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BEYOND CAFFEINE FOR MENTAL PERFORMANCE

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KEY POINTS

- Caffeine, when taken alone in a research context, is associated with consistent ergogenic and psychological benefits, although within differing optimal dose ranges. The effects of caffeine on mental performance are limited and do not typically encompass benefits to several sport-relevant cognitive domains.
- Caffeine has a number of mechanisms of action and enzyme substrate properties that predispose it to interact with other co-consumed bioactive compounds, including multifarious medicinal and psychoactive drugs.
- In a real-world sport/exercise context, caffeine is often consumed alongside other bioactive compounds in the form of manufactured energy drinks or naturally occurring, plant-derived, caffeinated products.
- Where relevant research has been conducted, the evidence suggests that caffeine-containing, multi-component, plant-derived products and energy drinks/shots can engender mental performance benefits that are broader than those expected from caffeine alone.
- Given the paucity of research designed to disentangle the comparative contributions of caffeine and other co-consumed bioactive ingredients to their combined effects, further research is required in this area.

INTRODUCTION

Three quarters of athletes consume caffeine before or during competition (Del Coso et al., 2011). Whilst caffeine has well-established ergogenic properties, it also exerts purely psychological effects. However, caffeine's beneficial effects here are largely restricted to improved alertness/fatigue and enhanced attention/concentration. Caffeine's effects do not generally extend to the other cognitive domains that can be conceived as being intrinsic to peak sporting performance, such as spatial and verbal working memory, executive function, and declarative memory (Scharfen & Memmert, 2019).

Caffeine's multifarious mechanisms of action predispose it to have interactive relationships with a wide range of bioactive medicinal and dietary compounds, potentially broadening, increasing, decreasing, or modulating the time course of their functional effects, or vice versa. This Sports Science Exchange article describes the mechanisms of action and functional effects of caffeine, and the psychological effects of commonly consumed multi-component caffeinated products. It also assesses whether the non-caffeine components of these products either have relevant independent effects on mental performance beyond those of caffeine, or whether they enjoy an interactive relationship with caffeine that potentiates their own functional effects, or indeed those of caffeine.

WHAT IS CAFFEINE?

Caffeine and related methylxanthines are alkaloid defence chemicals synthesized by a small group of unrelated plants, including those that give us tea, coffee, cocoa, and guaraná. Caffeine's primary role is to act as a toxic, neurological behaviour-modifier, dissuading insect and mollusc herbivores from eating the plant's most vulnerable tissue by increasing locomotor activity at low doses, with incapacitation and death following at higher doses. The mechanisms here are largely the same as those that drive caffeine's effects on human behaviour (Kennedy, 2014a).

In plants, methylxanthines are synthesized from ubiquitous purines, including adenine, guanine, and adenosine. Caffeine's biological effects are then directly related to its structural similarity to adenosine (Kennedy, 2014). Adenosine itself is an inhibitory neuromodulator that builds up in the cortex and basal forebrain as a direct consequence of neural activity throughout the waking hours, increasing fatigue and decreasing alertness. It then dissipates during sleep. However, adenosine is also the building block for a host of other functional cellular molecules, including anabolic and catabolic metabolism factors (e.g., adenosine di/triphosphate [ADP/ATP], S-adenosyl methionine [SAM-e]), second messenger molecules (e.g., cyclic adenosine monophosphate [cAMP]), and multiple enzymes (e.g., poly [ADP ribose] polymerase [PARP]).

CAFFEINE'S MECHANISMS OF ACTION

Orally consumed caffeine is rapidly absorbed and distributed with a circulating half-life of ~3–5 hours (McLellan et al., 2016). Caffeine's central nervous system effects are generally attributed to antagonism of A_1 and A_{2A} adenosine receptors and the resultant blockade of adenosine's inhibitory action. Downstream, this increases the neural activity associated with a variety of neurotransmitters, including dopamine, acetylcholine, noradrenaline, serotonin, glutamate, and gamma-aminobutyric acid. However, caffeine also inhibits the activity of several key enzymes, including those involved in the catalysis of neurotransmitters and amino acids, gluco-regulation, and cellular signalling and repair throughout the body (including phosphodiesterase and PARP). Caffeine at very high concentrations also mimics the role of ATP at ryanodine receptors, increasing muscle contractions.

In terms of ergogenic effects, these mechanisms translate into increased motor unit firing, suppression of exercise-related pain, reduced sensation of force, and decreased ratings of perceived physical effort, alongside related psychological benefits (Guest et al., 2021; Meeusen et al., 2013).

Based on the above mechanisms, caffeine also has potentially wide-ranging modulatory properties with regards to the effects of other bioactive molecules. However, caffeine also affects the absorption, distribution, metabolism, and excretion of many other bioactive molecules via complexation with other compounds, multiple gastrointestinal effects, and modulation of the distribution of molecules, by increasing the tightness of the blood-brain barrier. Caffeine and its metabolites are also metabolized by several members of the cytochrome P450 (CYP450) family of enzymes (CYP1A1, 1A2, 2A6, and 2E1) that manage the metabolism and clearance of endogenous and exogenous bioactive compounds. Caffeine can therefore interact with the many other compounds that also interact with these enzymes, increasing or decreasing their bioavailability, clearance, effectiveness, or toxicity of the compound/drug/nutrient, or vice versa. Unsurprisingly, caffeine has well-established interactive relationships with a wide range of medicinal and psychoactive drugs.

CAFFEINE'S FUNCTIONAL EFFECTS

In terms of ergogenic benefits, caffeine has been shown to enhance endurance exercise, muscular endurance and power, high-intensity and intermittent exercise, and sport-specific aspects of physical performance (for review, see Guest et al., 2021). The optimal dose range is 3–6 mg/kg body mass (bm), with some evidence from the limited literature that caffeine's effects extend down to 2 mg/kg bm (Pickering & Kiely, 2021; Spriet, 2014).

Caffeine's psychological effects are evident at much lower doses, with benefits evident from as low as 32 mg[1] (i.e., < 0.5 mg/kg bm), and consistent benefits apparent at 75 mg[2] (~1 mg/kg bm). Enhancement plateaus above 100 mg (~1.5 mg/kg bm), begin to decrease beyond 300 mg (~4 mg/kg bm) and can become negative in terms of anxiety and performance beyond 400 mg (~5.5. mg/kg) (McLellan et al., 2016). The psychological effects of caffeine within the optimal range are consistent but are restricted to increased subjective alertness/arousal or decreased fatigue and relatively modest improvements in the performance of tasks assessing attention or focussed attention/vigilance (Haskell et al., 2013). Caffeine's effects do not generally extend to other cognitive domains potentially relevant to sport, such as spatial or verbal working memory, executive function or long-term memory. There is little research addressing the cognitive effects of caffeine during sport/exercise, with most studies in a sport/exercise context measuring psychological function before and/or after rather than during exercise. These benefits are similar to the general psychological literature (Lorenzo-Calvo et al., 2021).

In general, the literature addressing caffeine's functional effects is complicated by a number of unresolved issues, such as the role that genetic polymorphisms (e.g., in CYP1A2), habituation, and withdrawal and tolerance may play with respect to caffeine's effects.

MULTI–COMPONENT CAFFEINATED PRODUCTS

In research, caffeine is most often administered in a pure, anhydrous form (Guest et al., 2021), whereas in the real world caffeine is usually consumed alongside other bioactive compounds, which may have independent effects or enjoy an interactive relationship with caffeine. The following summarizes the available information on the most common sources of caffeine.

Polyphenols and Caffeine

Natural sources of caffeine always contain significant concentrations of polyphenols. This group of phytochemicals engender global benefits to health and physiological functioning via interactions with, and modulation of diverse components of a wide range of mammalian cellular signal transduction pathways throughout the body, leading to multifarious metabolic, cardiovascular, and inflammatory status benefits. Within the brain these include modulation of neuro-inflammation, direct and indirect effects on neurotransmission and local blood flow, modulation of neurotrophin synthesis/function, and increased angiogenesis/neurogenesis (Kennedy, 2014a).

Meta-analyses of controlled-trial data suggest that polyphenols from diverse sources improve cardiovascular function, aid physiological recovery from exercise, and improve some aspects of physical performance (Ammar et al., 2020; Hepsomali et al., 2021). They also benefit cognitive function, including tasks assessing attention, executive function, and mental fatigue (Blake et al., 2021; Carey et al., 2021; Fraga et al., 2019). Caffeine and polyphenols also enjoy wide-raging interactive relationships, increasing both the bioavailability and functional effects of the polyphenols (e.g., Sansone et al., 2017).

Cocoa (seeds of Theobroma cacao). Cocoa contains caffeine (and theobromine) and high levels of polyphenolic flavanols and their oligomers, with the polyphenol levels dictated by the fermenting, roasting, and manufacturing process (Andres-Lacueva et al., 2008). Research generally employs high-flavanol extracts or dark chocolate with low levels of caffeine (< 40 mg). Meta-analyses of a substantive body of controlled trials show that both single doses and longer-term administration of high-flavanol extracts and chocolate engender a wide range of cardiovascular benefits. Cocoa-flavanols also reduce oxidative stress and modulate metabolism during or after exercise and enhance cerebral blood flow and the synthesis of neurotrophic factors such as brain-derived neurotrophic factor (BDNF) (Kennedy, 2019).

In terms of psychological benefits, a single study in a sport context

[1] Research outside of a sport context tends to administer a set dose for all participants. Where mg/kg bm is given, this is based on an average 70 kg body mass.

[2] The dose currently required for an EFSA (European Food Safety Authority) caffeine claim.

showed that cocoa-flavanols improved executive function task performance before and after exercise (Tsukamoto et al., 2018). This corresponds well with multiple studies showing that single doses of high-flavanol, low-caffeine extracts have potentially broader cognitive effects than caffeine alone (Kennedy, 2019). Two particularly thorough studies also reported that 4 weeks of supplementation with high-cocoa-flavanol extracts increased both attention and executive function task performance, alongside beneficial effects on multiple health related biomarkers, in 90 heathy elderly (Mastroiacovo et al., 2015) and 90 sufferers from age-related cognitive impairment (Desideri et al., 2012). In confirmation, a meta-analysis of chronic supplementation (2 weeks to 3 months) studies reported improvements in executive function task performance (Zhu et al., 2021), whilst a complementary meta-analysis also reported improved depression, anxiety, and positive affect (Fusar-Poli et al., 2021).

It is important to note that much of the human research has compared cocoa-flavanol extracts with caffeine matched control interventions. This approach differentiates the added value of cocoa-flavanols but clearly runs the risk of underestimating the effects of the cocoa-flavanol/caffeine combinations.

Guaraná (seeds of Paullinia cupana). Guaraná seed extracts have a similar polyphenol makeup as cocoa, with high levels of flavanols and their oligomers. Extracts also typically contain 2.5–5% caffeine and several triterpene compounds.

There is little research investigating the effects of guaraná on physical performance. However, a number of studies have demonstrated cognitive benefits following guaraná that are much broader than would be expected from caffeine. These include benefits to long-term memory, working memory, and executive function, alongside typical caffeine- like effects on mental fatigue and attention. Given that these effects are seen even when very low, sub-psychoactive doses of caffeine are involved (from ~0.05 mg/kg bm), it can be concluded that caffeine has not contributed directly to these effects (Haskell et al., 2013). In support of this, one study compared a guaraná extract with multi-vitamins to its comparatively high caffeine content (100 mg) and demonstrated significantly greater improvements in cognitive function for the guaraná condition compared both with placebo and caffeine alone (Pomportes et al., 2014). Of particular relevance here, a single study in a sport/exercise context also showed that single doses of a product combining guaraná extract (40 mg caffeine or ~0.6 mg/kg bm) and multi-vitamins improved working memory and episodic memory task performance both before and after 30 minutes of treadmill running in 40 young males (Veasey et al., 2015).

Coffee (Coffea genus). The coffee roasting process leads to depleted levels of polyphenols (mainly chlorogenic acids [CGA], alongside several simple phenolic acids and their derivatives). Unroasted or lightly roasted green coffee and coffee berry extracts made from the pulp surrounding the seed retain much higher levels of the same polyphenols.

Roasted Coffee. In ergogenic terms the small body of research that has directly compared coffee and caffeine has generated equivocal evidence as to their comparative efficacy. In terms of psychological functioning, there is a lack of research employing the requisite comparator arms to disentangle the effects of caffeine from those of the other bioactive components. One recent study did compare the cognitive and mood effects of caffeinated and decaffeinated coffee to an inert coffee flavoured placebo (Haskell-Ramsey et al., 2018). The results showed that both the caffeinated and decaffeinated coffee drinks led to increased alertness, but that the caffeine-containing drink alone revealed significant cognitive effects. However, the overall pattern of results showed that the decaffeinated drink fell between the placebo and caffeinated drink on most measures, leading the authors to surmise a modulatory effect of the non-caffeine components of coffee.

Green Coffee. There is some evidence that chronic consumption of high-CGA green coffee has beneficial effects on multifarious cardiovascular parameters, and that single doses of green coffee engender greater cardiovascular benefits than their caffeine content. However, a single physical exercise study found that whilst a high-CGA/caffeine coffee did improve overall mood, it was no more effective in ergogenic terms (Nieman et al., 2018). With regards to brain function, two single-dose studies have demonstrated that high-CGA decaffeinated green coffee improved the performance of attention tasks, subjective alertness, and other aspects of psychological state compared with placebo (see Haskell et al., 2013). Two recent studies also demonstrated some cognitive improvements, including in executive function tasks, following administration of caffeine-free green coffee to older adults over several months (Ochiai et al., 2019; Saitou et al., 2018).

Coffee Berry. Single doses of coffee berry extracts with very low caffeine levels have been shown to enhance cerebral blood flow and increase the synthesis of neurotrophic factors such as BDNF and attenuate the effects of extended performance of demanding cognitive tasks on alertness and mental fatigue. One study also investigated chronic effects. In this case, when coffee berry extract was taken in the morning or twice per day for 7 and 28 days by sufferers of mild, age-related cognitive impairment, the performance of a demanding working memory/executive function task was improved (Robinson et al., 2019). However, this effect was not seen when the extract was only taken in the evening.

Green tea (Camellia sinensis). Green tea contains significant levels of flavanols, including catechin, epicatechin, and the tea-specific polyphenol epigallocatechin gallate (EGCG), plus the tea-specific amino-acid L-theanine and caffeine. Meta-analysis of controlled-trial data showed that the consumption of green tea extracts was associated with a number of cardiovascular and anthropometric benefits, although the effects on exercise performance are unclear to date (see Golzarand et al., 2018; Rasaei et al., 2021).

There is little research assessing the mental performance effects of green tea extracts or tea catechins, and no studies in a sport/exercise context. However, a number of studies have investigated interactions between the green tea components caffeine and L-theanine. The general finding across a number of studies was that the combination of caffeine with L-theanine can potentiate the mental performance effects of caffeine alone, attenuate the reduction in cerebral blood-flow associated with caffeine, and elicit a synergistic, interactive effect on activation in brain regions associated with task performance. As an example of functional effects, one study found that whereas caffeine (150 mg) and caffeine combined with L-theanine (250 mg) elicited common improvements in the performance of a Rapid Visual Information Processing (RVIP) task and decreased subjective mental fatigue, the caffeine/L-theanine combination also led to a number of significant benefits over those seen following caffeine alone, including improved alertness and tiredness and enhanced working memory performance (Haskell et al., 2008). Whilst the balance here is in favour of beneficial caffeine/L-theanine interactions, it should be noted that two studies demonstrated that the addition of L-theanine simply attenuated caffeine's effects on cognitive function (Dodd et al., 2015; Giles et al., 2017).

Conclusion: Polyphenols and Caffeine. Caffeine enjoys a number of interactive relationships with polyphenols. Evidence suggests that the benefits to mental performance following plant-based sources of caffeine are broader than those following caffeine alone, and potentially include enhancement within cognitive domains relevant to sporting performance that are unaffected by caffeine. These benefits are also evident following products with lower doses of caffeine than would normally be considered psychoactive. The strongest evidence here, but also the most consistent research, relates to high cocoa-flavanol products and guaraná, with emerging evidence for high CGA coffee products. Whether these effects are entirely independent of caffeine or represent an interaction with the low dose of caffeine present remains to be explored by studies equipped with the appropriate comparator arms. The question of whether higher doses of caffeine will further potentiate the effects of low caffeine products also requires elucidation.

CAFFEINATED DRINKS

Caffeine/Carbohydrate Drinks. In general, carbohydrates consumed alone have very short-term effects on cognitive function, with improvements most often seen in long-term memory. However, whilst drinks containing caffeine and carbohydrate also have consistent effects on mental performance, there is little research disentangling their contributions. Just under half of the small number of studies published to date with the requisite arms for the comparison found evidence of a greater effect for the carbohydrate/caffeine combination than for the component parts, leaving the question unresolved (Boyle et al., 2018).

Energy Drinks/Shots. Energy drinks and shots typically contain caffeine and taurine, often in combination with carbohydrates, amino acids, vitamins, or herbal extracts. All of these components may have independent effects on brain function. In terms of ergogenic effects, a recent meta-analysis of the data from 34 studies found that energy drinks containing caffeine and taurine resulted in significantly improved endurance exercise test performance, jumping, muscle strength and endurance, and cycling and running performance (Souza et al., 2017). Importantly, these effects were evident from doses of caffeine (~1 mg/kg bm) that were lower than those typically considered to be ergogenic (Guest et al., 2021) and were correlated with the amount of taurine in the drinks rather than caffeine. The few studies on psychological functioning in a sport/exercise context are consistent with the findings from the general literature that energy drinks have reliable beneficial effects on attention task performance, although it is notable that these studies have not interrogated other cognitive domains.

Interestingly, in studies controlling for the effect of carbohydrates, the mental performance effects of multi-component energy drinks have extended to cognitive domains typically unaffected by caffeine. For example, a particularly thorough cross-over study, involving a large sample of healthy adults, compared a carbohydrate-free energy shot to placebo over 6 hours post-dose (Wesnes et al., 2013). The results demonstrated broad cognitive benefits that included improved attention task performance and improved alertness. More importantly, improvements were also seen in measures that would not be sensitive to caffeine, including across working memory and episodic memory tasks and in ratings of depression and anxiety. All of these improvements were also seen during the later assessments, when the effects of caffeine might be expected to be waning (Wesnes et al., 2013). With regards to specific interactions within ingredients, two studies suggest that taurine serves to attenuate caffeine's psychological effects, although again these studies did not interrogate the cognitive domains unaffected by caffeine (Giles et al., 2012; Peacock et al., 2013). Notably, irrespective of the direction of the functional relationship seen here, these results also confirm that both taurine and caffeine contribute to the effects of products that combine them.

NON-CAFFEINATED PHYTOCHEMICALS

A number of plant extracts and phytochemicals, several of which commonly appear in energy drinks[3], have been shown to have broader mental performance effects than caffeine. Recent evidence shows that single doses of mango leaf extracts containing high levels of the polyphenol mangiferin (> 60%) have physical performance–enhancing properties when combined with other polyphenols, and can engender broad improvements in cognitive function, including during mentally demanding tasks (Wightman et al., 2020). Several studies have also extended the psychological benefits of chronic supplementation with curcumin, the principal polyphenol in turmeric, typically seen as effective in depression, to include improved attention and working memory. Phytochemicals from other classes have also been shown to be effective in terms of improving attention and aspects of memory (working memory/long-term memory). These include single oral doses of volatile monoterpenes from sage (*Salvia officinalis/lavandulaefolia*) and peppermint (*Mentha piperita*); acute and chronic consumption of diterpene/polyphenol rich Ginkgo biloba extracts; and single doses of triterpene rich ginseng (*Panax ginseng/quinquefolius*) extracts. For a more detailed review, see Kennedy, 2019.

[3] The content of the bioactive components of plant extracts included in energy drinks is rarely stated.

Potential interactions with caffeine have not yet been investigated in humans for any of these plant extracts. However, given that many of their bioactive compounds share the same CYP enzymes as caffeine, and are potentially prone to caffeine's other modulatory effects on pharmacokinetics, there is real potential for boosted mental performance following combination products.

PRACTICAL APPLICATIONS

- Taking pure caffeine is likely to be the most impoverished method of consuming this phytochemical.
- Doses of caffeine at the higher end of the optimal ergogenic range (3 to 6 mg/kg bm) also coincide with doses that are liable to be detrimental in terms of anxiety and mental performance.
- The results from "pure caffeine" research cannot necessarily be extrapolated to everyday caffeine consumption.
- Plant caffeine sources will also provide significant levels of polyphenols, and energy drinks may contain significant levels of beneficial bioactives. These additional compounds may engender independent physiological or psychological benefits, and the additional compounds may enjoy functional interactive relationships with caffeine.
- Evidence suggests specific benefits for high-flavanol cocoa products (extracts or dark chocolate) and guaraná extracts, and high CGA coffee products. Regular tea and coffee would benefit from more research.
- Multi-component caffeinated products may deliver broader benefits to mental performance than caffeine alone, and at much lower doses of caffeine.

SUMMARY

In the real world, outside of a caffeine research context, athletes and participants in sport typically consume caffeine alongside a complex mixture of other bioactive compounds, potentially taking advantage of the many interactions that caffeine enjoys with phytochemicals and other bioactives. There is direct evidence of functional interactions between caffeine and polyphenols, L-theanine, and taurine. Additionally, multi-component caffeine-containing products or extracts can engender broader benefits to mental performance than expected from caffeine, even at higher doses. To what extent this is due to the independent effects of the non-caffeine bioactives or interactions with caffeine is not yet clear. Indeed, this area is typified by a lack of adequate research, and future research could usefully investigate the contributions of caffeine and the non-caffeine bioactive compounds in caffeinated products, the optimal level of caffeine in caffeinated products, the potential for additional caffeine to further enhance the functional benefits of low caffeine extracts, and the potential for caffeine to potentiate the functionality of multifarious other psychoactive phytochemicals. In general, this research effort should also include exercise or sporting contexts.

The views expressed are those of the authors and do not necessarily reflect the position or policy of PepsiCo, Inc.

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