Temporally Resolved Fluctuation Analysis of Sleep ECG

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Abstract The correlation behavior in the heart beat rate significantly differs with respect to light sleep, deep sleep, and REM sleep. We investigate whether fluctuations of the heart beat rhythm may serve as a surrogate parameter for rapidly changing sleep phenomena, and if these changes are accessible by progressive beat-by-beat analysis of the sleep electrocardiogram (ECG).

Keywords Heart rate variability · Correlation behavior · Fluctuation analysis · Sleep ECG · Arousals · REM detection · Sleep staging

1 Introduction

Although sleep is absolutely essential for our well-being, to date many questions are still left open as to the specific restorative purpose of the different sleep stages, i.e. light sleep, deep sleep, and rapid-eye-movement (REM) sleep. Generally, five sleep stages are recognized, two light sleep and two deep sleep stages, plus REM sleep, which differ in their characteristic patterns and waveforms in electroencephalographic (EEG) recordings. In order to explore the functions of sleep and sleep stages,

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many researchers are interested in the temporal pattern and in the sophisticated regulation of the sleep stages over the night. Apart from EEG data, the heart-rate variability (HRV) during the different sleep stages, which can easily, non-invasively, and precisely be monitored by recording the electrocardiogram (ECG), is believed to contain relevant information for healthy subjects as well as patients with, for example, breathing disorders [1, 2], since its regulation is determined by the autonomic nervous system. Indeed, the pulsation of the heart changes across the sleep stages. In the course of deep sleep, the heart beat rate is reduced, whereas a relative increase is noticed in REM sleep [3–5]. Furthermore, spontaneous movements in sleep are preceded by increases in heart beat rate [6]. These observations indicate a functional link between cardiac activity and sleep stages. HRV is shown to be mainly modulated during sleep by changes of the sympatho-vagal balance [7, 8]. Following Steyn-Ross et al. [9], the change from non-REM (NREM) sleep to REM sleep can be understood as a first-order phase transition of the cortical activity.

On some occasions, HRV is easily recognizable by the visual sleep scorer, particularly just before awakenings or during REM sleep. However, there is no conspicuous ECG pattern for visual classification of sleep phenomena. One reason for this is that changes of the HRV often evolve rather gradually than abruptly across the NREM-REM cycles. Furthermore, some inherent qualities of the pulsation of the heart are quite subtle. This is particularly true for cyclic alterations of the heart beat as a result of other periodic physiological functions such as breathing, and for the fluctuations in the timing of the individual beats. Numerical analyses of the ECG time series in the time and frequency domain and fluctuation analyses are utilized to access and quantify changes of the HRV that are not directly visible.

Frequencies around 0.25 Hz are found in the time series of the heart beats by fast Fourier transform (FFT) or wavelet analysis (WLT), corresponding to breathing of about 15 cycles per minute. This is due to an inhibiting afferent vagal action during inspiration that reaches the cardiac pacemaker. It leads to heart beat slowing during inspiration and to acceleration during expiration. Another phenomenon of the HRV is the fluctuation of the correlation between individual beats. Correlations are not random but coordinated as a function of the sleep stage or state of wakefulness. This is expressed in a dynamical alternation of long- and short-range correlations which is assessed by fluctuation-analysis algorithms, e.g. by detrended fluctuation analysis (DFA) and by the progressive DFA (PDFA), of the RR interval time series [10–12]. The heart may be utilized as a probe to identify shifts of the sympatho-vagal balance. Blood pressure and HRV analyses have been used to identify surrogate markers of sleep phenomena, e.g. arousals and sleep fragmentation, in the ECG time series [13, 14].

Although the role of arousals in normal and disordered sleep is under current debate, they are known to fragment sleep and reduce subjective sleep quality and cause daytime symptoms [15]. Increased arousal activity was found in insomniacs in addition to normal sleep stage architecture [16]. Just one in five insomniac patients showed distortions in the sleep stage architecture [17]. Even arousal on the autonomic level alone may lead to symptoms of disturbed sleep [18]. Temporally resolved ECG analyses may offer access to arousals of concomitant autonomic involvement. Sleep stage scoring according to Rechtschaffen and Kales (R&K) [19] often ignores arousals, since their duration does not exceed half the epoch. The scoring criteria do not recognize specific arousal features, and some arousals never reach EEG

accessible cortical level. There is evidence that in the hierarchy of compartmental arousal, cortical involvement is less frequent than autonomic [20, 21]. The majority of arousals should be assessed by detection of autonomic changes.

Sleep characterization on the basis of ECG analyses with a time resolution on the order of seconds may also contribute to the understanding of the biology of sleep. The timing of ECG events and sleep stages is often not synchronous. REM sleep is preceded by about 2 min of a relative activation of the sympathetic branch of the autonomic nervous system [7]. SWS onset is preceded by 12 ± 5 min of a relative vagal dominance [22]. Spontaneous behavioral arousals are preceded by around 8 s of pulse rate increase [6]. The central sleep regulation seems to affect the periphery before EEG changes appear. For the appearance of arousals during NREM sleep, a lead in the timing of changes in breathing and the heart beat rate by 15 and 5 s, respectively, before the onset of detectable central activation was found in the cat [23]. Superior regulatory input which modulates cardiac activity has been related to changes of the fluctuation of the heart beats. Long-term correlation seen in REM sleep and in the waking state is perceived as a highly regulated state despite the high variability of the heart beats [24, 25].

Here, we present a numerical analysis of sleep ECG to detect changes of the fluctuations with a few seconds time resolution. We have designed an algorithm to progressively screen the ECG for change-points in the correlation time of consecutive heart beats. We then investigated whether this algorithm can detect transitions to wake and REM sleep, and whether it would recognize movement time according to R&K. The aim of the study was to look at the sensitivity of the method and to test its temporal resolution in a well-defined experimental setting.

2 Methods

2.1 Subjects and Sleep Recording

Sleep recordings were performed on ten healthy male subjects (age 21–32 years) who signed an informed consent. The study was approved by the local ethics committee. Subjects did not take medication or illegal drugs at least 2 months before and during the recordings and had no history of any physical, mental or sleep related disease. Subjective sleep quality and daytime sleepiness (PSQI and ESS) scored within normal values. The timing of the sleep period was assessed by sleep logs for two weeks and matched the experimental time in bed. All subjects underwent a standardized experimental procedure implemented into the protocol of other sleep-related clinical studies. The following parameters were recorded on a Nihon Kohden polygraph and digitized at a sampling rate of 500 Hz: five channels EEG (Fz-A1, C3-A2, C4-A1, O1-A2, O2-A1 localizations of the 10/20 electrode placement system), EOG (electro-oculogram), submental and tibial EMG (electromyelogram), single channel ECG (corresponding to derivation V1-V4 at the chest wall), thoracic and abdominal breathing effort. The EEG was recorded with a sensitivity of 70 V/cm and high /low frequency filter cut-offs at 70 Hz and 0.53 Hz (the latter corresponding to a time constant of 0.3 s), respectively. For the ECG the settings were 500 V/cm and filtering cut-off frequencies of 70 and 0.1 Hz (time constant 1.6 s). The numerical processing was started at the beginning of the data acquisition (this started the

time-axis at 0 h). A total of 19 second and third nights in the sleep laboratory, which were considered regular nights, were subjected to the evaluation of the present study.

2.2 Sleep Scoring and Generation of ECG Time Series

All sleep recordings were scored at a resolution of 30 s epochs according to R&K by two independent visual scorers. For the specific stages of interest, i.e. transitions to wake, movement time (MT) and REM sleep, concordance of more than 85% was generally obtained. In some critical cases a consensus score by a third expert was used for further evaluation.

The raw ECG data was rendered into consecutive interbeat intervals, i.e. the time between two consecutive R waves, to create a time series of RR-intervals (RRI). This was achieved semi-automatically by a specially created program “RRI distiller” that allows supervision at any step of the conversion of the ECG into consecutive RRI [12]. The RRI time series can be edited *optionally* for visual assessment, for instance for persons with a highly irregular heart beat or when there were technical problems with the recording. By setting the parameters to very restrictive values, however, it is possible to exclude these parts from the analysis automatically, without the need for interaction.

2.3 Numerical Analyses

The ECG time series were analyzed by progressive detrended fluctuation analysis (PDFA), which we developed as a pointer on a time axis to temporally locate any changes of statistics occurring in the time series. We decided to focus on the changes in the correlation time, since it was shown both REM sleep and the waking state display a long-time memory that is absent in light sleep and deep sleep [10, 11]. Moreover, at some transitions between sleep stages of the ascending branch of a sleep cycle there is a rapid change in the correlation behavior [10, 26].

An algorithm, called detrended fluctuation analysis (DFA), proved to be very successful to detect changes of the correlation in physiological time series [27–29]. Based on the DFA technique, in the *progressive* variant of DFA (the PDFA), an intrinsic time axis is created by progressively incorporating heart beat by heart beat into the analysis. To this end, the time series is broken up into segments of a particular length, referred to as the “window size parameter n ,” which are progressively filled with data points. n is a parameter that is intrinsic to the *progressive* variant of DFA and has the following interpretation: for larger n the statistical estimation is carried out on more heart beats than for a small n , whereas smaller n means probing the data set with a finer temporal mesh-size. The latter allows the detection of statistical changes from a particular data point on. The parameter q , as in normal DFA, determines the polynomial orders of trends that are eliminated, as explained in the Appendix. All data sets were analyzed with first order PDFA ($q = 1$), which turned out to be sufficient in the present work, with window size n ranging from 3 to 80 data points, i.e., heart beats. A brief outline of the procedure is given in the Appendix. For a detailed mathematical definition of the analyzing procedure, see [12].

As additional graphical information for visual scoring of NREM versus REM we also look at the local slopes of the PDFA curves. The numerical “differentiation” is

carried out by calculating the slope of the straight line corresponding to the closest linear fit to the PDFA curves in a doubly logarithmic scale; for each point this linear fit is determined within an interval of a selectable number of data points around the point. Comparing several numbers, it has proven sufficient to choose five data point intervals. To get rid of uninteresting stochastic fluctuations on a very short time scale, which are unlikely to contain any physiologically relevant information, we carry out a smoothing by taking a moving average of the slope over a few data points. The more data points we use for averaging, the better the smoothing, naturally at a cost of time-resolution. By comparison, we found that an optimal trade-off between smoothing efficiency and time-resolution is reached for about 100 data points. Instead of applying this smoothing, one may alternatively include a larger number of data-points in the processing interval to start with. The times typically required for calculating a PDFA curve for a whole night ECG recording, sampled at 500 HZ, is 1–2 min. A complete analysis for 70 window sizes requires about 1 h.

Figure 1 demonstrates the typical behavior of the PDFA (in this case for sleep ECG data) for different window sizes, from 3 up to typically 80 data points. Small window sizes allow a higher temporal resolution, since less data points are involved than in large windows. PDFA localizes time changes in the correlation as well as

Fig. 1 Numerical PDFA analysis of a whole night sleep ECG recording (subject 9, second night): PDFA events graphically appear as *steps in the waterfall-like slope of the PDFA curves (a)*. Alternatively, one may identify PDFA events as peaks in the numerically differentiated curves (**b**). The manually scored hypnogram is shown *top* as a reference and the color-coded sleep stages are shown in the horizontal bar beneath each plot. The *window sizes in the gray-level coded bar on the right* are given in numbers of heartbeats

in the standard deviation of the numbers in the time series with high sensitivity and high temporal resolution. However, these two effects cannot be distinguished immediately, i.e. from one single curve alone, if they occur simultaneously. This problem can be resolved by taking more curves into consideration, as shown in the next paragraphs.

Applied to sleep ECG, transitions of sleep stages from deeper to lighter NREM sleep may be represented by changes in correlation as well as changes of the statistical spread of the RRI. Graphically, these changes appear as abrupt changes in the slope of the PDFA curves of each window size. The visibility of these “waterfall”-like PDFA events depends on the window size, as will be discussed below (cf. Fig. 2). Alternatively, numerically differentiated curves have been created (Fig. 1).

The resolution of the PDFA has been thoroughly investigated on artificially generated time series of correlated and uncorrelated segments. Figure 2 shows some examples of PDFA analyses of artificial time series containing three segments of random numbers with different correlation between the data points and/or different statistical variance: change points lead to abrupt changes in the slope of the PDFA curves (left in Fig. 2a and b, slope derived by numerical differentiation on the right). The parameter σ denotes the statistical variance of the data points, and α is a measure of the asymptotic behavior of the correlations chosen in each segment [10]. Uncorrelated white noise and time series with short-range correlations have $\alpha = 0.5$, and for long-range power law correlations $0.5 < \alpha \leq 1$ holds. In Fig. 2a the two change points, both in correlation of the time series, are clearly visible as abrupt changes in the slope of the PDFA curve (on the left) and as a corresponding prominent peak in the numerically differentiated curve (on the right). The solid line corresponds to a relatively large window size of 70 data points and the dashed line to a window size only half as long. This clearly illustrates that larger window size

Fig. 2 PDFA events in artificial data: The resolution in time of the PDFA method to localize changes in the statistics is demonstrated on artificial series of numbers containing two statistical change points. The *solid line* corresponds to a larger window size, the *dashed line* to a smaller one. In the *upper graphs (a)* the correlation coefficient of the time series has two sudden changes, whereas the *lower graphs (b)* treat the more challenging case of only a very slight change of statistical variance in the second change point

give rise to more pronounced steps, at the cost of cruder localization within a larger window (see, for instance, the graph on the right in Fig. 2a).

Figure 2b contains the more challenging case of two different types of change points, a change of the correlation behavior between the first and second segment and a slight difference in statistical variance between the second and third data point segments. By comparing curves for very small window sizes with curves for intermediate window sizes (e.g. $n = 5$ with $n = 35$), one can detect and distinguish both kinds of change points: The signature of an increase in α is a decrease in the slope for small window sizes and an increase for larger windows. Contrary to this, an increase in σ leads to an increase of slope for all window sizes [12]. The large fluctuations in the numerically differentiated curves (right hand side of Fig. 2) are neither PDFa-artifacts nor artifacts arising from the numerical differentiation, but are due to intrinsic short-time fluctuations in this time series. In other words, short-time excursions from the asymptotic expectation value of the time series lead to fluctuations in the differentiated PDFa curves. We have examined and confirmed this for stationary long-time-correlated time series.

Translated to the context of RRI time series, the onset of a sleep-disturbing event that imprints itself on the ECG, e.g. an arousal that changes the correlation and/or the statistical spread of the RRI, would be detected in the few initial RRI of different statistics. Visualization of the exact spot relates to the number of RRI taken into the analysis simultaneously, i.e. to the size of the analyzing window. A wider number of data-points implies a better visualization of the spots, but at the same time the temporal localization worsens. Therefore, the temporal resolution of PDFa in a RRI time series lies well below 10 s.

3 Results

3.1 Behavioral Arousal and Transitions to Wake

In order to test the temporal resolution of the progressive approach by analyzing heart beat by heart beat to detect the onset of a change in statistics, we focused on the detection of behavioral arousals and transitions to wake.

The sleep architecture of each of the 19 recorded nights was compared to the respective ECG-derived PDFa curve. We regarded movement time (MT) according to the scoring criteria of R&K as behavioral arousal, since large movement artifacts of duration of more than half the 30 s epoch are identified. Both MT and wake represent high-level activation that affects the ECG. Both are accurately accessed following the R&K criteria, independently from the ECG. As previously shown, the correlation behavior markedly differs in NREM compared to REM and wake [10, 11]. There is also evidence of uncorrelated intervals of the heart beats at transitions from deeper to lighter sleep [10, 26]. This gives rise to the assumption that high level arousals, i.e. the transitions to wake and MT, of abrupt onset and of short duration, will imprint on the ECG and be detectable by PDFa.

We find that the graphical presentation of the PDFa events derived from numerical differentiation provides a good indicator for a possible transition to wake or MT. Table 1 compares the absolute numbers of manually scored incidences of MT or wake for each of the 19 data sets (comprising second and third night recordings

Table 1 Number of incidences of MT or wake compared to the number of corresponding peaks in the numerically differentiated PDFA curves, i.e. “PDFA events,” for 19 recordings derived from ten subjects

	MT/wake	PDFA event
Subject 1, second night	5	5(= 100%)
Subject 1, third night	27	16 + 1(= 63%)
Subject 2, second night	2	2(= 100%)
Subject 2, third night	32	30 + 1(= 97%)
Subject 3, second night	26	26(= 100%)
Subject 3, third night	32	29 + 3(= 97%)
Subject 4, second night	29	29(= 100%)
Subject 4, third night	35	27 + 4(= 89%)
Subject 5, second night	33	29 + 2(= 94%)
Subject 5, third night	33	26 + 5(= 94%)
Subject 6, second night	39	32 + 5(= 95%)
Subject 6, third night	29	22 + 3(= 86%)
Subject 7, second night	39	36 + 3(= 100%)
Subject 7, third night	26	25 + 1(= 100%)
Subject 8, second night	8	8(= 100%)
Subject 8, third night	12	11 + 1(= 100%)
Subject 9, second night	22	18 + 2(= 91%)
Subject 10, second night	19	15(= 79%)
Subject 10, third night	26	15 + 5(= 77%)

The left column gives the absolute numbers of manually scored incidences of MT/wake, the right column the number of PDFA events, split up into a sum of pronounced PDFA peaks (first number) and doubtful (second number) events, with the sum of these expressed as percentage of the total number of scored events in parentheses.

The third night of subject 9 was not analyzed due to poor quality of the ECG recording

from ten healthy male subjects) with the numbers of matches with “PDFA events.” Here, a PDFA event is defined as a large, well-pronounced peak that reaches 10% of the height of the tallest peak in the numerically differentiated PDFA curve. The scoring of PDFA events was carried out by visual inspection by an unbiased person (blinded to the results of the visual sleep stage scoring according to R&K). Automated analysis seems possible, and we are currently testing several possibilities of implementation.

Figure 3 gives an example demonstrating the high time-resolution of the PDFA. Comparing the manually scored sequence of sleep stages in a segment of about 20 min with an EEG signal (moving FFT analysis of the C4A1 EEG recording) and the PDFA analysis (slope without smoothing) clearly reveals that the PDFA timing of the sleep changes closely matches the temporal pattern in the EEG, whereas the manual scoring with its time-resolution tied to the epoch is considerably “out of rhythm.” Small window sizes of *only three to four heart beats* (red curves) are sufficient to pick up the statistical changes. The blue peaks, corresponding to window sizes of a minute and longer, are typically higher (thus they were truncated in the image) and thus easier to detect, but their width is seen to be broader, which makes the localization of the physiological event in time less precise. Thus Fig. 3 is a visual illustration of the trade-off between sensitivity (large window-size, blue curves) and time resolution (small window-size, red curves). The smaller red peaks

Fig. 3 Demonstration of the time resolution of the PDFFA, with a manually scored hypnogram and a moving power spectrum of the C4A1 EEG recording. The PDFFA analysis corresponding to window sizes of only about three heart beats develops temporal structures simultaneously with the EEG spectrum, whereas the manual scoring according to the Rechtschaffen and Kales rules with their epoch-limited resolution is sometimes lagging behind. The example is taken from the same recording as in Fig. 5 (subject 4, third night): the time axis spans 23 min and covers MT/wake periods with lengths of one or two epochs (30 s/epoch)

in the illustration seem to correlate with K-complexes in the EEG, but a systematic investigation has yet to be carried out, before one can explain their origin.

Naturally there is certain amount of arbitrariness in our definition of a PDFFA event due to the specification of a threshold value for the minimal peak height to score as a PDFFA event. In order to illustrate the relative importance of this threshold, we have split the number of PDFFA events into a sum of two terms: the first number contains only very distinctive peaks, whereas the second number counts “doubtful” PDFFA events, which are either weaker or otherwise difficult to identify, for instance because of a “bunching” of several peaks in the vicinity which are hard to resolve as individual events. However, we have some preliminary results indicating that weaker peaks are indeed quite important for the detection of other features, as for instance EEG micro-arousals.

In Table 1, the percent in parentheses refer to successful identification of the total number of scored events. The percentage of identified incidences ranges from 63–100% for the 19 data sets, with a remarkable mean value of 93%. However, for a more detailed statistical analysis we have to keep in mind that, based on our hypothesis that sympathetic activation triggers PDFFA events, we expect all transitions to wake and movement time events to be accompanied by a PDFFA event, but also some transitions between sleep stages which involve such activation. The transition from stage IV to stage I, for example, gives rise to stronger PDFFA events [26], compared to a transition III to II, which may be explained by the different impact that these transition have in general (see editorial by Thomas [30] and references therein). Since some types of sleep stage transitions are typically also accompanied by PDFFA events, the usual evaluation of sensitivity and specificity of PDFFA events as indicators of MT/wake does not seem to be very meaningful, since all other PDFFA events (i.e. about 50% of all PDFFA events) would be counted as

“false positive.” Note that this does not rule out an automated assessment of NREM versus REM, since we suggest to make use of differences in the intervals *between* all statistical change points (as explained in Section 3.2).

Instead, we have calculated the 95% confidence interval (based on a binomial distribution) that MT/wake can be expected to be “heralded” by a PDFA event after pooling all data-sets. Pooling all 19 data-sets we have 461 transitions to MT/wake. 416 are accompanied by a PDFA event, 45 have only a weak or no PDFA signature. Thus the 95% confidence interval for a correct recognition of a MT/wake transition by a PDFA event was found to lie between 87.2 and 92.8%. Conversely, the 95% confidence interval for a missing PDFA event lies between 4.6 and 9.4%. In total, 763 PDFA events were recorded, that is 45,5% were independent of MT/wake transitions.

Most incidences that were missed (“false negative” events) were identified as rapid changes between short episodes of e.g. sleep stage 1 and MT/wake (for instance in the data set of the third night of subject 6) or of REM and MT/wake (for instance in the data set of the second and third night of subject 10). Data sets which contain regions with rapid switching between sleep stages at an already aroused level generally tend to be more problematic.

Figure 4a–d gives examples taken from four different second nights, (a) subject 4 (b) subject 7 (c) subject 10 (d) subject 3, of the graphical display of wake and MT detection. Both transitions to wake and MT are indicated by dotted vertical lines. Typically, as illustrated in Fig. 4a and b, almost all lines coincide with the most prominent peaks in the slope of the PDFA curves (i.e. with “PDFA events”). Arrows in Fig. 4a,c and d indicate some of the rare occasions of a mismatch in selected examples: Fig. 4c shows one of the rare “false negative” occasions, where a short epoch of wake is sandwiched between two short (one-epoch) episodes of sleep stage 3 and sleep stage 2, all of which preceded REM, was missed completely. Some “false positive” events that only exist for small window-sizes representing very short time

Fig. 4 Manually scored behavioral arousals (defined as movement time (MT) according to R&K) and transitions to wake are indicated by *dotted lines superimposed on the numerically differentiated PDFA curves* from four different data sets: peaks of the PDFA curves due to changes in correlation or standard deviation of the heart rate almost completely coincide with wake and MT (*dotted lines*). *Arrows* indicate critical points, where discrepancies arise, e.g. due to ECG recording artifacts (y-axis in arbitrary units, PDFA window sizes in numbers of heart beats)

Fig. 5 Differentiation of REM sleep and wake from NREM sleep (subject 4, third night): The degree of overlap of curves with small (red lines) and large (blue lines) window sizes, respectively, is strikingly different for REM and wake compared to NREM sleep

scales (“light grey” peaks, as e.g. the arrow in Fig. 4a) have been identified as artifacts derived from recording impurities of the ECG (causes and identification of these artifacts will be discussed below). The arrow in Fig. 4d does not derive from an ECG recording artifact, but coincides with an EMG arousal.

3.2 Differentiating REM Sleep and Wake from NREM Sleep

REM sleep and wake clearly differ from NREM sleep with respect to certain features in the HRV that are accessible by PDFa. Thus, these numerical findings may serve as “surrogate markers”: the PDFa curve derived from numerical differentiation shows an overlap of small and large window sizes, i.e. the scaling size parameter, only in REM sleep (see for instance extended region after 6 h in Fig. 1, taken from the second night of subject 9) and wake, but not in NREM sleep (see, for example, region in the middle between 4 and 5 h in Fig. 1). This qualitatively strikingly different dependence on the scaling size parameter, which may immediately be used for visual scoring, can be explained by the fact that, by scanning from the smallest to the largest window size, one crosses the correlation time typical for NREM sleep, which is around six heartbeats [10]. Since REM sleep is long-time correlated, with a correlation time much longer than the largest window size, changing this parameter has no relevance during periods of REM sleep. The same behavior is also seen in a wavelet analysis, if the scaling parameter (which now corresponds to the width of the chosen wavelet basis) is scanned in a similar range as the window size [26].

3.3 Artifacts

Artificial results in the PDFa curves appear if there are distorted or missing R waves, which may be either due to poor recording of the ECG or due to aberrant spread of the depolarization through the myocardium. We have checked very thoroughly that the RR-finding algorithm itself introduces no intrinsic error, as long as the ECG recording is of reasonably good quality.

Recording artifacts, for example, due to large motions of the subject, are clearly distinguishable in the numerically differentiated PDFa curves, since they create

unusually large peaks in the curves corresponding to small windows, i.e., lighter peaks in the gray-scale chosen in Fig. 4. This characteristic appearance becomes even more obvious, when small to large window slopes are superimposed as color-coded graphs. Thus “motional” ECG recording artifacts will become obvious, either already prior to PDFa analysis at the level of the RRI distiller by the manual correction mode of doubtfully allocated R waves, or after calculation of the PDFa by their characteristic appearance.

If the ECG data are corrupt throughout larger parts of the recording, such as due to inadequate electrode contacts, which unfortunately was the case for one of our recordings (third night of subject 9), the numerical analysis may of course be performed, but will not yield any meaningful information.

4 Discussion

With this work, we introduce an approach suitable to analyze whole-night sleep ECG recordings which provides more – and more subtle – information than a simple evaluation of changes in the mean value and standard deviation of the heart beat rate. The method is also intrinsically different from frequency analysis methods, since it progressively calculates the fluctuation of the timing of individual heart beats and their correlation. These fluctuations, in terms of RRI, occur typically within a range of 120 ms and appear to be related to physiological regulating mechanisms of sleep and wakefulness. As has been shown by Bunde et al. [10], the characteristics of fluctuations of the heart beats during sleep and wake are different. In NREM sleep, the pattern of the time lapse between two heart beats is comparatively irregular, i.e., consecutive beats are poorly correlated, and exact predictions of the occurrence of the next beat are difficult. In fact, in NREM sleep only three to six consecutive beats are correlated, whereas REM and wakefulness feature a much longer correlation time scale. These differences between REM and NREM sleep refer to manifest, but not at-a-glance obvious, changes in the statistical correlations. Some transitions between NREM sleep stages are accompanied by a pronounced change in the standard deviation of the RRI, presumably related to shifts of the sympatho-vagal balance of the autonomic nervous system [10, 26].

The advantage of *fluctuation* correlation analyses for the detection of short-lasting and slight systemic changes during sleep (e.g. autonomic arousals) relates to the fact that small changes of the fluctuation of the heart beats are not directly related to the cardiovascular regulation serving a hemodynamic purpose, but are perceived to be superimposed on the heart action. Changes of the fluctuations may appear much faster, with shifts of the sympatho-vagal balance, than changes of the frequency of the heart beats. A comparatively weak activation of frequency by arousal stimuli may be supported by the fact that blood pressure changes correlate better to EEG micro-arousals than to the heart beat rate [13].

If the changes of the fluctuation of heart beats are the ideal marker of subtle changes of the autonomic nervous system during sleep, they need to be detected by appropriate means. The difficulty of some numerical methods used to access fluctuation changes is the fact that the sleep ECG has to be divided into segments and analyzed with respect to the previously determined sleep stages. It is then not possible to register changes of the HRV as they occur along the RRI time series.

Here, we introduced a progressive analysis technique that takes in account every heart beat as it occurs. Practically speaking, any arousal or sleep stage change that is imprinted on the ECG should be localizable.

In this paper, we have demonstrated that our method is capable of localizing transitions to movement time/wake within seconds: Combining the information gained by a PDFA curve for a small window size providing better time resolution, with a larger window size (e.g., of 20 heart beats) providing better sensitivity, one can detect such events and localize them within very few heart beats. Thus, the strength of the approach lies in the detection and precise time-allocation of abrupt changes in the HRV, and not in its ability to discriminate between different types of such changes.

The onset of sleep stages according to R&K is sometimes difficult to determine and appears to be different from the onset of the changes in the respective heart activity [7, 22]. PDFA and other ECG analyzing methods should potentially be helpful for the definition and on-line detection of sleep stages, e.g., sleep-onset REM. In the future, arousal research may take advantage of ECG analyses to trace arousals travelling between central and peripheral nervous systems [6, 23]. However, the present paper was restricted to a direct comparison of HRV and visual scoring according to R&K, without alternative data acquisition or data processing in parallel which possesses higher time resolution than R&K; thus, we were not able to assess these issues.

Summarizing, we have demonstrated the good temporal resolution of the PDFA for artificial data as well as for “major” arousals, such as MT and transition to wake. It seems that the PDFA meets the requirements of ECG analyses proposed by Penzel [14] to accurately detect highly dynamic sleep-related events.

Moreover, we have outlined a new approach illustrating how to utilize the information gained by varying the scaling size parameter of the PDFA (i.e., the number of heart beats included in the active window that is moved across the data set during the numerical analysis) to record signatures that are typical for NREM sleep as opposed to REM and wakefulness. Currently we use a visual assessment to segregate NREM, but automated scoring seems possible in general. The broad spectrum of sleep-fragmenting events in normal and disordered sleepers remains to be tested for changes of heart rate fluctuations. So far, different arousal types and sleep stages appear to be identifiable in the RRI time series analysis using fluctuation criteria.

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Appendix A: Brief Outline of the Numerical PDFA Method

The data set containing the lengths of all RR-intervals as numbers in chronological order represents a time series $\{\tau_k\}$ of total length N . After having subtracted the mean value $\langle \tau \rangle = \frac{1}{N} \sum_{k=1}^N \tau_k$, we derive a cumulative time series $y(l) = \sum_{k=1}^l (\tau_k - \langle \tau \rangle)$ by integration. In a “random walk” with steps $\{\tau_k\}$, for example, $y(l)$ could be interpreted as the difference between the position *actually reached* after L steps, as compared to the position reached after taking L times the average step of length

(τ). Next, this cumulative time series is divided into non-overlapping segments of equal length n . We refer to n as the “window size” or the scaling size parameter. Similar to the detrended fluctuation analysis (DFA) of order q , in each segment, a polynomial of order q is fitted to the cumulative series and the deviations from this polynomial are calculated in order to eliminate local trends to the q^{th} order. The case $q = 1$ eliminates *linear* trends, i.e., in each segment a least-squares straight line is fitted to the cumulative data, representing the “local linear trend” $y_{\text{trend}}(l)$ in that segment.

In contrast to DFA, where the entire time series is divided into segments of length n and analyzed in *one step*, in PDFa, partial sums covering an increasing part of the total time series are created and analyzed *separately*. Each partial sum is divided into non-overlapping segments of length n starting from the beginning, and local trends are eliminated in each segment. This means that, in contrast to DFA, where the window size n is varied, here, the segments are all of *constant* length n (except for possibly the last one containing remaining points). For partial sums of length p increasing through the data-set ($p = 1, \dots, N$), the “PDFa curves” are defined by $P_{[n]}(p) = \sqrt{\sum_{l=1}^p [y(l) - y_{\text{trend}}(l, n)]^2}$. Apart from the length p of the evaluated time interval, $P_{[n]}(p)$ depends on the chosen window size n (as a reminder of this implicit dependence, we tag the fluctuation variance with the subscript $[n]$). Note that, by definition, the function $P_{[n]}(p)$ is not a scale-free measure. The whole procedure can be repeated for a different scaling parameter, i.e. a different window size n . In fact, a comparison of different scaling factors may yield useful additional information, as seen in the example of Fig. 4.

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