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Comparison of two different approaches in the detection of intermittent cardiorespiratory coordination during night sleep

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Abstract

Background: The objective was to evaluate and to compare two completely different detection algorithms of intermittent (short-term) cardiorespiratory coordination during night sleep. The first method is based on a combination of respiratory flow and electrocardiogram recordings and determines the relative phases of R waves between successive onsets of inspiration. Intermittent phase coordination is defined as phase recurrence with accuracy α over at least k heartbeats. The second, recently introduced method utilizes only binary coded variations of heart rate (acceleration = 1, deceleration = 0) and identifies binary pattern classes which can be assigned to respiratory sinus arrhythmia (RSA). It is hypothesized that RSA pattern class recurrence over at least k heartbeats is strongly related with the intermittent phase coordination defined above.

Results: Both methods were applied to night time recordings of 20 healthy subjects. In subjects <45 yrs and setting k = 3 and α = 0.03, the phase and RSA pattern recurrence were highly correlated. Furthermore, in most subjects the pattern predominance (PP) showed a pronounced oscillation which is most likely linked with the dynamics of sleep stages. However, the analysis of bivariate variation and the use of surrogate data suggest that short-term phase coordination mainly resulted from central adjustment of heart rate and respiratory rate rather than from real phase synchronization due to physiological interaction.

Conclusion: Binary pattern analysis provides essential information on short-term phase recurrence and reflects nighttime sleep architecture, but is only weakly linked with true phase synchronization which is rare in physiological processes of man.

Background

Synchronization between heartbeat and respiration has been intensively studied during the last century. As early as the 1960s Hildebrandt and coworkers [1,2] investigated the phase coordination between both oscillators in man. They used an apparatus named 'coincidence analyzer' which was able to determine the absolute time delay of the onset of inspiration precisely after the preceding R wave – see Footnote 1 – and which calculated the 'coupling rate' on the basis of the distribution of the detected time lags. The authors concluded that the 'coupling rate' is a prominent marker of physiological relaxation and regeneration after work load [2]. In recent years, cardiorespiratory coordination has again been brought into the focus of research [3–18]. The popularity has been mainly caused by the rise of nonlinear system or chaos theory and

by the rapid progress of computerized physics and mathematics. Surprisingly, the majority of analytical methods used are still very similar to the early methods, even though modern physical models have been applied to explain how complex systems might interact and how such interaction manifests itself in recorded data. The methods are based on the evaluation of synchrograms [3,4,9,14,18] or post event time series [8] and differ only in the definition of the respiratory or cardiac phase or in the statistical quantification of the strength of synchronization. Common goal of these studies was to demonstrate that phase differences between cardiac and respiratory cycle remain constant over a specific time period or that certain phase combinations or time lags are significantly more frequent than others. In this way, many different types of short-term synchronization between heartbeat and respiration could be shown in individual subjects under experimental resting conditions [3,4,8,9,12,13,15,18].

Common to all techniques, which are applied in the above cited literature to analyze synchronization, is that they rely on simultaneous measurements of the electrocardiogram (ECG) and respiratory flow. This method has its pros and cons. On the one hand, the combined registration guarantees reliable information on both oscillators and enables a high resolution of their phase relations in time. On the other hand, long-term respiratory flow measurements are not easy to perform, particularly without affecting respiration itself or even destroying the weak coupling between heartbeat and respiration. Therefore, we focused on respiratory sinus arrhythmia (RSA) in order to derive statistical information on cardiorespiratory coordination without respiratory flow measurements – see Footnote 2. In earlier studies we could show that the statistical evaluation of the 'musical rhythmicity' of heart rate (HRR), i.e. the predominance and cyclicity of so-called phase locking pattern classes in binary differential heart rate dynamics (binary RR differences), has certain advantages over other linear or nonlinear heart rate variability analytic tools [19–22]. Evidence was given that HRR reflects mainly the degree of cardiorespiratory coordination and also enables the determination of the weighted phase coordination ratio (PCR) that corresponds to the frequency ratio of heartbeat and respiration during intermittent periods of apparent cardiorespiratory coordination. However, a conclusive and detailed proof of this relationship on the basis of real respiratory data is still lacking and was addressed in the present study. The main question therefore was: How does the univariate binary RSA pattern analysis (Method 2) correspond to the bivariate analysis of phase relations between the cardiac and the respiratory cycle (Method 1)?

Results

Method 1 vs. Method 2

Only one nighttime recording is used to demonstrate visually and exemplarily the various interrelations between cardiorespiratory phase recurrence (PR) and binary pattern predominance (PP). Subject b05 reveals many of the features best, although the overall correlation between the gray-scale maps is not optimal (see parameter r_1 in Table 1). In Fig. 1 both gray-scale maps demonstrate visually high conformity but, going in detail, differences can be observed: in the lower diagram the overall 7-bit pattern recurrency is slightly higher than the recurrency of all other patterns, whereas in the upper diagram the phase recurrency indicates a pronounced 4:1 phase coordination shortly after falling asleep (sleeping time: 23:10 – 7:05). Moreover, the correlation coefficients demonstrate a high concordance of the gray-scale maps with respect to PCR_1 and PCR_2 (r_2 = 0.97) but not with respect to PR and PP (r_3= 0.62), i.e. PCR_1 could be reliably reproduced by PCR_2 (mean PCR_1 = 4.25, mean PCR_2 = 4.26, mean PCR_1 – PCR_2 = 0.12), but the strength of coordination (PR) was not likewise reproducible by PP (see also Fig. 2). However, in other subjects the PR-PP correlation (see linear correlation coefficient r_3 in Table 1) is much better.

Sleep architecture and HRV

Apart from the obvious but very subtle relationship between phase and pattern recurrence another trait is common to most recordings: a remarkable PP oscillation with an intra-individually constant period between 1 and 2 hours. The oscillation can also be observed for PR but in many subjects it is much more prominent for the pattern predominance data (see e.g. Fig. 1). As this oscillation most probably corresponds to the subjects' sleep stage rhythmicity a close relationship also to certain HRV parameters was expected (see discussion). Particularly HF, LF and BAL are supposed to be highly dependent on sleep stages [23–28] and might therefore help to identify the source of the PP oscillations. As can be seen in Fig. 3, BAL is indeed markedly correlated with PP (r_9 = -0.87) which is also reflected by the inverse time courses of PP and BAL in Fig. 4. Surprisingly, this close relationship is not a matter of course: Fig. 5 shows exemplarily the time courses from subject b06 which also discloses a pronounced periodic oscillation of PP between 23:00 and 4:00 (with obvious REM sleep minima) but reveals definitely no sleep architecture for BAL.

Verification of synchronization

The lower diagram of Fig. 6 displays the gray-scale map of the phase recurrency in the shuffled surrogate data of subject b05. The course of both type and strength of the phase recurrency is very similar to the original data (see upper diagram in Fig. 6) though slight differences can be observed. Whereas the 8:2 (4:1) coordination seems in no

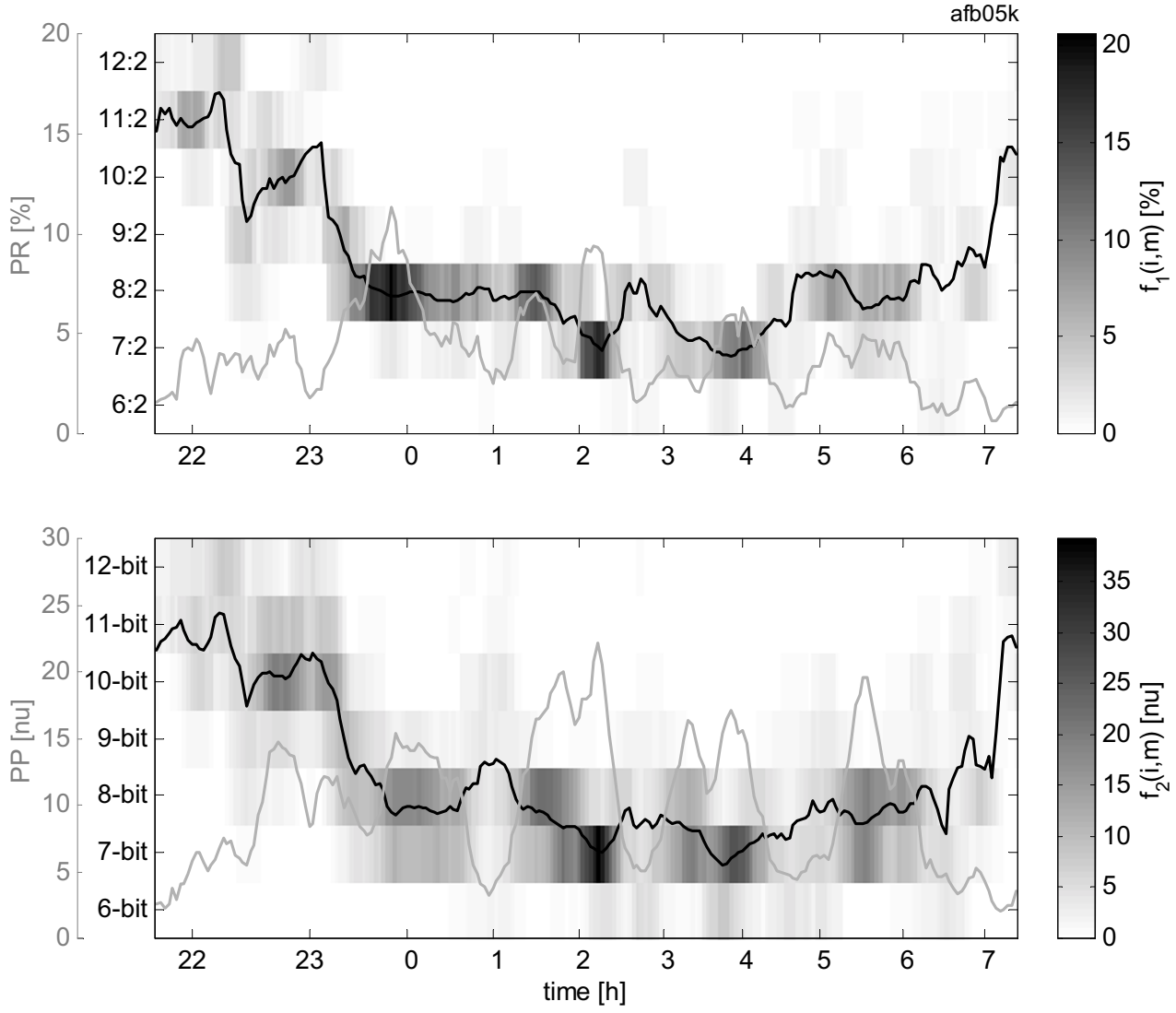

Figure 1

Method 1 vs. Method 2: Gray-scale maps of subject b05. Upper diagram: (a) gray-scale plot of the relative frequency $f_1(i,m)$ of intermittent m:2 phase coordination within a 1001-heartbeat window centered around the ith heartbeat and plotted against the time of day of the ith heartbeat; (b) weighted phase coordination ratio PCR_1 according to equation (6) (black line); (c) phase recurrency PR as the mean of the two maximal f_1 values in vertical direction (gray line) Lower diagram: (a) gray-scale plot of the corresponding normalized frequency $f_2(i,m)$ of m:2 RSA pattern recurrence within a 1001-heartbeat window centered around the ith heartbeat and plotted against the time of day of the ith heartbeat; (b) weighted phase coordination ratio PCR_2 according to equation (6) (black line); (c) pattern predominance PP as the mean of the two maximal f_2 values in vertical direction (gray line)

way to be dependent on the order of the RR series and therefore probably does not result from a beat-to-beat synchronization with respiration, the 7:2 phase recurrency decreases markedly in surrogate data. Thus it is more likely that the latter is caused by real phase couplings due to physiological interactions. These findings are confirmed by the parameter Δq. The bivariate variation of both signals, which is per se the same in the original and the surrogate data, decreases noticeably during 8:2 coordination but only slightly during 7:2 coordination. Moreover, the course of Δq reveals minima which are not accompanied by high phase recurrency. This shows that low bivariate signal variability does not automatically lead to spurious phase coordination since for the latter the average frequency ratio must also be close to m:2.

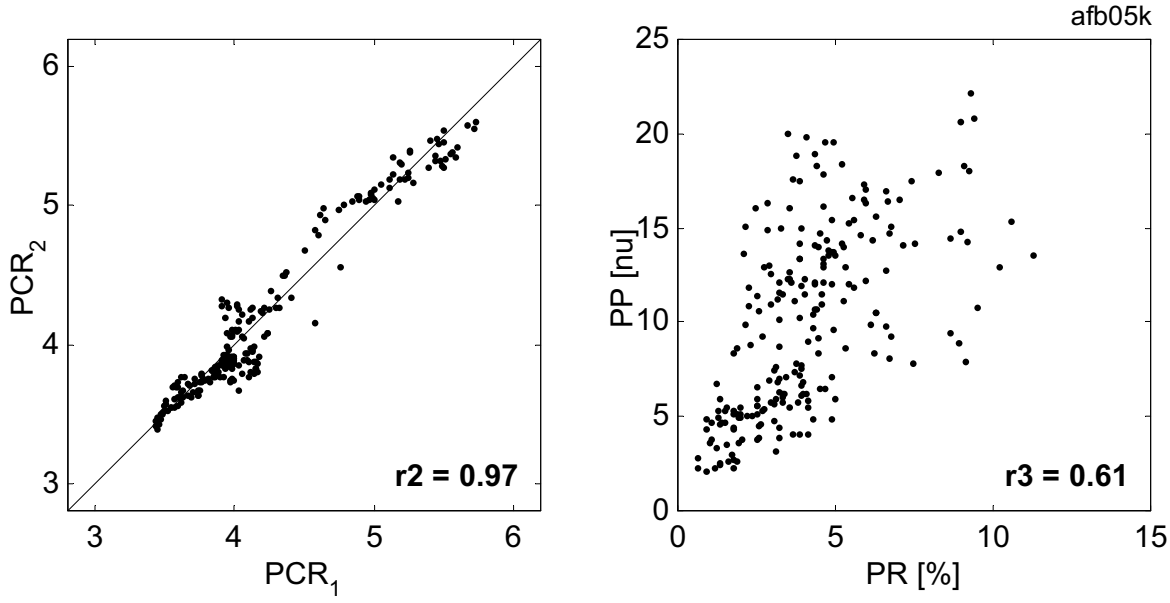

Figure 2
Method 1 vs. Method 2: Correlation diagrams of subject b05. PCR_1 vs. PCR_2 and PR vs. PP of the data (black and gray lines) in Fig. 1. In this subject only the weighted phase coordination PCR is highly reproducible. In other subjects also the PR-PP correlation (see linear correlation coefficient r_3 in Table 1) is striking.

Table 1: Correlation coefficients and age

	age	Method 1 vs. Method 2			Method 1 vs. HRV			Method 2 vs. HRV		
Subject	[yrs]	r_1	r_2	r_3	r_4	r_5	r_6	r_7	r_8	r_9
b05	25.4	0.80	0.97	0.60	-0.51	0.43	-0.61	-0.66	0.67	-0.87
a02	26.7	0.80	0.90	0.67	-0.43	-0.16	-0.31	-0.43	0.01	-0.49
b09	28.4	0.86	0.83	0.60	-0.58	-0.34	-0.33	-0.43	0.10	-0.81
b06	30.6	0.80	0.83	0.72	-0.35	0.12	-0.50	-0.40	0.03	-0.52
b08	30.6	0.91	0.80	0.61	-0.27	-0.37	-0.09	-0.40	-0.18	-0.33
b01	30.8	0.91	0.96	0.67	-0.53	-0.32	-0.25	-0.43	0.29	-0.79
b02	31.0	0.83	0.62	0.78	-0.07	0.32	-0.57	0.00	0.55	-0.79
a22	31.7	0.72	0.92	0.58	-0.63	-0.38	-0.27	-0.47	-0.07	-0.51
a01	32.2	0.79	0.94	0.53	-0.27	0.31	-0.60	-0.35	0.46	-0.83
a03	34.4	0.75	0.86	0.85	-0.36	0.27	-0.71	-0.17	0.48	-0.83
b03	35.4	0.79	0.81	0.70	-0.64	-0.55	-0.18	-0.67	-0.42	-0.45
b11	36.6	0.85	0.86	0.65	-0.43	-0.05	-0.48	-0.20	0.04	-0.30
b07	39.5	0.80	0.94	0.74	-0.44	-0.35	-0.16	-0.41	-0.15	-0.41
b51	39.9	0.75	0.85	0.71	-0.76	0.01	-0.55	-0.54	0.48	-0.81
a21	47.1	0.66	0.69	0.28	-0.49	0.06	-0.55	-0.28	0.47	-0.63
a20	48.4	0.65	0.76	0.09	-0.23	-0.14	0.06	-0.06	0.18	-0.24
b54	53.4	0.79	0.48	0.58	-0.56	-0.09	-0.56	-0.24	0.3	-0.62
b10	54.8	0.79	0.80	0.40	-0.35	-0.19	-0.11	-0.45	0.39	-0.77
b53	66.7	0.66	0.78	0.34	0.00	0.01	0.01	0.36	0.18	0.09
b52	75.3	0.62	0.66	0.48	0.12	0.54	-0.48	-0.18	0.08	-0.21

Linear correlation coefficients between both gray-scale maps (r_1), PCR_1 and PCR_2 (r_2), and PR and PP (r_3), are dependent on age. In most cases, the correlation between PR and LF (r_4), PR and HF (r_5), PR and BAL (r_6), PP and LF (r_7), and PP and HF (r_8) is significant but very low, suggesting that phase and pattern recurrency is related to linear HRV parameters but contain also additional information, e.g. on cardiorespiratory coordination. Only PP and BAL (r_9) are markedly anti-correlated, at least in 8 subjects ($r_9 < -0.76$) which may also be due to a methodological link between both parameters (see Discussion).

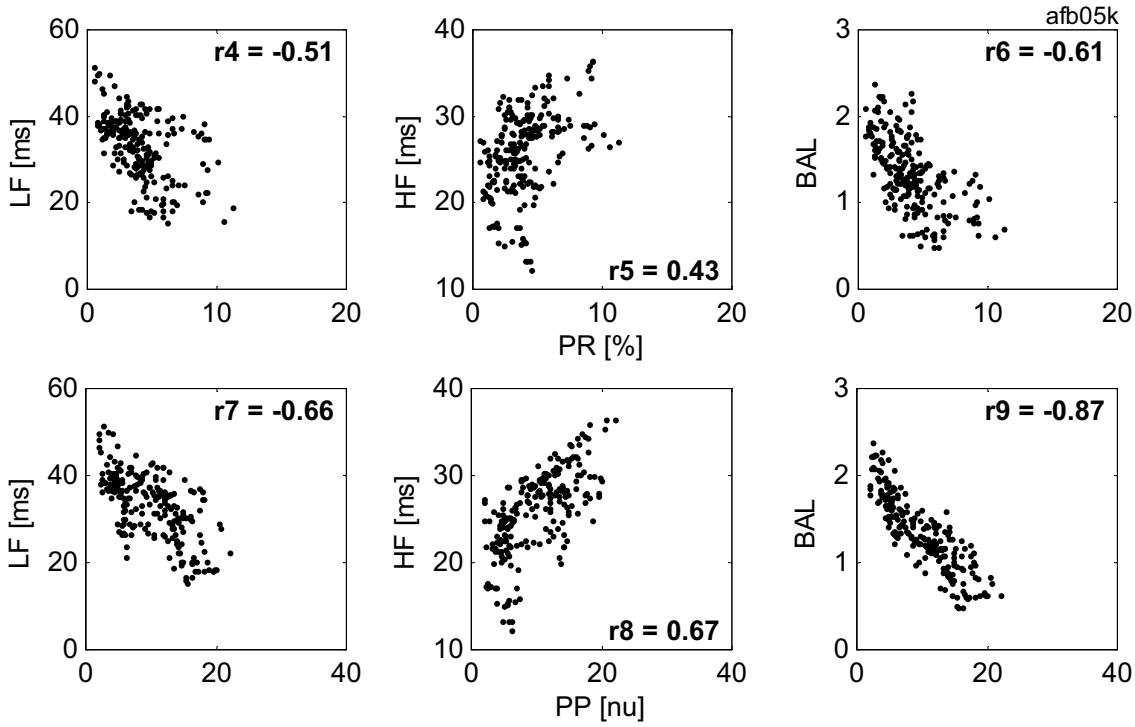

Figure 3
Coordination vs. HRV in subject b05. HRV parameters LF, HF and BAL vs. PR (upper diagrams) and PP (lower diagrams). The high correlation between PP and BAL confirms the methodological link between both parameters (see discussion) and supports the discussed dependency on sleep stages which has recently been shown for BAL.

Dependence on age

There is a remarkable decrease of mean PP with age (see upper diagram of Fig. 7), and also a notable dependence on age of the interrelations between cardiorespiratory phase recurrence and binary pattern recurrence (see Table 1). Particularly the correlation between the two gray-scale maps decreases with age (see lower diagram of Fig. 7).

Discussion

The first step towards a practical comparison of both methods was to describe cardiorespiratory coordination on a beat-to-beat basis. Phase coordination was assessed by determining the respiratory phases of R waves which follow a reference beat. The phase was defined as linear function of time between two onsets of inspiration. This is easier to calculate and yields similar phases when compared to the calculation of the phases via Hilbert transformation [12]. Intermittent phase coordination was then defined as phase recurrence with accuracy α after m heartbeats over a period of at least k heartbeats following the reference beat. In the context of this work, Method 1 is straightforward and not based on any physical model of coupled systems. It is merely descriptive while also allowing a confirmative statistical detection of epochs with deterministic synchronization when compared with appropriate surrogate data.

Whereas Method 1 is still very close to the synchrogram-based approaches [4], Method 2 is completely different and strictly based on the univariate analysis of the RR interval series. It has been adopted from earlier studies [19–22] and only slight modifications were made in order to ensure comparability with Method 1. Only recently, Galletly & Larson [29–31] described a technique to determine cardiorespiratory coupling during anaesthesia which is, like our method, based on HRV pattern repetition: "The specific pattern of heart rate acceleration and deceleration which occurs with breathing is determined by the pattern of vagal modulation and the positioning of heart beats within the ventilatory phases (...) Because the coupling interval (that between the initiating cardiac trigger and inspiratory onset) is fixed for a cardiac triggered breath at

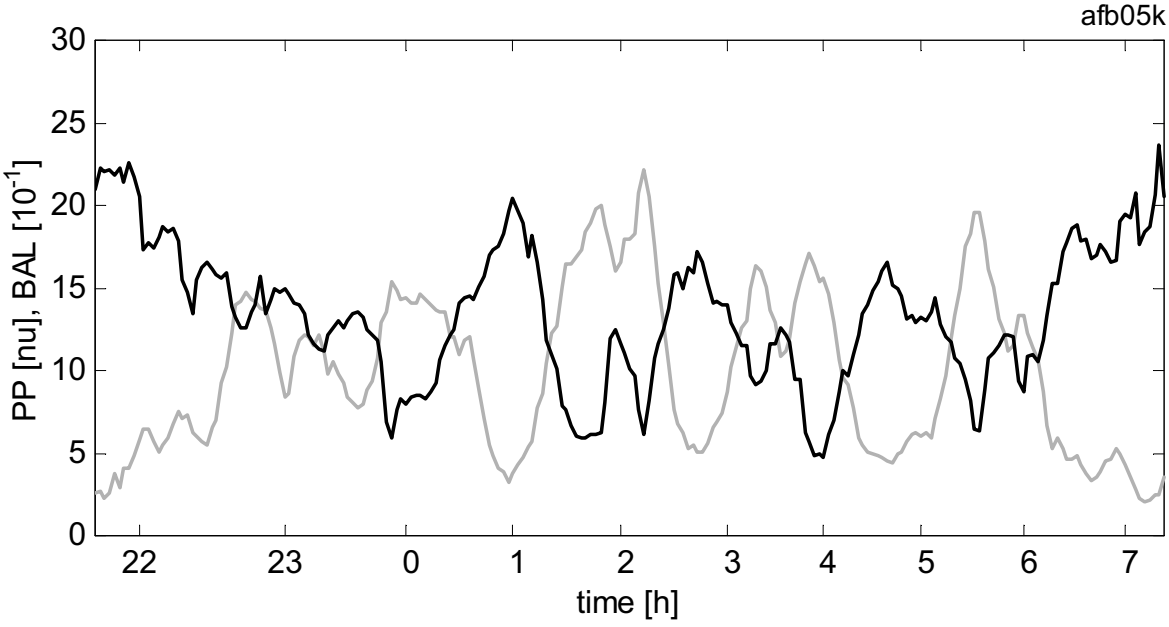

Figure 4
Night sleep oscillations of PP and BAL in subject b05. The negative correlation between PP (gray line) and BAL (black line) is also revealed by the mirrored time course of both parameters. In subject b05 BAL and PP show similar oscillatory fluctuations during sleep which probably relate to the periodic succession of sleep stages.

approximately 0.5 s, heart beats tend to fall in fixed relationship with the waxing an waning pattern of vagal tone." [31]. However, their quantitative approach to pattern repetition is a mix of linear and nonlinear analytic tools and is based on a pure triggering model. It does not consider nonlinear phase couplings. Moreover, the methods were only applied under anaesthesia which is not comparable with cardiorespiratory regulation under normal resting conditions. Janson et al. [32] also recently derived information on cardiorespiratory coordination solely from RR interval series which were called 'return times' in terms of nonlinear dynamics. From the maps of return times, better known as 'scatter plots', the authors calculated phase angles of vectors (RR_i RR_{i+1}) with respect to the 'center of mass' within a specific time window (a similar method is used also in [33]). The phase angles were then compared with the phases of the R peak within the respiratory cycle. In case of detectable RSA, both phases increase synchronously and result in very similar synchrograms. At first glance this method seems to be more accurate than the binary pattern analysis, but its practicability remains to be proven. Recently, Ashkenazy and Kantelhardt and coworkers [34,35] investigated binary coded variations of heart rate, which were called sign series of heart rate increments, by means of detrended fluctuation analysis (DFA). This method revealed high anticorrelations in the range between 8 and 13 heartbeats which were associated with linear dynamical properties by means of surrogate data analysis. But in their physical papers, the authors do not refer to RSA or even to cardiorespiratory coordination which would obviously explain this kind of (linear) sign series regularity.

In our study, the comparison of phase and binary pattern recurrence demonstrated high similarity between the frequency statistics of both methods. Particularly the weighted phase coordination ratio could be reliably reproduced by the pattern analysis, but also the phase recurrency PR, i.e. the frequency of intermittent coordination, is mirrored by the binary pattern predominance PP. In a group of 20 healthy subjects, the strong relationship between both methods could be confirmed, particularly for subjects younger than 45 years. The age dependence may be explained by the fact that that RSA decreases with age which inevitably leads to smaller detection rates of coordinated sequences by binary RSA pattern analysis (see upper diagram of Fig. 7).

Apart from the physiological correspondence with cardiorespiratory coordination, the binary HRV pattern technique also points to a strong relationship between sleep stages and cardiovascular regulation which is not revealed

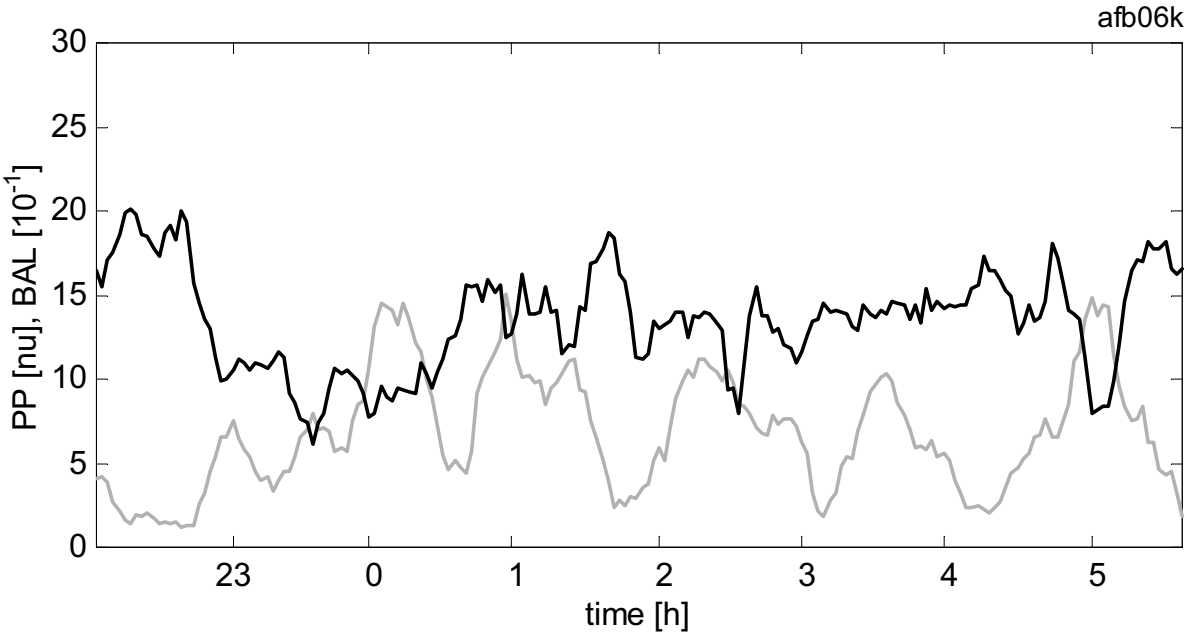

Figure 5
Night sleep oscillations of PP and BAL in subject b06. In subject b06 the correlation between PP (gray line) and BAL (black line) is weaker but, most interestingly, PP still oscillates while BAL does not. Is PP a better marker for sleep stage related alterations of cardiac control?

as clearly by classical HRV parameters. In most subjects, a large PP oscillation could be observed during the night which was present even when all other HRV parameters failed to unveil any periodicity (two data examples are presented in this article). In some cases PP was also highly correlated with the parameter BAL which is believed to be a very good HRV marker of REM sleep [24–27]. This suggests that PP oscillations with periods between 1 and 2 hours correspond to the periodic succession of sleep stages. On the other hand, as encephalographic registrations of sleep stages were not made in this study, such a conclusion can only be tentative. However, our findings are in accordance with the early results of Raschke and coworkers who already comprehensively discussed the dependencies between cardiorespiratory coordination and sleep. The authors emphasized that coupling is intensified during relaxation and that the 'coupling rate' changes systematically with sleep stages [36–40]. Moreover, in the above cited paper of Kantelhardt et al. [35], anticorrelations in heart rate increment sign series were also seen to be closely linked with sleep stages: "short-range anticorrelations ... are strong during deep sleep, weaker during light sleep, and even weaker during REM sleep". And these results are absolutely identical with our findings though, as already said, RSA and cardiorespiratory coordination was not a focus of their article. This is a bit surprising, as in an earlier paper by the same group [41], the correspondence between sleep-stage-dependent cardiorespiratory modulation (RSA) and correlations in heart rate series (but not in sign series) were already a main subject of discussion.

We have already discussed the methodological link between PP and BAL in a recent publication [22]. We assumed that a change of BAL, i.e. a shift from low- to high-frequency heart rate variations or vice versa, is accompanied by a shift in the distribution of predominant pattern classes. A decrease of BAL, for example, was thought to be related with a higher detection rate of cardiorespiratory phase locking patterns which also results in higher PP values. This assumption could be impressively confirmed in this study.

Both the analysis of bivariate variation and the use of surrogate data suggests that intermittent phase coordination, with $k = 3$ and $\alpha = 0.03$, results primarily from central adjustment of heart rate and respiratory rate and not from real beat-to-beat phase synchronization. This was not surprising because, in our experience, phase coordination over periods of more than 20 seconds, which correspond to sequences of at least three breathing cycles or 15–20 heartbeats, are relatively seldom in physiological data and can therefore not essentially contribute to the frequency

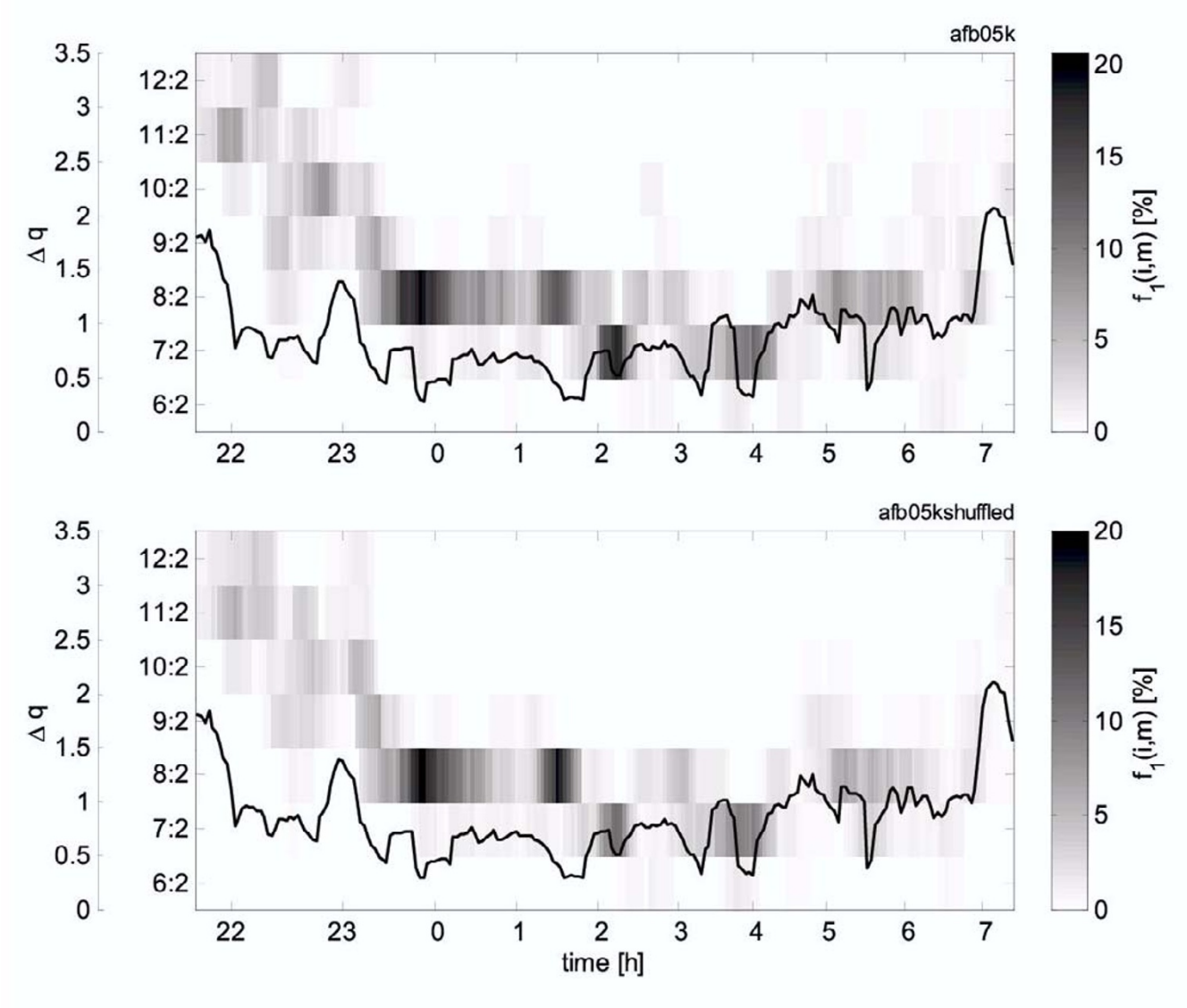

Figure 6

Shuffled surrogate data and bivariate variation (subject b05). Shuffling RR intervals within successive windows of 50 heartbeats destroyed all deterministic properties of the RR series on the LF-HF time scale while preserving long-term RR variability. The respiratory data remained unchanged. Despite this massive data manipulation the resulting gray-scale map of f_1 (lower diagram) does not change considerably compared to the original data (upper diagram). Only the 7:2 coordination after two o'clock is notably diminished. The course of Δq (black lines), which is per se identical for the original and the surrogate data, may explain this finding. During many periods of apparent coordination with k = 3 and α = 0.03, bivariate signal variation is low. Thus intermittent phase coordination most likely results mainly from a central adjustment of heart rate and respiratory rate but not from real beat-to-beat phase synchronization.

statistics of short-term phase coordination. Increasing the parameter k might help separating the effects of real synchronization from those of low bivariate signal variability or long-term frequency coordination, but it is not realistic to count only RSA patterns which are stable over at least k = 3 heartbeats. By increasing k, only very few sequences would be detected, resulting in statistically non-reliable frequency distributions. Fig. 8 shows this by way of example. The data are the same as in Fig. 1 but the stability condition has been set at k = 15. Only the sequences with 7:2 coordination shortly after two o'clock meet this requirement, corroborating the above finding (with respect to the surrogate data analysis and Δq, see results) that in subject b05 only the 7:2 phase recurrency partly indicates real phase couplings.

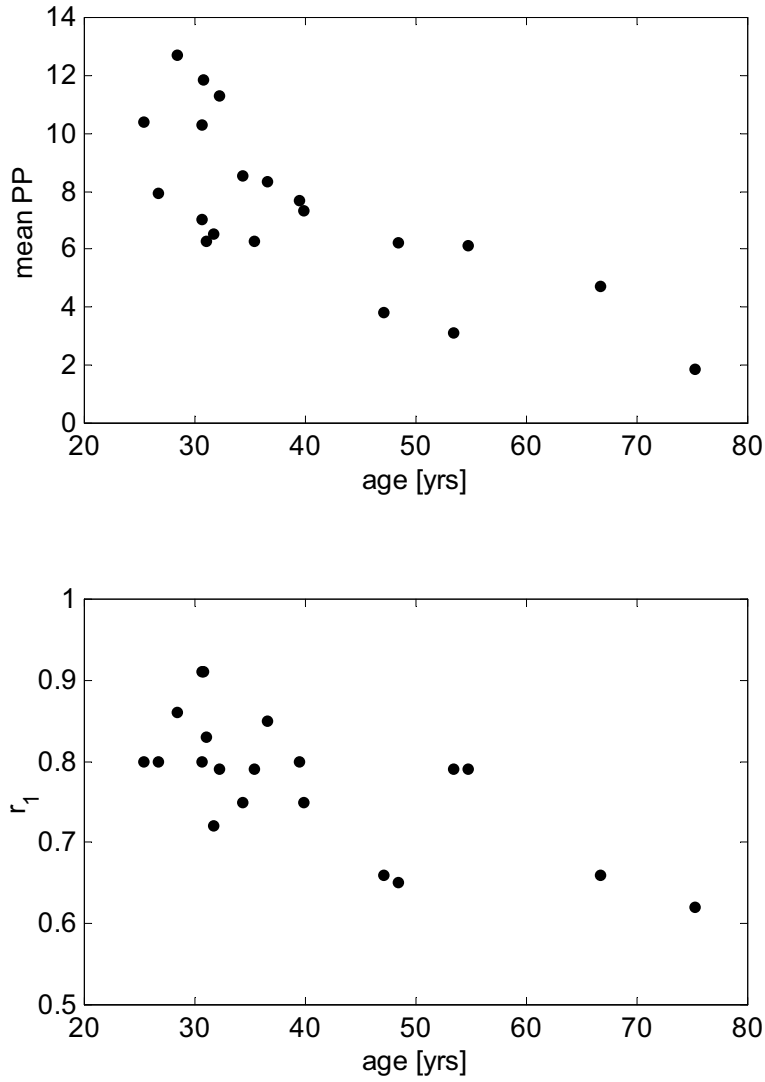

Figure 7
Dependence on age. There is a remarkable decrease of mean PP with age (upper diagram) which results from a loss in autonomic modulation of heart rate: Decreased RSA leads to lower detection rates of coordinated sequences by binary pattern analysis and to an inaccuracy of coordination analysis, e.g. expressed by lower overall correlation between phase and pattern recurrency (lower diagram, see also r_1 in Table 1).

Conclusions

Binary pattern analysis of heart rate differences is strongly linked with but does not substitute for bivariate cardiorespiratory phase coordination analysis. The univariate pattern analysis provides essential information on short-term phase recurrence and suggests a strong relationship between sleep architecture and cardiovascular regulation, but is only weakly linked with coupling processes and real phase synchronization.

We feel also encouraged to conclude that, if the primary goal is to analyze physiological phase synchronization and entrainment in the physical sense, it is necessary (i) to analyze highly resolved combined thermistor-ECG recordings, (ii) to find longer periods of continuous phase coordination, i.e. phase recurrence over several breathing cycles, and (iii) to require high bivariate signal variability. However, as all three criteria are seldom met, even during resting periods, it is thus questionable whether the application of physical synchronization criteria is appropriate in the identification and quantification of synergetic effects in physiological processes of man.

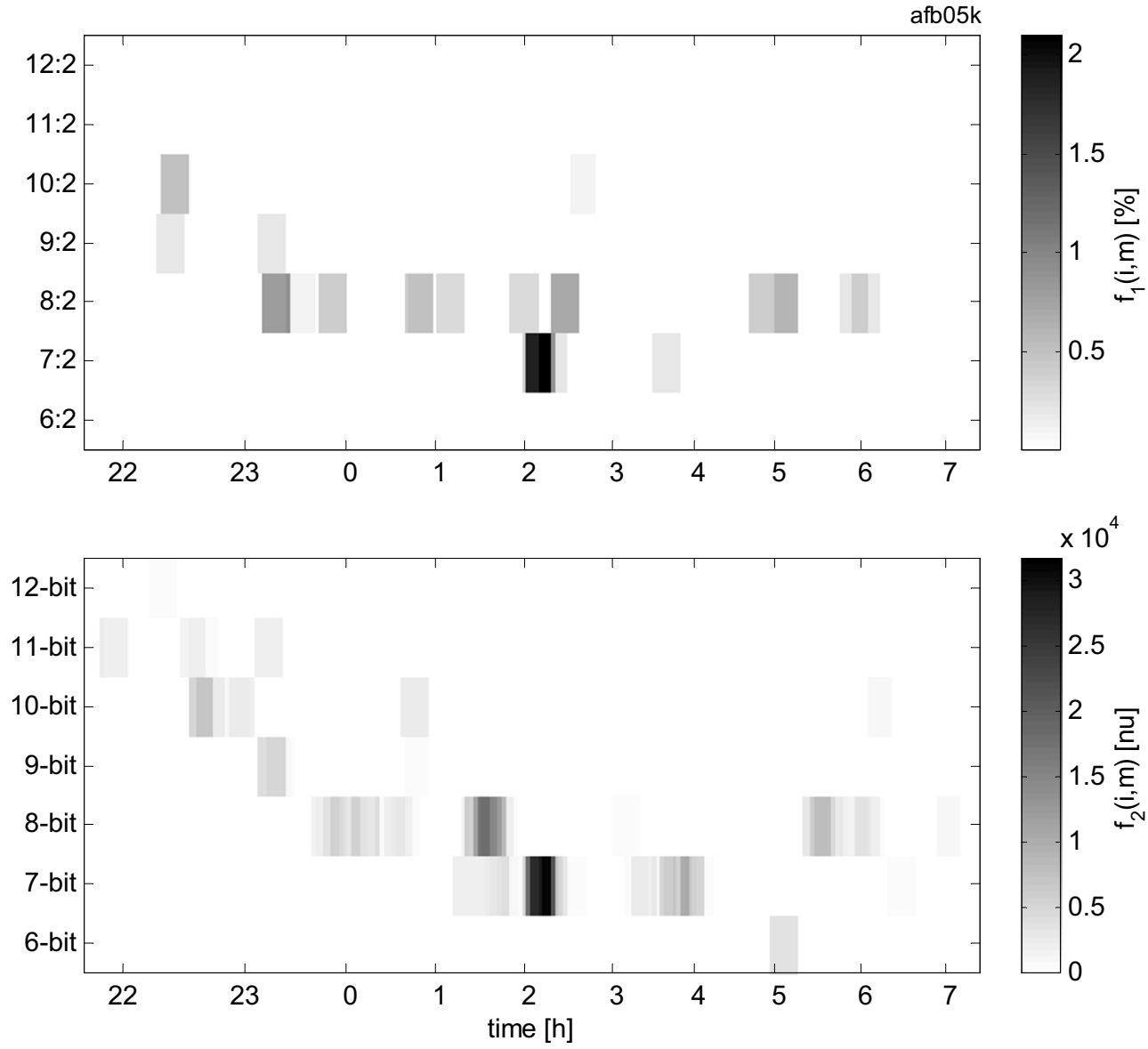

Figure 8

Gray-scale maps with *k* = 15 (subject b05). Phase synchronization should be revealed when solely longer periods (e.g. >20 seconds) of phase coordination are taken into consideration. To check for synchronization, the stability condition was set at *k* = 15 heartbeats which led to the sparse gray-scale maps in this figure. Only the 7:2 phase and RSA pattern recurrences seem to partially meet the strong synchronization criteria which supports the findings above (see legend of Fig. 6).

Methods

Subjects and data acquisition

In 22 healthy subjects, ECG (3000 Hz, including digital R wave detection) and airflow (100 Hz, using a nasal/oral thermistor) were recorded simultaneously with an ambulatory solid-state recorder (Medikorder, TOM-Signaltechnik, Graz, Austria) during night sleep over at least 5 hours (between 21:00 and 9:00). The ambulatory device provided Matlab data files which were further analyzed on a personal computer using C and Matlab routines. Two subjects had to be excluded from data analysis, one because of sustained ventricular arrhythmia, a second one because of losing the thermistor during night. The remaining 20 subjects were aged 25 to 75 years (mean ± SD: 40 ± 14 years), and included 13 males and 5 smokers.

The recordings are part of the multi-center study 'Respiratory rate detection from ECG recordings – a comparison of different detection methods' which is being carried out in cooperation with the Gemeinschaftskrankenhaus Havelhöhe (Berlin, Germany) and the Institute for Noninvasive Diagnostics, Joanneum Research (Weiz, Austria). The survey started in 2001 and is still in progress. All subjects gave their informed consent. Subjects with a known illness or pregnant women were excluded. The study protocol conforms to the ethical guidelines of the Declaration of Helsinki, Revision 2000.

Combined signal analysis (Method 1)

Taking the heartbeat as the reference (i.e. the data are calculated for each heartbeat) and the R wave as the reference point within the heartbeat cycle, cardiorespiratory phase coordination can be determined by calculating the phase φ of the respiratory cycle at all R times: $\varphi_i = \varphi(R_i)$. The easiest way to define the normalized continuous respiratory phase is to determine the relative time of R_i between the preceding and the subsequent onset of inspiration (I_j and I_{j+1}) and adding the index number j of the actual breathing cycle:

$$\varphi_i = j + \frac{R_i - I_j}{I_{j+1} - I_j}, \text{ with } I_j \le R_i < I_{j+1} \qquad (1)$$

The onsets of inspiration are defined as the minima of the thermistor curve. Practically, the following information for each R wave is obtained: index number i, R time R_i, index number of corresponding respiratory cycle j_i, phase of respiration φ_i, preceding RR interval RR_i, respiratory cycle duration II_j, and instantaneous frequency ratio $q_i = II_j/RR_i$. These parameters are registered for each heartbeat and written into the 'heartbeat table' (see Additional file 1).

On the basis of these definitions, intermittent phase coordination can be defined by the requirement that the phase φ must recur within the range φ ± α after m heartbeats for at least k subsequent heartbeats, comprising the same number n of breathing cycles:

$$\exists\, m, n \quad \forall l \in \{i \ldots i + k - 1\} \quad |\varphi_{l+m} - \varphi_l - n| < \alpha \qquad (2)$$

We denote this kind of statistical synchronization as m:n intermittent phase coordination with accuracy α and stability k (see illustration in upper diagrams of Fig. 9).

In the heartbeat table, the number of breathing cycles n is displayed for all heartbeats which meet requirement (2) with $k = 1$ and $m \in \{6 \ldots 12\}$ (see columns 8 to 14 in Table 2).

Binary RSA pattern analysis (Method 2)

Binary pattern analysis, which has been also denoted as 'musical heart rate rhythmicity' (HRR), is primarily based on simple binary coding of instantaneous heart rate fluctuations. It considers only the most important information from the time domain of heart rate variability (HRV), i.e. whether the heart rate accelerates or decelerates from one beat to the next. In the heartbeat table, R waves with RR differences (RR_{i+1} - RR_i) smaller than zero are marked with $b_i = 1$, which corresponds to an acceleration of heart rate, and RR differences greater than or equal to zero are marked with $b_i = 0$ which corresponds to a deceleration of heart rate (see Table 2 and lower diagram of Fig. 9). Subsequently, the algorithm looks for musical pattern classes in the resulting binary sequences. A binary musical pattern class is defined as a set consisting of all binary patterns with constant pattern length m. The patterns in a set can be transformed into each other either by rotation (shifts in origin) or by exchange (permutation) of 1s and 0s. This can be pictured as a closed necklace with white and black beads. Moving beads from one side to the other (rotation) or exchanging white and black beads (permutation) does not affect the symmetry type of the necklace. Alternatively, the 1s and 0s can be interpreted as strokes and rests or as strokes on two different drums. The formal musical rhythm, which results when repeatedly playing a pattern, does not depend on the entry point chosen (rotation) or on the type of the sounds played (permutation). In the music of African or African-American origin, for example, complementary rhythms (stroke-rest permuted patterns) are often played or thought simultaneously. If a complementary rhythm is not heard it can usually be still seen in the moving patterns of the drummers or dancers [42].

The pattern classification system used in this study had been derived from a scheme originally developed to classify timeline rhythms (bell patterns) in the music of African origin [43]. In a previous publication we constructed a scheme consisting of 42 pattern classes comprising all binary patterns with 3 to 8 bits (pulses, heartbeats) [19,20]. Later, the scheme was extended to 47 pattern classes to also include the most relevant pattern classes with up to 12 bits (applied in [21,22]). Many of these binary patterns are associated with RSA and are generated constantly and repeatedly when phase coordination between heart beat and respiration is present (see Table 3). Fig. 10 demonstrates this by way of example for a 7:2 phase locking which results in a cyclical recurrence of pattern class 22. The same effect is also shown in the lower panel of Fig. 9 using real data.

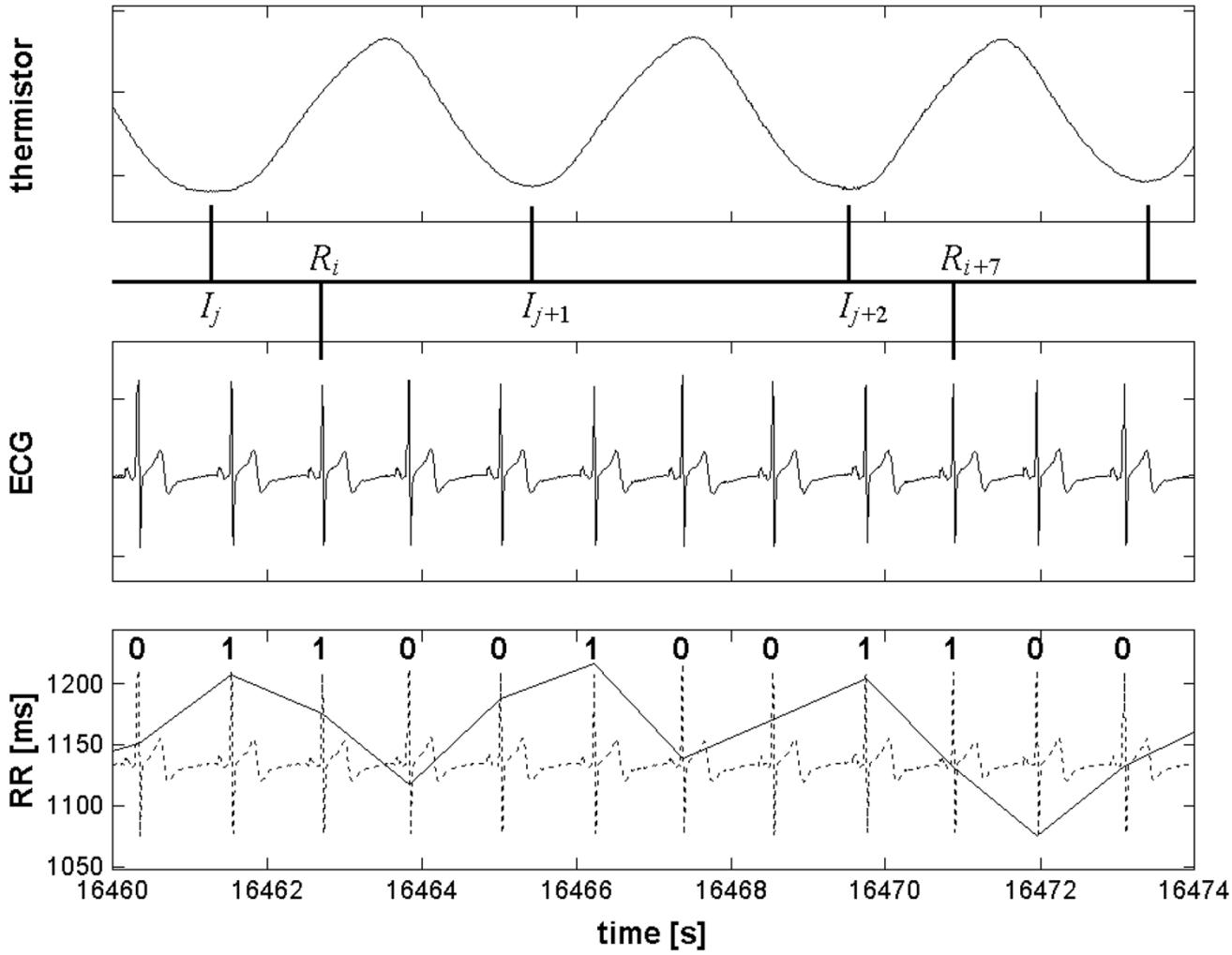

Figure 9

Intermittent phase coordination and binary pattern recurrence. Upper two panels: Real data example of a 7:2 phase recurrence, i.e. the relative phases of R waves between successive onsets of inspiration (II interval) recur after seven heartbeats and two respiratory cycles, and at least over a period of k = 3 heartbeats. This is denoted as 7:2 intermittent phase coordination. Lower panel: The corresponding RR tachogram shows a pronounced RSA which is synchronous with the thermistor signal and which leads to a cyclical 7-bit RSA pattern recurrence (of pattern class 22, see Fig. 10), i.e. binary values are repeated after seven heartbeats over a period of at least k = 3 heartbeats. This is equivalent to the rotation of the heart rate acceleration pattern 0110010 → 1100100 → 1001001 → 0010011 → etc.

The basic idea is to make use of the recurrence of RSA pattern classes in order to detect intermittent cardiorespiratory coordination. A detailed description of this method can be found in recent publications [19,20] – see Footnote 3. In the present study, the binary pattern analysis is reduced to detect only those patterns which belong to the pattern classes in Table 3. A second important modification of the standard method is that a one-bit or two-bit pattern deviation from a RSA pattern in Table 3 is allowed, i.e. all but one bit or two bits, respectively, of the pattern under consideration must coincide with the bits of a pattern in one of the pattern classes. This makes the algorithm more flexible as also asymmetrical breathing patterns are identified more effectively. Furthermore, the parameter k is introduced to preselect the required number of subsequent heartbeats for which a pattern class has to remain unchanged. This parameter corresponds to the phase coordination stability k in the previous section and is subsequently referred to as pattern stability. Then, RSA pattern recurrence could be formally defined by the following condition:

$$\exists\, m \quad \forall l \in \{0 \ldots k\} \quad class\ (\mathbf{b}_i^m) = class\ (\mathbf{b}_{i+l}^m) \in \{\text{RSA pattern classes}\} \quad (3)$$

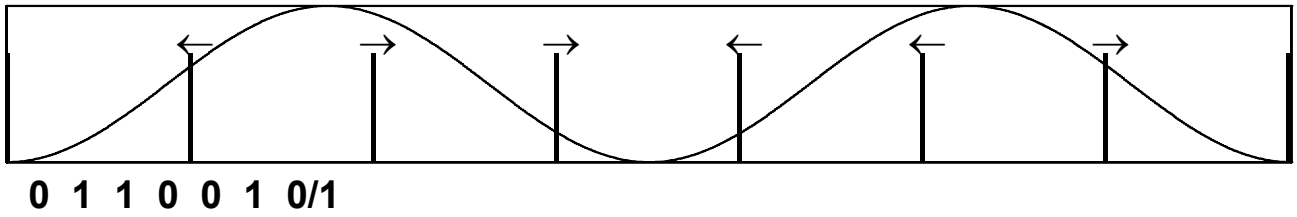

Figure 10
Example of a 7:2 phase locking pattern. A periodic and dominant frequency modulation of the heartbeat causes a predominance and cyclical recurrence of typical binary patterns of heart rate acceleration (1) and deceleration (0), as sketched here for a 7:2 phase-locked sinus modulator. The figure shows how a sinusoidal frequency modulation leads to a displacement of equidistant R peaks. The direction is indicated by arrows on top of the R peak bars. During inspiration (increase of idealized thermistor curve) R peaks are advanced and during expiration R peaks are retarded. The binary values below indicate the corresponding lengthening (0) or shortening (1) of RR intervals from one beat to the next. The two alternatively resulting patterns (0110011 and 0110010) belong to the same pattern class (the 7:2 phase locking pattern class which is designated as class 22 in [19,20]). In the range from 3:1 to 6:1 or 6:2 to 12:2, phase locking pattern predominance most likely originates from intermittent cardiorespiratory coordination as the binary constellations of these patterns correspond to high frequency heart rate variations, i.e. RSA. These classes are therefore denoted as RSA pattern classes without claiming a one-to-one correspondence to real cardiorespiratory synchronization. This relationship between RSA pattern predominance and cardiorespiratory synchronization is subject of the present study.

Table 3: *m*:2 RSA pattern classes

m	PLR	*class*	$\mu_m(0)$	$\mu_m(1)$	$\mu_m(2)$	2^m	basic pattern	basic compl. pattern
6	6:2	12	6	30	56	64	001001	011011
7	7:2	22	14	70	126	128	0010011	0011011
8	8:2	41	4	36	124	256	00110011	00110011
9	9:2	43	18	126	360	512	000110011	001100111
10	10:2	44	10	90	350	1024	0001100011	0011100111
11	11:2	45	22	198	770	2048	00011000111	00011100111
12	12:2	46	6	78	438	4096	000111000111	000111000111

In the present study, the binary pattern analysis is reduced to detect only those patterns which belong to the RSA pattern classes listed in this table. The strict condition is somewhat undermined by allowing a one-bit or two-bit pattern deviation (pattern tolerance τ) from the binary patterns listed, i.e. all but one bit or two bits, respectively, of the pattern under consideration must coincide with the bits of a pattern in one of the pattern classes. This makes the algorithm more flexible as asymmetrical breathing patterns are also taken into consideration. PLR : assigned phase locking ratio; $\mu_m(\tau)$: size of the pattern class with respect to τ (underlined values: tolerance chosen in this study); 2^m : number of possible *m*-bit combinations; basic pattern and its complement: (smallest) representatives of the pattern class. In the heartbeat table (Table 1) complementary patterns are indicated by negative class numbers.

with $\mathbf{b}_i^m = (b_i\, b_{i+1} \ldots b_{i+m-1})$. The term in braces denotes the set of the pattern classes summarized in Table 3, including those which are identical after permutation of τ bits (pattern tolerance). Definition (3) has to be extended as it ignores an important requirement: successive patterns must not only have the same class number but must also be identical after rotation. Thus in a single run, swapping 1s and 0s is not permitted in successive patterns, i.e. successive patterns may not be complementary. This restriction is taken into account by the following definition:

$$\exists\, m \quad class\,(\mathbf{b}_i^m) \in \{\text{RSA pattern classes}\} \quad \forall l \in \{i \ldots i + k - 1\}\ b_l = b_{l+m} \quad (4)$$

which is therefore more appropriate for the definition of RSA pattern recurrence. The form of (4) is also similar to the form of condition (2) in the previous section.

In the heartbeat table, the pattern class number is displayed for all heartbeats which meet the first part of (4) (i.e. $k = 0$) with $m \in \{6 \ldots 12\}$ (see columns 16 to 22 in Table 2 in Additional file 1). Negative class numbers denote complementary patterns.

Implementation

The heartbeat table is the basis for further analysis. Only phase coordination ratios in the range from 6:2 to 12:2 as well as 6-bit to 12-bit patterns are considered. This ensures comparability between the two kinds of statistics and allows equal treatment of the integer ratios 3:1 (6:2), 4:1 (8:2), 5:1 (10:2), 6:1 (12:2) and the non-integer ratios 7:2, 11:2 and 9:2.

Frequency statistics are performed in the same fashion for the combined signal analysis (Method 1) and the RSA pattern analysis (Method 2). A window of 1001 heartbeats centered around the *i*th heartbeat is moved in equidistant steps of 150 heartbeats over the entire heartbeat table. The stability requirement is set to $k = 3$ for both methods and the phase recurrence accuracy is set to $\alpha = 0.03$. Within the window, all heartbeats which comply with (2) and (4), respectively, are counted. These counts are referred to as absolute frequencies $F_1(i,m)$ and $F_2(i,m)$, respectively. The corresponding relative frequencies are denoted as $f_1(i, m) = F_1(i, m) / N$ and $f_2(i, m)$ (definition of f_2 see below).

A problem occurs when comparing the values of the resulting pattern class frequencies $F_2(i,m)$ with different pattern length m, because some of the pattern classes are per se more frequent than others. For example, class 22 encompasses 14 different patterns out of $2^7 = 128$ possible binary combinations (i.e. 11%) but class 41 only 4 (i.e. 1.6% of 256 possible patterns). Allowing a one-bit pattern tolerance, the relative number of all 8-bit patterns classified as RSA patterns increases to 14%, the number of all 7-bit patterns to 98%, i.e. only the 1111111 and the 0000000 pattern are not identified as RSA patterns (see parameter μ_m in Table 3). Therefore it is reasonable (i) to adjust the relative sizes $\mu_m(\tau)/2^m$ of the RSA pattern classes by choosing an appropriate tolerance value ($\tau = 0$, 1 or 2) and (ii) to normalize the absolute frequency by dividing by the respective relative pattern class size. Furthermore, to obtain relative values, the absolute frequency is also divided by the total number N of patterns within the window centered around the *i*th heartbeat and multiplied by 2^k to compensate for the stability requirement:

$$f_2(i,m) = F_2(i,m) \cdot \frac{2^{m+k}}{N \cdot \mu_m(\tau)} \quad (5)$$

The resulting normalized frequency f_2 is <1 if the pattern class recurrence is less frequent and >1 if the pattern class recurrence is more frequent than would be expected in equally distributed random symbol sequences (which corresponds to a random walk RR tachogram). In this study, the tolerance is set as follows: $\tau = 0$ for $m = 6,7$; $\tau = 1$ for $m = 8 \ldots 11$ and $\tau = 2$ for $m = 12$ (see underlined values in Table 3).

In comparing Method 1 and 2 quantitatively, different techniques are introduced. The first is a gray-scale map of the resulting seven frequency values $f_{1,2}(i,m)$ of each 1001-beat interval against the time of day (see Fig. 1). This map best illustrates coordination preferences during the nocturnal course.

Two types of parameters are calculated to reduce the information given by the frequency distribution: (i) the weighted phase coordination ratios PCR_1 and PCR_2 – see Footnote 4 – and (ii) the strength of coordination denoted as phase recurrency (PR) and pattern predominance (PP), respectively – see Footnote 5. The latter are simply defined as the mean of the two maximal f values in vertical direction and quantify the 'vertical gravity' of the gray-scale maps f_1 and f_2. PCR_1 and PCR_2 can be interpreted as the 'vertical centers of gravity' and are defined as the weighted averages of the m:2 frequency ratios:

$$PCR_{1,2}(i) = \frac{\sum_{m=6}^{12} \frac{m}{2} f_{1,2}(i,m)}{\sum_{m=6}^{12} f_{1,2}(i,m)} \quad (6)$$

All four parameters are plotted together with their corresponding gray-scale map (see Fig. 1) to reveal the type and the strength of phase and pattern recurrence respectively, and are plotted against each other to show their interrelation (see Fig. 2).

The correlations between pattern and phase recurrency are expressed by the linear correlation coefficients r_1 (overall correlation between both gray-scale maps), r_2 (PCR_1 vs. PCR_2) and r_3 (PR vs. PP).

Heart rate variability (HRV)

A Fast Fourier Transformation (FFT) based spectral analysis of HRV is performed on all 1001-heartbeat sequences. The resulting spectral power density function is integrated in the low frequency band (0.04–0.15 Hz, LF) and the high frequency band (0.15–0.40 Hz, HF). LF and HF power (LF, HF) are computed in milliseconds such that they correspond to the standard deviation of the LF and HF band-passed RR tachogram (times between R waves in milliseconds). Furthermore the balance BAL=LF/HF is calculated. The spectral analysis is performed according to the methods of Rottman and co-workers [44].

The linear correlations between HRV and coordination parameters are numerically demonstrated by the coeffi-

cients r_4 (PR vs. LF), r_5 (PR vs. HF), r_6 (PR vs. BAL), r_7 (PP vs. LF), r_8 (PP vs. HF) and r_9 (PP vs. BAL).

Verification of synchronization

Most interesting from the physical point of view is whether an apparent coordination of two oscillators in general is only an occasional coincidence or if it is really caused by coupling mechanisms. Only the latter deserves to be called 'synchronization' in the physical sense – see also Footnote 2. Answers can be found (i) by looking at the variability of both signals and (ii) by constructing appropriate bivariate surrogate data which preserve essential univariate properties of the original data but lack typical traces of phase coupling.

Intermittent phase coordination between heartbeat and respiration may appear if the two signals occasionally reveal both a reduced variability and a lower order rational frequency ratio. Then the signals seem to be coordinated although no entrainment or synchronization is necessarily present. Therefore a simple indicator of synchronization is a prominent phase recurrency together with high signal variation, i.e. high variability of heart rate and respiratory rate. In this study the bivariate variation of heart rate and respiratory rate is estimated with respect to their influence on the frequency ratio of heartbeat and respiration (according to the error propagation law):

$$\Delta q = \sqrt{\left(\frac{II}{RR^2}\Delta RR\right)^2 + \left(\frac{1}{RR}\Delta II\right)^2} \quad (7)$$

where II and RR can be replaced by the mean values and ΔII and ΔRR by the standard deviations of the II and RR differences respectively. Small values of Δq suggest spurious frequency coordination which results solely from low bivariate signal variability. If intermittent phase coordination is accompanied by small Δq values, phase synchronization is not likely or hard to detect.

Appropriate surrogate data are constructed by shuffling the RR differences within each part of a partitioned RR tachogram. A partition size of 50 heartbeats ensures that shuffling destroys all deterministic properties of the RR series on the LF-HF time scale while preserving long-term RR variability. The respiratory data remain unchanged. Within the windows of 1001 heartbeats, for which coordination statistics is performed, mean value and standard deviation of heart rate are the same in original and surrogate data but, due to the random order of RR intervals, deterministic phase relations between the heartbeat and any other oscillator (particularly respiration) are destroyed.

Footnotes

Footnote 1

The terms used by Engel et al. [1,2] are somewhat problematic. A time delay after the preceding R wave or inspiratory onset (e.g. [8,45]), which is also denoted as post event time [8], is not identical with a phase within the cardiac or respiratory cycle as only the 'beginning' of the cycle is regarded. Therefore, the term 'phase coupling' is inappropriate (e.g. [46]) in a strict physical sense. In the Hildebrandt group this problem was addressed by Raschke who determined real relative phases of inspiratory onset in the cardiac cycle [36–40]. Two different modes of coupling were discussed: modulation (RSA) and triggering. The latter is divided into the advancement of heartbeat by inspiration (when inspiration starts during the diastolic phase) and, vice versa, triggering of inspiration through the heartbeat which was called 'pure phase coupling' [37]. However, although calculating true phases, Raschke also focused solely on m:1 phase and frequency coordination.

Footnote 2

In physical applications, *synchronization* is understood as an entrainment or locking process due to interaction [3,4,9]. And strictly speaking one has to prove that an observed adjustment of rhythms is not an occasional coincidence but caused by coupling mechanisms. This proof often fails in living systems for two main reasons: First, periods of synchronization are naturally very short, and consequently testing for deterministic phase relations is not appropriate. Second, as the underlying dynamics are unknown, it is very difficult to decide whether rhythm adjustment is caused by couplings or not. In this context, the term *coordination* is less restrictive. It is widely used in a purely descriptive manner. Introduced by von Holst in the thirties of the last century (see references in [11,15–17]), (relative) coordination is equivalent to the existence of certain phase relations without claiming that these phase relations are due to real coupling mechanisms.

To avoid misinterpretations, it is also important to note that RSA and cardiorespiratory phase synchronization are both caused by cardiorespiratory couplings, but RSA results solely from modulation which is seen as a uni-directional interaction between heartbeat and respiration: breathing modulates heart rate but not vice versa. However, modulation does not lead to an adjustment of phases. Synchronization is typically bi-directional and, even more important, it depends on phase relations between two or more interacting oscillators.

Footnote 3

A detailed description of the HRR method can be found in [19] which can be downloaded free of charge from the website http://ajpheart.physiology.org/cgi/content/abstract/277/5/H1762.

Footnote 4

PCR was originally defined as the weighted average of phase locking ratios according to the frequency of the hourly predominance of binary phase locking patterns [20]. Thus the interpretation of PCR is different but the calculus is still the same.

Footnote 5

It has to be noted that the above definition of PP differs from the original definition in [19,20]: (i) it considers only the two maximal *f* values (not the difference between maximal and minimal values) and (ii) it includes the demand for pattern class stability over at least $k = 3$ heartbeats.

Authors' contributions

HB and DC designed the study, recruited the subjects and collected the data. HB developed the software for coordination analysis, performed the analysis and drafted the manuscript. DC wrote basic computer programs for data handling and participated in the analysis. PVL was involved in the interpretation of the data and participated in the final revision.

Additional material

Additional File 1

Table 2 – Excerpt from the heartbeat table (data of Fig. 9)
Click here for file
[http://www.biomedcentral.com/content/supplementary/1472-6793-2-18-S1.pdf]

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