

---

This is an uncorrected author post-print of the following article:

Mills, L., Boakes, R. A., & Colagiuri, B. (2016). Placebo caffeine reduces withdrawal in abstinent coffee drinkers. *Journal of Psychopharmacology*, 30(4), 388-394. doi: 10.1177/0269881116632374.

Please refer to the final published manuscript for the corrected version.

---

Post-print

**Placebo caffeine reduces withdrawal in abstinent coffee drinkers**

Llewellyn Mills<sup>1</sup>, Robert A Boakes<sup>1</sup>, Ben Colagiuri<sup>1</sup>

<sup>1</sup>University of Sydney, School of Psychology

**Corresponding author**

Llewellyn Mills

Room 310 Griffith Taylor Building (A19). University of Sydney. 2006.

Phone: +61 2 9036 7266 Fax: +61 2 9036 5223 Email: llew.mills@sydney.edu.au

**Acknowledgement of Funding**

There were no conflicts of interests involved in conducting this study. The research was funded by the University of Sydney School of Psychology. Mr Mills is receiving an Australian Postgraduate Award scholarship provided by Sydney University

# PLACEBO CAFFEINE REDUCES WITHDRAWAL

## Abstract

**Background:** Expectancies have been shown to play a role in the withdrawal syndrome of many drugs of addiction. However no studies have examined the effects of expectancies across a broad range of caffeine withdrawal symptoms, including craving.

**Aims:** The purpose of the current study was to use caffeine as a model to test the effect of expectancy on withdrawal symptoms, specifically whether the belief that one has ingested caffeine is sufficient to reduce caffeine withdrawal symptoms and cravings in abstinent caffeine drinkers.

**Methods** 24-h abstinent regular coffee drinkers completed the Caffeine Withdrawal Symptom Questionnaire (CWSQ) before and after receiving decaffeinated coffee. Half the participants were led to believe the coffee was regular caffeinated coffee (Told group) and half were told that it was decaffeinated (Low Expectancy group).

**Results:** Participants in the High Expectancy group reported a significantly greater reduction in craving, fatigue, lack of alertness and flu-like feelings factors of the CWSQ than those in the Low Expectancy.

**Conclusions:** These results indicate that the belief that one has consumed caffeine can affect caffeine withdrawal symptoms, especially craving, even when no caffeine has been consumed.

**Keywords:** withdrawal; addiction; craving; caffeine; expectancy; placebo

## Introduction

Numerous studies demonstrate that expectancies can affect the withdrawal symptoms of many addictive drugs (Colagiuri et al., 2009; Francis and Nelson, 1984; Gottlieb et al., 1987; Juliano and Brandon, 2002; Phillips et al., 1986; Senay et al., 1977; Tyrer et al., 1983). Caffeine is an addictive substance that is consumed by 80-90% of adults (Gilbert, 1984; Ressig et al., 2009) and has a well-established withdrawal syndrome (American Psychiatric Association and American Psychiatric, 2013; Juliano and Griffiths, 2004). However, despite the ubiquity of caffeine use, no study to date has tested the effect of expectancies on the full range of caffeine withdrawal symptoms including cravings using an empirically verified caffeine withdrawal symptom questionnaire.

The most commonly reported caffeine withdrawal symptoms are headache, fatigue or drowsiness, depressed or dysphoric mood, irritability, decreased alertness, difficulty concentrating and flu-like symptoms such as nausea, vomiting or muscle pains/stiffness (Juliano and Griffiths, 2004). Craving, while not listed as a withdrawal symptom in any of the DSM-5 substance withdrawal disorders (APA, 2013), is nevertheless important for the study of any withdrawal syndrome since it is an index of motivation to consume a drug (Sayette et al., 2000) that spikes following abstinence and is cited as a common cause of relapse (Kozlowski and Wilkinson, 1987; Shiffman, 1979).

In their review of caffeine withdrawal Dews, O'Brien, and Bergman (2002) propose two indirect lines of evidence suggesting that withdrawal from caffeine may be susceptible to the effect of expectancy. First, studies have found that caffeine withdrawal is most pronounced for subjective symptoms, often in the absence of corresponding declines in objective performance (Lane and Phillips-Bute, 1998; Phillips-Bute and Lane, 1997): Dews et al. (2002) argue that this dissociation indicates a negative expectancy

effect. Second, they argue that the considerable variability in onset and incidence of caffeine withdrawal symptoms cannot be explained by the pure pharmacological effects of caffeine, and implicates psychological factors like expectancy. For example, estimates of prevalence of headache in abstinent caffeine users range from 9% (Hughes et al., 1995) to 100% (Naismith et al., 1970) and, in the individuals that experience headaches, there is considerable variance in peak onset, ranging from 27 to 51 hours of abstinence (Griffiths et al., 1990).

Some evidence already supports these ideas. Instructions about the caffeine content of a beverage have been found to increase arousal and alertness (Flaten and Blumenthal, 1999; Kirsch and Rosadino, 1993; Kirsch and Weixel, 1988; Lotshaw et al., 1996) and contentedness and calmness (Mikalsen et al., 2001) irrespective of actual caffeine content. This suggests that expectancy about receiving caffeine can induce positive effects. Yet it remains to be seen whether the *negative* components of caffeine withdrawal, such as headaches, negative mood, and fatigue, can be reversed by instruction about beverage caffeine content alone. Harrell and Juliano (2009) examined the effect of instruction on a range of caffeine withdrawal symptoms; however the instructions given to participants pertained to the effect of caffeine on motor performance rather than whether or not they had ingested caffeine. Other studies have found evidence that expectancies mediated abstinence-induced headache, however these studies contained methodological weaknesses such as omission of important statistical information and details of the type of random-allocation instructions given to participants (Rubin and Smith, 1999; Smith 1996). To our knowledge no studies have examined whether instructions concerning the caffeine content of a beverage can reverse or reduce withdrawal across a wide range of withdrawal symptoms. Thus, the primary aim of the current study was to test, using an

empirically validated caffeine withdrawal questionnaire, whether the expectancy of having consumed caffeine can reduce withdrawal following 24 hours of abstinence, and to determine which specific withdrawal symptoms are most sensitive to expectancy effects.

A secondary aim of the study was to test whether information priming would influence the reported intensity of withdrawal symptoms. Written warnings about side-effects have been shown to increase subsequent report of those side-effects (Neukirch and Colagiuri, 2013; Myers et al. 1987; Colagiuri et al., 2012). This study sought to explore whether written information about the likelihood of withdrawal symptoms could similarly increase caffeine withdrawal, by priming half of participants with a warning about commonly experienced caffeine withdrawal symptoms.

## **Method**

### *Design*

The study used a 2 x 2 x (2) mixed design, as shown in Figure 1. The first factor was Priming, where participants were either given information suggesting that abstaining from caffeine could lead to substantial withdrawal symptoms (Prime group) or were not given this information (No Prime group). The second factor was Expectancy, where participants were given decaffeinated coffee and were either told that it was caffeinated (Told Caffeine group) or decaffeinated (Told Decaf group). The third factor was Time, either pre-coffee ingestion (pre-beverage) or post-coffee ingestion (post-beverage). The primary outcome of interest was self-reported caffeine withdrawal symptoms, however blood-pressure readings and a test of concentration were also performed and recorded at both time points.

### *Participants*

Participants were 89 (60 female) adult (mean age: 21.3; range 18-45) moderate to heavy coffee drinkers ( $\geq 3$  cups per weekday) studying at the University of Sydney and participating in exchange for either course credit ( $n=84$ ) or for \$30 payment. All participants gave informed consent to participate in a study on the effect of caffeine on cognitive performance and were fully debriefed at the conclusion of the study that the true purpose of the study was to understand the effect of expectancy on withdrawal symptoms.

A desired sample size of 20 per group (40 per main-effect group) was determined by consulting published studies examining caffeine placebo effects that had observed moderate to high effects sizes for outcomes equivalent to caffeine withdrawal (e.g. the Alertness and Tension variables in Kirsch and Weixel, 1988).

[Figure 1 near here; Caption for figure 1 below]

**Fig 1.** Design of study. The Prime group were given a written prime in their Participant Information Statement suggesting that they were likely to experience withdrawal symptoms. The No Prime group received no prime. The Told Caffeine group were told they were receiving caffeinated coffee. The Told Decaf group were told truthfully that they were receiving decaffeinated coffee. Pre- and post-beverage tests were, in order: 1) Blood Pressure; 2) CWSQ; 3) RVIP task.

### *Materials and Measures*

*Demographic and Caffeine Use Questionnaire:* Participants' demographic information and daily caffeine use across all beverages was ascertained via a computerised questionnaire (see supplementary materials ESM1). Estimates of caffeine content of

beverages were obtained from Barone and Roberts (1996) or from content listed by the manufacturer.

*Drinks:* Coffee was prepared in a DeLonghi Magnifica Automatic Coffee Machine using Peet's Major Dickason's Blend Decaffeinated coffee beans. These beans contain approximately 4% of the caffeine content of regular caffeinated coffee beans, amounting to 4mg or less of caffeine per cup.

*Caffeine Withdrawal Symptom Questionnaire:* A computerised version of the Caffeine Withdrawal Symptom Questionnaire (CWSQ; Juliano et al., 2012) was used to assess withdrawal symptoms. The 32-items comprising this version of the CWSQ are arranged in nine separate factors: Drowsiness/Fatigue; Decreased Alertness/Difficulty Concentrating; Mood Disturbances; Decreased Sociability/Motivation to Work; Nausea/Upset Stomach; Flu-like Feelings; Headache, Acute Caffeine Effects, and Craving. Participants were asked to rate to what extent they were experiencing each symptom on a 5-item response scale from 0 ('not at all') to 4 ('extremely'). The maximum possible score was 128. For a full list of items see supplementary materials ESM2.

*RVIP task:* In order to disguise the true purpose of the study participants were given a version of the Rapid Visual Information Processing (RVIP) task, a test of sustained attention used by Colagiuri and Boakes (2010). In this 5-min task participants were required to monitor single digits appearing on a screen in semi-random order and to detect strings of three consecutive odd or three consecutive even digits amongst the random digits. Performance on the test was measured via hit rate, false-alarm rate, reaction time, and a composite accuracy score.

*Blood Pressure:* Systolic and diastolic blood pressure was measured via an Omron HEM-7221 electronic sphygmomanometer.



*Exit Questionnaire/Manipulation Check:* A computerised exit questionnaire probed participants for awareness of the manipulation and their estimate of the caffeine content of the coffee they received (see supplementary materials ESM 5.)

### *Procedure*

To reduce the possibility of demand characteristics, participants were recruited under the guise of a study testing the effects of caffeine on cognitive performance. Participants signed up for the study by booking a test session on the University of Sydney's research participation website. Upon signing up participants were randomly allocated to either the Prime or No Prime condition. The priming manipulation was administered via a Participant Information Statement (PIS) sent to participants by email. In the email participants were instructed to read the PIS carefully prior to the test session. The PISs sent to the Prime and No Prime group were identical, except that those given the prime contained the additional text:

*"IMPORTANT: Because caffeine withdrawal symptoms become stronger over time it is likely that you will experience some withdrawal symptoms due to abstaining from coffee. These withdrawal symptoms can include headache, fatigue, difficulty concentrating, irritability, depression, flu-like feelings, nausea, upset stomach, and cravings. If any of these withdrawal symptoms become too severe please contact the researchers."*

See ESM3 and ESM4 for both versions of the PIS.

Participants were told in advertisements for the study, in the initial contact email, and on the PIS sent out with the contact email, that they must drink more than three cups of coffee on a standard weekday and be 24-h caffeine abstinent in order to be included in the

study. Using a ‘bogus pipeline’ procedure to enhance compliance with the 24-h abstinence requirement (Murray et al., 1987), participants were told in the email and PIS that abstinence would be verified upon arrival via a saliva test.

Participants were tested individually in a single 90-min test session. Prior to this session they were allocated to either Told Caffeine or Told Decaf conditions. In order to screen out participants who did not meet inclusion criteria, participants were asked upon arrival at the test session how many cups of coffee a day they drank and when they last consumed caffeine. If participants answered less than three cups per day or less than 24 h since last caffeine consumed they were not tested.

Participants meeting eligibility criteria had saliva samples collected, and the demographic and caffeine use questionnaire was administered. All questionnaires were completed on computers in the test lab during the 90-min test session. Following the demographic and caffeine use questionnaire participants had their blood pressure measured, and took the RVIP and CWSQ tests for the first time. Next, participants were given their cup of coffee, which was prepared in front of them in the test room. All participants received decaffeinated coffee. Beans used to make participants’ coffee were placed in the test room prior to participants’ arrival according to group allocation; either in original packaging or in decoy packaging of a popular (caffeinated) blend sold by Gloria Jean’s coffee chain. During preparation of the coffee, participants in the Told Decaf group were instructed that they had been allocated to a control condition of the study and would therefore receive decaffeinated coffee. The Told Caffeine group on the other hand were not given any further instructions, since all participants had been led to believe that they would be receiving caffeinated coffee as part of the general study description. Participants then consumed their coffee, after which they were allowed a 45-min ‘caffeine absorption

period' in which they remained in the lab but were free to study, browse the internet, or use their smartphones. Following the 'absorption period' participants had their blood pressure read and took the RVIP and CWSQ tests a second time. Finally, participants were given the exit questionnaire and debriefed as to the true nature of the study.

All the procedures in this study were approved by the University of Sydney Human Research Ethics committee and were conducted in accordance with the 1964 declaration of Helsinki.

## Results

### *Caffeine Use*

Mean caffeine consumption per weekday from all sources (e.g. coffee, tea, cola) was 554.1 mg ( $SD=295.8$ ). Coffee was the most commonly consumed caffeinated product. A two-way ANOVA revealed no significant between-group differences in daily caffeine consumption (Priming:  $F_{(1,88)} = 0.21, p=.647$ ; Expectancy: ( $F_{(1,88)} = 1.07, p=.304$ ).

### *Effect of Expectancy*

2 x 2 x (2) ANCOVAs, with Priming and Expectancy as the between-subjects factors and Time (pre- vs post-Beverage) as the within-subject factor, were conducted on CWSQ scores, blood-pressure, and RVIP scores. Eight participants from the Told Caffeine group and seven Participants from the Told Decaf group whose belief in the caffeine content of their beverage was incongruent with their instructions were excluded from analysis, leaving 37 in each group ( $N = 74$ ). The exclusion of these participants did not affect the overall pattern of significant results.

[Figure 2 near here; Figure 2 caption below]

**Fig. 2** Effect of expectancy before and after decaffeinated coffee, on total reported caffeine withdrawal symptoms (Left) and on cravings (Right). Higher scores indicate more severe withdrawal. All participants received decaffeinated coffee. The Told Caffeine group were told their coffee contained caffeine whereas the Told Decaf group were told theirs was decaffeinated.

There was a significant interaction between Expectancy and Time in total CWSQ scores ( $F_{(1,69)} = 8.36, p=.005, \eta^2=.108$ ), with the Told Caffeine group reporting a reduction of 14.6 points from pre- to post-beverage, compared to a 5.5-point reduction in the Told Decaf group. Figure 2 shows graphs of both mean Total CWSQ scores and CWSQ-Craving factor scores pre- and post-beverage according to Expectancy group allocation. There was no effect of Expectancy on blood pressure or any of the RVIP measures.

Between-group means pre- to post-beverage,  $F$ - and  $p$ -values and effect size estimates for total CWSQ scores and the nine CWSQ factors are reported in Table 2. Of the nine CWSQ factors, four showed significant interactions between Expectancy and Time, with significantly greater post-beverage reductions in Craving ( $F_{(1,69)} = 22.53, p<.001, \eta^2=.246$ ), Decreased Alertness/Difficulty Concentrating ( $F_{(1,69)} = 8.29, p=.005, \eta^2=.107$ ), Drowsiness/Fatigue ( $F_{(1,69)} = 4.64, p=.035, \eta^2=.063$ ) and Flu-like feelings ( $F_{(1,69)} = 4.22, p=.044, \eta^2=.058$ ) observed in the Told Caffeine group than the Told Decaf group.

Table 1. Mean CWSQ Total and Factor Scores Pre- and Post-Beverage According to Expectancy

CWSQ	Told Caffeine		Told Decaf				
	Pre	Post	Pre	Post			
	e	t				2	
Total Score	42.70 (13.4)	28.14 (8.9)	43.03 (12.8)	37.57 (11.1)	8.36	<b>.108</b>	<b>.005</b>
Factors							
1. Drowsiness/Fatigue	6.32 (3.6)	2.65 (2.3)	6.78 (3.3)	5.22 (2.8)	4.64	<b>.063</b>	<b>.035</b>
2. Decreased Alertness	9.70 (3.0)	7.84 (2.7)	10.56 (2.7)	10.51 (2.4)	8.29	<b>.107</b>	<b>.005</b>
3. Mood	1.89 (2.3)	0.89 (1.4)	2.35 (2.8)	1.65 (2.6)	0.17	.002	.681
4. Decreased Sociability	10.51 (2.6)	8.54 (2.4)	10.35 (.41)	9.57 (.39)	2.08	.029	.154
5. Nausea/Upset Stomach	0.81 (1.8)	0.43 (1.1)	1.08 (2.0)	0.46 (1.2)	0.33	.005	.566
6. Flu-like Feelings	4.70 (1.2)	4.27 (.87)	4.05 (1.4)	4.16 (.96)	4.22	<b>.058</b>	<b>.044</b>
7. Headache	1.97 (2.2)	0.81 (1.0)	1.65 (2.0)	1.19 (1.8)	2.04	.029	.158
8. Acute Caffeine Effects	1.78 (1.9)	1.13 (1.4)	1.38 (1.6)	1.02 (1.3)	0.45	.006	.504
9. Craving	5.00 (1.8)	1.57 (1.9)	4.81 (2.0)	3.78 (2.3)	22.53	<b>.246</b>	<b>&lt;.001</b>

Note: Significant *p*-values in bold. Standard deviation in parentheses.

### *Effect of Priming and Time*

There were significant main effects of Time, with CWSQ scores ( $F_{(1,69)} = 15.73$ ,  $p < .001$ ), systolic blood pressure ( $F_{(1,69)} = 15.80$ ,  $p < .001$ ), and RVIP False Alarm Rate ( $F_{(1,69)} = 21.40$ ,  $p < .001$ ) decreasing, and RVIP Hit Rate ( $F_{(1,69)} = 4.91$ ,  $p = .016$ ), and RVIP Accuracy scores ( $F_{(1,69)} = 12.72$ ,  $p = .001$ ) increasing significantly across all groups from pre- to post-beverage.

There was no significant main effect of Priming on CWSQ scores nor any of the other dependent variables. Nor were any significant two-way interactions observed between Priming and Time or Priming and Expectancy. There were no significant three-way interactions between Priming, Time, and Expectancy.

### *Belief About Beverage Caffeine Content*

In the exit questionnaire participants rated the likelihood that their beverage contained caffeine. Responses were coded as follows: 'Certainly Caffeinated' (7); 'Probably'

Caffeinated' (6); 'Possibly Caffeinated' (5); 'Don't Know' (4); 'Possibly Decaffeinated' (3); 'Probably Decaffeinated' (2); 'Certainly Decaffeinated' (1). A simple linear regression was performed to test the extent to which these beliefs predicted change in overall CWSQ scores (i.e., pre-beverage CWSQ – post-beverage CWSQ; with higher scores indicating a greater reduction in reported withdrawal symptoms) and cravings specifically. Since all participants, regardless of instruction, indicated some estimate of the likelihood that their beverage was caffeinated, the regression was conducted using all 89 participants. The strength of belief that the beverage was caffeinated significantly predicted the magnitude of the reduction in both total CWSQ score ( $R^2 = .047$ ,  $F_{(1,87)} = 4.282$ ,  $b = 8.175$ ,  $SEb = 3.95$ ,  $p = .041$ ) and for craving ( $R^2 = .087$ ,  $F_{(1,87)} = 8.241$ ,  $b = 0.36$ ,  $SEb = 0.13$ ,  $p = .005$ ). This meant that for every 1-point increase in participants' estimates of likelihood that there was caffeine in their beverage, there was a predicted 1.39-point decrease in their post-beverage total withdrawal score and a 0.36-point decrease in their craving score.

## Discussion

The results of this study demonstrate that caffeine withdrawal symptoms can be reduced by the simple belief that caffeine has been ingested, even when it has not. Participants who were led to believe that they were receiving caffeinated coffee showed a significantly greater reduction in total CWSQ scores following consumption of their beverage than those who were told that they had consumed decaf. Supporting this, participants' ratings of the likelihood that their beverage contained caffeine were positively correlated with the magnitude of the reduction in CWSQ scores.

Our novel symptom-by-symptom analysis indicated that four specific symptom clusters were susceptible to alteration by expectancy, namely Craving, Decreased Alertness/Difficulty Concentrating, Drowsiness/Fatigue, and Flu-like Feelings. It is particularly noteworthy that cravings for caffeine were significantly reduced by administration of placebo caffeine. This suggests that the belief that one has ingested caffeine is sufficient to reduce not only unpleasant withdrawal symptoms such as fatigue and diminished alertness, but also the motivation to consume caffeine. Previous research examining the effects of expectancy on cravings for other addictive substances, such as tobacco, has shown mixed results, with some studies finding expectancy-induced reductions in cravings (Darredeau and Barrett, 2010; Juliano and Brandon, 2002) and others finding no effects of expectancy (Gottlieb et al., 1987; Hughes et al., 1989; Tate et al., 1994). To our knowledge, this is the first study to demonstrate that expectancy alone can reduce cravings in abstinent caffeine users.

The findings for Drowsiness/Fatigue and Decreased Alertness/Difficulty Concentrating are consistent with other studies specifically targeting these symptoms, that have shown that abstinent caffeine users who believe they have ingested caffeine feel more alert and less fatigued (Flaten and Blumenthal, 1999; Kirsch and Rosadino, 1993; Kirsch and Weixel, 1988; Lotshaw et al., 1996). In contrast, other caffeine withdrawal symptoms, such as nausea, headache, and mood factors were not significantly influenced by the expectancy manipulation in the current study. This suggests that, in the context of caffeine withdrawal symptoms, sensations such as alertness, fatigue and craving are more susceptible to the type of top-down alteration of perception by expectancy that is thought to be involved in some placebo effects (Brown et al., 2008; Wall, 1993) than are sensations such as nausea, headache, and mood. It should be noted that nausea (see Quinn

and Colagiuri 2015) and mood (Dinnerstein and Halm, 1970) have been shown to be susceptible to manipulation by instruction in non-caffeine-related studies, therefore an alternative explanation is that these symptoms may take longer than 45 min to reverse than the symptoms that did show significant changes.

Like all withdrawal syndromes caffeine withdrawal is not a unitary phenomenon but is rather a cluster of symptoms across multiple modalities (e.g. cognitive, affective, somatic). Thus, it is not surprising that some clusters may be more affected by expectancy than others. Even within the affected symptoms there was some variation in the effectiveness of the expectancy manipulation, with a very large effect size for Cravings ( $\eta^2=.246$ ), a large effect size for Decreased Alertness/Difficulty Concentrating ( $\eta^2=.107$ ), and moderate effect sizes for Drowsiness/Fatigue ( $\eta^2=.063$ ) and Flu-like Feelings ( $\eta^2=.058$ ). By comparison, the effect size for Mood, which was not significantly changed by expectancy, was extremely small (Mood:  $\eta^2=.002$ ). It was interesting that Headache, which is generally the most robust and commonly reported of the caffeine withdrawal symptoms (Juliano & Griffiths, 2004), was not significantly affected by expectancy, with a small numerical change from 1.97 pre-beverage to 1.57 post-beverage out of 8. There is evidence that headaches due to caffeine withdrawal do not peak until 27-51 h after abstinence (Griffiths et al. 1990). Therefore, it is possible that the 24-hr abstinence period used in the current study created a floor effect in the sense that headaches prior to the intervention were already too low to be significantly reduced by the expectancy manipulation.

The finding that Time caused decreases in withdrawal irrespective of group allocation was interesting considering that one would expect participants in the Told Decaf groups, who knew their abstinence would continue because they were drinking decaf, to report an



increase in withdrawal between pre- and post-beverage. A possible explanation is that contextual cues relating to the taste, touch, and smell of coffee elicited conditioned withdrawal-reduction effects despite participants knowing they were receiving no caffeine.

It was also interesting to note that the written prime included in the Participant Information Statement did not appear to have any effect on reported pre-beverage withdrawal symptoms. It is possible that this was due to caffeine consumers being sufficiently well aware of the negative consequences of abstinence that a simple written prime had no effect on their expectancies (Rohsenow and Marlatt, 1981). However, given that a number of participants booked and attended the test session without having fully read even the prerequisites for admission to the study, it is possible simply that many failed to read the prime. Thus, it would be interesting to explore other priming manipulations that involve a more salient prime in future.

This study found that that expectancy-induced withdrawal reduction effects can persist for 45 min, a duration similar to that required for peak caffeine absorption from coffee (42 min: Liguori et al., 1997). This is well past the duration of placebo-induced increases in alertness of 15-20 min observed in previous studies (Kirsch and Weixel, 1988; Kirsch and Rosadino, 1993). Future research should further extend the period of time between administration of placebo caffeine and measurement of withdrawal symptoms in order to determine the durability of these expectancy effects.

The current study had several potential limitations. First, the study was single-blind only, which can result in increased demand characteristics. Second, since there was no objective test of abstinence from caffeine, confirmation that participants abstained from caffeine for 24 hours prior to testing relied on self-report. This could result in either under- or overreporting of symptoms due to biases such as social desirability. Third, there was no

measure of the pre-existing expectancies held by participants concerning withdrawal symptoms, which may have interacted with the priming and expectancy manipulations. In future research, a caffeine expectancy questionnaire such as the CaffEQ (Huntley and Juliano, 2012) could be administered to address this. Fourth, average daily consumption of participants in this study (554mg) was relatively high compared with the average US population (280mg; Barone and Roberts). Thus it is possible that both the withdrawal and the expectancy effects observed in this study were more pronounced than they would be in a sample whose consumption was lower. However participants in Griffiths et al. (1990) displayed marked withdrawal symptoms despite their daily caffeine consumption being considerably lower than the American average. Thus the effects of expectancy may occur irrespective of average consumption as long as the level of use leads to at least some withdrawal symptoms, although this needs to be tested. Lastly although the sample size for this study was based on sample sizes used by previous studies that found caffeine expectancy effects for withdrawal-related phenomena (e.g. Kirsch and Weixel, 1988) formal power analyses were not conducted.

Overall, the current study indicates that a number of caffeine withdrawal symptoms can be reduced by expectancy, namely craving, decreased alertness/difficulty concentrating, drowsiness/fatigue and flu-like feelings. These findings add to the growing body of research indicating that in addition to known pharmacological factors, expectancies concerning current levels of a drug in the body also play a significant role in the way individuals addicted to that drug perceive their withdrawal symptoms. Caffeine Withdrawal Syndrome has been added to list of substance use disorders in the most recent edition of the DSM (APA, 2013). These results suggest that expectancy-based interventions intended to reduce or eliminate drug intake may serve as a useful adjunct to

existing interventions, both for caffeine use specifically, and for other substance use disorders.

### **Acknowledgements**

This study and the resulting manuscript were designed, tested, edited, and written by Mr Llewellyn Mills, Professor Robert Boakes and Dr Ben Colagiuri.

### **Declaration of Conflicting Interest**

The authors declare that there is no conflict of interest

### **Funding**

This research was supported by Australian Research Council Grant DP150104026.

### References

- American Psychiatric Association DSMTF and American Psychiatric A (2013)  
*Diagnostic and statistical manual of mental disorders: DSM-5*. Arlington, Va:  
American Psychiatric Association.
- Barone J and Roberts H (1996) Caffeine consumption. *Food and Chemical Toxicology*  
34(1): 119-129.
- Brown CA, Seymour B, El-Derey W, et al. (2008) Confidence in beliefs about pain  
predicts expectancy effects on pain perception and anticipatory processing in right  
anterior insula. *PAIN* 139(2): 324-332.
- Colagiuri B, and Boakes RA (2010) Perceived treatment, feedback, and placebo effects in  
double-blind RCTs: an experimental analysis. *Psychopharmacology* 208(3): 433-  
441.
- Colagiuri B, McGuiness K, Boakes RA, et al. (2012) Warning about side effects can  
increase their occurrence: an experimental model using placebo treatment for sleep  
difficulty. *Journal of Psychopharmacology*, 26(12): 1540-1547.
- Colagiuri B, Morley KC, Boakes RA, et al. (2009) Expectancy in double-blind placebo-  
controlled trials: An example from alcohol dependence. *Psychotherapy and*  
*Psychosomatics* 78(3): 167-171.
- Darredeau C, and Barrett SP (2010) The role of nicotine content information in smokers'  
subjective responses to nicotine and placebo inhalers. *Human*  
*Psychopharmacology: Clinical and Experimental*, 25(7-8): 577-581.
- Dews PB, O'Brien CP, and Bergman J (2002) Caffeine: behavioural effects of withdrawal  
and related issues. *Food and Chemical Toxicology* 40(9): 1257-1261.

- Dinnerstein AJ and Halm J (1970) Modification of placebo effects by means of drugs: Effects of aspirin and placebos on self-rated moods. *Journal of Abnormal Psychology* 75(3): 308-314.
- Flaten MA, and Blumenthal TD (1999) Caffeine-associated stimuli elicit conditioned responses: an experimental model of the placebo effect. *Psychopharmacology* 145(1): 105-112.
- Francis D, and Nelson, A (1984) Effect of patient recognition of tranquilizers on their use in alcohol detoxification. *American Journal of Health-System Pharmacy* 41(3): 488-492.
- Gilbert RJ (1986) *Caffeine, the Most Popular Stimulant*. Chelsea House Publishers.
- Gottlieb AM, Killen JD, Marlatt GA, et al. (1987) Psychological and Pharmacological Influences in Cigarette Smoking Withdrawal: Effects of Nicotine Gum and Expectancy on Smoking Withdrawal Symptoms and Relapse. *Journal of Consulting and Clinical Psychology* 55(4), 606-608.
- Griffiths RJ, Evans SM, Heisham SJ, et al. (1990) Low dose caffeine physical dependence in humans. *Journal of Pharmacology and Experimental Therapeutics* 255(3): 1123-1132.
- Harrell PT and Juliano LM (2009) Caffeine expectancies affect the subjective and behavioural effects of caffeine. *Psychopharmacology* 207(2): 335-342.
- Hughes JR, Gulliver SB, Amori G, et al. (1989) Effect of instructions and nicotine on smoking cessation, withdrawal symptoms and self-administration of nicotine gum. *Psychopharmacology* 99(4): 486-491.
- Hughes JR, Oliveto AH, Bickel, et al. (1995) The ability of low doses of caffeine to serve as reinforcers in humans: A replication. *Experimental and Clinical Psychopharmacology* 3: 358-363.

Huntley ED, and Juliano LM (2012) Caffeine Expectancy Questionnaire (CaffEQ):

Construction, psychometric properties, and associations with caffeine use, caffeine dependence, and other related variables. *Psychological assessment* 24(3): 592-607.

Juliano LM, and Brandon TH (2002) Effects of nicotine dose, instructional set, and outcome expectancies on the subjective effects of smoking in the presence of a stressor. *Journal of Abnormal Psychology* 111(1): 88-97.

Juliano LM, and Griffiths RR (2004) A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. *Psychopharmacology* 176(1): 1-29.

Juliano LM, Huntley ED, Harrell PT, et al. (2012) Development of the caffeine withdrawal symptom questionnaire: caffeine withdrawal symptoms cluster into 7 factors. *Drug and Alcohol Dependence* 124(3): 229-234.

Kirsch I, and Rosadino MJ (1993) Do double-blind studies with informed consent yield externally valid results? An empirical test. *Psychopharmacology* 110(4), 437-442.

Kirsch I, and Weixel LJ (1988) Double-blind versus deceptive administration of a placebo. *Behavioral Neuroscience* 102(2): 319-323.

Kozlowski LT, and Wilkinson DA (1987) Use and misuse of the concept of craving by alcohol, tobacco, and drug researchers. *British Journal of Addiction* 82(1): 31-36.

Lane JD and Phillips-Bute BG (1998) Caffeine deprivation affects vigilance performance. *Physiology and Behaviour* 65(1): 171-175.

Liguori A, Hughes JR, and Grass JA (1997) Absorption and subjective effects of caffeine from coffee, cola and capsules. *Pharmacology, Biochemistry and Behavior* 58(3): 721-726.

- Lotshaw SC, Bradley JR, and Brooks LR (1996) Illustrating caffeine's pharmacological and expectancy effects utilizing a balanced placebo design. *Journal of drug education* 26(1): 13-24.
- Mikalsen A, Bertelsen B, and Flaten M (2001) Effects of caffeine, caffeine associated stimuli, and caffeine-related information on physiological and psychological arousal. *Psychopharmacology* 157(4): 373-380.
- Murray DM, O'Connell CM, Schmid LA, et al. (1987) The validity of smoking self-reports by adolescents: A reexamination of the bogus pipeline procedure. *Addictive Behaviors* 12(1): 7-15.
- Myers MG, Cairns JA, and Singer J (1987) The consent form as a possible cause of side-effects. *Clinical Pharmacology and Therapeutics* 42(3): 250-253.
- Naismith DJ, Akinyanju PA, Szanto S, et al. (1970) The effect, in volunteers, of coffee and decaffeinated coffee on blood glucose, insulin plasma lipids, and some factors involvd in blood clotting. *Journal of Nutrition and Metabolism* 12: 144-151.
- Neukirch N and Colagiuri B (2015) The placebo effect, sleep difficulty, and side effects: a balanced placebo model. *Journal of Behavioural Medicine* 38(2): 273-283.
- Quinn VF and Colagiuri B (2015) Placebo interventions for nausea: A systematic review. *Annals of Behavioral Medicine* 49(3): 449-462.
- Phillips GT, Gossop M, and Bradley B (1986) The influence of psychological factors on the opiate withdrawal syndrome. *British Journal of Psychiatry* 149(2): 235-238.
- Phillips-Bute BG and Lane JD (1997) Caffeine withdrawal symptoms following brief caffeine deprivation. *Physiology and Behavior* 63(1): 333-340.
- Reissig CJ, Strain EC, and Griffiths RR (2009) Caffeinated energy drinks – a growing problem. *Drug and Alcohol Dependence* 99(1): 1-10.

- Rohsenow DJ, and Marlatt GA (1981). The balanced placebo design: Methodological considerations. *Addictive Behaviours* 6: 107-122.
- Rubin GJ and Smith AP (1999) Caffeine withdrawal and headaches. *Nutritional Neuroscience* 2(2): 123-126.
- Sayette MA, Shiffman S, Tiffany ST, et al. (2000) The measurement of drug craving. *Addiction* 95(Suppl 2): 189-210.
- Senay EC, Dorus W, and Thornton W (1977) Withdrawal From Methadone Maintenance: Rate of Withdrawal and Expectation. *Archives of General Psychiatry* 34(3): 361-367.
- Shiffman SM (1979) The tobacco withdrawal syndrome. *Cigarette smoking as a dependence process*, 23: 158-184.
- Smith AP (1996) Caffeine dependence: An alternative view. *Nature Medicine* 2(5): 494-494
- Tate JC, Stanton AL, Green SB, et al. (1994) Experimental analysis of the role of expectancy in nicotine withdrawal. *Psychology of Addictive Behaviors* 8(3): 169.
- Tyrer P, Owen R, and Dawling S (1983) Gradual withdrawal of diazepam after long-term therapy. *Lancet* 1(8339): 1402.
- Wall PD (1993) Pain and the placebo response. In: Bock GR and Marsh J (eds) *Experimental and Theoretical Studies of Consciousness* Ciba Foundation Symposium 174. West Sussex, England: Wiley and Sons Ltd, pp.187-212



## Figures

Figure 1

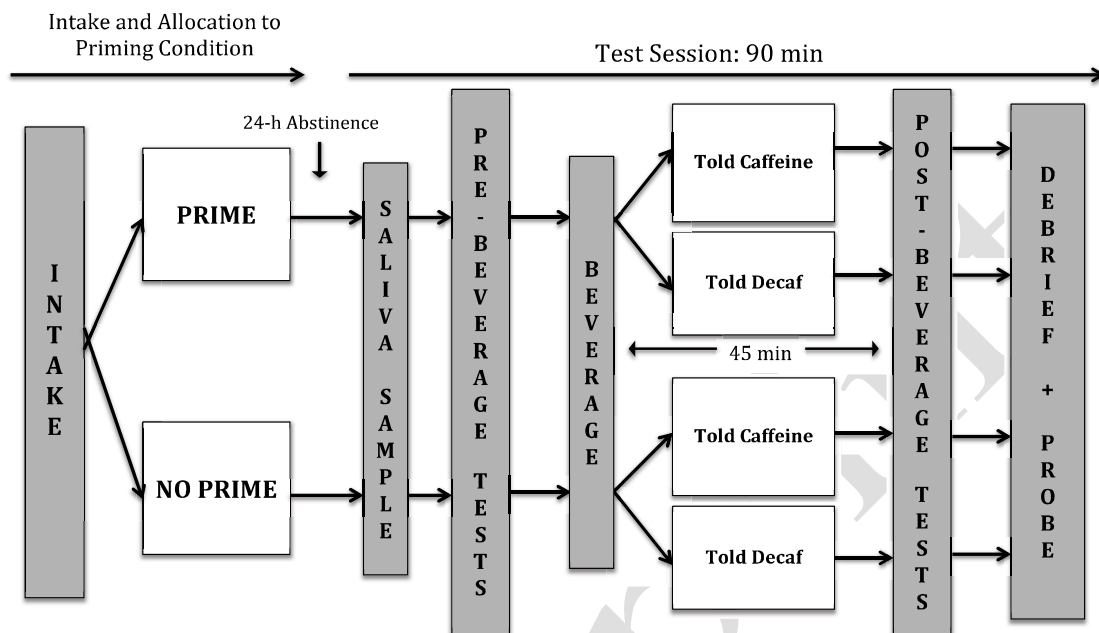


Figure 2

