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Research Article

The Distribution of Anisocoria is Related to Gender

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Abstract

Benign or physiologic anisocoria (BA) refers to a small difference in the size of the two pupils, which is likely caused by asymmetry of sympathetic nervous system (SNS) innervation. Here I measure BA in a large sample of young adults and find that its distribution varies with gender. Females presented a small but significant bias to the right (right pupil larger than left), whereas males exhibited a larger and significant bias to the left (left pupil larger than the right). The sex difference was primarily attributable to right-pupil size, which was significantly larger for females than males (no significant difference in left-pupil size). Based on the premise that BA is caused by SNS asymmetry, these results suggest that SNS lateralization is more common in males than females and biased to the opposite side of the brain. Future studies that measure bilateral brain activity in addition to pupil size and other measures of SNS function (e.g., electrodermal response) are needed to validate the relationship between BA and SNS lateralization.

Keywords: Pupil size; Asymmetry; Lateralization; Autonomic function; Anisocoria; Sex differences; Race

Introduction

Pupil-size asymmetry can be a sign of serious medical pathology, but small differences are common in healthy individuals. This condition is called benign or physiologic anisocoria (BA) and has been described in numerous ophthalmology publications [1-6]. [7] presents compelling evidence that this physiologic anomaly is caused by sympathetic nervous system (SNS) asymmetry, one eye receiving greater SNS activation than the other. Consistent with this thesis, asymmetry has been observed in several functional domains of the SNS, and most results suggest that the right side of the brain is more sympathetically active than the left. For example, stimulating the right-hemisphere with left-eye monocular viewing produces larger pupil dilation than when the left-hemisphere is stimulated [8,9]. Right-hemisphere lateralization has also been found in sympathetic cardiovascular control [10-15]. Likewise, many studies provide evidence that the right-hemisphere plays a special role in sympathetically-driven emotional experience [16-21].

While these studies present convincing evidence of SNS lateralization, the distribution of this asymmetry has not been quantified (owing in part to the relatively small sample sizes in these studies). Do most individuals exhibit right-lateralized SNS function? Are there sex differences in the direction and magnitude of SNS laterality, as there are in other domains of psychological function and brain structure? [22-26]. The distribution of BA may provide answers to these questions. BA is typically measured by subtracting the diameter of the left pupil from that of the right, so its sign indicates which pupil is larger, and thus which side of the brain is more active with regard to SNS function. If most individuals do in fact exhibit right-lateralized SNS function, then the central tendency of the BA distribution should reflect this laterality and be shifted or skewed away from a value of 0.0. Likewise, if gender, ethnicity, and other participant variables relate to the incidence and direction of SNS asymmetry, then these factors should also influence the BA distribution. One of the advantages of using BA as a marker of SNS asymmetry is that pupil size can be easily and unobtrusively collected in parallel with other physiologic and psychological variables, thus providing a new approach to studying the relationship between autonomic and psychological function.

In the present study, I will analyze anisocoria data from two large databases in order to develop an estimate of the population-wide distribution of SNS lateralization. [27] was the first to measure BA in the context of a psychology study, and demonstrated that it is related to psychological factors, including personality, gender, and attentional function. But in that study, the pupillometry data were collected while subjects engaged in tasks that varied in cognitive/attentional load and illumination levels. Thus, the BA distribution was likely influenced by variations in light-evoked and task-evoked pupillary responses [28] In the present study I use a large archive of facial photographs taken under conditions in which the subjects were at rest, with no cognitive demands, similar in that respect to ophthalmology studies cited earlier [5]. Results of this study will validate our earlier findings of 1) substantial individual differences in BA (and presumably SNS asymmetry), 2) a small but significant bias in the direction of lateralization (right pupil smaller than left), and 3) a sex difference in the direction and magnitude of Mean BA, suggesting a similar sex difference in SNS asymmetry.

Methods

A total of 397 high-resolution (3008 X 2000) color face photographs were obtained from the Chicago Face Database collection, which can be obtained at:

http://faculty.chicagobooth.edu/bernd.wittenbrink/cfd/download/download.html

[14] describes the purpose of the database, photographic methods, face-feature measurements, etc. Photographs were of relatively young individuals (Mean age = 29.6) posed in well-standardized front-facing posture and neutral facial expression (see Figure 1). The subjects were of 4 ethnic classes (Asian (F = 51, M = 50); Black (F = 48, M = 46); Latino (F = 48, M = 50); White (F = 52, M = 53)). A microscope photo-analysis software application (OMAX Toup View) was used to visually outline the pupil contour and thus measure pupil diameter (Figure 1b). Between 50-58 photos within each Gender X Ethnicity group were available for examination, but the luminance/color contrast between pupil contour and iris were in some instances too low to allow accurate measurement of pupil diameter. Two measurements were taken on each pupil at 600% magnification, and the average diameter used in further analysis (Figure 1).

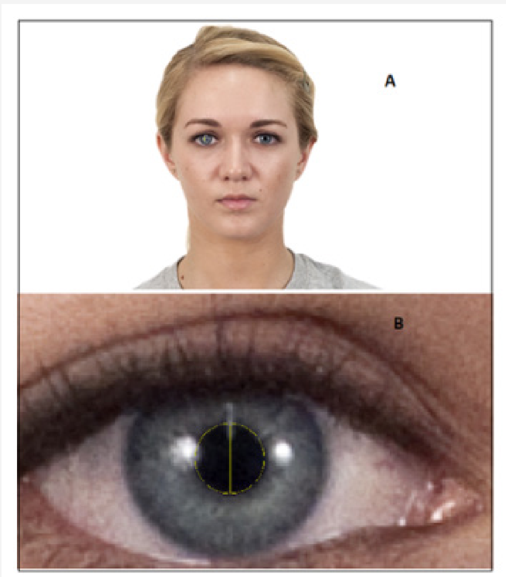

Figure 1: (A) face photograph from the Chicago Face Database (B) magnification of the left eye of the same photograph, showing software outline of pupil contour and diameter.

Result

BA equals right-pupil diameter (R) minus left-pupil diameter (L), in millimeters. Figure 2 presents frequency distributions for females and males. Mean values were offset from zero in opposite directions ($\overline{BA}_{male}$ = - 0.055; $\overline{BA}_{female}$ = + 0.024). Both Means were significantly (Figure 2). different from zero (females; t (197) = 2.3, p. = 0.02; males; t (198) = 4.1, p. < 0.001), and also significantly different from each other (t (395) = 4.95, p < 0.001). 30% of females exhibited a positive BA bias and 23% a negative bias; 42% of males exhibited a negative BA bias and 23% a positive bias. Sex differences were consistently observed across ethnicity levels, and ethnicity was not related to BA (Figure 3). Figure 4 shows that the sex difference was primarily driven by right-pupil size, which was significantly different between males and females (F = 2.85; M = 2.75: t (395) = 2.26, p. = 0.02). The difference in left pupil size was not significant (F = 2.83; M = 2.81: t (395) = 0.46, p. = 0.64).

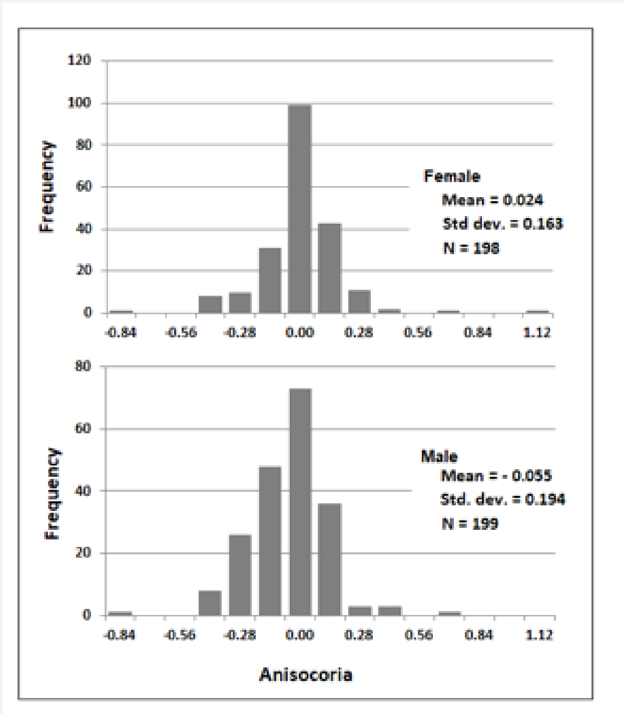

Figure 2: BA frequency distributions for females and males (Chicago Face Database only).

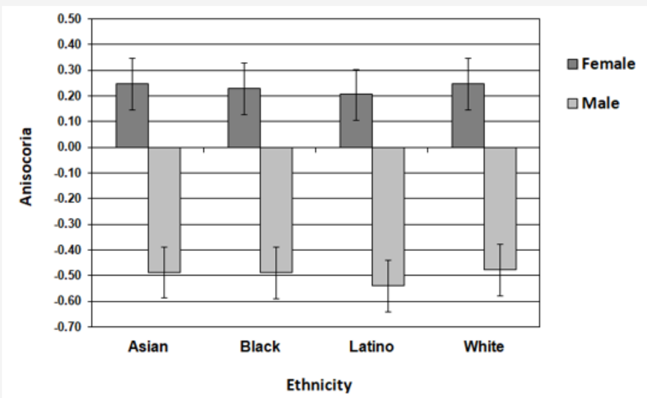

Figure 3: Sex differences were consistent across ethnicity levels, and ethnicity was not related to BA.

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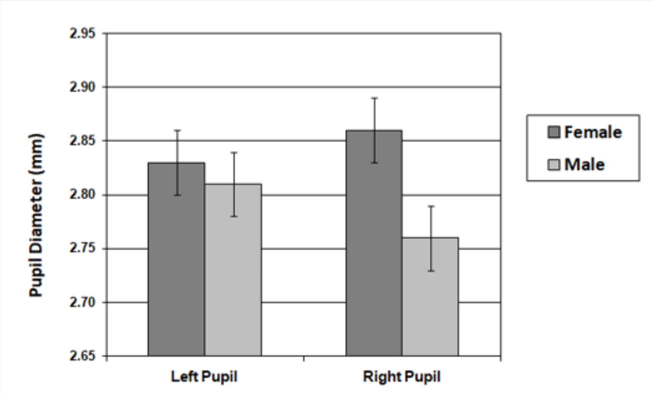

Figure 4: Difference in the size of the right pupil distinguished females and males.

(Figure 3&4).

Table 1: BA summary statistics.

Summary Statistic		Chicago Face Database N = 397)	Poynter Database (N = 310)	Combined (N = 707)
Mean	Overall	-0.016	-0.021	-0.017
	Female	0.024	0.008	0.019
	Male	-0.055	-0.051	-0.054
Standard Deviation	Overall	0.183	0.158	0.173
	Female	0.163	0.154	0.159
	Male	0.194	0.15	0.178
Significant Female-Male Difference?	BA	Yes	Yes	Yes
	Average Pupil Size	No	No	Yes \ Female > Male
	Right	Yes	Yes	Yes
	Pupil Size	Female > Male	Female > Male	Female > Male
	Left Pupil Size	No	No	No

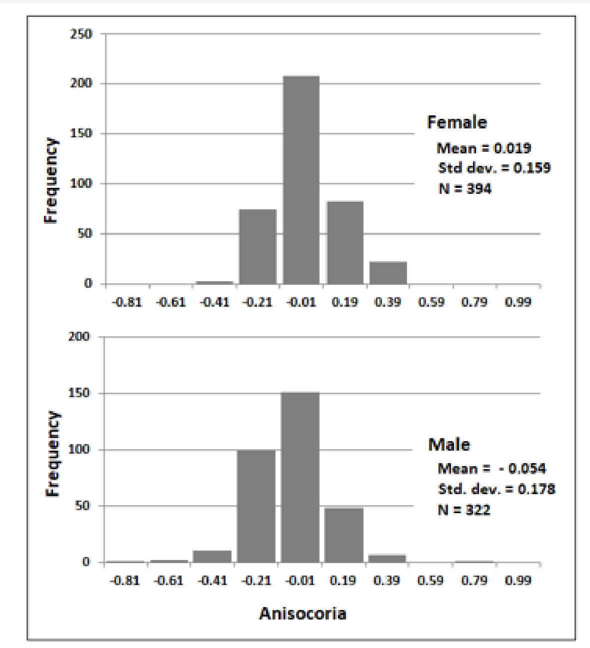

Figure 5: BA frequency distributions for females and males (both databases combined).

These same sex differences were observed in [27], but a different BA metric was used there. So, for purpose of comparison, (Table 1) presents summary statistics for both studies using the (R-L) metric. Despite substantial differences in the subject samples and context within which subjects were measured (e.g., age and ethnicity mix, illumination levels, subject's visual/mental activities during measurement), results were quite similar. Data from both studies were combined to provide an overall summary (Table 1 & Figure 5).

Discussion

Benign anisocoria was measured in two large pupillometry archives (total N = 707). The data were broadly distributed (Figure 2&5), and ¯BA for both archives was slightly negative, as found in previous ophthalmology studies (Loewenfeld (1977): BA = ~ - 0.03 , N = 850; Smith, et al. (1979): BA = - 0.06, N=150). If BA is in fact a marker of SNS asymmetry, then the later varies substantially across individuals, but exhibits a modest bias to one side of the brain -- probably the right side, given the right-hemisphere dominance reported in most SNS-lateralization studies [8,10,12,14,15,29]. Assuming such a right-brain bias for the SNS pathways controlling pupil dilation [8] provide evidence of), then the negative ¯BA value (left pupil more often larger than right) suggests that the left pupil receives sympathetic innervation from the right hemisphere (i.e., contralateral innervation).

The sex difference in BA indicates there is also a sex difference in SNS lateralization. In both archives, ¯BA was significantly > 0.0 for females and < 0.0 for males, and the absolute difference of ¯BA from 0.0 was larger for males than females see (Figures 2&5). Thus, SNS function appears to be more unilaterally asymmetric for males than females (i.e., males more often present a right-brain bias). Females, on the other hand, present a more symmetric lateralization distribution, with a small bias toward the left brain. The finding that BA (and presumably SNS function) are more lateralized for males than females is consistent with an extensive body of research indicating that the male brain is less symmetric than the female brain, both in terms of function and architecture [21-23,25,26].

The sex difference in BA appeared to be driven primarily by right pupil size (females presented a significantly larger right-pupil than males, but no significant difference in left-pupil size -see Figure 4). Thus, sex differences in SNS lateralization may be primarily related to sympathetic function in the left-brain, with females exhibiting greater function than males. I have used the terms right-brain and left-brain, versus right/left hemisphere, because it is not clear whether SNS asymmetry related to pupil dilation originates in the cortex, brainstem, or elsewhere in the SNS pathways to the pupil. That said, there is evidence of SNS asymmetry at the hemispheric level. [8], for example, demonstrated that pupil dilation is greater when the right- versus left-hemisphere is activated by way of left- versus right-eye monocular viewing, respectively.

Conclusion

This study helps to clarify the statistical distribution of benign anisocoria in the human population and may provide new information about the distribution of SNS asymmetry. The sexual dimorphism in BA indicates that there are sex differences in SNS lateralization, which may in turn relate to other physiologic, behavioral, and cognitive traits (e.g., personality and attentional function [27]). Males more often present a negative BA value (right pupil smaller than left), perhaps suggesting that the left-brain is less sympathetically active in males versus females. Future studies that directly measure bilateral brain activity in addition to pupil size and other measures of SNS function (e.g., electrodermal response) are needed in order to validate the relationship between BA and SNS lateralization. Assuming this relationship is confirmed, BA may have value in psychology as a relatively convenient and unobtrusive measure of SNS asymmetry.

Acknowledgement

None.

Conflicts of Interest

No conflicts of interest.

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