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# Entrainment of spontaneous cerebral hemodynamic oscillations to behavioral responses

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## HIGHLIGHTS

- Intrinsic hemoglobin oscillations can be entrained to periodic movements at 0.1 Hz.
- Voluntary movements can be entrained to intrinsic 0.1 Hz hemoglobin oscillations.
- Both types of entrainment are basically related.

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## ABSTRACT

Entrainment in physiological systems can be manifest in cases where phase-coupling (synchronization) between slow intrinsic oscillations and periodic motor responses, or vice versa, takes place. To test whether voluntary movement has something in common with entrainment of slow hemodynamic oscillations to motor responses, we studied blood pressure (BP), heart rate beat-to-beat intervals (RRI) and prefrontal (de)oxyhemoglobin ($Hb/HbO_2$) during 5 min of rest, 10 min of self-paced, voluntary movements and 10 min of stimulus-paced movements at 10 s intervals in 9 subjects. Subjects were divided into 2 groups according to the timing of voluntary finger movements. It appeared that these movements occurred at relatively regular intervals of approximately 10 s in 5 subjects (group A); while 4 subjects showed random or very short inter-movement intervals (group B).

Two remarkable results were obtained: first, the phase coupling ($COH^2$) between BP and RRI showed a significant ($p = 0.0061$) interaction between activity (rest vs. movement) and group (A vs. B), with an increased ($p = 0.0003$) coupling in group A. Second, the $COH^2$ between BP and Hb oscillations showed a significant ($p = 0.034$) interaction between activity and group, with a decreased ($p = 0.079$) coupling in group B.

These results suggest that subjects able to initiate self-paced, voluntary movements at relatively regular intervals of ~10 s show an entrainment potential between physiological oscillations and motor responses. This also provides the first evidence that not only physiological oscillations can be entrained to motor responses, but also motor responses (voluntary movements) can be entrained to slow intrinsic oscillations.



## 1. Introduction

Living systems are characterized by a great variety of physiological rhythms. One class includes the slow waves around 0.1 Hz in human arterial blood pressure (BP) known as Mayer or M-waves [1,2]. Such 0.1 Hz oscillations have also been reported in heart rate (HR), cerebral blood flow velocity, (de) oxyhemoglobin (Hb, $HbO_2$) concentration, EEG, and cerebral vasomotion [3–11]. Recently it was demonstrated that some healthy subjects initiated a spontaneous "willed" action (voluntary button press) phase-locked to the Mayer waves in BP and HR [12]. In two related papers it has been shown that a coupling exists not only between BP and $HbO_2$ but also between slow prefrontal $HbO_2$ and central beta power oscillations in the resting brain [13,14]. The global aim of the study is to try to clarify why EEG, cerebral hemodynamic signals and cere-

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brovascular signals oscillate preferentially with a period of ~10 s. Here we raise the questions, whether slow intrinsic BP, HR, Hb and $HbO_2$ oscillations can be entrained to stimulus-paced finger movements at 10 s intervals and whether such an entrainment can help to explain why some subjects and not others execute "willed" action related to the Mayer waves in BP.

## 2. Methods

### 2.1. Subjects and experimental paradigm

The investigation was carried out in 9 healthy subjects (2 male, 7 female) aged 20–31 years (24 ± 3.1, mean ± SD) selected from a group of 19 by the degree of phase coupling between slow $HbO_2$ and Hb oscillations ($COH^2$ >0.5; for details see [14,15]). All subjects were right-handed, had normal or corrected to normal vision, and were seated in a comfortable armchair for the experiments. The experiments were in compliance with the World Medical Association Declaration of Helsinki and the protocol was approved by the Ethics committee of the Medical University of Graz. The experiment started with an initial recording of EEG, HR, respiration, BP, $HbO_2$, and Hb during 5 min of awake rest ("rest"). The subjects were requested to rest with eyes open, stay awake, and avoid any movement. After a short pause, a 10 min recording period with self-paced voluntary brisk finger movements followed. Subjects were instructed to press a button voluntarily (at free will) with the right index finger. No prior instruction was given about the timing. After another short pause a session with 40 stimulus-paced (green cross at a TFT monitor approximately 1.5 m in front at eye level) movements in intervals of 10 s ("SPM") followed. Here only results from "rest" and "SPM" sessions are reported.

### 2.2. Data recording and processing

ECG was recorded bipolarly using electrodes placed on the thorax, BP from the finger using a continuous non-invasive monitoring system (CNAP™ Monitor 500, CNSystems, Austria), respiration by using a respiratory sensor placed on the chest (Respiratory Effort Sensor, Pro-Tech Services Inc., filter setup: 0.1–100 Hz) and $HbO_2$/Hb fluctuations with a custom made one-channel, continuous wave method-based NIRS system (details see [16]). The sources and the detector of the NIRS system were placed over the frontal cortex 1.5 cm to the left and right of position FP1. Three EEG signals were recorded (filter setup: 0.5–100 Hz) bipolarly over the sensorimotor cortex (electrodes were placed 2.5 cm anterior and posterior to C3, Cz and C4) using a biosignal amplifier (g.BSamp, g.tec, Austria). All signals were recorded with a sampling frequency of 500 Hz.

The EEG signals were band pass filtered in the frequency bands 9–14 Hz and 15–25 Hz, the data at each time point squared and then low pass filtered with a fourth-order Butterworth filter (cut-off frequency 0.13 Hz). The resulting band power time courses were log transformed and resampled at 2 Hz. The coupling between EEG band power and $HbO_2$ oscillations are reported elsewhere [14].

The beat-to-beat intervals in the ECG (RRI) and the diastolic pulse pressure amplitudes (BPdia) were linearly interpolated, resampled at 2 Hz, and displayed as RRI and diastolic (BPdia) time series. A transfer function model [17] was used to remove respiratory-related variability from instantaneous RRI- and BP-time series. Power spectra were estimated for all signals after detrending. For all spectral calculations, 1024 samples were used. The spectral values were smoothed using a 31-point triangular window, and cross-spectra were calculated between all variables (for details see [3,4]). After an automatic search for the largest peak in the cross-spectrum in the range 0.07–0.13 Hz, the corresponding coherence ($COH^2$) and phase-shift (PHA) values were determined.

### 2.3. Measurement of entrainment

In the periodic movement task two oscillatory phenomena have to be differentiated: first the intrinsic or spontaneous oscillations around 0.1 Hz, and second the sequence of movement-evoked BP, RRI, $HbO_2$ and Hb responses in the same frequency band. Entrainment is demonstrated if these 2 types of oscillations became phase-locked or synchronized. The entrainment is measured therefore by the change of phase coupling between BP–RRI, $HbO_2$–Hb and BP–Hb oscillations from the rest condition to the periodic, stimulus-paced movement. If an entrainment of 2 phase-coupled physiological signals (e.g. BP and Hb) is present, then the $COH^2$ between these signals should be enhanced. When no entrainment occurs the $COH^2$ should stay low.

### 2.4. Statistics

Results are presented as mean and standard deviation (SD). For statistical analysis of $COH^2$-changes with respect to activity (rest vs. movement), we applied a repeated measures ANOVA, with group as a between-subject factor. Statistical analysis was done using SAS 9.3.

## 3. Results

### 3.1. Phase coupling between BP, RRI, Hb and $HbO_2$ oscillations

The main focus of the study is the investigation of the coupling between slow cardiovascular and cerebral oscillations in the resting state (rest) and during the stimulus-paced movement task (SPM). For the statistical analysis the subjects were divided into 2 groups according to the timing of voluntary movements in the 10 min self-paced session. Five of 9 subjects performed voluntary movements at free will at relatively regular intervals of ~9 s (mean ± SD: 9.0 ± 2.0 s; group A). Of the 4 other subjects (group B), 3 showed movements at random intervals (between ~14 and ~31 s) and one showed movements at very short intervals of ~3 s. The grand average interval across the 4 subjects of group B was 19.4 ± 12.8 s.

Irrespective of the groups, stimulus-paced brisk finger movements (button press) at a frequency of 0.1 Hz were accompanied by a significant increase of the phase-coupling ($COH^2$) between slow oscillations in BP and RRI as compared to the rest condition (0.86 vs. 0.74; $p = 0.012$ using paired $t$-test). No significant changes were found in the coupling and phase shifts between slow BP and $HbO_2$, and prefrontal Hb and $HbO_2$ oscillations. The results for the whole group ($N = 9$) are summarized in Table 1.

Taking into account that subjects are divided into 2 groups (A and B), two significant results were obtained when cardiovascular and cerebral hemodynamic data recorded during movements at stimulus-paced 10 s intervals were compared with data from the resting state: First, the phase coupling ($COH^2$) between BP and RRI showed a significant ($p = 0.006$) interaction between activity (rest vs. movement) and group (A vs. B), with an increased coupling (0.86 vs. 0.66; $p = 0.0003$) in group A. Second, the $COH^2$ between BP and Hb oscillations showed a significant ($p = 0.034$) interaction between activity and group, with a decreased ($p = 0.079$) coupling in group B. These statistical results are summarized in Table 2 and displayed in Fig. 1.