Changes in regional cerebral blood volume in frontal cortex during mental work with and without caffeine intake: functional monitoring using near-infrared spectroscopy

Terumasa Higashi
Yukari Sone
Kanta Ogawa
Osaka University Graduate School of Medicine
Health Science
1-7 Yamadaoka, Suita
Osaka 565-0871
Japan
E-mail: thigashi@sahs.med.osaka-u.ac.jp

Yuri T. Kitamura
Osaka University Graduate School of Medicine
Division of Physiology and Biosignaling
2-2 Yamadaoka, Suita
Osaka 565-0871
Japan

Kayoko Saiki
Kobe Pharmaceutical University
4-19-1 Motoyamakitamachi
Higashinada-ku
Kobe, Hyogo 658-8558
Japan

Setsuko Sagawa
Osaka University Graduate School of Medicine
Health Science
1-7 Yamadaoka, Suita
Osaka 565-0871
Japan

Toshio Yanagida
Akitoshi Seiyama
Osaka University Graduate School of Medicine
Division of Physiology and Biosignaling
2-2 Yamadaoka, Suita
Osaka 565-0871
Japan
    and
Kansai Advanced Research Center
Brain Information Group
Communications Research Laboratory
588-2 Iwaoka
Nishi-ku
Kobe, Hyogo 651-2492
Japan

Abstract. Near-infrared spectroscopy (NIRS) was used to measure frontal regional cerebral blood volume (rCBV) in a person whose brain was under the influence of pharmacological agents while the person was performing a complex task. Fourteen healthy participants were administered Uchida-Kraepelin psychodiagnostic (UKP) tests before and after caffeine intake, and the concentration of caffeine in the urine was measured. The average number of answers and the average number of correct answers given by the participants improved significantly following caffeine intake. During the UKP testing, changes in the rCBV in the inferior frontal cortex were continuously measured using NIRS. The volume during the rest periods decreased as a result of caffeine-induced constriction of the cerebral arteriola. The volume increased during the mental work, but the degree of the increase was the same before and after caffeine intake. Although the performance of the mental work improved following caffeine intake, the improvement was not reflected in the rCBV in the inferior frontal cerebral cortex. These results suggest that caffeine helps to protect the brain from excessive hyperemia in addition to activating the neurons in the prefrontal cortex. © *2004 Society of Photo-Optical Instrumentation Engineers.*
[DOI: 10.1117/1.1755233]

1 Introduction

People at work often drink coffee or tea during break times, and the pharmacological effect of caffeine on the central nervous system and circulatory system is well understood. A typical cup of coffee contains 150 to 250 mg of caffeine, enough to stimulate the central nervous system and to con-

strict the cerebral arteriola.[1] This means that caffeine improves a person's abilities to think and to concentrate when doing mental work, while at the same time helping the person to recover from fatigue and to shake off drowsiness.

The association area in the prefrontal cortex (PFC) of the human brain has been shown to be related to mental work.[2] The Uchida-Kraepelin psychodiagnostic (UKP) test is a good mental task for investigating the changes in the regional cerebral blood volume (rCBV) in the inferior frontal cerebral cor-

Address all correspondence to Dr. Terumasa Higashi, Osaka University, School of Allied Health Sciences/Faculty of Medicine, 1-7 Yamadaoka, Suita, Osaka, 565-0871, Japan. Tel: 81-6-6879-2588; E-mail: thigashi@sahs.med.osaka-u.ac.jp

tex during mental work with and without caffeine intake since performance on the UKP test is improved by the intake of caffeine because caffeine directly affects the central nervous system.[3] In the UKP test, a subject is presented a paper on which multiple horizontal lines of random single-digit numbers are shown and asked to calculate as quickly and accurately as possible the sum of each pair of adjacent numbers from left to right at the rate of one line per minute. The results are used as a measure of the person's ability to perform work and personal character.[4] The UKP test is also frequently used in clinical psychiatry along with the Rorschach test to determine the patient's ability to perform simple mental work.[5]

Our first question is whether UKP testing induces changes in the rCBV in the inferior frontal cerebral cortex. Assuming that the answer is yes, our second question is How does the rCBV change during UKP testing after caffeine intake? Caffeine is often used to suppress headaches because it constricts the blood vessels in the brain, which suggests that caffeine intake also reduces the rCBV. Although mental work is known to induce various changes in the rCBV in the frontal region of the brain[6–9] and caffeine is known to induce vasoconstriction,[10] our two questions remain unanswered, at least to our knowledge.

It takes a person at least 1–2 h to perform the calculations in the UKP test. It also takes the same amount of time for caffeine intake to affect performance. A good way to continuously monitor changes in the rCBV in the inferior frontal cortex during lengthy experiments in which the participant may move around is to use near-infrared spectroscopy (NIRS) because it is noninvasive. The near-infrared light can penetrate a living body, owing to its high transmissivity, and the differences in the light absorption properties of oxyhemoglobin (Hb) and deoxy-Hb in the body can be used to estimate the Hb concentrations.[11,12] Using near-infrared spectroscopy (NIRS), we examined the changes in the rCBV in the prefrontal cortex and the effect of caffeine on the blood vessels in the brain during mental work (UKP tests) with and without caffeine intake.

2 Materials and Methods

2.1 Participants, Caffeine Intake, and Mental Work

Fourteen healthy men and women, aged 21 to 50, participated in our experiment. We obtained written informed consent from all participants beforehand. Each participant completed eight mental work sessions (I–VIII) lasting 15 min each. As shown in Fig. 1(a), each session consisted of five 1-min (UKP) test periods, each of which was preceded and followed by a 1-min rest period, with a 4-min rest period at the end. Immediately after finishing the third session, the participant drank coffee, either with or without caffeine.

The caffeine was administered following a double-blind protocol. CAF(+) indicates coffee with 180 mg of pharmacopoeia caffeine added to 2 g of caffeine-free coffee, while CAF(−) indicates caffeine-free coffee. The participants were asked not to consume anything containing caffeine for 24 to 48 h before the experiment. Each participant performed mental work under both the CAF(−) and CAF(+) conditions on different days after an interval longer than 1 week to minimize the effect of the experiment itself.
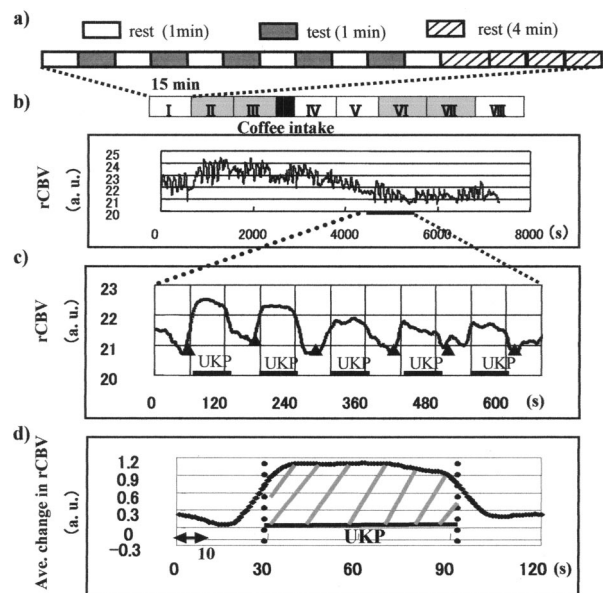
Fig. 1 (a) Rest and test periods in each work session; caffeine intake was after the third session. (b) Changes in rCBV over the course of eight sessions; rCBV is the concentration of Hb (a.u.). (c) Changes in rCBV during session VI; the periods labeled UKP were 1-min periods during which a mental work test was performed. The solid triangles show the lowest rCBV during each rest period. (d) Weighted average increase in rCBV for five test periods in session VI. Each participant started mental work at 30 s and finished it at 90 s; the double-headed arrow indicates a 10-s period used to calculate the average value of rCBV during the rest period.

At the start of each 1-min test period, a piece of paper with a horizontal line of random single-digit numbers was placed on a table in front of the participant, who was then asked to calculate as quickly and accurately as possible the sum of each pair of adjacent numbers from left to right and to write the totals on the paper in accordance with the UKP testing protocol. After completing sessions I–III, the participants took a brief break to drink coffee. They then performed sessions IV–VIII. Taking the learning effect and the length of the effectiveness of caffeine into consideration, we used the averages of the values obtained for sessions II and III as the pre-coffee-drinking values and the averages of the values obtained for sessions VI and VII as the post-coffee-drinking values.

2.2 rCBV Measurement

We measured the rCBV (the total Hb volume) in the frontal region using a three-wavelength (727, 803, and 827 nm) spatially resolved-spectroscopy (SRS)-based photometer (OM-200 NIRS monitor, Shimadzu, Tokyo). The incident light was directed though a guide onto the participant's head, and the light reflected back from the brain was collected with an optical probe consisting of two separate detectors, one 2.5 cm from the light guide and one 4 cm away. Using SRS enabled us to obtain the total volume of Hb in tissue in an arbitrary unit (a.u.).[13,14] The three laser diodes were activated sequentially to avoid interference. The temporal resolution of data acquisition was 1 s. Using this setup, we obtained continuous noninvasive measurement of the rCBV in the superficial portion of the brain (2 to 3 cm deep). To enable us to monitor the
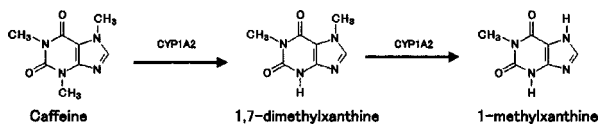
Fig. 2 Caffeine and its metabolites.

Fig. 3 (a) Average number of answers by one participant for five tests. (b) Average number of answers by one participant before (sessions II and III) and after (sessions VI and VII) drinking coffee. (c) Percentage change in average number of answers from before to after drinking coffee for CAF(−) and CAF(+), connected by a line.

rCBV of the association area in the PFC, the NIRS probe was placed against the participant's head, with the midpoint between the light emitter and light receptor 5 cm to the left of the midline of the frontal region and 3 cm above the supraorbital margin.[9]

As mentioned earlier, Fig. 1(a) shows the pattern of rest and test periods during each session. Figure 1(b) shows the rCBV measured over an entire session as an example, and Fig. 1(c) shows it for one session (VI). The lowest measured volumes during each rest period before and after each test period are shown by the solid triangles. The average value of these points was defined as the baseline for measurement during the test periods. During each test period, the increase in the frontal rCBV was calculated by summing the total increase in volume of Hb (a.u.) from the baseline using offline analysis with MS Excel. The average value for the five test periods in one session was defined as the average change in the rCBV [the hatched area in Fig. 1(d)]. For each 1-min rest period before and after each test period, an average volume of 10 s, indicated by the double-headed arrow in Fig. 1(d), was defined as the rCBV during the rest period. This 10-s period was the most stable period during which the effect of the pre- and post-UKP tests on the basal rCBV was at a minimum.

2.3 Scalp Blood Flow

To clarify the effect of blood flow in the scalp on the NIRS signal, we measured tissue blood flow in the same area of the scalp as measured with NIRS using a laser-Doppler flowmeter (LDF) (FLO-C1LDF, Omega Flow Inc., Tokyo) with a time constant of 1 s.

2.4 Caffeine Analysis

Urine samples were collected before and after the test session and frozen immediately after collection. To determine the amount of caffeine in the samples, we used a high-performance liquid column chromatography and mass spectroscopy (LC/MS) method partially modified from that described by Dobrocky et al.[15] Caffeine and its metabolites, 1,7-dimethylxanthine and 1-methylxanthine (Fig. 2), were measured with an LC/MS (LC: Hitachi L-4200 UV-VIS, L-6200 Intelligent Pump; MS: Hitachi M-1000 quadruple mass spectrometer). The caffeine and its metabolites were ionized using atmospheric pressure chemical ionization, and the ion concentration was measured using selected ion monitoring. The peak area method was used to determine the quantity of substances detected. The amounts of caffeine and its metabolites differed even though the concentrations of each in the samples were the same because the urine volumes varied among participants. Therefore creatinine was used as the standard for comparing samples because a specific quantity of creatinine is discharged during a given time. We measured the
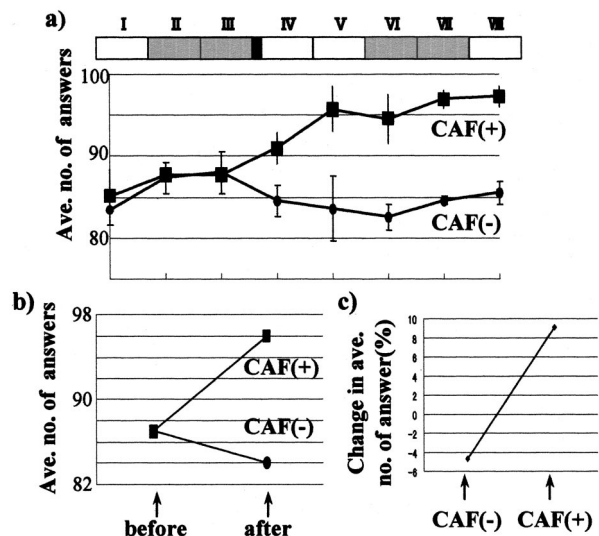
creatinine concentration with a creatinine analyzer (Creatinine Analyzer 2, Beckman Instruments) to determine the volume of urine equivalent to 0.2 mg of creatinine.

2.5 Statistics

Data are shown as the mean plus or minus the standard deviation (S.D.). The statistical significance (the P value) was evaluated using the paired t test. Significance was taken at $P < 0.05$.

3 Results

3.1 Effect of Caffeine on Mental Work

Figure 3(a) shows the average number of answers per session for one typical participant. It decreased slightly after CAF(−) intake, probably owing to growing fatigue, while it increased after CAF(+) intake. Compared with the average number of answers for the second and third sessions, the average number for the sixth and seventh sessions decreased 4.5% (from 88 to 84) after CAF(−) intake, while it increased 9.1% (from 88 to 96) after CAF(+) intake [Fig. 3(b)]. These percentage changes in the average number of answers (after/before) for CAF(−) and CAF(+), connected by a line, are shown in Fig. 3(c).

The percentage changes in the average number of answers for all 14 participants are shown in Fig. 4. Each participant's CAF(−) and CAF(+) are connected by a line. The average number increased $4.2 \pm 8.6\%$ after CAF(−) intake and $7.2 \pm 6.4\%$ after CAF(+) intake. Except for three instances, the average number was higher after CAF(+) intake than after CAF(−) intake. A paired t test showed that the differences between CAF(−) and CAF(+) were significant ($P < 0.05$).

The results for the number of correct answers were basically the same because most of the answers given were correct, so the data are not shown. The number of correct answers increased $2.4 \pm 4.1\%$ after CAF(−) intake and 7.4
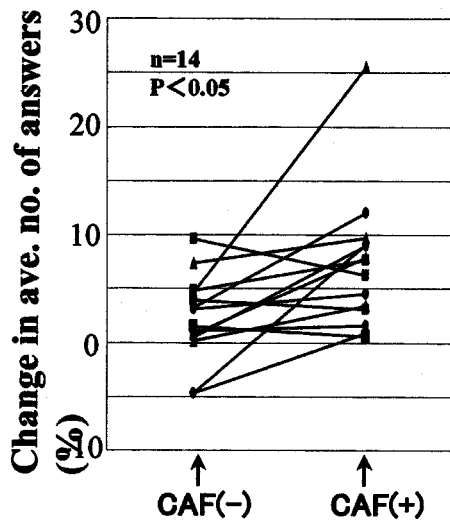
Fig. 4 Percentage changes in average number of answers from before to after drinking coffee for 14 participants. Each participant's CAF(−) and CAF(+) are connected by a line.

Fig. 5 (a) Change in rCBV for CAF(−) of one participant over the course of eight sessions. (b) Change in rCBV for CAF(+) for the same participant. (c) Percentage changes in rCBV between rest periods from before to after drinking coffee for 14 participants. (d) Percentage changes in rCBV between work periods from before to after drinking coffee for 14 participants. Each participant's CAF(−) and CAF(+) are connected by a line. Percentage change=[(average increase during sessions VI and VII)−(average increase during sessions II and III)]/ [average increase during sessions II and III]×100.

±6.8% after CAF(+) intake. Except for three instances, the average number of correct answers was higher after CAF(+) intake than after CAF(−) intake. Again, a paired t test showed that the differences between CAF(−) and CAF(+) were significant ($P<0.05$).

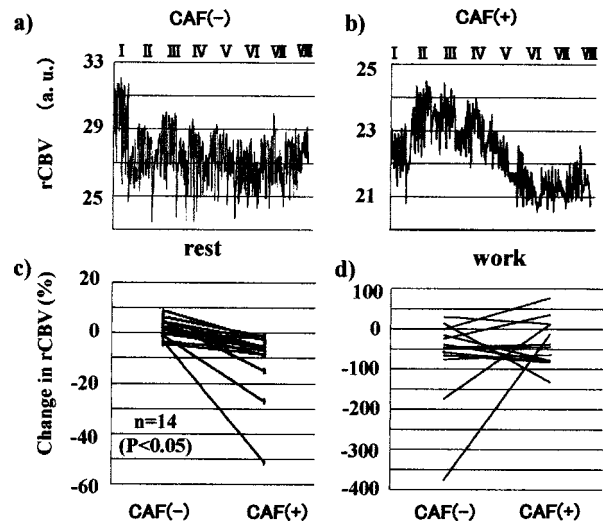## 3.2 Caffeine and its Metabolites in Urine Samples

Three of the 14 participants were unable to provide a second urine sample 2 h after the first one, and we did not subject them to collection using a catheter. Table 1 shows the average concentrations of caffeine, 1,7-dimethylxanthine, and 1-methylxanthine in the samples collected before and after CAF(−) or CAF(+) intake for the 11 participants from whom two samples were collected. The concentrations of caffeine and its metabolites in the samples are shown on the left, and the normalized volumes using the equivalent of 0.2 mg of creatinine are on the right. A paired t test showed that in both cases there were significant differences ($P<0.05$) between the average concentrations before and after CAF(+) intake in caffeine and 1,7-dimethylxanthine, while there were no significant differences in 1-methylxanthine.

3.3 Frontal rCBV Changes

The changes in the frontal rCBV during UKP testing for one participant for CAF(−) and CAF(+) intake as measured by NIRS are shown in Figs. 5(a) and 5(b), respectively. For both CAF(−) and CAF(+), there was no change in the tissue blood flow in the scalp as monitored with an LDF, indicating that the scalp blood flow did not affect the measured changes (data not shown). The baseline for CAF(−) remained unchanged after intake, while that for CAF(+) dropped. Figure 5(c) compares the changes in the rCBV resting value for CAF(−) with those for CAF(+); they were obtained by dividing the rCBV value between sessions VI and VII [i.e., the value in the double-headed arrow in Fig. 1(d)] by that between sessions II and III in each experiment. The CAF(−) and CAF(+) values for each participant are connected by a line. The average change in the rCBV for CAF

Table 1 Concentrations of caffeine and its metabolites in urine samples of 11 participants and concentrations normalized using 0.2-mg creatinine equivalent (mean+S.D.).

	CAF(−) (μg/ml)		CAF(+) (μg/ml)		CAF(−) (μg/0.2 mg Cr)		CAF(+) (μg/0.2 mg Cr)	
	Before	After	Before	After	Before	After	Before	After
Caffeine	0±0	0.1±0.2	0.3±0.7	4.5±0.8[a]	0±0	0±0	0.2±0.4	2.1±1.1[a]
1,7-diMX	0±0	3.3±6.5	3.9±7.6	12.3±5.2[a]	0±0	0.6±1.2	3.2±5.0	5.4±3.2[a]
1-MX	0±0	0.8±1.4	1.2±3.3	2.7±2.1	0±0	0.2±0.3	0.4±0.7	1.0±0.6

MX: methylxanthine
[a]$P<0.05$.

$(-)$ was $1.6 \pm 3.9\%$, and that for CAF$(+)$ was $-10.8 \pm 12.9\%$. A paired t test showed that the difference between CAF$(-)$ and CAF$(+)$ was significant $(P < 0.05)$, indicating that the frontal rCBV decreased after CAF$(+)$ intake.

The rCBV increased incrementally with each mental work task as a participant repeatedly went through rest and test periods. Figure 5(d) compares the changes in the rCBV during work for CAF$(-)$ and CAF$(+)$; they were obtained by dividing the average rCBV increase for sessions VI and VII by that for sessions II and III for each participant [Fig. 1(d)]. The CAF$(-)$ and CAF$(+)$ values for each participant are connected by a line. The average change in the rCBV for CAF$(-)$ was $-21 \pm 99\%$, and that for CAF$(+)$ was $10 \pm 57\%$. A paired t test showed no significant difference between CAF$(-)$ and CAF$(+)$ intake, indicating that caffeine intake had no significant effect on the rCBV during UKP testing.

4 Discussion

Although it is well known that caffeine directly affects the central nervous system and improves the performance of mental work[1] and that mental work affects the rCBV in the frontal region of humans,[6–9] there were no available reports on how caffeine affects the rCBV in the inferior frontal cortex during mental work like the UKP test. However, because mental calculation and number repetition, which are similar to the UKP test as mental work, are accompanied by the activation of the PFC,[16,17] the same phenomenon should occur during UKP testing. In the present study, therefore, we aimed to clarify the effect of caffeine on blood vessels in the brain, the change in the rCBV in the inferior frontal cortex during UKP testing, and the changes in the rCBV that are due to caffeine and UKP testing by using NIRS.

Caffeine is immediately absorbed in the gastrointestinal tract, and its plasma concentration reaches a peak within 15 to 45 min of intake.[1] It is then converted into 1,7-dimethylxanthine and 1-methylxanthine (Fig. 2) in the liver and excreted in urine from the kidney. The species of caffeine and the corresponding amounts of metabolic products in the urine depend on the length of time before urine collection and on the activity of the metabolic enzyme system in the liver.[15] For the 11 participants from whom two urine samples were collected, the amounts of caffeine and 1,7-dimethylxanthine in the urine increased after CAF$(+)$ intake (Table 1), indicating that their concentrations in the participants' blood were significantly elevated during the UKP testing. In contrast, there was no significant difference in the concentration of 1-methylxanthine between CAF$(-)$ and CAF$(+)$. The basal values of caffeine and its metabolic products for CAF$(+)$ were unexpectedly not zero, probably because some participants did not abide by our request not to eat or drink anything containing caffeine 24 to 48 h before the experiment.

The average number of answers in the UKP testing increased after CAF$(+)$ intake (Fig. 4), although 3 of the participants, who reported feeling heart palpitations and nausea after caffeine intake, had both fewer answers and fewer correct answers. The reactions were due to ingesting more caffeine than normally ingested at one time. In general, only the number of answers is presented for UKP testing because both the number of answers and the number of correct answers

show a similar tendency and result in the same conclusions.[4] Since our results follow this pattern, we show only the results for number of answers in Fig. 3 and Fig. 4.

Caffeine is often used as a curative medicine to suppress a headache.[1] This pharmacological effect is a result of constricting the blood vessels in the brain, which suggests that caffeine intake decreases the rCBV. This is the first report of the detection of a direct decrease in the rCBV in the human brain, as shown in Fig. 5(c), following caffeine intake. We also found that the frontal rCBV increased more during mental work than during rest. This was due to activation of the sympathetic nerve during UKP testing. Furthermore, our finding that the rCBV increased 10 s before the start of UKP testing suggests anticipatory elevation of mental tension and activation of the sympathetic nerve [Figs. 1(c) and 1(d)]. A decrease in the rCBV was observed during the course of every test period [Fig. 1(c)]. This may reflect the participant's becoming acclimated to the mental task.

The increases in the rCBV during each test period, which were described earlier, occurred to the same degree before and after caffeine intake [Fig. 5(d)]. Thus, the improvement in mental work following caffeine intake was not always accompanied by a volume change in the cerebral arteriola. Caffeine directly affects the central nervous system by inhibiting phosphodiesterase activity and the degradation of c-AMP, resulting in an increased concentration of c-AMP in the neurons.[1] As the quantity of mental work increases, the consumption of energy and oxygen should also increase. However, since the oxygen supply to the brain is 2.5 times the amount required even during resting,[18] the rCBV does not necessarily increase in proportion to the increase in oxygen consumption.

Based on our present results, we propose another hypothesis to explain the physiological significance of caffeine. When a person performs physical exercise, the temperature of the active muscles and the amount of blood supplied to the muscles are significantly increased by signals sent through the sympathetic nerve.[19] A similar phenomenon would not be beneficial for a working brain because an excess supply of blood leads to excessive hyperemia and a condition like the thermal runaway of a machine. The caffeine-induced constriction of the cerebral arteriola prevents this from happening.

5 Conclusion

Using near-infrared spectroscopy, we observed the effect of caffeine on blood vessels in the inferior frontal cortex. We found that the increase in the regional cerebral blood volume during mental work was the same before and after caffeine intake. These results suggest that caffeine helps protect the brain from excess hyperemia in addition to activating neurons in the prefrontal cortex.

References

1. C. P. O'Brien, "Drug addiction and drug abuse," Chap. 24 in *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, J. G. Hardman and L. E. Limbird, Eds., pp. 636, McGraw-Hill, New York (2001).
2. D. T. Stuss and D. F. Benson, "Neuropsychological studies of the frontal lobes," *Psychol. Bull.* **95**, 3–28 (1984).
3. H. Segawa and Y. Iikura, "Clinical effects of theophylline in the therapy of intractable asthmatic children. II. Theophylline therapy and behavior problems in children with asthma," *Allergy* **39**, 1427–1436 (1990) (Japanese).

4. H. Yamashita, T. Fujikawa, I. Yanai, S. Morinobu, and S. Yamawaki, "Cognitive dysfunction in recovered patients with silent cerebral infarction," *Neuropsychobiology* **45**, 12–18 (2002).

5. R. L. Adams and J. L. Culbertson, "Personality Assessment: Adults and Children," Chap. 7.5 in *Kaplan & Sadock's Comprehensive Textbook of Psychiatry Volume 1*, B. J. Sadock and V. A. Sadock, Eds., pp. 702–722, Lippincott Williams & Wilkins, Philadelphia (2000).

6. Y. Hoshi and M. Tamura, "Detection of dynamic changes in cerebral oxygenation coupled to neuronal function during mental work in man," *Neurosci. Lett.* **150**, 5–8 (1993).

7. Y. Hoshi and M. Tamura, "Dynamic multichannel near-infrared optical imaging of human brain activity," *J. Appl. Physiol.* **75**, 1842–1846 (1993).

8. Y. Hoshi, H. Onoe, Y. Watanabe, J. Andersson, M. Bergstrom, A. Lilja, B. Langstom, and M. Tamura, "Non-synchronous behavior of neuronal activity, oxidative metabolism and blood supply during mental tasks in man," *Neurosci. Lett.* **172**, 129–133 (1994).

9. Y. Hoshi and M. Tamura, "Near-infrared optical detection of sequential brain activation in the prefrontal cortex during mental tasks," *Neuroimage* **5**, 292–297 (1997).

10. D. Kerr, R. S. Sherwin, F. Pavalkis, P. B. Fayad, L. Sikorski, F. Rife, W. V. Tamborlane, and M. J. During, "Effect of caffeine on the recognition of and responses to hypoglycemia in humans," *Ann. Intern Med.* **119**, 799–804 (1993).

11. F. F. Jobsis, "Noninvasive infrared monitoring of cerebral and myocardial oxygen sufficiency and circulatory parameters," *Science* **198**, 1264–1267 (1977).

12. B. Chance, S. Nioka, J. Kent, K. McCully, M. Fountain, R. Greenfeld, and G. Holtom, "Time resolved spectroscopy of hemoglobin and myoglobin in resting and ischemic muscle," *Anal. Biochem.* **174**, 698–707 (1988).

13. D. T. Delpy and M. Cope, "Quantification in tissue near-infrared spectroscopy," *Philos. Trans. R. Soc. London, Ser. B* **352**, 649–659 (1997).

14. S. Homma and A. Kagaya, "Detection of oxygen consumption in different forearm muscles during handgrip exercise by spatially resolved NIR spectroscopy," *Adv. Exp. Med. Biol.* **428**, 327–332 (1997).

15. P. Dobrocky, P. N. Bennett, and L. J. Notarianni, "Rapid method for the routine determination of caffeine and its metabolites by high-performance liquid chromatography," *J. Chromatogr.* **652**, 104–108 (1994).

16. M. Pesenti, L. Zago, F. Crivello, E. Mellet, D. Samson, B. Duroux, X. Seron, B. Mazoyer, and N. Tzourio-Mazoyer, "Mental calculation in a prodigy is sustained by right prefrontal and medial temporal areas," *Nat. Neurosci.* **4**, 103–107 (2001).

17. S. F. Cowell, G. F. Egan, C. Code, J. Harasty, and J. D. Watson, "The functional neuroanatomy of simple calculation and number repetition: a parametric PET activation study," *Neuroimage* **12**, 565–573 (2000).

18. I. Kanno, K. Uemura, S. Higano, M. Murakami, H. Iida, S. Miura, F. Shishido, A. Inugami, and I. Sayama, "Oxygen extraction fraction at maximally vasodilated tissue in the ischemic brain estimated from the regional CO_2 responsiveness measured by positron emission tomography," *J. Cereb. Blood Flow Metab.* **8**, 227–235 (1988).

19. R. M. Berne and M. N. Levy, "Interplay of central and peripheral factors in the control of the circulation," Chap. 36 in *Physiology*, R. M. Berne and M. N. Levy, Eds., pp. 561–572, C. V. Mosby, St. Louis (1988).