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Review article

A review of caffeine's effects on cognitive, physical and occupational performance

Tom M. McLellan[a], John A. Caldwell[b], Harris R. Lieberman[c,*]

[a] TM McLellan Research Inc., Stouffville, ON L4A 8A7, CANADA, Canada
[b] Oak Ridge Institute for Science and Education, Belcamp, MD 21017, USA
[c] Military Nutrition Division, US Army Research Institute of Environmental Medicine (USARIEM), Natick, MA 01760-5007, USA

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ABSTRACT

Caffeine is consumed by over 80% of U.S. adults. This review examines the effects caffeine has on cognitive and physical function, since most real-world activities require complex decision making, motor processing and movement. Caffeine exerts its effects by blocking adenosine receptors. Following low (~40 mg or ~0.5 mg kg^{-1}) to moderate (~300 mg or 4 mg kg^{-1}) caffeine doses, alertness, vigilance, attention, reaction time and attention improve, but less consistent effects are observed on memory and higher-order executive function, such as judgment and decision making. Effects on physical performance on a vast array of physical performance metrics such as time-to-exhaustion, time-trial, muscle strength and endurance, and high-intensity sprints typical of team sports are evident following doses that exceed about 200 mg (~3 mg kg^{-1}). Many occupations, including military, first responders, transport workers and factory shift workers, require optimal physical and cognitive function to ensure success, workplace safety and productivity. In these circumstances, that may include restricted sleep, repeated administration of caffeine is an effective strategy to maintain physical and cognitive capabilities.

Contents

* Corresponding author.
E-mail addresses: DrTom.McLellan@gmail.com (T.M. McLellan), drjohncaldwell@gmail.com (J.A. Caldwell), harris.r.lieberman.civ@mail.mil (H.R. Lieberman).

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1. Introduction

Caffeine is one of the most widely consumed foods and supplements in the world. In the U.S., approximately 85% of adults consume caffeine (Fray et al., 2005; Fulgoni et al., 2015). Most caffeine is consumed as coffee (Barone and Roberts, 1996) but caffeine is also present in numerous foods, drugs and beverages (Table 1). Caffeine is psychoactive in doses found in single servings of many beverages (Lieberman et al., 1987a; Smith et al., 1999) and is the active ingredient in a relatively new product – energy drinks (McLellan and Lieberman, 2012). At the request of the US Food and Drug Administration, the Institute of Medicine recently convened a workshop to review the safe levels of caffeine consumption in many of the products identified in Table 1 (Institute of Medicine, 2014). A wide variety of benefits and risks have been attributed to caffeine, but it is generally agreed that for healthy adults, daily consumption of up to 400 mg (~5.5 mg kg^{-1} for a 75 kg individual) of caffeine does not present a health risk (Doepker et al., 2016; Higdon and Frei, 2006; Nawrot et al., 2003).

Numerous reviews have addressed the effects of caffeine on either physical or cognitive performance alone (Burke, 2008; Davis and Green, 2009; Graham, 2001; Lieberman et al., 2010; Shearer and Graham, 2014; Spriet, 2014). However, since Weiss and Laties did so in 1962 there have been only a few attempts to summarize caffeine's effects on both physical and cognitive function (Goldstein et al., 2010; Rogers and Dinges, 2005; Sökmen et al., 2008) and these latter reviews focussed on issues of interest to the sporting community. Nevertheless, it is clear that there are doses of caffeine available in foods and beverages that raise plasma concentration to levels which block adenosine receptors (Fredholm, 1979, 1995; Fredholm et al., 1999), and exert central nervous system (CNS) effects, to a degree that impacts both cognitive and physical function. It is also evident that there are many occupational settings, as well as sporting and leisure activities, where optimal physical and cognitive function is critical for performance success, safety and productivity. But what is the evidence-base that might support or refute the use of caffeine in these sporting and occupational settings, and is there a dose of the drug and timing of ingestion that will positively affect both cognitive and physical function or are the potential effects mutually independent or even antagonistic? These issues need to be carefully considered since rarely do the physical demands in sport or occupation occur in isolation from complex decision making, motor processing and movement. After briefly discussing the pharmacology and mechanisms of action of the drug, the effects of caffeine on various aspects of cognitive function will be addressed. Due to the immense literature on the behavioral effects of caffeine we have restricted our review to key aspects of cognitive function, especially those that may be related to occupational performance. This will be followed by a review of studies addressing various aspects of physical performance and then studies that have addressed the effects of caffeine on both physical and cognitive performance in various occupational settings. The review includes an assessment of peer-reviewed publications and reports available through end Spring 2016.

2. Pharmacology, metabolism and mechanisms of action

Caffeine (1,3,7-trimethylxanthine) is formed when three methyl groups are substituted on the parent compound xanthine. Following ingestion, caffeine is rapidly absorbed reaching peak concentrations in the circulation within an hour (Blanchard and Sawers, 1983; Robertson et al., 1981), although there is considerable individual variation (Desbrow et al., 2009; Skinner et al., 2013). In addition, absorption is slower when caffeine is consumed with a meal (Dews, 1982; Fleischer et al., 1999), but absorption is faster when it is provided in gum. Chewing caffeine-containing gum allows for rapid absorption through buccal tissue of the mouth (Kamimori et al., 2002). Caffeine is rapidly distributed to all tissues and readily crosses the blood-brain barrier to exert its effects. The half-life of caffeine in the circulation is normally 3–5 h (Fredholm, 1995), thus it interacts with many tissues for prolonged periods of time. Furthermore, smoking, certain dietary choices, liver disease, pregnancy or the use of oral contraceptives can alter the half-life of caffeine (Collomp et al., 1991; Curatolo and Robertson, 1983; Denaro et al., 1990; Peterson et al., 2006, 2009).

Caffeine is structurally similar to adenosine, a neuromodulator, whose formation is dependent on the relative rates of ATP breakdown and synthesis (Fredholm, 1995). Four distinct G-protein-coupled adenosine receptors, A_1, A_{2a}, A_{2b} and A_3, have been identified (Fredholm et al., 1994), each with a unique tissue distribution and pharmacological profile (Fisone et al., 2004; Landolt, 2008). Adenosine receptor density and sensitivity can vary among individuals (Martin et al., 2006), and receptors are up-regulated as caffeine intake increases (Varani et al., 2000). Caffeine's mechanism of action has been definitively established as explained by Fig. 1. Previously, caffeine's effects were thought to be due to inhibition of phosphodiesterase or by promoting intracellular Ca^{2+} release, but these effects occur with very high, non-physiological concentrations of caffeine. It is now known that the micromolar tissue concentrations of caffeine that result from ingestion of low to moderate doses of caffeine block A_1 and A_{2a} adenosine receptors (Fredholm, 1979). Nevertheless, as will be reviewed in Section 4.2, there is some evidence that the effects of caffeine on physical performance could be related to the release of calcium from the sarcoplasmic reticulum and inhibition of its reuptake, which subsequently increases nitric oxide via the activation of endothelial nitric oxide synthase (see Cappelletti et al., 2015). These actions may be associated with changes in neuromuscular function and increased contractile force in skeletal muscles that could be ergogenic (Tarnopolsky, 2008).

While both the A_1 and A_{2a} adenosine receptors are believed to be responsible for the behavioral effects of caffeine, their relative contributions have not been established. Both receptor subtypes are expressed in the brain and periphery. High levels of A_1 receptors are found in the hippocampus, cortex, cerebellum and hypothalamus

Table 1
Estimated caffeine content of beverages, foods and dietary supplements (Lieberman et al., 2010; McLellan and Lieberman, 2012).

Item	Caffeine content (mg/100 mL)	Serving size (mL)	Caffeine content (mg/serving)
Coffee			
Drip method	60–100	150	90–150
Instant	27–72	150	40–108
Decaffeinated	1–3	150	2–5
Tea			
1-min brew	6–22	150	9–33
5-min brew	13–33	150	20–50
Iced Tea	6–10	350	22–36
Chocolate Products			
Hot cocoa	1–5	175	2–8
Chocolate milk	1–3	235	2–7
Milk chocolate	3–50	30	1–15
Baking chocolate	115	30	35
Cola Beverages			
Coca-Cola®	10	350	35
Diet Coke®	13	350	47
Pepsi®	11	350	38
Diet Pepsi®	10	350	36
Other soft drinks			
Dr. Pepper®	11	350	40
Mountain Dew®	16	350	55
Barq's® Root Beer	7	350	23
Energy Drinks			
Amp®	30	235	71
Cocaine®	120	235	280
Monster®	34	235	80
Red Bull®	34	235	80
Rockstar®	34	235	80
Energy Shots			
5-h Energy®	333	60	200
10-h Time Release®	740	57	422
Over-the-counter Medication			
Anacin (1 tablet)	–	–	32
Excedrin (1 caplet)	–	–	65
Midol (1 pill)	–	–	60
NoDoz (1 tablet)	–	–	200

1 oz = 29.56 mL.

(Landolt, 2008). The A_{2a} subtype is present in regions of the brain such as the striatum, nucleus accumbens and olfactory tubercle, and are heavily innervated by dopamine-containing fibers (Nehlig, 1999). Adenosine appears to inhibit the release of many neurotransmitters in the central nervous system (Nehlig et al., 1992). In animal models, adenosine A_1 receptor agonists have been shown to inhibit release of glutamate (Ciruela et al., 2006; Flagmeyer et al., 1997; Marchi et al., 2002; Yang et al., 2013), serotonin (Okada et al., 1999), acetylcholine (Brown et al., 1990; Rainnie et al., 1994), noradrenaline (Fredholm, 1979) and dopamine (as discussed below). Adenosine receptor antagonists, such as caffeine, therefore would promote the release of these various neurotransmitters. For example, caffeine has been linked to the modulation of aggressive behavior through its inhibitory effects on serotonin release (Mahoney et al., 2011), and methylxanthines, such as theophylline and caffeine, have been implicated in lowering the epileptic seizure threshold through antagonism of adenosine on glutamatergic neurons (Boison, 2011; Dunwiddie, 1980; Fukuda et al., 2010).

As reviewed elsewhere (Ferré, 2010, 2016; Fuxe et al., 2005), adenosine A_1 and A_{2a} receptors form functional and pharmacologically active heteromers with dopamine D_1 and D_2 receptors in different regions of the brain. For example, by blocking A_{2a} receptors in the striatum caffeine antagonizes adenosine's effects and indirectly promotes dopamine's stimulatory effects on psychomotor activity, by acting on its D_2 receptor. Genetic polymorphisms of the A_{2a} and D_2 receptor in humans have also been associated with caffeine's effects on anxiety (Childs et al., 2008). Caffeine's effects on arousal, especially during prolonged periods of wakefulness, appear to involve both direct modulation of adenosine A_1 receptors in the basal forebrain as well as indirect effects on the noradrenergic and hypothalamic histaminergic and orexinergic systems, through modulation of both A_1 and A_{2a} receptors (Ferré, 2010). Neurochemical models have been proposed to explain the ability of adenosine A_1 and A_{2a} receptor antagonists to increase arousal during periods of sleep loss for treatment of daytime sleepiness and hypokinesia during Parkinson's disease (Sil'kis, 2009, 2014). According to these models, activation of adenosine A_1 receptors should induce long-term depression of excitatory inputs to striatonigral neurons, whereas A_{2a} receptor activation can induce long-term potentiation of inhibitory inputs to striatopallidal neurons. Therefore, the use of caffeine as an adenosine receptor antagonist can, in theory, promote excitation of striatonigral neuronal projections and reduce inhibitory signals to striatopallidal neurons. Both of these responses, therefore, are likely involved in the increase in arousal and enhanced psychomotor activity that follows ingestion of caffeine during sleep loss.

Single nucleotide polymorphisms of the ADORA2A gene, which codes for the A_{2a} receptor, have been identified as thymine and cytosine substitutions at position 1083. Between 15–20% of individuals are homozygous for thymine, whereas about 35% are homozygous for cytosine (Childs et al., 2008). These polymorphisms appear to influence an individual's response to the stimulant effects of caffeine (Bodenmann et al., 2012; Yang et al., 2010).

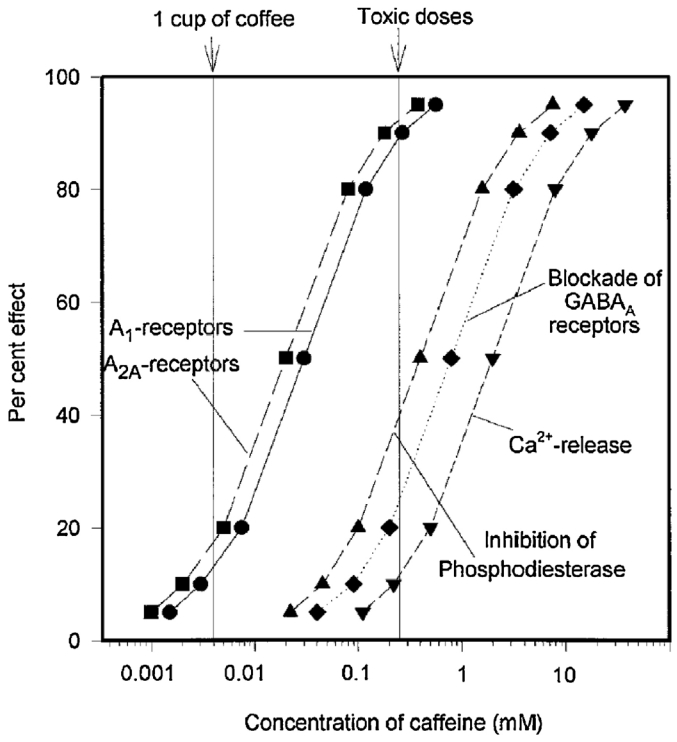

Fig. 1. Concentration-effect curves for caffeine at various potential sites of action. Caffeine markedly affects A_1 and A_{2a} receptors at low micromolar concentrations. To inhibit phosphodiesterase (PDE), concentrations 20 times as large are required. Approximate caffeine concentrations resulting from a single cup of coffee and toxic doses of caffeine are indicated. (Modified from Fredholm (1995) with permission from Elsevier.).

In summary, circulating levels of caffeine resulting from ingestion of caffeine-containing beverages or food products result in the antagonism of adenosine A_1 and A_{2a} receptors in the CNS and peripheral tissues. Clearance of caffeine is influenced by diet and genetics. Lifestyle and genetics affect adenosine receptor number and sensitivity and can impact how an individual responds to a given dose of caffeine.

3. Effects on cognitive performance

For centuries, caffeine, often in the form of coffee or tea, has been a popular means to enhance various aspects of mental or cognitive functions (Snel and Lorist, 2011). Although there is widespread scientific agreement about caffeine's behavioral effects, certain details regarding specific functional aspects remain controversial (Smith, 2011). For instance, there is general consensus that caffeine improves "lower" cognitive functions such as simple reaction time, whereas caffeine's effects on "higher" cognitive functions such as problem solving and decision making are often debated (Kosslyn and Smith, 2001). In part, this is because there are fewer published studies on higher-order cognitive function, and those that are available vary greatly with respect to methods employed (Brunyé et al., 2010a). The scientific consensus regarding basic cognitive functions is that caffeine in doses from 32 to 300 mg (or roughly 0.5–4 mg kg^{-1} for a 75 kg individual) enhance fundamental aspects of cognitive performance, such as attention, vigilance, and reaction time (Lorist and Snel, 2008; Nehlig, 2010; Snel et al., 2004). However, low and moderate doses of caffeine have not been shown to alter sensory functions (i.e., vision or hearing) to a significant degree (Lieberman, 1992).

Caffeine increases arousal in a dose-dependent manner; low doses can improve hedonic tone and may reduce anxiety, while high doses increase tension and symptoms of anxiety, nervousness and jitteriness (Stafford et al., 2007). How caffeine affects performance depends in part on the arousal level of the individuals under investigation, especially the extent to which subjects are sleep-deprived or fatigued versus well-rested. Nehlig (2010) suggested the classic inverted U-shaped arousal-performance function can partly explain the extent to which caffeine either improves or degrades function. According to the Yerkes-Dodson law (Yerkes and Dodson, 1908), there is an empirical relationship between arousal and performance, such that low arousal is associated with poor performance whereas increased physiological or mental arousal is associated with improved performance, but only up to a point. When arousal level becomes too high, performance decreases. Thus, a subject's pre-dose arousal level before consuming caffeine will influence the effects observed (Wood et al., 2014). Administration of a large dose of caffeine to an individual who is severely fatigued likely will improve performance because in this case, caffeine promotes a favorable arousal level (i.e., caffeine advances the subject's arousal into the middle range of the Yerkes-Dodson curve). Conversely, giving the same dose to someone who already is well-rested and highly aroused may degrade rather than improve performance because in this case, caffeine produces a state of over-arousal, which according to the Yerkes-Dodson law, will degrade cognition. Under normal day-to-day circumstances, there is evidence to suggest people use caffeine to achieve a self-perceived, peak state of arousal, as they modulate their caffeine usage until they reach their self-selected optimal level of arousal and cognitive performance (in accordance with the Yerkes-Dodson law) (Harvanko et al., 2015). In studies of caffeine where the doses under investigation are properly matched to the individual's arousal state, beneficial effects are likely to be observed.

Although the curvilinear relationship between caffeine-induced activation and performance may be contested, as well as the Yerkes-Dodson law itself, there is considerable support for both in many studies over the past 100 years (for example, see Anderson, 1994 and Watters et al., 1997). In any case a comprehensive examination of the validity of the Yerkes-Dotson law is well beyond the scope of this review. However, it should be noted the precise effects of caffeine or any other psychostimulants on behavior may be differentially influenced by the difficulty of the task under investigation (Diamond, 2005), individual differences in caffeine sensitivity (Renda et al., 2015), gender or body-weight differences (Wood et al., 2014), the motivational or emotional state of the volunteers (Diamond et al., 2007), impulsivity and sociability (Anderson, 1994), and/or other factors. Thus, while the dose-related impact of caffeine is generally curvilinear with the optimal dosage residing near the middle of the arousal/activation curve, it would be an oversimplification to assume that caffeine's effects precisely follow an inverted U-shaped function across all behaviors, emotional/motivational states, personality types, and unique individuals.

Given the qualifications noted above, it is generally the case that caffeine in doses up to approximately 300 mg (4 mg·kg^{-1}) enhances performance with minimal side effects across a wide variety of cognitive functions, often by preventing decrements in alertness and attention arising from suboptimal arousal (Lieberman et al., 2002). As will be discussed below and summarized in Supplementary Table 1, caffeine consistently improves mood, reaction time and vigilance when alertness is reduced, and given that some basic level of arousal is essential for the performance of any task, it is logical that caffeine is particularly useful in fatiguing circumstances. Rested (non-sleep-deprived) individuals engaged in long, monotonous activities such as military sentry duty or lengthy periods of highway driving can experience substantial performance benefits from 200-mg doses of caffeine (Carvey et al., 2012; Reyner and Horne, 1997, 2000) and for sleep-deprived individuals doses

ranging from 200 to 600 mg (~2.5–8 mg kg^{-1}) are helpful (Carvey et al., 2012; Lieberman et al., 2002; Penetar et al., 1993; Smith, 2005; Wesensten et al., 2002). Thus, the direct impact of sleep loss or the monotonous contextual factors shift alertness/activation toward the low end of the U-shaped arousal continuum where caffeine's energizing properties serve to prevent the manifestation of underlying physiological drowsiness.

3.1. Reaction time

Individual studies have demonstrated beneficial effects of caffeine on simple and/or visual-recognition reaction time (RT) (Balkin et al., 2004; Clubley et al., 1979; Kahathuduwa et al., 2016; Lieberman et al., 1987a; Lorist et al., 1994; Wesensten et al., 2002, 2004) and choice reaction time (Lieberman et al., 1987a); and reviews of the literature agree that caffeine improves reaction time (Lieberman et al., 2010; Nehlig, 2010; Smith, 2002). When administered in doses ranging from 12.5 to 400 mg (~0.2–5.5 mg kg^{-1}) to both rested and sleep-deprived individuals caffeine enhances reaction time (Einother and Giesbrecht, 2013). A few studies fail to support these positive results (Kuznicki and Turner, 1986; Lane, 1997), but such discrepancies appear attributable to differences in study populations (habitual versus non-habitual caffeine users, caffeine-deprived versus non-caffeine-deprived subjects) and/or divergent test methods and/or dosing levels (Lieberman, 1992; Weiss and Laties, 1962) rather than differential effects of caffeine itself.

3.2. Vigilance

The impact of caffeine on tasks requiring vigilance, the ability to sustain performance on lengthy, boring or tedious tasks, is clear. In fact, it appears that sustained tests of vigilance or tasks with substantial embedded vigilance components are the most sensitive to the behavioral effects of caffeine in rested individuals (Lieberman et al., 2010) as doses in the 200 mg (~2.5 mg kg^{-1}) range improve performance for several hours. Similar effects (with 200–300 mg, or 2.5–4.0 mg kg^{-1}, doses) also are seen in persons deprived of sleep continuously for as long as 3 days (Lieberman et al., 2002). In non-sleep deprived individuals, doses ranging from 32 to 256 mg (~0.5–3.5 mg kg^{-1}) of caffeine have been shown to increase the number of signal tones detected on the 1-h-long Wilkinson auditory vigilance test without altering the number of false alarms (Lieberman et al., 1987a,b). Rosenthal et al. (1991) found that twice-daily administrations of 75 and 150 mg (1–2 mg·kg^{-1}) doses of caffeine improved reaction time in an auditory vigilance task both in sleep-restricted and rested subjects, while performance on a shorter (15 min) divided attention task was unchanged. Visual vigilance detection rates improved in non-sleep-deprived individuals who were tested after administration of caffeine in doses of 32–256 mg (Amendola et al., 1998). Fine et al. (1994) confirmed and extended these findings by demonstrating that caffeine affected visual vigilance in rested young males. In that investigation, a 200 mg dose (~2.5 mg kg^{-1}) of caffeine significantly and consistently improved both number of stimulus detections and reaction times to stimuli in comparison to placebo across 12, 10-min test blocks for a total of 2 h of testing (see Fig. 2). Lanini et al. (2016) reported that personalized individual caffeine doses designed to match participants' habitual breakfast-time caffeine intake (doses ranged from 25 to 300 mg or ~ 0.3 to 4 mg·kg^{-1}) improved simple and sustained attention on the psychomotor vigilance task. In this study, caffeine significantly reduced mean reaction time and led to less variable response times from the beginning to the end of the 10 min task. Reyner and Horne (1997, 2000) reported that a 200 mg dose of caffeine significantly improved the lane-tracking

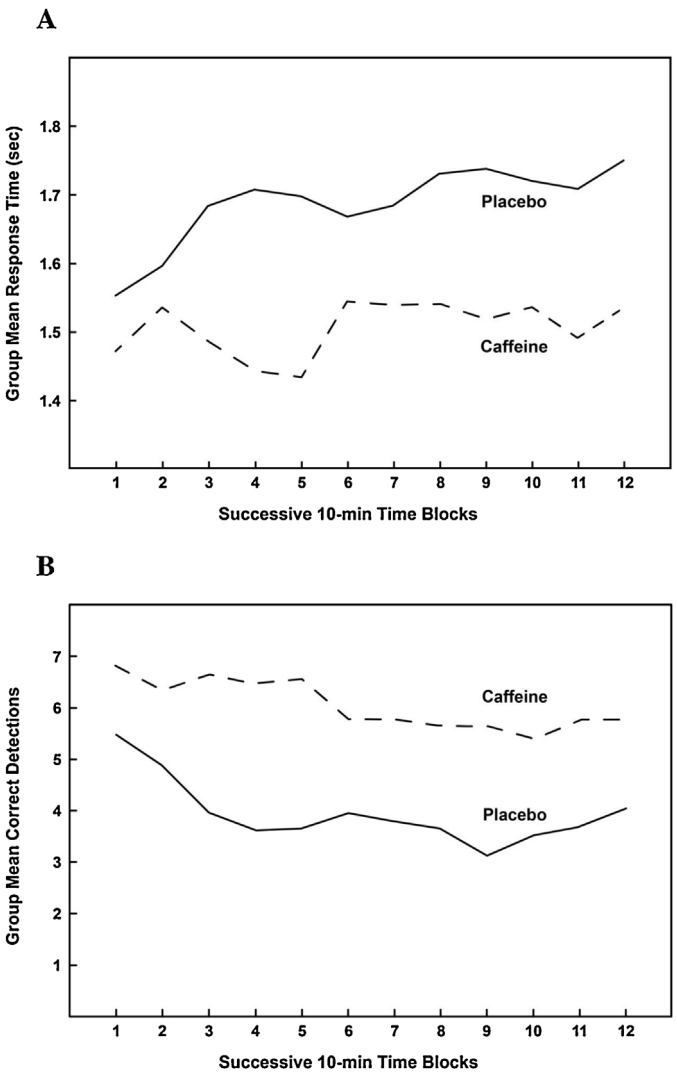

Fig. 2. Effect of 200 mg caffeine versus placebo on reaction time (A) and stimulus detection (B) in a visual vigilance task. Redrawn from Fine et al. (1994).

performance of sleep-restricted subjects during monotonous, 2-h, afternoon and early-morning drives in an automobile driving simulator. In a separate "real-world" relevant study with Air Force pilots, Doan et al. (2006) found that two 200-mg doses of caffeine (spaced 4 h apart) maintained several aspects of cognitive performance including vigilance over 9 h of overnight testing simulating a reconnaissance mission in a U-2 aircraft.

In summary, caffeine's effects on vigilance are very consistent from study to study. Even small doses (32 mg or ~0.5 mg kg^{-1}) can have beneficial effects, often regardless of whether subjects are well-rested or not (Lieberman, 1992; Nehlig et al., 1992). Reviews have noted that caffeine reliably enhances vigilance independent of gender, age, and the normal daily intake levels (at least within the 0–400 mg range or up to about 5.5 mg kg^{-1}) of the individuals studied (Lieberman, 1992; Smith, 2002).

3.3. Attention

Attention is the process of focusing on and selecting particular aspects of available task-relevant information while suppressing other less-relevant aspects (Smith and Kosslyn, 2007), and is different than vigilance- the ability to sustain performance on a task for a prolonged period of time (Oken et al., 2006). On a repeat digit detection task, caffeine in doses ranging from 40 mg

to approximately 280 mg (~0.5–4 mg kg^{-1}) improved both speed and accuracy in rested volunteers (Maridakis et al., 2009a, 2009b; Smith, 2009; Smith et al., 1992). On a focused-attention, choice-reaction-time test, caffeine (~100–150 mg or 1.2–2.0 mg kg^{-1}) significantly improved response speed in rested subjects, and sometimes simultaneously improved accuracy as well (Heatherley et al., 2005; Smith et al., 2005). There is some debate in the literature regarding the impact of caffeine on simple versus complex attention tasks, but Einother and Giesbrecht (2013) concluded that caffeine had positive effects on both. Simple tasks benefitted from doses ranging from 12.5–400 mg (~0.2–5.5 mg kg^{-1}); and more complex tasks, to include the rapid visual information processing task, the flanker task, and the switch task, benefitted from doses in the 60–400 mg (~0.75–5.5 mg kg^{-1}) range.

Evaluation of the impact of 3 mg kg^{-1} caffeine on categorical search, Stroop and flanker tasks led Renda et al. (2015) to conclude caffeine has a general positive impact on attention, and in tasks involving alerting, orienting and (verbal) executive control, caffeine positively affects different aspects of attention. These authors suggested some variability noted in previous studies of caffeine's effects may be in part due to variations in the genetic makeup of participants, especially in relation to genes affecting adenosine metabolism. Nevertheless, there appears to be consensus in the literature that a broad range of caffeine doses exert a positive impact on attention, appearing to reach an asymptote at doses of 200–300 mg (~2.5–4.0 mg kg^{-1}).

3.4. Acute effects on memory

Investigations on the effects of caffeine and short-term memory have produced mixed results. Warburton et al. (2001) tested 42 rested participants following ingestion of an energy drink containing 80 mg (~1 mg kg^{-1}) of caffeine, and found that while consumption of the beverage improved attention and verbal reasoning, there were no differences in verbal or non-verbal memory. These results tend to support those of Amendola et al. (1998) who found that caffeine in doses of 64, 128 and 256 mg (~1–3.5 mg kg^{-1}) resulted in a dose-dependent improvement in vigilance and mood, but had no significant effects on subjects' memory of words presented in a set word list. Terry and Phifer (1986) conducted a study on non-sleep-deprived college students and found that 100 mg (~1.5 mg kg^{-1}) of caffeine actually led to poorer recall of words, particularly words appearing in the middle or end of the memorized list. However, this study was not rigorously controlled.

Studies of the effects of caffeine on other aspects of memory also are inconsistent. Caffeine's effects on retrieval and recognition memory are variable, and its effects on encoding may depend on the subject's level of arousal [see Smith (2005) for a detailed review]. When caffeine has positive effects on specific aspects of memory, they may be mediated by its effects on lower order functions such as attention, and as previously noted, they often follow the U-shaped activation curve. For example, Mahoney et al. (2012) found an effect of caffeine on false memories in non-habitual users with as little as a 100 mg dose (~1.5 mg kg^{-1}), and while effects peaked at 200 mg (~2.5 mg kg^{-1}), a higher 400 mg (~5.5 mg kg^{-1}) dose did not result in a further increase. Subjects with the highest arousal increases due to caffeine administration also tended to produce the highest false recall and recognition rates, while veridical verbal memory was unaffected.

Evaluations of post-training effects of caffeine on cognitive- and motor-memory encoding and recall have produced mixed results. Hussain and Cole (2015) found that post-training administration of a 200 mg (~2.5 mg kg^{-1}) dose of caffeine exerted no significant impact on next-day patterns of re-learning, mean performance learning magnitudes, mean performance learning rates, or mean performance retention on a continuous isometric visuomotor tracking task. These results contrast with those of other investigators who have investigated effects of caffeine on memory encoding/recall in both animals and humans (Favila and Kuhl, 2014). In particular, they contradict Borota et al. (2014) who found administration of 200 mg caffeine during the memory encoding phase of testing improved subjects' next-day abilities to correctly discriminate between previously learned items and similar "lure items." Such discrepant findings may indicate the effects of caffeine on encoding and retention depend on the memory task being studied (Angelucci et al., 1999). Further study of the effects of caffeine on memory processing is essential to resolve these issues.

3.5. Chronic effects on memory

Most research on memory has focused on the acute effects of caffeine administration, but there have been a few investigations on the impact of long-term or habitual caffeine use. These generally suggest a beneficial effect of caffeine. Epidemiological reports have suggested a link between chronic caffeine consumption and a reduced risk of developing neurodegenerative diseases (Cappelletti et al., 2015), although a recent meta-analysis of observational studies called the association between coffee/tea consumption and cognitive disorders (specifically, dementia, Alzheimer's disease, cognitive impairment and cognitive decline) into question (Kim et al., 2015). Nevertheless, a study of 9003 adults by Jarvis (1993) found a positive relationship between habitual caffeine consumption and performance on verbal memory, visuospatial reasoning and reaction time tasks. These effects became stronger with increasing age. This is consistent with a study of 1875 adults conducted by Hameleers et al. (2000), which observed that habitual caffeine consumption was associated with better long-term, but not short-term, verbal memory. The results also were partially consistent with those of Johnson-Kozlow et al. (2002) who observed that elderly women (but not men) who consumed large amounts of caffeine throughout their lifetimes performed better than non-caffeine drinkers on memory and other cognitive tasks. Perhaps these memory effects in older adults are associated with the antiepileptic and neuroprotective improvements that have theoretically been linked to long-term caffeine consumption (Fredholm, 1995). Alternatively, they simply may be due to the fact that healthier (and therefore more cognitively intact) elderly subjects choose to consume more caffeine than their unhealthy counterparts as there is good evidence health concerns lead to curtailment of caffeine consumption (Soroko et al., 1996). Interestingly, Harvanko et al. (2015) failed to observe a positive relationship between routine self-regulated caffeine consumption and reaction time, vigilance, response inhibition or decision-making in young adults, suggesting that while higher average caffeine intake may attenuate cognitive declines in older adults, a similar effect is not present in younger subjects.

3.6. Executive function

Relatively few studies have examined the effects of caffeine intake on higher level "executive" skills that "manage" lower level functions such as reasoning and decision-making. Thus, there is little definitive information regarding the impact of caffeine on the ability to resolve cognitive conflicts, inhibit automatic or impulsive responses, plan strategic actions, and flexibly react to changing circumstances. These important skills of everyday life are difficult to evaluate. Also, as noted by Brunyé et al. (2010a), there are substantial methodological differences across the few studies examining caffeine's effects on executive function. The use of different caffeine doses, the testing of habitual vs. non-habitual consumers, the wide variations in the degree to which subjects are sleep deprived or

sleep restricted, and substantial disparities in the assessment tasks are just some of the factors contributing to discrepant findings in the literature concerning caffeine's impact on executive functions.

Brunyé et al. (2010b) used the Attention Network Test (ANT) to assess the effects of caffeine on conflict-resolution and impulsivity-inhibition in rested volunteers, and reported that caffeine improved executive control of low habitual caffeine users in a dose-dependent fashion (reaching an asymptote at 200 mg or ~2.5 mg kg^{-1}). Brunyé et al. (2010b) also found dose-dependent improvements in ANT performance among non-sleep-deprived, high habitual caffeine consumers (although a larger 400 mg (~5.5 mg kg^{-1}) dose of caffeine was required). Thus, since visual focus and impulse control are complex cognitive skills, data from the ANT support a positive role for caffeine enhancing higher-order processes.

In a study conducted with sleep-deprived volunteers, Gottselig et al. (2006) failed to detect a beneficial effect of caffeine on higher-order cognition assessed by the Random Number Generation (RNG) test which measures response inhibition and use of non-redundant, non-stereotypical strategies. The authors found that while 200-mg (~2.5 mg kg^{-1}) doses of caffeine administered at the 11th and 23rd hours of continuous wakefulness didn't mitigate sleepiness-related rule violations and stereotypical responses, it did partially prevent a decline in the number of responses generated. Therefore, the authors suggested caffeine has positive effects on sustainment of simple, but not complex cognitive processes degraded by sleep loss. However, an alternative interpretation, given caffeine's differential effects across the arousal continuum, is the extent of sleep deprivation generated by Gottselig et al. (2006) was not sufficiently severe to reveal caffeine's alerting properties.

In contrast to the above, Soar et al. (2016) found that even a low dose of caffeine (50 mg or ~0.7 mg kg^{-1}) enhanced executive functions as measured by performance on the Jansari assessment of Executive Functions (JEF©) task. Not only was overall performance on the JEF© enhanced, but individual constructs of planning, creative thinking, event-based prospective memory, time-based perspective memory and action-based perspective memory also were enhanced compared to a decaffeinated control condition. Interestingly, similar positive results were not observed on Stroop inhibitory control despite the fact caffeine generally improved speed of responding regardless of whether the stimuli were congruent or non-congruent. These findings call into question the validity of Stroop as a measure of executive function. However, since inhibitory control is not assessed by the JEF©, it is unclear whether different conclusions about caffeine and this particular higher-order process are due to methodological/validity issues or whether they are due to the fact caffeine actually exerts little control over response inhibition.

The Tower of London (TOL) and Tower of Hanoi (TOH) tasks have been used to assess the effects of caffeine on the executive skills of strategic planning and impulse control. These tasks require participants to rearrange stacks of colored objects on pegs to match a designated pattern. Optimal performance apparently relies on subtle differences in executive processing. As has been the case with other attempts to explore the effects of caffeine on executive function, the results from TOL and TOH studies appear confounded by inconsistent design characteristics. Killgore et al. (2009) found a single 600 mg (~8.0 mg kg^{-1}) dose of caffeine given after 44 h of sustained wakefulness led to improvements in TOH time-to-complete but failed to preserve TOL performance. Despite speculation as to why the results from these similar tasks were inconsistent, the authors did not reach any definitive conclusions. A subsequent multi-dose study conducted by Killgore et al. (2014) contradicted their earlier study. In that study, repeated 200 mg (~2.5 mg kg^{-1}) doses of caffeine given across 3 nights of continuous wakefulness significantly improved TOL performance by enhancing planning speed, average response time, and throughput efficiency despite having no effect on the overall number of moves required to solve the puzzles. The authors suggested the observed TOL improvements may have been the result of lower-level efficiency enhancements rather than better higher-order solution processing but, as is the case with other findings on caffeine and executive functioning, definitive conclusions will, as suggested by Stafford et al. (2007), require additional study.

3.7. Judgment and risk-taking

There is little research on the effects of caffeine on judging future consequences of current actions, maintaining emotional intelligence and control, rendering accurate self-appraisals, or making sound judgments. As with the executive skills discussed above, it is unclear whether caffeine exerts differential effects in rested versus sleep-deprived individuals, since virtually all studies on risk-taking and cognitive-affective (emotional) functions have been conducted on sleep-deprived volunteers. Thus, caffeine's observed impact in these studies may be secondary to caffeine's alerting properties. One study of caffeine's effects on non-sleep-deprived habitual users found no improvements in attention, concentration, processing and reaction speed; yet there were positive effects on self-reported energy and activity, and self-appraisals of performance capacity (Ullrich et al., 2015). Thus, the authors concluded caffeine made subjects "feel smarter" even in the absence of objective evidence that this was the case.

Overall, studies show that caffeine exerts little impact on complex judgment and risky-decision-making (Killgore, 2011). However, in one investigation 600 mg (~8 mg kg^{-1}) of caffeine improved ability of sleep-deprived subjects to make subtle judgments about complex emotional expressions (Huck et al., 2008). In contrast, Killgore et al. (2007) examined the impact of repeated 200 mg (~2.5 mg kg^{-1}) doses of caffeine (given every 2 h for a total of 800 mg or ~10.5 mg kg^{-1}) on the performance of a gambling task after 51 and 75 h of continuous wakefulness and found caffeine was ineffective at ameliorating sleepiness-related increases in risk-taking. In addition, an earlier study of effects of sleep loss and caffeine on ability to accurately judge the humor content of verbal statements and visual images (Killgore et al., 2006) found administration of a 600 mg dose did not restore humor appreciation (a highly-developed cognitive-affective ability) to pre-sleep-deprivation levels, even though caffeine-related improvements in vigilance were observed. The absence of caffeine's effect on humor is consistent with subsequent observations regarding the impact of caffeine (and other stimulants) on risk-taking. Killgore et al. (2008) found that a 600 mg dose of caffeine failed to normalize the propensity of sleepy subjects to engage in dangerous behaviors, to seek out loud and exciting activities, or to appropriately balance risk-taking cost/benefit perception (i.e., the cost of pushing limits versus the benefits of playing it safe). In summary, the limited evidence available suggests that while caffeine effectively promotes alertness and vigilance in sleep-deprived individuals, its impact on complex judgment, emotional discernment, and decision-making is uncertain.

3.8. Summary – cognitive performance

Caffeine increases alertness when individuals are rested or fatigued (Smith, 2011), and the effects are dose-related (Davidson and Smith, 1991; Nehlig, 2010). Moderate doses (100–300 mg or ~1.5–3.0 mg kg^{-1}) typically are beneficial while higher doses (above 400 mg or ~5.5 mg kg^{-1}) are more likely to result in anxiety and may, in non-sleep deprived non-users of caffeine, impair performance.

Caffeine exerts its most reliable beneficial effects on vigilance tasks. Caffeine's positive effects are present in rested individuals (Lieberman et al., 2010, 1987b, 1987a; Smith, 2005) and in sleep-deprived individuals (Lieberman et al., 2002; Smith, 2011; Weiss and Laties, 1962; Wesensten et al., 2002, 2004), and likely occur because caffeine reverses decrements in alertness associated with prolonged maintenance of attention. Caffeine also reliably enhances the fundamental cognitive processes that underlie all types of performance such as reaction time (Nehlig, 2010; Smith, 2002) and attention (Einother and Giesbrecht, 2013; Smith, 2011). The acute effects of caffeine on memory are less consistent and appear, among other things, to be influenced by whether or not the task is boring or engaging (Amendola et al., 1998; Anderson and Revelle, 1983). The chronic effects of caffeine intake on memory may be positive (Hameleers et al., 2000) perhaps due to neuroprotective effects (Fredholm, 1995). However, the evidence is not definitive and has been challenged by other studies (Boxtel et al., 2003). The effects of caffeine on higher-order executive functions are unclear as such functions are especially difficult to assess; therefore, additional research in rested, as well as sleep-deprived, individuals is warranted (Killgore, 2011; Lieberman, 1992).

In summary, across a wide array of circumstances, moderate doses of caffeine (approximately 32–300 mg or ~0.5–4.0 mg kg^{-1}) improve vigilance, learning, and mood. Caffeine may be particularly beneficial when factors that degrade performance are present.

4. Effects on physical performance

Caffeine's ergogenic properties were first reported over 100 years ago (Rivers and Webber, 1907). Differences in daily use of the drug and exercise routines were identified as important factors for interpreting responses to caffeine ingestion in this early report, which only had two participants. Other early reports also had low statistical power due to the small numbers of participants (Alles and Feigen, 1942; Asmussen and Bøje, 1948; Foltz et al., 1942a, 1942b; Ganslen et al., 1964; Haldi et al., 1941; Margaria et al., 1964; Thornton et al., 1939). In addition, it was noted there were 'responders' and 'non-responders' to caffeine (Alles and Feigen, 1942; Foltz et al., 1942a; Thornton et al., 1939). Reports also cited differences in response between exercise trained and untrained subjects (Foltz et al., 1942a, 1942b, 1942c), the duration of exhausting work (Asmussen and Bøje, 1948) or dose ingested (Alles and Feigen, 1942; Haldi et al., 1941) and the relationship between reduced sensations of pain and fatigue and improvements in work performance following the ingestion of the drug (Foltz et al., 1942a). Rarely were the doses normalized to the body mass of the participants (Haldi et al., 1941) but typically absolute amounts of 200–300 mg (or 3–4 mg kg^{-1}) were infused (Foltz et al., 1942a) or ingested (Alles and Feigen, 1942; Asmussen and Bøje, 1948; Haldi and Wynn, 1946; Margaria et al., 1964; Thornton et al., 1939).

Prior to 2004, athletes were disqualified from Olympic competition if urine levels of caffeine exceeded 12 μg mL^{-1}. Graham and Spriet (1991) examined running and cycling performance as well as urine concentrations of caffeine following a 9 mg kg^{-1} dose. Performance improved for both modes of exercise. Although mean urinary caffeine concentrations were below 12 μg·mL^{-1}, two participants exceeded this concentration following one or both of the performance tests, implying that a somewhat lower dose of caffeine would be required to ensure that these threshold limits of detection were not exceeded. Since caffeine was removed from the banned substance list of the World Anti-Doping Agency in 2004, there has been renewed research interest about the drug's impact in numerous sporting activities. In addition, use of caffeine by well-trained athletes during competition is common but athletes receive little information about the moral or ethical issues concerning the use of caffeine as an ergogenic aid (Chester and Wojek, 2008). The following section reviews evidence for the ergogenic effects of caffeine on physical performance and is subdivided into activities involving: 1) prolonged endurance exercise; 2) muscle strength and muscle endurance; and 3) high-intensity exercise and intermittent sprints. Section 4.4 also includes a discussion of the effects of caffeine on muscle pain and ratings of perceived exertion as they relate to changes in exercise performance following caffeine ingestion.

4.1. Endurance exercise

The evidence that either supports or refutes caffeine's effect on endurance exercise performance is summarized in Supplementary Table 2. Of the 59 studies described, 46 or 78% presented ergogenic findings for some or all of their experimental trials involving caffeine supplementation.

It was initially proposed by Costill and colleagues (Costill et al., 1978; Essig et al., 1980) that following a 4–5 mg kg^{-1} (~300–400 mg for a 75 kg individual) dose of caffeine, its stimulatory actions on free fatty acid release from adipose tissue could spare muscle glycogen utilization during exercise and prolong performance during exhaustive submaximal exercise. The drug's effect on intramuscular glycogen utilization during exercise, however, was not replicated in subsequent work following caffeine ingestion of 6 mg·kg^{-1} (~450 mg) (Graham et al., 2000; Greer et al., 2000; Jackman et al., 1996; Laurent et al., 2000). Graham et al. (2000) also conclusively demonstrated using direct Fick measures, from leg blood flow and arterial and venous blood sampling, and muscle biopsies that neither carbohydrate nor fat metabolism were altered during 60 min of exercise at 70% $\dot{V}O_{2max}$ following the ingestion of caffeine. The mechanism currently believed to account for the ergogenic effects of caffeine is CNS activation resulting from adenosine receptor A_1 and A_{2a} blockade (Davis et al., 2002; Zheng et al., 2014), not a shift in fuel utilization (Costill et al., 1978; Essig et al., 1980). As noted earlier in Section 2, adenosine A_1 and A_{2a} receptors form functional heteromers with dopamine D_1 and D_2 receptors. Blocking of adenosine A_{2a} receptors with caffeine, for example, promotes a direct excitatory potentiation of D_2 receptors and increases psychomotor activity in animals (Ferré, 2016).

The ergogenic response to caffeine during endurance exercise is affected by several factors, such as dose (Desbrow et al., 2009; Graham and Spriet, 1995), training status (O'Rourke et al., 2008), timing of ingestion (Conway et al., 2003; Cox et al., 2002), history of caffeine use (Bell and McLellan, 2002), withdrawal effects (Irwin et al., 2011; Van Soeren and Graham, 1998), source of caffeine (Graham et al., 1998; Hodgson et al., 2013) and the performance measures used (Bridge and Jones, 2006; Doherty and Smith, 2004; Ganio et al., 2009). In addition, studies have presented individual as well as mean changes to demonstrate there are 'responders' and 'non-responders' to the effects of caffeine (Desbrow et al., 2009; Jackman et al., 1996; Spriet et al., 1992). It remains unclear whether these differences in response are related to genetic polymorphisms discussed earlier (Graham et al., 2008) and/or are due to day-to-day individual variation in performance.

In most research studies, caffeine has been ingested as a capsule or dissolved in a drink approximately 1 h prior to the start of exercise, providing sufficient time for absorption and attainment of peak circulating concentrations (Blanchard and Sawers, 1983; Robertson et al., 1981), although peak performance has not necessarily coincided with attainment of peak caffeine concentrations (Skinner et al., 2013) and time to peak concentration varies considerably among individuals – anywhere from 0.5 to 3.0 h (Desbrow et al., 2009; Skinner et al., 2013). As depicted in Fig. 3, the ergogenic response to the drug is evident over a range of plasma concentrations. Dose response studies have typically reported optimal performance benefits with moderate doses between 3 and

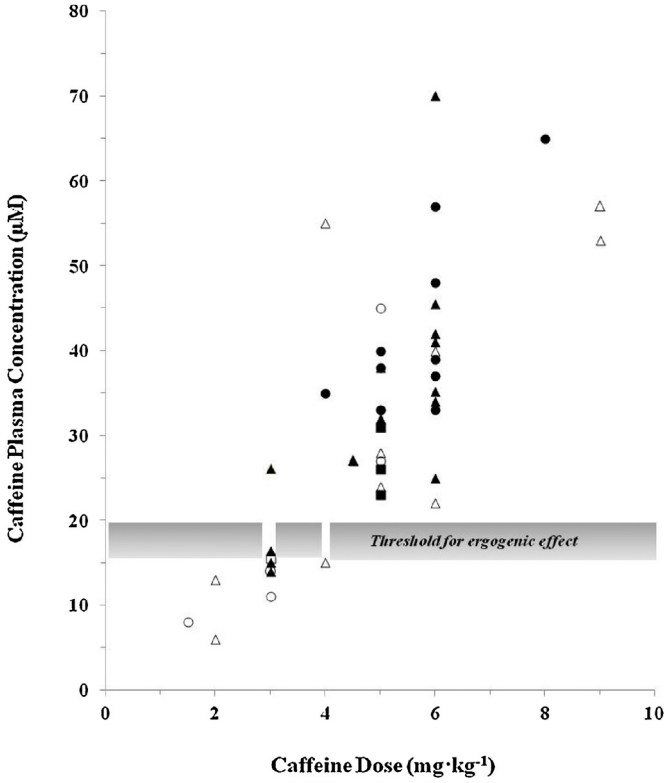

Fig. 3. The relationship between caffeine dose and circulating plasma concentrations for their effect on time-to-exhaustion or time-trial studies on endurance exercise performance. In these studies caffeine was provided approximately 1 h or longer before exercise. Open symbols indicate a non-significant finding whereas closed symbols reported significant effects. Circles, squares and triangles indicated that study participants were regular caffeine users, non-users or a mixture of both, respectively. Data are presented from 27 papers that reported circulating concentrations of caffeine following a given dose of caffeine. A threshold plasma concentration approximating 15–20 μM appears necessary before a predominance of positive findings become evident.

7 mg kg^{-1} (~250–500 mg) rather than with higher doses (Bruce et al., 2000; Cadarette et al., 1982; Graham and Spriet, 1995), as high doses can induce negative side-effects such as gastrointestinal distress, or an asymptotic ergogenic response in spite of increased dose and circulating concentration (Desbrow et al., 2012; McLellan and Bell, 2004). In addition, with one exception (Jenkins et al., 2008), performance is not improved when caffeine doses are below 3 mg kg^{-1} ingested approximately 1 h prior to exercise (Cadarette et al., 1982; Desbrow et al., 2009; Ryan et al., 2013). It should also be noted the ergogenic response to caffeine is maintained for several hours following ingestion of a moderate 5 mg kg^{-1} (~375 mg) dose of the drug despite falling circulating concentrations (Bell and McLellan, 2002, 2003).

Collectively, these data imply that the ergogenic response to caffeine is dependent upon attaining a threshold circulating concentration of approximately 15–20 μM (see Fig. 3), a concentration sufficient to block adenosine receptors. This observation is consistent with the lack of an ergogenic response observed by Van Soeren and Graham (1998) when plasma caffeine concentration was 10 μM prior to the placebo trial for the no withdrawal phase of their experimental design. This observation is also consistent with the ergogenic response observed by Graham and Spriet (1995) when plasma concentrations reached 18 μM prior to exercise following the ingestion of 3 mg kg^{-1} of caffeine. This threshold concentration appears to be lower for non-users of the drug (Bell and McLellan, 2002). Furthermore, exercise itself may alter the sensitivity of adenosine receptors and lower the threshold concentration such that a smaller dose provided during or at the beginning of exercise may be equally or more effective than similar or larger doses provided 1 h prior to exercise (Cox et al., 2002; Ryan et al., 2013). Likewise, smaller doses provided during warm-up exercise immediately prior to performance testing (Lane et al., 2014) or immediately prior to and during exercise (Hogervorst et al., 2008; Kovacs et al., 1998) can be ergogenic and may be as effective as a single larger dose ingested 1 h prior to exercise (Conway et al., 2003). Although the effects of acute exercise on adenosine receptor and caffeine sensitivity are not known, a single 1-h bout of exercise has been reported to alter the adenosine receptor-mediated response to insulin in the soleus muscle of the rat (Langfort et al., 1993). Thus, it is conceivable that sensitivity of the adenosine receptors to caffeine is altered during, and for several hours following, a single exercise bout.

Since absorption of caffeine is slowed following ingestion of food and the circulating concentration of the drug is reduced (Dews, 1982; Fleischer et al., 1999), a given dose ingested in a fasted or non-fasted state may lead to circulating concentrations that are below or above, respectively, the threshold concentration necessary to generate an ergogenic response. For example, doses of caffeine at or below 4 mg kg^{-1} (~300 mg) ingested following a meal and prior to exercise can lead to circulating concentrations that are non-ergogenic (Desbrow et al., 2009; Skinner et al., 2010), whereas this same dose provided in a fasted state prior to exercise can lead to improved performance (Lane et al., 2013; McLellan and Bell, 2004). In addition, although plasma caffeine concentrations may be lower when ingested following a meal, these concentrations may still lead to an ergogenic effect if exercise has been performed earlier in the day (Bell and McLellan, 2003), providing additional evidence that acute exercise itself increases adenosine receptor sensitivity to a given circulating concentration of the drug.

4.1.1. Exercise performance in the heat

Caffeine's ability to induce mild diuresis (Wemple et al., 1997) and thermogenic (Ely et al., 2011; Poehlman et al., 1985) effects at rest have been postulated to adversely impact exercise performance in the heat (Falk et al., 1990; Wemple et al., 1997). Some investigations have reported an increase in core temperature following caffeine ingestion during exercise in the heat (Cheuvront et al., 2009; Ely et al., 2011; Kim et al., 2011; Millard-Stafford et al., 2007), but often these increases are observed at rest and the change in heat storage during exercise is similar to placebo conditions (Cheuvront et al., 2009; Ely et al., 2011; Kim et al., 2011). In contrast, several studies have shown that caffeine, in doses ranging from 3 to 9 mg kg^{-1} (~250–700 mg), has no effect on the core temperature response during prolonged exercise in normal (~20 °C) (Dunagan et al., 1998; Ganio et al., 2011a), warm (~25–30 °C) (Falk et al., 1990; Wells et al., 1985) or hot environments (>30 °C) (Del Coso et al., 2009; Ganio et al., 2011a; Roti et al., 2006; Wemple et al., 1997). In addition, caffeine does not influence forearm blood flow (Del Coso et al., 2009), sweat rate or fluid-electrolyte balance (Del Coso et al., 2009; Ganio et al., 2011a; Millard-Stafford et al., 2007; Roti et al., 2006; Wemple et al., 1997), urine production (Ganio et al., 2011a; Millard-Stafford et al., 2007; Wemple et al., 1997) or heat storage (Ely et al., 2011) during exercise in the heat. Further, there is no evidence to support the contention that chronic consumption of caffeine alters fluid-electrolyte balance or hydration status (Armstrong, 2002; Maughan and Griffin, 2003; Roti et al., 2006). Thus the ingestion of caffeine in doses up to 9 mg kg^{-1} (~700 mg) prior to or during exercise in hot environments should not be avoided due to fear of increased fluid-electrolyte loss or a reduced exercise tolerance in the heat (Armstrong et al., 2007; Zhang et al., 2015).

Caffeine ingestion has been shown to increase peak cycling power throughout 2 h of exercise in the heat and prevent the

reduction in maximal voluntary contraction force and motor unit activation observed following exercise without drug ingestion (Del Coso et al., 2008). Since electrically evoked contractile properties were not affected by caffeine, the authors concluded caffeine had influenced CNS motor unit activation rather than directly affecting muscle function. To date, only one study has examined the ergogenic effects of caffeine in both cool and hot environments with the same well-hydrated participants (Ganio et al., 2011a). Under these conditions, although performance was decreased in the heat, the ergogenic effect of the 3 mg·kg^{-1} (~250 mg) dose of caffeine was similar in both the cool and hot environments (Ganio et al., 2011a). The available evidence clearly indicates caffeine does not exert a negative influence on exercise performance in the heat.

4.2. Muscle strength and endurance

The evidence-base that either supports or refutes caffeine's effect on muscle strength and associated tests of muscular endurance is summarized in Supplementary Table 3. Two-thirds of the 33 papers presented in this Supplementary Table described an ergogenic effect for experimental trials involving caffeine ingestion.

Very high, toxic doses of caffeine enhance intracellular Ca^{2+} release (see Fig. 1) and directly impact the excitation-contraction coupling process and generation of force. However, as reviewed elsewhere (Tallis et al., 2015), at a physiological concentration of 70 μM, caffeine increased contractility, cytosolic Ca^{2+} release and prolonged fatigue in an isolated mammalian skeletal muscle fiber preparation. Further, in intact human skeletal muscle, ingestion of low to moderate doses of caffeine has been shown to increase force generation during low-frequency stimulation (Lopes et al., 1983; Mora-Rodriguez et al., 2012; Tarnopolsky and Cupido, 2000), consistent with a direct effect of the drug on Ca^{2+} release. In contrast, Cafarelli and colleagues have shown that caffeine increased motor unit activation and maximal voluntary contraction force without affecting measures of motorneuron excitability or contractile properties, implying that the drug's effect on maximal force was occurring at a supraspinal level (Kalmar and Cafarelli, 1999; Plaskett and Cafarelli, 2001). It is not clear why some findings imply a direct effect of caffeine on intramuscular Ca^{2+} release whereas other findings do not.

Others have reported that maximal isometric force and isokinetic torque throughout a range of contraction velocities were increased following caffeine ingestion (Bazzucchi et al., 2011; Del Coso et al., 2012; Duncan et al., 2014; Park et al., 2008), an effect attributed to faster muscle fiber conduction velocity (Bazzucchi et al., 2011), as well as increased motor unit activation (Duncan et al., 2014; Park et al., 2008). Based on a meta-analysis, Warren et al. (2010) concluded caffeine increased strength of the leg extensors by enhancing motor unit activation and increasing muscular endurance during open-ended tests. These conclusions are consistent with the proposed central command and arousal and motivation mechanisms hypothesized to explain caffeine's effects on physical performance.

4.3. High-intensity exercise

Supplementary Table 4 summarizes the effects of caffeine on the performance of high-intensity exercise. Fifty-one or 69% of the studies described in Supplementary Table 3 were associated with an ergogenic effect following doses between 3–10 mg kg^{-1} (~250–750 mg) of caffeine within their experimental design.

The energy demand during high-intensity exercise is initially generated through anaerobic pathways but as the duration of effort increases a greater proportion of energy turnover is supplied through aerobic metabolism. The effects of caffeine in doses ranging from 3 to 10 mg kg^{-1} (~250–750 mg) have been studied during incremental exercise to maximum, tests that require maximal all-out efforts lasting 5–75 s, high-intensity repeated sprints, tests of agility and high-intensity tests to exhaustion or time-trials lasting several minutes. Typically, caffeine has no effect on total exercise time during an incremental test to maximum (Dodd et al., 1991; Powers et al., 1983). In addition, peak power and fatigue during all-out efforts lasting less than 60 s are most often unaffected by the drug (Bell et al., 2001; Glaister et al., 2012; Greer et al., 1998). However, as the duration of the all-out effort extends beyond 60 s, enhanced performance is observed (Bell et al., 2001; Jackman et al., 1996; Silva-Cavalcante et al., 2013; Simmonds et al., 2010; Wiles et al., 1992) and has been attributed to a direct effect on the active muscle through an increased glycolytic flux and accumulated oxygen deficit (Bell et al., 2001) or anaerobic power (Silva-Cavalcante et al., 2013), maintenance of intramuscular electrolyte homeostasis (Jackman et al., 1996; Simmonds et al., 2010), or CNS effects, as indicated by a reduced perception of effort (Wiles et al., 1992).

Repeated all-out brief sprints and intermittent high-intensity efforts are often required in team and court sports. Studies have reported mixed results for the impact of caffeine doses between 3–6 mg kg^{-1} (~250–450 mg) on speed, power and fatigue during these sports. For example, caffeine had no effect on 10 repeated 20-m sprints completed with about 6-s rest between each sprint (Paton et al., 2001) or repeated sets of all-out 4-s cycling sprints with 20-s rest between sprints (Lee et al., 2014a, 2014b). Others have also reported that following caffeine ingestion reduced peak and average power or the time to reach peak power during repeated all-out efforts lasting 30- or 60-s (Crowe et al., 2006; Greer et al., 1998). In contrast, caffeine has improved the motor skills necessary to be successful during simulated taekwondo, tennis, rugby and soccer matches (Hornery et al., 2007; Lara et al., 2014; Roberts et al., 2010; Santos et al., 2014), and improved agility, decision and movement time before and after four, 20-min circuits that replicated the movement patterns and exercise demands in team sports (Duvnjak-Zaknich et al., 2011). Some of the discrepancy across these findings can be attributed to the duration of the rest interval between the repeated high-intensity exercise bouts with no effects being observed following drug ingestion when recovery intervals are less than 10 s (Paton et al., 2001). Lee et al. (2012) reported that caffeine's ergogenic effects on peak and mean power during 4-s sprints remained evident during repeated sets with 90-s recovery intervals, but with shorter recovery intervals of 20 s performance on caffeine versus placebo actually decreased during the second set of 12 repeated sprints.

Although direct effects of caffeine on the muscle membrane potential have been suggested to explain the ergogenic effects of the drug during these high-intensity efforts (Simmonds et al., 2010), reports of CNS effects of caffeine that reduce sensations of pain and effort should not be discounted (Plaskett and Cafarelli, 2001; Roberts et al., 2010; Wiles et al., 1992).

4.4. Effects on muscle pain and perceived exertion

Adenosine levels increase during skeletal muscle contraction (Fredholm, 1995; Marshall, 2007). Because pain is induced by adenosine binding to A_1 receptors (Gaspardone et al., 1995; Sawynok, 1998), studies have examined whether caffeine can reduce the sensations of pain experienced during various types of exercise. These studies report reduced sensations of pain following caffeine ingestion during ischemic arm exercise (Myers et al., 1997), moderate- (Duncan and Hankey, 2013; Ganio et al., 2011b; Motl et al., 2006; O'Connor et al., 2004) and high-intensity (Gliottoni et al., 2009; Gliottoni and Motl, 2008) cycling, cross-country skiing (Stadheim et al., 2013, 2015) and following resistance exercise (Maridakis et al., 2007). The magnitude of the drug effect appears to be related to the intensity of exercise (Gliottoni et al., 2009;

O'Connor et al., 2004), level of pain (Gonglach et al., 2016), ambient temperature (Ganio et al., 2011b), sex (Motl et al., 2006; O'Connor et al., 2004) and anxiety sensitivity (Gliottoni and Motl, 2008), but appear unrelated to habitual use (Gliottoni et al., 2009). Following several sets of eccentric contractions that produce muscle soreness, caffeine has also been shown to reduce sensation of pain during maximal voluntary isometric or submaximal eccentric contractions 24- or 48-h post exercise (Maridakis et al., 2007).

In a similar context, ratings of perceived exertion during or following exercise are often reduced and time-to-exhaustion or total work increased following caffeine ingestion (Bell and McLellan, 2002, 2003; McLellan and Bell, 2004) or perceived exertion remains the same while time-trial performance improves (Bruce et al., 2000; Desbrow et al., 2012; Wiles et al., 1992), indicating more work can be accomplished or higher power outputs generated following the ingestion of the drug. Using meta-analysis, Doherty and Smith (2005) reported ratings of perceived exertion were reduced by approximately 6% with caffeine ingestion during constant load exercise and that change in these ratings could account for almost 30% of the variance in time-to-exhaustion tests following ingestion of caffeine. Together with lower ratings of perceived exertion, affective states of pleasure and arousal are increased during constant workrate exercise (Duncan and Hankey, 2013), which could further contribute to the ergogenic effects of the drug. The effects of caffeine on cognitive components of exercise such as perceived exertion and pain provide additional support for a predominantly central mechanism of action of the compound.

4.5. Summary – effects on physical performance

The antagonism of adenosine receptors in the CNS and the resultant interaction with dopamine receptors is now regarded as the principle mechanism of caffeine's action (Davis et al., 2002; Ferré, 2016). It is also now apparent that caffeine has ergogenic properties that can impact performance during many different types of exercise. Of the papers reviewed in Supplementary Tables 2–4, almost 80% reported positive findings during endurance exercise, whereas two-thirds reported ergogenic effects for measures of muscle strength and associated tests of muscular endurance or high-intensity exercise. Except for very short duration anaerobic exercise, there was also a common thread throughout these studies, regardless of the type of exercise, that caffeine reduced perception of effort (Doherty and Smith, 2005) and lowered sensations of pain (Gliottoni et al., 2009; Motl et al., 2003, 2006; O'Connor et al., 2004; Plaskett and Cafarelli, 2001; Stadheim et al., 2013, 2015). Notwithstanding the large body of evidence of caffeine's central effects via adenosine receptors, there have been studies revealing a direct action of caffeine following very high doses of 6–10 mg kg^{-1} (~450–750 mg) on skeletal muscle either through an effect on Ca^{2+} release from the sarcoplasmic reticulum (Lopes et al., 1983; Mohr et al., 1998; Tarnopolsky and Cupido, 2000) or through reduced K^+ efflux (Lindinger et al., 1993; Mohr et al., 2011). In addition, it is apparent that the ergogenic effects of the drug vary, and substantial individual differences in response to caffeine exist. Moreover, very high doses (6 or more mg kg^{-1} or greater than ~450 mg) can degrade physical and cognitive performance as they can produce anxiety and severe gastro-intestinal distress (see Section 6). These individual differences in response to the drug indicate that athletes should always test effects of caffeine on themselves prior to competition to optimize dose, timing of ingestion and period of abstinence prior to competition.

5. Combined effects on physical and cognitive performance

5.1. Exercise studies

Since caffeine has positive effects on cognitive and physical performance when they are studied separately, some experimental designs have tested the drug's effects on both measures of performance. Hogervorst and colleagues (Hogervorst et al., 1999; Kovacs et al., 1998) examined the impact of various doses of caffeinated carbohydrate electrolyte drinks on measures of cognitive function before and after a 1-h cycling time-trial. Moderate (3.2 mg kg^{-1} or ~250 mg) and high (4.5 mg kg^{-1} or ~350 mg) doses of caffeine improved time-trial performance (Kovacs et al., 1998), whereas the low (2.1 mg kg^{-1} or ~150 mg) and moderate doses improved many aspects of cognitive function, such as attention, recognition memory and complex psychomotor speed, following exercise (Hogervorst et al., 1999). Only selective attention was improved with the high dose of caffeine following exercise. Thus, lower doses favored cognitive function and higher doses improved exercise performance so a moderate dose should be recommended if both physical performance and cognitive function improvements are important. Subsequently, Hogervorst et al. (2008) reported that three 100 mg (~1.5 mg kg^{-1}) doses of caffeine consumed before and during exercise improved both time-to-exhaustion and concentration, response speed and detection, and complex processing during, as well as following, exercise.

The exercise challenge selected by Hogervorst and colleagues (Hogervorst et al., 1999; Kovacs et al., 1998), as well as the tests chosen to assess cognitive function, are also important to consider. Other studies have not reported consistent positive effects on both physical and cognitive function following caffeine ingestion (Bottoms et al., 2013; Carr et al., 2008; Crowe et al., 2006). For example, using a 6 mg kg^{-1} (~450 mg) dose of caffeine, Crowe et al. (2006) reported no effects on repeated all-out exercise lasting 60 s, as well as no effects on reaction time or recall assessed before or after the all-out efforts. Similarly, no effects on simple or complex reaction times measured before or after exercise were noted following 3 or 6 mg kg^{-1} (~250 or 450 mg) of caffeine, yet faster average sprint times were recorded during 5 repeated sets (Carr et al., 2008) or fewer misses were observed during a simulated fencing competition (Bottoms et al., 2013). Thus both the dose and timing of caffeine ingested, the exercise challenge selected and the tests chosen to assess cognitive function are important factors that could explain these discrepant findings.

In the next section strong evidence of caffeine's beneficial effect on both cognitive and physical performance is presented in the context of various real-world occupational activities.

5.2. Occupational studies

Military operations could benefit from the use of caffeine since soldiers are required to engage in physically and cognitively challenging activities in extreme environments, while carrying heavy loads (Nindl et al., 2013), with little opportunity to sleep, leading to extensive decrements in cognitive function (Lieberman et al., 2005). Lieberman et al. (2002) were the first to study the effectiveness of caffeine ingestion on cognitive function during a stressful military training exercise which involved 80-h of sleep restriction in combination with extensive physical and mental challenges. Following 72-h of sleep deprivation, a 200 or 300 mg (~2.5 or 4 mg kg^{-1}) dose of caffeine improved several measures of cognitive function including vigilance, reaction time, attention and mood, as well as improving marksmanship (Lieberman et al., 2002; Tharion et al., 2003). Unfortunately, tests of physical performance were not included in this study.

McLellan and co-workers expanded on the theme of caffeine as a physical and cognitive aid in the military environment with a series of laboratory (McLellan et al., 2004; Tikuisis et al., 2004) and field studies (McLellan et al., 2005a,b, 2007) designed to simulate the rigors of sustained operations for soldiers. The caffeine was provided in a gum due to its more rapid absorption through the buccal mucosa (Kamimori et al., 2002). During an initial laboratory study, both marksmanship and physical performance, as indicated by treadmill run times-to-exhaustion and a sandbag piling task, improved when a total caffeine dose of 600 mg (~8 mg kg^{-1}) was provided during overnight hours (McLellan et al., 2004; Tikuisis et al., 2004). A subsequent field study with personnel from a conventional unit assessed live-fire marksmanship accuracy and vigilance, running performance and overnight vigilance in an urban operation setting during a 50-h training exercise (McLellan et al., 2005a). Following the first overnight period that restricted sleep to 3 h, soldiers received either placebo or a total caffeine dose of 600 mg during the second overnight period. Marksmanship performance, assessed by ability to detect targets and shooting accuracy, and vigilance was maintained at control, non-sleep-deprived levels for those receiving caffeine, whereas both measures decreased significantly for the placebo group. However, 5-km run times performed approximately 5 h after the last caffeine dose slowed equally for both groups following the training exercise. This lack of ergogenic response is consistent with the lack of effects of caffeine observed when testing is more than 3 h after dosing and participants are regular users of caffeine (Bell and McLellan, 2002).

Two additional field studies were designed to assess the effectiveness of caffeine in highly-trained Special Forces personnel (McLellan et al., 2005b, 2007). During the first of these studies, vigilance, assessed with an observational field task, was maintained at control levels with administration of 200-mg (~2.5 mg kg^{-1}) doses of the drug but declined by 30% during the overnight testing period with placebo (McLellan et al., 2005b). Marksmanship accuracy, target engagement and response time were unaffected by caffeine in this study. In addition, 6.3 km run times significantly improved for those receiving 200 mg of caffeine approximately 1 h before the run, whereas run times slowed for those receiving placebo.

A subsequent field study was designed to assess caffeine's impact on physical and cognitive performance during repeated nights of sustained wakefulness followed by periods of restricted daytime sleep (Kamimori et al., 2015; McLellan et al., 2007). Vigilance was again maintained at control levels with the use of repeated 200-mg doses of caffeine, whereas performance decreased during the overnight periods with placebo. The use of caffeine also maintained and improved physical performance during an obstacle course test.

Clearly, these studies collectively demonstrate the benefits of using caffeine by both conventional and Special Forces personnel to maintain cognitive and physical performance during periods of sustained operations when opportunities for normal sleep are reduced or removed altogether. The U.S. Department of Defense has made caffeine gum available for uniformed personnel and included it in certain specialty rations (McClung et al., 2011). Repeated doses of approximately 200 mg every 2 h appear to be an effective strategy to maintain cognitive performance during an overnight period of sustained wakefulness, as well as to offset decrements in physical performance associated with sleep deprivation (Kamimori et al., 2015; McLellan et al., 2004, 2005a, 2005b, 2007).

In a similar context, the use of caffeine could prove useful for athletes who compete after travel across multiple time zones when their sleep is disrupted or in occupations demanding physical work and high levels of concentration and alertness with restricted opportunity for sleep, such as factory shift workers, truck drivers and pilots (Doan et al., 2006; Ker et al., 2010; Reyner and Horne, 2000; Ronen et al., 2014; Sharwood et al., 2013; Souissi et al., 2014). For example as highlighted in Section 3.2, the use of specially-formulated caffeinated foods provided to pilots during a simulated 10-h high-altitude nighttime mission maintained cognitive performance at baseline levels, whereas performance significantly decreased during placebo conditions (Doan et al., 2006). Consistent effects of caffeine, however, were not observed during performance of the flight simulator task. Realistic studies similar to these conducted by military researchers should be conducted to evaluate the benefits and risks of caffeine use in a variety of at-risk occupations.

The ability of caffeine to alleviate driver sleepiness has also been studied during both simulated and real driving tasks. Reyner and Horne (2000) reported that a 200 mg (~2.5 mg kg^{-1}) dose of caffeine provided following a night of restricted sleep (limited to 5 h) reduced the number of unintentional lane crossings compared with placebo throughout a subsequent 2-h simulated driving task. Following a night of total sleep deprivation, however, this same dose of caffeine was effective for only 30 min of the driving task, indicating that a larger and/or more frequent dosing of caffeine might be required to restore performance under these conditions. Fewer lane position and steering wheel deviations were also observed during a simulated driving task on a rural road for 150 min following the ingestion of 160 mg (~2 mg kg^{-1}) of caffeine, but driving performance was improved for longer if a short rest was included after 100 min of driving (Ronen et al., 2014). Nighttime performance assessed by unintentional line crossings during 200 km of real highway driving was also improved following the ingestion of coffee (with 200 mg caffeine) compared with decaffeinated coffee, although for 3 of 12 participants performance was not restored to baseline daytime conditions (Philip et al., 2006). Interestingly, the inclusion of a short nap prior to nighttime driving was an equally effective countermeasure as caffeine for younger (Philip et al., 2006) but not middle-aged participants (Sagaspe et al., 2007). It is also noteworthy that the reported use of caffeinated products by long-haul professional drivers for the purpose of staying awake was significantly associated with a 63% reduced likelihood of a road accident (Sharwood et al., 2013).

Without the added stress of sleep deprivation, repeated dosing that totals approximately 300 mg (~4 mg kg^{-1}) of caffeine appears sufficient to improve both physical and cognitive function (Hogervorst et al., 2008, 1999; Kovacs et al., 1998). That caffeine improves both physical and cognitive performance during periods of sleep deprivation suggests these effects are mediated by similar processes. Since sleep loss is known to degrade sensory information processing, attention, and motor activity, in part because of cortex-basal ganglia-thalamus-cortex circuit impairment associated with decreased dopaminergic activity in the striatum and increased adenosine in the cortex and striatum, caffeine's blockade of A_1 and A_2 receptor sites may be responsible for its positive effects in sleep-deprived individuals (Sil'kis, 2014).

To summarize, there are many occupational settings that demand optimal physical and cognitive function to ensure success, workplace safety and productivity. In these circumstances, which may include restricted overnight sleep or periods of sustained wakefulness, repeated dosing of caffeine is one strategy to maintain both physical and cognitive capabilities. The effective dose of caffeine required to affect both physical and cognitive performance is larger when the stress of additional sleep loss is present (McLellan et al., 2004, 2005a,b, 2007). Caffeine should not be considered as a replacement for sleep if opportunities for sleep exist, but the repeated ingestion of caffeine during overnight hours is an effective strategy to mitigate the adverse effects of sleep loss on physical and cognitive function (McLellan et al., 2004, 2005a,b) and caffeine use can extend for several days if there are reduced opportunities for sleep (McLellan et al., 2007). A summary of caf-

Table 2
Caffeine dose (mg kg^{-1} body mass) associated with cognitive and physical effects in both rested and sleep deprived individuals. The range of effective doses was obtained from the findings summarized in Supplementary Tables 1 through 4.

Cognitive/Physical Domain	Caffeine Dose for Effect (mg kg^{-1})	
	Rested	Sleep Deprived
Reaction Time	0.3–4.0 [1 h before testing]	3.0–8.5 [1 h before testing]
Vigilance	0.5–4.0 [1 h before testing]	3.0–8.5 [1 h before testing with smaller dose repeated during period of wakefulness]
Attention	0.3–5.5 [1 h before testing]	2.5–8.0 [1 h before testing]
Acute Memory	1.0–4.0 [equivocal findings]	Unknown
Chronic Effects on Memory	Positive relationship between habitual use (0–10) and performance	Unknown
Executive Function	0.7–5.5 [higher dose required for habitual user]	10.7 [2.7 repeated every 2 h for total 10.7/night for 3 nights]
Judgement/Risk Taking	Unknown	8.0–10.7 [equivocal findings, higher doses represent cumulative total from redosing during overnight]
Endurance Exercise	3.0–9.0 [1 h before, higher dose for users, effects last longer for non-users] 1.5–2.5 [during or following prior exercise]	8.0 [divided unequally over 7 h to restore to control] 8.0 [divided equally over 6 h to improve over control]
Muscle Strength/Power	3.0–6.0 [1 h before]	10.7 [2.7 repeated every 2 h for total 10.7/night for 3 nights]
High-Intensity/Sprint	3.0–10.0 [1 h before to immediately prior to exercise]	10.7 [2.7 repeated every 2 h for total 10.7/night for 3 nights]
Muscle Pain	3.0–10.0 [1 h prior to exercise with smaller dose repeated during exercise, independent of habitual use]	Unknown

feine doses documented to exert cognitive and physical effects in both rested and sleep deprived individuals is shown in Table 2.

6. Side-effects

Some individuals report experiencing negative side-effects of caffeine especially at high doses, such as increased levels of anxiety or gastrointestinal distress, possibly in part due to genetic factors such as the presence of certain adenosine receptor polymorphisms (Childs et al., 2008). Such individuals often are not regular consumers of caffeine (Yang et al., 2010) so their excessive sensitivity to the drug may reduce or eliminate its potential positive effects on physical and cognitive function. Individual differences in the response to a given dose of caffeine were identified as a confounding issue in some of the earliest reports on the ergogenic effects of the drug (Alles and Feigen, 1942; Foltz et al., 1942b; Rivers and Webber, 1907). In more recent work, participants are often asked to report any negative side-effects following caffeine ingestion and occasionally (Conway et al., 2003; Graham and Spriet, 1995; Spriet et al., 1992), but not always (Duvnjak-Zaknich et al., 2011; Graham et al., 1998), performance has been adversely affected among these individuals. At higher doses of caffeine, exceeding about 7 mg kg^{-1} (~500 mg), ergogenic effects sometimes are not observed (Cadarette et al., 1982; Graham and Spriet, 1995), especially among light users or non-users of the drug (Graham and Spriet, 1995), whereas regular users can tolerate higher doses and endurance performance is improved (Spriet et al., 1992). Adverse effects, such as tremors, nausea and nervousness have also been reported among light to moderate users of caffeine following a 600 mg (~8 mg kg^{-1}) dose of caffeine ingested after approximately 40 h of sleep deprivation (Wesensten et al., 2002, 2005). However, when similar or larger doses to 800 mg (~10.5 mg kg^{-1}) caffeine were provided by a gum administered in divided portions throughout 1–3 nights of sustained wakefulness no adverse effects were noted among both nonusers and habitual users of the drug (McLellan et al., 2005a, 2005b, 2007). The potential long-term negative health effects of these higher doses of caffeine, if continued for prolonged periods, is unknown but these doses are clearly greater than the daily limit of 400 mg (~5.5 mg kg^{-1}) recommended as safe for healthy adults (Nawrot et al., 2003) and much higher than the typical intake of the U.S. adult population (approximately 186 mg d^{-1}) (Fulgoni et al., 2015). Sleep patterns may also be adversely affected, especially if caffeine is ingested during exercise in the late afternoon or early evening (Ali et al., 2015; Miller et al., 2014; Salinero et al., 2014). Although extremely rare, very high doses of caffeine can be fatal (Jabbar and Hanly, 2013). Caffeine can be toxic if plasma concentrations of caffeine exceed 250 μM (see Fig. 1). Assuming a 5 mg kg^{-1} caffeine dose results in a circulating concentration between 30 and 40 μM (see Fig. 3), then a 7–8 fold greater dose of caffeine equivalent to 35–40 mg kg^{-1} could be fatal. The median lethal dose (LD50) of caffeine in various animal species approximates 200 mg kg^{-1} (Dews, 1982). Since caffeinated products provide an absolute dose for any given serving size, rather than a dose proportional to body mass (see Table 1), concern has been raised about the overuse of some products among adolescents (Wolk et al., 2012). Furthermore, many caffeine containing products do not provide caffeine content. In addition, the FDA recently issued warnings to certain distributors of pure powdered caffeinated products due to risk to consumers for overdosing (http://www.fda.gov/Food/DietarySupplements/ProductsIngredients/ucm460095.htm).

It has been hypothesized that the positive effects of caffeine reported in many studies may actually reflect a placebo effect (Beedie et al., 2006; Foad et al., 2008) or a rebound from the negative symptoms experienced during the withdrawal or abstinence period imposed by the experimental design prior to administration of the drug (James, 1994; James et al., 2005; James and Rogers, 2005). For some regular users of caffeine a period of abstinence for 24 h or longer is associated with symptoms of headache and irritability (Juliano and Griffiths, 2004) that might result in decreased performance under placebo conditions of a study. These concerns should be considered when caffeine research is designed. However, others believe this hypothesis could not explain the behavioral effects of caffeine observed among non-consumers (Addicott and Laurienti, 2009; Childs and deWit, 2006) and the observation that low doses of caffeine equivalent to 1 and 2 mg kg^{-1} (~75 and 150 mg, respectively) have improved cognitive function in regular users following an abstinence period of only 1 h (Warburton, 1995). Furthermore, regardless of whether there is 0, 2 or 4 days of abstinence, caffeine ingestion has similar ergogenic effects for regular users of the drug whether they are light-to-moderate (Irwin et al., 2011) or heavy consumers (Van Soeren and Graham, 1998).

7. Overall conclusions – cognitive and physical performance

This review examined the effects of caffeine on physical and cognitive function alone or in combination. The following conclusions appear justified based on the material presented:

a. Caffeine exerts its effects on cognitive and physical function through adenosine A_1 and A_{2a} receptor blockade in the CNS and peripheral tissues;
b. Caffeine, in doses up to approximately 300 mg (~4 mg kg^{-1}), enhances a wide array of basic cognitive functions with minimal side effects by preventing alertness and attention decrements associated with suboptimal arousal, consistent with the Yerkes-Dodson inverted U-hypothesis;
c. The effects of caffeine on higher-order executive skills, complex judgments, emotional discernment, and decision-making are unclear and require further study;
d. The ability of caffeine to enhance cognitive and physical function is dose-dependent. Doses of approximately 0.5–4.0 mg kg^{-1} (~40–300 mg) can improve cognitive function in rested individuals, whereas doses of 3–7 mg kg^{-1} (~200–500 mg) ingested approximately 1 h prior to exercise can enhance physical performance. However, response to a given dose shows large inter-individual variation;
e. The ergogenic effects of caffeine are present across a wide spectrum of exercise modalities including endurance tests to exhaustion or time-trials lasting several minutes to over an hour, tests of muscle strength and associated tests of muscular endurance, high-intensity efforts lasting longer than 60 s, or tests of speed, power and agility during repeated high-intensity intervals;
f. Threshold circulating plasma concentrations required to produce an ergogenic response may be as high as 15–20 μM when caffeine is ingested prior to exercise but may be as low as 5 μM when ingested during exercise. These threshold concentrations appear to be lower for caffeine naïve than non-naive individuals and the ergogenic response is present for several hours following ingestion;
g. The use of caffeine as an ergogenic aid need not be restricted during exposure to hot environments due to fears of increased fluid loss and rates of heat storage;
h. Caffeine is an effective strategy to counter both physical and cognitive degradation associated with sleep loss.

It is hoped that this review will stimulate conduct of additional research that examines: 1) the interplay between adenosine receptor genotype and its sensitivity to caffeine; 2) the behavioral effects of caffeine on higher order cognitive function; 3) whether exercise alters adenosine receptor sensitivity; 4) common central loci that can explain the dual effects of caffeine on cognitive and physical function; and 5) whether methods can be developed that change receptor sensitivity and create 'responders' from those who are classified as 'non-responders' without an associated increase in adverse effects that impact performance. Also when possible, collection of plasma or saliva samples should be included in the experimental designs to ensure caffeine abstinence prior to drug ingestion and to relate circulating concentrations of the drug to the observed physical and cognitive effects. In addition, participants' history of caffeine use together with lifestyle factors that might impact on caffeine clearance should be clearly identified, controlled for, and included when appropriate in the analyses of data. Similarly, the influence of caffeine withdrawal and placebo expectations on the performance metrics assessed should be addressed within the experimental design.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.neubiorev.2016.09.001.

References

Addicott, M.A., Laurienti, P.J., 2009. A comparison of the effects of caffeine following abstinence and normal caffeine use. Psychopharmacology 207, 423–431.
Ali, A., O'Donnell, J.M., Starck, C., Rutherfurd-Markwick, K.J., 2015. The effect of caffeine ingestion during evening exercise on subsequent sleep quality in females. Int. J. Sports Med. 36, 433–439.
Alles, G.A., Feigen, G.A., 1942. The influence of benzedrine on work-decrement and patellar reflex. Am. J. Physiol. 136, 392–400.
Amendola, C.A., Gabrieli, J.D.F., Lieberman, H.R., 1998. Caffeine's effects on performance and mood are independent of age and gender. Nutr. Neurosci. 1, 269–280.
Anderson, K., Revelle, W., 1983. The interactive effects of caffeine, impulsivity and task demands on visual search task. Pers. Indiv. Differ. 4, 127–132.
Anderson, K.J., 1994. Impulsivity, caffeine, and task difficulty: a within subjects test of the Yerkes–Dodson law. Pers. Indiv. Differ. 16, 813–829.
Angelucci, M.E., Vital, M.A., Cesário, C., Zadusky, C.R., Rosalen, P.L., DaCunha, C., 1999. The effect of caffeine in animal models of learning and memory. Eur. J. Pharmacol. 373, 135–140.
Armstrong, L.E., Casa, D.J., Maresh, C.M., Ganio, M.S., 2007. Caffeine, fluid-electrolyte balance, temperature regulation, and exercise-heat tolerance. Exerc. Sport Sci. Rev. 35, 135–140.
Armstrong, L.E., 2002. Caffeine, body fluid-electrolyte balance, and exercise performance. Int. J. Sport Nutr. Exerc. Metab. 12, 189–206.
Asmussen, E., Bøje, O., 1948. The effect of alcohol and some drugs on the capacity for work. Acta Phsyiol. Scand. 15, 109–113.
Balkin, T.J., Kamimori, G.H., Redmond, D.P., Vigneulle, R.M., Thorne, D.R., Belenky, G., Wesensten, N.J., 2004. On the importance of countermeasures in sleep and performance models. Aviat. Space Environ. Med. 75 (Suppl. (3)), A155–A157.
Barone, J.J., Roberts, H.R., 1996. Caffeine consumption. Food Chem. Toxicol. 34, 119–129.
Bazzucchi, I., Felici, F., Montini, M., Figura, F., Sacchetti, M., 2011. Caffeine improves neuromuscular function during maximal dynamic exercise. Muscle Nerve 43, 839–844.
Beedie, C.J., Stuart, E.M., Coleman, D.A., Foad, A.J., 2006. Placebo effects of caffeine on cycling performance. Med. Sci. Sports Exerc. 38, 2159–2164.
Bell, D.G., McLellan, T.M., 2002. Exercise endurance 1, 3, and 6 h after caffeine ingestion in caffeine users and nonusers. J. Appl. Physiol. 93, 1227–1234.
Bell, D.G., McLellan, T.M., 2003. Effect of repeated caffeine ingestion on repeated exhaustive exercise endurance. Med. Sci. Sports Exerc. 35, 1348–1354.
Bell, D.G., Jacobs, I., Ellerington, K., 2001. Effect of caffeine and ephedrine ingestion on anaerobic exercise performance. Med. Sci. Sports Exerc. 33, 1399–1403.
Blanchard, J., Sawers, S.J., 1983. The absolute bioavailability of caffeine in man. Eur. J. Clin. Pharmacol. 24, 93–98.
Bodenmann, S., Hohoff, C., Freitag, C., Deckert, J., Rétey, J.V., Bachmann, V., Landolt, H.P., 2012. Polymorphisms of ADORA2A modulate psychomotor vigilance and the effects of caffeine on neurobehavioural performance and sleep EEG after sleep deprivation. Br. J. Pharmacol. 165, 1904–1913.
Boison, D., 2011. Methylxanthines, seizures, and excitotoxicity. Handb. Exp. Pharmacol. 200, 251–266.
Borota, D., Murray, E., Keceli, G., Chang, A., Watabe, J.M., Ly, M., Toscano, J.P., Yassa, M.A., 2014. Post-study caffeine administration enhances memory consolidation in humans. Nat. Neurosci. 17, 201–203.

Bottoms, L., Greenhalgh, A., Gregory, K., 2013. The effect of caffeine ingestion on skill maintenance and fatigue in epee fencers. J. Sports Sci. 31, 1091–1099.
Boxtel, M.P.J., Schmidtt, J.A.J., Bosma, H., Jolles, J., 2003. The effects of habitual caffeine use on cognitive change: a longitudinal perspective. Pharmacol. Biochem. Behav. 75, 921–927.
Bridge, C.A., Jones, M.A., 2006. The effect of caffeine ingestion on 8 km run performance in a field setting. J. Sports Sci. 24, 433–439.
Brown, S.J., James, S., Reddington, M., Richardson, P.J., 1990. Both A1 and A2a receptors regulate striatal acetylcholine release. J. Neurochem. 55, 31–38.
Bruce, C.R., Anderson, M.E., Fraser, S.F., Stepto, N.K., Klein, R., Hopkins, W.G., Hawley, J.A., 2000. Enhancement of 2000-m rowing performance after caffeine ingestion. Med. Sci. Sports Exerc. 32, 1958–1963.
Brunyé, T.T., Mahoney, C.R., Lieberman, H.R., Taylor, H.A., 2010a. Caffeine modulates attention network function. Brain Cogn. 72, 181–188.
Brunyé, T.T., Mahoney, C.R., Lieberman, H.R., Giles, G.E., Taylor, H.A., 2010b. Acute caffeine consumption enhances the executive control of visual attention in habitual consumers. Brain Cogn. 74, 186–192.
Burke, L.M., 2008. Caffeine and sports performance. Appl. Phys. Nutr. Metab. 33, 1319–1334.
Cadarette, B.S., Levine, L., Berube, C.L., Posner, B.M., Evans, W.J., 1982. Effects of varied dosages of caffeine on endurance exercise to fatigue. In: Knuttgen, H. (Ed.), International Symposium on the Biochemistry of Exercise. Human Kinetics, Boston.
Cappelletti, S., Daria, P., Sani, G., Aromatario, M., 2015. Caffeine: cognitive and physical performance enhancer or psychoactive drug? Curr. Neuropharm. 13, 71–88.
Carr, A., Dawson, B., Schneiker, K., Goodman, C., Lay, B., 2008. Effect of caffeine supplementation on repeated sprint running performance. J. Sport Med. Phys. Fitness 48, 472–478.
Carvey, C.E., Thompson, L.A., Lieberman, H.R., 2012. Caffeine: mechanisms of action, genetics and behavioral studies conducted in simulators and the field. In: Wesensten, N.J. (Ed.), Sleep Deprivation, Stimulant Medications, and Cognition. Cambridge University Press, Cambridge, U.K, pp. 93–107.
Chester, N., Wojek, N., 2008. Caffeine consumption amongst British athletes following changes to the 2004 WADA prohibited list. Int. J. Sports Med. 29, 524–528.
Cheuvront, S.N., Ely, B.R., Kenefick, R.W., Michniak-Kohn, B.B., Rood, J.C., Sawka, M.N., 2009. No effect of nutritional adenosine receptor antagonists on exercise performance in the heat. Am. J. Physiol. 296, R394–R401.
Childs, E., deWit, H., 2006. Subjective, behavioral and physiological effects of acute caffeine in light, nondependent users. Psychopharmacology 185, 514–523.
Childs, E., Hohoff, C., Deckert, J., Xu, K., Badner, J., deWit, H., 2008. Association between ADORA2A and DRD2 polymorphisms and caffeine-induced anxiety. Neuropsychopharmacology 33, 2791–2800.
Ciruela, F., Casadó, V., Rodrigues, R.J., Luján, R., Burgueño, J., Canals, M., Borycz, J., Rebola, N., Goldberg, S.R., Mallol, J., Cortés, A., Canela, E.I., López-Giménez, J.F., Milligan, G., Lluis, C., Cunha, R.A., Ferré, S., Franco, R., 2006. Presynaptic control of striatal glutamatergic neurotransmission by adenosine $A_1 - A_{2A}$ receptor heteromers. J. Neurosci. 26, 2080–2087.
Clubley, M., Bye, C.E., Henson, T.A., Peck, A.W., Riddington, C.J., 1979. Effects of caffeine and cyclizine alone and in combination on human performance, subjective effects and EEG activity. Br. J. Clin. Pharmacol. 7, 157–163.
Collomp, K., Anselme, F., Audran, M., Gay, J.P., Chanal, J.L., Prefaut, C., 1991. Effects of moderate exercise on the pharmacokinetics of caffeine. Eur. J. Clin. Pharmacol. 40, 279–282.
Conway, K.J., Orr, R., Stannard, S.R., 2003. Effect of a divided caffeine dose on endurance cycling performance, postexercise urinary caffeine concentration, and plasma paraxanthine. J. Appl. Physiol. 94, 1557–1562.
Costill, D.L., Dalsky, G.P., Fink, W.J., 1978. Effects of caffeine ingestion on metabolism and exercise performance. Med. Sci. Sports Exerc. 10, 155–158.
Cox, G.R., Desbrow, B., Montgomery, P.G., ANderson, M.E., Bruce, C.R., Macrides, T.A., Martin, D.T., Moquin, A., Roberts, A., Hawley, J.A., Burke, L.M., 2002. Effect of different protocols of caffeine intake on metabolism and endurance performance. J. Appl. Physiol. 93, 990–999.
Crowe, M.J., Leicht, A.S., Spinks, W.L., 2006. Physiological and cognitive responses to caffeine during repeated, high-intensity exercise. Int. J. Sport Nutr. Exerc. Metab. 16, 528–544.
Curatolo, P.W., Robertson, D., 1983. The health consequences of caffeine. Ann. Intern. Med. 98, 641–653.
Davidson, R.A., Smith, B.D., 1991. Caffeine and novelty: effects on electrodermal activity and performance. Physiol. Behav. 49, 1169–1175.
Davis, J.K., Green, J.M., 2009. Caffeine and anaerobic performance: ergogenic value and mechanisms of action. Sports Med. 39, 813–832.
Davis, J.M., Zhao, Z., Stock, H.S., Mehl, K.A., Buggy, J., Hand, G.A., 2002. Central nervous system effects of caffeine and adenosine on fatigue. Am. J. Physiol. 284, R399–R404.
Del Coso, J., Estevez, E., Mora-Rodriguez, R., 2008. Caffeine effects on short-term performance during prolonged exercise in the heat. Med. Sci. Sports Exerc. 40, 744–751.
Del Coso, J., Estevez, E., Mora-Rodriguez, R., 2009. Caffeine during exercise in the heat: thermoregulation and fluid-electrolyte balance. Med. Sci. Sports Exerc. 41, 164–173.
Del Coso, J., Salinero, J.J., Gonzalez-Millan, C., Abian-Vicen, J., Perez-Gonzalez, B., 2012. Dose response effects of a caffeine-containing energy drink on muscle performance: a repeated measures design. J. Int. Soc. Sport Nutr. 9, 21.
Denaro, C.P., Brown, C.R., Wilson, M., JacobIII, P., Benowitz, N.L., 1990. Dose-dependency of caffeine metabolism with repeated dosing. Clin. Pharmacol. Ther. 48, 277–285.
Desbrow, B., Barrett, C.M., Minahan, C.L., Grant, G.D., Leveritt, M.D., 2009. Caffeine, cycling performance, and exogenous CHO oxidation: a dose-response study. Med. Sci. Sports Exerc. 41, 1744–1751.
Desbrow, B., Biddulph, C., Devlin, B., Grant, G.D., Anoopkumar-Dukie, S., Leveritt, M.D., 2012. The effects of different doses of caffeine on endurance cycling time trial performance. J. Sports Sci. 30, 115–120.
Dews, P.B., 1982. Caffeine. Annu. Rev. Nutr. 2, 323–341.
Diamond, D.M., Campbell, A.M., Park, C.R., Halonen, J., Zoladz, P.R., 2007. The temporal dynamics model of emotional memory processing: a synthesis on the neurobiological basis of stress-induced amnesia, flashbulb and traumatic memories, and the Yerkes-Dodson Law. Neural Plast. 2007, 60803.
Diamond, D.M., 2005. Cognitive, endocrine and mechanistic perspectives on non-linear relationships between arousal and brain function. Nonlinearity Biol. Toxicol. Med. 3, 1–7.
Doan, B.K., Hickey, P.A., Lieberman, H.R., Fischer, J.R., 2006. Caffeinated tube food effect on pilot performance during a 9-hour, simulated nighttime U-2 mission. Aviat. Space Environ. Med. 77, 1034–1040.
Dodd, S.L., Brooks, E., Powers, S.K., Tulley, R., 1991. The effects of caffeine on graded exercise performance in caffeine naive versus habituated subjects. Eur. J. Appl. Physiol. 62, 424–429.
Doepker, C., Lieberman, H.R., Smith, A.P., Peck, J.D., El-Sohemy, A., Welsh, B.T., 2016. Caffeine: friend or foe? Ann. Rev. Food Sci. Technol. 7, 117–137.
Doherty, M., Smith, P.M., 2004. Effects of caffeine ingestion on exercise testing: a meta-analysis. Int. J. Sport Nutr. Exerc. Metab. 14, 626–646.
Doherty, M., Smith, P.M., 2005. Effects of caffeine ingestion on rating of perceived exertion during and after exercise: a meta-analysis. Scand. J. Med. Sci. Sports 15, 69–78.
Dunagan, N., Greenleaf, J.E., Cisar, C.J., 1998. Thermoregulatory effects of caffeine ingestion during submaximal exercise in men. Aviat. Space Environ. Med. 69, 1178–1181.
Duncan, M.J., Hankey, J., 2013. The effect of a caffeinated energy drink on various psychological measures during submaximal cycling. Physiol. Behav. 116–117, 60–65.
Duncan, M.J., Thake, C.D., Downs, P.J., 2014. Effect of caffeine ingestion on torque and muscle activity during resistance exercise in men. Muscle Nerve 50, 523–527.
Dunwiddie, T.V., 1980. Endogenously released adenosine regulates excitability in the in vitro hippocampus. Epilepsia 21, 541–548.
Duvnjak-Zaknich, D.M., Dawson, B.T., Wallman, K.E., Henry, G., 2011. Effect of caffeine on reactive agility time when fresh and fatigued. Med. Sci. Sports Exerc. 43, 1523–1530.
Einother, S.J.L., Giesbrecht, T., 2013. Caffeine as an attention enhancer: reviewing existing assumptions. Psychopharmacology 225, 251–274.
Ely, B.R., Ely, M.R., Cheuvront, S.N., 2011. Marginal effects of a large caffeine dose on heat balance during exercise-heat stress. Int. J. Sport Nutr. Exerc. Metab. 21, 65–70.
Essig, D., Costill, D.L., vanHandel, P.J., 1980. Effects of caffeine ingestion on utilization of muscle glycogen and lipid during leg ergometer cycling. Int. J. Sports Med. 1, 86–90.
Falk, B., Burstein, R., Rosenblum, J., Shapiro, Y., Zylber-Katz, E., Bashan, N., 1990. Effects of caffeine ingestion on body fluid balance and thermoregulation during exercise. Can. J. Physiol. Pharmacol. 68, 889–892.
Favila, S.E., Kuhl, B.A., 2014. Stimulating memory consolidation. Nat. Neurosci. 17, 151–152.
Ferré, S., 2010. Role of the central ascending neurotransmitter systems in the psychostimulant effects of caffeine. J. Alzheimer's Dis. 20, S35–S49.
Ferré, S., 2016. Mechanisms of the psychostimulant effects of caffeine: implications for substance use disorder. Psychopharmacology, http://dx.doi.org/10.1007/s00213-016-4212-2.
Fine, B.J., Kobrick, J.L., Lieberman, H.R., Marlowe, B., Riley, R.H., Tharion, W.J., 1994. Effects of caffeine on diphenydramine on visual vigilance. Psychopharmacology 114, 233–238.
Fisone, G., Borgkvist, A., Usiello, A., 2004. Caffeine as a psychomotor stimulant: mechanism of action. Cell. Mol. Life Sci. 61, 857–872.
Flagmeyer, I., Haas, H.L., Stevens, D.R., 1997. Adenosine A1 receptor-mediated depression of corticostriatal and thalmostriatal glutamatergic synaptic potentials in vitro. Brain Res. 778, 178–185.
Fleischer, D., Li, C., Zhou, Y., Pao, L.H., Karim, A., 1999. Drug, meal and formulation interactions influencing drug absorption after oral administration: clinical implications. Clin. Pharmacokin 36, 233–254.
Foad, A.J., Beedie, C.J., Coleman, D.A., 2008. Pharmacological and psychological effects of caffeine ingestion in 40-km cycling performance. Med. Sci. Sports Exerc. 40, 158–165.
Foltz, E., Ivy, A.C., Barborka, C.J., 1942a. The use of double work periods in the study of fatigue and the influence of caffeine on recovery. Am. J. Physiol. 136, 79–86.
Foltz, E.E., Ivy, A.C., Barborka, C.J., 1942b. The influence of amphetamin (benzedrine) sulfate, d-deoxyephedrine hydrochloride (pervitin), and caffeine upon work output and recovery when rapidly exhausting work is done by trained subjects. J. Lab. Clin. Med. 28, 603–606.
Foltz, E.E., Schiffrin, M.J., Ivy, A.C., 1942c. The influence of amphetamine (benzedrine) sulphate and caffeine on the performance of rapidly exhausting work by untrained subjects. J. Lab. Clin. Med. 28, 601–603.

Fray, S.D., Johnson, R.K., Wang, M.Q., 2005. Food sources and intakes of caffeine in the diets of persons in the United States. J. Am. Diet. Assoc. 105, 110–113.
Fredholm, B.B., Abbracchio, M.P., Burnstock, G., Daly, J.W., Harden, T.K., Jacobson, K.A., Leff, P., Williams, M., 1994. Nomenclature and classification of purinoceptors. Pharmacol. Rev. 46, 143–156.
Fredholm, B.B., Battig, K., Holmen, J., Nehlig, A., Zvartau, E.E., 1999. Actions of caffeine in the brain with special reference to factors that contribute to its widespread use. Pharmacol. Rev. 51, 83–133.
Fredholm, B.B., 1979. Are methylxanthine effects due to antagonism of endogenous adenosine? Trends Pharmacol. Sci. 1, 129–132.
Fredholm, B.B., 1995. Adenosine, adenosine receptors and the actions of caffeine. Pharmacol Toxicol 76, 93–101.
Fukuda, M., Suzuki, Y., Hino, H., Kuzume, K., Morimoto, T., Ishii, E., 2010. Adenosine A1 receptor blockage mediates theophylline-associated seizures. Epilepsia 51, 483–487.
Fulgoni III, V.L., Keast, D.R., Lieberman, H.R., 2015. Trends in intake and sources of caffeine in the diets of US adults: 2001–2010. Am. J. Clin. Nutr. 101, 1081–1087.
Fuxe, K., Ferré, S., Canals, M., Torvinen, M., Terasmaa, A., Marcellino, D., Goldberg, S.R., Staines, W., Jacobsen, K.X., Lluis, C., Woods, A.S., Agnati, L.F., Franco, R., 2005. Adenosine A2A and dopamine D2 heteromeric receptor complexes and their function. J. Mol. Neurosci. 26, 209–220.
Ganio, M.S., Klau, J.F., Casa, D.J., Armstrong, L.E., Maresh, C.M., 2009. Effect of caffeine on sport-specific endurance performance: a systematic review. J. Strength Cond. Res. 23, 315–324.
Ganio, M.S., Johnson, E.C., Klau, J.F., Anderson, J.M., Casa, D.J., Maresh, C.M., Volek, J.S., Armstrong, L.E., 2011a. Effect of ambient temperature on caffeine ergogenicity during endurance exercise. Eur. J. Appl. Physiol. 111, 1135–1146.
Ganio, M.S., Johnson, E.C., Lopez, R.M., Stearns, R.L., Emmanuel, H., Anderson, J.M., Casa, D.J., Maresh, C.M., Volek, J.S., Armstrong, L.E., 2011b. Caffeine lowers muscle pain during exercise in hot but not cool environments. Physiol. Behav. 102, 429–435.
Ganslen, R.V., Balke, B., Nagle, F.J., 1964. Effects of some tranquilizing, analeptic and vasodilating drugs on physical work capacity and orthostatic tolerance. Aerosp. Med. 35, 630–633.
Gaspardone, A., Crea, F., Tomai f. Versaci, F., Iamele, M., Gioffrè, G., Chiariello, L., Gioffrè, P.A., 1995. Muscular and cardiac adenosine-induced pain is mediated by A1 receptors. J. Am. Coll. Cardiol. 25, 251–257.
Glaister, M., Patterson, S.D., Foley, P., Pedlar, C.R., Pattison, J.R., McInnes, G., 2012. Caffeine and sprinting performance: dose responses and efficacy. J. Strength Cond. Res. 26, 1001–1005.
Gliottoni, R.C., Motl, R.W., 2008. Effect of caffeine on leg-muscle pain during intense cycling exercise: possible role of anxiety sensitivity. Int. J. Sport Nutr. Exerc. Metab. 18, 103–115.
Gliottoni, R.C., Meyers, J.R., Arngrimsson, S.A., Broglio, S.P., Motl, R.W., 2009. Effect of caffeine on quadriceps muscle pain during acute cycling exercise in low versus high caffeine consumers. Int. J. Sport Nutr. Exerc. Metab. 19, 150–161.
Goldstein, E.R., Ziegenfuss, T., Kalman, D., Kreider, R., Campbell, B., Wilborn, C., Taylor, L., Willoughby, D., Stout, J., Graves, B.S., Wildman, R., Ivy, J.L., Spano, M., Smith, A.E., Antonio, J., 2010. International society of sports nutrition position stand: caffeine and performance. J. Int. Soc. Sport Nutr. 7, 5.
Gonglach, A.R., Ade, C.J., Bemben, M.G., Larson, R.D., Black, C.D., 2016. Muscle pain as a regulator of cycling intensity: effect of caffeine ingestion. Med. Sci. Sports Exerc. 48, 287–296.
Gottselig, J.M., Adam, M., Retey, J.V., Khatami, R., Achermann, P., Landolt, H., 2006. Random number generation during sleep deprivation: effects of caffeine on response maintenance and stereotypy. J. Sleep Res. 15, 31–40.
Graham, T.E., Spriet, L.L., 1991. Performance and metabolic responses to a high caffeine dose during prolonged exercise. J. Appl. Physiol. 71, 2292–2298.
Graham, T.E., Spriet, L.L., 1995. Metabolic, catecholamine, and exercise performance responses to various doses of caffeine. J. Appl. Physiol. 78, 867–874.
Graham, T.E., Hibbert, E., Sathasivam, P., 1998. Metabolic and exercise endurance effects of coffee and caffeine ingestion. J. Appl. Physiol. 85, 883–889.
Graham, T.E., Helge, J.W., MacLean, D.A., Kiens, B., Richter, E.A., 2000. Caffeine ingestion does not alter carbohdrate or fat metabolism in human skeletal muscle during exercise. J. Physiol. 529, 837–847.
Graham, T.E., Battram, D.S., Dela, F., El-Sohemy, A., Thong, F.S.L., 2008. Does caffeine alter muscle carbohydrate and fat metabolism during exercise? Appl. Phys. Nutr. Metab. 33, 1311–1318.
Graham, T.E., 2001. Caffeine and exercise: metabolism, endurance and performance. Sports Med. 31, 785–807.
Greer, F., McLean, C., Graham, T.E., 1998. Caffeine, performance, and metabolism during repeated Wingate exercise tests. J. Appl. Physiol. 85, 1502–1508.
Greer, F., Friars, D., Graham, T.E., 2000. Comparison of caffeine and theophylline ingestion: exercise metabolism and endurance. J. Appl. Physiol. 89, 1837–1844.
Haldi, J., Wynn, W., 1946. Action of drugs on the efficiency of swimmers. Res. Q. 17, 96–101.
Haldi, J., Bachmann, G., Ensor, D., Wynn, W., 1941. The effect of various amounts of caffeine on the gaseous exchange and the respiratory quotient in man. J. Nutr. 21, 307–320.
Hameleers, P.A., VanBoxtel, M.P., Hogervorst, W., Riedel, W.J., Houx, P.J., Buntinx, F., Jolles, J., 2000. Habitual caffeine consumption and its relation to memory, attention, planning capacity and psychomotor performance across multiple age groups. Hum. Psychopharm. Clin. 15, 573–581.
Harvanko, A.M., Derbyshire, K.L., Schreiber, L.R., Grant, J.E., 2015. The effect of self-regulated caffeine use on cognition in young adults. Hum. Psychopharmacol. 30, 123–130.
Heatherley, S.V., Hayward, R.C., Seers, H.E., Rogers, P.J., 2005. Cognitive and psychomotor performance, mood, and pressor effects of caffeine after 4, 6 and 8 h caffeine abstinence. Psychopharmacology 178, 461–470.
Higdon, J.V., Frei, B., 2006. Coffee and health: a review of recent human research. Crit. Rev. Food Sci. Nutr. 46, 101–123.
Hodgson, A.B., Randell, R.K., Jeukendrup, A.E., 2013. The metabolic and performance effects of caffeine compared to coffee during endurance exercise. PLoS One 8, e59561.
Hogervorst, E., Riedel, W.J., Kovacs, E., Brouns, F., Jolles, J., 1999. Caffeine improves cognitive performance after strenuous exercise. Int. J. Sports Med. 20, 354–361.
Hogervorst, E., Bandelow, S., Schmitt, J., Jentjens, R., Oliveira, M., Allgrove, J., Carter, T., Gleeson, M., 2008. Caffeine improves physical and cognitive performance during exhaustive exercise. Med. Sci. Sports Exerc. 40, 1841–1851.
Hornery, D.J., Farrow, D., Mujika, I., Young, W.B., 2007. Caffeine, carbohydrate and cooling use during prolonged simulated tennis. Int. J. Sports Physiol. Perform. 2, 423–438.
Huck, N.O., McBride, S.A., Kendall, A.P., Grugle, N.L., Killgore, W.D., 2008. The effects of modafinil, caffeine, and dextroamphetamine on judgements of simple versus complex emotional expressions following sleep deprivation. Int. J. Neurosci. 118, 487–502.
Hussain, S.J., Cole, K.J., 2015. No enhancement of 24-hour visuomotor skill retention by post-practice caffeine administration. PLoS One 10, e0129543.
Institute of Medicine, 2014. Caffeine in Food and Dietary Supplements: Examining Safety. The National Academies Press, Washington, D.C.
Irwin, C., Desbrow, B., Ellis, A., O'Keeffe, B., Grant, G., Leveritt, M., 2011. Caffeine withdrawal and high-intensity endurance cycling performance. J. Sports Sci. 29, 509–515.
Jabbar, S.B., Hanly, M.G., 2013. Fatal caffeine overdose: a case report and review of literature. Am. J. Forensic Med. Pathol. 34, 321–324.
Jackman, M., Wendling, P., Friars, D., Graham, T.E., 1996. Metabolic, catecholamine, and enduranced responses to caffeine during intense exercise. J. Appl. Physiol. 81, 1658–1663.
James, J.E., Rogers, P.J., 2005. Effects of caffeine on performance and mood: withdrawal reversal is the most plausible explanation. Psychopharmacology 182, 1–8.
James, J.E., Gregg, M.E., Kane, M., Harte, F., 2005. Dietary caffeine, performance and mood: enhancing and restorative effects after controlling for withdrawal reversal. Neuropsychobiology 52, 1–10.
James, J.E., 1994. Psychophysiological effects of habitual caffeine consumption. Int. J. Behav. Med. 1, 247–263.
Jarvis, M.J., 1993. Does caffeine intake enhance absolute levels of cognitive performance? Psychopharmacology 110, 45–52.
Jenkins, N.T., Trilk, J.L., Singhal, A., O'Connor, P.J., Cureton, K.J., 2008. Ergogenic effects of low doses of caffeine on cycling performance. Int. J. Sport Nutr. Exerc. Metab. 18, 328–342.
Johnson-Kozlow, M., Kritz-Silverstein, D., Barrett-Connor, E., Morton, D., 2002. Coffee consumption and cognitive function among older adults. Am. J. Epidemiol. 156, 842–850.
Juliano, L.M., Griffiths, R.R., 2004. A critical review of caffeine withdrawal: empirical validation of symptoms and signs, incidence, severity, and associated features. Psychopharmacology 176, 1–29.
Kahathuduwa, C.N., Dassanayake, T.L., Amarakoon, A.M., Weerasinghe, V.S., 2016. Acute effects of theanine, caffeine and theanine-caffeine combination on attention. Nutr. Neurosci., http://dx.doi.org/10.1080/1028415x.2016.1144845.
Kalmar, J.M., Cafarelli, E., 1999. Effects of caffeine on neuromuscular function. J. Appl. Physiol. 87, 801–808.
Kamimori, G.H., Karyekar, C.S., Otterstetter, R., Cox, D.S., Balkin, T.J., Belenky, G.L., Eddington, N.D., 2002. The rate of absorption and relative bioavailability of caffeine administered in chewing gum versus capsules to normal healthy volunteers. Int. J. Pharm. 234, 159–167.
Kamimori, G.H., McLellan, T.M., Tate, C.M., Voss, D.M., Niro, P., Lieberman, H.R., 2015. Caffeine improves reaction time, vigilance and logical reasoning during extended periods with restricted opportunities for sleep. Psychopharmacology 232, 2031–2042.
Ker, K., Edwards, P.J., Felix, L.M., Blackhall, K., Roberts, I., 2010. Caffeine for the prevention of injuries and errors in shift workers. Cochrane Database Syst. Rev. 5, CD008508.
Killgore, W.D., McBride, S.A., Killgore, D.B., Balkin, T.J., 2006. The effects of caffeine, dextroamphetamine and modafinil on human appreciation during sleep deprivation. Sleep 29, 841–847.
Killgore, W.D., Lipizzi, E., Kamimori, G.H., Balkin, T.J., 2007. Caffeine effects on risky decision making after 75 hours of sleep deprivation. Aviat. Space Environ. Med. 78, 957–962.
Killgore, W.D., Muckle, A.E., Grugle, N.L., Killgore, D.B., Balkin, T.J., 2008. Sex differences in cognitive estimation during sleep deprivation: effects of stimulant countermeasures. Int. J. Neurosci. 118, 1547–1557.
Killgore, W.D., Kahn-Greene, E.T., Grugle, N.L., Killgore, D.B., Balkin, T.J., 2009. Sustaining executive functions during sleep deprivation: a comparison of caffeine, dextroamphetamine, and modafinil. Sleep 32, 205–216.
Killgore, W.D., Kamimori, G.H., Balkin, T.J., 2014. Caffeine improves the efficiency of planning and sequencing abilities during sleep deprivation. J. Clin. Pharmacol. 34, 660–662.

Killgore, W.D., 2011. Asleep at the trigger: warfighter judgment and decision making during prolonged wakefulness. In: Barone, P.T., Pastel, R.H., Vaitkus, M.A. (Eds.), The 71F Advantage: Applying Army Research Psychology for Health and Performance Gains. National Defense University Press, Washington, D.C.
Kim, T.-W., Shin, Y.-O., Lee, J.-B., Min, Y.-K., Yang, H.-M., 2011. Caffeine increases sweating sensitivity via changes in sudomotor activity during physical loading. J. Med. Food 14, 1448–1455.
Kim, Y., Kwak, S.M., Myung, S., 2015. Caffeine intake from coffee or tea and cognitive disorders: a meta-analysis of observational studies. Neuroepidemiology 44, 51–63.
Kosslyn, M.S., Smith, E.E., 2001. Higher cognitive functions – introduction. In: Gassaniga, M.S. (Ed.), The New Cognitive Neurosciences. The MIT Press, Cambridge, U.K, pp. 961–964.
Kovacs, E.M.R., Stegen, J.H.C.H., Brouns, F., 1998. Effect of caffeinated drinks on substrate metabolism, caffeine excretion, and performance. J. Appl. Physiol. 85, 709–715.
Kuznicki, J.T., Turner, L.S., 1986. The effects of caffeine on caffeine users and non-users. Physiol. Behav. 37, 397–408.
Landolt, H.P., 2008. Sleep homeostasis: a role for adenosine in humans? Biochem. Pharmacol. 75, 2070–2079.
Lane, S.D., Areta, J.L., Bird, S.R., Coffey, V.G., Burke, L.M., Desbrow, B., Karagounis, L.G., Hawley, J.A., 2013. Caffeine ingestion and cycling power output in a low and normal muscle glycogen state. Med. Sci. Sports Exerc. 45, 1577–1584.
Lane, S.C., Hawley, J.A., Desbrow, B., Jones, A.M., Blackwell, J.R., Ross, M.L., Zemski, A.J., Bourke, L.M., 2014. Single and combined effects of beetroot juice and caffeine supplementation on cycling time trial performance. Appl. Phys. Nutr. Metab. 39, 1050–1057.
Lane, J.D., 1997. Effects of brief caffeinated-beverage deprivation on mood, symptoms, and psychomotor performance. Pharmacol. Biochem. Behav. 58, 203–208.
Langfort, J., Dudohoski, L., Dubaniewicz, A., Challiss, R.A., Newsholme, E.A., 1993. Exercise-induced improvement in the sensitivity of the rat soleus muscle to insulin is reversed by chloroadenosine – the adenosine receptor agonist. Biochem. Med. Metab. Biol. 50, 18–23.
Lanini, J., Galduroz, J.C.F., Pompeia, S., 2016. Acute personalized habitual caffeine doses improve attention and have selective effects when considering the fractionation of executive functions. Hum. Psychopharmacol. 31, 29–43.
Lara, B., Gonzalez-Millan, C., Salinero, J.J., Abian-Vicen, J., Areces, F., Barbero-Alvarez, J.C., Munoz, V., Portillo, L.J., Gonzalez-Rave, J.M., DelCoso, J., 2014. Caffeine-containing energy drink improves physical performance in female soccer players. Amino Acids 46, 1385–1392.
Laurent, D., Schneider, K.E., Prusaczyk, W.K., Franklin, C., Vogel, S.M., Krssak, M., Petersen, K.F., Goforth, H.W., Shulman, G.I., 2000. Effects of caffeine on muscle glycogen utilization and the neuroendocrine axis during exercise. J. Clin. Endocrinol. Metab. 85, 2170–2175.
Lee, C.-L., Cheng, C.-F., Lin, J.-C., Huang, H.W., 2012. Caffeine's effect on intermittent sprint cycling performance with different rest intervals. Eur. J. Appl. Physiol. 112, 2107–2116.
Lee, C.-L., Cheng, C.-F., Astorino, T.A., lee, C.-J., Huang, H.-W., Chang, W.-D., 2014a. Effects of carbohydrate combined with caffeine on repeated sprint cycling and agility performance in female athletes. J. Int. Soc. Sport Nutr. 11, 17.
Lee, C.-L., Cheng, C.-F., Lee, C.-J., Kuo, Y.-H., Chang, W.-D., 2014b. Co-ingestion of caffeine and carbohydrate after meal does not improve performance of high-intensity intermittent sprints with short recovery times. Eur. J. Appl. Physiol. 114, 1533–1543.
Lieberman, H.R., Wurtman, R.J., Emde, G.G., Roberts, C., Coviella, I.L., 1987a. The effects of low doses of caffeine on human performance and mood. Pyschopharmacology 92, 308–312.
Lieberman, H.R., Wurtman, R.J., Emde, G.G., Coviella, I.L.G., 1987b. The effects of caffeine and aspirin on mood and performance. J. Clin. Psychopharm. 7, 315–320.
Lieberman, H.R., Tharion, W.J., Shukitt-Hale, B., Speckman, K.L., Tulley, R., 2002. Effects of caffeine, sleep loss, and stress on cognitive performance and mood during U: S. Navy SEAL training. Psychopharmacology 164, 250–261.
Lieberman, H.R., Bathalon, G.P., Falcon, C.M., 2005. The fog of war: decrements in cognitive performance and mood associated with combat-like stress. Aviat. Space Environ. Med. 76, C7–14.
Lieberman, H.R., Carvey, C.E., Thompson, L.A., 2010. Caffeine. In: Coates, P.M. (Ed.), Encyclopedia of Dietary Supplements. Informa Healthcare USA, Inc., New York.
Lieberman, H.R., 1992. Caffeine. In: Jones, D., Smith, A. (Eds.), Factors Affecting Human Performance Vol. II The Physical Environment. Academic Press, London, U.K.
Lindinger, M.L., Graham, T.E., Spriet, L.L., 1993. Caffeine attenuates the exercise-induced increase in plasma [K^+] in humans. J. Appl. Physiol. 74, 1149–1155.
Lopes, J.M., Jardim, A.J., Aranda, J.V., Macklem, P.T., 1983. Effect of caffeine on skeletal muscle function before and after fatigue. J. Appl. Physiol. 54, 1303–1305.
Lorist, M.M., Snel, J., 2008. Caffeine, sleep and quality of life. In: Verster, J.C., Pandi-Permal, S.R., Steiner, D. (Eds.), Sleep and Quality of Life in Clinical Medicine. Human Press, Springer, New York, U.S, pp. 325–332.
Lorist, M.M., Snel, J., Kok, A., 1994. Influence of caffeine on information processing stages in well rested and fatigued subjects. Psychopharmacology 113, 411–421.
Mahoney, C.R., Brunyé, T.T., Giles, G.E., 2011. Caffeine effects on aggression and risky decision making. In: Kanarek, R.B., Lieberman, H.R. (Eds.), Diet, Brain, Behavior: Practical Implications. CRC Press, Boca Raton, FL, pp. 293–311.
Mahoney, C.R., Brunyé, T.T., Giles, G.E., Ditman, T., Lieberman, H.R., Taylor, H.A., 2012. Caffeine increases false memory in nonhabitual consumers. J. Cogn. Psychol. 24, 420–427.
Marchi, M., Raiteri, L., Risso, F., Vallarino, A., Bonfanti, A., Monopoli, A., Ongini, E., Raiteri, M., 2002. Effects of adenosine A_1 and A_{2A} receptor activation on the evoked release of glutamate from rat cerebrocortical snaptosomes. Br. J. Pharmacol. 136, 434–440.
Margaria, R., Aghemo, P., Rovelli, E., 1964. The effect of some drugs on maximal capacity of athletic performance in man. Int. Z. Angew. Physiol. Einschl Arbeitsphysiol. 20, 281–287.
Maridakis, V., O'Connor, P.J., Dudley, G.A., McCully, K.K., 2007. Caffeine attenuates delayed-onset muscle pain and force loss following eccentric exercise. J. Pain 8, 237–243.
Maridakis, V., Herring, M.P., O'Connor, P.J., 2009a. Sensitivity to change in cognitive performance and mood measures of energy and fatigue in response to differing doses of caffeine or breakfast. Int. J. Neurosci. 119, 975–994.
Maridakis, V., O'Connor, P.J., Tomporowski, P.D., 2009b. Sensitivity to change in cognitive performance and mood measures of energy and fatigue in response to morning caffeine alone or in combination with carbohydrate. Int. J. Neurosci. 119, 1239–1258.
Marshall, J.M., 2007. The roles of adenosine and related substances in exercise hyperaemia. J. Physiol. 583, 835–845.
Martin, E.A., Nicholson, W.T., Eisenach, J.H., Charkoudian, N., Joyner, M.J., 2006. Influences of adenosine receptor antagonism on vasodilator responses to adenosine and exercise in adenosine responders and nonresponders. J. Appl. Physiol. 101, 1678–1684.
Maughan, R.J., Griffin, J., 2003. Caffeine ingestion and fluid balance: a review. J. Hum. Nutr. Diet 16, 411–420.
McClung, H.L., Ely, M.R., Lieberman, H.R., Smith, J.E., McGraw, S.M., Niro, P.J., Davis, B.A., Young, A.J., Montain, S.J., 2011. A Snack-based Ration Containing Caffeine Increases Caloric Intake and Improves Cognitive Performance. U.S. Army Research Institute of Environmental Medicine, Natick, MA.
McLellan, T.M., Bell, D.G., 2004. The impact of prior coffee consumption on the subsequent ergogenic effect of anhydrous caffeine. Int. J. Sport Nutr. Exerc. Metab. 14, 698–708.
McLellan, T.M., Lieberman, H.R., 2012. Do energy drinks contain active compnents other than caffeine? Nutr. Rev. 70, 730–744.
McLellan, T.M., Bell, D.G., Kamimori, G.H., 2004. Caffeine improves physical performance during 24 h of active wakefulness. Aviat. Space Environ. Med. 75, 666–672.
McLellan, T.M., Kamimori, G.H., Bell, D.G., Smith, I.F., Johnson, D., Belenky, G., 2005a. Caffeine maintains vigilance and marksmanship in simulated urban operations with sleep deprivation. Aviat. Space Environ. Med. 76, 39–45.
McLellan, T.M., Kamimori, G.H., Voss, D.M., Bell, D.G., Cole, K.G., Johnson, D., 2005b. Caffeine maintains vigilance and improves run times during night operations for Special Forces. Aviat. Space Environ. Med. 76, 647–654.
McLellan, T.M., Kamimori, G.H., Voss, D.M., Tate, C., Smith, S.J.R., 2007. Caffeine effects on physical and cognitive performance during sustained operations. Aviat. Space Environ. Med. 78, 871–877.
Millard-Stafford, M.L., Cureton, K.J., Wingo, J.E., Trilk, J., Warren, G.L., Buyckx, M., 2007. Hydration during exercise in warm, humid conditions: effect of a caffeinated sports drink. Int. J. Sport Nutr. Exerc. Metab. 17, 163–177.
Miller, B., O'Connor, H., Orr, R., Ruell, P., Cheng, H.L., Chow, C.M., 2014. Combined caffeine and carbohydrate ingestion: effects on nocturnal sleep and exercise performance in athletes. Eur. J. Appl. Physiol. 114, 2529–2537.
Mohr, T., Van Soeren, M., Graham, T.E., Kjaer, M., 1998. Caffeine ingestion and metabolic responses of tetraplegic humans during electrical cycling. J. Appl. Physiol. 85, 979–985.
Mohr, M., Nielsen, J.J., Bangsbo, J., 2011. Caffeine intake improves intense intermittent exercise performance and reduces muscle interstitial potassium accumulation. J. Appl. Physiol. 111, 1372–1379.
Mora-Rodriguez, R., Pallarés, J.G., López-Samanes, A., Ortega, J.F., Fernández, V.E., 2012. Caffeine ingestion reverses the circadian rhythm effects on neuromuscular performance in highly resistance-trained men. PLoS One 7, e33807.
Motl, R.W., O'Connor, P.J., Dishman, R.K., 2003. Effect of caffeine on perceptions of leg muscle pain during moderate intensity cycling exercise. J. Pain 4, 316–321.
Motl, R.W., O'Connor, P.J., Tubandt, L., Puetz, T., Ely, M.R., 2006. Effect of caffeine on leg muscle pain during cycling exercise among females. Med. Sci. Sports Exerc. 38, 598–604.
Myers, D.E., Shaikh, Z., Zullo, T.G., 1997. Hypoalgesic effect of caffeine in experimental ischemic muscle contraction pain. Headache 37, 654–658.
Nawrot, P., Jordan, S., Eastwood, J., Rotstein, J., Hugenholtz, A., Feeley, M., 2003. Effects of caffeine on human health. Food Add Contam. 20, 1–30.
Nehlig, A., Daval, J.L., Debry, G., 1992. Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and pyschostimulant effects. Brain Res. Rev. 17, 139–170.
Nehlig, A., 1999. Are we dependent upon coffee and caffeine? A review on human and animal data. Neurosci. Biobehav. Rev. 23, 563–576.
Nehlig, A., 2010. Is caffeine a cognitive enhancer? J. Alzheimers Dis. 20, S85–S94.
Nindl, B.C., Castellani, J.W., Warr, B.J., Sharp, M.A., Henning, P.C., Spiering, B.A., Scofield, D.E., 2013. Physiological employment standards III: physiological challenges and consequences encountered during international military deployments. Eur. J. Appl. Physiol. 113, 2655–2672.

O'Connor, P.J., Motl, R.W., Broglio, S.P., Ely, M.R., 2004. Dose-dependent effect of caffeine on reducing leg muscle pain during cycling exercise is unrelated to systolic blood pressure. Pain 109, 291–298.
O'Rourke, M.P., O'Brien, B.J., Knez, W.L., Paton, C.D., 2008. Caffeine has a small effect on 5-km running performance of well-trained and recreational runners. J. Sci. Med. Sport 11, 231–233.
Okada, M., Kawata, Y., Murakami, T., Wada, K., Mizuno, K., Kondo, T., Kaneko, S., 1999. Differential effects of adenosine receptor subtypes on release and reuptake of hippocampal serotonin. Eur. J. Neurosci. 11, 1–9.
Oken, B.S., Salinsky, M.C., Elsas, S.M., 2006. Vigilance, alertness, or sustained attention: physiological basis and measurement. Clin. Neurophysiol. 117, 1885–1901.
Park, N.D., Maresca, R.D., McKibans, K.I., Morgan, D.R., Allen, T.S., Warren, G.L., 2008. Caffeine's beneficial effect on maximal voluntary strength and activation in uninjured but not injured muscle. Int. J. Sport Nutr. Exerc. Metab. 18, 639–652.
Paton, C.D., Hopkins, W.G., Vollebregt, L., 2001. Little effect of caffeine ingestion on repeated sprints in team-sport athletes. Med. Sci. Sports Exerc. 33, 822–825.
Penetar, D., McCann, U., Thorne, D., Kamimori, G.H., Galinski, C., Sing, H.C., Thomas, M., Belenky, G., 1993. Caffeine reversal of sleep deprivation effects on alertness and mood. Psychopharmacology 112, 359–365.
Peterson, S., Lampe, J.W., Bammler, T.K., Gross-Steinmeyer, K., Eaton, D.J., 2006. Apiaceous vegetable constituents inhibit cytochrome P-450 1A2 (hCYP1A2) activity and hCYP1A2-mediated mutagenicity of aflatoxin B1. Food Chem. Toxicol. 44, 1474–1484.
Peterson, S., Schwarz, Y., Li, S.S., Li, L., King, I.B., Chen, C., Eaton, D.L., Potter, J.D., Lampe, J.W., 2009. CYP1A2, GSTM1, and GSTT1 polymorphisms and diet effects on CYP1A2 activity in a crossover feeding trial. Cancer Epidemiol. Biomarkers Prev. 18, 3118–3125.
Philip, P., Taillard, J., Moore, N., Delord, S., Valtat, C., Sagaspe, P., Bioulac, B., 2006. The effects of coffee and napping on nighttime highway driving. Ann. Intern. Med. 144, 785–791.
Plaskett, C.J., Cafarelli, E., 2001. Caffeine increases endurance and attenuates force sensation during submaximal isometric contractions. J. Appl. Physiol. 91, 1535–1544.
Poehlman, E.T., Després, J.-P., Bessette, H., Fontaine, E., Tremblay, A., Bouchard, C., 1985. Influence of caffeine on the resting metabolic rate of exercise-trained and inactive subjects. Med. Sci. Sports Exerc. 17, 689–694.
Powers, S.K., Byrd, R.J., Tulley, R., Callender, T., 1983. Effects of caffeine ingestion on metabolism and performance during graded exercise. Eur. J. Appl. Physiol. 50, 301–307.
Rainnie, D.G., Grunze, H.C.R., McCarley, R.W., Greene, R.W., 1994. Adenosine inhibition of mesopontine cholinergic neruons: implications for EEG arousal. Science 263, 689–692.
Renda, G., Committeri, G., Zimarino, M., DiNicola, M., Tatasciore, A., Ruggieri, B., Ambrosini, E., Viola, V., Antonucci, I., Stuppia, L., DeCaterina, R., 2015. Genetic determinants of cognitive responses to caffeine drinking identified from a double-blind, randomized, controlled trial. Eur. Neuropsychopharmacol. 25, 798–807.
Reyner, L.A., Horne, J.A., 1997. Suppression of sleepiness in drivers: combination of caffeine with a short nap. Psychophysiology 37, 251–256.
Reyner, L.A., Horne, J.A., 2000. Early morning driver sleepiness: effectiveness of 200 mg caffeine. Psychopharmacology 37, 251–256.
Rivers, W.H.R., Webber, H.N., 1907. The action of caffeine on the capacity for muscular work. J. Physiol. 36, 33–47.
Roberts, S.P., Stokes, K.A., Trewartha, G., Doyle, J., Hogben, P., Thompson, D., 2010. Effects of carbohydrate and caffeine ingestion on performance during a rugby union simulation protocol. J. Sports Sci. 28, 833–842.
Robertson, D., Wade, D., Workman, R., Woosley, R.L., 1981. Tolerance to the humoral and hemodynamic effects of caffeine in man. J. Clin. Invest. 67, 1111–1117.
Rogers, N.L., Dinges, D.F., 2005. Caffeine: implications for alertness in athletes. Clin. Sports Med. 24, e1–e13.
Ronen, A., Oron-Gilad, T., Gershon, P., 2014. The combination of short rest and energy drink consumption as fatigue countermeasures during a prolonged drive of professional truck drivers. J. Safety Res. 49, 39–43.
Rosenthal, L., Roehrs, T., Zwyghuizen-Doorenbos, A., Plath, D., Roth, T., 1991. Alerting effects of caffeine after normal and restricted sleep. Neuropsychopharmacol 4, 103–108.
Roti, M.W., Casa, D.J., Pumerantz, A.C., Watson, G., Judelson, D.A., Dias, J.C., Ruffin, K., Armstrong, L.E., 2006. Thermoregulatory responses to exercise in the heat: chronic caffeine intake has no effect. Aviat. Space Environ. Med. 77, 124–129.
Ryan, E.J., Kim, C.-H., Fickes, E.J., Williamson, M., Muller, M.D., Barkley, J.E., Gunstad, J., Glickman, E.L., 2013. Caffeine gum and cycling performance: a timing study. J. Strength Cond. Res. 27, 259–264.
Sökmen, B., Armstrong, L.E., Kraemer, W.J., Casa, D.J., Dias, J.C., Judelson, D.A., Maresh, C.M., 2008. Caffeine use in sports: considerations for the athlete. J. Strength Cond. Res. 22, 978–986.
Sagaspe, P., Taillard, J., Chaumet, C., Moore, N., Bioulac, B., Philip, P., 2007. Aging and nocturnal driving: better with coffee or a nap? A randomized study. Sleep 30, 1808–1813.
Salinero, J.J., Lara, B., Abian-Vicen, J., Gonzalez-Millan, C., Areces, F., Gallo-Salazar, C., Ruiz-Vicente, D., DelCoso, J., 2014. The use of energy drinks in sport: perceived ergogenicity and side effects in male and female athletes. Br. J. Nutr. 112, 1494–1502.
Santos, V.G.F., Santos, V.R.F., Felippe, L.J.C., Almeida, J.W., Bertuzzi, R., Kiss, M.A.P.D.M., Lima-Silva, A.E., 2014. Caffeine reduces reaction time and improves performance in simulated-contest of taekwondo. Nutrients 6, 637–649.
Sawynok, J., 1998. Adenosine receptor activation and nociception. Eur. J. Pharmacol. 347, 1–11.
Sharwood, L.N., Elkington, J., Meuleners, L., Ivers, R., Boufous, S., Stevenson, M., 2013. Use of caffeinated substances and risk of crashes in long distance drivers of commercial vehicles: case-control study. BMJ 346, f1140.
Shearer, J., Graham, T.E., 2014. Performance effects and metabolic consequences of caffeine and caffeinated energy drink consumption on glucose disposal. Nutr. Rev. 72 (S1), 121–136.
Sil'kis, I.G., 2009. Search for approaches to correction of daytime sleepiness induced by dopaminergic drugs during treatment of Parkinson's disease: neurochemical aspects. Neurochem. J. 3, 253–265.
Sil'kis, I.G., 2014. Possible mechanisms for impairments to learning, memory, and attention due to sleep deprivation. Neurosci. Biobehav. Physiol. 44, 1200–1212.
Silva-Cavalcante, M.D., Correia-Oliveira, C.R., Santos, R.A., Lopes-Silva, J.P., Lima, H.M., Bertuzzi, R., Duarte, M., Bishop, D.J., Lima-Silva, A.E., 2013. Caffeine increases anaerobic work and restores cycling performance following a protocol designed to lower endogenous carbohydrate availability. PLoS One 8, e72025.
Simmonds, M.J., Minahan, C.L., Sabapathy, S., 2010. Caffeine improves supramaximal cycling but not the rate of anaerobic energy release. Eur. J. Appl. Physiol. 109, 287–295.
Skinner, T.L., Jenkins, D.G., Coombes, J.S., Taaffe, D.R., Leveritt, M.D., 2010. Dose response of caffeine on 2000-m rowing performance. Med. Sci. Sports Exerc. 42, 571–576.
Skinner, T.L., Jenkins, D.G., Taafe, D.R., Leveritt, M.D., Coombes, J.S., 2013. Coinciding exercise with peak serum caffeine does not improve cycling performance. J. Sci. Med. Sport 16, 54–59.
Smith, E.E., Kosslyn, S.M., 2007. Cognitive Psychology: Mind and Brain. Pearson Education, Columbus, OH.
Smith, A., Kendrick, A., Maben, A., 1992. Use and effects of food and drinks in relation to daily rhythms of mood and cognitive performance. Effects of caffeine, lunch and alcohol on human performance. Proc. Nutr. Soc. 51, 325–333.
Smith, A., Sturgess, W., Gallagher, J., 1999. Effects of a low dose of caffeine given in different drinks on mood and performance. Hum. Psychopharmacol. Clin.Exp. 14, 473–482.
Smith, A., Sunderland, D., Christopher, G., 2005. Effects of repeated doses of caffeine on mood and performance of alert and fatigued volunteers. J. Psychopharmacol. 19, 620–626.
Smith, A., 2002. Effects of caffeine on human behavior. Food Chem. Toxicol. 40, 1243–1255.
Smith, A., 2005. Caffeine. In: Lieberman, H.R., Kanarek, R.B., Prasad, C. (Eds.), Nutritional Neuroscience. Taylor and Francis Group, Boca Raton, FL, pp. 341–361.
Smith, A., 2009. Effects of caffeine in chewing gum on mood and attention. Hum Psychopharm Clin 24, 239–247.
Smith, A.P., 2011. Caffeine, practical implications. In: Kanarek, R., Lieberman, H. (Eds.), Diet, Brain, Behavior: Practical Implications. CRC Press, Boca Rotan, Florida, pp. 271–292.
Snel, J., Lorist, M.M., 2011. Effects of caffeine on sleep and cognition. Prog. Brain Res. 190, 105–117.
Snel, J., Lorist, M.M., Tieges, Z., 2004. Coffee, caffeine, and cognitive performance. In: Nehlig, A. (Ed.), Coffee, Tea, Chocolate and the Brain. CRC Press LLC, Boca Raton, FL, pp. 53–73.
Soar, K., Chapman, E., Lavan, N., Jansari, A.S., Turner, J.J.D., 2016. Investigating the effects of caffeine on executive functions using traditional Stroop and a new ecologically-valid virtual reality task, the Jansari assessment of Executive Functions (JEF©). Appetite 105, 156–163.
Soroko, S., Chang, J., Barrett-Connor, E., 1996. Reasons for changing caffeinated coffee consumption: the Rancho Bernardo Study. J. Am. Coll. Nutr. 15, 97–101.
Souissi, M., Chtourou, H., Abedelmalek, S., Ghozlane, I.B., Sahnoun, Z., 2014. The effects of caffeine ingestion on the reaction time and short-term maximal performance after 36 h of sleep deprivation. Physiol. Behav. 131, 1–6.
Spriet, L.L., MacLean, D.A., Cyck, D.J., Hultman, E., Cederblad, G., Graham, T.E., 1992. Caffeine ingestion and muscle metabolism during prolonged exercise in humans. Am. J. Physiol. 262, E891–E898.
Spriet, L.L., 2014. Exercise and sport performance with low doses of caffeine. Sports Med. 44 (Suppl. (2)), S175–S184.
Stadheim, H.K., Kvamme, B., Olsen, R., Drevon, C.A., Ivy, J.L., Jensen, J., 2013. Caffeine increases performance in cross-country double-poling time trial exercise. Med. Sci. Sports Exerc. 45, 2175–2183.
Stadheim, H.K., Nossum, E.M., Olsen, R., Spencer, M., Jensen, J., 2015. Caffeine improves performance in double poling during acute exposure to 2,000-m altitude. J. Appl. Physiol. 119, 1501–1509.
Stafford, L.D., Rusted, J., Yeomans, M.R., 2007. Caffeine, mood, and performance. A selective review. In: Smith, B.D., Gupta, U., Gupta, B.S. (Eds.), Caffeine and Activation Theory: Effects on Health and Behavior. Taylor and Francis, Boca Raton, FL, pp. 284–310.
Tallis, J., Duncan, M.J., James, R.S., 2015. What can isolated skeletal muscle experiments tell us about the effects of caffeine on exercise performance? Br. J. Pharmacol. 172, 3703–3713.

Tarnopolsky, M.A., Cupido, C., 2000. Caffeine potentiates low frequency skeletal muscle force in habitual and nonhabitual caffeine consumers. J. Appl. Physiol. 89, 1719–1724.
Tarnopolsky, M.A., 2008. Effect of caffeine on the neuromuscular system – potential as an ergogenic aid. Appl. Phys. Nutr. Metab. 33, 1284–1289.
Terry, W.S., Phifer, B., 1986. Caffeine and memory performance on the AVLT. J. Clin. Psychol. 42, 860–863.
Tharion, W.J., Shukitt-Hale, B., Lieberman, H.R., 2003. Caffeine effects on marksmanship during high-stress military training with 72 hour sleep deprivation. Aviat. Space Environ. Med. 74, 309–314.
Thornton, G.R., Holck, H.G.O., Smith, E.L., 1939. The effect of benzedrine and caffeine upon performance in certain psychomotor tasks. J. Abnorm. Soc. Psychol. 34, 96–113.
Tikuisis, P., Keefe, A.A., McLellan, T.M., Kamimori, G.H., 2004. Caffeine restores engagement speed but not shooting precision following 22 h of active wakefulness. Aviat. Space Environ. Med. 75, 771–776.
Ullrich, S., deVries, Y.C., Kühn, S., Repantis, D., Dresler, M., Ohla, K., 2015. Feeling smart: effects of caffeine and glucose on cognition, mood and self-judgment. Physiol. Behav. 151, 629–637.
Van Soeren, M.H., Graham, T.E., 1998. Effect of caffeine on metabolism, exercise endurance, and catecholamine responses after withdrawal. J. Appl. Physiol. 85, 1493–1501.
Varani, K., Portaluppi, F., Gessi, S., Merighi, S., Ongini, E., Belardinelli, L., Borea, P.A., 2000. Dose and time effects of caffeine intake on human platelet adenosine A_{2a} receptors. Circulation 102, 285–289.
Warburton, D.M., Bersellini, E., Sweeney, E., 2001. An evaluation of a caffeinated taurine drink on mood, memory and information processing in healthy volunteers without caffeine abstinence. Psychopharmacology 158, 322–328.
Warburton, D.M., 1995. Effects of caffeine on cognition and mood without caffeine abstinence. Psychopharmacology 119, 66–70.
Warren, G.L., Park, N.D., Maresca, R.D., McKibans, K.I., Millard-Stafford, M.L., 2010. Effect of caffeine ingestion on muscular strength and endurance: a meta-analysis. Med. Sci. Sports Exerc. 42, 1375–1387.
Watters, P.A., Martin, F., Schreter, Z., 1997. Caffeine and cognitive performance: the nonlinear Yerkes-Dodson law. Hum. Psychopharm. 12, 249–257.
Weiss, B., Laties, V.G., 1962. Enhancement of human performance by caffeine and the amphetamines. Pharmacol. Rev. 14, 1–36.
Wells, C.L., Schrader, T.A., Stern, J.R., Krahenbuhl, G.S., 1985. Physiological responses to a 20-mile run under three fluid replacement treatments. Med. Sci. Sports Exerc. 17, 364–369.
Wemple, R.D., Lamb, D.R., McKeever, K.H., 1997. Caffeine vs caffeine-free sports drinks: effects on urine production at rest and during prolonged exercise. Int. J. Sports Med. 18, 40–46.
Wesensten, N.J., Belenky, G., Kautz, M.A., Thorne, D.R., Reichardt, R.M., Balkin, T.J., 2002. Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine. Psychopharmacology 159, 238–247.
Wesensten, N.J., Belenky, G., Thorne, D.R., Kautz, M.A., Balkin, T.J., 2004. Modafinil vs caffeine: effects on fatigue during sleep deprivation. Aviat. Space Environ. Med. 75, 520–525.
Wesensten, N.J., Kilgore, W.D., Balkin, T.J., 2005. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. J. Sleep Res. 14, 255–266.
Wiles, J.D., Bird, S.R., Hopkins, J., Riley, M., 1992. Effect of caffeinated coffee on running speed, respiratory factors, blood lactate and perceived exertion during 1500-m treadmill running. Br. J. Sports Med. 26, 116–120.
Wolk, B.J., Ganetsky, M., Babu, K.M., 2012. Toxicity of energy drinks. Curr. Opin. Pediatr. 24, 243–251.
Wood, S., Sage, J.R., Shuman, T., Anagnostaras, S.G., 2014. Psychostimulants and cognition: a continuum of behavioral and cognitive activation. Pharmacol. Rev. 16, 193–221.
Yang, A., Palmer, A.A., deWit, H., 2010. Genetics of caffeine consumption and responses to caffeine. Psychopharmacology 211, 245–257.
Yang, C., Franciosi, S., Brown, R.E., 2013. Adenosine inhibits the excitatory synaptic inputs to basal forebrain cholinergic, GABAergic, and parvalbumin neurons in mice. Front. Neurol. 4, 77.
Yerkes, R.W., Dodson, J.D., 1908. The relation of strength of stimulus to rapidity of habit-formation. J. Compd. Neurol. Psycho 18, 459–482.
Zhang, Y., Coca, A., Casa, D.J., Antonio, J., Green, J.M., Bishop, P.A., 2015. Caffeine and diuresis during rest and exercise: a meta-analysis. J. Sci. Med. Sport 15, 569–574.
Zheng, X., Takatsu, S., Wang, H., Hasegawa, H., 2014. Acute intraperitoneal injection of caffeine improves endurance exercise performance in association with increasing brain dopamine release during exercise. Pharmacol. Biochem. Behav. 122, 136–143.