Could caffeine be used to treat cognitive impairments in Alzheimer's disease?

Lisa Bouwman
S3445062
MSc Biomedical Sciences

Supervisor:
Prof. dr. Robbert Havekes
GELIFES
University of Groningen

6 December 2021

Abstract

Cognitive impairments are one of the main symptoms of Alzheimer's disease (AD). There is currently no long-term treatment that reverses these cognitive impairments in AD, and the approved drugs do not target the pathology directly. Interestingly, epidemiological studies have found an association between caffeine consumption and a reduced risk of developing AD. Furthermore, caffeine is thought to be a cognitive enhancer. Since caffeine is found in many foods and drinks that are consumed on a daily basis, caffeine might be an efficient treatment for cognitive symptoms in AD. This review summarizes studies about the effects of caffeine on cognition and memory in both humans and rodents. Furthermore, the effects of caffeine on learning and memory in animal models of AD will be discussed, as well as the molecular mechanisms underlying these effects. In conclusion, caffeine could potentially be an efficient treatment for cognitive impairments in AD that might not only improve cognitive symptoms, but also act on the pathology directly by increasing amyloid-beta clearance and inhibiting neuroinflammation. Although there is no clear evidence that caffeine improves cognition in healthy humans, it seems to prevent and reverse memory impairments in animal models of AD. Investigation of the effects of caffeine on cognition in patients with AD is a crucial next step to gain more insight in the possibility of caffeine as a treatment for Alzheimer's disease.

Table of Contents

1. Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease that accounts for more than half of all cases of dementia (Londzin et al. 2021). The neuropathology of AD is characterized by amyloid-beta (Aβ) plaques and hyperphosphorylated tau aggregates (Masters et al. 1985; Arnold et al. 1991; Lane et al. 2018). This eventually leads to brain atrophy which is mainly present in the medial temporal lobe, including the hippocampus (Jack 2011). Atrophy in the hippocampal areas leads to cognitive decline. Cognitive symptoms of AD include memory loss, having trouble with planning, losing track of time and dates, and poor judgment (Alzheimer's Association 2021). These symptoms interfere with the lives of patients, as well as the lives of the people around them.

Currently, there are only four drugs for Alzheimer's disease that are approved by The U.S. Food and Drug Administration (FDA): rivastigmine, galantamine, donepezil and memantine (Alzheimer's Association 2021). Rivastigmine, galantamine and donepezil are cholinesterase inhibitors, which cause an increase in acetylcholine levels (Khoury et al. 2018). This improves the cognitive functioning of patients. Memantine is a N-methyl-D-aspartate (NMDA) receptor antagonist, which inhibits the action of the excitatory neurotransmitter glutamate (Reisberg et al. 2003). Unfortunately, none of these drugs are able to slow the progression of Alzheimer's disease, and these drugs only improve cognitive impairments temporarily. Furthermore, since acetylcholine also acts on the periphery, cholinesterase inhibitors often lead to gastrointestinal side effects (Inglis 2002). It is therefore crucial to keep searching for ways to improve cognitive impairments in Alzheimer's disease.

Interestingly, the association between Alzheimer's disease and caffeine consumption has been getting attention from scientists. Caffeine (1,3,7-trimethylxanthine) is one of the most consumed psychoactive stimulants worldwide (Heckman et al. 2010). It can be found in many different foods and drinks, but it is mainly consumed via coffee and tea. Although caffeine is mainly consumed to decrease fatigue and increase arousal, several studies suggest that is also has beneficial effects on health. For example, caffeine consumption has been associated with a decreased risk of developing several diseases, such as liver diseases, type 2 diabetes and Parkinson's disease (Poole et al. 2017). Furthermore, many epidemiological studies have associated daily intake of a moderate caffeine dosage with a decreased risk of developing AD (Zhou & Zhang 2021). Since caffeine is also thought to be a cognitive enhancer (Ruxton 2008), caffeine might improve cognition and memory in patients with AD. If caffeine is indeed able to improve cognitive impairments in AD, increasing caffeine consumption through dietary interventions would be a cheap and efficient treatment for cognitive impairments in AD.

This literature study reviews current knowledge on the effect of caffeine on cognition in Alzheimer's disease. Studies about the effect of caffeine on cognitive performance in humans and rodents are discussed, as well as the molecular mechanisms underlying these effects. Finally, a suggestion for further research on the potential of caffeine as a treatment for AD will be given.

2. Caffeine consumption: neuroprotection and cognitive enhancement in humans

2.1 Epidemiological studies

Many epidemiological studies have been able to find an association between caffeine consumption and a decreased risk of developing AD. A case-control study found that patients with AD had a lower average daily caffeine intake compared to controls (Maia & De Mendonça 2002), indicating that there is an association between caffeine consumption and the risk of developing AD. In a systematic review, Chen et al. (2020) concluded that moderate caffeine consumption may reduce the risk of dementia and cognitive decline. Furthermore, a 10-year prospective cohort study with 676 European men showed that consuming coffee reduces cognitive decline in elderly men (Van Gelder et al. 2007). Similar results were found in women (Ritchie et al. 2007). In a follow-up study among 4,615 elderly, coffee consumption was associated with a decreased risk of developing AD (Lindsay et al. 2002). In another study among 3494 men, however, no association between caffeine consumption and the risk of developing AD was found (Gelber et al. 2011). A cohort-study in Portugal found that caffeine intake was only significantly associated with a lower risk of cognitive decline in women (Santos et al. 2010). In an Italian study, constant coffee consumption was associated with a lower rate of developing mild cognitive impairments, while an increase in habitual coffee consumption of more than 1 extra cup a day was associated with an increased rate of developing mild cognitive impairments (Solfrizzi et al. 2015). In contrast to low coffee consumption, consumption of more than 6 cups per day was associated with 53% higher risk of dementia compared to consumption of 1–2 cups per day (Pham et al. 2021).

A meta-analysis by Larsson & Orsini (2018) did not find a significant association between caffeine intake and the risk of developing dementia. Of the eight studies that they analysed, five specifically focused on the effect of caffeine on AD (Eskelinen et al. 2009; Gelber et al. 2011; Loftfield et al. 2015; Park et al. 2017; Larsson & Wolk 2018). However, it must be noted that the studies by Loftfield et al. (2015) and Park et al. (2017) only looked at mortality rates, not at the risk of developing AD. Furthermore, Eskelinen et al. (2009) did actually find a lower risk of developing AD in people who drank 3–5 cups of coffee per day. The conclusion of Larsson & Orsini can therefore be questioned.

In summary, there is epidemiological evidence that caffeine consumption is associated with a decreased risk of developing AD, suggesting neuroprotective effects of caffeine in humans. However, in order to use caffeine as a treatment for cognitive impairments in AD, it needs to have cognition-enhancing effects. In the next section, studies about the effect of caffeine on cognitive performance will be discussed.

2.2 Caffeine as a cognitive enhancer

Multiple studies have shown that caffeine increases alertness (Hewlett & Smith 2007; Einöther & Giesbrecht 2013). There is evidence that caffeine decreases recognition visual reaction time, simple reaction time, audial reaction time and choice reaction time (Adan & Serra-Grabulosa 2010; Kahathuduwa et al. 2017; Balko et al. 2020). A study by Bruyné et al. (2010) found that caffeine enhanced both vigilance and the executive control of visual attention, but only with a dose of 400 mg. In a Stroop task, participants that consumed coffee had faster executive speed with a higher accuracy rate than the control group (Yuan et al. 2020; Figure 1). A study by

Jarvis (1993) found that caffeine intake was related to simple reaction time, choice reaction time, incidental verbal memory, and visuo-spatial reasoning. Hameleers et al. (2000) showed that habitual caffeine consumption was significantly related to better long-term memory performance and faster locomotor speed, but not to short-term memory, information processing, planning and attention. In a study among over 2500 elderly (>60 years old), a significant association was found between caffeine intake (coffee, caffeinated coffee and caffeine from coffee) and cognitive performance (Dong et al. 2020). This relation between caffeine consumption and cognitive performance has also been shown by other studies (Haller et al. 2018). Caffeine also improved performance in a visually focussed selective search task (Lorist et al. 1995).

When looking at the effects of caffeine on short-term memory, the results are inconclusive. In a test where participants had to recall a list of words in random order, no beneficial or negative effect of caffeine was seen on learning and memory (Loke 1988). Warburton et al. (2001) studied the effects of a caffeinated taurine drink, but saw no effect of this drink on memory. Some studies even found a negative effect of caffeine on short-term memory. A moderate dose of caffeine impaired motor sequence learning and declarative verbal memory (Mednick et al. 2008). Caffeine also impaired word recall in an auditory-verbal learning test (Terry & Phifer 1986). Kim et al. (2021) did not find a significant effect of coffee consumption on short-term memory. However, they did find a significant improvement of working memory after coffee consumption (Table 1). fMRI studies have shown that acute caffeine intake enhances working memory-related brain activation (Koppelstaetter et al. 2008; Haller et al. 2013). Smith et al. (1999) concluded that caffeine consumption had no effect on initial working memory, but improved encoding of new information. Rees et al. (1999), on the other hand, found a small but significant improvement in working memory after caffeine consumption. Schmitt et al. (2003) found no effect of caffeine on either short-term memory or long-term memory.

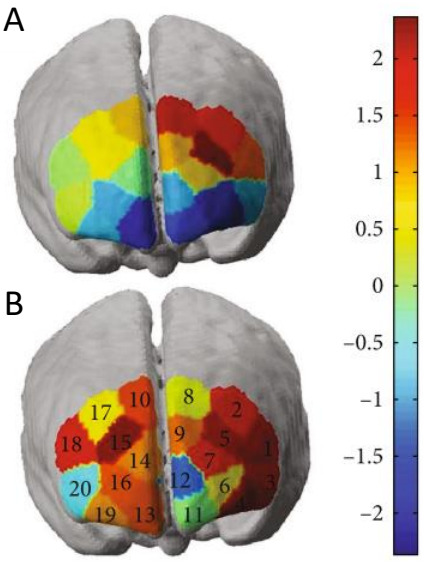

Figure 1. Brain activation during a Stroop task with or without coffee consumption. The figure shows a t-statistic map for Oxy-Hb. **A**. Brain activity during a Stroop task without caffeine consumption. **B**. Brain activity during a Stroop task after coffee consumption. More channels were activated during the Stroop task after coffee consumption (for a specification of the channel numbers see Yuan et al. 2020). Adapted from Yuan et al. (2020).

In conclusion, it seems like caffeine mainly has a positive effect on attention, but there is little evidence that it is able to improve short-term or long-term memory. However, studying the effects of pure caffeine in humans is very difficult. Many drinks and foods that are consumed on a daily basis contain caffeine. Creating a control group of people that have consumed no caffeine at all is therefore almost impossible, and if participants are instructed to avoid caffeine before participating in the experiment, the performance on cognitive tasks might be affected by caffeine withdrawal (Nehlig 2010). Therefore, it is hard to draw a conclusion on the effect of caffeine consumption on cognition. To have more control over the caffeine dosages and other factors that might influence the outcome of behavioural tests, the effect of caffeine on memory has been tested in animals. Testing the effects of caffeine in rodents can tell us more about the possibilities of caffeine as a treatment in Alzheimer's disease. In the next section, studies on the effect of caffeine on learning and memory in rodents will be discussed.

Table 1. Effect of coffee consumption on performance in neuropsychological tests. Performance in the Digit Span Test and Trail Making Test were significantly improved after coffee consumption, indicating an improvement in attention, working memory and executive function. No effect of coffee consumption on global function or short-term memory was seen. Adapted from Kim et al. (2021).

	Baseline	After coffee consumption	P value
<Global function>			
Mini-mental status examination (correct/30 items)	30	30	–
<Attention and working memory>			
Digit Span Test forward (correct/9 digits)	8.52 ± 0.75	8.95 ± 0.22	0.025
Digit Span Test backward (correct/8 digits)	6.24 ± 1.76	7.29 ± 1.10	0.001
Target Detection Task (correct/11 syllable targets)	11	11	–
<Executive function>			
Trail Making Test Part B (s)	5.80 ± 1.41	4.87 ± 1.17	0.002
<Memory>			
Short-term memory recall (correct/5 words)	5	5	–
Delayed recall (correct/5 words)	4.57 ± 0.68	4.81 ± 0.40	0.135

3. Experimental studies on the effects of caffeine in rodents

3.1 Effect of caffeine on learning and memory in rodents

There is some controversy about the effect of caffeine on learning and memory in rodents. Some studies show that caffeine, in contrast to what is often believed, impairs memory retention in rodents (Angelucci et al. 1999). Mice that were given caffeine before acquisition or retrieval in a fear condition test showed impaired conditioning (Dubroqua et al. 2015). A study by Sanday et al. (2013) found that moderate pre-training caffeine administration (20 mg/kg) impaired memory retention. However, pre-test administration of caffeine was able to counteract this memory deficit. They also demonstrated that caffeine had an anxiogenic effect. Mice that were given a moderate dose of caffeine for one week (20 mg/kg) performed significantly better in a water maze than control mice or mice that were given a high dosage of caffeine (200 mg/kg) (Almosawi et al. 2018; Mahdi et al. 2019; Figure 2). Poole et al. (2016) showed that chronic caffeine at 1.0 mg/ml enhanced contextual conditioning in pre-adolescent and adolescent mice, whereas chronic caffeine at 3.0 mg/ml led to deficits in contextual conditioning in pre-adolescent and adolescent mice. However, they did not find any significant effects of caffeine in adult mice.

In rats, caffeine seems to disrupt the acquisition of hippocampal-dependent learning (Corodimas et al. 2000). Another study in rats showed that moderate and high dosage of caffeine (0,3 mg/ml and 1,0 mg/ml) improved performance in an object recognition task (Ardais et al. 2014). However, when given the dosage of 1,0 mg/ml, rats did not habituate when tested in an open field test. Not being able to habituate is a sign of non-associative memory

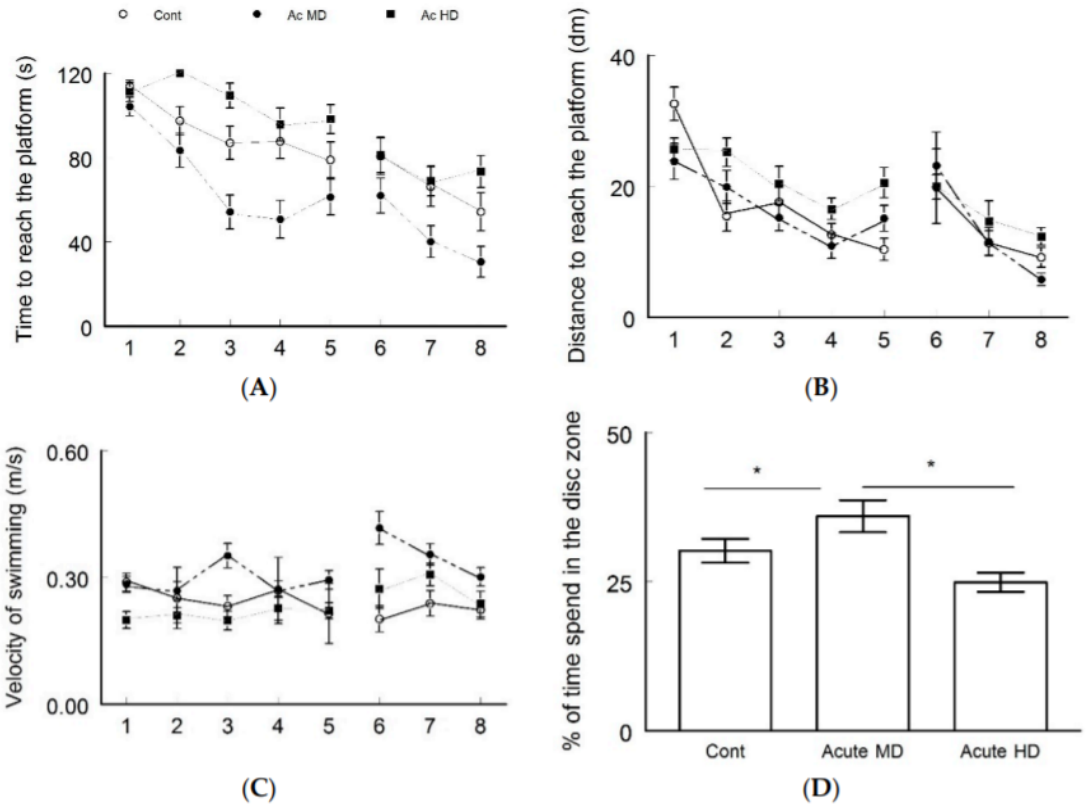

Figure 2. Performance of mice in the Morris water maze after no caffeine (Cont), moderate caffeine (Ac MD) or high caffeine (Ac HD) dosage. A. Time to reach the platform. The Ac MD group showed a lower latency compared to the Cont or Ac HD group. **B**. Distance to reach the platform. The Ac MD group showed a shorter distance to reach the platform. **C**. Velocity of swimming (m/s). The velocity of swimming was the highest in the Ac MD group **D**. Percentage of time spent in the disc zone. The Ac MD group spent significantly more time in the disc zone than the Cont or Ac HD group ($P < 0,05$). Adapted from Almosawi et al. (2018).

impairment. Rats that were given chronic caffeine from a young age (6 months in a row, starting at the age of 4 months) showed less cognitive decline at a later age compared to control rats (Vila-Luna et al. 2012). Angelucci et al. (2002) found that post-training administration of 0.3-10 mg/kg caffeine improved memory retention in the Morris water maze. However, when given a dosage of 30 mg/kg caffeine post-training, no improvement in memory was found. Pre-test caffeine administration also caused a small increase in memory retrieval, while pre-training caffeine did not have any effect on performance. In 12 and 18 month-old rats that exhibited significantly impaired olfactory discrimination and short-term social memory, acute caffeine administration was able to reverse olfactory deficits (Prediger et al. 2005).

It seems that caffeine can increase learning and memory in rodents, but only when given a moderate or high dosage. Furthermore, the effect seems to be dependent on the age of the animals. These results do not provide strong evidence for cognition-enhancing effects of caffeine. However, these studies have been using wildtype animals. It might be possible that lower dosages of coffee do not improve normal levels of cognition, but can reverse memory deficits in animal models of Alzheimer's disease. To test this hypothesis, the effect of caffeine on learning and memory has been studied in animal models of AD, as described in the next section.

3.2 Effects of caffeine on cognitive impairments in animal models of AD

There are three genes that have been associated with familial AD: PS1, PS2 and APP. The APP gene codes for amyloid precursor protein (APP), which is cleaved into Aβ molecules (Ridge 2013). Mutations in this gene can lead to an increased formation of insoluble $A\beta_{1-42}$ molecules, which are able to self-aggregate and form plaques (Sleegers et al. 2006). Similarly, mutations in the genes presenilin 1 (PS1) and presenilin 2 (PS2) increase the formation of formation of $A\beta_{1-42}$ molecules (Ridge et al. 2013). Mouse models of AD are therefore often created by manipulating these genes.

One of the most studied AD mouse models is the Swedish mutation transgenic mouse (APPsw Tg mouse). APPsw mice show increased Aβ production (Esquerda-Canals et al. 2017), and show learning and memory impairments at a later age (Hsiao et al. 1996; Evans et al. 2020). The APPsw mice are therefore commonly used the study the effect of caffeine on cognition in AD. A study by Arendash et al. (2006) found that APPsw mice that were given 1,5 mg of caffeine daily (comparable to 500 mg in humans) performed significantly better on tasks requiring spatial learning/reference memory, working memory, and recognition/identification. Not only was caffeine able to prevent Aβ-induced cognitive impairments, it also reversed cognitive impairments in aged APPsw mice that already showed cognitive symptoms (Arendash et al. 2009; Figure 3). In animals with both Swedish and Indiana familial APP mutations, both pure caffeine and crude-caffeine (a by-product of the decaffeination of coffee) were able to partially prevent memory impairment (Chu et al. 2012). In PS1/APP double transgenic mouse, a daily caffeine dose of 0,75 mg or 1,5 mg per day was able to reverse memory impairment in a water maze (Han et al. 2013).

Alzheimer's disease is not only characterized by Aβ plaques, but also by tau aggregates. One of the most commonly used models of tau pathology is the THY-Tau22 mouse model. THY-Tau22 mice show major tau expression in the hippocampus and are therefore a good model to study the effects of AD on the hippocampus and cognition (Schindowski et al. 2006). Chronic caffeine intake is able to prevent the development of spatial memory deficits in THY-Tau22 mice (Laurent et al. 2014). However, no other studies have investigated the effect of caffeine on cognitive performance in this mouse model.

Next to transgenic mouse models of AD, the effects of caffeine have also been investigated in non-transgenic AD rodent models. One study shows that in mice that have been injected with Aβ, caffeine prevented Aβ-induced cognitive impairments (Dall'Igna et al. 2007). Another non-transgenic model is D-galactose. Administration of D-galactose induces oxidative stress, which leads to memory impairments and neurodegeneration (Wei et al. 2005; Cui et al. 2006). Chronic treatment with caffeine (3 mg/kg/day) improved memory impairments in D-galactose rats (Ullah et al. 2015). Espinosa et al. (2013) studied the effect of caffeine on rats after intracerebroventricular streptozotocin (STZ) administration. STZ administration induces memory deficits and is therefore a model for sporadic AD. Caffeine (1 g/L) prevented STZ-induced memory impairments in rats.

Overall, we can conclude that caffeine is able to improve memory in animal models of AD. Not only does it seem to prevent the development of memory deficits, it also has been shown to reverse memory impairments in AD models. These results suggest that caffeine might be able to reverse memory impairments in patients with AD as well. The question remains how caffeine is able to have neuroprotective and cognition-enhancing effects in animal models of AD. Investigation of the molecular mechanisms underlying these effects tells us more about how caffeine affects cognition, and whether caffeine is able to mimic current treatments for AD.

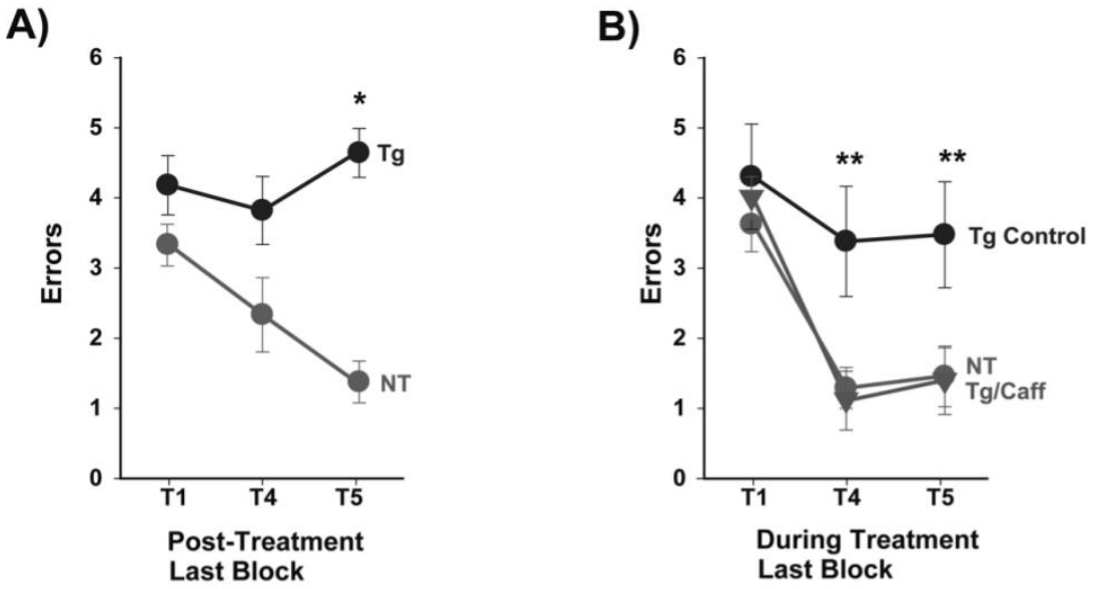

Figure 3. Effect of caffeine on memory impairment in aged APPsw mice. A. Number of errors of non-transgenic mice (NT) and APPsw mice (Tg) in the radial arm maze prior to caffeine treatment. The Tg mice showed significantly more errors than the NT mice ($P < 0{,}000005$). **B**. Number of errors of NT, Tg and Tg + caffeine mice 4-5 weeks into caffeine treatment. The Tg mice that did not receive caffeine treatment showed significantly more errors than both the NT and Tg + caffeine mice ($P < 0{,}025$). Adapted from Arendash et al. (2009).

4. Molecular mechanisms of caffeine

4.1 The role of adenosine A2A receptors in cognitive impairments

One way in which caffeine affects cognition is through adenosine A2A receptors (A2AR). Caffeine is an antagonist of the A2A receptor. There is numerous evidence that the A2AR plays a role in memory dysfunction. Adenosine A2A receptor blockade is able to prevent memory impairment induced by $A\beta_{1\text{-}42}$ (insoluble Aβ) administration in rodents (Cunha et al. 2008; Canas et al. 2009). Overexpression of A2AR increases tau hyperphosphorylation in THY-Tau22, leading to tau-induced memory deficits (Carvalho et al. 2019). It has also been shown that upregulation of A2AR abolishes long-term synaptic potentiation, which could be reversed by A2AR antagonists (Da Silva et al. 2016). Treatment with A2AR antagonist MSX-3 prevented the development of cognitive deficits in APP/PS1dE9 mice (Faivre et al. 2018).

The role of A2AR in memory is also shown by deletion of this receptor. In A2AR knock out mice, performance in the Morris water maze and radial arm maze was improved compared to wildtype mice (Zhou et al. 2009). It has also been shown that A2AR deletion in mice improves spatial recognition memory (Wang et al. 2006). Selective A2AR deletion in the forebrain or striatum enhanced working memory and reversal learning in mice (Wei et al. 2011). This study however, in contrast to Wang et al. (2006), did not find an effect of A2AR deletion on spatial memory. A2A receptor deletion also seems to have beneficial effects in animal models of AD. Deleting A2A receptors protects THY-Tau22 mice from Tau pathology-induced memory deficits (Laurent et al. 2016). Overall, it seems that overexpression of A2AR leads to cognitive deficits, while deletion of the receptor reverses or prevents memory impairments. It

is therefore likely that the antagonistic action of caffeine on the A2A receptor improves memory in animal models of AD.

4.2 Reduction of amyloid-β and neuroinflammation

As described in the previous section, the main hallmark of AD is the formation of Aβ plaques. These plaques, that are also referred to as senile plaques, are mainly present in the hippocampus of AD patients (Cheignon et al. 2018) and can lead to memory impairment. Furthermore, Aβ is thought to have pro-inflammatory effects (Tuppo & Arias 2005). Reducing Aβ levels in the hippocampus would therefore be an ideal treatment for cognitive impairments in AD.

Long-term caffeine administration is able to reduce Aβ levels in the hippocampi and plasma of APPsw mice (Arendash et al. 2006; Cao et al. 2009; Figure 4). Even in aged APPsw mice that already showed cognitive dysfunction, caffeine was able to reduce Aβ levels and reverse cognitive impairment (Arendash et al. 2009). In cultured cells, treatment with caffeine prevented Aβ-induced neuronal cell death (Dall'Igna et al. 2003). A study by Li et al. (2015) found that caffeine suppresses adenosine A3 receptor (A3R)-mediated internalization of Aβ. Caffeine also increases expression of P-glycoprotein, a protein that is involved in Aβ clearance (Qosa et al. 2012). However, Mancini et al. (2018) found no effect of caffeine on Aβ aggregation.

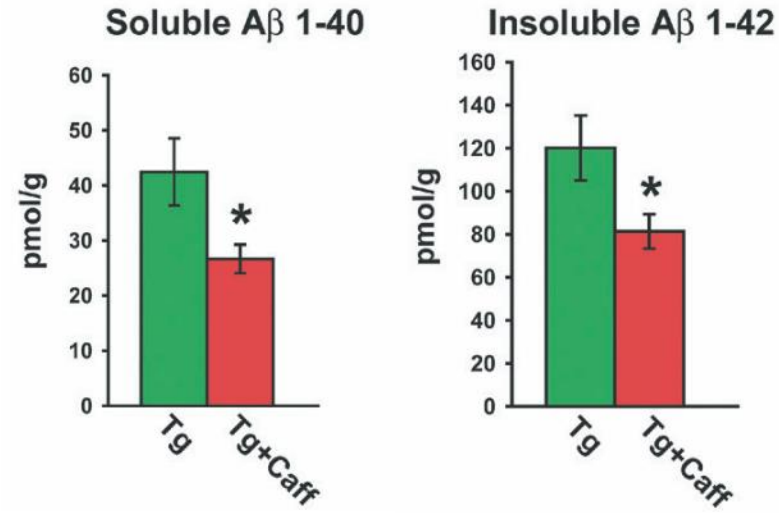

Figure 4. Levels of soluble and insoluble Aβ in the hippocampus of transgenic mice. Caffeine administration significantly lowered both soluble and insoluble Aβ levels in the hippocampus of transgenic mice. Adapted from Arendash et al. (2006).

Other hallmarks of Alzheimer's disease are the activation of microglia and neuroinflammation (Lull et al. 2010). Neuroinflammation can lead to neurodegeneration. Inhibiting neuroinflammation might prevent the progression of AD and reduce symptoms. Studies have shown that caffeine is able to inhibit neuroinflammation. A measurement of cytokines in human blood showed that caffeine supresses the production of proinflammatory cytokine TNF-α (Horrigan et al. 2004). In rats, caffeine significantly inhibited sleep deprivation-induced inflammation by down-regulating the pro-inflammatory cytokines and up-regulating the anti-inflammatory cytokines (Wadhwa et al. 2018). Caffeine also reduced microglial immunoreactivity in the hippocampal areas of these rats. Another study shows that caffeine is able to restore increased TNF-α levels that are the result of aluminium chloride-induced neurotoxicity (Hosny et al. 2019). In rodents with lipopolysaccharide-induced

neuroinflammation, caffeine reduced the number of activated microglia in the hippocampus as well as brain cytokine levels (Brothers et al. 2010; Basu Mallik et al. 2021). Furthermore, caffeine was able to fully prevent 3,4-methylenedioxymethamphetamine (MDMA)-induced activation of microglia and astroglia (Ruiz-Medina et al. 2013).

The anti-inflammatory effect of caffeine has also been shown in AD models. In transgenic AD mice, higher plasma caffeine levels were associated with lower inflammatory cytokine levels in hippocampus (Cao et al. 2009). Caffeine treatment also reduced several proinflammatory markers that were upregulated in the hippocampus of THY-Tau22 mice (Laurent et al. 2014). D-galactose-induced neuroinflammation was reduced by caffeine through reduction of inflammatory mediators COX-2, NOS-2, TNFα and IL-1β (Ullah et al. 2015).

In summary, caffeine seems to improve cognition and AD pathology in three ways: 1) by antagonism of A2A receptors, 2) by increasing AB clearance, thereby inhibiting microglia activation, and 3) by lowering the levels of pro-inflammatory cytokines (Figure 5). These pathways are not targeted by the current treatments for AD. Caffeine might therefore have beneficial effects in AD by targeting the pathology directly, instead of only relieving cognitive symptoms.

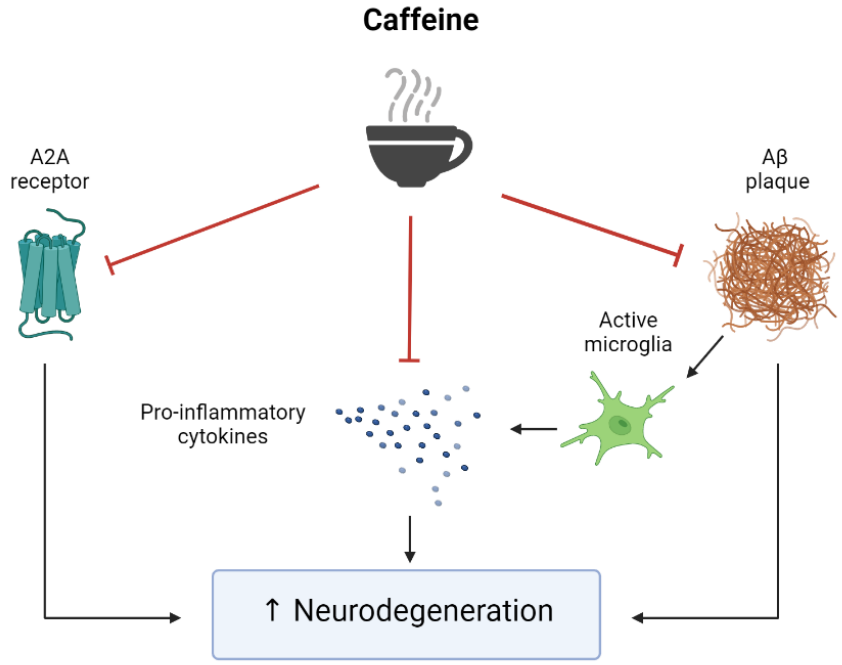

Figure 5. Effects of caffeine on molecular and cellular hallmarks of Alzheimer's disease. Three pathways that lead to neurodegeneration in AD are 1) activation of A2A receptors, 2) activation of microglia, which leads to an increase in pro-inflammatory cytokines, and 3) formation of Aβ plaques. Studies have shown that caffeine blocks A2A receptor responses, inhibits inflammatory responses by reducing the level of pro-inflammatory cytokines, and reduces Aβ levels. These mechanisms are likely associated with the neuroprotective and cognition-enhancing effects of caffeine in animal models of AD. Created in BioRender (www.biorender.com).

5. Discussion

In this review, several aspects of the association between caffeine, cognition and Alzheimer's disease have been discussed: 1) epidemiological studies on the association between caffeine and AD, 2) the cognition-enhancing effects of caffeine in humans, 3) the cognition-enhancing effects of caffeine in rodents, 4) the effect of caffeine on AD pathology in animal models for AD, and 5) the molecular mechanisms of cognitive improvement by caffeine. Although the results of experiments are inconclusive, caffeine might have some beneficial effects on cognition. In healthy subjects, caffeine did not always improve cognition, and sometimes it even worsened learning and memory. However, in animal models for AD, caffeine is able to both prevent and reverse cognitive deficits. Furthermore, there is evidence that caffeine is able to reduce Aβ levels and neuroinflammation, which are hallmarks of AD.

As discussed in the introduction, there are currently only four drugs for Alzheimer's disease that are approved by The U.S. Food and Drug Administration (FDA): rivastigmine, galantamine, donepezil and memantine (Alzheimer's Association 2021). As stated in the introduction, the problem with these drugs is that they do not slow down the progression of the disease, but only improve cognitive symptoms temporarily (Fish et al. 2019). Furthermore, most drugs are only effective in early stages of AD. Memantine is the only drug that works as a treatment for severe AD (Reisberg et al. 2003). As discussed in this review, caffeine does not only relieve cognitive symptoms in animal models of AD, it also seems to act directly on the pathology by decreasing Aβ levels and neuroinflammation (Arendash et al. 2006; Han et al. 2013; Dall'Igna et al. 2007). Another benefit of caffeine as a treatment for AD is that caffeine, in contrast to many other potential AD treatments, can cross the blood brain barrier (McCall et al. 1982; Banks 2012). This means that no high dosage of caffeine is needed to have an effect on the brain. Furthermore, caffeine is cheap and very easy to consume. There are many foods and drinks that contain different levels of caffeine. Since most studies show that moderate caffeine consumption has the most beneficial effects on cognition, simple dietary interventions leading to increased caffeine consumption might be sufficient to improve cognitive symptoms in patients with AD.

Unfortunately, the effects of caffeine on cognition and memory in patients with AD remain unknown. The human studies discussed in this review either focussed on cognition-enhancing effects of caffeine in healthy subjects, or on the association between caffeine and the risk of developing AD. The ability of caffeine to reverse memory impairment has only been tested in animal models of AD. However, it has been shown that caffeine is able to improve scopolamine-induced memory impairment in humans (Riedel et al. 1995). Even though no correlation has been found between caffeine consumption and Aβ levels in patients with AD (Travassos et al. 2015), it might still have beneficial effects due to the antagonistic effects of caffeine on A2A receptors and the reduction of pro-inflammatory cytokines. Improvement of cognitive functioning through caffeine consumption could be a cheap and easy way to improve the quality of life of patients with AD, as well as the lives of their relatives and caregivers. Therefore, it could be worth starting clinical trials with caffeine as a treatment for AD.

It should be noted that there is a difference between coffee and pure caffeine. Coffee contains many more substances that might have an effect on cognition. 5-caffeoylquinic acid, a coffee polyphenol, has been proven to improve cognitive functioning and reduce Aβ plaque formation in APP/PS2 transgenic mice (Ishida et al. 2020). Another component of coffee, eicosanoyl-5-hydroxytryptamide, was able to improve cognitive functioning in different rodent models for AD (Basurto-Islas et al. 2014; Asam et al. 2017). It would therefore be interesting to compare the effects of pure caffeine and coffee on cognition in patients with AD. The effect of caffeine also depends on the dosage. In general, higher levels of coffee consumption are

associated with a reduced risk of developing AD (Pham et al. 2021). However, experimental studies in rodents show that when caffeine levels are too high, caffeine either has no effect on memory or can even impair memory (Angelucci et al. 2002; Almosawi et al. 2018; Mahdi et al. 2019). In humans, it is on average safe to consume 400 mg of caffeine per day without experiencing adverse effects (Nawrot et al. 2003). More research is needed to find the optimal dosage of caffeine to improve cognitive impairments in AD without exceeding the 400 mg/day limit.

In conclusion, caffeine potentially has beneficial effects on cognition in patients with Alzheimer's disease. Although there is no clear evidence that caffeine has beneficial effects on memory in healthy humans, caffeine seems to have both neuroprotective effects and cognition-enhancing effects in animal models of AD through A2A receptor antagonism, reduction of Aβ levels and inhibition of neuroinflammation. If the same findings could be replicated in patients with AD, this would be a great step towards treatment of cognitive impairments in AD. Caffeine consumption could be increased in patients with AD by simple dietary interventions. This makes caffeine a cheap and efficient potential therapy for AD, with minimal side effects. In order to gain more insight in the potential of caffeine as a treatment for AD, it is crucial to investigate the effect of caffeine in patients with AD.

References:

2021 alzheimer's disease facts and figures. (2021). Alzheimer's & Dementia : The Journal of the Alzheimer's Association, 17(3), 327–406.

Adan, A., & Serra-Grabulosa, J. M. (2010). Effects of caffeine and glucose, alone and combined, on cognitive performance. Human Psychopharmacology: Clinical and Experimental, 25(4), 310-317.

Almosawi, S., Baksh, H., Qareeballa, A., Falamarzi, F., Alsaleh, B., Alrabaani, M., ... & Kamal, A. (2018). Acute administration of caffeine: The effect on motor coordination, higher brain cognitive functions, and the social behavior of BLC57 mice. Behavioral Sciences, 8(8), 65.

Angelucci, M. E. M., Cesario, C., Hiroi, R. H., Rosalen, P. L., & Cunha, C. D. (2002). Effects of caffeine on learning and memory in rats tested in the Morris water maze. Brazilian Journal of medical and biological Research, 35(10), 1201-1208.

Angelucci, M. E., Vital, M. A., Cesário, C., Zadusky, C. R., Rosalen, P. L., & Da Cunha, C. (1999). The effect of caffeine in animal models of learning and memory. European journal of pharmacology, 373(2-3), 135-140.

Ardais, A. P., Borges, M. F., Rocha, A. S., Sallaberry, C., Cunha, R. A., & Porciúncula, L. O. (2014). Caffeine triggers behavioral and neurochemical alterations in adolescent rats. Neuroscience, 270, 27-39.

Arendash, G. W., Mori, T., Cao, C., Mamcarz, M., Runfeldt, M., Dickson, A., ... & Potter, H. (2009). Caffeine reverses cognitive impairment and decreases brain amyloid-β levels in aged Alzheimer's disease mice. Journal of Alzheimer's disease, 17(3), 661-680.

Arendash, G. W., Schleif, W., Rezai-Zadeh, K., Jackson, E. K., Zacharia, L. C., Cracchiolo, J. R., ... & Tan, J. (2006). Caffeine protects Alzheimer's mice against cognitive impairment and reduces brain β-amyloid production. Neuroscience, 142(4), 941-952.

Arnold, S. E., Hyman, B. T., Flory, J., Damasio, A. R., & Van Hoesen, G. W. (1991). The topographical and neuroanatomical distribution of neurofibrillary tangles and neuritic plaques in the cerebral cortex of patients with Alzheimer's disease. Cerebral cortex, 1(1), 103-116.

Asam, K., Staniszewski, A., Zhang, H., Melideo, S. L., Mazzeo, A., Voronkov, M., ... &

Nicholls, R. E. (2017). Eicosanoyl-5-hydroxytryptamide (EHT) prevents Alzheimer's disease-related cognitive and electrophysiological impairments in mice exposed to elevated concentrations of oligomeric beta-amyloid. PLoS One, 12(12), e0189413.

Balko, S., Simonek, J., Balko, I., Heller, J., Chytry, V., Balogova, K., & Gronek, P. (2020). The influence of different caffeine doses on visual and audial reaction time with different delay from its consumption. Science & Sports, 35(6), 358-363.

Banks, W. A. (2012). Drug delivery to the brain in Alzheimer's disease: Consideration of the blood–brain barrier. Advanced drug delivery reviews, 64(7), 629-639.

Basu Mallik, S., Mudgal, J., Hall, S., Kinra, M., Grant, G. D., Nampoothiri, M., ... & Arora, D. (2021). Remedial effects of caffeine against depressive-like behaviour in mice by modulation of neuroinflammation and BDNF. Nutritional Neuroscience, 1-9.

Basurto-Islas, G., Blanchard, J., Tung, Y. C., Fernandez, J. R., Voronkov, M., Stock, M., ... & Iqbal, K. (2014). Therapeutic benefits of a component of coffee in a rat model of Alzheimer's disease. Neurobiology of aging, 35(12), 2701-2712.

Brothers, H. M., Marchalant, Y., & Wenk, G. L. (2010). Caffeine attenuates lipopolysaccharide-induced neuroinflammation. Neuroscience letters, 480(2), 97-100.

Brunyé, T. T., Mahoney, C. R., Lieberman, H. R., Giles, G. E., & Taylor, H. A. (2010). Acute caffeine consumption enhances the executive control of visual attention in habitual consumers. Brain and cognition, 74(3), 186-192.

Canas, P. M., Porciúncula, L. O., Cunha, G. M., Silva, C. G., Machado, N. J., Oliveira, J. M., ... & Cunha, R. A. (2009). Adenosine A2A receptor blockade prevents synaptotoxicity and memory dysfunction caused by β-amyloid peptides via p38 mitogen-activated protein kinase pathway. Journal of Neuroscience, 29(47), 14741-14751.

Cao, Chuanhai, John R. Cirrito, Xiaoyang Lin, Lilly Wang, Deborah K. Verges, Alexander Dickson, Malgorzata Mamcarz et al. "Caffeine suppresses amyloid-β levels in plasma and brain of Alzheimer's disease transgenic mice." Journal of Alzheimer's Disease 17, no. 3 (2009): 681-697.

Carvalho, K., Faivre, E., Pietrowski, M. J., Marques, X., Gomez-Murcia, V., Deleau, A., ... & Blum, D. (2019). Exacerbation of C1q dysregulation, synaptic loss and memory deficits in tau pathology linked to neuronal adenosine A2A receptor. Brain, 142(11), 3636-3654.

Cheignon, C., Tomas, M., Bonnefont-Rousselot, D., Faller, P., Hureau, C., & Collin, F. (2018). Oxidative stress and the amyloid beta peptide in Alzheimer's disease. Redox biology, 14, 450-464.

Chen, J. Q., Scheltens, P., Groot, C., & Ossenkoppele, R. (2020). Associations between caffeine consumption, cognitive decline, and dementia: a systematic review. Journal of Alzheimer's Disease, (Preprint), 1-28.

Chu, Yi-Fang, Wen-Han Chang, Richard M. Black, Jia-Ren Liu, Pradoldej Sompol, Yumin Chen, Huilin Wei, Qiuyan Zhao, and Irene H. Cheng. "Crude caffeine reduces memory impairment and amyloid β1–42 levels in an alzheimer's mouse model." Food chemistry 135, no. 3 (2012): 2095-2102.

Corodimas, K. P., Pruitt, J. C., & Stieg, J. M. (2000). Acute exposure to caffeine selectively disrupts context conditioning in rats. Psychopharmacology, 152(4), 376-382.

Cui, X. U., Zuo, P., Zhang, Q., Li, X., Hu, Y., Long, J., ... & Liu, J. (2006). Chronic systemic D-galactose exposure induces memory loss, neurodegeneration, and oxidative damage in mice: Protective effects of R-α-lipoic acid. Journal of neuroscience research, 83(8), 1584-1590.

Cunha, G. M., Canas, P. M., Melo, C. S., Hockemeyer, J., Müller, C. E., Oliveira, C. R., & Cunha, R. A. (2008). Adenosine A2A receptor blockade prevents memory dysfunction caused by β-amyloid peptides but not by scopolamine or MK-801. Experimental neurology, 210(2), 776-781.

Dall'Igna, O. P., Fett, P., Gomes, M. W., Souza, D. O., Cunha, R. A., & Lara, D. R. (2007). Caffeine and adenosine A2a receptor antagonists prevent β-amyloid (25–35)-induced cognitive deficits in mice. Experimental neurology, 203(1), 241-245.

Dall'Igna, O. P., Porciúncula, L. O., Souza, D. O., Cunha, R. A., & Lara, D. R. (2003). Neuroprotection by caffeine and adenosine A2A receptor blockade of β-amyloid neurotoxicity. British journal of pharmacology, 138(7), 1207-1209.

Da Silva, S. V., Haberl, M. G., Zhang, P., Bethge, P., Lemos, C., Gonçalves, N., ... & Mulle, C. (2016). Early synaptic deficits in the APP/PS1 mouse model of Alzheimer's disease involve neuronal adenosine A 2A receptors. Nature communications, 7(1), 1-11.

Dong, Xue, Shiru Li, Jing Sun, Yan Li, and Dongfeng Zhang. "Association of Coffee, Decaffeinated Coffee and Caffeine Intake from Coffee with Cognitive Performance in Older Adults: National Health and Nutrition Examination Survey (NHANES) 2011–2014." Nutrients 12, no. 3 (2020): 840.

Dubroqua, S., Low, S. R., Yee, B. K., & Singer, P. (2015). Caffeine impairs the acquisition and retention, but not the consolidation of Pavlovian conditioned freezing in mice. Psychopharmacology, 232(4), 721-731.

Einöther, S. J., & Giesbrecht, T. (2013). Caffeine as an attention enhancer: reviewing existing assumptions. Psychopharmacology, 225(2), 251-274.

Eskelinen, M. H., Ngandu, T., Tuomilehto, J., Soininen, H., & Kivipelto, M. (2009). Midlife coffee and tea drinking and the risk of late-life dementia: a population-based CAIDE study. Journal of Alzheimer's disease, 16(1), 85-91.

Espinosa, J., Rocha, A., Nunes, F., Costa, M. S., Schein, V., Kazlauckas, V., ... & Porciuncula, L. O. (2013). Caffeine consumption prevents memory impairment, neuronal damage, and adenosine A 2A receptors upregulation in the hippocampus of a rat model of sporadic dementia. Journal of Alzheimer's Disease, 34(2), 509-518.

Esquerda-Canals, Gisela, Laia Montoliu-Gaya, Jofre Güell-Bosch, and Sandra Villegas. "Mouse models of Alzheimer's disease." Journal of Alzheimer's Disease 57, no. 4 (2017): 1171-1183.

Evans, C. E., Miners, J. S., Piva, G., Willis, C. L., Heard, D. M., Kidd, E. J., ... & Kehoe, P. G. (2020). ACE2 activation protects against cognitive decline and reduces amyloid pathology in the Tg2576 mouse model of Alzheimer's disease. Acta neuropathologica, 139(3), 485-502.

Faivre, E., Coelho, J. E., Zornbach, K., Malik, E., Baqi, Y., Schneider, M., ... & Blum, D. (2018). Beneficial effect of a selective adenosine A2A receptor antagonist in the APPswe/PS1dE9 mouse model of Alzheimer's disease. Frontiers in molecular neuroscience, 11, 235.

Fish, P. V., Steadman, D., Bayle, E. D., & Whiting, P. (2019). New approaches for the treatment of Alzheimer's disease. Bioorganic & medicinal chemistry letters, 29(2), 125-133.

Gelber, R. P., Petrovitch, H., Masaki, K. H., Ross, G. W., & White, L. R. (2011). Coffee intake in midlife and risk of dementia and its neuropathologic correlates. Journal of Alzheimer's disease, 23(4), 607-615.

Haller, S., Montandon, M. L., Rodriguez, C., Herrmann, F. R., & Giannakopoulos, P. (2018). Impact of coffee, wine, and chocolate consumption on cognitive outcome and MRI parameters in old age. Nutrients, 10(10), 1391.

Haller, S., Rodriguez, C., Moser, D., Toma, S., Hofmeister, J., Sinanaj, I., ... & Lovblad, K. O. (2013). Acute caffeine administration impact on working memory-related brain activation and functional connectivity in the elderly: a BOLD and perfusion MRI study. Neuroscience, 250, 364-371.

Hameleers, P. M., Van Boxtel, M. J., Hogervorst, E., Riedel, W. J., Houx, P. J., Buntinx, F., & Jolles, J. (2000). Habitual caffeine consumption and its relation to memory, attention, planning capacity and psychomotor performance across multiple age groups. Human Psychopharmacology: Clinical and Experimental, 15(8), 573-581.

Han, K., Jia, N., Li, J., Yang, L., & Min, L. Q. (2013). Chronic caffeine treatment reverses memory impairment and the expression of brain BNDF and TrkB in the PS1/APP double transgenic mouse model of Alzheimer's disease. Molecular medicine reports, 8(3), 737-740.

Heckman, M. A., Weil, J., & De Mejia, E. G. (2010). Caffeine (1, 3, 7-trimethylxanthine) in foods: a comprehensive review on consumption, functionality, safety, and regulatory matters. Journal of food science, 75(3), R77-R87.

Hewlett, P., & Smith, A. (2007). Effects of repeated doses of caffeine on performance and alertness: new data and secondary analyses. Human Psychopharmacology: Clinical and Experimental, 22(6), 339-350.

Horrigan, L. A., Kelly, J. P., & Connor, T. J. (2004). Caffeine suppresses TNF-α production via

activation of the cyclic AMP/protein kinase A pathway. International immunopharmacology, 4(10-11), 1409-1417.
Hosny, E. N., Sawie, H. G., Elhadidy, M. E., & Khadrawy, Y. A. (2019). Evaluation of antioxidant and anti-inflammatory efficacy of caffeine in rat model of neurotoxicity. Nutritional neuroscience, 22(11), 789-796.
Hsiao, K., Chapman, P., Nilsen, S., Eckman, C., Harigaya, Y., Younkin, S., ... & Cole, G. (1996). Correlative memory deficits, Aβ elevation, and amyloid plaques in transgenic mice. Science, 274(5284), 99-103.
Inglis, F. (2002). The tolerability and safety of cholinesterase inhibitors in the treatment of dementia. International journal of clinical practice. Supplement, (127), 45-63
Ishida, K., Misawa, K., Nishimura, H., Hirata, T., Yamamoto, M., & Ota, N. (2020). 5-Caffeoylquinic acid ameliorates cognitive decline and reduces Aβ deposition by modulating Aβ clearance pathways in APP/PS2 transgenic mice. Nutrients, 12(2), 494.
Jack Jr, C. R. (2011). Alliance for aging research AD biomarkers work group: structural MRI. Neurobiology of aging, 32, S48-S57.
Jarvis, M. J. (1993). Does caffeine intake enhance absolute levels of cognitive performance?. Psychopharmacology, 110(1), 45-52.
Kahathuduwa, C. N., Dassanayake, T. L., Amarakoon, A. T., & Weerasinghe, V. S. (2017). Acute effects of theanine, caffeine and theanine–caffeine combination on attention. Nutritional neuroscience, 20(6), 369-377.
Khoury, R., Rajamanickam, J., & Grossberg, G. T. (2018). An update on the safety of current therapies for Alzheimer's disease: focus on rivastigmine. Therapeutic advances in drug safety, 9(3), 171-178.
Kim, H., Kang, S. H., Kim, S. H., Kim, S. H., Hwang, J., Kim, J. G., ... & Kim, J. B. (2021). Drinking coffee enhances neurocognitive function by reorganizing brain functional connectivity. Scientific Reports, 11(1), 1-11.
Koppelstaetter, F., Poeppel, T. D., Siedentopf, C. M., Ischebeck, A., Verius, M., Haala, I., ... & Krause, B. J. (2008). Does caffeine modulate verbal working memory processes? An fMRI study. Neuroimage, 39(1), 492-499.
Lane, C. A., Hardy, J., & Schott, J. M. (2018). Alzheimer's disease. European journal of neurology.
Larsson, S. C., & Orsini, N. (2018). Coffee consumption and risk of dementia and Alzheimer's disease: A dose-response meta-analysis of prospective studies. Nutrients, 10(10), 1501.
Larsson, S. C., & Wolk, A. (2018). The role of lifestyle factors and sleep duration for late-onset dementia: A cohort study. Journal of Alzheimer's Disease, 66(2), 579-586.
Laurent, C., Burnouf, S., Ferry, B., Batalha, V. L., Coelho, J. E., Baqi, Y., ... & Blum, D. (2016). A 2A adenosine receptor deletion is protective in a mouse model of Tauopathy. Molecular psychiatry, 21(1), 97-107.
Laurent, C., Eddarkaoui, S., Derisbourg, M., Leboucher, A., Demeyer, D., Carrier, S., ... & Blum, D. (2014). Beneficial effects of caffeine in a transgenic model of Alzheimer's disease-like tau pathology. Neurobiology of aging, 35(9), 2079-2090.
Li, S., Geiger, N. H., Soliman, M. L., Hui, L., Geiger, J. D., & Chen, X. (2015). Caffeine, Through Adenosine A 3 Receptor-Mediated Actions, Suppresses Amyloid-β Protein Precursor Internalization and Amyloid-β Generation. Journal of Alzheimer's Disease, 47(1), 73-83.
Lindsay, J., Laurin, D., Verreault, R., Hébert, R., Helliwell, B., Hill, G. B., & McDowell, I. (2002). Risk factors for Alzheimer's disease: a prospective analysis from the Canadian Study of Health and Aging. American journal of epidemiology, 156(5), 445-453.
Loftfield, E., Freedman, N. D., Graubard, B. I., Guertin, K. A., Black, A., Huang, W. Y., ... & Sinha, R. (2015). Association of coffee consumption with overall and cause-specific mortality in a large US prospective cohort study. American journal of epidemiology, 182(12), 1010-1022.
Loke, W. H. (1988). Effects of caffeine on mood and memory. Physiology & behavior, 44(3), 367-372.
Londzin, P., Zamora, M., Kąkol, B., Taborek, A., & Folwarczna, J. (2021). Potential of Caffeine in Alzheimer's Disease—A Review of Experimental Studies. Nutrients, 13(2), 537.
Lorist, M. M., Snel, J., Mulder, G., & Kok, A. (1995). Aging, caffeine, and information

processing: an event-related potential analysis. Electroencephalography and Clinical Neurophysiology/Evoked Potentials Section, 96(5), 453-467.
Lull, M. E., & Block, M. L. (2010). Microglial activation and chronic neurodegeneration. Neurotherapeutics, 7(4), 354-365.
Mahdi, S., Almosawi, S., Baksh, H., Qareeballa, A., Alsaleh, B., Falamarzi, F., ... & Kamal, A. (2019). Effect of chronic administration and withdrawal of caffeine on motor function, cognitive functions, anxiety, and the social behavior of BLC57 mice. International journal of health sciences, 13(2), 10.
Maia, L., & De Mendonça, A. (2002). Does caffeine intake protect from Alzheimer's disease?. European journal of neurology, 9(4), 377-382.
Mancini, R. S., Wang, Y., & Weaver, D. F. (2018). Phenylindanes in brewed coffee inhibit amyloid-beta and tau aggregation. Frontiers in neuroscience, 12, 735.
Masters, C. L., Simms, G., Weinman, N. A., Multhaup, G., McDonald, B. L., & Beyreuther, K. (1985). Amyloid plaque core protein in Alzheimer disease and Down syndrome. Proceedings of the National Academy of Sciences, 82(12), 4245-4249.
McCall, A. L., Millington, W. R., & Wurtman, R. J. (1982). Blood-brain barrier transport of caffeine: Dose-related restriction of adenine transport. Life sciences, 31(24), 2709-2715.
Mednick, S. C., Cai, D. J., Kanady, J., & Drummond, S. P. (2008). Comparing the benefits of caffeine, naps and placebo on verbal, motor and perceptual memory. Behavioural brain research, 193(1), 79-86.
Nawrot, P., Jordan, S., Eastwood, J., Rotstein, J., Hugenholtz, A., & Feeley, M. (2003). Effects of caffeine on human health. Food Additives & Contaminants, 20(1), 1-30.
Nehlig, A. (2010). Is caffeine a cognitive enhancer?. Journal of Alzheimer's Disease, 20(s1), S85-S94.
Park, S. Y., Freedman, N. D., Haiman, C. A., Le Marchand, L., Wilkens, L. R., & Setiawan, V. W. (2017). Association of coffee consumption with total and cause-specific mortality among nonwhite populations. Annals of internal medicine, 167(4), 228-235.
Pham, K., Mulugeta, A., Zhou, A., O'Brien, J. T., Llewellyn, D. J., & Hyppönen, E. (2021). High coffee consumption, brain volume and risk of dementia and stroke. Nutritional Neuroscience, 1-12.
Poole, R. L., Braak, D., & Gould, T. J. (2016). Concentration-and age-dependent effects of chronic caffeine on contextual fear conditioning in C57BL/6J mice. Behavioural brain research, 298, 69-77.
Poole, R., Kennedy, O. J., Roderick, P., Fallowfield, J. A., Hayes, P. C., & Parkes, J. (2017). Coffee consumption and health: umbrella review of meta-analyses of multiple health outcomes. bmj, 359.
Prediger, R. D., Batista, L. C., & Takahashi, R. N. (2005). Caffeine reverses age-related deficits in olfactory discrimination and social recognition memory in rats: involvement of adenosine A1 and A2A receptors. Neurobiology of aging, 26(6), 957-964.
Qosa, H., Abuznait, A. H., Hill, R. A., & Kaddoumi, A. (2012). Enhanced brain amyloid-β clearance by rifampicin and caffeine as a possible protective mechanism against Alzheimer's disease. Journal of Alzheimer's Disease, 31(1), 151-165.
Rees, K., Allen, D., & Lader, M. (1999). The influences of age and caffeine on psychomotor and cognitive function. Psychopharmacology, 145(2), 181-188.
Reidel, W., Hogervorst, E., Leboux, R. L. A. M., Verhey, F., Van Praag, H., & Jolles, J. (1995). Caffeine attenuates scopolamine-induced memory impairment in humans. Psychopharmacology, 122(2), 158-168.
Reisberg, B., Doody, R., Stöffler, A., Schmitt, F., Ferris, S., & Möbius, H. J. (2003). Memantine in moderate-to-severe Alzheimer's disease. New England Journal of Medicine, 348(14), 1333-1341.
Ridge, P. G., Ebbert, M. T., & Kauwe, J. S. (2013). Genetics of Alzheimer's disease. BioMed research international, 2013.
Ritchie, K., Carrière, I., De Mendonca, A., Portet, F., Dartigues, J. F., Rouaud, O., ... & Ancelin, M. L. (2007). The neuroprotective effects of caffeine: a prospective population study (the Three City Study). Neurology, 69(6), 536-545.

Ruiz-Medina, J., Pinto-Xavier, A., Rodríguez-Arias, M., Miñarro, J., & Valverde, O. (2013). Influence of chronic caffeine on MDMA-induced behavioral and neuroinflammatory response in mice. Psychopharmacology, 226(2), 433-444.

Ruxton, C. H. (2008). The impact of caffeine on mood, cognitive function, performance and hydration: a review of benefits and risks. Nutrition Bulletin, 33(1), 15-25.

Sanday, L., Zanin, K. A., Patti, C. L., Fernandes-Santos, L., Oliveira, L. C., Longo, B. M., ... & Frussa-Filho, R. (2013). Role of state-dependent learning in the cognitive effects of caffeine in mice. International journal of neuropsychopharmacology, 16(7), 1547-1557.

Santos, C., Lunet, N., Azevedo, A., de Mendonça, A., Ritchie, K., & Barros, H. (2010). Caffeine intake is associated with a lower risk of cognitive decline: a cohort study from Portugal. Journal of Alzheimer's Disease, 20(s1), S175-S185.

Schindowski, K., Bretteville, A., Leroy, K., Bégard, S., Brion, J. P., Hamdane, M., & Buée, L. (2006). Alzheimer's disease-like tau neuropathology leads to memory deficits and loss of functional synapses in a novel mutated tau transgenic mouse without any motor deficits. The American journal of pathology, 169(2), 599-616.

Schmitt, J. A., Hogervorst, E., Vuurman, E. F., Jolles, J., & Riedel, W. J. (2003). Memory functions and focussed attention in middle-aged and elderly subjects are unaffected by a low, acute dose of caffeine. The Journal of nutrition, health & aging, 7(5), 301-303.

Sleegers, K., Brouwers, N., Gijselinck, I., Theuns, J., Goossens, D., Wauters, J., ... & Broeckhoven, C. V. (2006). APP duplication is sufficient to cause early onset Alzheimer's dementia with cerebral amyloid angiopathy. Brain, 129(11), 2977-2983.

Smith, A. P., Clark, R., & Gallagher, J. (1999). Breakfast cereal and caffeinated coffee: effects on working memory, attention, mood, and cardiovascular function. Physiology & Behavior, 67(1), 9-17.

Solfrizzi, V., Panza, F., Imbimbo, B. P., D'Introno, A., Galluzzo, L., Gandin, C., ... & Scafato, E. (2015). Coffee consumption habits and the risk of mild cognitive impairment: the Italian longitudinal study on aging. Journal of Alzheimer's Disease, 47(4), 889-899.

Terry, W. S., & Phifer, B. (1986). Caffeine and memory performance on the AVLT. Journal of clinical psychology, 42(6), 860-863.

Travassos, M., Santana, I., Baldeiras, I., Tsolaki, M., Gkatzima, O., Sermin, G., ... & de Mendon, A. (2015). Does caffeine consumption modify cerebrospinal fluid amyloid-β levels in patients with Alzheimer's disease?. Journal of Alzheimer's Disease, 47(4), 1069-1078.

Tuppo, E. E., & Arias, H. R. (2005). The role of inflammation in Alzheimer's disease. The international journal of biochemistry & cell biology, 37(2), 289-305.

Ullah, F., Ali, T., Ullah, N., & Kim, M. O. (2015). Caffeine prevents d-galactose-induced cognitive deficits, oxidative stress, neuroinflammation and neurodegeneration in the adult rat brain. Neurochemistry international, 90, 114-124.

Van Gelder, B. M., Buijsse, B., Tijhuis, M., Kalmijn, S., Giampaoli, S., Nissinen, A., & Kromhout, D. (2007). Coffee consumption is inversely associated with cognitive decline in elderly European men: the FINE Study. European journal of clinical nutrition, 61(2), 226-232.

Vila-Luna, S., Cabrera-Isidoro, S., Vila-Luna, L., Juarez-Diaz, I., Bata-Garcia, J. L., Alvarez-Cervera, F. J., ... & Góngora-Alfaro, J. L. (2012). Chronic caffeine consumption prevents cognitive decline from young to middle age in rats, and is associated with increased length, branching, and spine density of basal dendrites in CA1 hippocampal neurons. Neuroscience, 202, 384-395.

Wadhwa, M., Chauhan, G., Roy, K., Sahu, S., Deep, S., Jain, V., ... & Panjwani, U. (2018). Caffeine and modafinil ameliorate the neuroinflammation and anxious behavior in rats during sleep deprivation by inhibiting the microglia activation. Frontiers in cellular neuroscience, 12, 49.

Wang, J. H., Ma, Y. Y., & van den Buuse, M. (2006). Improved spatial recognition memory in mice lacking adenosine A2A receptors. Experimental neurology, 199(2), 438-445.

Warburton, D. M., Bersellini, E., & Sweeney, E. (2001). An evaluation of a caffeinated taurine drink on mood, memory and information processing in healthy volunteers without caffeine abstinence. Psychopharmacology, 158(3), 322-328.

Wei, H., Li, L., Song, Q., Ai, H., Chu, J., & Li, W. (2005). Behavioural study of the D-galactose induced aging model in C57BL/6J mice. Behavioural brain research, 157(2), 245-251.
Wei, C. J., Singer, P., Coelho, J., Boison, D., Feldon, J., Yee, B. K., & Chen, J. F. (2011). Selective inactivation of adenosine A2A receptors in striatal neurons enhances working memory and reversal learning. Learning & memory, 18(7), 459-474.
Yuan, Y., Li, G., Ren, H., & Chen, W. (2020). Caffeine effect on cognitive function during a stroop task: fNIRS study. Neural Plasticity, 2020.
Zhou, X., & Zhang, L. (2021). The Neuroprotective Effects of Moderate and Regular Caffeine Consumption in Alzheimer's Disease. Oxidative Medicine and Cellular Longevity, 2021.
Zhou, S. J., Zhu, M. E., Shu, D., Du, X. P., Song, X. H., Wang, X. T., ... & He, J. C. (2009). Preferential enhancement of working memory in mice lacking adenosine A2A receptors. Brain research, 1303, 74-83.