Caffeine Withdrawal: A Parametric Analysis of Caffeine Dosing Conditions

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ABSTRACT

Although caffeine is the most widely used behaviorally active drug in the world, caffeine physical dependence has been only moderately well characterized in humans. Four double-blind experiments were conducted in independent groups of healthy participants to assess the conditions under which withdrawal symptoms occur upon cessation of low to moderate doses of caffeine. In experiment 1, there was no evidence that the range or magnitude of caffeine withdrawal symptoms differed when 300 mg of caffeine was consumed as a single dose in the morning versus 100 mg at three time points across the day. In experiment 2, both the range and severity of withdrawal increased as a function of caffeine maintenance dose (100, 300, and 600 mg/day), with even the lowest dose (100 mg) producing significant caffeine withdrawal. Experiment 3 showed that when individuals were maintained on 300 mg caffeine/day and tested with a range of lower doses (200, 100, 50, 25, and 0 mg/day), a substantial reduction in caffeine consumption (≥100 mg/day) was necessary for the manifestation of caffeine withdrawal. Experiment 4 manipulated duration of exposure to caffeine (1, 3, 7, or 14 days of 300 mg/day) and showed that caffeine withdrawal occurred after as little as 3 days of caffeine exposure, with a somewhat increased severity of withdrawal observed after 7 or 14 days of exposure. As a whole, this set of experiments provides the most complete parametric characterization of caffeine withdrawal to date and suggests that caffeine physical dependence can occur under more modest conditions (i.e., fewer doses per day, lower daily dose, shorter duration of exposure) than previously recognized.

Caffeine physical dependence and withdrawal in humans has been documented in numerous case reports and experimental studies (cf. Griffiths and Woodson, 1988a; Griffiths and Mumford, 1995). The most common withdrawal symptoms include increases in headache, drowsiness, and work difficulty (including impaired concentration) and decreases in feelings of contentment and sociability (e.g., Griffiths et al., 1990a; Silverman et al., 1992; Hughes et al., 1993; Strain et al., 1994; cf. Griffiths and Mumford, 1995). Although severity of caffeine withdrawal can vary within and across individuals, it can produce clinically significant functional behavioral impairment (Silverman et al., 1992; Strain et al., 1994; Streufert et al., 1995) and has been implicated in a weekend migraine headache syndrome (Couturier et al., 1992) and postoperative headache (Galletly et al., 1989; Fennelly et al., 1991; Weber et al., 1993). There is convincing evidence that caffeine withdrawal symptoms enhance the reinforcing effects of caffeine and thus are integrally related to the maintenance of long-term patterns of caffeine self-administration (e.g., Griffiths et al., 1986a; Hughes et al., 1993; Evans et al., 1994; Richardson et al., 1995; Rogers et al., 1995; Schuh and Griffiths, 1997; Garrett and Griffiths, 1998).

Although caffeine withdrawal has been well documented, prospective parametric studies of dosing conditions for inducing physical dependence are almost nonexistent. The present set of experiments was undertaken to examine the effects on caffeine withdrawal of manipulating several major caffeine dosing parameters (within-day dosing frequency, maintenance dose, magnitude of dose reduction, and duration of dosing).

Although previous studies have demonstrated caffeine withdrawal occurs under widely varying within-day dosing conditions [e.g., daily dose divided into either 2 (Garrett and Griffiths, 1998) 3 (Evans and Griffiths, 1992), or 10 (Griffiths et al., 1990a) equal portions over the day], the effect of varying within-day dosing pattern has not been studied systematically, and, to our knowledge, no study has examined whether caffeine withdrawal occurs after once-a-day dosing. Thus, the first experiment was designed to explore the role of within-day caffeine dosing frequency by examining caffeine withdrawal in participants who were maintained on 300 mg...
of caffeine each day either as a single dose in the morning or as three 100-mg doses spaced 4 to 6 h apart over the day.

To our knowledge, there have been no prospective experimental studies of the effects of caffeine maintenance dose on caffeine withdrawal. Although previous studies have shown that the incidence of caffeine withdrawal increased as a function of daily self-reported caffeine dose (e.g., Goldstein and Kaizer, 1969; Goldstein et al., 1969; Galletly et al., 1989; Fennelly et al., 1991; Weber et al., 1993), these studies provide only suggestive evidence that caffeine withdrawal is related to the amount of caffeine consumed because caffeine dose was not manipulated directly, but was self-selected by the individuals themselves. The second experiment examined the role of daily caffeine dose on caffeine withdrawal by maintaining subjects on different doses of caffeine (100, 300, and 600 mg/day) before withdrawal.

Another dosing parameter that has remained unstudied is the magnitude of the caffeine dose required to prevent (i.e., suppress) caffeine withdrawal in individuals already physically dependent on caffeine. Therefore, the third experiment was designed to determine the extent to which lower doses of caffeine would suppress or reduce caffeine withdrawal symptoms in individuals chronically maintained on a constant dose of caffeine. This was assessed by maintaining individuals on 300 mg/day caffeine throughout the study and periodically substituting a range of lower caffeine doses (200, 100, 50, 25, and 0 mg/day).

Finally, no previous study has systematically explored the effect of duration of daily caffeine exposure on subsequent caffeine withdrawal. Although it is well established that long-term daily exposure (e.g., for a period of months) to moderate or high doses of caffeine can result in subsequent caffeine withdrawal, two studies suggested that caffeine withdrawal can occur after relatively short-term (i.e., 6–15 days) exposure to caffeine (Dreisbach and Pfeiffer, 1943; Griffiths et al., 1986a). The fourth experiment was designed to determine directly the minimum duration of chronic caffeine exposure necessary for the expression of caffeine withdrawal. This was assessed by maintaining individuals on placebo throughout the study and intermittently switching them to caffeine (300 mg/day) for periods of 1, 3, 7, or 14 days, followed by a return to placebo for 1 week.

Materials and Methods

Subjects

Volunteers were recruited from the Francis Scott Key Medical Center campus via posters and flyers. All participants were medically healthy based on medical history, a complete physical examination, electrocardiogram, urine toxicology for abused drugs, and, for female participants, a urine pregnancy test. In addition, no one had any current psychiatric disorders including psychoactive substance abuse or dependence (other than nicotine) based on a psychiatric interview using DSM-III-R criteria (American Psychiatric Association, 1987). All participants had at least a high school education to ensure an adequate understanding of the consent form, questionnaires, and protocol requirements. Individuals with any medical problems contraindicating caffeine consumption, as well as individuals who did not report current daily caffeine consumption, were excluded.

These studies were approved by the Institutional Review Boards of the Francis Scott Key Medical Center and Johns Hopkins University School of Medicine. Before research participation, experimental procedures were discussed with participants and they signed a consent form that outlined the procedures to be used and listed possible side effects of the drugs. Participants were told that the purpose of the study was to evaluate the effects of compounds found in coffee, tea, chocolate, and soda on mood and behavior. To maintain the double-blind and minimize expectancy effects related to caffeine, participants were told that the compounds they might receive included chlorogenic acids, diterpenes, caffeine, tannin, theophylline, and inactive placebo and that the drugs and doses could vary from day to day. Participants were paid for their participation. Before beginning the experimental phase, all participants completed a detailed dietary survey from which daily caffeine intake was calculated for 7 days immediately before starting the study.

Table 1 shows the demographics for participants across the four experiments, which were conducted sequentially over a 4-year period. Different individuals participated in each of the four experiments: 15, 17, 19, and 25 participants completed experiments 1, 2, 3, and 4, respectively. The majority of participants were women, and the average age was between 28 and 30 years across the experiments. The average prestudy caffeine consumption ranged from 241 mg/day in experiment 1 to 294 mg/day in experiment 3 and was similar to estimated daily average caffeine consumption of 280 mg per adult consumer in the United States (Barone and Roberts, 1996).

Dietary Restrictions

In all experiments, participants were instructed to abstain completely from caffeinated and decaffeinated coffee, caffeinated and decaffeinated tea, all chocolate-containing products, caffeinated soft drinks, and various over-the-counter medications for the full duration of the study (ranging between 54 days in experiment 3 to 73 days in experiment 2). Participants were given a detailed list of allowed and restricted beverages and over-the-counter medications. Participants were instructed to report any use of prescription or nonprescription medications, except those previously approved by the investigator (e.g., oral contraceptives). Participants were permitted alcohol in moderation after the evening capsule until bedtime, and cigarette smoking was not restricted. To verify compliance with the dietary restrictions, saliva samples were collected on an unspecified schedule throughout the study and intermittently switching them to caffeine. Participants were told that failure to comply with the dietary restrictions could result in discontinuation from the study and/or loss of study payments. Overall, data from seven participants (8.4% of those who

<table>
<thead>
<tr>
<th>Number of participants</th>
<th>Expt. 1</th>
<th>Expt. 2</th>
<th>Expt. 3</th>
<th>Expt. 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)</td>
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<td>4/13</td>
<td>8/11</td>
<td>5/20</td>
</tr>
<tr>
<td>Number of smokers</td>
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<td>5</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>Age (mean ± S.E. yr)</td>
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<td>29.5 ± 1.6</td>
<td>29.4 ± 1.6</td>
<td>30.4 ± 1.5</td>
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<tr>
<td>Prestudy caffeine</td>
<td>241 ± 30</td>
<td>277 ± 27</td>
<td>294 ± 65</td>
<td>263 ± 32</td>
</tr>
</tbody>
</table>

* An additional three participants in exp. 3 and four participants in exp. 4 were excluded from data analysis because of lack of compliance with caffeine dietary restrictions.
completed an experiment) were excluded from the data analyses because of noncompliance (Table 1).

### Daily Experimental Procedures

In all experiments, participants reported to the research unit in the morning (Monday through Friday) between 7:00 and 10:00 AM. As described below, they filled out a caffeine withdrawal questionnaire and the Profile of Mood States (POMS) questionnaire each morning (before the first capsule of the day). They then ingested a single capsule under the supervision of a research assistant and nurse and left the research unit. Participants returned to the research unit 4 to 6 h later at midday (12:00 PM) to fill out the two questionnaires and ingest another single capsule. Before leaving the unit at midday, participants were given two more sets of questionnaires to be filled out at 4:00 and 8:00 PM (in experiment 1, participants also were given another single capsule in a blister pack for 4:00 PM). Participants were instructed to fill out the third set of questionnaires and take the third capsule (experiment 1 only) approximately 4 to 6 h after the midday capsule (4:00 PM); the last set of questionnaires was to be filled out at approximately 8:00 PM. Participants recorded the times at which they filled out the forms and ingested capsules. The next morning (with the exception of weekends and holidays) participants returned the 4:00 and 8:00 PM forms. When participants returned to the research unit on Fridays for their midday capsule, they were provided with capsules and questionnaires for the remainder of Friday (4:00 and 8:00 PM) and the weekend. On Monday mornings, participants returned the empty blister packs and the questionnaires. On occasion, when participants knew they would be unable to return to the research unit on a weekday (e.g., doctor’s appointment, sick child, funeral, holiday, etc.), they were provided their capsules and questionnaires to take with them. Each participant was issued a digital watch (Casio Data Bank), which permitted setting of daily, multiple alarms to remind the participant when to take capsules, complete questionnaires, and provide saliva samples.

### Subjective-Effects Questionnaires

In all four experiments, participants completed a caffeine withdrawal questionnaire four times each day (approximately 8:00 AM before the first capsule of the day), 12:00 PM, 4:00 PM, and 8:00 PM. The 26 items were selected based on previous research (Griffiths et al., 1990a,b) as representing dimensions that are sensitive to caffeine withdrawal. In experiment 1, the caffeine withdrawal questionnaire had an additional seven items, but these were not used in the data analysis. Participants rated each of the 26 items on a 4-point scale from “not at all” (0) to “very much” (3), based on how they felt at the present time. The items included: 1) irritable/cross/grumpy, 2) alert/attentive/observer, 3) lightheaded/dizzy, 4) upset stomach, 5) well being, 6) blurred vision, 7) desire to socialize/talkativeness, 8) anxious/nervous, 9) urge to do task/work-related activities, 10) drowsy/sleepy, 11) ability to concentrate, 12) cerebral fullness, 13) muscle pain or stiffness, 14) yawning, 15) energy/active, 16) runny nose, 17) jittery/shaky, 18) depressed, 19) lethargy/fatigue/tired/sluggish, 20) muzzy/foggy/not clear-headed, 21) content/satisfied, 22) headache, 23) flu-like feelings, 24) sweating, 25) self-confidence, and 26) limb tremor.

In all four experiments, participants also completed the 65-item POMS questionnaire four times daily (approximately 8:00 AM before the first capsule of the day), 12:00 PM, 4:00 PM, and 8:00 PM. The POMS questionnaire is an adjective-rating questionnaire generally considered to be a standardized mood-state inventory (McNair et al., 1971) and has been shown previously to be sensitive to the effects of caffeine and caffeine withdrawal (Griffiths et al., 1990a,b; Evans and Griffiths, 1992; Silverman et al., 1992). Participants rated each of the 65 items on a 5-point scale from “not at all” (0) to “extremely” (4), based on how they felt at the present time. Seven empirically derived scales were scored for the 65-item version of the POMS: Tension-Anxiety, Depression-Dejection, Anger-Hostility, Vigor, Fatigue, Confusion-Bewilderment, and Friendly. One additional factor, Total Mood Disturbance, was calculated as a composite factor.

### Capsule Preparation and Dosing

For all experiments, caffeine and placebo capsules (size 0 gelatin) were prepared from combinations of caffeine-anhydrous (United States Pharmacopeia) and powdered lactose. The color of the capsules varied across participants, but the capsule color for a given participant remained the same throughout the study. Placebo and caffeine capsules were identical in appearance. In experiment 1 participants received one capsule three times each day and in experiments 2 through 4 they received one capsule two times each day. Capsules were ingested with approximately 150 ml of water in the presence of a nurse or research assistant, with the exception of the 4:00 PM (experiment 1) and weekend capsules. Participants, nurses, and research assistants were blind to drug conditions.

### Saliva Samples

On an unannounced quasi-random schedule, participants provided a 5-ml saliva sample in the morning before taking the first capsule of the day and again at 4:00 PM by expectorating directly into a test tube. On weekends and holidays participants were provided saliva tubes and labels in the event that samples were required; participants opened an envelope in the morning (before filling out the morning forms) that contained a piece of paper with “please give saliva samples today” or “no saliva samples today.” Participants were instructed to freeze or refrigerate saliva samples over the weekend and return them on Monday morning. All saliva samples were frozen and stored. Caffeine concentrations in selected samples were analyzed (Labstat Incorporated, Kitchener, Ontario, Canada) using gas chromatography with nitrogen-phosphorous detection and capillary column (modified from Jacob et al., 1981) with 5-methylcytosine as the internal standard for caffeine. If saliva samples indicated noncompliance with the dietary restrictions, all data from the participant were excluded from the analyses. The criterion for compliance was that, for a given individual, the caffeine concentration from a saliva sample after 2 days of placebo administration was 25% or less than the caffeine concentration from a saliva sample taken on the morning after receiving 300 mg of caffeine the previous day. There was no evidence of noncompliance in experiments 1 and 2; data from three participants in experiment 3 and from four participants in experiment 4 were excluded because of noncompliance.

### Individual Experiments

All four experiments used a within-subject, double-blind, crossover design with the order of dosing conditions in each experiment counterbalanced across participants.

#### Experiment 1: Interval of Caffeine Dosing.

Throughout the 63-day study, 15 participants ingested three capsules daily spaced 4 to 6 h apart (e.g., 8:00 AM, 12:00 PM, and 4:00 PM). Participants were maintained on 300 mg/day caffeine in capsules either as a single 300-mg dose in the morning and two placebo capsules in the afternoon or as 100-mg capsules three times a day. On the first day of the experiment, all participants received 100 mg of caffeine three times. When participants were exposed to the single 300-mg dose in the morning, the morning dose of caffeine was increased by 50 mg/capsule (with a corresponding decrease in the caffeine dose of the other two daily capsules) over a period of 4 days. To assess caffeine withdrawal, participants were administered caffeine for 5 to 9 consecutive days followed by the substitution of placebo capsules for 2 consecutive days. Participants then were returned to caffeine maintenance for 5 to 9 consecutive days. This sequence was repeated two more times, such that participants were exposed to three 2-day placebo substitutions at each dosing interval. At this time, participants were switched to the other dosing interval (i.e., either 300 mg...
in the morning or 100 mg three times a day) and were maintained on
the second dosing interval for 5 to 9 consecutive days before a 2-day
placebo substitution. As with the first dosing interval, participants
were exposed to three 2-day placebo substitutions.

**Experiment 2: Caffeine Maintenance Dose.** Throughout the
73-day study, 17 participants ingested two capsules daily spaced 4 to
6 h apart (e.g., 8:00 AM and 12:00 PM). Participants were main-
tained on either 100, 300, or 600 mg/day of caffeine given in two
equally divided doses each day. On the first day of the experiment all
participants received 50 mg of caffeine two times (100 mg/day). For
those participants assigned to one of the higher maintenance doses
first, the dose of caffeine was increased by 50 mg/capsule (100 mg/
day) to the scheduled maintenance dose. The scheduled maintenance
dose was maintained for at least 7 consecutive days before placebo
was substituted for 2 consecutive days. Participants then were re-
turned to caffeine maintenance dose for at least 7 consecutive
days. Then, participants were exposed to another 2-day placebo
substitution. This sequence was repeated for the other two caffeine
maintenance doses such that each participant was exposed to two
2-day placebo substitutions at each maintenance dose. Between dose
conditions, the dose of caffeine was gradually increased or decreased
by 100 mg/day (50 mg/capsule) until the new maintenance dose was
reached.

**Experiment 3: Suppression of Caffeine Withdrawal.** Throughout the
54-day study, 19 participants ingested two capsules daily spaced 4 to
6 h apart (e.g., 8:00 AM and 12:00 PM). Initially, participants were main-
tained on 300 mg/day of caffeine given in two
equally divided doses each day. Approximately every 7 days, a lower
dose of caffeine (300, 200, 100, 50, and 25 mg/day) or placebo was
substituted for 2 consecutive days. Within a given day, the substitu-
tion dose was divided equally between the two capsules. Participants
then were returned to the caffeine maintenance dose of 300 mg/day
for at least 7 consecutive days before participants were exposed to
another 2-day dose substitution. This sequence was repeated such
that each participant was exposed to all six dose substitutions.

**Experiment 4: Duration of Caffeine Exposure.** Throughout the
60-day study, 25 participants ingested two capsules daily spaced 4 to
6 h apart (e.g., 8:00 AM and 12:00 PM). For the first 7 days, all
participants were maintained on placebo in capsules given twice a
day. After this placebo “washout” week, participants were adminis-
terminated caffeine (300 mg/day given in two equally divided doses)
for either 1, 3, 7, or 14 consecutive days. Each duration of caffeine
exposure was followed by 7 consecutive days of placebo, and each
participant was exposed to all caffeine durations.

**Data Analysis**

**Cluster Analysis.** The 26 items of the caffeine withdrawal ques-
tionnaire were subjected to a hierarchical cluster analysis. This was
done to reduce the number of measures and facilitate the analyses
because the symptoms and severity of caffeine withdrawal for any
single dimension can vary both within and across individuals (see
Griffiths et al., 1990a; Griffiths and Mumford, 1995). All participants
across the four experiments were exposed to a condition in which
they were maintained on 300 mg/day caffeine followed by a 2-day (or
more) placebo substitution. Thus, a total of 76 individuals were
included in the cluster analysis. For experiments 1 through 3, the
peak ratings over the 2 caffeine days immediately preceding placebo
substitution were compared with the peak ratings over the 2 placebo
days for each item separately, using the first exposure to a 300-mg/
day caffeine and 2-day placebo substitution. For experiment 4, the
peak ratings over the last 2 days of the 14 consecutive 300-mg/day
caffeine condition were compared with the peak ratings over the first
2 days of placebo after the 14-day caffeine condition. Peak effect over
2 days was used because maximal withdrawal symptoms occur
within 24 to 48 h after the cessation of caffeine (e.g., Dreisbach and
Pfeiffer, 1943; Griffiths et al., 1990a; Evans and Griffiths, 1992).
Peak effect for each item was based on the expected direction during
caffeine withdrawal. The maximum value was calculated for items 1,
3, 4, 6, 8, 10, 12, 13, 14, 16, 17, 18, 19, 20, 22, 23, 24, and 26. The
minimum value was calculated for items 2, 5, 7, 9, 11, 15, 21, and 25.

A biostatistician blind to the experimental designs, as well as to
the actual items from the caffeine withdrawal questionnaire, con-
ducted the cluster analysis. The hierarchical cluster analysis began
with as many clusters as variables. The two variables “closest” to-
gether (based on a Euclidean distance measure) were combined to
form a new cluster at the first step. Succeeding steps combined the
two variables (or a variable with an already created cluster) “closest”
together. This process continued until the original variables were
reduced to a small number of clusters. Solutions of two through five
clusters were examined, and the five-cluster solution was deemed
reasonable. The choice of the actual number of clusters was based on
scientific, rather than statistical, grounds. Cluster 1 (Headache/Poor
Mood) consisted of four items: irritable/cross/grumpy, anxious/nerv-
ous, depressed, and headache. Cluster 2 (Activity/Alertness) con-
stisted of eight items: alert/attentive/observant, well being, desire to
socialize/talkativeness, urge to do task-work-related activities, abil-
ity to concentrate, energy/active, content/satisfied, and self-confi-
dence. Cluster 3 (Physical Symptoms) consisted of eight items: light-
headed/dizzy, upset stomach, blurred vision, cerebral fullness,
jittery/shaky, buzzy/foggy/not clear-headed, sweating, and limb
tremor. Cluster 4 (Tiredness) consisted of three items: drowsy/
sleepy, yawning, and lethargy/fatigue/tired/sluggish. Cluster 5 (Flu-
Like Symptoms) consisted of three items: muscle pain or stiffness,
runny nose, and flu-like feelings.

For each of the four experiments, all data for the caffeine with-
drawal questionnaire were analyzed using the five derived clusters
described above. In addition, because headache is often considered to
be a cardinal feature of caffeine withdrawal and is the most fre-
quently reported symptom in caffeine withdrawal studies (Griffiths
and Mumford, 1995), this item was analyzed separately for each
experiment. Lastly, for the POMS questionnaire, each of the eight
subscapes was analyzed separately, again using the peak ratings of
the 2 caffeine days compared with the peak ratings of the 2 placebo
(or caffeine) substitution days (experiments 1–3) or the peak ratings
of the last 2 days of the 14 consecutive 300 mg/day caffeine condition
compared with the peak ratings of the first 2 days of placebo after
the 14-day caffeine condition (experiment 4). The minimum value was
calculated for Vigor and Friendly, and the maximum value was
calculated for the other six subscales.

**Experiment 1: Interval of Caffeine Dosing.** A three-factor
repeated-measures ANOVA was conducted for each of the five
clusters from the caffeine withdrawal questionnaire, headache, and each
of the eight subscales of the POMS questionnaire, using the peak
ratings (i.e., maximum or minimum values as defined above) over
the 2 caffeine days immediately preceding each 2-day placebo
substitution and the peak ratings over each 2-day placebo substitution.
The three factors were Drug (caffeine versus placebo), Number of
daily doses (once a day versus three times a day), and Replication
(three replications). Planned comparisons (two-tailed tests) were
conducted to examine differences between caffeine and placebo by
collapsing data across the number of daily doses and replications.

**Experiment 2: Caffeine Maintenance Dose.** A three-factor
repeated-measures ANOVA was conducted for each of the measures
as described above for experiment 1. The three factors were Drug
(caffeine versus placebo), Maintenance dose (100 versus 300 versus
600 mg/day), and Replication (two replications). Planned compari-
sions (two-tailed tests) were conducted to 1) examine differences
between caffeine and placebo for each caffeine maintenance dose
and 2) examine differences between the placebo substitution at the
600-mg dose and the placebo substitution at the 100-mg dose.

**Experiment 3: Suppression of Caffeine Withdrawal.** A two-
factor repeated-measures ANOVA was conducted for each of the
measures using the peak ratings over the 2 caffeine maintenance
days immediately preceding each 2-day dose substitution and the
peak ratings over each 2-day dose substitution. The two factors were
Drug (caffeine maintenance versus dose substitution) and Dose Sub-
stitution (300 mg versus 200 mg versus 100 mg versus 50 mg versus 25 mg versus placebo). Planned comparisons (two-tailed tests) were conducted to 1) examine differences between caffeine maintenance and dose substitution for each of the six dose substitutions and 2) examine differences between the placebo dose substitution and each of the other five dose substitutions.

Experiment 4: Duration of Caffeine Exposure. A one-factor repeated-measures ANOVA was conducted for each of the measures. There were five drug conditions in the ANOVA: peak ratings over the last 2 days of the 14 consecutive 300-mg/day caffeine condition and peak ratings over the first 2 days of placebo immediately after each caffeine duration (1, 3, 7, and 14 days). Planned comparisons (two-tailed tests) were conducted to 1) examine differences between caffeine and placebo after each duration of caffeine and 2) examine differences between the placebo days.

Effects were considered to be significant for \( p \leq 0.05 \), using Huynh-Feldt corrections when appropriate.

**Results**

Caffeine Withdrawal Across All Participants. Caffeine withdrawal for all 76 participants across the 4 experiments was determined using their initial exposure to placebo after maintenance on 300 mg/day caffeine. Table 2 shows that substitution of placebo for caffeine significantly increased Headache, Headache/Poor Mood, Tiredness, Fatigue (POMS), Confusion-Bewilderment (POMS) and Total Mood Disturbance (POMS) and decreased Activity/Alertness, Vigor (POMS), and Friendly (POMS).

Experiment 1: Interval of Caffeine Dosing. The ANOVA showed no significant differences between the two dosing intervals with regard to caffeine withdrawal symptoms. As shown in Table 2, the planned comparisons between caffeine and placebo, collapsed across the two dosing intervals and the three replications, revealed significant changes on eight scales. Figure 1 shows that compared with days on which participants were maintained on caffeine, substitution of placebo was associated with significant increases in Headache (\( p < 0.001 \)), Headache/Poor Mood (\( p = 0.017 \)), Tiredness (\( p = 0.003 \)), Flu-Like Symptoms (\( p = 0.001 \)), Fatigue (POMS; \( p = 0.036 \)), and decreases in Vigor (POMS; \( p = 0.025 \)). Activity/Alertness (\( p = 0.018 \)) and Friendly (POMS; \( p = 0.043 \)) also showed decreases. Taken together, these results indicate that 300 mg/day caffeine results in a reliable caffeine withdrawal syndrome when placebo is substituted and that caffeine withdrawal occurs whether 300 mg of caffeine is ingested as a single dose in the morning or as three divided doses over the day.

**TABLE 2**

Summary of significant results for all 76 participants and for each of the four experiments

<table>
<thead>
<tr>
<th>Measure**</th>
<th>All Participants** (( n = 76 ))</th>
<th>Expt. 1***</th>
<th>Expt. 2****</th>
<th>Expt. 3****</th>
<th>Expt. 4****</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Dose Effects</td>
<td>Suppression of Withdrawal</td>
<td>Duration of Exposure (No. Days)</td>
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<tr>
<td></td>
<td></td>
<td>300 versus 0</td>
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<td>300 versus 0</td>
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<tr>
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<td>0.005</td>
<td>0.001</td>
<td>0.001</td>
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<tr>
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<td>0.018</td>
<td>0.016</td>
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<td>Physical symptoms</td>
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<td>Tiredness</td>
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<td>0.011</td>
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<td>POMS**</td>
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<td>0.009</td>
<td>0.043</td>
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<tr>
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<td>0.013</td>
<td>0.013</td>
<td>0.027</td>
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For all significant effects shown, substitution of placebo or lower caffeine doses (expt. 3) increased all measures relative to caffeine except for Activity/Alertness, Vigor (POMS), and Friendly (POMS), which were decreased significantly, as indicated by down arrow.

Comparison between last 2 days of caffeine (300 mg/day) and first 2-day placebo substitution (0 mg/day) across all four experiments.

Comparison between last 2 days of caffeine (300 mg/day) and 2-day placebo substitutions for data collapsed across two dosing intervals and three replications.

Comparison between last 2 days of each caffeine maintenance dose and corresponding 2-day placebo substitution.

Comparison between last 2 days of caffeine (300 mg/day) and corresponding 2-day dose substitution.

Comparison between last 2 days of 14-day caffeine condition (300 mg/day) and first 2 days of placebo substitution after each of the caffeine exposures (i.e., 1, 3, 7, or 14 days of 300 mg/day caffeine).

Comparison between last 2 days of caffeine (300 mg/day) and 2-day placebo substitutions for data collapsed across two dosing intervals and three replications.

Comparison between last 2 days of caffeine (300 mg/day) and corresponding 2-day dose substitution.

Comparison between last 2 days of 14-day caffeine condition (300 mg/day) and first 2 days of placebo substitution after each of the caffeine exposures (i.e., 1, 3, 7, or 14 days of 300 mg/day caffeine).

No value indicates comparison was not statistically significant at \( p \geq 0.05 \).

Three POMS scales (Anger-Hostility, Depression-Dejection, Tension-Anxiety) are not shown in this table because they did not show significant caffeine withdrawal effects in any experiment.
To assess compliance with the dietary restrictions, caffeine concentrations in 8:00 AM saliva samples were analyzed from mornings immediately after 300 mg/day of caffeine, after 1 day of placebo, and after 2 days of placebo administration. A minimum of two caffeine samples and four placebo samples were analyzed for each participant. Caffeine concentrations were clearly elevated after overnight abstinence from 300 mg/day (0.98 ± 0.26 µg/ml), and these concentrations dropped considerably over the first 0.13 ± 0.05 µg/ml) and second day (0.06 ± 0.04 µg/ml) of placebo substitution, indicating compliance with the dietary restrictions. These concentrations are consistent with previous studies of caffeine abstinence (Griffiths et al., 1990a; Evans and Griffiths, 1992; Evans et al., 1994).

Experiment 2: Caffeine Maintenance Dose. Based on the ANOVA, significant Drug × Dose interactions were obtained on 9 of the 14 scales (Headache, Headache/Poor Mood, Activity/Alertness, Tiredness, Vigor (POMS), Fatigue (POMS), Confusion-Bewilderment (POMS), Friendly (POMS), Total Mood Disturbance (POMS); data not shown). Consistent with the ANOVA, the planned comparisons shown in Table 2 indicate that relative to data from days on which participants received caffeine, substitution of placebo was associated with significant changes in 5 scales when maintained on 100 mg/day, 6 scales when maintained on 300 mg/day, and 10 of the 14 scales when maintained on 600 mg/day caffeine. In addition, when the placebo substitution after 600 mg/day caffeine was compared with the placebo substitution after 100 mg/day caffeine, there were significant differences in the magnitude of effect, with the highest dose showing greater caffeine withdrawal. Placebo substituted after 600 mg caffeine was significantly different than placebo substituted after 100 mg caffeine for Headache (p < .001), Headache/Poor Mood (p < .001), Depression-Dejection (POMS; p = 0.016), Friendly (POMS; p = 0.007), and Total Mood Disturbance (POMS; p < .001).

Figure 2 shows the results from four representative measures that showed a significant caffeine-versus-placebo difference for at least one caffeine maintenance dose. Placebo substitution significantly increased Tiredness scores at each caffeine maintenance dose, and there were no significant differences in the magnitude of caffeine withdrawal between the caffeine maintenance doses. In contrast, Headache/Poor Mood, Activity/Alertness, and Headache all showed a dose-related caffeine withdrawal. Headache/Poor Mood scores were increased significantly only when placebo was substituted for 600 mg/day caffeine. For Activity/Alertness scores, there was no evidence of withdrawal when placebo was substituted for 100 mg/day caffeine, whereas substitutions of placebo for 300 and 600 mg/day caffeine were significantly different from caffeine, with the magnitude of withdrawal similar at both of these maintenance doses. Ratings of Headache were increased significantly when placebo was substituted for each of the caffeine maintenance doses, although the magnitude was significantly higher when placebo was substituted for 600 mg/day caffeine than when substituted for 100 mg/day caffeine.

To assess caffeine concentrations and compliance with the dietary restrictions, a caffeine and a placebo sample were analyzed for each dose condition in each participant. For the caffeine conditions, the 8:00 AM saliva samples were analyzed from days immediately after each of the three caffeine maintenance dose conditions (100, 300, or 600 mg/day caffeine), thus reflecting residual caffeine levels. Morning caffeine concentrations were an increasing function of caffeine maintenance dose (mean ± SE: 0.02 ± 0.07 µg/ml, 0.90 ± 0.26 µg/ml, and 2.60 ± 0.78 µg/ml at 100, 300, and 600 mg, respectively). For the placebo conditions, saliva samples were collected on the morning after the second placebo day, which was approximately 60 h after the last caffeine dose. Although caffeine concentrations continued to be an increasing function of previous caffeine maintenance dose (mean ± SE: 0.008 ± 0.003 µg/ml, 0.012 ± 0.005 µg/ml, and 0.028 ± 0.014 µg/ml at 100, 300, and 600 mg, respectively), the absolute caffeine concentrations were substantially lower, thus indicating compliance with the dietary restrictions.

Experiment 3: Suppression of Caffeine Withdrawal. The ANOVA showed no overall effects of Drug, but did show significant Dose Substitution effects for Activity/Alertness (p = 0.029), Tiredness (p = 0.002), Fatigue (POMS; p = 0.009), and Total Mood Disturbance (POMS; p = 0.039) and Drug × Dose Substitution interactions for Headache (p = 0.009) and Vigor (POMS; p = 0.026). The planned comparisons between each 2-day dose substitution and the corresponding 2-day period of 300-mg/day caffeine maintenance showed that substitution of lower caffeine doses or no caffeine (placebo) resulted in an increased number of withdrawal symptoms. Table 2 shows that relative to when participants received 300 mg/day caffeine, substitution of either the maintenance dose (300 mg/day caffeine) or 200 mg/day caffeine was not associated with any significant changes in mood. In contrast, substitution of 100, 50, 25, or 0 mg/day caffeine was associated with significant changes in two, one, three, and seven scales, respectively.
Figure 3 shows the results from four representative measures that showed a significant caffeine maintenance versus dose substitution difference for at least one dose substitution. Ratings of Headache and Headache/Poor Mood were significantly increased compared with the caffeine maintenance dose condition only when placebo was substituted, although ratings of Headache and Headache/Poor Mood scores tended to increase as the dose of caffeine substituted decreased. Activity/Alertness scores were decreased significantly compared with the caffeine maintenance dose when both 25 mg/day caffeine and placebo were substituted. Lastly, Tiredness scores showed the broadest range of effects in that scores were decreased significantly after the substitution of 100, 50, and 25 mg/day caffeine and placebo.

Similar to experiment 2, only 8:00 AM saliva samples were analyzed from mornings immediately after participants received 300 mg/day caffeine and from mornings after the second day of the 2-day placebo substitution. For each participant, a 300-mg/day caffeine and a placebo sample were analyzed. The concentrations of caffeine in saliva from the caffeine maintenance condition of 300 mg/day were 0.70 ± 0.20 μg/ml, whereas the concentrations of caffeine after the second day of the 2-day placebo substitution were 0.02 ± 0.01 μg/ml, indicating compliance with the dietary restrictions.

Experiment 4: Duration of Caffeine Exposure. Based on the ANOVA, significant Drug effects were obtained on 5 of the 14 scales [Headache, Headache/Poor Mood, Physical Symptoms, Tiredness, Fatigue (POMS); data not shown]. Table 2 shows that compared with when participants were maintained on caffeine (300 mg/day), substitution of placebo was associated with significant changes on no scales after a single day of caffeine exposure, and on four or more scales after 3 or more days of caffeine exposure. These findings indicate that caffeine withdrawal can develop when placebo is substituted for caffeine after a brief period of exposure to caffeine, i.e., as little as 3 days.

Figure 4 shows the results from four representative measures that showed a significant caffeine versus placebo difference for at least one duration of caffeine exposure. Both Headache/Poor Mood and Tiredness scores were increased significantly compared with caffeine when placebo was substituted after a duration of 3, 7, and 14 consecutive days of 300 mg/day caffeine. Furthermore, the magnitude of Headache/Poor Mood scores after 7 and 14 days of caffeine exposure were significantly greater than after 1 day of caffeine exposure. Similarly, ratings of Headache tended to increase when placebo was substituted after 3 days of caffeine exposure (p < .057) and were increased significantly compared with caffeine when placebo was substituted after a duration of 7 and 14 consecutive days of 300 mg/day caffeine. In addition, the magnitude of Headache was significantly different between the single day of caffeine exposure and the 14 days of caffeine exposure. Lastly, Activity/Alertness scores were decreased significantly compared with the caffeine maintenance dose only when placebo was substituted after 3 and 7 days of caffeine exposure.

Saliva samples from 8:00 AM were analyzed for caffeine content from mornings immediately after participants were maintained on 300 mg/day caffeine for at least 5 consecutive days (i.e., the 7- and 14-day caffeine duration) and when
participants were maintained on placebo. Thus, for each participant, two caffeine samples and a placebo sample from each of the 5 placebo weeks were analyzed. The concentrations of caffeine in saliva from the caffeine maintenance condition of 300 mg/day were 1.07 ± 0.16 μg/ml, whereas the concentrations of caffeine after the second day of the 2-day placebo substitution were 0.02 ± 0.01 μg/ml, indicating compliance with the dietary restrictions.

Discussion

The present study provides the most comprehensive parametric experimental analysis to date of the dosing conditions necessary for the development of caffeine physical dependence as expressed by caffeine withdrawal symptoms upon abrupt cessation of caffeine administration. A particular strength of the present study is that each of the four parametric experiments was conducted using the same general procedure in a different group of moderate daily caffeine consumers.

Caffeine Withdrawal Symptoms

The present study confirms and extends previous findings regarding the symptoms associated with the cessation of caffeine consumption. The major symptom clusters that were affected significantly in each of the four experiments (cf. Table 2) were increases in Headache, Headache/Poor Mood (including irritability, anxiety, feelings of depression), Tiredness (drowsy, yawning, lethargy), Fatigue (POMS), and Total Mood Disturbance (POMS) and decreases in Activity/Alertness (alertness, well being, desire to socialize, urge to do task-related activities, concentration, energy, satisfaction, self-confidence) and Vigor (POMS). These symptom clusters overlap with the four most prominent symptom clusters summarized in a recent comprehensive review by Griffiths and Mumford (1995) of the caffeine withdrawal literature: headache, drowsiness, work difficulty (decreased motivation for work/tasks, impaired concentration), and decreased well being/contentment (including decreased self-confidence, increased irritability). The present results also provide weak support for two less prominent symptom clusters cited in the Griffiths and Mumford (1995) review: decreased friendliness and flu-like symptoms. As shown in Table 2, decreased Friendly (POMS) and Flu-Like Symptoms were intermittently sensitive to the caffeine withdrawal manipulations across the four experiments.

Frequency of Caffeine Dosing

In experiment 1 (caffeine dosing interval), there was no clear evidence that the range or magnitude of caffeine withdrawal symptoms differed when 300 mg caffeine was consumed as a single dose in morning versus as 100 mg at three time points across the day. These findings, in combination with the existing literature, are intriguing given that caffeine withdrawal has been well documented after caffeine consumption in a number of studies that have varied widely with respect to dose and dosing frequency across the day. For example, many studies allowed participants to self-administer caffeine, ranging from 25 to 400 mg/dose, anywhere from four times a day to ad libitum consumption (e.g., Griffiths et al., 1986a,b; Hughes et al., 1991; Oliveto et al., 1992; Evans et al., 1994). Similarly, other studies using experimenter-determined caffeine intake documented caffeine withdrawal when individuals were consuming caffeine twice a day (Silverman et al., 1992; Schuh and Griffiths, 1997) or up to 10 times per day (Griffiths et al., 1990a). Taken together with the present findings, it appears that daily consumption of caffeine, irrespective of the pattern of intake across the day, can result in physical dependence and subsequent withdrawal upon the termination of caffeine intake.

It is intriguing that even once-a-day dosing with caffeine is sufficient to produce physical dependence. Although caffeine is eliminated relatively quickly, its mean half-life of about 5 h (Denaro and Benowitz, 1991) is apparently long enough to maintain significant caffeine exposure even under a once-a-day dosing regimen. It is well established that there is wide interindividual variation in caffeine elimination rates, with half-lives varying over a 13-fold range (Denaro and Benowitz, 1991; Balough et al., 1992). Thus, it is plausible that individuals who have very short caffeine half-lives (e.g., <2 h) might not develop caffeine physical dependence if they restricted their caffeine intake to a short period each day.

Caffeine Maintenance Dose

The results of experiment 2 (dose effects) provide the first prospective experimental demonstration that both the range and magnitude of caffeine withdrawal symptoms are related to the caffeine maintenance dose. The number of symptom/cluster scales that were altered significantly after the substitution of placebo increased as a function of the daily caffeine maintenance dose (5, 6, and 10 scales at 100, 300, and 600 mg/day caffeine, respectively). In addition, the magnitude of withdrawal effect was greater at 600 mg/day caffeine than 100 mg/day caffeine on several measures including Headache, Headache/Poor Mood, Depression-Depression (POMS), Friendly (POMS), and Total Mood Disturbance (POMS). These results are consistent with previous studies that reported that the incidence of caffeine withdrawal increased as a function of daily self-reported caffeine dose (e.g., Goldstein and Kaizer, 1969; Goldstein et al., 1969; Galletly et al., 1989; Fennelly et al., 1991; Weber et al., 1993).

Experiment 2 also documented that significant caffeine withdrawal symptoms can occur after maintenance on as little as 100 mg/day caffeine. The only other study to document caffeine withdrawal after such a low caffeine dose (100 mg/day) involved a select subject population, i.e., a group of behavioral pharmacologists who had been maintained on this dose for a relatively long period of time and had been trained previously to discriminate low doses of caffeine from placebo (Griffiths et al., 1990a,b). A provocative implication of the results of experiments 1 and 2, taken together, is that individuals who consume as little as a single 6-oz. cup of brewed coffee (which is known to deliver about 100 mg of caffeine; Barone and Roberts, 1996) each morning are at risk for experiencing headache and other withdrawal symptoms should they omit their daily single cup of coffee.

Suppression of Caffeine Withdrawal

The results of experiment 3 (suppression of caffeine withdrawal) indicate that when individuals are maintained on 300 mg/day caffeine, a substantial reduction in caffeine consumption, or complete elimination, is necessary for the manifestation of the full, classic withdrawal syndrome. Only when the dose was reduced to 100 mg/day (one-third the maintenance dose) was there any evidence of caffeine withdrawal. In fact, the withdrawal observed tended to be relatively mild and variable even when a mere 25 mg of caffeine was substituted for the maintenance dose of 300 mg, although ratings of Headache tended to increase as the dose of caffeine decreased (cf.
Fig. 4). Based on this experiment, the most sensitive caffeine withdrawal symptoms to emerge after a reduction in caffeine dose were Tiredness and Fatigue (POMS). This is consistent with observations from other studies of caffeine withdrawal suggesting that the onset of symptoms such as fatigue and sleepiness occurs before the onset of headache (Dreisbach and Pfeiffer, 1943; Goldstein et al., 1969; Bruce et al., 1991).

The observation that caffeine withdrawal is largely suppressed by even low caffeine doses emphasizes the methodological importance that research involving caffeine withdrawal or requiring caffeine abstinence should confirm abstinence by assessing caffeine concentrations in biological samples such as saliva. Unfortunately, many studies have failed to biologically confirm caffeine abstinence, which may reduce the apparent prevalence of caffeine withdrawal symptoms (e.g., Smith, 1996). Also, the suppression of caffeine withdrawal by low caffeine doses may account for different estimates of the incidence of caffeine withdrawal based on experimental studies versus retrospective questionnaires. In experimental studies that have biologically verified caffeine abstinence, the incidence of withdrawal headache ranges between 42 and 86% (52%, Silverman et al., 1992; 86%, Griffiths et al., 1990a; 45%, Lader et al., 1996; 42%, van Dusseldorp and Katan, 1990). In contrast, retrospective surveys often have indicated that a smaller proportion of moderate or heavy caffeine users report experiencing caffeine withdrawal headache (8–9%, Goldstein and Kaizer, 1969; ≤10%, Winstead, 1976; 11%, Greden et al., 1978; 27%, Hughes, 1992). It seems possible that, in the retrospective surveys, people who report not experiencing headache after caffeine abstinence may have been unaware of relatively low-dose sources of caffeine (such as caffeinated soft drinks or chocolate) that might effectively suppress withdrawal headache on occasions when they do not consume their usual source of caffeine (such as coffee), and thus erroneously assumed themselves to be caffeine abstinent.

The observation that low doses of caffeine suppress caffeine withdrawal may also explain some of the variability observed in studies assessing the reinforcing effects of caffeine in regular caffeine consumers. Among several double-blind studies using caffeine-versus-placebo-choice procedures in normal volunteers, the percentage of individuals showing significant caffeine choice has ranged from a low of 10% (Oliveto et al., 1992) to a high of 82% (Evans et al., 1994), even though caffeine withdrawal was observed in most of these studies on days when participants were exposed to placebo (e.g., Griffiths and Woodson, 1988b; Hughes et al., 1992). Studies that use a concurrent caffeine-versus-placebo-choice procedure (e.g., Oliveto et al., 1992), do not provide as strong a test of caffeine reinforcement as studies that use a mutually exclusive choice procedure (e.g., Evans et al., 1994). For example, a recent study (Mitchell et al., 1995) assessed caffeine (coffee) self-administration after various levels of caffeine deprivation by using a money-versus-coffee concurrent schedule procedure. These authors concluded that caffeine withdrawal was not a reliable predictor for subsequent caffeine self-administration because the volume of coffee consumed did not increase with increases in deprivation time. Given that even low doses of caffeine can suppress withdrawal, the failure to use a mutually exclusive choice procedure provides a relatively weak test of the hypothesis that deprivation affects caffeine reinforcement. Indeed, several recent studies that have used mutually exclusive choice procedures have shown that deprivation clearly increases the reinforcing effects of caffeine (Schuh and Griffiths, 1997; Garrett and Griffiths, 1998).

**Duration of Caffeine Exposure.** Experiment 4 (duration of caffeine exposure) showed that relatively short-term exposure (as few as 3 consecutive days) to intermediate doses of caffeine (300 mg/day) is sufficient to produce withdrawal symptoms when caffeine dosing is terminated. As shown in Table 2 and Fig. 4, the withdrawal tended to be somewhat greater after 7 days of caffeine exposure, with no further increases after 14 days of caffeine exposure. To our knowledge, only two previous studies have provided information suggesting that caffeine withdrawal can occur after relatively short durations of caffeine exposure (Dreisbach and Pfeiffer, 1943; Griffiths et al., 1988a). Both studies showed caffeine withdrawal headache upon termination of high caffeine doses (terminal doses ≥600 mg/day) administered for 6 to 15 days. Thus, the present study documents caffeine withdrawal after lower doses and shorter exposure durations than previously shown.

**Limitations.** Although the present series of experiments represents the most complete analysis to date of caffeine physical dependence in humans, there were some uncontrolled factors that could have affected the data. First, urine drug screens were not performed on individuals during these experiments. However, an interview, a questionnaire, and a urine drug screen before the study indicated that none of these individuals used illicit drugs. Second, menstrual cycle and related symptoms were not tracked in female participants. Thus, it is unknown how any possible extraneous drug use and any menstrual cycle phase changes could have affected the results. However, given the robust and orderly parametric findings across the four experiments (which were each of about 2 months duration) and the fact that the experiments used double-blind, counter-balanced designs, it seems unlikely that these uncontrolled factors would have altered the major conclusions of these experiments.

In summary, the present series of parametric experiments confirms and extends previous studies of caffeine withdrawal (see reviews by Griffiths and Woodson, 1988a; Griffiths and Mumford, 1995) and suggests that caffeine physical dependence can occur under more modest conditions (i.e., fewer doses per day, lower daily dose, and shorter duration of exposure) than previously recognized. Significant caffeine withdrawal symptoms can occur reliably when individuals are maintained on as little as 100 mg caffeine each day, and the severity of caffeine withdrawal is an increasing function of the caffeine maintenance dose. Administration of caffeine as a single daily dose produces physical dependence similar to that produced by three divided doses over the day, suggesting that the daily dose of caffeine consumed is more relevant to the development of caffeine dependence than the pattern of caffeine intake within the day. Furthermore, caffeine withdrawal occurs after as little as 3 consecutive days of caffeine exposure, with a somewhat increased severity of withdrawal observed after a week of caffeine exposure. A final experiment showed that, when individuals were maintained on 300 mg caffeine/day, a substantial reduction in caffeine consumption, or complete elimination, is necessary for the manifestation of the full, classic withdrawal syndrome. As a whole, this set of experiments provides the most
complete parametric characterization of caffeine withdrawal to date.

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References