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Acetaminophen Reduces Distrust in Individuals With Borderline Personality Disorder Features

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Abstract

People with borderline personality disorder (BPD) tend to distrust others. We hypothesized that acetaminophen might reduce distrust in people with high BPD features because disordered affective responses are partially responsible for the interpersonal difficulties of people with BPD features, and acetaminophen has been shown in multiple studies to reduce negative affect. Using a double-blind, parallel-arm design, 284 young adult participants were administered either acetaminophen (1,000 mg; acute) or placebo and subsequently completed an economic trust game. BPD features were assessed with the Personality Assessment Inventory–Borderline Features scale. Participants with elevated BPD features showed less trust in their partners in the placebo condition but increased trust in the acetaminophen condition. Acetaminophen did not change expectations of trustee's trustworthiness and did not impact trusting behavior in participants low in BPD features. Our results indicate that acetaminophen may reduce the behavioral distrust exhibited at high levels of BPD features.

Keywords

borderline personality, paracetamol, personality disorder, psychopharmacology, trust

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Impaired social functioning is a core diagnostic feature of borderline personality disorder (BPD), which is characterized by instability in close relationships and fear of abandonment (American Psychiatric Association, 2013). These interpersonal difficulties may stem, in part, from the tendency of those with BPD to judge others as untrustworthy (Miano, Fertuck, Arntz, & Stanley, 2013). Distrust is likely to be particularly detrimental to interpersonal relationships because trustworthiness is an important and desirable characteristic for interaction partners across a wide range of social contexts (Cottrell, Neuberg, & Li, 2007) and is critical to the development and maintenance of relationships (Simpson, 2007). Therefore, addressing the distrust of patients with BPD may be particularly beneficial for both personal and therapeutic relationships.

Increasingly, the social behaviors associated with BPD and BPD features are being examined within controlled experiments (Lazarus, Cheavens, Festa, & Rosenthal, 2014). For example, people with BPD diagnoses and high BPD features appraise neutral faces as appearing less trustworthy (Fertuck, Grinband, & Stanley, 2013; Miano et al., 2013). Several other studies have used a trust game in which the participant (i.e., the investor) is given an endowment of money and asked to decide how much to send to a partner (i.e., trustee). The investment is multiplied (e.g., by 4) and the trustee decides how much of the multiplied investment to return to the investor (Berg, Dickhaut, & McCabe, 1995). In this task, patients diagnosed with BPD entrusted less money to an anonymous partner

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and expected their partner to return less money relative to participants in the healthy control (HC) condition (Unoka, Seres, Aspán, Bódi, & Kéri, 2009). The BPD group did not risk less in a nonsocial risky gamble task, suggesting that their reduced risk taking was specific to social exchanges. Other studies have found that participants with BPD, relative to HC participants, reacted more strongly to trustees' facial cues when entrusting money (Ebert et al., 2013; Franzen et al., 2011). Furthermore, when people with BPD are the trustees, they tend to respond in ways that erodes trust as the interaction unfolds (King-Casas et al., 2008). Thus, an emerging body of research has demonstrated deficits in trusting behavior among participants with BPD when compared to HC participants.

Unfortunately, there are currently no pharmacological therapies that have been approved by the U.S. Food and Drug Administration specifically for the treatment of BPD that might help ameliorate this general distrust. There was initial optimism that intranasal oxytocin (OT) might reduce distrust in patients with BPD, because studies found it to increase trust in HC participants (Kosfeld, Heinrichs, Zak, Fischbacher, & Fehr, 2005). However, this optimism has since been tempered by methodological challenges (Walum, Waldman, & Young, 2016) as well as the lack of translation to patients with BPD. Two studies found OT to *reduce* trust in those with BPD (Bartz et al., 2011; Ebert et al., 2013). One explanation for OT having opposite effects on trust in HC participants and participants with BPD is that OT may increase the salience of social cues and, thus, exacerbate the effects of the negative relationship representations associated with BPD (Bartz et al., 2011). Therefore, a drug that reduces the negative affect that people with BPD associate with social interactions might be more effective.

Recent studies have shown acetaminophen (i.e., paracetamol) to reduce negative affective responses, beyond analgesia, across a variety of social contexts. For example, acetaminophen reduced self-reports of hurt feelings and neural responses associated with experiences of social pain (DeWall et al., 2010; Fung & Alden, 2017). Acetaminophen also dampened the emotional experience associated with aversive stimuli such as making difficult decisions (DeWall, Chester, & White, 2015), thinking about one's own mortality (Randles, Heine, & Santos, 2013), and empathy for another person's physical and social pain (Mischkowski, Crocker, & Way, 2016). Acetaminophen also reduced affective responses to both negative and positive emotional images (Durso, Luttrell, & Way, 2015). In this last study, acetaminophen had no effect on the extremity of a nonevaluative judgment (i.e., the amount of blueness in the images)—providing suggestive evidence that acetaminophen may selectively dampen affect. Therefore, there is emerging and consistent evidence that acetaminophen reduces affective responses.

These acetaminophen-induced reductions in affect may be particularly relevant for those with BPD. BPD is associated with heightened rejection sensitivity (Berenson, Downey, Rafaeli, Coifman, & Paquin, 2011; Miano et al., 2013; Staebler, Helbing, Rosenbach, & Renneberg, 2011). It is intriguing that acetaminophen has been shown to reduce hurt feelings from rejection in HC participants (DeWall et al., 2010; Fung & Alden, 2017). In a context of interpersonal trust, deciding to place one's trust in another person inherently comes with increased interpersonal vulnerability and the possibility of betrayal regardless of what is expected of a particular trustee. Individuals with BPD, possibly related to their increased rejection sensitivity, experience negative affect when deciding how much to trust an individual who is unfamiliar to them (Unoka et al., 2009). Therefore, it is possible that acetaminophen could help to alleviate the distrust of people with high BPD features, perhaps by reducing negative affect.

To test whether acetaminophen would increase trust behavior in people high in BPD features, we randomly assigned participants to receive an acute dose of acetaminophen or placebo and then had them complete an economic trust game in the role of the investor. To get an initial assessment of whether acetaminophen's effects are mediated by a shift in expectations or not, we also asked participants how much they expected their partners to return. To accrue a relatively large sample and to test BPD features dimensionally, we recruited an undergraduate sample and measured BPD features with the Personality Assessment Inventory–Borderline Features scale (PAI-BOR; Morey, 1991). Testing the effect of acetaminophen on trusting behavior as a function of borderline features was our primary clinically relevant goal and serves as a companion to our current research into the tolerability of chronic acetaminophen in patients with BPD (NCT02108990).

Method

Participants

Participants were 284 undergraduates at the Ohio State University (Experiment 1: 73 males, 45 females, 4 declined to respond; Experiment 2: 60 males, 95 females, 7 declined to respond). Because our two studies were nearly identical in design, we combined the data, in line with recent statistical recommendations (Schimmack, 2012). The sample sizes for each experiment were based on effect sizes observed in other acetaminophen studies conducted in our lab (Cohen's

d = 0.55 in Durso et al., 2015; Hedges's g = 0.45 in Mischkowski et al., 2016). In Experiment 1, all participants received course credit for participating. Those in Experiment 2 participated either in exchange for course credit or for payment.

One participant from Experiment 1 was excluded for only responding to 13 of the 24 PAI-BOR items. In addition, the PAI-BOR data for one participant from Experiment 1 and four participants from Experiment 2 were lost due to technological error, and, therefore, those participants could not be included in the analyses. All participants in Experiment 2 were tested on task comprehension. There were no quizzes in Experiment 1. We excluded participants (n = 6) in Experiment 2 who did not perform significantly above chance on the comprehension questions (for more details, see the Supplemental Material available online). After exclusions, 272 participants (137 acetaminophen, 135 placebo) were included in the final analyses.

General procedures

Both experiments followed the same general procedure. After signing up for the experiments, participants received an email asking them to refrain from participation if they met any of a list of risk factors associated with acetaminophen use (see Durso et al., 2015). To facilitate drug absorption, we asked participants to refrain from consuming food for 3 hr before the experiment.

Upon arrival, all participants were randomly assigned to take either an acute dose of 1,000 mg of acetaminophen or a placebo, both in a liquid vehicle. Assignment of drug condition followed a double-blind procedure in which bottles containing the drug and placebo mixtures were labeled with codes. Drug condition was decoded after data collection was completed. Acetaminophen and placebo solutions were prepared by Pharmacy Specialists Compounding Pharmacy (Altamonte Springs, Florida; http://www.makerx.com/). The drug solution consisted of acetaminophen (100 mg/ml) dissolved in Ora-Plus suspension liquid and flavored with Ora-Sweet Syrup. The placebo solution consisted of Avicel Microcrystalline powder (100 mg/ml) dissolved in the same vehicle.

Immediately after receiving the drug, participants completed a set of self-report questionnaires that contained the PAI-BOR. After completing the questionnaires, participants were allowed to rest until approximately 60 min had elapsed since drug administration. This uptake period was to allow sufficient time for the drug to enter the brain (Singla et al., 2012). Then participants completed the trust game in the role of investor as part of a larger battery of social and cognitive assessments (to be reported separately). Participants completed the experiment within individual cubicles. In addition to receiving course credit or payment for participation, participants were financially compensated based on one randomly selected decision. Each participant had one trial randomly paired with an anonymous participant from a separate study and both were paid according to the decisions made. Payments earned based on the randomly selected decision ranged from \$0 to \$10. After completing all tasks, participants were asked to guess which drug they received.

Trust game as investor

The trust games used in both experiments were nearly identical. Any differences are noted in the Supplemental Material. Groups of participants completed the experiment simultaneously in a session in individual cubicles. In both experiments, participants had multiple trials. With each trial they were given an initial endowment, which varied in size across trials. They were then asked to decide how much, if any, of each endowment they wished to send to a partner who they were informed would be another participant taking part in a similar experiment. The amount sent to the partner (i.e., the trustee) was multiplied by 4 and participants were instructed that their partner would decide how much of this new amount to keep for himself or herself and how much to return to the participant. After each investment decision, participants were asked how much they expected their partner to return to them unless they did not send anything. In the latter case, the question was skipped. No feedback on trustee decisions in response to participant investments was provided during the task. Participants were informed that all players in the games would be anonymous. Furthermore, all participants were informed that one of their decisions would be selected at random to be paired with a partner who was a participant in a separate experimental session. Both they and their partners would receive monetary payments in accordance with their combined decisions. Thus, there was no deception in the study. To help bolster participants' confidence that they and a partner would be receiving money based on their decisions, participants were asked to sign a slip of paper with a statement confirming their understanding of the payment procedure before beginning the task.

Data analysis

All analyses were conducted in the R statistical package (R Core Team, 2015). For analyses, the average proportion of the initial endowment invested as well as the average proportion of the investment expected to be returned were calculated for each participant. In

regression analyses, drug condition and PAI-BOR status, when using the Trull (1995; ≥ 38) cutoff, were effects coded (*acetaminophen* = 1, *placebo* = 0 and *high BPD features* = 1, *low BPD features* = 0). In continuous analyses, orthogonal polynomials were used.

Because the dependent variable (i.e., average proportion of endowment invested) was bounded (i.e., [0, 1]), we used beta regression for our analyses (Smithson & Verkuilen, 2006). A beta distribution more accurately reflects the distribution of responses with upper and lower bounds and indeed examining the *AIC* for beta and Gaussian versions of our models confirmed that beta regression provided a better account of the data than regression that assumes a Gaussian distribution (*AIC*: –11.99 and 51.65, respectively). The R package *betareg* (Cribari-Neto & Zeileis, 2010) was used to fit the beta regression models. Because beta regression requires the response variable to be in the open interval (0, 1), we applied the transformation recommended by Smithson and Verkuilen (2006): $y' = [y(N - 1) + 0.5]/N$, where N is the number of participants. Beta regression also features the simultaneous estimation of location and precision (i.e., the inverse of dispersion), which allows for the prediction of both the mean and variance in trusting investment behavior. This way we are able to analyze both parameters and how they differ between groups.

Results

Participants were unable to guess which drug they had received, $\chi^2(1, N = 256) = 0.24$, $p = .63$ (N differs because some participants did not provide a guess). There was no difference in BPD features among participants who received acetaminophen ($M = 24.27$, $SD = 11.21$) relative to placebo ($M = 24.19$, $SD = 10.46$) as measured by the PAI-BOR, $t(270) = 0.06$, $p = .95$.

First, we fit a fixed dispersion beta regression model (i.e., intercept only in the precision submodel; Cribari-Neto & Zeileis, 2010) predicting trust game investment with PAI-BOR, drug condition, and their interaction in the location submodel. This revealed a significant interaction between PAI-BOR and drug condition ($b = 4.48$, $SE = 2.25$, $z = 1.99$, $p = .047$) such that there was a significantly positive relationship between PAI-BOR and amount invested in the acetaminophen condition ($b = 3.49$, $SE = 1.53$, $z = 2.28$, $p = .023$), but no relationship in the placebo condition ($b = -1.00$, $SE = 1.65$, $z = -0.60$, $p = .55$).

The absence of a negative relationship between BPD features and trusting behavior in the placebo condition is counter to past research that found reduced trust in BPD patients (Unoka et al., 2009). One possibility is that the general distrust exhibited by people with BPD becomes observable primarily at high levels of BPD features (e.g., BPD patients). In line with this hypothesis, inspection of the scatterplot (see Fig. 1a) and a quintile plot (see the Supplemental Material) suggested a nonlinear relationship between PAI-BOR and the average amount invested in the placebo condition so a model including a second-degree polynomial term for PAI-BOR was fit to the data. Again, there was a significant interaction between the linear polynomial of PAI-BOR and drug condition ($b = 5.29$, $SE = 2.04$, $z = 2.59$, $p = .010$; see Table 1 location submodel) such

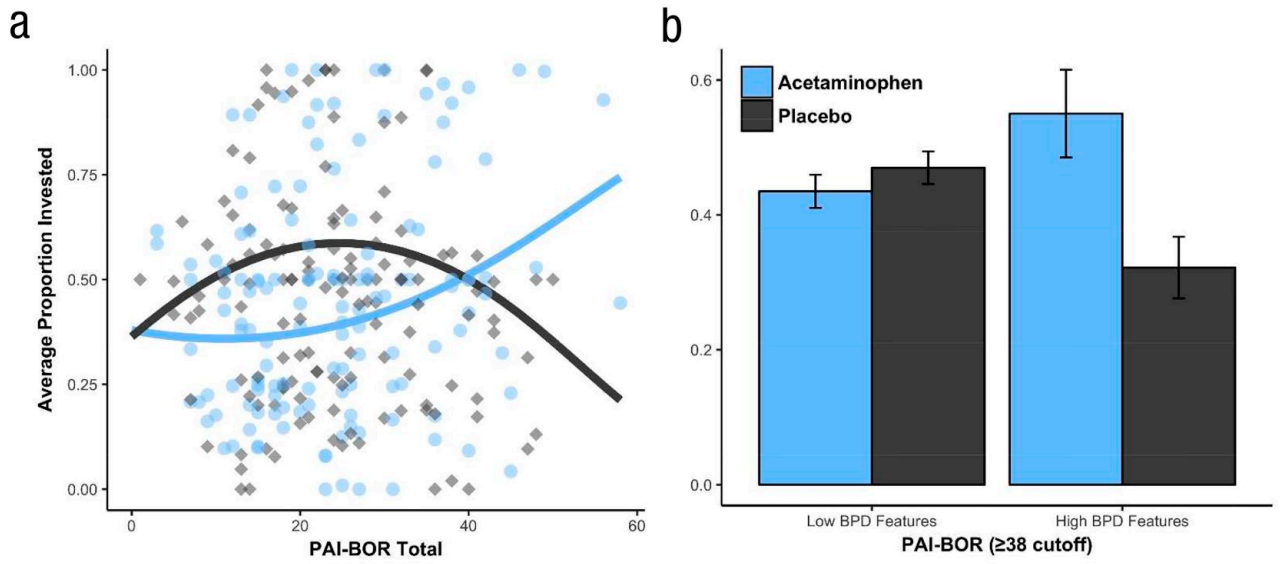

Fig. 1. (a) Predicted mean proportion of endowment invested. (b) Mean proportion of endowment invested by participants with high and low BPD features (cutoff from Trull, 1995). Error bars represent standard error.

Table 1. Investment Behavior as a Function of Personality Assessment Inventory–Borderline Features Scale (PAI-BOR) Score and Drug Condition

Parameter	Coefficient	*SE*	*p*
Location submodel			
Intercept	–0.12	0.09	.210
PAI-BOR	–1.66	1.51	.271
PAI-BOR^2	–3.24	1.53	.034
Drug	0.00	0.13	.974
PAI-BOR × Drug	5.29	2.04	.010
PAI-BOR^2 × Drug	4.84	1.97	.014
Precision submodel			
Intercept	0.68	0.07	< .001
PAI-BOR	–3.20	1.23	.010
PAI-BOR^2	4.90	1.26	< .001
Drug	0.03	0.07	.636
PAI-BOR × Drug	–3.10	1.26	.012

Note: Pseudo-R^2 = .03; log-likelihood = 16.99

that there was a significantly positive linear relationship between PAI-BOR and the average amount invested in the acetaminophen condition (b = 3.63, SE = 1.37, z = 2.65, p = .008) but a nonsignificant negative relationship in the placebo condition (b = −1.66, SE = 1.51, z = −1.10, p = .27). There was also a significant interaction between the quadratic term and drug condition (b = 4.84, SE = 1.97, z = 2.46, p = .014; see Table 1 location submodel). As suggested by the scatterplot and quintile plot, the model revealed a significant quadratic relationship between PAI-BOR in the placebo condition (b = −3.24, SE = 1.53, z = −2.12, p = .03). A negative quadratic term indicates concave curvature in the relationship between PAI-BOR and the amount invested in the placebo condition. Because the linear polynomial for participants who received placebo was negative, this reveals that the negative relationship between PAI-BOR and amount invested strengthens at higher levels of PAI-BOR. There was no quadratic relationship in the acetaminophen condition (b = 1.60, SE = 1.23, z = 1.30, p = .19).

Because beta regression also models a precision parameter, it is possible to investigate effects on variance as well. Adding predictors to the precision submodel improved the overall model fit. There was a significant interaction between the linear polynomial of PAI-BOR and drug (see Table 1 precision submodel) such that in the acetaminophen group there was a significantly negative linear relationship between PAI-BOR and precision (b = –6.30, SE = 1.68, z = –3.75, p < .001). There was no relationship on placebo (b = −0.09, SE = 1.82, z = –0.05, p = .96). Because variance decreases as precision increases, this indicates that in the acetaminophen condition the variance in the amount invested between participants increased with BPD features. There was also a significant quadratic relationship between PAI-BOR and precision (see Table 1 precision submodel) such that there was an inverted-U relationship between BPD features and variance in average amount invested. The quadratic term was not moderated by drug condition and including it did not improve the model fit so it was removed from the final model.

The nonlinear relationship between BPD features and average investment in the location submodel suggests that another way to examine the data might be to use a preestablished threshold for PAI-BOR scores. A score of 38 or higher on the PAI-BOR has been previously validated as a marker of significant BPD features in a nonclinical sample (Trull, 1995) and so in an additional set of analyses to further explore the relationship between PAI-BOR and trusting behavior, participants were grouped based on whether they surpassed this threshold or not. Based on this criterion, 37 participants (about 13.6%) had significant BPD features (20 acetaminophen, 17 placebo), which is similar to the prevalence observed in other undergraduate samples (Ayduk et al., 2008; Trull, 1995). A beta regression with a dichotomized PAI-BOR was fit to the data (see the Supplemental Material for table of results). The results revealed a significant interaction between PAI-BOR grouping (≥ 38 vs. < 38) and drug condition (b = 1.34, SE = 0.39, z = 3.48, p < .001; see Fig. 1b). Among participants who received placebo, those with low BPD features (M = 0.47, SD = 0.26) entrusted their partners with a significantly greater proportion of their monetary endowments than those who had high BPD features (M = 0.32, SD = 0.19; b = –0.84, SE = 0.27, z = –3.19, p = .001). Meanwhile, participants with high BPD features who were given acetaminophen, relative to those with high BPD features who were given placebo (M = 0.32, SD = 0.19), were significantly more trusting (M = 0.55, SD = 0.29; b = 1.19, SE = 0.36, z = 3.31, p < .001). Participants with low BPD features who received acetaminophen (M = 0.43, SD = 0.27) did not differ from those with low BPD features on placebo. Within the acetaminophen condition, there was a marginal effect such that participants with high BPD features were more trusting than those with low BPD features (b = 0.50, SE = 0.28, z = 1.78, p = .08).

To test whether acetaminophen increased trusting behavior by reducing expectations of betrayal, we tested whether acetaminophen had any effect on how much investors expected their trustees to return. Because expectations could not be collected on trials where participants chose not to invest anything, these trials were excluded from analyses, but inferring expectations to be zero for these trials did not change the results. There were no significant effects of PAI-BOR or

any interactions with drug condition on expectation whether PAI-BOR was treated continuously or dichotomously (see the Supplemental Material). Thus, acetaminophen did not change expectations of betrayal and there were no differences in expectations between those with high and those with low BPD features.

Discussion

We found evidence that people with high BPD features exhibited less trusting behavior than people with low BPD features using a widely accepted economic trust paradigm. This result is in line with a previous study that found patients with BPD to exhibit less trusting behavior using the same trust paradigm (Unoka et al., 2009). Most important, acetaminophen reduced the behavioral distrust of those with elevated features of BPD.

Treating PAI-BOR as a continuous predictor revealed a nonlinear relationship between BPD features and trusting behavior among participants who received placebo. This is noteworthy because, to our knowledge, this is the first time that the relationship between BPD features and trusting behavior in this paradigm has been assessed continuously. Past studies using the trust game have all compared BPD patients to HC participants (Ebert et al., 2013; Franzen et al., 2011; Unoka et al., 2009). It is interesting that these analyses suggest that distrust is most observable at higher levels of BPD features and that acetaminophen may have primarily affected the trusting behavior of people with higher levels of BPD features.

Differing from a prior study where participants with BPD expected their partners to be less trustworthy (Unoka et al., 2009), our study found that people with high and low BPD features had similar expectations about trustee behavior. Because acetaminophen reduced the behavioral distrust of participants with high levels of BPD features, it appears to have influenced trusting behavior by a process other than changing expectations. There are multiple plausible mechanisms for this effect. One could be that people find the experience of making themselves vulnerable to the actions of another aversive and therefore tend to avoid it by not placing trust in others. Behavioral economists have labeled this tendency betrayal aversion (Bohnet, Greig, Herrmann, & Zeckhauser, 2008; Bohnet & Zeckhauser, 2004) and consistent with the results reported here betrayal aversion is independent of expectations about outcomes (Aimone & Houser, 2012; Aimone, Houser, & Weber, 2014). In other words, people invest less money when playing a trust game with another person than with a computer, even when expected outcomes are held constant (Aimone & Houser, 2012; Aimone et al., 2014). Disordered affective responding (Rosenthal et al., 2008), specifically in the context of interpersonal situations (Lazarus et al., 2014), in people with high BPD features could produce heightened betrayal aversion relative to HC participants because of a stronger affective response to vulnerability. In line with this hypothesis, people with BPD reported greater discomfort when completing a trust game but not when completing a nonsocial risk game with a computer (Unoka et al., 2009).

Discomfort with the mere potential for betrayal is also consistent with greater rejection sensitivity among people with BPD diagnoses (Berenson et al., 2011; Staebler et al., 2011) and those with heightened BPD features (Miano et al., 2013). In fact, rejection sensitivity has been found to mediate the relationship between BPD features and appraising faces as untrustworthy (Miano et al., 2013). Our study suggests that people with high BPD features may show greater distrust due to heightened anxiety about possible outcomes (i.e., betrayal aversion) independent of actual expectations, and reducing this anxiety could be how acetaminophen increases trust. That is, acetaminophen could make people with high BPD features more comfortable with taking interpersonal risks. Similar to how rejection sensitivity is composed of (a) anxiety about the outcome of a social interaction and (b) expectations of rejection (Downey & Feldman, 1996), acetaminophen could increase trust in people with high BPD features by either (a) decreasing anxiety about the outcome or (b) producing more optimistic expectations. Our data could be taken to suggest that acetaminophen increased trust by reducing negative affect about the possibility of an unpleasant outcome regardless of expectations. This could be akin to the recent finding that acetaminophen reduced anxiety in anticipation of and during social interactions that have the potential for social exclusion (Fung & Alden, 2017). Such a finding would also be consistent with acetaminophen reducing hurt feelings in healthy samples (DeWall et al., 2010; Fung & Alden, 2017). Future work is needed to clarify whether betrayal aversion, general baseline negative affect, or another unidentified mechanism mediates the effect of acetaminophen on behavioral distrust for individuals at high levels of BPD.

An alternative explanation of the current results could be that acetaminophen reduced the affective response to rewarding stimuli, such as money, in people with high BPD features. People with BPD are frequently impulsive and they tend to choose smaller amounts of money that will be received sooner over larger amounts that would be received after a delay (Lawrence, Allen, & Chanen, 2010). Because the

investor begins each trial of the trust game with a small endowment of money that can be either kept or invested with the hope of receiving more later, it is possible that distrust reflects an impulsive preference for the smaller-sooner reward. Thus, acetaminophen could be making people with high BPD features less impulsive by reducing positive affect responses to the more immediate reward (i.e., the money that was initially endowed). Acetaminophen has indeed been shown to reduce positive evaluations of pleasant emotional images (Durso et al., 2015) in the general population. Contrary to this interpretation, people with BPD have also been shown to have attenuated evaluations of pleasant emotional stimuli (Rosenthal et al., 2008). Still, research is needed to investigate this possibility.

It is interesting that there was some evidence in our study that acetaminophen actually *increased* trusting behavior in people with high BPD features above what was observed in people low in BPD features. It is possible that reducing the usual betrayal aversion experienced by people with BPD features may facilitate trusting behavior. This might reflect the tendency of patients with BPD to view people more dichotomously in terms of valence (Veen & Arntz, 2000) and to exhibit greater vacillations in interpersonal behaviors across social interactions (Russell, Moskowitz, Zuroff, Sookman, & Paris, 2007). Therefore, acetaminophen may have induced people with high BPD features to shift from one extreme (i.e., heightened distrust) to another (i.e., heightened trust). Indeed, inspecting the scatterplot (Fig. 1) suggests that some participants with high levels of BPD features in the acetaminophen condition entrusted almost all their money, demonstrating an extremitization of interpersonal behavior. Our findings could suggest possible mechanisms for the vacillating interpersonal behaviors of people with BPD observed in longitudinal studies (e.g., Russell et al., 2007). For example, if acetaminophen is indeed dampening the negative affect of betrayal aversion, it suggests that interpersonal behaviors could vary dramatically, in part, based on the affect experienced in a given moment. This is in line with theories that individuals with BPD are more emotionally reactive than others (e.g., Linehan, 1993). The increased variance in responses across participants with high levels of BPD features who received acetaminophen may suggest that this extremitizing behavioral shift happened particularly in a subset of participants. In future work, researchers may need to consider what factors might influence responsiveness to acetaminophen and should explore the role of emotion in predicting extreme interpersonal behaviors in people with BPD.

Because of the pressing need for improved therapies for BPD, some may find it tempting to suggest acetaminophen as a possible therapeutic adjunctive for patients with BPD, assuming that acetaminophen might reduce behavioral distrust and potentially facilitate BPD patients' formation and maintenance of some interpersonal relationships. Similarly, if the reduction in hurt feelings by acetaminophen in HC participants (DeWall et al., 2010; Fung & Alden, 2017) also occurs in patients with BPD, this could potentially reduce the aggressive and self-injurious behaviors associated with heightened rejection sensitivity (e.g., Berenson et al., 2011). Such speculations should be treated with extreme caution given the limited nature of available data and the absence of randomized trials in clinical populations. It is important to note that acetaminophen could also have potential detrimental consequences for people with BPD and their relationships. For example, acetaminophen has been shown to reduce affective responses to positive stimuli (Durso et al., 2015) and to reduce empathy for others (Mischkowski et al., 2016). If acetaminophen has either of these effects in people with BPD, it could have harmful effects for their well-being and interpersonal relationships. Furthermore, increased trust is likely only beneficial in situations where the trustee is indeed trustworthy. Our study also suggests that acetaminophen may increase the variability in trusting behavior among people with high BPD features. Therefore, any future research examining acetaminophen as a therapeutic agent should consider these and other possible negative outcomes. Because nearly a quarter of the U.S. population takes acetaminophen each week (Kaufman, Kelly, Rosenberg, Anderson, & Mitchell, 2002), it would also be valuable to explore whether standard acetaminophen use has unintended negative consequences in the daily lives of people with BPD.

In light of these potential safety concerns, one place for further testing of acetaminophen would be in the well-controlled context of meeting with a therapist. For example, patient-clinician trust is reported by both clinicians and patients with BPD as being one of the most important factors for positive therapeutic outcomes (Langley & Klopper, 2005). However, because patients with BPD are characterized by high levels of distrust, it may take longer for them to develop trust with their therapists. Our study suggests that an avenue for future research is to test whether an acute dose of acetaminophen given before a therapy session facilitates the patient-therapist relationship by dampening distrust. Another area for future research is to examine the incorporation of acetaminophen use into skills-based psychotherapies to potentially facilitate skill acquisition by reducing the anticipated negative affect associated with making difficult behavioral changes.

The precise biological mechanisms accounting for acetaminophen's effects are unclear. Acetaminophen

has effects on multiple neurochemical systems, but its effects on two systems in particular might be relevant here. First, acetaminophen inhibits prostaglandin production in the brain (Graham, Davies, Day, Mohamudally, & Scott, 2013). This is noteworthy because an omega-3 polyunsaturated fatty acid in fish oil, eicosapentaenoic acid (EPA), is an inhibitor of prostaglandin synthesis (Culp, Titus, & Lands, 1979; Dong et al., 2016; Wada et al., 2007), and there is suggestive evidence that omega-3's may have therapeutic effects for people with BPD (Amminger et al., 2013; Hallahan, Hibbeln, Davis, & Garland, 2007; Zanarini & Frankenburg, 2003). Second, acetaminophen increases levels of serotonin in the brain (Pini, Sandrini, & Vitale, 1996). Although the results are mixed, some studies have shown that selective serotonin reuptake inhibitors can have therapeutic effects for people with BPD (Stoffers & Lieb, 2015). Alternatively, acetaminophen's behavioral effects could be due to the combined effects of these systems, as well as others.

One important potential limitation to our study is that we did not include diagnostic assessments of BPD. However, people who meet or exceed a score of 38 on the PAI-BOR are more likely to receive a BPD diagnosis when subsequently interviewed and also show disturbances in reports of affect, personality, psychopathology symptoms, personality, and interpersonal issues relative to people who score below the cutoff (Trull, 1995). It is possible that individuals diagnosed with BPD might show a greater response to acetaminophen than those with elevated features. In fact, the curvilinear nature of the relationship between PAI-BOR and trusting behavior observed in our study suggests this would be the case. That said, the size of the effect in the current study is slightly larger than would be anticipated by our prior studies and suggests the need for future work, particularly in clinical populations.

Our study is the first to show a pharmacological agent increases trusting behavior in people with high BPD features. This is especially noteworthy because, thus far, studies with pharmacological interventions have only resulted in *reduced* trusting behavior in BPD patients (Bartz et al., 2011; Ebert et al., 2013). However, acetaminophen also increased the variability of trusting behavior in people with high BPD features. Because of how many people take acetaminophen every day, it is important for future research to investigate any potential therapeutic or harmful effects acetaminophen could have for people with BPD.

Author Contributions

I. D. Roberts, I. Krajbich, J. S. Cheavens, and B. M. Way developed the study concept. I. D. Roberts, I. Krajbich, and B. M. Way designed the study. Data collection and data analysis were performed by I. D. Roberts under the supervision of I. Krajbich, J. S. Cheavens, and B. M. Way. I. D. Roberts and B. M. Way drafted the manuscript, and I. Krajbich, J. S. Cheavens, and J. V. Campo provided critical revisions. All authors approved the final version of the manuscript for submission.

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Declaration of Conflicting Interests

The authors declared that they had no conflicts of interest with respect to their authorship or the publication of this article.

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Supplemental Material

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References

Aimone, J. A., & Houser, D. (2012). What you don't know won't hurt you: A laboratory analysis of betrayal aversion. *Experimental Economics*, *15*, 571–588.

Aimone, J. A., Houser, D., & Weber, B. (2014). Neural signatures of betrayal aversion: An fMRI study of trust. *Proceedings of the Royal Society B: Biological Sciences*, *281*, 20132127.

American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders* (5th ed.). Washington, DC: Author.

Amminger, G. P., Chanen, A. M., Ohmann, S., Klier, C. M., Mossaheb, N., Bechdolf, A., . . . Schäfer, M. R. (2013). Omega-3 fatty acid supplementation in adolescents with borderline personality disorder and ultra-high risk criteria for psychosis: A post hoc subgroup analysis of a double-blind, randomized controlled trial. *Canadian*

Journal of Psychiatry. Revue Canadienne de Psychiatrie, *58*, 402–408.

Ayduk, Ö., Zayas, V., Downey, G., Cole, A. B., Shoda, Y., & Mischel, W. (2008). Rejection sensitivity and executive control: Joint predictors of borderline personality features. *Journal of Research in Personality*, *42*, 151–168.

Bartz, J., Simeon, D., Hamilton, H., Kim, S., Crystal, S., Braun, A., . . . Hollander, E. (2011). Oxytocin can hinder trust and cooperation in borderline personality disorder. *Social Cognitive and Affective Neuroscience*, *6*, 556–563.

Berenson, K. R., Downey, G., Rafaeli, E., Coifman, K. G., & Paquin, N. L. (2011). The rejection-rage contingency in borderline personality disorder. *Journal of Abnormal Psychology*, *120*, 681–690.

Berg, J., Dickhaut, J., & McCabe, K. (1995). Trust, reciprocity, and social history. *Games and Economic Behavior*, *10*, 122–142.

Bohnet, I., Greig, F., Herrmann, B., & Zeckhauser, R. (2008). Betrayal aversion: Evidence from Brazil, China, Oman, Switzerland, Turkey, and the United States. *American Economic Review*, *98*, 294–310.

Bohnet, I., & Zeckhauser, R. (2004). Trust, risk and betrayal. *Journal of Economic Behavior and Organization*, *55*, 467–484.

Cottrell, C. A., Neuberg, S. L., & Li, N. P. (2007). What do people desire in others? A sociofunctional perspective on the importance of different valued characteristics. *Journal of Personality and Social Psychology*, *92*, 208–231.

Cribari-Neto, F., & Zeileis, A. (2010). Beta regression in R. *Journal of Statistical Software*, *34*, 1–24.

Culp, B. R., Titus, B. G., & Lands, W. E. M. (1979). Inhibition of prostaglandin biosynthesis by eicosapentaenoic acid. *Prostaglandins and Medicine*, *3*, 269–278.

DeWall, C. N., Chester, D. S., & White, D. S. (2015). Can acetaminophen reduce the pain of decision-making? *Journal of Experimental Social Psychology*, *56*, 117–120.

DeWall, C. N., MacDonald, G., Webster, G. D., Masten, C. L., Baumeister, R. F., Powell, C., . . . Eisenberger, N. I. (2010). Acetaminophen reduces social pain: Behavioral and neural evidence. *Psychological Science*, *21*, 931–937.

Dong, L., Zou, H., Yuan, C., Hong, Y. H., Kuklev, D. V., & Smith, W. L. (2016). Different fatty acids compete with arachidonic acid for binding to the allosteric or catalytic subunits of cyclooxygenases to regulate prostanoid synthesis. *Journal of Biological Chemistry*, *291*, 4069–4078.

Downey, G., & Feldman, S. I. (1996). Implications of rejection sensitivity for intimate relationships. *Journal of Personality and Social Psychology*, *70*, 1327–1343.

Durso, G. R. O., Luttrell, A., & Way, B. M. (2015). Over-the-counter relief from pains and pleasures alike: Acetaminophen blunts evaluation sensitivity to both negative and positive stimuli. *Psychological Science*, *26*, 750–758.

Ebert, A., Kolb, M., Heller, J., Edel, M.-A., Roser, P., & Brüne, M. (2013). Modulation of interpersonal trust in borderline personality disorder by intranasal oxytocin and childhood trauma. *Social Neuroscience*, *8*, 305–313.

Fertuck, E. A., Grinband, J., & Stanley, B. (2013). Facial trust appraisal negatively biased in borderline personality disorder. *Psychiatry Research*, *207*, 195–202.

Franzen, N., Hagenhoff, M., Baer, N., Schmidt, A., Mier, D., Sammer, G., . . . Lis, S. (2011). Superior "theory of mind" in borderline personality disorder: An analysis of interaction behavior in a virtual trust game. *Psychiatry Research*, *187*, 224–233.

Fung, K., & Alden, L. E. (2017). Once hurt, twice shy: Social pain contributes to social anxiety. *Emotion*, *17*, 231–239.

Graham, G. G., Davies, M. J., Day, R. O., Mohamudally, A., & Scott, K. F. (2013). The modern pharmacology of paracetamol: Therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology*, *21*, 201–232.

Hallahan, B., Hibbeln, J. R., Davis, J. M., & Garland, M. R. (2007). Omega-3 fatty acid supplementation in patients with recurrent self-harm: Single-centre double-blind randomised controlled trial. *British Journal of Psychiatry*, *190*, 118–122.

Kaufman, D., Kelly, J., Rosenberg, L., Anderson, T., & Mitchell, A. (2002). Recent patterns of medication use in the ambulatory adult population of the United States: The Slone survey. *JAMA*, *287*, 337–344.

King-Casas, B., Sharp, C., Lomax-Bream, L., Lohrenz, T., Fonagy, P., & Montague, P. R. (2008). The rupture and repair of cooperation in borderline personality disorder. *Science*, *321*, 806–810.

Kosfeld, M., Heinrichs, M., Zak, P. J., Fischbacher, U., & Fehr, E. (2005). Oxytocin increases trust in humans. *Nature*, *435*, 673–677.

Langley, G. C., & Klopper, H. (2005). Trust as a foundation for the therapeutic intervention for patients with borderline personality disorder. *Journal of Psychiatric and Mental Health Nursing*, *12*, 23–32.

Lawrence, K. A., Allen, J. S., & Chanen, A. M. (2010). Impulsivity in borderline personality disorder: Reward-based decision-making and its relationship to emotional distress. *Journal of Personality Disorders*, *24*, 785–799.

Lazarus, S. A., Cheavens, J. S., Festa, F., & Rosenthal, M. Z. (2014). Interpersonal functioning in borderline personality disorder: A systematic review of behavioral and laboratory-based assessments. *Clinical Psychology Review*, *34*, 193–205.

Linehan, M. M. (1993). *Cognitive-behavioral treatment of borderline personality disorder*. New York, NY: Guilford.

Miano, A., Fertuck, E. A., Arntz, A., & Stanley, B. (2013). Rejection sensitivity is a mediator between borderline personality disorder features and facial trust appraisal. *Journal of Personality Disorders*, *27*, 442–456.

Mischkowski, D., Crocker, J., & Way, B. M. (2016). From painkiller to empathy killer: Acetaminophen (paracetamol) reduces empathy for pain. *Social Cognitive and Affective Neuroscience*, *11*, 1345–1353.

Morey, L. C. (1991). *Personality Assessment Inventory: Professional manual*. Odessa, FL: Psychological Assessment Resources.

Pini, L. A., Sandrini, M., & Vitale, G. (1996). The antinociceptive action of paracetamol is associated with changes in the serotonergic system in the rat brain. *European Journal of Pharmacology*, *308*, 31–40.

Randles, D., Heine, S. J., & Santos, N. (2013). The common pain of surrealism and death: Acetaminophen reduces compensatory affirmation following meaning threats. *Psychological Science*, *24*, 966–973.

R Core Team. (2015). *R: A language and environment for statistical computing*. Retrieved from https://www.r-project.org/

Rosenthal, M. Z., Gratz, K. L., Kosson, D. S., Cheavens, J. S., Lejuez, C. W., & Lynch, T. R. (2008). Borderline personality disorder and emotional responding: A review of the research literature. *Clinical Psychology Review*, *28*, 75–91.

Russell, J. J., Moskowitz, D. S., Zuroff, D. C., Sookman, D., & Paris, J. (2007). Stability and variability of affective experience and interpersonal behavior in borderline personality disorder. *Journal of Abnormal Psychology*, *116*, 578–588.

Schimmack, U. (2012). The ironic effect of significant results on the credibility of multiple-study articles. *Psychological Methods*, *17*, 551–566.

Simpson, J. A. (2007). Psychological foundations of trust. *Current Directions in Psychological Science*, *16*, 264–268.

Singla, N. K., Parulan, C., Samson, R., Hutchinson, J., Bushnell, R., Beja, E. G., . . . Royal, M. A. (2012). Plasma and cerebrospinal fluid pharmacokinetic parameters after single-dose administration of intravenous, oral, or rectal acetaminophen. *Pain Practice*, *12*, 523–532.

Smithson, M., & Verkuilen, J. (2006). A better lemon squeezer? Maximum-likelihood regression with beta-distributed dependent variables. *Psychological Methods*, *11*, 54–71.

Staebler, K., Helbing, E., Rosenbach, C., & Renneberg, B. (2011). Rejection sensitivity and borderline personality disorder. *Clinical Psychology and Psychotherapy*, *18*, 275–283.

Stoffers, J. M., & Lieb, K. (2015). Pharmacotherapy for borderline personality disorder: Current evidence and recent trends. *Current Psychiatry Reports*, *17*, 534.

Trull, T. J. (1995). Borderline personality disorder features in nonclinical young adults: 1. Identification and validation. *Psychological Assessment*, *7*, 33–41.

Unoka, Z., Seres, I., Aspán, N., Bódi, N., & Kéri, S. (2009). Trust game reveals restricted interpersonal transactions in patients with borderline personality disorder. *Journal of Personality Disorders*, *23*, 399–409.

Veen, G., & Arntz, A. (2000). Multidimensional dichotomous thinking characterizes borderline personality disorder. *Cognitive Therapy and Research*, *24*, 23–45.

Wada, M., DeLong, C. J., Hong, Y. H., Rieke, C. J., Song, I., Sidhu, R. S., . . . Smith, W. L. (2007). Enzymes and receptors of prostaglandin pathways with arachidonic acid-derived versus eicosapentaenoic acid-derived substrates and products. *Journal of Biological Chemistry*, *282*, 22254–22266.

Walum, H., Waldman, I. D., & Young, L. J. (2016). Statistical and methodological considerations for the interpretation of intranasal oxytocin studies. *Biological Psychiatry*, *79*, 251–257.

Zanarini, M. C., & Frankenburg, F. R. (2003). Omega-3 fatty acid treatment of women with borderline personality disorder: A double-blind, placebo-controlled pilot study. *American Journal of Psychiatry*, *160*, 167–169.