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Pupillary unrest correlates with arousal symptoms and motor signs in Parkinson disease

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Abstract

Background—Arousal symptoms (e.g., sleepiness) are common in Parkinson disease and pupillary unrest (spontaneous changes in pupil diameter) is positively associated with sleepiness. We explored pupillary unrest in Parkinson disease.

Methods—Arousal symptoms (Epworth sleepiness scale and sleep/fatigue domain of the non-motor symptoms scale for Parkinson disease (NMS-sleep)) and pupillary unrest were assessed in 31 participants (14 PD, 17 controls). Effect sizes and t-tests compared Parkinson disease with control participants. Correlation coefficients were calculated among arousal symptoms, pupillary unrest and UPDRS-III. Linear regression was performed with arousal symptoms or pupillary unrest as outcome.

Results—Parkinson disease participants reported more arousal symptoms than controls. Pupillary unrest, arousal symptoms and UPDRS-III were positively correlated. The association between NMS-sleep score and pupillary unrest was higher in Parkinson disease versus controls, and higher in those with more Parkinsonian motor signs. UPDRS-III was positively associated with pupillary unrest.

Conclusions—Pupillary unrest correlates with motor and non-motor features associated with Lewy-related pathology, suggesting it may be a non-motor marker of progression in Parkinson disease.

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Introduction

There is a great need for earlier recognition of Parkinson disease (PD) and non-motor markers of disease progression so that agents which alleviate motor symptoms may be evaluated for neuroprotective effect. Non-motor features have a prevalence of 90% in PD¹. They may predate motor signs and include dysautonomia and disorders of arousal such as daytime sleepiness and sleep disorders².

Pupillary unrest refers to the extent of spontaneous changes in pupil diameter in darkness which reflects spontaneous fluctuations in autonomic tone. In middle-aged healthy adults, pupillary unrest is positively associated with sleepiness³. Consequently, the application of pupillary unrest in PD may address the need for non-motor markers of PD progression as it may measure dysautonomia and disorders of arousal. The objectives of this exploratory study were to determine whether pupillary unrest can be measured in PD, characterize differences in pupillary unrest between PD and control groups, and investigate the extent to which pupillary unrest correlates with sleepiness or Parkinsonism in an elderly population.

Participants and Methods

Participants were recruited from the University of Pittsburgh Medical Center. PD participants fulfilled the UK PD Society Brain Bank Clinical Criteria, scoring Hoehn and Yahr Stage (HY) < 5, taking either no anti-parkinsonian medication, carbidopa/levodopa or dopamine agonists. Controls were age and sex matched to PD participants. Exclusion criteria included: pyramidal and/or cerebellar signs, any other organic brain disorder, prior intracranial surgery, uncorrectable eyesight, bilateral cataract surgery, diabetes, uncontrolled hypertension, inability to participate due to motor disability (HY=5), taking medications affecting autonomic measures which could not be safely withheld, history of polyneuropathy or failure to pass a toxicology screen for substances that could influence results (alcohol, opiates, cocaine, cannabis, benzodiazepines and amphetamines).

Design and Measures

Baseline measures included age, sex, HY Stage and the Unified Parkinson Disease Rating Scale Part-III Motor signs (UPDRS-III). Arousal measures were the Epworth Sleepiness Scale and the sleep/fatigue domain of the Non-motor symptoms scale for PD (NMS-sleep). Both scales have established validity and reliability. The Epworth is an index of sleepiness (0–3) in eight situations (range 0–24)⁴. The NMS-Sleep has four items: daytime sleepiness, fatigue, restless legs and insomnia. Severity (0–3) and frequency (1–4) are scored and then multiplied and items are summed (range 0–48)⁵. In both measures, higher scores indicate more symptoms.

Testing sessions began at 0900. Pupillary unrest was assessed as in the Pupillary Sleepiness Test⁶, using infrared video pupillography, which digitized measurement of the horizontal pupil diameter of one eye (ISCAN RK726 sampling at 60 Hz with a resolution of 0.04mm). Participants were seated in front of a computer monitor in darkness (illumination=0.027 foot candles with monitor on) resting comfortably on a head and chin rest. They were instructed to stare at a dim red fixation point (intensity <0.03 candelas/m²) at eye level at a distance of

28.75" subtending a visual angle of 0.25° for 11 min. Due to concerns as to whether PD participants could remain adequately still off anti-parkinsonian medication, the first five PD participants were tested without anti-parkinsonian medications being withheld. Once feasibility was established, anti-parkinsonian medications were withheld for at least 12 hours prior to testing.

Signal Processing and Statistical Analyses

As described by Lüdtke et. al.⁶, pupillary unrest was quantified employing a fast Fourier transform and summing spectral power from 0–0.8 Hz for 82 sec segments of data. Because several participants were unable to stay awake and keep their eyes open for 11 min, pupillary unrest was quantified as the spectral power for the first 164 sec of pupil signal collected.

Two-sided T-tests or Wilcoxon rank-sum tests compared PD vs. controls group, $\alpha=0.1$). Effect sizes (Cohen's *d*) and their 95% confidence intervals were calculated. The Shapiro-Wilk normality test showed pupillary unrest was not normally distributed. This was normalized by logarithmic (base 10) transformation for correlations and regression analyses. Pearson correlation coefficients were used to determine linear associations among arousal measures (Epworth and NMS-Sleep), pupillary unrest and Parkinsonian motor signs (UPDRS-III). A one-sided t-test for the difference between two dependent correlations compared associations of arousal measures (Epworth or NMS-Sleep) with UPDRS-III. Linear regressions were performed to test if associations between arousal (outcome) and pupillary unrest were different for PD and control based on a PD diagnosis (categorical) or UPDRS-III score (continuous) (test for interaction $\alpha=0.1$). A univariate model with log(pupillary unrest) as outcome and UPDRS-III as the predictor was also tested. Given the sample size, regression models were limited to no more than three predictors. A secondary analysis compared those PD participants in which anti-parkinsonian medications were withheld with those in whom they were not. Analyses were performed with Stata® (StatCorp LP, version 10 or R version 2.11⁷).

Results

PD and control participants were of similar age (mean(SD): 64.5(3.2) vs. 59.4(3.3), respectively, Table 1). The PD group had HY=1.7(0.6) and UPDRS-III=10.1(3.7). The PD group scored higher in measures of arousal-related symptoms (Epworth effect size (ES): 0.71, $p=0.05$; NMS Sleep ES: 1.07, $p=0.007$) and pupillary unrest (ES: 0.90, $p=0.07$). There were no significant differences in any outcome measure between the PD participants in which anti-parkinsonian medications were withheld and those in which they were not.

Positive correlations were seen between arousal-related measures and pupillary unrest (Epworth: $r=0.39$, $p=0.03$; NMS Sleep: $r=0.41$, $p=0.02$) as well as arousal-related measures and UPDRS-III (Epworth $r=0.38$, $p=0.04$; NMS Sleep: $r=0.66$, $p=0.001$). Correlation was higher with UPDRS-III for NMS-Sleep than for Epworth scores ($r=0.66$ vs. 0.38 , $p=0.06$). UPDRS-III was positively associated with pupillary unrest ($r=0.32$, $p=0.08$).

Epworth scores were positively associated with PD diagnosis ($R^2=0.13$, $p=0.05$), log(pupillary unrest) ($R^2=0.15$, $p=0.03$) and UPDRS-III ($R^2=0.14$, $p=0.04$) in univariate models but not in a simultaneous regression. Multiple linear regression (Figure 1) demonstrated the association between pupillary unrest and NMS-Sleep score was higher for PD than for controls with a difference in slope between the PD and control group of 1.07 ($p=0.09$). The association between NMS-Sleep score and pupillary unrest was higher with more severe Parkinsonian motor signs (difference in simple slopes of 0.85 ($p=0.10$) for UPDRS-III 1 SD above and below then mean).

Discussion

Pupillary unrest has not been previously evaluated in PD. Compared to controls, we observed more severe arousal symptoms in the PD group which were positively correlated with pupillary unrest. A positive interaction on NMS-sleep scores was seen involving PD diagnosis (PD diagnosis $\times$ log(pupillary unrest)) and severity of Parkinsonian motor signs (UPDRS-III $\times$ log(pupillary unrest)). Parkinsonian motor signs were also positively associated with pupillary unrest.

This study found an association between pupillary unrest and arousal in older adults with PD. The pupil sympathetic pathway integrates input from frontal, limbic hippocampal-amygdaloid and thalamic sources. The pupil parasympathetic pathway integrates information in the Edinger-Westphal nucleus (cranial nerve III) from ascending reticular fibers and descending fibers from cortical regions³. Therefore, pupillary unrest is influenced by neural structures which underlie arousal. Though the possibility of processes peripheral to the Edinger-Westphal contributing to pupillary unrest have not been excluded (glaucoma may be associated with higher parasympathetic tone resulting in less pupillary unrest³), this is unlikely given the exclusion criteria for participants. The correlation of pupillary unrest with Parkinsonian motor signs was higher for NMS-Sleep scores vs. Epworth scores ($r=0.66$ vs. 0.41 , $p=0.06$) possibly because the Epworth scale assesses only daytime sleepiness, while the NMS-sleep scale captures additional symptoms which coexist in PD.

The positive correlation between arousal symptoms or pupillary unrest and Parkinsonism suggests either that one contributes to the other, or that both motor function and arousal are affected by the same underlying process in PD. Although it is possible that Parkinsonism contributes to symptoms such as daytime sleepiness, or that fatigue could lead to bradykinesia, this does not explain why arousal disorders (e.g., REM sleep behavior disorder) predate motor signs². Furthermore, neuropathologic studies in PD have demonstrated Lewy-related pathology in the structures that influence pupillary autonomic pathways detailed above^{8, 9}. Thus, a possible explanation is that higher UPDRS-III scores and pupillary unrest are measures which both reflect impairments due to PD neuropathology. The UPDRS-III reflects motor impairment of the basal ganglia while pupillary unrest may reflect disorders of arousal involving the reticular activating system. Because PD pathology also involves structures which influence pupillary unrest but not arousal, pupillary unrest may not only reflect disorders of arousal as seen in healthy adults, but additional PD pathology as well. This may explain the significant positive interactions observed between PD diagnosis or parkinsonian motor signs and pupillary unrest.

Limitations of this study include its small sample size, limited range of PD severity (HY=1.7 (0.6)), limited range of arousal symptoms and cross-sectional design. Nonetheless, results demonstrate the feasibility of measuring pupillary unrest in PD and suggest that pupillary unrest is a marker of disorders of arousal. As such disorders can occur prior to motor signs¹⁰, pupillary unrest may increase in PD prior to Parkinsonism becoming apparent. In later stage PD, correlation between pupillary unrest and motor signs may be higher as motor signs and arousal symptoms accumulate. Longitudinal investigation of pupillary unrest in a more heterogeneous PD population and those at risk for PD (REM sleep behavior disorder) is needed to assess the potential of pupillary unrest as an objective non-motor marker of PD progression.

Glossary

UPDRS-III Unified Parkinson Disease Rating Scale Part-III Motor signs

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Figure 1. Regression models and interactions on arousal-related measures*
*PU = Pupillary Unrest

Table 1

Participant Characteristics, arousal-related measures, pupillary unrest and correlations

<i>Participant Characteristics</i>	PD	Controls				
	N=14	N=17				
Age	64.5 (3.2)	59.4 (3.3)				
#Women (%)	9 (52.9)	4 (28.8)				
Hoehn and Yahr	1.7 (0.6)	0				
UPDRS-III	10.1 (3.7)	0				

<i>Arousal measures and Pupillary Unrest</i>	PD	Controls	P-value	Effect size	95% CI
Epworth	8.6 (4.4)	5.7 (3.4)	0.05	0.71	0.01–1.41
NMS-Sleep	3.9 (4.3)	0.24 (0.75)	0.007	1.07	0.34–1.80
Pupillary Unrest ($\times 10^{-2}$ sec ² /Hz) *	8.0 (7.6)	2.7 (3.3)	0.07	0.90	0.23–1.57
Log (Pupillary Unrest)	−1.5 (0.8)	−1.9 (0.6)	0.12	0.56	0.16–1.28

<i>Pearson Correlations</i>	r	P-value
Log(Pupillary Unrest) and Epworth	0.39	0.03
Log(Pupillary Unrest) and NMS-Sleep	0.41	0.02
UPDRS-III and Epworth	0.38	0.04
UPDRS-III and NMS-Sleep	0.66	0.001
UPDRS-III and log (Pupillary Unrest)	0.32	0.08

* Spectral Power