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TRANSCRANIAL NEAR-INFRARED SPECTROSCOPY OF SMOKING BRAINS

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We used a mobile wireless near-infrared sensor for the noninvasive recording of cerebral hemoglobin concentration changes during cigarette smoking. Each measurement included 5 min of rest, 5 min of smoking imitation, and 5 min of actual smoking. We observed significant effects of the tobacco smoking on temporal changes in the human brain at time scales ranging from 200 ms to about 1 min. The most reproducible effects were an increase of the heartbeat rate and a decrease in the heartbeat power spectral density during smoking. Significant but highly individual changes due to smoking were observed in temporal patterns of hemodynamic fluctuations in 5–50 s time scales. We have also found statistically significant slow increases in both oxy- and deoxy-hemoglobin concentrations during smoking.

Keywords: Near-infrared spectroscopy; hemoglobin; brain; smoking.

1. Introduction

There is a general consensus between the medical and scientific communities that cigarette smoking causes lung cancer, heart disease, emphysema, and other serious diseases.[1] Smoking is one of the leading causes of deaths in North America, where approximately 5 million Canadians alone aged 15 years and older smoke.[2,3] The chemicals inhaled during cigarette smoking may cause a number of physiological changes in the human body.[1] However, very few studies have been carried out on the immediate short-term physiological effects of smoking. The only relevant work on the effects of nicotine on human brain was by Giessing *et al.*,[4] who used functional magnetic resonance imaging (fMRI) to show that nicotine reduced the blood oxygenation level dependent (BOLD) signal in the right intraparietal sulcus during a cognitive task. The disadvantages of the fMRI study were that nicotine was administered through Nicorette polacrilex gum rather than through natural tobacco smoking, and that fMRI provided only a qualitative indicator of oxygenation changes.

There is, however, another method to measure cerebral blood oxygenation, which is free from some of the limitations immanent to MRI. Near-infrared (NIR) light in the range of 700–1000 nm travels easily through body tissues.[5] The noninvasiveness, low cost, and portability of NIR spectroscopy (NIRS) makes it a valuable tool to measure continuous real-time changes in tissue oxygenation.[6] In recent years, researchers have started using NIRS to monitor and measure changes in oxygenated (HbO2) and deoxygenated (HHb) hemoglobin concentrations during brain functional activities.[7–9] A typical device has a light source that emits light of different NIR wavelengths on the scalp, and detectors that detect backscattered light.[6,7] Changes in the amount of backscattered light can be transformed into the changes in HbO2 and HHb using modified Beer–Lambert law.[7,9] There are several advantages of NIRS over other imaging modalities. NIRS provides accurate quantitative information about physiological parameters, such as the hemodynamic parameters, that are not available in other modalities. NIRS has a much higher temporal

resolution (in the order of milliseconds), compared to other imaging modalities such as fMRI. This allows for measurements of not only hemodynamic but also neuronal signals in the brain.[7] NIRS equipment can be made mobile thus providing the capability to monitor physiological changes in subjects while they perform their daily routines, which allows for a vast range of important physiological factors to be examined.

Siafaka *et al.*[10] used NIRS to study effects of long-term smoking on skeletal muscle microcirculation. In Ref. 10 vascular responses to brachial artery occlusion measured by NIRS were compared for groups of smokers and nonsmokers. The conclusion of the study was that vascular microcirculation in skeletal muscles in smokers is significantly impaired. This was the only NIRS study of the effects of tobacco smoking carried out so far.

While the fMRI study[4] have demonstrated that nicotine can affect cerebral hemodynamics, it could not directly address the effects of naturally administered tobacco smoke, which contains hundreds of chemicals. Commercial cigarettes are manufactured by blending tobacco leaves and processed tobacco. During the processing of these two substances, humectants increasing the amount of moisture the tobacco holds are added to the mix, as well as other flavors to mask the harsh taste of the smoke.[11–13] The majority of these extra ingredients added to the tobacco of the cigarettes does not pyrolyse extensively during smoking and hence are inhaled into the body along with the nicotine.[1] To examine the effects of chemicals contained in tobacco smoke on cerebral hemodynamics smoke must be ingested naturally during a measurement, as opposed to administration of nicotine using gum. Mobile NIRS devices can be used on test subjects in natural environments, rather than in an MRI scanner. These devices also eliminate influential negative factors such as stress of an unknown place, noisy machinery, and high equipment usage costs.

This study uses a mobile wireless NIRS sensor to determine immediate short-term effects of cigarette tobacco smoking on temporal characteristics of cerebral hemodynamics.

2. Methods and Materials

2.1. *Mobile NIR sensor*

A mobile NIR sensor (Arquatis GmbH, Rieden, Switzerland) was used for acquiring changes in cerebral HbO2 and HHb concentrations during smoking. The battery-powered portable sensor was small in size ($90 \times 30 \times 20$ mm) and light in weight (about 50 g), making the device easily wearable on the body. The device had four bi-wavelength (at 760 and 870 nm) light emitting diode sources, and four photodiode detectors. The source–detector distances were 25 mm (the optimal distance for the adult human brain measurements[8]). Data acquired by the sensor at the sampling rate of 100 Hz was transmitted to a personal digital assistant (PDA) via a 10 m range Bluetooth channel and then retransmitted to a server via the GSM wireless network using the HTTP protocol. We have developed Java software loadable to PDA which supports the above wireless data transfers.[14]

2.2. *Human subjects and experimental protocol*

20 measurements were performed on 11 different adult subjects of ages between 19 and 51. All subjects gave consent after being informed of the nature of the study. The protocol of the study was approved by the Ryerson University Research Ethics Board (file number REB 2008-003). All subjects reported themselves as smokers with at least one year smoking experience. During experiments subjects smoked their own cigarettes of various brands legally purchased in Canada. Subjects were required not to use alcohol at least during one day before the experiment.

All measurements were performed outdoors at a shelter covering subjects from precipitations and direct sunlight at daylight and at air temperatures between 17° and 26°C. During measurements subjects stayed relaxed in a comfortable chair. The NIR sensor was attached to the right side of the forehead using elastic band. Each measurement consisted of the following epochs: rest (5 min), smoking imitation (5 min), and actual smoking (5 min). Smoking imitation included repetitive inhalations of air through an unlit cigarette. During actual smoking exactly the same kind of inhalation was performed through a smoking cigarette. During both imitation and actual smoking epochs inhalations were repeated each 30 s following commands of the investigator. The accuracy of timing was within 1 s. Subjects were instructed to follow their usual smoking habits, not to push themselves while inhaling smoke or air, and to move a cigarette to mouth very slowly. The insensitivity of data to slow hand movements was tested in a number of control measurements.

2.3. *Data analysis*

All data processing was performed using MATLAB 2008b (The MathWorks^{TM}). Seven of 20 datasets with indications of artifacts due to motion or ambient light were excluded from the analysis. Remaining 13 high quality datasets were analyzed. Changes in oxy- and deoxy-hemoglobin concentrations were computed from changes in the optical signals at 760 and 870 nm using modified Lambert–Beer's law.[7,9] We analyzed effects of smoking on cerebral hemodynamics at three frequency/time scales: fast effects associated with the heartbeat (time intervals shorter than 1 s, or 1–6 Hz frequency band), slow effects (5–50 s or 0.02–0.1 Hz) associated with Mayer waves, respiration, and local vasodilation,[15] and long-time effects (1–5 min). Fast effects were analyzed using power spectral density (PSD).[16] Slow effects were revealed using band-pass filtering of the hemoglobin concentration traces. Long-time effects were separated using the third-order polynomial data fit. Statistical analysis was performed using Matlab Statistics Toolbox. In particular, the *t*-tests were performed using the *t*-test function and the regression analysis was performed using the *regstats* function.

3. Results

3.1. *Fast effects*

Two major effects of cigarette smoking were an increase of heartbeat frequency and a reduction of the heartbeat peaks in the oxy-hemoglobin PSD compared with those during both rest and imitated smoking. These effects are illustrated in Table 1 and Figs. 1 and 2, corresponding to measurements 8 and 11, respectively. No frequency increases were observed only in three out of 13 measurements presented in Table 1, i.e., in measurements 9, 17, and 18. Decreases in heartbeat PSD occurred in nine measurements; in three measurements PSD remained almost unchanged (measurements 9, 13, and 20), and in only one case the heartbeat PSD increased (measurement 19). As one can see from Table 1, the heartbeat frequency changes between imitated and real smoking ranged from 0 to 0.4 Hz (measurement 16). The average frequency increase was 0.28 Hz. The paired *t*-test performed on the heartbeat frequency data from Table 1 revealed no change between the rest and pretended smoking conditions ($p < 0.25$) and a significant ($p < 0.018$) increase of the peak frequency during smoking. The *t*-test also showed a significant decrease in the heartbeat PSD with $p < 0.04$.

Figures 1 and 2 show typical oxy-hemoglobin PSDs in 0.5–5.5 Hz range for rest, imitated smoking, and real smoking. All PSDs shown were normalized and scaled to show changes in decibels from the peak fundamental heartbeat frequency (nearest to 1 Hz) at rest. One can see that the PSD curves corresponding to actual smoking were obviously different from the curves corresponding to rest and imitated smoking. Figure 2 shows also a significant widening of the heartbeat peaks during smoking.

Table 1. Effects of smoking on heartbeat.

Experiment ID#	Age	Frequency, rest (Hz)	Frequency, imitated (Hz)	Frequency, smoking (Hz)	Peak difference (dB)*
8	19	1.21	1.22	1.33	−5
9	50	1.23	1.14	1.23	0
10	51	1.24	1.30	1.43	−2
11	43	1.31	1.32	1.52	−6
12	43	1.17	1.19	1.37	−2
13	20	1.07	1.07	1.12	0
14	22	1.42	1.54	1.82	−4
15	21	1.31	1.33	1.51	−3
16	23	1.37	1.41	1.82	−3
17	23	1.17	1.27	2.27	−1
18	45	1.51	1.46	1.46	−2
19	45	1.32	1.32	1.37	+5
20	20	1.12	1.12	1.17	0

*Peak difference is the difference between imitated smoking and actual smoking for the PSD peak at fundamental heartbeat frequency.

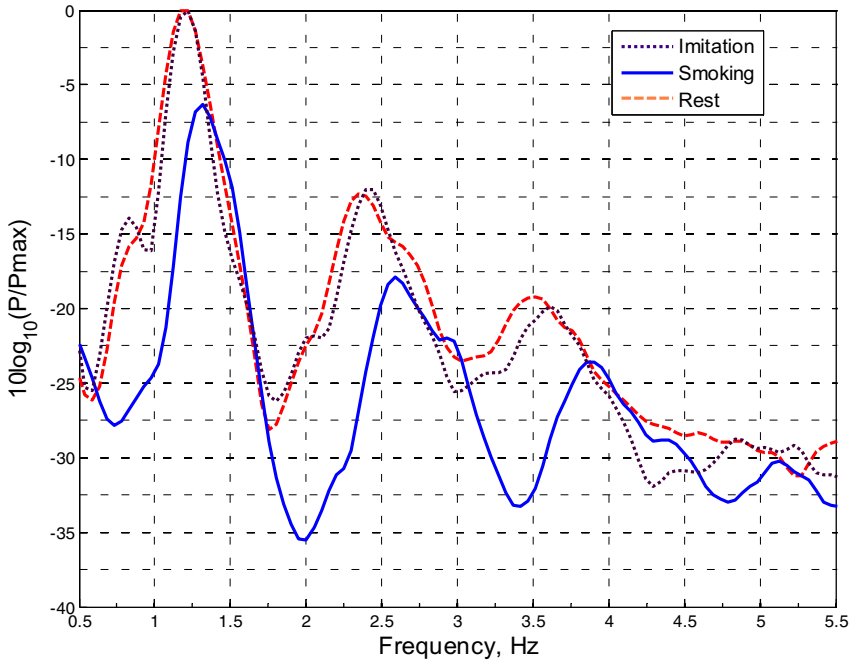


Fig. 1. Power spectral densities of oxy-hemoglobin pulsations for experiment 8.

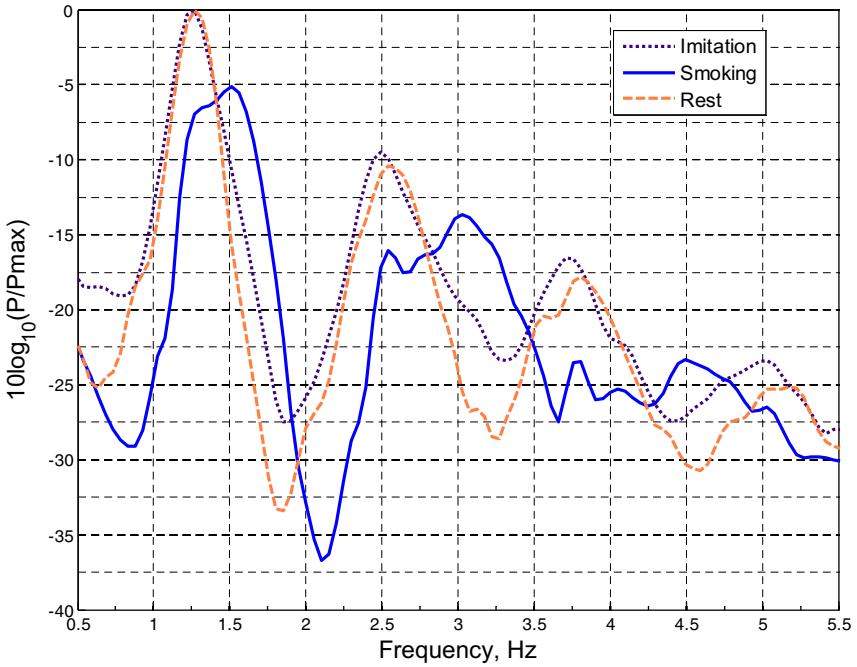


Fig. 2. Power spectral densities of oxy-hemoglobin pulsations for experiment 11.

3.2. *Slow effects*

In most experiments we observed obvious differences between temporal patterns of oxy- and deoxy-hemoglobin changes within 10–50 s time scale during imitated and real smoking. However, unlike fast effects, the temporal patterns of slow changes were highly individual and often nonstationary. Examples of the hemoglobin traces are shown in Figs. 3–5. These traces appear "flat" because they were detrended using a third-order polynomial fit in order to separate slow changes from long-time changes. In each of Figs. 3–5 the first half (300 s) of

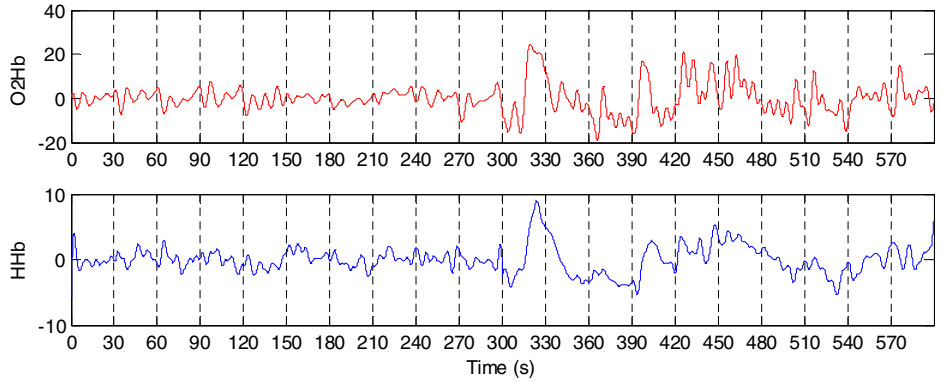


Fig. 3. Experiment 8: Slow changes in oxy- and deoxy-hemoglobin concentrations during imitated (0–300 s) and actual smoking (300–600 s).

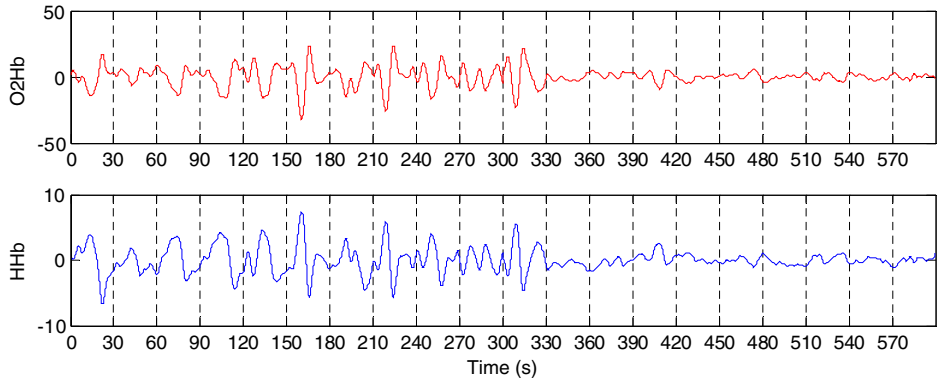


Fig. 4. Experiment 10: Slow changes in oxy- and deoxy-hemoglobin concentrations during imitated (0–300 s) and actual smoking (300–600 s).

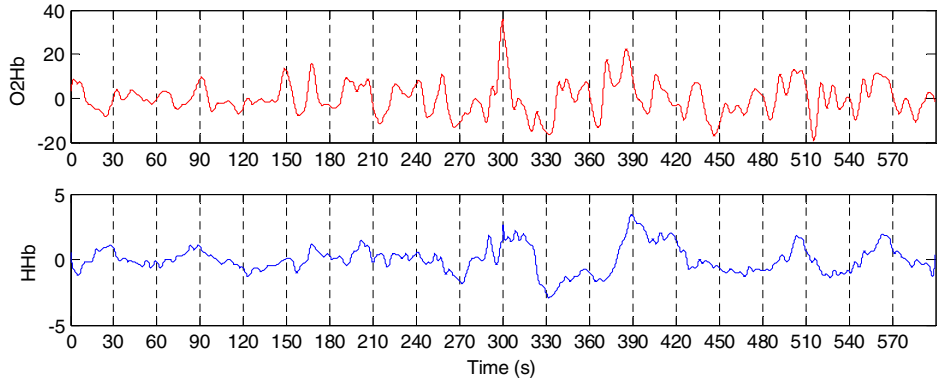


Fig. 5. Experiment 19: Slow changes in oxy- and deoxy-hemoglobin concentrations during imitated (0–300 s) and actual smoking (300–600 s).

the epoch corresponded to pretended smoking, and the second half — to the actual smoking. Figure 3 shows much higher activity during smoking than during imitated smoking, while hemoglobin variations shown in Fig. 4 had much less amplitude during actual smoking than during imitated smoking. In Fig. 5 the smoking period differs from the control one mostly by the behavior of deoxy-hemoglobin.

Each line of the vertical grid in Figs. 3–5 corresponded to an inhalation onset. Some of the waves in Figs. 3 and 4 appeared to be synchronized with inhalations. However, a detailed visual inspection

of the temporal patterns lead us to the conclusion that overall the degree of synchronization between inhalations and hemoglobin changes is relatively low. Temporal patterns in Figs. 3 and 5 appeared to be nonstationary.

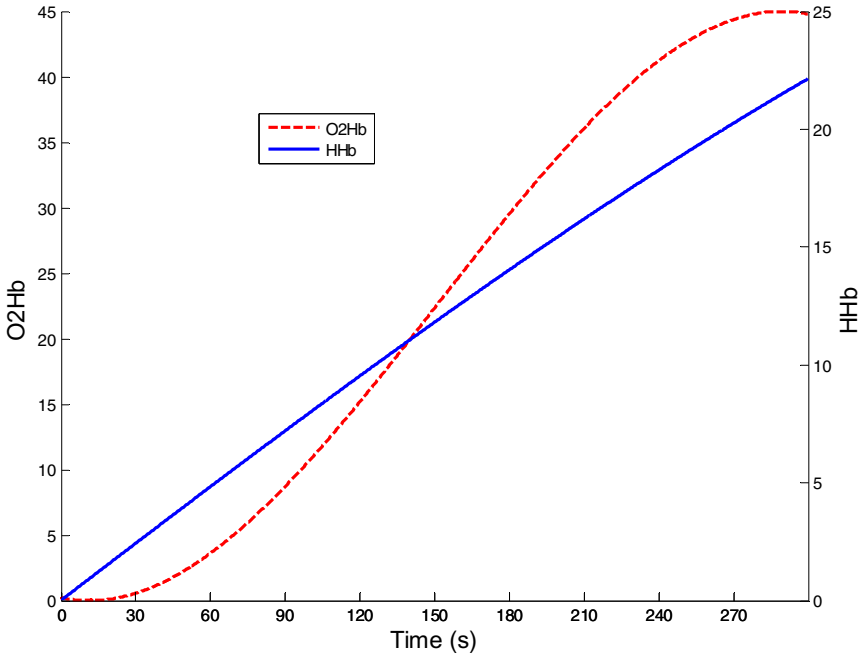
3.3. *Long-time effects*

We observed a monotonic increase in oxy- and deoxy-hemoglobin concentrations during smoking (such as the one shown in Fig. 6(a)) only in three measurements. In all other experiments the behaviors of long-time changes revealed by the third-degree polynomial data fitting were nonmonotonic and often different across four different channels. However, we never observed a significant monotonic decrease in either oxy- or deoxy-hemoglobin concentrations during smoking. The linear regression analysis performed on 52 data samples (four channels per 13 measurements) revealed statistically significant increases in both oxy- and deoxy-hemoglobin concentrations during smoking. Although the low R^2 values (0.09 and 0.10 for oxy- and deoxy-hemoglobin, respectively), indicated high data variability, the large F-values (36 and 43 for oxy- and deoxy-hemoglobin, respectively) showed the statistical significance of the effect. Figure 6(b) shows the average oxy- and deoxy-hemoglobin time traces. No significant trends in hemoglobin concentrations were found during rest or pretended smoking.

4. Discussion and Conclusion

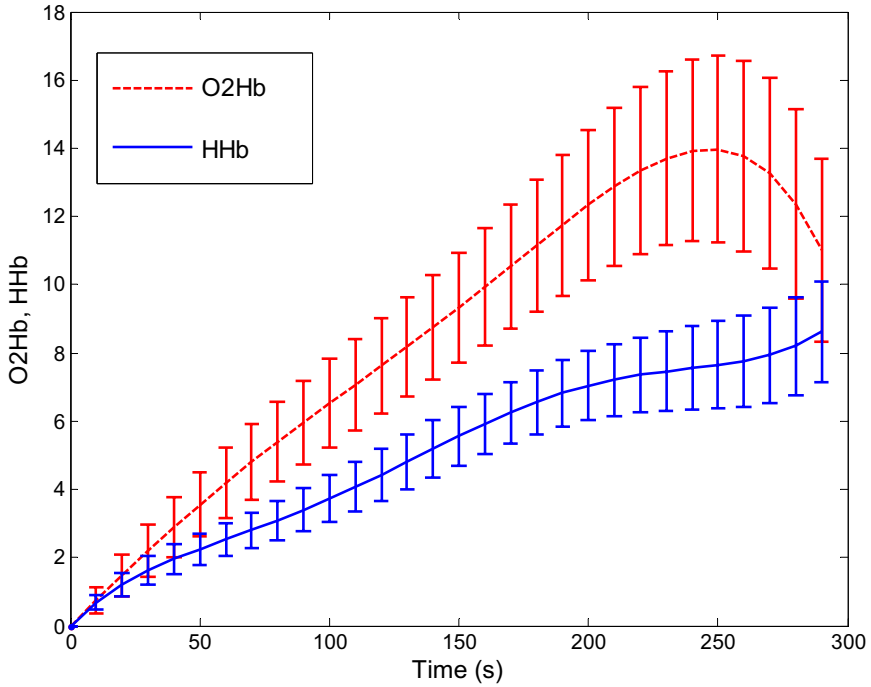
To the best of our knowledge we report here a first NIRS observation of smoking effects on cerebral hemodynamics. A previous fMRI study of the nicotine influence on the brain activity[4] used nicotine administration by Nicorette gum. The use of natural tobacco smoke in our present study became possible due to the development of a mobile NIR sensor.[14] The feasibility of mobile sensors is one of the valuable features of NIRS, and this study demonstrates the benefits of mobile NIRS devices.

Most reproducible effects of smoking we found were those on the heartbeat-related hemodynamics, i.e., the temporal changes in the frequency bandwidth of 1–5 Hz. Certainly, the increase in the heartbeat rate was a systemic effect. However, we should outline that the NIRS signals we measured depended not only on the dynamics of the heart as a source of the pulsations, but also on the vascular responsivity to the pressure waves generated by the heart. In particular, the decreases on the magnitude and widening of the PSD peaks could be due to both changes in the heart dynamics and to local changes in the vascular tone caused by smoking.



(a)

Fig. 6. (a) Experiment 18, long-time hemodynamic changes. (b) Group averaged long-time hemodynamic changes during smoking. Traces were averaged over four channels in 13 subjects. Error bars show the standard error.



(b)

Fig. 6. (*Continued*)

We have also observed significant effects of smoking on the temporal patterns of slow cerebral hemodynamic fluctuations with characteristic times from 5 to 50 s, which have been attributed to Mayer waves, spontaneous local vasodilations, and contractions, and to respiration.[15] However, unlike fast effects, these slow temporal patterns were not well reproducible across subjects. This initial study reveals the need in a further broad study, which would include a larger number of subjects sufficient to identify and to classify changes in slow temporal patterns.

A recent positron emission tomography (PET) study by Brody *et al.*[17] showed that smoking a regular cigarette resulted in 88% occupancy of the human brain nicotinic acetylcholine receptors. The PET images in Ref. 17 showed receptor saturation in most parts of the brain, in particular in the frontal lobe. Since binding of the nicotine molecules to these receptors results in an excitatory postsynaptic potential in neurons and in the release of neurotransmitters, one can expect that smoking can also cause continuous and monotonous changes in such parameters as cerebral blood volume, flow, or oxygenation. Although we observed long-time monotonic hemodynamic changes induced by smoking in a limited number of individual experiments, the averaged data showed statistically significant monotonic increases in both oxy- and deoxy-hemoglobin (and, consequently, in the blood volume). The blood volume increase can indicate an increase in the cerebral blood flow.

To conclude, this first noninvasive study has revealed significant effects of the tobacco smoking on temporal changes in the human brain at time scales ranging from 200 ms to about 1 min. This study was greatly facilitated by the use of a mobile wireless NIRS sensor, which significantly simplified measurements during smoking by allowing subjects to remain relaxed in natural conditions, outdoors, and, in particular, by eliminating the need to ventilate the room. In future studies involving larger numbers of subjects and comprehensive signal processing techniques we plan to address such questions arising from the current results as the physical and physiological origins of the observed effects and their significance for the cerebral health of smokers.

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