ORIGINAL ARTICLE

A Case of Synchronised Pupillary and Nasal Cycling: Evidence for a Central Autonomic Pendulum?

Fion D. Bremner^a and Jonas Gälldin Nordström^b

^aNational Hospital for Neurology & Neurosurgery, London, UK; ^bHusie Health Centre, Department of General Practice, Skane University Hospital, Malmö, Sweden

ABSTRACT

We previously reported that some healthy individuals show alternating anisocoria. We now describe one such individual who also exhibits a classic nasal cycle (alternating periods of nasal congestion and decongestion). We made measurements of his pupil asymmetry and nasal asymmetry at 21 different time points and found that these variables were always synchronised such that greater nasal airflow was invariably found on the same side as the larger pupil. We hypothesise that a common central oscillator may be responsible for co-modulating the sympathetic outflow to both nasal vessels and iris dilator muscles in some healthy individuals.

ARTICLE HISTORY

Received 28 February 2017
Revised 29 March 2017
Accepted 30 March 2017

KEYWORDS

Anisocoria; autonomic; nasal cycle; pupil

Introduction

Physiological anisocoria is common: around 20% of the normal population have at least 0.4 mm difference in the sizes of their right and left pupils.¹ However, the cause of this pupillary asymmetry in healthy individuals remains unexplained. On the one hand, it may be due to local factors within the eye (for example, differences in the anatomy or physiology of the iris muscles, stroma, or anterior segment between the two eyes). Alternatively, physiological anisocoria may have a neural basis as a result of asymmetric outflow from the autonomic nervous system. Some support for the latter mechanism was provided by Rosenberg² who used the friction sweat test to assess sudomotor activity on the forehead of healthy subjects with anisocoria; his data showed good correlation between sweating and pupil size, implying there is “sympathetic dominance” on the side of the larger pupil. In our own study some years later, we described a rare but interesting phenomenon seen in a small number of otherwise healthy individuals that we called “benign alternating anisocoria”.³ In these cases the pupil asymmetry “flips” every few hours, with no observed instances when both pupils are equal in size. We hypothesised that this unusual pupil behaviour is due to a

central oscillator causing alternating (reciprocal) variation in the sympathetic pupillomotor outflow.

Another example of alternating lateralisation of sympathetic outflow is the nasal cycle. This phenomenon, which was first described over 100 years ago,⁴ consists of periods of reciprocal congestion and decongestion of the right and left nasal spaces, typically with a cycle time of a few hours. It is present in 20–40% of the normal population and can also be demonstrated in other mammals, although its function remains a subject of continued debate.⁵ The effector for this phenomenon appears to be variations in the sympathetic outflow to the nasal venous sinusoids, an increase in sympathetic activity causing increased airflow by decongesting the nasal space.⁶ The central control of this cycle is thought to be both in the hypothalamus and also in the reticular formation of the brainstem, and it is in the latter location that it has been proposed that there are reciprocal oscillators giving rise to this alternating cycle.⁷ The question of whether the autonomic lateralisation evident in the nasal cycle is confined to the nasal mucosa or is part of a more generalised ultradian rhythm has attracted much interest. There is some evidence that the nasal cycle is synchronized, with alternating patterns of activity in the two cerebral hemispheres,⁸ and also affected by rapid eye

movement (REM) and non-REM sleep cycles.⁹ However, there is no good evidence of spread of autonomic lateralisation to other functions within the face in subjects with a classic nasal cycle—indeed, in one study, measurements of the skin temperature on the cheek showed no correlation with the nasal cycle¹⁰ despite both variables being under the control of sympathetic vasomotor fibres.

We wondered if the sympathetic supply to the pupil varies with the nasal cycle. We are not aware of any studies specifically designed to address this question, but Eccles and Eccles¹¹ refer to a paper from 1951 in the German literature in which transient alternating anisocoria was observed after unilateral stellate ganglion blockade. However, the cycle time was rather short (1 hour) and the oscillation persisted only for a few hours, so this may simply be an example of an unstable system reaching a new equilibrium rather than evidence of an intrinsic naso-pupillary rhythmicity. Part of the challenge in answering this question is that most healthy people have only small degrees of anisocoria. Moreover, in our previous study,³ we provided evidence that physiological anisocoria generally does not show reciprocal cycling. However, in the present study, we present new data from one individual who exhibits *both* benign alternating anisocoria and a classic nasal cycle. Our results show that in this unusual situation, the sympathetic vasomotor outflow to the nose and pupillomotor outflow to the eye are synchronised—implying that they are both under the central control of the same hypothalamic or brainstem oscillator.

Materials and methods

The subject is a 34-year-old Caucasian male in good general health who takes no regular medications. Both prenatal and post-natal development was entirely normal, and there is no history of any subsequent trauma or disease affecting the eyes, the nose, or the central nervous system. Whilst a medical student the subject became aware that he has unequal pupils but that the larger pupil is sometimes in the right eye, sometimes in the left eye; however, photographs confirm that this pupil behaviour has been present all of his life. Similarly, he has always known that there are times when he can breathe more easily through one nostril but at other times through the other nostril, apparently

switching every few hours. The subject gave informed consent to participate in these experiments, which adhered to the guidelines proposed in the Declaration of Helsinki.

For the purposes of this study, the subject used a webcam on his laptop computer to record a short video segment each day for 21 consecutive days. All recordings were done in the same place under similar (artificial) lighting conditions, maintaining a similar distance between subject and camera; the timing of the recording was determined only by the convenience to the subject and varied from day to day (ranging between 12:00 and 21:26). In each recording, the subject was first instructed to look at the camera for a few seconds, allowing the relative size of his pupils to be determined (Figure 1A). He was then asked to breathe out through his nostrils onto a mirror and hold it up to the camera so that the relative amounts of condensation from each nostril could be compared (the “hygrometric method for assessing nasal airflow; see Figure 2A). A typical recording lasted less than 30 seconds.

All 21 video segments were transferred to London for further analysis. For each video segment, two single frames were extracted—one showing the pupil sizes, the other showing the areas of condensation on the mirror corresponding to the air breathed out through each nostril. Although the choice of which frame to extract was arbitrary (and based in practice on which image was clearest), it was observed in all cases that the same relative differences between right and left pupil sizes or between right and left nasal

Figure 1. Single frames extracted from the same video segment showing (A) pupil sizes and (B) areas of condensation on a mirror caused by breathing out through both nostrils. In this video segment, both the larger pupil and the larger area of nasal condensation lie on the right side.

Figure 2. Pupil asymmetry. (A) Consecutive estimates of the difference in pupil area (right – left) across all 21 time points. (B) Frequency histogram of these estimates showing a bimodal distribution.

condensation areas persisted throughout each video segment—in other words, frame choice did not affect this comparison. The image analysis software supplied with the Topcon TRC-50DX mydriatic retinal camera was used to manually draw round these images, allowing quantitative estimations of the difference in right and left pupil areas, or right and left nasal condensation areas. Since it is the relative sizes rather than the absolute measurements that are of interest, no attempt was made to calibrate these images; all measurements have therefore been expressed in the proprietary units (pixels squared). Standard statistical methods were used to evaluate the distribution of these pupil or nasal asymmetry estimates and their degree of concordance across the 21 separate time points.

Results

Measurements of pupil area showed that on some occasions, the right pupil was larger than the left, whereas on other occasions the anisocoria reversed (Figure 2A). However, there were no occasions when the pupils were the same size, and a frequency

histogram of these estimates of pupil asymmetry confirms that their distribution is bimodal (Figure 2B), with approximately equal numbers of occurrences of a larger right pupil and a larger left pupil. Measurements of the nasal condensation area showed a similar alternating pattern. Greater nostril patency was sometimes observed on the right side and sometimes on the left side (Figure 3A), but there were no occasions when the condensation areas were similar from both nostrils. Accordingly, a frequency histogram of these nasal asymmetry estimates also shows their distribution to be bimodal (Figure 3B).

The concordance of this pupil and nasal asymmetry across the 21 different time points has been evaluated. Figure 4A shows both pupil and nasal asymmetry estimates for each consecutive observation. It can be seen that whenever the right pupil was larger than the left, there was also a larger area of nasal condensation from the ipsilateral nostril (upward bars), and vice versa (downward bars). No instances were observed in which the larger pupil and the more patent nostril were on opposite sides. The estimates of pupil asymmetry and nasal asymmetry have been displayed on a scatter plot in Figure 4B.

Figure 3. Nasal asymmetry. (A) Consecutive estimates of the difference in nasal condensation area (right – left) across all 21 time points. (B) Frequency histogram of these estimates showing a bimodal distribution.

Figure 4. Comparing pupil and nasal asymmetry. (A) Consecutive estimates of the differences in pupil area (black) and nasal condensation area (grey) across all 21 time points. The estimates of nasal asymmetry were scaled down by a factor of 30 to allow them to be plotted on the same scale. (B) Scatter plot of pupil (abscissa) and nasal (ordinate) asymmetry estimates; there is perfect concordance, with no instances observed when the larger pupil and the larger nasal condensation area were on opposite sides.

This confirms perfect concordance between these variables, with an approximately equal chance of observing asymmetry in both directions, and no instances found of symmetry (i.e., similarly sized pupils or nostrils) or discordant asymmetry.

Discussion

Asymmetry in pupil size or nasal patency is not uncommon within the healthy population, and in some cases it may be attributed to structural differences between the eyes or nasal passages (for example, a deviated nasal septum). However, in this case, the asymmetry swaps direction every few hours, behaviour that is more likely to reflect changes in the neural balance of autonomic outflow to these organs. The parasympathetic supply to the nasal cavity is mainly responsible for controlling nasal secretions and is not thought to make any significant contribution to nasal patency.¹² Short-term variations in nasal patency associated with the nasal cycle are therefore considered to be driven by changes in the sympathetic outflow.¹³ Variations in physiological anisocoria over time may of course be caused by changes to either parasympathetic or sympathetic outflow, and in this study we do not have any pupillometric data that would allow us to distinguish which mechanism is responsible. However, the subject, who is medically qualified, has confirmed that both pupils seem to show symmetric constriction to a light stimulus despite their asymmetric resting sizes, soft evidence that there is no lateralisation of parasympathetic outflow. On this basis, we suggest

that both the changes in nasal patency and pupil size in our subject are primarily caused by changes to the sympathetic outflow. Interestingly, the post-ganglionic sympathetic fibres supplying the nose and the iris arise from the same superior cervical ganglion.

The data presented in this report show for the first time that these variations in the sympathetic “tone” to nasal vessels and iris muscles are synchronised—over 21 different time points there was perfect concordance in our subject, implying they are both under the control of the same central oscillator. Moreover, the quantitative analysis suggests not only a common underlying rhythmicity but also reciprocity: when one pupil becomes larger, the other becomes smaller (and vice versa), and similarly the areas of nasal condensation show opposite changes in different phases of the nasal cycle. Stoksted¹⁴ originally proposed the hypothalamus as responsible for the nasal cycle, but later work in cats showed that hypothalamic outflow is distributed equally to both sides and cannot alone account for asymmetric outflow.¹⁵ Further studies identified an area of the brainstem that probably loosely corresponds to the reticular activating system that when stimulated produced reciprocal effects on the nasal mucosa, with ipsilateral vasoconstriction and contralateral vasodilation.⁶ We assume the same oscillator is responsible for the benign alternating anisocoria exhibited by our subject, although the precise location within the brainstem has yet to be established.

This report describes observations made on just one individual subject, and the question arises as to

whether our findings apply more generally. We have not yet extended our study to other individuals with benign alternating anisocoria, although we have no reason to doubt that similar results would be obtained. However, classical nasal cycling is found in less than half the normal population,¹⁶ and the prevalence of benign alternating anisocoria is unknown but probably also uncommon. It therefore follows that most healthy people have no asymmetry in pupil size and nasal patency, or an asymmetry that remains stable over time. It remains to be seen whether there is any concordance between pupil and nasal asymmetry at a population level in those more typical individuals who show no cyclical variation in these parameters. Moreover, there are other patterns of temporal variation described both for nasal patency and pupil size. Some otherwise healthy individuals exhibit unilateral intermittent mydriasis (sometimes called a “springing pupil”)¹⁷; this phenomenon differs from benign alternating anisocoria insofar as the pupil change is unilateral rather than reciprocal, and episodic not cyclical. However, it would be interesting to investigate whether there is any corresponding change to nasal patency ipsilateral to the dilated pupil during these “attacks”.

Our subject confirms that he has been aware of alternating nasal and pupil asymmetry all his life; in other words, this behaviour appears to be “constitutional” rather than any transient response to an environmental stressor or illness. He is not consciously aware of the relative sizes of his pupils but knows which nostril he can breathe more easily through and can use that information to predict with complete accuracy which pupil is larger. The cycle period seems to be of the order of a few hours, although this has not been formally measured and varies over time. Similar changes over time to the nasal cycle have been reported in other studies,¹⁸ and there is also a tendency for the nasal cycle to become less apparent with age.¹⁹ Our subject is not aware of any other synchronised changes in neural function—either affecting the central nervous system or the autonomic nervous system. However, other studies have reported changes in various neural (verbal and spatial task performance²⁰) and endocrine (circulating catecholamines²¹) functions that synchronise with the nasal cycle, and it would be interesting to investigate whether there are

subtle changes in these functions that have not been noticed by our subject.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

References

- [1] Lam BL, Thompson HS, Corbett JJ. The prevalence of simple anisocoria. *Am J Ophthalmol* 1987;104:69–73.
- [2] Rosenberg ML. Physiologic anisocoria: a manifestation of a physiologic sympathetic asymmetry. *Neuro-Ophthalmology* 2008;32:147–149.
- [3] Bremner FD, Booth A, Smith SE. Benign alternating anisocoria. *Neuro-ophthalmology* 2004;28:129–135.
- [4] Kayser R. Die exacte messung der luftdurchgangigkeit der nase [The exact measurement of the air permeability of the nose]. *Arch Laryngol* 1895;3:101–120.
- [5] White DE, Bartley J, Nates RJ. Model demonstrates functional purpose of the nasal cycle. *Biomed Eng Online* 2015;14:38.
- [6] Bamford OS, Eccles R. The central reciprocal control of nasal vasomotor oscillations. *Pflügers Arch Eur J Physiol* 1982;394:139–143.
- [7] Williams M, Eccles R. A model for the central control of airflow patterns within the human nasal cycle. *J Laryngol Otol* 2016;130:82–88.
- [8] Werntz DA, Bickford RG, Bloom FE, Shannahoff-Khalsa DS. Alternating cerebral hemispheric activity and the lateralization of autonomic nervous function. *Hum Neurobiol* 1983;2:39–43.
- [9] Kimura A, Chiba S, Capasso R, Yagi T, Ando Y, Watanabe S, Moriyama H. Phase of nasal cycle during sleep tends to be associated with sleep stage. *Laryngoscope* 2013;123:2050–2055.
- [10] Preece M, Eccles R. The relationship of skin temperature to the nasal cycle in normal subjects. *Rhinology* 1994;32:20–24.
- [11] Eccles R, Eccles KS. Asymmetry in the autonomic nervous system with reference to the nasal cycle, migraine, anisocoria and Meniere’s syndrome. *Rhinology* 1981;19:121–125.
- [12] Änggård A. The effects of parasympathetic nerve stimulation on the microcirculation and secretion in the nasal mucosa of the cat. *Acta Otolaryngol* 1974;78:98–105.
- [13] Eccles R, Wilson H. The autonomic innervation of the nasal blood vessels of the cat. *J Physiol* 1974;238:549.
- [14] Stoksted P. Rhinometric measurements for determination of the nasal cycle. *Acta Otolaryngol* 1953;43(Suppl 109):159–175.
- [15] Eccles R, Lee RL. The influence of the hypothalamus on the sympathetic innervation of the nasal vasculature of the cat. *Acta Otolaryngol* 1981;91:127–134.

- [16] Flanagan P, Eccles R. Spontaneous changes of unilateral nasal airflow in man. A re-examination of the 'nasal cycle'. *Acta Otolaryngol* 1997;117:590–595.
- [17] Jacobson DM. Benign episodic unilateral mydriasis: clinical characteristics. *Ophthalmology* 1995;102:1623–1627.
- [18] Williams MR. *A Pilot Study on the Stability of the Human Nasal Cycle* [doctoral dissertation]. Cardiff, UK: Cardiff University; 2016.
- [19] Williams MR, Eccles R. The nasal cycle and age. *Acta Otolaryngol* 2015;135:831–834.
- [20] Klein R, Pilon D, Prosser S, Shannahoff-Khalsa D. Nasal airflow asymmetries and human performance. *Biol Psychol* 1986;23:127–137.
- [21] Kennedy B, Ziegler MG, Shannahoff-Khalsa DS. Alternating lateralization of plasma catecholamines and nasal patency in humans. *Life Sci* 1986;38:1203–1214.