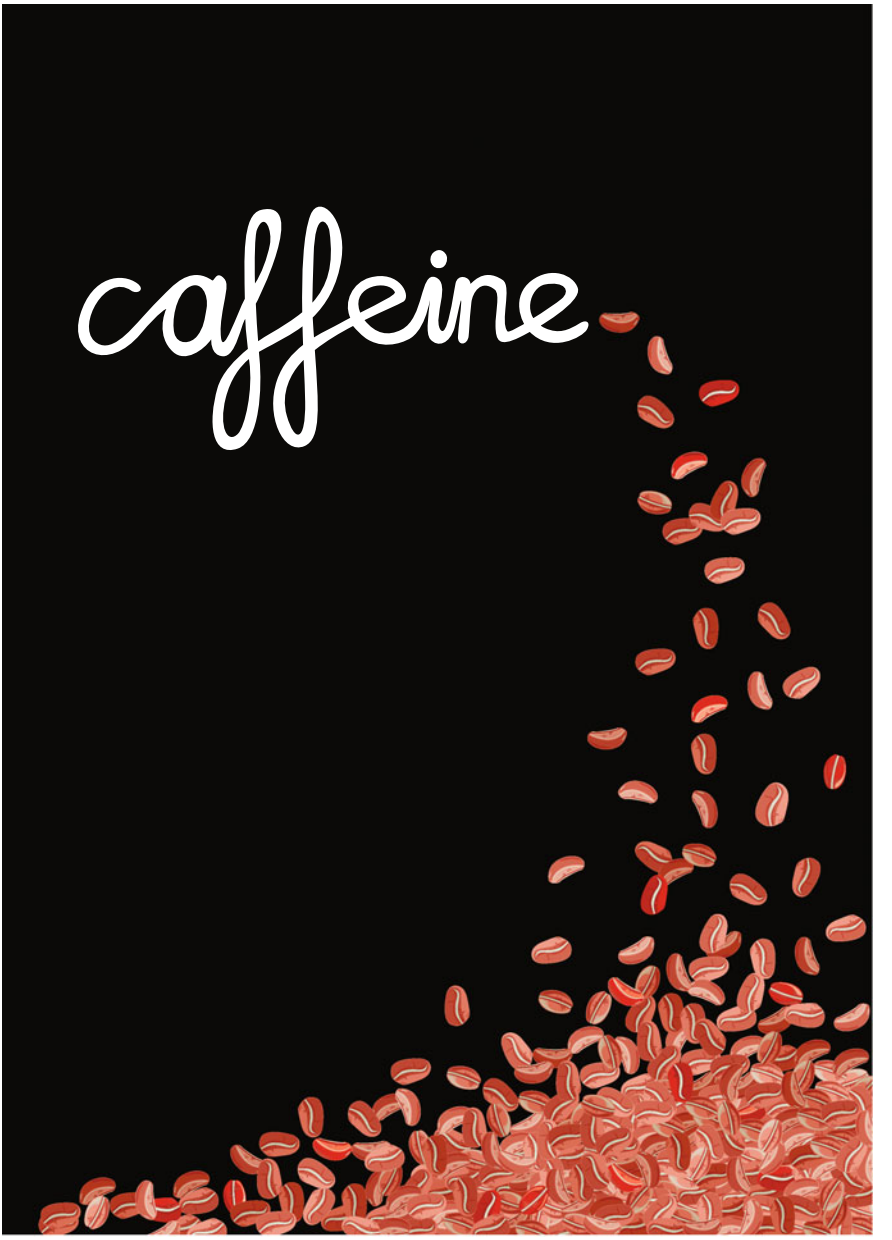
caffeine

Caffeine

Pauline van der Wel, Olga D. Boer and Lorenza S. Colzato

Introduction

Caffeine (1,3,7-trimethylxanthine) is a plant alkaloid that acts as a competitive antagonist of adenosine, thereby increasing the excitability of the sympathetic nervous system (SNS, Biaggioni et al. 1991). The psychostimulant effects of caffeine have been known for centuries and include increased levels of resting energy, enhanced physical and motor performance, increased alertness and wakefulness, and improved mood (for a review see Glade 2010). Given that caffeine has these stimulant properties, a lot of studies investigated the short- and long-term effectiveness of caffeine as cognitive enhancer (for reviews see Cappelletti et al. 2015; Panza et al. 2015). Unfortunately, reports on the effects of caffeine on cognitive performance in healthy humans are inconsistent and there is much variety in methodology and design (James 2014). A major issue that has been the topic of debate for many years is the hypothesis that caffeine derives its stimulant properties by reversal of withdrawal symptoms (James 1994, 2005). This hypothesis is supported by some studies (Ullrich et al. 2015), but rejected by others (Childs and De Wit 2006). The aim of this chapter is to provide a summary of available studies on the short- and long-term effects of caffeine on cognition in regular and nonusers in order to better understand under which circumstances caffeine has the potential to act as a cognitive enhancer.

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In this chapter we will first describe the working mechanisms of caffeine and current issues in the debate on its effectiveness. Second, we will outline the available studies that investigate short- and long-term effects of caffeine on cognition. Studies on the short-term effects indicate that caffeine has the potential to enhance cognition in both regular and nonusers. Studies on the long-term effects indicate that long-term moderate caffeine consumption potentially decreases the risk of cognitive decline and dementia later in life.

Mechanism of Action

Approximately 45 min after oral ingestion, 99% of the administered dose of caffeine is absorbed from the gastrointestinal tract after which it immediately crosses the blood–brain barrier (Fredholm et al. 1999). Peak plasma levels are reached between 15 and 120 min and half-life values range from 1.5 to 9.5 h (Bonati et al. 1982). The length of these periods depends on individual absorption and metabolism rate, which are influenced by factors like age (Jarvis 1993) and smoking (Hart et al. 1976). Caffeine metabolism takes place in the liver and is mainly controlled by cytochrome CYP1A2 and to a lesser extent by xanthine oxidase and *N*-acetyltransferase (NAT2) (Fenster et al. 1998). Demethylation by these enzymes results in the release of three active metabolites: paraxanthine (84%), theobromine (12%), and theophylline (4%) (Bonati et al. 1982; Cappelletti et al. 2015) (see Fig. 1).

Caffeine modulates the activity of the sympathetic nervous system by blocking the effects of the naturally occurring neuromodulator adenosine. Adenosine in the brain inhibits the release of excitatory transmitters in the synaptic cleft, such as acetylcholine, dopamine, norepinephrine, and serotonin (Snyder 1985). Caffeine blocks A_1 and A_{2a} receptors, causing an increased release of dopamine, norepinephrine, and glutamate (Smits et al. 1987; Cappelletti et al. 2015). The relationship between A_{2a} receptors and D_1 and D_2 receptors also becomes obvious in their localization, both in a high concentration in dopamine rich areas in the brain (Smits et al. 1987; Cappelletti et al. 2015). When caffeine is ingested in higher doses (>500 to 600 mg), which is not likely to happen from dietary sources, other suggested mechanisms of action are mobilization of intracellular calcium and inhibition of phosphodiesterases (for a review see Cappelletti et al. 2015).

The European Food Safety Authority (2015) recommends a maximum caffeine intake of 400 mg/day with single doses not exceeding 200 mg. A regular cup of coffee is assumed to contain approximately 85–100 mg caffeine. The highest total caffeine concentrations (mg/100 g) are contained in 70–85% cacao dark chocolate (80 mg), coffee (40 mg), energy drink (30 mg), and tea (20 mg) (Somogyi 2010). At high single doses (e.g., >500 to 600 mg) caffeine can cause anxiety, tremor, and increased resting heart rate. Long-term health risks of high coffee consumption are cardiovascular diseases, negative shifts in calcium balance, and mineral

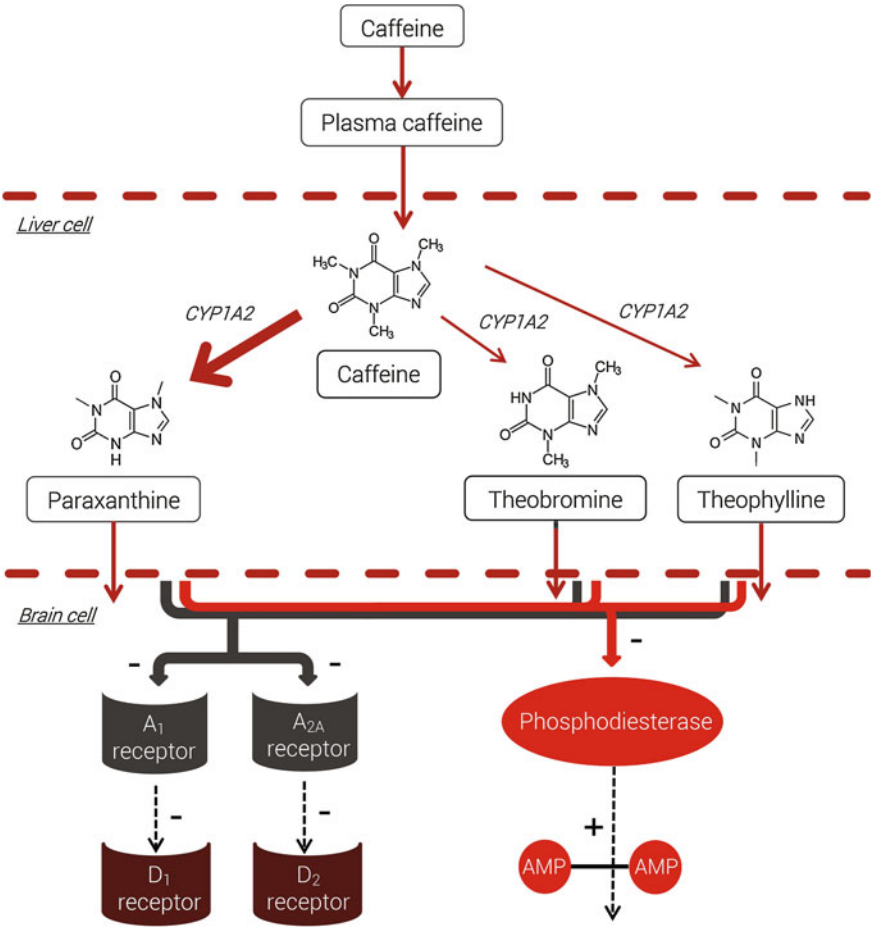

Fig. 1 Schematic representation of metabolism of caffeine and its mechanism of action. Caffeine is metabolized by CYP1A2 to paraxanthine (84%), theobromine (12%) and theophylline (4%) in the liver. After passing the blood–brain barrier, these substances block adenosine A1 and A2A receptors, that usually decrease the affinity of dopamine receptors for agonists. The substances also inhibit the enzyme phosphodiesterase, that breaks bonds in adenosine monophosphate (AMP), leading to more cyclic AMP (cAMP). The combination of both processes leads to the stimulatory effects of caffeine

deficiencies. However, these risks are mainly the result of a dose that is difficult to reach from dietary sources (Higdon and Frei 2006). Moreover, all lethal cases of caffeine intoxication known are the consequence of caffeine intake by non-dietary sources like pills (Cappelletti et al. 2015).

Short-Term Effects of Caffeine

The psychostimulant effects of caffeine are suggested to be beneficial not only for mood and alertness, but also for cognitive performance. In this section we will give an overview of findings on the acute cognitive enhancing properties of caffeine. We will first give a summary of a debate that dominated research on the effects of caffeine for years: the withdrawal reversal hypothesis of caffeine.

James (1994, 2005) was the first to argue that the acute effects of caffeine are largely due to reversal of withdrawal symptoms. Withdrawal symptoms of caffeine include headache, fatigue, decreased energy and alertness, and depressed mood (Juliano and Griffiths 2004). The withdrawal reversal hypothesis states that there are no net benefits of caffeine consumption, but rather that caffeine consumption after overnight abstention brings regular users back to their performance and energy baseline (Rogers et al. 2003). Several studies indeed show that their performance and alertness is impaired after overnight abstention (Richardson et al. 1995; for a review see James and Rogers 2005), but others do not (Haskell et al. 2005), or find even higher cognitive performance (Smit and Rogers 2000). Methodological issues such as the definition of caffeine-naivety, the possible self-selection of people that are caffeine naïve, and individual differences in caffeine sensitivity could be the cause of these inconsistent results (James 2014). Because it is yet unclear whether cognitive enhancing effects of caffeine are due to withdrawal reversal, short-term effects of caffeine will be discussed separately for regular and nonusers respectively.

Effects in Regular Users

Studies show a large variety in their definition of regular users. In line with the categorization of Cappelletti et al. (2015), we define regular users as people that consume 200–400 mg of caffeine on a daily basis. The results of studies investigating the acute cognitive enhancing effects of caffeine in regular users are mixed. Rogers et al. (2013) did not find an acute benefit of a single dose of 100–150 mg caffeine on mental alertness or mental performance in medium-high consumers after overnight abstention. However, the group of medium-high consumers was indicated by consuming >40 mg/day, which corresponds to the low-users group indicated by Cappelletti et al. (2015). In contrast, a study by Haskell et al. (2005) did show increased performance on two accuracy tasks after administrating 75 or 150 mg caffeine to regular consumers. The discrepancy between these studies shows that administrating a dose that lacks an effect in low consumers can have an effect in moderate consumers, which may point to support for the withdrawal reversal hypothesis. However, the study by Haskell et al. (2005) did not find lower performance on these tasks before caffeine administration after overnight abstention, so there were no apparent withdrawal symptoms.

A study that investigated the effect of low doses revealed a dose as low as 12.5 mg significantly improved cognitive performance on a simple reaction task and a rapid visual interaction task. These effects were more apparent in high

caffeine consumers (>200 mg/day), as compared to low caffeine consumers (<100 mg/day). Only the highest dose (100 mg) significantly increased levels of energetic arousal, equally for both groups (Smit and Rogers 2000). This study nicely shows two findings that are more or less consistent in the literature: Caffeine seems to be more beneficial for performance on simple cognitive tasks, and improvements in alertness and mood are possible confounds. A recent study in which there were no differences in cognitive performance between participants that received caffeine, placebo, water, or no treatment, supports that mood and alertness are possible confounds: the only trend to significance was found in subjective reports of preserved mental energy and activation after caffeine intake. Moreover, 24-h of caffeine abstinence did not result in an effect of caffeine or coffee placebo on cognitive performance (Ullrich et al. 2015).

From the Ullrich et al. (2015) and Smit and Rogers (2000) study we can conclude that the effect, or lack of effect, of caffeine on cognitive performance in regular users seems to be influenced by changes in mood. Besides mood, also the level of expectancy (Richardson et al. 1995) and baseline levels of arousal or alertness (Chait 1992) are suggested to have an influence on the effect of caffeine on cognitive performance. Since regular users are always aware of their overnight caffeine abstention, it is difficult to determine whether improved performance is a consequence of changes in expectancy, alertness, and mood, reversal of withdrawal symptoms, or the caffeine. Nonetheless, most studies hypothesize that the beneficial effect is largest when the baseline levels of alertness are low and expectancy of the effects of caffeine is high (Smith 2002).

A proper way to deal with the issues of caffeine research in regular users is to investigate if and how caffeine affects performance in nonusers. The results of these studies will be discussed in the next section.

Effects in Nonusers

Studies on caffeine supplementation to nonusers show significant subjective and objective effects in mood and performance. A study (Childs and de Wit 2006) showed that caffeine administration to nondependent, light users significantly increased blood pressure, feelings of arousal, positive mood reports, and measures of attention. However, an administration of the highest dose (450 mg) significantly impaired performance on a working memory task called the backward digit span task. Haskell et al. (2005) showed that in nonusers 150 mg of caffeine significantly improved performance on digit vigilance accuracy and reaction time, working memory reaction time, sentence verification accuracy (also after 75 mg), and delayed picture recognition time. Also, mental fatigue was significantly reduced after a dose of 75 mg. Thus, although more studies on the acute effects of caffeine in nonusers are needed, preliminary results suggest that caffeine administration to nonusers affects their subjective and objective state, which raises serious doubts about the withdrawal reversal hypothesis.

In sum, administration of caffeine affects mood, alertness, and cognitive performance in both regular- and nonusers. The largest effect is found when the task is easy, baseline alertness is low, and expectancy is high. More research is needed on the effects of caffeine in nonusers and the potential mediating or moderating role of mood, alertness, and expectancy in regular users.

Long-Term Effects of Caffeine

In a recent review of 28 cross-sectional and longitudinal studies, it was concluded that moderate intake of caffeine has the potential to decrease the risk on cognitive decline and dementia or Alzheimer's disease (AD) later in life (Panza et al. 2015). A survey including 9003 British adults showed a dose-response trend to improved performance with higher levels of caffeine consumption in simple reaction time, and memory tasks (Jarvis 1993). These promising findings lead us to the following section to discuss studies investigating the protective effect of caffeine in cognitive decline and impairment, and in dementia and AD.

Late-life cognitive decline, also called mild cognitive impairment (MCI), is defined as a reduction in cognitive abilities, usually in the domain of memory, that is unexpected at the particular age and level of education (Petersen et al. 1999). A large population study among 4197 women and 2820 men showed that the psychostimulant properties of caffeine are associated with a reduction in cognitive decline, especially in women. No relation was found in men (Ritchie et al. 2007). Other review studies point in the same direction (Arab et al. 2013; Panza et al. 2015), except one study that lacks an association when the model is fully adjusted for age, intelligent quotient score, and social class. When controlled for age and gender only, a significant positive association between caffeine intake and global cognitive functions was found (Corley et al. 2010).

Thus, these studies suggest that there is an association between caffeine intake and reductions in cognitive decline, but that confounds may play a large part in this association and possibly could account for a lack of a dose-response trend in some studies. In the next section, we will discuss studies on the effects of caffeine on prevention of dementia and AD, after which we will address some possible confounds and proposed working mechanisms.

AD is a neurodegenerative disease that is characterized by a progressive impairment of cognitive functions like memory and learning (Canas et al. 2009). The amyloid hypothesis states that AD is caused by accumulation of amyloid β-peptide (Aβ) in the brain. This accumulation is suggested to be the consequence of an imbalance between Aβ production and Aβ clearance due to mutations in the APP gene. As a consequence of Aβ accumulation, neuronal homeostasis and other processes on the cellular level are dysregulated, eventually leading to cell death and widespread neuronal dysfunction (Hardy and Selkoe 2002). Control of potential risk factors is thought to be the most beneficial treatment by preventing the early symptoms of Aβ accumulation. Dietary factors, such as caffeine, are becoming

more and more promising as they are recently associated with the risk for developing Alzheimer's disease (Eskelinen and Kivipelto 2010). Several studies suggest that caffeine is associated with a significantly lower risk of AD even when accounting for variables such as medical disorders, drugs, and education (Eskelinen and Kivipelto 2010; Maia and De Mendonça 2002). Animal research suggests that caffeine protects against Aβ accumulation by blockade of adenosine A_{2a} receptors, which otherwise would cause a loss of nerve terminal markers, resulting in Aβ imbalance and, consequently, memory dysfunction (Canas et al. 2009). Other suggested mechanisms are more indirect, but are also thought to be beneficial for reduction of cognitive decline. These indirect mechanisms include, among others, late-life health benefits of caffeine like prevention of type 2 diabetes, Parkinson's disease, and colorectal cancer (Higdon and Frei 2006).

Thus, according to the current knowledge, caffeine on the long term acts as a protective rather than a restorative factor and is associated with reduced cognitive decline and a lower risk of AD. It has also become clear that in research on the association between caffeine intake and cognitive decline or AD, there are many possible confounding variables. Both caffeine consumption and cognitive decline are associated with a wide range of sociodemographic, lifestyle and clinical variables, such as gender, social class, and intelligence (Ritchie et al. 2014). Although some studies corrected for these confounds, others did not, which can lead to biased results. Furthermore, research on AD and dementia are often of a retrospective nature and participants are usually of a high age. These factors may increase the chance of biased and incorrect consumption reports, which should be taken into account when interpreting the results. (Arab et al. 2013).

We conclude that the long-term effects of caffeine on cognitive performance are very promising, but since possible confounds are not addressed in many of the studies, more research is needed on this topic before firm conclusions can be drawn.

Conclusion

As an adenosine receptor antagonist, caffeine has the potential to exert a psychostimulant effect. Although more research is needed to explain contradictory results, the literature suggests that on the short term, caffeine can positively influence cognitive performance, in particular when the task is easy, baseline alertness is low, and expectancy is high. This effect is more consistent in regular users than in nonusers, which is why more research into the acute effects of caffeine in nonusers is needed. Furthermore, future studies should take into account participants' mood, alertness, and expectancy levels, since these confounds seem to play a large role in modulating the cognitive enhancing effect of caffeine.

Besides the suggested beneficial short-term effects, studies on the effects of long-term use of caffeine show very promising findings. Although results are still inconsistent, caffeine might be beneficial for reducing cognitive decline and lowering the risk of AD. More research is needed into direct and indirect working

mechanisms and on possible confounds such as lifestyle factors and gender differences.

Future studies should take into consideration adding genetic information as a covariate in their analyses, in order to achieve a better understanding of the role that particular polymorphisms might play in the effects of caffeine. A recent study suggested that a part of the interindividual variability in effects of caffeine on performance can be explained by variability in genes, in particular genes that affect adenosine metabolism (Renda et al. 2015). Caffeine in interaction with genes has not yet received much attention in the literature, but available studies point to polymorphisms in the CYP1A2 enzyme, adenosine A_{2a} receptor, or dopamine receptors to account for interindividual differences in caffeine sensitivity and caffeine effects on performance on both the short- and long-term (Yang et al. 2010).

In sum, even though more research is necessary, we can conclude that caffeine is a promising tool for enhancing cognitive performance on the short-term in both regular and non-regular users and might exert neuroprotective effects across the life span.

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