Published in final edited form as:

Parkinsonism Relat Disord. 2011 February ; 17(2): 119–122. doi:10.1016/j.parkreldis.2010.11.005.

Autonomic Insufficiency in Pupillary and Cardiovascular Systems in Parkinson's Disease

Samay Jain^{1,3}, Greg J. Siegle¹, Chen Gu¹, Charity G. Moore¹, Larry S. Ivanco¹, J. Richard Jennings¹, Stuart R. Steinhauer^{1,2}, Stephanie Studenski¹, and J. Timothy Greenamyre^{1,3}

¹ University of Pittsburgh School of Medicine

² VA Pittsburgh Healthcare System

³ Pittsburgh Institute for Neurodegenerative Diseases

Abstract

Background—In Parkinson's disease (PD), neurodegenerative changes have been observed in autonomic pathways involving multiple organ systems. We explore pupillary and cardiac autonomic measures as physiological manifestations of PD neurodegeneration.

Methods—Pupil measures (pupillary unrest (spontaneous changes of pupil diameter in darkness), constriction velocity and redilation velocity) were assessed in 35 participants (17 PD, 18 controls). Simultaneous cardiac measures (respiratory sinus arrhythmia during deep breathing, Valsalva ratio, resting heart rate variability (HRV), orthostatic change in blood pressure and orthostatic change in heart rate) were obtained. Nonparametric statistics were used to compare PD with control participants and to calculate correlation coefficients between pupillary and cardiac measures.

Results—Pupillary unrest and orthostatic decreases in systolic blood pressure were greater in PD than controls. Respiratory sinus arrhythmia during deep breathing and resting HRV were lower in PD. Among all participants, there was a negative correlation between HRV and redilation velocity and a positive correlation between orthostatic change in heart rate and pupillary unrest. A modifying effect of PD was found on the association between high frequency HRV and pupillary unrest.

Conclusions—Results demonstrate simultaneous autonomic dysfunction in both pupillary and cardiac systems in PD. The correlations between pupillary and cardiac measures suggest shared central centers of autonomic integration, while the modifying effect of PD may reflect autonomic effects of PD-related pathology not present in controls.

Keywords

non-motor features; Parkinson's disease; pupillography; pupil; cardiac physiology; autonomic dysfunction

Correspondence: Samay Jain, M.D., M.S., Assistant Professor of Neurology, Clinical Director, Movement Disorders Division, Department of Neurology, University of Pittsburgh Medical Center, 3471 Fifth Ave., Suite 811, Kaufmann Medical Building, Pittsburgh, PA 15213-3232, Phone: (412) 692-4916, Fax: (412) 692-4601, jains@upmc.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Introduction

Parkinson's disease (PD) neuropathology suggests neurodegenerative changes involve neurons in autonomic pathways affecting multiple organ systems[1] which may lead to widespread changes in autonomic physiology which if quantified may serve as non-motor markers of PD. Such markers could allow earlier diagnosis and better treatment of PD as non-motor features of PD occur earlier and contribute more to the burden of disease than do motor features[2]. Both the pupillary and cardiovascular systems may provide such physiological markers.

The pupil can provide a unique window into brain function as it integrates inputs from both cortical and subcortical structures which influence its autonomic function - parasympathetic constriction or sympathetic dilation. Pupillary measures include pupillary unrest, constriction velocity and redilation velocity. Pupillary unrest refers to spontaneous fluctuations in autonomic tone which lead to changes in pupil diameter in darkness. It is positively associated with arousal related symptoms such as sleepiness which are common in PD[3]. The cardiovascular system is also of clinical significance, as evidenced by the high prevalence of orthostatic hypotension in PD[2]. Cardiac measures include respiratory sinus arrhythmia with deep breathing, resting heart rate variability, the Valsalva ratio and orthostatic blood pressure and heart rate. Cardiac measures in PD have been reported, but mostly in isolation without taking account of how other autonomic end-organs are functioning. Our objective in this exploratory study is to simultaneously acquire measures in the pupillary and cardiovascular systems, allowing correlations of autonomic function between the two systems. Results of such analyses would reveal information on hierarchically higher centers of autonomic integration in elderly controls and how such systems may be affected in PD[4].

Methods

All participants were recruited from the University of Pittsburgh Medical Center. The IRB gave ethical approval and the participants signed informed consent. 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. As a group, 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, cardiac dysrhythmia, 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).

Baseline measures included age, sex, HY Stage and the Unified Parkinson's Disease Rating Scale (UPDRS). All physiological assessments were conducted in a quiet room free of distracting stimuli. Session were done at the same time every morning (0900), at the same ambient temperature (22-24°C) in the same seated position to minimize effects of circadian variation, temperature and position on autonomic measures. At first, it was not clear medications could be safely or practically withheld so the first five participants were tested on medication. All subsequent participants withheld all dopaminergic medications and agents that would influence autonomic measures (e.g. anti-hypertensives) for at least 12 hours prior to testing. Pupillary and cardiac measures at rest were obtained simultaneously in darkness. Pupillary measures included pupillary unrest, constriction velocity and redilation velocity. Pupillary unrest was assessed as in the Pupillary Sleepiness Test[3], 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. Pupil constriction and redilation velocity were measured by administering the light reflex. After three minutes in darkness, 11 "flashes" (a white circle subtending a visual angle of 4.60°) were presented (1 second duration, every 10 seconds) at eye level at a distance of 73 cm with an intensity of 13 cd/m². The light reflex was performed separately from cardiac measures to avoid any potential cardiac orienting responses. Stimulus presentation was programmed with E-prime routines. ECG (modified lead II placement) was sampled at 1000 Hz utilizing Grass model 7 neurodata amplifiers. Resting ECG was recorded for 11 min during pupillography. The Valsalva ratio was measured with the Valsalva maneuver by asking participants to force expiration against a closed glottis at a pressure of 15 mmHg for 15 sec. Respiratory sinus arrhythmia was measured by asking participants to take six deep breaths at a pace of 0.1 Hz, visually cued by a breathing metronome. Orthostatic blood pressure and heart rate were measured after the participant was in a supine position for five minutes, and then again after the participant had been standing for two minutes.

Signal Processing

All physiological recordings were manually inspected for artifacts and proper signal processing. For pupillography, this consisted of removal of blink artifact and for ECG this consisted of removing motion artifact and confirming R-wave detection. As described by Lüdtker et al [3], 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, the pupillary unrest measure reported is the spectral power for the first 164 sec of pupil signal collected. For light reflex responses, the pupil response was averaged across the last 10 trials. Constriction velocity is the maximum velocity during contraction (mm/s) and redilation velocity is the change in diameter divided by time elapsed from 50% to 75% redilation [5]. For cardiac measures, resting heart rate variability (HRV) was the spectral power of a 5 min ECG recording of two frequency bands (low: 0.04-0.15 Hz and high: 0.15-0.40 Hz) calculated using Fast Fourier Transform on interbeat (RR) intervals of a five minute recording. Valsalva Ratio was calculated by dividing the maximum RR interval by the minimum RR interval during Valsalva and within 30 sec after the maneuver. Respiratory sinus arrhythmia was the average difference between maximum and minimum heart rate during deep breathing. Orthostatic variables were the standing systolic blood pressure or heart rate subtracted from their supine values.

Statistical Analysis

Wilcoxon rank-sum tests (for HRV in low and high frequency bands) or 2-sided T-tests (for all other measures) were used for comparisons between groups. Combining data from both PD and control groups, Spearman correlation coefficients were used to determine associations among pupil and cardiovascular measures. Tests for modifying the effect of PD on the correlations between each paired pupillary and cardiovascular measure were performed. Levodopa equivalent dose was calculated for each participant [6]. 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). Because this exploratory study is intended for planning research and hypotheses generation, an $\alpha=0.10$ was selected *a priori* and effect sizes (Cohen's *d*

((difference between group means divided by the pooled standard deviation)) were also calculated.

Results

Characteristics of PD and control groups are summarized in Table 1. Pupillary unrest was higher in PD and four of the six cardiovascular measures were lower in PD compared to controls. Medications in the first five participants were not withheld and included: no medications in the first participant; selegiline 5 mg/day and levodopa 800 mg/day in the second; amantadine 200 mg/day and ropinirole 12 mg/day in the third; levodopa 600 mg/day in the fourth; and levodopa 300 mg/day in the fifth. There were no significant differences in any outcome measure between the PD participants in which anti-parkinsonian medications were withheld vs. those in which they were not with the exception of redilation velocity (0.37(0.05) vs. 0.25(0.04)mm/s, respectively, (Wilcoxon rank-sum, $p=0.09$)).

Significant correlations were seen between low frequency HRV and redilation velocity ($r_s=-0.35$), high frequency HRV and redilation velocity ($r_s=-0.36$), and orthostatic heart rate and pupillary unrest ($r_s=0.34$). One correlation demonstrated a significant modifying effect by PD: the correlation between high frequency HRV and pupillary unrest was lower in PD than in controls ($r_s=0.19$ vs. 0.51). Because combining data from both groups for correlations may introduce bias, we conducted a supplementary analysis looking at correlations within each group. The three significant correlations were in the same direction within each group and no significant differences were seen between PD and controls.

Discussion

Simultaneous recordings of pupillary and cardiovascular autonomic measures in PD have not been previously reported. We observed lower HRV in both low and high frequency bands, greater decreases in supine to standing (orthostatic) systolic blood pressure and higher pupillary unrest in PD relative to controls. This represents lower sympathetic and parasympathetic cardiac function, as well as higher autonomic variability in pupillary function in PD.

Given the known association of pupillary unrest with sleepiness, the observation of higher pupillary unrest in PD is consistent with the fact that disorders of arousal such as daytime sleepiness and REM sleep behavior disorder are common in PD[2]. To distinguish parasympathetic from sympathetic function in the pupil, we conducted the light reflex. When the pupil is exposed to a brief light stimulus, it constricts and then redilates. The measure of constriction velocity is parasympathetic while the latter portion of redilation (after initial parasympathetic withdrawal) is sympathetic. We did not find lower pupil constriction velocity in PD as reported by others[7]. This could be because our light stimulus was of longer duration or that our PD population limited in severity (mean Hoehn and Yahr stage = 1.7) compared to other studies. We know of no previous reports of redilation velocity in PD, which was not significantly different when compared to controls. Five participants taking anti-parkinsonian medications had lower redilation velocities than PD participants in which such agents were withheld, suggesting possible sympathetic withdrawal secondary to medication. This interpretation is limited, however, as data from these same participants off anti-parkinsonian agents is not available.

Our findings of cardiovascular autonomic dysfunction in PD is consistent with other studies[8,9]. Specifically, lower resting HRV in high frequency bands indicates lower parasympathetic function, while lower resting HRV in low frequency bands typically reflects lower sympathetic and parasympathetic function[10]. The greater reduction in

orthostatic blood pressure along with the lower HRV in high and low frequency bands in PD are consistent with lower sympathetic and parasympathetic cardiac function, respectively.

The simultaneous acquisition of cardiovascular and pupillary measures allowed us to see if autonomic function from the two organ systems correlate with one another, revealing information on centers of autonomic integration in elderly controls and how such systems may be affected in PD. Among all participants, we found that HRV in both high and low frequency bands negatively correlates with pupillary redilation velocity. Furthermore, orthostatic change in heart rate positively correlates with pupillary unrest. This indicates lower parasympathetic cardiac function is negatively associated with measures of sympathetic pupillary function and positively associated with pupillary unrest. This suggests involvement of either central autonomic networks which influence both pupil and cardiac autonomic function, or widespread multi-focal involvement of peripheral autonomic pathways in both organ systems. There is evidence supporting both possibilities. 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 both ascending reticular fibers and descending fibers from cortical regions [5]. Central nuclei which modulate cardiac autonomic function include preganglionic cardiovagal neurons in the parasympathetic nucleus ambiguus and sympathetic neurons in the rostral ventrolateral medulla. The paraventricular nucleus of the hypothalamus, amygdala or anterior cingulate cortex are structures that influence general autonomic tone for different organ systems and are candidate structures for affecting both pupil and cardiac measures[4]. In PD, Lewy pathology has been found in virtually all of the aforementioned structures [11,12]. Peripheral, post-ganglionic sympathetic cardiac denervation has also been established in PD [1]. Thus, both central autonomic networks and peripheral autonomic pathways are affected in PD. A modifying effect of PD on the correlation between high frequency HRV and pupillary unrest was observed which may reflect autonomic effects of PD-related pathology not present in controls.

Due to the small number of participants, we were unable to determine if Parkinsonian motor signs (UPDRS-III) correlated with autonomic measures, though another study found HRV to be negatively correlated with severity of Parkinsonism [9]. Participants were also limited in their range of PD severity. It is possible that with more participants or more advanced stage PD, we would detect more differences in autonomic function between PD and controls, more associations among cardiac and pupillary autonomic measures, or more modifying effects of PD. Although medications were withheld for at least 12 hours, residual effects of longer acting dopamine agonists may have still been present. Despite these limitations, this exploratory study establishes the feasibility of novel autonomic measures acquired simultaneously in multiple organ systems and illustrates how such studies can provide insight to our understanding of pathophysiology in PD. Understanding mechanisms of autonomic dysfunction will aid in the development of treatments for dysautonomia in PD. Additional studies are underway to relate autonomic changes with motor signs in PD in an effort to determine if autonomic physiology can be utilized as a non-motor marker of progression in PD.

Acknowledgments

Disclosures: Funded by NIH grants KL2 RR024154, KMH082998, MH55762, UL1 RR024153, P30 AG-024827, Department of Veterans Affairs, and the American Parkinson's Disease Association Center for Advanced Research at the University of Pittsburgh.

References

1. Beach TG, Adler CH, Sue LI, Vedders L, Lue L, White Iii CL, et al. Multi-organ distribution of phosphorylated alpha-synuclein histopathology in subjects with Lewy body disorders. *Acta Neuropathologica* Jun;119(6):689–702. [PubMed: 20306269]
2. Chaudhuri KR, Healy DG, Schapira AH. Non-motor symptoms of Parkinson's disease: diagnosis and management. *Lancet Neurology* 2006 Mar;5(3):235–45. [PubMed: 16488379]
3. Ludtke H, Wilhelm B, Adler M, Schaeffel F, Wilhelm H. Mathematical procedures in data recording and processing of pupillary fatigue waves. *Vision Research* 1998;38(1998):2889–96. [PubMed: 9797985]
4. Bar KJ, Schulz S, Koschke M, Harzendorf C, Gayde S, Berg W, et al. Correlations between the autonomic modulation of heart rate, blood pressure and the pupillary light reflex in healthy subjects. *Journal of the Neurological Sciences* 2009 Apr 15;279(1-2):9–13. [PubMed: 19195664]
5. Loewenfeld, IE. *The Pupil: Anatomy, Physiology, and Clinical Applications*. 1. Detroit: Wayne State University Press; 1993.
6. Smith, C. Levodopa Dose Equivalency: A Systematic Review. Annual PD MED Collaborator's Meeting; 2010 June 8th; Birmingham. 2010.
7. Stergiou V, Fotiou D, Tsiptsios D, Haidich B, Nakou M, Giantselidis C, et al. Pupillometric findings in patients with Parkinson's disease and cognitive disorder. *Int J Psychophysiol* 2009 May;72(2):97–101. [PubMed: 19047001]
8. Kallio M, Haapaniemi T, Turkka J, Suominen K, Tolonen U, Sotaniemi K, et al. Heart rate variability in patients with untreated Parkinson's disease. *Eur J Neurol* 2000 Nov;7(6):667–72. [PubMed: 11136353]
9. Haapaniemi TH, Pursiainen V, Korpelainen JT, Huikuri HV, Sotaniemi KA, Myllylä VV. Ambulatory ECG and analysis of heart rate variability in Parkinson's disease. *Journal of Neurology, Neurosurgery, and Psychiatry* 2001 Mar;70(3):305–10.
10. Berntson GG, Bigger JT Jr, Eckberg DL, Grossman P, Kaufmann PG, Malik M, et al. Heart rate variability: origins, methods, and interpretive caveats. *Psychophysiology* 1997 Nov;34(6):623–48. [PubMed: 9401419]
11. Hunter S. The rostral mesencephalon in Parkinson's disease and Alzheimer's disease. *Acta Neuropathologica* 1985;68(1):53–8. [PubMed: 2996284]
12. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K. Stages in the development of Parkinson's disease-related pathology. *Cell and Tissue Research* 2004 Oct;318(1):121–34. [PubMed: 15338272]

Table 1

Participant characteristics and autonomic measures

<i>Participant Characteristics</i>		PD N=17	Control N=18	p-value	
Age		64.9 (11.7)	60.3 (13.5)	0.35	
#Women (%)		4 (24%)	9 (50%)	0.16	
Hoehn and Yahr		1.7 (0.6)	0		
UPDRS Part III (motor signs)		11.1 (4.5)	0		
UPDRS total score		20.5 (9.6)	0		
Mean levodopa equivalent dose(mg)**		516 (376)			
Number of participants taking dopamine agonists (%)		5 (29.4%)			
<i>Autonomic Measures</i>					
Organ System	Measure	PD	Control	Effect size	Autonomic domain assessed
Pupillary system	Pupillary Unrest ($\times 10^{-2}$ sec ² /Hz)*	7.7 (7.6)	2.7 (1.4)	0.90	Autonomic variability
	Constriction velocity (mm/s)	4.61 (1.33)	4.58 (1.17)	0.03	Parasympathetic
	Redilation velocity (mm/s)	0.33 (0.15)	0.26 (0.14)	0.64	Sympathetic
CV system	Low frequency HRV ($\times 10^{-1}$ sec ² /Hz)*	6.7 (4.6)	10.37 (8.4)	0.91	Sympathetic & Parasympathetic
	High frequency HRV ($\times 10^{-1}$ sec ² /Hz)*	2.7 (1.8)	7.4 (5.2)	1.00	Parasympathetic
	Respiratory Sinus Arrhythmia (bpm)*	8.25 (4.22)	13.13 (6.88)	0.80	Parasympathetic
	Orthostatic systolic blood pressure (mmHg)*	-15.53 (11.04)	-2.83 (11.75)	0.98	Sympathetic
	Orthostatic heart rate (bpm)	-8.73 (3.17)	-10.39 (12.09)	0.18	Parasympathetic
	Valsalva Ratio	1.49 (0.24)	1.63 (0.23)	0.60	Parasympathetic

* p <0.05, HRV=heart rate variability, for those on dopamine,

** levodopa equivalent dose conversion factors [6]: 0.75 for controlled release L-dopa; 20 for ropinirole; 100 for pramipexole; 1 for amantadine or rimantadine; 10 for selegiline; 0.33 for entacapone;