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ABSTRACT

Interactions between the cardiac and respiratory systems play a pivotal role in physiological functioning. Nonetheless, the intricacies of cardio-respiratory couplings, such as cardio-respiratory phase synchronization (CRPS) and cardio-respiratory coordination (CRC), remain elusive, and an automated algorithm for CRC detection is lacking. This paper introduces an automated CRC detection algorithm, which allowed us to conduct a comprehensive comparison of CRPS and CRC during sleep for the first time using an extensive database. We found that CRPS is more sensitive to sleep-stage transitions, and intriguingly, there is a negative correlation between the degree of CRPS and CRC when fluctuations in breathing frequency are high. This comparative analysis holds promise in assisting researchers in gaining deeper insights into the mechanics of and distinctions between these two physiological phenomena. Additionally, the automated algorithms we devised have the potential to offer valuable insights into the clinical applications of CRC and CRPS.

The cardiac and respiratory systems are key in maintaining healthy physiologic function. Pathological deviations from normal cardiac and respiratory dynamics have been linked to increased risk of disability and mortality, and often, heart diseases affect respiratory health and vice versa due to their mutual coupling. Quantifying cardio-respiratory coupling is a challenging problem, as little is known about the specific nature of this interaction and how it changes with different physiologic states, such as sleep/wake transitions and sleep stages. In our work, we focus on two phenomena of cardio-respiratory coupling: cardio-respiratory phase synchronization and cardio-respiratory coordination. We suggest two methods to detect and quantify these interactions automatically and apply these methods to sleep recordings that include heart rate, breathing, and wrist actigraphy. We find that heart rate and breathing are more in sync or coordinated during deep sleep than during rapid eye movement sleep. We also find that the kind of interaction and coexistence of synchronization and coordination depends on how stable or variable the breathing rate is. Our work can contribute to a better understanding of the mechanisms and benefits of cardio-respiratory interactions and help diagnose diseases that affect them.

I. INTRODUCTION

The cardiac and respiratory systems are integral to human life and interact through various complex mechanisms, such as

vagal afferent and efferent activity, baroreceptor coupling, and other unknown factors.[1–3] These mechanisms can result in synchronized rhythms between the systems, which, in turn, improves the efficiency of pulmonary gas exchange.[4] A long-known phenomenon of cardio-respiratory interaction is respiratory sinus arrhythmia (RSA), which, during normal breathing frequencies, shows an increase in heart rate during inspiration and a decrease during expiration.[5] Besides RSA, researchers have found other, less noticeable cardio-respiratory couplings, including cardio-respiratory phase synchronization (CRPS)[6,7] and cardio-respiratory coordination (CRC),[8] which both were shown to be independent of RSA.[9,10]

Weakly coupled oscillators can synchronize their phases even when the amplitudes vary chaotically and are actually uncorrelated.[11] However, phase synchronization is only one form of synchronization, and over the past decades, various other states of synchronization have been extensively investigated. These include complete or identical synchronization, lag synchronization, generalized synchronization, intermittent lag synchronization, imperfect phase synchronization, and almost synchronization (for more details, see the review papers of Refs. 12–14).

Phase synchronization is also observed in the cardio-respiratory system,[6,7,9,15] and cardio-respiratory phase synchronization (CRPS) is detected when the R peaks in the electrocardiogram (ECG) consistently appear at the same respiratory phases. This can be visualized conveniently by the cardio-respiratory synchrogram,[6] in which epochs of CRPS are identified through horizontal parallel lines. Recent studies have enriched our understanding of CRPS, indicating that physical fitness enhances CRPS, and athletes show higher levels of synchronization.[16] Additionally, controlled breathing based on heartbeat detection and biofeedback has been found to significantly increase CRPS, emphasizing the impact of respiratory patterns on heart–lung interaction.[17] Moreover, analyses under free-running conditions reveal a complex array of synchronization patterns in healthy humans.[18] CRPS has also been found to change significantly across sleep stages[9] and is affected by aging[19] and obstructive sleep apnea.[20] Since CRPS has such strong sleep-stage dependency, it has also been used as a feature in automatic sleep-stage classification.[21]

Another form of cardio-respiratory interaction is cardio-respiratory coordination (CRC). First described by Riedl *et al.*,[8] CRC is a generalized form of cardioventilatory coupling found by Galletly and Larsen.[22] The main difference between CRPS and CRC is that the latter is in the time domain and focuses on the time difference between R peaks and respiration onsets. In contrast, CRPS works in the phase domain utilizing the respiratory phase at a heartbeat (i.e., the R peak). Just as analyzing CRPS requires the use of a synchrogram, a coordigram is used for CRC analysis, and, accordingly, horizontal parallel lines in the coordigram indicate epochs of CRC. CRC has been found to increase during sleep apnea[8] and in preeclampsia.[23] Even though previous articles have demonstrated the association of CRC with certain diseases, these works have obtained their findings from a rather small number of samples. At this stage, studying CRC in large databases is hampered by the lack of automated methods for CRC detection.

At first glance, the coordigram and synchrogram methods seem very similar; however, CRC and CRPS are very different physiological phenomena as discussed in Krause *et al.*[24] Additionally, phase synchronization is known from nonlinear dynamics and thought to minimize the overall energy of coupled systems for certain phase values;[25] thus, CRPS could be modeled by considering the cardiovascular and respiratory systems as two coupled oscillators.[26] On the contrary, for CRC, there is no nonlinear dynamics-inspired model yet, but Galletly and Larsen have proposed an empirical model based on their experimental results. According to this model, CRC develops when inspiration is triggered by some unknown afferent signal related to the heartbeat.[27]

In our study, we will elaborate on the differences between CRC and CRPS by analyzing an extensive dataset of cardio-respiratory signals collected during nocturnal sleep. To this end, we introduce an automated method for the detection of CRC, while automated procedures for CRPS detection in long-term data are already available (for a comprehensive review and comparison, please refer to Ref. 28). Our findings reveal that akin to CRPS, CRC also exhibits sleep-stage dependence. Furthermore, we observe that CRPS and CRC can co-occur when fluctuations in breathing frequency remain sufficiently limited. Demonstrating the robustness of CRPS and CRC detection, even when utilizing cardio-respiratory data reconstructed from actigraph recordings, could potentially pave the way for investigating these phenomena in large cohort studies such as the German National Cohort (GNC),[29] which includes about 200 000 subjects. Such investigations could also facilitate correlations with clinical parameters, ultimately shedding light on the physiological mechanisms that trigger and influence CRPS and CRC.

II. DATA

We conducted the comparative analysis using data from 226 subjects recorded at the Charité Hospital Berlin in Germany during a project funded by the German–Israeli Foundation (GIF). The study received ethical approval from the hospital's ethics committee, and all participants provided written informed consent prior to the study. During their initial diagnostic night at the sleep laboratory, all subjects wore a SOMNOwatch™ plus device (SOMNOmedics, Randersacker, Germany). This device simultaneously recorded 3D wrist acceleration of the non-dominant arm at a sampling rate of 128 Hz, as well as a single-channel electrocardiogram (ECG) at 256 Hz.

Additionally, full polysomnography (PSG) was conducted, capturing various physiological signals such as electroencephalography (EEG), electrooculography (EOG), electromyography (EMG), ECG, photoplethysmography (PPG), oxygen saturation, respiratory effort, and more. The PSG data was recorded using either an ALICE system (Philips, Amsterdam, Netherlands), an Embla® system (Natus, Pleasanton, USA), or a SOMNOscreen™ PSG system (SOMNOmedics, Randersacker, Germany). Sleep stages based on 30-s epochs have been determined from the PSG data by trained experts following standard guidelines of the American Academy of Sleep Medicine (AASM)[30] to distinguish light sleep (stages N1 and N2), deep sleep (stage N3), and rapid eye movement (REM) sleep.

Due to the differential recording capabilities of the devices used, namely, the SOMNOwatch™ for accelerometry and the PSG systems for sleep stages and reference respiratory activity, it was necessary to synchronize the recordings as an initial step. Synchronization was achieved by utilizing the R-peak positions detected in

TABLE I. Overview of the GIF dataset used in this study.

	Mean ± STD
Male / female	117 / 109
Age (y)	48.6 ± 13.9
Weight (kg)	83.7 ± 18.8
BMI (kg/m^2)	27.9 ± 5.7
Apnea–hypopnea index (/h)	14.5 ± 18.7
Periodic limb movement index (/h)	13.8 ± 23.7
Time in bed (min)	455.3 ± 46.3
Sleep onset latency (min)	18.4 ± 15.9
Total sleep time (min)	377.1 ± 72.3
Wake after sleep onset (min)	59.8 ± 49.1
Fraction of N1	0.204 ± 0.150
Fraction of N2	0.440 ± 0.123
Fraction of N3	0.186 ± 0.101
Fraction of REM	0.170 ± 0.081

the ECG recordings of both devices. For a more comprehensive description, we refer to.[31–33] Subsequently, each measurement was trimmed to include data solely between the "lights off" and "lights on" time stamps, which demarcated the sleep opportunity period. We also note that respiratory data need to be "narrow-banded" before determining the respiratory phase through the analytic signal approach. Thus, we applied a second-order Butterworth filter in the frequency range [0.1, 0.8] Hz. For an overview and detailed information about the database, see Table I.

In this paper, we analyzed the heartbeat and respiration data recorded by the PSG systems as well as heartbeat and respiration signals reconstructed from accelerometry (ACT). The reconstruction procedure employed the algorithms detailed in Zschocke *et al.*,[33] which were applied to the SOMNOwatch actigraphy data. In brief, the derivation of heartbeat signals involved extracting information from pulse pressure waves that induce subtle, high-frequency vibrations at the wrist. Similarly, respiratory activity was reconstructed through the detection of minuscule, periodic turns of the wrist. Both of these phenomena are discernible through the employment of the high-resolution accelerometer recordings of the SOMNOwatch.

III. METHODS

A. Synchrogram and coordigram

The most common methods used to probe for cardio-respiratory phase synchronization (CRPS) and cardio-respiratory coordination (CRC) are synchrogram and coordigram, respectively. The synchrogram has been introduced by Schäfer *et al.*[6] and is obtained by plotting the times of heartbeat occurrences on the x axis and the corresponding respiratory phases on the y axis. Horizontal parallel lines in the synchrogram indicate epochs of synchronization between heartbeat and respiration [gray shaded area in Fig. 1(a)]. Heartbeat timings are computed using the open-source package biosppy[34] by either detecting the R peaks in the ECG (PSG data) or the maximum of the reconstructed pulse wave (ACT data). The analytic signal approach yields the instantaneous respiratory phase $\Phi(t) = \arg(x_s(t))$, where the analytic signal $x_s(t)$ is calculated using the Hilbert transform of the respiratory signal.[25]

While the synchrogram reveals the synchronization or phase-locking between heartbeat and respiration, the coordigram tracks the time coordination between respiratory onset and heartbeats.[22] Thus, for creating a coordigram, the times of respiratory onset are plotted on the x axis, and the time differences between the onset of respiration and the occurrence of heartbeats are plotted on the y axis (we chose the respiratory onset to coincide with the maximum of the respiratory signal as suggested by Riedl *et al.*[8]). Again, horizontal parallel lines in the coordigram indicate cardio-respiratory coordination [Fig. 2(a)].

B. Reduced synchrogram method (RSM)

There are several reliable methods to detect cardio-respiratory phase synchronization automatically; for a review, see Kuhnhold *et al.*.[28] The reduced synchrogram method (RSM)[15] is particularly well-suited to avoid the detection of spurious synchronization.[28] For RSM, the synchrogram is divided into overlapping time windows, and then, within each window, the phase points are arranged into n subgroups of heartbeats. The phase points in the synchrogram are labeled as $\Phi^m(t) = \Psi(t) \bmod 2m\pi$, where $\Psi(t)$ is the cumulative respiratory phase of m respiratory cycles. To detect CRPS automatically, many $n:m$ synchronization ratios are probed systematically. If phase synchronization occurs in a particular time window, the subgroups will form n parallel horizontal lines. For an illustration of the typical CRPS ratios, we refer to Fig. 3 in Bartsch *et al.*[7]

Specifically, the steps of RSM for each $n:m$ ratio are as follows:

- Arrange the phase points $\Phi^m(t_i)$ into n subgroups.
- Calculate the mean phase for each subgroup by using the superposition of unit vectors. Thus, for the jth subgroup, the mean phase is defined as
$$\left\langle \Phi_j^m \right\rangle = \arg \sum_l e^{i\Phi^m(t_{nl+j})}. \tag{1}$$
- Subtract the mean phase from the phase points of each subgroup
$$\Phi^{m*}(t_{nl+j}) = \Phi^m(t_{nl+j}) - \left\langle \Phi_j^m \right\rangle, \tag{2}$$
thus centering all phase points around zero to obtain a reduced synchrogram.
- Calculate the width W_S of the reduced synchrogram as the difference between the maximum and minimum phase value.
- Repeat the procedure for $m = 1, n = 1, \ldots, 6$, and $m = 2$, $n = 5, \ldots, 12$ until all $n:m$ ratios have been tested. Of all ratios, choose the lowest value of $W_S \cdot n/m$.
- If this $W_S \cdot n/m$ value is smaller than a threshold T_S (Table II), the window is classified as synchronized. The threshold T_S has been determined by surrogate data analysis (see below).

Figure 1(b) shows an example of the RSM; the gray-shaded region indicates CRPS.

C. Automated coordigram method (ACM)

Although there are several methods for the automated detection of CRPS, to our knowledge, suitable algorithms to automatically

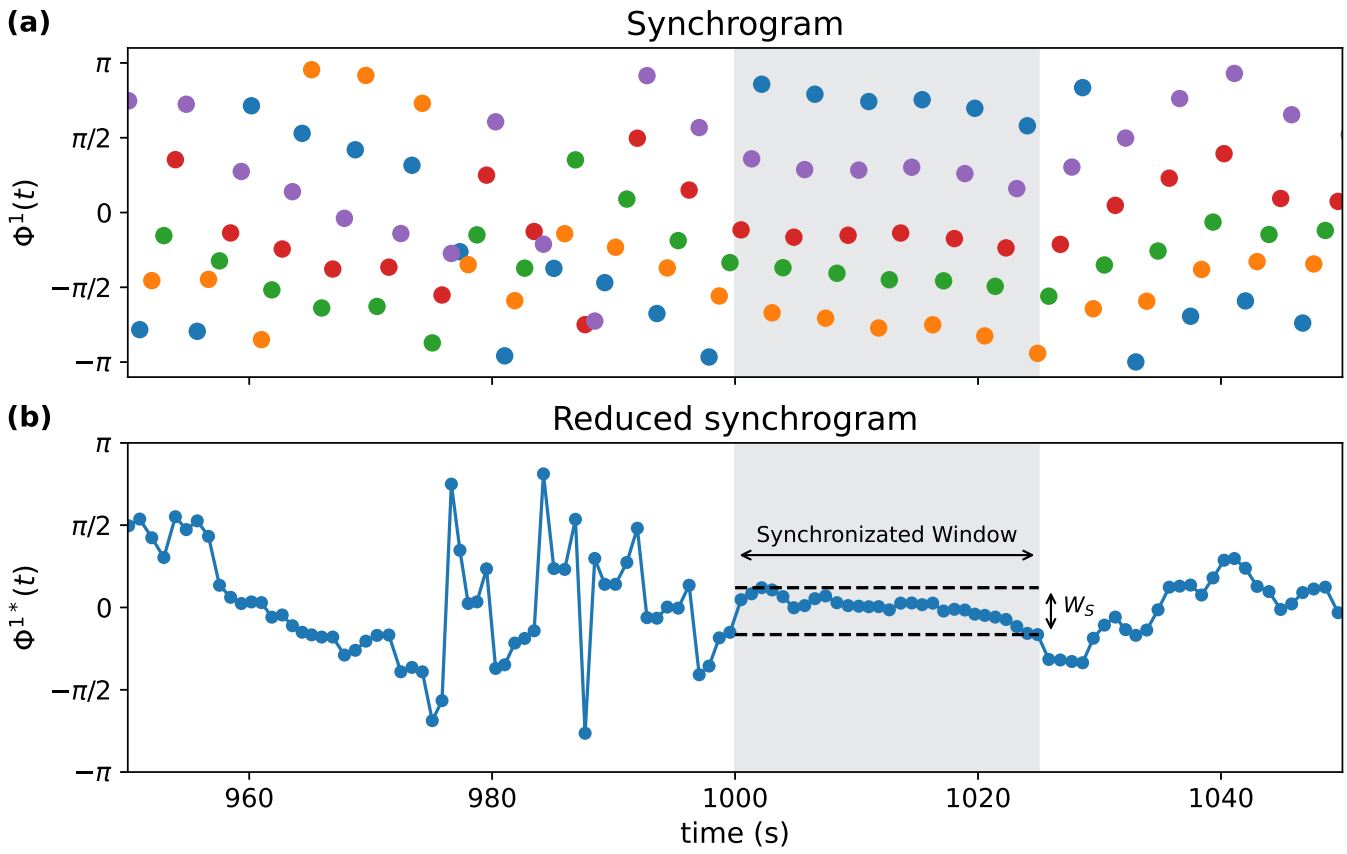


FIG. 1. Reduced synchrogram method (RSM) to detect cardio-respiratory phase synchronization (CRPS). (a) Synchrogram for a 5 : 1 synchronization ratio. Here, five heartbeats are assumed to fall within one breathing cycle; the heartbeats are plotted at the respective phases $\Phi^1(t_{5l+1}) \ldots \Phi^1(t_{5l+5})$ of the lth breathing cycle; the order of the heartbeats within the breathing cycle is color-coded, same colors correspond to the same subgroup. To detect CRPS automatically, several $n : m$ synchronization ratios are probed systematically (see Methods section). (b) Reduced synchrogram is obtained by subtracting the mean phase of the jth subgroup from each phase $\Phi^1(t_{5l+j})$ within a fixed window size [Eq. (2)]. Heartbeat and respiration are synchronized if the width W_S of the reduced synchrogram within a 25-s window is below a threshold (Table II). Following this procedure, the gray-shaded region between 1000 and 1025 s is identified as exhibiting CRPS.

determine epochs of CRC in long-term recordings are missing. Galletly and Larsen[35] calculate the Shannon entropy of the RI plot (which is similar to the coordigram, and the time intervals between each R wave and the following inspiratory onset are plotted against the time of R wave occurrence). However, this measure is strongly affected by the heart rate as higher heart rates or lower breathing rates yield more lines in the RI plot, making higher entropy values more likely. For our automated coordigram method (ACM), we consider R-peak time differences between all neighboring heartbeats in a chosen time window. As a first step, we obtain the times of respiratory onsets when the respiratory phase is equal to $\Phi^1 = \pi$. These times of respiratory onsets are plotted on the horizontal axis; see Figs. 2(a) and 2(b). For all heartbeats within 4 s before and 0.5 s after a respiratory onset, the differences between respiratory onset time and the time of heartbeats are plotted on the vertical axis, forming the cardio-respiratory coordigram. Note that a given heartbeat will appear twice in the coordigram if it occurred less than 4 s before one respiratory onset but also less than 0.5 s after the subsequent respiratory onset. For ACM, the coordigram is divided into overlapping time windows (Table II), and the points in the coordigram are paired to examine the time shifts [e.g., within the red ovals in Figs. 2(a) and 2(b)]. Specifically, the steps of ACM are:

TABLE II. Choice of parameters for the reduced synchrogram method (RSM) and automated coordigram method (ACM). Parameters were optimized using surrogate data analysis (see Methods); note that the threshold for RSM depends on the number of subgroups n (i.e., the number of lines in the synchrogram.).

Method	Window size	Overlap	Threshold
RSM	25 s	20 s	$T_s = 5.9$ rad
ACM	25 s	20 s	$T_c = 0.25$ s

- Calculate the time shifts between each pair of neighboring heartbeats [e.g., red ovals in Figs. 2(a) and 2(b)], but also for all pairs that appear below them in the considered time window.

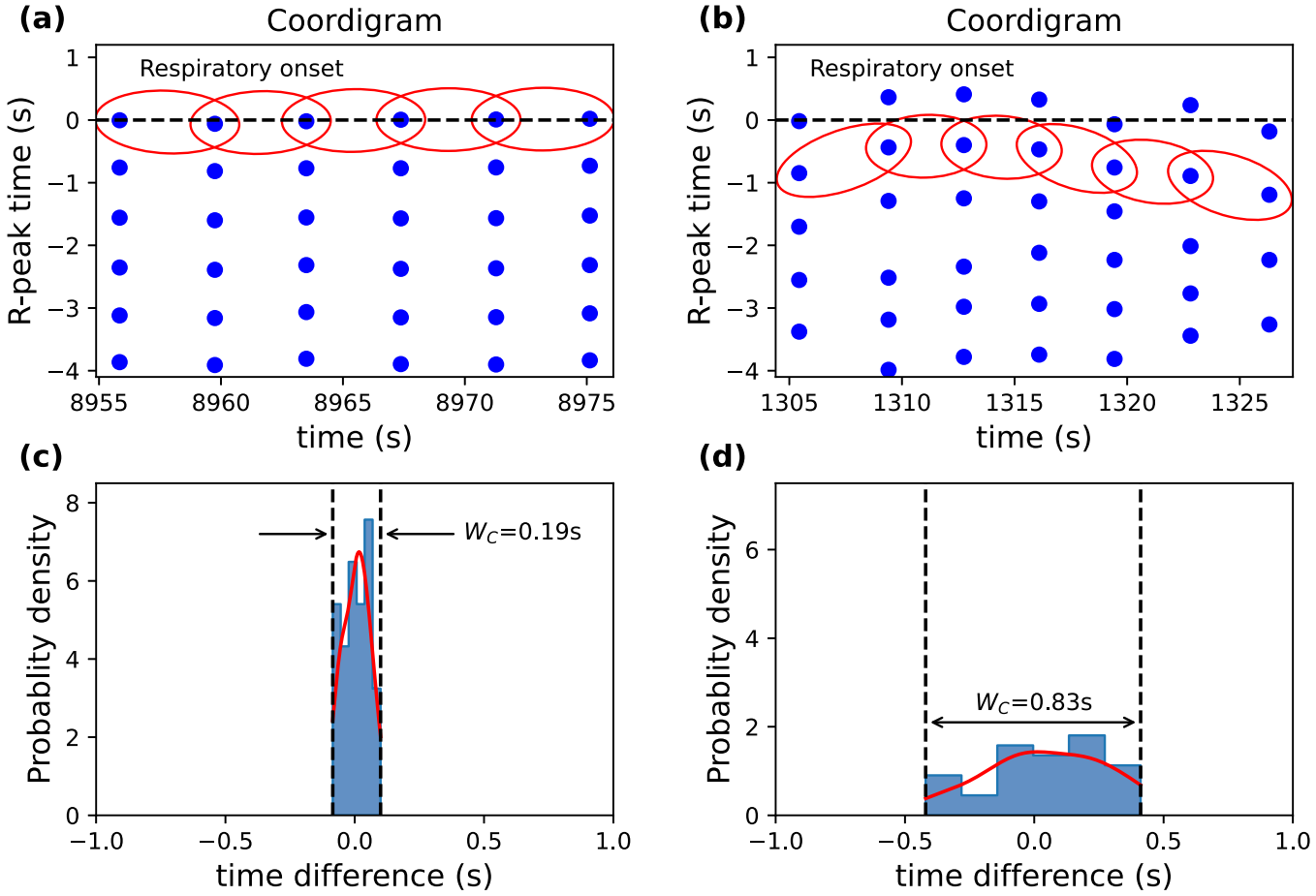


FIG. 2. Automated coordigram method (ACM) to detect cardio-respiratory coordination (CRC). (a) and (b) Coordigrams are obtained by plotting the difference between respiratory onset time and R-peak time (y axis) vs respiratory onset time (x axis) (i.e., the dashed line indicates the simultaneous occurrence of R-peak and respiratory onset). Similar to CRPS in the synchrogram, CRC occurs when heartbeats organize in horizontal parallel lines. For automatic CRC detection, we calculate the R-peak time differences between all neighboring heartbeats within a time window (red ovals highlight the first line for the heartbeats closest to respiratory onsets). (c) In the case of CRC, the distribution of these time differences is narrow, and the width of the distribution, $W_C = 0.19$ s, is below the threshold 0.25 s. (d) In contrast, a broad distribution of time differences suggests the absence of CRC (here, $W_C = 0.83$ s). The red line in (c) and (d) depicts the estimated histogram by using kernel density estimation.

- If the distribution of the time shifts does not significantly deviate from zero mean (as probed by a t-test; $p < 0.05$) and the width W_C of the distribution (i.e., the difference between maximum and minimum) is smaller than a threshold T_C (Table II), CRC is detected in this window [Figs. 2(c) and 2(d)]. Again, the threshold has been determined by surrogate data analysis (see below).

Figure 2 shows two examples for the ACM—for coordinated data (a) and (c) and non-coordinated data (b) and (d). Note that perfect CRC would yield a delta distribution of time shifts and $W_C = 0$.

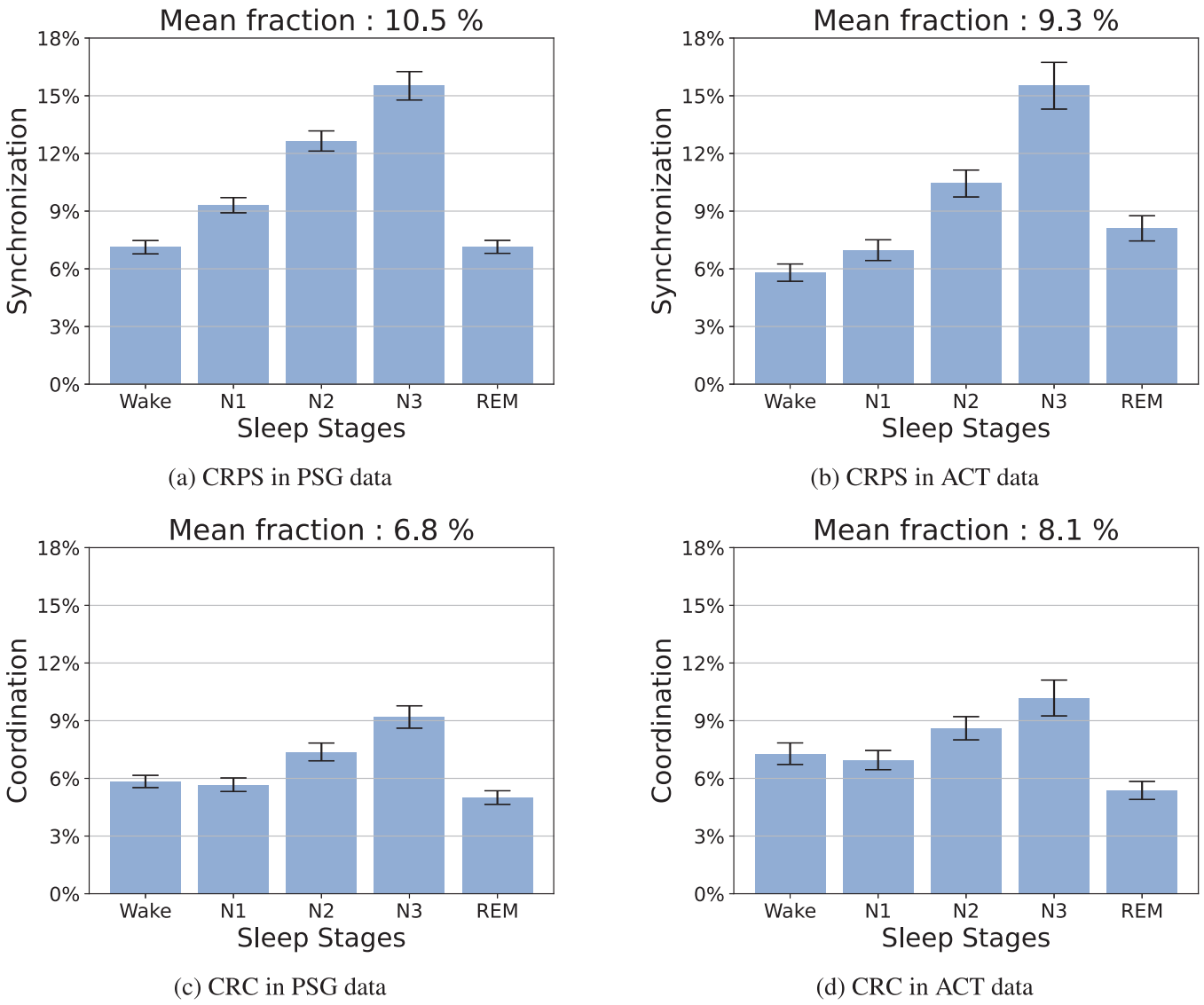
D. Surrogate tests and parameter optimization

We have determined the thresholds T_S and T_C using surrogate data and applying RSM and ACM, respectively. The surrogate data were generated by taking the heartbeat signal from one subject and randomly pairing it with the respiratory signal from a different subject. Then, for a given threshold T_S for RSM (or T_C for ACM), one obtains a percentage of CRPS (or CRC) for both real and surrogate data.

The optimized thresholds are determined by identifying the largest Kullback–Leibler divergence between the real and surrogate results. The Kullback–Leibler divergence is a measure of how one probability distribution P differs from a second reference probability distribution Q. It is defined by[36]

$$D_{\mathrm{KL}}(P \parallel Q) = \sum_{x \in \mathcal{X}} P(x) \log\left(\frac{P(x)}{Q(x)}\right). \tag{3}$$

The parameters optimized through surrogate data tests are shown in Table II. Despite the availability of two datasets, namely, the PSG and ACT data, the optimization of parameters was done



(a) CRPS in PSG data

(b) CRPS in ACT data

(c) CRC in PSG data

(d) CRC in ACT data

FIG. 3. CRPS and CRC are most pronounced during deep sleep N3 and much lower during REM sleep. The figures show the group average and standard error of CRPS and CRC percentages of time for the different sleep stages. (a) CRPS calculated from heartbeat and respiration data obtained from PSG. (b) CRPS when heartbeats and respiration were reconstructed from actigraphy data recorded by a smartwatch (see Methods). (c) and (d) show the results for CRC when using PSG and ACT data, respectively. Note that the sleep-stage stratification is most pronounced for CRPS applied to PSG data and is somewhat reduced when reconstructed heartbeat and respiration are used. On the other hand, CRC slightly increases for ACT data. Our results indicate that CRPS and CRC can reliably be determined at home by reconstructing heartbeat and respiration signals from the actigraphy recordings of wrist-worn smart devices. The mean fraction represents the average time CRPS and CRC are observed across all subjects throughout the night, calculated by averaging individual subject measures regardless of sleep stage.

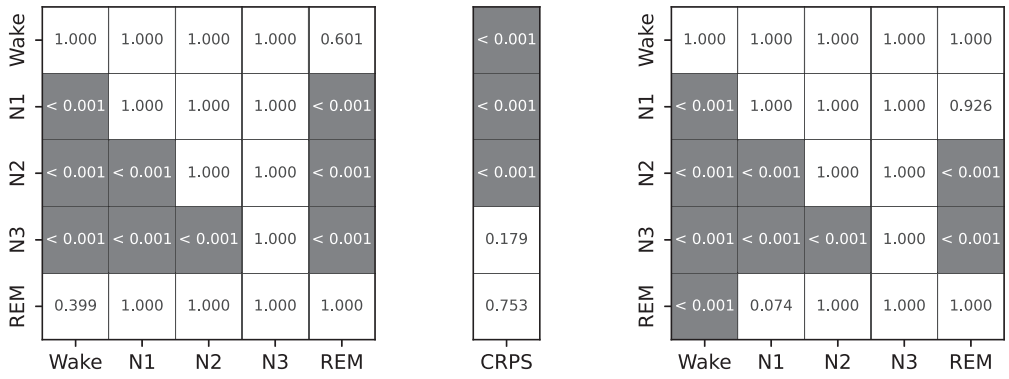
solely on the ECG and respiration signals derived from the PSG dataset. It is important to note that the optimal window size of 25 s and overlap of 20 s, as shown in Table II, facilitate the most effective differentiation between actual and surrogate data. These specific values do not need to be in correspondence with sleep-stage scoring, which is typically done in 30 s windows. Alterations to these parameters can significantly influence the outcomes; for example, a reduced window size may increase the detection of spurious synchronization. The comprehensive analysis provided in Ref. 28 validates that a window size of 25 s and an overlap of 20 s are optimal for RSM. The RSM and ACM algorithms were employed on the PSG and ACT datasets of each participant to systematically identify episodes of CRPS and CRC across various sleep stages.

TABLE III. Group average percentage of CRPS and CRC for the different sleep stages for both PSG and ACT datasets.

	Wake	N1	N2	N3	REM
CRPS(PSG)	7.12%	9.31%	12.65%	15.52%	7.15%
CRPS(ACT)	5.80%	6.97%	10.44%	15.52%	8.10%
CRC(PSG)	5.84%	5.67%	7.38%	9.19%	5.00%
CRC(ACT)	7.28%	6.95%	8.61%	10.18%	5.37%

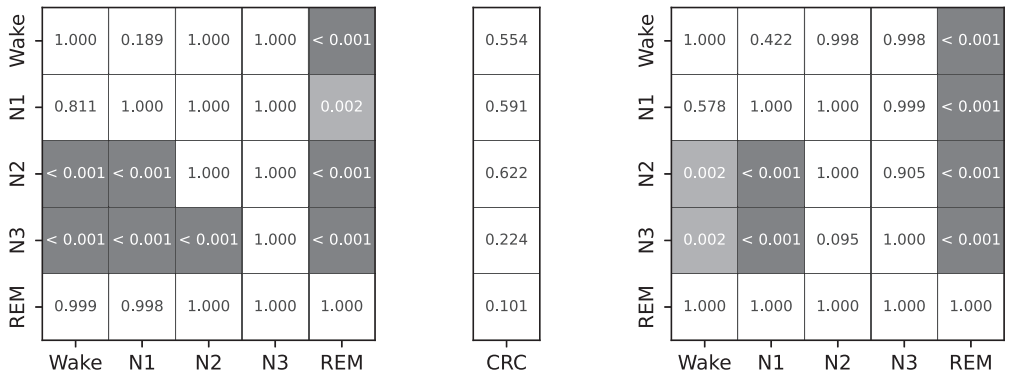
IV. RESULTS AND DISCUSSION

The means and standard errors of the group-averaged percentages of CRPS and CRC for the different sleep stages for PSG and ACT data sets are presented in Fig. 3 and Table III. The comparison between the results obtained from PSG (recorded heartbeat and respiration activity) and ACT data (heartbeat and respiration activity reconstructed from wrist acceleration) demonstrates a high level of agreement for both CRC and CRPS. These group-averaged results are also confirmed by the analysis of the data from individual subjects (Fig. 4). However, we note that there is a significant reduction in CRPS for wake and light sleep in the reconstructed data (Fig. 4, top panel in middle column). This could be explained by the variability in pre-ejection and pulse arrival times, which may modulate the cardiac phase in the reconstructed signal but not the respiratory phase. This, in turn, would reduce overall CRPS. In contrast, changes in pre-ejection and pulse arrival times represent an offset in the difference between R-peak time and respiratory onset and thus



(a) CRPS in PSG data

(b) CRPS in ACT data



(c) CRC in PSG data

(d) CRC in ACT data

FIG. 4. Statistical comparisons of CRPS and CRC based on PSG and reconstructed data. We applied a one-sided Wilcoxon rank test to the results of individual subjects to probe for significant differences in CRPS and CRC in the different sleep stages. Each matrix depicts the significance level for this pairwise comparison given the hypothesis that CRPS (CRC) in the sleep stage indicated on the y axis is larger than the CRPS (CRC) in the sleep stage indicated on the x axis. A matrix element in white recommends rejection of the hypothesis ($p > 0.05$), whereas colored elements show statistical significance at different levels (gray for $p < 0.01$ and dark gray for $p < 0.001$). The middle column depicts the significance levels for the direct comparison between PSG and reconstructed data using a two-sided Wilcoxon rank test. Overall, these results confirm the observation of a sleep-stage stratification pattern in CRPS and CRC in both PSG and reconstructed data, as shown in Fig. 3. The significant difference between CRPS in PSG and reconstructed data during wake and light sleep could be due to the variability in pre-ejection and pulse arrival times that modulate the cardiac phase in the reconstructed signal.

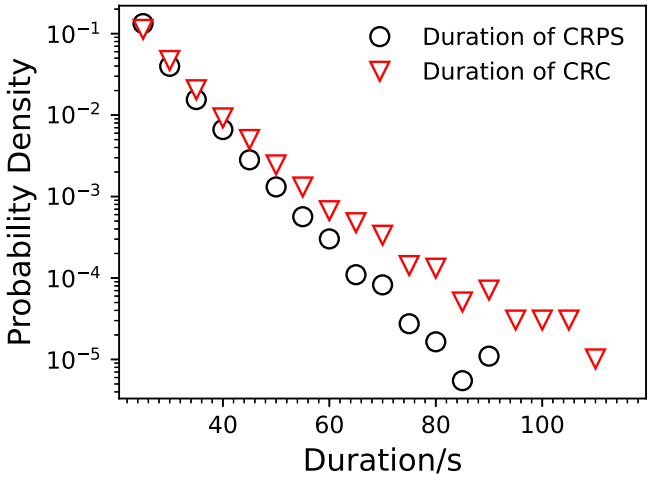


FIG. 5. Distributions of the durations of CRPS and CRC episodes. This log-linear plot displays the durations of CRPS and CRC episodes as detected by the automatic algorithms. Notably, both distributions exhibit a nearly exponential decay. Although CRPS is detected more frequently (Fig. 3), long CRC episodes are slightly more frequent.

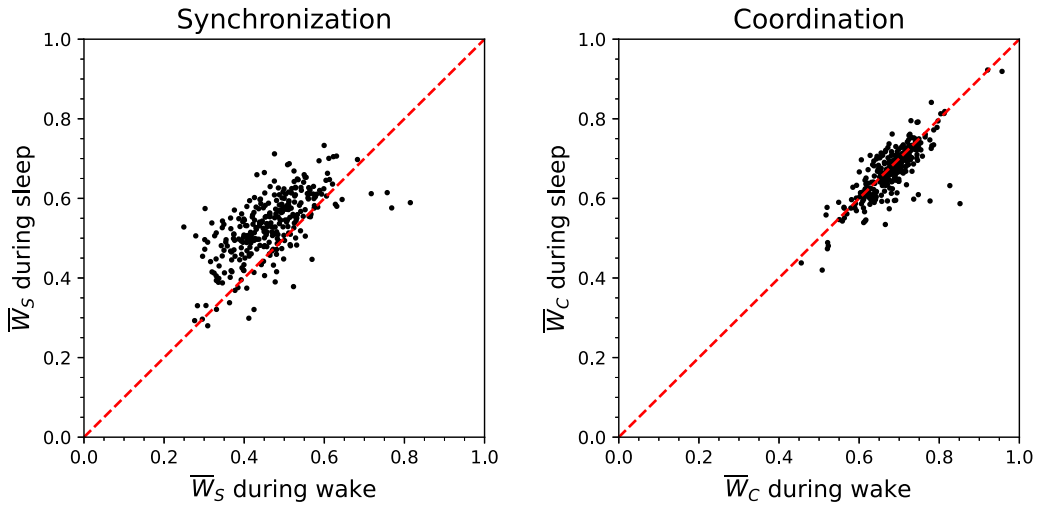
should not affect the coordigram very much so that no significant changes occur.

Previous studies[7,9] have reported a pronounced stratification pattern of CRPS across different sleep stages in healthy individuals. While the GIF database contains mainly patients with mild to moderate obstructive sleep apnea (see Leube *et al.*[32] for a table of diagnoses), we find that this sleep-stage stratification pattern is preserved. CRPS is more frequent in NREM sleep and most robust for N3 (deep) sleep. In contrast, CRC does not show such a clear sleep-stage stratification pattern, but nevertheless, CRC is highest during N3 sleep and lowest during REM. During N1, CRC occurrences are as frequent as during wake, unlike CRPS occurrences. For CRC, the percentage increases by 1.6 from wake to N3, while the corresponding factor is 2.2 for CRPS.

In Fig. 5, we compare the durations of CRPS and CRC episodes. Both distributions exhibit an exponential decay. However, longer durations are slightly more frequent for CRC than for CRPS, albeit CRC is less frequent overall.

In addition to the overall group-averaged percentages of CRPS and CRC during different sleep stages, we are also interested in CRPS and CRC on an individual level, i.e., whether subjects with more CRPS or CRC during sleep also have more CRPS/CRC during wake. To this end, we investigate the width of the reduced synchrogram W_S and the width of the CRC time-shift distribution W_C during wake and sleep. For better comparison, we rescaled both measurements to the range between 0 and 1, $\overline{W}_S = 1 - \frac{W_S}{2\pi}$ and $\overline{W}_C = 1 - \frac{W_C}{1.5\,\mathrm{s}}$, since we only consider shifts between two R peaks shorter than 1.5 s. The closer the observed value is to one, the higher the degree of CRPS or CRC. The averaged $\overline{W}_S$ and $\overline{W}_C$ for wake and sleep have been calculated for each subject.

Figure 6 illustrates a strong correlation between sleep and wake in both CRPS and CRC measurements, indicating that individuals with a high degree of wake CRPS (or CRC) are likely to exhibit a high degree of CRPS (or CRC) during sleep. However, we note that for CRPS, the measurements during sleep are higher than during wake [as shown also in Figs. 6(a), 3(a), 3(b)]. In contrast, for CRC, the



(a) CRPS (b) CRC

FIG. 6. Sleep–wake correlations for (a) CRPS and (b) CRC. Subjects who show high values of synchronization or coordination during sleep are likely also to have high synchronization or coordination during wake and vice versa. Degrees of CRPS and CRC are characterized by the normalized values of the widths, $\overline{W}_S$ and $\overline{W}_C$, respectively; all four sleep stages have been combined. Spearman's rank correlation coefficients are (a) $\rho = 0.68$ ($p < 10^{-5}$, for CRPS) and (b) $\rho = 0.76$ ($p < 10^{-5}$, for CRC). Only the PSG data were used for this analysis.

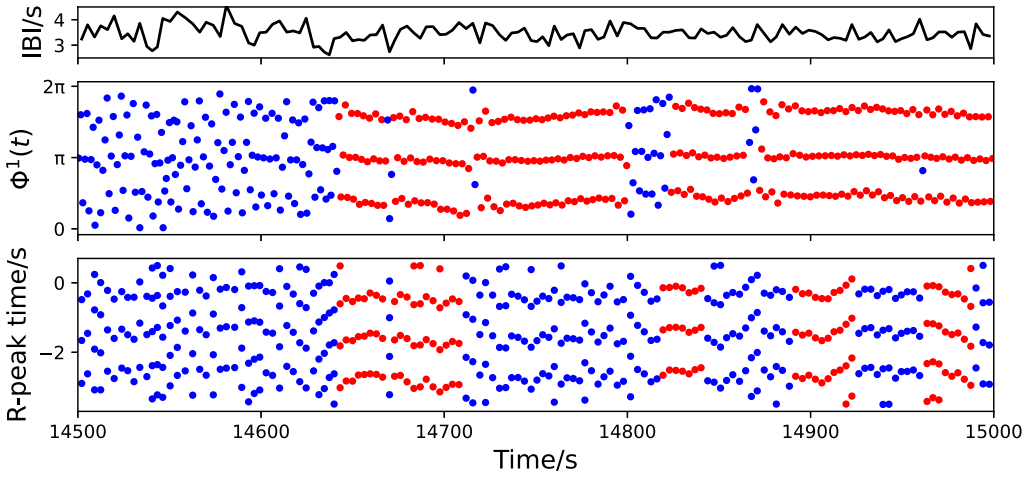


FIG. 7. CRPS and CRC coexist and are influenced by breathing rate fluctuations. Sleep data from a single subject indicate that despite considerable fluctuations in the inter-breath intervals (IBI, top panel), i.e., fluctuations in breathing rate, the cardiac and respiratory rhythms can synchronize (red dots, middle panel) or coordinate (red dots, bottom panel). Particularly interesting is the period from about 14 710–14 800 s with pronounced CRPS and no CRC, perhaps because of high fluctuations in the breathing rate. Of note, for relatively constant breathing frequencies, CRPS and CRC coexist (e.g., from 14 650 to 14 710 s—interrupted by a fast breathing cycle at around 14 680 s—and from 14 820 to 14 850 s).

differences between sleep and wake are relatively small (in accordance with Figs. 3(c) and 3(d).

Another interesting question is about the relationship between CRPS and CRC, as both were shown to coexist but are believed to be independent of respiratory sinus arrhythmia (RSA).[10,37] To shed light on this, we investigated the dynamics of CRPS and CRC, simultaneously plotting reduced synchrograms and coordigrams for individual subjects. Figure 7 shows an example of the coexistence of CRPS and CRC, which may be affected by fluctuations in the breathing rate. In fact, for moderately to highly fluctuating breathing rates, lower levels of CRC but a high level of CRPS could occur if the phase of the heart rate oscillator changes in synchronization with the respiratory oscillator (see, e.g., the time period between 14 710 and 14 800 s in Fig. 7; note that the opposite can also be observed[10]). The figure also suggests that for relatively constant breathing rates, CRPS, and CRC coexist.

The breathing-rate dependence of CRPS–CRC correlations during sleep is systematically investigated in Fig. 8. Our results indicate a transition from positive CRPS–CRC correlations at relatively constant breathing rates to CRPS-CRC anti-correlations if fluctuations in the breathing rate are large. This anti-correlation and strong dependence on the stability of the breathing cycle implies that different physiological mechanisms could trigger CRPS and CRC.

V. SUMMARY AND OUTLOOK

In this paper, we introduced the automated coordigram method (ACM)—an algorithm to detect epochs of CRC in long-term data and quantify the degree of CRC. Applying ACM to sleep data, we found a pronounced sleep-stage dependence, with the highest level of CRC during N3 (deep) sleep and the lowest during REM. This dependence is similar to the sleep-stage stratification pattern that we observe in CRPS and which was previously reported for a cohort of healthy subjects.[9] Specifically, our findings are in close agreement with the age groups of 35–49 and 50–64 years in Ref. 9 (corresponding to the mean age ± STD of 48.6±13.9 years of our database). While the overall percentage of CRC during sleep is lower than for CRPS, and the sleep-stage differences are less distinct, episodes of CRC tend to be slightly longer than CRPS episodes.

Our algorithms work similarly well for ACT data, recovering the same sleep-stage stratification pattern so that data from smart watch devices could be used for CRPS and CRC analysis. These findings demonstrate that reconstructed data can also be used to reliably measure both CRPS and CRC, offering a cost-effective and widely accessible method for detecting these conditions at home without the need for a sleep lab and medical devices to measure ECG and respiration. We note that sleep-stage classification can also be obtained from wrist acceleration data (and reconstructed heartbeats), as was recently shown with an approach using a convolution neural network combined with a dilated convolution neural network and transfer learning.[38]

Generally, subjects with higher synchronization during sleep are also more likely to have higher synchronization in the wake; the same holds for CRC. It should be noted that CRPS and CRC should come from different physiological mechanisms, even though the synchrogram and coordigram look similar. They respond to the change of sleep stages and certain chronic diseases differently.[8,10,39] Also, the synchrogram and coordigram cannot show a perfect horizontal line at the same time when the breathing frequency fluctuates, but CRC and CRPS will be indistinguishable when the breathing frequency shows no fluctuation. This hypothesis is supported by the transition from a positive correlation to a negative correlation as the standard deviation of IBI increases.

Our systematic research shows that CRPS and CRC are two independent phenomena that result from different physiological mechanisms. Although CRPS is more sensitive to sleep-stage

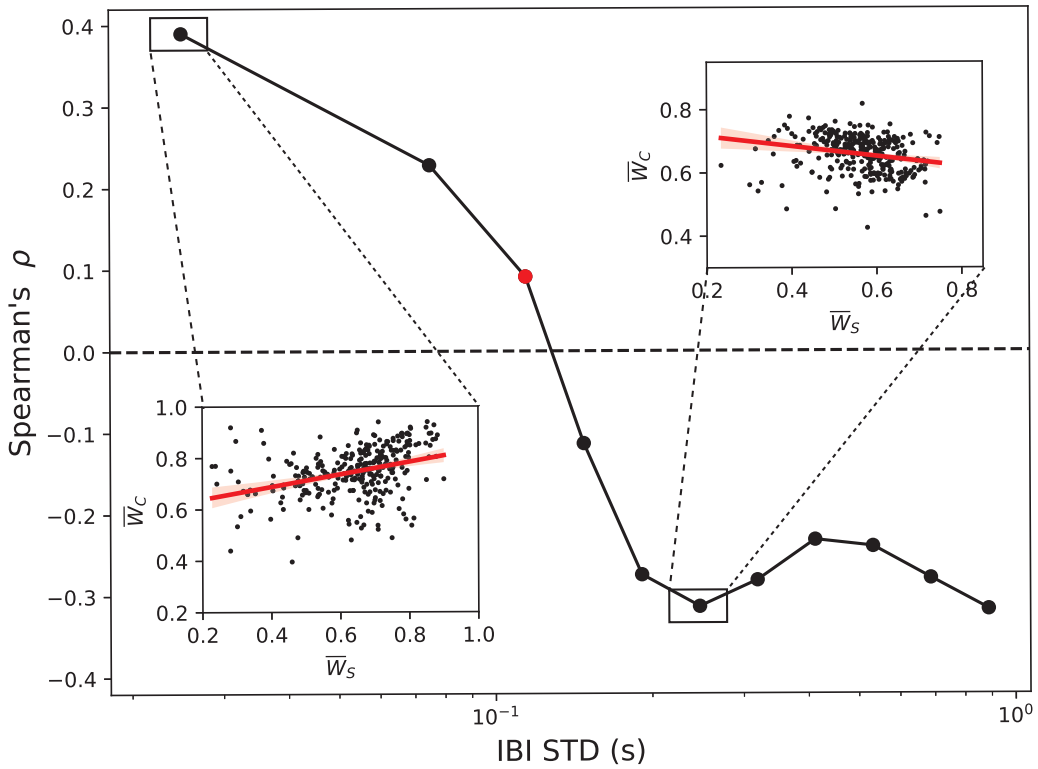


FIG. 8. The nature of CRPS and CRC correlation during sleep depends on fluctuations of the breathing frequency. For small fluctuations in the breathing frequency (i.e., the standard deviation (STD) of IBI < 0.1 s), CRPS and CRC are positively correlated; for moderate to highly fluctuating breathing frequencies, CRPS and CRC are anti-correlated, showing the highest level of anti-correlations at an IBI STD of about 0.25 and 0.9 s. CRPS–CRC correlations were calculated from the scatter plots of $\overline{W}_C$ vs $\overline{W}_S$ using Spearman's rank correlation (see the two insets for positive and negative correlations for different IBI STD). Each point in the scatterplot represents a single subject from the GIF-PSG database, for which their corresponding $\overline{W}_C$ and $\overline{W}_S$ values for windows in the selected interval of IBI STD were averaged. Spearman's ρ-values are significant ($p < 0.05$) for all IBI STDs except for the range of 0.1–0.13 s (red dot).

transitions, CRC is highly affected by disorders such as sleep apnea,[8] or preeclampsia.[39] Both measures have the potential to be used in clinical diagnosis, and they are very likely to respond differently to various cardiovascular diseases. They become indistinguishable only under constant breathing rates but exhibit rather similar change directions with sleep stages, also when studied for individual subjects. We have shown that these changes can be reliably retrieved using fully automated annotation algorithms for CRPS and CRC, even if respiration and heartbeat activity are not measured but merely reconstructed from actigraphy data. Using these reconstruction algorithms will, therefore, help to investigate CRPS and CRC in large population-based cohort studies, where physiological data are commonly recorded by wrist (or hip) actigraphy. Such a study with thousands of subjects as available, for example, in the German Cohort Study,[29] would be essential to prove significant relationships of CRC and CRPS to diseases and risk factors.

AUTHOR DECLARATIONS

Conflict of Interest

The authors have no conflicts to disclose.

Author Contributions

Yaopeng J. X. Ma: Data curation (equal); Formal analysis (equal); Investigation (equal); Methodology (equal); Software (equal); Visualization (equal); Writing – original draft (equal); Writing – review & editing (equal). **Johannes Zschocke:** Data curation (equal); Formal analysis (equal). **Martin Glos:** Data curation (equal). **Maria Kluge:** Data curation (equal). **Thomas Penzel:** Data curation (equal); Funding acquisition (equal); Project administration (equal). **Jan W. Kantelhardt:** Conceptualization (equal); Data curation (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Validation (equal); Writing – original draft (equal); Writing – review & editing (equal). **Ronny P. Bartsch:** Conceptualization (equal); Funding acquisition (equal); Investigation (equal); Methodology (equal); Supervision (equal); Validation (equal); Writing – original draft (equal); Writing – review & editing (equal).

DATA AVAILABILITY

All analyses were performed using Python scripts. The code is publicly available at https://github.com/AlexMa123/CRC_CRPS_Detection. Further inquiries can be directed to the corresponding

authors. We utilize de-identified multi-channel recordings, including ECG, respiration, wrist actigraphy, and sleep hypnograms from clinical sleep laboratories at the Charité Hospital Berlin, Germany. These data can be obtained upon reasonable request by contacting Dr. Martin Glos (martin.glos@charite.de).

REFERENCES

[1]T. E. Dick, Y.-H. Hsieh, R. R. Dhingra, D. M. Baekey, R. F. Galán, E. Wehrwein, and K. F. Morris, "Cardiorespiratory coupling: Common rhythms in cardiac, sympathetic, and respiratory activities," in *The Central Nervous System Control of Respiration*, Progress in Brain Research, edited by G. Holstege, C. M. Beers, and H. H. Subramanian (Elsevier, 2014), Vol. 209, Chap. 10, pp. 191–205.

[2]R. P. Bartsch, K. K. Liu, Q. D. Ma, and P. C. Ivanov, "Three independent forms of cardio-respiratory coupling: Transitions across sleep stages," in *Computing in Cardiology 2014* (IEEE, 2014), pp. 781–784.

[3]T. Penzel, Y. Ma, J. Krämer, N. Wessel, M. Glos, I. Fietze, and R. P. Bartsch, "Sleep-related modulations of heart rate variability, ECG, and cardio-respiratory coupling," in *Physics of Biological Oscillators: New Insights into Non-Equilibrium and Non-Autonomous Systems* (Springer, 2021), pp. 311–327.

[4]F. Yasuma and J.-I. Hayano, "Respiratory sinus arrhythmia: Why does the heartbeat synchronize with respiratory rhythm?," Chest **125**, 683–690 (2004).

[5]A. Angelone and N. A. Coulter, Jr., "Respiratory sinus arrhythmia: A frequency dependent phenomenon," J. Appl. Physiol. **19**, 479–482 (1964).

[6]C. Schäfer, M. G. Rosenblum, J. Kurths, and H.-H. Abel, "Heartbeat synchronized with ventilation," Nature **392**, 239–240 (1998).

[7]R. Bartsch, J. W. Kantelhardt, T. Penzel, and S. Havlin, "Experimental evidence for phase synchronization transitions in the human cardiorespiratory system," Phys. Rev. Lett. **98**, 054102 (2007).

[8]M. Riedl, A. Müller, J. F. Kraemer, T. Penzel, J. Kurths, and N. Wessel, "Cardiorespiratory coordination increases during sleep apnea," PLoS One **9**, e93866 (2014).

[9]R. P. Bartsch, A. Y. Schumann, J. W. Kantelhardt, T. Penzel, and P. C. Ivanov, "Phase transitions in physiologic coupling," Proc. Natl. Acad. Sci. **109**, 10181–10186 (2012).

[10]H. Krause, J. F. Kraemer, T. Penzel, J. Kurths, and N. Wessel, "On the difference of cardiorespiratory synchronisation and coordination," Chaos: An Interdisciplinary Journal of Nonlinear Science **27**, 093933 (2017).

[11]M. G. Rosenblum, A. S. Pikovsky, and J. Kurths, "Phase synchronization of chaotic oscillators," Phys. Rev. Lett. **76**, 1804–1807 (1996).

[12]S. Boccaletti, J. Kurths, G. Osipov, D. Valladares, and C. Zhou, "The synchronization of chaotic systems," Phys. Rep. **366**, 1–101 (2002).

[13]L. M. Pecora and T. L. Carroll, "Synchronization of chaotic systems," Chaos **25**, 097611 (2015).

[14]T. Stankovski, T. Pereira, P. V. E. McClintock, and A. Stefanovska, "Coupling functions: Universal insights into dynamical interaction mechanisms," Rev. Mod. Phys. **89**, 045001 (2017).

[15]E. Toledo, S. Akselrod, I. Pinhas, and D. Aravot, "Does synchronization reflect a true interaction in the cardiorespiratory system?," Med. Eng. Phys. **24**, 45–52 (2002).

[16]S. Perry, N. Khovanova, and I. Khovanov, "Physical fitness contributes to cardio-respiratory synchronization," in *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)* (IEEE, 2019), pp. 4957–4960.

[17]Y. Ren and J. Zhang, "Increased cardiorespiratory synchronization evoked by a breath controller based on heartbeat detection," Biomed. Eng. Online **18**, 1–13 (2019).

[18]C. Schäfer, M. G. Rosenblum, H.-H. Abel, and J. Kurths, "Synchronization in the human cardiorespiratory system," Phys. Rev. E **60**, 857–870 (1999).

[19]D. Iatsenko, A. Bernjak, T. Stankovski, Y. Shiogai, P. J. Owen-Lynch, P. Clarkson, P. V. McClintock, and A. Stefanovska, "Evolution of cardiorespiratory interactions with age," Philos. Trans. R. Soc. A **371**, 20110622 (2013).

[20]M. M. Kabir, H. Dimitri, P. Sanders, R. Antic, E. Nalivaiko, D. Abbott, and M. Baumert, "Cardiorespiratory phase-coupling is reduced in patients with obstructive sleep apnea," PLoS One **5**, e10602 (2010).

[21]M. Radha, P. Fonseca, A. Moreau, M. Ross, A. Cerny, P. Anderer, X. Long, and R. M. Aarts, "Sleep stage classification from heart-rate variability using long short-term memory neural networks," Sci. Rep. **9**, 14149 (2019).

[22]D. Galletly and P. Larsen, "Cardioventilatory coupling during anaesthesia," Br. J. Anaesth. **79**, 35–40 (1997).

[23]K. Berg, J. F. Kraemer, M. Riedl, H. Stepan, J. Kurths, and N. Wessel, "Increased cardiorespiratory coordination in preeclampsia," Physiol. Meas. **38**, 912 (2017).

[24]H. Krause, J. F. Kraemer, T. Penzel, J. Kurths, and N. Wessel, "On the difference of cardiorespiratory synchronisation and coordination," Chaos **27**, 0 (2017).

[25]A. S. Pikovsky, M. G. Rosenblum, and J. Kurths, *Synchronization: A Universal Concept in Nonlinear Sciences* (Cambridge University Press, Cambridge, 2001).

[26]K. Kotani, K. Takamasu, Y. Ashkenazy, H. E. Stanley, and Y. Yamamoto, "Model for cardiorespiratory synchronization in humans," Phys. Rev. E **65**, 051923 (2002).

[27]D. Galletly and P. Larsen, "Inspiratory timing during anaesthesia: A model of cardioventilatory coupling," Br. J. Anaesth. **86**, 777–788 (2001).

[28]A. Kuhnhold, A. Y. Schumann, R. P. Bartsch, R. Ubrich, P. Barthel, G. Schmidt, and J. W. Kantelhardt, "Quantifying cardio-respiratory phase synchronization—A comparison of five methods using ECGs of post-infarction patients," Physiol. Meas. **38**, 925 (2017).

[29]German National Cohort (GNC) Consortium, "The German National Cohort: Aims, study design and organization," Eur. J. Epidemiol. **29**, 371–382 (2014).

[30]R. B. Berry, S. F. Quan, A. R. Abreu, M. L. Bibbs, L. DelRosso, and S. M. Harding *et al.*, "The AASM manual for the scoring of sleep and associated events: Rules, terminology and technical specifications, version 2.6" (American Academy of Sleep Medicine, 2020).

[31]J. Zschocke, M. Kluge, L. Pelikan, A. Graf, M. Glos, A. Müller, R. Mikolajczyk, R. P. Bartsch, T. Penzel, and J. W. Kantelhardt, "Detection and analysis of pulse waves during sleep via wrist-worn actigraphy," PLoS One **14**, e0226843 (2019).

[32]J. Leube, J. Zschocke, M. Kluge, L. Pelikan, A. Graf, M. Glos, A. Müller, R. P. Bartsch, T. Penzel, and J. W. Kantelhardt, "Reconstruction of the respiratory signal through ECG and wrist accelerometer data," Sci. Rep. **10**, 14530 (2020).

[33]J. Zschocke, J. Leube, M. Glos, O. Semyachkina-Glushkovskaya, T. Penzel, R. P. Bartsch, and J. W. Kantelhardt, "Reconstruction of pulse wave and respiration from wrist accelerometer during sleep," IEEE Trans. Biomed. Eng. **69**, 830–839 (2021).

[34]C. Carreiras, A. P. Alves, A. Lourenço, F. Canento, H. Silva, and A. Fred *et al.*, "BioSPPy: Biosignal processing in Python," available at https://biosppy.readthedocs.io/en/stable (2015).

[35]D. Galletly and P. Larsen, "Cardioventilatory coupling in heart rate variability: Methods for qualitative and quantitative determination," Br. J. Anaesth. **87**, 827–833 (2001).

[36]S. Kullback and R. A. Leibler, "On information and sufficiency," Ann. Math. Stat. **22**, 79–86 (1951).

[37]R. P. Bartsch, K. K. Liu, Q. D. Ma, and P. C. Ivanov, "Three independent forms of cardio-respiratory coupling: Transitions across sleep stages," in *Computing in Cardiology 2014* (IEEE, 2014), pp. 781–784.

[38]Y. J. Ma, J. Zschocke, M. Glos, M. Kluge, T. Penzel, J. W. Kantelhardt, and R. P. Bartsch, "Automatic sleep-stage classification of heart rate and actigraphy data using deep and transfer learning approaches," Comput. Biol. Med. **163**, 107193 (2023).

[39]K. Berg, J. F. Kraemer, M. Riedl, H. Stepan, J. Kurths, and N. Wessel, "Increased cardiorespiratory coordination in preeclampsia," Physiol. Meas. **38**, 912 (2017).