

# Fourteen well-described caffeine withdrawal symptoms factor into three clusters

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## Abstract

**Rationale** Abrupt cessation of caffeine often results in several withdrawal symptoms among habitual caffeine consumers.

**Objective** The objective of the study was to determine whether caffeine withdrawal symptoms co-exist as clusters in some individuals.

**Materials and methods** Withdrawal symptoms and caffeine intake were assessed for men ( $n=126$ ) and women ( $n=369$ ), aged 20–29, using a caffeine habits questionnaire and a semi-quantitative food frequency questionnaire, respectively. Principal components factor analysis was used to identify common underlying factors among 14 well-described caffeine withdrawal symptoms. Odds ratios (OR) and 95% confidence intervals (CI) were calculated to determine if the likelihood of reporting a withdrawal factor was associated with habitual caffeine consumption.

**Results** The 14 withdrawal symptoms were grouped into three factors termed “fatigue and headache”, “dysphoric mood”, and “flu-like somatic”. The likelihood of reporting the fatigue and headache and dysphoric mood factors increased with higher levels of habitual caffeine consumption. Compared to <100 mg/day of caffeine, the ORs (95% CI) of reporting the fatigue and headache factor with a habitual intake of 100–200 mg/day and >200 mg/day were 1.97 (1.21, 3.21) and 4.44 (2.50, 7.86), respectively. The corresponding ORs (95% CI) for the dysphoric mood factor were 1.55 (0.96, 2.52) and 3.34 (1.99, 5.60).

**Conclusions** The 14 well-described caffeine withdrawal symptoms factor into three clusters, suggesting the existence

of three distinct underlying mechanisms of caffeine withdrawal. Increasing habitual caffeine consumption is associated with an increased likelihood of reporting the fatigue and headache and dysphoric mood symptoms, but not the flu-like somatic symptoms.

**Keywords** Caffeine · Cessation · Withdrawal · Dependence · Fatigue · Mood · Dysphoria · DSM · ICD · Human

## Introduction

Approximately 80–90% of North American adults report consuming caffeine regularly (Hughes and Oliveto 1997), with a mean intake of 280 mg/day (Barone and Roberts 1996). Caffeine has been shown to be a mild reinforcer (Evans et al. 1994; Hughes et al. 1991), and some individuals experience great difficulty abstaining from caffeine despite having medical problems that are aggravated by caffeine (Hughes et al. 1998; Strain et al. 1994). Regular use of caffeine can result in tolerance to some of its acute effects, which could then lead to increasing levels of daily intake in order to experience the desired effects (Griffiths and Mumford 1996). Consequently, chronic intake of caffeine can produce a form of physical dependence as evidenced by the withdrawal symptoms experienced upon the cessation or significant reduction of daily caffeine intake. Thus, regular use of caffeine is thought to be motivated, at least in part, by the desire to avoid caffeine withdrawal symptoms (Rogers 2007). Caffeine withdrawal can cause significant distress in daily functioning and is included as an official diagnosis in the International Statistical Classification of Diseases and Related Health Problems (ICD-10; World Health Organization 1992a, b) and a topic requiring further research as a

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potential official diagnosis in the Diagnostic and Statistical Manual of Mental Disorders, DSM-IV-TR (American Psychiatric Association 2000).

Caffeine withdrawal has been hypothesized to generally be a result of increased sensitivity to adenosine through neuro-adaptation (Griffiths and Mumford 1996), whereby the central nervous system neurons adapt to compensate for the continuous presence of caffeine in the brain (Satel 2006). Symptoms of caffeine withdrawal have been described for more than 170 years, but have only recently been reviewed empirically through an analysis of published studies (Juliano and Griffiths 2004). The symptoms that were deemed valid include headache, fatigue, decreased energy, decreased alertness, drowsiness, decreased contentedness, depressed mood, difficulty concentrating, irritability, foggy headedness, flu-like symptoms, nausea, and muscle pain (Juliano and Griffiths 2004). Anxiety did not fulfill the validity criteria set by Juliano and Griffiths, but is proposed in the DSM-IV-TR as a potential symptom of the caffeine withdrawal syndrome. Although the individual caffeine withdrawal symptoms have been well characterized, it is unclear whether the symptoms co-exist as clusters in some individuals. Juliano and Griffiths proposed that part of the DSM criteria be changed to indicate that a potential diagnosis for caffeine withdrawal syndrome requires abrupt cessation of caffeine use or reduction in the amount of caffeine used, closely followed by three or more of the following: (1) headache, (2) fatigue or drowsiness, (3) dysphoric mood, depressed mood, or irritability, (4) difficulty concentrating, and (5) flu-like somatic symptoms, nausea, vomiting, or muscle pain/stiffness (Juliano and Griffiths 2004). Although these clusters of symptoms were derived conceptually, the authors recognized the need to empirically establish the groupings.

Withdrawal symptoms have been reported to occur between 6 and 43 h after abstinence (Griffiths et al. 1990; Roller 1981) and last from 2 to 9 days (Griffiths et al. 1986). Symptoms have been shown to occur following abstinence from a habitual daily intake of as little as 100 mg (Evans and Griffiths 1999; Griffiths et al. 1990) and after as little as 3 days of caffeine exposure (Evans and Griffiths 1999). However, caffeine withdrawal symptoms can be prevented or reversed by consuming as little as 25 mg of caffeine (Evans and Griffiths 1999). The lowest caffeine dosing condition examined appears to have been 100 mg per day (Evans and Griffiths 1999; Griffiths et al. 1990), and it is unclear whether lower levels of daily consumption produce caffeine withdrawal symptoms. The incidence and severity of some caffeine withdrawal symptoms increase with higher amounts of daily caffeine consumption (Evans and Griffiths 1999; Goldstein 1964; Goldstein and Kaizer 1969; Lader et al. 1996; Lane 1997; Lane and Phillips-Bute 1998; Silverman et al. 1992).

However, this relationship has not been demonstrated in some studies assessing caffeine withdrawal and may depend on the type of symptoms experienced (Dews et al. 1999; Hofer and Battig 1994; Hughes et al. 1993; Verhoeff and Millar 1990).

The aim of the present study was to use a principal components method of factor analysis to determine if the 14 well-characterized caffeine withdrawal symptoms co-present in factors and to investigate whether the likelihood of reporting the factors of symptoms is associated with habitual intake levels of caffeine.

## Materials and methods

### Study population and data collection

Men ( $n=253$ ) and women ( $n=589$ ) aged 20–29 years were recruited by advertisement from the University of Toronto campus to participate in the Toronto Nutrigenomics and Health Study. Pregnant or nursing females were excluded from the study. Anthropometric measurements were taken, and a general health and lifestyle questionnaire was used to provide information on medical history, use of medication, cigarette smoking, and physical activity.

### Caffeine intake assessment

Caffeine intake was assessed using a semi-quantitative food frequency questionnaire (FFQ), which is a method that has been shown to be a valid and reliable approach to capture average daily caffeine intake (Kabagambe et al. 2001). The FFQ assessed dietary intake over the past month and included questions related to the consumption of caffeinated coffee, tea, cola, and other caffeinated soda beverages, chocolate, and “energy drinks.” The standard portion size for caffeinated tea, coffee, and energy drink beverages in the FFQ was fixed as 1 cup equivalent to 8 oz. The standard portion size for cola and other soda beverages was fixed as 1 can/glass/bottle equivalent to 12 oz. In order to help subjects report their beverage portion sizes more accurately, three portion cup sizes of 8, 12, and 16 oz were presented to them as examples. Subjects were asked to select one of ten categories of caffeinated beverage intake: never, 1 cup/week or less, 2 to 4 cups/week, 5 to 6 cups/week, 1 cup/day, 2 cups/day, 3 cups/day, 4 cups/day, 5 cups/day, or 6 or more cups/day. Daily caffeine intake levels derived from the FFQ were calculated using the US Department of Agriculture food composition data file (USDA 2007). Subjects were asked if they ever and how often they purchased and consumed coffee outside of the home or workplace. Subjects were also asked to indicate their usual method of preparing coffee at home or work. Caffeine

intake values from coffee consumption were determined after taking into account the variable caffeine content and the frequency of the usual brand of coffee purchased outside of the home or workplace, as well as the caffeine content of coffee according to the usual method of preparation (Cornelis and El-Soheby 2007). The caffeine intake values were then used to calculate the daily intake of caffeine in milligrams per kilogram body weight (bw) to provide two different measures of daily caffeine exposure as previously described (Barone and Roberts 1996). Caffeine intake from over-the-counter medications was determined using the general health and lifestyle questionnaire.

### Caffeine habits questionnaire

Subjects were asked “Do you currently, or have you ever, consumed caffeine-containing beverages (e.g., coffee, tea, cola) regularly?” and chose one of three responses: (1) “Yes, I currently consume them regularly”, (2) “Yes, I used to consume them regularly but do not anymore”, or (3) “No, I have never regularly consumed them”. Subjects were informed that “regularly” should be considered as daily or several days per week. Subjects were then asked “If yes, please indicate next to each of the following withdrawal symptoms the degree to which you experience(d) them up to 48 hours after ceasing to consume caffeine-containing beverages”, and chose one of five responses for each of the 14 caffeine withdrawal symptoms: (1) “do not know”, (2) “none”, (3) “mild”, (4) “moderate”, or (5) “severe”. Subjects were also given the option to select do not know if they had never abstained from caffeine, do not recall abstaining from caffeine, or do not know if they ever experienced a particular symptom. Subjects who responded “No, I have never regularly consumed them” to the question “Do you currently, or have you ever, consumed caffeine-containing beverages (e.g., coffee, tea, cola) regularly?” ( $n=245$ ) were excluded from all analyses, since they were instructed to skip the caffeine withdrawal symptoms questions in the questionnaire. Subjects who responded “Yes, I used to consume them regularly but do not anymore” ( $n=102$ ) were also excluded from all analyses, since some of these subject may have been dealing with long-term retrospective memory and may have had difficulty recalling their caffeine withdrawal symptoms.

### Statistical analysis

Population characteristics were assessed for the 495 subjects remaining after exclusions between three different categories of habitual caffeine intake. The cut points for the three categories of intake were 100 and 200 mg/day, which are equivalent to approximately 1 and 2 cups of coffee per day, respectively. The reported severities of the caffeine

withdrawal symptoms were dichotomized into “no” (none) and “yes” (mild, moderate, and severe) because of the relatively low number of subjects reporting moderate or severe symptoms, which may reflect the relatively low average habitual caffeine consumption level (168.1 mg/day) in this population of young adults. We conducted a principal components analysis method of factor analysis using the outcome measures yes or no for each withdrawal symptom to identify any underlying connection within the data (Kim and Mueller 1978). The number of factors for the withdrawal symptoms was determined using a scree test as well as the Kaiser criterion for eigenvalues, as only those factors with values above 1 indicate that the variance explained by the factor is greater than any one input variable (Kaiser 1958). Factor structure was simplified by using orthogonal rotation to maximize the variance of the squared loadings for each factor. Items with factor loadings  $>0.50$  were considered as a distinct symptom of that factor. Factor strength and the level of correlation between the items considered to be part of a factor were measured using Cronbach’s  $\alpha$  coefficients. Subjects reporting a history of mood disorder were excluded from analyses on the “dysphoric mood” factor ( $n=75$ ). Unconditional multivariate logistic regression models were adjusted for covariates and used to calculate odds ratios (OR) and 95% confidence intervals (CI). This was done in order to determine the likelihood of reporting a factor of withdrawal symptoms with increasing categories of caffeine consumption. Models were adjusted for age, sex, cigarette smoking (current vs. past or never), history of mood disorder (anxiety or depression), use of oral contraceptives (among women only), physical activity, and body mass index (BMI); however, only covariates that materially altered the effect estimates were included in the final adjusted models. Tests for multiplicative interactions between habitual caffeine intake and covariates on the outcome variables were conducted using Wald statistics. All statistical analyses were two-sided, and  $P$  values  $<0.05$  were considered statistically significant. All data were analyzed using the Statistical Analysis Systems software (SAS V9.1; SAS Institute, Cary, NC, USA).

### Results

Characteristics of subjects who reported current regular caffeine consumption among different categories of habitual caffeine intake are presented in Table 1. A summary of the caffeine withdrawal symptoms reported is presented in Table 2. Factor loadings and Cronbach’s alpha coefficients for the withdrawal symptoms are displayed in Table 3. The 14 caffeine withdrawal symptoms listed in Table 2 were grouped into three factors, and each symptom was included

**Table 1** Subject characteristics by habitual caffeine intake category

Characteristic	Caffeine intake category		
	<100 mg/day (n=192)	100–200 mg/day (n=149)	>200 mg/day (n=154)
Age, years	22.5±2.3 <sup>a</sup>	23.0±2.6 <sup>ab</sup>	23.1±2.5 <sup>b</sup>
Sex			
Men, n (%)	58 (30)	33 (22)	35 (23)
Women, n (%)	134 (70)	116 (78)	119 (77)
Weight, kg	64.9±14.1	62.0±13.3	64.9±12.0
BMI, kg/m <sup>2</sup>	22.9±3.9	22.3±3.6	23.3±3.6
Physical activity (MET h/week)	12.4±2.4	12.2±2.2	12.3±2.2
Smoking status, n (%)			
Current	10 (5) <sup>a</sup>	8 (5) <sup>a</sup>	25 (16) <sup>b</sup>
Past	17 (9) <sup>a</sup>	12 (8) <sup>a</sup>	27 (18) <sup>b</sup>
Never	165 (86) <sup>a</sup>	129 (87) <sup>a</sup>	102 (66) <sup>b</sup>
History of mood disorder, n (%)	24 (12)	25 (17)	30 (19)
Oral contraceptive use, n (% of women)	45 (34)	36 (31)	42 (35)
Mean caffeine intake			
mg/day	53.5±26.7 <sup>a</sup>	140.7±28.4 <sup>b</sup>	337.6±143.9 <sup>c</sup>
mg/kg bw/day	0.8±0.4 <sup>a</sup>	2.4±0.7 <sup>b</sup>	5.3±2.2 <sup>c</sup>

Values are mean±standard deviation (SD) for continuous variables and percent for category. Values not sharing the same letter are significantly different between intake categories ( $P<0.05$ ).

as a factor item based on a factor loading score >0.50. Of the 14 caffeine withdrawal symptoms, two (foggy/not clearheaded and difficulty concentrating) loaded on to more than one factor. The first factor, which we termed “fatigue and headache”, included decreased energy/activeness, decreased alertness/attentiveness, tiredness/fatigue, drowsiness/sleepiness, headache, foggy/not clearheaded, and difficulty concentrating. The second factor was termed dysphoric mood and included depressed mood, anxiety/nervousness, irritability, decreased contentedness/well-being, and also foggy/not clearheaded and difficulty concentrating. The third factor was referred to as “flu-like somatic” and included nausea/vomiting/upset stomach, flu-like symptoms, and muscle pain/stiffness. The most common caffeine

withdrawal symptom factor reported was the fatigue and headache (72%), factor followed by dysphoric mood (53%), then flu-like somatic (11%).

The crude and adjusted ORs (95% CI) for reporting the withdrawal symptoms in all three factors with increasing habitual caffeine consumption are shown in Table 4. Compared to <100 mg/day, the adjusted ORs (95% CI) for reporting the fatigue and headache factor with a habitual intake of 100–200 and >200 mg/day were 1.97 (1.21, 3.21) and 4.44 (2.50, 7.86), respectively. After excluding subjects who reported a history of mood disorder, the adjusted ORs (95% CI) for reporting the dysphoric mood factor with a habitual intake of 100–200 and >200 mg/day, compared to <100 mg/day, were 1.55 (0.96, 2.52) and 3.34 (1.99, 5.60),

**Table 2** Caffeine withdrawal symptoms reported up to 48 h after ceasing to consume caffeine

Withdrawal symptom	None	Mild	Moderate n (%)	Severe	Do not know
Headache	294 (59)	95 (19)	55 (11)	16 (3)	35 (7)
Tiredness/fatigue	183 (37)	164 (33)	99 (20)	23 (5)	26 (5)
Decreased energy/activeness	214 (43)	158 (32)	74 (15)	19 (4)	30 (6)
Decreased alertness/attentiveness	219 (44)	148 (30)	76 (15)	19 (4)	33 (7)
Drowsiness/sleepiness	219 (44)	149 (30)	82 (17)	15 (3)	30 (6)
Decreased contentedness/well-being	322 (65)	88 (18)	41 (8)	6 (1)	38 (8)
Depressed mood	358 (72)	68 (14)	24 (5)	2 (<1)	43 (9)
Difficulty concentrating	282 (57)	112 (23)	49 (10)	9 (2)	43 (9)
Irritability	320 (65)	84 (17)	47 (9)	8 (2)	36 (7)
Foggy/not clearheaded	310 (63)	97 (20)	40 (8)	12 (2)	36 (7)
Flu-like symptoms	436 (88)	20 (4)	6 (1)	1 (<1)	32 (6)
Nausea/vomiting/upset stomach	446 (90)	17 (3)	4 (1)	2 (<1)	26 (5)
Muscle pain/stiffness	442 (89)	12 (2)	5 (1)	1 (<1)	35 (7)
Anxiety/nervousness	402 (81)	45 (9)	13 (3)	1 (<1)	34 (7)

**Table 3** Factor loads from principal components factor analysis of caffeine withdrawal symptoms

Withdrawal symptom	Factor 1 Fatigue and headache	Factor 2 Dysphoric mood	Factor 3 Flu-like somatic
Decreased energy/activeness	<b>0.88</b>	0.20	0.15
Decreased alertness/attentiveness	<b>0.88</b>	0.26	0.03
Tiredness/fatigue	<b>0.88</b>	0.22	0.09
Drowsiness/sleepiness	<b>0.82</b>	0.24	0.08
Headache	<b>0.61</b>	0.17	0.19
Foggy/not clearheaded	<b>0.60</b>	<b>0.53</b>	-0.02
Difficulty concentrating	<b>0.59</b>	<b>0.58</b>	0.11
Depressed mood	0.24	<b>0.81</b>	0.13
Anxiety/nervousness	0.05	<b>0.73</b>	0.37
Irritability	0.45	<b>0.69</b>	0.13
Decreased contentedness/well-being	0.45	<b>0.68</b>	0.06
Nausea/vomiting/upset stomach	0.11	-0.02	<b>0.75</b>
Flu-like symptoms	0.13	0.15	<b>0.73</b>
Muscle pain/stiffness	0.04	0.26	<b>0.72</b>
Cronbach's $\alpha$ coefficient	0.92	0.89	0.54

Values in bold indicate item loads on a single factor with loading criteria of >0.50. Cronbach's  $\alpha$  coefficients represent the correlation between items with bold values within a factor.

respectively. The likelihood of reporting the flu-like somatic factor did not increase with increasing habitual caffeine intake. The corresponding ORs (95% CI) for the flu-like somatic factor were 1.05 (0.52, 2.14) and 0.84 (0.40, 1.77).

## Discussion

In the present study, we observed that 14 well-described caffeine withdrawal symptoms factored into three distinct clusters that we termed fatigue and headache, dysphoric mood, and flu-like somatic. Of the 14 caffeine withdrawal symptoms, two (foggy/not clearheaded and difficulty concentrating) loaded on to both the fatigue and headache

and dysphoric mood factors. Juliano and Griffiths proposed that part of the DSM criteria be changed to indicate that a potential diagnosis for caffeine withdrawal syndrome requires abrupt cessation of caffeine use or reduction in the amount of caffeine used, closely followed by three or more of the following: (1) headache, (2) fatigue or drowsiness, (3) dysphoric mood, depressed mood, or irritability, (4) difficulty concentrating, and (5) flu-like somatic symptoms, nausea, vomiting, or muscle pain/stiffness (Juliano and Griffiths 2004). These proposed five clusters of symptoms were based on the 13 symptoms describing the caffeine withdrawal syndrome (Juliano and Griffiths 2004) and did not include anxiety. Although these five clusters of symptoms were derived conceptually, the authors recognized the need to establish this empirically.

**Table 4** Frequency and OR (95% CI) of reporting the clusters of caffeine withdrawal symptoms among habitual caffeine intake categories

Factor/caffeine intake category	No <i>n</i> (%)	Yes	OR (95% CI) <sup>a</sup>	OR (95% CI) <sup>b</sup>
Factor 1 "Fatigue and headache"				
<100 mg/day	75 (40)	111 (60)	1.00	1.00
100–200 mg/day	38 (26)	106 (74)	1.88 (1.17, 3.02)	1.97 (1.21, 3.21)
>200 mg/day	21 (14)	129 (86)	4.15 (2.40, 7.17)	4.44 (2.50, 7.86)
Factor 2 "Dysphoric mood" <sup>†</sup>				
<100 mg/day	97 (59)	67 (41)	1.00	1.00
100–200 mg/day	57 (47)	64 (53)	1.63 (1.01, 2.61)	1.55 (0.96, 2.52)
>200 mg/day	35 (29)	84 (71)	3.47 (2.10, 5.74)	3.34 (1.99, 5.60)
Factor 3 "Flu-like somatic"				
<100 mg/day	164 (89)	20 (11)	1.00	1.00
100–200 mg/day	125 (88)	17 (12)	1.11 (0.56, 2.22)	1.05 (0.52, 2.14)
>200 mg/day	130 (90)	15 (10)	0.95 (0.47, 1.92)	0.84 (0.40, 1.77)

<sup>†</sup> Model excludes subjects reporting a mood disorder ( $n=79$ ).

<sup>a</sup> Unadjusted logistic regression

<sup>b</sup> Logistic regression model adjusted for age, sex, physical activity, and smoking

A previous study conducted hierarchical cluster analysis of a 26-item caffeine withdrawal questionnaire on 76 subjects to determine the effects of different caffeine doses on withdrawal (Evans and Griffiths 1999). In that study, the authors identified two to five possible cluster combinations and determined their cluster structure based on scientific reasons or biological plausibility rather than empirical findings. In the present study, we conducted a principal components analysis, and, in contrast to the Evans and Griffiths study, our factor selection was empirically driven using a scree test as well as the Kaiser criterion for eigenvalues. Our analysis examining 14 commonly described withdrawal symptoms was also performed among a larger sample of 495 subjects and may have more validity in the factors identified. Our findings suggest that caffeine withdrawal symptoms co-exist in three distinct factors. Although there is no prior evidence to suggest that these factors represent distinct mechanisms, we speculate that the observed factors may represent either the adenosinergic, dopaminergic, serotonergic, or adrenergic pathways, since these pathways have been shown to mediate many of the physiological effects of caffeine (Fredholm et al. 1999). Future studies involving controlled dosing conditions should investigate whether caffeine withdrawal symptoms are experienced in clusters similar to the factors we identified and explore the underlying mechanisms of these distinct clusters. One way to begin investigating which biological mechanism mediates a specific factor would be to determine if functional genetic variations in the receptors or other targets involved in the mechanism of action of caffeine are associated with the incidence or severity of the factors of withdrawal symptoms. Any variability in incidence or severity of a factor between the genotypes of a specific polymorphism would suggest an involvement of that gene and pathway in the mediation of the symptoms in that factor.

The findings from the present study suggest that caffeine withdrawal headaches are often accompanied by fatigue. Although previous studies have suggested that non-headache symptoms of caffeine withdrawal, including tiredness, fatigue, and drowsiness, represent distinct features of the caffeine withdrawal syndrome that can occur in the absence of headaches (Griffiths et al. 1990; Griffiths and Woodson 1988), our findings suggest that headaches are more likely to co-exist with fatigue rather than exist on their own. Headache was included in the fatigue and headache factor after meeting the loading criteria that was set a priori. Caffeine withdrawal headaches are thought to be due to an increase in cerebral blood flow, caused by vasodilatory effects of increased adenosine activity. However, the EEG activity changes observed during fatigue and drowsiness could also arise from a similar mechanism (e.g., adenosinergic pathway) that would mediate caffeine withdrawal headaches (Jones et al. 2000). As such, it is reasonable to

suggest that headaches co-exist with the fatigue symptoms. We also observed that foggy/not clearheaded and difficulty concentrating as withdrawal symptoms were associated with both the fatigue and headache and dysphoric mood factors, although both symptoms had a higher factor load on the fatigue and headache factor. Our findings suggest that both these symptoms are co-presented with the remaining symptoms included in the fatigue and headache and dysphoric mood factors. Interestingly, difficulty concentrating has been proposed to be a cluster of its own (Juliano and Griffiths 2004). In the present study, the variation in responses for foggy/not clearheaded and difficulty concentrating appear to be related to the variation within the responses to withdrawal symptoms in both fatigue and headache (Factor 1) and dysphoric mood (Factor 2) factors leading to the factor loading split. This split is not surprising and is biologically plausible since both Factor 1 and Factor 2 are comprised of neurologic-type effects. “Fogginess” and difficulty concentrating, although still related to neuro-endocrine processes, are less objective than the other neurologic-type withdrawal symptoms contained in Factors 1 and 2. These two variables represent an intersection between the two factors, since subject interpretation of these symptoms may have varied more than the other variables contained in the two factors. Their factors scores are thus representative of this reduced objectivity and relationship with both groups of symptoms.

The frequency of reporting the specific withdrawal symptoms in the present population are consistent with those reported in previous studies (Juliano and Griffiths 2004). The most common factor of symptoms reported was the fatigue and headache factor, which consisted of the symptoms previously reported to have the highest incidence among all caffeine withdrawal symptoms (Griffiths and Woodson 1988; Hughes et al. 1998). The likelihood of reporting the fatigue and headache and dysphoric mood factors increased with increasing habitual caffeine intake. The least common factor of symptoms reported was the flu-like somatic factor. Although flu-like symptoms, including nausea and muscle pain, have been validated as caffeine withdrawal symptoms, they have also been shown to be relatively uncommon (Griffiths and Woodson 1988; Juliano and Griffiths 2004). Increasing daily caffeine intake was not associated with an increase in the likelihood of reporting the flu-like somatic factor. Consistent with our findings, some studies have observed that the severity of flu-like symptoms of withdrawal, including nausea and muscle pains, does not increase with increasing daily caffeine consumption (Juliano and Griffiths 2004). One reason for this finding could be that regardless of habitual consumption level, a small subset of the population may have a genetic variation that results in an increased susceptibility to the flu-like somatic symptoms of caffeine

withdrawal. This may also explain why these symptoms are relatively uncommon.

The present study has some limitations. Examining the withdrawal symptoms of stimulants such as caffeine usually involves randomized controlled intervention designs executed under specified conditions. However, retrospective study designs have been shown to be valid and reliable methods of testing novel hypotheses, and our findings provide the first empirical evidence that caffeine withdrawal symptoms present in three distinct groups. We attempted to reduce recall bias and measurement error in both measures of caffeine intake and withdrawal symptoms by asking subjects to recall their dietary habits within a relatively recent time period (1 month) and utilizing a dietary assessment tool (FFQ) that has been shown to be a reliable method of measuring habitual caffeine intake (Kabagambe et al. 2001). Furthermore, we excluded subjects who did not consume caffeine regularly at the time that they completed the caffeine habits questionnaire, since some of them might not have accurately recalled their caffeine withdrawal symptoms.

Because the onset of withdrawal symptoms has previously been reported to occur at different time points for certain individuals (Juliano and Griffiths 2004), subjects were asked to report the type and severity of symptoms they recall experiencing up to 48 h after abstaining from caffeine. Subjects who never tried abstaining or were unsure if they had previously abstained from caffeine were instructed to indicate do not know on the questionnaire and were excluded from further analyses. The aim of the present study was to assess whether withdrawal symptoms group into factors. However, we did not aim to assess the frequency of withdrawal symptoms following abstinence after a fixed duration. Therefore, the findings of our factor analysis should not be affected by subjects who had abstained from caffeine only overnight, since this can also produce caffeine withdrawal symptoms in some individuals (Juliano and Griffiths 2004).

Because the severity of some withdrawal symptoms increases with increasing daily caffeine intake, the number of subjects indicating none, mild, or do not know likely reflects the relatively low level of habitual caffeine consumption in our population. The proportion of subjects in our population indicating moderate or severe for a common withdrawal symptom such as headache is 14%, which is consistent with previous findings that have reported the incidence of significantly distressing withdrawal headaches to be approximately 13% (Juliano and Griffiths 2004). The reason for dichotomizing responses was to assess incidence rather than severity given the relatively low proportion reporting any severe symptoms. It is possible that some subjects may have never actually experienced a period of sustained abstinence, since as little as 25 mg of caffeine can prevent some

withdrawal symptoms (Evans and Griffiths 1999), and small amounts of caffeine that are unknowingly consumed on days believed to be “caffeine-free” may lead to an underestimation of the severity of withdrawal symptoms. However, a potential underestimation of the severity of symptoms would likely bias associations toward the null. Any underestimation of caffeine withdrawal symptoms would likely have been non-differential across caffeine consumption groups and, therefore, have not materially altered the results.

Habitual caffeine consumption in significant amounts usually begins in early adulthood. Sampling a population of young adults in relatively good health allows us to collect the data on consumption behavior at the early stages of a developing habit and could possibly help us better understand the early stages of caffeine dependency. Although caffeine withdrawal symptoms have been shown to occur following abstinence from a habitual daily intake of as little as 100 mg, this appears to be the lowest caffeine dosing condition examined so far. Thus, it is possible that habitual daily intakes of less than 100 mg could produce caffeine withdrawal symptoms upon abrupt cessation. Furthermore, in the study by Evans and Griffiths (1999), subjects were exposed to caffeine for 1, 3, 7, or 14 days of 300 mg/day, and it was observed that caffeine withdrawal occurred after as little as 3 days of caffeine exposure. Although it was not examined, caffeine withdrawal symptoms might have also occurred from caffeine abstinence after as little as 2 days of consecutive caffeine use. As such, young adults using caffeine regularly only on weekdays or weekends could also experience caffeine withdrawal symptoms.

In summary, 14 well-described caffeine withdrawal symptoms factored into three clusters of caffeine withdrawal symptoms that we termed fatigue and headache, dysphoric mood, and flu-like somatic. The three factors may represent different underlying mechanisms of caffeine withdrawal. Increasing caffeine intake was associated with an increase in the likelihood of reporting symptoms of the fatigue and headache and dysphoric mood factor, but not the flu-like somatic symptoms.

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## References

- American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders: DSM-IV-TR, 4th edn. American Psychiatric Association, USA

- Barone JJ, Roberts HR (1996) Caffeine consumption. *Food Chem Toxicol* 34:119–129
- Cornelis MC, El-Sohemy A (2007) Coffee, caffeine, and coronary heart disease. *Curr Opin Lipidol* 18:13–19
- Dews PB, Curtis GL, Hanford KJ, O'Brien CP (1999) The frequency of caffeine withdrawal in a population-based survey and in a controlled, blinded pilot experiment. *J Clin Pharmacol* 39:1221–1232
- Evans SM, Griffiths RR (1999) Caffeine withdrawal: a parametric analysis of caffeine dosing conditions. *J Pharmacol Exp Ther* 289: 285–294
- Evans SM, Critchfield TS, Griffiths RR (1994) Caffeine reinforcement demonstrated in a majority of moderate caffeine users. *Behav Pharmacol* 5:231–238
- Fredholm BB, Battig K, Holmen J, Nehlig A, Zvartau EE (1999) Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. *Pharmacol Rev* 51:83–133
- Goldstein A (1964) Wakefulness caused by caffeine. *Naunyn Schmiedebergs Arch Exp Pathol Pharmacol* 248:269–278
- Goldstein A, Kaizer S (1969) Psychotropic effects of caffeine in man. 3. A questionnaire survey of coffee drinking and its effects in a group of housewives. *Clin Pharmacol Ther* 10:477–488
- Griffiths RR, Mumford GK (1996) Caffeine reinforcement, discrimination, tolerance and physical dependence in laboratory animals and humans. In: Balster RL, Kuhar MJ, Schuster CR (eds) *Pharmacological aspects of drug dependence: toward an integrated neurobehavioral approach* (Handbook of experimental pharmacology, v. 118). Springer, Berlin
- Griffiths RR, Woodson PP (1988) Caffeine physical dependence: a review of human and laboratory animal studies. *Psychopharmacology (Berl)* 94:437–451
- Griffiths RR, Bigelow GE, Liebson IA (1986) Human coffee drinking: reinforcing and physical dependence producing effects of caffeine. *J Pharmacol Exp Ther* 239:416–425
- Griffiths RR, Evans SM, Heishman SJ, Preston KL, Sannerud CA, Wolf B, Woodson PP (1990) Low-dose caffeine physical dependence in humans. *J Pharmacol Exp Ther* 255:1123–1132
- Hofer I, Battig K (1994) Cardiovascular, behavioral, and subjective effects of caffeine under field conditions. *Pharmacol Biochem Behav* 48:899–908
- Hughes JR, Oliveto AH (1997) A systematic survey of caffeine intake in Vermont. *Exp Clin Psychopharmacol* 5:393–398
- Hughes JR, Higgins ST, Bickel WK, Hunt WK, Fenwick JW, Gulliver SB, Mireault GC (1991) Caffeine self-administration, withdrawal, and adverse effects among coffee drinkers. *Arch Gen Psychiatry* 48:611–617
- Hughes JR, Oliveto AH, Bickel WK, Higgins ST, Badger GJ (1993) Caffeine self-administration and withdrawal: incidence, individual differences and interrelationships. *Drug Alcohol Depend* 32: 239–246
- Hughes JR, Oliveto AH, Liguori A, Carpenter J, Howard T (1998) Endorsement of DSM-IV dependence criteria among caffeine users. *Drug Alcohol Depend* 52:99–107
- Jones HE, Herning RI, Cadet JL, Griffiths RR (2000) Caffeine withdrawal increases cerebral blood flow velocity and alters quantitative electroencephalography (EEG) activity. *Psychopharmacology (Berl)* 147:371–377
- Juliano LM, Griffiths RR (2004) A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. *Psychopharmacology* 176:1–29
- Kabagambe EK, Baylin A, Allan DA, Siles X, Spiegelman D, Campos H (2001) Application of the method of triads to evaluate the performance of food frequency questionnaires and biomarkers as indicators of long-term dietary intake. *Am J Epidemiol* 154:1126–1135
- Kaiser HF (1958) The varimax criterion for analytic rotation in factor analysis. *Psychometrika* 23:187–200
- Kim J-o, Mueller CW (1978) *Factor analysis: statistical methods and practical issues*. Sage Publications, California
- Lader M, Cardwell C, Shine P, Scott N (1996) Caffeine withdrawal symptoms and rate of metabolism. *J Psychopharmacol* 10:110–118
- Lane JD (1997) Effects of brief caffeinated-beverage deprivation on mood, symptoms, and psychomotor performance. *Pharmacol Biochem Behav* 58:203–208
- Lane JD, Phillips-Bute BG (1998) Caffeine deprivation affects vigilance performance and mood. *Physiol Behav* 65:171–175
- Rogers PJ (2007) Caffeine, mood and mental performance in everyday life. *British Nutrition Foundation* 32:84–89
- Roller L (1981) Caffeinism: subjective quantitative aspect of withdrawal syndrome. *Med J Aust* 1:146
- Satel S (2006) Is caffeine addictive?—a review of the literature. *Am J Drug Alcohol Abuse* 32:493–502
- Silverman K, Evans SM, Strain EC, Griffiths RR (1992) Withdrawal syndrome after the double-blind cessation of caffeine consumption. *N Engl J Med* 327:1109–1114
- Strain EC, Mumford GK, Silverman K, Griffiths RR (1994) Caffeine dependence syndrome. Evidence from case histories and experimental evaluations. *Jama* 272:1043–1048
- USDA (2007) *National Nutrient Database for Standard Reference*
- Verhoeff FH, Millar JM (1990) Does caffeine contribute to postoperative morbidity. *Lancet* 336:632
- World Health Organization (1992a) *ICD-10: international statistical classification of diseases and related health problems, 10th revision*. edn. World Health Organization, Geneva
- World Health Organization (1992b) *The ICD-10 classification of mental and behavioural disorders: clinical descriptions and diagnostic guidelines*. World Health Organization, Geneva