The Postprandial Increase in Blood Triglycerides Has No Direct Effect on the Brain BOLD Response

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Abstract: A previous study showed that ingestion of a liquid meal high in polyunsaturated lipids decreased the blood-oxygenation-level-dependent (BOLD) response measured by functional magnetic resonance imaging (fMRI) during a finger-tapping motor task, and suggested that this effect was due to a direct effect of blood lipids on the cerebral vasculature. This study compared the time course and magnitude of the BOLD response in fixed anatomic locations before and 3 h after ingestion of high versus low lipid content liquid meals (235 ml Ensure Plus [Abbot Labs] with or without 50 ml added canola oil). Blood triglyceride content peaked 3 h after the high lipid meal and was elevated by 33% compared with the low lipid meal. There was no significant effect of meal composition on the time course or magnitude of the BOLD response in fixed-location clusters of voxels which were activated during either a motor (finger-tapping), a visual (flashing checkerboard), or an integrative/cognitive (number addition) block-design task paradigm. The results indicate that increased blood total triglyceride content after a meal with relatively high polyunsaturated fat does not directly alter the hemodynamic BOLD response to neural activity. However, the postprandial effect on BOLD response of other meals with varying fat types and amounts, as well as other nutrients and phytochemicals, remains to be determined. *Hum Brain Mapp* 30:749–756, 2009. © 2008 Wiley-Liss, Inc.

Key words: functional magnetic resonance imaging; visual; motor; addition; diet

INTRODUCTION

The blood-oxygenation-level-dependent (BOLD) effect is the physiological response to neural activity which underlies many human brain functional magnetic resonance

imaging (fMRI) studies [Buxton et al., 2004; D'Esposito et al., 2003; Logothetis and Pfeuffer, 2004; Nair, 2005; Ogawa et al., 1998]. A positive BOLD effect occurs when local perfusion of an active brain region increases to a greater extent than local oxygen consumption, resulting in increased venous PO₂, decreased paramagnetic deoxyhemoglobin content, and decreased apparent transverse relaxation rate of venous blood and nearby tissue. Because BOLD-based fMRI depends directly on local vascular and metabolic events, rather than on neural activity per se, results of these fMRI studies can be dramatically affected by vascular health, by baseline metabolic state, or by vasoactive drugs. For example, vascular reactivity can be diminished by cerebrovascular disease, such that a

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negative rather than positive BOLD response is observed during neural activity [Rother et al., 2002]. Increased arterial PCO₂ decreases the magnitude of the BOLD response because it increases global brain blood flow, increases baseline venous PO₂, and decreases baseline deoxyhemoglobin [Cohen et al., 2002]. Conversely, caffeine decreases brain blood flow and increases the magnitude of BOLD response [Mulderink et al., 2002], although this effect may be limited to chronic caffeine users [Laurienti et al., 2002]. Therefore, it seems plausible that acute or chronic variations in exposure to other vasoactive substances, for example, in the diet [Francis et al., 2006], might also alter the BOLD response and contribute to variability in BOLD-based fMRI studies.

Noseworthy et al. [2003] recently reported that lipid ingestion (addition of 50 ml of canola oil to a liquid nutritional drink) decreased the magnitude of the sensorimotor cortical BOLD response to a simple finger tapping task performed 40 and 100 min after the test meals. The observed decrease in single voxel BOLD magnitude translated into a 56% decrease in the number of voxels judged "active" after 100 min by standard statistical criteria. Thus, Noseworthy et al. [2003] suggested that postprandial variations in blood lipid content might be a significant source of variability in fMRI studies. However, the mechanism for this reported effect of blood lipid on the brain BOLD response is not clear. Although chronic hyperlipidemia is well known to be associated with vascular endothelial dysfunction [Nitenberg et al., 2006], and increased saturated triglyceride content after a high fat meal does attenuate flow-mediated dilation in large peripheral conduit arteries [Marchesi et al., 2000; Vogel et al., 1997], there is little evidence that acute increases in blood triglyceride content alter the functional reactivity of cerebral microvessels. Furthermore, canola oil contains relatively little saturated fatty acid and is relatively high in omega-3 polyunsaturated fatty acid, which may actually enhance flow-mediated dilation in peripheral arteries [Cortes et al., 2006; West et al., 2005]. Therefore, the purpose of this study was to reexamine the reported effect of canola oil ingestion and blood total triglyceride content on brain BOLD responses. Specifically, the purpose was to determine whether or not total blood triglycerides alter the magnitude and/or time course of the BOLD response in locations which are unambiguously "active" during various standard fMRI tasks.

METHODS

Experimental Design

Ten healthy adult subjects (age 21 ± 4 [SD] years, range 19–30, two female) were recruited for the study, which was approved by the Michigan State University Committee on Research Involving Human Subjects, and all subjects gave informed, written consent. Each subject was studied during two 4-h experimental sessions conducted at least 2 days apart. Subjects were asked to fast and to drink only

water for at least 10 h before each study session. On each study day, the subjects underwent two identical fMRI exams (see later), the first immediately before and the second 3 h after ingestion of a liquid meal consisting of 235 ml of Ensure Plus (Abbott Labs, Abbott Park, IL; fat content 11 g), shaken either with (lipid meal) or without (control meal) 50 ml (46 g) of added canola oil. These are the same test meals used in the previous study [Noseworthy et al., 2003]. The postmeal fMRI exams were performed 3 h after the meals because blood triglyceride content typically peaks 3–4 h after a high fat meal [e.g., Marchesi et al., 2000; Rueda-Clausen et al., 2007; Vogel et al., 1997]. Half of the subjects received the high fat meal on the first study day and half on the second study day, and subjects were nominally blinded to the meal identity. Blood glucose, total cholesterol, and triglyceride contents were measured on 50 μ l arterialized samples taken from the fingers immediately before, and at 1.5, 3, and 4 h after meal ingestion using Cholestech LDX lipid panel/glucose kits (Cholestech, Haywood, CA).

The fMRI exam consisted of three short block-design paradigms intended to invoke activity in motor, visual, and integrative/cognitive areas. The motor paradigm consisted of four 30 s duration task periods of bilateral finger tapping at a target rate of 2 Hz, flanked by 30 s rest periods, similar to the paradigm described by Noseworthy et al. [2003]. However, in this study, the subjects tapped their thumbs and index fingers against a rubber sphingomanometer bulb. The bulb was attached to the respiratory monitor of the scanner, and changes in bulb pressure were continuously recorded at 40 Hz, enabling measurement of the tapping rate. Timing cues (30 s "TAP," 29 s "REST," 1 s "READY") were displayed on an optically coupled 6×4.5 inch LCD screen throughout the 4 min 30 s duration motor paradigm. The visual paradigm was an 8×10 black and white checkerboard pattern with the square colors alternated at 8 Hz. This pattern was displayed on the same LCD screen, extending 22° across the subject's visual field. The flashing checkerboard was displayed for four 10 s duration task periods flanked by 50 s duration control periods, during which a white crosshair was displayed in the center of the black screen. Subjects were instructed to look continuously at the screen throughout the 4 min 50 s duration visual paradigm. The cognitive paradigm was a mental addition task, somewhat similar to the paced visual serial addition test [Lazeron et al., 2003; Rachbauer et al., 2006]. During each of four 30 s duration task blocks, 10 random single digits (1–9) were displayed on the LCD screen (3 s per digit). These task blocks were flanked by 30 s control periods, during which random nonvowel capital letters were displayed in the same large font at the same rate. The subjects were instructed to examine the letters and digits, and when each display of digits began, to mentally add the 10 digits of that individual block together. At the end of this 4 min 30 s duration paradigm, the subjects were asked to report the sum of the last block of digits. Each

subject completed this three part, 15–20 min duration fMRI paradigm four times, that is, prelipid, postlipid, precontrol, and postcontrol.

MRI Acquisition

Images were acquired via a standard clinical eight channel head coil on a GE 3T Excite system (GE Medical Systems, Milwaukee, WI). Subjects were positioned supine and head motion was limited by foam padding packed within the coil housing. Functional images were axial, single-shot gradient-recalled echo-planar (27–33 slices, 4.5 mm slice thickness, 0.5 mm slice gap, 22 cm field-of-view, 64×64 matrix, TR 2 s, TE 30 ms, 90° flip angle) acquired continuously throughout each functional paradigm after an 8 s period of dummy acquisitions. T1-weighted anatomical images (sagittal 3D inversion-prepped fast spoiled gradient-recalled-echo, 256×192 acquisition matrix, 1 mm slice, $22 \times 22 \times 17.4$ cm³ FOV, TR 2 s, TE 1.5 ms, TI 450 ms, 15° flip angle) were acquired at the end of each imaging session.

Data Analysis

MRI data were analyzed using the AFNI software package [Cox and Hyde, 1997]. In contrast to many fMRI studies, the goal of the analysis in this study was not to determine the location of the activity per se, but rather to compare the blood-oxygenation-level-dependent (BOLD) response in the same active locations within each individual across the four exams. This was accomplished as follows. Each functional dataset was motion-corrected using the AFNI two-pass, Fourier method. Nonbrain and low signal-to-noise regions were excluded using the 3dAutomask threshold function, and the signal intensity time courses of the remaining voxels (typically near 30,000) were temporally smoothed with a 0.167 Hz low pass filter. The functional images were then temporally cross-correlated against smoothed boxcar waveforms corresponding to the appropriate task paradigm, yielding correlation maps, which were thresholded to $P < 0.01$ (motor, visual paradigms) or $P < 0.05$ significance (addition paradigm) with Bonferroni correction for the total number of brain voxels examined. Data from each exam session were then transformed into Talairach space, and contiguous clusters of voxels exceeding the threshold and in the expected anatomical locations (i.e., adjacent to central sulcus for motor, occipital lobes for visual, and medial frontal gyrus for serial addition) were chosen from one of the four exams, selected at random. These cluster locations (saved in Talairach space) were then used as masks to extract the average time course of intensity changes in those clusters from all four exams in the same subject. The mean time course and magnitude of the BOLD response to the task for each trial were then obtained by averaging the four 1-min duration task + rest blocks.

Figure 1.

Blood triglyceride content (mg/dl, mean $\pm$ SE, $n = 8$) before and for up to 4 h after ingestion of control (○) and high lipid (●) meals.

Statistics

Blood triglyceride and glucose contents, peak BOLD magnitude, total number of active voxels, and the tapping rate measured during the motor task were compared across conditions by two-factor (meal composition, exam time) repeated measures analysis of variance using SPSS (SPSS, Chicago, IL).

RESULTS

Data from two male subjects were excluded from the repeated measures analyses because their blood triglyceride levels were elevated on arrival (201 and 137 mg/dl), such that their triglyceride levels actually decreased (to 173 and 86 mg/dl) 3 h after drinking the lipid meal. On subsequent questioning, these subjects were somewhat vague concerning their adherence to the overnight fast. Figure 1 shows triglyceride levels in the remaining eight subjects before and after meal ingestion. As expected, in these subjects blood triglyceride increased after the lipid meal and decreased after the lower fat control meal, such that there was a significant interaction ($P = 0.03$) between time and meal. Thus, blood triglyceride content was 33% higher 3 h after ingestion of the high lipid meal (100 ± 13 [SE] mg/dl) compared to the control meal (75 ± 8 mg/dl). This difference is comparable with the increase in blood triglyceride measured in a previous study 3 h after ingestion of a similar volume of various vegetable oils [Rueda-Clausen et al., 2007]. Blood glucose had returned to fasting level (89 ± 2 mg/dl) by 3 h after meal ingestion, and was not significantly different between meals. Total cholesterol averaged 139 ± 6 mg/dl in this relatively lean ($BMI = 26 \pm 1$) group of young subjects.

During the motor task the finger tapping rate, measured from the bulb pressure fluctuations, averaged 2.09 ± 0.27 Hz

Figure 2.

Talairach group-averaged axial slices with functional overlay of task-correlated activity during the four trials of the three paradigms. Top row is motor paradigm (Talairach $z + 48$), middle row is visual paradigm ($z + 6$), and bottom row is addition paradigm ($z + 50$).

($\pm$ SE, $n = 8$), and did not significantly vary between trials. Figure 2 (top row) shows a representative axial slice from the Talairach-averaged group response to the motor task for each of the four trials. As expected from previous studies [e.g., Noseworthy et al., 2003; Papke et al., 2000], this simple bilateral finger tapping task was associated with robust activity in left and right primary sensorimotor areas, the supplementary motor area, and in the cerebellum (not shown). The mean, block-averaged BOLD time courses extracted from contiguous clusters in the left sensorimotor areas of each subject for each trial are shown in Figure 3. Interestingly, in all four trials the cluster signal intensity tended to fall and then rise during the 30 s task period. However, there was no apparent effect of either meal composition or exam time on the time course of the response. ANOVA revealed no significant effect of meal or time on the BOLD magnitude within this cluster (Table I), or on the total number of active voxels across the whole brain (Table II). There was a significant interaction ($P = 0.03$) between meal versus time for total number of voxels after this task, that is, the number of active voxels decreased after the control meal but not after the lipid meal.

As expected [e.g., Cohen et al., 2002], visual stimulation was associated with robust activation of the occipital primary visual area (Fig. 2, middle row). Again, however, there was no apparent effect on the time course of the BOLD response in the largest contiguous cluster within this area (Fig. 4), and there was no significant effect of meal composition on either the magnitude of the cluster response (Table I) or on the total number of active voxels (Table II). However, there was a trend toward decreased total number of active voxels in both postmeal trials compared with the pre-meal trials for this paradigm ($P = 0.056$).

After the addition paradigm, subjects reported the correct sum for the last task block for 28 of the 32 trials (two errors before and two after the lipid meal). For this paradigm, the largest group-averaged clusters of activation were in the medial and left middle frontal gyrus (Fig. 2, bottom row). Activation in these areas was also observed in three previous fMRI studies of mental addition [Kamashima et al., 2004; Lazerion et al., 2003; Rachbauer et al., 2006]. However, in those studies, in which the only visual stimulus during the control blocks was a constant visual fixation point, there was also widespread task-correlated

Figure 3.

Block-averaged time course of signal intensity changes (% mean $\pm$ SE, $n = 8$ subjects) in left primary sensorimotor cluster during and after 30 s of bilateral finger tapping before ($\circ$) and 3 h after ($\bullet$) ingestion of the control meal (top panel) and lipid meal (bottom panel).

activation in occipital and parietal areas. Apparently, the display of random letters during the control blocks in this study suppressed much of that task-correlated activation, revealing more focal clusters which are presumably more uniquely related to the number interpretation or computational components of the task. Again, however, ANOVA revealed no significant effects of either meal composition or exam time on the total number of active voxels (Table II), and there was no difference across trials in either the

TABLE I. Cluster BOLD magnitude (maximum percent change in signal intensity, mean $\pm$ SE, $n = 8$)

Paradigm	Precontrol	Postcontrol	Prelipid	Postlipid
Motor	1.77 $\pm$ 0.12	1.83 $\pm$ 0.22	1.84 $\pm$ 0.11	1.98 $\pm$ 0.18
Visual	2.91 $\pm$ 0.21	3.04 $\pm$ 0.36	3.17 $\pm$ 0.18	2.57 $\pm$ 0.24
Addition	1.24 $\pm$ 0.07	1.38 $\pm$ 0.13	1.33 $\pm$ 0.21	1.74 $\pm$ 0.15

TABLE II. Number of active voxels (mean $\pm$ SE, $n = 8$)

Paradigm	Precontrol	Postcontrol	Prelipid	Postlipid
Motor ^a	2074 $\pm$ 340	1261 $\pm$ 207 ^b	1475 $\pm$ 271	1528 $\pm$ 247
Visual	795 $\pm$ 65	671 $\pm$ 90	907 $\pm$ 160	572 $\pm$ 131
Addition	579 $\pm$ 128	625 $\pm$ 232	708 $\pm$ 196	661 $\pm$ 297

^aSignificant interaction between meal and time, $P = 0.03$.

^bSignificant difference, pre- versus postmeal, $P = 0.01$.

magnitude (Table I) or time course (Fig. 5) of the BOLD response in the medial frontal gyrus cluster.

DISCUSSION

In contrast to the previous study of Noseworthy et al. [2003], this study provides no evidence that a postprandial

Figure 4.

Block-averaged time course of signal intensity changes (% mean $\pm$ SE, $n = 8$ subjects) in occipital cluster during and after 10 s of flashing checkerboard stimulus before ($\circ$) and 3 h after ($\bullet$) ingestion of the control meal (top panel) and lipid meal (bottom panel).

Figure 5.

Block-averaged time course of signal intensity changes (% mean $\pm$ SE, $n = 8$ subjects) in medial frontal gyrus cluster during and after 30 s number addition task before ($\circ$) and 3 h after ($\bullet$) ingestion of the control meal (top panel) and lipid meal (bottom panel).

increase in blood total triglyceride content per se directly decreases the BOLD response in healthy young subjects. One possible explanation for this difference in results is that the postmeal exam in this study was conducted 3 h after meal ingestion, whereas in the previous study post-meal exams were conducted 40 and 100 min after meal ingestion. Both this study (Fig. 1) and many previous studies [e.g., Marchesi et al., 2000; Rueda-Clausen et al., 2007; Vogel et al., 1997] show that the peak in blood triglyceride content after a high fat meal occurs after 3 h. If the decrease in BOLD response reported previously were because of a direct effect of blood triglyceride on the cerebral vasculature, then the effect should have been magnified in this study, and it was not. Therefore, it seems unlikely that the decreased response reported previously was due to a direct effect of blood triglyceride content. In fact, acute fat ingestion invokes other physiological and behavioral responses which can occur more rapidly than

the rise in blood triglyceride. In particular, cholecystokinin [Liddle et al., 1985] and other centrally acting peptides [Chaudhri et al., 2006] are released by the gastrointestinal tract after a high-fat meal. It may be that these substances directly or indirectly influence subject mood or attention after a high fat meal [Wells et al., 1997, 1998], leading to altered task performance and decreased neural activity during simple, repetitive tasks such as finger tapping. For example, in as much as the magnitude of the BOLD response to finger tapping depends strongly on tapping frequency [Rao et al., 1996], and the tapping rate was not measured in the previous study, decreased tapping rate after fat ingestion might explain the previous result.

Another difference between this and the previous study is that the main outcome measurement in this study was the signal intensity change within fixed cluster locations, whereas in the previous study the main reported outcome measure was total number of active voxels. Statistical classification of individual voxels as active or inactive depends on image quality and physiologic noise [Kruger and Glover, 2001], as well as on the magnitude of the task-correlated signal change. Thus, the variability of the voxel counting measurement (Table II) was generally higher than the variability of the BOLD magnitude measurement (Table I). Surprisingly, in this study, there was a statistically significant decrease in number of active voxels for the motor paradigm after the control (but not the high lipid) meal compared with before the meal, but no significant change in BOLD magnitude in the fixed-location sensorimotor cluster. Whether the observed decrease in active voxels reflects a true difference in the spatial extent of neural activity, or is an artifact caused by time-dependent changes in physiologic noise or other factors is not clear. However, in either case, the fact that the cluster BOLD response was unchanged suggests that the decrease in active voxels was not because of a change in the local hemodynamic response to activity.

There are other methodological differences which might have contributed to the difference between the results of this study versus the previous study of Noseworthy et al. [2003]. For example, this study was conducted at 3 T versus 1.5 T, and used echo-planar versus spiral acquisitions, either of which could alter BOLD contrast-to-noise. Tapping against the sphingomanometer bulb in this study might have required more force or increased subject attention to task performance compared with the tapping task in the previous study. Finally, although both studies used relatively young subjects, there may be other factors, such as physical activity level, fasting triglyceride or glucose levels, or circadian and/or circannual rhythms which differed between subject groups in the two studies, and which influenced subject responses during repeated exams. Again, however, consideration of these methodological differences does not reinforce the view that the result reported by Noseworthy et al. [2003] can be directly attributed to blood lipid content per se.

Of course, the results of this study do not rule out the possibility that chronic hyperlipidemia, or larger, acute increases in postprandial blood total triglyceride (e.g., to over 200 mg/dl, or clinically hyperlipidemic) could directly alter the BOLD response to neural activity during fMRI studies. Furthermore, it is possible that lipids with different fatty acid composition or additional nutrients (e.g., tocopherols, polyphenols) might have different effects on cerebral hemodynamics. For example, canola oil contains relatively large amounts of α -linolenic acid, an omega-3 polyunsaturated fatty acid. Unlike saturated and monounsaturated fats, meals high in α -linolenic acid do not attenuate flow-mediated dilation in peripheral vessels [Cortes et al., 2006; Vogel et al., 2000]. It is also possible that blood-borne free fatty acids might have more direct vascular effects than triglycerides. In fact, infusion of α -linolenic acid was recently shown to increase cerebral blood flow in mice by direct activation of the TREK-1 potassium channel in cerebral vessels [Blondeau et al., 2007]. Finally, as noted earlier, meal ingestion invokes changes in cholecystokinin, insulin, and other hormones which might alter subject mood, and indirectly influence fMRI studies. Therefore, as suggested by Noseworthy et al. [2003], the potential influence of subjects' dietary habits and prandial state, as well as other factors such as smoking, caffeine ingestion, or circadian rhythm ought to be considered in the design and interpretation of BOLD-based fMRI studies.

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