

THE EFFECTS OF ACETAMINOPHEN ON NEURAL INDICATORS OF EMOTIONAL REACTIONS

An Undergraduate Research Scholars Thesis

by

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ABSTRACT

The effects of acetaminophen on neural indicators of emotional reactions

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Acetaminophen, the active ingredient in Tylenol, is a popular over-the-counter pain reliever. Recent studies suggest that acetaminophen blunts not only physical pain but also emotional pain (DeWall et al., 2010; Durso, Luttrell, & Way, 2015). The current experiment expands previous research beyond self-report measures to study the effects of acetaminophen administration on emotional responding at the neural level. This study was conducted with a sample of undergraduates from Texas A&M University ($n = 97$). Participants viewed positive, negative and neutral images on a computer screen while their brain activity was monitored using electroencephalography (EEG). Participants were randomly assigned to either the acetaminophen condition or the control (placebo) condition. On the basis of previous research, we predicted that participants who ingested acetaminophen would have less intense emotional reactions to the negative stimuli as revealed by the late positive potential (LPP, an event-related potential derived from EEG), compared to those who ingested placebo. Personality questionnaires, including the behavioral inhibition and behavioral activation scales (BIS/ BAS; Carver & White, 1994), were included to explore moderating effects. We quantified the LPP as the mean EEG activity in the time window 500-1000 ms after picture onset, separately for each picture type. Results revealed a main effect of picture type, such that positive and negative images elicited larger LPPs than

neutral images. However, there was no effect of pill condition and no interaction between pill condition and picture type. This finding is not consistent with our hypothesis or Durso et al.'s self-reported emotion results. We explored moderating effects of BIS on the LPP. A regression analysis found that BIS predicted LPP magnitudes in the placebo condition, but this relationship disappeared in the acetaminophen condition. Within-cell correlations revealed that acetaminophen disrupts the relationship between BIS and LPP for both positive and negative images. These results suggest that trait BIS moderates the effects of acetaminophen on a neural measure of emotional responding.

DEDICATION

I dedicate this research to my grandmother, Patsy McDonald. Without your continued support this opportunity would not have been possible.

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NOMENCLATURE

EEG	Electroencephalography
ERP	Event Related Potential
Hz	Hertz
IAPS	International Affective Picture System
LPP	Late Positive Potential
ms	Milliseconds
n	Number of Participants

CHAPTER I

INTRODUCTION

Acetaminophen, the active ingredient in the popular over-the-counter drug Tylenol, is well known as an effective pain reliever for a variety of physical ailments. But can acetaminophen also treat emotional ailments? An accumulating body of evidence suggests that acetaminophen has a much more widespread psychological effect than previously believed (Durso, Luttrell, & Way, 2015; DeWall, Chester & White, 2015; DeWall et al., 2010, Randles, Heine, & Santos, 2013).

Overview of previous research

One influential study found evidence that acetaminophen reduces the emotional pain of being socially excluded and ostracized (DeWall et al, 2010). In this experiment participants took either acetaminophen or placebo for three weeks. They also reported on experiences in their social relationships, and participants in the acetaminophen condition reported less intense hurt feelings compared to those who took a placebo over the same duration.

Other research has found that just one dosage of acetaminophen can blunt individuals' negative reactions to emotionally charged stimuli. One study found that an acute dose of acetaminophen reduces the use of psychological defenses in response to unsettling or aversive events such as thinking of one's own mortality (Randles et al., 2013). A dose of acetaminophen has also been observed to ease the discomfort or dissonance associated with making a difficult decision (DeWall et al., 2015).

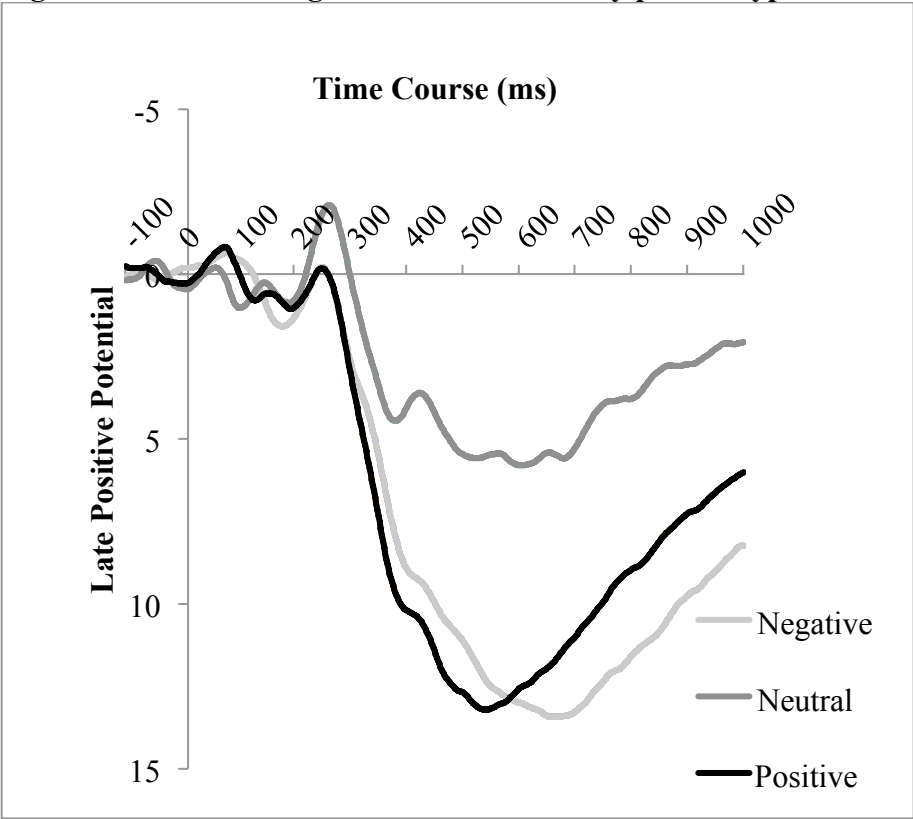
A more recent study found that acetaminophen blunts both positive and negative emotions (Durso et al., 2015). This experiment involved participants taking a one-time dosage of either acetaminophen or placebo. Later, participants viewed and rated a series of emotionally charged images selected from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2008). Images ranged from extremely pleasant to view (e.g., children playing, people laughing) to extremely unpleasant to view (e.g., mutilated body parts, gun pointed at viewer). Participants rated how positive or negative the photos were, and then they viewed the photos again and rated how emotionally aroused the images made them feel. The results revealed that acetaminophen, compared to placebo, reduced individuals' reactions to both positive and negative images, suggesting a general blunting effect of acetaminophen on emotional and evaluative processing. The research team postulated that the emotion-blunting effects of Tylenol may stem from an overlap in brain systems involved in both physical pain and psychological pain.

Overview of present research

The current study extended past research by examining the effects of acetaminophen on emotional responding measured at the neural level. Previous research has found that Tylenol reduces self-reports of emotional experience, but self-reports are subject to a host of biasing influences, including perceived social appropriateness and demand characteristics. Neural measures are virtually impervious to these reporting biases. Hence, in the current study we used electroencephalography (EEG) to record emotion-related patterns of electrical activity in the brain.

We analyzed an EEG waveform known as the late positive potential (LPP). The LPP is a component of an event-related potential (ERP) that occurs in response to emotionally arousing stimuli (Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Schupp, Junghöfer, Weike, & Hamm, 2004). More specifically, the LPP has been linked to the selective processing of emotional stimuli, particularly pictures, such that the LPP is larger in amplitude while viewing arousing positive and negative pictures relative to neutral and non-arousing pictures (Schupp, et al., 2000). Please refer to Figure 1, which depicts typical LPP waveform as a function picture type.

Figure 1. Grand average of LPP waveform by picture type.



As in the study by Durso et al. (2015), participants in the current study consumed acetaminophen or a placebo before viewing emotionally charged images. Unlike the previous study, electrical activity in the brain was monitored during picture viewing using EEG sensors. If the findings support our hypothesis, then this study will provide further support for idea that acetaminophen influences neural systems involved in emotion processing. The possible implications of this study, and future studies, are important for the millions of people who take acetaminophen yet may be unaware of its impact on their emotional states.

Based on prior evidence that acetaminophen may serve as an “all-purpose emotion reliever,” we predicted that acetaminophen would show a similar blunting effect on a neural indicator of emotionality. Specifically, we predicted that ingesting acetaminophen (versus placebo) would blunt neural responding (i.e., smaller LPPs from centroparietal electrode sites) to emotional pictures. We therefore sought to replicate the findings of Durso et al. (2015) and extend them by studying the neural consequences of acetaminophen consumption. We also included measures of personality traits to test the possibility that the effects of acetaminophen would be more or less impactful for certain individuals.

CHAPTER II

METHODS

Participants and design

Ninety-seven undergraduate students from Texas A&M University completed the experiment in exchange for credit toward a course requirement. This study was approved by the University's Institutional Review Board. Additional participants completed the study but were removed from analysis for the following reasons: 5 had electrode impedances greater than 5 Kohms and 3 did not complete the questionnaires.

This experiment used a 2 (Drug Type: acetaminophen vs. placebo) \times 3 (Picture Type: positive, negative, neutral) mixed-factorial design. Participants were randomly assigned to either the acetaminophen ($n = 56$) or placebo ($n = 41$) condition; both the experiment and the participant were blind to condition. After taking the dose, participants viewed a series of emotional images on a computer screen while their brain activity was monitored using EEG.

Procedures

After providing informed consent participants received a brief description about the experiment. Participants were randomly assigned to ingest either 1000 mg of acetaminophen or placebo (cornstarch capsule) prior to sensor placement. Sensors were attached to participants' heads using 59 tin electrodes in a stretch-lycra electrode cap. Sensor placement lasted approximately 1 hour and thereby allowed time for the drug (in the Tylenol condition) to enter the bloodstream (Smith, 2009). During EEG hookup participants completed a series of questionnaires including a

BIS/BAS questionnaire (Carver & White, 1994) and provided basic demographic information. Most relevant for present purposes, participants completed a measure of behavioral inhibition system (BIS) sensitivity, which assesses reactivity to threat and punishment (Carver & White, 1994). The BIS measure includes items such as “I worry about making mistakes,” and “Criticism or scolding hurts me quite a bit.” Participants responded to these items using a scale from 1 (*very true for me*) to 4 (*very false for me*). Higher BIS scores indicated heightened sensitivity to non-reward, punishment and novel experience.

After sensor placement a 4-minute recording was made of the brain at rest. Participants then completed a picture-viewing task in which they viewed a series of emotional pictures on a computer screen. Pictures were presented using DMDX software. Participants viewed 19 positive, 19 neutral, and 19 negative pictures borrowed from the international Affective Picture System (IAPS; Lang et al., 2008).¹ Positives pictures depicted exciting or fun activities. Neutral pictures featured ordinary objects and mundane scenes. Negative pictures include mainly scenes of violence or mutilation. The first four images were neutral practice trials and were not analyzed. Each trail consisted of a fixation cross that appeared on screen for 3 seconds, followed by a picture for 6 seconds, and an inter-trial interval of 8-12 seconds. The image-viewing task lasted 22 minutes.

¹ The following IAPS photos were used. Negative valence: 1052, 1205, 1270, 1300, 2811, 3000, 3022, 3071, 3130, 3150, 3250, 3400, 3550, 6230, 6550, 6560, 7380, 9300, 9405. Neutral valence: 2038, 2190, 2393, 2394, 2397, 2405, 2487, 2516, 2850, 5534, 7000, 7009, 7025, 7035, 7041, 7053, 7058, 7100, 7161, 7180, 7185, 7236. Positive valence: 4608, 4651, 4656, 4658, 4659, 4670, 4681, 4695, 5621, 7200, 7260, 7350, 7390, 7460, 7470, 8031, 8161, 8186, 8260

Following the end of the experiment participants reported whether they believed they had received acetaminophen or placebo and how sure they were of their answer. Lastly, participants were debriefed about the purpose of the study and dismissed.

Psychophysiological recording and quantification

EEG was recorded with 59 tin electrodes in a stretch-lycra electrode cap using Neuroscan software for impedance checking and data collection. EEG signals were amplified with Neuroscan SynAmps2 (El Paso, TX), bandpass filtered (0.05-100Hz), notch filtered (60 Hz) and digitized at 500 Hz. Eye movements were recorded from an electrode at FP2 (10-20 placement system). Data was visually inspected and portions of the data that contained artifacts (e.g. horizontal eye movements, muscle movements) were first removed by hand. Then a regression-based eye movement correction was applied to correct vertical eye movements (Semlitsch, Anderer, Schuster, & Presslich, 1986), after which the data were again visually inspected to ensure proper correction.

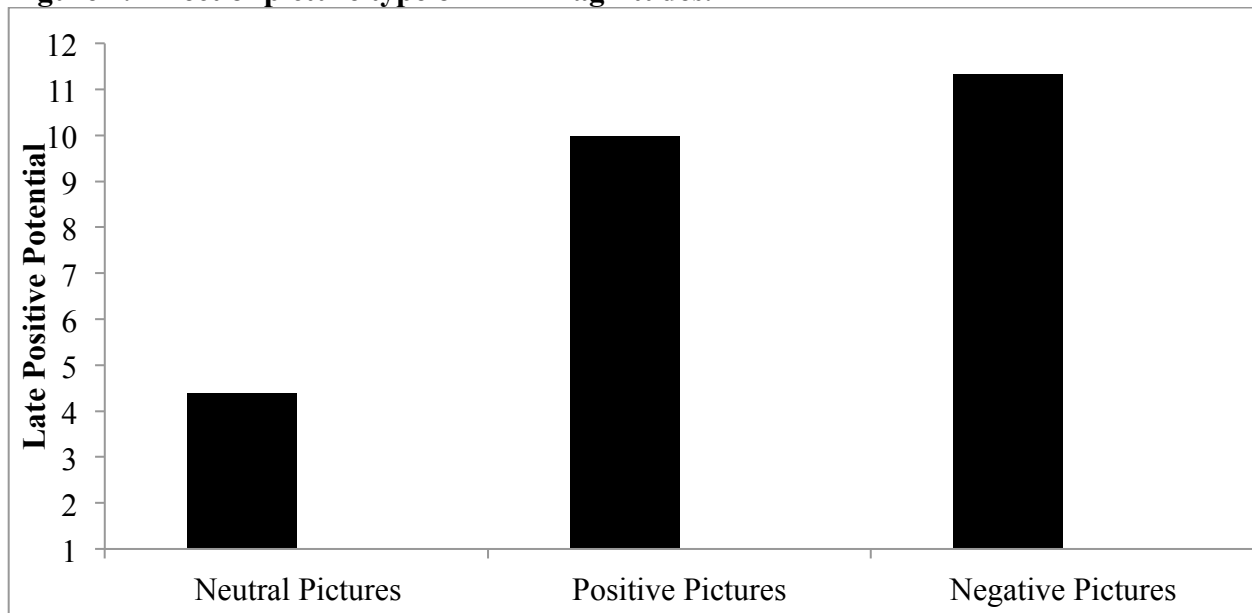
CHAPTER III

RESULTS

The early LPP is typically observed at centroparietal sites between 400 and 1000 ms after stimulus onset (Hajcak et al., 2012). We quantified the LPP as the mean EEG activity in the window of 500-1000 ms after picture onset, separately for each picture type. We analyzed activity at electrode sites CZ, CPZ, and PZ and chose to focus on activity at PZ for all subsequent analysis because the LPP was the largest at this site.

A 2 (Drug Type: acetaminophen vs. placebo) \times 3 (Picture Type: positive, negative, neutral) mixed-factorial analysis of variance (ANOVA) found a main effect of picture type, such that positive and negative images elicited larger LPP magnitudes than neutral images, $F(2, 190) = 73.18, p < .001$. Pairwise comparisons (Bonferroni corrected) revealed that the LPP was significantly different between all picture types: largest during negative pictures ($M = 11.24, SE = 0.711$), smallest during neutral pictures ($M = 4.19, SE = 0.67$), with positive in between other two ($M = 9.72, SE = 0.66$), $ps < .05$. See Figure 1.

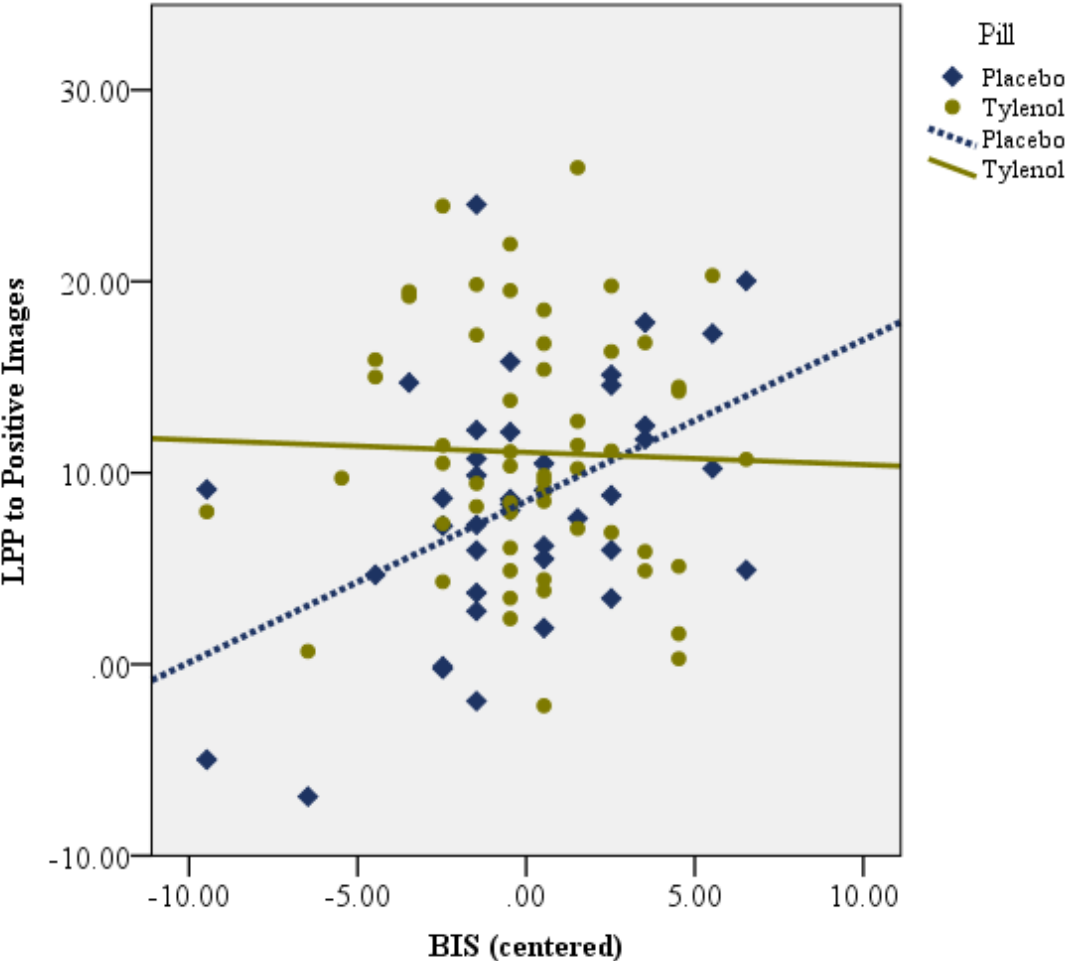
Figure 1. Effect of picture type on LPP magnitudes.



However, we found no main effect of pill condition, $F(1, 95) = 2.47, p = .120$, and no interaction between pill condition and picture type, $F(2, 190) = 1.19, p = .306$. This finding is not consistent with our original hypothesis or Durso et al.'s (2015) finding that acetaminophen blunts self-reported emotional experience.

We explored moderating effects of trait BIS on LPP magnitudes. Regression analysis results predicting LPP magnitudes during positive and negative pictures, controlling for LPPs to neutral pictures, as a function of BIS (centered), pill condition, and their interactions found that BIS and pill condition interacted to predict LPP magnitudes to both negative pictures, $\beta = -0.28, p = .020$, and positive pictures $\beta = -0.22, p = .049$. To further unpack these interactions we examined the correlations between BIS and LPP magnitudes in the acetaminophen and placebo conditions separately. In the placebo condition, BIS predicted LPP magnitudes to both positive pictures, $r(39) = .47, p = .002$, and negative pictures, $r(39) = .48, p = .002$. In the acetaminophen

Figure 3. Scatterplot of the correlation between BIS and LPP magnitudes during positive images by pill condition.



CHAPTER III

SUMMARY AND CONCLUSIONS

On the basis of previous research we expected acetaminophen to blunt neural reactivity to emotional images. However, we found no effect of ingesting acetaminophen (versus placebo) on LPP magnitudes during the picture-viewing task. In general, whether a person ingested Tylenol or not, they exhibited an enhanced LPP while viewing emotional (positive or negative) versus neutral images. This evidence does not support the hypothesis that acetaminophen (vs. placebo) blunts neural responses to emotional images, as measured by the LPP at centro-parietal electrode sites.

The results did reveal that acetaminophen breaks the link between trait behavioral inhibition system (BIS) sensitivity and the LPP. Previous research found that BIS sensitivity is positively related to vigilance and defensive responding to threats, including larger LPPs to negative emotional images (Balconi, Falbo, & Conte, 2012). We replicated this pattern in the placebo condition in the current experiment. Evidence further suggests that higher BIS activation is associated with enhanced attention, arousal, vigilance, and anxiety, and very strong BIS corresponds to anxiety-related disorders (Fowles, 1988; Leen-Feldner, Zvolensky, & Feldner, 2004). Insofar as acetaminophen breaks the link between BIS and LPP magnitudes to emotional images, this suggest that acetaminophen may be particularly impactful on emotional responding for individuals who are prone to anxiety.

Although acetaminophen did not affect our neural measure of emotional responding in all participants, it did disrupt the relationship between trait BIS and LPP to both positive and negative pictures. How Tylenol affects people's emotions on a day to day basis is still largely unknown, but the current findings lend additional support the idea that Tylenol has an effect on emotional processing that is moderated by individual differences in behavioral inhibition tendencies.

Limitations and future directions

The current study did not directly address how acetaminophen breaks the link between BIS and the LPP to emotional images. More research is needed to understand the boundary conditions of the effects of acetaminophen on emotional reactivity. For example, what are the precise neural mechanisms acetaminophen works on to influence emotional reactivity? Do the observed acetaminophen effects generalize to more profoundly anxious or clinical populations? For now, what exactly Tylenol does to the brain and how deeply it may influence emotion remains to be seen.

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