Social Pain and Physical Pain Overlap Theory:

A Pharmacological Evaluation of the Neural Alarm System Hypothesis of Social Pain

THESIS

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Abstract

Past research has suggested that shared neural processes and computational mechanisms may underlie experiences of physical pain as well as social pain. Indeed, both physical and social pain have been associated with neural activity in the anterior cingulate cortex (ACC). Meanwhile, computational modeling work in the field of cognitive neuroscience has suggested that the ACC functions as a monitor for conflicts in information-processing. Based on ACC's association with physical and social pain as well as detecting conflicts, Eisenberger and Lieberman (2004) proposed that the ACC functions as a neural alarm system by (1) detecting discrepancies from desired set points and (2) triggering an alarm in the form of negative affect and autonomic responses. However, to date, there has been little work investigating the neural alarm system hypothesis. Therefore, the present work sought to examine the neural alarm system's prediction that conflict-monitoring processes are involved in social pain responses and drew on the recent finding that acetaminophen decreases social pain and ACC activity associated with social exclusion (DeWall et al., 2010). Specifically, it was predicted that acetaminophen would interfere with conflict-monitoring processes and that this effect would be associated with reductions in social pain. Two experiments tested this hypothesis. While the results did not provide support for the neural alarm system hypothesis, reduced social pain as a result of an acute dose of acetaminophen is demonstrated. Implications for the neural alarm system model and future research directions are discussed.

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Chapter 1: Introduction

It has been proposed that humans are fundamentally social beings who require social interactions. Indeed, if stable, positive interpersonal relationships are not maintained people suffer both physically and psychologically (Baumeister & Leary, 1995; Cohen, 2004; Eisenberger, 2012a). For example, the quality and diversity of a person's social interactions have been associated with improved health outcomes in domains ranging from upper respiratory illness (Cohen, Doyle, Skoner, Rabin, & Gwaitney, 1997) to cardiovascular health (Uchino, Holt-Lunstad, Uno, Campo, & Reblin, 2007). Furthermore, the level of mortality risk associated with having poor social relationships has been suggested to be comparable to that of smoking (Holt-Lunstad, Smith, & Layton, 2010).

Thus, research has demonstrated that social connections are critical to human well-being. In accordance with the great benefits of positive social relationships as well as the detriments of social disconnection, it would be highly adaptive for humans to possess heightened sensitivity to cues of social disconnection. Detection of social disconnection cues could trigger a signal that would rapidly draw attention to the situation. Such a mechanism would lead people to avoid situations and behaviors that threaten their social integration and actively seek out reparations when indications of potential damage to their connections within a social network are detected. In this way, people could maintain positive, stable social relationships and the vast benefits that accompany them. A great deal of research has focused on determining the nature of the mechanisms that promote social connection maintenance.

One experience that prioritizes attention and stimulates avoidance is pain. Thus, if threats of social disconnection were painful then people would be likely to become motivated to avoid actions that may result in damaged social bonds as well as to actively seek to repair weakened social ties. Indeed, most people would describe experiences of social disconnection as painful. For example, people use words such as "painful" or even "heart-breaking" to convey feelings associated with romantic break-ups. Beyond the use of similar language when describing physical and social pain though, research has suggested that experiences of "social pain" may even rely on some of the same neural systems and computations that underlie physical pain.

Social Pain

Beginning in the 1970s, research conducted by Panksepp and colleagues suggested that endogenous opioids are involved in separation distress and attachment behaviors (Nelson & Panksepp, 1998). As support for this hypothesis, Herman and Panksepp (1978) demonstrated that morphine, a drug that stimulates opiate receptors, decreased separation distress vocalizations in guinea pigs. Furthermore, naloxone, which blocks opioid receptors, increased separation distress vocalizations (Herman & Panksepp, 1978). Because opioids are critically involved in the experience of physical pain (Price, Von der Gruen, Miller, Rafii, & Price, 1985), the findings of Panksepp and colleagues led to the idea that in evolutionary development the mechanisms for social pain co-opted preexisting physical pain neural pathways (Nelson & Panksepp, 1998). Thus, both physical and social pain experiences might rely on similar neural systems.

More recent work in social neuroscience has contributed to the hypothesized existence of a physical-social pain neural overlap (for a review, see Eisenberger, 2012b). In a highly-influential study, participants were socially excluded while they were in an fMRI scanner (Eisenberger, Lieberman, and Williams, 2003). In this experiment, social exclusion was manipulated with the widely-used Cyberball paradigm (Williams, Cheung, Choi, 2000). In Cyberball, participants are told that they will be playing a

computerized game of catch with other participants via the internet. In reality, the computer program controls the other participants. In the inclusion condition, participants receive a proportionate number of ball tosses from the other players throughout the game. However, in the exclusion condition, after receiving a few ball tosses at the beginning the other players stop passing the ball to the participant and exclude him/her from the game. By being excluded from the game, participants experience disconnection from the other players and report increased social pain in the form of a decreased sense of belonging, self-esteem, meaningful existence, sense of control, and mood (Williams et al., 2000; for a review, see Williams, 2009). Results from Eisenberger and colleagues (2003) revealed increased activity in dorsal anterior cingulate cortex (dACC) and anterior insula (AI) during exclusion relative to inclusion. Furthermore, dACC activation was highly positively correlated with self-reported social distress. Activation of dACC and AI has been frequently observed during physical pain and has been mostly associated with the affective component (e.g. unpleasantness) of the experience (Talbot et al., 1991; Rainville et al., 1997; Hutchinson et al., 1999). Thus, because dACC and AI activations have been observed during both social exclusion and physical pain, it was suggested that these similar brain activation patterns might reflect the involvement of shared neural and computational processes underlying both experiences (Eisenberger et al., 2003).

Since Eisenberger and colleagues' (2003) initial study, numerous others have built on the theory of a physical-social pain neural overlap (pain-overlap theory; Eisenberger & Lieberman, 2005). In a behavioral study, participants who were not included during Cyberball showed a negative correlation between social distress and physical pain unpleasantness threshold suggesting that individuals with heightened physical pain sensitivity are also more sensitive to social pain (Eisenberger, Jarcho, Lieberman, & Naliboff, 2006). In additional work, neural activation during Cyberball exclusion has been shown to be moderated by variables that support the overall hypothesis that dACC activity indeed reflects experienced pain. For example, attachment style has been shown to interact with exclusion such

that dACC activation was positively correlated with anxious attachment but negatively correlated with avoidant attachment (DeWall et al., 2012). Other experiences of social disconnection have also been used to elicit neural activity in brain areas associated with pain. When participants viewed photographs of former romantic partners who had recently dumped them, dACC and AI were activated when viewing the ex-partner relative to familiar, neutral acquaintances (Fisher et al., 2010). Using the same ex-romantic partner paradigm, dACC and AI activity was shown to overlap with activity during actual physical pain (Kross et al., 2011). Finally, a recent study demonstrated that taking acetaminophen (the active ingredient in Tylenol) for 3 weeks led to a decrease in daily reported hurt feelings relative to placebo as well as decreased dACC and AI activations during Cyberball exclusion (DeWall et al., 2010).

Thus, in conclusion, experiences which produce physical pain as well as those that produce social pain are frequently associated with neural activity in many of the same regions. Additionally, physical pain-killers have been shown to dampen social pain. However, the psychological process reflected by dACC activation during social exclusion remains unknown. Therefore, the question remains, what is the role of the dACC in experiences of social pain?

Conflict-Monitoring

As reviewed above, ACC activation is a common finding associated with experiences of pain and correlates with reports of distress. However, many other processes seemingly unrelated to pain have been attributed to ACC activation. Indeed, much work in the areas of cognitive neuroscience and computational modeling has focused on conceptualizing the central psychological process represented by ACC activity. One highly-influential theory has proposed that a key function of the ACC is to detect conflicts in information-processing and recruit prefrontal cognitive control regions to resolve the conflict (Botvinick et al., 2001; 2004). For example, according to the conflict-monitoring hypothesis, the ACC is 'triggered' whenever competing, incompatible responses are simultaneously activated (Botvinick et al., 2001; 2004). Tasks that frequently produce response conflicts and thus ACC activation involve the

overriding of prepotent responses (Carter et al., 1998; Botvinick et al., 1999; Kerns et al., 2004), selection from a set of equally permissible responses (Barch, Braver, Sabb, & Noll, 2000), and error commissions (Gehring, Goss, Coles, Meyer, & Donchin, 1993; Dehaene, Posner, & Tucker, 1994; Yeung, Botvinick, & Cohen, 2004). In addition to responding to response level conflicts, ACC has been shown to activate during conflicts at other levels of processing (e.g. perceptual; Weissman, Giesbrecht, Song, Mangun, & Woldorff, 2003). Thus, it has been suggested that ACC acts as a general conflict-monitor across levels of information processing. Finally, upon detecting a conflict, the ACC recruits prefrontal regions (Kerns et al., 2004) that increase processing of task-relevant information (Egner & Hirsh, 2005; King, Korb, van Cramon, & Ullsperger, 2010) and modify behavioral performance.

The conflicting-monitoring hypothesis has found support in numerous behavioral, neuroimaging, and computational modeling studies. For example, one task that has been used regularly to elicit both behavioral and neural indices of conflict is the Eriksen flanker task (Eriksen & Eriksen, 1974). Other frequently used tasks include the Stroop (Stroop, 1935) and Simon (Simon & Small, 1969) tasks. During the flanker task participants are presented with central, target stimuli surrounded by distractor stimuli (i.e. flankers) and are asked to identify the target stimulus with a button press. For example, in some versions arrows are used as the stimuli and arranged horizontally (e.g. >>>>>). By varying these two features of the overall display independently (i.e. target vs. distractor), two basic trial types are created: congruent and incongruent. On congruent trials the target stimulus and the distractor stimuli are associated with the same response (e.g. >>>>>) while on incongruent trials they are associated with different responses (e.g. <<><<). Because both the target and the distractors prompt the same response on congruent trials, these trials do not evoke any conflict in the form of competing responses being simultaneously activated. Meanwhile, on incongruent trials, incompatible responses are activated by the target stimulus prompting a response different from the distractor stimulus response. Therefore, as might be expected due to the required resolution of conflicting responses on

incongruent trials, reaction times (RTs) are slower in incongruent relative to congruent trials. This difference in RTs is called the *interference effect* and has been positively associated with ACC activity (Carter et al., 2000; Botvinick et al., 1999).

Another commonly observed effect in the conflict-monitoring literature results from an interaction between current trial type (incongruent vs. congruent) and previous trial type (Gratton, Coles, & Donchin, 1992). According to the conflict-monitoring hypothesis (Botvinick et al., 2001; 2004), the detection of response conflict on incongruent trials by the ACC results in the recruitment of prefrontal regions that increase processing of task-relevant information in order to improve performance. The increase in task-focused processing evoked by conflict on a trial carries over to the following trial and thus decreases the influence of task-irrelevant information. Therefore, when preceded by an incongruent trial, an immediately subsequent incongruent flanker trial will elicit less activation of the distractor-triggered response and thus less conflict. This effect is sometimes called the *conflict adaptation effect.* In line with this theorizing, RTs on incongruent trials that were preceded by an incongruent trial (iI) versus a congruent trial (cI) are faster (Gratton et al., 1992; Kerns et al., 2004; Botvinik et al., 1999). Furthermore, the level of ACC activation on the preceding trial has been shown to be negatively associated with the RT for the following incongruent trial (Kerns et al., 2004). Additionally, prior ACC activation was positively associated with immediately subsequent dorsolateral prefrontal cortex (dlPFC) activity and dlPFC activation was negatively related with the RT on a given incongruent trial (Kerns et al., 2004).

In addition to being active during trials which elicit competing responses (e.g. incongruent flanker trials), neural activity in the ACC has been frequently associated with the detection of errors (Gehring et al., 1993; Dehaene et al., 1994; Yeung et al., 2004; Kerns et al., 2004). Computational modeling has suggested that conflict-monitoring processes may underlie error detection and the associated ACC responses (Yeung et al., 2004). Specifically, error trials are likely to involve activation of

both correct and incorrect responses and therefore elicit conflict. A commonly observed behavioral response to committing an error is a slower RT on the trial immediately following the error (Rabbitt, 1966; Gehring et al., 1993; Danielmeier & Ullsperger, 2011). This *post-error slowing* is positively associated with ACC activity during error commission (Gehring et al., 1993). Thus, greater conflict during an error is associated with greater post-error slowing. In all, experimental data has been supportive of the conflict-monitoring hypothesis of ACC function.

Neural Alarm System

Based on the theory and work surrounding conflict-monitoring (Botvinick et al., 2001; 2004), Eisenberger and Lieberman (2004; see also Eisenberger, 2012) proposed that ACC activity during painful events represents the engagement of a 'neural alarm system'. Specifically, it was hypothesized that in the case of physically or socially painful experiences the ACC performs two main processes: 1) detection of the discrepancy from a desired set point and 2) triggering of increased attention as well as distress in the form of affective responses and autonomic activity. Thus, the capacity to detect information-processing conflicts was proposed to underlie negative affective responses to social exclusion as well as to aversive physical stimuli.

In support of the neural alarm system hypothesis, a recent meta-analysis demonstrated a shared region of ACC to be activated by pain, tasks involving conflict, and negative affect (Shackman et al., 2011). Thus, all three psychological processes appear to involve a shared region on the brain, suggesting the ACC plays a potentially similar computational role. Additional bolstering evidence for the neural alarm system hypothesis is provided by a study in which participants with obsessive-compulsive disorder (a disorder involving heightened anxiety and chronic distress) showed greater ACC activation during conflict trials and error commission (Ursu et al., 2003). Similarly, participants high in neuroticism (the tendency to experience distress and negative affect) tended to show greater dACC activity during a discrepancy detection task (Eisenberger, Lieberman, & Satpute, 2005). A recent study has demonstrated

that ACC activation during error commissions on a stop-signal task is associated with self-reported negative affect, particularly frustration (Spunt, Eisenberger, & Cohen, 2012).

Seemingly in line with the neural alarm system hypothesis, Botvinick (2007) has recently re-conceptualized the conflict-monitoring theory to propose that conflict serves as an aversive learning signal. In support of the suggestion that conflict is aversive, after being primed with an incongruent Stroop trial participants evaluated negatively valenced stimuli more quickly but positive stimuli more slowly (Dreisbach & Fischer, 2012). Additionally, incongruent primes also produced more negative evaluations of neutral stimuli (Fritz & Dreisbach, 2013). Other evidence suggests that negative affect may even have a role in typical conflict-monitoring behavioral indices (e.g. conflict adaptation). In one experiment, the conflict adaptation effect was reduced when incongruent trials were followed with a stimulus indicating monetary reward (van Steenbergen, Band & Hommel, 2009). Thus, it was suggested that negative affect plays a role in enacting cognitive control and that inducing positive affect can counteract the effects of conflict-induced negative affect. Furthermore, participants induced to experience negative affective states relative to those induced to experience positive affective states demonstrated greater conflict adaptation (van Steenbergen, Band, & Hommel, 2010). Therefore, information-processing conflicts appear to produce negative affect and this affect may be involved in behavioral adjustments associated with conflict. The propensity for conflict to produce negative affect is in line with the neural alarm system hypothesis of ACC function.

Even so, the neural alarm system was proposed in order to integrate cognitive neuroscience research on conflict-monitoring and ACC with other research demonstrating a role for ACC in experiences of pain. Therefore, a critical question is whether conflict-monitoring processes are associated with pain. A few studies have sought to investigate the relationship between physical pain and such cognitive processes. In a PET study of six participants, Derbyshire, Vogt, and Jones (1998) demonstrated some instances of overlapping ACC activation during pain and the Stroop task though, at

the individual participant level, most of the activity was adjacent. Another study had participants perform a cognitive task (but not a conflict-monitoring task) and a pain task while in an fMRI scanner and found that ACC activations did not overlap (Davis, Taylor, Crawley, Wood, & Mikulis, 1997). Thus, there has not been a clear test of the neural alarm system hypothesis of ACC function with a larger sample size.

In conclusion, the neural alarm system hypothesis has been proposed as an integrative interpretation of the process reflected by ACC activation during social exclusion and physical pain paradigms. Specifically, it has been suggested that the ACC detects discrepancy from a desired state and as a result triggers negative affect and autonomic responses. However, evidence directly linking conflict-monitoring processes to experiences of social pain has yet to be produced.

Present Research

In order to clarify the mechanisms underlying neural activations associated with both physical and social pain, the present research sought to investigate the proposed role of conflict-monitoring processes in the experience of social pain. Past work has demonstrated acetaminophen (a widely-used physical pain-killer) to be capable of reducing experiences of social pain as well as the associated ACC activity (DeWall et al., 2010). Therefore, observing effects of acetaminophen on conflict-monitoring task performance as well as responses to social exclusion would provide initial evidence suggesting a shared mechanism underlying social pain and provide support for the neural alarm system hypothesis.

Besides the neural alarm system theory, there are additional reasons to believe that acetaminophen may affect conflict-monitoring processes. First, a recent study has demonstrated acetaminophen to attenuate compensatory responses following expectancy violations (an experience theorized to rely on conflict-monitoring processes; Randles, Heine, & Santos, 2013). Thus, acetaminophen appears to have effects beyond experiences generally considered to be painful. Another area of research that is relevant to the current work is research on marijuana. Both acetaminophen

(Ottani et al., 2006) and marijuana (Lupica et al., 2004) are thought to have some of their effects via action on cannabinoid 1 (CB1) receptors in the brain. Therefore, both drugs are likely to affect similar processes. Indeed, one study has suggested that marijuana use may dampen social pain (Deckman, DeWall, Way, Gilman, & Richman, 2013). Furthermore, additional evidence suggests that marijuana influences conflict-monitoring processes. In one study, acute administration of delta-9-tetrahydrocannabinol (THC) decreased the amplitude of the error-related negativity (ERN; Spronk, Dumont, Verkes, & de Bruijn, 2011). The ERN is a neurophysiological response that has been localized to the ACC and interpreted as reflecting conflict-detection (Gehring et al., 1993; Dehaene et al., 1994; Yeung et al., 2004). An acute dose of marijuana has also been shown to been demonstrated to increase the interference effect during the Stroop task (Hooker & Jones, 1987). Thus, past work has presented the possibility that drugs that act on the CB1 receptor may impact conflict-monitoring processes as well as social pain.

In the first study, participants were given an acute dose of either acetaminophen or placebo and then performed a commonly used conflict-monitoring task. Due to acetaminophen's dampening effects on ACC activity (DeWall et al., 2010) and the positive relationship between ACC activation and behavioral indices of conflict-monitoring (Botvinick et al., 2001; 2004), it was hypothesized that acetaminophen would reduce interference, post-error slowing, and conflict adaptation effects. If acetaminophen decreases behavioral indices of conflict-monitoring this would provide tentative initial evidence that conflict-monitoring may be a shared mechanism underlying both physical and social pain to the extent that acetaminophen is also capable of dampening both types of pain experiences. Furthermore, observing effects of acetaminophen on conflict-monitoring would lend support to the neural alarm system hypothesis given that acetaminophen has been shown to moderate ACC activity.

Chapter 2: Study 1

Methods

Participants. Participants were 73 introductory psychology students at the Ohio State University who voluntarily completed the experiment in exchange for course credit. The data for 13 participants was excluded from analyses; 2 were dropped for failing to follow task instructions, 7 for not responding on greater than 25% of all trials (100 trials), and 4 for computer program malfunctions that caused the computer task to crash mid-completion. Thus, the final analyses included 60 participants (29 males, 30 females, and 1 who declined to respond) with a mean age of 19.02 years (SD = 1.70).

Flanker Task. All participants completed the Eriksen flanker task (Eriksen & Eriksen, 1974). The flanker task has been widely used in the conflict-monitoring literature and shown to reliably elicit ACC activity (Gratton et al., 1992; Gehring et al., 1993; Botvinick et al., 1999; 2001; van Steenbergen et al., 2009; 2010). In this task, stimuli were five arrows (e.g. <<<<<) presented in white on a black background on a computer screen above a central fixation dot. Participants were instructed to indicate the orientation of the central arrow (the target) by pressing a button as quickly and as accurately as possible. On all trials, four additional arrows flanked (two on each side; the distractors) the target arrow. On congruent trials, all arrows pointed in the same direction (e.g. <<<<<); on incongruent trials, the target and flanker arrows pointed in opposite directions (e.g. >><>>).

Each trial began with a grey central fixation dot. The duration of this fixation (the intertrial interval) was randomly varied from 1500ms to 3500ms. At the end of the intertrial interval, the fixation dot brightened to white. The brightening served as a warning cue and occurred 1000ms before the onset of the arrow display. The arrow display was presented for 100ms just above the fixation dot.

There was a 1500ms time window starting with the onset of the arrow display during which participants could provide a response. At the end of the 1500ms time window, the fixation dot returned to grey and the next intertrial interval began.

Participants first completed a practice block of 16 trials in order to familiarize themselves with the task. After this, all participants completed 4 blocks of 100 trials each. Each block consisted of 50% congruent and 50% incongruent trials, randomly ordered. Before beginning, participants were instructed to maintain approximately one meter between their eyes and the screen throughout the task.

Procedure. At the beginning of each experimental session, participants were told that the purpose of the experiment was to investigate the effects of acetaminophen on "how information is processed in the brain". Participants completed a consent form packet and then were given either 1000mg of acetaminophen or placebo in the form of two capsules (30 participants received acetaminophen and 30 received placebo). Participants were randomly assigned to drug condition and the experimenter was blind to the participants' conditions.

Next, participants completed a series of questionnaires. Simultaneous to completion of the online questionnaires, participants were asked to provide a 2mL saliva sample for genotyping. Following completion of the questionnaires, participants were told to relax quietly until about 50 minutes had elapsed since drug administration. This time was allotted to allow for drug absorption and participants were permitted to engage in quiet activities such as school course work or texting on their cellular phones.

After the wait period, participants received instructions about the flanker task and completed a 16 trial practice block. At about 50 minutes after drug administration, participants started the first block of the flanker task. After completing the flanker task, participants completed a brief questionnaire. Finally, all participants were asked to guess which drug they had received, were debriefed about the study purposes, and dismissed.

Results

In line with past work (Verbruggen et al., 2006; van Steenbergen et al., 2009), any reaction times (RTs) greater than 2.5 standard deviations from the mean for each participant were excluded from all analyses. Furthermore, only RTs from trials on which the participant gave the correct response were included in the analyses. The drug conditions did not differ in terms of overall RT speed and thus it does not appear that acetaminophen affects general processing speed, $t(58) = 1.2183$, $p = .23$. Participants were not able to guess the drug they received, $\chi^2(3, N = 55) = .7$, $p = .87$, and thus the study was indeed double-blind.

Interference Effects

In order to test the hypothesis that acetaminophen would reduce the interference effect, a mixed ANOVA was run with drug condition as a between-subjects variable and flanker trial type as a within-subjects variable. For this analysis, all RTs following an error were excluded (Verbruggen et al., 2006; van Steenbergen et al., 2009). Participants demonstrated the standard interference effect with slower RTs on incongruent trials relative to congruent trials, $F(1, 58) = 607.553$, $p < .0001$. The interaction of drug (acetaminophen vs. placebo) and trial type (incongruent vs. congruent) on RT was significant, $F(1, 58) = 5.119$, $p = .03$, but in the opposite direction as was predicted. The interference effect was present in both the acetaminophen, $t(29) = 16.1252$, $p < .0001$, and the placebo, $t(29) = 20.3105$, $p < .0001$, conditions. However, contrary to the hypotheses, participants who received acetaminophen demonstrated a greater interference effect ($RT_{incongruent} - RT_{congruent}$; $M = 94.22$, $SD = 32.00$) than participants who received placebo ($M = 78.37$, $SD = 21.14$; $t(50.254) = 2.2625$, $p = .03$; See Figure 1).

Post-Error Slowing

In order to determine whether participants on acetaminophen made more errors than those on placebo, error rates were calculated by dividing the number of errors made by the number of trials on

which a response was given. For analyses, error rates were transformed by taking the cubic root in order to make the distributions normal. A mixed ANOVA revealed that participants had a higher error rate on incongruent trials (M = .08, SD = .09) relative to congruent trials (M = .01, SD = .02), $F(1,58) = 290.125$, $p < .0001$, as expected. Drug conditions did not differ in terms of overall error rate, $F(1,58) = 0.254$, $p = .62$, and drug did not interact with trial type, $F(1,58) = 0.314$, $p = .58$.

In order to determine whether acetaminophen affected how much participants slowed their RTs following making an error, post-error slowing was calculated by subtracting RTs following correct trials from RTs following error trials. One participant in the acetaminophen condition was excluded from these analyses for not making any errors. After excluding an outlier in the acetaminophen condition (>4 *SD*s above the mean), results revealed a significant difference in the predicted direction such that participants on acetaminophen showed less post-error slowing than those on placebo, $t(56) = 2.1971$, $p = .03$ (See Figure 2). Thus, participants on acetaminophen slowed down less following an error (M = -5.35, SD = 36.04) relative to participants on placebo (M = 13.99, SD = 28.94).

Conflict Adaptation

In order to test whether acetaminophen reduced the conflict adaptation effect, a mixed ANOVA was run with drug condition as a between-subjects variable and previous and current flanker trial types as within-subjects variables. All RTs following an error were excluded from these analyses. The conflict adaptation effect was observed in the present data as indicated by a previous X current trial type interaction, $F(1, 58) = 30.488$, $p < .0001$. Indeed, the interference effect was greater following congruent trials (M = 92.77, SD = 32.34) than incongruent trials (M = 79.31, SD = 26.24), $t(59) = 5.5404$, $p < .0001$. However, the non-significant 3-way interaction showed that drug did not moderate the conflict adaptation effect, $F(1, 58) = 0.599$, $p = .44$. Further analysis revealed that the conflict adaptation effect was significant in both the placebo, $F(1,29) = 10.99$, $p = .002$, and acetaminophen conditions, $F(1, 29) = 20.34$, $p < .0001$.

Discussion

The present results yielded mixed support for the neural alarm system prediction that if acetaminophen decreases social pain by dampening ACC activity it is occurring via disruption of a conflict-monitoring mechanism. That is, based on recent data showing that acetaminophen dampens ACC activation during social exclusion (DeWall et al., 2010), the neural alarm system hypothesis would predict that acetaminophen would interrupt conflict-monitoring and would decrease the interference effect in a flanker task. However, the current data revealed a significant effect in the opposite direction such that participants who had taken acetaminophen actually showed greater interference. Meanwhile, as predicted, acetaminophen decreased post-error slowing. Finally, acetaminophen failed to decrease the magnitude of the conflict adaptation effect as would be predicted by the neural alarm system hypothesis. Thus, while not all of the results were as predicted, the present data provide tentative support for the neural alarm system hypothesis in that acetaminophen does appear to affect conflict-monitoring processes.

Although study 1 provided some preliminary evidence than acetaminophen affects conflict-monitoring, a critical limitation is that the current experiment did not measure participant experiences of social pain. Thus, it is possible that the acute dosage of acetaminophen utilized did not affect any of the mechanisms underlying social pain. If the current drug administration procedures were not effective in reducing pain, then observing drug effects on conflict-monitoring would suggest that this process is actually not involved in pain. Indeed, the efficacy of an acute dose of acetaminophen on social pain is uncertain because in the study by DeWall and colleagues (2010) acetaminophen was administered chronically for 3 weeks prior to the fMRI session with Cyberball. However, a more recent paper has shown an acute dosage to have effects on responses to tasks theorized to involve conflict-monitoring processes (Randles et al., 2013). Nevertheless, incorporating a measure of social pain to the study design would allow for this issue to be addressed.

Study 2 sought to address this critical issue from study 1 by having participants complete the first block of the same flanker task used in study 1. The flanker task was shortened to just 100 trials because data from study 1 revealed that both the interference effect ($t(59) = 18.3499$, $p < .0001$) and the conflict adaptation effect ($F(1, 59) = 13.77$, $p < .001$) were significant in the first block. Thus, 100 trials were sufficient to elicit the effects under examination. Next, participants underwent the Cyberball social exclusion manipulation and completed subsequent measures of social pain. Overall, the objectives of study 2 were three-fold. First, the association between flanker task indices of conflict-monitoring and social pain measures was examined. According to the neural alarm system hypothesis, to the extent that social pain relies on conflict-monitoring processes, measures of one should be related to the other. Second, the effect of acetaminophen on flanker task conflict-monitoring indices and measures of social pain were directly compared. Demonstrating similar acetaminophen-induced reductions in both conflict-monitoring and social pain would lend support to the neural alarm system hypothesis of ACC function and may suggest that acetaminophen reduces social pain via ACC-related conflict-monitoring mechanism. Alternatively, observing an effect of acetaminophen on social pain but not conflict-monitoring would suggest that acetaminophen-induced reductions in social pain are not the result of interference with conflict-monitoring processes as the neural alarm system hypothesis would predict. Third, by using an acute dose of acetaminophen, the ability of acute drug administration to reduce social pain was investigated.

Chapter 3: Study 2

Methods

Participants. Participants were 88 introductory psychology students at Ohio State University who voluntarily completed the experiment in exchange for course credit (M_{age} = 19.62, *SD* = 1.98; 47 males). One participant left after completing the questionnaires and did not complete the computer tasks. Therefore, computer task data was available for 87 participants.

Procedure. Participants were run in groups of three with each of the participants in separate rooms. Because the Cyberball social exclusion manipulation requires deception, if there were not enough participants the experimenter faked the late arrival of additional participants out-of-sight from where the participants were seated. As a cover story, all participants were told that the purpose of the experiment was to investigate the effects of acetaminophen on the accuracy, speed, and vividness with which visual information is processed. Participants completed a consent form packet and were randomly assigned to receive either 1000mg of acetaminophen or placebo in the form of two capsules (44 participants received acetaminophen and 43 received placebo). The experimenter was blind to the participants' conditions.

Immediately after drug administration, participants completed a series of questionnaires on Qualtrics. Simultaneous to completion of the questionnaires, participants were asked to provide a 2mL saliva sample for genotyping. Following the questionnaires, participants read computerized instructions for computer tasks they would be completing later.

About 50 minutes after drug administration, participants completed a state emotions measure in which they rated the extent to which they currently felt 15 emotional adjectives on a scale from 1

(not at all) to 7 (extremely). The emotional adjective ratings were used to compute composite measures of happiness (cheerful and pleased), anxiety (anxious and tense), hurt feelings (hurt, pained, and wounded), anger (angry, irritated, and mad), sadness (sad and down), and strength (strong, tough, and powerful). Following the initial state emotion measure, participants completed 16 practice trials followed by one 100-trial block of the same flanker task used in Study 1. Next, participants answered a few questions about the flanker task and then completed a couple filler tasks. Participants then completed the Cyberball social exclusion paradigm (Williams et al., 2000). Cyberball was presented as a mental visualization task and participants were instructed to visualize surroundings and the other people as if the game of catch were occurring in-person. During Cyberball, 44 participants received the ball on 33% of the 40 total tosses while 43 participants never received the ball again after the tenth toss. Thus, participants were either included or excluded, respectively. Following Cyberball, in order to further bolster the cover story, participants answered a few questions about the vividness of their visualization experience during Cyberball. Lastly, participants reported their state emotions again and completed a final task. After completing all tasks, participants were probed for suspicion, asked to guess which drug they had received, and fully debriefed.

The filler tasks completed between the flanker task and Cyberball were the Information Sampling Task (IST; Clark et al., 2006) and a temporal discounting task (Weber et al., 2007). The final task completed following Cyberball was the Competitive Reaction Time task (Taylor, 1967). Data from these tasks are not presented in the current report.

Results

Participants were unable to guess which drug they received and thus the experiment was double-blind, χ^2 (1, N = 81) = .3196, p = .57.

Flanker task

For all flanker task analyses, any participants who did not respond on more than 25% of the trials were excluded. Furthermore, because only correct RTs are analyzed, any participants who made errors on greater than 25% of the total trials were excluded. Thus, 74 participants were included in the flanker task analyses (38 acetaminophen; 36 placebo). As in study 1, any RTs greater than 2.5 standard deviations from each participant's mean were excluded from analyses. Only RTs from trials on which the correct response was given were analyzed.

Interference Effect

To test hypothesis that acetaminophen would reduce the interference effect, a mixed ANOVA was run with drug as a between-subjects variable and trial type (congruent vs. incongruent) as a within-subjects variable. As in study 1, any RTs that followed an error were excluded from these analyses. Results revealed the familiar interference effect in that RTs on incongruent trials were slower than RTs on congruent trials, $F(1,72) = 325.076$, $p < .0001$. Furthermore, there was a marginal main effect of drug such that participants on acetaminophen had faster RTs than those on placebo, $F(1,72) = 3.107$, $p = .08$. Finally, the interaction between drug and trial type reached trend level, $F(1,72) = 2.426$, $p = .12$. Contrary to the results of study 1, calculating the interference effect ($RT_{incongruent} – RT_{congruent}$) for both drug conditions revealed that the interference effect was non-significantly smaller among participants in the acetaminophen condition ($M = 83.38$, $SD = 25.47$) relative to those in the placebo condition ($M = 99.11$, $SD = 56.52$; $t(72) = 1.5574$, $p = .12$). However, the main effect of drug and drug X trial type interaction were partially driven an outlier in the placebo condition (incongruent RT 4.18 SDs above the mean). After excluding this participant from analyses, the main effect of drug was reduced to a trend ($F(1,71) = 2.306$, $p = .13$) and the drug X trial type interaction was also reduced ($F(1,71) = 1.364$, $p = .25$).

Error Rate

In order to determine whether acetaminophen increased the number of errors, error rates were calculated by dividing the number of errors by the number of trials on which a response was given.

Furthermore, error rates were transformed by taking the cubic root in order to create normal distributions. As expected, a mixed ANOVA revealed that participants had higher error rates on incongruent trials (M = .09, *SD* = .10) relative to congruent trials (*M* = .006, *SD* = .01), $F(1,72) = 175.782$, $p < .0001$. However, there was no main effect of drug condition, $F(1,72) = 0.04$, $p = .84$, and no interaction between drug condition and trial type, $F(1,72) = 0.639$, $p = .43$. With the shortened flanker task (100 trials), there were not enough errors to analyze post-error slowing.

Conflict Adaptation

To test the hypothesis that acetaminophen would reduce the conflict adaptation effect, a mixed ANOVA with drug as a between-subjects variable and current and previous trial types as within-subjects variables was run. Participants demonstrated the conflict adaptation effect (current trial type X previous trial type; $F(1,72) = 15.155$, $p = .0002$) such that the interference effect was greater following congruent trials (*M* = 98.01, *SD* = 51.86) than incongruent trials (*M* = 83.29, *SD* = 38.71; $t(73) = 3.8556$, $p < .001$). The 3-way interaction reached trend level, $F(1,72) = 2.419$, $p = .12$. Calculating the conflict adaptation effect ((cI – cC) – (iI – iC); where cI is the mean RT for incongruent trials preceded by a congruent trial, cC is the mean RT for congruent trials preceded by a congruent trial, and so on) revealed that although participants on acetaminophen demonstrated decreased conflict adaptation (*M* = 9.00, *SD* = 31.13) relative to those on placebo (*M* = 20.77, *SD* = 33.95) the difference between the drug conditions did not reach significance (see Figure 3). However, closer examination revealed that while the conflict adaptation effect was significant in the placebo condition ($F(1,35) = 13.47$, $p < .001$) it was marginally significant in the acetaminophen condition ($F(1,37) = 3.174$, $p = .08$).

Cyberball Emotions

As a manipulation check for Cyberball condition, participants were asked to estimate the percentage of total ball tosses they received. The manipulation was successful in that participants in the exclusion condition reported receiving the ball on a smaller percentage of tosses than those in the

inclusion condition, $t(85) = 11.6849$, $p < .0001$. In order to calculate emotional responses to Cyberball, state emotion ratings just prior to and following Cyberball were each averaged. Then the pre-Cyberball emotions were subtracted from the post-Cyberball emotions. The following analyses did not differ if participants who expressed suspicion about whether they were actually interacting with the other participants were excluded so the analyses reported include all participants. The effects of drug, Cyberball condition, and their interaction on change in happiness, anxiety, anger, sadness, and strength were not significant (ps > .13). The main effect of Cyberball condition on change in hurt feelings was not significant, $F(1,83) = .2319$, $p = .63$, and neither was the effect of drug, $F(1,83) = 2.6688$, $p = .11$. However, in line with the hypothesis that acetaminophen would reduce hurt feelings in response to social exclusion, there was a significant interaction of drug and Cyberball condition on change in hurt feelings, $F(1,83) = 8.4918$, $p < .005$. Planned comparisons revealed that participants on placebo reported a marginally significant increase in hurt feelings when excluded relative to inclusion, $t(83) = 1.712$, $p = .09$. Unexpectedly, participants on acetaminophen showed significantly decreased hurt feelings when excluded relative to inclusion, $t(83) = 2.412$, $p = .02$.

Association between Conflict-Monitoring and Hurt Feelings

For all analyses in this section, the same participants excluded during the flanker task analyses (see above) were also excluded. To examine whether conflict-monitoring indices were associated with responses to social exclusion, Pearson's correlations were conducted. Results revealed no relationship between change in hurt feelings and either conflict adaptation ($r(74) = -.05$, $p = .7$) or the interference effect ($r(74) = .03$, $p = .8$). Neither behavioral index of conflict-monitoring was associated with change in any other emotion (ps > .15).

In order to assess whether differences in conflict-monitoring accounted for hurt feelings in response to Cyberball exclusion, a set of hierarchical regressions were run. If including behavioral indices of conflict-monitoring in the model eliminates the interactive effect of Cyberball and drug on hurt

feelings then this would suggest that conflict-monitoring may underlie responses of social pain. For step 1 of the regression, both Cyberball and drug conditions were effects-coded and their main effects and interaction were entered into a regression predicting change in hurt feelings. The overall model was non-significant, $F(3,70) = 1.734$, $p = .17$. However, closer examination revealed that two outliers (studentized residuals > 4) were heavily influencing the model (DFFITS > 1; covariance ratio < .43) and so these data points were excluded from further analyses. Excluding these participants, the step 1 model was marginally significant, $F(3,68) = 2.51$, $p = .066$ (see Table 1). Furthermore, the interaction between drug and Cyberball significantly predicted change in hurt feelings, $ß = -0.07$, $t = 2.11$, $p < .04$. Next, for step 2a, conflict adaptation and its interactions were entered into the model. Adding conflict adaptation as a predictor resulted in a poor overall model, $F(7,64) = 1.27$, $p = .28$ (see Table 1). Furthermore, the interaction of Cyberball and drug remained a significant predictor of change in hurt feelings, $ß = -0.08$, $t = 2.16$, $p < .04$. Thus, controlling for conflict adaptation did not eliminate the effect of Cyberball and drug on change in hurt feelings. In to examine whether another behavioral measure of conflict-monitoring could account for the effect of Cyberball and drug on change in hurt feelings, the interference effect and its interactions were added to the step 1 model to create step 2b. Adding the interference effect as a predictor reduced the fit of the overall model, $F(7,64) = 1.412$, $p = .22$ (see Table 1). Furthermore, the interaction of Cyberball and drug remained a marginally significant predictor of change in hurt feelings, $ß = -0.06$, $t = 1.81$, $p = .07$. Therefore, controlling for either conflict adaptation or the interference effect failed to eliminate the effect of the interaction of exclusion and acetaminophen on hurt feelings.

Discussion

The results of study 2 demonstrated that an acute dosage of acetaminophen is capable of influencing experiences of social pain. Specifically, participants who had taken acetaminophen reported less hurt feelings following exclusion relative to those who had taken placebo. However, acetaminophen

did not influence behavioral measures of conflict-monitoring as previously observed in study 1 and thus does not appear to be reducing social pain by dampening conflict-monitoring processes. Furthermore, conflict-monitoring performance was not correlated with hurt feelings and statistically controlling for conflict-monitoring did not eliminate the effect of social exclusion and drug condition on hurt feelings. Therefore, differences in conflict-monitoring abilities do not appear to be related to social pain sensitivity, as the neural alarm system hypothesis would predict.

A puzzling aspect of the results from study 2 is that participants in the acetaminophen condition revealed a smaller interference effect relative to placebo when an effect in the opposite direction had been observed in study 1. Although most of the procedure preceding the flanker task remained the same in both studies, there are a few differences that may have contributed the current results. First, while both studies were mostly run at the end of semesters, study 1 was collected at the end of the autumn semester while study 2 was collected at the end of the spring semester. Thus, it is possible that some feature of the student environment for that time of year interacted with the drug to produce the opposing effects. Second, perhaps the experimental instructions used in each study elicited different levels of motivation for engaging the flanker task. Indeed, a comparison of RTs from the two studies revealed that participants in study 1 had significantly slower RTs overall compared to those in study 2, $t(132) = 2.4174$, $p = .017$. Therefore, it might be that acetaminophen interacted with participants' overall motivation for the task. It is worth noting that, among participants in study 2, acetaminophen did not affect self-reported motivation, focus, or interest in the flanker task (p's > .12). Future research should consider possibility interactions between drug and task framing.

A critical limitation of study 2 is the time difference between when participants completed the flanker task and Cyberball. The flanker was completed about 50 minutes after drug administration while Cyberball came significantly later. Therefore, it is possible that the acetaminophen was not sufficiently active to have an effect at the time of the flanker task but was active by the time participants underwent

the social exclusion manipulation. A future study should have participants wait longer after drug administration before completing a conflict-monitoring task. Alternatively, a quicker acting form of drug could be used (e.g. liquid acetaminophen).

Chapter 4: General Discussion

The studies reported here were designed to investigate the neural alarm system's hypothesis that ACC activation during social exclusion reflects the involvement of a conflict-monitoring process. Based on prior work that has shown acetaminophen to decrease ACC activity during social exclusion as well as reports of hurt feelings, it was hypothesized that acetaminophen might enact its pain-reducing effects by disrupting conflict-monitoring processes. Therefore, in study 1, participants were given either acetaminophen or placebo and then asked to complete a widely-used conflict-monitoring task. It was predicted that acetaminophen would reduce the magnitude of the interference and conflict adaptation effects. In addition, it was hypothesized that acetaminophen would reduce how much participants slowed down after committing an error. The data from study 1 provided mixed support for these hypotheses. The goal of study 2 was to address some of the concerns regarding study 1's design by including a measure of hurt feelings in response to social exclusion. Adding a measure of social pain allowed for associations between social pain responses and conflict-monitoring to be investigated. Although acetaminophen reduced hurt feelings following social exclusion, it did not significantly affect conflict-monitoring performance and conflict-monitoring was not associated with emotional responses to exclusion. Because past research has demonstrated the magnitude of ACC activation to correlate with response conflict (Botvinick et al., 1999; Kerns et al., 2004) as well as social distress during social exclusion (Eisenberger et al., 2003), the neural alarm system hypothesis would predict that individual differences in conflict should correlate with social pain. Thus, observing no relationship between flanker task performance and hurt feelings in response to exclusion suggests that the neural alarm system hypothesis may require revisions.

Overall, the data from the current studies failed to provide clear support for the neural alarm system hypothesis and a role for conflict-monitoring in social pain. These results are in line with recent studies which have demonstrated event-related potentials (ERPs) associated with attention allocation, but not those associated with conflict-monitoring, to be related to emotional responses to social exclusion (Kawamoto, Nittono, & Ura, 2010; Themanson, Khatcherian, Ball, & Rosen, 2012). Combining evidence from the current studies with the recent work by other researchers, it is becoming apparent that conflict-monitoring indices are not associated with self-reported measures of social pain. Therefore, the neural alarm system hypothesis is likely to require modifications. Future work should examine the role of other candidate processes in the generation of social pain responses to social disconnection and clarify whether or not conflict-monitoring is involved.

Although the studies reported here did not support the neural alarm system hypothesis, study 2 did provide critical new evidence for the social pain-reducing effects of acetaminophen. In line with past research (DeWall et al., 2010), acetaminophen reduced hurt feelings in response to exclusion relative to placebo. To the extent that acetaminophen also alleviates physical pain, these data provide additional support for the general theory that both physical and social pain rely on shared neural systems. By demonstrating shared neural mechanisms, other treatments for physical pain might be adopted for the treatment of socially painful experiences. Critically, because acetaminophen is a readily available over-the-counter medication, its usage could quickly be adapted for the treatment of social pain. With careful implementation, acetaminophen could become an effective treatment for people suffering from the death of a loved one or a romantic breakup. Furthermore, this study has produced the first demonstration that an acute dose of acetaminophen can reduce social pain. Observing acute dose effects is important because it suggests that acetaminophen may be capable of offering rapid relief and does not necessarily need to be administered chronically. Altogether, the effect of acetaminophen on

hurt feelings observed in the current data provides support for pain-overlap theory and the development of an inexpensive, widely-available pharmacological treatment.

Limitations and Future Directions

In contrast to the neural alarm system hypothesis, the present studies suggest that conflict-monitoring may not be a mechanism underlying social pain. However, it is important to consider possible design limitations that provide reasons to avoid dismissing the neural alarm system hypothesis prematurely. Indeed, there are several potential explanations for the non-significant results in the present studies. First, one reason for the failure to observe an effect of acetaminophen on flanker task performance might be that acetaminophen is reducing social pain via effects on neural processes other than those associated with the ACC. That is, although acetaminophen was previously shown to decrease ACC activation during social exclusion (DeWall et al., 2010), the neural alarm system hypothesis states that ACC activity during exclusion reflects the detection of a discrepancy from a desired set point (Eisenberger & Lieberman, 2004). Thus, ACC activation relies on competing activation of representations of the desired set point as well as the individual's actual state. If acetaminophen affects the construction of either of these representations then it could eliminate the presence of a discrepancy for ACC to detect. For example, if acetaminophen reduces the desire for social integration then being excluded would not be detected as discrepant from an individual's goals. In this way, ACC activation during social exclusion could be dampened by acetaminophen without affecting the conflict-monitoring process itself. By not affecting conflict-monitoring or the ACC, the associated processes should still be functional during tasks such as the flanker task. Without any measures of neural activity, it is impossible to determine whether acetaminophen influenced ACC-generated neural responses to response conflict during the flanker task. If acetaminophen did not reduce neural responses indicative of conflict-monitoring during the flanker task but did reduce ACC activation during social exclusion, this would provide evidence that acetaminophen may be affecting neural regions and processes that temporally

precede any activation of the neural alarm system. Therefore, a future study might be to compare the effect of acetaminophen on neural responses to both response conflict and social exclusion.

Second, although no relationship was observed between self-reported hurt feelings and conflict-monitoring performance in study 2, it is still possible that conflict-monitoring processes play a role in social pain. According to the neural alarm system hypothesis, the ACC detects a discrepancy and then triggers negative affect. Exclusion during Cyberball may be so apparent that even participants with less sensitivity for conflict detection are capable of detecting the discrepancy from their desired inclusion status. Once exclusion is detected and negative affect has been triggered, other processes unrelated to conflict-monitoring (such as reappraisal processes which rely on ACC-recruited prefrontal regions) may begin to operate and adjust the affective experience. Indeed, prefrontal activations during social exclusion have been shown to be negatively correlated with distress (Eisenberger et al., 2003). Thus, conflict-monitoring may be related to the initial detection of social exclusion but not necessarily the emotions reported following the experience. If this is the case, then emotional responses to more subtle instances of social exclusion should be more likely to be associated with a person's sensitivity to conflict because those with less sensitivity will be less likely to detect the exclusion.

In line with the above hypothesis that conflict-monitoring might be associated with the detection of exclusion rather than the emotional response, another prediction is that people with heightened conflict-monitoring should be quicker to detect exclusion when it occurs. One hypothesis that follows from this prediction is that conflict-monitoring should be negatively related with the amount of time it takes to realize that one is being excluded during Cyberball. The emotional time course of participants during Cyberball has been previously measured with a dial that participants turned in order to provide a continuous measure of overall affective positivity (Wesselmann, Wirth, Mroczek, & Williams, 2012). Using a 'feelings dial', it may be the case that heightened conflict sensitivity during the flanker task would be associated with earlier decreases in affect during exclusion.

Alternatively, it might be possible to use a continuous physiological measure such as pupillary dilation, which has been shown to be associated with both social rejection (Silk et al., 2012) and response conflict (Brown et al., 1999; Siegle et al., 2004; Laeng et al., 2011), as a measure of social exclusion detection.

Conclusion

The present studies sought to test the neural alarm system hypothesis of ACC activation during social exclusion. Although the data did not support the theory, it remains possible that procedural modifications and different measures could produce supportive results in the future. Meanwhile, study 2 provided the first evidence of acute acetaminophen administration reducing social pain. Acetaminophen's ability to dampen social pain has many important implications for both theory and clinical application. Given the severe detriments of social disconnection, this program of research certainly warrants continued investigation.

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Appendix A: Figures

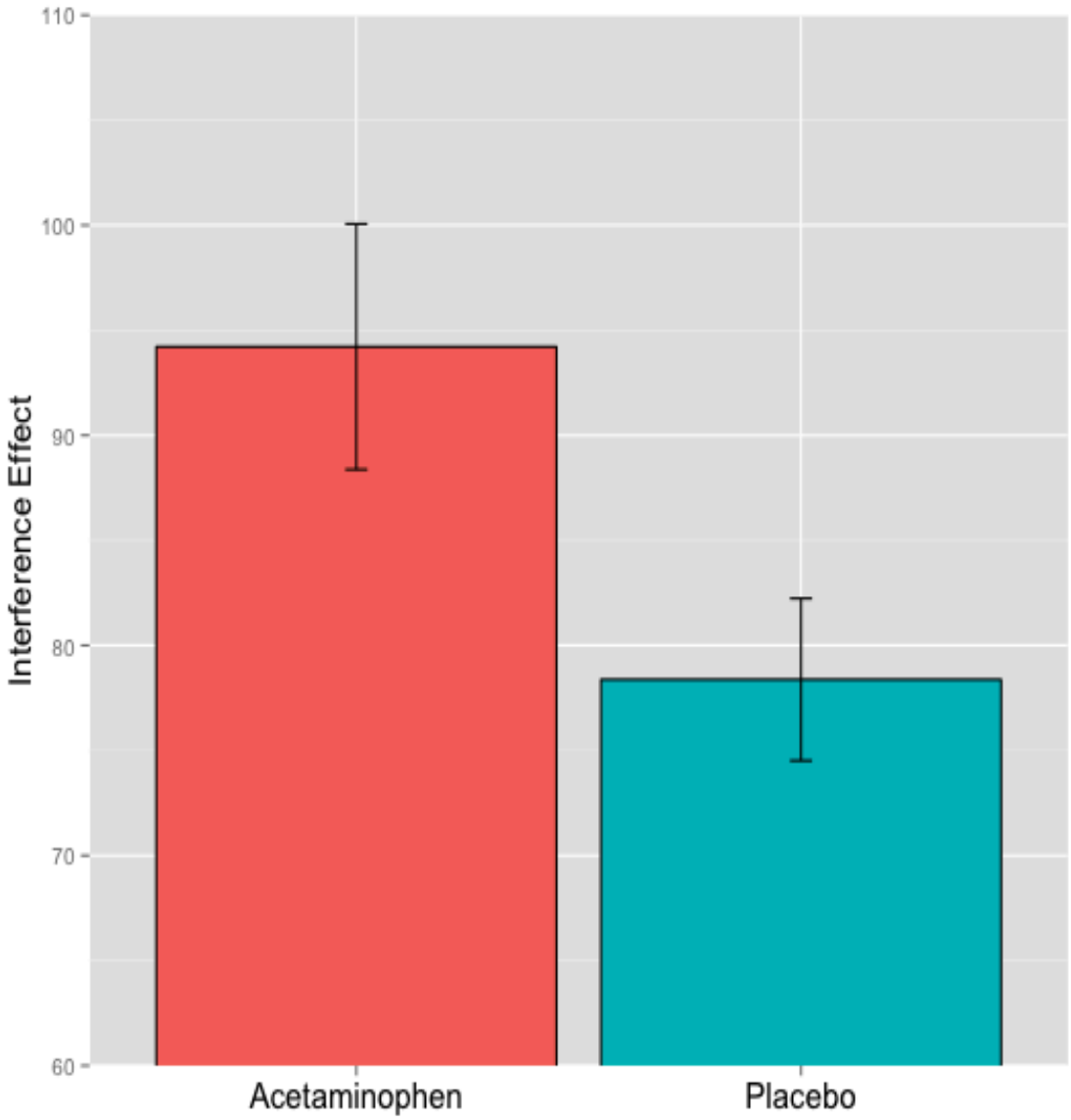

Figure 1: Study 1 – Interference Effect

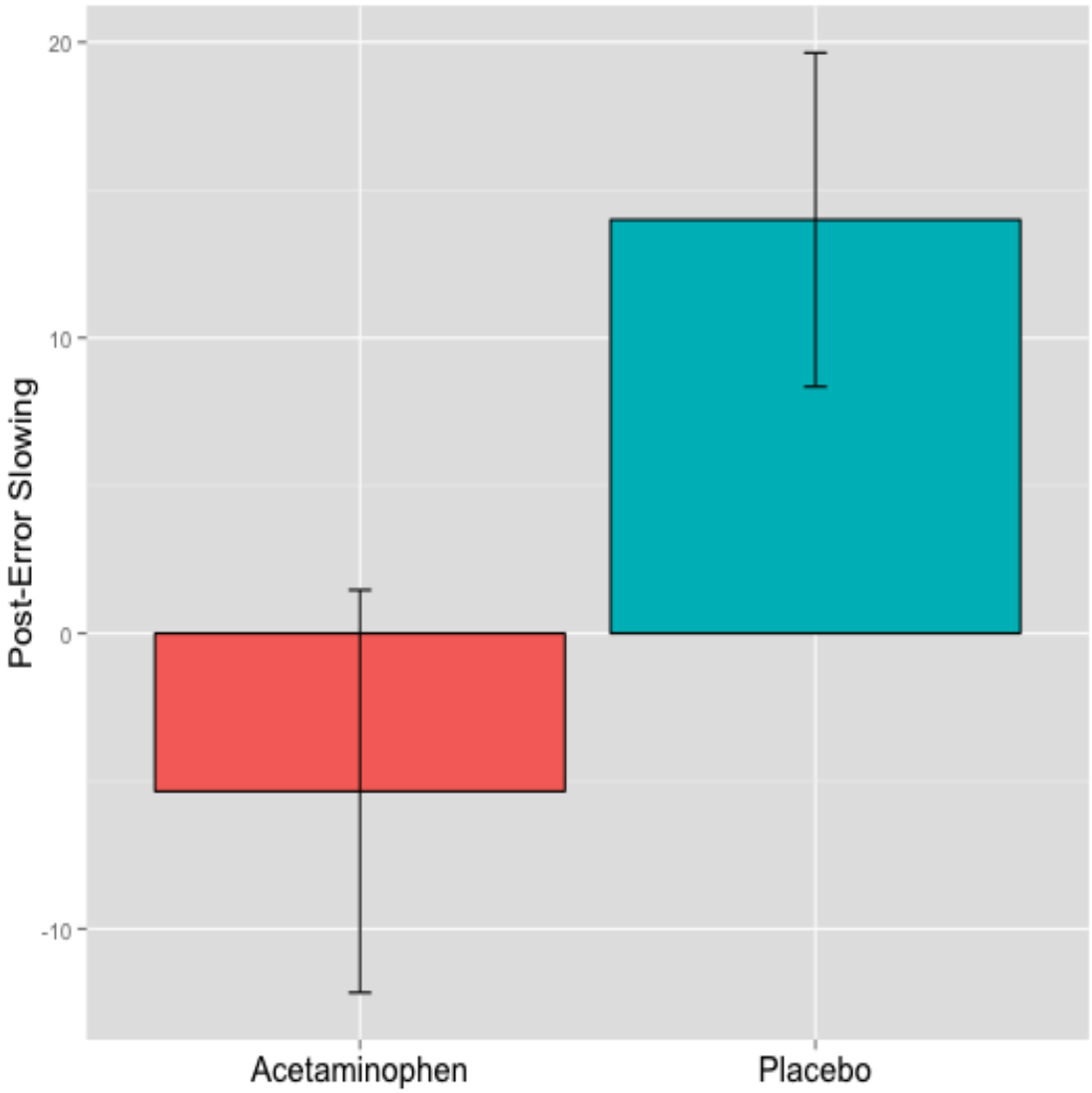

Figure 2: Study 1 – Post-Error Slowing

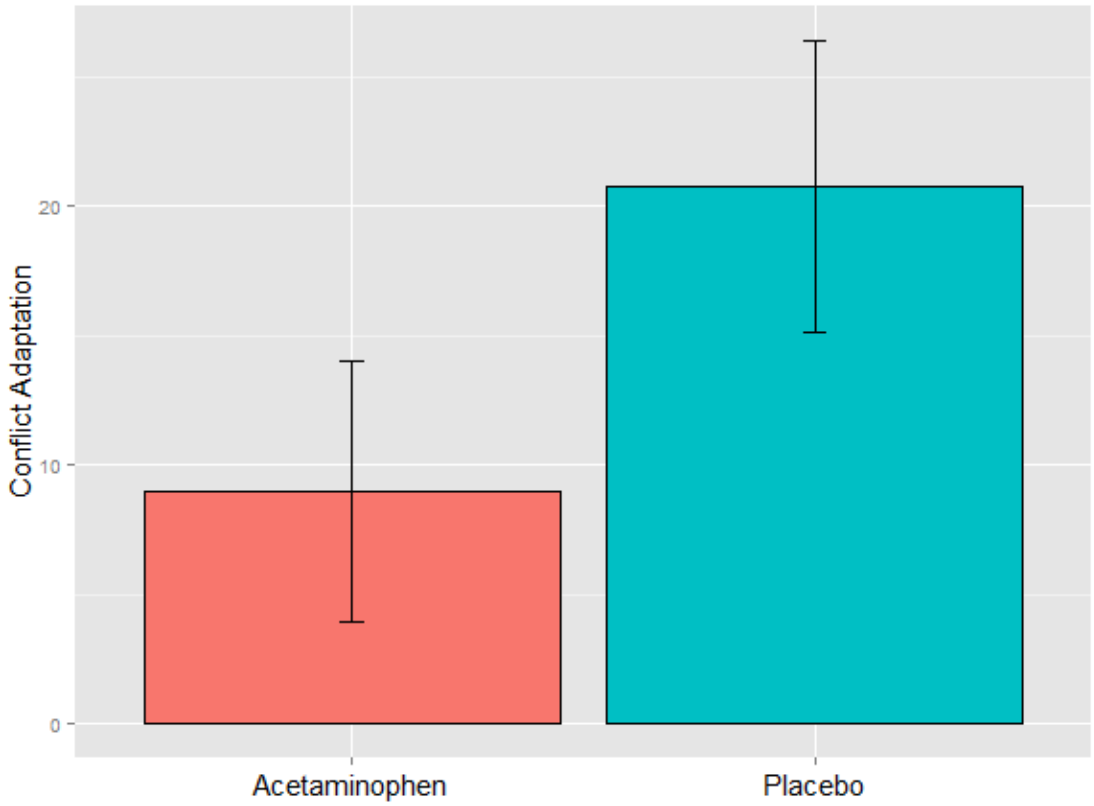

Figure 3: Study 2 – Conflict Adaptation Effect

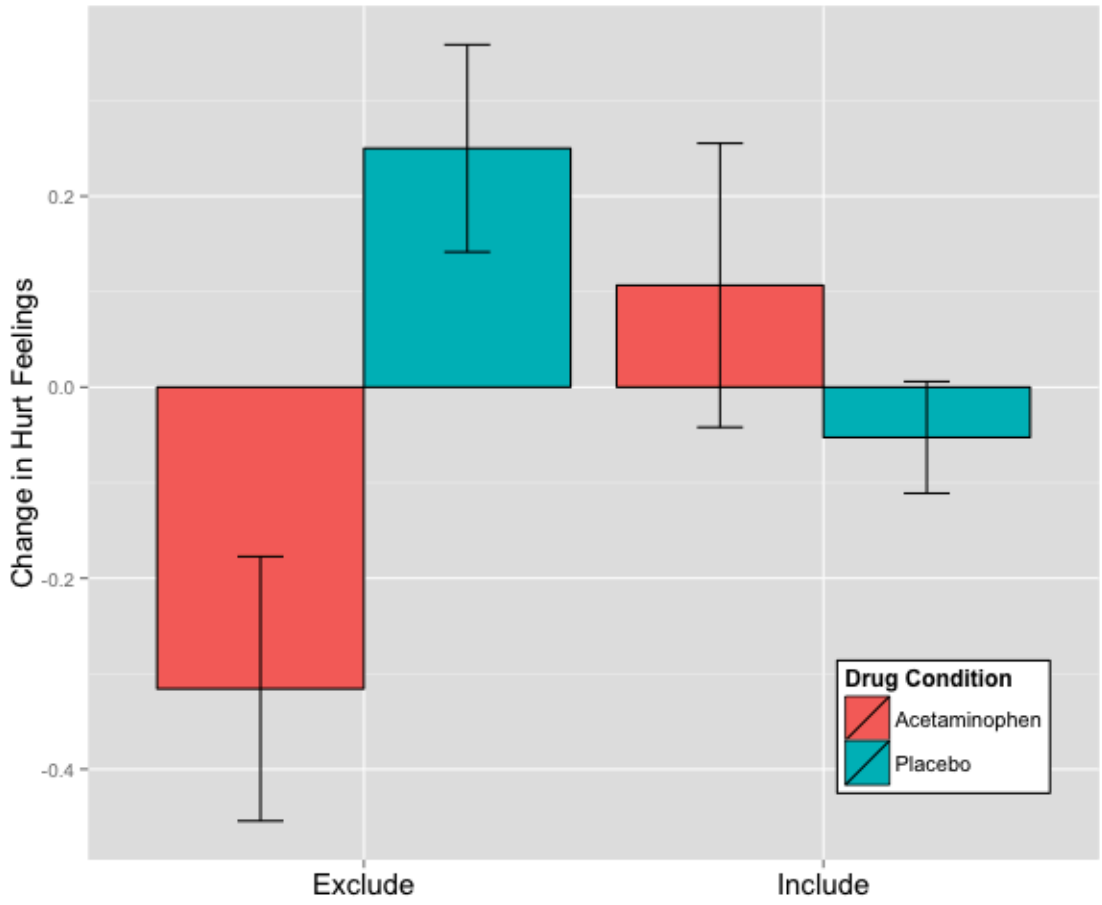

Figure 4: Study 2 – Effect of Cyberball by Drug on Hurt Feelings

Appendix B: Tables

Table 1. Cyberball, Drug, & Flanker Task Predicting Hurt Feelings

	Δ adj. R^2	***B***	***SE B***	***t***	***p***
Step 1	0.06				
Intercept		-0.08	0.04	-2.35	<.03
Drug		-0.06	0.04	-1.68	.10
Cyberball		0.02	0.04	0.50	.62
Drug X Cyberball		-0.07	0.04	-2.11	<.04
Step 2a – Conflict adaptation	-0.03				
Intercept		-0.09	0.04	-2.36	<.03
Drug		-0.07	0.04	-1.71	.09
Cyberball		0.01	0.04	0.30	.76
Conflict		-0.00	0.00	-0.71	.48
Drug X Cyberball		-0.08	0.04	-2.16	<.04
Drug X Conflict		-0.00	0.00	-0.48	.63
Cyberball X Conflict		-0.00	0.00	-0.38	.71
Drug X Cyberball X Conflict		-0.00	0.00	-0.52	.61
Step 2b – Interference Effect	-0.02				
Intercept		-0.09	0.04	-2.38	<.02
Drug		-0.06	0.04	-1.57	.12
Cyberball		0.02	0.04	0.63	.53
Interference		-0.00	0.00	-0.79	.43
Drug X Cyberball		-0.06	0.04	-1.81	.07
Drug X Interference		0.00	0.00	-0.58	.57
Cyberball X Interference		0.00	0.00	-1.18	.24
Drug X Cyberball X Interference		0.00	0.00	0.68	.50

Change in R^2 for both step 2a and 2b models is relative to step 1 model.