Published in final edited form as:
Biol Psychol. 2014 July ; 100: 79–85. doi:10.1016/j.biopsycho.2014.05.006.

The Effects of Constrained Left versus Right Monocular Viewing on the Autonomic Nervous System

D. Brandon Burtis, D.O.[1,2,4], **Kenneth M. Heilman, M.D.**[1,2,4], **Jue Mo, B.S.**[3], **Chao Wang, M.S.**[3], **Gregory F. Lewis, Ph.D.**[5], **Maria I. Davilla, Ph.D.**[6], **Mingzhou Ding, Ph.D.**[3], **Stephen W. Porges, Ph.D.**[6,7], and **John B. Williamson, Ph.D.**[1,2,4]

[1]Department of Neurology, University of Florida, College of Medicine, Gainesville, FL

[2]Center for Neuropsychological Studies, Gainesville, FL

[3]J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Gainesville, FL

[4]Malcom Randall Veteran's Affairs Hospital, Gainesville, FL

[5]Research Triangle Institute (RTI) International, Research Triangle Park, NC

[6]Department of Psychiatry, University of Illinois at Chicago, College of Medicine, Chicago, IL

[7]Department of Psychiatry, University of North Carolina. School of Medicine, Chapel Hill, NC

Abstract

Asymmetrical activation of right and left hemispheres differentially influences the autonomic nervous system. Additionally, each hemisphere primarily receives retinocollicular projections from the contralateral eye. To learn if asymmetrical hemispheric activation induced by monocular viewing would influence relative pupillary size and respiratory hippus variability (RHV), a measure of parasympathetic activity, healthy participants had their left, right or neither eye patched. Pupillary sizes were then recorded with infrared pupillography. Pupillary dilation was significantly greater with left than right eye viewing. RHV, however, was not different between eye viewing conditions. These differences in pupil dilatation may have been caused by relatively greater activation of the right hemispheric-mediated sympathetic activity induced by left monocular viewing or relatively greater deactivation of the left hemispheric-mediated parasympathetic activity induced by right eye patching. The absence of an asymmetry in RHV, however, suggests that hemispheric asymmetry of sympathetic activation was primarily responsible for this ocular asymmetry of pupil dilation.

Contact: D. Brandon Burtis, D.O. Department of Neurology, McKnight Brain Institute, University of Florida, Gainesville, FL 32610, Telephone: 352-273-5550, Fax: 352-273-5575, dbrandon.burtis@mail.ufl.edu.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Keywords

Constrained Monocular Viewing; Autonomic Nervous System; Laterality; Pupillary Light Reflex; Hippus; Respiratory Sinus Arrhythmia; Monocular Occlusion; Eye Patching; Sprague effect; Pupillary Diameter

Introduction

The autonomic nervous system (ANS) plays a critical role in the involuntary control and regulation of the organs and systems involved in maintaining homeostasis and helping the body adapt to its environment. The two major divisions of the ANS are the sympathetic and parasympathetic systems. Beginning with Lowenstein and Loewenfeld (1950a,b), it has been demonstrated that the ANS controls the size of the pupils with activation of the cholinergic parasympathetic nervous system (PNS) constricting the pupil (miosis) and the adrenergic sympathetic nervous system (SNS) dilating the pupil (mydriasis).

Both animal and human studies suggest lateralized hemispheric differentiation of ANS control. For example, researchers (Hoffman & Rasmussen, 1953; Oppenheimer et al., 1992; Oppenheimer et al., 1996) demonstrated that right insular cortex stimulation increases sympathetic activity (increase heart rate) and left insular cortex increases parasympathetic activity (decreases heart rate). Right hemispheric infarction in the rat is associated with elevated catecholamines with corresponding increases in heart rate and blood pressure (Hachinski et al., 1992) and in the human with tachyarrhythmias (Lane et al., 1992). The volume of right insular cortex infarction correlates well with the degree of catecholamine elevation (Sander & Klingelhofer, 1995). A right insular lesion is also associated with greater probability of death within one year, possibly related to pathological sympathetic activation of the cardiovascular system (Colivicchi et al., 2005).

Further, using tachistoscopic visual half-field stimulation, Wittling et al. (1998) provided evidence that the left hemisphere appears to be dominant in the parasympathetic control heart rate. Measures of hand perspiration reflect sympathetic arousal levels of the brain. Whereas right hemispheric strokes reduce shock-induced hand sweating, left hemispheric strokes increase hand sweating (Heilman et al., 1978). This finding is consistent with the subsequent demonstration that the right hemisphere tends to have stronger connection with the lateral (sympathetic) than medial (parasympathetic) hypothalamus (Lemaire et al., 2011).

While additional studies also appear to support these asymmetries of cerebral hemispheric control of the ANS (Hilz et al., 2001; Zamrini et al., 1990; Rosen et al., 1982), there are also some studies which suggest right hemispheric dominance in parasympathetic control of heart rate (Ahern et al., 2001; Thayer & Lane, 2009). These investigators reported that with selective hemispheric anesthesia, by means of injecting a barbiturate into the right or left carotid artery, heart rate variability decreased more with right than left carotid injections, suggesting greater right hemisphere dominance for vagal control.

Though beyond the scope of the current paper, there appears to be some inter and intra-hemispheric relationships in the control of the ANS. One possibility is that the hemispheric laterality of autonomic control functions in a manner that is similar to the hemispheric control of attention and emotion in that the right hemisphere may be dominant for both sympathetic and parasympathetic nervous system control and the left hemisphere may be more facile in the allocation of parasympathetic resources than sympathetic.

Whereas each side of the retina primarily projects to the ipsilateral hemisphere's geniculo-calcarine system, there is also evidence the entire retina in each eye has greater projections to the contralateral superior colliculus. According to Perry and Cowey (1984), about 7 to 10 percent of retinal ganglia cells project to the superior colliculus. Furthermore, these investigators as well as others (Pollack & Hickey, 1979; Rafal et al., 1990) reported that the majority (∼70%) of the retinocollicular pathway project to the contralateral superior colliculus. Additionally, tectoreticular fibers from the colliculus project to the mesencephalic reticular formation that mediates hemispheric arousal, with ipsilateral fibers more abundant than contralateral fibers (Truex and Carpenter, 1964) and stimulation of the each colliculus induces an ipsilateral hemispheric arousal response (Jefferson, 1958). Thus, each superior colliculus via the tectoreticular system appears to be able to activate-arouse the ipsilateral hemisphere. Based on this connectivity, monocular visual input into the brain may be able to asymmetrically activate the cerebral hemispheres; however, little research has been performed in an attempt to understand the influence of monocular visual input on the cerebral hemispheric interactions with the components of the ANS as assessed by measuring alterations of pupillary size, a sensitive and reliable means of assessing autonomic function (Bar et al., 2005).

A demonstration of this shift in hemispheric arousal can be inferred from behavioral studies of neglect. Studies of animals and patients have revealed that damage to elements of one hemisphere's thalamic and mesencephalic reticular activating system can induce the ipsilesional attentional and action-intentional biases that are characteristic of the unilateral neglect syndrome (Watson et al., 1974; Watson et al., 1981). Patients with unilateral neglect have revealed that their injured hemisphere is relatively hypoaroused (Watson et al., 1977). Thus, these patients' ipsilesional attentional and action-intentional bias appears to be caused by the relative hyperactivity of the unlesioned contralesional hemisphere (Heilman, 1979), and this relative contralesional hemispheric hyperactivity can be related to an injury-induced hemispheric reduction of activity, as well as perhaps a lesion-induced loss of inter-hemispheric inhibition of the uninjured hemisphere. Support for the loss of inter-hemispheric hypothesis comes from studies which have demonstrated improvement in patients with hemispatial neglect who are treated with slow transcranial magnetic stimulation (TMS) applied to the unlesioned hemisphere, which reduces the unlesioned hemisphere's activation (Koch et al., 2008).

Sprague (1966) induced what appeared to be contralesional neglect in animals with a posterior cortical lesion. Subsequently, by ablating the contralesional colliculus, he demonstrated the reversal of this neglect-like behavior. Since the retinocollicular pathway primarily projects contralaterally, Posner and Rafal (1987) posited that occlusion of the eye on the same side as the hemispheric lesion would reduce the activation of the contralateral colliculus, and thereby reduce the spatial bias associated with neglect. Thus, in those patients with a right posterior cortical lesion who have left hemispatial neglect, patching the ipsilesional (right) eye should theoretically produce relative deactivation of the superior colliculus contralateral to the lesion while reducing the relatively heightened activation of the unlesioned hemisphere (the Sprague effect). However, studies on unilateral neglect have revealed that ipsilesional eye patching showed mixed results by helping some, but not all patients (Butter & Kirsch, 1992; Serfaty et al., 1995; Barrett et al., 2001).

Based on the above studies demonstrating right-left hemispheric asymmetries in autonomic control and the potential impact of monocular viewing on hemispheric activation, the goal of this study was to learn if monocular viewing would affect pupillary size as controlled by the sympathetic and parasympathetic divisions of the autonomic nervous system. Occlusion of the left eye may reduce the activation of the right superior colliculus and induce relative inactivation of the right hemisphere. Since the right hemisphere appears to preferentially mediate activity of the sympathetic nervous system, occlusion of the left eye may lead to a relative reduction of pupillary diameter, miosis. In contrast, right eye occlusion and relative reduced inactivation of the left hemisphere, which may mediate the parasympathetic nervous system, may induce pupillary dilation, mydriasis.

In healthy individuals without hemispheric injury, it remains uncertain if the change in pupillary diameter results from deactivation of the colliculus-hemisphere from contralateral eye patching or activation of the opposing hemisphere from the viewing eye, or a combination of both via inter-hemispheric inhibition (i.e., activation of one hemisphere inhibits the other via callosal communication, affecting both sympathetic and parasympathetic behaviors). With pupillary dilation, this effect could be explained solely from activation of the sympathetic mediated right hemisphere with *left (versus right) eye monocular viewing*. However, pupillary dilation can result from both a direct inactivation induced by reduced left collicular-hemispheric arousal with left (versus right) eye patching according to the Sprague effect, as well as inter-hemispheric inhibition with further deactivation of the left hemisphere mediated parasympathetic system from the opposing activated right collicular-hemisphere. Similarly, but opposite effects may be seen with *right (versus left) eye monocular viewing*.

To learn if these alterations in pupil diameter during monocular viewing can be explained primarily by alterations of either the sympathetic or parasympathetic components of the autonomic nervous system or an interaction of both systems, it may be valuable to have an additional measurement to aid in determining this distinction. Experimental spectral analysis of respiratory frequency rhythmic oscillations of pupil diameter, or hippus variability (RHV), may offer a further means of assessing the degree of parasympathetic activation. Hippus oscillations are presumed to reflect the autonomic nervous system's influence on the pupillary muscles; and there is evidence to suggest that the oscillations are specifically related to parasympathetic activity (Huang, 2000; Borgdorff, 1975). The midbrain Edinger-Westphal nucleus, which gives rise to the parasympathetic nerves that help control pupillary size, receives connections from the rostral ventral respiratory neuronal cell group (Gaytan and Pasaro, 1998). Spectral decomposition of the changing pupil diameter reveals distinct oscillations that correspond to respiratory rhythm (Calcagnini, 2000), a rhythm that is associated with activity of the myelinated vagal pathway and has been related to cerebral influence on autonomic behavior (e.g., Friedman and Thayer, 1998). Parnandi and

Gutierrez-Osuna (2012) demonstrated significant correlations between heart rate variability and hippus variability using analogous spectral analysis methods. Thus, there are anatomical and behavioral data to indicate that the application of spectral analysis techniques to the examination of hippus in response to monocular viewing may be helpful in learning the relative independent contributions of PNS activity to pupil size. Therefore, if pupillary asymmetries with right versus left eye viewing are detected, but without simultaneous alterations of RHV, it would suggest that the pupillary changes are primarily being induced by alterations of sympathetic activity. In contrast, if there are asymmetries of RHV that mirror pupillary constriction, it would suggest that the pupillary changes are related to the effect of monocular viewing on the parasympathetic nervous system.

Based on previous studies demonstrating right-left hemispheric asymmetries in sympathetic versus parasympathetic control (Hoffman & Rasmussen, 1953; Oppenheimer et al., 1992; Oppenheimer et al., 1996; Hilz et al., 2001; Zamrini et al., 1990; Rosen et al., 1982), as well as the influence of collicular ablation on ipsilateral hemispheric activation (Sprague, 1966) and the possible influence of monocular occlusion reducing contralateral collicular activation (Posner and Rafal, 1987), we predicted that with left eye patching (right eye viewing), there would be a reduction of right hemisphere mediated sympathetic activity and a relative enhancement of left hemisphere mediated parasympathetic activity producing pupillary constriction. In contrast, with right eye patching and relative left hemisphere inactivation, we expected a reduction of parasympathetic activation with a relatively greater sympathetic activation producing pupillary dilation. The purpose of this study is to learn if right and left monocular viewing can differentially influence the sympathetic versus parasympathetic components of the ANS as evidenced by pupillary changes.

Method

Participants

Subjects for this study were 14 healthy volunteers (4 women). One participant was excluded due to lack of sleep and also appearing to be sleepy during the evaluation. A second subject was excluded due to being left-handed. Thus, 12 self-reported right-handed participants were included in this study. These participants had a mean age of 22.5 years, +/- 5.2, and age range of 18-31 years. All participants were screened for adequate visual acuity to prevent any unnatural strain and discomfort during the experimental session. The visual acuity required to visualize the targeted crosshairs (+) as described below was estimated at approximately 20/100 according to the Snellen chart. The participants were free of diagnosed neurological, ophthalmological or psychiatric diseases. Participants denied taking any ‘over the counter’ or prescribed medications and were asked to refrain and/or denied any caffeine intake or other stimulants within a 12-hour period prior to testing.

Apparatus-Monocular Viewing Goggles

A set of specially designed goggles was used for eye patching (Figure 1a, 1b). In order to control for an asymmetrical somatosensory input due to a typical eye patch, these goggles were designed from protective eye wear normally purchased at a local store. The goggles were comfortably fitted over each eye without placing excessive pressure at any point of contact with the skin. The clear goggle lens was removable from the supporting frame, thus allowing a black nylon patch to be placed over the front and back of the lens unilaterally for complete monocular obstruction of all light. Furthermore, the nylon overlapped along the perimeter of the leading edge of the lens to further obstruct any light from penetrating on all sides. Thus, direct light entered the participants' eyes from the monitor and ambient light from the room was limited. In order to symmetrically balance the tactile sensation from the nylon perimeter strip in contact with the skin surrounding the orbit of the occluded, a thin nylon strip was also applied only along the perimeter of the clear lens of the contralateral viewing eye.

A goggle for binocular viewing (or unpatched condition) was designed with strips of nylon also placed along the perimeter and overlapped in order to provide an equal and symmetrical tactile sensation similar to the monocular viewing goggles (Figure 2a,b).

Procedure

Each subject signed an informed consent form in accordance with the Institutional Review Board at the University of Florida. The experiment took place in an acoustically and magnetically shielded room. The lighting of the recording room was controlled to be consistent across subjects by 36 LED bulbs on the ceiling. Light from the left side and the right side of the ceiling were symmetric. Subjects sat comfortably in a chair in the center of the recording room facing a monitor. After verifying from each subject the absence of any light perception to the occluded eye and any tactile asymmetry between left and right, subjects were asked to place their head on a chin-and-forehead rest to begin recording. Luminance was measured by LX1010B digital light meter. With the overhead lights on, the luminance in the direction from the chinrest horizontally to the front of the computer monitor was 20 cd/m^2. The luminance in the direction from the chinrest horizontally to the left wall and the right wall were the same, equal to 25 cd/m^2. With the overhead lights off, the average luminance of the computer monitor itself was 7 cd/m^2. The luminance of the fixation point was 11 cd/m^2. There was no difference in luminance between left and right portions of the monitor. All the surfaces of the walls of the recording room were made by black fabric and the reflective luminance of the surfaces was only approximately 1 cd/m^2 despite the overhead lighting.

Each subject's pupil size was recorded for 3 sessions in a random order with either the left, right or neither eye(s) being covered. Each recording session lasted for 4 minutes. The randomly chosen goggle was donned before each session and assured by each subject for comfort prior to testing. Instructions were to sit quietly while maintaining a fixated gaze on a cross-hair “+” measuring 9 × 9 mm displayed on a 20.1″ LCD 1024×768 resolution monitor at approximately 85 cm from the viewing eye(s). The height and width of the monitor measured 30.5 × 40.7cm, respectively. The visual angle of the monitor measured approximately 0.35 degrees for the height and 0.47 degrees for the width.

The size of the pupils and eye movements were recorded with a desktop mounted infrared eye-tracker (EyeLink 1000) at a sampling rate of 1000 Hz. The experimental paradigm was delivered by E-Prime software.

Analysis

Artifact rejection

All the saccade events were automatically detected by the data acquisition system (following the manual of Eyelink 1000). In addition, the blinks were detected when the pupillary size dropped to zero. To eliminate the artifact caused by the saccade and blink events, linear interpolation was performed around each onset of saccade/blink event within a [0 - 500] millisecond interval.

Statistic of the pupillary size

Time course of pupillary size was low-pass filtered with cutoff frequency at 100 Hz and then down sampled to 200Hz. The average pupil size for each condition was assessed separately by the temporal mean of the pupillary time course. The average pupil size was normalized within each individual subject by dividing the binocular viewing condition.

The reported values for pupil size were assigned an arbitrary unit as a measure for pupil area according to the Eyelink manual. Pupil size data is not calibrated and the units of pupil measurement will vary with subject setup. Pupil size is an integer number, in arbitrary units. Typical pupil area is 100 to 10000 units, with a precision of 1 unit.

Statistic of the hippus variability analysis

The magnitude of the respiratory frequency (RF, 0.12 – 0.50 Hz) component of the pupil diameter signal was calculated by modifying the Porges-Bohrer method used to quantify respiratory sinus arrhythmia (Porges, 1985). The pupil diameter time series, sampled at 200 Hz, was convolved with a third order polynomial filter to produce a new time series containing the variance of trend occurring below the low cut-off frequency (for RF, f_c = 0.095 Hz). This baseline was then subtracted from the original time series to generate a time series representing the hippus variability in the frequency band of spontaneous breathing. The filtered time series was then down sampled at 5 Hz and processed by a 6^{th} order Butterworth band-pass filter (for RF, f_{c1} = 0.12 Hz) to restrict the variance to the frequency range of interest. Hippus associated with spontaneous breathing was defined as the peak amplitude within the frequency band of 0.12-0.4 Hz. To conform to assumption for parametric analyses, the spectral densities representing RFHV were logarithmically transformed.

Results

Dilation

Average pupillary area was compared using a repeated measures analysis of variance (ANOVA) with repeated measures of both eyes open, left eye occluded and right eye occluded. Since the descriptive analyses of the data indicated significant skewing and kurtosis, a log transformation was performed on the data. The ANOVA performed on this transformed data indicated a significant difference in pupil size across conditions, $F(2, 22) = 16.142$, $p < 0.001$ [right eye patch] (Mdn [non-log] = 1916.2); left eye patch (Mdn [non-log] = 1558.7); binocular viewing (Mdn = 1240.1)]. Post-hoc analyses comparing the left and right eye block conditions with one-way repeated measures ANOVA indicated a significant difference, $F(1, 11) = 4.159$, $p = 0.033$ with left eye viewing yielding greater dilation than right eye viewing.

See Figure 3.

Respiratory Hippus Variability

Comparison of the respiratory hippus spectral variability shows a significant difference between experimental conditions, $F(2, 22)$, $= 8.139$, $p = 0.002$. Post-hoc analyses demonstrate that the RHV is larger during monocular viewing (mean = 9.47, SD = 0.85) than binocular viewing (mean = 8.84, SD = 0.85) conditions (both eye viewing versus left eye viewing $t(11) = -4.281$, $p = 0.001$; both eye viewing versus right eye viewing $t(11) = -2.700$, $p = 0.021$). However, no significant difference is observed between the left eye patching (right monocular viewing) and the right eye patching (left monocular viewing) condition, $t(11) = .500$, $p = 0.627$ (Left eye patch mean RHV = 9.51, SD = 0.87; Right eye patch mean RHV = 9.43, SD = 0.92). Power analysis, assuming stability of the data, revealed that a total sample size of 5424 would be necessary to demonstrate a statistically significant laterality effect.

Discussion

In the introduction, evidence that the left hemisphere primarily mediates parasympathetic activity and the right hemisphere mediates sympathetic activity was introduced. Based on this hemispheric asymmetry, we hypothesized that activation of the left hemisphere may reduce pupil size and activation of the right hemisphere may increase pupil size and that changes in RHV would be greater with left hemisphere activation and lesser with right hemisphere activation. Since the superior colliculus receives the majority of its retinal afferents from the contralateral eye and collicular activation induces ipsilateral hemispheric activation, it was predicted that left eye patching (right eye viewing) would reduce right hemispheric mediated sympathetic activity along with relative enhancement of left hemispheric mediated parasympathetic activity producing constriction of the pupil and greater RHV. In contrast, with right eye patching (left eye viewing) and relative left hemisphere inactivation, there would be relative reduction of parasympathetic activity and greater sympathetic activation with an induction of pupil dilation and reduced RHV. The primary findings of this study were suggestive of a laterality effect for sympathetic but not parasympathetic control.

In general, the pupils were smaller with binocular viewing than with either right or left eye monocular viewing. This difference may be related to the greater amount of light activating the retinal pathways when both eyes are open. When both eyes are viewing, the stimulus (light) will activate, via both optic nerves and pretectal nuclei, both parasympathetic Edinger–Westphal nuclei and induce greater constriction of the pupils than when light enters just one eye. This difference in pupil diameter between binocular and monocular exposure to light has also been previously reported (Weinhold & Bigelow, 1993).

The relative pupil size was greater with left than right eye viewing. The reason for this laterality effect could be primarily from light entering the left eye activating the right superior colliculus and the right hemisphere, which in turn induced sympathetic activation. An alternative explanation is that occlusion of the right eye reduced the activation of the left superior colliculus and left hemisphere, thereby inducing a reduction of parasympathetic activity, or a combination of both. Therefore, in order to clarify this relationship, RHV was analyzed.

Since RHV appears to be primarily mediated by the PNS, the finding that monocular occlusion of either eye resulted in an equal increase in high frequency hippus variability suggests that the reason for the laterality effect in pupil dilation was primarily due to the activity of the SNS. The reason that no laterality effect was evident in PNS activity is not known but may be related to either light intensity or to the novelty of monocular viewing as a task or, further, differences in laterality of parasympathetic versus sympathetic control in regulating pupillary response from other approached to autonomic assessment that have been previously reported. The effect size for the difference of RHV with monocular viewing was quite small and a sample size of more than 5000 would be necessary for enough power to detect a difference. Thus, this result may also reflect more bilateral influence in parasympathetic control than in sympathetic control.

Lowenstein and Loewenfeld (1950a,b) introduced the concept of the “psychosensory reflex” where all forms of sensory input, except for light with accommodation, lead to pupillary dilation. In addition to controlling for light entry into the eyes, the experimental apparatus was designed to control for other possible asymmetrical afferent sensations that may potentially influence brain activation. Thus, other than light from the monitor directly penetrating the eye with monocular viewing, the authors are unaware of any asymmetric sensory stimuli that could potentially affect the diameter of the pupil by a sympathetic response according to the “psychosensory reflex.” There could be, however, the effect of novelty in that monocular occlusion in a laboratory setting is a novel procedure. Novelty can result in the greater allocation of attention and may explain the uniform shift in RHV observed with monocular viewing regardless of eye (i.e., effect size for novelty>effect size for monocular viewing).

There have been a few prior studies that have examined the size of the pupil in relation to hemispheric stimulation. For example, in a study with transcranial magnetic stimulation (TMS), Niehaus et al. 2001 found that independent of location, TMS induced pupillary dilation. However, they also found that stimulation over the right central region evoked a larger dilatation of the pupil than stimulation over the left. These results are consistent with our findings and also correlate with previous literature that has provided evidence that the right hemisphere primarily mediates the activity of the sympathetic nervous system.

Case studies and prior experiments have described cardiac-related changes related to alterations of the ANS induced by cerebral hemispheric damage and especially to the insular region (Oppenheimer et al., 1992; Oppenheimer & Cechetto, 1990, Hoffman & Rasmussen, 1953). However, the authors are unaware of prior studies reporting alterations of pupil size as a function of right versus left hemispheric cortical infarctions. Although seizure induced ictal pupillary dilation is a common clinical finding, there are only a few cases reported of pupillary miosis as a clinical manifestation of partial epileptic seizures. For example, Sadek et al. (2011) reported a patient with epileptic seizures that started in the left hemisphere. These seizures were associated with miosis, suggesting these left hemispheric seizures activated the parasympathetic system. Whereas clinical and experimental data suggest the presence of a “cortical pupillary constrictor area” the localization remains elusive. Some have argued that the area localizes to the occipitoparietal region (Wang et al., 1931). However, cases have reported localization to the temporal lobe (Afifi et al., 1990), temporo-occipital region (Rosenberg, 1991) and middle parietal gyrus (Sadek et al., 2011).

Pupillography is an inexpensive, non-invasive and under-utilized measure (Low, 1997) of ANS activity with high sensitivity and reproducibility (Bar et al., 2005). As stated by others, perhaps this tool may further provide a “complimentary assessment of different aspects of the ANS” (Daluwatte et al. 2012) and “reveal differential patterns in certain disease states” (Bar et al., 2009). Pupillography also has strong potential applications as a noninvasive measure of alterations in the ANS. The ability to derive reliable sympathetic and parasympathetic measures without contact with a person is valuable in that it potentially improves ecological validity and experimental efficiency. Evaluation of pupillography and specifically the relationship of RHV to cognitive functions together with typical measures of RSA will help further validate this technique. Furthermore, future studies directly examining lateralized hemispheric activation with monocular viewing, by using other physiological techniques, as well as studies of patients with specific lateralized lesions are needed to help further examine the implications of our results. Finally, since our study suggests that monocular viewing can systematically alter sympathetic functions, perhaps future studies using monocular viewing as a therapy to restore ANS homeostasis may prove to be useful.

Acknowledgments

Supported in part by NIDCD/NIH Grant (1T32DC008768-01), the Veteran's Affairs Hospital Research Service and the State of Florida Memory Disorder Clinics

References

Afifi AK, Corbett JJ, Thompson HS, Wells KK. Seizure-induced miosis and ptosis: association with temporal lobe magnetic resonance imaging abnormalities. Journal of Child Neurology. 1990; 5:142–146. [PubMed: 2345281]

Ahern GL, Sollers JJ, Lane RD, Labiner DM, Herring AM, Weinand ME, Hutzler R, Thayer JF. Heart rate and heart rate variability changes in the intracarotid sodium amobarbital test. Epilepsia. 2001; 42:912–21. [PubMed: 11488892]

Bär KJ, Boettger MK, Till S, Dolicek J, Sauer H. Lateralization of pupillary light reflex parameters. Clinical Neurophysiology. 2005; 116:790–798. [PubMed: 15792888]

Bär KJ, Schulz S, Koschke M, Harzendorf C, Gayde S, Berg W, Voss A, Yeragani VK, Boettger MK. Correlations between the autonomic modulation of heart rate, blood pressure and the pupillary light reflex in healthy subjects. Journal of the Neurological Sciences. 2009; 279:9–13. [PubMed: 19195664]

Barrett AM, Crucian GP, Beversdorf DQ, Heilman KM. Monocular patching may worsen sensory-attentional neglect: a case report. Archives of Physical Medicine and Rehabilitation. 2001; 82:516–518. [PubMed: 11295013]

Borgdorff P. Respiratory fluctuations in pupil size. American Journal of Physiology. 1975; 228:1094–1102. [PubMed: 1130509]

Butter CM, Kirsch N. Combined and separate effects of eye patching and visual stimulation on unilateral neglect following stroke. Archives of Physical Medicine and Rehabilitation. 1992; 73:1133–1139. [PubMed: 1463376]

Calcagnini G, Censi F, Lino S, Cerutti S. Spontaneous fluctuations of human pupil reflect central autonomic rhythms. Methods of Information in Medicine. 2000; 39:142–145. [PubMed: 10892249]

Colivicchi F, Bassi A, Santini M, Caltagirone C. Prognostic implications of right-sided insular damage, cardiac autonomic derangement, and arrhythmias after acute ischemic stroke. Stroke. 2005; 36:1710–1715. [PubMed: 16020766]

Daluwatte C, Miles JH, Yao G. Simultaneously measured pupillary light reflex and heart rate variability in healthy children. Physiological Measurement. 2012; 33:1043–1052. [PubMed: 22563002]

Friedman BH, Thayer JF. Autonomic balance revisited: panic anxiety and heart rate variability. Journal of Psychosomatic Research. 1998; 44:133–151. [PubMed: 9483470]

Gaytan SP, Pasaro R. Connections of the Rostral Ventral Respiratory Neuronal Cell Group: an Anterograde and Retrograde Tracing Study in the Rat. Brain Research Bulletin. 1998; 47:625–42. [PubMed: 10078619]

Hachinski VC, Turner GR, Thompson WF. Asymmetry of sympathetic consequences of experimental stroke. Archives of Neurology. 1992; 49:697–702. [PubMed: 1497495]

Heilman KM, Schwartz HD, Watson RT. Hypoarousal in patients with the neglect syndrome and emotional indifference. Neurology. 1978; 28:229–232. [PubMed: 564476]

Heilman, KM. Neglect and related disorders. In: Heilman, KM.; Valenstein, E., editors. Clinical Neuropsychology. New York: Oxford University Press; 1979. p. 268-307.

Hilz MJ, Dütsch M, Perrine K, Nelson PK, Rauhut U, Devinsky O. Hemispheric influence on autonomic modulation and baroreflex sensitivity. Annals of Neurology. 2001; 49:575–584. [PubMed: 11357947]

Hoffman BL, Rasmussen T. Stimulation studies of insular cortex of Macaca mulatta. Journal of Neurophysiology. 1953; 16:343–351. [PubMed: 13070046]

Huang WX, Yu Q, Cohen MI. Fast (3 Hz and 10 Hz) and slow (respiratory) rhythms in cervical sympathetic nerve and unit discharges of the cat. Journal of Physiology. 2000; 523(Pt. 2):459–477. [PubMed: 10699089]

Jefferson, G. Substrates for integrative patterns in the reticular core. In: Scheibel, ME.; Scheibel, AB., editors. Reticular Formation. Boston: Little Brown; 1958.

Koch G, Oliveri M, Cheeran B, Ruge D, Lo Gerfo E, Salerno S, Torriero S, Marconi B, Mori F, Driver J, Rothwell JC, Caltagirone C. Hyperexcitability of parietal-motor functional connections in the intact left-hemisphere of patients with neglect. Brain. 2008; 131:3147–3155. [PubMed: 18948300]

Lane JD, Adcock RA, Burnett RE. Respiratory sinus arrhythmia and cardiovascular response to stress. Psychophysiology. 1992; 29:461–470. [PubMed: 1410177]

Lemaire JJ, Frew AJ, McArthur D, Gorgulho AA, Alger JR, Salomon N, Chen C, Behnke EJ, De Salles AA. White matter connectivity of human hypothalamus. Brain Research. 2011; 1371:43–64. [PubMed: 21122799]

Low, PA. Laboratory evaluation of autonomic function. In: Low, PA., editor. Clinical autonomic disorders. Boston: Little, Brown and Company; 1997. p. 173-204.

Lowenstein O, Loewenfeld IE. Role of sympathetic and parasympathetic systems in reflex dilation of the pupil; pupillographic studies. Archives of Neurology & Psychiatry. 1950a; 64:313–340.

Lowenstein O, Loewenfeld IE. Mutual role of sympathetic and parasympathetic in shaping of the pupillary reflex to light; pupillographic studies. Archives of Neurology & Psychiatry. 1950b; 64:341–377.

Niehaus L, Guldin B, Meyer B. Influence of transcranial magnetic stimulation on pupil size. Journal of Neurological Sciences. 2001; 182:123–128.

Oppenheimer SM, Gelb A, Girvin JP, Hachinski VC. Cardiovascular effects of human insular cortex stimulation. Neurology. 1992; 42:1727–1732. [PubMed: 1513461]

Oppenheimer SM, Kedern G, Martin WM. Cardiovascular effects of human insular cortex stimulation. Neurology. 1996; 42:1727–1732. [PubMed: 1513461]

Parnandi, A.; Gutierrez-Osuna, R. Technical Report. Department of Computer Science and Engineering; Texas A&M University: 2012. Contactless Measurement of Heart Rate Variability from Pupillary Fluctuations.

Perry VH, Cowey A. Retinal ganglion cells that project to the superior colliculus and pretectum in the macaque monkey. Neuroscience. 1984; 12:1125–1137. [PubMed: 6483194]

Pollack JG, Hickey TL. The distribution of retino-collicular axon terminals in rhesus monkey. Journal of Comparative Neurology. 1979; 185:587–602. [PubMed: 109475]

Porges, SW. Method and apparatus for evaluating rhythmic oscillations in aperiodic physiological response systems. US Patent 4510944.

Posner, MI.; Rafal, RD. Cognitive theories of attention and the rehabilitation of attentional deficits. In: Meir, MJ.; Benton, A.; Diller, L., editors. Neuropsychological rehabilitation. New York: Guildford Press; 1987. p. 182-201.

Rafal R, Smith J, Krantz J, Cohen A, Brennan C. Extrageniculate vision in hemianopic humans: saccade inhibition by signals in the blind field. Science. 1990; 250:118–121. [PubMed: 2218503]

Rosen AD, Gur RC, Sussman NM, Gur RE, Hurtig H. Hemispheric Asymmetry in the control of heart rate. Neuroscience Abstracts. 1982; 8:917.

Rosenberg ML, Jabbari B. Miosis and internal ophthalmoplegia as a manifestation of partial seizures. Neurology. 1991; 41:737–739. [PubMed: 1902918]

Sadek AR, Kirkham F, Barker S, Gray WP, Allen D. Seizure-induced miosis. Epilepsia. 2011; 52:e199–203. [PubMed: 22050551]

Sander D, Kingelhofer J. Changes of circadian blood pressure patterns and cardiovascular parameters indicate lateralization of sympathetic activation following hemispheric brain infarction. J Neurol. 1995; 242:313–318. [PubMed: 7643140]

Serfaty C, Soroker N, Glicksohn J, Sepkuti J, Myslobodsky MS. Does monocular viewing improve target detection in hemispatial neglect? Restorative Neurology and Neuroscience. 1995; 9:77–83. [PubMed: 21551835]

Sprague JM. Interaction of cortex and superior colliculus in mediation of visually guided behavior in the cat. Science. 1966; 153:1544–1547. [PubMed: 5917786]

Thayer JF, Lane RD. Claude Bernard and the heart–brain connection: Further elaboration of a model of neurovisceral integration. Neuroscience and Biobehavioral Reviews. 2009; 33:81–88. [PubMed: 18771686]

Truex, RC.; Carpenter, MB. Human Neuroanatomy. Baltimore: Williams & Wilkins; 1964.

Wang GH, Lu TW, Lau TT. Pupillary constriction from cortical stimulation. Chinese Journal of Physiology. 1931; 5:205–216.

Watson RT, Andriola M, Heilman KM. The electroencephalogram in neglect. Journal of Neurological Sciences. 1977; 34:343–348.

Watson RT, Heilman KM, Miller BD, King FA. Neglect after mesencephalic reticular formation lesions. Neurology. 1974; 24:294–298. [PubMed: 4205158]

Watson RT, Valenstein E, Heilman KM. Thalamic neglect. Possible role of the medial thalamus and nucleus reticularis in behavior. Archives of Neurology. 1981; 38:501–506. [PubMed: 7247787]

Weinhold LL, Bigelow GE. Opioid miosis: effects of lighting intensity and monocular and binocular exposure. Drug and Alcohol Dependence. 1993; 31:177–81. [PubMed: 8436062]

Wittling W. The right hemisphere and the human stress response. Acta Physiol Scand Suppl. 1997; 640:55–59. [PubMed: 9401607]

Wittling W, Block A, Genzel S, Schweiger E. Hemisphere asymmetry in parasympathetic control of the heart. Neuropsychologia. 1998; 36:461–468. [PubMed: 9699952]

Zamrini EY, Meador KJ, Loring DW, Nichols FT, Lee GP, Figueroa RE, Thompson WO. Unilateral cerebral inactivation produces differential left/right heart rate responses. Neurology. 1990; 40:1408–1411. [PubMed: 2392227]

Highlights

1. Based on the Sprague effect, constrained monocular viewing potentially activates the contralateral hemisphere via the retinocollicular pathway.
2. Measures of pupil diameter and size fluctuation within the frequency of respiration during constrained monocular viewing suggest a lateralized sympathetic nervous system response.
3. Pupillary measures including diameter and hippus variability within the respiration spectrum (RHV), may add a valuable, non-invasive means of determining fluctuations of the ANS.

Figure 1. a, b: Goggles for Left Monocular Viewing

Figure 2. a, b: Goggles for Binocular Viewing

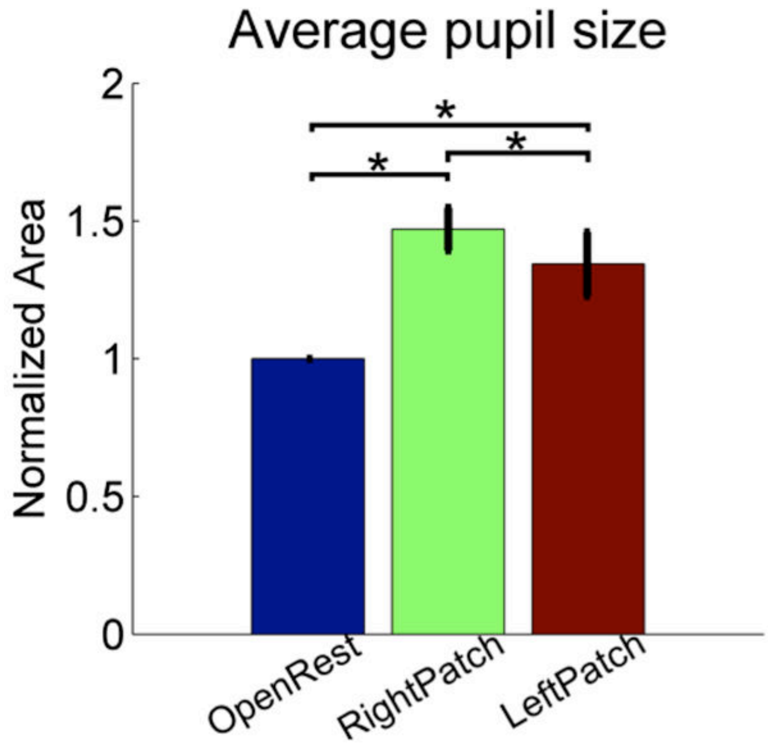

Figure 3. Average pupil size under binocular viewing and monocular viewing condition (*p<0.05 with Repeated Measures ANOVA) [error bars = standard deviation]