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NeuroImage 39 (2008) 492–499

Does caffeine modulate verbal working memory processes? An fMRI study

F. Koppelstaetter,[a,1] T.D. Poeppel,[b,1] C.M. Siedentopf,[a] A. Ischebeck,[c] M. Verius,[a] I. Haala,[a] F.M. Mottaghy,[d] P. Rhomberg,[a] S. Golaszewski,[e] T. Gotwald,[a] I.H. Lorenz,[f] C. Kolbitsch,[f] S. Felber,[a,g,*] and B.J. Krause[a,h]

[a]*Department of Radiology II, Medical University of Innsbruck, University Hospital of Innsbruck, Anichstr. 35, A-6020 Innsbruck, Austria*
[b]*Department of Nuclear Medicine, University of Essen, Germany*
[c]*Department of Neurology, Medical University of Innsbruck, Austria*
[d]*Department of Nuclear Medicine, Catholic University of Leuven, Belgium*
[e]*Department of Neurology, Christian Doppler Klinik Salzburg, Austria*
[f]*Department of Anaesthesiology, Medical University of Innsbruck, Austria*
[g]*Department of Radiology, Stiftungsklinikum Mittelrhein Koblenz, Germany*
[h]*Department of Nuclear Medicine, Technical University Munich, Germany*

Received 25 May 2007; revised 24 July 2007; accepted 17 August 2007
Available online 31 August 2007

To assess the effect of caffeine on the functional MRI signal during a 2-back verbal working memory task, we examined blood oxygenation level-dependent regional brain activity in 15 healthy right-handed males. The subjects, all moderate caffeine consumers, underwent two scanning sessions on a 1.5-T MR-Scanner separated by a 24- to 48-h interval. Each participant received either placebo or 100 mg caffeine 20 min prior to the performance of the working memory task in blinded crossover fashion. The study was implemented as a blocked-design. Analysis was performed using SPM2.

In both conditions, the characteristic working memory network of frontoparietal cortical activation including the precuneus and the anterior cingulate could be shown. In comparison to placebo, caffeine caused an increased response in the bilateral medial frontopolar cortex (BA 10), extending to the right anterior cingulate cortex (BA 32).

These results suggest that caffeine modulates neuronal activity as evidenced by fMRI signal changes in a network of brain areas associated with executive and attentional functions during working memory processes.

Keywords: Caffeine; Verbal working memory; Functional magnetic resonance imaging (fMRI)

Introduction

Methyltheobromine, also known as caffeine, is one of the most widely used stimulants worldwide. Caffeine is found in a variety of foods and beverages, although it is mainly consumed in the form of coffee, tea or soft drinks. Depending on the type and preparation, a cup of coffee contains between 19 and 177 mg of caffeine (Nehlig, 1999).

Caffeine is generally thought to provide benefits such as enhanced mental alertness, energy and a sense of well-being. Psychopharmacological studies investigated the different aspects of the effects of caffeine. Caffeine has been found to enhance mental performance, mood and vigilance (Brice and Smith, 2002; Lieberman et al., 1987; Van Duinen et al., 2005). Most of the observed beneficial effects on learning, memory and performance, however, have been attributed to caffeine increasing arousal and overcoming fatigue rather than to a direct enhancement of specific cognitive functions.

Caffeine exerts its action through a nonselective antagonism on adenosine A_1 and A_2 receptors within the brain (Laurienti et al., 2003). Since adenosine receptors display a general inhibitory effect on neural activity (Dunwiddie and Masino, 2001), a receptor antagonist has stimulant properties through disinhibitory mechanisms (Dunwiddie and Masino, 2001; Ralevic and Burnstock, 1998). Brain regions mediating sleep, mood and concentration show substantial increases in activity at low doses of caffeine (Nehlig and Boyet, 2000). However, caffeine acts not only as an excitatory neurostimulant but also as a vasoconstrictor and can cause reductions in cerebral blood flow (CBF) (Fredholm, 1995). At doses of 200 mg caffeine may decrease the resting-state CBF in humans by as much as 20–30% (Cameron et al., 1990; Mathew and Wilson,

* Corresponding author. Department of Radiology, Stiftungsklinikum Mittelrhein, Gesundheitszentrum ev. Stift St. Martin Koblenz, Johannes Mueller Strasse 7, D-56068 Koblenz, Germany. Fax: +49 261 137 1935.
E-mail address: stephan.felber@stiftungsklinikum.de (S. Felber).
[1] Authors contributed equally to the study.
Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2007 Published by Elsevier Inc.
doi:10.1016/j.neuroimage.2007.08.037

1991). Because increased neuronal activity is thought to be exerted mainly through action on A_1 receptors, whereas vasoconstriction is mediated mainly through action on A_2 receptors (Laurienti et al., 2003), a nonselective antagonist can have both neural and vascular effects depending on the ratio of A_1 to A_2 receptors in a given brain region (Laurienti et al., 2003). Hence, caffeine affects the brain by a localised combination of neural and vascular responses (Laurienti et al., 2003).

Blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (fMRI) is sensitive to regional cerebral perfusion. It is a matter of debate, however, whether global CBF changes caused by caffeine interfere with regional CBF changes in BOLD fMRI.

In an fMRI study, Mulderink and colleagues (2002) investigated the effects of caffeine on resting and sensorimotor activation. They suggested that caffeine decreases resting perfusion, thus lowering the BOLD signal baseline from which subsequent BOLD activation changes are measured. The lowered baseline is assumed to provide a greater range for the BOLD signal during activation, thus leading to a measurably larger BOLD response. The authors concluded that caffeine serves as a "contrast booster" for fMRI experiments. In a similar manner, it has been argued, that the magnitude of the BOLD signal can increase or decrease due to caffeine, by a combination of effects on the vascular and neural level, which depend on many factors, such as receptor number and affinity (Laurienti et al., 2003). Laurienti and colleagues could demonstrate that the effect of caffeine on the variation of the BOLD signal is dependent on the individual baseline caffeine intake. A greater BOLD signal change was observed in high than in low caffeine users (Laurienti et al., 2002). In contrast, other researchers (Bendlin et al., 2007) found no support for the hypothesis that changes in perfusion are directly associated with caffeine-related modulations of the baseline BOLD signal.

So far, only a few fMRI studies investigated the effects of caffeine on cognitive functions other than relatively pure perceptual or motor tasks. In 1998, Portas et al. used fMRI to measure the brain activity during the performance of an attentional task under different levels of arousal including caffeine stimulation. Recently, Bendlin and colleagues (2007) investigated the effects of caffeine with fMRI using a word stem completion task.

Many higher cognitive functions depend on the temporary storage of information, which is also referred to as working memory. According to Baddeley (1992), working memory consists of two components, a short-term storage of information that is domain-specific (verbal and visuo-spatial) and executive processes that operate on the contents of this storage (Smith and Jonides, 1999). Working memory relies on a frontoparietal network consisting of brain areas within the prefrontal and parietal cortex, the anterior cingulate and parts of the basal ganglia (Cabeza and Nyberg, 2000; Krause et al., 2006; Smith and Jonides, 1998). The distinct cortical areas have been associated with specific cognitive functions. Executive processes are assumed to involve orbitofrontal as well as prefrontal brain areas, whereas the storage of information is supposed to be mediated by the parietal cortex (Cabeza and Nyberg, 2000; Smith and Jonides, 1998).

The aim of this fMRI study was to assess the effect of caffeine on the fMRI signal during a verbal working memory task in healthy moderately caffeine consuming males after the administration of caffeine or placebo. Since the beneficial effects of caffeine on mental performance have been attributed to an enhancement of arousal, vigilance and attention we hypothesise that caffeine might, among others, selectively modulate the fMRI signal in frontal cortical brain areas related to attention and executive functions.

Materials and methods

Participants

Sixteen healthy Caucasian males (age 25–47 years; ±5.58 years) were recruited for the study (university students and departmental staff under following inclusion criteria: no history of migraines, stroke, hypertension, diabetes, any neurological/psychiatric or vascular disease; no history of alcohol or drug abuse). All subjects were right-handed and handedness was affirmed by the Edinburgh Handedness Inventory (Oldfield, 1971). The study was approved by the local ethics committee of the University of Innsbruck and signed consent was obtained from every participant. One volunteer was excluded due to signal artefacts caused by braces. The final sample consisted of 15 subjects (age 25–47 years; ±5.63 years). In a prescan interview, all subjects were classified as moderate caffeine consumers (Nehlig, 1999). All participants were free of medication and reported an undisturbed sleep period of at least 6 h during the night prior to the fMRI scan sessions.

Experimental design

Each subject underwent two fMRI scan sessions on two different days separated by a 24- to 48-h interval. The participants abstained from caffeine and nicotine intake by a minimum of 12 h and fasted for at least 4 h prior to each scan session (see Fig. 1).

Caffeine dose and administration

Subjects received an oral dose of either caffeine (100 mg) or placebo in crossover fashion and pseudo-randomised order. Subjects were blind to the order of caffeine and placebo. Caffeine is absorbed rapidly and 100% bioavailable. It has a 3- to 8-h plasma half-life, with stable brain levels for at least 1 h (Nehlig, 1999). According to the pharmacokinetics of caffeine, fMRI-sessions were started 20 min after oral intake. A moderate caffeine dosage was chosen to reflect caffeine intake of common drinking habits and to avoid changes of heart rate and blood pressure that might be noticed by the volunteers.

Physiological parameters

Heart rate, systolic and diastolic blood pressure (in mmHg), mean arterial pressure (MAP, in mmHg) and pulse oximetry (percentage oxyhaemoglobin saturation) measurements were recorded prior to drug administration, as well as immediately before and after the scanning session. Data were analysed with paired *t*-tests. A Bonferroni correction was applied.

Behavioural measures

Behavioural performance was assessed as percentage of correct responses (accuracy) and the time (in ms) taken to respond (reaction time). The effects of caffeine on response accuracy and reaction time over the 0-back and 2-back condition were analysed separately in a repeated measures analysis of variance (ANOVA) with the within-subjects factors Drug condition (caffeine, placebo) and Task (0-back, 2-back).

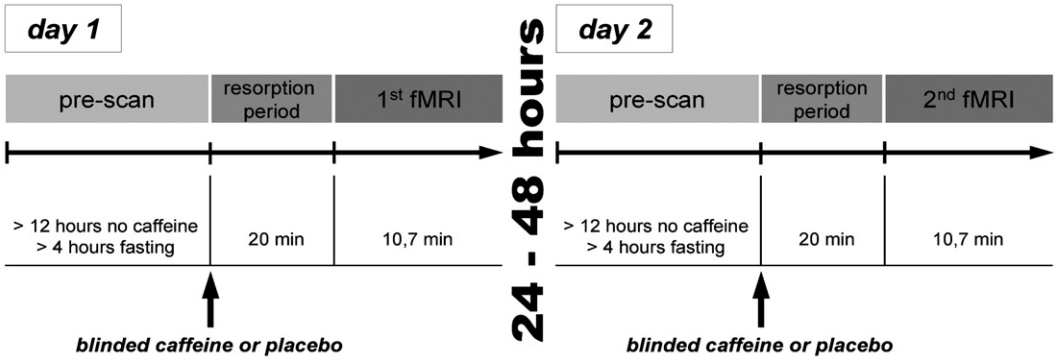

Fig. 1. Experimental design. Each subject underwent two fMRI scan sessions on two different days separated by a 24- to 48-h interval. Subjects abstained from caffeine and nicotine intake by a minimum of 12 h and fasted for at least 4 h prior to each scan session. Subjects received an oral dose of either caffeine (100 mg) or placebo in crossover fashion and pseudo-randomised order 20 min prior to the individual fMRI scan sessions.

fMRI procedure

Participants had to perform a 2-back verbal working memory task. They were trained on the task for 30 min before entering the scanner. A pseudo-randomised successive presentation of the letters "B", "D", "H" and "M" served as stimuli. Subjects had to decide by button press whether the letter presented was identical to the letter two trials before (2-back task). They were instructed to respond as fast as possible with their right index finger for 'yes' and the left index finger for 'no' on every presentation of a letter. Two response pads fixated to both sides of the subjects' body were used. A 0-back task served as reference condition. In the 0-back task the letters X and Y were presented in a pseudo-randomised order. Subjects had to press the right button for an "X" and the left in case of "Y". In a further reference condition a fixation cross was presented repeatedly on the screen. The subjects had to press the right and left button alternately on each appearance of the fixation cross (fix-cross condition). Each stimulus was presented for 1300 ms with an interstimulus interval (ISI) of 200 ms (Hautzel et al., 2002).

The experiment was realised as a conventional fMRI blocked-design. Three randomisations/runs of the experiment were generated and randomly assigned to the participants. All three versions differed with regard to the sequence of blocks pertaining to the three conditions (2-back, 0-back and fix-cross). Each task condition was repeated 6 times yielding 18 blocks per run. Each session consisted of a single run with a duration of approximately 10.7 min.

For stimulus presentation, the Eloquence fMRI device (InvivoMDE, MRI Devices Corporation Inc., Orlando, Florida, USA; http://www.mridevices.com/Funct/Eloquence.asp) was used. The experiment was programmed using the integrated software tool "E-Prime" (Psychology Software Tools, Inc.; Pittsburgh, USA; http://www.pstnet.com/products/e-prime/). Stimulus presentation was triggered by the MR-scanner.

fMRI data acquisition

The fMRI experiments were performed on a 1.5-T MR-Scanner (Siemens Sonata, MR Syngo 2002b, Erlangen, Germany; Echo

Table 1
Physiological parameters during caffeine and placebo condition

Caffeine condition		Placebo condition	
HR[a] before drug	67±6	HR[a] before placebo	69±12
HR[a] before scanning	63±6	HR[a] before scanning	68±14
HR[a] after scanning	66±9	HR[a] after scanning	69±10
Systolic blood pressure before drug[b,*]	125±8	Systolic blood pressure before placebo[b,*]	119±10
Systolic blood pressure before scanning[b]	124±10	Systolic blood pressure before scanning[b]	118±9
Systolic blood pressure after scanning[b]	129±13	Systolic blood pressure after scanning[b]	118±8
Diastolic blood pressure before drug[b]	76±9	Diastolic blood pressure before placebo[b]	73±8
Diastolic blood pressure before scanning[b]	77±9	Diastolic blood pressure before scanning[b]	71±7
Diastolic blood pressure after scanning[b,*]	79±8	Diastolic blood pressure after scanning[b,*]	71±9
Mean arterial pressure before drug[b]	92±13	Mean arterial pressure before placebo[b]	88±9
Mean arterial pressure before scanning[b]	92±11	Mean arterial pressure before scanning[b]	86±7
Mean arterial pressure after scanning[b,*]	98±14	Mean arterial pressure after scanning[b,*]	88±7
SaO_2[c] before drug	97±1	SaO_2[c] before placebo	96±7
SaO_2[c] before scanning	97±1	SaO_2[c] before scanning	95±10
SaO_2[c] after scanning	97±2	SaO_2[c] after scanning	96±8

Values are expressed as mean±standard deviation.
[a] HR=heart rate in beats per minute.
[b] In mmHg.
[c] SaO_2=percentage oxyhaemoglobin saturation.
* Statistically different between the two conditions ($p<0.05$).

planar imaging (EPI), repetition time = 3 sec, echo time = 60 ms, flip angle (α) = 90°, field of view (FoV) = 250, 24 slices parallel to intercommissural (AC–PC) plane, matrix size = 64 × 64, thickness = 5 mm, distance factor = 0.25, giving a voxel size of 3.95 × 3.95 × 5 mm^3 covering the whole brain) using an eight channel head coil. Each subject underwent an anatomical 3D scan with a spatial resolution of 0.98 × 0.98 × 1 mm^3 prior to the functional scan.

fMRI data analysis

fMRI data analysis was accomplished using SPM2 (SPM2, Wellcome Department of Cognitive Neurology, London, UK; http://www.fil.ion.ucl.ac.uk/spm/software/spm2/) under MATLAB 6.5 (MathWorks Inc., Natick, MA, USA; http://www.mathworks.com/). The functional data sets of each subject were motion corrected. Anatomical high-resolution images were coregistered to a mean functional image of each participant and nonlinearly transformed into a standard stereotactic space using the T1 template provided by SPM2 (MNI template). The parameters of this transformation were then applied to the functional images. Finally, the functional images were spatially smoothed using an 8-mm FWHM Gaussian kernel. A statistical analysis on the basis of the general linear model was conducted as implemented in SPM2. The delta function of the block onsets was convolved with the canonical form of the haemodynamic response function for a duration corresponding to the length of the blocks to generate the model time courses for the conditions. A high-pass filter (1/288 Hz) was used to remove low frequency drifts. No global normalisation was used.

A comparison of 2-back *minus* 0-back was calculated for each condition (caffeine and placebo) to obtain the general activation pattern for working memory. After that single subject model estimation calculated contrasts were entered into a second level analysis (random effects model) to assess group effects (Friston et al., 1999).

To investigate the differential effect of caffeine compared to placebo on brain activations attributed to the working memory system the following interaction contrast was computed: (2-back *minus* 0-back)$_{caffeine}$ *minus* (2-back *minus* 0-back)$_{placebo}$.

In all comparisons, clusters of activations were reported as significant, when they surpassed an initial threshold of $p < 0.001$ (uncorrected) and had a corrected *p*-value of $p < 0.05$ on cluster level.

Results

Physiological parameters

Subjects reported no awareness to the condition applied (caffeine or placebo). All recorded physiological parameters remained within physiological ranges (see Table 1). No significant changes were present during or between the conditions, with the following exceptions: Systolic blood pressure was significantly higher before and after completing the working memory task in the caffeine compared to placebo condition ($p < 0.05$). Diastolic and mean arterial blood pressure were significantly different between the conditions (caffeine/placebo) after completing the working memory task ($p < 0.05$).

Behavioural measures

0-back trials were answered faster and more accurate than 2-back trials, yielding a significant main effect of task (accuracy: $F(1,14) = 117{,}710$, Mean Squared Error (MSE) = 407.51, $p < 0.001$; reaction time: $F(1,14) = 16.9$, MSE = 323519, $p < 0.001$). There was no main effect of drug condition and no significant interaction in either reaction times or accuracy. Mean response accuracy and reaction time during the working memory conditions for both the caffeine and placebo condition are presented in Figs. 2a and b.

fMRI

The contrast 2-back *minus* 0-back was computed to investigate task-related effects. A network of frontal and parietal cortical areas was observed to be more active in both, the caffeine and placebo condition for 2-back than for 0-back (Fig. 3). The network included bilateral activations in the middle and inferior frontal gyrus, in the anterior cingulate gyrus, the superior and inferior parietal lobule, the precuneus and the cuneus. Additionally activations could be found

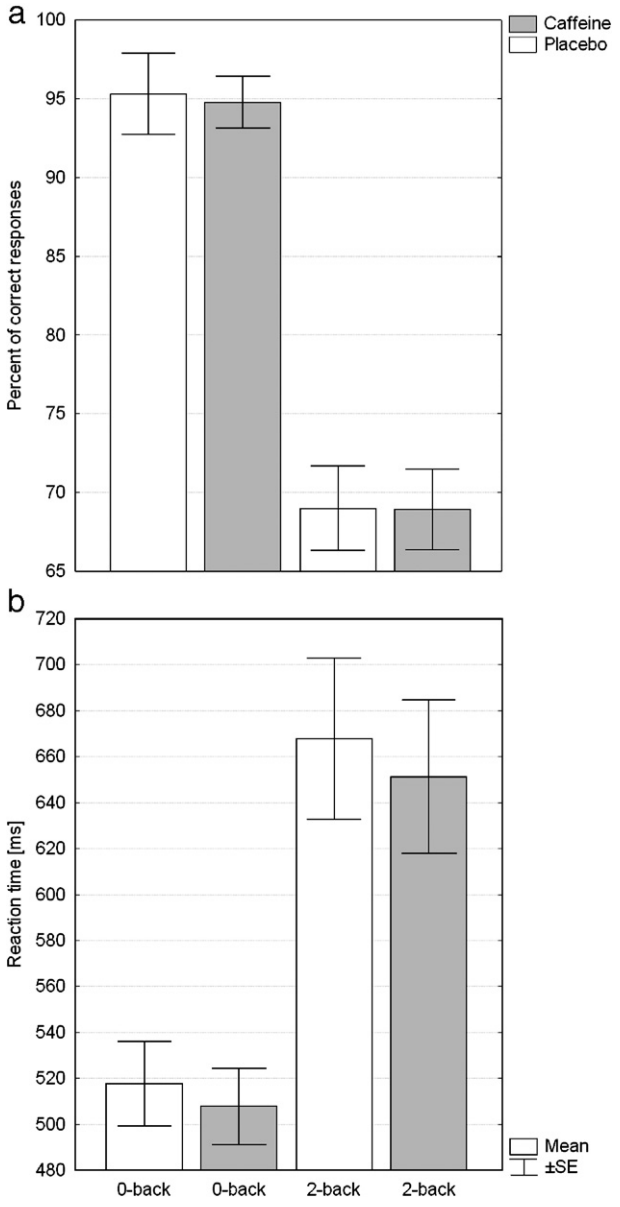

Fig. 2. Response accuracy (percentage of correct responses; panel a) and reaction time (in ms; panel b) for the 0-back and 2-back task in the caffeine and placebo condition showing no significant differences between the conditions. Error bars demonstrate standard error of the mean.

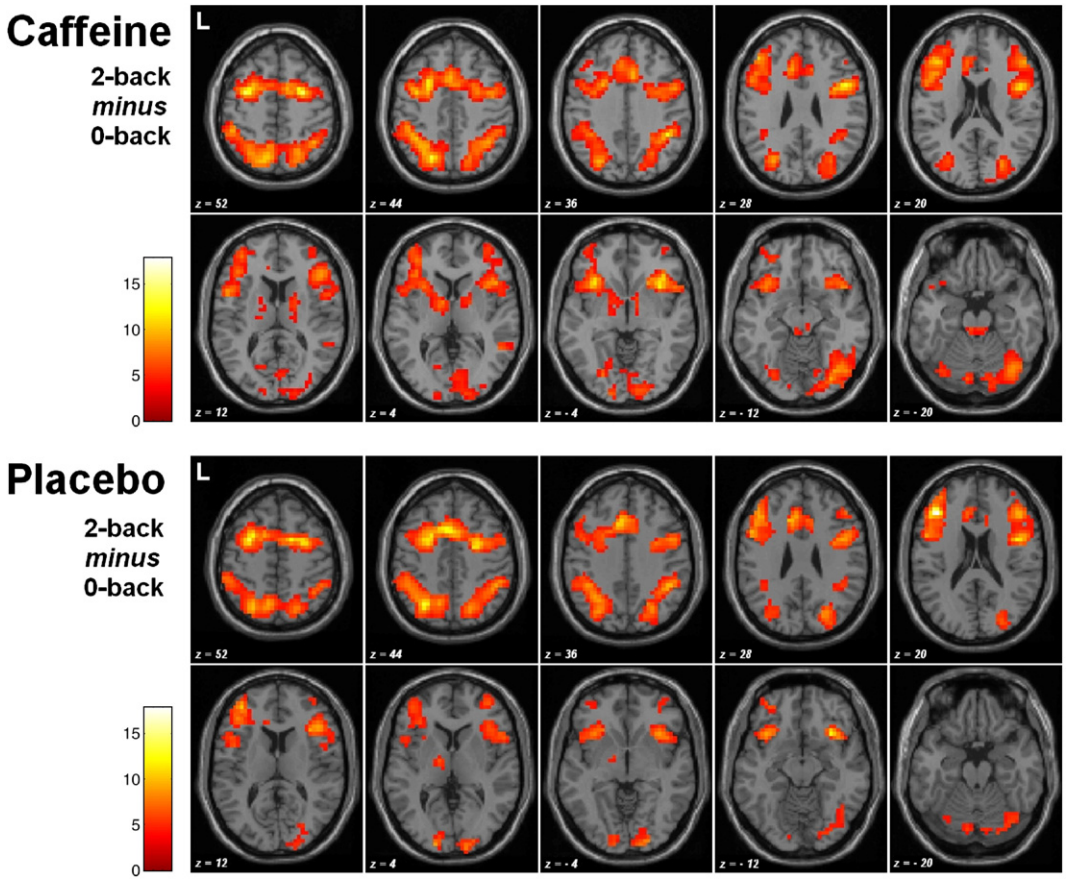

Fig. 3. Second level analysis for each condition (caffeine and placebo) *minus* reference (i.e. 2-back *minus* 0-back) of the whole group superimposed on the canonical SPM2 T1 image revealing the widespread pattern of cortical activation seen in working memory. Activations were reported for clusters that surpassed an initial uncorrected threshold of $p<0.001$ and had a corrected p-value of $p<0.05$ on cluster level.

bilaterally in the visual cortex, the basal ganglia including the thalamus as well as the brainstem and cerebellum. Table 2 displays the activations for caffeine and placebo conditions separated by hemisphere.

The interaction contrast task × pharmaco-intervention (Fig. 4) revealed a caffeine-related effect on the medial frontopolar cortex (BA 10) of both hemispheres (Talairach coordinates: $x=-4$, $y=58$, $z=-6$; $x=8$, $y=58$, $z=-6$), extending to the right anterior cingulate (BA 32) when the initial threshold was lowered to a $p<0.005$ (uncorrected). The reverse contrast did not show any significant result even with a more lenient threshold.

Discussion

In the present fMRI study, we investigated the effects of caffeine on the fMRI signal during a working memory task in healthy moderately caffeine consuming males to examine the pharmacological influence of caffeine during verbal working memory processes.

Modulation of the cortical activation pattern induced by caffeine

The main finding in the interaction analysis (task × pharmaco-intervention) revealed a distinct caffeine-related effect on the medial frontopolar cortex (BA 10) of both hemispheres extending to the right anterior cingulate (BA 32), brain regions, that have been associated with attentional and executive functions.

There are functionally distinct types of supramodal attentional systems, which are mediated through different cortical and subcortical networks (Portas et al., 1998; Raz and Buhle, 2006). Frontal brain areas are part of the neural networks underlying these attentional abilities (Mottaghy et al., 2006; Sturm et al., 1999), in particular sustained attention and vigilance (Lawrence et al., 2003). Another key player in this context is the anterior cingulate cortex (ACC), which has frequently been hypothesised to play a critical role in motivated attention, allocation of attention and error detection (Carter et al., 1999). Brain imaging studies have identified the ACC as an important node in the network of executive attention (Raz and Buhle, 2006). They have consistently demonstrated activation of different parts of the ACC in cognitive conflict tasks and in error detection/monitoring (Fan et al., 2002; Raz and Buhle, 2006). These different aspects of attention are essential requirements for working memory processes. Moreover, a right-sided hemispheric asymmetry of ACC involvement is described for attentional and executive functions (Markela-Lerenc et al., 2004), particularly in working memory (Kondo et al., 2004). The prefrontal cortex (PFC) and the ACC are strongly functionally interconnected and modulate each other (Mottaghy et al., 2006). Therefore, an effect of caffeine on any of these areas may directly or indirectly influence the others. The frontopolar prefrontal cortex (FPPFC) plays a central role in executive functions like planning, monitoring and problem solving (Baker et al., 1996; Christoff and Gabrieli, 2000) and has been associated with monitoring processes

Table 2
Activation foci of the contrasts of experimental conditions vs. reference (displaying the working memory network)

	Left					Right			
	x	*y*	*z*	*t*-value		*x*	*y*	*z*	*t*-value
Caffeine									
Anterior cingulate	−8	25	25	8.57	Anterior cingulate	8	17	32	9.18
Inferior frontal gyrus	−44	20	17	8.72	Inferior frontal gyrus	48	28	13	10.32
Middle frontal gyrus	−32	44	16	6.69	Inferior frontal gyrus	40	54	1	5.48
Dorsolateral prefrontal cortex	−51	12	10	8.49	Inferior frontal gyrus	48	20	3	8.56
Middle frontal gyrus	−32	2	48	14.04	Middle frontal gyrus	28	2	48	13.89
Inferior frontal gyrus	−51	13	21	9.14	Inferior frontal gyrus	48	9	22	17.84
Precuneus	−20	−64	44	13.01	Precuneus	20	−68	48	8.88
Inferior parietal lobule	−36	−44	43	9.96	Submarginal gyrus	44	−41	35	12.4
Lingual Gyrus	−24	−74	0	7.18	Inferior occipital gyrus	32	−78	−6	9.03
Cerebellum	−32	−60	−27	6.68	Cerebellum	40	−60	−27	11.8
Brainstem	−4	−28	−15	5.81	Brainstem	8	−28	−12	6.49
Placebo									
Anterior cingulate	−4	18	40	11.47	Anterior cingulate	4	18	40	11.47
Middle frontal gyrus	−40	32	17	16.61	Inferior frontal gyrus	48	28	13	9.15
Middle frontal gyrus	−28	6	48	12.45	Middle frontal gyrus	28	2	44	11.42
Superior parietal lobule	−28	−60	44	11.92	Superior parietal lobule	24	−60	40	7.42
Inferior parietal lobule	−48	−37	46	6.99	Inferior parietal lobule	48	−41	39	10.89
Precuneus	−8	−60	47	9.12	Precuneus	20	−64	47	8.17
Cuneus	−16	−93	5	8.4	Cuneus	20	−93	5	7.59
Cerebellum	−32	−63	−24	6.37	Cerebellum	28	−64	−32	6.18

Coordinates are reported corresponding to the Talairach space (Talairach and Tournoux, 1988) after conversion of the original SPM2 (MNI space) coordinates with the transformation by Matthew Brett as previously described (Calder et al., 2001). Anatomical labels are given on the basis of the "Talairach Daemon" (Lancaster et al., 2000).

and the integration of subgoals during working memory tasks while maintaining information (Braver and Bongiolatti, 2002). The 2-back task demands attention and concentration, first to process the fast sequence of letters, second, to store and finally to retrieve these information simultaneously. Executive functions like scheduling processes and updating and checking the contents of working memory to determine the next step in a sequence of letters are further indispensable features of this task (for a review, see Braver and Bongiolatti, 2002). A possible role of the frontopolar cortex (BA 10) for updating information in working memory was suggested by Van der Linden et al. (1999). The medial anterior prefrontal and mediopolar prefrontal cortex seem to play an essential role in planning. Koechlin et al. (2000) reported on medial anterior prefrontal (BA 32/10) and mediopolar prefrontal activity depending on predictable or unpredictable sequences. In the current study, subjects received information and instructions about the general procedure of the task prior to the experiment, however the pseudo-randomised sequences of letters itself was unpredictable. Beside the missing interaction effect in the ventral striatum, the effects we observed in BA 10 and BA 32 are similar to the activations described by Koechlin et al. (2000).

Taken together, caffeine seems to influence the brain area network subserving the executive and attentional functions involved in working memory processes.

Behavioural effects of caffeine

In this study, caffeine had no significant effect on cognitive performance. Other psychopharmacological studies, however, have shown a beneficial effect of caffeine on mental performance, mood

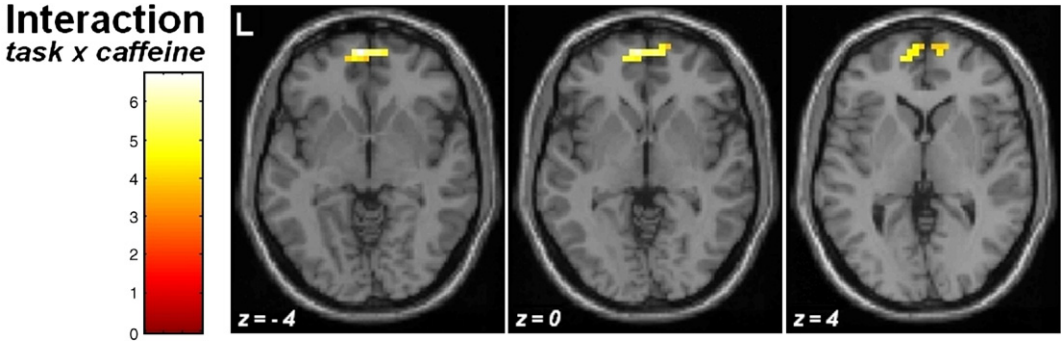

Fig. 4. Second level cognitive subtraction/interaction analysis ((2-back *minus* 0-back)$_{caffeine}$ *minus* (2-back *minus* 0-back)$_{placebo}$) of the whole group superimposed on the canonical SPM2 T1 image revealed a caffeine-related effect on the frontomedial cortex (BA 10) of both hemispheres. Activations were reported for clusters that surpassed an initial uncorrected threshold of $p<0.001$ and had a corrected *p*-value of $p<0.05$ on cluster level.

and vigilance (Brice and Smith, 2002; Durlach, 1998; Lieberman et al., 1987; Van Duinen et al., 2005). This difference could be due to the rather low dosage of caffeine used in this study, which was chosen to avoid physiological side-effects noticeable to the volunteers, as well as to reflect caffeine intake of common drinking habits. Therefore, the present study differs from psychopharmacological and fMRI-studies that used higher caffeine dosages (Laurienti et al., 2002; Mulderink et al., 2002). All subjects were moderate consumers of caffeinated beverages. Habituation to caffeine might therefore have disguised clear-cut behavioural effects. It is also necessary to take into consideration that there is substantial interindividual variability of behavioural changes through caffeine depending on vigilance, personality traits and gender (Linde, 1995). However, fMRI studies can exhibit meaningful changes in patterns of brain activation without corresponding changes in overt behaviour (Wilkinson and Halligan, 2004), which holds for pharmacological studies as well (Ghatan et al., 1998; Hershey et al., 2004). Moreover, the absence of significant behavioural effects holds the advantage that the neuroimaging results observed here are likely to reflect specific actions of caffeine and cannot be alternatively explained by task difficulty effects and different task performance.

Neurophysiological effects of caffeine

A well-known constraint on studying the effects of caffeine on cognitive functions with functional imaging concerns the substantial effects that caffeine exerts on vascular structures (Dager and Friedman, 2000; Laurienti et al., 2002). Although caffeine was termed a "BOLD booster" (Mulderink et al., 2002), its effects on BOLD signal intensity are complex and discussed controversially in literature. The magnitude of the BOLD signal has been observed to be modulated by a variety of neural and vascular factors, such as receptor number and affinity (Laurienti et al., 2003). In our study, the comparison of cortical activation under working memory demands within the caffeine and placebo condition shows a modulating effect of caffeine on frontal brain regions that are related to attentional and executive processes and can be associated with the cognitive processes involved in working memory. This regional specificity renders an explanation solely by a vascular effect unlikely, since the prefrontal or frontal cortex do not display a specifically high concentration of adenosine A_2 receptors (Moreau and Huber, 1999), which are mainly responsible for vasoconstrictive effects of caffeine (Laurienti et al., 2003). Moreover, A_1 receptors, which mediate the neuroexcitatory effect of caffeine, are distributed differentially throughout the brain. As evidenced from both in-vitro (Fastbom et al., 1986, 1987) and from combined in-vitro/in-vivo studies in humans (Bauer et al., 2003) there is a significant amount of A_1 receptors in the cortex (among a high receptor density in the parts of the basal ganglia). Thus, the differential distribution of A_1 receptors makes some cortical and subcortical regions more likely to be affected by caffeine than others. Since the effects of caffeine on the brain are mediated by a combination of neural and vascular responses (Laurienti et al., 2003), we hypothesise that the observed modulation is mediated mainly by the neuroexcitatory action of caffeine on the specific brain regions that are involved in executive and attentional functions.

Another possible confound has been pointed out by Field et al. who proposed that withdrawal of caffeine in regular caffeine consumers might affect cerebral blood flow depending on the drinking habits (Field et al., 2003). However, other authors do not consider the withdrawal hypothesis as an adequate explanation for the effects of caffeine (Smith et al., 2006). It is unlikely that the results of the present study are due to individual caffeine withdrawal effects, as all studied subjects were moderate consumers of caffeine. However, additional studies are required to investigate the influence of different dosages of caffeine as well as using additional scanning techniques (e.g., arterial spin labelling) for evaluating regional changes in cerebral blood flow during the test procedure.

Conclusion

Caffeine modulates the fMRI signal during working memory processes in brain regions that have been associated with attentional and executive functions. The fact that the modulation is only seen in specific cortical regions (medial frontopolar cortex and ACC) suggests an effect on brain areas engaged in specific cognitive processes rather than a general effect due to the influence of caffeine on the vasculature. We hypothesise that the results may reflect a neuromodulatory effect on the medial frontopolar and anterior cingulate cortex.

Acknowledgment

This article is dedicated to Prof. Dr. med. Dieter Zur Nedden, Innsbruck, Austria, on the occasion of his 65th birthday.

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