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OSCILLATIONS IN CEREBRAL HAEMODYNAMICS

Implications for Functional Activation Studies

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1. INTRODUCTION

The blood oxygenation level dependent (BOLD) contrast signal in functional magnetic resonance imaging (fMRI) provides highly spatially resolved deoxygenation maps of the activated cortex (Turner 1995). In common with many other activation measurement techniques, (including optical measurements) fMRI relies upon multiple repetition of the stimulus followed by signal averaging, baseline subtraction and extensive thresholding techniques to provide difference images of activation.

One of the roles of this type of data manipulation is to account for non activation related changes in the measured cerebral parameters. It is well known that the "resting" brain is in a constant state of haemodynamic redistribution (Halsey & McFarland 1974, Dóra & Kovách 1980) and hence may not be considered to provide a static baseline for activation studies. An important aspect of the status of the resting brain is the phenomena of vasomotion—the name given to rhythmical oscillatory behavior of capillary blood flow of different frequencies caused by the contraction and relaxation of the pre-capillary vessels (Berne & Levy 1997). The phenomenon of vasomotion has been known for some time and was in fact first described in 1854 (Schniff 1854). Several studies have been designed to elucidate its origin however many of the techniques employed have the disadvantage of requiring exposed cortex preparations and anaesthesia. An example of one such study on the exposed cortex of the rat has revealed slow (typically 0.1 Hz) oscillations in optical attenuation signal, which have been ascribed to the phenomenon of vasomotion (Mayhew et al., 1996). Laser doppler studies have also demonstrated the presence of "spontaneous" oscillations in flow (Hudetz et al., 1992). The advent of non

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invasive optical techniques has provided new opportunities for investigating the resting brain. Near infrared spectroscopy (NIRS) has found widespread use as a monitor of tissue oxygenation and in the past decade has been applied specifically to measurements of cerebral activation related changes in haemodynamics (Villringer et al., 1993, Meek et al., 1994).

The purpose of this study was (i) to use near infrared spectroscopy to investigate the presence and characteristics of vasomotion type signals in the intact resting adult human brain and (ii) to assess the implications of these signals upon the design of functional activation studies.

2. METHODS

2.1. Experimental Methods

The subjects for the study comprised 10 healthy adult volunteers, of median (range) age 31 (25–43) years. Light from a stabilized tungsten halogen light source was filtered with a 610 nm long pass filter and transmitted to the head of the subject using a fibre optic bundle. Transmitted light was collected with a second fiber bundle and focused onto the entry slits of a spectrograph (270 M, Instruments SA). Spectra with a resolution of 0.27 nm/pixel were collected between 650 and 980 nm on a cooled CCD detector (Wright Instruments, Enfield, London). The exposure time was set to allow a sampling rate of 19 Hz. The optodes were placed 3 cm apart over the occipital cortex, 1 cm above and to the right of the inion. Nasal airflow was measured using a pair of thermistors and the subject's pulse waveform was recorded using a pulse oximeter (Model 520, Novametrix, USA). These data were collected and stored simultaneously with the spectral information. Measurements were taken over a period of seven minutes in each subject during which they were awake in a darkened room with no auditory or visual stimuli. In all cases a support was used to prevent head movement.

2.2. Data Analysis

Changes in concentration of oxy (ΔHbO_2) and deoxyhaemoglobin (ΔHb) were obtained by fitting changes in the attenuation spectra between 780 and 900 nm to in-vitro absorption spectra of HbO_2 and Hb which had been corrected for wavelength dependence of pathlength (Wray et al., 1988, Essenpreis et al., 1993). Changes in total haemoglobin concentration (ΔHbT) were calculated from the sum of the ΔHbO_2 and ΔHb signals. Throughout this paper all concentration changes will be expressed in units of µmolar.cm.

Labview (National Instruments, Texas, USA) was used to provide a power spectrum of the raw, unaveraged ΔHbO_2, ΔHb and ΔHbT data. A power spectrum of both the nasal airflow and heart pulse waveform data was also performed to calculate the respiratory rate and heart rate for each subject.

To determine the implications of the presence of relatively slow oscillations in cerebral oxygenation and haemodynamics on BOLD fMRI data, the NIRS data was averaged to mimic a typical echo planar imaging (EPI) BOLD data acquisition sequence. This was achieved by averaging 110 ms of data every 4 seconds where 110 ms represents the echo time (TE) and 4 seconds repetition time (TR) of an EPI sequence.

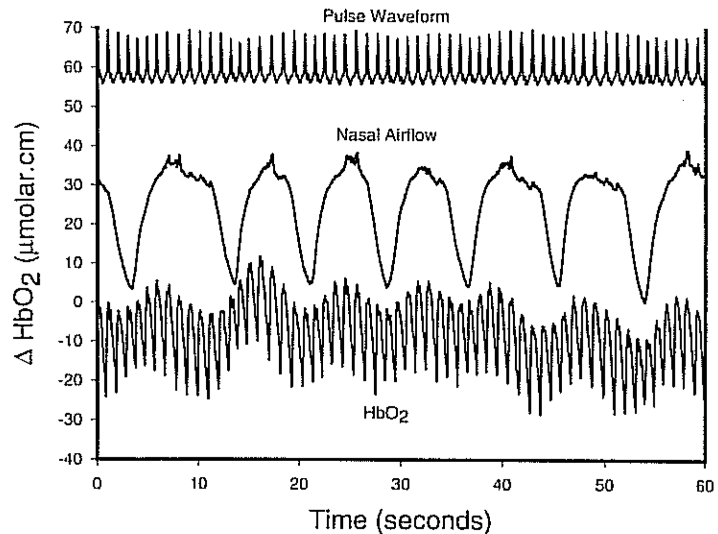


Figure 1. An example of the HbO_2, respiratory and cardiac data collected from one subject.

3. RESULTS

Figure 1 shows an example of the nasal airflow, pulse waveform and ΔHbO_2 data collected from one subject clearly demonstrating the presence of both respiratory and heart pulse related oscillations in the cerebral HbO_2 signal. Figure 2 shows a longer section of data in which a mean filter (rank 15) has been used to filter out the heart pulse effects and to reveal a slower oscillatory signal.

Figure 3 summarises the results of frequency analysis of the ΔHbO_2 signal for all subjects. A persistent slow oscillation was seen in all subjects at a range of frequencies associated with vasomotion (mean $\pm$ SD $= 0.082 \pm 0.016$ Hz) which could be clearly separated from those related to cardiac and respiratory changes.

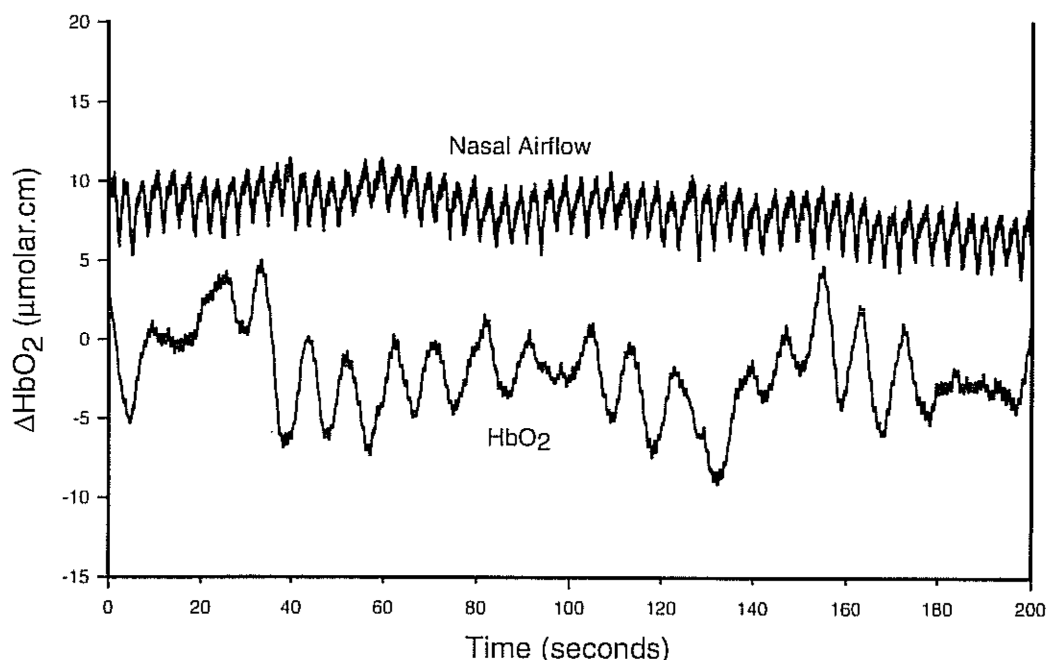
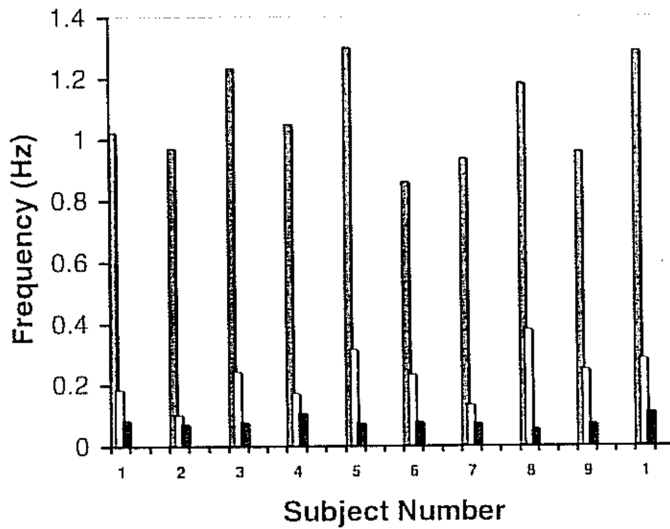


Figure 2. Evidence of the slow oscillations in HbO_2 signal in a single subject.



	Frequency (Hz)	Period (s)
heart rate	**1.08** ± 0.16	**0.9** ± 0.15
breathing rate	**0.22** ± 0.07	**4.5** ± 0.81
vasomotion	**0.082** ± 0.016	**12.2** ± 2.3

Figure 3. A histogram of the frequency components of the HbO_2 signal for each subject. The table documents the mean ± SD frequency and period for each of the three oscillations.

The cardiac, respiratory and vasomotion related oscillations were evident on each of the ΔHbO_2, ΔHb and ΔHbT signals. The relative magnitudes of the amplitudes of the three frequency components in each signal are shown in Figure 4.

It was clear that in all subjects there were a range of vasomotion frequencies. Figure 5 shows the power spectrum of the ΔHbO_2 data for a single subject illustrating the cardiac, respiratory and vasomotion peaks. Viewed on an expanded frequency scale (Figure 6) the range of vasomotion frequencies can be seen.

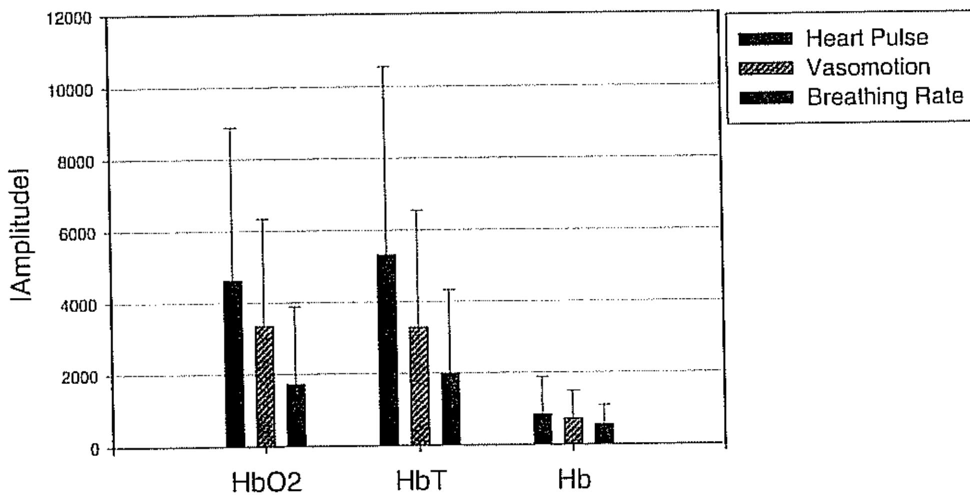


Figure 4. The relative amplitudes of the frequency components of the HbO_2, HbT and Hb data for all subjects.

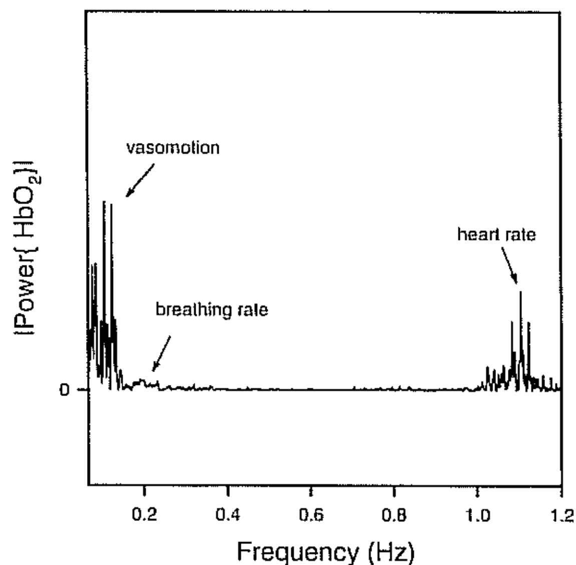


Figure 5. Power spectrum of the HbO_2 signal for a single subject.

Following the fMRI averaging, vasomotion oscillations were still visible in the NIRS data at a mean ± SD frequency of 0.075 ± 0.012 Hz in the ΔHbO_2 and ΔHbT signals and 0.082 ± 0.017 in the ΔHb signal. Figure 7 demonstrates the effect of fMRI averaging on the ΔHbT data for a single subject. The power spectrum of the HbO_2, Hb and HbT signal for this subject, after fMRI averaging, is shown in Figure 8.

4. DISCUSSION

This study has shown that in the intact, resting adult brain, cardiac and respiratory related oscillations in cerebral haemodynamics are clearly visible. In addition, oscillations in cerebral HbO_2 associated with vasomotion have also been confirmed. These oscillations, which appear to be predominantly arterial, have periods between 9 and 17 seconds.

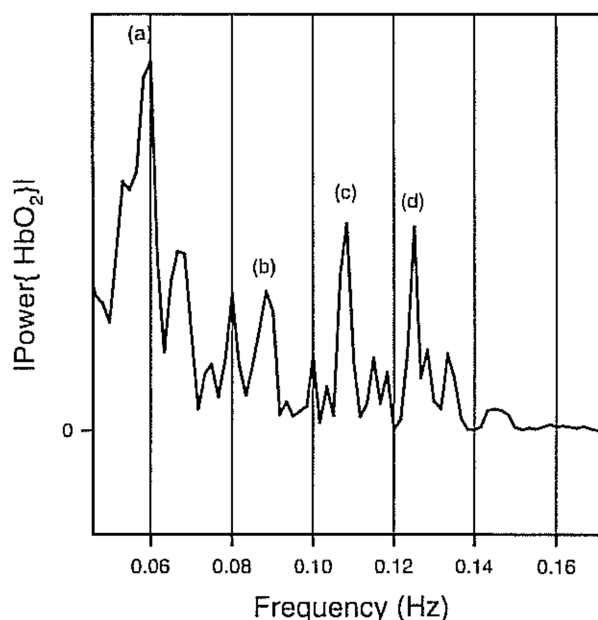


Figure 6. Expanded plot of Figure 5 demonstrating the distribution of vasomotion frequencies. The corresponding periods of the peaks shown are (a) 16.7 s, (b) 11.4 s, (c) 9.3 s and (d) 8 s.

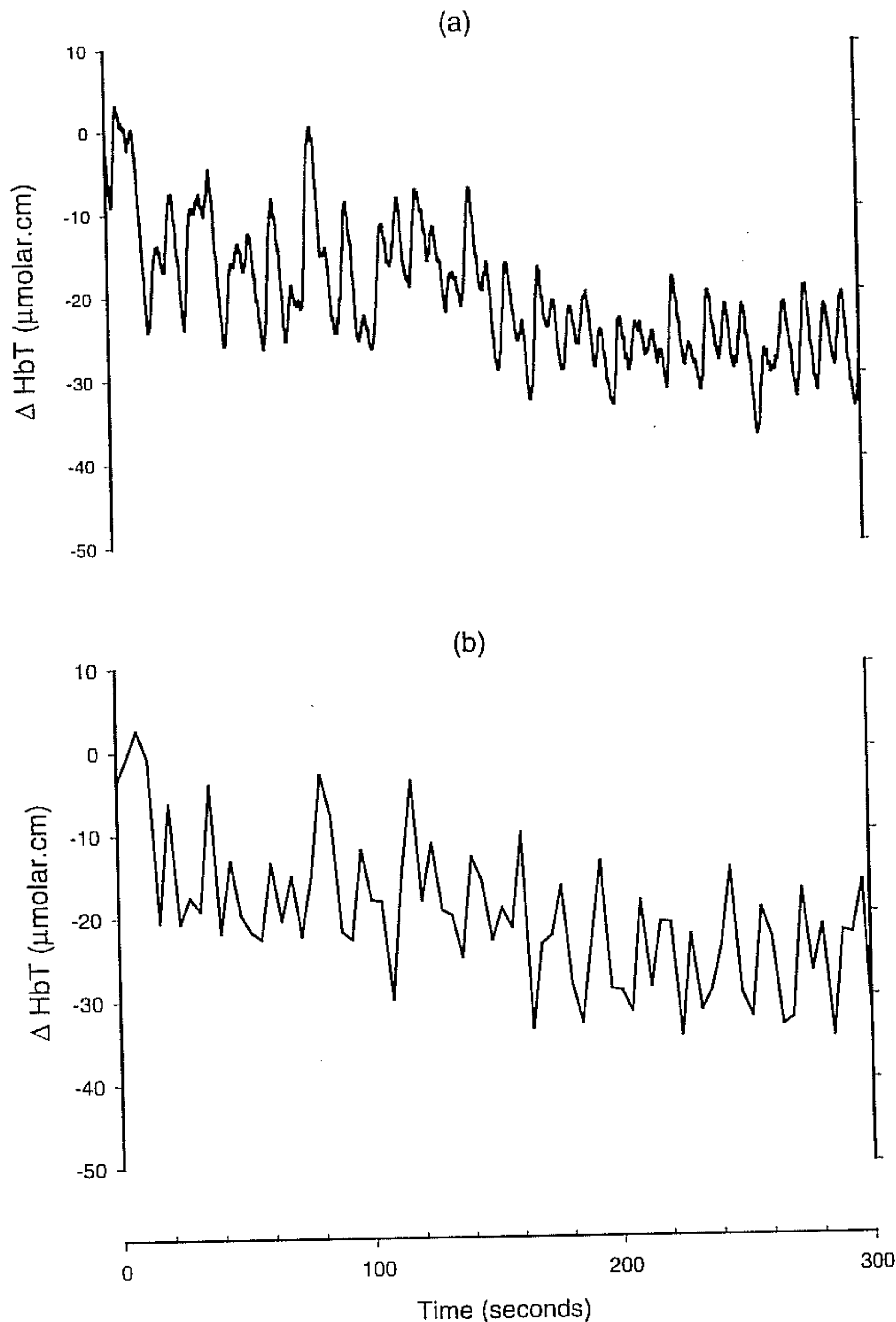


Figure 7. The ΔHbT signal (a) before and (b) after the simulated fMRI averaging assuming TE = 110 ms and TR = 4 s. The slow vasomotion oscillations are still clearly visible after averaging.

Since it was first described, vasomotion has been demonstrated in a variety of species including bats, frogs and guinea pigs and in a number of organs including skin, skeletal muscle, intestine and the brain. It is believed to originate from the spontaneous activity of the vascular smooth muscle that exhibits patterns of continuous contraction and dilation (Funk & Intaglietta, 1983). For some time research in this field was hindered by the invasive nature of available techniques for the continuous monitoring of haemodynamics. This, coupled with the sensitivity of any observations to the use of anaesthet-

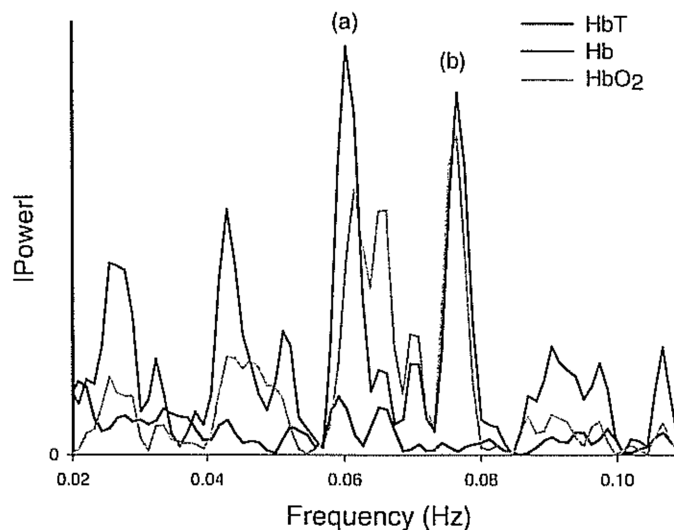


Figure 8. The power spectra of the HbO_2, Hb and HbT signals of a single subject after simulated fMRI averaging. The labelled peaks correspond to periods of (a) 16.7 s and (b) 13 s.

ics, prevented truly *spontaneous* haemodynamic events to be routinely monitored. NIRS provides the opportunity for the continuous, non invasive assessment of quantitative cerebral haemodynamics and oxygenation in the intact adult brain. Data from other groups using related technology for exposed cortex preparations indicate the presence of oscillations similar to those described here. Vern et al. (Vern et al., 1998) used visible reflectance spectroscopy to measure local light intensity changes in the exposed cortex of the cat during stages of waking and sleep. Oscillations were seen in the 590 nm signal (related to blood volume) and 603–590 nm signal (related to cytochrome aa_3) in all behavioral states at a mean ± SEM frequency of 0.14 ± 0.001 Hz which did not differ significantly between sleep states. Hoshi et al. (Hoshi & Tamura 1997), using interoptode spacings between 2 and 3 cm over the temporal, occipital and frontal regions, describe fluctuations in cerebral Hb and HbO_2 in resting adult subjects with frequencies ranging from 0.003–0.03 Hz, although no likely explanation for these oscillations is discussed.

It is important to note that most *in vitro* studies have investigated vasomotion effects at a very local level (<2 mm^2 or even single capillary loops (Hudetz et al., 1992)). In NIRS studies however, a much larger elliptical region approximately 4 cm long, 2–3 cm wide and 1–3 mm deep is interrogated (Okada et al., 1997, Firbank et al., 1998), yet significant effects are still seen over this larger volume. Further investigation is required to determine whether the relatively "macroscopic" events recorded with NIRS are likely to have the same origin as those observed in the exposed cortex.

The paramagnetic tracer responsible for the BOLD contrast signal is deoxyhaemoglobin, although the exact contribution to the BOLD signal of changes in cerebral blood volume and flow is still under debate (Buxton et al., 1998). Our data suggests that the vasomotion effects are primarily seen in the ΔHbO_2 signal, and are less prominent in the ΔHb signal. However, as demonstrated in Figure 8, there are significant vasomotion oscillations present in the ΔHbT (or cerebral blood volume) signal, the magnitude of which may well impact on BOLD measurements.

In most functional activation studies, the low signal/noise ratio makes necessary the repetition of stimulus presentation (alternating with the "rest" condition) over a number of cycles. Given the typical time constant of the haemodynamic response (6–10 s) (Bandetti et al., 1995), stimulation protocols are very often based around repetition periods between 10 and 20 s. Using a combination of experimental and theoretical

methods, Hutton et al. (1998) determined an optimal inter-stimulus interval for visual stimuli of 18 s. The possible aliasing artifacts which could be incurred by running activation protocols at these frequencies in the presence of the described vasomotion signals are obvious. In addition, the possibility of entraining the vasomotion signal to the stimulus must also be taken into account. In fMRI the problem is compounded by the relatively poor temporal resolution of the technique where standard acquisition sequences result in an effective sampling rate of approximately 0.25 Hz. As shown by the data presented in this paper, vasomotion related oscillations can still be seen at this sampling rate and may not be adequately dealt with by averaging and thresholding techniques.

Furthermore the magnitude of these resting oscillations can be equivalent to, or even exceed those of the haemodynamic changes observed during functional activation. In an identical experimental setup to the one described here, (data not presented) NIRS measurements were recorded over the occipital cortex of a subject during a visual stimulus activation study. The stimulus comprised of a black and white checkerboard pattern (reversing at 8 Hz) for 18 seconds alternating with a blank screen for 36 seconds. During activation the mean increase in HbO_2 was 8 μmolar.cm compared to mean changes during vasomotion in the resting brain of approximately 10 μmolar.cm.

Recent NIRS studies using systems with adequate signal to noise to observe single evoked responses have demonstrated that the magnitude of the evoked response itself varies with each stimulus (Colier et al., 1997). Since this characteristic is lost in repeated averaging techniques, further work with this type of instrumentation may be the key to providing more information about the effects of the slow oscillations in cerebral oxygenation haemodynamics on functional activation studies.

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