hydroxytryptamine, or 5-HT) neurotransmitter activity (for reviews, see Berman, Tracy, & Coccaro, 1997; Moore, Scarpa, & Raine, 2002; Siever, 2008; van Goozen, Fairchild, Snoek, & Harold, 2007). For example, compared with individuals exhibiting low levels of aggression, highly aggressive individuals have lower levels of the 5-HT metabolite 5-HIAA in their cerebrospinal fluid (Moore et al., 2002) and lower 5-HT-dependent hormonal responses to serotonergic agents (Berman et al., 1997; Siever, 2008). However, the processes linking serotonin to aggression are poorly understood (Berman et al., 1997), and a causal relationship between 5-HT activity and aggression in humans has not yet been unequivocally demonstrated (Berman et al., 1997; Moore et al., 2002; van Goozen et al., 2007).

A causal role for 5-HT in aggression in lower animal species has been supported by an extensive experimental literature showing that manipulation of central 5-HT is followed by changes in aggressive behavior (see Miczek, Fish, de Bold, & de Almeida, 2002, for a review). Similarly, researchers have experimentally manipulated 5-HT in human aggression studies by (a) altering dietary precursors necessary for the manufacture of central 5-HT (Bjork, Dougherty, Moeller, Cherek, & Swann, 1999; Bjork, Dougherty, Moeller, & Swann, 2000; Bond, Wingrove, & Critchlow, 2001; Cleare & Bond, 1995; Dougherty, Bjork, Marsh, & Moeller, 1999; LeMarquand, Benkelfat, Pihl, Palmour, & Young, 1999; Marsh,

Dougherty, Moeller, Swann, & Spiga, 2002; Moeller, Dougherty, Swann, Collins, Davis, & Cherek, 1996; Pihl, Young, Harden, Plotnick, Chamberlain, & Ervin, 1995; Smith, Pihl, Young, & Ervin, 1986) or (b) administering drugs that raise 5-HT levels acutely (Cherek & Lane, 1999, 2001; Cherek, Spiga, & Creson, 1995). Aggression is then prospectively observed in the laboratory. Nonexperimental studies showing an inverse relationship between serotonin status and aggression suggest that lowering central 5-HT bioavailability should increase aggression and raising 5-HT bioavailability should diminish aggression.

Results of the human experimental studies have been mixed, with some providing support for a causal relation between serotonin activity and aggression, and others obtaining null results. However, most of these studies have not incorporated placebo controls and double-blind drug-administration procedures. The results of studies meeting these design standards are not particularly supportive of the 5-HT hypothesis of aggression. In men, acutely raising (Pihl et al., 1995; Smith et al., 1986) or lowering (LeMarquand et al., 1999; Pihl et al., 1995; Smith et al., 1986) 5-HT did not alter aggression, relative to a placebo condition. One placebo-controlled study in women, however, did find that lowering 5-HT increased aggression (Bond et al., 2001).

These equivocal findings could be due to the presence of two moderating variables: (a) provocation or attack and (b) individual differences in aggressive tendencies. Researchers have long thought that 5-HT may serve to regulate response to provocation or attack (Berman et al., 1997; Coccaro, 1989; Miczek et al., 2002). According to this perspective, reduced 5-HT does not lead people to behave in a generally aggressive manner, but rather impairs their ability to inhibit aggressive responding to provocation (Coccaro, 1989). Studies in lower animals provide support for this model, with 5-HT depletion exerting its strongest effects on aggression when threat or provocation is high (Miczek et al., 2002). Extrapolated to humans, these results suggest that individuals with intact 5-HT systems may be able to modulate their response to provocation or attack, but that individuals with a history of aggressive behavior may fail to inhibit their response to provocation because of compromised 5-HT activity (Berman et al., 1997; Coccaro, 1989). If so, acutely raising 5-HT levels should attenuate response to provocation in aggressive individuals. Laboratory tasks measuring human aggression generally include some form of provocation to elicit an aggressive response (e.g., noise or electric shock). Often, the level of provocation is held constant if it is not a variable of interest (e.g., Dougherty et al., 1999; Moeller et al., 1996). However, provocation can be manipulated by systematically increasing the level of attack by a fictitious opponent (e.g., increasing the intensity of a noxious stimulus delivered to the participant). Placebo-controlled studies in which provocation has been manipulated have failed to show a relation between altered levels of 5-HT and response to provocation in humans (Bond et al., 2001; LeMarquand et al., 1999; Pihl et al., 1995; Smith et al., 1986). In these studies, however, the highest level of provocation available has not represented a clear and unequivocal attack, so these studies provide a less than robust test of the role of provocation in 5-HT-related aggression.

Failure to consider individual differences in history of aggression may also account for the null findings (Berman et al., 1997). Aggressive individuals are more likely than nonaggressive individuals to be hyperresponsive to provocation (Bettencourt, Talley, Benjamin, & Valentine, 2006), a difference that may be due to deficits in the 5-HT system (Berman et al., 1997). For this reason, aggressive individuals may be more sensitive to experimentally altered levels of 5-HT than nonaggressive individuals are. That is, it is reasonable to propose that raising serotonin levels in aggressive individuals should lower their response to provocation.

The aim of the study reported here was to examine whether 5-HT regulates human aggression by attenuating response to provocation, and to determine whether this effect is observed predominantly in aggressive individuals. Eighty participants (42 men and 38 women), with or without a marked history of aggression, were randomly assigned to receive either 40 mg of paroxetine hydrochloride or a placebo, administered orally using double-blind procedures. Paroxetine is a selective serotonin reuptake inhibitor that has been used as a single-dose probe to stimulate presynaptic 5-HT activity (e.g., Kojima et al., 2003; Reist, Helmeste, Albers, Chhay, & Tang, 1996). We predicted that aggression in response to a highly provocative attack would be reduced in the paroxetine condition, compared with the placebo condition. We also predicted that this effect would be limited to individuals with a life history of aggression, that is, those individuals who are thought to have compromised 5-HT activity and who are hyperresponsive to provocation.

METHOD

Participants

We recruited 42 men and 38 women ($N = 80$), ages 18 through 48 years ($M = 24.33$, $SD = 7.27$), for a study on “personality and psychomotor skills.” Advertisements for the study indicated that we were looking for “healthy volunteers” and (to recruit aggressive individuals) individuals with “a short fuse who sometimes feel out of control.”

The Aggression Scale (AG) of the Life History of Aggression semistructured interview (LHA; Coccaro, Berman, & Kavoussi, 1997) was used to assess aggression history from adolescence onward. The AG consists of five items (temper outbursts, physical fighting, verbal aggression, assaults, and aggression toward objects) and has good interrater agreement (intraclass correlation = .94), internal consistency ($\alpha = .87$), and test-retest reliability ($r > .80$; Coccaro et al., 1997). Respondents with a score of 9 or higher were characterized as aggressive (+AG) on the basis of pilot data showing this that score discriminated individuals with and without clinical aggression, defined as a diagnosis of intermittent explosive disorder (IED) according to criteria of the Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision (DSM-IV-TR; American Psychiatric Association, 2000). Respondents who scored below 9 were characterized as nonaggressive (−AG). The utility of this cutoff score was supported by findings from a subset of the participants ($n = 68$) who completed a self-report screen for IED. In this subset, the participants in the +AG group had higher scores for history of damaging or destroying someone else's property ($p < .001$), history of physical violence ($p < .001$), history of injuring someone ($p < .001$), and having problems in their lives as a result of aggressive behavior ($p < .05$).

Individuals who had current major depression; who had a history of bipolar disorder, psychosis, or substance dependence; who were nursing or pregnant; or who had a medical reason not to take paroxetine were excluded. DSM-IV-TR psychiatric diagnoses were assigned using the Structured Clinical Interview for the DSM-IV (SCID; First, Gibbon, Spitzer, & Williams, 1998), which was administered by psychology doctoral students. A positive alcohol or toxicological screen (opiates, THC, methamphetamine, benzodiazepine, and cocaine) was also exclusionary. Participants were required to abstain from alcohol for 48 hr before the experimental session and to refrain from taking any medication for the 7 days leading up to the session.

The sample consisted of 40 aggressive (+AG; 26 men, 14 women) and 40 nonaggressive (−AG; 16 men, 24 women) participants. Participants identified themselves as Caucasian (73.8%), African American (20%), Hispanic (3.8%), or “other” (2.4%). Most were never married (76.3%) and had some college experience (60%). The +AG and −AG groups did not

differ significantly with respect to mean age, racial composition, or educational attainment (all p s > .18). Participants received \$10 per hour as compensation. The consent process and study procedures were approved by the Institutional Review Board for the Protection of Human Subjects at the University of Southern Mississippi.

The Taylor Aggression Paradigm

The Taylor aggression paradigm (TAP; Taylor, 1967) is a laboratory task designed to assess physical aggression. More than 40 years of research have provided evidence for the task's validity and robustness to various modifications (see Anderson & Bushman, 1997; Giancola & Chermack, 1998; McCloskey & Berman, 2003). In the TAP, the participant competes against a fictitious opponent in a reaction time game during which electric shock is administered and received. For this study, we used a version of the TAP designed to assess an unequivocal aggressive response to clear provocation (Taylor, Schmutte, Leonard, & Cranston, 1979). Specifically, we manipulated provocation by having the "opponent" select increasingly intense shock levels for the participant, eventually attempting to administer a purportedly severe shock well above the participant's shock-tolerance threshold.

Paroxetine Manipulation

Participants were randomly assigned to receive either an inert placebo (lactose) or 40 mg of paroxetine (Paxil®), administered in capsule form at 9:30 a.m. using double-blind procedures (+AG group: 20 received paroxetine and 20 received placebo; -AG group: 22 received paroxetine and 18 received placebo). Paroxetine acutely elevates central 5-HT activity (Kojima et al., 2003; Reist et al., 1996), resulting in a rapid increase in 5-HT concentration in serotonergic synapses (Schatzberg & Nemeroff, 2001).

In healthy volunteers, administration of paroxetine stimulates the hypothalamus (via central 5-HT), which in turn elevates cortisol levels after 3 to 4 hr (Kojima et al., 2003; Reist et al., 1996). It is well replicated that aggressive individuals exhibit an attenuated hormonal response to various serotonergic agents (Berman et al., 1997; Siever, 2008), but whether or not this is true for paroxetine has not yet been examined. Therefore, we assessed cortisol levels at baseline and 1, 3, and 5 hr after drug administration to determine if +AG and -AG participants differed on this biological index. Plasma cortisol was determined using a direct competitive chemiluminescent immunoassay procedure (Chiron Diagnostic ACS: 180; Bayer HealthCare LLC Diagnostic Division, New York, NY). Specimen collection and handling followed industry standards.

Procedure

Participants made two visits to the lab, scheduled 1 to 4 weeks apart. During the first visit, they completed the SCID and LHA. During the second visit, toxicological and pregnancy screening was followed by the capsule administration and then the TAP. For women, the second visit occurred during the first 10 days of the menstrual cycle (the luteal phase may be associated with greater instability in 5-HT functioning; Bond et al., 2001). Blood samples were obtained via venipuncture at baseline (just before the capsule was administered) and 1, 3 (pre-TAP), and 5 hr later. The TAP was started about 4 hr after the capsule administration, by which time significant drug-dependent changes in 5-HT functioning would be expected to occur (Kojima et al., 2003; Reist et al., 1996).

For the TAP, fingertip electrodes were attached to the index and middle fingers of the nondominant hand. The participant was then told that he or she would be competing in a task against another subject in the adjoining room. After a short delay, the participant's shock-tolerance threshold was determined by administering increasingly intense shocks, at 100- μ A intervals, until the participant reported that the shock was "very unpleasant" and that

he or she could not tolerate any further increase. To enhance the credibility of the experimental situation, we arranged for the participant to overhear an audiotape ostensibly portraying the same procedure being conducted with the fictitious other subject (a same-sex confederate).

Instructions for the reaction time task were then provided via intercom to the two competitors. Before each trial on this task, the participant (and ostensibly the opponent) pressed 1 of 12 buttons on a panel to select a shock level (0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or 20), and the person (participant or opponent) who had the slower reaction time on that trial would receive the shock set by the other person before the trial. The faster person would not receive a shock, but would see what shock level the other person had set via panel lights also labeled “0” through “10” and “20.” The 10 shock was equivalent to the tolerance-threshold current. The 9 shock was set at 95% of this maximum, the 8 shock at 90%, and so forth. The 20 shock would ostensibly administer a “severe” shock “twice the intensity” of the tolerance threshold. For the “0” response, no shock would be administered. This nonaggressive response option was included to increase the ecological validity of the task (but was rarely selected by participants).

Each participant completed 28 reaction time trials. An initial trial was followed by four 6-trial blocks of increasing provocation by the opponent. Note that the frequency of wins and losses for the participant (50%) was preprogrammed by the experimenter and computer controlled. The average shocks set by the opponent in Blocks 1, 2, 3, and 4 were 2.5, 5.5, 8.5, and 8.5, respectively. The second and third blocks were each preceded by a trial on which the opponent selected a shock of intermediate intensity (4 and 7, respectively), to smooth the transition between blocks. However, between the third and fourth blocks, the opponent selected a 20 shock (extreme provocation). The participant won this trial and therefore did not receive this shock. Aggression was measured by the number of 20 shocks the participant set for the opponent. The average number of 20 shocks set by the participant in the fourth block, after extreme provocation by the opponent, was of particular interest to test our hypothesis.

RESULTS

Aggression History

Mean LHA Aggression scores were 15.33 (SD = 3.94) for the AG+ group and 4.13 (SD = 2.56) for the -AG group. The paroxetine (M = 9.21, SD = 6.75) and placebo (M = 10.29, SD = 6.32) groups did not differ with respect to Aggression scores, $t(78) = 0.73$, $p = .47$, $p_{\text{rep}} = .52$, $d = 0.16$. Although men were overrepresented in the +AG group (65%) compared with the -AG group (40%), $\chi^2(1, N = 80) = 5.01$, $p < .05$, average aggression scores did not differ significantly between men (M = 15.38, SD = 4.02) and women (M = 15.21, SD = 3.95) in the +AG group, $t(38) = 0.13$, $p = .90$, $p_{\text{rep}} = .18$, $d = 0.04$, or between men (M = 4.69, SD = 1.78) and women (M = 3.75, SD = 2.95) in the -AG group, $t(38) = 1.14$, $p = .26$, $p_{\text{rep}} = .67$, $d = 0.37$.

Aggressive Responding

A 2 (drug condition) $\times$ 2 (aggression history) $\times$ 2 (gender) $\times$ 4 (trial block) analysis of variance (ANOVA) with trial block treated as a repeated measures factor revealed that +AG participants used the 20 shock more than 6 times more often (M = 0.50, SD = 0.94) than -AG participants (M = 0.075, SD = 0.18), $F(1, 72) = 5.10$, $p = .03$, $p_{\text{rep}} = .91$, $\eta_p^2 = .07$, and that this shock was used more frequently as provocation increased (i.e., in later trial blocks), $F(3, 228) = 9.85$, $p < .001$, $p_{\text{rep}} = .99$, $\eta_p^2 = .12$. No main or interaction effects involving gender were found.

A significant Drug Condition $\times$ Aggression History $\times$ Trial Block interaction was found, $F(3, 216) = 3.41$, $p = .02$, $p_{\text{rep}} = .93$, $\eta_p^2 = .03$ (see Fig. 1). We conducted a separate Drug Condition $\times$ Trial Block ANOVA for each aggression group to explore the three-way interaction. These analyses revealed a Drug Condition $\times$ Trial Block interaction for the +AG group, $F(3, 228) = 7.39$, $p < .001$, $p_{\text{rep}} = .99$, $\eta_p^2 = .09$, but not for the -AG group, $F(3, 228) = 0.08$, $p = .97$, $p_{\text{rep}} = .09$, $\eta_p^2 < .01$. As Figure 1 shows, -AG participants, on average, rarely chose the 20 shock in either drug condition at any level of provocation (i.e., from Block 1 through Block 4). In contrast, +AG participants who received placebo used the 20 shock after being highly provoked (i.e., in Block 4, after the opponent attacked with a 20 shock) more than 4 times as often ($M = 1.70$, $SD = 2.34$) as +AG participants who received paroxetine ($M = 0.40$, $SD = 0.75$), $F(1, 78) = 8.47$, $p < .01$, $p_{\text{rep}} = .97$, $\eta_p^2 = .10$. Moreover, in Block 4, aggressive participants who received paroxetine behaved similarly to nonaggressive participants in both drug conditions. That is, the number of 20 shocks selected in the fourth block by +AG participants who received paroxetine did not differ significantly from the number of 20 shocks selected in the fourth block by -AG participants in either the placebo ($M = 0.22$, $SD = 0.55$, $p = .68$, $p_{\text{rep}} = .37$) or the paroxetine ($M = 0.32$, $SD = 0.84$, $p = .84$, $p_{\text{rep}} = .24$) condition.

Cortisol Response to Paroxetine Challenge

Complete cortisol data were available for 76 participants (results for some participants were not available because of collection-tube breakage or spoilage). A 2 (drug condition) $\times$ 2 (aggression history) $\times$ 2 (gender) $\times$ 4 (collection time) ANOVA revealed main effects for drug condition and collection time that were qualified by a Drug Condition $\times$ Aggression History $\times$ Collection Time interaction, $F(3, 204) = 3.79$, $p = .01$, $p_{\text{rep}} = .95$, $\eta_p^2 = .053$. No main or interaction effects involving gender were found. We conducted a separate Drug Condition $\times$ Collection Time ANOVA for each aggression group to explore the three-way interaction. A Drug Condition $\times$ Collection Time interaction emerged for -AG participants, $F(3, 216) = 4.16$, $p = .01$, $p_{\text{rep}} = .96$, $\eta_p^2 = .10$, but not for +AG participants, $F(3, 216) = 0.34$, $p = .81$, $p_{\text{rep}} = .26$, $\eta_p^2 < .01$. Hence, -AG participants had the expected cortisol response to paroxetine, but +AG participants appeared to have a blunted cortisol response to paroxetine. Follow-up comparisons of means within the -AG group revealed no effect of drug condition at baseline, $F(1, 36) = 0.19$, $p = .67$, $p_{\text{rep}} = .38$, $\eta_p^2 < .01$, or at 5 hr, $F(1, 36) = 2.00$, $p = .17$, $p_{\text{rep}} = .75$, $\eta_p^2 = .05$. However, cortisol levels in the -AG group were higher in the paroxetine than in the placebo condition at 1 hr ($M = 14.54$, $SD = 5.76$, vs. $M = 10.84$, $SD = 5.00$), $F(1, 36) = 4.34$, $p = .04$, $p_{\text{rep}} = .89$, $\eta_p^2 = .11$. Similarly, cortisol levels in the -AG group were higher in the paroxetine than in the placebo condition at 3 hr ($M = 14.72$, $SD = 4.74$, vs. $M = 9.83$, $SD = 3.37$), $F(1, 36) = 12.84$, $p = .001$, $p_{\text{rep}} = .97$, $\eta_p^2 = .26$. In contrast, no effect of drug condition on cortisol level was found for the +AG group at any time point.

Drug Effects on Shock-Tolerance Threshold

Although +AG participants had higher average shock-tolerance thresholds ($M = 1.49$ μA , $SD = 0.82$) than did -AG participants ($M = 0.94$ μA , $SD = 0.57$), $F(1, 76) = 12.49$, $p = .001$, $p_{\text{rep}} = .99$, $\eta_p^2 = .14$, shock-tolerance thresholds showed neither a main effect of drug condition, $F(1, 76) = 0.67$, $p = .42$, $p_{\text{rep}} = .56$, $\eta_p^2 < .01$, nor an interaction of drug condition and aggression history, $F(1, 76) = 0.06$, $p = .81$, $p_{\text{rep}} = .27$, $\eta_p^2 < .01$. Because paroxetine did not seem to affect shock-tolerance thresholds, the anti-aggressive effects observed were probably not due to analgesia.

DISCUSSION

We found that (a) acutely augmenting 5-HT activity reduces response to provocation in aggressive individuals, and (b) a history of aggression is associated with attenuated hormonal response to an acute dose of paroxetine. These findings support the notion that the role of 5-HT in human aggression is complex, and that theoretically meaningful environmental (provocation) and individual difference (aggression history) variables must be considered to better understand this relationship.

In the standard TAP, average shock across trials is of interest. For this study, we modified the standard TAP by adding a severe (20) shock option. The inclusion of this shock option enhances the paradigm both as a means of provocation and as an index of aggressive responding. Specifically, having the opponent select a 20 shock to administer to the participant allows attack or provocation to be unequivocally manipulated by providing a clear intent to attack or harm the participant. Similarly, intent to harm the opponent is easier to discern when the participant uses the 20 shock (intent to harm is a cardinal feature of aggression; Baron & Richardson, 1994). In addition, use of the 20 shock may be more sensitive to the anti-aggressive effects of drugs (Myerscough & Taylor, 1985). Finally, aggression in both humans and lower animal species seems to occur in intermittent outbursts (Miczek et al., 2002), which are ecologically similar to decisions to try to administer a 20 shock. For these reasons, we recommend using the modified TAP when provocation effects are central to a study.¹

The biological and psychological processes by which 5-HT regulates response to provocation bear consideration. Spont (1992) suggested that 5-HT stabilizes information flow via its effects on other neurotransmitter systems (e.g., dopamine, gamma-aminobutyric acid), resulting in controlled behavioral, cognitive, and affective output when the organism is confronted with changing environmental demands, such as those that elicit fight-or-flight behaviors. Studies in lower animal species support this idea, showing that reduced 5-HT activity is associated with increases in punishment-suppressed behavior, and that intact or elevated 5-HT functioning is associated with effective decision making and prosocial behaviors (Miczek et al., 2002; Spont, 1992).

Most research on 5-HT and aggression has focused on men (but see Bond et al., 2001; Marsh et al., 2002). Although women tend to behave less aggressively overall than men, they do respond similarly to men when provoked (Bettencourt & Miller, 1996). Accordingly, we saw no reason to exclude women from participation. Although this study was not designed to explore gender differences in the relationship between 5-HT and aggression, we found no moderating effects of gender, perhaps because of the similar aggression histories of the men and women in both the high- and the low-aggression groups.

Aggressive individuals showed a blunted cortisol response to paroxetine. Many studies have demonstrated that aggressive individuals have an attenuated hormonal response to various serotonergic agents, including d- and d,l-fenfluramine, buspirone, and ipsapirone (see Siever, 2008). To our knowledge, this is the first demonstration that cortisol response to 40 mg of paroxetine can serve as a pharmacological probe for 5-HT function in aggressive individuals. Given this drug's good safety profile, researchers should consider using paroxetine in future studies of linkages between 5-HT and behavior.

¹Average shock in the modified task can be analyzed by first recoding 20 as 11, to minimize the effects of outliers (McCloskey & Berman, 2003). When we used average shock as our index of aggression, we found no significant effects of paroxetine, which supports the notion that 5-HT specifically controls extreme aggressive outbursts.

Our two main findings may seem contradictory at first blush. That is, participants with a history of aggression were sensitive to the aggression-suppressing effects of paroxetine, but also had attenuated 5-HT activity as indicated by lower hormonal response to the drug. Attenuated hormonal response to 5-HT agents is a relatively static condition dependent on both hypothalamic activity and reduced postsynaptic receptor sensitivity (Cowen & Sargent, 1997), but hormonal response per se is not thought to mediate the relation between 5-HT and aggression (Siever et al., 1999). Indeed, administration of 5-HT agents, even in individuals with attenuated hormonal response, increases the bioavailability of 5-HT in the synapse and activates pathways in orbital and ventral medial prefrontal cortices that are responsible for behavioral control in response to environmental challenge (Siever, 2008; Siever et al., 1999). For this reason, experimentally enhancing 5-HT activity can alter behavior in more aggressive individuals despite their tonically lower postsynaptic serotonergic sensitivity.

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Fig. 1. Participants' mean use of extreme (20) shock as a function of drug condition and trial block. Results are shown separately for participants with and without a history of aggression. Provocation increased from the first through the final trial block. Error bars represent standard errors of the means.