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Can One Detect Sleep Stage Transitions for On-Line Sleep Scoring by Monitoring the Heart Rate Variability?

Sind Schlafstadienwechsel durch eine on-line Analyse der Herzschlagvariabilität erkennbar?

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Summary

Question of the study Sleep stages are known to differ in the heart rate variability (HRV). REM sleep and wakefulness are characterized by long-range correlations in the heart beat rate. In SWS, a statistical correlation extends only to very few (3–6) of the heart beats that follow. In the present paper, this difference is utilized to separate NREM sleep from REM sleep and wakefulness on-line in polysomnographic whole-night sleep recordings.

Methods So far, 48 whole-night recordings of 19 healthy subjects have been subjected to numerical analysis. Extracting the RR intervals from the ECG channels of the polysomnographies, a time series was established and analysed with a variety of numerical methods. In particular, we have applied the progressive detrended fluctuation analysis (PDFA), a tool that we recently developed to find and localize statistical 'change points', and a continuously moving wavelet analysis that we adapted for this purpose. Spectral methods were applied to gain indirect information on the sympathetic activity.

Results PDFA and the wavelet method were found to be sensitive to transitions between particular sleep stages and consistently insensitive to others when superimposed on a sleep chart of visually scored colour-coded sleep stages: Short embedded periods of wakefulness are detected with excellent sensitivity and reliability. 'Numerical events' reliably mark transitions from deeper to lighter sleep (e.g. from stage 4 to stage 3 or 2) but are consistently *missing* for transitions from deep to light sleep (e.g. from stage 3 or 2 to stage 4). By varying a built-in scaling parameter of the method, a visual display is generated that clearly differentiates REM sleep and wakefulness from NREM sleep. Wakefulness and REM cannot be distinguished in this way. The examples discussed are typical of the 48 whole-night polysomnographies.

Conclusions The fact that our numerical method is not sensitive to the more gradual settling from the initiation of sleep into SWS rules out the possibility of progressive on-line sleep staging based on the PDFA approach. The discrimination between REM sleep/wake and NREM sleep gives rise to an automated aid to visual scoring. Since PDFA events seem to be related to the occurrence of autonomic arousals, our approach has the potential to provide an alternative way to detect and classify arousals.

Keywords heart rate variability – time series analysis – sleep stage reconstruction – autonomic arousal.

Zusammenfassung

Fragestellung Schlafstadien unterscheiden sich in der Herzschlagvariabilität. Statistische Analysen des Herzschlags ergeben kurz- und lang-reichweitige sehr unterschiedliche Korrelationszeiten in der Zeitreihe der RR-Intervalle. REM-Schlaf und Wachstadien sind charakterisiert durch statistische Korrelation über viele RR-Intervalle. Im SWS erstreckt sich

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eine statistische Korrelation nur über 3–6 RR-Intervalle. In der vorliegenden Arbeit wird der Versuch einer automatisierten und fortlaufenden Unterscheidung von NREM-Schlafstadien und REM-Schlaf bzw. Stadium Wach auf der Basis von numerischen RR-Intervall-Analysen dargestellt.

Methodik Zeitreihen von RR-Intervallen wurden aus dem EKG von bisher insgesamt 48 Polysomnographien von 19 gesunden, männlichen Probanden ermittelt und mit verschiedenen numerischen Methoden analysiert. Mittels der von uns entwickelten PDFA (Progressive Detrended Fluctuation Analysis) und einer Wavelet-Analyse wurden statistische Wechsel berechnet und zeitlich lokalisiert. Indirekte Hinweise auf den Sympathotonus lieferte die gefensterte Fourier-Transformation von 1 Minutenabschnitten der RR-Zeitreihe.

Ergebnisse Vor dem Hintergrund einer visuell ermittelten, farblich kodierten Schlafstadientapete ergeben PDFA und Wavelet-Methode dieselben Hinweise auf Übergänge von Schlafstadien: die Ergebnisse beider numerischen Analysen sind wenig sensitiv für die Progression vom Einschlafen bis zu Tiefschlaf. Wechsel von Tiefschlaf- in Leichtschlafstadien bzw. Wach werden dagegen mit hoher Verlässlichkeit und guter zeitlicher Übereinstimmung mit der Schlafstadienklassifizierung nach R&K erkannt. Die Darstellung der Steigungen der PDFA-Verläufe lässt eine klare Trennung von REM-Schlaf (beziehungsweise Wach) und NREM-Schlafstadien erkennen. REM und Wach lassen sich daraus nicht direkt unterscheiden. Die diskutierten typischen Beispiele wurden exemplarisch ausgesucht aus bisher insgesamt 48 untersuchten Polysomnographien, die von 19 Probanden stammen.

Schlussfolgerungen Die Tatsache, dass Schlafstadienübergänge nur in Richtung leichteren Schlafs erkannt werden, spricht gegen eine Anwendung der Methode zur automatisierten und fortlaufenden Bestimmung der Schlafstadien während der nächtlichen Schlafaufzeichnung im Labor. Die Methode der Trennung von REM und Wach von NREM-Stadien ist hingegen viel versprechend in der Assistenz des visuellen Scorings. PDFA-Ereignisse sind hinweisend auf vegetative und EEG-Arousals und für die Erkennung von fragmentiertem Schlaf verwertbar.

Schlüsselwörter Herzfrequenz Variabilität – Zeitreihen-Analyse – Schlafstadien Rekonstruktion – vegetative Arousal.

Introduction

The present standard of sleep stage definition by *Rechtschaffen* and *Kales* (*R & K*) was established 35 years ago [22]. However, to date no method has replaced the standard procedure of visual analysis by an expert polysomnographer, although visual sleep stage scoring is a tedious and time-consuming task that is also prone to subjectiveness, as e.g. a non-negligible inter-rater variability.

Furthermore, it has been criticized that conceptual deviations as regards the biology of sleep may be inherent in the scoring definitions, resulting e.g. from the rigid one-epoch resolution, from a focus exclusively on vertex EEG, from the sparse number of modalities sampled from the sleeping body, and from their deduction exclusively from healthy male adults. Therefore, many attempts at a comprehensive definition of sleep are currently being made.

The progress in digital data acquisition and processing that has been made over the past years opens up entirely new possibilities to test hypotheses along these lines. Information on system conditions such as the vegetative state, for instance, can be gained from analysing the heart rate variability (HRV) of the sleep ECG [3, 17]. Recently, *Bunde* et al. [4, 5] have shown that sleep stages (light sleep, deep sleep, REM sleep) significantly differ in the correlation time of the heart beat rate. Standard sleep evaluation according to the rules of *R & K* represents a visual decision-making process on the basis of a global impression of 30-s epochs of restricted polysomnographic information, therefore resulting in poor time resolution for arousal detection.

In the following, we report on our main conclusions drawn from an ECG fluctuation analysis and discuss the possibility of applications for sleep stage reconstruction. We will show that a numerical on-line time series analysis of ECG may contribute specific information, valuable e.g. for arousal detection, and thus complement EEG-based sleep evaluation.

Methods

Subjects and procedures

So far we have subjected 48 ECG data sets of whole-night recordings from 19 healthy male subjects (aged 22–36 years) to numerical analysis. The subjects participated in other sleep-related clinical studies, which were approved by the local ethics committee and which provided the raw data for the present purely numerical work. Each subject signed an informed consent and underwent a clinical interview and evaluations (PSQI, ESS, sleep diary over a period of 2 weeks, evening and morning protocol) to confirm the absence of any sleep-related or other disease. None of the subjects complained about non-restorative sleep or daytime somnolence. All were free of any prescribed medication and in good physical condition. None presented evidence of illegal drug consumption.

The first night of polysomnographic recording allowed the subjects to become habituated to the recording procedure. Owing to the first-night effect, numerical data from these recordings were not included here. The recording procedure remained the same throughout the entire study and followed the guidelines of the German Sleep Research

Society (DGSM) [21]. At about 19.00 hours, the preparation of the subjects for the recording began. The recording started at about 23.00 hours. Time in bed averaged about 8 hours.

Data acquisition

The following variables were systematically recorded on a 17-channel analogue Nihon Kohden polygraph and digitized at a sampling rate of 500 Hz: five channels of electroencephalogram (EEG; frontal Fz-A1, central C3-A2, C4-A1, occipital O1-A1, O2-A2 localizations of the 10/20 electrode placement system), electro-oculogram (EOG; left eye-A2, right eye-A2), electromyogram (EMG; submental muscle, left anterior tibial muscle), electrocardiogram (ECG; single channel chest lead at V1-V4), thoracic and abdominal breathing effort.

All sleep data were available on paper as well as in digitized format. Sleep staging was carried out following the standard criteria of *R & K* by two independent raters from our sleep lab. In some of the illustrations, a sleep chart of colour-coded sleep stages resembled the background against which the numerical results were depicted.

RR intervals were extracted from the digitized ECG curve by a computer program developed by the authors with the option to monitor the results interactively; at any stage of processing it was possible to check and correct manually the outcome of the identification of the R waves. This allowed the estimation and monitoring of the quality of the time series data generated from the raw data, i.e. from the digitized ECG curve of the recording.

Exact synchronization of all types of recordings is of paramount importance for the analysis (no time leaps, omissions, etc.). For the sake of having as little difference in the data acquisition of all included recordings as possible, we chose four more recent data sets scored by one particular scorer from the total of 48 data sets to be included in the quantitative assessment presented in the Results section (accumulated in table 1). However, all analysed data sets (except one set with very frequently occurring extrasystoles) have confirmed our findings detailed below. The inter-rater variability between the two sleep scorers was within acceptable limits of about 70%, which lies within the range of published assessments of inter-rater variability [9]. For particular sequences of interest (i.e. in cases of obvious discrepancy between numerical prediction and manual scoring), a third consensus scorer, acquainted with the previous scoring and the results of the numerical analysis, was asked for an interpretation. We decided on such a procedure because – at this state of evaluation of the PDFA method – it was not clear what information was to be extracted from the heart beat time series.

Numerical methods

Recently, new statistical methods have been developed to investigate the heart rate variability in healthy subjects and patients [1, 2, 8, 11, 12, 19]. Physiological time series are typically affected by nonstationarities, which make the

Table 1. Juxtaposition of manually scored sleep stage transitions and numerical 'PDFA events' (indicated by significant peaks in the slope of the PDFA curves) for four data sets. Transitions that are strongly correlated with PDFA events and transitions that are very rarely accompanied by PDFA events are both accentuated by boldface.

	Manual scoring	PDFA event	No PDFA event
Transitions to wake:			
Data set 1	**13**	**13**	**0**
Data set 2	**31**	**30**	**1**
Data set 3	**16**	**16**	**0**
Data set 4	**19**	**18**	**1**
Transitions 4 to 3:			
Data set 1	5	2	3
Data set 2	15	4	11
Data set 3	4	3	1
Data set 4	0	0	0
Transitions 3 to 4:			
Data set 1	**7**	**0**	**7**
Data set 2	**19**	**0**	**19**
Data set 3	**7**	**1**	**6**
Data set 4	**1**	**0**	**1**
Transitions 3 to 2:			
Data set 1	10	5	5
Data set 2	47	16	31
Data set 3	6	4	2
Data set 4	8	3	5
Transitions 2 to 3:			
Data set 1	**12**	**0**	**12**
Data set 2	**52**	**0**	**52**
Data set 3	**8**	**3**	**5**
Data set 4	**10**	**0**	**10**

detection of subtle changes in the correlation of the heart beats challenging. In this context, especially the detrended fluctuation analysis (DFA), which is able to detect the presence of long-range power-law correlations in a data set, has proven very successful. For a detailed list of references on the DFA and its applications in various research fields including meteorology, physiology, neurology, economics and more, see [10] and [7]. Originally DFA was developed by *Peng* et al. [18] to distinguish non-coded from coded areas of DNA sequences, since coded areas are lacking the long-range correlations typically present in the often highly repetitious non-coded areas. Similarly, DFA has also revealed that REM sleep and periods of wakefulness display a long-time memory that is absent in light sleep and deep sleep [4, 13].

The aim of the present work was to exploit these differences in HRV in order to recognize transitions between sleep stages while processing a night recording from evening to morning. To this end, we developed a new time-series analysis method, which we will refer to as progressive detrended fluctuation analysis (PDFA). Mathematical definitions can be found in the Appendix. More details on the new method will be presented elsewhere; here we restrict ourselves to describing it briefly and demonstrating its ability to detect changes in the statistics occurring at a particular time on artificially generated data (cf. fig. 1).

As in the DFA, local linear (or polynomial) trends are subtracted from a cumulative (i.e. integrated) time series derived from the time series of RR intervals. However, in contrast to DFA, where one first divides the whole cumulative time series into 'time windows' of increasing window size in order to calculate the local trends and then derives the slope of a fluctuation variance versus window size in doubly logarithmic scale, PDFA uses only a particular window size and progressively adds more and more data points from the time series to fill more and more of these time windows. This introduces an intrinsic time axis, which allows the detection of statistical changes from a particular data point on.

Applying this method to the distribution of the RR intervals in the ECG data set allows the localization of sleep stage transitions in time with high sensitivity and resolution (cf. Results). Strictly speaking, the method is not sensitive exclusively to changes in correlation time, but also to changes in standard deviation of the numbers in the time series; thus these two effects cannot be distinguished. Nevertheless, it has proven an excellent tool to detect certain sleep stage transitions, which are probably characterized by both a change in correlation time and a change in statistical spread of the heart beat intervals.

To validate our new method, we carried out a corresponding calculation on another scale-dependent measure that allows analysis across the data set. We have chosen the wavelet transform standard deviation outlined in *Teich* et al. [26]. In order to get extra information on sympathetic activation, we additionally carried out a Fast Fourier Transformation (FFT), which delivers information on the vegetative state [3, 17].

Results

Sleep stage transitions

The following figures exemplify results of PDFA applied to whole-night recordings. In all of these example images, PDFA has been carried out several times for a window size (= scaling parameter) varying from 3 up to about 80 data points. Strikingly, almost every transition from deep sleep (e.g. stage 4) to lighter sleep (stage 3) is marked by a PDFA event, i.e. a pronounced step in the PFDA curves (for a mathematical definition of the quantity plotted in the graphs, we refer to the Appendix). However, such steps are missing for the progression from stage 3 to 4. This asymmetry in time is a significant and general feature that can be observed for various combinations of sleep stages. Visual examples of this effect are given in figure 2. It is not an artefact of the method because it remains if the data set is processed reversely, i.e. from 'morning to evening'.

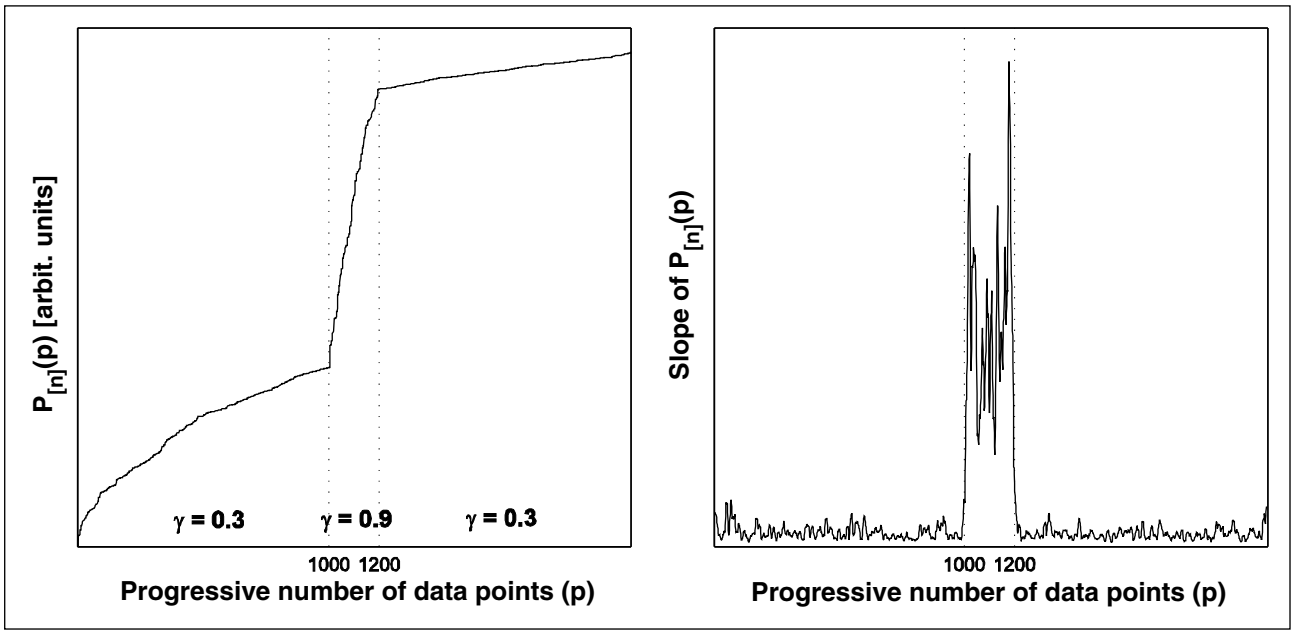

Figure 1. The capability of the PDFA method to localize changes in the statistics in a time series is exemplified on an artificially generated time series containing three data-point segments of long-range power-law correlated Gaussian random numbers having equal statistical spread but different correlation between the data points: The parameter γ (with $0 < \gamma < 1$) is a measure for the correlation length chosen in each segment. The two deliberately built-in statistical change points are clearly visible as abrupt changes in the slope of the PDFA curve (on the left) or, alternatively, in the numerically differentiated curve (on the right).

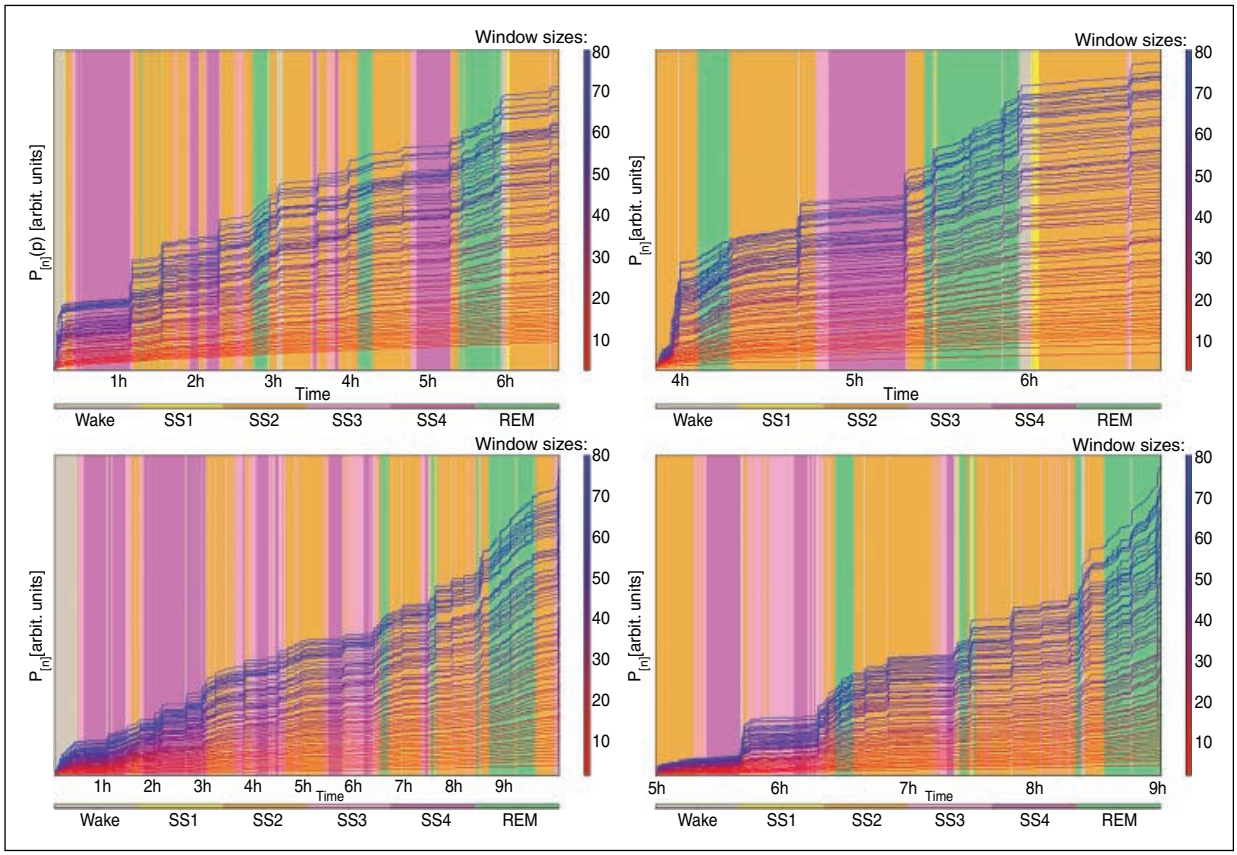

Figure 2. PDFA curves (in arbitrary units) of various window sizes superimposed on a visually scored sleep chart for comparison. Two whole-night recordings are shown, each with an enlarged detail on the right. The example at the bottom shows a night following sleep deprivation.

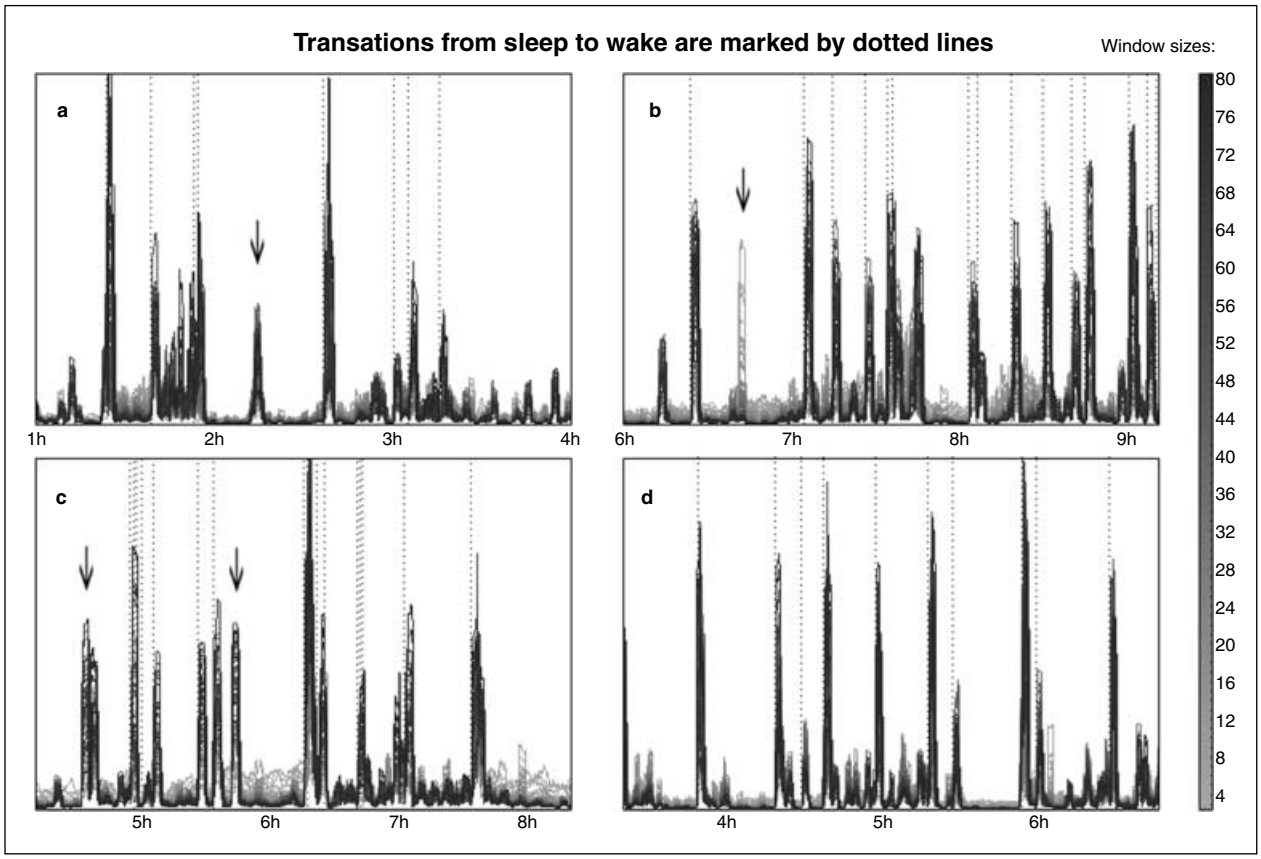

Figure 3. Numerically differentiated PDFA curves (in arbitrary units) from recording excerpts from four different data sets. Note that most of the higher peaks in the curves (corresponding to sharp changes in the slope of the PDFA curve) are related to transitions to wake, as can be seen by means of vertical dotted lines indicating the manually scored transitions into wakefulness.

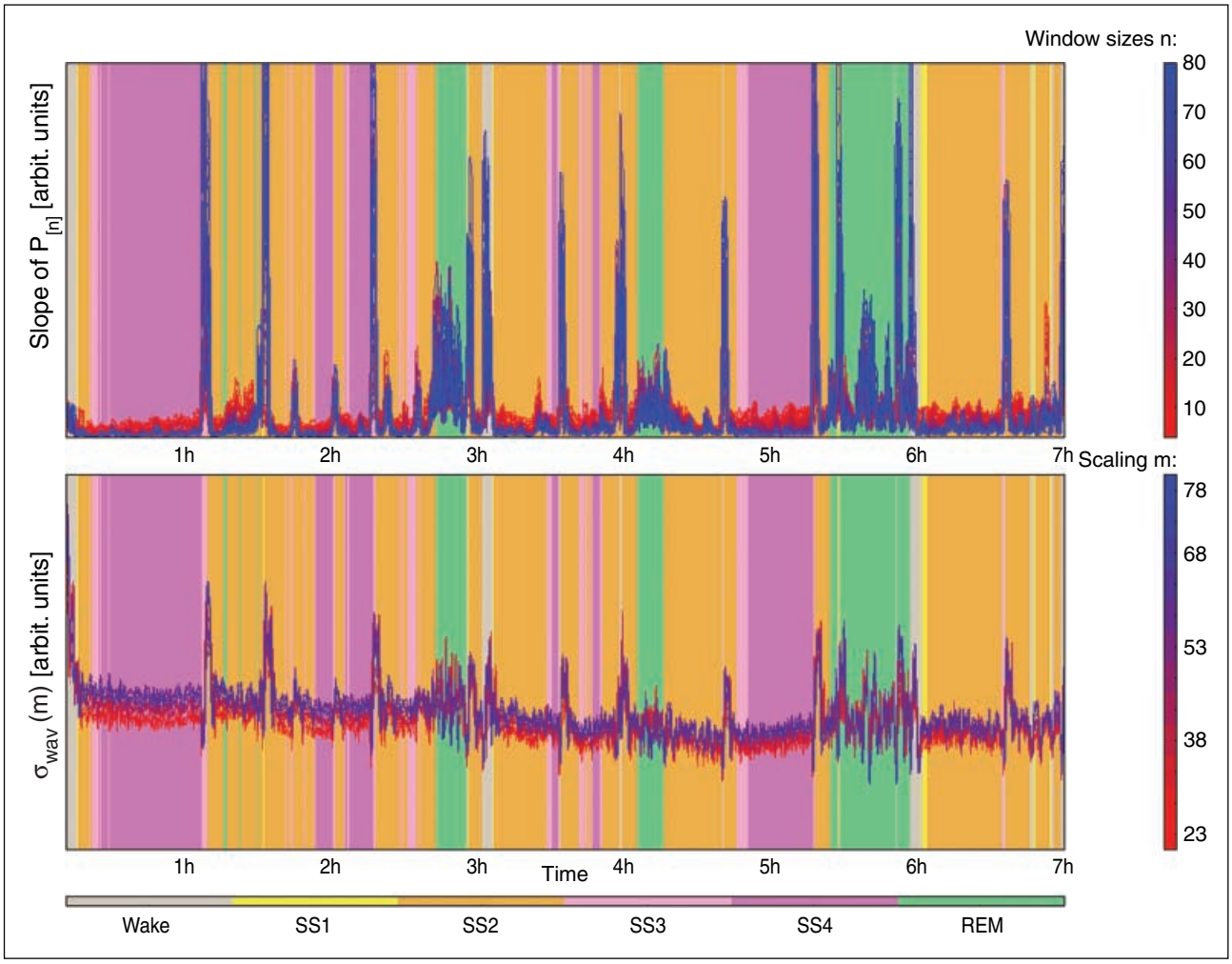

Figure 4. NREM sleep is characterized by a strong dependence on the size of the scaling parameter chosen for the numerical analysis, i.e. the blue and red curves are well separated. On the contrary, in REM sleep (green) there is no such 'scaling parameter dispersion'. Top: PDFA (with the window size as scaling parameter), bottom: wavelet transform standard deviation (with the size of the wavelet basis as scaling parameter). The graphs also demonstrate that the peaks indicating changes in the heart rate statistics coincide for both, completely independent, numerical methods throughout the data set.

In view of our experience with artificially generated correlated and uncorrelated data, it seems that the transitions to lighter sleep are characterized by short intermediate intervals of very strong fluctuations in the heart beat rate. This has also been noticed by *Bunde* et al. [4]. Possibly it is related to the occurrence of short autonomic arousals (cf. Discussion).

It turned out that by using the slope of the PDFA curve derived from numerical differentiation, one gains a good numerical indicator for a possible sleep stage transition. A particularly striking example is visualized in figure 3: the highest peaks in the slope of the PDFA curves are shown to correlate very well with transitions to wakefulness in data set samples from four different whole-night recordings. The manually scored transitions to wakefulness are indicated as dotted vertical lines. Here we have chosen four 'typical' examples, which allow us to discuss possible pitfalls: the strong peak (indicated by an arrow) in figure 3a was caused by an elevation in muscle tonus preceding a transition from 4 to 3; in figure 3b the marked structure was identified as a momentary problem with the digital recording; and in figure 3c we can see that movement artefacts can also give rise to false-positive indications of wakefulness. These problematic points, however, usually make up just a small percentage, except for some more challenging irregular data sets with e.g. extended motion times. Motoric events seem to influence the analysis in any case.

From our data set pool, we chose four data sets from four different subjects, all among our most recent 'normal' night sleep recordings (i.e. no first nights, no nights following sleep deprivation), for an especially detailed investigation of all occurring types of transitions determined by manual scoring. As numerical indicators we used what we call 'PDFA events', i.e. peaks in the slope of the PDFA curves that lie above a chosen threshold. Unfortunately, no *universal* threshold can be chosen for all data sets, but choosing the threshold just above the typical peak height for the smallest window size has worked well for most samples.

Some of our results on contrasting numerical PDFA events with sleep stage transitions for the chosen data sets are summarized in table 1. Any uncertainty about PDFA events (e.g. due to the peak being too close to the fringe of the sample or due to crowding of several narrow peaks together, etc.; cf. fig. 3) was counted as 'no PDFA event'. Table 1 illustrates that non-gradual 'ascending' transitions (into wake, from 4 to 3, or 3 to 2) are predominantly accompanied by a PDFA event, as already illustrated in figure 3 for the case of wake. The important thing here to note is the fact that we almost never find a PDFA event for the corresponding 'descending' transitions (settling into deeper sleep, e.g. 2 to 3

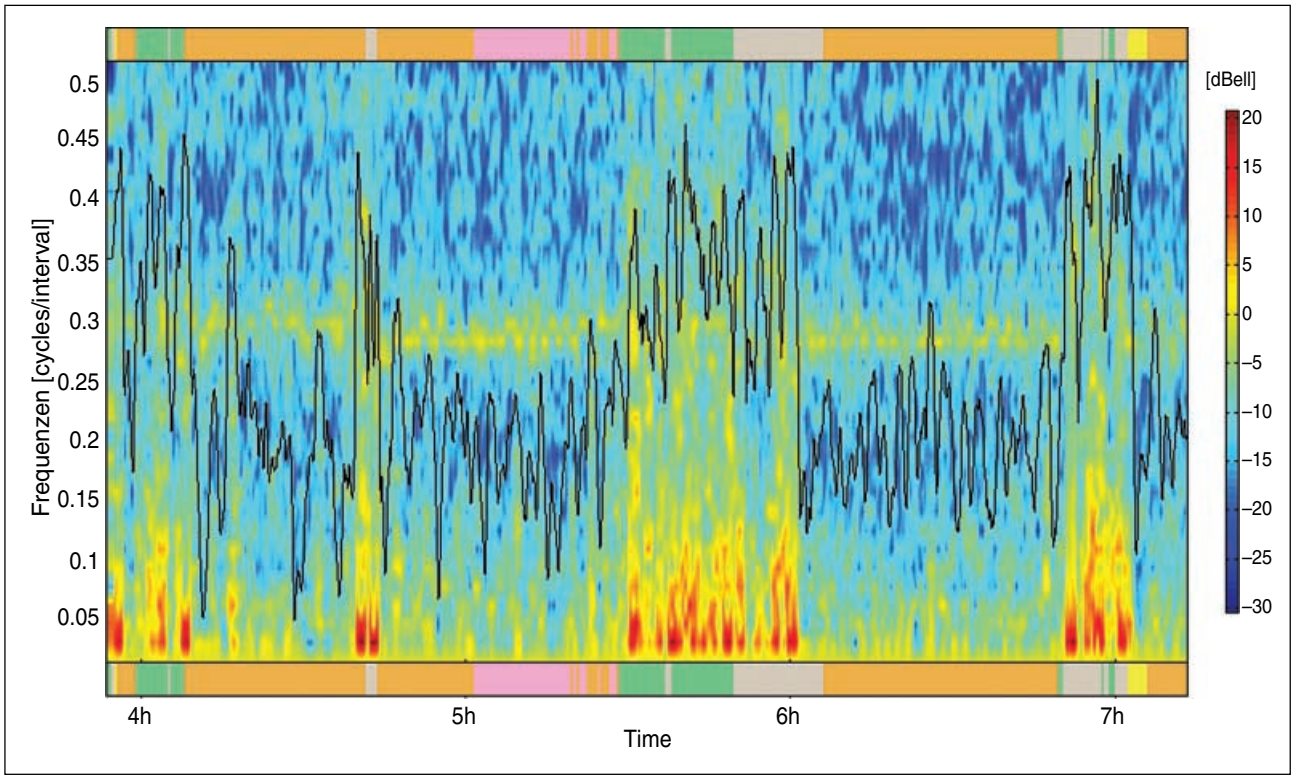

Figure 5. Spectral sympathetic index (ratio of the LF and HF spectral bands) derived by an FFT analysis performed on 1-min window RR intervals 'moving' through the data set. In comparison with the manually scored sleep chart at the top and bottom of the graph, in this example sympathetic activity is seen to coincide with REM sleep (green) and wake (grey).

or 3 to 4). A possible explanation for this striking imbalance will be proposed under Discussion.

Differentiating REM sleep from NREM sleep

In numerically differentiating the PDFA curves, one finds an interesting behaviour that may be used to distinguish REM sleep (and wake) from NREM sleep: while periods of REM sleep show no 'dispersion' in the scaling parameter (i.e. the window size), the curves corresponding to small window sizes (in red) clearly separate from the curves corresponding to wide window sizes (in blue). The same behaviour is seen in the 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. Furthermore, figure 4 convincingly demonstrates that the PDFA measure and the wavelet-transform standard-deviation measure are sensitive to the *same* features in the heart rate statistics, as indicated by coinciding peaks.

This dependence on the scaling size parameter, which is present in NREM sleep and absent in REM sleep, 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 6 heart beats for light sleep [4]) but not for REM sleep with its long time correlation.

Discussion

Having analysed a multitude of data sets, we can conclude that automatic sleep staging based on changes in HRV alone does *not* seem possible, at least not in the outlined approach, since not all transitions from one sleep stage to another give rise to a PDFA (or wavelet) event: Generally only non-gradual transitions from deeper to lighter sleep or wakefulness can be seen. Moreover, in general it is impossible to determine *which* sleep stage transition has taken place based on this type of numerical information alone, except for transitions to wake, which are associated with the largest change in the slope of the numerical curves.

But it seems that this fact in itself indicates the possibility of gaining information on the state of the autonomic nervous system during sleep: Variations in sleep EEG activity are related to changes in cardiac variables and thus are extractable to a certain degree from the ECG. Possibly the imbalance concerning the occurrence of PDFA events along the sleep cycle ('waking up vs. falling asleep') is related to the prevalence of autonomic arousals. Interspersed autonomic arousals, i.e. autonomic activation of short duration terminating in a subcortical level, are *not* recognized by the brain-centred sleep stage scores of *R & K* and ASDA criteria [24]. However, autonomic arousals appear to be indicated as 'PDFA events' by our ECG fluctuation analysis method; thus PDFA could be used to detect autonomic arousals.

In view of our hypothesis that absolute or relative sympathetic activation relates to a PDFA event, we have carried out another independent numerical evaluation to gain additional information on the autonomic state. We have calculated FFT power spectra of windows containing 64 RR intervals to derive what's called the low frequency (LF) band (0–0.15 Hz) and the high frequency (HF) band (0.15–0.5 Hz). This was motivated by the ongoing controversial discussion on sympathetic activity and HRV. It has been argued [3], for instance, that the HF band can be associated with parasympathetic activity, while the LF band corresponds to mixed sympathetic and parasympathetic activity. It was suggested to introduce a sympathetic index as the ratio of LF band/HF band to assess the sympathetic activity.

In figure 5, our results are seen to support this suggestion: the sympathetic index is consistent with sympathetic nervous system activation during REM sleep and wake. NREM sleep on the other hand is characterized by relatively low

sympathetic activity and a corresponding decrease in the LF and increase in the HF band. Possibly the initial increase in sympathetic activation is responsible for PDFA events detecting even very short periods of wakefulness so efficiently. It has to be mentioned, however, that the correspondence between the level of the spectral sympathetic indices and the sleep stages is not always as convincing as in the example shown in figure 5. It seems that this correspondence is more pronounced in some subjects than in others, which will also have to be looked into more thoroughly. To date, these issues remain a hypothesis that has to be tested further. Recently developed new methods for the non-invasive assessment of sympathetic activity such as the pulse transit time (PPT) and the peripheral arterial tonometry (PAT) [20] would be very appropriate means to investigate this issue.

Conclusions

Answering the question raised in the title, one can summarize as follows. Firstly, non-gradual 'ascending' transitions from deep sleep to lighter sleep stages and transitions into wakefulness correlate very well with our numerical indicators and can be located as pronounced steps in the PDFA curves (cf. examples in fig. 2). Secondly, differentiation between REM sleep (and wake) and NREM sleep is possible: Scanning the window size across the correlation time of NREM leads to a 'dispersion' of short and large window sizes in the numerically differentiated curves, which is seen only in NREM sleep. Scanning the scaling parameter of a wavelet analysis 'mirrors' this behaviour exactly, in spite of the fact that this is a completely independent mathematical method. This represents evidence that there is some underlying physiological pattern both methods are sensitive to: autonomic changes such as spells of sympathetic rise parallel PDFA events at transitions from deeper to lighter sleep. With spectral analyses of the heart rate, we established that the onset of periods with increased occurrence of autonomic arousals, as indicated by sympathetic tonus elevation and unaffected EEG, are indicated by PDFA.

Our on-line analysis of sleep ECG might provide an easy-to-administer method – complementing other non-invasive methods such as PTT and PAT [20] – to shed light on sleep distortion caused by an altered arousal threshold [24]. Patients' frequent complaint of non-restorative sleep and daytime fatigue gives speech to a lack of sleep continuity [23]. Sleep fragmentation seems to be the underlying distortion [6, 15, 16]. Sleep fragmentation may be assessed by autonomic arousal detection [16]; moreover, EEG arousal seems to be associated with autonomic arousal together as a functional pair [14, 25]. Therefore, we plan to extend our research to sleep data of artificially altered arousal thresholds and sleep pressure and to ECG recordings of polysomnographies from patients with sleep-related diseases (e.g. depressive disorders, anxiety and panic disorder) that are known to have a low arousal threshold, poor subjective sleep quality and daytime sleepiness on top of relatively normal sleep scores according to *R & K*. A systematic evaluation of sensitivity and specificity of PDFA and other numerical methods (e.g. wavelet analysis methods) to EEG arousal and autonomic arousal on a larger and more variate pool of data sets is going to be performed. We also plan to implement additional assessment techniques for the autonomous nervous system during sleep in order to validate the ECG-based assessment as a reliable tool for tracing autonomic changes.

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Appendix: Mathematical definitions

Let us assume that we wish to analyse the time series $\{\tau_k\}$ of total length N, in our case the data set containing the lengths of all N RR intervals as numbers in chronological order. First the time series, from which the mean value $\langle\tau\rangle = \frac{1}{N}\sum_{k=1}^{N}\tau_k$ has been subtracted, is integrated according to $y(l) = \sum_{k=1}^{l}(\tau_k - \langle\tau\rangle)$. In a 'random walk' with steps $\{\tau_k\}$, for example, $y(l)$ would correspond to the difference between the position actually reached after l steps and the position reached after taking the average step $\langle\tau\rangle$ l times. Next, this integrated (or cumulative) time series is divided into non-overlapping segments of equal length n, the 'window size'. Similar to the detrended fluctuation analysis (DFA) [10], in order to eliminate local trends to qth order, in each segment a polynomial of order q is fitted to the cumulative series and the deviations from the polynomial are calculated. In this work we restrict ourselves to the elimination of *linear* trends, i.e. $q = 1$, thus in each segment a least-squares straight line is fitted to the cumulative data, representing the 'local linear trend' $y_{trend}(l)$ in that segment.

However, in contrast to DFA, not the *total* time series is divided into segments of length n and analysed in one step, but partial sums covering an increasing part of the total time series are created and analysed separately. Each partial sum is divided into non-overlapping segments of length n starting from the beginning, and the local trends are eliminated in each segment. Note that in contrast to DFA, where the window size n is varied, here the segments are all of *constant* length n (except for the last one containing the remaining points). For partial sums of length p increasing through the data set ($p = 1,\ldots,N$), the 'PDFA curves' shown in figure 2 (in arbitrary units) are defined as $P_{[n]}(p) = \sqrt{\sum_{l=1}^{p}[y(l) - y_{trend}(l,n)]^2}$. 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 scaling independent measure [26]. The procedure can be repeated for a different scaling parameter, i.e. a different window size n. In fact, in figures 2–4 many curves belonging to window size parameters in a wide range (from about 4 to 80 data points or heart beats) are shown simultaneously.