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INTERRELATION OF CARDIOVASCULAR DYSFUNCTION AND PUPILLARY FLUCTUATIONS IN PATIENTS WITH MAJOR DEPRESSION

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Abstract: *Autonomic dysregulation in patients suffering from major depression is expressed in cardiovascular regulation as well as in the pupillary light reflex. We used spectral analysis and unrest indices to uncover indications of autonomic imbalance in resting pupillographic recordings. Significantly increased unrest and mean pupil diameters were observed in depressed patients. Pupillometric parameters correlated to symptom severity suggesting clinical relevance.*

Keywords: *autonomic regulation, heart rate, pupil diameter, major depression*

Introduction

Besides cardiovascular dysregulation, pupil sizes of patients suffering from major depression (MD) were found to reflect autonomic imbalance [1]. Pupil size is modulated by sympathetic and parasympathetic impacts. The objective of this study was to find indications of autonomic dysfunction in resting pupillographic recordings and their relation to cardiovascular function.

Methods

Cardiovascular and pupillographic recordings of 23 MD-patients and 23 matched controls were conducted using the MP150 polygraph (BIOPAC Systems Inc, Goleta, CA, USA). During the 20 minutes of measurement the room was absolutely quiet and fully shaded. To guarantee constant illumination level we used an indirect light source. An ellipse filling the whole 22 inch monitor was presented to enable focus movements within the acquisition window. Assuming participants to calm down at the beginning of the recording the first five minutes were not analyzed.

ECG and blood pressure were band-pass filtered between 0.05 to 35 Hz and digitized at 1000 Hz. Pupil size was assessed every 4 seconds by the infrared camera system RED 250 (SensoMotoric Inc., Boston, MA). Interruptions of pupillographic acquisition were substituted by interpolating adjacent data points. Eye blinks expressed as sudden drops of pupil diameter were eliminated using wavelet analysis. Affected segments were detected after signal decomposition using Daubechies wavelet of 10^{th} order and replaced by linear interpolation.

To analyse sympathetic and parasympathetic influence on pupil diameter fluctuation we exploited the different reaction times. The rapid signal conduction of parasympathetic pathways was demonstrated in pupil diameter modulation enabling the discriminative interpretation of the pupillary light reflex [2]. Vagal heat rate variability estimation is also based on the slow sympathetic reaction. Regarding the pupillary light response reaction times of pupil size similar to cardiac modulation can be assumed. We defined intervals for low (LF: 0.01-0.25 Hz) and high (HF: 0.25-0.5 Hz) frequency components representing the two autonomic branches. Their ratio was calculated to estimate balance.

Analyzing pupil size fluctuation we eliminated temporal mean. The Welch spectrum was estimated using a Blackman window lasting 128 s with 95 % overlap. Pupillary unrest index (PUI) was calculated based on the algorithm introduced by Lüdtke et al. [3]. Briefly, deviation of mean values of 80 s segments is computed. Additionally RMSSD and baroreflex sensitivity by sequence method were calculated estimating cardiovascular autonomic regulation in time domain.

Statistical analysis was conducted by a MANOVA of pupillary and cardiovascular parameters. If results were not normal distributed natural logarithmic transformation was performed. Spearman correlation was used to estimate linear relation of assessed parameters and to symptom severity assessed by Beck's Depression Inventory (BDI).

Results

Cardiovascular indices confirmed our assumption of autonomic imbalance suggesting diminished vagal activity. RMSSD and baroreflex sensitivity were reduced in MD patients (see Tab. 1).

Patients had larger pupil sizes with higher unrest indices.

Low frequency component and overall Spectral power for $0.01\ \text{Hz} \leq f \leq 0.5\ \text{Hz}$ was increased in patients. In contrast high frequency power and LF/HF ratio were not significantly higher. Mean diameter and unrest index of the left pupil were significantly correlated to symptom severity assessed by BDI. Spectral pupillometric parameters were not correlated with cardiovascular autonomic indices but with global calculation of pupillary unrest.

Table 1: MANOVA of cardiovascular and pupillographic parameters (RMSSD: root mean square of successive heart beat intervals, BRS: baroreflex sensitivity, PUI: pupillary unrest index, DIA: mean pupil diameter, LF/HF: ratio of low and high frequency power of pupil size fluctuations, subscripts r and l stand for right and left pupil, HR: heart rate)

Parameter	Controls	Depressed	Significance
Heart rate [min^{-1}]	65.5	75,8	$p<0.01$
RMSSD [ms]	51.8	37,0	$p<0.05$
BRS [ms/mmHg]	22.0	13.0	$p<0.01$

Parameter	Controls	Depressed	Significance
PUI_l [mm]	0.093	0.140	$p<0.01$
PUI_r [mm]	0.097	0.139	$p<0.05$
DIA_l [mm]	3.82	4.26	$p<0.05$
DIA_r [mm]	3.65	4.20	$p<0.05$
LF [ms²]	38.01	76.33	$p<0.05$
HF [ms²]	12.97	24.67	n.s.
LF/HF [%]	3.92	3.32	n.s.

Discussion

An elevated sympathetic activity of patients with major depression was shown in cardiovascular parameters. In pupillometric data we also found significant differences. An increased mean pupil diameter was already reported in studies analyzing pupillary light reflex and is generally related to sympathetic predominance.

Pupillary unrest is commonly related to sleepiness [3]. Spectral power of pupil size fluctuations was increased in patients and highly correlated to PUI. This indicates an augmented daytime sleepiness in MD patients that is related to their symptom severity. An elevated low frequency power suggests that especially sympathetic influence contributes to increased pupil fluctuations. High frequency power does not reflect parasympathetic attenuation.

Pupillary fluctuations by central autonomic regulation are not as intensively investigated as at the cardiovascular level. Maybe influences like cognitive load or sleepiness complicate estimation of autonomic impact. However pupillographic indices correlating with symptom severity but not with cardiovascular autonomic markers demonstrate that pupillometry can give important information additionally to standard analysis.

Bibliography

[1] K.-J. Bär, W. Greiner, T. Jochum, M. Friedrich, G. Wagner, and H. Sauer, “The influence of major depression and its treatment on heart rate variability and pupillary light reflex parameters.,” *Journal of affective disorders*, vol. 82, no. 2, pp. 245–52, Oct. 2004.

[2] K. Yamaji, Y. Hiratai, and S. Usui, “The pupil as a possible monitor of the autonomic nervous system,” *Proceedings of the 19th International conference, Biology Society, 1997*, vol. 2777, no. C, pp. 2777–2781, 1997.

[3] H. Lüdtke, B. Wilhelm, M. Adler, F. Schaeffel, and H. Wilhelm, “Mathematical procedures in data recording and processing of pupillary fatigue waves.,” *Vision research*, vol. 38, no. 19, pp. 2889–96, Oct. 1998.