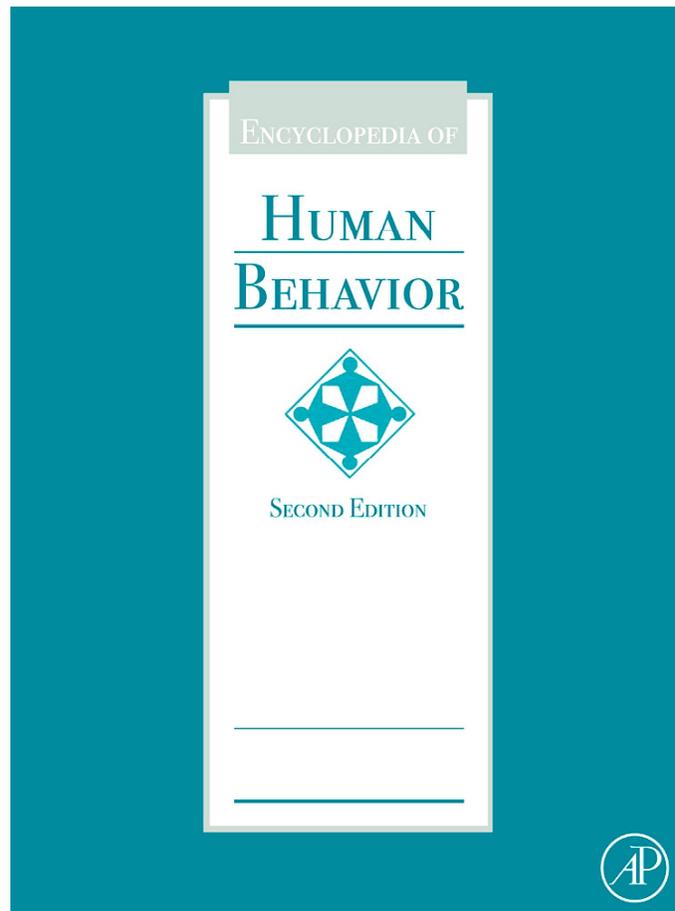


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Revelle W., Condon D.M., and Wilt J. (2012) Caffeine. In: V.S. Ramachandran (ed.) The Encyclopedia of Human Behavior, vol. 1, pp. 423-429. Academic Press.

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## Caffeine

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### Glossary

**Adenosine** A neuromodulator associated with regulating the degree of alertness in central nervous system functioning. A1 adenosine receptors inhibit excitatory neurotransmitters, while A2 receptors facilitate neurotransmission by inhibiting A1 receptors.

**Affect** The feeling state associated with an emotion. Affect is typically used in terms of direction of approach (positive affect) and avoidance (negative affect). It is most typically measured by self-reports of positive and negative affect.

**Arousal** A construct used to organize the common behavioral effects of exercise, stimulant drugs, sleep deprivation (negatively), time of day, and time on task. Arousal is associated with feelings of energy and tension. It is better thought of in terms of the two independent dimensions of energetic arousal and tense arousal. It typically involves increases in heart rate, blood pressure, skin conductance, and other autonomic indicators.

**Caffeinism** Chronic psychological distress, including sleep and anxiety disorders, associated with high levels of caffeine consumption.

**Dose response** The shape of the relationship between increasing dosage levels (measured in mg of caffeine/kg of body weight) with physical or psychological responses.

**Energetic arousal** One of the two dimensions of arousal, associated with self-reports of feeling energetic, lively, alert versus sleepy, tired, and drowsy. It is correlated with but separable from positive affect.

**Negative affect** A second unipolar dimension of affect. It is associated with self-reports of feeling sad, blue, unhappy, and depressed.

**Positive affect** One of the two unipolar dimensions of affect. It is associated with self-reports of feeling happy, pleased, delighted, and satisfied.

**Tense arousal** A second dimension of arousal, associated with self-reports of feeling scared, tense, nervous, afraid versus calm, relaxed, and at ease. It is correlated with but separable from negative affect.

**Vigilance task** It is a monotonous task, typically requiring a rapid response to the detection of an infrequently occurring event. Most vigilance tasks require sustained performance over a long period.

**Withdrawal** Symptoms associated with an abrupt cessation of consumption of a drug (e.g., caffeine).

### Introduction

Caffeine and its fellow xanthines, theophylline and theobromine, are the most consumed drugs in the world, surpassing alcohol and nicotine for popularity and universality. Caffeine, normally associated with coffee, is also a major ingredient of tea, as is theophylline, and is even found in chocolate, a source of theobromine. Caffeine may also be found in the kola nut (chewed in Africa), yerba mate (taken with hot water in South America), and guarana seeds (primarily added to soft drinks in Brazil but also included in various 'natural food supplements'). Moderate doses of caffeine enhance mood, alertness, and physical endurance, but at the cost of increased tolerance with use and withdrawal symptoms of severe headache, fatigue, and dysphoria. The affective, behavioral, and cognitive consequences of caffeine consumption are generally positive for moderate doses, but can lead to clinical diagnoses of anxiety disorder, as well as to physical tremor, twitching, and cognitive impairment at higher levels. Besides the obvious sources of coffee and tea, caffeine is also included as an active ingredient of colas, energy drinks, and energy bars, sold in over-the-counter pill or lozenge form, and is added to many over-the-counter and prescription drugs to alleviate other side effects.

Perhaps because of its common usage and lack of apparent danger, caffeine is generally not even considered a drug. Indeed, its very ubiquity makes it very much a part of modern society and hard to think of as a psychoactive drug. However,

given that its effects are similar to those of many other psychoactive drugs, if caffeine were to be discovered today, it is quite likely that it would be illegal or at least seriously regulated. Indeed, unsuccessful attempts at regulating caffeine have occurred since coffee's first introduction into Arabia and Europe.

Coffee came to Europe and then the rest of the world from Arabia (probably starting in Yemen) or Ethiopia where the legendary Ethiopian goat herder, Kaldi, saw his goats chew on the red berries of a bush and then show great energy. Trying the berries himself is said to have led him to the joys of coffee. More likely is that warriors of Ethiopia used a mixture of ground coffee beans and animal fat to provide nourishment and energy while conducting raids on their neighbors. This mixture spread to Arabia and then by the late sixteenth century to the rest of the world. However, tea had been consumed in India and China for millennia before being introduced to Europeans searching for spices. The guarana seed was a source of caffeine in pre-Columbian South America and remains a major source of caffeine in South America and in 'health food' stores. The introduction of coffee and tea into Europe as sources of caffeine had a revolutionary impact.

The ubiquity of caffeine and its cousins as drinks and candies around the world testifies to the ease of preparation and its perceived benefits for thinking clearly and feeling alert. Some attribute the European Enlightenment and subsequent Industrial Revolution to the introduction of coffee to Europe

in the early seventeenth century and the resulting replacement of beer by coffee or tea in workers' and intellectuals' diet. (The boiling of water necessary for tea and coffee purified the drinking water, making it a safe alternative to beer for breakfast. Workers could thus work longer and intellectuals argue with greater logic than had they started their day with beer.) Joining the classic association with writers and musicians who praised (and used) the powers of coffee (cf. Balzac, Johnson, Bach, Mozart), it is difficult today to think of software developers or college students without a nearby espresso maker, cans of cola, or more powerful forms of caffeine ('energy drinks'). A wonderful statement about the powers of caffeine frequently is attributed to the Hungarian mathematician, Erdos, although probably was made by his colleague, Rényi, who claimed that 'A mathematician is a machine for turning coffee into theorems.'

A negative consequence of the introduction of coffee and tea to Europe and then to the rest of the world was similar to the later introduction of electric lights: By allowing people to stay awake when tired or when it is dark, caffeine and the electric light have modified our sleep patterns in a manner that leads to sleep deprivation and insomnia. A society without caffeine or electricity is bound to the natural rhythms of daylight and spends more time sleeping than does one with caffeine and artificial lighting.

### Sources and Consumption of Caffeine

Caffeine is typically consumed by drinking coffee or tea, although it is also found in chocolate, many soft drinks, and a variety of over-the-counter medicines. The amount of caffeine in these various preparations differs drastically with more variance in tea (at least a factor of 10 between the weakest and the strongest tea in one study) than in coffee (only a factor of 4 between the weakest and the strongest coffee). What makes estimates of caffeine consumption difficult is that the standard 'coffee cup' unit of 5 oz (150 ml) is probably used less often than a 'coffee mug' of 8 oz (237 ml) or the 'Grande' size (16 oz or 473 ml) of some coffee chains. A further difficulty is that coffee differs in the way it is prepared. In a comparison of coffees, home-brewed filtered coffee tends to be stronger than does instant coffee, perhaps because the process of making the latter is more efficient in extracting caffeine, as well as some of the other bitter flavors than found in a cup of freshly brewed and filtered coffee. (Table 1)

In the United States, 95% of the adult population consumes caffeine in some form, with an average daily consumption increasing with age to the late 50s and then declining slightly (Figure 1). Typically taken with breakfast, the serving of coffee or tea to visitors is an expected custom for many. In Europe and North America, the social aspect of caffeine consumption began with the establishment of coffee houses in seventeenth century Britain and continues to this day with the popularity of various coffee shop chains. Given caffeine's prevalence in modern society, it is hard to believe that four centuries ago, coffee and tea were considered revolutionary, and there was a move to ban coffee houses as sources of rebellion.

There are vast individual differences in the consumption of caffeine, probably due to self-titration, in that people

self-administer as much caffeine as they find to yield the positive effects on mood and alertness but not enough to produce some of the negative side effects of tension. As is true of most psychological variables, there are reliable individual differences in caffeine consumption and these differences are moderately heritable ( $h^2 \geq 0.4$ ) with a higher heritability for heavy use ( $h^2 \geq 0.7$ ). In addition to individual differences within countries, the consumption of caffeine varies a great deal between nations. While the average intake in the United States is roughly 2–3 mg kg<sup>-1</sup>, this varies drastically, with the top 10% of the population consuming as much as 5 mg kg<sup>-1</sup>. In the United Kingdom, the per capita consumption is about 4 mg kg<sup>-1</sup>, with the top 10% consuming as much as 7 mg kg<sup>-1</sup>, while in Scandinavia, the average is about 7.5 mg kg<sup>-1</sup>, with the top 10% consuming almost 15 mg kg<sup>-1</sup>!

Although given GRAS status (generally recognized as safe) by the US Food and Drug Administration as a supplement to cola-like beverages, in 2009, the FDA announced that it did not view it as GRAS as an additive to alcoholic beverages. This led to some controversy, as a variety of alcohol-producing and -marketing companies complained that this would limit their sale of caffeinated alcoholic beverages (CABs). The US Center for Disease Control has issued warnings about the use of CABs, as well as the mixing of 'energy drinks' containing caffeine with alcoholic beverages. The warning is that the stimulating effects of the caffeine when combined with the disinhibiting effects of alcohol can lead to binge drinking and increase the likelihood of driving under the influence of alcohol or to unsafe or undesired sexual behavior.

### Physiology of Caffeine

The full chemical name for caffeine is 1,3,7-trimethylxanthine, and its chemical formula is C<sub>8</sub>H<sub>10</sub>N<sub>4</sub>O<sub>2</sub>. Caffeine is a member of the purine family of compounds, meaning that it has a double-ringed, crystalline organic base, C<sub>5</sub>H<sub>4</sub>N<sub>4</sub>. When consumed orally, caffeine is rapidly and completely absorbed into the bloodstream through the gastrointestinal tract. Individual differences in the amount of time it takes to achieve peak plasma levels in the bloodstream can range from 15 to 120 min, with the majority of individuals reaching peak plasma levels approximately about 30–60 min after ingestion. Caffeine is broken down extensively by the liver into three primary metabolites, paraxanthine (84%), theobromine (12%), and theophylline (4%), each of which have their own effects on the body. The liver further breaks down these three metabolites into xanthine by removal of methyl groups. Xanthine is either excreted in urine or reused by the body. The average half-life of caffeine, the time it takes for half of the caffeine consumed to be eliminated, is 2.5–4.5 h. The half-life may vary depending on a number of factors; it is much longer in individuals with liver disease, reduced by up to 50% in smokers, may be doubled in women taking contraceptives, and increases throughout pregnancy (reaching a maximum time of 15 h during the last trimester of pregnancy). The half-life also depends on the amount of caffeine consumed. The pharmacokinetics for ~70–100 mg of caffeine are linear, but the clearance of caffeine is significantly reduced and its elimination half-life is prolonged at higher doses of 250–500 mg, indicating nonlinearity. Caffeine has no nutritional value.

**Table 1** Common sources of caffeine

Source	Serving	Dose/serving	Dose per ml
<i>Coffee &amp; tea</i>			
Espresso, generic	30 ml	30–90 mg <sup>a</sup>	1.00–3.00 mg ml <sup>-1</sup>
Coffee, generic, drip	237 ml	96–288 mg <sup>a</sup>	0.41–1.22 mg ml <sup>-1</sup>
Coffee, generic, percolated	237 ml	64–272 mg <sup>a</sup>	0.27–1.15 mg ml <sup>-1</sup>
Coffee, generic instant	237 ml	27–192 mg <sup>a</sup>	0.11–0.81 mg ml <sup>-1</sup>
Starbucks brewed coffee (Grande)	473 ml	320 mg	0.68 mg ml <sup>-1</sup>
Dunkin' donuts medium coffee	473 ml	206 mg	0.50 mg ml <sup>-1</sup>
Starbucks vanilla latte (Grande)	473 ml	150 mg	0.32 mg ml <sup>-1</sup>
Black tea, 1 teabag brewed 3 min	237 ml	25–110 mg <sup>b</sup>	0.11–0.46 mg ml <sup>-1</sup>
Starbucks chai tea latte (Grande)	473 ml	100 mg	0.21 mg ml <sup>-1</sup>
Oolong tea, 1 teabag brewed 3 min	237 ml	12–55 mg <sup>b</sup>	0.05–0.23 mg ml <sup>-1</sup>
Snapple-flavored iced teas	473 ml	42 mg	0.09 mg ml <sup>-1</sup>
Green tea, 1 teabag brewed 3 min	237 ml	8–30 mg <sup>b</sup>	0.03–0.13 mg ml <sup>-1</sup>
Arizona iced tea, black	473 ml	32 mg	0.07 mg ml <sup>-1</sup>
Coffee, generic decaffeinated	237 ml	3–12 mg <sup>a</sup>	0.01–0.05 mg ml <sup>-1</sup>
Arizona iced tea, green	473 ml	15 mg	0.03 mg ml <sup>-1</sup>
<i>Soft drinks</i>			
Jolt Cola	355 ml	140 mg	0.39 mg ml <sup>-1</sup>
Mountain Dew	355 ml	54 mg	0.15 mg ml <sup>-1</sup>
Diet Coke	355 ml	47 mg	0.13 mg ml <sup>-1</sup>
Dr. Pepper	355 ml	41 mg	0.12 mg ml <sup>-1</sup>
Pepsi	355 ml	38 mg	0.11 mg ml <sup>-1</sup>
Coca-Cola	355 ml	35 mg	0.10 mg ml <sup>-1</sup>
Diet Pepsi	355 ml	36 mg	0.10 mg ml <sup>-1</sup>
Guarana sodas	355 ml	30 mg	0.08 mg ml <sup>-1</sup>
<i>Energy drinks</i>			
AMP Energy	237 ml	80 mg	0.34 mg ml <sup>-1</sup>
Monster Energy	473 ml	160 mg	0.34 mg ml <sup>-1</sup>
Red Bull	250 ml	80 mg	0.32 mg ml <sup>-1</sup>
<i>Chocolate</i>			
Hershey's special dark chocolate bar	41 g	31 mg	
Hershey's unsweetened baking chocolate	14 g	15 mg	
Hershey's milk chocolate bar	43 g	9 mg	
Hershey's chocolate milk	237 ml	4 mg	0.02 mg ml <sup>-1</sup>
Starbucks coffee ice cream	101 g	40 mg	
<i>Over-the-counter medications</i>			
NoDoz (maximum strength)	1 tablet	200 mg	
Excedrin (extra strength)	2 tablets	130 mg	
Anacin (maximum strength)	2 tablets	64 mg	
<i>Other</i>			
AMP caffeinated gum	2 pieces	80 mg	
Enerjets lozenges	1 lozenge	75 mg	
GU energy gel	32 g pack	20 mg	

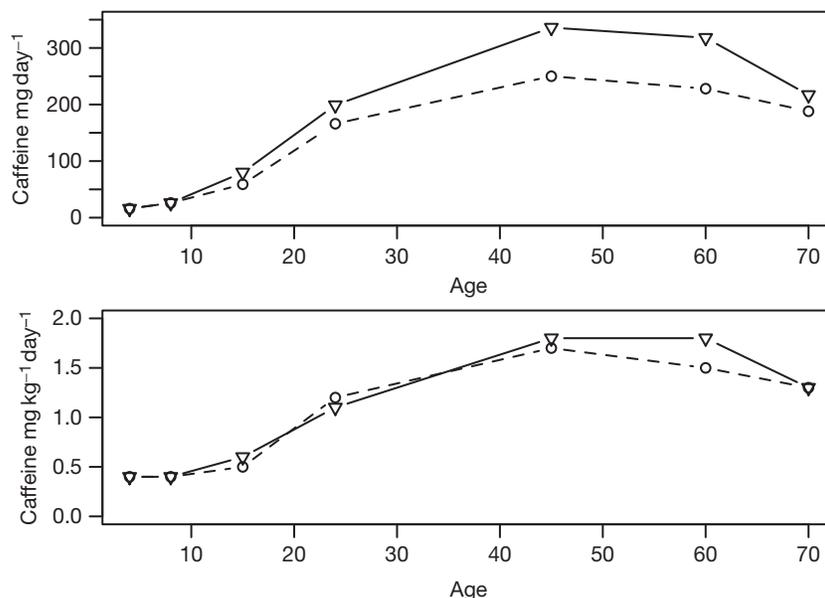
Adapted from the Center for Science in the Public Interest, the USDA National Nutrient Database for Standard Reference, Release 22 (2009), the International Coffee Organization, and company Web sites.

<sup>a</sup>Factors affecting the range of caffeine in coffee include the type and origin of the coffee bean, roasting method, grinding method, and brewing method.

<sup>b</sup>Factors affecting the range of caffeine in tea include the type, origin, and age of the tea plant, the location of the leaf on the plant, the method of steeping (loose leaf, bagged, etc.), and the length of steeping time (where longer steeping times release more caffeine). 1 fluid oz = 30 ml; 1 oz weight = 28 g.

Not only does caffeine rapidly disperse to all cells in the body, its chemical structure also allows it to easily cross the blood–brain barrier. Once in the brain, the principal mode of action is as a nonselective antagonist of adenosine receptors. The caffeine molecule is structurally similar to adenosine and binds to adenosine receptors on the surface of cells without activating them, therefore acting as a competitive inhibitor or 'antagonist' of adenosine. Caffeine's physiological and psychostimulant effects are thought to derive largely from inhibiting the effects of adenosine, particularly at the A1 and A2a

adenosine receptors. The A1 receptors are located in all parts of the brain with the heaviest concentration in the hippocampus, cerebral cortex, cerebellum, and certain thalamic nuclei. The A2a receptors are located in the dopamine-rich areas of the brain, including the striatum, nucleus accumbens, and olfactory tubercle. Adenosine transmission normally decreases the neuronal firing rate and inhibits both synaptic transmission and the release of most neurotransmitters; it promotes sleepiness, dilates blood vessels, reduces the contractions of the stomach and intestines, slows the reaction to stress, and lowers



**Figure 1** Caffeine consumption increases by a factor of 21 with age and differs between men and women. However, when considering body weight, the sex difference is diminished, and the increase with age is less than a factor of 5.

the heart rate, blood pressure, and body temperature. After caffeine connects to the A1 and A2a receptors, an adenosine blockage forms, thus reversing the effects of adenosine. Caffeine is classified as a psychostimulant because it produces heightened central nervous system (CNS) arousal, which increases the dominance of the sympathetic branch of the autonomic nervous system. The result of this shift is to increase the levels of activity in physiological systems that mobilize the body for aggressive or defensive activity, including the cardiovascular system, the respiratory apparatus, and the digestive system. Under continued stress, the pituitary gland is instructed by the hypothalamus to increase the release of hormones that cause the adrenal glands to produce epinephrine and cortisol. These hormones cause increased heart rate, dilation of the bronchi, a release of sugar into the bloodstream from the liver, increased blood flow to the muscles, and a tightening of muscles for action.

Caffeine also affects dopaminergic transmission. By inhibiting adenosine A2a receptors, caffeine reduces the negative modulatory effects of adenosine receptors on dopamine D2r receptors, thus causing potentiation of dopaminergic neuro transmission. This mechanism is thought to be related to the ability of caffeine to induce a positive mood state that includes mild euphoria. However, in contrast to the drugs of abuse that selectively lead to a release of dopamine in the shell of the nucleus accumbens, caffeine increases dopamine release in the caudate nucleus. Dopamine release in the caudate nucleus relates to the stimulatory properties of caffeine on locomotor activity. Only at doses not likely to be consumed by humans does caffeine cause release of dopamine in the nucleus accumbens; however, this dose is associated with nonspecific activation in the brain and aversive effects such as anxiety. Repeated administration of caffeine quickly leads to tolerance of the physiological effects previously described; tolerance refers to an acquired change in responsiveness after repeated exposure to a drug. Usually developing within a few days, tolerance to caffeine's effects on blood pressure, heart rate, diuresis, plasma

epinephrine and norepinephrine levels, renin activity, tension, anxiety, jitteriness, and nervousness has also been demonstrated. Tolerance to sleep disruption can develop within 1 week with doses as low as two cups of coffee per day. Nonhuman animals also develop a tolerance to caffeine-induced locomotor stimulation, cerebral electrical activity, and reinforcement thresholds for electrical brain stimulation. The alerting and attentional focus effects of the drug do, however, continue.

### Withdrawal

Physiological dependence is a state induced by repeated drug use that results in a withdrawal syndrome when the drug is discontinued or an antagonist is administered. It is important to distinguish a withdrawal syndrome from a rebound phenomenon. Withdrawal comprises a number of signs and symptoms not present during administration of the drug, whereas rebound refers to a single sign or symptom that is the reverse of the drug effect. Additionally, withdrawal most often occurs after discontinuation of repeated drug administration; rebound can occur after single administrations of a drug. The most oft-reported symptoms of caffeine withdrawal are headaches, fatigue, weakness, drowsiness, impaired concentration, work difficulty, depression, anxiety, irritability, increased muscle tension, decreased energy and activeness, decreased alertness, drowsiness, and irritability. Onset of symptoms can appear within only 3–6 h after abstinence and can last for one week, although the incidence or severity of the symptoms increases with increases in daily dose; symptoms can appear with doses as low as 100 mg day<sup>-1</sup>. It is important to note, however, that the intensity of withdrawal symptomatology is subject to substantial individual differences, based, in part, on genetic predispositions. Some people experience quite extreme withdrawal symptoms, while others experience almost none.

Although there is an overall, general withdrawal factor, withdrawal symptoms can be grouped into lower-level factors

of fatigue/headache, dysphoric mood, and flu-like symptoms. The effects of withdrawal are most clearly dose-dependent for the first two sets of symptoms: compared to light caffeine consumers (less than 100 mg day<sup>-1</sup>), heavy consumers (greater than 200 mg day<sup>-1</sup>) are more than four times as likely to report headache and fatigue as well as more than three times as likely to report dysphoric mood.

The effect of acute withdrawal from caffeine is seen commonly in headache and fatigue. Indeed, office workers who consume high doses during the week and then do not consume caffeine on the weekend find that the resulting weekend headaches are easily treated with pain relievers that contain caffeine. Perhaps one cause of postoperative headache is the preoperative withdrawal from caffeine rather than the acute aftereffects of anesthesia.

Some of the physiological underpinnings of common withdrawal effects have just recently been discovered. Acute caffeine abstinence results in increases in blood flow velocity in middle and anterior cerebral arteries and decreases in variability of blood flow velocity in the middle cerebral artery. These effects suggest that a vascular mechanism causes the caffeine withdrawal symptom of headache. Acute caffeine abstinence also produces significant changes in electrical activity in the brain corresponding with increased drowsiness and decreased alertness.

Withdrawal effects complicate the study of caffeine effects on mood and performance. Because most participants normally consume caffeine, it has been proposed that the beneficial effects of caffeine on mood, behavior, and cognitive performance are actually due to antiwithdrawal effects. That is, caffeine does not elevate mood or improve alertness, but rather withdrawal leads to tension and sleepiness. The logic of this position is that most double-blind caffeine studies are done after 12–24 h of caffeine withdrawal (e.g., participants are requested not to consume any caffeine after 8 pm prior to a morning study), and thus, participants are in acute caffeine withdrawal. Evidence against this proposal comes from comparing predrug administration measures of mood and performance for heavy and light caffeine consumers as well as the observation that both nonconsumers and normal consumers of caffeine report increased alertness following caffeine consumption when compared to a placebo. Further evidence against the withdrawal hypothesis comes from the pattern of cognitive performance effects of caffeine as they interact with personality and the time of day.

### Affective, Behavioral, and Cognitive Effects of Caffeine

Caffeine is most commonly consumed because it improves alertness, attentional focus, and mood and fights off the effects of fatigue, though it is also used by athletes because of its effects on motor speed, power, and endurance. However, as with most things, moderation is important, for too much caffeine will mimic the symptoms of anxiety, induce hand tremor, and hinder performance in a variety of ways. Though the cognitive, affective, and behavioral effects of caffeine are addressed in turn in the following sections, it is important to acknowledge that the distinct causal mechanisms for these effects are often complicated by the fact that caffeine affects

several physiological systems simultaneously. In addition to the central nervous system, each of the cardiovascular, muscular, pulmonary, hormonal, and metabolic systems are affected by the presence of caffeine in the bloodstream.

### Affective Effects of Caffeine

Coffee and tea are part of the morning routines for many around the world because they help people to feel more awake. In low to moderate doses, caffeine consumption enhances mood, increases levels of self-reported alertness, and decreases self-reported fatigue. While some effects of caffeine consumption decrease with increasing tolerance, this is generally not the case with enhancements to mood and mental alertness, though considerable evidence suggesting an interaction effect of caffeine and expectancy may play a role in the preservation of these effects.

The effect of caffeine on affect needs to be considered in terms of at least four distinct but correlated constructs. Energetic arousal (EA), indicated by such terms as alert, energetic, and wide awake as contrasted to tired, sleepy, or drowsy, is increased with caffeine. This is, after all, why coffee and tea are consumed! Orthogonal to EA is Tense arousal (TA), which is indicated by words such as tense, anxious, nervous, or afraid as contrasted with calm, relaxed, or at ease. State levels of TA are seen as a response to stressful situations, while more stable individual differences (trait levels) are associated with anxiety and neuroticism. TA increases with caffeine, particularly at higher doses (i.e.,  $\geq 4$  mg kg<sup>-1</sup>). Positive affect (PA), although highly correlated with energetic arousal and indexed by words such as cheerful, pleased, and happy, is an interactive effect of caffeine and situational cue for happiness. Without such cues, caffeine has a small positive effect on PA. The dimension of negative affect (NA) as indicated by unhappy, depressed, and blue, is highly positively correlated with TA and slightly negatively correlated with PA. NA is less affected by caffeine than it is by situational manipulations of affect (e.g., sad or depressing movies or other negative mood inductions).

In higher doses, and among individuals with lower tolerances, caffeine also increases 'jitteriness,' nervousness, and general anxiety, and these side effects are more common among clinically anxious individuals. Indeed, caffeinism is a recognized anxiety disorder associated with high levels of caffeine intake. The current diagnostic and statistical manual of mental disorders (DSM-IV-TR) lists four caffeine-related psychiatric disorders: caffeine intoxication, caffeine-induced anxiety disorder, caffeine-induced sleep disorder, and other caffeine disorders not otherwise specified. Caffeine intoxication is shown by having recently consumed more than 250 mg of caffeine and showing at least five of the following symptoms: restlessness, nervousness, excitement, insomnia, flushed face, diuresis, gastrointestinal disturbance, muscle twitching, rambling flow of thought and speech, tachycardia or cardiac arrhythmia, periods of inexhaustibility, or psychomotor agitation. For a diagnosis, these symptoms must be causing clinically significant distress or impairment of functioning. Caffeine-induced anxiety disorder includes symptoms of anxiety associated with high levels of caffeine intake. Caffeine-induced sleep disorder is associated with high caffeine consumption and sleep disorders not otherwise explained. Because the symptoms of high levels of caffeine

consumption are similar to those of the anxiety disorders, physicians are encouraged to inquire about the level of caffeine intake for patients complaining about anxiety symptoms.

### Behavioral Effects of Caffeine

Of course, many of these affective effects carry over into more overtly physical behaviors. The most renowned behavioral effect of caffeine is increased alertness. Performance on monotonous tasks that require detection of rare events (e.g., vigilance tasks such as long distance truck driving or looking for weapons in airport scanners) normally deteriorates over time. Moderate doses of caffeine ameliorate this decrease. A more subtle, but equally reliable effect is the speeding up of reaction time, particularly when choice is not required.

In addition to these benefits, moderate doses of caffeine enhance physical endurance by increasing both work output and the time to exhaustion. Caffeine's effect on shorter-term physical behavior is less well documented, perhaps because shorter durations make effects more difficult to reliably detect. Nevertheless, the effect of caffeine on physical exercise of short duration suggests that peak power output, speed, and isokinetic strength are improved for very short bouts (lasting less than 10 s). For longer bouts (greater than 15 s), which rely on the glycolytic system, these same improvements are not maintained; in fact, some findings suggest a detrimental effect of caffeine on power for bouts of 15 s to 3 min. These discrepancies reflect the likelihood that the effects of caffeine result from a combination of mechanisms at work simultaneously. In addition to the central nervous system, these mechanisms result from changes to the cardiovascular, muscular, pulmonary, hormonal, and metabolic systems.

The effects of caffeine on physical performance have led to its widespread use among elite athletes and performers, even though the benefits are not well established across activities. With respect to elite athletic performance, it is important to note that very small variations in performance are the difference between being on the victory stand and being one of the crowd. The unit of analysis is thus not the percent change in performance so much as change as a percent of the coefficient of variation in performance, that is, the size of the effect in terms of the standard deviation rather than in terms of the raw performance.

In an effort to maintain parity, the International Olympic Committee classified caffeine as a doping agent in 1984 by setting an acceptable threshold level of  $15 \mu\text{g ml}^{-1}$  in urinary samples (the level was reduced to  $12 \mu\text{g ml}^{-1}$  the following year). In 2004, however, this prohibition was revoked when doping for most international sporting events (including the Olympics) fell under the administration of the world anti-doping agency (WADA). Under the current WADA policy, the concentration of caffeine in the bloodstream is monitored through urine samples for signs of potential abuse, though the threshold level constituting abuse has not been officially declared. In the past, threshold levels have been subject to criticism on the basis that they fail to take into account high interindividual variability in terms of caffeine metabolism (several studies suggest a 15–20-fold range across individuals) as well as the fact that most performance-enhancing benefits of caffeine have been documented at levels consistent with

moderate daily use. Estimates vary dramatically depending on many factors, but peak urinary caffeine concentrations of  $12 \mu\text{g ml}^{-1}$  would be expected to occur 105 min after a mean caffeine intake of at least  $10.5 \text{ mg kg}^{-1}$  of body weight.

### Cognitive Effects of Caffeine

The effects of caffeine on cognitive performance are not as clear-cut as they are for feelings of alertness. They are complex, for they depend upon the type of task, the situational demands, and characteristics of the individual. To make it more complicated, there is reliable evidence for systematic interactions with the various combinations of person, situation, and task variables.

To understand these effects, it is useful to organize a number of cognitive tasks along three dimensions: the requirements for sustained attention, the requirements for working or immediate memory, and the requirements for integrating long-term memories with immediate memory. Tasks can be high or low on each of these three dimensions. The positive effects of caffeine on the first (sustained attention) are quite clear, whereas effects on the latter two dimensions are more complicated.

Sustained attention tasks such as long distance truck driving, security scanning at airports, or other examples of vigilance that require detection of rare events in the presence of many repetitive but nontarget signals are correlated with general alertness. Performance on these tasks is hindered by manipulations that lead to lower alertness: alcohol, sleep deprivation, the time of day (the optimal time depends upon the participant), or the time on task. In particular, performance on these tasks decays over time, with very good performance upon starting with a (negatively accelerating) exponential decay over time. Performance may be indexed by reaction time or by accuracy. Reaction time increases and accuracy diminishes over time. Caffeine as well as brief exercise, or even an increase in the signal frequency inhibits this decay, although effort instructions ('try harder' or 'do not go to sleep') do not. The clearest evidence for caffeine effects on vigilance are found following sleep deprivation and after a period of time on the task. That is, caffeine helps the most when the subject is most fatigued. These effects are associated with increases in energetic arousal.

Although the effect of caffeine on vigilance is quite clear, the pattern on working memory tasks is much less so. Part of the confusion is that caffeine facilitates alertness which is, in turn, related to detection of the material to be remembered. In addition, caffeine enhances speed of performance which in turn can reduce accuracy. Thus, in some studies, memory for recent events is enhanced, probably because the detection was better, rather than improvements in storage or retrieval. An example of the complexity of the results may be seen in proof-reading where caffeine hinders the detection of interword errors (e.g., subject-verb agreement) which requires more working memory than does the detection of intraword errors (e.g., spelling or broken typography) which has a more complicated relationship with caffeine (a small decrease in detection is associated with an increase in the speed of processing).

Information acquired when one is alert is recalled better later (after at least a day) than is information acquired when

one is sleepy. This effect may be shown using sleep deprivation, the time of day, exercise, and variation in personality dimensions associated with arousal (impulsivity and extraversion). Similar effects are found with caffeine: caffeine taken when learning new material facilitates long-term recall and recognition of that material.

For complex cognitive tasks, similar to the sort of ability tests given for admission to graduate school, the effects of caffeine are even more complicated and are an interactive function of individual differences in impulsivity and the time of day. In a series of studies using these complex tasks, it was shown that caffeine facilitated the performance of subjects thought to be less aroused (high impulsive participants in the morning, low impulsive participants in the evening) but had deleterious effects for those thought to be more highly aroused (low impulsiveness in the morning, high impulsiveness in the evening.)

The general conclusion for cognitive performance is that caffeine facilitates performance on tasks that require (sustained) attention, particularly among participants who are fatigued or less aroused. The beneficial effects of caffeine are harder to detect for alert subjects or for tasks that require more memory. For especially complicated tasks with highly aroused participants, caffeine can have a deleterious effect.

### Caffeine as a Tool for Psychological Research

Much of the research on caffeine is just that: studies of the effects of caffeine on various psychological variables. A less recognized use of caffeine is as a tool for psychological research. By increasing the ways in which a participant's

energetic and tense arousal may be manipulated, caffeine allows the careful researcher to tease apart the effects of putative arousal and motivational-related variables such as the time of day, introversion–extraversion, impulsivity, exercise, or incentives. For example, in the study of the association between positive affect and energetic arousal, and negative affect and tense arousal, the differential effect of caffeine on these variables as contrasted to more typical mood manipulations allows for distinctions that would otherwise be difficult to achieve.

### Conclusion

Caffeine, particularly in the form of coffee or tea, is used by a majority of adults worldwide. The benefits on feelings of alertness and positive affect, as well as on endurance and simple cognitive performance are clear, particularly in situations that would otherwise normally lead to fatigue or when sleep-deprived. However, the benefits come with some cost, in that performance on complex reasoning tasks can be hindered, and that high doses lead to unpleasant levels of tension. Although the effects of low to moderate doses seem positive, higher doses can lead to discomfort and impaired cognitive performance.

### Further Reading

- Fredholm BB (2011) Notes on the history of caffeine use. In: Starke K, et al. (ed.) *Methylxanthines*, vol. 200, pp. 1–9. Berlin: Springer.
- James JE (2011) Caffeine. In: Johnson BA (ed.) *Addiction Medicine*, pp. 551–583. New York: Springer.
- Nehlig A (1999) Are we dependent upon coffee and caffeine? A review on human and animal data. *Neuroscience & Biobehavioral Reviews* 23(4): 563–576.