Published in final edited form as:
*J Ultrasound Med*. 2010 July ; 29(7): 1017–1022.







# BRAIN BLOOD FLOW AND VELOCITY: CORRELATIONS BETWEEN MAGNETIC RESONANCE IMAGING AND TRANSCRANIAL DOPPLER

**Farzaneh Sorond, M.D., Ph.D.**[1], **Norman K. Hollenberg, M.D., Ph.D**[2], **Lawrence P. Panych, Ph.D.**[3], and **Naomi D.L. Fisher, M.D.**[4]

[1] Department of Neurology, Brigham and Women's Hospital, Boston MA 02115

[2,3] Department of Radiology, Brigham and Women's Hospital, Boston MA 02115

[4] Department of Medicine, Brigham and Women's Hospital, Boston MA 02115

## Abstract

**Objective—**Because transcranial Doppler TCD is unable to measure arterial diameter, it remains unproven whether the changes in cerebral blood velocity it measures are representative of changes in cerebral blood flow. Our study was designed to compare velocity changes to flow changes measured by two MRI techniques, perfusion MRI and arterial spin labeling, using flavanol-rich cocoa to induce cerebral blood flow changes in healthy volunteers.

**Methods—**We enrolled 20 healthy subjects aged 62 to 80 years (mean 73 years). Each was studied at baseline and after consuming standardized servings of cocoa for 7–14 days.

**Results—**Changes in middle cerebral artery flow by TCD were significantly correlated with changes in perfusion assessed by gadolinium MRI ($r=0.63$; $p<0.03$). Measures with arterial spin labeling showed a stronger correlation with borderline significance.

**Conclusions—**Changes in flow velocity in the middle cerebral artery associated with drinking cocoa were highly correlated with changes in cerebral blood flow measured by two MRI techniques, using the tracer gadolinium and arterial spin labeling. These results validate Doppler measures of cerebral blood flow velocity as representative assessments of cerebral blood flow.

### Keywords

TCD; cerebral blood flow; MRI; cocoa

## INTRODUCTION

The introduction of transcranial Doppler ultrasound (TCD) to measure cerebral blood flow (CBF) velocity [1] has provided a powerful tool for non-invasive assessment of dynamic CBF velocity responses to drugs, nutritional supplements as well as various other stimuli [2–4]. TCD, which can provide continuous beat-to-beat measurement of the CBF velocity in the basal cerebral arteries with a high temporal resolution, has become the most commonly utilized tool to study relative CBF changes and regulation in humans.

Address for Correspondence: Farzaneh A. Sorond, MD, PhD, Brigham and Women's Hospital, Department of Neurology, Stroke Division, 75 Francis St, Boston, MA 02117, Fax: 617-278-6963, Tel: 617-732-6857, fsorond@partners.org.

One inherent problem with TCD is the inability to measure diameter of the artery at the point of insonation due to the scatter of the ultrasound beam through the bone plate of the skull. While several previous studies using a variety of techniques ($^{133}$Xe, SPECT, MRI) have confirmed that relative changes in CBF velocity are representative of changes in CBF [5–14], othergroups have found poor correlations between changes in CBF velocity andCBF during drug stimulation [15–18].

Our study was designed to compare CBF velocity changes to CBF changes using two different MRI techniques, perfusion magnetic resonance imaging (MRI) and arterial spin labeling (ASL) [19]. We have previously reported a substantial increase in blood flow velocity to the brain following the consumption of flavanol-rich cocoa by healthy elderly humans [2]. Therefore, in this study we used flavanol-rich cocoa to induce cerebral blood changes in healthy volunteers.

## MATERIALS AND METHODS

### Subjects

We enrolled 20 healthy right-handed subjects aged 62 to 80 years (mean 73 years) to participate in this study. Subjects were recruited from the Harvard Cooperative Program on Aging subject registry, and were carefully screened with a medical history, physical examination, and electrocardiogram. All were healthy nonsmokers with normal blood pressure and without diabetes. They refrained from alcohol, caffeine, and chocolate and cocoa intake for at least twelve hours prior to each study. The protocol was approved by the Partners Healthcare Human Subjects Institutional Review Board and followed institutional guidelines. Informed consent was obtained from all study participants.

### Experimental Protocol

Each subject was studied on two different days. On the first study day, baseline measurements of blood flow velocity in the middle cerebral artery (MCA) and cerebral perfusion measured by MRI were made. Subjects were then discharged with instructions to drink a standardized cocoa for 7 to 14 days, in two equal servings (Table 1). The follow-up visit was performed at the same time of day as the baseline study to minimize the effect of diurnal variations in cerebral blood flow, always two to four hours following their last cocoa dose.

Subjects reported to the General Clinical Research Center at the Brigham and Women's Hospital at least two hours after their last meal. TCD ultrasonography (MultiDop-X4 DWL —Transcranial Doppler Systems, Inc.; Sterling, VA) was used to measure right middle cerebral artery (MCA) mean flow velocity (MFV). The same technician performed all of the studies, and the depth of insonation was recorded so they could be duplicated in the follow-up study. The MCA signal was identified according to the criteria of Aaslide and Colleagues [1] and recorded at a depth of 50 to 60 mm. A Mueller-Moll probe fixation device was used to stabilize the Doppler probe for the duration of the study. The envelope of the velocity wave form derived from a fast-Fourier analysis of the Doppler frequency signal was displayed in digitized and real time at 500 Hz with commercially-available data acquisition software (Windaq, Dataq Instruments).

### MRI Measurements

In the first subset of 14 subjects, perfusion data were acquired based on contrast infusion, using a spin-echo planar technique with TE-TR at 80 and 1,900 milliseconds respectively. Each volume consisted of 16 axial slices of 7 mm thickness with a 1 mm gap. A bolus of 30

NIH-PA Author Manuscript

NIH-PA Author Manuscript

cc gadolinium was infused over 8 seconds and MR images were acquired continuously for a period of 114 seconds. Data were acquired using a using a GE Signa CVI 1.5 Tesla Scanner.

In the second MRI subset, involving six different subjects, arterial spin labeling was used as the flow tracer in place of gadolinium [19]. Data were acquired using a 3.0 Tesla GE Scanner and a custom fast-spin-echo sequence with continuous labeling and background suppression.

In all MRI studies, high-resolution T1-weighted 3D scans were obtained for each subject as anatomical reference for the perfusion studies. The high-resolution anatomic images were segmented to obtain subject-specific maps of gray matter and white matter and to identify specific brain regions-of-interest (ROI). Perfusion results in both studies were registered to these anatomical reference maps. The changes in flow before and after cocoa were computed for 90 different ROI (45 each on the right and left side). In this, blood flow in each region was normalized to the total blood flow over the whole brain.

All our images were reviewed by our neuroradiologists. There were no structural abnormalities (vascular or parenchymal) reported on any of the images

**Diet—**FRC (CocoPro™, Masterfoods, Inc., Hackettstown, NJ) beverage used in the study was dairy-based and formulated to deliver 900 mg of cocoa flavanols daily in two servings delivering 450 mg each. The drink packet was a dry blend that was reconstituted with water just prior to consumption. Contents of the cocoa beverage and nutritional values are presented in Table 1.

**Analysis—**Absolute values for MFV in the MCA territory were reported as the mean ± SEM and were compared using repeated measures of ANOVA. Correlation statistics were used to correlate blood flow measured by TCD and by MRI. Significance was set at $p<0.05$.

## RESULTS

### MRI-TCD Correlation

The percentage change in middle cerebral artery flow by TCD showed a significant positive correlation with percentage change in perfusion assessed by MRI using gadolinium ($r=0.63$; $p<0.03$; $N=12$; Fig. 1). The correlation was based on 12 subjects; two of the cases had to be excluded due to technical difficulties with measurement. In the 6 subjects in whom arterial spin labeling replaced gadolinium the correlation was stronger (Fig. 1; $r= 0.80$); statistical significance was borderline.

### Regional Perfusion (CBF) by MRI

We measured cerebral blood flow by region of brain, employing both MR techniques. Table 2 lists the top 20% of brain areas (18 of the 90 areas segmented) in the two studies showing the greatest effect due to cocoa, averaged over all subjects. The areas so identified by both modalities are bolded. Figure 2 shows the areas listed in Table 2. The sagittal MR images with color overlays identify the locations (Fig 3). Note that in both studies, there appeared to be more involvement from areas more frontal and inferior in location. Further, two thirds of these areas were on the left side of the brain.

## DISCUSSION

Recent developments in Doppler technology have enabled researchers to measure beat-by-beat changes in cerebral flow velocity in the major cerebral arteries that feed the pial arteries of the brain [1]. Our study was designed to ascertain whether the increase in flow velocity in the MCA associated with drinking flavanol-rich cocoa, assessed by TCD, reflected a true

NIH-PA Author Manuscript

NIH-PA Author Manuscript

increase in volume flow to the brain. Both MRI techniques of assessing CBF, using the tracer gadolinium and arterial spin labeling, yielded responses to cocoa consumption that were highly correlated to velocity responses measured by Doppler. The correlation was significant despite the intrinsic noisiness of the methods. Sorteberg, et al [20] examined the variability of the TCD flow velocities show that the standard deviation of day-to-day differences was about 12% for the MCA. Similarly, for the MRI measures Grandin et al [21] looked at the reproducibility of cerebral blood flow measured with contrast-based MRI on three separate trials and also compared the absolute values of these measures with those obtained with the gold-standard PET technique in the same subjects. A variation of 22% was found for the MRI-derived CBF measures using contrast injection. For ASL, a study based on trials at 28 sites by Petersen et al [22] found an overall 10% variation in CBF on two trials separated by 2 weeks duration.

Several approaches have been employed to ascertain whether TCD measurements are confounded by potential changes in vascular dimensions --and all have concluded that such dimensional changes did not lead to a misleading outcome [5–7, 10, 11, 23].

The most significant increases in flow occurred in the areas summarized in Table 2. Given that all of our subjects were right handed, the higher observed changes in the left hemisphere may be a reflection of their hemispheric dominance. While there may be significant amount of variability in blood flow distribution of various structural regions of the brain, it is generally acceptable that the MCA supplies the putamen, pallidum, amygdale, superior temporal pole and inferior and lateral frontal lobes. Interestingly, these areas may be involved in control of emotion and memory, supporting the future potential for flavanol-rich cocoa in clinical trials of cognitive function.

Our study demonstrated that changes in flow velocity in the middle cerebral artery associated with drinking cocoa were highly correlated with changes in cerebral blood flow measured by two MRI techniques. These results validate Doppler measures of cerebral blood flow velocity as representative assessments of cerebral blood flow.

## Acknowledgments

Mars, Inc. provided research support and cocoa. Dr. Sorond was supported by NIA K23-AG030967. Dr. Fisher was supported by NIH RO3 AG023896

## References

1. Aaslid R, Markwalder TM, Nornes H. Noninvasive transcranial Doppler ultrasound recording of flow velocity in basal cerebral arteries. J Neurosurg 1982;57:769–774. [PubMed: 7143059]
2. Sorond FA, Lipsitz LA, Hollenberg NK, et al. Cerebral blood flow response to flavanol-rich cocoa in healthy elderly humans. Neuropsychiatr Dis Treat 2008;4:433–440. [PubMed: 18728792]
3. Panerai RB. Assessment of cerebral pressure autoregulation in humans--a review of measurement methods. Physiol Meas 1998;19:305–338. [PubMed: 9735883]
4. Tiecks FP, Lam AM, Aaslid R, et al. Comparison of static and dynamic cerebral autoregulation measurements. Stroke 1995;26:1014–1019. [PubMed: 7762016]
5. Bishop CC, Powell S, Rutt D, et al. Transcranial Doppler measurement of middle cerebral artery blood flow velocity: a validation study. Stroke 1986;17:913–915. [PubMed: 3764963]
6. Clark JM, Skolnick BE, Gelfand R, et al. Relationship of 133Xe cerebral blood flow to middle cerebral arterial flow velocity in men at rest. J Cereb Blood Flow Metab 1996;16:1255–1262. [PubMed: 8898699]
7. Dahl A, Russell D, Nyberg-Hansen R, et al. A comparison of regional cerebral blood flow and middle cerebral artery blood flow velocities: simultaneous measurements in healthy subjects. J Cereb Blood Flow Metab 1992;12:1049–1054. [PubMed: 1400642]

8. Larsen FS, Olsen KS, Ejlersen E, et al. Cerebral blood flow autoregulation and transcranial Doppler sonography in patients with cirrhosis. Hepatology 1995;22:730–736. [PubMed: 7657276]
9. Larsen FS, Olsen KS, Hansen BA, et al. Transcranial Doppler is valid for determination of the lower limit of cerebral blood flow autoregulation. Stroke 1994;25:1985–1988. [PubMed: 7916502]
10. Serrador JM, Picot PA, Rutt BK, et al. MRI measures of middle cerebral artery diameter in conscious humans during simulated orthostasis. Stroke 2000;31:1672–1678. [PubMed: 10884472]
11. Sorteberg W, Lindegaard KF, Rootwelt K, et al. Blood velocity and regional blood flow in defined cerebral artery systems. Acta Neurochir (Wien) 1989;97:47–52. [PubMed: 2785744]
12. Sugimori H, Ibayashi S, Fujii K, et al. Can transcranial Doppler really detect reduced cerebral perfusion states? Stroke 1995;26:2053–2060. [PubMed: 7482649]
13. Ulrich PT, Becker T, Kempski OS. Correlation of cerebral blood flow and MCA flow velocity measured in healthy volunteers during acetazolamide and CO2 stimulation. J Neurol Sci 1995;129:120–130. [PubMed: 7608725]
14. Vorstrup S, Zbornikova V, Sjoholm H, et al. CBF and transcranial Doppler sonography during vasodilatory stress tests in patients with common carotid artery occlusion. Neurol Res 1992;14:31–38. [PubMed: 1351256]
15. Dahl A, Russell D, Nyberg-Hansen R, et al. Effect of nitroglycerin on cerebral circulation measured by transcranial Doppler and SPECT. Stroke 1989;20:1733–1736. [PubMed: 2512693]
16. Dahl A, Russell D, Nyberg-Hansen R, et al. Simultaneous assessment of vasoreactivity using transcranial Doppler ultrasound and cerebral blood flow in healthy subjects. J Cereb Blood Flow Metab 1994;14:974–981. [PubMed: 7929661]
17. Kaufman MJ, Levin JM, Ross MH, et al. Cocaine-induced cerebral vasoconstriction detected in humans with magnetic resonance angiography. Jama 1998;279:376–380. [PubMed: 9459471]
18. Kontos HA, Wei EP, Navari RM, et al. Responses of cerebral arteries and arterioles to acute hypotension and hypertension. Am J Physiol 1978;234:H371–383. [PubMed: 645875]
19. Honey G, Bullmore E. Human pharmacological MRI. Trends Pharmacol Sci 2004;25:366–374. [PubMed: 15219979]
20. Sorteberg W, Langmoen IA, Lindegaard KF, et al. Side-to-side differences and day-to-day variations of transcranial Doppler parameters in normal subjects. J Ultrasound Med 1990;9:403–409. [PubMed: 2197422]
21. Grandin CB, Bol A, Smith AM, et al. Absolute CBF and CBV measurements by MRI bolus tracking before and after acetazolamide challenge: repeatabilily and comparison with PET in humans. Neuroimage Jun 2005;26:525–535.
22. Petersen ET, Mouridsen K, Golay X. The QUASAR reproducibility study, Part II: Results from a multi-center Arterial Spin Labeling test-retest study. Neuroimage 2010;41:104–113. [PubMed: 19660557]
23. Newell DW, Aaslid R, Lam A, et al. Comparison of flow and velocity during dynamic autoregulation testing in humans. Stroke 1994;25:793–797. [PubMed: 7909175]

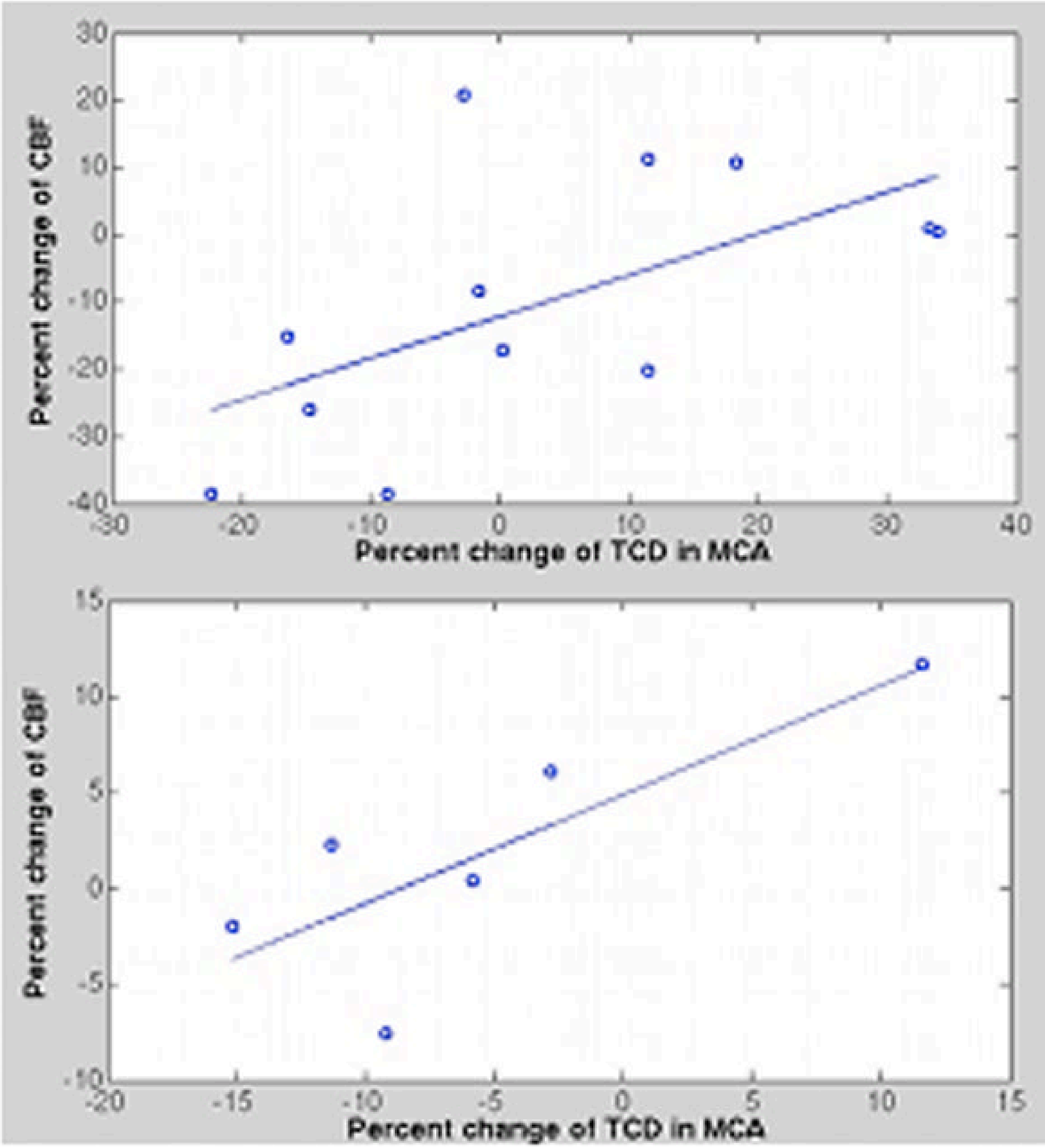


**Figure 1.**

Upper Plot: Percent change of middle cerebral artery (MCA) blood flow velocity by transcranial Doppler plotted against percentage change in cerebral blood flow measured by MRI with gadolinium.

Lower Plot: Percent change of middle cerebral artery (MCA) blood flow velocity by transcranial Doppler plotted against percent change in cerebral blood flow measured by MRI with arterial spin labeling.

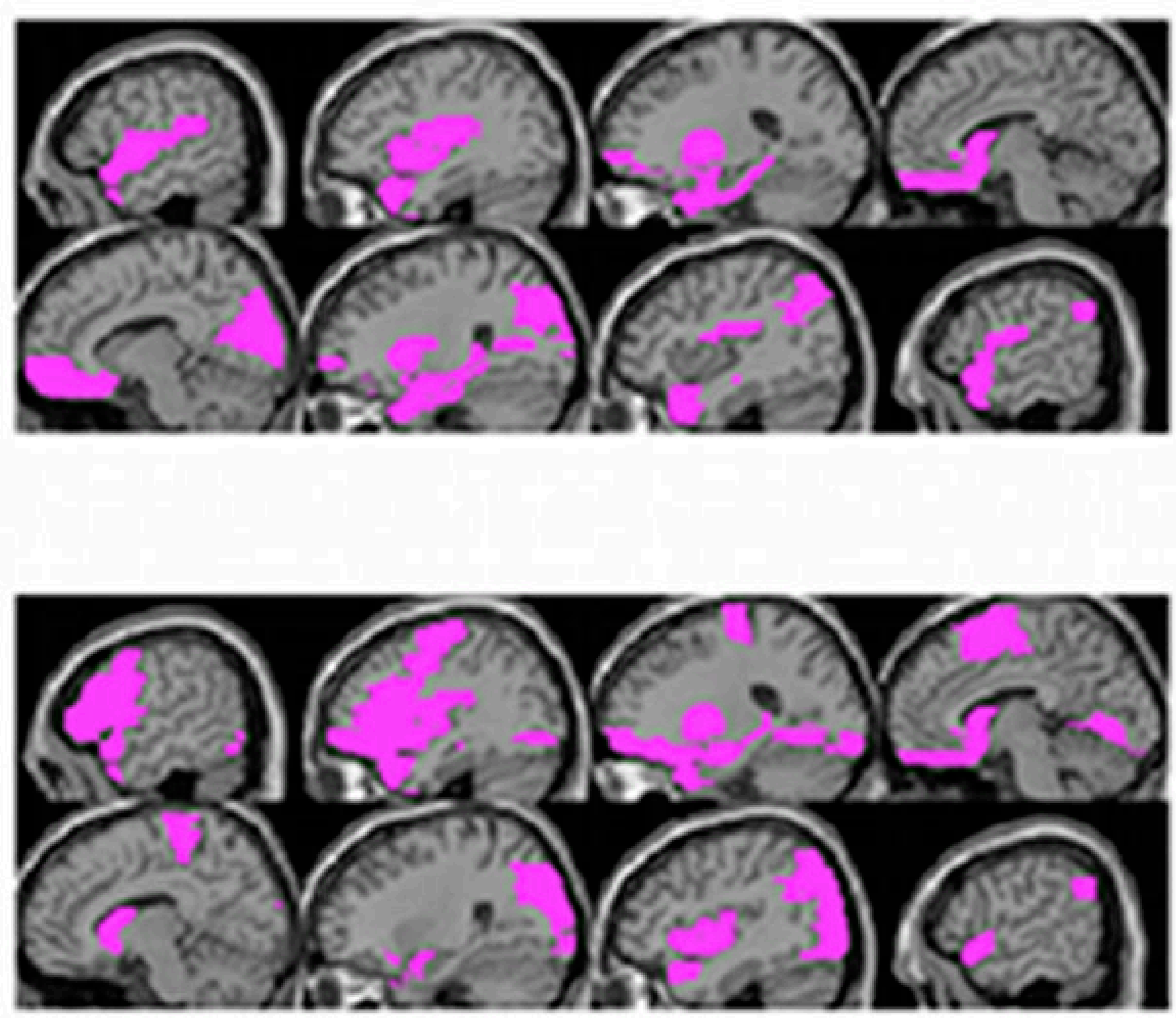

**Figure 2.**
Images identifying the locations of the areas listed in Table 2. Images in the upper panel identify the top 20% of areas from the gadolinium perfusion study where there was the greatest effect (increase) in cerebral blood flow due to cocoa, averaged over all subjects. Images in the lower panel identify the regions of greatest effect from the ASL study.

NIH-PA Author Manuscript
NIH-PA Author Manuscript

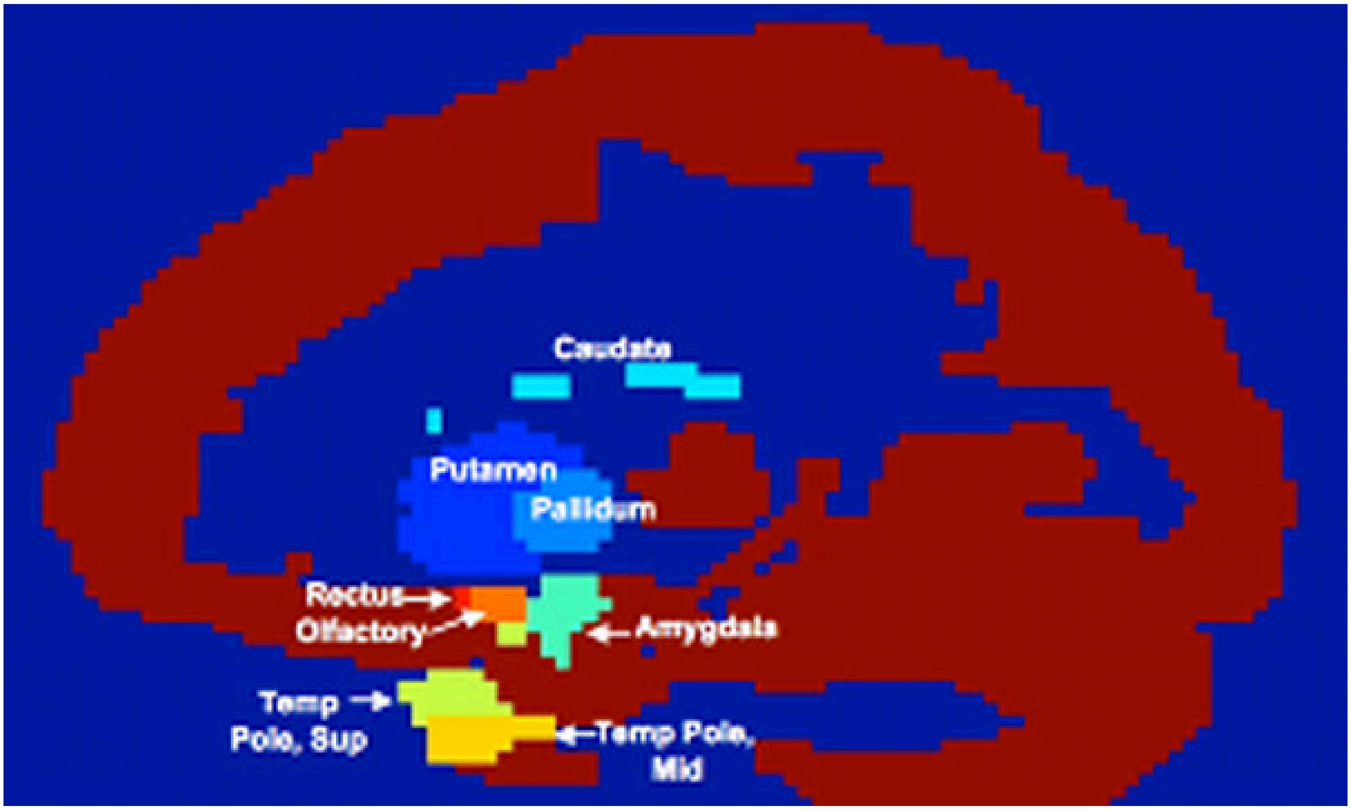


**Figure 3.**
The eight areas identified by both the gadolinium and the ASL perfusion studies as being among the most likely to show an increase in CBF due to cocoa (see Table 2): Putamen (dark blue), Pallidum (light blue), caudate (Cyan), Amygdala (light green), Rectus (light red), Olfactory (orange), Temporal Pole Superior (light yellow), Temporal Pole Mid (yellow). Areas outside the gray matter are displayed in deep blue. Gray matter areas outside the eight regions are displayed in red.

**Table 1**

Cocoa contents per serving

| | Cocoa |
|---|---|
| Cocoa flavanols, mg | 451.1 |
| Calories | 118.1 |
| Total fat, g | 1.4 |
| Cholesterol, mg | 4.4 |
| Total Carbohydrates, g | 17.1 |
| Dietary fiber, g | 3.0 |
| Sugars, g | 9.4 |
| Protein, g | 9.4 |
| Caffeine, mg | 18.3 |
| Theobromine, mg | 336.5 |
| Sodium, mg | 105.1 |
| Potassium, mg | 530.1 |
| Calcium, mg | 243.7 |
| Iron, mg | 1.9 |
| Phosphorous, mg | 280.2 |
| Magnesium, mg | 85.9 |
| Zinc, mg | 1.6 |
| Copper, mg | 0.4 |
| Manganese, mg | 0.6 |

NIH-PA Author Manuscript

NIH-PA Author Manuscript

## Table 2

Top 20% of areas showing greatest increase using the two different MRI techniques.

| Areas of Maximum Effect in Gadolinium Study | | Areas of Maximum Effect in ASL Study | |
|---|---|---|---|
| **Left** | **Right** | **Left** | **Right** |
| Rolandic Operculum | | Precentral | |
| **Olfactory** | | **Olfactory** | |
| | Frontal Mid Orbital | | |
| **Rectus** | Rectus | **Rectus** | |
| ParaHippocampal | ParaHippocampal | Hippocampus | |
| **Amygdala** | **Amygdala** | **Amygdala** | **Amygdala** |
| | Calcarine | Insula | Insula |
| | Cuneus | | |
| **Caudate** | | **Caudate** | |
| **Putamen** | | **Putamen** | |
| **Pallidum** | | **Pallidum** | |
| Heschl | | | |
| **Temporal Pole, Superior** | **Temporal Pole, Superior** | **Temporal Pole, Superior** | **Temporal Pole, Superior** |
| **Temporal Pole, Mid** | | **Temporal Pole, Mid** | |
| | | | Occipital, Superior |
| | | | Occipital, Mid |
| | | Occipital, Inferior | Occipital, Inferior |