

**THE INFLUENCE OF ACETAMINOPHEN ON TASK RELATED ATTENTION**

by

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### The Influence of Acetaminophen on Task Related Attention

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the degree of                 Master of Arts  
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## **ABSTRACT**

The attenuating effects of acetaminophen on neuroaffective and neurocognitive processing, bear striking similarity to those of event-related processing observed during periods of off-task thoughts. The current study was designed to investigate whether acetaminophen impacts or alters normal patterns of neurocognitive disengagement with events in the external environment during off-task attentional states. In a placebo-controlled, between-groups design, participants performed a sustained attention to response task (SART) while event-related potentials (ERPs) to target events were recorded. At random intervals participants were queried for their attentional reports at the time of stoppage – either “on-task” or “off-task”. The frequency of off-task attentional reports and the ERPs generated by target events immediately preceding these subjective reports were assessed. Behaviourally, the frequency of off-task attentional reports was comparable between groups. Electrophysiologically, there were two findings of note. First, there was an overall main effect of attentional state on the amplitude of the P300 ERP component elicited target events, such that the mean amplitude was significantly attenuated during off-task vs. on-task attentional states in both the acetaminophen and placebo groups. Second, the amplitude of the LPP ERP component elicited by target events showed a significant decrease in amplitude during off-task attentional states that was specific to the acetaminophen group. Take together, my findings suggest that acetaminophen impacts neurocognitive disengagement during off-task attentional states, but not by increasing the attenuation of more basic stimulus categorization processes as indexed by the P300 ERP component, but rather, by catalyzing the attenuation of deeper, more contemplative stimulus evaluations, as indexed by the LPP ERP component.

## **LAY SUMMARY**

Acetaminophen is a common over-the-counter medication used by millions of people worldwide for relieving physical pain. However, recent studies have shown that acetaminophen can numb more than just the pain of physical injury – more specifically, the pain from social rejection or the mental discomfort of making a decision. These reductions in physiological pain share similarities to the blunting effects observed during off-task thoughts. The present study showed that taking acetaminophen leads to reduction in the sensitivity to tasks that extends to shorter timescales of having off-task thoughts. In other words, in a person that has taken acetaminophen, engagement with the outside world will be normal while they are still paying attention to the outside world but when they start having off-task thoughts, the brain becomes even better at reducing the sensitivity to the outside world, leading to a mind that is less empathetic.

## **PREFACE**

This thesis is original and unpublished work by the author S. Mutti. All research described in this report was conducted through the Department of Psychology at the University of British Columbia under the supervision of Dr. Todd Handy.

Data from this experiment was presented at the annual meetings of Cognitive Neuroscience Society 2017, NorthWest Cognition and Memory 2017, and PsychFest 2018.

This research was approved by the UBC Clinical Research Ethics Board, and the Certificate Number of the Ethics Certificate is H15-01130-A004.

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## **Chapter 1: Introduction**

Acetaminophen—also known as paracetamol or Tylenol®—is a common non-prescription, centrally-acting pain reliever that has been recognized in recent years to have a number of substantive cognitive and affective side-effects (e.g., DeWall et al., 2010). The origins of this work centered on testing a model in social psychology that proposed social pain and physical pain rely on a common or shared underlying neural mechanism. Within this context, acetaminophen was an ideal way to test the validity of this model owing to its central impact on pain. In the initial study it was found that social pain was indeed attenuated by chronic doses of acetaminophen taken over a period of three weeks (DeWall et al., 2010). The finding from this initial study has since been followed up in several different critical ways, all in studies using single, acute doses of acetaminophen, and as reviewed below, all demonstrating that acetaminophen attenuates various aspects of cognitive-affective processes. Given this body of evidence, the goal of my thesis was to examine whether the attenuating effects of acetaminophen extend to neurocognitive process that operate at shorter timescales and in particular, timescales associated with transient fluctuations in task related attentional states.

### **1.1 Acetaminophen and Processing Attenuation**

In DeWall et al.’s (2010) original experiment, the primary behavioural experiment was a between-groups design that had participants taking two daily doses of 1000 mg of acetaminophen or placebo for a treatment period of three-weeks, once in the morning and once in the evening just before going to sleep. Every evening during treatment, participants also filled out the Hurt Feelings Scale (Leary & Springer, 2001), a cross-culturally validated

measure that quantifies the degree or intensity of one's daily social pain. Relative to the placebo group, DeWall et al. (2010) found that the participants taking acetaminophen showed a significant reduction over the treatment period in the intensity of their reported social pain. These findings support that acetaminophen does in fact attenuate sensitivity to socially painful situations. Since this original experiment by DeWall et al. (2010), the attenuating effects of acetaminophen on social and cognitive processing have been expanded on in a number of different ways and all in experiments using single, acute doses of acetaminophen in placebo-controlled, between-groups designs.

In the first follow-up experiment, Randles, Heine, and Santos (2013) assessed affective responses to cognitively threatening experiences following acute 1000mg dose of acetaminophen. The experimenters placed participants in either unsettling or control conditions and measured the ways in which acetaminophen influenced participants' disciplinary actions towards lawbreakers. In one version of the experiment, participants were placed in a mortality-threat condition - involving a writing probe about their own death, or a control condition - involving a writing probe about dental pain. In another version of the experiment, the meaning-threat condition was achieved by having participants watch a surrealist film, as compared to a control film condition. Participants were then asked by what amount they would increase the set bond amount either for a hypothetical arrest of a prostitute (Experiment 1), or for Vancouver Canucks hockey rioters (Experiment 2). In both versions of the experiment acetaminophen disrupted compensatory responses to unsettling experiences. In other words, acetaminophen attenuated affective responses to cognitively threatening events.

In a more recent experiment, Durso, Luttrell, and Way (2015) explored the blunting effects of acetaminophen on the evaluation of affectively salient stimuli. In this experiment, participants viewed a set of 40 images from the International Affective Picture System (IAPS; Lang, Bradley, & Cuthbert, 2001). After taking either 1000mg of acetaminophen or placebo, participants then rated each image on three separate scales—one targeting the intensity of felt negative vs. positive emotion towards the image, one targeting the intensity of emotion felt towards the image regardless of polarity, and as a control, how much of the colour blue was in each image. As compared to the placebo condition, participants in the acetaminophen condition evaluated images as being less polarizing and having overall less emotionality, while there were no significant between-groups differences in the blue ratings. Again, as seen with previous experiments, Durso et al. (2015) demonstrated the attenuating effect of acetaminophen on individuals' evaluative and emotional processing.

Extending these aforementioned findings further, DeWall et al. (2015) investigated the effects of acute doses of acetaminophen on the cognitive dissonance generated by sub-optimal decision-making. In their first experiment, the authors used a paradigm designed to generate cognitive dissonance over making decisions about what hypothetical tasks they would vs. would not like to perform. Compared to the placebo condition, participants in the acetaminophen condition self-reported reduced levels of cognitive dissonance in the decision task. In their second experiment the researchers used a classic endowment-effect paradigm to induce a sense of loss aversion. The results showed that if participants "owned" the mug but had taken acetaminophen, they set the lower prices for selling the mug relative to

participants in the placebo condition. In other words, acetaminophen attenuated the magnitude of felt loss aversion. Taken together, the findings from these two experiments are consistent with an attenuating impact of acetaminophen on cognitive-affective evaluative processing.

Finally, in the latest experiment reported on acetaminophen, Randles et al. (2016) assessed the effects of acute doses of acetaminophen on behavioural performance monitored as measured via event-related potentials (or ERPs). In their experiment, participants performed a classic go/no-go task, with the intention of measuring to different ERP responses to any errors in the task—the error related negativity (ERN) and the error positivity (Pe), which index automatic error detection and implicit evaluation of the error, respectively. Compared to the placebo conditions, participants that took acetaminophen had a reduced propensity to detect and respond to the “go” targets. Importantly, while the ERN was unaffected by acetaminophen, the Pe was significantly attenuated in the acetaminophen group. This suggests that while acetaminophen did not alter the automatic detection of errors, it significantly reduced participants’ implicit evaluation of the error made.

In sum total, across these different experiments, a common pattern of cognitive and affective attenuation for acetaminophen emerges. When participants ingest a dose of acetaminophen, there is a systematic reduction in the intensity of cognitive-affective responses to on-going events, an attenuating effect that appears to persist for the several hours duration of the drug’s influence. Considering this conclusion, the aim of my thesis is to examine whether the attenuating effects of acetaminophen can be seen at shorter

timescales, and in particular, during transient fluctuations in task related attentional states that take place on the order of seconds to tens of seconds.

## 1.2 Task Related Attention

When our thoughts drift off-task, such as when we are mind wandering, our neurocognitive and neuroaffective engagement with on-going events in the outside world attenuates for the brief transient periods when we are off in the clouds. In many respects, these brief periods of attenuated processing resemble the attenuating effects ascribed to acetaminophen over longer time scales as reviewed above. For example, in the first study to directly investigate how periods of off-task thinking alter our engagement with events in the external environment, Smallwood et al. (2008) asked participants to perform a modified sustain attention to response task (SART) while the ERP responses to target events were recorded. At the end of each trial block participants were then queried as to whether they had their attention directed to the task as the block was ending. They found that the amplitude of the P300 ERP component elicited by target events was significantly attenuated in the time period immediately preceding off-task attentional reports, relative to when attention was reported as on-task. As such, this study was the first to provide direct evidence that our cognitive engagement with the external environment is attenuated during periods of off-task thinking. In the years since, these attenuating effects have now been documented several additional processing domains.

Both behavioural and EEG-based studies have confirmed that sensory-level processing is attenuated during off-task attentional states. Analogous to Smallwood et al.

(2008), Kam et al. (2011) assessed sensory-evoked responses to task-irrelevant probes in the visual and auditory domains, via P1 and N1 ERP components, respectively. The visual and auditory cortices showed decreased sensory-evoked responsivity in the time periods immediately preceding off-task attentional reports relative to when attention had been reported as on-task. Likewise, using a pupillometry-based measure of perceptual processing, Smallwood et al. (2011) had participants complete either a working memory or choice reaction time task. They found that the participants' pupils did not dilate during off-task attentional states, suggesting a lack of perceptual engagement with task events during these periods. Similarly, in an EEG-based experiment that assessed brain-evoked responses to perceptual stimuli during off-task thoughts, Braboszcz and Delorme (2011) had participants perform an introspective judgment experiment. To test the participants' response to task-irrelevant stimuli, the experimenters evaluated auditory oddball stimuli as a function of whether the participants responded on-task vs. off-task attentional states. They found a significant decrease in sensory-level processing during off-task thoughts. Taken together, these studies demonstrate that the sensory-perceptual processing of external events is significantly attenuated during periods of off-task thought.

Similar to the cognitive and sensory-level attenuations found during off-task thoughts, studies have also looked at attention-related attenuations in the monitoring of our own behavioural performance. In one such study, Kam et al. (2012) had participants track a moving dot across the computer screen by moving a cursor that controlled an annulus that was to remain centered over the dot. Using a root mean squared measure of tracking error, they found that tracking was less accurate when the participants reported being in an off-task

vs. on-task attentional state (Kam et al., 2012, Experiment 1). In a second experiment they then asked participants to perform a time-estimation task and assessed the sensitivity to performance feedback on the task via the error-related negativity (fERN) ERP component (Kam et al., 2012, Experiment 2), again while also asking participants to report on their attentional states. Consistent with an attenuating effect of off-task attention states on performance monitoring, they found that the amplitude of the fERN elicited by feedback signals was significantly attenuated in the time period immediately preceding off-task vs. on-task reports. Taken together, these results suggest that there are indeed significant attenuations in performance monitoring processes during off-task thoughts.

Finally, off-task thoughts also appear to be associated with attenuations in affective processing as well. In an ERP-based experiment, Kam, Xu, and Handy (2014, Experiment 1) showed participants images of either painful (e.g., getting a locker door shut on the hand) or neutral situations (e.g., hand next to a locker door) and asked them to evaluate whether the image looked painful or not, while measuring the P300 component elicited by each image. The results showed that the P300 amplitude elicited by the painful images significantly decreased in the moments immediately preceding an off-task vs. on-task attentional report. To investigate whether off-task attentional states actually reduce the subjective sensitivity to painful images, Kam and colleagues (2014, Experiment 2) had participants simply rate how painful each image looked on a 7-point Likert scale. Consistent with the first experiment, the ratings for painful images were indeed lower when participants were in off-task relative to on-task attentional states. In sum, the findings support the proposal that the attenuating

effects of off-task attentional states on our processing of events in the external environment do in fact extend to the affective domain.

Viewed together, these studies indicate that when our minds drift off-task, we broadly attenuate our neurocognitive and neuroaffective engagement with on-going events in the external environment. What the collective findings have shown is that during the brief moments of off-task thoughts, there are significant reductions in the processing of external events that have been demonstrated in the cognitive, sensory, performance monitoring, and affective domains. This then provides the evidential background for the motivating hypothesis on my thesis—if acetaminophen has a general attenuating impact of the cognitive and affective processing of external events during the period of the drug’s effect, would this state-related attenuation effect interact with processing attenuations that play out over shorter time scales, as identified during periods of off-task vs. on-task attentional states?

### **1.3 Hypotheses**

My thesis examines whether acetaminophen impacts or alters normal patterns of neurocognitive disengagement with events in the external environment during off-task attentional states. This will be determined via two complimentary measures as taken in the context of a placebo-controlled, between-groups experiment that has participants perform a standard SART paradigm as the ERPs to target events are recorded. First, behaviourally, I will measure the frequency of off-task attentional reports to determine whether acetaminophen alters normative patterns of how much time we spend in off-task attentional states. If acetaminophen impacts the amount of time we spend in off-task attentional states,

this predicts that there should be a significant between-group difference in the frequency of off-task attentional reports—the more time spent in off-task thinking, the greater the number of expected off-task attentional reports. Second, I will discern if acetaminophen alters the depth of neurocognitive disengagement normally seen during off-task attentional states, as indexed via the mean amplitude of the P300 and LPP ERP components elicited by target events. If acetaminophen impacts the depth of neurocognitive disengagement during off-task attentional states, it predicts that the amplitude of the P300 and/or LPP should significantly differ between the acetaminophen relative to placebo group.

## **Chapter 2: Methods**

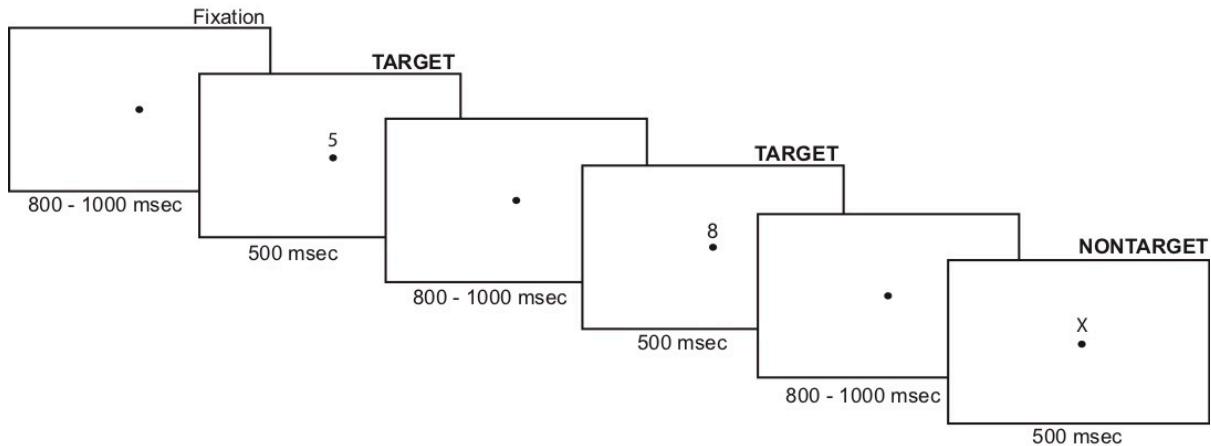
### **2.1 Participants**

Participants were recruited through the community via posting at the Paid Participants Study List hosted by Psychology Graduate Student Council website, and remunerated \$20 (CAD) for their participation. A total of 60 participants from the community were recruited, but data from 20 participants was excluded from final analyses due to excessive eye movement and other recording artifacts identified in their data during initial data analysis (see below). Of the remaining forty participants (26 females;  $M = 23.4$  years old,  $SD = 6.61$ ; 39 were right-handed), all had no history of neurological problems, and had normal or corrected-to-normal vision. Participants provided written informed consent to the experimental procedure, and the UBC Behavioural Review Ethics Board approved all procedures and protocols of this experiment.

### **2.2 Stimuli and Task**

Participants performed a SART adapted from Smallwood et al. (2008) and Kam et al. (2011). The task involved presentation of a serial stream of stimuli at foveal centered fixation dot. The stimuli were black numbers or a letter on a white background. Participants were asked to make a manual button press for “targets” (numbers 0– 9, which were presented frequently), and were asked to withhold a button press response when presented with a “nontarget” (letter X, which was presented infrequently). The timing and sequence of stimuli are shown in Figure 2.1. Within each block of stimuli, nontarget probability was quasi-randomized, with the constraints that (1) one to two nontargets were presented during each block, and (2) for blocks having two nontargets, the nontargets would be separated by at least

ten target events, and (3) the last 6 trials of each block included no nontarget events. The block duration was randomly varied between 30 to 90 seconds, meaning each block had anywhere from 15 to 45 trials, and with a total of at least 20 trial blocks being completed by each participant.



**Figure 2.1. Task Paradigm.** Timing and sequence of stimuli in the present experiment.

To measure task-related attention, the procedures from Smallwood and colleagues (2008), and Kam and colleagues (2011) were also replicated. Participants were instructed to report their “attentional state” at the end of each trial block. Specifically, they were asked to identify their state immediately prior to the block termination as either being “on-task” (fully attentive to task performance), or “off-task” (inattentive to the task). Importantly, participants were provided with verbal descriptions and examples of these two “attentional states” prior to starting the testing session. On-task states were defined as when one’s attention is firmly directed towards the task, whereas off-task states were described as when one is aware of other things than just the task at hand. Examples of these attentional states were given in the context of reading, during which “one may be fully attentive to the content

of the reading material, or thinking about something completely unrelated to the content, reflective of on-task and off-task states, respectively.” Attentional reports were recorded by the investigator at the conclusion of each trial block, and these reports were then used to sort ERP data based on on-task versus off-task states as described below. The block duration itself was randomly varied between 30 and 90 seconds to (1) minimize predictability of block completion and (2) maximize variability of attentional state at the time of block completion.

### **2.3 Experimental Manipulation**

Our procedures for the between-group pharmacological manipulation replicated Randles et al. (2016). Participants in the experimental condition consumed two capsules each containing 500mg tablets of Kirkland-brand acetaminophen (1000mg total), while participants in the placebo condition consumed two identical-looking capsules that were filled with white granulated sugar. Participants were informed that they were being randomly assigned to an experimental condition through double-blind procedure, where each participant’s dose was assigned a unique ID prior to the study that matched it to the correct condition. While the researcher running the study was blind to condition assignment, they could request access to identify the condition if it became medically necessary. Participants were sorted into condition beginning at the group averaging stage of data analysis.

### **2.4 Procedure**

Participants provided written consent and then consumed their assigned capsules. The participant was then prepared for recording his or her electroencephalogram (EEG), and instructed in the SART while seated at the task computer running MATLAB R2010a (The

MathWorks, Inc.) with Psychtoolbox. This task began approximately 60 min after consuming the pills, ensuring that most participants experienced peak pharmacological activation; typically requiring 45–60 min for adults consuming acetaminophen orally (Bertolini et al., 2006). The half-life of acetaminophen in healthy subjects has been reported to be 1.9 to 2.5 hours (Forrest, Clements, & Prescott, 1982). Once commenced, the EEG testing session itself took approximately 1 hour, giving participants a total study time of approximately 2 hours.

## **2.5 Electrophysiological Recording and Analysis**

Continuous EEG was recorded during the task via 64 Ag/AgCl active electrodes mounted in an elastic cap (BioSemi Active-Two amplifier system; BioSemi, Amsterdam, Netherlands) in spatial accordance with the international 10–20 system. Two additional electrodes located over the medial-parietal cortex (Common Mode Sense and Driven Right Leg) were used as ground electrodes. Recordings were digitized at 256 Hz, digitally filtered offline between 0.1 and 30 Hz (zero phase-shift Butterworth filter) and then referenced offline to the average of two mastoid electrodes. EEG data processing was performed using ERPLAB, a toolbox within MATLAB 2012a (The MathWorks, Inc.) used in conjunction with EEGLAB. To ensure proper eye fixation and allow for the removal of events associated with eye movement artifacts, vertical and horizontal electrooculograms (EOGs) were also recorded—the vertical EOGs from an electrode inferior to the right eye, and the horizontal EOGs from two electrodes on the right and left outer canthus. Offline, computerized artifact rejection was used to eliminate trials during which detectable eye movements and blinks occurred. These eye artifacts were detected by identifying the minimum and maximum

voltage values on all recorded EOG channels from -200 to 800ms post-stimulus for each event epoch, and then removing the trial from subsequent signal averaging if that value exceeded 200 uV, a value calibrated to capture all blinks and saccades. This was followed by visual inspection of the data. If additional artifacts (e.g. muscle movements and loose connections) were observed, the threshold was reduced by 25 uV until artifacts were not present or a minimum of 100 uV was reached. Participants (N = 20) with more than 50% rejected trials were excluded from analysis; the remainder of participants (N = 40) had an average of 17.84% trials rejected due to these signal artifacts. The percentage of rejected trials did not significantly differ between individuals in the acetaminophen vs. placebo conditions ( $p = 0.53$ ). ERP data analyses were based on mean amplitude measures using mixed design analyses of variance (ANOVAs), with time-windows centered on the peaks of the components of interest identified in the grand-averaged waveforms presented below. A -200 to 0 ms pre-stimulus baseline was used for taking all the measures.

The ERP waveforms for the two attentional conditions of interest were derived by averaging together the EEG epochs for the six target events preceding each categorical instance of a subjective attentional report (on-task vs. off-task). Although it is never certain how long participants have actually been in a particular attentional state at the time a subjective report is given, analyses were based on the assumption that the 12 s prior to each report (the time window capturing the 6 preceding targets) would, on average, reliably capture the given attentional state—an assumption consistent with the presumed time course of off-task thinking (e.g., Christoff et al., 2009; Sonuga-Barke & Castellanos, 2007) and the time windows of analyses we have adopted previously (Kam et al., 2011, 2012; Kam &

Handy, 2013; Kirschner, Kam, Handy, & Ward, 2012; Smallwood et al., 2008). Although a shorter pre-report time window for averaging nontarget EEG epochs would more accurately capture attentional state, it would also reduce the number of events included in the ERP analysis. The choice of how many pre-report events to include in the averages was therefore an attempt to maximize the number of events in each waveform average while not extending the window back so far in time as to consistently capture the preceding attentional state or transition between states.

## **Chapter 3: Results**

### **3.1 Behaviour**

Participants completed an average of 36.2 trial blocks during the 1-hour testing session, with 49.4% of the attentional reports being given as "off-task." However, there was no effect of the experimental manipulation on the reported frequency of "off-task" thinking (acetaminophen = 51.0%, placebo = 47.9%;  $t(19) = 0.62, p = 0.54$ ). In other words, the acute dose of acetaminophen did not influence the frequency rates of off-task thoughts.

### **3.2 Electrophysiology**

For brevity, main effects and interactions involving scalp electrode site are not reported in the statistical analyses below, as they do not address the main question or conclusions drawn.

#### **3.2.1 P300 Mean Amplitude**

The P300 a component is reliably elicited by target events and is typically maximal over midline lateral-central scalp electrode (Donchin, 1981; Polich, 2007), therefore data analysis was constrained to the central electrode locations CPz, Pz, and POz, along with the immediately distal locations to each over the left (CP1, P1, and PO1) and right (CP2, P2, and PO2) cerebral hemispheres. The P300 elicited by target events is shown in Figure 3.1 and the mean amplitude as measured across a 250 to 350 ms time window capturing the peak latency of the P300 are reported in Table 3.1 as a function of attentional report (on-task vs. off-task) and experimental condition (acetaminophen vs. placebo). An omnibus, mixed-model, repeated-measures ANOVA was conducted, with experimental group (acetaminophen

vs. placebo) was included as a between-groups factor, and attentional report (on-task vs. off-task) and electrode site were included as within-groups factors. There was an overall significant main effect of attentional report [ $F(1, 38) = 4.64, p = 0.038$ ], but there was no significant main effect of experimental group [ $F(1, 38) = 2.22, p = 0.14$ ] or a significant interaction between attentional report and experimental group [ $F(1, 38) = 0.11, p = 0.75$ ].

### 3.2.2 LPP Mean Amplitude

Similar to P300, the LPP is believed to be maximal over the midline parietal-central scalp electrode sites, and we thus constrained analysis of this component to the central electrode locations (C, CP, and P) along with the distal locations to each over the left (C1, CP1, and P1) and right (C2, CP2, and P2) cerebral hemispheres. The LPP elicited by target events is shown in Figure 3.1 and the mean amplitude as measured across a 375 to 525 ms time window capturing the peak latency of the LPP is reported in Table 3.2 as a function of attentional report (on-task vs. off-task) and experimental condition (acetaminophen vs. placebo). Data were again analyzed using an omnibus, mixed-model, repeated-measures ANOVA, with experimental group (acetaminophen vs. placebo) was again included as a between-groups factor, and attentional report (on-task vs. off-task) and electrode site were included as within-groups factors. There was an overall significant main effect of attentional report [ $F(1, 38) = 21.66, p < 0.001$ ] and a significant interaction between attentional report and group [ $F(1, 38) = 5.84, p = 0.021$ ], but there was no significant main effect of group [ $F(1, 38) = 0.13, p = 0.91$ ]. Separate ANOVAs within each group confirmed a main effect of attentional report for the acetaminophen group [ $F(1, 38) = 25.00, p < 0.001$ ], but not for the placebo group [ $F(1, 38) = 2.50, p = 0.12$ ]. This finding thus confirmed that while

participants in the acetaminophen group showed a significant attenuation in LPP amplitude during off-task relative to on-task attentional states, there was no comparable effect of attention on LPP amplitude in the placebo group.

**Table 3.1** P300 ERP results

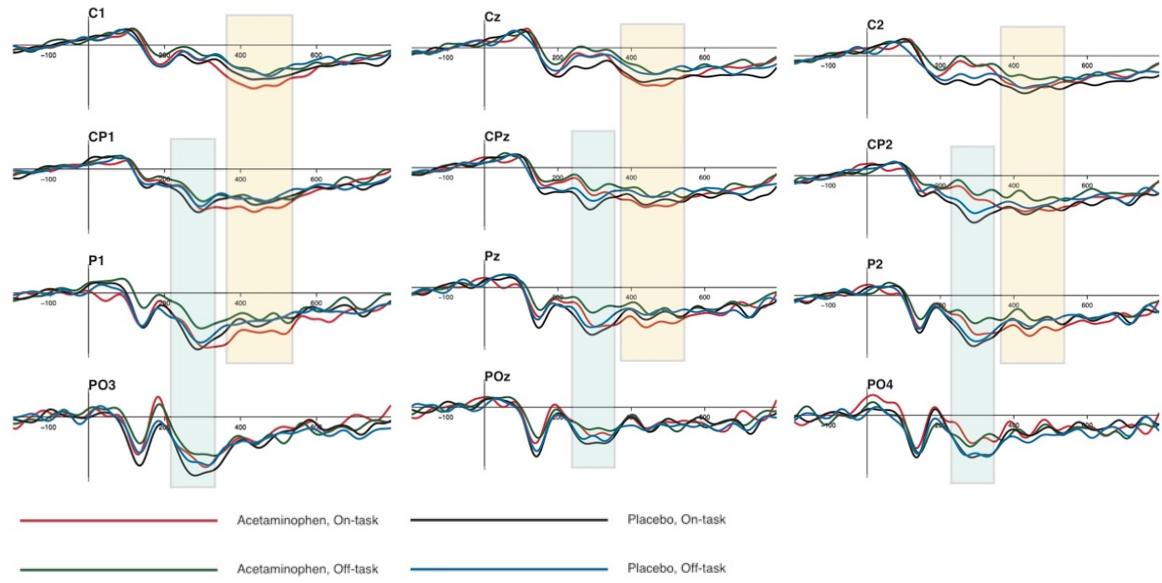
P300		Attention State	
Condition	Electrodes	On-Task	Off-Task
<i>Placebo</i>	CP1	2.02(1.42)	1.67 (1.48)
	CPz	2.03 (1.23)	1.63 (1.78)
	CP2	2.36 (1.36)	1.91 (1.70)
	P1	2.74 (1.07)	2.38 (1.50)
	Pz	2.40 (1.28)	2.00 (1.70)
	P2	2.59 (1.34)	2.33 (1.74)
	PO3	3.01 (1.66)	2.43 (1.90)
	POz	1.99 (1.36)	1.75 (1.61)
	PO4	2.24 (1.25)	2.24 (1.42)
<i>Acetaminophen</i>	CP1	1.93 (1.53)	1.48 (1.15)
	CPz	1.33 (1.96)	0.99 (1.40)
	CP2	1.24 (2.01)	0.82 (1.54)
	P1	2.68 (2.96)	1.66 (1.46)
	Pz	1.91 (2.16)	1.14 (1.67)
	P2	1.96 (1.96)	1.33 (1.77)
	PO3	2.36 (1.97)	2.03 (1.57)
	POz	1.45 (2.21)	1.22 (1.72)
	PO4	1.35 (3.63)	1.42 (2.01)

**Table 3.1** The mean P300 amplitudes (and standard deviation) for targets as a function of attentional state (on task vs mind wandering) and experimental group (acetaminophen vs placebo). Mean amplitudes were taken across a 250-350 ms post-stimulus time window, measured relative to a -200 to 0 baseline.

**Table 3.2** LPP ERP results

LPP		Attention State	
Condition	Electrodes	On-Task	Off-Task
<i>Placebo</i>	C1	1.78 (1.43)	1.47 (1.37)
	Cz	1.78 (1.73)	1.33 (1.77)
	C2	1.92 (1.57)	1.63 (1.55)
	CP1	1.76 (1.14)	1.62 (1.20)
	CPz	1.87 (1.38)	1.52 (1.55)
	CP2	1.96 (1.15)	1.67 (1.36)
	P1	1.60 (1.11)	1.55 (1.11)
	Pz	1.54 (1.25)	1.37 (1.20)
	P2	1.54 (1.25)	1.52 (1.04)
<i>Acetaminophen</i>	C1	2.22 (1.63)	1.39 (1.27)
	Cz	2.00 (1.65)	1.19 (1.43)
	C2	1.74 (1.48)	1.23 (1.31)
	CP1	2.18 (1.40)	1.63 (1.29)
	CPz	2.11 (1.77)	1.41 (1.53)
	CP2	1.96 (1.55)	1.22 (1.41)
	P1	2.19 (2.07)	1.32 (1.21)
	Pz	2.00 (1.59)	1.24 (1.40)
	P2	1.98 (1.77)	1.22 (1.34)

**Table 3.2** The mean LPP amplitudes (and standard deviation) for targets as a function of attentional state (on task vs mind wandering) and experimental group (acetaminophen vs placebo). Mean amplitudes were taken across a 375-525 ms post-stimulus time window, measured relative to a -200 to 0 baseline.



**Figure 3.1. ERP waveforms for acetaminophen and placebo experimental groups.**

Averaged waveforms showing cognitive effects of P300 and LPP ERP components elicited by targets at 12 electrode sites as a function of attentional state and experimental condition. The time-windows used in the P300 amplitude analyses are highlighted in blue (250-350 ms), and the ones used in the LPP amplitude analyses are highlighted in yellow (375-525 ms). These ERP waveforms are time-locked to visual target events in the 12 seconds preceding an attentional report.

## **Chapter 4: Conclusion**

This thesis project examined the effects of acetaminophen on patterns of neurocognitive disengagement during off-task attentional states. Participants were randomly assigned to either an acetaminophen or placebo condition, and then performed a SART as they were queried on their attentional states and the ERPs elicited by target events were recorded. In terms of behaviour, I found no significant differences in the frequency of off-task attentional reports for acetaminophen vs. placebo experimental groups. This suggests that there was no significant difference in the amount of time the participants spent having off-task thoughts between the two experimental groups. In terms of ERPs, there were two main findings of interest. First, there was an overall main effect of attentional state on the P300, such that the mean amplitude was significantly attenuated during off-task vs. on-task attentional states in both the acetaminophen and placebo groups. This suggests that while acetaminophen didn't impact neurocognitive disengagement in cognitive processing indexed by the P300, it provides important normative validity for the current study in replicating previous studies showing that the P300 attenuates during off-task relative on-task attentional states (Barron, Riby, Greer, & Smallwood, 2011; Kam et al., 2011; Smallwood et al., 2008). However, in contrast to this finding in the P300, the LPP showed a significant decrease in amplitude during off-task attentional states that was specific to the acetaminophen group. This suggests that acetaminophen can in fact impact off-task attentional states, and in particular, it appears to facilitate transient reductions in the implicit evaluative analysis of on-going events in the external environment—an effect that is not present in the absence of acetaminophen intoxication. In other words, acetaminophen is a

catalyst for enhanced or more extensive neurocognitive disengagement during off-task attentional states.

#### **4.1 Research Significance and Potential Implications**

Given the conclusions and findings, several key questions and points follow. First, how should the differential effect of acetaminophen on the P300 vs. LPP be construed at a functional level? At issue here is understanding how these components differ in terms of what they are believed to capture in terms of neurocognitive processing. The P300 is taken to index the degree to which a stimulus is initially evaluated or categorized at a basic cognitive level (e.g., Donchin, 1981; Polich, 2007), while the LPP is believed to index deeper or more contemplative aspects of evaluative analysis (e.g., Cacioppo & Berntson, 1994; Cacioppo, Crites, & Gardner, 1996; Crites, Cacioppo, Gardner, & Berntson, 1995; Cuthbert, Schupp, Bradley, Birbaumer, & Lang, 2000; Ito & Cacioppo, 2000). For example, while the P300 modulates in amplitude with stimulus frequency (van Dinteren, Arns, Jongsma, & Kessels, 2014), the LPP modulates with emotional intensity (Brown, van Steenbergen, Band, de Rover, & Nieuwenhuis, 2012) and implicit aesthetic preference (Handy, Smilek, Geiger, Liu, & Schooler, 2010; Miller, Rietschel, McDonald, & Hatfield, 2011). Given this distinction, my findings here suggest that acetaminophen impacts neurocognitive disengagement during off-task attentional states not by increasing the attenuation of more basic stimulus categorization processes beyond what is normally seen, but rather, by catalyzing the attenuation of deeper, more contemplative stimulus evaluations. Whether this is restricted to implicit evaluative analysis as captured in the current paradigm or extends to

situations where stimuli are being explicitly evaluated on emotional and/or aesthetic dimensions remains an open question.

Second, my findings extend our understanding of acetaminophen and its psychopharmacological impacts in several key ways. For one, all previous studies of acetaminophen's psychological effects have been predicated on state-related comparisons between when an individual is on acetaminophen relative to when taking a placebo. My findings here demonstrate that acetaminophen can impact neurocognitive processing at much shorter, more transient time scales as well. For another, individuals on acetaminophen present as less empathetic towards the physical plight of others (Mischkowski, Crocker, & Way, 2016), less sensitive to the pain of social rejection (DeWall et al., 2010), less prone to cognitive dissonance with respect to behavioural outcomes (DeWall et al., 2015), less affected by existential threats (Randles et al., 2013), less reactive to emotionally valanced imagery (Durso et al., 2015), and less perturbed by performance errors (Randles et al., 2016). All of these situations can be described as having some degree of affective salience of one form or another. By way of contrast, the stimuli used in the current study were affectively neutral visual events presented in the context of a simple target detection task. Given that acetaminophen nevertheless was found to induce a significant decrease in the implicit evaluative analysis of target events as captured in the LPP ERP component, my findings suggest that the psychological impacts of acetaminophen extend to affectively benign stimuli. That is, the effects of acetaminophen on neurocognitive processing are not specific to emotion-related or emotion-inducing events.

Finally, to what extent do the current findings align with what we understand about the site of acetaminophen's impacts on cortical processing? Previous neuroimaging studies have shown that acetaminophen reduces responsivity in the dorsal anterior cingulate cortex (dACC) to both social (DeWall et al., 2010) and physical (Pickering et al., 2015) pain, evidence that aligns with the psychological effects reported in previous studies of acetaminophen – including the reported attenuation of social pain (DeWall et al., 2010), cognitive dissonance (DeWall et al., 2015), and affective responses (Randles et al., 2013). Although debate continues over how best to situate dACC functions within a more detailed neurocognitive architecture (Ebitz & Hayden, 2016; Kolling et al., 2016; Shenhav, Cohen, & Botvinick, 2016), it can be generally understood that the dACC exerts a high degree of control over our behavioural interactions with the external environment (Heilbronner & Hayden, 2016), such as orienting our attention to task-relevant external events (Weissman, Gopalakrishnan, Hazlett, & Woldorff, 2005) and mediating the saliency of both internal or external events (Bonnelle et al., 2012; Jilka et al., 2014; Menon, 2015). If acetaminophen does indeed reduce the responsivity of the dACC to on-going events in the external environment, it would certainly fit with the reported effects here.

## 4.2 Limitations

While this project contributes to our understanding of the influence of acetaminophen on neurocognitive disengagement during off-task attentional states, several limitations must be noted. First, my thesis is not providing direct definitive evidence that acetaminophen downregulates activity in the dACC; that question goes beyond the scope and goals of the

current study. Rather, my thesis is presenting results that are consistent with this model of how acetaminophen induces its psychological effects.

Second, the null behavioural results concerning the frequency of off-task attentional reports for acetaminophen vs. placebo experimental groups raises an important question: Based on these non-significant results, can we conclude that acetaminophen does not alter the amount of time spent in off-task attentional states? *Post hoc* analyses on the behavioural analyses of 20 participants per experiment group, showed that the resulting behavioural analyses had a power of .15 to detect the effect size of .19, indicating that the statistical tools used in the present study had a good chance of failing to reject the null hypothesis even if an effect were present. *Post hoc* power analyses with effect size from this sample was used because to our knowledge, a study on this style with psychopharmacological manipulation of task related attention has not been done in the literature so far. Therefore, I did not have an *a priori* effect size to run my power calculation for the desired sample size. Moreover, only the 40 participants with corresponding ERP-based data were used for behavioural data to keep consistency in my overall analyses. The behavioural null result from this low-powered analyses are nevertheless at a concern of over-interpreting what it might or might not mean. A follow-up study with more experience sampling from a bigger sample size is required in order to have interpretable results of whether acetaminophen alters the relative amount of time one spends in off-task attentional states.

### **4.3 Future directions**

Since in my study affectively benign stimulus of the SART resulted in an LPP attenuation, a component that is typically modulated by emotional intensity of a stimulus (Brown et al., 2012), it would be interesting to observe the effects of acetaminophen on an otherwise affectively benign stimuli, that elicits a salient response in particular populations. One such special population would be hoarders, whom gather a larger body of objects with little discrimination. Hoarders report feeling pain when their cherished items are discarded (Brown & Pain, 2014), and are more likely to demonstrate tendencies of anthropomorphism towards hoarded items – attributing human-like characteristics to non-human items (Neave, Tyson, McInnes, & Hamilton, 2016; Timpano & Shaw, 2013). Since hoarders ascribe human qualities to inanimate objects, they might also elicit an affectively salient response towards images of broken or damaged objects. Therefore, it is reasonable to assume that images that would be considered affectively benign to clinically typical populations would be highly polarizing to hoarders. We could investigate whether acetaminophen influences attentional disengagement differently in hoarders with anthropomorphism. In a double-blind, placebo-controlled study paradigm similar to Kam et al. (2014) with subjective ratings of pain and ERP-based measures, hoarders with anthropomorphism would look at images of broken or intact items. If the affective profile of the image is important in eliciting a cognitive response, then we would see a difference in the frequency or depth of disengagement during attentional reports between hoarders with anthropomorphism and clinically typical participants upon taking acetaminophen. This study could help us identify potential areas for intervention research by understanding how acetaminophen influences disengagement when viewing stimuli that might elicit an affectively salient response in particular populations.

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