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Review article

How does caffeine influence memory? Drug, experimental, and demographic factors

Ruo-Chong Zhang *, Christopher R. Madan

School of Psychology, University of Nottingham, Nottingham, UK

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ABSTRACT

Caffeine is a widely used nootropic drug, but its effects on memory in healthy participants have not been sufficiently evaluated. Here we review evidence of the effects of caffeine on different types of memory, and the associated drug, experimental, and demographical factors. There is limited evidence that caffeine affects performance in memory tasks beyond improved reaction times. For drug factors, a dose-response relationship may exist but findings are inconsistent. Moreover, there is evidence that the source of caffeine can modulate its effects on memory. For experimental factors, past studies often lacked a baseline control for diet and sleep and none discussed the possible reversal of withdrawal effect due to pre-experimental fasting. For demographic factors, caffeine may interact with sex and age, and the direction of the effect may depend on the dose, individual tolerance, and metabolism at baseline. Future studies should incorporate these considerations, as well as providing continued evidence on the effect of caffeine in visuospatial, prospective, and implicit memory measures.

1. Introduction

Most of us believe that caffeine can make us more alert, focused, and productive. Indeed, caffeine is the most consumed psychoactive and nootropic drug worldwide (Nehlig, 1999). It is estimated that worldwide around two billion cups of coffee are consumed daily (British Coffee Association, n.d.). Further caffeine intake comes from tea, energy or sports drinks, and various chocolate products (Fitt et al., 2013). While many advocates for the neuroprotective and cognitive-enhancing effects of caffeine (McLellan et al., 2016; Panza et al., 2015), others proposed that the magnitude of these benefits are negligible, furthermore, a higher dose can have detrimental effects on physical and mental health (Nehlig, 2010, 1999). As past literature tended to treat memory as a subset of cognitive functions, the specific effect of caffeine on memory has not been thoroughly discussed. As with all other nootropics, research on caffeine faces many issues regarding ethical challenges in drug administration and treatment reliability across experimental settings (Crespo-Bujosa and Suárez Rodríguez, 2019; Ricci, 2020). Few studies have considered individual differences in caffeine tolerance and metabolism due to genetic, or demographic variations in the number of adenosine receptors (Nehlig, 2018).

Although there has been a large body of literature examining the effects of caffeine in animal models, these effects cannot be directly translated to human participants due to two major concerns. Firstly, in animal models, the treatment effects of a drug can be established causally through rigorous control over confounding factors, such as diet, access to the drug, animals' immediate environment, stress levels, metabolism, and circadian rhythms (Gallagher and Rapp, 1997; Granholm, 2010). It is also possible to add or remove a single factor at a time to systematically explore its interaction with the drug. Moreover, animals can be screened with an injection of radioactive tracers or sacrificed post-treatment for a more detailed study of the drug pharmacodynamics and pharmacokinetics. In contrast, human studies have limited control over many confounding factors. Although it is possible to engage participants in multiple sessions (Baur et al., 2021), these designs can still be challenged by attrition. Alternatively, information about individual caffeine consumption and other confounding factors can be collected at a greater resources cost, as a result, few studies have yet to take a comprehensive approach. The second reason is based on the differences in experimental design and procedures between animal and human memory studies. Animal studies typically assess memory through visuospatial learning tasks such as maze navigation, new objects or environmental exploration (Vorhees and Williams, 2014), whereas human memory studies can employ various visuospatial

* Corresponding author at: School of Psychology, University Park, University of Nottingham, Nottingham, NG7 2RD, UK.
E-mail address: ruochong.zhang@nottingham.ac.uk (R.-C. Zhang).

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and verbal stimuli. This distinction suggests that testing different types of memory in animal studies is less feasible. For example, human working memory (WM) incorporates temporary information maintenance, manipulation, and information updating (Bledowski et al., 2010, 2009), assessing these separate elements has yet to be achieved in animal studies (Keeler and Robbins, 2011; Vorhees and Williams, 2014). Additionally, the existing definition of human episodic memory involves a "self-awareness" process that can be examined through behavioural testing (Tulving, 2002), but is difficult to establish in animal models (Madan, 2020). Tasks probing source memory has provided valuable insights into the dissociation between familiarity and recollection in human participants (Yonelinas, 2002, 2001; Yonelinas et al., 2010), but are far less used in animal studies (Crystal, 2016). The lack of distinction between familiarity and recollection in animal studies questions the validity of using animal models to test human episodic memory (Madan, 2020). With regards to long-term memory, while humans can be assessed at random intervals after the initial learning phase, separating learning from performance can be more ambiguous in animal models. Equally challenging is individual differences in animal's motivation or consistency in reward responses in prolonged training and testing (Keeler and Robbins, 2011; Vorhees and Williams, 2014).

Given the difficulty of comparing across human and animal studies, in this review, we focus on the treatment effect of caffeine in healthy human participants. We explore how caffeine and the associated drug administrative, experimental, and demographic factors affect memory in healthy participants, as well as caffeine as a cognitive enhancer by comparing its effectiveness with other approaches, such as glucose intake and sleeping. In discussion, we describe several animal studies which examined caffeine's effects on memory and associated drug mechanisms. While similar mechanisms may appear in healthy humans, changes in these biomolecular pathways do not always manifest as memory outcomes. Therefore, we focus on discussing human studies, and direct interested readers to other reviews with more detailed animal work.

2. Does caffeine affect memory?

We examined the effect of caffeine based on the types of memory. Due to the wide range of memory measures employed by reviewed studies, we categorised the findings by the type of memory measures used. In each section, we first briefly defined the type of memory, followed by describing studies adopting relevant measures.

Among reviewed literature, the findings generally map onto *acute* or *long-term* effects of caffeine. Here we refer to the *acute* effect as studies investigating the one-off, short-term effects of caffeine administered in laboratory experiments. Although some studies required participants to return for multiple testing sessions, few regularly administered caffeine during the inter-session intervals. Given that in human participants, the maximum caffeine tolerance is achieved after two to seven days of regular consumption (Denaro et al., 1990; Griffiths and Woodson, 1988; Hewlett and Smith, 2007; James, 1998; Nehlig, 1999), this type of design does not permit observation of the *long-term* effects of caffeine associated with regular consumption over an extended period. Conversely, *long-term* effects refer to studies analysing the associations between *habitual* consumption and memory, such as studies using epidemiological or time-series designs. Although having better ecological validity and allowing for longitudinal analysis, in most instances, these studies adopted a quasi-experimental design that had limited control over confounding factors, such as dietary intake and sleep cycles. Therefore, any differences may reflect the effects of habitual caffeine consumption or other confounding factors. In each section, we also grouped the findings by these two designs. We will discuss the issues of tolerance, withdrawal, and withdrawal reversal related to these designs in later sections.

2.1. Working memory (WM)

Working memory (WM) is defined as the memory system which simultaneously holds and manipulate information of different modalities (Baddeley, 2012, 2000, 1992; Baddeley and Hitch, 1974). By this definition, WM measures are tasks involving multimodal attentional control, rapid information processing, temporary maintenance, and manipulation of mental representations. Here, we organise the findings on the effect of caffeine by types of WM tasks.

2.1.1. Reaction time

Jarvis (1993) and Hameleers et al. (2000) examined long-term outcomes of habitual caffeine consumption in a self-reported survey, and both used the simple (SRT)/choice reaction time (CRT) tasks to evaluate information processing and psychomotor skills. As both skills depend on WM capacity (WMC), the reaction time (RT) task can be considered as a WM task (Hülür et al., 2019). In SRT, participants respond to a single predefined stimulus as quickly as possible, whereas in CRT, participants respond correspondingly to two or more stimuli as quickly as possible. Both Jarvis (1993) and Hameleers et al. (2000) reported a significant dose-response relationship between the amount of caffeine habitually consumed from preferred daily drinks and improved performance in these RT tasks.

In studies examining the acute effects of caffeine, intake of a personally preferred amount of caffeine via oral capsules improved performance in SRT (Lanini et al., 2016). Furthermore, a standard dose of 4 mg/kg bodyweight caffeine also improved accuracy and RTs in digit vigilance (Smith et al., 1992). One longitudinal study evaluating the effect of regular daily caffeine consumption on sleep deprivation provided participants with regular drop coffee (101 $\pm$ 0.6 mg caffeine per 200 g) or decaffeinated coffee prepared in the same way (2.4 $\pm$ 0.05 mg caffeine per 200 g) two times a day. The researchers elaborated that this administration procedure mimics the real world European consumption habits ($\sim$ 300 mg daily). They found that when sleep-deprived (restricted to five hours per night) over the course of five days, those receiving regular coffee improved in speed, lapses, and accuracy in the RT task through the first and second testing days, whereas the decaffeinated group showed a persistent decline across five days (Baur et al., 2021). However, another study comparing 100 mg caffeine added into decaffeinated coffee with regular decaffeinated coffee (control) and water with coffee flavouring (placebo) reported the performance-enhancing effect of caffeine only in digit vigilance, but not the SRT (Haskell-Ramsay et al., 2018).

2.1.2. Digit span

Several studies used digit span as a measure of WM, which examines the maximum amount of information one can temporarily hold in memory (Conway et al., 2005). Lesk et al. (2009) found that participants' performance in this task was not affected by consumption of caffeine-containing foodstuffs (CCFS) (assessed through self-report questionnaire) within four hours before testing, though there was a trend for worse performance associated with CCFS consumption. Where a standard dose of caffeine was administered, both Schmitt et al. (2003) (100 mg) and Walters and Lesk (2016, 2015) (200 mg) failed to find an effect of caffeine on this task. Lastly, Lanini et al. (2016) tested participants with a dual-task digit span by using a concurrent, paper and pencil based visuospatial task, they also did not find any impact of caffeine.

2.1.3. Sternberg and N-back

These tasks require participants to maintain monitoring of a continuous stream of stimuli and respond to only a subset (Jaeggi et al., 2010; Sternberg, 1966). Compared to RT tasks, these tasks involve retaining a larger amount of information; compared to the digit span, these tasks require more complex and continuous updating of mental representations in addition to information retention (Conway et al.,

2005). Performance in these tasks is indexed through accuracy, RTs, or both. Klaassen et al. (2013) and Haskell-Ramsay et al. (2018) tested the effects of 100 mg caffeine added to decaffeinated coffee and both failed to find any effects on the Sternberg task. Similarly, ingesting 100 mg (Koppelstaetter et al., 2008) or 200 mg (Haller et al., 2017) caffeine capsules, or direct inhalation from 1 % caffeine-containing vaporiser (Ueda and Nakao, 2019) did not affect performance in the N-back tasks, regardless of task difficulty (0, 2, or 3 back) or type of stimuli (letters or numbers) used. Baur et al. (2021) demonstrated that among sleep-deprived but otherwise healthy young adults, ingesting regular coffee that matches their daily consumption habits improved speed, but not accuracy in the N-back tasks (1, 2, or 3 back) relative to their baseline performance. Conversely, the decaffeinated group showed a persistent decline compared to baseline in speed (in 1 back only) and accuracy.

2.1.4. Other

An oddball task (visual or auditory) requires participants to respond mentally or physically to an infrequent target presented amid frequently occurring stimuli and infrequently occurring distractors. This process involves ongoing attentional control and memory updating (Yurgil and Golob, 2013). Using this task, Trunk et al. (2015) reported that caffeine capsules (5, 10, 20, and 100 mg) added to water significantly reduced RTs in trials with high target frequencies. Furthermore, using a comprehensive cognitive battery, Soar et al. (2016) found that even 50 mg caffeine added into decaffeinated coffee improved performance in a planning task, but not a prioritisation task, compared to the decaffeinated coffee alone.

Despite the enhancing effects reported in these two studies, many have reported a smaller magnitude or no effects of caffeine on other WM measures: Haskell-Ramsay et al. (2018) did not find any main effect of caffeine on a visuospatial WM task. Hameleers et al. (2000) and Alharbi et al. (2018) included a letter-digit substitute task, assessing processing speed and WM capacity (Van der Elst et al., 2012). While the former did not find any effect of habitual caffeine consumption, the latter found that a single dose of caffeine from a specific type of coffee, café *arabica* (Qahwa), a traditional Arabic and Middle Eastern coffee made from raw or lightly roasted beans and cardamom improved performance. Loke (1988) and Lanini et al. (2016) used procedures involving mental operations (addition, subtraction, multiplication), which involves rapid information processing, retention, and manipulating mental representations (Imbo et al., 2007). In Loke (1988), ingesting 200 mg caffeine capsules improved performance in selected mental operations compared with placebo or 400 mg caffeine capsules, whereas Lanini et al. (2016) reported no effects of ingesting a personally preferred amount of caffeine.

2.1.5. Summary

There is limited evidence for the effect of caffeine on aspects of WM, other than improved RTs. However, the improved performance on psychomotor vigilance and RT tasks implies that caffeine can improve overt attentional control in WM, such as facilitating faster initiation of the already prepared response. Regardless of dose or the form of administration, caffeine is unlikely to influence other WM processes, such as information maintenance and manipulation, especially in complex tasks where multiple WM processes are involved.

2.2. Short term memory (STM)

Here we distinguished WM from short term memory (STM), which can be viewed as a "passive" information repository involving short-term maintenance and recounting (Unsworth and Engle, 2007). The verbal learning task (VLT), including both immediate recall and recognition memory tests, and the memory scanning task, are widely used procedures across the reviewed studies as STM measures. In VLT, to-be-remembered words are presented in visual or auditory form. Hameleers et al. (2000) did not find an association between habitual caffeine consumption and immediate recall in VLT. In contrast, based on self-reported habitual caffeine consumption, Loke (1988) categorised participants into three groups: *low* users (< 387.5 mg/week); *moderate* users (387.5–927.5 mg/week); and *high* users (> 927.5 mg/week). Participants were also given 200 mg caffeine capsules and completed a recall task immediately, 15 min, and 50 min after treatment. Low users recalled fewer words relative to moderate and high users at 15 min posttreatment, however, this study did not find the effect of a single dose of caffeine administered in these habitual users.

Erikson et al. (1985) and Arnold et al. (1987) used similar procedures to examine the effect of 0, 2, or 4 mg/kg bodyweight caffeine dissolved in a sports drink on immediate recall. Arnold et al. (1987) found improvements in male participants under either 0 or 4 mg dose at fast presentation, as well as in female participants under either 2 or 4 mg dose at the third level of practice. Ryan et al. (2002) showed that a cup of regular coffee (estimated caffeine 220–270 mg), but not decaffeinated coffee (estimated caffeine 5–10 mg) improved immediate recall in older adults (> 65 years). In contrast, Erikson et al. (1985) showed that recall was unaffected in male participants, but impaired in female participants at 2 or 4 mg. A standard dose of 100 mg caffeine added in sports drink was also shown to reduce overall retention in immediate recall and recall after an interfering list was presented, compared with placebo (Terry and Phifer, 1986). In line with Erikson et al. (1985), several other studies did not find any effect of caffeine on immediate recall, regardless of the number of trials or lists (Smith et al., 1992), or the dose of caffeine (Walters and Lesk, 2016, 2015).

Only a few studies assessed recognition STM; among these, consuming 100 mg caffeine added to decaffeinated coffee did not affect performance in either immediate recall or memory scanning as an STM recognition task (Schmitt et al., 2003). Alharbi et al. (2018) reported a tendency for a selected type of coffee in improving accuracy in picture recognition (*arabica*) relative to placebo, but this did not reach statistical significance. Other studies adopting STM measures reported an interaction between caffeine and age-related factors, and are described further in Section 5.2.

2.2.1. Summary

While a few studies identified the effect of caffeine on STM measures, others found no reliable evidence that caffeine affects STM measures, irrespective of presentation modality. Where effects were found, there is a lack of clarity in the direction of the effect as studies reported both enhanced and impaired memory outcomes. Here task procedures were relatively consistent, and the effect of caffeine does not seem to depend on the type of STM assessment but possibly the caffeine administration process or other demographic characteristics.

2.3. Long term memory (LTM)

Long-term memory (LTM) differs from STM and WM in duration and capacity: information stored in LTM is not susceptible to time-based decay, and the LTM storage is not capacity-limited (Cowan, 2008). Thus, LTM is assumed to store a vast amount of stabilised information for an unlimited period. In Jarvis (1993) and Hameleers et al. (2000), the LTM measures include delayed VLT and verbal fluency, a semantic memory task (Shao et al., 2014). The length of the retention interval ranged from "a few minutes" to 20 min. Both studies reported a positive relationship between habitual consumption and performance in these LTM measures. However, Lesk et al. (2009) reported a negative effect of CCFS use on performance in paired associative learning (PAL) tasks and the general naming task (GNT). PAL requires learning the association between unique, unfamiliar patterns and their locations in a display of six boxes, thereby assessing visuospatial associative memory (Barnett et al., 2016). GNT asks participants to name black-and-white outline drawings of objects graded for familiarity as fast as possible, thereby assessing semantic memory (McKenna and Warrington, 1980).

Subsequent studies examining the effect of 200 mg caffeine on the same measures showed performance decline in GNT, but not PAL (Walters and Lesk, 2016, 2015). Studies using administered caffeine found limited or no effect of caffeine on delayed VLT recall, recognition, or verbal fluency, regardless of the type of stimuli (words, pictures), length of retention interval (20 min to 48 h), or the dose of caffeine (Haskell--Ramsay et al., 2018; Herz, 1999; Hogervorst et al., 1998; Lanini et al., 2016; Schmitt et al., 2003).

Two studies reported the negative effect of caffeine on LTM outcomes. Terry and Phifer (1986) demonstrated that 100 mg dissolved in a sports drink impaired delayed recall. Furthermore, the group who received caffeine also showed a trend for increased intrusion errors. Additionally, on a list of 15 items, those who received caffeine had a poorer recall for words at serial position 5–14 and showed a weak relationship for maintaining item order. The researchers suggested that the group receiving caffeine forget more words at recency positions and recalled less strategically compared to the placebo group. Mednick et al. (2008) demonstrated that compared with a placebo and a nap group, the group that received a 200 mg caffeine pill had significantly impaired recall but not recognition at 20 min, despite reporting themselves as feeling more alert. At seven hours delay, the nap group outperformed the other two groups in both recall and recognition.

A few studies reported an LTM facilitating effect of caffeine. Smith et al. (1992) showed that tablets containing 4 mg/kg bodyweight of caffeine added to decaffeinated coffee improved performance in logical reasoning (Baddeley, 1968) and semantic processing (Baddeley, 1981) when tested in the morning or a few hours after lunch, relative to control. However, no group difference in delayed recognition was observed. Loke (1988) noted an inverted U-shaped relationship between habitual intake and recall. Borota et al. (2014) showed the consolidation-enhancing effect of 200 mg caffeine administered immediately post-learning, reflected by the improved discrimination between old and new items in 24 -h delayed recognition. However, Aust and Stahl (2020) failed to replicate the findings of this study, suggesting that in Borota et al. (2014), likely the reversal of withdrawal symptoms from caffeine abstinence escalated the positive treatment effect. Furthermore, similar to Herz (1999); Borota et al. (2014) found no effect of caffeine on LTM when administered before memory tests. Lastly, Ryan et al. (2002) reported a memory-enhancing effect of a regular cup of drip coffee, compared with decaffeinated coffee, in both delayed recall and recognition.

2.3.1. Summary

There is no reliable effect of caffeine on LTM, and the effect was characterised by either an LTM enhancing or impairing direction, depending on the type of tasks used and the drug administration process. LTM tasks such as PAL or GNT may require the recruitment of additional cognitive processes compared with delayed recall or recognition, thus evoking more varied performance.

2.3.2. Which memory stage does caffeine affect?

The process of forming LTM can be divided into three stages: encoding, where selected information is processed voluntarily and enters WM or STM; consolidation, where some information is reorganised or rehearsed, and integrated into LTM; retrieval, where information is retrieved spontaneously or through associative cues (Atkinson and Shiffrin, 1968; Broadbent, 1971; Waugh and Norman, 1965). Caffeine may likely play different roles at these stages. We examined this topic from two aspects. First, where caffeine was experimentally administered, drug administration can occur immediately before or after learning, or the encoding phase; or immediately before the memory test, or retrieval phase. Furthermore, when a longer retention interval was used (Borota et al., 2014; Mednick et al., 2008), caffeine administered immediately after learning is likely to affect memory consolidation. Here a "long" retention interval is only loosely defined as studies having separate sessions for learning and delayed memory tests. Comparing results from studies adopting these different procedures can help us understand which memory stage is affected. Second, several studies using multiple recall trials reported serial position analyses, providing further insights on how caffeine affects recall dynamics.

Most studies administered caffeine 15 min to an hour before the learning phase, providing sufficient time for caffeine metabolise. In contrast, Borota et al. (2014) and Herz (1999) examined caffeine administered after the learning phase. Herz (1999) found that 5 mg/kg bodyweight (participants' mean weight was 71.6 kg) caffeine capsule administered before retrieval (i.e., 48 h after learning) did not affect LTM recall following a 48 -h delay. Nevertheless, this finding does not rule out the possibility that caffeine did facilitate memory encoding or consolidation, but the effect was negligible after the delay. Borota et al. (2014) found that 200 mg caffeine immediately following incidental learning significantly improved correct identification of similar lure items in a 24 -h delayed recognition (Experiment 1). However, the same amount of caffeine administered one hour before the memory test (24 h after learning) did not affect performance (Experiment 2), replicating Herz's (1999) results. These two experiments provide evidence that caffeine can facilitate consolidation but not retrieval.

Terry and Phifer (1986) reported that 100 mg caffeine tablet dissolved in sports drink moderated recall dynamics in three ways. First, participants recalled substantially fewer words in the middle positions (positions 5–14, in a list of 15 items). Second, caffeine substantially reduced the correlation between the recalled word positions and the presented word positions ($r = -.01$) compared with control ($r = -.52$). The researchers elaborated that high correlation is usually expected in free recall. Third, compared to the caffeine group, the control group tended to recall more items from recency positions. These findings suggest that caffeine impairs memory search during retrieval after a short delay.

On the contrary, Arnold et al. (1987) demonstrated that at higher caffeine dose (4 mg/ kg bodyweight, compared to 2 mg/kg bodyweight or the placebo control), participants outputted words in later positions first, followed by words at primacy and middle positions. They suggested that caffeine may especially strengthen STM and support encoding of recent events at the cost of earlier events, thus, to compensate for this attention cost, participants strategized recall by unloading recency items first and then shift their attention to output items at other positions. This interpretation indicates that caffeine can affect encoding through attention modulation, or retrieval through strategized recall. Note that Arnold et al. (1987) is one of the few studies which reported the STM-enhancing effect of caffeine. The researchers' interpretation cannot be extrapolated to other studies which did not find a reliable effect of caffeine on STM. In line with this, Loke (1988) showed that both moderate and high users recalled more difficult words at primacy positions compared to low users, and moderate users also recalled more easy words at primacy positions, but fewer easy words at recency positions than low users, suggesting that caffeine can also affect recall of items at earlier serial positions.

2.3.2.1. Summary. There is some evidence that caffeine can affect memory encoding and consolidation. Despite that caffeine may not directly affect retrieval, it can modulate the focus of attention during memory search and recall output. The direction of this influence remains unclear: while caffeine can impair item encoding at specific serial positions, this process prompts strategized recall, which may improve overall retention.

2.4. Other memory measures

Soar et al. (2016) used JEF©, a comprehensive executive assessment battery involving three tests of action-based, event-based, and time-based prospective memory. They showed that 1.8 g of Nescafe® coffee granules (estimated 50 mg caffeine) dissolved in hot water

improved performance in all three sub-categories of the memory task compared to the placebo group who received decaffeinated coffee. Additionally, Lesk and Womble (2004) examined the effect of a 200 mg caffeine tablet on tip-of-tongue as an implicit memory measure. The group receiving caffeine showed a larger phonological priming effect compared to the placebo group by demonstrating decreased tip-of-tongue on the related list and blocking interference produced by the unrelated list.

2.4.1. Summary

When prospective or implicit memory measures are used, the administration of a small amount of caffeine shows a promising facilitating effect. Prospective memory and implicit memory can add ecological validity and clinical applications to the aforementioned LTM measures. For example, the tip-of-tongue effect can reflect retrieval from both STM and LTM. More studies are needed to determine the reliability and dose effect.

3. Drug factors

3.1. Is there a dose-response relationship between caffeine and memory?

Three studies reported dose-response associations between habitual caffeine intake and memory outcomes (Hameleers et al., 2000; Jarvis, 1993; Loke, 1988). Among these, two reported a linear relationship of better memory performance in higher habitual consumers (Hameleers et al., 2000; Jarvis, 1993). On the other hand, Loke (1988) found that moderate users outperformed the high and low users in the problem solving WM task and delayed recall, implying an inverted U relationship between habitual consumption and memory. Borota et al. (2014, Experiment 3) showed performance increment in the delayed recognition memory task at both 200 mg and 300 mg caffeine dose, compared with the placebo and 100 mg dose groups, suggesting that the optimal dose is a minimum of 200 mg.

Several other studies also implied a dose-response relationship via other moderators. Terry and Phifer (1986) found a correlation between trait anxiety and recall. Although this factor did not interact with the effect of caffeine, they mentioned that participants probably already experienced situational anxiety, hence "…*the additional arousal from the caffeine probably exceed the optimal level beneficial to performance*" (p. 862). This implies that the effect of caffeine on memory is moderated by trait anxiety and arousal levels, and this effect is characterised by an inverted U shape. Similarly, Lanini et al. (2016) reported no effect of a personally preferred amount of caffeine on memory, but improved RTs in the psychomotor vigilance, executive function assessment (Random Number Generation task) (Towse and Neil, 1998), and metacognition (subjective ratings of perceived performance on a Visual Analogue Scale). The researchers argued that a dose-response is likely to exist when the administered dose exceeds the dose individual habitually consumes, and the direction of this relationship depends on task-specific memory processes.

Erikson et al. (1985) and Arnold et al. (1987) both reported a more complex dose-response relationship. Erikson et al. (1985) reported an interaction between dose and stimuli presentation speed in female participants only: while no caffeine effect was observed in fast presentation, the increment of recall under slow presentation was the lowest in the 2 mg (19 %), followed by 4 mg (22 %), and highest at 0 mg (33 %) dose. When participants were then divided into high (> 150 mg daily) and low users (< 150 mg daily) based on habitual consumption, low users recalled more than high users, but the correlation between habitual consumption and recall was not significant. These results led Erikson et al. (1985) to conclude a negative linear relationship between caffeine and recall, further moderated by sex and encoding duration. Arnold et al. (1987) demonstrated that male participants recalled more under 0 mg and 4 mg relative to under 2 mg dose in slow presentation condition, they also recalled more under 4 mg relative to under the other two doses in fast presentation condition. Whereas female participants recalled more under 2 and 4 mg conditions than under control in the third practice only. The researchers suggested that these results point to a positive linear relationship between caffeine consumption and memory outcomes.

3.1.1. Summary

There is no evidence for a reliable dose-response relationship between caffeine consumption and memory outcomes. Where a dose-response association is implied, the direction of the relationship can be both positive or negative. Studies using self-report approach are more likely to report a positive dose-response, suggesting a possible placebo effect of daily caffeine consumption in personally preferred drinks. Studies reporting indirect dose-response relationships with additional moderating factors are harder to interpret. Likely dose-response can be observed under specific task conditions, or that there is no dose-response relationship once these task conditions are removed.

3.2. Are all caffeine sources equal?

Caffeine is ubiquitous in a variety of food items such as coffee, tea, coke, sports drinks, and chocolate (Carman et al., 2014). Different sources of caffeine may have specific drug properties mediating metabolic efficiency (Choi and Curhan, 2007). This is because i) food items containing naturally occurring caffeine may also consist of other components which can affect memory outcomes with regular consumption. For example, there is established evidence that the specific type and amount of polyphenols and ascorbic acids presented in tea, but not coffee, has a greater observable neuroprotective effect (Noguchi-Shinohara et al., 2014); ii) when comparing the same type of caffeine-containing foodstuff such as coffee, caffeine contents can differ by the grinding and brewing processes used (Bell et al., 1996; McCusker et al., 2003). These raised the question of whether caffeine from different sources can have different effects on memory.

In studies measuring habitual caffeine intake, participants reported the source of consumption by responding to a single question asking how many cups of "coffee" or "tea" do they usually drink in a day (Hameleers et al., 2000; Jarvis, 1993; Lesk et al., 2009; Loke, 1988). Jarvis (1993) computed average intake by assigning weights of 1.0 to coffee and 0.5 to tea. A dose-response relationship was observed between coffee consumption and performance in all cognitive tasks, but an association between tea and performance in only two tasks (SRT and visuospatial reasoning). Hameleers et al. (2000) assigned weights of 0.85 to coffee and 0.35 to tea based on the industrial standards of 85 mg and 30 mg caffeine in a cup of coffee and tea, respectively. Such estimation is likely unrepresentative of the actual caffeine content. For example, a cup of freshly brewed coffee may contain a higher amount of caffeine than a cup of blended instant coffee. In both studies, the effect of other caffeine-containing food was not accounted for. Loke (1988) reported a significant effect of habitual consumption, but not a single dose of experimentally administered caffeine capsule, on recall. The screening process for habitual consumption was not reported in this study, thus participants may ambiguously report caffeine intake from a variety of food items. The findings also raised the question of caffeine tolerance. Chronic caffeine use causes increased caffeine tolerance (Addicott et al., 2009; Evans and Griffiths, 1992; Shi et al., 1993), thus a standard dose assigned by the experimenter may not have observable effects due to inter-individual differences in tolerance.

Caffeine from the same beverage, coffee, can also have different effects due to the stage of beans, brewing process, and biochemistry profiles (Alharbi et al., 2018). In this study, participants receiving a cup of 3.02 g coffee arabica and 2.04 g ground cardamom showed performance increment in all memory tests, compared to those receiving a cup of 12 g '*2 in 1 City Café*' instant coffee (robusta) (with an optional 4.6 g sugar sachet). Coffee arabica also increased ratings on clear-headedness and decreased ratings on sleepiness compared to control and the group

receiving robusta. In comparison, coffee robusta only improved performance in one task (Trail making set B). However, the robusta group was given highly processed instant coffee which may also contain a high amount of noncoffee ingredients. The arabica group was given fresh ground coffee and cardamom, which was used to enhance the flavour but can also independently enhance learning and memory (Abu-Taweel, 2018). The researchers did not report the estimated caffeine contents in these two types of coffee, but likely that these beans differed in caffeine contents. Taken together, this study suggests the treatment effect of caffeine can be mediated by the source of caffeine, either due to the quantity of the caffeine content, or other presenting bioactive ingredients.

In laboratory settings, caffeine is typically administered via oral capsules and pills; tablets dissolved in sports drink, water, or decaffeinated coffee; or regular commercially accessible coffee. These procedures involve minimal costs or risks for participants and are easy to include a placebo-controlled condition, but limit the analysis of caffeine effects derived from other food sources. Furthermore, coffee craving can impair performance in cued recall and recognition memory (Palmer et al., 2017). This suggests that regular coffee consumers may underperform in memory tasks if they were only given a capsule or tablets (odourless) dissolved in a cup of water after a prolonged caffeine fasting, as they have been deprived of the sensory experiences (i.e., the sight of a familiar café, smell, or taste) of their regular coffee. As most studies reported a required period of caffeine, food, or other substances fasting, reversal withdrawal can inflate the treatment effects (Aust and Stahl, 2020). This effect can be further inflated in habitual consumers who received regular coffee, than those receiving caffeinated capsules or pills. Regular consumers should also be able to distinguish between regular and decaffeinated coffee due to the subtle differences in texture and taste. Nonregular consumers should be able to distinguish between caffeine and placebo due to the larger magnitude of caffeine-induced physical symptoms in low tolerant users (Shirlow and Mathers, 1985). Additionally, consuming different types of caffeine-containing beverages is mapped by geographical, historical, and cultural characteristics (Grigg, 2002). Participants receiving coffee (or caffeine added to decaffeinated coffee) treatment would not experience the effect of caffeine if they prefer to obtain their daily dose of caffeine from other types of beverages.

3.2.1. Summary

Caffeine from different sources may contain other bioactive ingredients that independently affect cognitive functioning and performance in memory tasks. Most studies did not control for confounding factors such as caffeine metabolism, caffeine intake from other food sources, consumption habits, and baseline tolerance, warranting more research to compare the effect of caffeine from different sources.

4. Experimental factors

Most studies included prescreening or other controlled processes to ensure the effectiveness of drug administration. These include using well defined exclusion criteria, fasting, controlling for the diurnal cycle (e.g., sleep scheduling, restricting testing time), and specifying absorption time. As nicotine interferes with caffeine absorption (Nehlig, 2018; Snel and Lorist, 2013), most studies included prescreening for a history of smoking. Others used prescreening to exclude participants with health conditions that can be affected by the use of caffeine or other stimulants, such as neuropsychiatric, kidney, or cardiovascular problems, pregnancy, and female participants taking oral contraceptives. Ten studies screened participants for physical measures (Arnold et al., 1987; Baur et al., 2021; Erikson et al., 1985; Hogervorst et al., 1998; Jarvis, 1993; Koppelstaetter et al., 2008; Lanini et al., 2016; Lesk et al., 2009; Smith et al., 1992; Soar et al., 2016). Among these, blood pressure and heart rate are most commonly screened. Additional measures include pupil diameter and blood samples for fasting glucose and insulin (Lanini et al., 2016), pulse oximetry (Koppelstaetter et al., 2008), and polymorphism of the gene ADORA2A through saliva samples (Baur et al., 2021). Studies recruiting older adults also included more rigorous cognitive prescreening, such as driving ability (Haskell-Ramsay et al., 2018), clinical diagnosis of mild cognitive impairment (Haller et al., 2017), and MMSE (Haller et al., 2017; Lesk et al., 2009; Walters and Lesk, 2016, 2015).

To ensure caffeine absorption, all but three (Borota et al., 2014; Smith et al., 1992; Ueda and Nakao, 2019) mentioned the requirements for pretreatment fasting. Caffeine fasting is not explicitly reported in Borota et al. (2014), however, a subsequent replication study (Aust and Stahl, 2020) elaborated a fasting procedure, implying that this has been required in Borota et al. (2014). Though Terry and Phifer (1986) and Klaassen et al. (2013) did not mention fasting requirements, participants completed a questionnaire detailing their food and beverage before the experiment, and data was removed for those who reported having consumed caffeinated food items two hours before the experiment. The type of fasting ranged from caffeine or CCFS (Erikson et al., 1985; Haller et al., 2017; Soar et al., 2016), to alcohol, OTC medications, and general beverage and food fasting (Alharbi et al., 2018; Arnold et al., 1987; Baur et al., 2021; Haskell-Ramsay et al., 2018; Herz, 1999; Hogervorst et al., 1998; Koppelstaetter et al., 2008; Lanini et al., 2016; Lesk and Womble, 2004; Loke, 1988; Mednick et al., 2008; Ryan et al., 2002; Schmitt et al., 2003; Trunk et al., 2015; Walters and Lesk, 2016, 2015). The time of the required caffeine fasting ranged from two (Soar et al., 2016) to 24 h (Alharbi et al., 2018; Haskell-Ramsay et al., 2018; Loke, 1988; Mednick et al., 2008). One study investigating sleep deprivation adopted a more rigorous pre-experimental protocol restricting participants' naps, caffeine, alcohol, and medication intake, as these were known factors to interfere with sleep (Baur et al., 2021). According to Borota's et al. (2014) assessments on salivary caffeine metabolites, a dose of up to 300 mg (amount to 1.5 cups of regular coffee) caffeine can be fully washed out after 24 h. Nevertheless, due to the variations in source intake and individual metabolism, whether a short period of caffeine fasting (2–4 h) can reset the absorption rate is less clear (Kalow, 1985; Nehlig, 2018). As diet, alcohol and OTC medications also affect caffeine absorption and metabolism, future studies may benefit from stricter fasting protocols (Nehlig, 2018). Conversely, Aust and Stahl (2020) warned against pretreatment fasting, as the reversal of withdrawal symptoms can be mistakenly taken as the treatment effect. Future studies using habitual caffeine consumer samples and fasting procedures may benefit from measuring the withdrawal symptoms at baseline and posttreatment. A better approach is to use alternating phases of caffeine treatment and abstinence: participants are given a standard amount of caffeine three times daily over several consecutive days to establish habitual consumption and tolerance, followed by the last day, during which they receive either the same amount of caffeine or a placebo (James, 1998). This protocol can effectively control for tolerance and withdrawal associated with habitual consumption, allowing for disaggregation of the acute (performance on the last day) and long-term effects (performance across previous days).

All but three studies (Trunk et al., 2015; Walters and Lesk, 2016, 2015) reported using an absorption period of 15 (Loke, 1988) to 60 min (Alharbi et al., 2018; Borota et al., 2014; Mednick et al., 2008), with 30 min being the most prevalent (Arnold et al., 1987; Erikson et al., 1985; Haller et al., 2017; Haskell-Ramsay et al., 2018; Hogervorst et al., 1998; Lanini et al., 2016; Ryan et al., 2002; Schmitt et al., 2003). An exception is Klaassen et al. (2013), who reported that the functional magnetic resonance imaging (fMRI) scanning session began 10 min after caffeine administration, however, considering the procedures involved in fMRI data collection, likely the actual absorption was longer before task exposure. All of these studies administrated caffeine through oral ingestion, the chosen absorption time is validated by caffeine pharmacokinetics data suggesting that peak concentration is usually reached between 15–120 min after intake (Fredholm et al., 1999). However, few justified the use of a particular absorption period, except Ueda and

Nakao (2019) who administered caffeine through transpulmonary inhalation, they clarified that this method ensures peak plasma caffeine be reached within seconds, hence tests were administered immediately after the drug treatment. Saliva sampling is a reliable, non-invasive method for frequent measurement of caffeine pharmacokinetics (Newton et al., 1981; Suzuki et al., 1989), albeit only a few reported collecting participants' salivary samples (Baur et al., 2021; Borota et al., 2014; Haskell-Ramsay et al., 2018; Hogervorst et al., 1998; Klaassen et al., 2013; Trunk et al., 2015). Among these, Trunk et al. (2015) mentioned the procedure of salivary sample collection but did not report this data in further detail. Haskell-Ramsay et al. (2018) and Hogervorst et al. (1998) compared salivary caffeine concentrate before and after the experiment (75–110 min posttreatment) and excluded data from participants who did not adhere to the caffeine fasting instruction. Both studies also demonstrated higher post-experiment caffeine concentration in the treatment compared to the placebo control group. Klaassen et al. (2013) compared concentration at baseline, 25, and 90 min after administration, and found greater concentration in the treatment group at 25 min, and marginally higher concentration at 90 min compared to the placebo group. This finding is in line with Borota et al. (2014), who compared salivary caffeine metabolites at the baseline, one, three, and 24 h after treatment, and found the peak concentration at around one hour window, which gradually declines and was fully metabolised at 24 h. However, Baur et al. (2021) reported that caffeine metabolites levels continued to increase after regular daily doses until the fourth day, and gradually decreased after the termination of caffeine administration.

Controlling for sleeping schedules and time of testing can help regulate overall arousal and alertness, which can affect both caffeine absorption and memory outcomes (Nehlig, 2018). Some studies reported a requirement of "a normal night of sleep" before the experiment (Alharbi et al., 2018; Lanini et al., 2016; Loke, 1988), while others reported a minimum of five (Arnold et al., 1987; Baur et al., 2021; Erikson et al., 1985) to eight (Mednick et al., 2008) hours of sleep. Four studies measured participants' sleepiness in the Karolinska Sleepiness Scale (Alharbi et al., 2018; Baur et al., 2021; Klaassen et al., 2013; Mednick et al., 2008), whereas others mostly included measurements of mood states, including levels of alertness and arousal. Additionally, Smith et al. (1992) mentioned that the placebo and treatment groups did not differ in their lengths of sleep the night before the experiment. The remaining studies did not report a minimum required amount of sleep nor compared the sleep schedule between the treatment and placebo groups at baseline. In particular, participants' sleep schedules have not been reported in studies examining the interaction between caffeine and the time-of-day effect (Ryan et al., 2002; Walters and Lesk, 2016, 2015). However, these studies did specify the restricted testing window or the use of the same testing time if participants returned for a second session. The use of a restricted testing window has been reported in all the reviewed studies.

4.1. Summary

Most studies elaborated the experimental control for confounding factors, such as health conditions, physiological state, fasting, and diurnal cycles. However, sleep schedules have not been consistently examined. Fasting schedules used by different studies are largely inconsistent, with little justifications on the type and time of fasting. Possible inflation of treatment effect from the reversal of caffeine withdrawal symptoms has not been discussed in these studies. Where appropriate, future studies may benefit from including pre-experimental food and sleep diaries.

5. Demographic factors

5.1. Are caffeine effects on memory different in males and females?

The effects of caffeine were exclusively observed in female participants in Erikson et al. (1985). Arnold et al. (1987) hypothesised that the caffeine effect is mediated by sex hormones (Sisti et al., 2015), they subsequently recruited females who were within the first five days of their menstruation cycle and found that recall in female participants benefited more from caffeine compared to male participants. A similar performance-enhancing effect of caffeine in female participants was observed in Smith et al. (1992), who found that 4 mg/kg bodyweight of caffeine tablets added in decaffeinated coffee improved female participants' performance in a sustained attention task, but impaired male participants' performance. Despite the evidence that the effect of hormonal fluctuation on caffeine metabolism is dose-related (Sisti et al., 2015), a dose-response relationship between caffeine and sex is often not examined.

Haskell-Ramsay et al. (2018) reported a significant interaction between sex and caffeine in LTM but provided no further details. They also found higher ratings of jitteriness in younger females compared to the same age placebo group and older males in either caffeine or placebo groups, and significantly lower ratings of jitteriness in decaffeinated groups in older males. They proposed several sex-related factors, including sex-steroid levels (Ascherio et al., 2004; Ferrini and Barrett-Connor, 1996), haemodynamic mechanisms (Hartley et al., 2004), uric acid responses (Kiyohara et al., 1999; Perna et al., 2016), and genetic polymorphisms (Rasmussen et al., 2002) which can modulate caffeine metabolism. Particularly relevant to this study is the finding that females were more susceptible to the anxiogenic effects of caffeine under the same dose than males (Domschke et al., 2012; Gajewska et al., 2013). In comparison, a study examining the resting functional connectivity between habitual and non-coffee drinkers found an association between the increased frequency of caffeine consumption and anxiety in males only (Magalhães et al., 2021). However, this study did not assess participants' memory nor provide further explanations for this sex difference.

Loke (1988) and Herz (1999) failed to find any main or interaction effect of sex in memory tasks. Noteworthy is a number of studies that recruited only males (Klaassen et al., 2013; Koppelstaetter et al., 2008; Lanini et al., 2016; Ueda and Nakao, 2019), and one that recruited only females (Alharbi et al., 2018). Most of these studies did not justify the rationale for males or females only recruitment, except Lanini et al. (2016), who mentioned that females were excluded due to "changes in caffeine metabolism during menstrual cycling and contraceptive steroid use." (p. 31).

5.1.1. Summary

Given the underlying physiological mechanisms, caffeine is likely to affect memory differently in males and females through metabolic pathways, although this is not fully evident in the studies which examined sex and caffeine interaction. Female participants are likely to benefit more from an acute dose of caffeine than their male counterparts, but they are also likely to experience higher levels of physical side effects of caffeine. On the other hand, recruitment of only males or females indicates that researchers might have already anticipated some sex-related differences in the caffeine effect. Future studies should also examine how female participants' hormonal fluctuations may synchronise with the effects of caffeine on memory.

5.2. Does ageing interact with caffeine to influence memory?

Where the long-term consequence of habitual caffeine consumption was examined, Jarvis (1993) reported a greater memory-enhancing effect of caffeine in older adults (55 years and older) compared to younger adults. In contrast, Lesk et al. (2009) found the detrimental effect of consuming CCFS on LTM, but not WM tasks in older adults (67 years and older). Hameleers et al. (2000) reported no interaction between habitual caffeine consumption and age (from 24 to 81 years) in memory outcomes. These disparities may be due to methodological differences. In Jarvis (1993) the cut-off age for older adults were loosely defined and

group performance might be inflated by the relatively younger participants in the older adult age group (i.e., the researchers grouped all participants aged 55 years and older). In Lesk et al. (2009), participants who consumed CCFS might also have other foods which simultaneously altered their cognitive performance.

Walters and Lesk (2016, 2015) re-examined the impact of 200 mg administered caffeine in a group of older adults (> 60 years) using the same set of cognitive measures as Lesk et al. (2009). Both found caffeine, compared to placebo, worsened performance in WM, LTM, and the processing speed tasks as the time-of-day effect increases. In contrast, Ryan et al. (2002) found that a cup of regular drip coffee compared to a decaffeinated coffee could ameliorate performance decline caused by time-of-day in older adults (> 65 years). Hogervorst et al. (1998) reported an interaction between different age groups and a dose of 225 mg caffeine (a total of three cups of coffee received within 15 min), whereby the middle-aged adults (46–54 years) showed performance increments in both STM and LTM tasks, and younger adults (26–34 years) showed RTs slowing in the STM task, but no effect of caffeine on older adults (66–74 years). However, analysis of salivary caffeine metabolites also revealed that the middle age group had higher levels of pretreatment caffeine concentration, indicating that they failed to adhere to the required caffeine fasting. This group also reported higher levels of habitual consumption compared to the other two age groups, indicating a possible larger placebo effect. Lastly, two studies did not find any effects of 100 mg caffeine added in decaffeinated coffee in different age groups (Haskell-Ramsay et al., 2018; Schmitt et al., 2003).

5.2.1. Summary

There is adequate evidence that the treatment effect of caffeine manifests differently in different age groups. Older adults may be more sensitive to the effect of caffeine than younger or middle age adults. Furthermore, in older adults, caffeine can interact with the time-of-day effect to facilitate or impair memory performance. There is room for future studies to compare the caffeine effect in different age groups.

6. How effective is caffeine as a memory enhancer?

Cognitive resources are defined as a limited quantity enabling (Abreu et al., 2011) cognitive functions and processes (Oberauer et al., 2016; Shenhav et al., 2017). In this view, memory is a resource-limited process (Anderson et al., 1996; Barrouillet et al., 2004; Bjork and Bjork, 2011; Borragán et al., 2017; Just and Carpenter, 1992; Logie, 2011; Ma et al., 2014; Popov et al., 2019; Vergauwe and Cowan, 2015). This resource limit can occur during encoding, such as when the amount of processing resource cannot cope with task demand (Camos and Portrat, 2015); consolidation, such as when multiple representations are competing for storage resources (McFarlane and Humphreys, 2012; Zhang and Luck, 2008); or retrieval, such as when previously retrieved information interferes with the ongoing retrieval process (Wixted and Rohrer, 1993). In all these examples, the amount of available cognitive resources can determine if information can be remembered.

Some studies have analogised cognitive resources to muscle strength, which depletes with sustained use and recovers over time (Popov and Reder, 2020). As muscle strength, stamina, and repair can be promoted by diet or exercise (Maughan, 2002), the amount and availability of cognitive resources may also be enhanced through behavioural or pharmacological interventions (Popov et al., 2019; Popov and Reder, 2020). Existing evidence suggests that in healthy adults, sleeping, physical activities, noninvasive brain stimulation, and nootropics can be applied to boost global cognitive functions (Boggio et al., 2009; Manenti et al., 2013). To the best of our knowledge, the efficacy of these resource enhancing approaches in influencing memory processes has not been compared. Among different types of nootropics, caffeine is an adenosine receptor antagonist associated with acute improvement in vigilance and motor reaction times (Nehlig, 2010, 1999) and has been widely used as a cognitive enhancer (Hameleers et al., 2000; Jarvis, 1993; Madan, 2014; Nehlig, 2010). Here we compare the effects of caffeine with other cognitive enhancement approaches, including breakfast and nap.

Regular breakfast intake is associated with improved learning and memory outcomes (Galioto and Spitznagel, 2016). In typical Western societies, adults also have a regular cup of caffeinated drink during breakfast, raising the question of whether the cognitive enhancing effect of breakfast was due to glucose intake or caffeine. According to Maridakis et al. (2009), a dose of 100 mg or 200 mg caffeine capsule improved performance in tasks involving psychomotor vigilance and sustained attention, which was comparable to the effect of breakfast. Moreover, the treatment effect of 200 mg caffeine on psychomotor tasks was independent of carbohydrate intake (Maridakis et al., 2009). However, memory outcomes were not examined in these studies. Similarly, Lanini et al. (2016) found that a personally preferred caffeine amount delivered via oral capsules improved performance in psychomotor vigilance tasks and metacognition, but not in memory tasks. These effects were independent of breakfast. In contrast, Smith et al. (1992) found a memory-enhancing effect of caffeine in selected WM and LTM tasks, while breakfast had either no effect or impaired performance in selected LTM tasks. The WM enhancing effect of caffeine relative to placebo carried over to the second round of testing after participants were provided with a portion controlled lunch. Furthermore, both Maridakis et al. (2009) and Smith et al. (1992) reported a mood enhancing effect of caffeine, whereas, in Smith et al. (1992), participants who received breakfast reported being more tranquil and calm only when they also received caffeine rather than placebo.

Given the established role of caffeine in modulating arousal and sleepiness, its treatment effect on memory outcomes may be indirectly attributed to these factors. This has been demonstrated in studies that measured participants' mood, arousal, and sleepiness. For example, Alharbi et al. (2018) showed that coffee robusta compared to arabica did not improve ratings on clear-headedness or sleepiness, in keeping with the finding that only arabica but not robusta improved performance in WM and STM measures. Mednick et al. (2008) found that although participants receiving caffeine reported higher levels of alertness, there is a detrimental effect of a 200 mg caffeine pill on delayed recall relative to placebo or napping, after either a short (20 min) or long (7 h) retention interval. Thus, sleep may be more effective than caffeine in elevating memory resources independent of state arousal and alertness. Conversely, Baur et al. (2021) observed the effects of regular consumption over five days in sleep-deprived young adults (20–40 years), and reported no differences in subjective ratings of sleepiness between those receiving regular coffee and decaffeinated coffee, except on the first day. Furthermore, the reported sleepiness remained high in the regular coffee group even after the night of an eight-hour recovery sleep. This reflects the short-lasting effect of an acute dose of caffeine in improving subjective sleepiness. This study found that, compared to the decaffeinated group, regular daily caffeine consumption prevented performance decline in several WM tasks in sleep-deprived participants, suggesting that instead of an enhancer, regular consumption normalises WM deficits due to sleep deprivation.

6.1. Summary

Compared with breakfast, caffeine demonstrated promising cognitive enhancing effect, especially in tasks involving psychomotor and attentional control. There is some evidence that this positive treatment effect of caffeine also applies to WM or STM tasks, whereas the effect of breakfast is more unreliable. However, compared with sleep, an acute dose of caffeine may have short-term detrimental effects on memory, independent of participants' perceived arousal and alertness. While regular daily consumption overtime can prevent WM decline associated with sleep disturbances, it does not restore subjective sleepiness.

7. Discussion

7.1. Summary of findings

Caffeine is the most popular psychoactive drug used worldwide. However, its impact on cognitive performance remains controversial. Here we exclusively examined the effect of caffeine on performance in a wide range of memory tasks based on drug factors, experimental factors, and demographic factors. As a nootropic, caffeine is related to the enhancement of cognitive resources in memory processes. Therefore, we explored the effects of caffeine in comparison with other common cognitive enhancement approaches, such as glucose intake and sleeping.

There is substantial evidence of caffeine in improving RTs in tasks involving psychomotor vigilance or overt attentional control. This may be due to the faster initiation of already prepared responses. However, there is limited treatment effect of caffeine in WM tasks involving information maintenance, updating, or manipulation of memory representations. Caffeine also does not have a reliable, unidirectional effect on performance in immediate or delayed recall and recognition tasks, but some positive effects on prospective or implicit memory measures. The inconsistent effects may be due to the heterogeneous LTM measures and drug administration procedures used, or treatment effects at different memory stages. While pre-learning administration can directly moderate memory encoding, post-learning administration can affect consolidation depending on the length of the retention interval. There is no evidence that caffeine can affect retrieval administered post-learning.

The direction of caffeine's treatment effect may depend on drug factors and administration processes. Despite the lack of a reliable dose-response relationship, likely there is a minimum amount for the treatment effect to be observed. Furthermore, most studies assumed a common metabolic process of caffeine ingested from different sources, albeit the evidence that caffeine from various caffeine-containing foodstuffs can have different effects on cognition (Alharbi et al., 2018; Choi and Curhan, 2007). In particular, habitual users may experience the drug effect differently from their preferred caffeine-containing foodstuffs than administered pills or tablets. Most required a pre-experimental caffeine fasting procedure, which can lead to withdrawal effects detrimental to memory performance (Nehlig, 1999). The extent to which the treatment effect was caused by the reversal of withdrawal effect has not been examined (Aust and Stahl, 2020). Although all studies have reported a prescreening procedure and included a placebo control group where possible, only a few collected salivary samples to validate caffeine absorption across individuals.

There is extensive evidence that demographic characteristics such as sex and age can mediate the treatment effect of caffeine on memory. Females compared to males may be more sensitive to the physical effect of caffeine, such as reporting higher levels of jitteriness or alertness, while also more likely to experience the memory-enhancing effect of caffeine. However, more research examining the interaction between sex and caffeine effect in memory outcomes is needed, particularly how the treatment effect interacts with female participants' hormonal cycles. Additionally, older adults may also be more sensitive to the treatment effects of caffeine or the interaction between caffeine and the time of day effect than their younger counterparts. Where effects were found in older adults, caffeine can either enhance or impair memory outcomes. Compared to younger adults, older adults may be lifelong caffeine consumers having different metabolic profiles or having been exposed to other lifestyle factors that can interact with caffeine in affecting memory.

Lastly, we examined the effectiveness of caffeine as a memory enhancer when compared with glucose intake and sleep. There is some evidence that caffeine can benefit performance more than breakfast, especially in tasks requiring psychomotor and attentional control. Conversely, depending on participants' state arousal and alertness, caffeine can have short term detrimental effect compared to a nap, which can benefit memory consolidation. On the other hand, regular caffeine consumption over an extended period has working memory normalising effects among sleep-deprived healthy young adults.

7.2. Drug mechanisms

Drug mechanisms of caffeine have been well established in animal models. Compared with laboratory experiments using human participants, animals can be maintained under rigorously controlled diets and restrictions to caffeine access, permitting experimental designs that can potentially establish causality. Several animal studies have suggested that a single moderate dose of caffeine (1–30 mg/kg or 3–10 mg/kg in 0, 1, 3, 10, 30, or 100 mg/kg) administered immediately post-learning, or 30 min before testing improved the retention of inhibitory avoidance (avoiding a footshock), but not habituation (decreased free exploration) in a new environment; conversely, caffeine administered 30 min at the same dose before learning impaired memory acquisition, possibly through interfering with attentional processes (Angelucci et al., 1999). Similarly, a moderate dose of caffeine (0.3–10 mg/kg in 0, 0.3, 10, or 30 mg/kg) administered immediately post-learning, or 30 min before testing improved rats' memory retention and retrieval in the Morris water maze task, while pre-learning administration did not alter performance during learning or testing (Angelucci et al., 2002). These suggest that, in rats, caffeine directly participate in consolidation, but can only affect encoding through interfering with the attentional processes. This is in line with the findings in human studies described in Section 2.3.2, where a single dose of caffeine can affect both encoding and consolidation, and the direction of this influence may depend on individual or task specific factors. On the other hand, in these animal studies, the finding that pre-testing (after the retention interval) administration improved memory retrieval indicates that caffeine at a moderate dose may facilitate memory retrieval, which was not reported in human studies (Borota et al., 2014; Herz, 1999).

Animal studies are particularly useful in providing insights into the therapeutic potential of caffeine and its biomolecular mechanisms. In the animal model of Parkinson's disease, a single dose of caffeine administered 45 min pre-learning could effectively reverse the memory deficit in the rat model of Parkinson's disease, suggesting that caffeine may affect learning and memory through the interaction between dopamine and adenosine systems (Gevaerd et al., 2001). Habitual caffeine use is associated with several other pathways downregulating disease progression and preserve memory (Kalampokini et al., 2019; Victorino et al., 2021), including increasing anti-inflammatory microbiome (Nakayama and Oishi, 2013), attenuating neuroinflammation (Brothers et al., 2010), and improving the bioavailability of levodopa (Deleu et al., 2006), although the reliability of this effect is yet to be demonstrated in humans (Postuma et al., 2017).

Additionally, the effect of caffeine on adenosine receptors A_1 and A_{2a} has been widely established in animal models. A_{2a} receptors are ubiquitously distributed in brain areas known as primary memory regions, including ventral and dorsal striatum, selected areas of cortex, and hippocampus (Borea et al., 2018; Snyder et al., 1981). Habitual caffeine can reverse memory impairments in the animal model of Alzheimer's disease by mimicking the effects of selective inhibitors of A2a receptors (Da Silva et al., 2016), while acute coffee treatment increased plasma level of anti-inflammatory cytokines and granulocyte-colony stimulating factors associated with WM improvements (Cao et al., 2011). Importantly, Cao et al. (2011) also found no effects of caffeine solution alone or decaffeinated coffee treatments, suggesting that these neuroprotective effects are only presented when caffeine is synergised with other bioactive ingredients in coffee. Furthermore, both acute and chronic caffeine prevented amyloid beta induced neurotoxicity and cognitive impairment (Canas et al., 2009; Dall'Igna et al., 2007). The effect of an acute dose of caffeine in mimicking adenosine A_{2a} receptor antagonists has also been demonstrated in animal models of other neuropsychiatric diseases, such as preventing memory deficits in attention deficit and hyperactivity disorder (ADHD) (Pires et al., 2009;

Prediger et al., 2005b, 2005c). While an acute dose of caffeine administered before learning did not alter performance in learning or testing in healthy animals (Angelucci et al., 2002, 1999), here, it reversed the spatial learning deficits exhibited in the spontaneously hypertensive rats (animal model of ADHD) (Prediger et al., 2005c). There is also converging evidence on the role of caffeine in preventing secondary memory deficits in animal models of chronic diseases, such as traumatic brain injury (Ning et al., 2015) and diabetes (Duarte et al., 2012), likely through attenuating neuroinflammation and glutamate excitotoxicity (Ning et al., 2015).

In animal models of ageing, habitual consumption (80 days before testing) of a controlled diet with either brewed coffee or caffeine supplements, compared to a controlled diet alone, improved animals' LTM in an object recognition task (Abreu et al., 2011). This study also found reduced lipid peroxidation of brain membranes and increased concentration and activities of antioxidants in rats ingesting the coffee or caffeine diet, indicating that chronic intake can protect the antioxidant system in age-associated memory functions. Although there is less evidence on the acute effects of caffeine in ageing, an acute dose at 10 or 30 mg/kg administered together with A_{2a} receptor antagonists reversed the ageing-related deficits in olfactory memory (Prediger et al., 2005a). To the best of our knowledge, there is no review of animal studies examining the chronic or acute effect of caffeine on learning and memory in healthy animals. However, interested readers may refer to Victorino et al. (2021) for a review of caffeine in the animal model of Parkinson's disease, Ferré et al. (2018) for caffeine in the animal models of neuropsychiatric diseases, and Kolahdouzan and Hamadeh (2017) for caffeine's neuroprotective mechanisms in animal and human studies. Note that these highlighted reviews are established on neurological or neuropsychiatric disease models, suggesting caffeine as a therapeutic tool, rather than a cognitive enhancer.

In keeping with animal studies, in humans, the physical and cognitive outcomes are attributed to caffeine's drug effect on adenosine receptors A_1 and A_{2a} and rapid turnover of neurotransmitters (Nehlig, 1999). Lesk and Womble (2004) proposed that caffeine alters short-term plasticity in neurons of the phonological retrieval system through blocking A_1 adenosine receptors. It is believed that the interaction between A_{2a} and D_2 receptors in the striatum underlies some of the drug effects of caffeine (Nehlig, 1999). Moreover, the neuroprotective effects of habitual caffeine use shown in animal studies have also been substantiated in human studies (Borea et al., 2018; Carman et al., 2014), demonstrating the therapeutic potential of caffeine in preventing memory deficits associated with these neurological diseases. However, compared to animal studies, limited evidence from human studies have shown the effects of acute caffeine or coffee in preventing age-related memory decline (Haller et al., 2013; Haskell-Ramsay et al., 2018; Schmitt et al., 2003). Taken together, in humans, likely habitual, but not acute consumption can ameliorate some memory deficits associated with ageing or neurodegenerative disease.

Although we did not focus on neuroimaging findings, in studies reviewed there is also evidence that an acute dose of caffeine is related to activation of attentional networks, such as bilateral medial frontopolar cortex extending to anterior cingulate gyrus (Koppelstaetter et al., 2008), bilateral dorsolateral prefrontal cortex (PFC), and the left thalamus (Haller et al., 2017, 2013; Klaassen et al., 2013). Furthermore, lifelong habitual caffeine consumers compared to non-coffee drinkers showed increased functional connectivity between cerebellar and several subcortical areas known to be involved in attention, arousal, and memory acquisition, including the thalamus, lingual and inferior occipital gyrus, and parahippocampus (Magalhães et al., 2021). In electroencephalography studies, caffeine is associated with increased prestimulus alpha amplitude (Trunk et al., 2015), and an increase in the theta activity in the right PFC, central, and temporal areas (Ueda and Nakao, 2019). Together, these results suggested the role of caffeine in modulating the top-down attention network. However, these studies either did not include memory assessments or find the treatment effects of caffeine on any memory measures beyond improved reaction times, making interpretation of the neuroimaging data difficult.

Given these pharmacological mechanisms and neural associations, it is surprising that our results showed very limited treatment effects of caffeine on memory performance. Moreover, despite the established neuroprotective effects, several studies reported that caffeine administered before learning impaired memory performance. This effect may be dose-related, at low levels, caffeine can be a cognitive enhancer, while at high levels it inhibits working memory dependent learning (Nehlig, 2010). Our findings correspond to a recent meta-analysis identifying no association between habitual consumption and long term memory functions after controlling for genetic variations, except a small positive effect on prospective memory (Zhou et al., 2018). Where effects were found, participants' improved mood and arousal may underly the elevated memory encoding. In other words, caffeine can indirectly participate in the memory processes by increasing attentional control and processing resources or modulating learning factors including mood, concentration, arousal, and alertness. As increased attentional control and processing resources no longer modifies the strengths of memory representations during retrieval, caffeine administered after a long retention interval and immediately before testing does not impact retrieval.

Similar interactions between caffeine and sex, where a larger protective effect for females than males has been reported in a systematic review (Panza et al., 2015). However, Panza et al. (2015) focused on the role of habitual caffeine consumption in preventing cognitive decline and dementia, without detailing mechanisms underlying this sex effect. Given the various metabolic pathways of caffeine, habitual consumption may participate in physiological processes that affect global cognition (de Mejia and Ramirez-Mares, 2014), but this does not translate to the effect of caffeine on memory tasks in the healthy population. Taken together, an acute dose of caffeine does not have a direct effect on memory but can affect performance in either direction through other modulating pathways. On the other hand, habitual consumption influences memory included global cognition mainly in clinical populations, indicating that caffeine should not be viewed as a memory enhancer, but instead a normaliser which attenuates memory decline associated with ageing or neurodegenerative diseases (Cunha and Agostinho, 2010).

7.3. Limitations and future directions

With respect to drug factors, only a few studies compared the effects of different doses and often did not justify the selected dose categories (Arnold et al., 1987; Borota et al., 2014; Erikson et al., 1985; Loke, 1988). Despite reported memory outcomes under different doses, none systematically examined a dose-response relationship with more nuanced statistical approaches. There is also a lack of disaggregation of the treatment effect for caffeine from various sources of caffeine-containing foodstuffs (Noguchi-Shinohara et al., 2014). In the discussed epidemiological studies and those adopted quasi-experimental designs, participants' diet (Verly et al., 2017), sleep-wake cycles (Park et al., 2018), and time of the day of assessments (Anderson et al., 1991; Hasher et al., 2005) might have independently affected memory or interacted with habitual caffeine consumption to confound the latter's effect. For experimental factors, none of the studies using oral administration justified the specific absorption time used (Fredholm et al., 1999), or considered participants' baseline tolerance or individual variations in caffeine metabolism (Kalow, 1985; Nehlig, 2018). In terms of the demographic factors, some studies have reported the interaction between caffeine and sex, but this was limited by the lack of a defined dose-response relationship (Arnold et al., 1987; Erikson et al., 1985), or a more detailed description of the effects (Haskell-Ramsay et al., 2018). Given the evidence that polymorphisms in A1 and A2a adenosine receptor genes play a role in anxiety regulation (Alsene et al., 2003), individual genetic variability is associated with the tendency to habitually

consume caffeine, acute caffeine-related responses such as level of anxiety and insomnia, magnitude of withdrawal, and the risks to certain health outcomes (Alsene et al., 2003; Kendler, 1999; Yang et al., 2010). Furthermore, in complex cognitive control tasks involving attention and executive functioning, the effect of caffeine can be partly explained by genetic polymorphisms of adenosine and adrenergic receptors (Renda et al., 2015). These evidence highlight the need for recruiting more homogenous samples in future studies. A few studies recruiting unisex samples also failed to provide justifications on their sampling approach (Alharbi et al., 2018; Klaassen et al., 2013; Koppelstaetter et al., 2008; Lanini et al., 2016; Ueda and Nakao, 2019). Similarly, despite some studies recruiting only older participants reported the interaction between caffeine and age-related factors, such as the time of day effect, whether this effect can exhibit in younger adults have not been examined. Studies investigating the age-related caffeine effect also rarely examined changes in caffeine metabolism due to lifelong habitual consumption (Addicott et al., 2009).

Future experiments assessing the effect of caffeine on memory can benefit from several considerations. First, clearly defined dose categories, duration, and types of caffeine exposure based on the pharmacokinetics and pharmacodynamics of caffeine should be used to further establishment of a dose-response relationship (Shi et al., 1993). Analysis of additional demographic factors should take into consideration of the dose-response relationship, for example, how sex-related hormonal variations or age can moderate dose-response. Second, baseline evaluation should include habitual consumption of caffeine-containing foodstuffs, detailing caffeine intake from various source. Where possible, pre-experimental dietary and sleep schedules should be collected. Instead of using pre-experimental fasting, an ad libitum study without fasting, or an alternating exposure-abstinence protocol can prevent withdrawal effect or inflation of treatment effect when paired with appropriate statistical procedures controlling for caffeine intake (Aust and Stahl, 2020; James, 1998). Furthermore, periodical, noninvasive physical measures such as pupil diameter and salivary caffeine metabolites can provide supporting information on tolerance and absorption, allowing for analysis of individual variances in treatment effects. Finally, despite heterogeneity in working memory and long term memory measures, most relied on verbal stimuli. There is currently insufficient research on visuospatial long term memory performance under the effects of caffeine. The positive treatment effects of caffeine on prospective memory and implicit memory measures also highlight an area of future exploration. The effects of caffeine compared with other cognitive enhancers should be continuously examined in future research.

7.4. Conclusion

Based on the studies reviewed, there is no reliable evidence that habitual consumption or an experimentally administered dose of caffeine can affect healthy participants' performance in various working memory, short term memory, or long term memory tasks. However, most studies found a positive effect on reaction times. Due to the lack of baseline control or appropriate statical procedures, most studies including dose-response analysis found an inconsistent relationship between caffeine and memory. Only a few reported an interaction between caffeine and demographic factors such as sex and age. Where effects were found, the direction of the treatment effect may depend on the given dose and individual tolerance and metabolism at baseline. Future studies should include a more comprehensive assessment of i) drug factors, such as clearly defined dose categories, and source or type of caffeine, ii) experimental factors, such as a wider variety of visuospatial, prospective, and implicit memory measures, and iii) individual factors, such as habitual caffeine consumption, tolerance, and metabolism.

Declaration of Competing Interest

The authors reported no conflict of interest.

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