Neuropharmacology 64 (2013) 160–167

Contents lists available at SciVerse ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

The effect of caffeine on working memory load-related brain activation in middle-aged males

Elissa B. Klaassen [a,f,*], Renate H.M. de Groot [a,b,f], Elisabeth A.T. Evers [c], Jan Snel [d], Enno C.I. Veerman [e], Antoon J.M. Ligtenberg [e], Jelle Jolles [f], Dick J. Veltman [g]

[a] School for Mental Health and Neuroscience (MHeNS), Department of Psychiatry and Neuropsychology, Maastricht University, The Netherlands
[b] Centre for Learning Sciences and Technologies (CELSTEC), Open University, The Netherlands
[c] Center for Functional Magnetic Resonance Imaging, Department of Radiology, University of California San Diego (UCSD), San Diego, USA
[d] Department of Psychology, Workgroup Brain and Cognition, University of Amsterdam, The Netherlands
[e] Department of Oral Biochemistry, Academic Centre for Dentistry Amsterdam, The Netherlands
[f] AZIRE Research Institute & Faculty of Psychology and Education, VU University Amsterdam, The Netherlands
[g] Department of Psychiatry, VU University Medical Centre, & Neuroscience Campus Amsterdam, The Netherlands

ARTICLE INFO

Article history:
Received 29 March 2012
Received in revised form
13 June 2012
Accepted 14 June 2012

Keywords:
Caffeine
Working memory
fMRI
Dorsolateral prefrontal cortex
Thalamus

ABSTRACT

Caffeine is commonly consumed in an effort to enhance cognitive performance. However, little is known about the usefulness of caffeine with regard to memory enhancement, with previous studies showing inconsistent effects on memory performance. We aimed to determine the effect of caffeine on working memory (WM) load-related activation during encoding, maintenance and retrieval phases of a WM maintenance task using functional magnetic resonance imaging (fMRI). 20 healthy, male, habitual caffeine consumers aged 40–61 years were administered 100 mg of caffeine in a double-blind placebo-controlled crossover design. Participants were scanned in a non-withdrawn state following a workday during which caffeinated products were consumed according to individual normal use (range = 145–595 mg). Acute caffeine administration was associated with increased load-related activation compared to placebo in the left and right dorsolateral prefrontal cortex during WM encoding, but decreased load-related activation in the left thalamus during WM maintenance. These findings are indicative of an effect of caffeine on the fronto-parietal network involved in the top-down cognitive control of WM processes during encoding and an effect on the prefrontal cortico-thalamic loop involved in the interaction between arousal and the top-down control of attention during maintenance. Therefore, the effects of caffeine on WM may be attributed to both a direct effect of caffeine on WM processes, as well as an indirect effect on WM via arousal modulation. Behavioural and fMRI results were more consistent with a detrimental effect of caffeine on WM at higher levels of WM load, than caffeine-related WM enhancement.

This article is part of a Special Issue entitled 'Cognitive Enhancers'.

1. Introduction

Caffeine (a methylxanthine) is one of the most widely consumed psychoactive substances in the world, with coffee generally accounting for the majority of dietary caffeine intake (Nehlig, 1999). As a result of its stimulant properties, caffeine is often consumed in an attempt to enhance performance and combat the detrimental effects of fatigue. However, although caffeine has consistently been shown to diminish tiredness, increase energy and improve mood, findings regarding its ability to enhance cognitive performance are more complex (Nehlig, 2010; Snel et al., 2004).

Relatively consistent effects have been found with regard to the enhancement of psychomotor function (e.g. speeded reaction time) and sustained attention following caffeine consumption. Effects on learning and memory performance, however, appear to be more variable. Variable effects may be attributed to the diversity of caffeine research protocols in terms of caffeine dosage, cognitive task type and the characteristics (e.g., age, gender and habitual

* Corresponding author. Educational Neuroscience, Centre of Brain and Learning, Vrije Universiteit Amsterdam, Van der Boechorststraat 1, 1081 BT Amsterdam, The Netherlands. Tel.: +31 20 59 88894.
E-mail addresses: e.b.klaassen@vu.nl, elissa.klaassen@maastrichtuniversity.nl (E.B. Klaassen), Renate.deGroot@ou.nl (R.H.M. de Groot), eevers@ucsd.edu (E.A.T. Evers), J.Snel@uva.nl (J. Snel), e.veerman@acta.nl (E.C.I. Veerman), a.ligtenberg@acta.nl (A.J.M. Ligtenberg), j.jolles@psy.vu.nl (J. Jolles), DJ.Veltman@vumc.nl (D.J. Veltman).

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http://dx.doi.org/10.1016/j.neuropharm.2012.06.026

caffeine consumption levels) and state (e.g., fatigue level, arousal level and caffeine abstinence) of the participant. Fortunately, insight into the effects of psychoactive agents, such as caffeine, on cognitive processes (regardless of whether significant changes in performance are evident at the behavioural level) can be provided by functional magnetic resonance imaging (fMRI). In the present study, we used fMRI to investigate the effect of caffeine on working memory (WM).

To date, just one study has investigated the effect of caffeine on learning or memory using fMRI. Koppelstaetter et al. (2008) demonstrated increased WM load-related activation (N-back task, block design) following caffeine (compared to placebo) administration in prefrontal cortex areas (PFC) associated with executive and attentional functions (in the absence of a significant effect on WM performance). This finding was suggested to reflect a direct effect of caffeine on WM processes. Behavioural findings, on the other hand, are generally considered to indicate an indirect effect of caffeine on WM via changes in arousal state.

We aimed to extend on findings by Koppelstaetter et al. (2008) by investigating the effect of caffeine on WM load-related activation during encoding, maintenance and retrieval phases of a WM maintenance task (modified Sternberg task) using an event-related fMRI design. In contrast to Koppelstaetter et al. (2008), we tested participants following a day of habitual caffeine consumption, rather than requiring an extended period of caffeine abstinence prior to testing. The advantage of this approach is that the effects of caffeine are investigated in the context of each participant's usual levels of caffeine in the body, instead of in the context of a caffeine withdrawal state. This design addresses the criticism that the beneficial effects of caffeine in abstained habitual consumers may in fact reflect the removal of the negative effects of caffeine withdrawal (Field et al., 2003; Heatherley, 2011; James, 1994). Caffeine withdrawal is associated with headaches, fatigue, dysphoric mood changes and flu-like somatic symptoms (Ozsungur et al., 2009), as well as changes in cerebral blood flow (CBF), the effect of which will be elucidated further below in relation to fMRI. In line with Koppelstaetter et al. (2008), we examined the effects of a 100 mg dose of caffeine (equivalent to 1–1.5 cups of coffee) in male caffeine consumers (250–800 mg per day).

Our study focused on middle-aged males aged 40–61 years. Cognitive performance, including WM, has already started to decline by middle age (e.g. Bopp and Verhaeghen, 2005; Myerson et al., 2003; Park et al., 2002), as have energetic resources (Salthouse, 1988). Nevertheless, middle-aged adults commonly still work fulltime in positions that demand a high level of cognitive performance. There is some indication that caffeine can exert a more pronounced enhancement of cognition in older individuals (Nehlig, 2010). Therefore, the possible memory enhancing effects of caffeine are of particular interest in this age group; middle-aged adults may stand to benefit more from caffeine in terms of work-related performance enhancement than young adults (or retired old adults in whom daily cognitive demands are probably reduced). Since the memory enhancing effects of caffeine may be more evident when participants are in a suboptimal state (Nehlig, 2010), we tested participants immediately after a full day of work, when work-related fatigue levels are high.

When investigating the effect of caffeine on the blood oxygen level-dependent (BOLD) response utilised by fMRI as an indirect measure of neural activity, it is important to recognise that changes in the BOLD response can arise from both neural and cerebrovascular mechanisms (for a review see Koppelstaetter et al., 2010; Laurienti et al., 2003). Caffeine, a non-selective adenosine receptor antagonist (Pelligrino et al., 2010), elicits: 1) neurostimulant effects, primarily via A_1 receptors and the dopamine system (Ferre, 2008; Pelligrino et al., 2010); 2) cerebrovascular effects, primarily via A_{2A} and A_{2B} receptors located on blood vessels (Pelligrino et al., 2010); and 3) arousal enhancing effects, via A_{2A} receptors and the histaminergic arousal system (Ferre, 2008); with tolerance thought to arise as the brain regulates its population of adenosine receptors to reach a new state of equilibrium in response to levels of caffeine chronically present in the body (Jacobson et al., 1996; Ralevic and Burnstock, 1998; Sousa et al., 2011). Studies have shown that administration of 200–250 mg of caffeine results in reduced CBF (Addicott et al., 2009; Field et al., 2003; Laurienti et al., 2003; Liau et al., 2008; Mulderink et al., 2002; Perthen et al., 2008), possibly accompanied by a reduction in the baseline BOLD signal (during simple motor and visual tasks) (Chen and Parrish, 2009b; Perthen et al., 2008) and changes in the magnitude (Griffeth et al., 2011; Laurienti et al., 2002) and temporal dynamics of the BOLD response (Liau et al., 2008; Liu et al., 2004; Rack-Gomer et al., 2009). Furthermore, increased CBF has been found during caffeine withdrawal (Addicott et al., 2009; Field et al., 2003). Therefore, findings from studies examining the effect of caffeine on brain activation in the context of caffeine withdrawal (compared to the withdrawal state as a control condition) may represent the resolution of withdrawal-related activation changes as well as changes relating to the effects of caffeine on CBF and cognition (Field et al., 2003). However, there is evidence that lower caffeine doses do not affect the amplitude or timing of the BOLD response (Chen and Parrish, 2009a) and have a smaller effect (Chen and Parrish, 2009a), or no significant effect (Kennedy and Haskell, 2011), on CBF. Furthermore, caffeine-related CBF changes are smaller in non-abstained higher consuming habitual users (Addicott et al., 2009). Therefore, our decision to administer a lower caffeine dosage to non-abstained moderate to high habitual caffeine consumers was intended to minimise the potential cerebrovascular effects of caffeine administration and avoid caffeine withdrawal effects.

In summary, we investigated the effect of caffeine on WM load-related activation in middle-aged, male habitual caffeine consumers. Participants were tested following a workday during which they consumed caffeine according to their own habitual regime. Based on findings by Koppelstaetter et al. (2008), we hypothesised that (although this dose may not significantly affect WM performance at the behavioural level) caffeine would increase WM load-related activation in the fronto-parietal network associated with the top-down control of attention and executive functions.

2. Methods

2.1. Participants

Twenty-one right-handed Dutch male participants (aged 40–61) were recruited via advertisements in local newspapers. Inclusion criteria specified a high level of education, fulltime employment in a white-collar profession (to ensure greater sample homogeneity with regard to cognitive demands throughout the workday and the resulting cognitive fatigue state) and consumption of 250–800 mg of caffeine daily. Daily caffeine consumption estimates at screening were based on participants' self-reports, with the estimate in mg calculated according to a recent overview of caffeine-containing products in the Netherlands (Wendte et al., 2003). The most commonly consumed products were estimated as follows: one cup (125 ml) of filter coffee = 85 mg of caffeine, instant coffee (125 ml) = 60 mg, espresso (50 ml) = 65 mg, and black tea (125 ml) = 30 mg. Exclusion criteria were significant past or present physical or psychiatric illness, medication use, illicit substance or nicotine use, or MRI contraindications. Females were not included due to gender differences in caffeine consumption and metabolism (Carrillo and Benitez, 1996; Magkos and Kavouras, 2005). The study was approved by the medical ethical committee at Maastricht University academic hospital. Volunteers gave informed consent prior to their (paid) participation.

2.2. Design

The study employed a randomised double-blind placebo-controlled crossover design. Participants were tested once after drinking caffeinated coffee (caffeine condition) and once after decaffeinated coffee (placebo condition) (treatment order