User Research

The neural and vascular effects of caffeine revealed by simultaneous EEG-fMRI by Richard G. Wise
Cardiff University Brain Research Imaging Centre, School of Psychology, Cardiff University, Cardiff, United Kingdom

Acknowledgement

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Introduction

You may, at this moment, be drinking coffee in the hope that it will keep you alert while reading this article. What effect is the caffeine having on your brain? Neuroimaging methods have recently been brought to bear in answering this question. Caffeine is a nonselective antagonist of A<sub>1</sub> and A<sub>2A</sub> adenosine receptors ( Dunwiddie and Masino, 2001). Increased neuronal activity is mediated through action on A<sub>1</sub> and A<sub>2A</sub> adenosine receptors, while vasoconstriction and as a consequence, reduction in cerebral blood flow (CBF), is mediated through action on A<sub>2A</sub> receptors. Caffeine, therefore, can have both neuronal and vascular effects depending on the presence of A<sub>1</sub> and A<sub>2A</sub> receptors in different brain regions ( Laurienti et al., 2003).

fMRI in its most common form, exploiting the blood oxygenation level dependent (BOLD) signal, depends on increases in blood flow associated with increases in neuronal activity ( Logothetis, 2008). The presence of caffeine, in having effects both on blood flow and neuronal activity, may lead to changes in this ‘neurovascular’ relationship and erroneous conclusions in conventional BOLD fMRI experiments in which the aim is normally to equate changes in BOLD signal with changes neuronal activity ( Iannetti and Wise, 2007; Griffeth et al., 2011).

EEG and fMRI, performed simultaneously, offer both an electrophysiological and a haemodynamic window onto the brain, a very useful toolkit for studying caffeine with its dual neuronal and vascular effects. With this in mind, our study published in Neuroimage ( Diukova et al., 2012), investigated the neuro-cognitive effects of a single dose of caffeine using simultaneous EEG-fMRI in an attempt to identify both general vascular and specific neural effects of caffeine. We aimed to determine the effect of caffeine on non- and infrequent caffeine consumers during performance of a cognitively demanding (auditory oddball) task and lower level visual and motor tasks. Non- and infrequent consumers were selected to avoid influences of the effects of frequent caffeine intake ( Rogers et al., 2010). We expected that caffeine might selectively increase the task-related BOLD signal in frontal cortex associated with attention and executive functioning during the auditory oddball task and that this would be reflected in the ERPs. Furthermore, we regarded the fMRI responses to the lower level visual and motor tasks as an index of the general influence of caffeine on the cerebral haemodynamic response.

Methods

Data are presented from 14 healthy, non or infrequent caffeine consuming, right handed male volunteers (aged 20–32 years). On each of two visits participants were scanned once with the stimulus paradigm described below, removed from the MRI magnet at which point they received an oral dose of either a gelatine capsule containing 250mg caffeine (equivalent to that present in 2 cups of ground coffee) or placebo (cornflour) and were then scanned again 30 mins later (Fig. 1).

Fig. 1. Experimental design:
Each participant was scanned twice on each of two separate visits at the same time of the day at least one week apart. Each visit’s first or baseline scan was without placebo or caffeine, while the ‘drug’ scan was preceded by 30 mins by an oral dose of either a gelatine capsule containing 250mg caffeine or placebo (corn flour). Caffeine was given in a double-blind, crossover, placebo-controlled manner. The abbreviations used in the text, BP, BC, DP, DC, refer to baseline scan for placebo session, baseline scan for caffeine session, ‘drug’ scan for placebo session and ‘drug’ scan for caffeine session, respectively. Copyright Elsevier 2012, reprinted with permission from, Diukova A, Ware J, Smith JE, Evans CJ, Murphy K, Rogers PJ, Wise RG. Separating neural and vascular effects of caffeine using simultaneous EEG-fMRI: differential effects of caffeine on cognitive and sensorimotor brain responses. Neuroimage. 2012;62(1):239-49. doi:10.1016/j.neuroimage.2012.04.041.

Participants were presented with 3 different tasks (“Presentation” Version 11.3, http://www.neurobs.com):
1) Visual task: A black and white square checkerboard, reversing at 4Hz, (5 x 40s on and 20s off).
2) Finger tapping task: A visually cued finger tapping (1 Hz) task (right hand) was employed for motor activation (5 x 26 s on and 26 s rest).
3) Auditory ‘oddball’ task (20 mins): A three-stimulus continuous (20 min) auditory ‘oddball’ task was utilised to elicit a cognitive...
response. The frequent (70% of 576 trials) standard auditory stimuli (5kHz, lasting 100 ms), the rare target auditory stimuli (1.5kHz, lasting 100 ms, 15% of trials) and the novel auditory stimuli (15% of trials), consisting of noises (e.g. dog barks, whistle, etc.), were presented randomly via headphones with a mean inter-stimulus interval of 2.05 s. Participants were asked to respond quickly and accurately to the target stimuli only by pressing the button under the right index finger.

Data acquisition

MRI was conducted on a General Electric Excite HDx 3T MRI scanner. BOLD (T2* weighted) fMRI was performed using standard acquisition parameters (Diukova et al., 2012). A T1 weighted structural scan was acquired to facilitate registration of the functional data to the common standard space of the MNI.

Continuous EEG data were collected during MRI from 30 standard scalp electrodes using the BrainAmp MR, a high-input impedance amplifier specifically designed for recordings in high magnetic fields (Brain Products, Munich, Germany). Sintered Ag/AgCl ring electrodes with built-in 5kΩ resistors mounted into an electrode cap according to the 10–20 system (EASYCAP; http://www.easycap.de/easycap/) were used. One additional electrode was placed below the left eye and one on the lower back to monitor eye-blinks and electrocardiogram, respectively. Electrode impedances were maintained below 10 kΩ before recording began. All 32 channels were recorded with FCz as reference. The data were recorded with a passband of 0.016–250 Hz and a sampling rate of 5kHz.

Data analysis

BOLD fMRI data were analysed for each subject using the fMRIB Software Library (FSL) version 5.98 (www.fmrib.ox.ac.uk/fsl) using a standard pipeline (Diukova et al., 2012). For EEG data analysis BrainVision Analyzer software version 1 (Brain Products) was used for correction of MR gradient and then ballistocardiographic (BCG) artifacts (Allen et al., 2000). Gradient artifacts were removed by subtracting an artifact template from the data, using a baseline-corrected sliding average of 20 consecutive volumes. Pulse artifact subtraction works analogously by averaging EEG signal synchronized to the ECG. Segments contaminated by artifacts due to gross movements were removed following visual inspection (maximum total 20% rejected from the data in a given subject). After removal of any bad channels, all channels were re-referenced to the common average. EEG data were filtered with a 0.2 Hz high-pass filter and a 30 Hz low-pass filter. The filters used were phase-shift-free Butterworth filters with a 24 dB/octave slope. ICA was performed on the continuous EEG data using the infomax algorithm and components representing eye-blinks were removed from the data (Srivastava et al., 2005). The data were then segmented into stimulus-locked segments. Automatic artifact rejection was then performed before response averaging to reject trials contaminated by residual artifacts. Specifically, trials with a difference of 100 μV or greater between the largest negativity and largest positivity, and trials with 60 or more data points in a row with the same value were rejected automatically. All segments were then baseline corrected using pre-stimulus data. Finally, segments were averaged within trial types to produce single-participant averages, then further averaged into grand-averages.

Two-way repeated-measures (within subject) analysis of variance (ANOVA) was performed to isolate the caffeine effect while accounting for between day variations by the inclusion of the baseline scans. The main factors in the ANOVA were dosing within scan session i.e. baseline (B) or post-dose (D) scan and drug i.e. placebo (P) or caffeine (C). The drug effect of interest was given by the interaction of factors “dosing” x “drug”.

Results

The visual stimulation elicited widespread activation (a BOLD response) in visual cortex (Fig. 2a). The BOLD signal change in visual cortex was significantly reduced by caffeine (Fig. 2b). Analysis of visual evoked potentials (VEPs) (Fig. 2c) revealed no significant effect of caffeine on amplitude or latency. The finger tapping (motor) task elicited fMRI-measured activation in the
left sensorimotor cortex, supplementary motor area, thalamus, putamen and right superior cerebellum. The BOLD signal change in left sensorimotor cortex was significantly reduced by caffeine (refer to Diukova et al., 2012 for further results). In addition to BOLD fMRI, arterial spin labelling measurements showed a caffeine-induced reduction of 19% in cerebral blood flow across grey matter.

fMRI results for the auditory oddball task showed that target vs. non-target stimulation was associated with significant hemodynamic activity (Fig. 3a). There was a significantly more positive BOLD response for target vs. non-target stimuli induced by caffeine in superior frontal gyrus, frontal pole and paracingulate gyrus (Fig. 3b). The midline electrodes Fz, Cz and Pz were used for analysis of the ERPs (Fig. 3c). The response for the target stimulus, the P300 amplitude, was defined as the largest positive peak (relative to the 100 ms pre stimulus baseline) within the time window of 300-550 ms post stimulus presentation. There was a significant shortening of the P300 response latency (target stimuli only) with caffeine. Caffeine significantly reduced the number of missed responses to the target oddball stimulus but had no significant effect of caffeine on the number of false alarms or on reaction times.

Conclusions

Our results are consistent with earlier studies that suggested altered haemodynamic responses after caffeine administration. We were able to identify caffeine’s vasoconstrictive effects and hence altered neurovascular coupling through the reduction in amplitude of low-level task fMRI (haemodynamic) responses while electrophysiological responses (VEPs) were preserved. However, our experiment suggests that, despite this general vasoconstrictive action, caffeine had a positive effect on the frontal BOLD signal consistent with the shortening of oddball ERP response latency and with the observed improved task performance. The combined use of EEG-fMRI is a promising methodology for investigating alterations in brain function in drug and disease studies where neurovascular coupling may be altered on a regional basis.

References


