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NeuroImage

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NeuroImage 32 (2006) 9 – 15

Caffeine reduces the initial dip in the visual BOLD response at 3 T

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Received 13 January 2006; revised 22 February 2006; accepted 7 March 2006
Available online 25 April 2006

Localized changes in oxygen consumption related to increased neural activity can result in a small and transient "initial dip" of the blood oxygenation level-dependent (BOLD) signal used in functional magnetic resonance imaging (fMRI). The initial dip has been of great interest to the fMRI community because it may provide a more accurate and localized measure of neural activity than the conventional BOLD signal increase. Although potentially useful as a technique for human brain mapping, the initial dip is not always detected and has been a source of some controversy. In this study, the BOLD response to a 4-s long visual stimulus was measured with a 3-T MRI system in 5 healthy volunteers both before and immediately after a 200-mg oral caffeine dose. The caffeine dose significantly ($P < 0.001$) reduced or eliminated the initial dip in all subjects. These findings suggest that caffeine usage may be a key factor in the detection of the initial dip in human fMRI studies.

Introduction

The blood oxygenation level-dependent signal (BOLD) used in most functional magnetic resonance imaging (fMRI) studies reflects local changes in deoxyhemoglobin (dHb). With increased neural activity, there are increases in both the rate of oxygen metabolism ($CMRO_2$) and the delivery of oxygen via cerebral blood flow (CBF). In most cases, the increase in oxygen delivery eventually exceeds the rate of oxygen consumption, leading to a prolonged decrease in dHb and an increase in the BOLD response (Buxton et al., 1998). This signal increase, referred to as the positive BOLD response, is the basis for most fMRI applications. However, a number of optical imaging and functional magnetic resonance imaging (fMRI) studies have shown that, in the first few seconds following the onset of increased neural activity, $CMRO_2$ may increase more quickly than CBF, leading to an initial transient increase in dHb and an associated "initial dip" in the BOLD signal (Ernst and Hennig, 1994; Menon et al., 1995; Malonek and Grinvald, 1996; Hu et al., 1997; Thompson et al., 2004). In addition, it has been shown that the initial dip is better localized to areas of neural activity (e.g., cortical columns), as compared to the more diffuse positive BOLD response (Duong et al., 2000; Yacoub et al., 2001; Kim et al., 2000; Yacoub and Hu, 2001). These observations are consistent with a view in which the early portion of the BOLD signal reflects changes in dHb that are primarily localized to the microvasculature, whereas the later part of the BOLD signal reflects dHb changes in both the microvasculature and the macrovasculature, due to the draining of dHb into larger vessels (Duong et al., 2000; Fukuda et al., 2006; Yacoub et al., 2001).

Although the initial dip has been observed in a number of human and animal studies (Ernst and Hennig, 1994; Malonek and Grinvald, 1996; Hu et al., 1997; Vanzetta and Grinvald, 1999; Duong et al., 2000; Kim et al., 2000; Yacoub and Hu, 2001; Yacoub et al., 2001), some animal studies have found no evidence for an initial dip (Mandeville et al., 1999; Marota et al., 1999; Silva et al., 2000; Lindauer et al., 2001). It has been suggested that differences in imaging methodology, brain regions, animal species, and anesthesia are responsible for the conflicting observations in animal studies (Buxton, 2001; Ances, 2004). One human fMRI study suggested that the initial dip may be an experimental artifact that arises when stimuli are too closely spaced in time (Fransson et al., 1998), but a subsequent study found an initial dip even with wider spacings (Yacoub et al., 1999). While there do not appear to be additional human fMRI studies that explicitly focus on the absence of the initial dip, there are many studies of the dynamics of the BOLD response that either do not find or simply do not mention the initial dip. For example, the initial dip was not observed in studies examining the effects of carbon dioxide on the BOLD response (Kemna and Posse, 2001; Cohen et al., 2002). Cohen et al. attributed the lack of detection to differences in experimental methodology, which can be an important factor given the relatively small amplitude of the initial dip.

In addition to methodological differences, variations in the baseline vascular state due to factors such as pharmacological

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Available online on ScienceDirect (www.sciencedirect.com).

1053-8119/$ - see front matter © 2006 Elsevier Inc. All rights reserved.
doi:10.1016/j.neuroimage.2006.03.005

agents, disease, and age have been shown to alter the dynamics of the BOLD response and may therefore affect the detection of the initial dip in humans (D'Esposito et al., 2003). As an example, the carbon dioxide studies mentioned above found that vasodilation caused by hypercapnia significantly slowed down the dynamics of the BOLD response, while vasoconstriction caused by hypocapnia led to a quickening of the response. In a recent study using a 4-T MRI system, we showed that caffeine, a known vasoconstrictor, led to a quickening of the visual BOLD response in a manner similar to that observed with hypocapnia (Liu et al., 2004). Due to technical considerations (e.g., scanner instabilities), the initial dip was not easily detected in that study. In the present study, performed on a 3-T MRI system, we demonstrate robust detection of the initial dip and show that a 200 mg caffeine dose can significantly reduce the initial dip.

Methods

Experimental protocol

Five healthy subjects (ages 23 to 39) participated in the study after giving informed consent. Each subject refrained from ingesting any food or drink containing caffeine for at least 12 h prior to the experiment. The estimated daily caffeine usage of the subjects based on self-reports of coffee, tea, and caffeinated soda consumption is summarized in Table 1. The assumed caffeine contents for an 8-oz coffee, tea, and soda were 100 mg, 40 mg, and 20 mg, respectively (Fredholm et al., 1999). Each experiment lasted approximately 3 h and consisted of a 1-h pre-dose imaging session followed by a 1-h post-dose session. In addition to the actual time spent on imaging, the length of each session included time for preparation (e.g., ensuring that physiological monitoring equipment was working properly), parameter set-up and execution of pre-scan routines (as necessary), and instruction of the subject prior to each scan. Between sessions, the subject ingested an over-the-counter tablet containing 200 mg of caffeine and rested outside the scanner for approximately 30 min. The first functional run began approximately 45 min post-ingestion. This interval was chosen based on studies showing that the absorption of caffeine from the gastrointestinal tract reaches 99% about 45 min after ingestion, with a half-life of 2.5 to 4.5 h (Fredholm et al., 1999).

During both the pre-dose and post-dose imaging sessions, each subject viewed two repeats of a periodic single trial visual stimulus consisting of a 20-s initial "off" period followed by 5 cycles of a 4-s "on" period and a 40-s "off" period. During the "on" periods, a full-field, full contrast radial 8-Hz flickering checkerboard was displayed, while the "off" periods consisted of a gray background of luminance equal to the average luminance of the "on" period. Three of the five subjects viewed two additional repeats of the periodic single trial design. As described below, these were acquired with a smaller imaging slice thickness than the first two repeats. In addition, a resting-state scan, during which the subject was presented with the "off" condition for 3 min, was performed and used to characterize the resting CBF level.

Imaging protocol

Imaging data were collected on a GE Signa Excite 3 Tesla whole body system with a body transmit coil and an eight channel receive coil. Laser alignment was used to landmark the subject and minimize differences in head position between sessions. During the resting-state scan, data were acquired with a PICORE QUIPPS II (Wong et al., 1998) arterial spin labeling (ASL) sequence (TR = 2 s, TI1/TI2 = 600/1500 ms, 10-cm tag thickness, and a 1-cm tag-slice gap) with a dual echo spiral readout (TE1/TE2 = 9.1/30 ms, FOV = 24 cm, 64 × 64 matrix, and a flip angle = 90°). Small bipolar crusher gradients were included to remove signal from large vessels (b = 2 s/mm^2). Three oblique axial 8-mm slices were prescribed about the calcarine sulcus for this ASL run. During the periodic single trial runs, BOLD-weighted images were acquired with a spiral readout (TE = 25 ms, TR = 500 ms, FOV = 24 cm, 64 × 64 matrix, and a flip angle of 45°). In all five subjects, these BOLD runs used the same slice prescription as the ASL runs (e.g., three 8-mm slices). The choice of the 8-mm slice thickness reflects the fact that the experiments on two of the subjects (labeled as Subjects 4 and 5 in Results) were not originally intended to examine the initial dip. To determine whether there was an effect of the large slice thickness, the experiments in the three remaining subjects (labeled 1 to 3 in Results) included two additional BOLD-weighted runs using the periodic single trial design and acquired with six oblique 4-mm slices covering the same volume as the three 8-mm slices. For all periodic single trials acquired at either slice thickness, 480 volumes at a TR of 500 ms were acquired.

A high-resolution structural scan was acquired with a magnetization prepared 3D fast spoiled gradient acquisition in the steady-state (FSPGR) sequence (TI 450 ms, TR 7.9 ms, TE 3.1 ms, 12° flip angle, FOV 25 × 25 × 16 cm, matrix 256 × 256 × 124). In addition, a cerebrospinal fluid (CSF) reference scan and a minimum contrast scan were acquired for use in CBF quantification. The CSF scan consisted of a single-echo, single repetition scan acquired at full relaxation and echo time equal to 9.1 ms, while the minimum contrast scan was acquired at TR = 2 s and TE = 11 ms. Both scans used the same in-plane parameters as the ASL scans, but the number of slices was increased to cover the lateral ventricles.

Table 1
Pre-dose and post-dose baseline CBF values shown as mean (standard deviation)

Subject	Estimated daily caffeine usage (mg)	Pre-dose baseline CBF ml/(100 g min)	Post-dose baseline CBF ml/(100 g min)	Paired t test P Value
1	200	53.4 (28.1)	33.5 (16.1)	3.9 e−18
2	<50	57.6 (23.3)	35.1 (16.8)	2.4 e−20
3	200	55.4 (22.6)	38.9 (20.2)	1.7 e−11
4	<50	73.1 (14.0)	35.8 (15.9)	1.0 e−19
5	250	88.2 (25.2)	47.4 (21.8)	1.8 e−19

Mean and standard deviation were computed across voxels in each subject's respective ROI_{dip}. For each subject, significance was computed with a paired t test (two-sided).