

Experimental Evidence for Phase Synchronization Transitions in the Human Cardiorespiratory System

Ronny Bartsch,¹ Jan W. Kantelhardt,² Thomas Penzel,³ and Shlomo Havlin¹

¹*Minerva Center, Department of Physics, Bar-Ilan University, Ramat-Gan 52900, Israel*

²*Institute of Physics, Theory Group, Martin-Luther-Universität Halle-Wittenberg, 06099 Halle (Saale), Germany*

³*Division of Pulmonary Diseases, Department of Internal Medicine, Hospital of Philipps-University, 35033 Marburg, Germany*

(Received 3 April 2006; published 1 February 2007)

Transitions in the dynamics of complex systems can be characterized by changes in the synchronization behavior of their components. Taking the human cardiorespiratory system as an example and using an automated procedure for screening the synchograms of 112 healthy subjects we study the frequency and the distribution of synchronization episodes under different physiological conditions that occur during sleep. We find that phase synchronization between heartbeat and breathing is significantly enhanced during non-rapid-eye-movement (non-REM) sleep (deep sleep and light sleep) and reduced during REM sleep. Our results suggest that the synchronization is mainly due to a weak influence of the breathing oscillator upon the heartbeat oscillator, which is disturbed in the presence of long-term correlated noise, superimposed by the activity of higher brain regions during REM sleep.

DOI: 10.1103/PhysRevLett.98.054102

PACS numbers: 05.45.Xt, 87.19.Hh, 87.19.Uv

Periodic events are ubiquitous in many natural systems [1]. If two oscillatory processes are weakly coupled, they can become phase synchronized. Transitions in the synchronization behavior have been shown to be important characteristics of coupled oscillatory model systems [2]. It has also been found that noise, when applied identically to different nonlinear oscillators, can induce, enhance, or destroy synchronization among them [3–5]. However, phase synchronization is difficult to study in experimental data which are very often inherently nonstationary and thus contain only quasiperiodic oscillations. Among the few recent experimental studies are coupled electrochemical oscillators [4], laser systems [5], and climate variables [6]. In physiology, the study of phase synchronization focuses on cardiorespiratory data (see below) and encephalographic data [7]. Here, in order to obtain reliable experimental evidences of transitions in phase synchronization behavior, we consider cardiorespiratory synchronization in humans during sleep, because homogeneous long-term data for well-defined conditions of a complex system are available in this particular example.

First approaches for the study of cardiorespiratory synchronization have been undertaken by the analysis of the relative position of inspiration within the corresponding cardiac cycle [8]. More recently, phase synchronization between heartbeat and breathing has been studied during wakefulness using the synchrogram method [9–12]. While long synchronization episodes were observed in athletes and heart transplant patients (several hundreds of seconds) [10,11], shorter episodes were detected in normal subjects (typical duration less than hundred seconds) [11–13]. For two recent models of cardiorespiratory synchronization, see [14,15].

In this Letter we use the concept of phase synchronization to develop an automated synchrogram based proce-

dure and study interactions between cardiac and respiratory oscillations under different well-defined physiological conditions. We focus on the sleep stages, where external stimuli are absent. It is well known that healthy sleep consists of cycles of roughly 1–2 hours duration. Each cycle is characterized by a sequence starting usually with light sleep, followed by deep sleep and rapid-eye-movement (REM) sleep [16]. We find the intriguing result that during REM sleep cardiorespiratory synchronization is suppressed by approximately a factor of 3 compared with wakefulness. On the other hand, during non-REM sleep, it is enhanced by a factor of 2.4, again compared with wakefulness. In addition, we find that these significant differences between synchronization in REM and non-REM sleep are very stable and occur in the same way for males and females, independent of age and independent of the body mass index (BMI). Hence, it seems likely that—similar to the long-term correlations [17] occurring in both heartbeat [18] and breathing [19] during REM sleep but not during non-REM sleep—the differences are caused by the influence of the activity of higher brain regions on both oscillators [20].

First, we developed an algorithm, which detects epochs of synchronization automatically and systematically. The algorithm is applied on simultaneous records of respiration (from a thermistor placed close to the subject's nose) and heartbeat (from electrocardiograms) obtained for 112 healthy subjects during sleep. The data were recorded in the EU project SIESTA in several European sleep laboratories [21], and the average length of the records is 7.9 hours with a standard deviation of 25 minutes. Sleep stages have been determined by visual evaluation of electrophysiological recordings of brain activity [16]. We can thus assign the synchronization episodes to the specific sleep stages. In addition, we constructed surrogate data

by random combination of heartbeat and breathing signals from different subjects [11]. We found that the total duration of the detected synchronization episodes in real data is increased by a factor 2.3 as compared with the surrogate data, suggesting that most of the detected episodes are real [22].

Our algorithm for the detection of phase synchronization episodes is based on the study of cardiorespiratory synchograms [9–12]. For each record, the times t_k of heartbeats are mapped on the continuous cumulative phase $\Phi_r(t)$ of the respiratory signal, which we obtain by unfolding the phase of the Hilbert transform of the normalized thermistor recording. Figure 1(a) shows a representative synchrogram, where $\Phi_r(t_k) \bmod 2\pi$ is plotted versus t_k . In the case of $n:1$ synchronization (i.e., if n heartbeats fit to one breathing cycle) one observes n parallel horizontal lines in the synchrogram [$n = 3$ in Fig. 1(a)]. In general, to find different ratios $n:m$ of phase synchronization, we plot $\Psi_m(t_k) = \Phi_r(t_k) \bmod 2\pi m$ versus t_k .

While most earlier work relies on a visual evaluation of the synchograms [10,12], we detect the episodes in a fully systematic way. For each synchronization ratio $n:m$ we first replace the n phase points $\Psi_m(t_k)$ in each m respiratory cycles by the averages $\bar{\Psi}_m(t_k)$ calculated over the corresponding points in the time windows from $t_k - \tau/2$ to $t_k + \tau/2$ [Fig. 1(b)]. In the second step, the algorithm deletes all phase points $\bar{\Psi}_m(t_k)$ where the mean standard deviation of

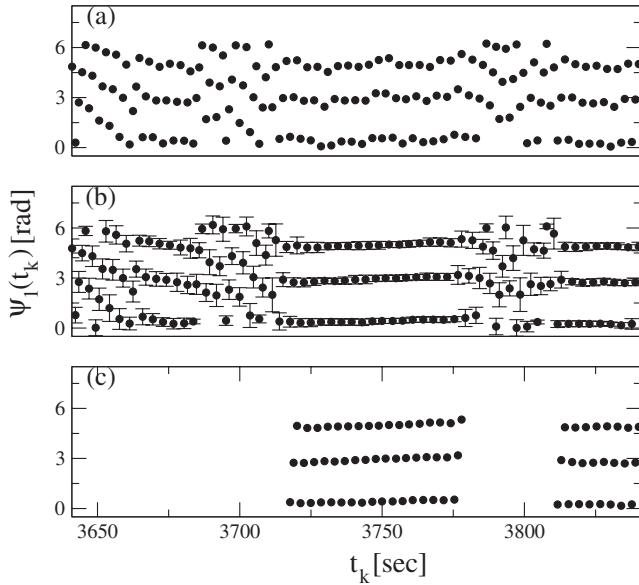


FIG. 1. Illustration of our automated phase synchronization detector: (a) section of a typical synchrogram in raw form, (b) the same section as in (a) after applying a moving average filter with windows of $\tau = 30$ s around each breathing cycle; the window averages are shown together with their standard deviations (error bars), (c) contiguous phase points of (b) where the standard deviation is below a threshold (see text) are detected as synchronization episodes if their durations exceed T seconds (here $T = 30$ s).

the n points in each m breathing cycles, $\langle \sigma \rangle_n$, is larger than $2m\pi/n\delta$. In the third step, only the phase points $\bar{\Psi}_m(t_k)$ in uninterrupted sequences of durations exceeding T seconds are kept [Fig. 1(c)].

Figure 2(a) shows a comparison of the detected synchronization rates in real data and in surrogate data for several values of the parameter T . The ratio of the mean percentage of synchronization in real data over the mean percentage in surrogate data increases from 1.6 for $T = 20$ s to 3.4 for $T = 40$ s. There is no generic limit for T . However, we choose $T = 30$ s in order to keep the number of arbitrary detection of synchronization at an acceptable low level ($\approx 1\%$ in the surrogate data) while at the same time still detecting synchronization episodes during all kinds of sleep stages. In addition, for $T = \tau = 30$ s we have only one effective time scale parameter, which is identical with the standardized time frame used for the detection of sleep stages [16]. We note that changing the parameter δ has a similar effect on the results as changing T , and we chose $\delta = 5$ based on similar considerations as for T . Our results do hardly depend on the duration τ of the initial running average.

When studying the percentages of synchronized episodes in real data separately during wakefulness, REM sleep and non-REM sleep, we obtain a highly significant difference in the frequency of cardiorespiratory synchronization between the two major physiological states during sleep. We find 3.8% synchronization in non-REM sleep compared with just 0.6% in REM sleep—a difference by a factor of 6.3. Wakefulness is clearly intermediate, since we

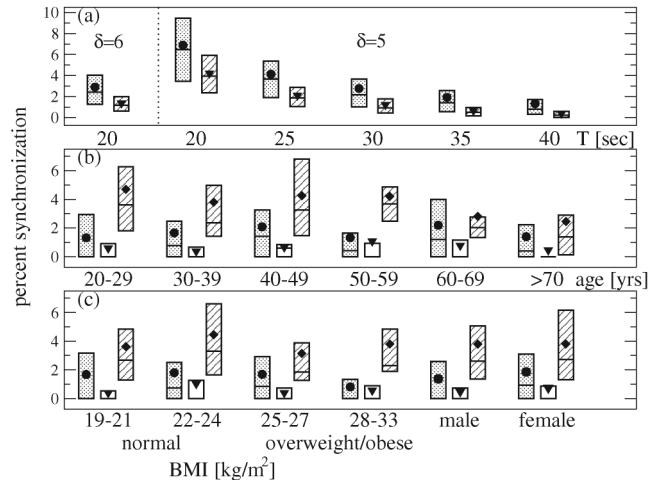


FIG. 2. Medians, upper and lower quartiles (bars) and means (filled symbols) for the detected synchronization rates (a) versus T for all original data (dotted bars and circles) and surrogate data (striped bars and triangles), (left of dotted line $\delta = 6$, right of dotted line $\delta = 5$); (b),(c) versus age, BMI, and gender, for wakefulness (dotted bars and circles), REM sleep (blank bars and triangles), and non-REM sleep (striped bars and diamonds) for $T = 30$ s. Note the similar synchronization behavior in all groups.

find 1.6% for it. Similar differences are observed for other values of T and δ . Since our data base contains records of 112 subjects, we can also study synchronization separately for several age groups, several groups with different body mass index (BMI), and men and women. Figures 2(b) and 2(c) show that the results, for wakefulness, REM sleep, and non-REM sleep are practically the same for both genders, all BMI groups, and all age groups, although both heart rate and breathing rate are known to depend on BMI and age. These results prove that our finding of significant differences between the cardiorespiratory synchronization in REM and non-REM sleep is very stable.

Similar stable differences between REM and non-REM sleep were found in the correlation properties of both heartbeat [18] and breathing [19] fluctuations, but hardly in the magnitude of these fluctuations [20]. The differences were attributed to the influence of the central nervous system with its sleep stage regulation in higher brain regions on the autonomous nervous system. The similarity leads us to suggest that the diminished synchronization during REM sleep is also caused by influences of the central nervous system. As long as the heartbeat oscillator and the breathing oscillator (as parts of the autonomous nervous system) are only affected by uncorrelated noise from higher brain regions, they run like two weakly coupled oscillators—and they clearly show synchronization as expected, possibly enhanced by the noise [3]. However, if the higher brain regions are more active and impose long-term correlated noise on the two oscillators, as is the case during REM sleep, the noise disturbs the emergence of synchronized patterns, leading to a drastic reduction of synchronization episodes. Hence, we suggest from the experimental data that correlated noise is rather suppressing synchronization while uncorrelated noise might increase it.

Our interpretation is consistent with the result that cardiorespiratory synchronization is enhanced in heart transplanted patients, where correlated signals from the brain can hardly affect the heartbeat oscillator [11]. Hence, it supports that any relation of the synchronization patterns with cardiac impairments can only be an indirect one as reported recently [23]. Diminished long-term correlated regulation activity might explain the increase of synchronization in well-trained athletes [10], where fluctuations of heartbeat and breathing might be avoided to optimize the cardiovascular system for optimal performance.

In order to gain insight into the mechanism of cardiorespiratory phase synchronization we have studied, again for all 112 subjects, the distribution of the synchronization ratios $n:m$, where n cardiac cycles are synchronized with m breathing cycles. Figure 3 shows the normalized histograms of the synchronization ratios during (a) wakefulness, (b) REM sleep, (c) light sleep, and (d) deep sleep. The underlying continuous curves in Figs. 3(a)–3(d) show the distributions of the frequency ratios between heartbeat and breathing independent of synchronization.

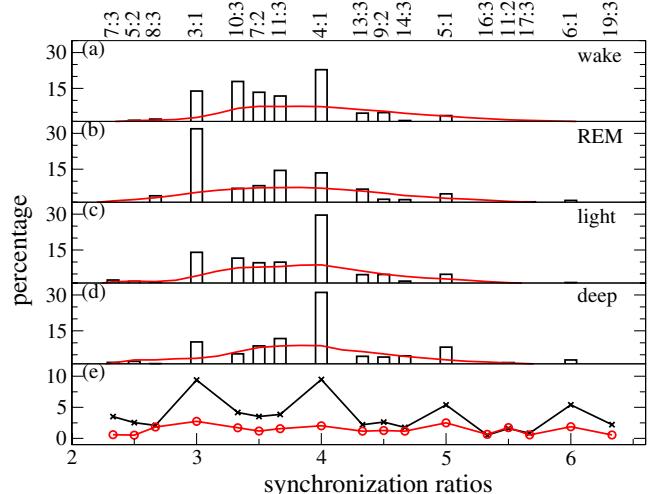


FIG. 3 (color online). Normalized histograms of all detected synchronization ratios as well as distributions of the frequency ratios between heartbeat and breathing during (a) wakefulness, (b) REM sleep, (c) light sleep, and (d) deep sleep. Note that 4:1 synchronization is remarkably increased in light sleep and deep sleep, whereas in REM sleep 3:1 synchronization dominates. In (e) the quotient of the synchronization ratio histogram with the distribution of the frequency ratios is shown for the original data (crosses) as well as for the surrogate data (circles).

To clarify the efficiency of the synchronization mechanism, we show the quotient of the synchronization rate histogram with the distribution of the frequency ratios (crosses) in Fig. 3(e). When comparing with the corresponding curve for surrogate data (circles) it becomes obvious that $n:1$ synchronization is preferred. This involves not just the common ratios of 3:1, 4:1, and 5:1, but also clearly 6:1 synchronization. In particular, we do not find any indication of a suppression of 4:1 synchronization as has been reported recently based on modelling [14]. This suggests that the feedback from baroreceptors to the respiratory centers introduced in the model is probably not very important in the healthy subjects we studied. The synchronization ratios $n:2$ and $n:3$ are weakly efficient if n is low, but not efficient at all for large values of n . Hence, Fig. 3(e) proves that cardiorespiratory synchronization is nearly limited to frequency ratios $n:m$ with very small m , but quite independent of the number of heartbeats n .

From this behavior we suggest that the physiological synchronization mechanism is mainly based on an interaction of the respiratory cycle upon heartbeat and not vice versa. This assumption can explain the weak (or absent) efficiency of $n:m$ synchronization with $m > 1$. If the heartbeat oscillator gets a synchronizing kick at a particular phase of each respiratory cycle and $m > 1$, only half or even less of the kicks coincide with a heartbeat and thus $n:m$ synchronization cannot be effective. The assumption is consistent with the result obtained when studying the direction of synchronization in children and adults [24] and

in a recent model [15]. It is also coherent with the result that synchronization is enhanced under paced respiration [13].

In conclusion, we have studied cardiorespiratory phase synchronization during different well-defined physiological stages in sleep for a large data base of healthy subjects. We observed clearly reduced synchronization during REM sleep and enhanced synchronization during non-REM sleep. The result is stable for all studied subgroups of subjects; it is neither affected by gender, nor by age, nor by BMI. Since REM and non-REM sleep differ mainly in the type of activity of higher brain centers, it seems probable that the differences in cardiorespiratory synchronization are caused by the more and less long-term correlated regulation actions of the brain during REM and non-REM, respectively. Heart rate and breathing rhythm generators behave like two weakly coupled oscillators, where the coupling direction is from breathing to heartbeat. They become synchronized if uncorrelated noise is imposed from the brain while long-term correlated noise disturbs the emergence of the synchronized patterns. Hence, the experimental data suggest that correlated noise is suppressing synchronization while uncorrelated noise might increase it.

We thank Shay Moshel, Meir Plotnik, and Diego Rybski for discussions. This work has been supported by the Deutsche Forschungsgemeinschaft (Grants No. KA 1676/3 and No. PE 628/3), by the Minerva Foundation, by the Israel Science Foundation, and by the EU project DAPHNet (Grant No. 018474-2).

- [1] S. H. Strogatz and I. Stewart, *Sci. Am.* **269**, 102 (1993); L. Glass, *Nature (London)* **410**, 277 (2001); S. H. Strogatz, *Sync: How Order Emerges from Chaos in the Universe, Nature, and Daily Life* (Penguin, Toronto, 2004).
- [2] M. G. Rosenblum *et al.*, *Phys. Rev. Lett.* **76**, 1804 (1996); E. Rosa, Jr. *et al.*, *ibid.* **80**, 1642 (1998); K. J. Lee *et al.*, *ibid.* **81**, 321 (1998); G. V. Osipov *et al.*, *ibid.* **91**, 024101 (2003); Z. Liu *et al.*, *Europhys. Lett.* **71**, 200 (2005); D. A. Smirnov and R. G. Andrzejak, *Phys. Rev. E* **71**, 036207 (2005); Y.-Ch. Lai *et al.*, *ibid.* **73**, 026214 (2006); K. Wood *et al.*, *Phys. Rev. Lett.* **96**, 145701 (2006).
- [3] A. Maritan and J. R. Banavar, *Phys. Rev. Lett.* **72**, 1451 (1994); Ch. Zhou and J. Kurths, *ibid.* **88**, 230602 (2002); J. N. Teramae and D. Tanaka, *ibid.* **93**, 204103 (2004); B. Blasius, *Phys. Rev. E* **72**, 066216 (2005); Sh. Guan *et al.*, *Phys. Rev. E* **73**, 046210 (2006); S. F. Brandt *et al.*, *Phys. Rev. Lett.* **96**, 034104 (2006).
- [4] Ch. Zhou *et al.*, *Phys. Rev. Lett.* **89**, 014101 (2002); I. Z. Kiss *et al.*, *Phys. Rev. E* **70**, 026210 (2004).
- [5] S. Boccaletti *et al.*, *Phys. Rev. Lett.* **89**, 194101 (2002); C. S. Zhou *et al.*, *Phys. Rev. E* **67**, 066220 (2003).
- [6] D. Maraun and J. Kurths, *Geophys. Res. Lett.* **32**, L15 709 (2005).
- [7] P. Tass *et al.*, *Phys. Rev. Lett.* **81**, 3291 (1998); L. Angelini *et al.*, *ibid.* **93**, 038103 (2004).
- [8] P. Engel *et al.*, *Pflügers Arch.* **298**, 258 (1968); H. Passenhofer and T. Kenner, *Pflügers Arch.* **355**, 77 (1975); F. Raschke, in *Temporal Disorder in Human Oscillatory System*, edited by L. Rensing *et al.* (Springer, Berlin, 1987), p. 152.
- [9] M. G. Rosenblum *et al.*, in *Handbook of Biological Physics*, edited by S. Gielen and F. Moss (Elsevier, New York, 2001), Vol. 4; A. S. Pikovsky *et al.*, *Synchronization—A Universal Concept in Nonlinear Science* (Cambridge University Press, Cambridge, England, 2001).
- [10] C. Schäfer *et al.*, *Nature (London)* **392**, 239 (1998); *Phys. Rev. E* **60**, 857 (1999).
- [11] E. Toledo *et al.*, *Med. Engin. Phys.* **24**, 45 (2002).
- [12] M. B. Lotric and A. Stefanovska, *Physica (Amsterdam)* **283A**, 451 (2000); A. Stefanovska *et al.*, *Phys. Rev. Lett.* **85**, 4831 (2000); M.-Ch. Wu and Ch.-K. Hu, *Phys. Rev. E* **73**, 051917 (2006).
- [13] M. D. Prokhorov *et al.*, *Phys. Rev. E* **68**, 041913 (2003).
- [14] K. Kotani *et al.*, *Phys. Rev. E* **65**, 051923 (2002).
- [15] V. N. Smelyanskiy *et al.*, *Phys. Rev. Lett.* **94**, 098101 (2005).
- [16] A. Rechtschaffen and A. Kales, *A Manual of Standardized Terminology, Techniques, and Scoring System for Sleep Stages of Human Subjects* (U.S. GPO, Washington, DC, 1968).
- [17] C.-K. Peng *et al.*, *Phys. Rev. Lett.* **70**, 1343 (1993); P. Ch. Ivanov *et al.*, *Europhys. Lett.* **48**, 594 (1999); *Nature (London)* **399**, 461 (1999).
- [18] A. Bunde *et al.*, *Phys. Rev. Lett.* **85**, 3736 (2000); J. W. Kantelhardt *et al.*, *Phys. Rev. E* **65**, 051908 (2002); *Europhys. Lett.* **62**, 147 (2003); T. Penzel *et al.*, *IEEE Trans. Biomed. Eng.* **50**, 1143 (2003).
- [19] J. W. Kantelhardt *et al.*, *Physica (Amsterdam)* **319A**, 447 (2003); S. Rostig *et al.*, *Sleep* **28**, 411 (2005).
- [20] We note that there is very little ($\approx 14\%$) increase in the amplitude of heartbeat or breathing fluctuations during REM sleep when compared with non-REM sleep. The changes in the synchronization behavior can thus not be due to variations in the strength of the influences from the brain. Rather, they must be due to the correlation structure imposed by these influences. Long-term correlations are nearly absent in both heartbeat and breathing during non-REM sleep [18, 19].
- [21] G. Klösch *et al.*, *IEEE Eng. Med. Bio. Mag.* **20/3**, 51 (2001); H. Danker-Hopfe *et al.*, *J. Sleep Res.* **13**, 63 (2004).
- [22] We note that the detection of phase synchronization in oscillators affected by the same uncorrelated noise might be spurious if band-pass filtering techniques (Fourier filtering) are applied [L. Xu *et al.*, *Phys. Rev. E* **73**, 065201(R) (2006)]. However, our synchrogram based algorithm works without any band-pass filtering.
- [23] D. Hoyer *et al.*, *Med. Eng. Phys.* **24**, 33 (2002).
- [24] M. G. Rosenblum *et al.*, *Phys. Rev. E* **65**, 041909 (2002); M. Palus and A. Stefanovska, *Phys. Rev. E* **67**, 055201(R) (2003).