In Press, *International Journal of Psychophysiology*

Sympathetic and Parasympathetic Innervation of Pupillary Dilation During Sustained Processing

Stuart R. Steinhauer[ab,*], Greg J. Siegle[ab], Ruth Condray[ab], Misha Pless[c]

[a]Biometrics Research Program, 151R, VA Pittsburgh Healthcare System,
7180 Highland Drive, Pittsburgh, PA 15206, USA
and
Departments of Psychiatry[b] and Ophthalmology[c]
University of Pittsburgh School of Medicine, Pittsburgh, PA USA

*Corresponding Author:
Stuart R. Steinhauer, Ph.D.
Biometrics Research, 151R
VA Pittsburgh Healthcare System
7180 Highland Drive
Pittsburgh, PA 15206 USA
Tel: (412) 365-5251
Fax: (412) 365-5259
Email: sthauer@pitt.edu
www.wpic.pitt.edu/research/biometrics/

Abstract

The contributions of separate sympathetic and parasympathetic pathways to pupillary dilation during a sustained processing task were studied through environmental and pharmacological manipulations. In Experiment 1, 22 healthy volunteers (11 female) performed a serial Subtract 7 task while pupil diameter was recorded both during moderate room light and in darkness. In a control for verbalization, subjects performed an easier Add 1 task. In all conditions, pupil diameter increased significantly during the response period as compared to a pre-verbalization baseline period. Pupillary dilation was increased for the difficult task, and further increase in dilation was associated with recording in light. This suggests a major differential contribution to task difficulty mediated through inhibition of the parasympathetic pathway. In Experiment 2, a subgroup of 12 volunteers (7 female) repeated all conditions at three additional sessions in which one eye was instilled with tropicamide (to block the parasympathetic sphincter muscle), dapiprazole (to block the sympathetic dilator muscle) or placebo. All pharmacological conditions resulted in overall dilation during task performance. Differential performance similar to the placebo condition was seen only in the dapiprazole condition, when parasympathetic activation was intact. The findings suggest that sustained performance during a difficult task is modulated by cortical inhibition of the parasympathetic pathway at the oculomotor nucleus. Moreover, modulation of both ambient light intensity and pharmacological blockade of the final pupillary musculature were observed to provide converging approaches for quantifying the activity of identifiable central autonomic pathways.

Keywords: Pupillary dilation; sustained processing; sympathetic and parasympathetic pathways; pharmacology

1. Introduction

Many cognitive processes result in dilation of the pupil (Beatty, 1982b; Janisse, 1977; Loewenfeld, 1993). Experimental studies relating cognitive activity to pupillary changes have often used discrete stimuli, resulting in characteristic waveforms associated with reception and processing activities (e.g., Friedman et al., 1973, Steinhauer and Zubin, 1982). When task demand is increased over time (e.g., with increasing numbers of stored items in the digit span task) the pupil is observed to increase following presentation of each stimulus (Kahneman and Beatty, 1966; Peavler, 1974; Granholm et al., 1996). In such situations, the pupil decreases in diameter as stored information is then reported by the subject (Beatty and Kahneman, 1966). When overall diameter throughout the course of a task is examined, pupil diameter is larger as overall task demand is increased (see, for example, Karatekin, in press).

If processing demands are continuous, then pupil dilation is maintained (Beatty, 1982a). Such dilation is likely to be associated with brain regions having the ability to sustain attention and ongoing processing of information. Frontal cortical regions have been implicated as subserving such functions as indicated indirectly by neuropsychological deficits in patients with frontal damage (Sarter et al., 2001), and more directly by concurrent pupillometry and functional neuroimaging studies (Siegle et al., 2003). Yet, the extent to which cognitive activity is uniquely associated with sympathetic or parasympathetic activity is unclear. This is of importance because current knowledge regarding the neurophysiological systems that contribute to cognitive activities can be evaluated by monitoring pupillary dynamics; differential activation of these pathways can provide quantitative measurements of activation underlying central nervous system mechanisms.

Methodological Approaches for Dissociating Autonomic Pathways in the Pupil: Though a variety of invasive approaches can be used to explore relative parasympathetic and sympathetic contributions to pupillary motility in animal models, the possibility of utilizing similar approaches to study higher cognitive function in humans is necessarily limited. The specific problem is in determining the extent of contributions by the sympathetic and parasympathetic divisions of the autonomic nervous system to pupillary dilation. The sympathetic branch, mediated by posterior hypothalamic nuclei, produces enlargement of the pupil by direct stimulation of the dilator muscles. The contribution of the parasympathetic pathway is mediated by central inhibition of the Edinger-Westphal complex of the oculomotor nucleus (n. III) in the midbrain, which is the motor center for parasympathetic pathway. Inhibition of this complex results in relaxation of the sphincter muscles and thus, dilation. Two paradigms for exploring these relative autonomic contributions have been suggested (Steinhauer and Hakerem, 1992).

Differential Effects of Recording in Dark and Light Adapted Conditions: One method for manipulating the parasympathetic pathway is to modulate ambient light intensity. In darkness, active parasympathetic tone is minimal. Neural and muscular systems typically exhibit a resting level of activity even in the absence of specific stimulation. A tonic level of activity is present in the pupillary sphincter, so that even in the dark adapted pupil, there is still minimal constriction of the pupillary sphincter (Loewenfeld, 1993). Consequently, active inhibition of the parasympathetic center will have the least residual effect of dilation due to relaxation of the sphincter muscles for recordings obtained in darkness. In contrast, stimulation of the dilator should be present. Dilation occurring in response to cognitive activation during dark adapted conditions is well documented (Friedman et al., 1973; Steinhauer and Hakerem, 1992;

Steinhauer and Zubin, 1982). Such findings indicate a significant sympathetic contribution to dilation in response to specific cognitive events.

As ambient light intensity is increased, the sphincter muscle is stimulated, resulting in a smaller overall diameter. When central activity now reaches the same Edinger-Westphal sites, the effect is to result in relaxation of the sphincter muscle as an additional component of dilation. The extent of this dilation should be related to the initial stimulation of the pupil, i.e., brighter light and a smaller diameter should provide greater dilation amplitude mediated by the parasympathetic pathway, thus allowing differential measurement of sympathetic and parasympathetic contributions. This method is employed in Experiment 1.

Pharmacological Dissociation of Sympathetic and Parasympathetic Innervation: The second method for dissociating the pathways involves direct pharmacological blockade of the musculature. It is possible to use topical administration of standardly employed ophthalmological agents to produce transient blockade of the iris neuromusculature. Blocking the sympathetically-mediated alpha-adrenergic receptor of the dilator allows parasympathetic contributions to be measured uniquely. In contrast, blocking of the muscarinic receptor of the sphincter muscles limits pupillary activity to the sympathetically mediated dilator muscles. What is critical to this approach is that neither blockade results in any changes to central neural activation related to cognitive tasks that may be conducted. This method is employed in Experiment 2.

There are numerous neuropsychological tests that involve continuing mental load, including continuous performance tests of vigilance as well as mathematical processing paradigms. Among these, we selected the serial seven subtraction task. This task is widely used to impose a difficult cognitive load, both in mental status examinations and in the psychology

and psychophysiology laboratories. The task remains demanding even over repeated test sessions, making it useful for repeated measures designs as employed in the current study.

2. Experiment 1: Materials and Methods

2. Subjects

The subject group for Experiment 1 consisted of 22 healthy volunteers (11 female), with a mean age of 30.6 years (s.d. = 7.9), education 15.2 years (s.d. = 2.1), 21 Caucasian, 1 African-American, with three left-handed. All subjects signed informed consent approved by the VA Pittsburgh Healthcare System and University of Pittsburgh IRBs. Subjects were screened to exclude history of DSM-IV AXIS I psychiatric disorder or other major medical disorder (e.g., head trauma, diabetes, heart disease). No ophthalmologic problems (other than correctable vision) were reported by any of the subjects.

2.2. Methods

Subjects were seated in a darkened chamber. Three red LEDs masked by pinholes at optical infinity formed a small triangle for fixation. Background luminance in darkness was not detected above 0.03 cd/m^2. Background room illumination in light was measured at 0.59 cd/m^2. Head position was maintained by a head and chin rest.

Each subject was tested under a number of different experimental conditions, including those reported here, either first in light or first in darkness, randomized across subjects.

There were two experimental conditions compared in the current study: Sustained performance on the difficult serial subtraction task (Subtract 7), and an easy control task designed to elicit verbalizations (Add 1), also presented randomly under each lighting condition.

For each task, subjects were first given a randomly generated seed number between 100 and 900. They were then told that they either should sequentially subtract 7 and continue until told to stop, or that they should slowly add 1 and continue until told to stop. The Add 1

condition was expected to provide a control for the verbalization aspect of the task, although typically subjects reported more often in the Add 1 than in the Subtract 7 condition.

Because of variability in pupil diameter measured in the light when there is no task demand, it was difficult to obtain an accurate "no task" baseline for these experiments. Consequently, subjects were requested not to begin responding until they heard a single auditory tone (100 ms, 800 Hz , 70 dB). Pupillary recording was initiated 5 s before the cue, to provide a non-response baseline, and continued for 60 s after the cue, for a total duration of 65.1 s. Data for the four conditions were obtained: Add 1 – Light, Add 1 – Dark, Subtract 7 – Light, Subtract 7 – Dark.

2.3. Pupillary Measurement

An ISCAN, Inc., Model RK-406 Pupillometer was used to record pupil diameter. Resolution of individual measurements was better than .05 mm. An infra-red light source permitted measurement of the pupil in either light or complete darkness. The analog output was digitized at 62.5 Hz (16 ms intersampling time) and stored. A remote control system was used to keep the eye within recording limits during any small head movements produced by verbalizations.

2.4. Data Analysis

Off-line, individual trial data were filtered using a 9.2 Hz two-pass digital filter and scaled to mm. Each 65.1 s recording was displayed on a video monitor, evaluated for blinks, and edited if necessary. The automatic editing algorithm attempted to define beginning and end points for blinks, which could be modified by the experimenter. A linear interpolation was then applied.

Baseline diameter was defined as the average diameter during the five s interval preceding the auditory cue to respond. Response diameter was defined as the average diameter over the entire 60 s response period.

In Experiment 1, data were analyzed as a repeated measures design for the factors of task condition (Add 1 vs. Subtract 7) x light condition (dark vs. light). Baseline was first examined separately, followed by changes across the baseline and response periods.

3. Experiment 1: Results

Baseline Pupil Diameter: Pupil diameter measured during the five s period before the subject began to respond was significantly smaller during recording in light than during recording in darkness (as expected, due to the normal effect of light; Figure 1) ($F_{1,21} = 30.6$, $p < 0.001$, $\eta^2 = 0.593$). In addition, there was a significant main effect for Task, with larger diameters during the Subtract 7 task than during the Add 1 task ($F_{1,21} = 4.6$, $p = 0.043$, $\eta^2 = 0.181$).

Insert Figure 1 about here

Pupil Diameter During Response Period Compared to Baseline: Given the effects seen for baseline, a three way ANOVA was then conducted examining interval (Baseline vs. Response), Task, and Light condition. There was a significant main effect for dilation during the response period above baseline ($F_{1,21} = 388.4$, $p < 0.001$, $\eta^2 = 0.949$). All conditions resulted in dilations above baseline diameter, ranging from .53 to .62 mm (Figure 2). In addition, the main effects observed for the individual baseline periods were still present across both periods (Light: $F_{1,21} = 35.1$, $p < 0.001$, $\eta^2 = 0.626$; Task: $F_{1,21} = 8.7$, $p = 0.008$, $\eta^2 = 0.292$).

There was also a significant interaction of Task x Light ($F_{1,21} = 5.5$, $p = 0.029$, $\eta^2 = 0.208$). Simple effects analysis indicated no significant differential effects between tasks in darkness, but a significantly greater pupil diameter in light for the Subtract 7 than Add 1 condition ($F_{1,21} = 7.8$, $p = 0.011$, $\eta^2 = 0.271$).

Insert Figure 2 about here

---

4. Discussion, Experiment 1

Pupil diameter was increased when a demanding task was imposed (Subtract 7) as compared to a simple addition and verbalization requirement (Add 1). The increase in diameter was observed in both the baseline and response periods. This suggests that as soon as the nature of the task was told to the subject, differential preparation and processing were already occurring, and were responsible for the primary effects associated with task difficulty. The modulation of light intensity resulted in increased diameter over baseline levels during performance of both tasks.

In both light and darkness, pupil diameter was increased with the onset of the task. It suggests that at least part of the change in diameter is associated with the sympathetic pathway. The increased extent of dilation for recordings in light also suggests a specific contribution to dilation resulting from central inhibition of the parasympathetic pathway. Moreover, the further increase of diameter in the light, observed only for the Subtract 7 condition, suggests the presence of an additional component of parasympathetic inhibition that is present only in the cognitively demanding situation. The specificity of these likely contributions was explored by repeating the experiment during selective isolation of the final autonomic pathways in Experiment 2.

5. Method, Experiment 2

Subjects for Experiment 2 were 12 of the subjects (7 female) who participated in Experiment 1, with mean age = 28 years, (s.d. = 5.7), education 15.7 years (s.d. = 1.6), all Caucasian, one left-handed. Before further participation, an ophthalmologic screening was conducted to exclude the presence of the condition called narrow angle, since use of mydriatics such as tropicamide can lead to increased intraocular pressure in the presence of narrow angle, resulting in acute narrow angle glaucoma. No subject was excluded on this basis.

Each subject participated in three additional sessions involving administration of drops in the left eye by nursing or medical staff. Otherwise, the laboratory session was identical to

Experiment 1: subjects were tested in both light and darkness, on both the Add 1 and the Subtract 7 tasks at each session.

At one session, ophthalmologic saline (Muro 128® 2%) was employed as a placebo condition. At a second session, 1.0% tropicamide (Mydriacil®) was used to provide temporary blockade of the sphincter muscle. At a third session, 0.5% dapiprazole HCl (Rev-Eyes®) was used to provide temporary blockade of the dilator muscle. The order of instillation by session was randomized across subjects. The concentrations of mydriacil and dapiprazole are those normally employed in the ophthalmology clinic. Each agent produces temporary blockade for up to several hours. At least 2 days intervened between drug testing sessions.

At each session, resting diameter was first measured in darkness and light. Next, a single drop of saline, tropicamide, or dapiprazole was placed onto the lower limbus of the left eye by nursing or medical staff. The subject was instructed to move his/her eye around to facilitate absorption. To verify stabilization of resting diameter in the treated eye, pupil diameters of both eyes were monitored at 5-10 minute intervals in light and darkness for approximately 25 minutes, at which time recording was initiated. Based on pilot testing, 23-25 minutes after administration was found to be optimal for maximal blockade of the sphincter and dilator. No attempt was made to provide absolute blockade through use of additional drops. Other than the expected effects of a possible brief sting when the drop was first placed in the eye and reddening of the sclera after dapiprazole, no additional side effects were reported by any of the subjects.

Data were initially analyzed as a repeated measures design for the factors of drug (3 levels: placebo, dapiprazole, or tropicamide) x measurement period (baseline vs. response) x task condition (Add 1 vs. Subtract 7) x light condition (dark vs. light). Greenhouse-Geisser corrected probability levels are reported for ANOVAs where appropriate when comparing across the three drug conditions, as indicated by fractional degrees of freedom.

6. Results, Experiment 2

Effects of drug administration are depicted for each experimental condition for both baseline and response period diameters (Figure 3) and extent of pupillary dilation (response minus baseline, see Figure 4). As previously noted, use of tropicamide to block the post-synaptic receptor site of the sphincter muscle (Loewenfeld, 1993) results in activity that is attributable to the sympathetically-mediated dilator muscle. Conversely, use of dapiprazole to block the alpha-adrenergic receptor site of the dilator muscle (Larson et al., 1996) results in activity that is attributable to the parasympathetically-mediated sphincter muscle.

Baseline Diameter vs. Response Period: As anticipated on the basis of pharmacological properties, a strong effect was observed related to differences in overall diameter related to drug effects (see Figure 3), with smallest diameters after dapiprazole when the dilator muscle was blocked (circles), larger diameters in the placebo condition (squares), and largest diameters after tropicamide when the sphincter muscle was blocked (triangles) ($F_{1.3,13.9} = 35.9$, $p < 0.001$, $\eta^2 = 0.766$). Simple effects analyses indicated that overall diameters among all three conditions differed significantly from each other.

Insert Figure 3 about here

Across all conditions, there was significant dilation during the response period (heavy lines, filled symbols) compared to the baseline period (thin lines, open symbols) ($F_{1,11} = 365.1$, $p < 0.001$, $\eta^2 = 0.971$). Note that dilation occurred both when the parasympathetic system was blocked by tropicamide, resulting in dilation attributable to sympathetic activation, and also when the sympathetic system was blocked by dapiprazole, resulting in dilation attributable to inhibition of the parasympathetic pathway.

As in Experiment 1, there also was a significant effect related to larger diameters in darkness than light ($F_{1,11} = 39.3$, $p < 0.001$, $\eta^2 = 0.781$), and larger diameters associated with the

Subtract 7 than the Add 1 conditions in both the baseline and response periods (task: $F_{1,11} = 15.9$, $p = 0.002$, $\eta^2 = 0.590$). However, an interaction of measurement period and task indicated greater dilation between baseline and response period to the Subtract 7 than the Add 1 task (($F_{1,11} = 12.9$, $p = 0.004$, $\eta^2 = 0.541$).

The only significant interaction involving pharmacological administration was related to drug x light condition (($F_{1.7,18.8} = 14.3$, $p < 0.001$, $\eta^2 = 0.565$). In order to examine the nature of this interaction, paired comparisons of the pharmacological conditions were examined for remaining interactions with drug administration. When placebo and dapiprazole were compared, the drug x light interaction was not significant. However, the drug by light interaction remained when comparing tropicamide to placebo ($F_{1,11} = 11.23$, $p = 0.007$, $\eta^2 = 0.503$) and tropicamide to dapiprazole ($F_{1,11} = 41.9$, $p < 0.001$, $\eta^2 = 0.792$). In both of the latter comparisons, it is the decreased responsivity to variation of light after tropicamide administration, apparent in Figure 3, which accounts for the significant interaction.

Pupil Diameter During Response Interval compared to Baseline: As in Experiment 1, the extent of dilation during the response period was examined after subtraction of baseline diameter, in order to evaluate the change during response period more clearly. Amplitude of dilation is plotted in Figure 4. There were no significant differences in overall amplitude of dilation by drug administration ($p = .285$), as also indicated in the previous set of analyses. There was a significant task effect ($F_{1,11} = 15.4$, $p = 0.002$, $\eta^2 = 0.583$), and a significant task x light interaction ($F_{1,11} = 7.61$, $p < 0.019$, $\eta^2 = 0.409$).

There also was a marginal drug x task interaction ($F_{1.6,17.6} = 3.8$, $p = 0.052$, $\eta^2 = 0.254$). Given the interest on drug effects, this interaction was followed by simple effects analyses.

Insert Figure 4 about here

In paired comparisons, there were no significant differences in dilation between placebo and dapiprazole conditions, nor were there any interactions of drug condition with task or light effects. Task remained significant (Subtract 7 > Add 1, $F_{1,11} = 14.8$, $p = 0.003$, $\eta^2 = 0.574$), as was the interaction of Task x Light, due to enhancement of the response to Subtract 7 in the light as compared to the dark ($F_{1,11} = 7.8$, $p = 0.017$, $\eta^2 = 0.415$). That is, effects of task interacted with lighting condition whenever the parasympathetic pathway was intact.

When dapiprazole and tropicamide were contrasted, a significant drug x task effect was observed ($F_{1,11} = 13.6$, $p = 0.004$, $\eta^2 = 0.554$). A similar but non-significant pattern was observed for the drug x task interaction when placebo and tropicamide were contrasted ($F_{1,11} = 13.6$, $p = 0.116$, $\eta^2 = 0.209$). These effects appear associated with the relative lack of differential dilation across conditions in the tropicamide condition.

When the tropicamide data were examined alone, there were no significant differences in dilation associated with either task or light condition, or in the interaction of task and light. Note the dilation amplitudes across all conditions still showed significant increases as compared to baseline, as determined in the earlier analysis of baseline to response period changes.

7. Discussion

Two approaches for isolating contributions of the sympathetic and parasympathetic pathways to pupillary dilation indicated differential contributions of these pathways during a sustained processing task. Increasing task complexity was associated with greater pupillary diameter and dilation. Moreover, manipulations of light intensity indicated an enhanced effect mediated through inhibition of the parasympathetic system, which was best observed when light intensity was increased, and was most marked for the difficult task.

A significant but relatively constant amplitude effect was present in the sympathetic pathway, leading to activation of the dilator muscle. There was little differential activation to the two tasks when recordings in darkness were compared in Experiment 1 and the placebo condition of Experiment 2. Furthermore, blockade of the sphincter muscle by tropicamide, while

still resulting in overall dilation attributable to the dilator muscle, still showed little differential effect of task condition.

In contrast, multiple effects of task demands were indicated by activity in the parasympathetic pathway. In Experiment 1, when lighting was increased, there was differential dilation to the more demanding task, as well as larger initial diameter in light during this task than to simple addition. The contribution of this pathway was defined more clearly when the sympathetic dilator was blocked by dapiprazole: the pattern of dilation was most similar to the placebo response, but with greater differential reactivity between dark and light conditions for the Subtract 7 task. By isolating the activity of the parasympathetic pathway, significant effects for lighting condition, task requirements, and an interaction between lighting and task were clearly indicated.

The pattern of findings indicates contributions of both the sympathetic and parasympathetic pathways to dilation during sustained processing. However, more than one aspect of dilation due to inhibition in the parasympathetic pathway was indicated. The requirement to attend and verbalize was sufficient to activate inhibitory processes reflected in pupillary dilation in all conditions. When greater task demand was imposed, additional inhibitory influence was observed as an even greater dilation during light-adapted recording.

The findings parallel previous data indicating that cognitive load utilizing the same tasks has a differential inhibitory effect on the light reaction, which is modulated through the Edinger-Westphal complex (Steinhauer et al., 2000). In that study, as compared to a simple light reflex in the dark, pupil diameter was increased by the Add 1 manipulation, but no decrement of the light reaction was observed. However, imposition of the Subtract 7 task resulted in even greater dilation, as well as significant reduction of the light reaction.

From those as well as the present findings, it is clear that multiple pathways impinge on the Edinger-Westphal complex, resulting in pupillary dilation through inhibition of the parasympathetic pathway. Demanding cognitive load, most likely associated with frontal cortical functioning, contributes heavily to this inhibitory process; both direct cortical and

indirect cortico-thalamic-hypothalamic pathways producing inhibition at the Edinger-Westphal region have been described (Lowenstein, 1955). The general increase in inhibition across all task conditions may well include contributions of reticular pathways contributing to arousal, which also impinge on the Edinger-Westphal complex (Bonvallet and Zbrozyna, 1963). In contrast, sympathetic contributions to dilation during sustained activity appear to be less differentially affected by task activity.

It is notable that similar amplitudes of dilation were seen among all three drug conditions. This may seem counterintuitive at first: if there is dilation associated with relaxation of the parasympathetic system, as well as dilation associated with the sympathetic system, it might be expected that the extent of these dilations should be additive, resulting in greater overall dilation amplitude in the placebo condition. However, in the normal eye, there is tonic activity of both the constrictor (sphincter) and dilator muscles, making the resultant more complex. Thus, under normal stimulation, there is always some opposition of these muscles, so that what is being reflected at any time is a combination of the tonic effects of pupillary constriction via the parasympathetic pathway, and dilation via the sympathetic pathway. With the administration of tropicamide, the dilator muscle remains unopposed, but the lack of differential activity could reflect either a general response that is non-differential for the tasks conditions, or it may reflect a ceiling effect for pupillary diameter. When dapiprazole has been administered, tonic levels of constriction are unopposed, so that the beginning diameter is substantially smaller, and all increases in diameter must be related only to central inhibition at the oculomotor nucleus.

One of the major observations of the study was that pupil diameter increased more even during the baseline period for a difficult task than for an easy task. This appears to reflect brain activity associated with the immediate demands for preparing to perform a challenging mental operation. Neuroimaging data suggest that the dorsolateral prefrontal cortex is more active following instructions to complete a difficult as compared to easy task, even before the task begins (MacDonald et al, 1999). As pupil dilation has been observed to increase with

dorsolateral prefrontal cortex activity (Siegle et al, 2003), increased pupil dilation preceding the difficult task may reflect preparatory and dorsolateral prefrontal cortex activity.

One difficulty encountered during sustained processing tasks is the establishment of a non-task control condition. Merely asking a subject to fixate without any instructions, especially during light adaptation, results in highly variable pupil diameters over time. Thus, confidence in such "pure" baseline conditions is somewhat suspect, and no attempt was made to use a pure baseline in the present study. The current findings indicated, in fact, that as soon as any instructions are given, processing load related to the task is immediately reflected in the pupil.

Finally, this study demonstrates converging findings provided by two experimental approaches for examining autonomic activity in the pupillary system. Direct pharmacological blockade was able to isolate activity within each pathway. As a complementary method, comparison of pupillary dynamics in darkness and in light provided differential evidence for contributions of the parasympathetic component of pupillary dilation. The latter procedure may be especially appropriate to study of cognitive dynamics in patient populations, without requiring even the mild administration of mydriatic or miotic agents to the eye of the subject.

Acknowledgements

This work was supported by USPHS Grant MH55762, and by the Dept. of Veterans Affairs. We thank Annette Holcomb, B.S., for valuable assistance, and the nursing staff and pharmacy service of the VA Pittsburgh Healthcare System for their support.

References

Beatty, J., 1982a. Phasic not tonic pupillary responses vary with auditory vigilance performance. Psychophysiology, 19, 167-172.

Beatty, J., 1982b. Task-evoked pupillary responses, processing load, and the structure of processing resources. Psychol. Bull., 91, 276-292.

Beatty, J., Kahneman, D. L., 1966. Pupillary changes in two memory tasks. Psychonomic Science, 5, 371-372.

Bonvallet, M., Zbrozyna, A., 1963. Les commandes reticulaires du systeme autonome et en particulier de l'inervation sympathetique et parasympathetique del la pupille. Archs. Ital. Biol., 101, 174-207.

Friedman, D., Hakerem, G., Sutton, S., Fleiss, J.L., 1973. Effects of stimulus uncertainty on the pupillary dilation response and the vertex evoked potential. Electroencephalogr. Clin. Neurophysiol., 34, 475-484.

Granholm, E., Asarnow, R.F., Sarkin, A.J., Dykes, K.L., 1996. Pupillary responses index cognitive resource limitations. Psychophysiology, 33, 457-61.

Janisse, M.-P., 1977. Pupillometrics: The psychology of the pupillary response. Hemisphere Publishing Corp., Washington, D.C., 304 pp.

Kahneman, D., 1973. Attention and Effort. Prentice-Hall, Englewood Cliffs, N.J.

Kahneman, D., Beatty, J.,1966. Pupil diameter and load on memory. Science, 154, 1583-1585.

Karatekin, C. (in press). Development of attentional allocation in the dual task paradigm. Int. J. Psychophysiology.

Larson, M.D., MD; Tayefeh, F., Sessler, D.I., Daniel, M., Noorani, M.,1996. Sympathetic nervous system does not mediate reflex pupillary dilation during desflurane anesthesia. Anesthesiology, 85, 748-754.

Loewenfeld, I.E., 1993. The pupil: Anatomy, physiology, and clinical applications. Iowa State University Press, Ames, Iowa, 1594 pp.

Lowenstein, O., 1955. Pupillary reflex shapes and topical clinical diagnosis. Neurology, 5, 631-644.

Lowenstein, O., Loewenfeld, I.E., 1963. The pupil. In: Davson, H. (Ed.), The Eye, vol 3. Academic Press, New York, pp. 231-267.

MacDonald, A.W. 3rd; Cohen, J.D., Stenger V.A., Carter, C.S., 2000. Dissociating the role of the dorsolateral prefrontal and anterior cingulate cortex in cognitive control. Science, 288, 1835-1838.

Peavler, W. S., 1974. Pupil size, information overload, and performance differences. Psychophysiology, 11, 559-566.

Sarter, M., Givens, B., Bruno, J.P., 2001. The cognitive neuroscience of sustained attention: where top-down meets bottom-up. Brain Res. Reviews, 35, 146-160.

Siegle, G.J., Steinhauer, S.R., Stenger, V.A., Konecky, R., and Carter, C.S., 2003. Use of concurrent pupil dilation assessment to inform interpretation and analysis of fMRI data. NeuroImage, 20, 114-124.

Steinhauer, S.R., Condray, R., Holcomb, A., 2000. Cognitive modulation of midbrain function: Task-induced reduction of the pupillary light reflex. Int. J. Psychophysiol., 39, 21-30.

Steinhauer, S.R., Hakerem, G., 1992. The pupillary response in cognitive psychophysiology and schizophrenia. Annals N.Y. Aca. Sciences, 658, 182-204.

Steinhauer, S. R., Zubin, J. 1982. Vulnerability to schizophrenia: Information processing in the pupil and event-related potential. In E. Usdin & I. Hanin, (Eds.) Biological markers in psychiatry and neurology (pp. 371-385). Oxford: Pergamon Press.

List of Figures

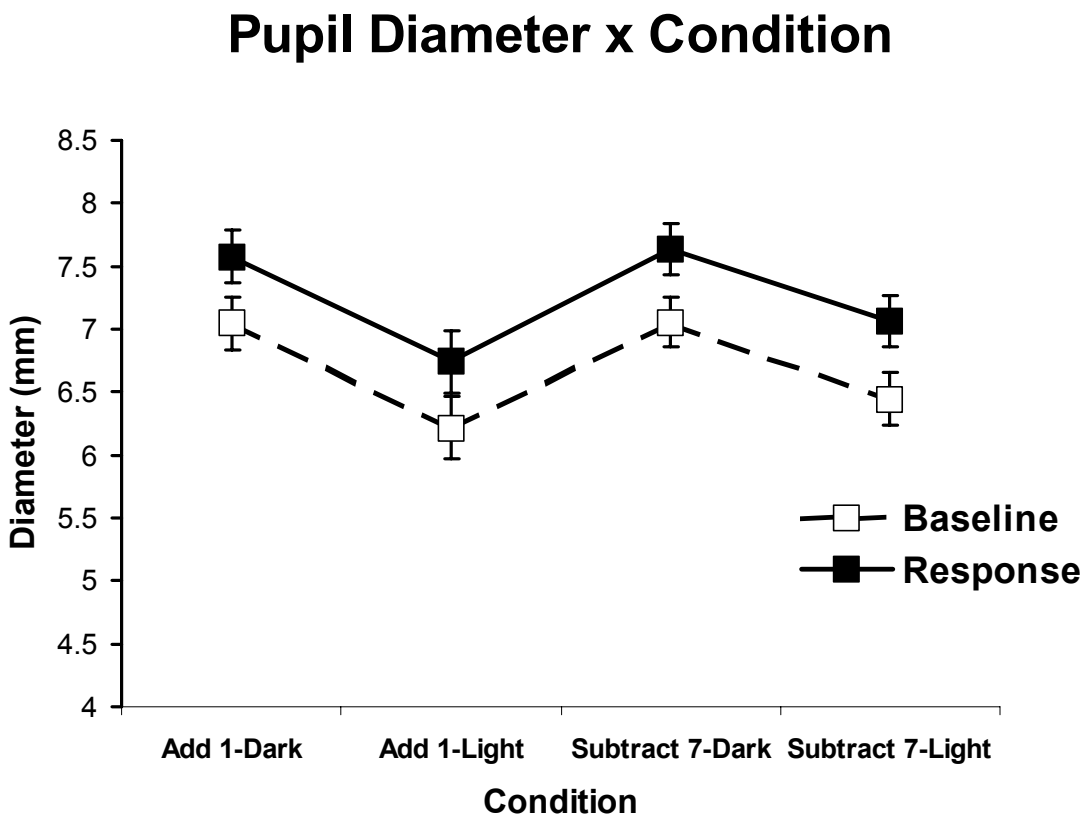

Figure 1: Absolute pupil diameter (all figures indicate mean +/- 1 s.e.) during 5 s baseline (dashed-open squares) and 60 s response periods (solid line- filled squares).

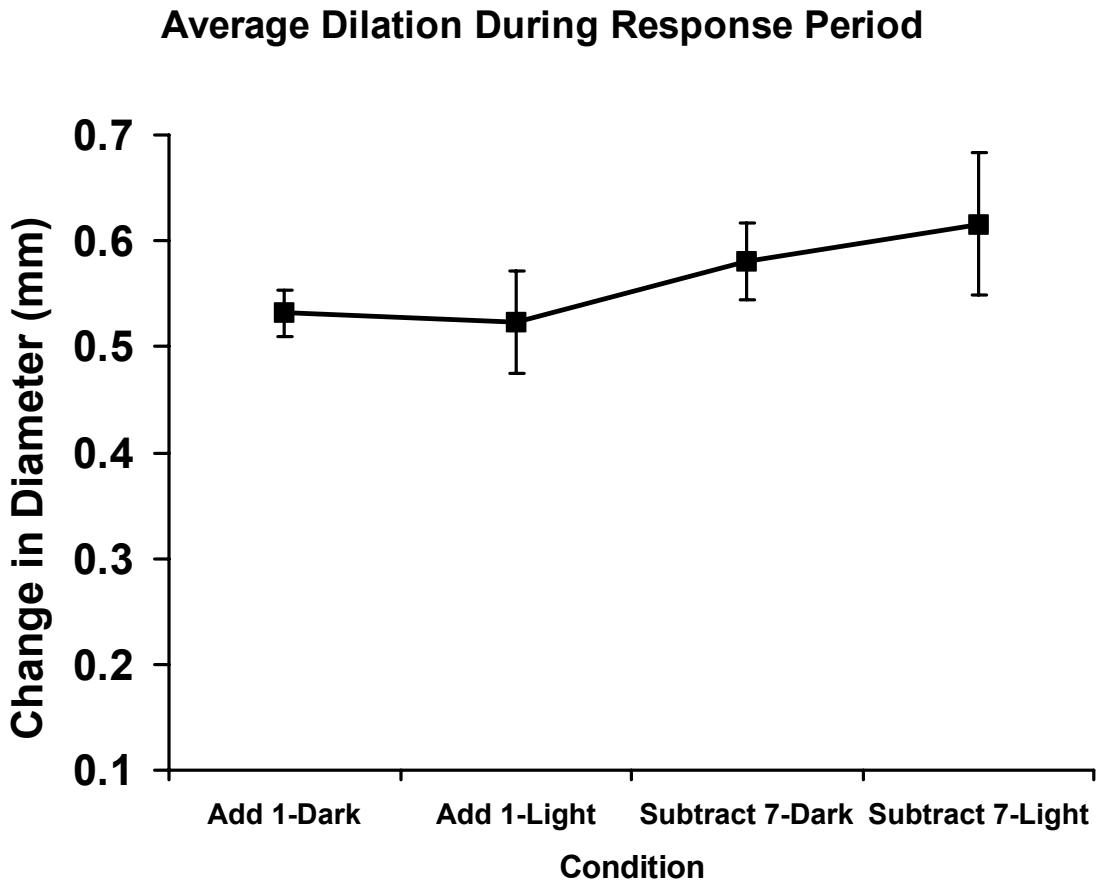

Figure 2: Change in diameter from baseline to response period, by task, in darkness and light.

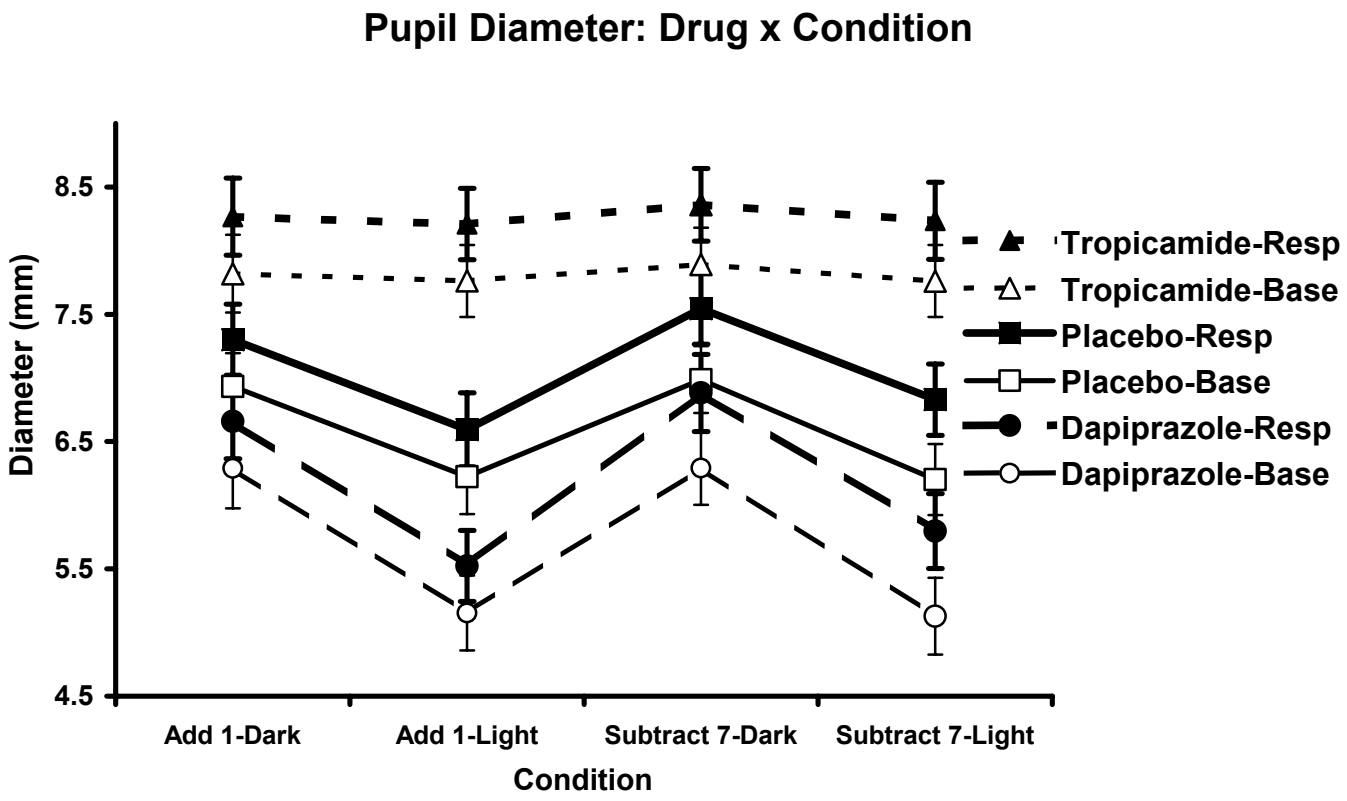

Figure 3: Absolute pupil diameter (mean +/- 1 s.e.) during 5 s baseline and 60 s response periods for all conditions, separately for placebo (solid line-square), tropicamide (dotted-triangle) and dapiprazole (dashed-circle) treatment sessions. Baseline measures are indicated by open symbols, response period measures are indicated by filled symbols and thicker lines.

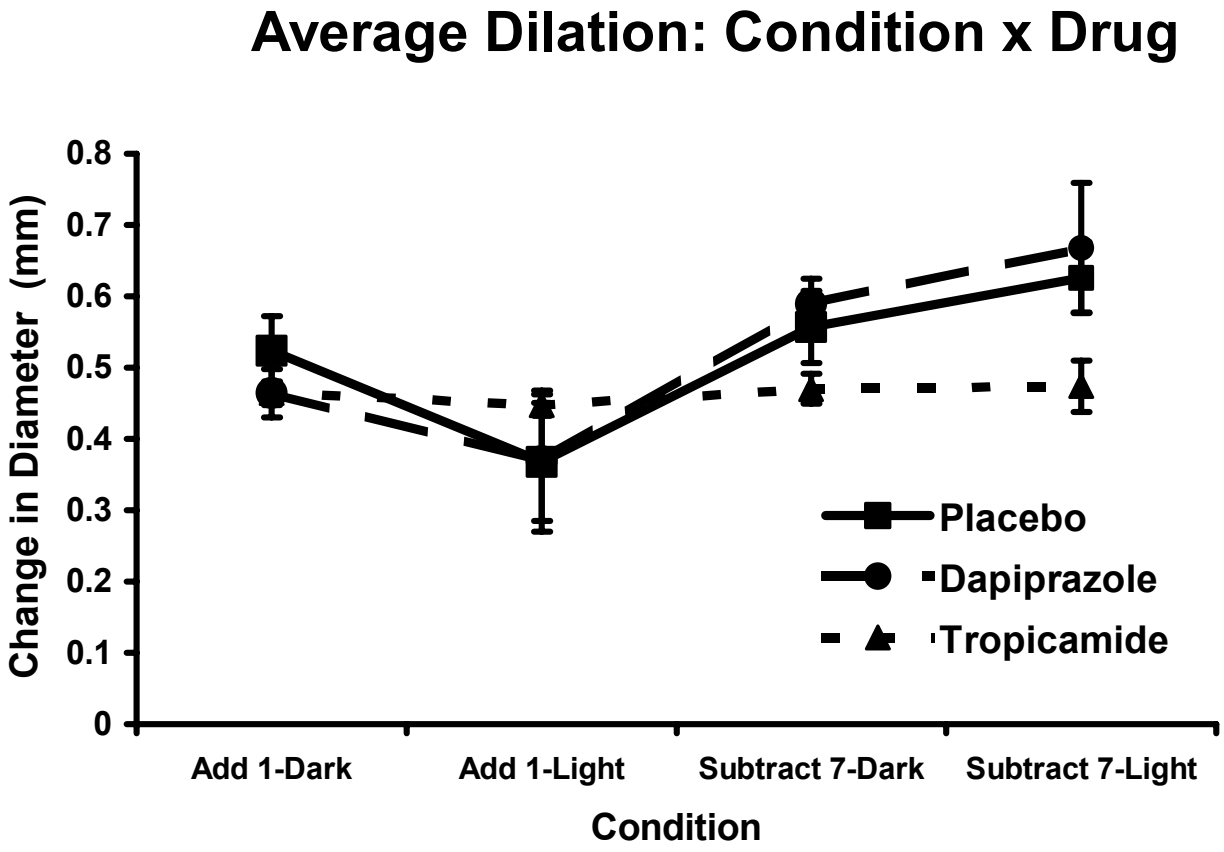

Figure 4: Change in pupil diameter (mean +/- 1 s.e.) from baseline to response period for all conditions, separately for placebo (solid line-square), tropicamide (dotted-triangle) and dapiprazole (dashed-circle) treatment sessions.