Andy Schumann*, Juliane Ebel and Karl-Jürgen Bär

Forecasting transient sleep episodes by pupil size variability

Abstract: The ability to predict when a person is about to fall asleep is an important challenge in recent biomedical research and has various possible applications. Sleepiness and fatigue are known to increase pupillary fluctuations and the occurrence of eye blinks. In this study, we evaluated the use of the pupil diameter to forecast sleep episodes of short duration (>1s). We conducted multi-channel physiological and pupillometric recordings (diameter, gaze position) in 91 healthy volunteers at rest in supine position. Although they were instructed to keep their eyes open, short sleep episodes were detected in 20 participants (16 males, age: 26.2±5.6 years), 53 events in total. Before each sleep event, pupil size was extracted in a window of 30s (without additional sleep event). Mean pupil diameter and its standard deviation, Shannon entropy and wavelet entropy in the first half (15s) were compared to the second half of the window (15s). Linear and nonlinear measures demonstrated an elevation of pupil size variability before sleep onset. Most obviously, WE and SD increased significantly from 0.054±0.056 and 0.38±0.16 mm to 0.113±0.103 ($T(102)=2.44$, $p<0.001$) and 0.46±0.18 mm ($T(104)=3.67$, $p<0.05$) in the second half of each analysis window. We were able to identify 83% of the pre-sleep segments by linear discriminant analysis. Although our data was acquired in an experimental condition, it suggests that pupillary unrest might be a suitable predictor of events related to transient sleep or inattentiveness. In the future, we are going to involve the other recorded physiological signals into the analysis.

Keywords: Microsleep, entropy, pupillary unrest

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1 Introduction

For human beings, sleep is essential to recover. In periods of sleep deprivation or prolonged attentional effort, transient unintentional sleep episodes (micro-sleeps) become likely to occur [1]. Even short intrusions of sustained wakefulness might have fatal consequences, e.g. while car-driving. Therefore, a solid forecast of events related to microsleeps or inattentiveness is in focus of recent biomedical research.

The pupillary system is known to react to sleepiness. Spontaneous pupillary fluctuations and their relation to fatigue were first observed by Lowenstein et al. [2]. The increase of slow pupil diameter oscillations with high amplitude were called ‘fatigue waves’. According to their findings an elevated state of arousal and attention is expressed by a fixed constant pupil diameter while an instable variable diameter indicates fatigue and sleepiness. The characteristic pattern of pupil size fluctuations can be quantified by the pupillary unrest index (PUI) which estimates the deviation of pupil diameter at low frequencies. The pupillary sleepiness test (PST) has been used as objective tool to assess if a person is ‘fit for duty’ [3]. The occurrence of eye blinks and the dynamic of eyelid closure are also reliable signs of sleepiness and fatigue [4]. Incorporating both phenomena in one measure of pupillary unrest promises to enhance micro-sleep detection.

The objective of this study was to evaluate, whether pupil size variability can be used for prediction of transient sleep events. We expected an increase of low frequency pupillary fluctuations and the occurrence of sudden drops of pupil diameter values due to blinks before sleep events. Thus, the variability of PD is assumed to be affected in a nonlinear fashion and on multiple time scales. We used different indices to capture these changes. Besides, the standard deviation of pupil size, we assessed nonlinear (Shannon entropy) and nonlinear time-frequency variability (wavelet entropy) of pupil diameter.

2 Methods

2.1 Data acquisition and participants

Multi-channel resting state recordings in supine position were conducted using the MP150 polygraph (BIOPAC Systems Inc., Goleta, CA, USA) in 91 healthy controls. Participants had no present or past history of psychiatric, neurological or other clinically significant disorders. All subjects gave their informed written consent in accordance with the protocol approved by the local Ethics Committee.

During the 20 minutes of measurement the room was absolutely quiet and fully shaded. To guarantee constant illumination level a beamer was used as an indirect light source. An ellipse filling the whole 22 inch monitor was presented to enable focus movements within the acquisition window of the pupillometric system. In spite the instruction to keep their eyes open and to stay awake, we detected transient episode of sleep in 20 of the subjects (16 males, age: 26.2±5.6 years).

Electrocardiogram, non-invasive blood pressure, respiration and skin conductance were recorded at 1000Hz. Pupil diameter (PD) was assessed every 4 ms by the infrared camera system RED 250 (SensoMotoric Instruments Inc., Boston, MA, USA).

2.2 Extraction of micro-sleep events (MSE)

Closed eyes lead to a loss of the pupillometric signal. Interruptions of the pupil size data can easily be detected. Typically, eye blinks take about half a second and are prolonged in drowsy subjects [4]. A minimum duration of one second was used to separate MSE from long blinks. Pupil diameter signal of the left eye prior to MSEs was investigated in intervals that were free of additional MSE events.

2.3 Estimation of pupil size variability

Pupil diameter signal (PD) was resampled to 25Hz and underwent no further pre-processing. In time windows of 30 s (750 samples) before MSE onset, variability of pupil diameter was estimated using three different measures: standard deviation, Shannon entropy, and wavelet entropy. We compared the first (*preMSE_1*) and second half (*preMSE_2*) of the analysis window with both lasting 15s.

2.3.1 Standard deviation

A straight-forward and simple way to estimate variability of a time series is the calculation of its standard deviation. The variation of data points around the mean value (μ) can be assessed by

$$\boldsymbol{S_x = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(x_i - \mu)^2}.} \tag{1}$$

2.3.2 Shannon entropy

Entropy is a measure of uncertainty, complexity or unpredictability of a time series. Shannon introduced his concept of entropy H_x quantifying the information contained in a message.

$$\boldsymbol{H_x = -\sum_{i=1}^{N}[p(x_{i,j}) \cdot log(p(x_{i,j}))]} \tag{2}$$

Probabilities $p(x_i)$ were approximated by accumulating data points in 0.1 mm bins.

2.3.3 Wavelet entropy

Iterative wavelet transform was conducted in MATLAB (R2012a, The Mathworks Inc, Natick, MA, USA) using a standard biorthogonal wavelet ('bior2.6') that is dilated and rescaled to approximate the input signal. Entropy was estimated across wavelet components based on their energy distribution [5]. The energy $E_{j,i}$ of wavelet coefficient sets $C_{j,i}$ at each resolution level j ($j \leq N$, $i=2^j$) was averaged over time t to estimate energy distribution across wavelet components.

$$\boldsymbol{E_{i,j} = \frac{1}{T}\sum_{t=1}^{T}|C_{i,j}(t)|^2} \tag{3}$$

Relative wavelet energy $p_{j,i}$ was assessed by level-wise (j) normalization of $E_{j,i}$ to total energy of all coefficient sets (i). These can be interpreted as spectral or time scale densities, on which Shannon entropy was computed by

$$\boldsymbol{WE = -\sum_{i=1}^{N}[p_{i,j} \cdot log(p_{i,j})].} \tag{4}$$

Wavelet entropy was calculated at decomposition level N=8 corresponding to frequency resolution of Δf=0.1Hz.

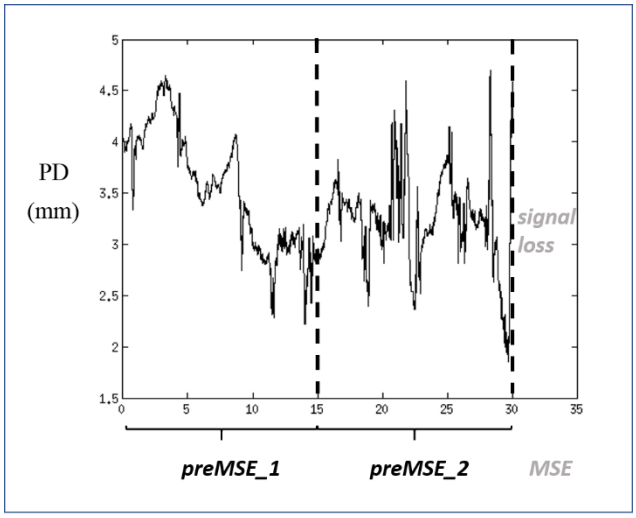

Figure 1 Example pupil diameter time course (PD) before signal loss due to MSE. The 30s preMSE-interval was divided into two analysis windows: *preMSE_1* and *preMSE_2* (dashed lines). Variability of PD was significantly increased in *preMSE_2*.

2.3.4 Statistical analysis

Estimates of pupil size variability were compared across participant by a two-sample t-test. We tested the capability of pupillary fluctuation to identify pre-MSE segments by linear discrimination analysis involving all measures. *preMSE_1* segments served as baseline recording supposing no effect of later MSE on pupillary variation.

3 Results

An exemplary time course of the pupil diameter signal 30s prior to MSE onset is illustrated in **Figure 1**. The preMSE-interval was divided into two analysis windows lasting 15s (*preMSE_1* and *preMSE_2*). It is easy to see that variability in *preMSE_2* is higher when compared to *preMSE_1*. This increase might be due to blinks or pupillary motility in general but can consistently be observed before the onset of MSE.

In **Table 1**, mean values and standard deviations of the three different approaches to estimate pupil size variability are listed. Mean pupil diameter (PD) and Shannon entropy (H_x) was not significantly different in the two analysis windows. Standard deviation of pupil size (S_x) increased from 0.38 ± 0.16 mm to 0.46 ± 0.18 mm in the second half of each analysis window (T(102)=3.67, p<0.05). In preMSE_2, wavelet entropy (*WE*) was significantly elevated to 0.113 ± 0.103 when compared to baseline, 0.054 ± 0.056 (T(102)=2.44, p<0.001). In a linear discriminant analysis involving the three measures of pupil size variability, we were able to identify 83.0% of *preMSE_2* intervals. The remaining 17.0% were missed. 62.3% of *preMSE_1* segments were correctly classified as baseline and 37.7% as pre-sleep.

Table 1: Mean value (PD) and variability of pupil diameter prior to MSEs assessed by standard deviation (S_x), Shannon entropy (H_x) and wavelet entropy (*WE*)

	preMSE_1	preMSE_2	Significance
PD (mm)	3.89 ± 0.58	3.87 ± 0.70	*n.s.*
S_x (mm)	0.381 ± 0.164	0.464 ± 0.184	p<0.05
H_x	1.135 ± 0.475	1.239 ± 0.375	*n.s.*
WE	0.054 ± 0.056	0.113 ± 0.103	p<0.001

Results are given in mean value ± standard deviation. Statistical significance of the two-sample t-test is reported as p-value threshold or marked as not significant instead (n.s.)

4 Discussion

In this study, we demonstrated an increase of pupil size variability in 15s prior to the onset of MSE. Variability was assessed by three different approaches and compared to baseline. Especially nonlinear wavelet entropy of pupil diameter was considerably elevated before MSE.

Spontaneous fluctuations of pupil diameter are most probably generated by an imbalance between the central sympathetic and parasympathetic nervous system [2, 6]. It was proposed that loss of constant sympathetic inhibition of the Edinger-Westphal nucleus determines pupillary fluctuations [6]. These variations are rather slow and might not primarily contribute to the elevation of pupil size variability as it was assessed here. More likely, saccades and incomplete as well as complete (blinks) eye lid closures might increase variation of the recorded pupil diameter prior to MSE. The identification of *preMSE_2* windows by pupil size variability was quite accurate (83%). Especially, the increase of WE in the second window was consistent across participants. But high inter-individual differences impeded a precise classification.

Usually, microsleep episodes are detected by more than one human experts analysing EEGs or video streams of the participant's face [7]. Thus, the retrospective detection of MSE by loss of the pupillary signal might be limitation of

this study with regard to microsleeps. Considering a possible application to warn a driver getting sleepy, we think the reason for his or her closed eyes is secondary. Every lack of visual attention lasting longer than one second might be a risk especially at high driving speed.

In this study, no signal other than pupillometric recordings was used to forecast MSE. However, several physiological signals were acquired during the experiment that might carry additional information about the participants' drowsiness. We focussed on the pupils because pupillometry is contactless and secure to detect the absence of visual attention. But future analyses are going to involve other recorded physiological signals, like skin conductance.

Although our results were obtained in an experimental condition, they indicate that pupillary unrest might be a suitable predictor of transient sleep or inattentiveness.

Author's Statement

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