Caffeine Withdrawal and Cold Pressor Test Performance

A Senior Honors Thesis for the Department of Psychology

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Abstract

Caffeine is the most widely used central nervous system (CNS) stimulant in the world. Whether through coffee, soft drinks, food, or medication, caffeine is ingested habitually by most of the human population. As a stimulant, caffeine causes wakefulness, sustained intellectual activity, and even mood elevation (Hodgman, 1998), making it a popular additive to daily human food and beverage intake.

In addition to benefits, however, caffeine has addicting qualities, and thereby causes deleterious effects once consumers go through withdrawal of the drug. This study will further investigate the nature of caffeine dependence through analysis of pain perception once a habitual consumer is in caffeine withdrawal. The analgesic effects of caffeine, although confirmed by numerous studies, are poorly understood. This study will contribute to the knowledge regarding the conditions under which analgesia is experienced upon caffeine consumption.

Introduction

Caffeine is the most widely consumed psychoactive drug in the world. It is found in many commonly consumed products such as coffee, soft drinks, food, and over-the-counter pain relievers. As a result, caffeine is ingested habitually by most of the human population. As a stimulant, caffeine causes wakefulness, sustained intellectual activity, and even mood elevation (Hodgman, 1998), making it a popular additive to daily human food and beverage intake.

Physiological and Behavioral Effects of Caffeine

Caffeine has a number of behavioral and physiological effects, and they are mainly dependent upon the strength of caffeine dosage. Caffeine significantly increases diastolic blood pressure, plasma concentration of epinephrine, and free fatty acids in humans (Benowitz, Jacob, Mayan, & Denaro, 1995). While less severe pharmacological effects include mild central nervous system stimulation, wakefulness, sustained intellectual activity and decreased reaction timing (Hodgman, 1998). More extreme side effects of caffeine include restlessness, nervousness and irritability. Symptoms can also progress to delirium, emesis, neuromuscular tremors and convulsions, tachycardia, and increased respiration (Gilman, Rall, Nies & Taylor, 1990). Caffeine can also, at acute dosage of 150-200 mg/kg body weight, have fatal effects (Hodgman, 1998).

Caffeine acts as a vasoconstrictor of the cerebral arteries, reducing regional blood flow in the brain (Cameron, Modell & Harihaven, 1990; Mathew, Barr & Weinman, 1983), particularly blood flow velocity in the medulla-cerebral artery (Perod, Roberts & McKinney, 2000). Withdrawal also causes changes in cerebral blood flow, leading to vasodilation in high caffeine users that is thought to be associating with a throbbing, vascular-type headache- one of the

commonly observed symptoms of caffeine withdrawal (Couturier, Laman, van Duijn & van Duijn, 1997; Lader, 1999; Matthew & Wilson, 1985).

In addition to blood flow, caffeine is also known to have influence on adenosine receptors A_1 and A_2, both of which play roles in the heart, regulating myocardial oxygen consumption and coronary blood flow (Daly, Shi, Nikodyivic & Jacobson, 1999). It acts as a non-selective competitive antagonist, inhibiting the receptors and consequently effecting behavior and cognitive function. Results from the competitive binding of caffeine and paraxanthine to adenosine receptors are important to CNS effects. Due to the blockage of the adenosine receptors, caffeine indirectly affects the release of many neurotransmitters. gamma-aminobutyric acid (GABA), it increases spontaneous glutamate release from nerve terminals (Sharma & Vijayaraghavan, 2003), dopamine levels increase, norepinephrine, dopamine, acetylcholine, serotonin, and perhaps neuropeptides (Daly et al, 1999), thereby causing an effect in a number of physiological systems.

Metabolism

In humans, peak plasma blood concentrations of caffeine occur between 15 and 120 minutes after oral dosage (Arnaud, 1987). Caffeine is both hydrodrophilic and lipophilic, so it distributes feely into intracellular tissue water as well as through all biological membranes (Bonati et al, 1982). It also readily crosses the blood-brain barrier, resulting in prompt impact on brain function (Bonati et al, 1982). The half-life of caffeine in plasma of humans is approximately 5 hours, although it can range from 1.5 to 9.5 hours. Pregnancy, obesity, use of oral contraceptives, smoking, and altitude all affect the metabolism of caffeine (Brachtel & Richter, 1992). For example in adult males, caffeine half-life is reduced by 30% to 50% in smokers compared to nonsmokers (Hart, Farrel, Cooksley & Powerll, 1976; Joeres, Klinker,

Hesuler,, Epping, Zilly & Richter, 1998; Murphy, McIvor, Yap, Cooksley, Halliday & Powerll, 1988) whereas its half-life is approximately doubled in women taking oral contraceptives (Patwardhan, Desmond, Jonson & Shenker, 1980). There are no apparent differences, however, in caffeine metabolism and age, as the drug's half-life is the same in both young and elderly humans (Blanchard & Sawers, 1983b).

In healthy humans, repeated caffeine ingestion does not alter its absorption or its metabolism (George, Murphy, Roberts, Cooksley, Halliday & Powell, 1986). With long-term exposure to caffeine, there is a substantial accumulation of paraxanthine, its chief metabolite (Benowitz et al, 1995). As a result, paraxanthine would almost certainly contribute to the pharmacological activity of caffeine (Benowitz et al, 1995). It would also be reasonable to expect then, that with long-term caffeine exposure, paraxanthine would also contribute to development of tolerance to caffeine and subsequent withdrawal symptoms.

Tolerance and Withdrawal

Caffeine does not have a convincing profile among the psychological community as an addictive drug, and is not classified as such in the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV). Furthermore, researchers have argued that caffeine withdrawal is not clinically significant and is primarily determined by expectancies (Dews, O'Brien & Bergman, 2002; Rubin & Smith, 1999). Despite these arguments, caffeine dependence can occur. Chronic administration results in tolerance to a number of its physiological, subjective and behavioral effects (Griffiths & Mumford, 1996). This, in combination with the development of withdrawal symptoms amongst chronic caffeine consumers, might indicate that caffeine has addictive properties.

Repeated administration of caffeine does not change its pharmacokinetics, but in many cases development of tolerance to the drug does occur. Specifically, certain behavioral actions, such as those resulting from stimulation, become less potent as tolerance for caffeine develops (Finn & Holtzman, 1986). Following cessation of caffeine use, withdrawal-like symptoms are also may be seen in humans (Griffiths , Bigleow & Leibson, 1986; Griffiths, Evans, Heishman, Preston, Sannerud, Wolf & Woodson, 1990). These withdrawal symptoms typically are presented as the opposite effects of those resulting from caffeine administration. Frequency of occurrence of withdrawal, as reported in survey studies and clinical trials, varies anywhere from 4% to 100% (Goldstein et al, 1965; Griffith et al, 1986; Griffiths & Woodson, 1988; Naismith et al, 1970; Robertson et al, 1981; Weber et al, 1993). They generally begin approximately twelve to twenty-four hours after sudden cessation of caffeine consumption and reach a peak after forty-eight hours. However, in some individuals, these symptoms can appear within only three to six hours; consequently, even a short abstinence equivalent to missing a single cup of coffee can lead to significantly unpleasant effects (Phillips-But & Lane, 1998). Symptoms of caffeine cessation, although typically short lasting, can last as long as one week (Barone & Roberts, 1984; James, 1991; Nehlig & Debry, 1994; Phillips-Bute & Lane, 1998).

It is also important to mention the lack of relationship between withdrawal symptoms and the quantity of caffeine that is ingested daily (Strain, Mumford, Silverman & Griffiths, 1994). Signs and symptoms of caffeine withdrawal can range from mild to severe, following withdrawal from both low and high doses of caffeine (Silverman, Evans, Strain & Griffiths, 1992). In the aforementioned study conducted by Strain, Mumford, Silverman and Griffiths (1994) for example, withdrawal symptoms were found in subject with a daily caffeine intake ranging from low (only 1 to 2 cups) to those whose intake was significantly higher (about 20 to 30 cups).

These withdrawal symptoms typically included headaches, drowsiness, irritability, fatigue, low vigor, and flu-like symptoms including muscle pain, nausea, and vomiting (Griffiths et al, 1986; Griffiths et al, 1990; Silverman et al, 1992). Nervousness was also a common withdrawal symptom (Griffiths et al, 1986; Griffith et al, 1990).

Dependence

A condition known as caffeinism can occur when individuals become dependent on caffeine, and it describes a set of behavioral and physiological symptoms caused by the excessive consumption of caffeine-containing substances (Greden, 1974; McManamy and Schube, 1936; Powers, 1925; Reimann, 1967). The symptoms include irritability, tremulousness, occasional muscle twitching, insomnia, sensory disturbances, tachypnea (an abnormally rapid rate of breathing), palpitations, flushing, arrhythmias (an alteration or abnormality of normal cardiac rhythm), diuresis and gastrointestinal disturbances (Greden, 1974; Powers, 1925; Reimann, 1967; Truitt, 1971). Individuals suffering from caffeinism are sometimes misdiagnosed as anxiety neurotics because of the similarity of the symptoms (Greden, 1974), particularly when they consume more than 250 mg of caffeine per day.

Caffeine intoxication is also recognized in the DSM-IV, and is characterized by demonstration of 5 or more of the following signs during or shortly after caffeine use (usually in excess of 250 mg): Restlessness, Nervousness, Excitement, Insomnia, Flushed Face, Diuresis, Gastrointestinal disturbance, Muscle Twitching, Rambling flow of though and speech, Tachycardia or cardiac arrhythmia, Periods of inexhaustibility, or Psychomotor agitation. In

addition, these symptoms must cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Caffeine has also been shown to function as a reinforcer in humans (Hughes et al 1991; Evans et al 1994), and some individuals become clinically dependent on caffeine as indicated by being unable to quit and continuing its use despite having medical problems made worse by it (Strain et al, 1994; Hughes et al, 1998). Physical dependence on caffeine has been documented in both pre-clinical and clinical research, and biological basis has been hypothesized to be increased functional sensitivity to endogenous adenosine (Griffiths & Mumford, 1996).

The extent to which dependence can affect behavior was investigated in a study conducted by Schuh and Griffiths (1997) using twenty subjects who were moderate consumers of caffeine (average daily intake 379 mg). By means of saliva measurements, it was ascertained that the subjects generally complied with an admonition to refrain from caffeine during the study. They were then asked to rate their subjective impression of the randomly assigned placebo or caffeine capsules and to assign a cash value to receiving the same type of capsule again. These symptoms of headache, feeling "worn out" and experiencing "flu-like symptoms" were, as expected, higher in the subjects that received placebo than in those that received caffeine. Conversely, caffeine capsules were associated with subjective alertness, well being, and symptoms of stomach upset (Schuh and Griffiths, 1997). Importantly, the subjects chose caffeine and were willing to forfeit money to avoid receiving placebo. Because this behavior correlated with the symptoms of headache, the authors concluded that choice of coffee is potently controlled by avoiding withdrawal. In fact, in this study, avoiding withdrawal was a stronger controller of caffeine intake than were the positive effects of caffeine. This conclusion was later confirmed in another study (Garrett and Griffiths, 1998).

Earlier studies also established this idea of behavior intending to lessen the potency of withdrawal symptoms. In one such study, sixty-two daily caffeine consumers were assessed while consuming normal caffeine intake (Silverman et al, 1992). After a two-day period in which they consumed caffeine-free diets, they were administered capsules containing caffeine (matched to usual intake) or a placebo. Results of the study showed that subjects administered the placebo increased their use of analgesics despite discouragement from the experimenters (Silverman et al, 1992). In another study conducted by Strain, Mumford, Silverman and Griffiths (1994), eleven subjects who met DSM-IV criteria for substance dependence on caffeine were assessed after two-day periods during which they were administered capsules containing caffeine (matched to usual intake) or placebo. Results of this study showed that 82% of subjects showed evidence of caffeine withdrawal during placebo and that 45% reported analgesic use despite discouragement (Strain et al, 1994).

A study conducted by Höfer and Bättig (1994a) reported results similar to the two aforementioned studies. One hundred and twenty habitual coffee drinkers, after a three-day baseline period, received either nine days of caffeinated instant coffee, or nine days of intermittent instance coffee, and decaffeinated instant coffee. In the intermittent group, decaffeinated days compared with baseline days produced increased analgesic use.

Analgesic Properties

A number have studies have linked caffeine dependence to analgesic use, since it has been reported to increase plasma β-endorphins (endogenous opioid peptide neurotransmitters) during endurance exercise (Laurent et al, 2000). A possible explanation for this may be related to the presence of adenosine A_2 receptors in, or close to sensory nerve endings that cause hyperalgesic effects in certain types of pain (Myers, Shaikh & Zullo, 1997). The analgesic effects are small

(Bättig & Welzl, 1993), but under conditions of pain, caffeine could have an indirect beneficial effect by elevating mood and clear-headedness (Lieberman, Wurtman, Emde & Coviella, 1987). Patients rate caffeine-containing analgesics as superior to caffeine-free preparations for the treatment of headache (Migliardi, Armellino, Friedman, Gillings & Beaver, 1994). The study conducted by Lieberman, Wurtman, Emde and Coviella (1987) found that both mood and vigilance were improved when aspirin was combined with caffeine than when aspirin was given alone or with a placebo.

There is another possibility that caffeine might have analgesic properties for specific types of pain. In addition, caffeine may exert an analgesic effect in the brain. For example, caffeine antagonized pain-related behavior in mice following injection into brain (Ghelardini, Galeotti & Bartolini, 1997). Analgesic effects have also been seen when treating human headache (Ward et al, 1991), whereby headache intensity was significantly and dose-dependently reduced by caffeine administration under double-blind conditions.

Present Study

The present study examined the analgesic properties of caffeine through investigation of pain perception under specific withdrawal conditions. Given the results of the aforementioned studies (Bättig & Welzl, 1993; Ghelardini et al, 1997; Höfer & Bättig,1994a ; Liberman, Wurtman, Emde & Coviella, 1987; Silverman et al, 1992; Ward et al, 1991; Migliardi et al, 1994), when an individual is experiencing caffeine withdrawal, his or her pain threshold should be lower, indicating that the analgesic effects from which they once benefited with caffeine

consumption are no longer present once caffeine is eliminated. This relationship was examined using a cold pressor test, which has been used experimentally to stimulate acute pain. Studies show that the cold pressor is an effective model of acute pain conditions due to the discomfort it causes (Mitchell, MacDonald & Brodie, 2004).

We hypothesized that when in caffeine withdrawal, participants would be unable to keep their arm submerged in cold water for as long as they would when receiving caffeine and thereby exhibit decreased pain threshold when in caffeine withdrawal.

Methods

Participants

Twenty-eight individuals were be recruited from the greater Tufts community, specifically students between the ages of 18 and 22. Compensation was in the form of monetary payment of $10/hr. (The Tufts University Psychology Department standard volunteer rate.) The $10 payment was given at the end of each session. If a volunteer did not complete all test sessions, they were compensated based on the number of sessions they attended (but did not necessarily complete). Recruitment was made through tuftslife.com or through recruitment flyers.

Subjects recruited were non-smokers. They also did not take any prescription medication or report any hypersensitivity to caffeine. Individuals who suffered from anxiety, panic attacks, hypertension, cardiac disease, hepatic dysfunction, peptic ulcer disease, severe reflux, or insomnia were not eligible to participate.

Recruited subjects were habitual consumers of various dosages of caffeine. Individuals who never consumed caffeine, were excluded since they had no experience with the drug. Habitual caffeine intake levels were assessed using a questionnaire onto which the participant recorded the caffeine containing products they consume on a daily basis.

Caffeine Administration:

Both the caffeine and placebo treatements were administered in capsule form (Dr. Michael Roberge, RPh, Compounded Solutions, Monroe, CT). Capsules contained either 0mg or 300 mg of caffeine, but looked identical. They were also coded to ensure volunteer and administrator blindness during the procedure. Caffeine dose level was equivalent to that found in two cups of coffee.

Manipulation Checks:

To verify the effects of caffeine withdrawal and caffeine consumption, various questionnaires were provided. The profile of Mood States Questionnaire (POMS) is an questionnaire assessing the subjective mood and state of arousal of the respondant (McNair et al., 1971). The respondant rated 65 mood-relateed adjectives on a five-point scale, with their present state in mind. According to previous studies, the POMS is sensitive to caffeine (Amendola et al., 1998; Lieberman et al., 2002).

Before administration of both treatments, participants completed a Questionnaire of Caffeine Cravings (West & Roderique-Davies, 2008). This questionnaire is an adaptation of that created by West & Roderique-Davies in which participants recorded their level of agreement to a number of statements suggesting the features of caffeine withdrawal. For example, participants

were asked questions to rate their agreement to statements such as "I will have caffeine as soon as I get the chance." The administration of this questionnaire helped to assess the level of withdrawal the participant was in after each treatment and cold-pressor test administration.

Fake Saliva Sample:

Participants were told that to ensure they have not consumed caffeine prior to the cold pressor test, they would be asked to provide a saliva sample by rinsing their mouth with water and then spitting into a saliva collection tube. However, the saliva was never for caffeine. Previous studies (Kanarek & Carrington, 2004) have shown that the fake saliva sample is an effective way of ensuring participant compliance when they are asked to cease caffeine intake before testing.

Cold Pressor Test:

Pain perception was evaluated using a cold pressor test, a model by which acute pain is measured. The experimentor measured the time it takes for an individual to withdraw their arm from a cold water bath. To ensure that all participants began the experiment under similar thermal conditions, each participant placed his/her non-domininant arm in a water bath maintained at body temperature (37° Celsius) for two minutes. The participant then placed his/her arm in a cold water bath maintained at 2 ±1°C. Participants then rated their discomfort during the cold-pressor test using the Borg Category-Ratio (CR) 10 scale, a standardized scale used to measure perceived exhertion, aches or pain. The experimenter also recorded the amount of time that elapsed as the subject reported each level of the scale and the time until the subject

could no longer keep his or her arm submerged in the icy water. If after two minutes the participant did not remove his or her arm, the experimenter terminated the test.

Before the first session, volunteers were contacted and asked not to consume caffeine for 24 hours prior to their arrival in the laboratory. Once they arrived for the first session, volunteers were given the opportunity to thoroughly read the consent form (see Appendix A), asked any questions and then signed the consent form. Aftwards, they were given two other forms to assess their habitual caffeine consumption and a health questionnaire.

Recruited participants completed two sessions, approximately one week apart. During these sessions, participants gave consent and were then tested under two conditions: receiving 300 mg of caffeine or a plecebo capsule after 24 hours of caffeine withdrawal. The time for measuring the effects of caffeine withdrawl was based on previous studies indicating that withdrawal symptoms begin about 12 hours and peak between 24 and 48 hours after cessation of caffeine consumption.

Following the saliva sample, an initial cold-pressor test was then given. The participant was then given a capsule containing either 300 mg of caffeine or a placebo along with a cup of water. After 30 minutes, during which time the participant watched a television show, the participant was given the second cold-pressor test. During this time, the participant stated his or her level of increasing discomfort using the Borg CR-10 scale (see Appendix E) until he or she pulled her arm out of the water or until 2 minutes maximum had elapsed (whichever comes first). The participant then completed a Questionnaire of Caffeine Cravings (QCC; see Appendix D) to help assess their level of caffeine craving after each treatment, and the POMS (see Appendix C)

to assess their current mood after each treatment. The television shows were presented in the Psychology Department, and had been previously used as filler tasks during experiments.

All procedures for the present study were approved by the Institutional Review Board (IRB) at Tufts University.

Results

Data Analysis

Data were analyzed using SPSS 16.0 for Windows. All data presented as Mean ± SD. Two factor repeated measures ANOVA were used throughout. Average daily caffeine intake for each participant was also factored in as a covariate in the repeated measures ANOVA analyses. Alpha level of 0.05 set for all analyses.

POMS

The POMS scores for fatigue, vigor, anger, depression, tension, and confusion yielded varying results. Data show that when given caffeine, subjects reported more vigor (M=12.5, SD=6.17) than when given the placebo (M=9.26, SD=5.9). However analysis shows no significant difference in reported vigor between the two treatments ($F=3.434$, $p<.081$); (See Figure 1). Participants also reported less fatigue (M=8.05, SD =4.42) when given caffeine than when in given placebo (M=10.35, SD=5.31); (See Figure 2).

There was a difference in tension scores for participants when given caffeine (M=5.4, SD=3,69) and given the placebo (M=7.26, SD=6.79). This difference was statistically

significant (F=4.503, p<.048), indicating that when given the placebo, participants were significantly more tense than when presented with caffeine.

Results show a difference in confusion between caffeine (M=5.3, SD=2.9) and placebo (M=7.05, SD=4.88) treatments. This difference is also significant (F=4.697, p<.043), indicating that when given placebo, participants report being more confused than when given caffeine (See Figure 3).

Data show no significant difference between anger of particpants when given caffeine (M=2.25, SD=3.24) and placebo (M=2.75, SD=4.12) treatments (F=.263, p<.614). However, when the amounts of caffeine habitually consumed by participants was factored in as a covariate, the difference in the two treatments became statistically signficant (F=14.481, p<.001), indicating that the amount of caffeine ingested by a participant has an effect on the difference in anger they report between the caffeine and placebo treatments. Pearson product correlation indicates that increased caffeine intake correlates positively with increased anger when presented with placebo (R=.714, p<.001).

Similarly, no statistically significant difference in depression was found between caffeine (M=2.85, SD=3.18) and placebo (M=4.75, SD=6.77) treatments (F=.807, p<.381). However, when the amounts of caffeine habitually consumed by participants was factored in as a covariate, the difference in the two treatments became statistically signficant (F=10.738, p<.004), indicating that the amount of caffeine ingested by a participant has an effect on the difference in depressed state they report between the caffeine and placebo treatments. Pearson product correlation indicates that increased caffeine intake correlates positively with depressive mood state when presented with placebo (R=.600, p<.005).

Questionnaire of Caffeine Cravings

Participants reported a higher craving score (M=71.11, SD=20.51) when given placebo than when given caffeine (M=63.95, SD=15.112), however this difference was not statistically significant (F=.202, p<.659); (See Figure 5). When average daily caffeine consumption was factored as a co-variate, this difference indicates a trend (F=3.909, p<.064), indicating the the amount of caffeine consumed daily influences the difference in reported craving between caffeine and placebo treatments.

When analyzing craving scores with daily caffeine intake considered by mean split, significance was found. There was a significant difference in craving between the participants who consumed the above-average amount of caffeine daily and those who consumed the below-average amount of caffeine daily (F=8.403, p<0.01). When factoring daily caffeine intake as a covariate, data indicated that those participants who consumed more than the average amount of caffeine for the participant population reported significantly higher craving scores than those who consumed less than the average daily amount of caffeine (F=9.709, p<.006); (See Figure 8).

Withdrawal Latency

Withdrawal latencies for participants before receiving each treatment was nearly identical. Prior to receiving the caffeine capsule, average withdrawal latency was 70.59±39.8 seconds. Prior to receiving placebo, withdrawal latency was 70.96±39.0 seconds.

Results from cold pressor test indicate a larger difference in withdrawal latency for participants when given the caffeine capsule (M=5.9439, SD=22.13), than adminitered the placebo (M=0.976, SD=18.8). This result showed that participants held their arm in the water longer after receiving the caffeine than when receiving the placebo. However, this difference

was not statistically signficant (F=.719, p<.404); (See Figure 9). When average daily caffeine intake was included as a covariate, there was no effect (F=.019, p<.891).

Discussion

The present study examined the effects of caffeine withdrawal on cold pressor test performance. The design was within subjects, thus each participant was given both caffeine and a placebo treatment during different sessions approximately one week apart. The presentation of treatments was counterbalanced in the hopes of eliminating confounds pertaining to order of presentation. Although the results showed that when given caffeine, participants were able to hold their arm in the ice water longer than when in withdrawal, the difference was not significant. This may be the result of a number of things. Firstly, it may have been the result of confounding factors. For instance, all of the participants were tested in the late afternoon. Perhaps depending on their food intake or various activities during a particular day, other factors may have been influencing their cold pressor performance aside from caffeine. What's more, given the fact that caffeine is in many commonly ingested foods, participants simply may not have realized that they could have ingested some caffeine despite their attempts to avoid it 24 hours before arriving in the laboratory.

When the amount of caffeine habitually ingested by each participant was included in the withdrawal latency analysis as a co-variate, we again found no significance between withdrawal time of the caffeine and placebo treatments. In fact, even less of an effect was seen. This is consistent with past studies that state that the amount of caffeine habitually consumed by an individual does not influence the severity of withdrawal symptoms once individuals cease

caffeine consumption. In fact, individuals who consumed as little as 47mg of caffeine daily showed longer withdrawal latency when presented with caffeine than placebo.

In the future, perhaps all participants should be tested in the morning after having fasted, since that will ensure that no inadvertent caffeination from ingested foods. It would also be more consistent with an individual's typically routine, since caffeine is often taken as a "morning coffee" as a way to start one's day.

The Questionnaire of Caffeine Cravings (QCC) analysis indicated a higher craving score for participants when presented with the placebo than when presented with the caffeine. However, this difference was not significant until the data was analyzed via a mean split of the population with caffeine intake acting as a covariate. Many things could explain this. Firstly, since 11 of the participants reported a daily caffeine consumption level less than 100 mg, the majority of those who consumed less than the average caffeine intake may not have felt any craving for caffeine whatsoever. Studies show that the effects of withdrawal can be felt in individuals who habitually consume as little as 100 mg a day, yet there is not much data for those who consume less than that. Secondly, the lack of effect could be explained by the nature of caffeine cravings. That's to say, perhaps there is more to craving fulfillment than simply ingesting the drug that causes the craving. Take, for example, the fact that many people consume a mug of coffee or as an iced soft drink when they intake caffeine. Perhaps these results support the fact that an individual would have to physically taste the coffee or soft drink in their habitual manner to truly fulfill the craving. When the drug that they crave is presented in a capsule, it's possible that they truly wouldn't feel satisfied. When considering those of the above-average population, however, this craving fulfillment seems to be satisfied by the drug alone. These results suggest a potential relationship between the amount of drug one consumes

daily and the extent to which delivery preference controls craving fulfillment. That's to say, when one consumes large amount of a drug, the way in which they receive that drug is less important to someone who consumes low to moderate amounts of the same drug.

The results of the POMS indicate a trend in which individuals when caffeinated reported higher vigor, and less fatigue. This is to be expected, since caffeine is a known stimulant. However, these results were not statistically significant. One possible explanation for this could be the result of other confounding factors. For example, as previously stated these participants arrived to the lab towards the late afternoon, typically around 4 pm. It is possible that activities during the day may have made them more or less fatigued for each session, thereby influencing their POMS reporting. What's more, it is possible that the individuals who reported a habitual caffeine intake below 100 g did not feel the effects of caffeine withdrawal, and therefore did not feel more fatigued or less vigorous as a result of avoiding caffeine for 24 hours. One should also consider the fact that a treatment of 300 mg may not have been potent enough to take those who consumed very high amounts of caffeine completely out of withdrawal. In this case, such an individual would still feel fatigue and lack of vigor despite having received a caffeine treatment. It should also be noted that only 20 of the 28 subjects reported POMS scores that were analyzed. This is because the order in which the POMS scale was presented changed during the course of the experiment, and therefore the original 8 subjects' responses were disregarded. This change may have resulted in insufficient power for statistical significance to be possible.

The results of the POMS investigating confusion and tension yielded significant results. We find that individuals when in withdrawal from caffeine reported more confusion and more tension that those who received caffeine. This is consistent with previous studies that found that, in conjunction with fatigue and headache, tension was a symptom of withdrawal (Griffiths,

Bigleow & Leibson, 1986; Griffiths, Evans, Heishman, Preston, Sannerud, Wolf & Woodson, 1990). The results for the difference in confusion could be consistent with the established idea that among its ergogenic properties, caffeine increases alertness and concentration in individuals performing cognitive tasks along with sustained intellectual activity (Hodgman, 1998). The POMS assessment of depression and anger yielded no statistical significance when analyzed for difference in scores under caffeinated and withdrawal conditions. This was also consistent with our expectations that withdrawal would not influence one's anger or depressed mood state. This is consistent with previous studies (Evans & Griffiths, 1999).

A possible limitation of this study was that the time participants were asked to cease caffeine consumption might have been too short. While we decided that 24 hours would be sufficient, considering that withdrawal onset typically occurs between 12 and 24 hours. Past research shows, however, that caffeine consumption reaches a peak after around 48 hours. Given the fact that our population of caffeine consumers tended to consume what is considered to be low levels of caffeine habitually, perhaps 48 hours would have been a better way to ensure maximal withdrawal symptoms at the time of testing. Another limitation was that the time of day during which the participants were tested was not ideal. For college students, late afternoon seems to be a time when fatigue is at its peak. This, in combination with the fact that students are undoubtedly exposed to varying environmental stimuli every day, may have confounded their performance on the cold-pressor test. This is supported by the fact that the average withdrawal time for participants before each treatment varied greatly when it should have been consistent. Even before having received the placebo or the caffeine capsule, participants were performing differently on each of the two pre-tests administered during the study. This leads one to assume that factors beyond the realm of this study were influencing the performance of the participants.

In the future, I recommend that the withdrawal time be increased to 48 hours prior to treatment. This will ensure that most of the participants should be in peak withdrawal, thereby maximizing the potential for an effect. Furthermore, I would perform the experiments first thing in the morning, to minimize the likelihood of inadvertent caffeine consumption by the participant, and also to remain consistent with the "morning coffee" idea as a way of isolating the time at which people are most likely to consume caffeine. Given the magnitude of the variation in withdrawal times across the participant population, I feel that future studies should also increase the number of participants.

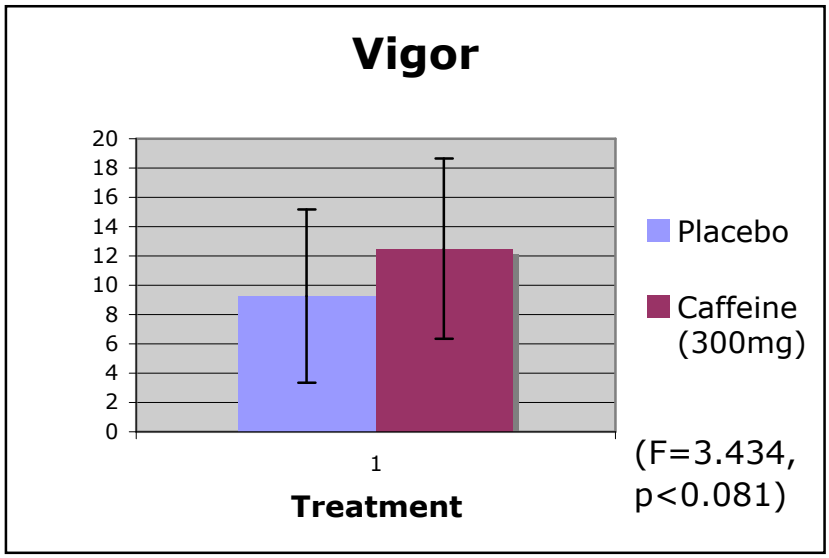

Fig. 1: When given caffeine, subjects reported more vigor (M=12.5, SD=6.17) than when in withdrawal (M=9.26, SD=5.9). However analysis shows no significant difference in reported vigor between the two treatments (F=3.434, p<.081);

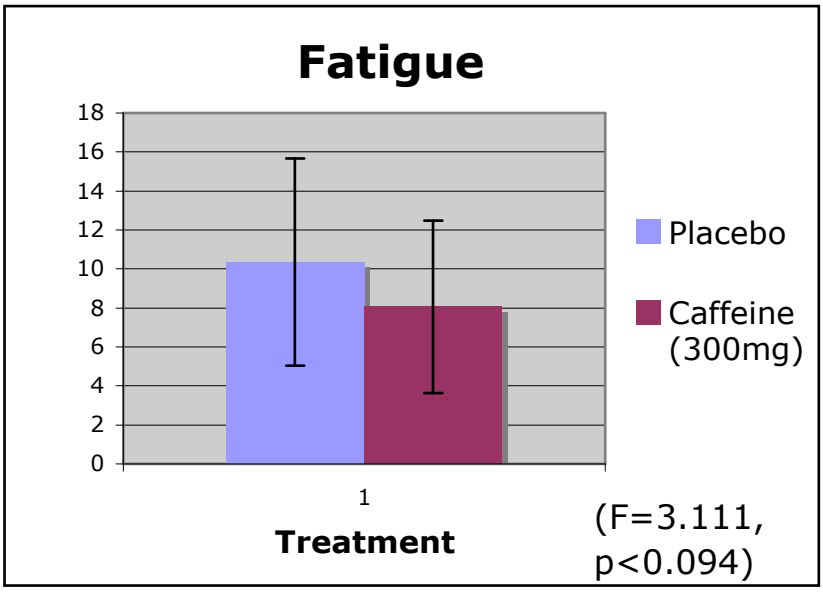

Fig. 2: Participants reported less fatigue (M=8.05, SD =4.42) when caffeinated than when presented with placebo (M=10.35, SD=5.31). No significant difference was shown between the reported fatigue for the two treatments (F=3.111, p<0.094).

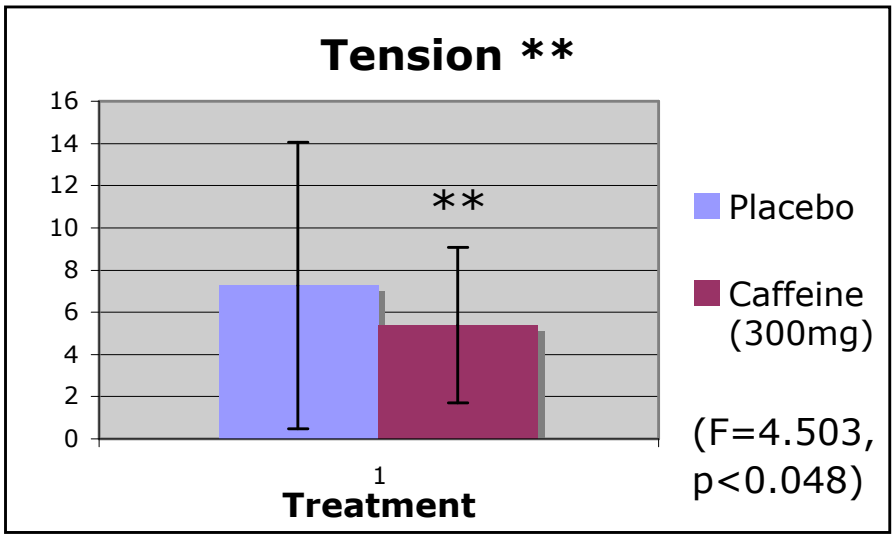

Fig. 3: There was a difference in tension scores for participants when caffeinated (M=5.4, SD=3,69) and in withdrawal (M=7.26, SD=6.79). This difference was statistically significant (F=4.503, p<.048), indicating that when in caffeine withdrawal, participants were significantly more tense than when presented with caffeine.

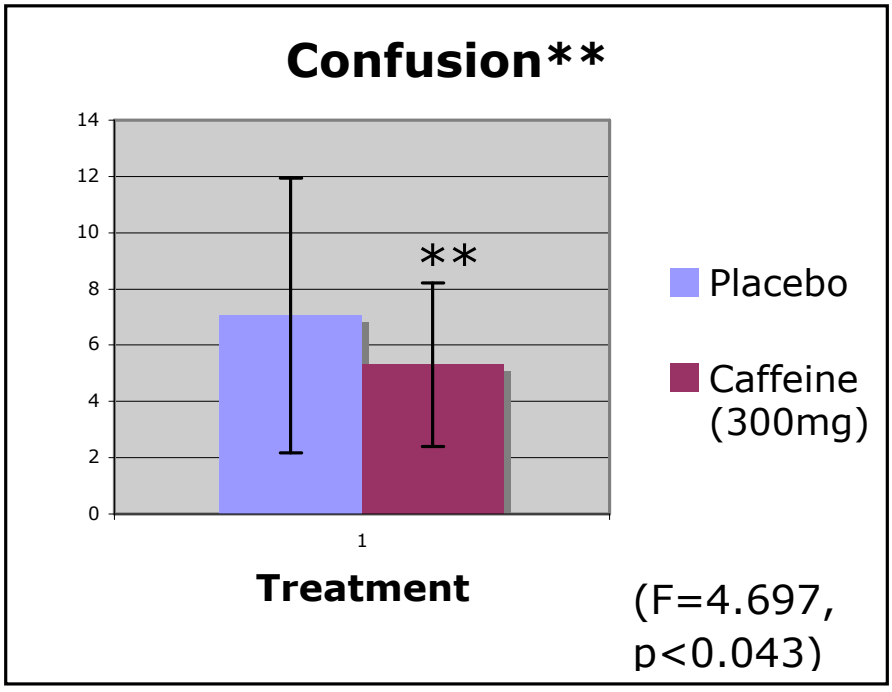

Fig. 4: Results show a difference in confusion between caffeinated (M=5.3, SD=2.9) and withdrawal (M=7.05, SD=4.88) groups. This difference is also significant (F=4.697, p<.043), indicating that when in caffeine withdrawal, participants report being more confused than when not in withdrawal

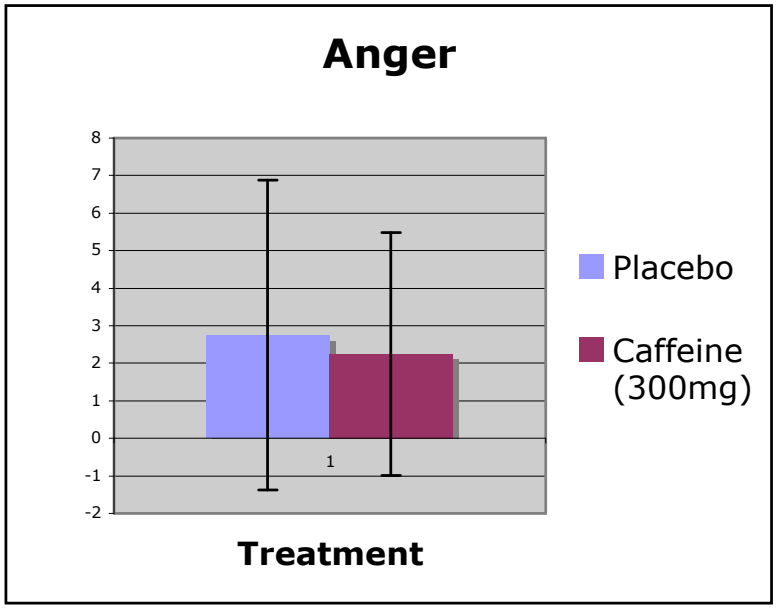

Fig. 5: Data show no significant difference between anger of particpants in the caffeinated (M=2.25, SD=3.24) and withdrawal (M=2.75, SD=4.12) treatments (F=.263, p<.614).

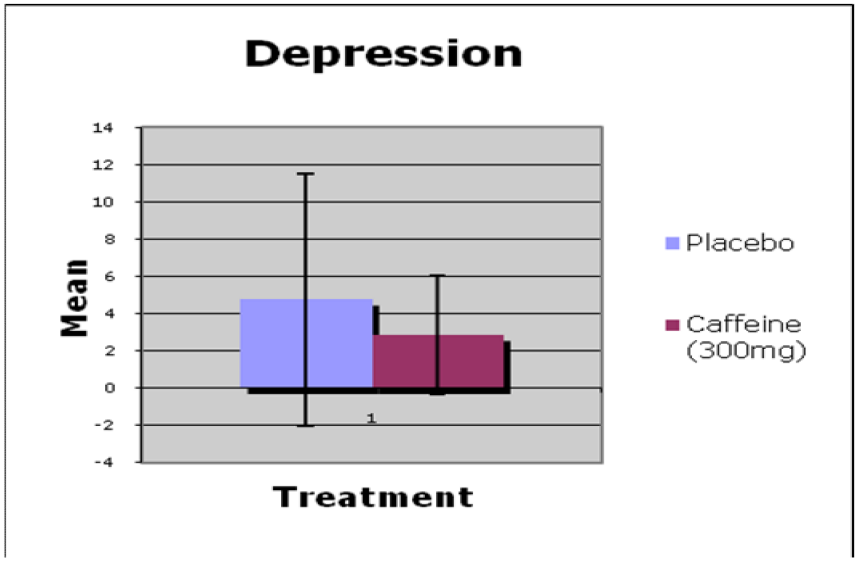

Fig. 6: Data show no statistically significant difference in depression was found between caffeinated (M=2.85, SD=3.18) and withdrawal (M=4.75, SD=6.77) treatments (F=.807, p<.381).

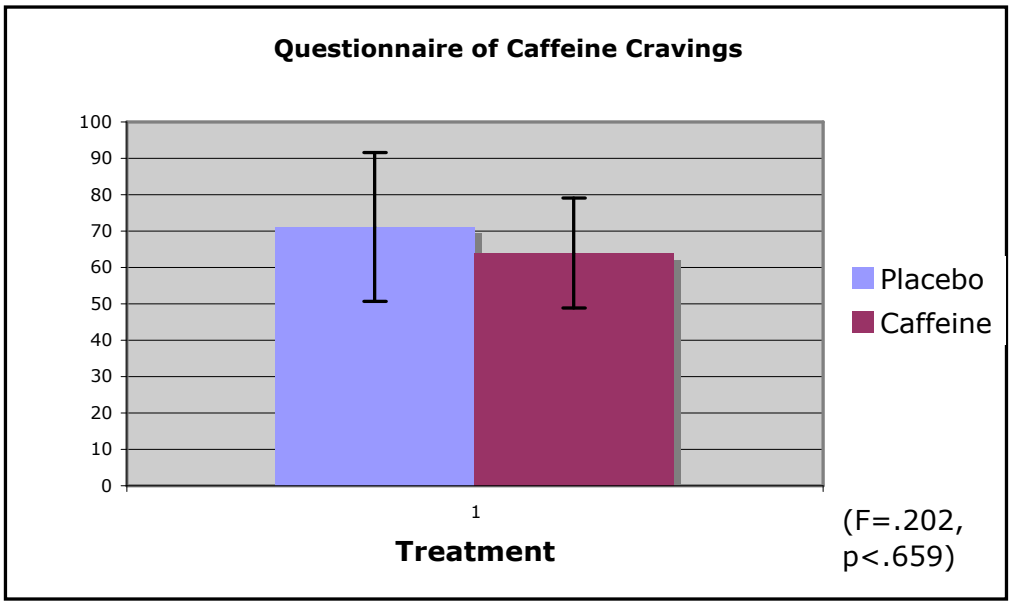

Fig. 7: Participants reported a higher craving score (M=71.11, SD=20.51) when in caffeine withdrawal then when not in withdrawal (M=63.95, SD=15.112), however this difference is not statistically significant (F=.202, p<.659); (See Figure 5).

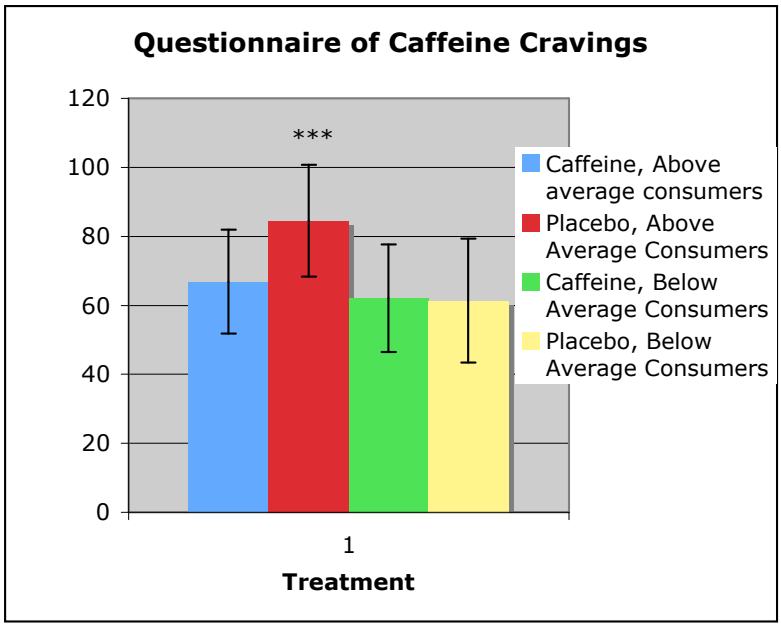

Fig. 8: When considering daily caffeine intake as a covariate, data indicate that those participants who consumed more than the average amount of caffeine for the participant population reported significantly higher craving scores than those who consumed less than the average daily amount of caffeine (F=9.709, p<.006).

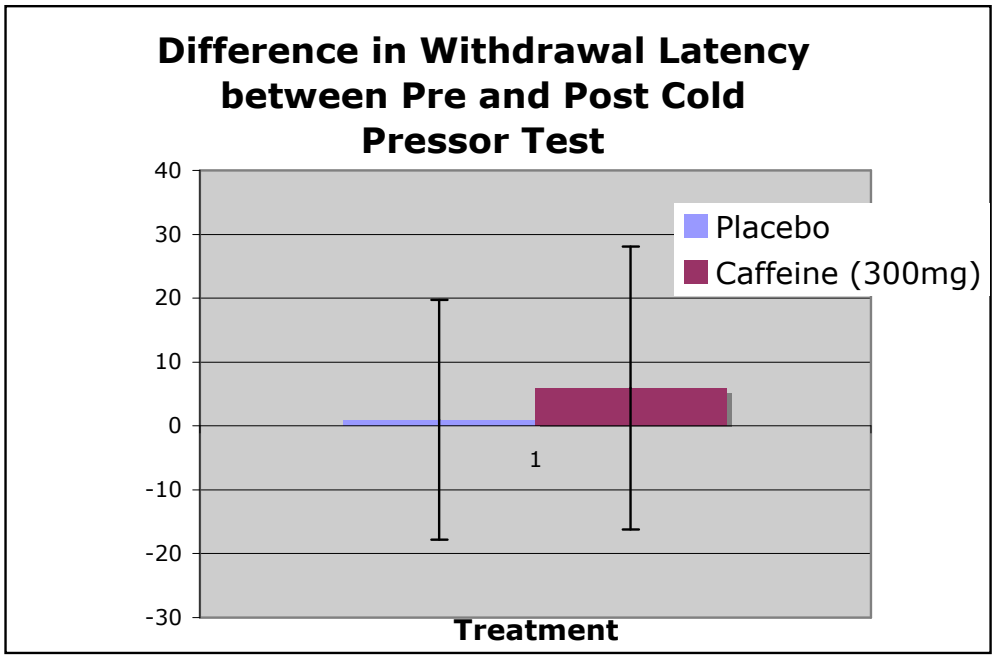

Fig. 9: Results from cold pressor test indicate a larger difference in withdrawal latency for participants when caffeinated (M=5.9439, SD=22.13), than when in caffeine withdrawal (M=0.976, SD=18.8). However, this difference is not statistically signficant (F=.719, p<.404).

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Appendix A

Informed Consent Form for Monetary Payment

Title of Study: Caffeine and Cold Pressor Test
Principal Investigator: Kaitlyn Mula, kaitlyn.mula@tufts.edu, (941) 587-7148
Co-Investigator and Emergency Contact: Dr. Robin Kanarek, Psychology Building, 490 Boston Avenue, Medford, MA 02155. (617) 627-5902, robin.kanarek@tufts.edu
IRB Contact: Yvonne Wakeford, IRB Administrator, Office of the Vice Provost, 20 Professors Row, Medford, MA 02155, (617) 627-3417.

Purpose, Duration and Procedures: You are being asked to participate in a research study investigating cold sensitivity that involves two sessions. Before coming to each session, we will ask you to cease all caffeine consumption for 24 hours. At the start of the first session of the experiment, we will take a saliva sample to ensure that you have not consumed caffeine, and you will be asked to fill out a series of questionnaires asking about your health and the medications you are taking (if any), your daily caffeine consumption, your current mood, and the level of caffeine withdrawal you are currently experiencing. Then, you will be given a capsule that may contain 300 mg of caffeine, or 0 mg of caffeine. The 300 mg of caffeine you will receive is roughly equivalent to that found in a Grande Starbucks regular coffee. Immediately after, you will select and watch a 30 minute television show from our archives. Finally you will be asked to place your arm in a cold water bath for as long as you can. If after two minutes, if you have not removed your arm, we will ask you to remove it from the water bath. During the time that your arm is in the bath, we will ask you to state aloud the levels of discomfort you are feeling. The procedure for the second session will be identical to that of the first, except you will not need to fill out the health and medications questionnaire, nor the daily caffeine consumption questionnaire. We will debrief you at the end of the second session.

Withdrawal of Participation and Compensation: Your participation is completely voluntary. You may decide to discontinue your participation at any time without penalization. You may also opt out of parts of the experiment if you want to. You will be paid $10 for each session you attend. Should you decide to stop participating midway through the session, you will be paid $10 anyway.

Benefits and Risks: The results from this experiment will help us to understand the role of caffeine withdrawal in cold sensitivity. There are no direct benefits to you besides the experience gleaned from participating in research studies, and there are no foreseeable risks associated with this study. Sometimes 300 mg of caffeine can cause some stomach upset, jitteriness or slight headache, although this is rare. However, if you suffer from: diabetes, depression, anxiety disorders, panic attacks, cardiac disease, liver disease, hypertension, insomnia, Raynaud's disease, cold intolerance, cold allergies (ie: skin when exposed to cold temperatures breaks out in rash), Peptic Ulcer disease, or severe reflux, we must insist that you not participate. If you are also taking prescription medications or are pregnant, you cannot participate.

Confidentiality: The data you provide us in this experiment will be coded for anonymity and will be kept confidential. All documents that you complete will placed in a manila folder and locked in a cabinet in Room 321 of the Psychology Building at Tufts University.

Request for more information: If you feel so inclined, you may contact Kaitlyn Mula (kaitlyn.mula@tufts.edu) or Robin Kanarek (robin.kanarek@tufts.edu) to find the results of this study after its completion.

If you have any questions, please ask the investigator.
I affirm that I understand the procedures and purposes of this experiment. I understand that I may ask questions at any time and can stop participation at any time without penalization. I have read this consent form, and by signing I indicate my willingness to be a participant in this study.
Participant's signature: _____ Date: _____
Printed name of participant: _____

Experimenter's signature: _____ Date: _____

Appendix B

Caffeine and Cold Sensitivity
Health Screening Questionnaire

Age: ____ Height: ____ Weight: _____

Sex: Male Female

Please answer each of the following questions by circling either "yes" or "no".

Are you a smoker? YES NO

Are you currently pregnant or nursing? YES NO

Do you plan on becoming pregnant during the study? YES NO

Are you currently taking oral contraceptives? YES NO

Do you have problems swallowing pills? YES NO

Is English your native language? YES NO

Are you currently using drugs or medication of any kind? YES NO
(Does not include oral contraceptives)

Do you have a history of:

Diabetes YES NO
Depression YES NO
Anxiety disorders YES NO
Panic attacks YES NO
Cardiac Disease YES NO
Liver Disease YES NO
Hypertension YES NO
Insomnia YES NO
Raynaud's Disease YES NO
Cold Intolerance YES NO
Cold Allergies (ie: cold temperatures when exposed to bare skin will give you rashes) YES NO
Peptic Ulcer Disease YES NO
Severe Reflux YES NO
Other Gastrointestinal Disease YES NO

Would you characterize yourself as overly sensitive to caffeine? YES NO
If yes, please explain:

Do you typically avoid caffeine consumption for any reason? YES NO
If yes, please explain:

Are you currently participating in any other research studies? YES NO
If yes, please explain

Appendix C

Caffeine Consumption Survey

Please indicate the amount of servings you consume daily for each of the following products.

Coffee	# of Servings	[Please do not write in boxes below]
Percolated (1 small mug: 7 oz.)		
Drip (1 small mug: 7 oz.)		
Espresso (1 shot: 1.5-2 oz)		
Brewed (1 small mug: 7 oz.)		
Instant (1 small mug: 7 oz.)		
Decaf, brewed (1 small mug: 7 oz.)		
Decaf, instant (1 small mug: 7 oz.)		

other : _____

Tea	# of Servings	
Iced (12 oz)		
Black (1 small mug: 7 oz.)		
Green (1 small mug: 7 oz.)		

other: _____

Soft Drinks	# of Servings	
Coca-Cola (12 oz)		
Diet Coke (12 oz)		
Pepsi (12 oz)		
Diet Pepsi (12 oz)		
Pepsi One (12 oz)		
Jolt (12 oz)		
Vault (12 oz)		
Mountain Dew (12 oz)		
Mellow Yellow (12 oz)		
Nestea (12 oz) please specify flavor		
Snapple (12 oz) please specify flavor		
A & W Cream Soda (12 oz)		

other: _____

Energy Drinks & Syrups	# of Servings	
Powershot (1 oz)		
Sky Rocket Syrup (1 oz)		
Redline RTD (8 oz)		
Sobe Adrenaline Rush (8.3 oz)		
Red Bull (1 can: 8.3 oz)		

other: _____

Foods	# of Servings	
Milk Chocolate (1 oz)		
Dark Chocolate (1 oz)		
Dannon Coffee Flavored Yogurt (8 oz)		
Chocolate Flavored Syrup (2 tbs)		

Supplements & Medications	# of Servings	
No-Doz (1 tablet)		
No-Doz Maximum Strength (1 tablet)		
Excedrin (1 tablet)		
Midol (1 tablet)		
Midol Maximum Strength (1 tablet)		

Appendix D

Profile of Mood States

Subject Number: _____ Date: _____

Below is a list of words that describe feelings people have. Please read each one carefully; then mark ONE circle around the answer to the right which best describes HOW YOU FEEL RIGHT NOW.

The numbers refer to these phrases:

0 = Not at all
1 = A little
2 = Moderately
3 = Quite a bit
4 = Extremely

·iendly	0 1 2 3 4	Unworthy	0 1 2 3 4	Desperate	0 1 2 3 4
ɛnse	0 1 2 3 4	Spiteful	0 1 2 3 4	Sluggish	0 1 2 3 4
ngry	0 1 2 3 4	Sympathetic	0 1 2 3 4	Rebellious	0 1 2 3 4
'orn Out	0 1 2 3 4	Uneasy	0 1 2 3 4	Helpless	0 1 2 3 4
nhappy	0 1 2 3 4	Restless	0 1 2 3 4	Weary	0 1 2 3 4
learheaded	0 1 2 3 4	Unable to concentrate	0 1 2 3 4	Bewildered	0 1 2 3 4
·vely	0 1 2 3 4	Fatigued	0 1 2 3 4	Alert	0 1 2 3 4
ɔnfused	0 1 2 3 4	Helpful	0 1 2 3 4	Deceived	0 1 2 3 4
ɔrry for things done	0 1 2 3 4	Annoyed	0 1 2 3 4	Furious	0 1 2 3 4
ıaky	0 1 2 3 4	Discouraged	0 1 2 3 4	Efficient	0 1 2 3 4
·stless	0 1 2 3 4	Resentful	0 1 2 3 4	Trusting	0 1 2 3 4
ɛeved	0 1 2 3 4	Nervous	0 1 2 3 4	Full of pep	0 1 2 3 4
ɔnsiderate	0 1 2 3 4	Lonely	0 1 2 3 4	Bad-tempered	0 1 2 3 4
ıd	0 1 2 3 4	Miserable	0 1 2 3 4	Worthless	0 1 2 3 4
ctive	0 1 2 3 4	Muddled	0 1 2 3 4	Forgetful	0 1 2 3 4
n edge	0 1 2 3 4	Cheerful	0 1 2 3 4	Carefree	0 1 2 3 4
·rouchy	0 1 2 3 4	Bitter	0 1 2 3 4	Terrified	0 1 2 3 4
·lue	0 1 2 3 4	Exhausted	0 1 2 3 4	Guilty	0 1 2 3 4
·nergetic	0 1 2 3 4	Anxious	0 1 2 3 4	Vigorous	0 1 2 3 4
anicky	0 1 2 3 4	Ready to fight *	0 1 2 3 4	Uncertain about things	0 1 2 3 4
lopeless	0 1 2 3 4	Good natured	0 1 2 3 4	Bushed	0 1 2 3 4
.elaxed	0 1 2 3 4	Gloomy	0 1 2 3 4		

* This means you are ready to get in a physical fight

MAKE SURE YOU HAVE ANSWERED EVERY ITEM

Appendix E

Questionnaire of Caffeine Cravings (QCC)

Please report your level of agreement with each statement AT THIS MOMENT by circling 1 (strongly disagree) through 7 (strongly agree)

Having caffeine would make me less depressed	1 2 3 4 5 6 7
All I want right now is some caffeine	1 2 3 4 5 6 7
My desire for caffeine seems overpowering	1 2 3 4 5 6 7
I will have caffeine as soon as I get the chance	1 2 3 4 5 6 7
I crave some caffeine right now	1 2 3 4 5 6 7
I would feel more nauseous if I was having caffeine	1 2 3 4 5 6 7
Having caffeine right now would make me feel less drowsy	1 2 3 4 5 6 7
Right now, I am not making plans to have caffeine	1 2 3 4 5 6 7
Having caffeine right now would make me feel less fatigued	1 2 3 4 5 6 7
I need to have caffeine now	1 2 3 4 5 6 7
I would not enjoy some caffeine right now	1 2 3 4 5 6 7
I would do almost anything for some caffeine now	1 2 3 4 5 6 7
If I was having caffeine now, I could think more clearly	1 2 3 4 5 6 7
Nothing would be better than having some caffeine right now	1 2 3 4 5 6 7
I am not missing having caffeine right now	1 2 3 4 5 6 7
Some caffeine would not be very satisfying right now	1 2 3 4 5 6 7
Caffeine would not taste good right now	1 2 3 4 5 6 7
I am going to have caffeine as soon as possible	1 2 3 4 5 6 7
Having caffeine now would make things seem just perfect	1 2 3 4 5 6 7
Having caffeine would not help me calm down now	1 2 3 4 5 6 7
I would be more able to concentrate if I could have some caffeine now	1 2 3 4 5 6 7

Appendix F

Borg Category-Ratio (CR) 10 Scale

Please state aloud your feelings of discomfort on the scale as they arrive.

Trial 1 (s)	Trial 2 (s)	
		0 Nothing at all
		0.5 Extremely weak (just noticeable)
		1 Very weak
		2 Weak (light)
		3 Moderate
		4 Somewhat strong
		5 Strong (heavy)
		6
		7 Very strong
		8
		9
		10 Extremely strong (almost max)
		** Maximal
		TOTAL TIME

Appendix G

Debriefing Form

Study Title: Caffeine and Cold Pressor Test
Study Number:
Principal Investigator: Kaitlyn N. Mula
Co-Investigator: Dr. Robin Kanarek

This research was an Undergraduate Senior Honor's Thesis.

Thank you for participating!

Purpose of the Study:

You just participated in a study designed to help us understand the effect of caffeine withdrawal on cold sensitivity. We were also interested to see if individuals who typically consumed a lot of caffeine daily would exhibit lower cold tolerance than individuals who did not consume caffeine or consumed low amounts daily. On each of the test days, you were given either 300 mg of caffeine (about two cups of coffee's worth of caffeine) or you were given a placebo (0 mg caffeine). We expected you to have a lower cold tolerance when you were given the placebo than when you were given the caffeine. This would have supported our theory that caffeine users gain analgesic (pain relieving) elements from their daily caffeine use, and that these analgesic properties no longer exist once they stop consuming caffeine for more than 24 hours.

Deception was also involved in this study. The saliva samples you provided the researchers were never actually tested for caffeine. It was merely an exercise to motivate you to comply with caffeine cessation prior to the sessions.

If you have any other questions or concerns, or if you would like to know the results of the experiment once it is completed, please contact:

- Investigators

Kaitlyn Mula
kaitlyn.mula@tufts.edu
(941) 587-7148

or

Dr. Robin Kanarek
robin.kanarek@tufts.edu
(617) 627-5902
490 Boston Ave., Medford, MA 02155

You may also search the following keywords if you want to seek more information about this type of research: caffeine, addiction, withdrawal, pain perception, cold-sensitivity, Roland Griffiths, PhD.

If you have any concerns about this study or your rights as a participant of this experiment, we encourage you to contact the Tufts University IRB Administrator, Yvonne Wakeford, at (617) 627-3147.

Appendix H

Caffeine Study seeking participants!

Interested in research participation? Want to earn $10/hr?

You can earn $20 for participating in a study on caffeine and cold sensitivity.

- 2 separate sessions ($10 each)
- Must not drink caffeine 24 hrs before each session.
- You will be asked to consume caffeine or a placebo at each session and complete a simple task to measure your sensitivity to cold temperatures.

Criteria to participate:

- 18 to 22 years old
- Non-smoker
- Not taking prescriptions (including birth control)
- No history of heart, liver, or anxiety disorders
- No history of gastrointestinal disorders, including peptic ulcers and severe reflux.
- No cold allergies (ie: when your skin is exposed to cold temperatures you break out in a rash).

Scheduling is flexible, and this study has been approved by the Institutional Review Board (IRB) at Tufts University.

For more information, please email kaitlyn.mula@tufts.edu