Monochromatic Ultra-Slow (~0.1 Hz) Oscillations in the human electroencephalogram and their relation to hemodynamics

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Abstract

Previous studies demonstrated the presence of Monochromatic Ultra-Slow Oscillations (MUSO) in human EEG. In the present study we explored the biological origin of MUSO by simultaneous recordings of EEG, Near-Infrared Spectroscopy (NIRS), arterial blood pressure, respiration and Laser Doppler flowmetry. We used a head-up tilt test in order to check whether MUSO might relate to Mayer waves in arterial blood pressure, known to be enhanced by the tilting procedure. MUSO were detected in 8 out of 10 subjects during rest and showed a striking monochromatic spectrum (0.07–0.14 Hz). The spatial topography of MUSO was complex, showing multiple foci variable across subjects. While the head-up tilt test increased the relative power of Mayer waves, it had no effect on MUSO. On the other hand, the relative spectral power of 0.1 Hz oscillations in EEG, NIRS and blood pressure signals were positively correlated across subjects in the tilted condition. Eight subjects showed a coherence between MUSO and NIRS/arterial blood pressure. Moreover, MUSO at different electrode sites demonstrated coherence not reducible to volume conduction, thus indicating that MUSO are unlikely to be generated by one source. We related our experimental findings to known biological phenomena being generated at about 0.1 Hz, i.e.: arterial blood pressure, cerebral and skin vasomotion, respiration and neuronal activity. While no definite conclusion can yet be drawn as to an exact physiological mechanism of MUSO, we suggest that these oscillations might be of a rather extraneuronal origin reflecting cerebral vasomotion.

Keywords:
Neuronal oscillations
EEG
NIRS
Brain hemodynamics

Introduction

Neuronal oscillations are involved in many brain processes including perceptual, motor and cognitive activity. EEG and MEG are particularly relevant for studying oscillations since they provide a direct and real-time measure of neuronal activity. The majority of previous studies have focused on theta (~4–7 Hz), alpha (~8–12 Hz), beta (~15–12 Hz) and gamma (~30 Hz) oscillations. Ever since Hans Berger’s discovery of alpha oscillations they are recognized as the most pronounced rhythmic activity in the human brain, being identified by a well defined spectral peak. In contrast, for EEG activity in the very low frequency range (~0.1 Hz), which has been topic of previous studies (Vanhatalo et al., 2004, 2005). In addition, very slow oscillations in a restricted frequency range were found in invasive recordings in rabbits (7–9 cycles/min, Aladjawola, 1957) and in human scalp EEG recordings (~0.1 Hz, Girton et al., 1973; Trimmel et al., 1990). Although these oscillations were recorded with electrophysiological techniques, there is no unambiguous evidence that they were due to neuronal activity. In addition, only one or few electrodes were used to record these slow oscillations, thus restricting the interpretation of the obtained results.

Apart from neuronal activity, very slow fluctuations also occur in cerebral hemodynamics as detected with fMRI (Balduzzi et al., 2008; Biswal et al., 1995; Fox and Raichle, 2007; Khader et al., 2008; Magnuson et al., 2010; Mantini et al., 2007), however these fluctuations are not strictly periodic, and are well described by 1/f spectrum. On the other hand, hemodynamic activity recorded with Near-Infrared Spectroscopy (NIRS) (Obrig et al., 2000; Sirotin and Das, 2009), does show pronounced oscillations at 0.1 Hz. These 0.1 Hz oscillations are also present in fluctuations of arterial blood pressure and are called Mayer waves (Julien, 2006). Interestingly, NIRS signals and Mayer waves show pronounced coherence at 0.1 Hz range (Obrig et al., 2000; Pfurtscheller et al., 2011). Another prominent source of 0.1 Hz in hemodynamic fluctuations is due to cerebral vasomotion, as shown in

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animals (Golanov et al., 1994; Mayhew et al., 1996) and more recently in humans (Rayshubskiy et al., 2013).

In the present study we combined multichannel electrophysiological and hemodynamic measures in order to investigate the biological origin of electroencephalographic Monochromatic (very narrow frequency range) Ultra-Slow Oscillations (MUSO) centered around 0.1 Hz. Given that EEG MUSO, found in the present study, peak at the same frequency (−0.1 Hz) as previously reported NIRS and blood pressure oscillations, we hypothesized that MUSO might relate to hemodynamic activity. In order to differentiate the contribution of systemic effect (blood pressure) and brain hemodynamics to the generation of MUSO, we performed recordings of EEG, arterial blood pressure and NIRS, before and after perturbation of hemodynamic activity with head-up tilt test (Cooke et al., 1999; Furlan et al., 2000). In particular, we conjectured that MUSO might be due to hemodynamic fluctuations having an electric counterpart. This idea would be in agreement with the recent findings showing that some EEG responses can be generated by cerebral hemodynamics modulating DC potential created by blood brain barrier (Vanhatalo et al., 2004; Voipio et al., 2003). If this were the case one should also observe a coupling between MUSO and oscillations in NIRS/blood pressure signals as extensively addressed in the present study.

Material and methods

We studied ten healthy male subjects (age: 29.3 ± 4.4 years, mean ± standard deviation). In order to address the origin of EEG MUSO we used a combination of different techniques such as: electroencephalography (EEG), Near Infrared Spectroscopy (NIRS), non-invasive blood pressure monitoring, measurement of respiration and Laser Doppler flowmetry. Below we will provide details on each of these techniques.

The experimental protocol was approved by the Ethics Committee of the Charité – University Medicine Berlin, and written informed consent was provided by all subjects.

We observed MUSO at a frequency of −0.1 Hz thus being in the frequency range of Mayer waves, which are known to reflect fluctuation in arterial blood pressure (Julien, 2006). Therefore, we aimed at investigating how MUSO would be modulated by the experimental manipulations known to affect Mayer waves. One of the standard procedures, leading to the increase of the amplitude of 0.1 Hz oscillations in blood pressure, is a head-up tilt test (Cooke et al., 1999; Furlan et al., 2000) where the subject it tilted on a table by about 60–75°. In order to investigate whether changes in MUSO, recorded with EEG, can be due to the changes in Mayer waves, we utilized a passive head-up tilt test, tilting the head up to 60° on a special table providing a foot support.

Protocol

After EEG and NIRS preparation, the subject was placed in a supine position on a special table equipped with a foot support. A finger cuff was applied on the left-hand index finger and calibrated for blood pressure measurements. The subject was instructed to relax with eyes open.

We performed four consecutive recording sessions of 10 min each, alternating supine and tilted positions: during the supine session the subject was lying on the bed; in the tilted position the bed was at 60° with respect to the horizontal plane. Recordings from the four different devices (EEG, NIRS, blood pressure, respiration) were synchronized by a continuous train of TTL pulses.

Experimental setup

Electroencephalography

EEG was acquired with BrainAmp MR-plus (Brain Products, Germany) amplifiers, using 58 electrodes (Fig. 1, Ag/AgCl sintered ring electrodes, EasyCap, Germany) with nose being a reference. During data acquisition EEG signals were band-pass filtered between 0.016 and 250 Hz and digitized at a rate of 1000 Hz. For later calculations data were low-pass filtered at 80 Hz and down-sampled to 200 Hz.

Blood pressure

Arterial blood pressure was measured non-invasively on a beat-to-beat basis by finger photoplethysmography (Finometer® midi, FMS, Amsterdam, Netherlands). The brachial arterial pressure was then reconstructed using a general inverse anti-resonance model correcting for the difference in pressure waveforms after individual forearm cuff calibration (Bogert and van Lieshout, 2005). Sampling frequency was set to 1 kHz. For later calculations data were low-pass filtered at 80 Hz and down-sampled to 200 Hz. In this paper we generally refer to brachial arterial pressure as blood pressure (BP).

NIRS

The NIRS-System (NIRScout 8–16, NIRx Medizintechnik GmbH, Germany) consisted of 24 optical fibers (8 sources with wavelengths of 850 nm and 760 nm) and 16 detectors thus resulting in 26 measurement channels, as shown in Fig. 1. Concentration changes of hemoglobin were calculated according to the modified Lambert–Beer law on the NIRS data (differential path length factor of 5.98 (higher wavelength) and 7.15 (lower wavelength), extinction coefficients for HbO = 2.5264/1.4866 (higher/lower wavelength) and HbR 1.7986/3.8437 (higher/lower wavelength), and an inter-optode-distance of 3 cm). As already used in Fazli et al. (2012), the extinction coefficients were calculated according to publicly available data (see e.g. http://www.spectros.com/fileadmin/user_upload/library/Data_Hemoglobin_Standards.pdf) provided by W.B. Gratzer, Med. Res. Council Labs, Holly Hill, London and N. Kollias, Wellman Laboratories, Harvard Medical School, Boston. The differential pathlength factors (DPF) are taken from Essenpreis et al. (1993). This procedure converts attenuation changes measured by the NIRS system into concentration changes of oxygenated (Oxy-Hb) and deoxygenated hemoglobin. In agreement with a previous study (Obrist et al., 2000), 0.1 Hz oscillations were detected primarily in Oxy-Hb and thus we restrict the following analysis to Oxy-Hb signals. Frontal, parietal and occipital regions of the left and right hemispheres were studied.
motor and parietal areas of the head were covered with optodes as shown in Fig. 1. The sampling frequency was 6.25 Hz (for further calculations involving EEG we up-sampled the data to 200 Hz). NIRS probes and EEG electrodes were integrated in a standard EEG cap (extended 10–20 system) with inter-optode distances 2–3 cm. The optical probes were constructed such that they fit into the ring of standard electrodes. This allowed us to place NIRS fibers at the same locations as EEG electrodes.

Respiration

The respiratory activity was monitored with a respiration belt (Brain Products, Germany) placed around the subject's torso, at the level of the stomach.

Laser Doppler flowmetry

In a separate experimental session we recorded EEG (15 electrodes over the right hemisphere) in three subjects while simultaneously measuring cutaneous skin blood microcirculation with Laser Doppler technique (PeriFlux System 5000 by Perimed AB, Stockholm, Sweden).

During the recording the subjects were sitting in a comfortable chair with their eyes being open. The Laser-Doppler instrument operated at 780 nm (red wavelength) and a short emitter detector distance (0.25 mm); hence the penetration depth was between 0.5 and 1 mm. Its probe (Probe 407 by Perimed AB, Stockholm, Sweden) was placed at three different locations during three 10-minute sessions: at the forehead close to the position of AF4 electrode, at a central position close to a position of C4 electrode and at a parietal position close to a P4 electrode. The probe was placed into a holder integrated in the EEG cap and fixed at the subject's scalp by an adhesive strip. The instrument and subjects were acclimatized for around 30 min before the actual measurement in the same room and the instrument was calibrated just before the start of the experiment.

Analysis

For EEG data we used 1) nose-referenced potentials and 2) spatially filtered EEG potentials using Laplacian transformation (Graimann and Pfurtscheller, 2006; Hjorth, 1975) by subtracting activity from four neighboring electrodes from the activity in a given electrode. In the following text nose-referenced EEG is labeled as EEG-N and Laplacian-transformed EEG as EEG-L.

Spectral estimation

For EEG, NIRS, blood pressure, Laser Doppler, and respiration we performed a power spectral density analysis. The data from the two tilt sessions and two supine sessions were combined for the analysis thus resulting in about 20 min of recordings for each condition. Power Spectral Density was estimated with 80-second segments (Hanning window) and a corresponding frequency resolution $\Delta f = 0.0125$ Hz.

Then we identified the frequency bins at the base of the MUSO peak, the corresponding frequency bins are designated here as $f_1$ and $f_2$ and the integral (1) of the spectral density was calculated in this range. In order to estimate how much a given peak stands above the 1/f part of the spectra we used a cubic interpolation taking into account only spectral power in $f_1 - 0.0375$ and in $f_2 + 0.125$ Hz frequency range and calculated an integral of the spectral power between $f_1$ and $f_2$ using interpolated spectrum (12). Relative Power was calculated as $\frac{f_1}{f_2}$. The statistics for $f_1$ and $f_2$ were as follows (mean ± standard deviation): EEG-N: from 0.0725 ± 0.022 to 0.13 ± 0.21 Hz; EEG-L: from 0.08625 ± 0.019 to 0.14125 ± 0.029 Hz; NIRS: from 0.06 ± 0.015 to 0.135 ± 0.03 Hz; blood pressure: from 0.05625 ± 0.013 to 0.13375 ± 0.029 Hz.

We then have chosen channels showing Relative Power $> 1$ and averaged corresponding spectra. On average 44 ± 12 (mean ± standard deviation) and 13 ± 4 channels had Relative Power $> 1$ for Nose Reference and Laplacian recordings, respectively. Relative Power of the average spectrum was then used for across-subjects statistics.

Coherence estimation

In order to study the relation between MUSO in EEG and NIRS, blood pressure and Laser Doppler signals, we used magnitude squared coherence. The following coherence measures were calculated: EEG-N/L vs. NIRS, EEG-N/N vs. blood pressure, NIRS vs. blood pressure, and EEG-N/N vs. Laser Doppler. For assessing the significance of coherence we used permutation tests where 30-second segments were permuted in one of the vectors thus destroying the true order of segments between the two signals while preserving their spectral content. Such permutation was performed 200 times. The significance was determined as a percentage of coherence values (from permuted sequence) exceeding the coherence value corresponding to not permuted data. In the present study the threshold for critical significance was set to 1%. The coherence estimation was calculated for the tilted condition only since the spectral peak for blood pressure was clearly detected in all subjects only in this condition. The significance of multiple coherence calculations was assessed with binomial testing (Montez et al., 2009). Using this approach we calculated a probability of obtaining $m$ pairs with significant peak coherences (at $P < 0.01$) out of $n$ tested pairs.

Testing for multiple sources in the EEG

In order to determine whether MUSO were generated by one or multiple sources, the following analysis was performed. For EEG-L signals, we used synchronization index (SI, Rosenblum et al., 2001) and Phase Lag Index (PLI, Stam et al., 2007). The phase of MUSO was extracted from the Hilbert transform of the signal after band-pass filtering centered at individual peak frequencies (band width 0.06 Hz). SI indicates the strength of the phase coupling and PLI shows whether phase synchronization between the two signals is due to phase lag being 0 (thus most likely reflecting a volume conduction effect). Significant non-zero value of PLI indicates the presence of interacting sources with a phase lag different from 0. The significance of SI and PLI was validated also with permutation tests. The following logic was applied to deduce whether there was more than one source of MUSO: Given that a few channels show a peak at MUSO range, the following situations were possible.

1. SI is 0, PLI is 0. This case indicates the presence of more than one MUSO source because more than one EEG channel shows a spectral peak around 0.1 Hz. Had it been due to volume conduction, SI would not have been 0.
2. SI is not 0, but PLI is 0. This indicates that while there is a phase synchronization, the phase difference is symmetric around zero, thus most likely indicating a volume conduction. Thus this case is not indicative for the presence of multiple MUSO generators.
3. SI is not 0 and PLI is not 0. This case like in (1) indicates the presence of more than one MUSO source. However, different from (1) these sources also demonstrate a genuine phase synchronization with time lag.
4. SI is 0 but PLI is not 0. We include this case only for the completeness of the association between SI and PLI. However, theoretically this result is unlikely to happen since non-zero PLI should also indicate phase synchronization and thus SI should be non-zero as well. It was indeed the case in our data as we observed this situation in less than 5% of the data, which is most likely due to statistical fluctuation in the calculation of SI and PLI.

As it follows from the description, the presence of cases described in (1) and (3) is associated with multiple sources of MUSO.

Results

We detected EEG-MUSO in 8 of 10 subjects. Fig. 2A shows a time course of 10 min from unfiltered Laplace-transformed EEG recordings.
(EEG-L, see Methods). Fig. 2B provides an enlarged segment of MUSO in EEG-N and in EEG-L. In addition, the three lower panels of Fig. 2B show 0.1 Hz oscillations obtained in NIRS (Oxy-Hb), blood pressure and respiration. All traces are shown only with low-pass filtering at 80 Hz (see Methods section Electroencephalography) in order to demonstrate that the oscillatory nature of the signal is not due to the narrow band-pass filtering. In general we observed that MUSO are best detectable after the Laplacian transformation compared to nose-referenced recordings as visible from comparing traces in corresponding panels of Fig. 2B. MUSO showed waxing-and-waning behavior but in some cases the oscillations could last without a considerable attenuation for a hundred of seconds (Fig. 2A). Fig. 2C shows corresponding spectra for the activities presented in Fig. 2B. Note the well-shaped and pronounced spectral peaks at about 0.1 Hz for EEG-N and EEG-L. Fig. 2D shows a topographic map of the spectral power density of oscillations in EEG-N, EEG-L, and Oxy-Hb recordings, respectively. A characteristic feature of MUSO in EEG was their relatively sparse power topography. In general, there were no apparent similarities in the topographies of 0.1 Hz oscillations in EEG and Oxy-Hb recordings. In addition we have not observed similarities in the spatial patterns of EEG-MUSO across subjects. In some subjects electrodes showing strong MUSO were located over the frontal areas, while in other subjects strongest MUSO were detected over the parietal areas.

Effect of head-up tilt on 0.1 Hz oscillations in EEG, NIRS and blood pressure

We compared changes in the Relative Power of 0.1 Hz oscillations in EEG, NIRS, and blood pressure between supine and tilted conditions. Fig. 3B shows that only for blood pressure 0.1 Hz oscillations were significantly increased in amplitude in the tilted condition (Wilcoxon signed rank test) while no amplitude changes between the two conditions were detected in EEG or NIRS. In addition, we also compared peak frequencies of oscillations between the conditions. We observed significant increase in peak frequency for Oxy-Hb signal in

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NIRS recordings (Fig. 3A, \(P < 0.05\)) in supine compared to the tilted condition, while no changes in peak frequency were detected in EEG and blood pressure.

Head-up tilt test also did not change the frequency of respiration, which was on average \(-0.25\) Hz, being significantly larger (by a factor of 2) than the frequency of MUSO in EEG \((P < 0.001)\).

3.2. Relationship between Relative Power of 0.1 Hz oscillations in EEG and NIRS/blood pressure

For the tilted condition, where the 0.1 Hz oscillations were detected in blood pressure, EEG and NIRS recordings, we performed a correlation of Relative Power between signals from different measuring modalities and across subjects. Fig. 4A shows that Relative Power in EEG-N and blood pressure were positively correlated (Spearman correlation, \(R = 0.71, P < 0.05\)). We also observed a significant positive correlation between Relative Power in EEG-N and Oxy-Hb (Fig. 4B, Spearman correlation, \(R = 0.82, P < 0.05\)). In addition we found a significant correlation between Relative Power of 0.1 Hz oscillations in Oxy-Hb and blood pressure (Fig. 4C, Spearman correlation, \(R = 0.7, P < 0.05\)). No correlation was detected between Relative Power of 0.1 Hz oscillations in EEG-L and NIRS/blood pressure recordings.

Coherence analysis between 0.1 Hz oscillations in EEG, NIRS and blood pressure

For this analysis we calculated all pairwise coherences between channels belonging to different measurement techniques. For instance for 26 NIRS channels and 58 EEG-N channels in a given subject, we would obtain \(26 \times 58\) pairs of signals which can be used for the calculation of coherences. Fig. 5 shows an example of coherence spectra for EEG-N vs. NIRS and EEG-N vs. blood pressure. The figure shows a pronounced statistically significant peak at about 0.1 Hz for both EEG-N vs. NIRS and EEG-N vs. blood pressure coherences.

In 8/10 subjects we detected significant values of coherence at about 0.1 Hz between EEG-N/EEG-L and blood pressure signals and between EEG-N/EEG-L and Oxy-Hb signals. Fig. 6A shows the average percentage of EEG channels (nose referenced or Laplace-transformed) showing at least one significant (at \(\alpha = 0.01\)) coherence value at about 0.1 Hz with Oxy-Hb or blood pressure signals. Although for EEG-N/EEG-L vs NIRS the number \(m\) of significant pairs (out of a total number of tested pairs \(n\)) varied across subjects, the binomial testing for multiple comparisons (see Methods) showed that even for the subject with the smallest number of significant pairs, the probability of multiple significant coherences was at most \(P < 5e-09\). For coherences between EEG-N/EEG-L and BP binomial testing was at most \(P < 0.001\).

While Fig. 6A shows how many EEG channels showed coherence, another interesting question is how many EEG channels were coherent with a given NIRS or blood pressure signal. Fig. 6B shows the average percentage of EEG-N/EEG-L channels demonstrating significant coherence with the activity in a given NIRS channel or with blood pressure signal. These percentages were quite high, usually \(>40\%\) and considerably higher than what would be expected for the signals with random coherences at \(\alpha = 0.01\), e.g. only about 1% of the cases would show the significance.

3.4. EEG-MUSO are generated by more than one source

In order to clarify whether MUSO originate from more than one source, we used a combination of Synchronization Index (SI) and Phase Lag Index (PLI). Table 1 shows the percentage of interactions between EEG-L channels at MUSO frequency range for each of the combinations of these two measures. In total 39% of the pairwise interactions had SI and PLI not being significantly different from zero (Case 1, see Methods). This indicates that there were different sources of MUSO in EEG not showing any interactions but indicating that MUSO is not due to one source, since spectral peaks were detected in multiple channels. In 32% of all pair-wise interactions both, SI and PLI were significantly different from zero (Case 3). This in turn indicated that there might have been multiple MUSO sources also showing some phase locking which was not due to the volume conduction. In 25% of the data SI was significantly different from 0, but PLI was not. This indicates that the interactions corresponding to these pairs of EEG channels are most likely due to the volume conduction.

3.5. Laser Doppler flowmetry and EEG

In three subjects we performed additional recordings measuring skin blood flow with Laser Doppler technique in combination with EEG. On average we observed a peak in the Laser Doppler signal at \(-0.096\) Hz. Fig. 7 shows an example of spectra of EEG and Laser Doppler signals for one subject. For all three subjects we calculated coherence between EEG-N/EEG-L channels and Laser Doppler signals and used permutation tests to check for the significance. In two subjects we observed a significant coherence between the Laser Doppler signals and EEG-L. In both subjects the coherence peak was lower than the corresponding peaks in Laser Doppler. In one of these subjects (Fig. 7), we detected a significant interaction between EEG-N and Laser Doppler.

![Fig. 4](https://example.com/fig4.jpg)

Fig. 4. Correlation between Relative Power values of blood pressure, NIRS and EEG across different subjects (Spearman’s correlation coefficient, \(P < 0.05\)). A. BP vs. EEG, B. NIRS vs. EEG, C. BP vs. NIRS.

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The main idea of the present study was to describe MUSO in EEG recordings and to show their possible relation to the hemodynamic responses. While more experiments are required in order to address further aspects of MUSO, here we used six different recordings techniques (EEG/NIRS/blood pressure/Laser Doppler/Respiration) as well as head-up tilt test to characterize the nature of MUSO. Although a complete understanding of MUSO origin is still pending, we found an unequivocal evidence for their relation to NIRS and blood pressure signals thus providing a basis for further experiments in this area.

Using our findings and the evidence reported in other studies, we consider different interpretations for the generation of MUSO.

Fig. 5. Coherences between different measuring modalities. A. Coherence between blood pressure and EEG-N signals in a representative subject. B. Coherence between EEG-N and 26 NIRS signals (Oxy-Hb). Red dashed line: the highest confidence interval (P < 0.01) for the shuffled data. C and D correspond to A and B where only three largest coherences are shown. In panel C the blue, green and red traces correspond to the interaction of BP with EEG-N electrodes Pz, FC3, C2, respectively. In panel D the coherence is between EEG-N and NIRS such as: electrode P2 vs source 7/detector 13 (close to Pz, blue), electrode O1 vs source 2/detector 2 (close to F2, green), electrode O1 vs source 3/detector 7 (close to FC1, red).

Finally, in the third subject with a peak at about 0.1 Hz in Laser Doppler and EEG, no significant peak in coherence was observed. Thus only in one out of three subjects and only in EEG-N we observed a relatively small peak of coherence corresponding to a spectral peak in Laser Doppler and MUSO.

Discussion

This study demonstrated the presence of monochromatic EEG oscillations at about 0.1 Hz and their coherence with blood pressure and NIRS signals. Importantly, spectral/coherency peaks of MUSO clearly stand out above the 1/f part of the spectrum, thus representing a truly oscillatory phenomenon in EEG. MUSO was detected in 8 out of 10 subjects. We hypothesize that the absence of MUSO in two subjects could be due to insufficient signal-to-noise ratio.

The main idea of the present study was to describe MUSO in EEG recordings and to show their possible relation to the hemodynamic responses. While more experiments are required in order to address further aspects of MUSO, here we used six different recording techniques (EEG/NIRS/blood pressure/Laser Doppler/Respiration) as well as head-up tilt test to characterize the nature of MUSO. Although a complete understanding of MUSO origin is still pending, we found an unequivocal evidence for their relation to NIRS and blood pressure signals thus providing a basis for further experiments in this area.

Using our findings and the evidence reported in other studies, we consider different interpretations for the generation of MUSO.

Previous reports on MUSO

Two previous studies presented an evidence for the presence of MUSO in human scalp EEG (Girton et al., 1973; Trimmel et al., 1990). There was no spectral analysis performed in those studies, but the presented time traces showed oscillatory EEG activity at about 0.1 Hz. The amplitude and frequency of MUSO in those studies were comparable to the parameters obtained in our study. In addition, another study in rabbits, using invasive cortical recordings, suggested that these oscillations were generated directly by brain tissue (Aladjalova, 1957). No attempt was made in any of these studies to test the hypothesis that MUSO might be linked to hemodynamic activity. Interestingly, the authors (Girton et al., 1973) also commented on the fact that none of the stimuli (tactile or visual) as well as none of other types of mental activity (mental arithmetic calculation, meditation, memory recollections) had any effect upon eliciting MUSO.

Neural generators

When one uses EEG, the main assumption is that it is a real time measure of electrical neuronal activity in contrast to purely hemodynamic responses measured for instance with fMRI/NIRS. Current wisdom holds that apart from easily identifiable muscle artifacts and eyes movements, EEG primarily reflects a neuronal activation. Therefore, if someone records

Table 1

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<thead>
<tr>
<th>Case 1</th>
<th>Case 2</th>
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<tr>
<td>No synch no phase lag</td>
<td>Synch no phase lag</td>
<td>Synch phase lag</td>
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<tr>
<td>Significant SI</td>
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<td>Significant PLI</td>
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<tr>
<td>Occurrence %</td>
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oscillations with EEG, then these are habitually interpreted in neuronal terms.

Ultra-slow EEG fluctuations (at and below 0.1 Hz) have been previously reported (Aladjalova, 1957; Girton et al., 1973; Trimmer et al., 1990; Vanhatalo et al., 2004, 2005). Although the possibility of a neuronal interpretation of the obtained data is mentioned in those studies, the unimodal nature of such recordings did not allow for an unequivocal evidence of primarily neuronal generation. Notably, some invasive intracortical recordings in cats showed that ~0.1 Hz hemodynamic activity can coincide with rhythmic bursting (intra-burst frequency 5–10 Hz), recorded with ECoG activity, which is likely to reflect neuronal processing (Golanov et al., 1994).

Large amplitude of MUSO would be in agreement with the fact that slower oscillations are usually generated by the greater number of neurons (Hughes et al., 2011). In addition, the fact that our analysis revealed a presence of multiple generators of MUSO might also be considered as an evidence for distributed neuronal sources. Although such interpretations are possible we consider below extraneuronal sources of slow oscillations which might have contributed to the generation of MUSO.

Respiration

One of the most straightforward explanations for the presence of MUSO might have been due to respiration. In this scenario slight movement of the body during breathing might have lead to the movement of electrodes and correspondingly to the changes in EEG potentials. However, the frequency of respiration was twice larger than the frequency for MUSO, e.g. 0.25 Hz vs. 0.12 Hz. The mean respiratory rate, obtained in the present study (~15 breaths/min or 0.25 Hz), was similar to the mean normative rate (~16 breaths/min) reported in Tobin et al. (1983). Moreover, the presence of multiple sources and the complexity of MUSO topographies with multiple foci rule out a possibility for their generation through a single common source such as a respiratory activity.

4.4. Skin vasomotion

Low-frequency oscillations at about 0.1 Hz are known to occur in skin blood flow due to the vasomotion (Bari et al., 2005; Silverman and Stout, 2002). Although Mayer waves can also be observed in vessels, particularly in large ones, the presence of local vasomotion indicates that not all changes in vessel tone are due to systemic blood flow changes (Nilsson and Aalkjaer, 2003). In agreement with this statement it was shown that the low-frequency oscillations in the microvasculature in response to a vasoconstrictive challenge were not a consequence of oscillations in heart rate or systemic blood pressure (Silverman and Stout, 2002). Interestingly, Laser Doppler flowmetry also demonstrated that the highest perfusion values were seen on the face and forehead with much lower perfusion being detected at the extremities and at the trunk (Stücker et al., 2001). In line with this, it was found that oscillations at about 0.13 Hz were strongest on the forehead compared to forearm skin (Bari et al., 2005), as also reported previously (Lossius and Erikson, 1995). This indicates that vasomotion is particularly pronounced in scalp skin from where EEG signals are usually recorded.

Given that there is a trans-epidermal potential (De Talhouet and Webster, 1996) mechanical fluctuations due to skin vasomotion might give rise to electric potentials oscillating at the frequency of vasomotion, potentially recordable with EEG. The coherence between EEG and NIRS at 0.1 Hz is an indication that MUSO might have a contribution from skin vasomotion, since in addition to cerebral blood flow NIRS also detects skin hemodynamics (Kirilina et al., 2012). Also the presence of multiple sources of EEG MUSO as well as their complex topographies would be in agreement with spatially diverse activation of vasomotion oscillations (Nilsson and Aalkjaer, 2003).

Yet, in more specific flow-metric measurements we detected only some cases of significant coherence between MUSO and Laser-Doppler signals where the frequency of interaction was not necessarily at the peak frequency of MUSO and there was only one marginally significant instance of coherence corresponding to the frequency range of EEG MUSO.

Notwithstanding, we cannot completely exclude the possibility that MUSO might have some contribution from skin potentials, and as almost all EEG studies are performed with surface electrodes, the understanding of electrical phenomena in such condition is imperative for a proper interpretation of the obtained results.

Mayer waves in head-up tilt test

Oscillations in arterial blood pressure at about 0.1 Hz (Mayer waves) are prominent in humans and animals and reflect baroreflex activity in the cardiovascular system (see for review Julien, 2006). A head-up tilt
test was used in the present study as Mayer waves have also a mono- 
chronic spectrum peaking at about 0.1 Hz and thus could be related 
to MUSO in EEG. In agreement with previous studies we showed that 
the head-up tilt test resulted in an increase in the amplitude of 0.1 Hz 
oscillations in blood pressure (Cooke et al., 1999; Furlan et al., 2000). 
This increase in the amplitude of 0.1 Hz oscillations is most likely due 
to high sympathetic outflow during the head-up test (Taylor and 
Eckberg, 1996). The amplitude of 0.1 Hz oscillations in Oxy-Hb signals 
was not affected by the head-up tilt, but the frequency of these oscilla-
tions was significantly smaller in the tilted than supine position. The ab-
sence of increase of Oxy-Hb peak at 0.1 Hz in NIRS might be due to 
cerebral autoregulation, which maintains blood flow at appropriate 
levels during the changes in systemic arterial blood pressure. However, 
one can still observe coherence between fluctuations in blood pres-
sure and cerebral blood flow measured with transcranial Doppler ultrasound 
(Diehl et al., 1995; Panerai et al., 2006). This in turn might be a reason 
for the coherence between blood pressure and NIRS signals observed 
in the previous studies (Obrig et al., 2000; Pfurtscheller et al., 2011) 
and also in the present study. Because of the coupling of cerebral 
blood flow and arterial pressure, we also observed a positive correlation 
between Relative Power in NIRS and blood pressure signals.

Interestingly, despite the changes in the amplitude of 0.1 Hz oscilla-
tions in blood pressure and frequency changes in NIRS signals, the am-
plitude and frequency of MUSO were not significantly affected by the 
head-up tilt either in EEG-N or in EEG-L recordings. In addition, the 
presence of multiple generators of EEG MUSO would also be at odds 
with a hypothesis about a single systemic factor, such as arterial blood 
pressure, generating MUSO. Although this finding might indicate that 
MUSO are not directly related to changes in blood pressure, other as-
pects of blood-pressure vs. EEG, namely correlations between mean 
amplitudes and coherences provide a complementary perspective.

MUSO and mechanical artifacts

We also assume that skin vasomotion or Mayer waves alone are un-
likely to explain MUSO due to pure mechanical movement-related 
factors. In case of mechanical artifacts, we should have observed an in-
crease of MUSO amplitude in the tilted condition, since this condition 
significantly increased blood-pressure related oscillations at 0.1 Hz 
(Fig. 3). Yet, the amplitude of MUSO was not different between the su-
pine and tilted conditions. Moreover, for the control of skin vasomotion 
we performed simultaneous Laser-Doppler recordings and EEG and we 
have not observed a consistent coherence between skin blood flow and 
EEG signals. However, such coherence should be very high and easily 
replicable in different subjects if MUSO were due to mechanical artifacts 
caused by the skin vasomotion, the latter being fully described by Laser 
Doppler technique which has a penetration depth of 0.5–1 mm, thus 
being primarily sensitive to skin blood flow. In addition, in another 
study (Girton et al., 1973) the authors directly tested whether 
MUSO can be produced by deliberate moving of the body with fre-
quency 5–8 cycles/min, yet no oscillatory contribution could be de-
tected in EEG from these maneuvers. Moreover, in the same study 
the authors showed that MUSO cannot be due to the changes in 
skin potential by showing that the oscillations were absent when 
activity was recorded from the hand.

We also believe that large scale pulsatile brain movements are un-
likely to explain the generation of MUSO. This is because a presence of 
multiple interacting MUSO sources as well as non-coherent MUSO 
 sources are rather incongruent with a strong common movement 
source.

Cerebral vasomotion and DC potentials due to blood barrier

Another source of 0.1 Hz oscillations in the brain is due to cerebral 
vasomotion as shown in animals (Galovan et al., 1994; Mayhew et al., 
1996) and humans (Rayshubskiy et al., in press). Invasive Laser Doppler 
measurements in rats demonstrated spatial heterogeneity in 0.1 Hz 
oscillations even on sub-millimeter scale, which in turn indicated that 
cerebral vasomotion could not be reduced to a common general system-
ic influence or a motion artifact (Mayhew et al., 1996). Recently it was 
also found that sinusoidal hemodynamic oscillations at 0.1 Hz in the 
human brain were spatially localized and exhibited wave-like propaga-
tion thus further confirming that they were not a result of systemic 
blood pressure (Rayshubskiy et al., in press). As vasomotion affects 
blood flow, it is also likely to be reflected in NIRS signals in addition to 
fluctuations in blood pressure, since NIRS measures blood volume in 
arterial and venous vascular beds (Watzman et al., 2000).

Here, we would like to emphasize a theoretically plausible conse-
quence for EEG signal generation when one considers a combination 
of vasomotion and electrical potentials created at the blood brain barrier 
(BBB). Previous studies showed the existence of an electrical near-DC 
potential between cerebrospinal fluid and blood measuring up to a 
few millivolts (Kjallquist, 1970; Sorensen et al., 1978) due to partial per-
meability of plasma solutes across BBB. A model was suggested (Voipio 
et al., 2003) where BBB forms a voltage source that generates a volume 
current flowing through the distributed resistance, coupling brain po-
tential to the surrounding extracortical tissue layers, and also through 
the distributed resistance of the layers between brain surface and skin 
surface thus giving rise to a voltage drop which can be measured on 
the scalp. This mechanism was hypothesized to be responsible for 
large (hundreds of microvolts) slow DC oscillations in EEG recorded 
during bilateral jugular vein compression, head-up tilt, Valsalva maneu-
ver (Varhatalo et al., 2003). Interestingly the authors also showed that 
the time course of slow EEG responses was paralleled by a similar activ-
ity of hemodynamic measures such as total hemoglobin, recorded with 
NIRS. The authors concluded that hemodynamic changes in the brain in 
combination with their modulation of BBB potential may give rise to 
extraneuronal generation of EEG signals.

Here we extend this idea of generation of EEG through changes in 
BBB potentials due to cerebral hemodynamics also to spontaneous he-
modynamic oscillations occurring in the brain due to local vasomotion 
and changes in systemic blood pressure. As these are primarily generated 
at about 0.1 Hz, as we discussed above, corresponding changes in EEG 
should also appear in the same frequency range and, specifically, a co-
herence between NIRS and EEG signals should be observed, which, in-
deed, was detected in abundance in the present study. Moreover, our 
analysis indicated that EEG-MUSO oscillations are generated by multi-
ples sources. In many cases these sources were coupled, showing a 
strong phase synchronization which is not reducible to volume conduc-
tion. In other cases MUSO in different electrodes were not synchronous, 
thus also indicating a presence of independent generators. Such pat-
terns of MUSO in EEG as well as often mosaic-like MUSO topographies 
would also be in agreement with locally specific and diverse patterns 
of cerebral vasomotion (Mayhew et al., 1996; Rayshubskiy et al., in 
press).

Interestingly, the fact that we observed coherence between EEG-N/ 
EEG-L MUSO and NIRS/blood pressure, indicates that MUSO consist 
not only of spatially restricted but also of globally distributed 0.1 Hz os-
cillations. This is because EEG-N recordings reflect rather more global 
brain activation without spatial high-pass filtering of Laplacian transfor-
mation. Another evidence for a global character of MUSO is reflected in 
the finding that Relative Power of NIRS and systemic blood pressure was 
correlated only with the Relative Power of EEG-N but not with the 
Relative Power of EEG-L recordings. Taken together our analysis 
does not show that EEG MUSO most likely contain both global and local features. 

Fig. 8 summarizes the main findings related to the interpretation of 
EEG MUSO. A respiration is unlikely to be involved in the generation 
of MUSO. On the other hand, there were no experimental findings 
contradicting the generation of MUSO by the cerebral vasomotion. At 
the same time skin vasomotion and arterial blood pressure (Mayer 
waves) had evidence for and against their involvement in the genera-
tion of MUSO. Ironically, although we used EEG, we do not have a direct
### Hemodynamics and EEG

One possible conclusion from the present data is that not only hemodynamic activity might reflect neuronal activity, but that EEG responses can also reflect hemodynamic fluctuations, while not being the cause for these hemodynamic responses — this idea being in line with a similar hypothesis suggested earlier, but for the case of special experimental maneuvers (Vanhatalo et al., 2003).

This hypothesis would imply that EEG MUSO might represent an electric counterpart of the hemodynamic response. This situation would call for a consideration in combined EEG and fMRI/NIRS studies, as it would indicate that the last two techniques would not exclusively measure neuro-vascular coupling, and thus one would rather study an association between the two manifestations of the same hemodynamic activity. We studied oscillations in 0.1 Hz as they were the common and easily identifiable binding factor across different recording modalities. However, it is also known that hemodynamic responses as well as EEG/MEG/LFP signals have a $1/f$ part of spectra (Fox and Raichle, 2007; Pan et al., 2013; Thompson et al., 2014). This in turn potentially might imply that, if the idea of hemodynamic responses having an electric counterpart is feasible, other parts of the spectra of EEG signals might also have a hemodynamic contributions thus complicating the conventional interpretation of EEG/MEG/LFP signals reflecting primarily electrical neuronal activity.

### References


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