Nasal airflow and hand preference: Is there a link?

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Summary

In recent years, evidence has emerged suggesting that nasal airflow asymmetry and brain asymmetry may be linked. The nose is unique in that it exhibits asymmetrical airflow with the dominant airflow alternating from one nasal passage to the other over a period of hours. The cerebral hemispheres also exhibit both functional and structural asymmetry, and one of the most obvious manifestations of this is hand preference. Over ten years ago, it was suggested that nasal airflow dominance and hand preference were linked. The aims of this thesis were to explore the literature relating to nasal airflow and brain activity and to conduct a cross-sectional observational study looking for a correlation between nasal airflow and hand preference in healthy individuals.

The modified Glatzel Mirror was used to record the dominant nasal passage at 15-minute intervals over a 6-hour period in 29 healthy subjects, of whom 15 were left-handed and 14 were right-handed, as measured by the Edinburgh Handedness Inventory (Short Form).

As expected based on previous studies, there was considerable variability in the nasal airflow patterns of the individuals observed, but over half demonstrated at least one definite and sustained reversal of nasal airflow dominance. No correlation between nasal airflow dominance and hand preference was identified.

Asymmetrical cerebral organisation may offer advantages for complex actions such as speech and hand gestures. Nasal airflow is controlled by the autonomic nervous system and the function of asymmetrical nasal airflow is most likely immune defence and air-conditioning. Having a dominant nasal passage, comparable to having a dominant hand, would not therefore be physiologically advantageous. The results presented here, along with further evidence from the literature, do not support the previously reported correlation between hand preference and nasal airflow.

Contents

Chapter 1: Introduction A (Overview)

1.1: Nasal airflow asymmetry

The nose is a unique organ in that it exhibits asymmetrical airflow with the dominant airflow alternating from one nasal passage to the other over a period of hours (1). Changes in nasal airflow are mediated by alternating dilation and constriction of the venous erectile tissue in the nasal mucosa, by action of the sympathetic nervous system (2). This alternation of nasal airflow is often described as a "nasal cycle" as it can be regular and reciprocal (1, 3-5). The first description of this phenomenon is attributed to Kayser in 1895 (6). Sen (1901) documented observations of his own nasal mucosa, stating that the alternating congestion and decongestion of the nasal erectile tissue occurred with "clockwork-like regularity" (7). More recent evidence has suggested that regular periodicities are not always present and that there is significant inter-individual variation in both reciprocity and rhythmicity (8, 9), contradictory to the term "cycle". Patterns of nasal airflow also vary within individuals, with a lack of reproducibility seen when measurements of airflow are repeated on different days (10, 11). Nonetheless, the presence of asymmetrical nasal airflow that fluctuates spontaneously throughout the day has been established by multiple studies (4, 8-13).

1.2: Defining the nasal cycle

As mentioned above, there is some confusion in the literature surrounding the definition of the nasal cycle. Gilbert and Rosenwasser (1987, p.180) suggest that according to the classical idea of reciprocal and regular alternations of nasal airflow referred to as the nasal cycle, "the left and right sides have identical periods, are 180 degrees out of phase, and have similar mean airflow and amplitude" (8). However this is not necessarily the case, and in many studies the term nasal cycle is used to

describe any asymmetries or patterns seen in nasal airflow. Without a clear definition of what constitutes a nasal cycle, results of research studies can be difficult to interpret. This issue was highlighted by Flanagan and Eccles (1997) who developed numerical parameters to define the spontaneous changes in nasal airway resistance commonly referred to as the nasal cycle (13). The numerical parameters suggested were the correlation co-efficient (r value) and airflow distribution ratio (ADR) (13). The correlation co-efficient is a measure of reciprocity ranging from -1, which would indicate a strict reciprocal relationship, to +1, which would indicate a strictly in-phase relationship (13). The ADR is a measure of the relative volume of airflow through each nasal passage calculated as a percentage of the total volume of airflow over an eight-hour period, with a range of zero to one, where one indicates that the distribution of airflow between the two nasal passages has been equal over time (13). The authors argue that in order to be classed as a nasal cycle, patterns of nasal airflow should exhibit a certain degree of reciprocity as well as equal volume distribution between the nasal passages, and define this as an r value above 0.6 and an ADR above 0.7 (13). Using these numerical definitions, only 21% of healthy subjects demonstrated a nasal cycle, although the majority exhibited a trend towards reciprocity and equalisation of airflow suggesting some sort of pattern in nasal airflow changes (13).

Hasegawa and Kern (1978) defined the nasal cycle in rhinomanometric terms as a change of nasal airway resistance of 20% or more comparing each nasal passage for two consecutive observations at least 15 minutes apart (10). Using this definition they found that 72% of 50 subjects observed over a 7-hour period had at least one nasal cycle (10).

Huang et al. (2003) defined the nasal cycle as significant negative correlation between the two nasal passages, but did not specify what they deemed to be significant (14). In their analysis of 10 subjects, only 5 exhibited a nasal cycle as per this definition (14).

Kern (1981) suggested the term “non-cycle nose” to describe individuals without the classical features of a nasal cycle (9). After studying nasal airflow patterns in 14 subjects who did not have a nasal cycle, he suggested three categories for the non-cycle nose (9):

1. No change in nasal resistance.
2. Moderate fluctuations in nasal resistance in one nasal passage but no change in the opposite side.
3. Fluctuations in nasal resistance in both nasal passages but no reversal of dominance i.e. greater airflow from one side to the other (in-phase relationship).

Gallego et al. (2006) looked at the patterns of nasal airflow in children aged 2-11 years and categorised the nasal cycle into four types (15):

- Classic – congestion in one nasal passage with accompanying decongestion in the other but no change in the total nasal airway volume, i.e. a reciprocal relationship.
- Parallel – alternating congestion and decongestion with an in-phase relationship.
- Irregular – changes in total nasal airway volume but with no discernable pattern.
- No pattern – no changes in the unilateral or total nasal airway volume i.e. no nasal cycle.

Interestingly, all subjects demonstrated some sort of nasal cycle, but the majority (50%) had an irregular pattern (15). It should be noted however that this was a short study with a measurement period of only 3 hours, and it could be argued that patterns may have emerged or changed over a longer time period.

Whilst several authors have attempted to define what constitutes a nasal cycle using different methods, a general consensus has not yet been reached. The presence of fluctuating patterns of nasal airflow is not disputed, but the term “cycle” is probably not appropriate given that in many individuals rhythmic and reciprocal alternations

in nasal airflow do not occur. For the purposes of brevity and clarity, fluctuating patterns of nasal airflow will be referred to as the nasal cycle in subsequent introductory chapters.

1.3: Function of the nasal cycle

The nasal passages are the natural point of entry for air into the respiratory tract in healthy humans, despite having a greater resistance to air flow compared to the oral cavity (16). The principal function of the nose is to prepare inspired air for rapid gaseous exchange in the lungs (17). This requires cleaning and filtering, heating and humidification. However the exact purpose of the nasal cycle remains unclear.

Since the nasal mucosa continuously comes into contact with pathogens encountered in inspired air, Eccles (1996) suggested that the nasal cycle may have a role in respiratory defence (18). The nasal mucosa has a rich blood supply, with arteries that emerge from the bony walls of the nasal cavity to terminate in capillary networks situated in the subepithelial layers of the mucosa (17). These capillaries drain into venous sinusoids which form venous plexuses deeper in the mucosa (17). The venous plexuses are often referred to as erectile tissue as they contain smooth muscular walls and can be closed by sphincter muscles (17, 19). Histological studies in rabbits revealed the presence of endothelial fenestrations in the subepithelial venous sinusoids of the nasal mucosa in the regions of the nasal septum and turbinates (20, 21). Interestingly, these fenestrations were seen to open towards the adjacent epithelium, and were not present in the veins situated deeper in the nasal mucosa (21). Based on these findings, Grevers (1993) suggested that these fenestrated veins were probably involved in the regulation of nasal fluid secretion (21). The exudation of plasma from the nasal mucosal vessels is important as a first line defence mechanism (22). Not only does the plasma exudate contain immunoglobulins and pro-inflammatory proteins, but in addition the flow of exudate onto the mucosal surface could help wash away pathogens and foreign material (18).

The alternating congestion and decongestion of the venous sinusoids, known to produce the nasal cycle, could in fact be acting as a pump mechanism for the secretion of plasma exudate (18). During the congested phase, hydrostatic pressure will be increased in the venous sinusoids due to the higher blood volume, and this could aid the formation of plasma exudate (18). Following on from this, contraction of the smooth muscle in the walls of the veins during the decongestive phase could squeeze the exudate through the fenestrations towards the mucosal surface (18). This theory is supported by observations of an increase in the amplitude of the nasal cycle associated with upper respiratory tract infection (23), wherein the exaggerated congestion and decongestion in the venous system could lead to increased production of plasma exudate that is rich in immunoglobulins and pro-inflammatory proteins (18).

It has also been suggested that the nasal cycle may be involved in controlling the balance of heat and water exchange required to condition inspired air in preparation for gaseous exchange in the lungs (16). The nasal airway is lined with liquid, sometimes termed airway surface liquid (ASL), which is derived from the epithelium and submucosal glands and consists of a periciliary layer with overlying mucus (24). This fluid is required for the humidification of inspired air and for the transport of trapped pathogens (24). Effective mucus clearance, and hence clearance of trapped pathogens and particles, is inhibited if the ASL becomes dehydrated (25). Using computer models, White et al. (2015) demonstrated a possible role for the nasal cycle in dealing with the difficulties of simultaneously carrying out both of these important functions, i.e. air-conditioning and mucociliary clearance (26). Efficient heating and humidification requires higher airflow velocities, whereas efficient mucociliary transport requires lower airflow velocities (26). During the decongested phase of the nasal cycle, severe dehydration of the ASL occurs due to the greater airflow though the nasal passage (26). Conversely, during the congested phase, the reduced airflow results in only minor dehydration of the ASL which leads to improved mucociliary clearance (26). Alternating the partitioning of airflow through each nasal passage allows for one side (the congested side) to maintain its ASL and carry out effective mucociliary clearance, whilst the other side receives the greatest

proportion of inspired air which can be efficiently heated and humidified but consequently leads to ASL dehydration (26). This then switches over, reducing the amount of time that each nasal passage is exposed to drying conditions and perhaps more efficiently carrying out the principle functions of the nose – filtering, heating and humidification of inspired air (26).

1.4: Duration of the nasal cycle

The reported duration of the nasal cycle varies widely in the literature. This may in part be due to the problems surrounding the definition of the nasal cycle, as discussed above. In addition there is significant variability both within and between individuals, and a lack of reproducible findings when the same measurements are repeated in the same individuals but on different days (10, 11). Table 1 gives some examples of average nasal cycle durations previously reported in the literature. There are varying methods of measurement and sampling intervals, which again could be a factor for the significant variability seen. As shown in Table 1 the shortest duration recorded is 20 minutes (27) and the longest is 7.3 hours (8). The short duration of 20 minutes was recorded using continuous portable rhinoflowmetry during wakefulness, and the device was given to participants so that recording could take place during their normal daily activities (27). A longer cycle duration was recorded during sleep (27), which has been echoed in other studies (28). Tahamiler et al. (2009) recorded another short duration of 30 minutes using Odiosoft-Rhino, a software programme that detects the sounds generated during normal nasal breathing (29). Their sampling period was 30 minutes, longer than some of the other studies that failed to demonstrate a periodicity of less than 1 hour (10, 30). Interestingly, they made their recordings by installing the programme on the subjects' own computers so that again the test could be carried out in the subjects' own environment rather than in a laboratory (as is the case for most studies) (29). They defined a nasal cycle as a statistically significant difference in the values obtained from each nasal passage (29), which does not take into account the

reciprocity and regularity usually considered to be the hallmarks of a cycle.

Table 1: Examples of nasal cycle durations reported in the literature and the different methods used to record them.

Study	Number of subjects	Age range (years)	Method of measurement	Duration of measurement (hours)	Sampling period (minutes)	Cycle length (hours)		
						Mean	S.D.	Range
Hasegawa and Kern 1978 (10)	50	24	Posterior rhinomanometry	7	15	2.9		1-6
Gilbert and Rosenwasser 1987 (8)	16	18-34	Anterior rhinomanometry	8	10	4.3	1.3	2.4-7.3
Gilbert 1989 (31)	9	18-30	Anterior rhinomanometry	8	5	4.5	1.0	3.5-6
Huang et al. 2003 (14)	10	18-32	Posterior rhinomanometry	6	10	3.5		2.3-4.4
Ohki et al. 2005 (30)	20	Mean age: 45.8	Portable rhinoflowmeter	12	Continuous	1.8	-	-
Tahamiler et al. 2009 (29)	20	24-30	Odiosoft-Rhino	12 hours on 4 different days	30	-		0.5-2.5
Rorhmeier et al. 2014 (27)	20	22-66	Portable rhinoflowmeter	23	Continuous	1.5		0.3-5.6

1.5: Control of nasal airflow

Changes in nasal airflow are mediated by alternating dilation and constriction of the venous erectile tissue in the nasal mucosa, by action of the sympathetic nervous system (2). The presence of a vasomotor supply to the nasal mucosa was first noted by Tschalussow in 1913 (32). Experiments on cats demonstrated that stimulation of the cervical sympathetic chain led to immediate vasoconstriction in the nasal veins, indicating the origin of the vasomotor fibres in the cervical sympathetic chain (33). Application of topical sympathomimetics causes decongestion of the nose and a marked increase in nasal airflow (34, 35). Conversely, blockade of the stellate ganglion or performance of a cervical sympathectomy are known to cause venous congestion and reduced nasal airflow (36, 37). In summary, increased sympathetic

tone causes vasoconstriction of the nasal veins, leading to an increase in nasal conductance, and reduction or blockade of sympathetic tone causes vasodilation of the nasal veins, leading to an increase in nasal resistance.

There is growing evidence for a central control mechanism of nasal airflow. Studies on anaesthetised cats led to the notion of collections of sympathetic neurons in the brainstem, so-called "oscillators", with an asymmetry in sympathetic discharge between the left and right oscillators resulting in asymmetry of nasal airflow between the left and right nasal passages (38). The dominance of sympathetic output alternates from left to right and vice versa, causing the reciprocal changes in nasal airflow, both spontaneously and in response to electrical stimulation of the brainstem (38). However it has been postulated that overall control occurs at the level of the hypothalamus, as in animal studies, electrical stimulation here caused an overall increase in sympathetic tone and greater nasal airflow bilaterally (33, 39). Therefore, with the hypothalamus as the generator of a rhythmic nasal cycle, increased or decreased hypothalamic output will stimulate the brainstem oscillators symmetrically, but these brainstem oscillators will influence nasal airflow asymmetrically due to their reciprocal differences in sympathetic discharge (11). This is summarised in Figure 1.

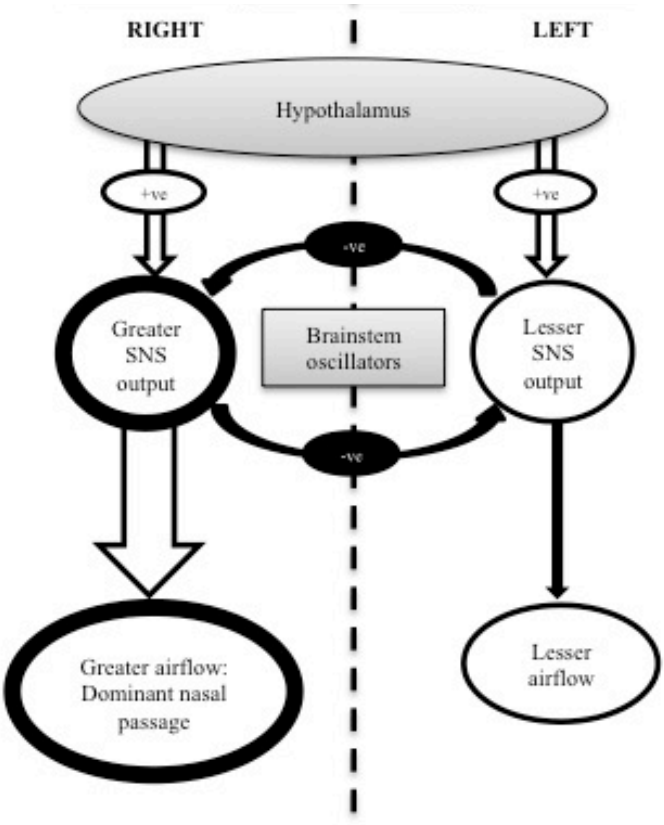

Figure 1: Model to explain the control of nasal airflow. The overall alternation in sympathetic activity over a period of hours is controlled by the hypothalamus and the asymmetry in sympathetic outflow is determined by the activity of brainstem oscillators which act as a flip flop mechanism, with each centre inhibiting the activity of the other centre and only one centre having dominant activity at any one time. These hypothalamic and brainstem mechanisms have been studied in the anaesthetised cat (38, 39).

Support for the existence of a central control mechanism determining the rhythmicity and asymmetry of nasal airflow has been gained from observational human studies. In a study of nasal airway resistance and axillary sweat production in 7 subjects, reciprocal alternating cycles with the same periodicity were seen for both nasal airflow and axillary sweat production (40). Although not present in every subject, it was found that an increase in right axillary sweating was associated with an increase in left nasal airflow (40). As sweating is controlled by the thermoregulatory centre in the hypothalamus via the sympathetic nervous system (41), the authors postulated the presence of a central cycle (40). Galioto et al. (1991) observed an anomalous or absent nasal cycle in a small cohort of patients

with Kallman syndrome, a disorder caused by hypothalamic hypoplasia (42). Studies on patients who had undergone laryngectomy revealed preservation of the alternations in nasal airflow patterns as seen in healthy individuals but in the absence of nasal airflow, reinforcing the notion of a central rather than local control mechanism (43, 44). Although the periodicities of the nasal cycle were similar in both the laryngectomy and control groups, the amplitude was significantly lower in the former group, and the authors have suggested that nasal airflow receptors could be modifying the underlying centrally-generated patterns of nasal airflow (44).

Cortical influence on the hypothalamus and brainstem in terms of the nasal cycle is yet to be established, however there is some evidence to support a link between cortical functions and nasal airflow, which will be discussed in detail later.

1.6: Sensing nasal airflow

The sensation of nasal airflow is believed to be mainly determined by stimulation of nasal trigeminal nerve endings that are sensitive to temperature changes, especially cooling of the nasal mucosa, as occurs during inspiration of air (1, 45, 46). This phenomenon has been reflected in studies on the effect of menthol on nasal airflow. Menthol caused a cooling sensation and a subjective improvement in nasal airflow in healthy subjects without any change in the total nasal airway resistance (47). Following the application of local anaesthetic to the nasal mucosa, the sensation of nasal airflow was diminished, as was the effect of menthol (48). Under physiological conditions, the spontaneous changes in nasal airway resistance between the nasal passages occur without being detected since the total nasal resistance remains relatively constant (18).

1.7: Measuring nasal airflow

Multiple techniques can be used to measure nasal patency, either in clinical practice or for research purposes. Subjective methods include use of a visual analogue scale (VAS) to assess the perception of nasal airflow (49), and questionnaires such as the sino-nasal outcome test 20 (SNOT-20) (50). Objective methods include evaluation of nasal cavity anatomy for example with computed tomography or acoustic rhinometry, and measurements of nasal airflow such as rhinomanometry or peak nasal flow rates (49, 51, 52). An objective measurement of nasal airflow is useful for the clinician as it will aid in the diagnosis of nasal obstruction and quantification of its severity, as well as in the assessment of treatment outcomes such as topical decongestant agents or surgical intervention. It is for these reasons that the ability to measure the airflow through each nasal passage separately is useful (53).

Any method used to measure nasal airflow should ideally preserve normal nasal anatomy and physiology, be easy to use and comfortable for the subject or patient, measure physiological flow and pressure, and provide reproducible and relevant results (54, 55). One of the challenges encountered when measuring nasal airflow is the physiological variability of resistance that occurs between inspiration and expiration and between each nasal passage due to the nasal cycle (53). As air is inspired through the nasal passages, the cartilages are drawn inwards, thereby increasing the resistance to nasal airflow. The opposite occurs during expiration.

The first attempts at objectively measuring nasal airflow were documented by Zwaardemaker in 1889, who used a cold mirror placed horizontally under the nose to measure the condensation area produced by expired air from each nasal passage (54, 56). This was the first hygrometric method used to measure nasal airflow (57). Although many more techniques have since been developed, no single method has become commonplace in clinical practice (53). Some examples of other methods used today to measure nasal patency are described below.

Peak nasal inspiratory flow rate (PNIF)

PNIF is a non-invasive method of measuring nasal airflow during maximal forced nasal inspiration (51). It therefore provides an indirect measurement of nasal airway resistance, as an increased resistance alters the peak flow rate achievable (58). However it is not a reflection of nasal resistance during normal breathing (51) and can miss smaller obstructions to nasal airflow (52). The device used is portable, relatively simple and requires minimal training of staff and subjects (58). Another advantage is the availability of baseline values for adults which can be used for comparison (52). Subject cooperation is required, and lack of effort or fatigue can affect the results (58). The subject's respiratory function and the presence of secretions can also have a confounding effect (51, 58).

Rhinomanometry

Nasal airflow occurs due to the pressure difference between the environment and the nasopharynx (51, 59). Rhinomanometry measures the pressure and airflow differences between the anterior and posterior nasal cavity that occur during the inspiration and expiration of air through the nose (59). These measurements of nasal airflow and pressure can then be used to calculate nasal airway resistance (58). Rhinomanometry can provide an assessment of each nasal passage separately or together, depending on the technique used. During anterior rhinomanometry, the sensing tube is taped to each nostril in turn providing a value for the nasal airway resistance for the left and right nasal passages separately (59). During posterior rhinomanometry, the sensing tube is placed in the subject's mouth, providing a measurement of the total nasal airway resistance (59). This technique requires subject co-operation and training which can be difficult (58). Rhinomanometry is considered to be more sensitive and specific than acoustic rhinometry (52). However it involves the use of more complex and bulky equipment, which is expensive, and as such it is more useful in research laboratories than in clinical practice (51, 58).

Acoustic rhinometry

Acoustic rhinometry involves the use of acoustic reflection to demonstrate the geometry and cross-sectional area of the nasal cavity (60). A sound wave is transmitted into the nasal passages, and the reflected wave patterns are detected and analysed (58). Variations in the size or contour of the nasal airway, for example septal deviation or the presence of a nasal polyp, will distort the reflected sound wave (51). Acoustic rhinometry does not require any nasal airflow to obtain measurement values, meaning that it can be used for the subject with a completely occluded nose (60). In addition, it does not require much subject participation or cooperation (60) and therefore is useful in children who could struggle with other methods. Studies have demonstrated good reproducibility, with a low coefficient of variation between repeated measurements (60). Acoustic rhinometry does however have several disadvantages. Should an obstruction in the anterior nasal cavity prevent transmission of sound waves, there is no way of measuring the area posterior to that obstruction, thus limiting the view of the overall nasal airway (60). It does not provide information about nasal airflow i.e. a measurement of nasal function (58), which can be more relevant to the patient and clinician than anatomical findings. It is also unable to measure each nasal passage separately, but provides a cross-sectional reflection of the nasal cavity (52).

Nasal spirometry

The technique of nasal spirometry was devised in 2001 as a method of measuring the distribution of nasal airflow through each nasal passage, termed the nasal partitioning of airflow ratio (NPR) (61). It provides a measure of the laterality of nasal airflow. A device is used to measure the volume of air expired from each nasal passage following maximal inspiration (61). It is easy to use by both the subject and the investigator, requiring minimal training (62). Other advantages of this method include its good correlation with rhinomanometry (61) and the availability of a reference range for healthy adults (63). The accuracy and reproducibility of nasal spirometry was demonstrated in a study using a model of the nasal cavity (64). It has also been used successfully in clinical studies, for example as an objective

measure of nasal septal deviation (62) and for detecting postural changes in nasal airflow in patients with acute rhinitis (65).

The modified Glatzel Mirror (GM)

Following on from the cold mirror method invented in the late 1800s, in 1904, Glatzel described a metallic mirror marked with four lines that could be used to quantify nasal airflow. This was modified by Cocks (1915) who added multiple horizontal curved lines and parallel vertical lines, both 1cm apart (66). To obtain a measurement, the mirror is held horizontally beneath the nostrils, and the subject is instructed to breath out through the nose normally, with the mouth closed (54, 66). The temperature difference between the nasal cavity and the plate causes condensation of the vapour in the expired air, producing a brief reflection of the nasal airway on the plate (54).

Gertner et al. (1984) described their technique in detail (54), and the reproducibility of this method specifically has been analysed more recently (55). The plate used was a 10cm x 12cm polished chrome-coated metal plate marked with arches at 1cm apart (54). The plate was positioned horizontally immediately under the collumela with the vertical axis at 90 degrees towards the upper lip (54). The patient was then asked to exhale through the nose slowly with the mouth closed (54) (see Figure 2). The area of condensation produced during nasal exhalation was then measured, and in the absence of nasal pathology this was typically an oval shaped area 7-8cm long and 4-5cm wide (54) (see Figure 3).

The advantages of this method are immediately obvious; it is easy to use, non-invasive, quick, inexpensive and does not distort nasal anatomy (54, 55). It does however have limitations, for example the user technique can cause variability in the results obtained, and there is no method of regulating air flow which could also lead to erroneous readings (67).

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Figure 2: Taken from Gertner et al.'s paper (1984) (54). A photograph of a subject exhaling through the nose onto a modified GM.

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Figure 3: Taken from Gertner et al.'s paper (1984) (54). An illustration of the condensation areas expected to be produced by a normal individual with no nasal pathology.

It has been suggested that the only reliable results obtained by the modified GM are qualitative in nature, as quantitative values may be unreliable due to potential variability between readings and the short-lived appearance of condensation areas (49). However one could argue that the reliability and usefulness of results depend on the purpose, for example a brief view of nasal patency for the purpose of diagnosing the presence and laterality of nasal obstruction in clinical practice can be extremely useful.

Brescovici and Roithmann (2008) assessed the reproducibility of the modified GM method in the assessment of nasal patency, specifically utilising the technique described by Gertner et al. (1984) (55). They analysed the minute-by-minute and hour-by-hour variability of measurements in a cohort of healthy individuals (55). The mean variation coefficient was found to be less than 15% for unilateral measurements and less than 12% for total measurements at different time intervals, which is comparable to other methods of measuring nasal patency (55). It was also able to reliably demonstrate the changes in nasal airflow caused by the nasal cycle (55). Another study comparing the efficacy of the modified GM with peak nasal inspiratory airflow measurements in children identified the modified GM as superior in the diagnosis of nasal obstruction (68).

Several factors can affect the reliability and reproducibility of measurements obtained by use of the modified GM. These include patient factors, such as vital capacity and nasal obstruction, environmental factors such as temperature and humidity, and positional factors such as the position of the plate relative to the nasal passages (66). Particularly for research purposes, these can be minimised by using anatomical landmarks to correctly position the plate, using the same examiner for repeated measurements, and allowing subjects to acclimatise to the room temperature and humidity for 30 minutes prior to taking measurements (55). In addition, using the average of 3-5 readings can improve reliability (55).

The modified GM has been used as an outcome measure in several studies attempting to analyse the effects of nasal surgery (54, 67, 69). Gertner et al. (1984)

demonstrated that the modified GM was useful in clinical practice, as it could detect differences in nasal airflow before and after septal surgery used to treat nasal obstruction (54). However another study assessing changes to nasal airflow following rhinoplasty procedures with the modified GM failed to show a significant difference in the values obtained pre- and post-operatively (67). The authors of this study commented that this could have been due to the effects of the nasal cycle (67). It should be noted however that this study only involved a small cohort of 20 patients who were undergoing cosmetic rhinoplasty, and therefore the aim of surgery may not have been to improve nasal airflow. As with other methods, studies have identified a poor correlation between subjective measures of nasal airflow (e.g. patient questionnaires) and objective measures taken using the modified GM (55, 67).

The modified GM is particularly useful in children as it is non-invasive and easy to use, not requiring any training. It has been used successfully in several studies involving children (68, 70). The cold mirror method has even been used in animal studies in order to demonstrate the presence of a nasal cycle (71). A cold metal mirror was placed under the nostrils of tranquilised rats and rabbits, and the side of the nose (left or right) producing the greatest area of condensation was recorded (71). This was compared with measurements of airflow recorded in millilitres per minute by collecting air that escaped from each nostril under water following insufflation into the trachea (71). The cold mirror recordings were shown to correlate with the measurements of flow (71), supporting its reliability and accuracy.

Recently, the cold mirror method has been adapted further by the addition of video technology which is termed the video-rhino-hygrometer (49). This involves the recording of the condensation areas produced by nasal expiration followed by computer processing in order to extract more detailed quantitative parameters (49). When this method was used to evaluate the post-operative outcome following septoplasty, it was able to identify an improvement in comparison to pre-operative measurements (49). However in the same group of patients, there was no

statistically significant correlation between measurements obtained by video-rhino-hygrometry and those obtained by anterior rhinomanometry (49).

1.8: Factors that affect nasal airflow

Numerous studies have demonstrated that nasal airflow can be influenced by both pathologic and physiologic conditions. Some significant examples are discussed below.

Age

Cross-sectional studies of adults aged 16 to 82 years have demonstrated that age does not affect nasal airflow rate, nasal cross-sectional area or nasal resistance (72, 73). However cross-sectional studies may not be reliable due to the high degree of variability between subjects seen in studies of nasal airflow, and the authors suggest that changes to the nasal mucosa thickness and elasticity are a likely consequence of ageing (72). It seems that ageing can affect the rhythmicity and reciprocity in patterns of nasal airflow typically associated with the nasal cycle. In a study of 60 subjects aged 18 to 85 years, nasal airflow was measured every 15 minutes over 6 hours (74). In subjects under the age of 50 years, 22% exhibited a classical nasal cycle, defined by the authors as statistically significant negative r values (i.e. significant reciprocity), compared to 9% of subjects aged over 50 years (74). In addition, the presence of acyclic patterns, defined as no fluctuations in nasal airflow in either nasal passage, was more likely with advancing age (74). In a longitudinal study of a single subject, nasal airflow measurements were taken almost 40 years apart, and a significant decline in reciprocity was identified (75). Although the reasons for these age-associated changes have not been fully established, it is likely that they are due to age-related changes in the central nervous system, since fluctuations in nasal airflow patterns are controlled by the hypothalamus and brainstem (74, 75).

Posture

Positional changes can affect nasal airflow. Changing from a sitting position to a recumbent position causes a rise in jugular venous pressure, increasing blood flow to the head, including the nose (76). This will lead to vasodilation of the nasal veins, increasing the total nasal airway resistance, and one study identified an 8.4% increase in nasal resistance when changing from a sitting to a supine position (77). A pressure stimulus to one side of the body, for example when in the lateral decubitus position, leads to ipsilateral vasodilation (congestion) and contralateral vasoconstriction (decongestion) in the nasal passages (78-80). This has been demonstrated by application of axillary pressure by means of a small crutch, and when applied to the same side as the dominant nasal passage, it caused reversal of nasal passage dominance within 5 minutes (80). Twelve minutes of lateral recumbency was shown to induce the same changes in nasal airway resistance, which interestingly were found to continue after the pressure stimulus was removed (79). It has been proposed that this phenomenon is mediated by a reflex arc, sometimes called the corporo-nasal reflex, involving sensory receptors in the skin and sympathetic innervation to the nasal mucosa (78). These are likely to be pressure sensors situated in the thorax, pectoral and pelvic girdles with efferent fibres travelling via the cervical sympathetic chain to the venous sinuses in the nose (79).

Sleep

Spontaneous fluctuations in nasal resistance also occur during sleep (28, 81). Sleep seems to affect the nasal cycle, causing an increased periodicity when compared to wakefulness in the same subjects (27, 28). In a study of 20 healthy subjects, there was a significant reduction in the number of cycles, i.e. reversals of nasal passage dominance, that occurred during sleep compared to wakefulness when nasal airflow was measured continuously over a 24 hour period (28). In another similar study, reversals of nasal passage dominance were preceded by a change in body position almost 60% of the time (27). There is also an increase in nasal cycle amplitude during sleep, caused by increased congestion in the congested nasal passage, however this is more likely a result of recumbency rather than sleep, consistent with

the existence of the corporo-nasal reflex (27). It should be noted however that both of these studies used portable rhinoflowmetry to continuously measure nasal airflow, which requires the insertion of nasal prongs into the anterior nares. Nasal prongs have been shown to significantly increase nasal airway resistance even in the absence of nasal pathology, as they reduce the cross-sectional area of the nasal passages (82). There is also a chance that they could become dislodged or misplaced especially during sleep, or cause irritation to the nasal mucosa, which again could affect the accuracy of measurements.

There is some evidence to suggest that reversal of nasal passage dominance predominantly occurs during rapid eye movement (REM) sleep (28, 83), even when postural effects are taken into account (28). REM sleep is associated with sympathetic nervous system activation which could explain this finding (27).

Exercise

Exercise reduces the total nasal airway resistance, abolishing the asymmetry between the nasal passages (84, 85). Re-breathing (resulting in an elevated plasma carbon dioxide level) also reduces the total nasal airway resistance (84). It is likely that the increased metabolic demand caused by these scenarios leads to a sympathetic response resulting in vasoconstriction and reduced nasal airway resistance (84).

Environment

One study used acoustic rhinometry as an objective measure of nasal patency in 50 healthy subjects at two different room temperatures; 30-33°C and 18-22°C, and found no statistically significant difference caused by the change in room temperature (86). In a study of eight healthy subjects, ingestion of hot water and nebuliser treatment (i.e. heat and humidification) caused a significant decrease in the volume of the nasal cavity that was already the most congested, although there was no change in total nasal cavity volume, again measured by acoustic rhinometry (87). Drinking cold water and placement of an ice pack on the neck did not have any significant effect (87).

Hormones

There is some evidence to suggest that female reproductive hormones may be associated with changes in nasal airflow, however conflicting findings have been reported. During pregnancy, it is thought that hormonal changes are responsible for pregnancy-induced rhinitis, which is relatively common in the later stages of gestation (88, 89). In this condition, nasal symptoms develop during pregnancy and resolve spontaneously soon after delivery (90). In a longitudinal cohort study of over 2000 pregnant women, self-reported "nasal stuffiness" increased throughout pregnancy, occurring in 42% of women at 36 weeks gestation (91).

This phenomenon led to analyses of the effects of the menstrual cycle and contraceptive drugs on nasal airflow. In a study of 41 healthy women, nasal peak expiratory flow rate was found to be significantly lower during menstruation compared with the rest of the menstrual cycle, indicating increased nasal congestion at this time (92). It has been suggested that elevated levels of oestrogen may be responsible for fluctuations in nasal congestion occurring during the menstrual cycle, however oestrogen levels are lowest during menstruation (92). Using rhinostereometry, Haeggstrom et al. (2000) observed nasal hyperreactivity during ovulation (when oestrogen levels are highest) by challenging the nasal mucosa with histamine (93). However when acoustic rhinometry was used to measure nasal congestion, no significant differences were identified at different phases of the menstrual cycle (93). The authors suggest therefore that the sensation of nasal congestion associated with pregnancy could be due to hyperreactivity of the nasal mucosa caused by high oestrogen levels, rather than increased congestion of the nasal mucosa (93).

The opposite was found in another study, where nasal resistance was found to be significantly higher around the time of ovulation compared to the menstrual phase as measured by anterior rhinomanometry (94). Biopsies of the nasal mucosa taken during different phases of the menstrual cycle showed no differences compared to male controls in seven out of ten women (95). The three women with histological changes demonstrated increased vascularity with dilated and congested capillaries

and glandular hyperactivity, which the authors suggested may be related to emotional disturbances influencing the autonomic nervous system (95).

A large study of over 300 women found that olfactory sensitivity reached its peak during the ovulatory phase of the menstrual cycle and was higher at this stage compared to controls (96). The lowest sensitivity was found during the menstrual phase of the menstrual cycle (96). It is thought that changes in oestrogen levels throughout the menstrual cycle could be altering olfactory function peripherally and centrally (96). These findings are particularly interesting given that some studies on nasal airflow have suggested that nasal congestion and hyperreactivity occur at the time of ovulation (93, 94), which would usually reduce olfactory sensitivity. Clearly this relationship between female sex hormones, nasal airflow and olfactory sensitivity is complex, and its definitive existence has not been fully established.

Animal studies have revealed that administering oestrogens causes vasodilation with an increase in the size of vascular spaces in the nasal mucosa, with the same histological changes occurring in pregnancy (97). Similar effects have been demonstrated in human histological studies. Toppozada et al. (1984) took nasal biopsies from 25 women on the combined oral contraceptive pill, 15 of these women had developed nasal symptoms after starting the drug (98). Although minor changes such as glandular hyperactivity were observed in the asymptomatic group, the symptomatic group had changes similar to those seen in hypertrophic non-allergic rhinitis, such as interepithelial oedema, glandular hyperplasia and congested capillaries (98). However a more recent study found that the modern combined oral contraceptive pill did not have any effect on nasal airflow as measured by a variety of methods (99).

It would seem that the effects of hormones such as oestrogen and progesterone have the potential to cause changes in the nasal mucosa and even symptomatic rhinitis, however significant variability has been identified in the prevalence, duration and severity of symptoms. Whether these changes alter nasal airflow is even more controversial, and conflicting results have been presented in the

literature. Even if there are minor changes in nasal airflow occurring throughout the menstrual cycle or with use of contraceptives, this does not necessarily mean that the nasal cycle will be affected. Equally, there is evidence to suggest that men have a greater nasal airflow rate than women (72), most likely due to their increased vital capacity which should not affect the nasal cycle duration, only it's amplitude. Most importantly, a relationship between gender and the nasal cycle has not been identified. Mirza et al. (1997) measured nasal airflow every 15 minutes for a 6-hour period in 60 subjects to determine factors that affect nasal cycle patterns, and found that gender had no significant effect (74). Tahamiler et al. (2009) found no significant differences in nasal cycling between male and female subjects when nasal airflow was measured every 30 minutes for 12 hours on 4 different days in 20 subjects (29).

Drugs

Many drugs have been shown to affect nasal airflow generally and also alter the nasal cycle. For example alcohol, known to have vasodilatory effects, has been shown to increase total nasal airway resistance (100, 101). Cigarette smoking also has an effect. In a study of over 2500 adults, those who were cigarette smokers had lower nasal cavity volumes and peak nasal inspiratory flow values compared to non-smokers, even after decongestion (102). It is likely that chronic damage to the nasal mucosa caused by cigarette smoke is responsible for these changes (102). Topical decongestants such as adrenaline and xylometazoline cause vasoconstriction of the dilated veins, leading to symmetrical nasal airflow (12, 14). Anti-inflammatory medication such as anti-histamines and corticosteroids also decongest the nose by reducing inflammation (103, 104). Nasal obstruction and rhinitis have been reported in patients taking anti-hypertensives such as ACE-inhibitors (105) and beta-blockers (106).

Disease

Several pathologic factors can influence nasal airflow and the nasal cycle, including local factors such as anatomical obstruction or mucosal inflammation, and general factors such as respiratory function. Anatomical obstruction such as septal deviation

reduces nasal airflow through the affected nasal passage (54). In a comparative study, the amplitude of fluctuation in nasal airflow was greater in the wider nasal passage in patients with anterior septal deviation compared to those without, although there was no change in the duration of the nasal cycle (107). It is possible that severe nasal septal deviation can eliminate the nasal cycle i.e. prevent any reversal in the dominance of nasal airflow (28), although the evidence for this is weak and as discussed previously the great variation in nasal airflow patterns generally could account for this observation.

Nasal resistance is increased in allergic and chronic hypertrophic rhinitis (77). In addition, acute rhinitis, for example in upper respiratory tract infection, exaggerates the nasal cycle, causing a greater maximal nasal airway resistance and an increase in the amplitude of reciprocal changes between to the two nasal passages (12, 23). Restricted or reduced lung movement leads to reflex venous dilatation in the nasal mucosa and reduced nasal airflow (37).

Over the past decade, evidence has emerged to suggest that nasal airflow patterns are altered in neurodevelopmental and psychiatric disorders (70, 108, 109), although this notion remains controversial with only a few studies published on the topic. This concept will be discussed in more detail later.

Summary

There are many factors that can influence nasal airflow but most of these do not affect the characteristics of the nasal cycle. There are a few exceptions. Asymmetry between the nasal passages can be abolished by stimulation of the sympathetic nervous system, for example during exercise (84, 85) or following the application of topical sympathomimetics (12). Increasing age is associated with reduced reciprocity in the alternating fluctuations of nasal airflow (74, 75). Changes in posture, specifically resulting in a pressure stimulus to lateral aspects of the body for example during lateral recumbency, trigger a reversal in nasal passage dominance, such that the greater airflow is observed in the nasal passage contralateral to the pressure stimulus (78, 80). Pathological conditions such as severe septal deviation

have the potential to prevent fluctuations in nasal airflow (28), and acute rhinitis exaggerates the amplitude of reciprocal changes between the two nasal passages (12, 23). These influences need to be considered carefully when designing studies that aim to assess the nasal cycle, and should be adequately controlled for wherever possible.

1.9: Nasal airflow and hand preference

The cerebral hemispheres exhibit both functional and structural asymmetry (110). Perhaps one of the most obvious signs of cerebral asymmetry is hand preference. Broca proposed that the hemisphere controlling speech was contralateral to the dominant hand, suggesting that in most people the left hemisphere is dominant, however this relationship is actually more complex (111). The majority of the population is right-hand dominant, has speech controlled by the left hemisphere and visuospatial processing controlled by the right hemisphere (110, 112).

In 2005, Searleman and colleagues hypothesised the existence of a correlation between nasal airflow and handedness (113). They described two principle reasons for the basis of their hypothesis. First, there is a tendency for a positive correlation between lateral preferences, including both limb sidedness and sense organ sidedness, so that left-handers tend also to be left-footed, left-eyed and left-eared (113). Secondly, there are two separate nasal passages which function independently. As discussed in detail earlier, airflow through each nasal passage fluctuates spontaneously over a period of hours (1, 3, 4), unlike airflow through the bronchi and lungs, which under normal circumstances (i.e. in the absence of pathology) is divided equally between the left and right sides. At any given time point one nasal passage is decongested, i.e. has greater airflow making it the dominant side, whilst the other is congested, i.e. has less airflow thus making it the non-dominant side. Since the exact nature and purpose of these fluctuating patterns

of nasal airflow remain elusive, it seems reasonable to consider structural influences such as cerebral organisation and lateral preferences.

Searleman et al. (2005) aimed to answer two questions; is there a dominant nasal passage and if so, is it consistent with other lateral preferences, for example hand dominance (113)? They predicted that the left nasal passage would be dominant for the majority of the time in left-handers, and vice versa in right-handers (113). Searleman et al.'s (2005) study involved 20 healthy male participants, aged 18-22 years, 11 of whom were right-handed and 9 of whom were left-handed (113). Women were excluded due to concerns that alterations in hormone levels could influence nasal airflow (113). Handedness was determined by self-report and observation of hand-writing (113). Nasal airflow was measured using two hot wire anemometers positioned just inside the nares, and the maximum airflow rate was used as the measure of nasal passage dominance (113). Measurements were performed at 15-minute intervals over a continuous 6-hour period (113). Attempts were made to minimise potential confounding factors by performing anterior rhinoscopy to rule out obstructive nasal pathology, excluding smokers or those with an abnormal sense of smell, ensuring correct and consistent positioning during nasal airflow measurements, and prohibiting exercise and lying down on the test day (113).

In order to look for a correlation between hand preference and nasal passage dominance, Searleman et al. (2005) analysed the percentage of time each nasal passage was dominant, based on maximum airflow rates recorded from each side (113). In left-handers, the left nasal passage was dominant for 59.3% of the study period, whereas in right-handers, the right nasal passage was dominant for 59.5% of the study period (113). The *p* value for both of these findings was less than 0.01, however the methods of statistical analysis were unclear (113). They also looked for any correlation between the number of nasal cycles and handedness. Left-handers had an average of 5.67 nasal cycles in the 6-hour measurement period, whereas right-handers had an average of 3 (113). Using this information, they calculated that the average duration of a nasal cycle was 63.1 minutes in left-handers and 120

minutes in right-handers (113). These findings were not statistically significant, although again the statistical methods used were not specified.

There are several issues with both the methodology and data interpretation in this article:

1. A small sample size of only 20 subjects has been used. As there is no previous similar literature, power calculations would not have been possible. In addition, studies that require measurement and analysis of the nasal cycle are, by definition, time consuming, and therefore the majority of published reports only have a small number of subjects.
2. The method of measuring nasal airflow required the insertion of hot wire anemometers just inside the nares, which could have interfered with the accuracy of measurements.
3. No formal test was used to determine handedness despite the availability of validated objective and subjective measures. Handedness is not as simple as left or right, but is in fact a continuum, with degrees of left and right-handedness (114). Studies that utilise hand preference as a variable can therefore be difficult to interpret.
4. Data analysis and statistical methods have not been described in any detail, making it difficult to reliably interpret the results. It would appear that the number of times each nasal passage was dominant during the 6-hour measurement period has been calculated and used to produce a percentage value for the amount of time each side was dominant. A subject has then been defined as being left nasal passage dominant if the left nasal passage had the greatest airflow for more than 50% of the time points, and vice versa for the right nasal passage. This figure has then been used to show a correlation with handedness. As there is significant inter- and intra-individual variability in nasal airflow patterns, using 50% as the cut off for nasal passage dominance could be unreliable. With only a few more measurements, extending the sampling period to 7 hours for example, the percentage of time one nasal passage was dominant could easily change to just above or just below 50%, completely altering the outcomes.

5. When calculating the average number of nasal cycles in left-handers and right-handers, there is no description or definition of what is meant by the term “nasal cycle” in the context of this data.

The finding of a correlation between nasal airflow and hand preference is unusual for several reasons. Many different research groups have performed observational studies on nasal airflow in healthy individuals, and although they have not explicitly looked for a relationship between nasal airflow and hand preference, it has not been identified incidentally. Since 90% of the population is right-handed, surely other studies of nasal airflow would have noted that the majority of their participants had right nasal passage dominance. Although the exact function of the nasal cycle has not been firmly established, there is evidence to suggest that it has functional significance with potential roles in immune defence and air conditioning (18, 26). A correlation between nasal airflow and hand preference would conflict with these theories by suggesting that nasal airflow patterns were linked with cortical organisation rather than having a functional role in respiratory defence or preparation of inspired air for gaseous exchange.

The article by Searleman et al. (2005) (113), published over 10 years ago, is the only available literature concerning hand preference and nasal airflow in healthy subjects, and it is not commonly cited in the more recent literature base for the nasal cycle. In 2007, Dane and Balci published a study that compared hand preference and nasal airflow patterns in 37 autistic children and 20 healthy controls (70). Autism is a neurodevelopmental disorder in which cerebral lateralisation is abnormal (70). Children with autism have a lesser degree of handedness, i.e. are less lateralised than controls and more likely to demonstrate mixed or left-handedness (70). When nasal airflow was measured 24 times over a 12-hour period using the modified GM, the majority of autistic children demonstrated left nasal passage dominance for the majority of the time period (70). Of the 24 measurements, the left nasal passage was on average dominant 19.59 times in the autistic group, compared to 11.75 times in the control group, and this difference was found to be statistically significant, with a *p* value of 0.00 (70). The authors did not look specifically for a correlation between

hand preference and nasal passage dominance but did find that in their group of 37 autistic children, there was a higher prevalence of left or mixed handedness and of left nasal passage dominance compared to controls (70).

Two similar studies investigated nasal airflow patterns in right-handed adults with schizophrenia and mood disorders. The modified GM was used to measure nasal airflow every 30 minutes over a 12-hour period in 83 patients with schizophrenia (108), 26 patients with unipolar depression and 44 patients with bipolar disorder (109) and compared with 64 healthy controls. Psychotic disorders may be associated with abnormal brain asymmetry, and there have been reports of increased rates of mixed and left-handedness in patients with schizophrenia (112, 115, 116). All subjects in these studies were right-handed. In schizophrenic patients, the rate of left nasal passage dominance was 65.1%, compared to a rate of 22.9% for right nasal passage dominance, a finding with a *p* value of 0.00. In healthy controls, the rate of left nasal passage dominance was 25%, the rate of right nasal passage dominance was 21.9%, and the majority had no significant lateralisation of nasal airflow over the 12-hour measurement period (108). Patients with bipolar disorder had a higher rate of right nasal passage dominance, whereas those with unipolar depression had a higher rate of left nasal passage dominance, however these findings were only significant in female subjects (109). The authors of these studies have suggested that the altered nasal airflow patterns apparently associated with these disorders may be contributing the hypo- or dys-function in the cerebral hemispheres (108, 109). Specifically, Ozan et al. (2009) proposed that greater airflow through the left nasal passage for the majority of the time corresponds to increased sympathetic tone and therefore reduced electrical activity in the left cerebral hemisphere, contributing to the left hemispheric dysfunction seen in schizophrenia (108).

The above findings in healthy control subjects are particularly relevant. Over a 12-hour period, 53.1% had no overall lateralisation of nasal airflow, meaning that the left and right nasal passages were dominant for roughly equal amounts of time (108). The rate of left nasal passage dominance was 25%, and the rate of right nasal passage dominance was 21.9% (108). All subjects were right-hand dominant as

measured by the Edinburgh Handedness Inventory, a validated questionnaire for handedness. These results directly contradict the findings of Searleman et al. (2005) (113).

1.10: Handedness

Around 90% of the population is right-handed and 10% is left-handed (117). Although these figures may vary slightly, right-handers have been predominant throughout history and across the world (117).

Handedness can be defined by either preference or skill. Preference is a subjective measure that is assessed by asking subjects which hand they use for a particular task i.e. a questionnaire, whereas skills tests compare a subject's ability to perform tasks with each hand (118). The Edinburgh Handedness Inventory is the most widely used preference questionnaire (119), in which participants are asked which hand they use for a number of activities such as writing, throwing a ball and using a spoon (120). There is good correlation between measures of preference and skill, particularly for complex movements such as writing, however whether preference precedes skill or *vice versa* is difficult to establish (118).

Some studies fail to differentiate mixed-handers from left- or right-handers, which could confound results (121). Preference tests produce a J-shaped distribution, with the majority of individuals showing a clear right preference, some showing a clear left preference and hardly any being indifferent (122).

Defining an individual as either right-handed or left-handed may seem very simple, but in actual fact it can be quite complicated. When preferences for several different actions are observed (i.e. not just hand-writing), the patterns of preference are surprisingly variable (122). In 1970, Annett (p. 316) suggested that "to talk about asymmetry in terms of left and right might be like talking about height in terms of

“tall” or “short”” (122). Handedness is therefore best viewed as being a continuum, with mixed handers being part of the left-right continuum rather than a separate classification of hand preference (122). That said, for the purpose of research a cut-off point is required in order to classify handedness. The degree of handedness can be measured using laterality indices; questionnaire responses are assigned scores that are combined, for example a pure right-hander will score +100, a pure left-hander will score -100 and an ambidextrous subject will score zero (118).

Handedness is often regarded as a reflection of cerebral hemisphere dominance, and Broca proposed that the hemisphere controlling speech was contralateral to the dominant hand (111). Around 5-6% of right-handers have speech controlled by the right hemisphere, compared to 30-35% of left-handers, so the correlation between cerebral hemisphere dominance and handedness is actually more complex (117). It is important to remember therefore that handedness does not necessarily correlate with cerebral hemisphere dominance. In addition, whilst right-handers are usually consistent in their hand preference e.g. for performing different tasks, left-handers are less so (123).

There is a fundamental difference in the cerebral organisation of those that are right-handed and those that are left-handed, however the underlying reason for this is controversial. Factors other than neural control can influence handedness, and these include imitation, specific instruction, social prejudice and tool design (124). Annett (1972) proposed three potential mechanisms that could explain the variation in handedness seen in humans (121):

1. Genetics. A familial trend for handedness has been demonstrated, however simple genetic transmission cannot explain these findings.
2. Translational errors. The accidental effects of minor translational errors could lead to variation.
3. Cultural differences. Imitation and practice could affect handedness.

It is likely that all of these factors are involved to some extent in the development of handedness (121). Twin and familial studies suggest that a genetic factor is involved

in the development of handedness, however this cannot be explained by a Mendelian model (118).

The differences between humans and animals with regard to lateral preferences are interesting. Animals with bilaterally symmetrical limbs also exhibit preferences for the left or right side, however this seems to occur by chance and is not heritable (125). Both humans and animals exhibit a bell-shaped distribution of asymmetry of skill, however in humans the bell-shaped curve is shifted to the right, meaning that there is a bias towards right-handedness, termed the right shift (121). If this right shift was not present, the distribution of hand preference would be the same in humans and non-humans; 25% would be left-handed, 25% would be right-handed and 50% would have mixed handedness (121). The right shift factor, which is specific to humans, may be related to speech development which usually occurs in the left hemisphere (121). It is possible that the lateralisation of speech may confer advantages for speech development (125). When a complex action originates in the brain, there may be advantages to having it arise in only one hemisphere, such as avoiding unnecessary conduction between the hemispheres and duplication of specialised areas when neural space is limited (119).

1.11: Aims of thesis

The principle aim of this thesis was to look for a correlation between nasal airflow and hand preference in healthy individuals. Since hand preference is considered to be a reflection of brain asymmetry, a secondary aim was to conduct a literature review in order to gain a better understanding of the theories and evidence suggesting a link between brain activity and nasal airflow.

Over the past few decades, evidence has emerged from different research groups in different areas suggesting that asymmetrical brain activity may influence asymmetrical nasal airflow, and *vice versa*. The research findings have been

obtained using many different methods with numerous variables, and have often yielded contradictory results, making this field difficult to interpret. These ideas and controversies are presented and summarised in Chapter 2.

A possible relationship between nasal airflow and hand preference in healthy individuals was identified in a single study by Searleman et al. (2005) (113). Since then there has been no further specific research in this area. There are several reasons to doubt the reliability of this study. First, issues with the methodology were identified and have been described in detail above (see Chapter 1.9). Secondly, numerous studies have analysed nasal airflow patterns in healthy individuals, and although 90% of the population is right-handed, none have commented that there was a preponderance of right nasal passage dominance, which would be expected if Searleman et al.'s (2005) findings (113) were applicable to the general population. Thirdly, alternating nasal passage dominance appears to have a function related to immune defence and air-conditioning, both of which would require equal division of labour between the two nasal passages, and therefore having an overall dominant nasal passage would not make sense.

Using a different method of measuring nasal airflow and analysing the data, this study aimed to reproduce the experiment conducted by Searleman et al. (2005) (113) in order to test the theory of a correlation between nasal airflow and hand preference. The methodology and results are presented in Chapters 3 to 6.

Chapter 2: Introduction B (Nasal airflow and brain activity – literature review)

2.1: Introduction

For many centuries the ancient art of yoga in India has studied nasal breathing and developed techniques to switch the dominant nasal passage from one side to the other by use of a yoga danda or small crutch applied to the axilla (126). The yoga belief is that nasal airflow influences brain activity and cognition depending on whether airflow is dominant through the right or left nasal passage, and therefore by controlling left and right nasal airflow with the yoga danda, the yoga student could control brain activity (127). This theory may appear implausible to sceptics from the scientific community, however the asymmetrical effects of the yoga danda on nasal airflow have been confirmed in several studies in different research centres and this ancient practice now has scientific support. Reciprocal changes in nasal airflow can be readily caused by pressure applied to the axilla by means of a small crutch, or by adopting the lateral recumbent position (78-80), but whether this in turn influences brain activity remains controversial.

Over the past few decades, some evidence has emerged suggesting that nasal airflow asymmetry and brain asymmetry are linked. Different theories have been proposed, with varying strengths of evidence from human studies. The following section will discuss the evidence that links nasal airflow and brain activity in relation to two ideas; firstly the proposal that asymmetrical brain activity causes asymmetrical nasal airflow, and secondly that asymmetrical nasal airflow causes asymmetrical brain activity. Both the theories and evidence are contradictory and must be interpreted with caution.

2.2: Methods

A Medline® search was conducted in November 2015 using the following key words: *nasal airflow, nasal cycle, nasal hyperventilation, forced nostril breathing, brain asymmetry, electroencephalogram (EEG), cerebral activity, cognition, cerebral lateralisation, epilepsy, autism and schizophrenia.*

Reference lists were hand searched for other articles of interest.

2.3: Results

Does asymmetrical brain activity cause asymmetrical nasal airflow?

The peripheral control of nasal airflow via the autonomic nervous system is well documented (2, 36), and involves the vasoconstrictor sympathetic nerves that supply the large veins in the turbinates. The asymmetry in brain activity and sympathetic tone extend to the brainstem region where left and right oscillators cause reciprocal changes in nasal airflow (38). The hypothalamus may give the overall rhythmicity to a cycle of reciprocal changes in nasal airflow, but there is no evidence for asymmetry at this level (39). Cortical involvement in nasal airflow asymmetry has been suggested by studies on hand preference (113), lateralisation disorders such as schizophrenia (112) and autism (70) and ultradian rhythms of cerebral activity (128), but the evidence for these influences is weak and this area of research is controversial.

Fixed cerebral asymmetries and nasal airflow

In the early 1800s, the widespread belief was that the two cerebral hemispheres functioned as a single unit (111). However following studies on brain damaged patients, it became apparent that different areas of the brain were specialised for different functions (111), and nowadays it is known that the cerebral hemispheres exhibit both functional and structural asymmetry (110). In the majority of the population, the left hemisphere is dominant for language and speech whereas the

right hemisphere is dominant for visuospatial processing (110). Broca suggested that the hemisphere controlling speech was opposite to the dominant hand, so that in left-handers speech is controlled by the right hemisphere and in right-handers it is controlled by the left hemisphere (111). In reality, the relationship between speech and handedness is more complex and can be influenced by brain damage and neuronal plasticity (111).

Searleman and colleagues (2005) hypothesised a correlation between nasal airflow and handedness, based on the observation that there is often a consistency in lateral preferences e.g. left- handers tend to be left-footed, left-eyed *etc.* (113). Given the existing knowledge of the alternations in nasal airflow between the right and left nasal passages, they predicted that the left nasal passage would be dominant for the majority of the time in left-handers, and *vice versa* in right-handers. Their study proved the hypothesis to be correct, in that the dominant nasal passage positively correlated with the dominant hand for almost 60% of the time (113). However, among other issues outlined in section 1.9, the study only involved a small group monitored over a short time period and as previously demonstrated there is great variability in patterns of nasal airflow (13). It is also unusual that this relationship has not been noted in other observational studies of the nasal cycle in healthy individuals, since 90% of them were probably right-handed.

Non-right handedness (left-handedness or inconsistent handedness) seems to be more prevalent than expected in certain neurodevelopmental and psychiatric disorders such as autism and schizophrenia and this may be related to cerebral lateralisation abnormalities (70, 112, 116). One study analysed hand preference and nasal airflow in autistic children, and found that the majority were left-handed and had left nasal passage dominance for most of the time (12-hour measurement period) (70). A similar study in right-handed schizophrenics revealed that there was a significant increase in left nasal passage dominance in this group compared with controls (108).

Handedness is not as simple as left or right, but is in fact a continuum, with degrees of left and right-handedness (114). Studies that utilise hand preference as a variable can therefore be difficult to interpret. There are also different methods of measuring handedness, including objective performance tests and subjective inventories (129), and these are not standardised across different studies. It should be noted as well that the aforementioned studies are relatively small and there could have been confounding factors that were not controlled for, such as the use of psychoactive medication.

Fluctuating cerebral asymmetries and nasal airflow

The idea of rhythmic, spontaneous fluctuations in cerebral hemisphere activity first appeared in the 1960s. Following the discovery of the REM/non-REM (NREM) sleep cycle (130), Kleitman (1967) proposed that this phenomenon was the nocturnal part of a "Basic Rest Activity Cycle" (BRAC), which involves fluctuations in central nervous system activity approximately every 90 minutes (131). These fluctuations are often referred to as ultradian rhythms in cerebral activity. However the exact nature of these changes in brain activity remain contentious, and conflicting results have been presented. A few studies with small numbers of participants have suggested rhythmic fluctuations in electroencephalographic (EEG) activity (132) and cognitive performance in this time frame (133, 134), such that verbal performance is better than spatial performance, switching to the reverse approximately every 90-100 minutes (133).

Several studies have suggested the existence of a correlation between the alternating pattern of nasal airflow and cerebral hemisphere activity (128), this again is based on the regular periodicity associated with the BRAC (131) which has not been a consistent finding (133, 135). Werntz et al. (1983) reported increased EEG activity in the hemisphere contralateral to the dominant nasal passage as measured by nasal airflow (128). The EEG activity was observed across the cortex rather than focussed at the olfactory centres, suggesting a mechanism other than olfactory stimulation (128). Alternation of the predominant nasal airflow to the opposite side occurred after alternation of cerebral hemisphere dominance (128). A larger study

involving 126 right-handed participants found a tendency for enhanced performance in verbal tasks at times of right nasal passage dominance, and enhanced performance in spatial tasks at times of left nasal passage dominance, i.e. a link between nasal passage dominance and activity in the contralateral cerebral hemisphere (136).

Not only do the authors of these articles often reach different conclusions, they utilise different methods of testing, analysis and reporting, usually in small groups of subjects, at times failing to consider potentially confounding factors such as gender and handedness. EEG studies in particular are difficult to interpret and have varying methods of analysis. There is also a high level of inter-individual variability (132). It must be noted that the authors who have identified an ultradian rhythm in cognitive performance have supported Kleitman's theory of the BRAC (131), potentially introducing bias (128, 133).

Model of how the brain influences nasal airflow

A model of how the brain influences nasal airflow is illustrated in Figure 4. The model summarises the evidence and ideas presented in this section and for simplicity the control is discussed from the peripheral nerves and moving upwards through the hierarchy of central nervous control centres. The peripheral control of nasal airflow via the autonomic nervous system involves the vasoconstrictor sympathetic nerves that supply the large veins in the turbinates (2, 36). The asymmetry in brain activity and sympathetic tone extend to the brainstem region where left and right oscillators cause reciprocal changes in nasal airflow (38). The hypothalamus may give the overall rhythmicity to a cycle of reciprocal changes in nasal airflow, but there is no evidence for asymmetry at this level (39). Cortical involvement in nasal airflow asymmetry has been suggested by studies on handedness (113), ultradian rhythms of cerebral activity (128) and lateralisation disorders such as schizophrenia (108) and autism (70), but the evidence for these influences is weak.

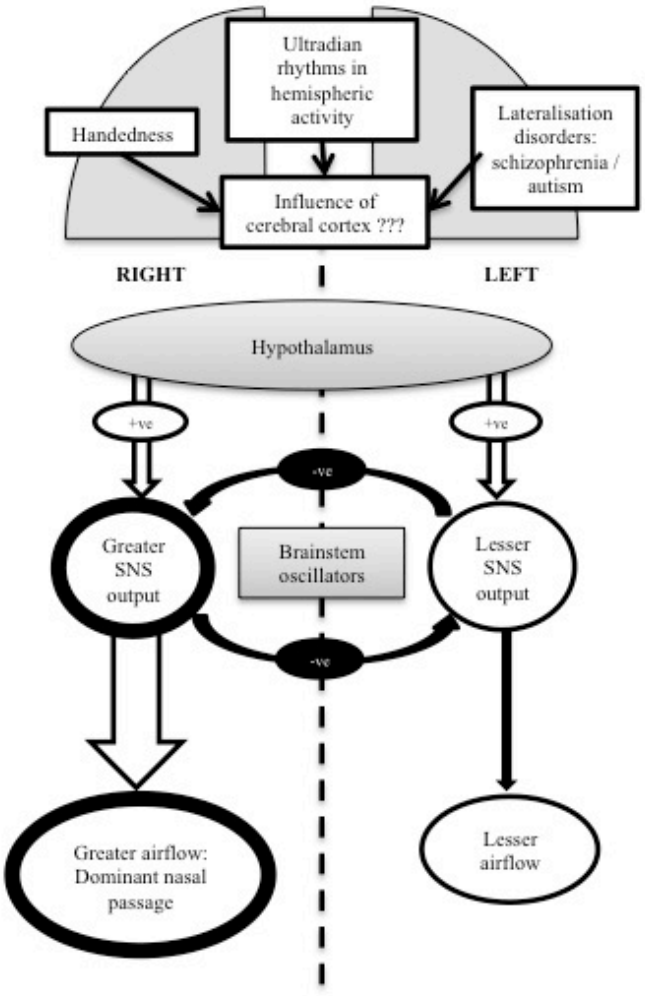

Figure 4: Model to explain the influence of brain activity on nasal airflow. The overall alternation in sympathetic activity over a period of hours is controlled from the hypothalamus and the asymmetry in sympathetic outflow is determined by the activity of brainstem oscillators which act as a flip flop mechanism, with each centre inhibiting the activity of the other centre and only one centre having dominant activity at any one time. These hypothalamic and brainstem mechanisms have been studied in the anaesthetised cat (38, 39). Higher centres in the cerebral cortex may also influence nasal airflow leading to asymmetry and most of the supporting evidence for this has come from experimental work in man (70, 113, 128). (SNS = sympathetic nervous system, +ve = positive, -ve = negative.)

Does asymmetrical nasal airflow cause asymmetrical brain activity?

The sensation of nasal airflow is believed to be mainly determined by stimulation of nasal trigeminal nerve endings that are sensitive to temperature changes, especially cooling of the nasal mucosa, which occurs during inspiration of air (1, 45, 46). A

purely trigeminal stimulus has been shown to increase arousal frequency and duration during sleep (137), whereas no effect was seen with an olfactory stimulus (138). Therefore, it seems that a nasal airflow stimulus can influence brain activity, and further evidence is discussed below.

Nasal hyperventilation and epileptic activity

It has been known for some time that deep breathing can activate epileptic foci in the brain, triggering seizure activity (139). This phenomenon was previously explained by hypocarbia leading to vasoconstriction and cerebral ischaemia, but it appears that airflow stimulation of the nasal mucosa could be the trigger (139). Animal studies have demonstrated that insufflation of air into the nasal cavity can trigger epileptic areas in the brain (139). In studies of some epileptic patients, nasal hyperventilation was more likely than oral hyperventilation to stimulate epileptic EEG activity, and unilateral nostril breathing had a greater effect on the abnormalities in the ipsilateral hemisphere (139, 140). This was suppressed following the application of local anaesthetic to the nasal mucosa in the region of the superior meatus (139, 141). The exact mechanism of this phenomenon has not been fully established, however the authors of these studies have suggested a reflex involving stimulation of the olfactory nerve by nasal airflow (139, 141).

Unilateral forced nostril breathing

Asymmetrical nasal airflow with unilateral forced nostril breathing (UFNB), where one nostril is occluded either manually by the subject or with cotton wool, has been used to analyse the influence of asymmetrical nasal airflow on the brain as measured by EEG activity (142) and cognitive performance (136, 143). In fact, these concepts have their basis in ancient yogic practices, and there is a relatively large literature discussing the nostril breathing methods utilised in yoga and their effects on mood and cognition, for examples see (144-149). Several studies have demonstrated an effect on the autonomic nervous system, for example changes in cardiovascular parameters (150-152) and intraocular pressure (153-155). In a study of five subjects, UFNB caused a shift in the dominant cerebral hemisphere, defined by relatively greater EEG activity, often within two minutes (142). Whether and how

this correlates with cognitive performance remains contentious. In general, studies have used hemisphere-specific tasks to measure cognitive performance, i.e. verbal tasks to reflect left hemisphere activity and spatial tasks to reflect right hemisphere activity. Using these methods, one study identified significant improvements in verbal test scores with right UFNB and spatial test scores with left UFNB (156). Others have found that left UFNB significantly improved right hemisphere performance whereas right UFNB had no effect (149, 157), but the opposite effect has also been demonstrated, wherein right UFNB improved left hemisphere performance but left UFNB had no effect (146). One study suggested that UFNB affected task performance differently in males and females (143), although again this finding has not been reproducible (157). Others have failed to show that UFNB had any effect on EEG measurements (158) or cognitive performance (128). It has been suggested that UFNB can influence mood, and it has been reported to affect emotional responses (159).

Often these studies are difficult to interpret accurately and have conflicting results. Criticisms include small numbers of participants (142, 143, 156), differing methods of UFNB (142, 143, 149), differing methods of measuring cerebral activity (142) and cognitive performance (143, 156), and failure to consider potential confounding factors such as sex (149) and handedness (142).

Following their study of nasal airflow patterns in children with autism, Dane and Balci (2007) suggested that autism is associated with the absence of a normal nasal cycle, the left nasal passage being dominant for the majority of the time (70). They have likened this finding to continuous left UFNB, and suggested that this may be causing continuous stimulation of the right cerebral hemisphere whilst depriving the left cerebral hemisphere of stimulation, possibly accounting for the delayed language development often seen in this group (70). The issue with this theory is that there is no evidence that right nasal blockage, for example septal deviation or nasal polyposis, leads to developmental delay. In these pathological conditions, the difference between the amount of airflow in each nasal passage is far greater than the difference caused by the nasal cycle under physiological conditions.

Shannahoff-Khalsa and his colleagues have suggested in multiple articles that UFNB has potential as a non-invasive treatment for psychiatric disorders (142, 160), and have recorded a correlation between left nasal passage dominance and hallucination occurrence in one schizophrenic female (160). A recent article suggested that UFNB may have beneficial effects for recovery of speech in stroke patients (161).

How could a nasal airflow stimulus affect cerebral activity?

A proposed mechanism for a correlation between nasal airflow and cerebral hemisphere activity involves the sympathetic nervous system (128, 142, 157), supported in part by the other autonomic effects demonstrated to occur during UFNB (150-152). As autonomic nerve fibres connecting the nose and hypothalamus do not decussate, vasoconstriction in the nasal vessels has been postulated to reflect concurrent vasoconstriction in the ipsilateral cerebral hemisphere, leading to a decrease in cerebral blood flow ipsilaterally and relative increase contralaterally (128, 142, 157). In this way, the increased blood flow could improve cognitive function as measured by performance in hemisphere-specific tasks (157).

However the physiological basis for this theory is questionable. Task performance has been shown to increase overall blood flow to both hemispheres, and more specifically verbal tasks cause a left lateralisation and spatial tasks a right lateralisation in right-handed subjects (162, 163). However the effect of the sympathetic nervous system on cerebral blood flow under physiologic conditions is thought to be minimal due to the action of cerebral autoregulation (164). In fact, whilst blockade of the stellate ganglion i.e. inhibition of sympathetic activity increases blood flow in extracranial vessles, it has no effect intra-cranially (165).

Therefore a different mechanism for the effect of nasal airflow on brain activity is proposed here, incorporating the activating effect of a nasal airflow stimulus on the cerebral cortex via the reticular formation. This is illustrated in Figure 5.

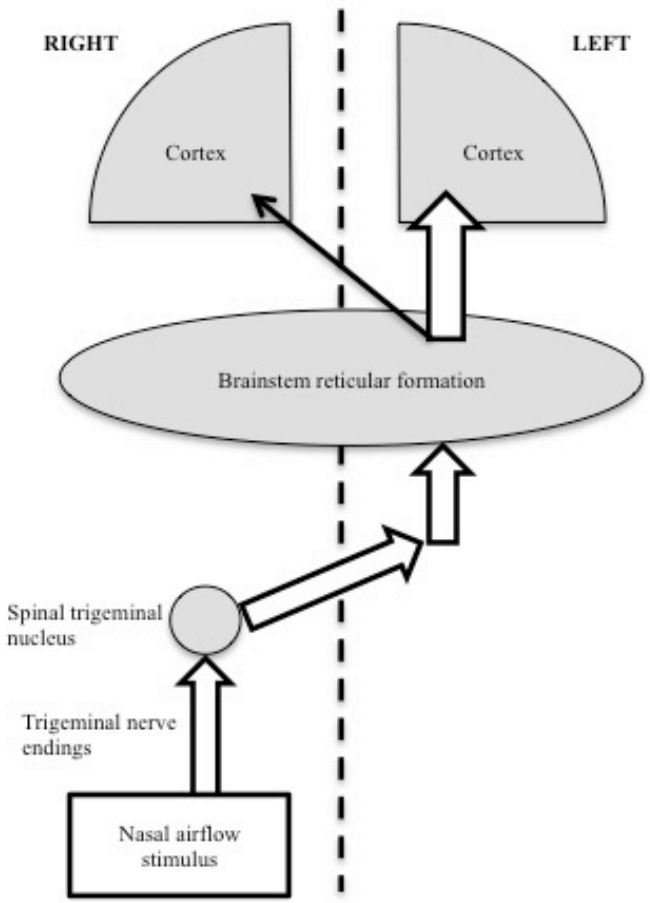

Figure 5: Model to explain the influence of nasal airflow on brain activity. A nasal airflow stimulus such as UFNB stimulates trigeminal nerve endings on one side of the nose. Trigeminal neurons transmitting temperature signals synapse in the spinal trigeminal nucleus and then cross the midline, travelling up to the thalamus through the brainstem. Studies on cats have suggested that via the brainstem reticular formation, a nasal airflow stimulus could lead to enhanced arousal and brain activity in both cerebral cortices (166). EEG studies and cognitive performance testing in human subjects have intimated that the greatest stimulating effect occurs in the hemisphere contralateral to the nasal airflow stimulus (128, 156).

One major challenge is that the laterality of cerebral hemisphere stimulation by nasal airflow is unclear, with some studies suggesting an ipsilateral response (139, 143), and others a contralateral response (142, 156, 157). Olfactory nerve fibres do not decussate and therefore stimulate mostly the ipsilateral cortex, whereas trigeminal fibres relaying temperature signals cross over in the spinal cord before passing through the brainstem. The trigeminal nerve detects nasal airflow, but experimental insufflation of air into the nasal passages could stimulate the olfactory

nerve due to the inadvertent presence of an olfactory stimulus. In addition, the olfactory cortex is unable to sense the laterality of a stimulus unless the trigeminal nerve is also stimulated (167). Suppression of the EEG stimulation caused by nasal airflow by application of local anaesthetic to the nasal mucosa (141) is more suggestive of trigeminal nerve involvement. Although sleep studies have demonstrated arousal secondary to a trigeminal nerve stimulus, this stimulus was an irritant (carbon dioxide) (137) and is therefore difficult to compare with nasal inspiration of air as with UFNB.

It is possible that nasal airflow causes bilateral cortical stimulation, with a greater effect on one side. Experimental stimulation of the reticular formation in anaesthetised cats caused EEG changes indicating increased alertness, and at lower levels of stimulation this effect was only seen in the ipsilateral hemisphere (166). It is unclear whether the trigeminal or olfactory nerves are involved in this mechanism.

Model of how nasal airflow influences brain activity

A model of how nasal airflow influences the brain is illustrated in Figure 5. The model summarises the evidence and ideas presented in this section. Inspired air stimulates cold receptors in the nasal mucosa that are innervated by the trigeminal nerve, providing the sensation of nasal airflow. Environmental sensory stimuli such as noise or smells can enhance arousal, and this effect is mediated by the reticular formation – an area in the brainstem involved in arousal and consciousness (166). Experimental stimulation of the reticular formation in anaesthetised cats caused EEG changes indicating increased alertness (166). Insufflation of air into the nose had the same effect on EEG patterns i.e. increased arousal (168). Therefore, a nasal airflow stimulus, for example insufflation of air or UFNB could activate the reticular formation and increase arousal, leading to EEG changes and possibly improved cognitive performance. There is evidence to suggest both an ipsilateral (139, 143) and contralateral (142, 149, 156, 157) stimulating effect. However it is more likely that a unilateral nasal airflow stimulus has an activating effect on both cerebral hemispheres, but with a greater effect on one side. As trigeminal neurons

transmitting temperature signals cross the midline in the medulla, it seems logical that the greatest effect would be seen contralaterally.

2.4: Conclusions

The ancient yogic practice of "pranayama" or breath control exercises are thought to promote health and well-being, improve circulation and prepare for concentration (169). Whilst this notion may have been met with scepticism from the scientific community, it inspired clinical studies into the effects of nasal breathing on cognition. There is a growing body of evidence to suggest that nasal airflow can influence brain activity, however the mechanism, extent and significance are debatable. Considering the evidence from studies in epileptic patients (139, 141) and arousal during sleep (137), it seems that a nasal airflow stimulus potentially has some sort of activating effect on the brain. Putting this into an everyday context, stepping outside into a cold environment and inhaling cool air through the nose often makes us feel more alert, and the cooling effects of menthol on nasal receptors may also cause arousal (170). Smelling salts were used in Victorian times to revive unconscious patients, and even nowadays some athletes use smelling salts as a stimulant prior to competing (171). However the role of higher centres and cortical organisation remains uncertain, with some conflicting theories suggested. For example, if nasal airflow dominance correlates with hand preference (113), it could not also correlate with fluctuating ultradian rhythms of cerebral activity (136), as hand preference is normally fixed.

Chapter 3: Methodology

3.1: Ethical approval

The study was designed and conducted according to the World Medical Association's Declaration of Helsinki and the International Council for Harmonisation's Good Clinical Practice guidelines. Prior to commencement all documentation was reviewed and approved by the School of Biosciences Research Ethics Committee and Cardiff University's Research Governance Department. The patient information leaflet and informed consent form are included in Appendices 2 and 3.

3.2: Study design

The study was designed as a prospective pilot study, based on the methods used by Searleman et al. (2005) (113). The handedness of each subject was recorded as part of the screening procedure. Following this, nasal airflow was measured at 15-minute intervals over a continuous 6-hour period using a modified GM, as described by Gertner et al. in 1984 (54). At each measurement, the investigator examined the condensation areas formed on the metal plate and determined whether the left or right nasal passage had produced the largest area, and therefore was dominant. The same investigator (AP) carried out all measurements in an attempt to minimise user variation.

Although similar in design to Searleman et al.'s 2005 study (113), a different method of measuring nasal airflow was chosen. Part of the reason for this was related to the aim of the study. In order to determine the dominant nasal passage in terms of airflow, the only variables of importance are left or right. The modified GM provides a snapshot view of nasal airflow through each nasal passage, allowing the investigator to instantaneously judge which nasal passage has the greatest airflow

and therefore is dominant. Other advantages of this technique are discussed in the introduction (see section 1.7).

3.3: Study population and recruitment

Participants were recruited from Cardiff University campus by an advertisement email and posters seeking out normal, healthy, non-smoking adults. Participants were excluded if they had a history of nasal disease or were taking medication that could affect nasal physiology. In contrast to Searleman et al.'s (2005) study (113), women were included providing they were not pregnant or lactating. The potential effects of female sex hormones on nasal airflow were discussed in detail in the Introduction (see section 1.8), however in brief, during pregnancy it is thought that hormonal changes are responsible for pregnancy-induced rhinitis, which is relatively common in the later stages of gestation (88, 89). There is some evidence to suggest that nasal airway resistance may be higher during menstruation, although changes in the nasal cycle have not been identified (92). In addition, there is little evidence to suggest that the contraceptive pill has a significant effect on the nasal cycle (99). Many other studies specifically analysing the nasal cycle have involved both male and female participants, without significant differences identified.

For the full exclusion and inclusion criteria, see Appendix 1.

Participants were paid an honorarium of £70 on completion of the study. Those excluded from the study following the screening assessment were paid £5 for their time.

3.4: Sample size and power

As this was a pilot study, the aim was to recruit between 25 and 30 participants, with the final number dependent on the number of left-handed participants included. A power calculation based on the previous study (113) was not possible due to limited data presented, however statistical significance was reportedly achieved with 20 participants (113).

3.5: Measurement of handedness

A test of handedness was performed to exclude those categorised as mixed-handed and to identify the hand preference of each participant. This involved observation of handwriting, followed by completion of the Edinburgh Handedness Inventory (Short Form) to obtain a handedness categorisation (172) (see Appendix 4). If there was any disparity between the participant's statement of hand preference and observation of handwriting, the participant was excluded. Participants were also excluded if they demonstrated mixed handedness.

Handedness can either be measured by preference or skill, and there is good correlation between both types of test especially for complex movements such as writing (118). Observation of handwriting alone as a test for handedness can miss those with mixed handedness, which could be a confounding factor. A questionnaire was therefore used to ascertain subjects' hand preference for several different activities. The Edinburgh Handedness Inventory is the most widely used preference questionnaire (119), and the Short Form is a revised version that has been shown to have good validity and reliability (172). Subjects were asked which hand they prefer to use for four different actions; writing, throwing, using a toothbrush and using a spoon. They were assigned scores that were used to calculate whether they were categorised as left-handed, right-handed or mixed-handed (see Appendix 4).

3.6: Measurement of nasal airflow

Nasal airflow was assessed using the modified GM, as described by Gertner et al. (1984) (54). This method allows the investigator to obtain a momentary assessment of nasal airflow by comparing the condensation area formed by expired air from each nasal passage. The instrument used was a polished metal plate made from aluminium measuring 10cm x 12cm and marked with arches 1cm apart (see Figure 6). The plate was positioned horizontally just beneath the columella with the vertical axis at 90 degrees towards the upper lip. Each participant was instructed to exhale through the nose slowly with the eyes and mouth closed. The temperature difference between the expired air and the metal plate is what causes the vapour to condense on the plate. By observing which nasal passage produced the largest condensation area, the dominant nasal passage was recorded.

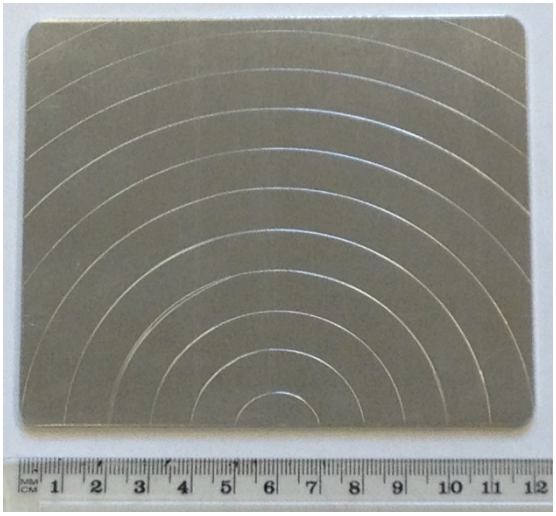

Figure 6: A photograph of the metal plate (i.e. modified GM) used in the study.

3.7: Trial environment and procedure

All visits and testing procedures were carried out at the Common Cold Centre. Potential participants attended for a screening visit, where they were provided with a participant information sheet (see Appendix 2) and signed a study consent form (see Appendix 3). They were then assessed by the study clinician (AP) to ensure all

inclusion and exclusion criteria were met, which involved eliciting a medical history and examining the nose by anterior rhinoscopy. Those enrolled onto the study attended at a later, convenient date for testing.

Every attempt was made to minimise factors known to affect nasal airflow that could potentially affect the study results. Since upper respiratory tract infection has been shown to increase the nasal airway resistance and the amplitude of the nasal cycle (23), participants with common cold symptoms at the screening visit or on the test day were delayed for two weeks to ensure resolution. Alcohol ingestion increases nasal airway resistance (100, 101), therefore participants were asked not to drink more than four units of alcohol the night before testing. Exercise effectively abolishes the reciprocal changes in nasal airway resistance, leading to an overall increase in nasal airflow (84), therefore participants were asked to refrain from any vigorous exercise such as running, cycling or swimming for three hours prior to testing.

On the test day, participants arrived 30 minutes prior to the start time for nasal measurements to ensure any effects of exertion and the external environment on the nasal mucosa were eliminated, and to allow for acclimatisation to the temperature and humidity of the test environment. During the test period, participants remained at rest and in the same room, with allowances for use of the bathroom. They were permitted to read, use their computers or watch television but were not permitted to lie down, as changes in posture and pressure stimuli can lead to alteration of nasal airflow (78, 79). Although menthol has not been shown to affect nasal airway resistance *per se*, it can cause a subjective change in nasal airflow (47), therefore participants were not permitted to eat any menthol containing products such as mints. They were provided with a standard cold lunch between 12 and 12.30pm. No hot drinks were permitted.

Recordings of the dominant nasal passage using the modified GM were performed at 15-minute intervals over a 6-hour period, giving a total of 24 recordings. Participants

were positioned sitting upright with the head in a neutral position. Once sitting comfortably, they were given the following instructions:
"I will ask you to take a deep breath in using the word inhale. You will then hold this breath until I inform you to exhale. When you exhale, keep your eyes and mouth closed and gradually breath out through your nostrils."

Whilst the participant held their breath, the modified GM was positioned under the collumela as described above (see Figure 7). This procedure was repeated three times at each 15-minute interval. A judgement was made by the investigator as to which nasal passage produced the largest condensation area, and was therefore dominant, and this was recorded as either left or right. If it was unclear which nasal passage had produced the largest condensation area, the result was recorded as equal. Of the three measurements taken, the majority reading was used as the final result.

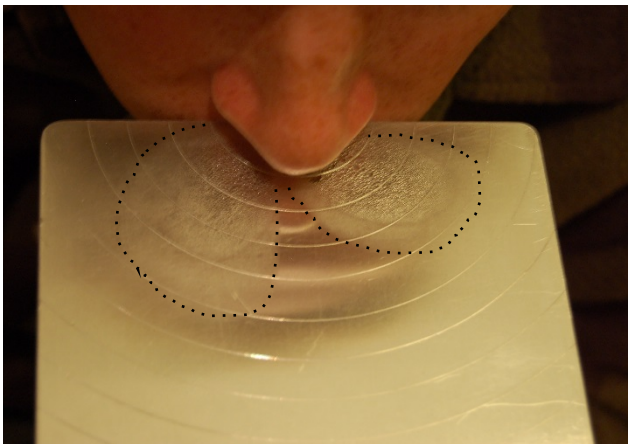

Figure 7: A photograph of the modified GM in use. The participant is exhaling through the nose with the modified GM positioned horizontally just beneath the columella. The condensation areas produced during exhalation can be seen on the plate and are marked with a dotted line. On this occasion the right nasal passage produced a larger condensation area than the left, indicating right nasal passage dominance at that time.

A trial run was performed during the 30-minute rest period after each participant arrived at the test centre to allow them to become familiar with the testing method. Results from this trial run were not be recorded or included in the data analysis. Care was taken to minimise positional errors whilst recording. The subject was sat

upright with the head in a neutral position and the same investigator (AP) performed and interpreted each measurement.

3.8: Blinding

In order to avoid potential investigator bias (given the subjective nature of the recordings), as much as possible the investigator taking the nasal airflow measurements (AP) was blinded to the participants' handedness. Handedness questionnaires were completed by participants and checked by another researcher. Participants were asked not to reveal their hand preference or write when the investigator was in the room. Throughout data collection, participant demographics were monitored by another researcher and discussed with the investigator to ensure roughly equal numbers of right-handed and left-handed participants and to guide recruitment. Therefore the investigator was not blinded to the last three subjects' hand preference as only left-handed volunteers were recruited (subject numbers 034, 035 and 036). The handedness of all participants was revealed once all data had been collected and analysed.

3.9: Statistical analysis

The data collected was compiled into a Microsoft Excel® spreadsheet for further analysis. In order to define each subject as either left or right nasal passage dominant based on the measurements collected, binomial distribution was used to look for consistent differences in each subject.

Once all data had been analysed, the hand preference of each participant was revealed. The Chi-square test was used to look for a statistically significant correlation between nasal passage dominance and hand preference.

Chapter 4: Subjects

4.1: Introduction

Over the past few decades, many studies have found that certain physiological and pathological conditions can influence nasal airflow. These include subject factors, such as age (74) and nasal pathology (54), positional factors such as posture (79) and other influences such as sleep (28) and exercise (84). During recruitment, efforts were made to minimise factors known to influence nasal airflow using strict inclusion and exclusion criteria. The test environment and methods used to take measurements were also carefully considered. The following section discusses the recruitment procedure and subjects in detail with reference to the relevant literature that informed the process.

4.2: Methods

Volunteers for the study were recruited by email and poster advertisements placed around Cardiff University campus. There were two periods of recruitment and testing that coincided with university semesters, one in the autumn and another in the spring. The first group of volunteers were recruited and tested between November 5th 2015 and December 17th 2015 (subject numbers 001 – 019). The second group were recruited and tested between April 11th 2016 and May 20th 2016 (subject numbers 020 – 036). Both groups contained a mixture of male and female subjects and left-handed and right-handed subjects. All volunteers were students at the University.

Each subject was required to attend the test centre on two separate days. On the first day, after providing informed consent, subjects were screened for suitability to take part. To ensure that all inclusion and exclusion criteria were met, subjects were asked about their medical history and had a nasal examination using anterior

rhinoscopy (for full list see Appendix 1). A convenient date was then arranged for the test day.

4.3: Results

In total, 36 subjects were recruited into the study. Of those, 7 were excluded. The reasons for exclusion are listed in Table 2.

Table 2: A summary of the demographics and reasons for exclusion. *Subject 014 was taking isotretinoin for acne, which can cause dryness of the nasal mucosa (173).

Subject number	Age (years)	Gender	Hand preference	Reason for exclusion
001	22	M	Left	Significant nasal septal deviation
014	18	F	Left	Concominant confounding medication*
016	19	F	Left	Rhinitis
017	19	M	N/A	Mixed handedness
021	22	M	N/A	Mixed handedness
026	27	F	Right	Significant nasal septal deviation
029	20	M	N/A	Mixed handedness

Efforts were made to recruit roughly equal numbers of left- and right-handed subjects and males and females (see Tables 5 and 6). Of those included, 14 were male and 15 were female. The average age was 20.8 years, with a range of 18 – 30 years. Fifteen subjects were left-hand dominant (LHD), including 6 males and 9 females, and 14 were right-hand dominant (RHD), including 8 males and 6 females. The demographics of all included patients are listed in Table 3.

Table 3: Demographics of all included subjects.

Subject number	Age (years)	Gender	Hand dominance	Significant medical history	Concominant medication
002	19	Female	Right	None	None
003	19	Male	Left	Seasonal rhinitis – asymptomatic during study period	None
004	18	Female	Left	None	None
005	19	Female	Left	None	None
006	18	Female	Left	None	Progesterone – only contraceptive pill
007	20	Female	Left	Mild asthma during childhood – asymptomatic for 8 years	None
008	20	Female	Left	None	Combined oral contraceptive pill
009	18	Female	Left	Cholecystectomy for gallstones	Combined oral contraceptive pill
010	20	Female	Left	Mild asthma during childhood – asymptomatic for 8 years	Combined oral contraceptive pill
011	20	Male	Left	Seasonal rhinitis – asymptomatic during study period	None
012	21	Female	Left	Mild asthma during childhood – asymptomatic for 4 years	None
013	20	Male	Right	None	None
015	21	Female	Left	None	None
018	21	Female	Right	Appendicectomy	None
019	19	Female	Right	None	Contraceptive implant (slow release progesterone)
020	21	Female	Right	None	Contraceptive implant (slow release progesterone)
022	20	Female	Right	None	Combined oral contraceptive pill
023	23	Male	Right	None	None
024	25	Male	Right	None	None
025	21	Male	Right	Depression	Sertraline (selective serotonin reuptake inhibitor)
027	21	Female	Right	None	Combined oral contraceptive pill
028	20	Male	Right	None	None
030	22	Male	Right	None	None
031	30	Male	Right	None	None
032	21	Male	Left	None	None
033	25	Male	Right	None	None
034	21	Male	Left	None	None
035	22	Male	Left	None	None
036	19	Male	Left	Migraine	None

Table 4: Summary of included subjects.

Summary of included subject demographics	
Average age (years)	20.8
Median age (years)	20
Age range (years)	18 - 30
Number of males	14
Number of females	15
Male to female ratio	1:1.07
Number of left-handers	15
Number of right-handers	14
Left to right-handed ratio	1:0.93

Table 5: Comparison of basic demographics for male and female subjects.

	Male subjects	**Female subjects**
Number of subjects	14	15
Average age (years)	22	19.7
Median age (years)	21	19
Age range (years)	19 – 30	18 – 21
Number of left-handers	6	9
Number of right-handers	8	6

Table 6: Comparison of basic demographics for left- and right-handed subjects.

	Left-handers	**Right-handers**
Number of subjects	15	14
Average age (years)	19.8	21.9
Median age (years)	20	21
Age range (years)	18 – 22	19 – 30
Number of males	6	8
Number of females	9	6

During screening, all subjects were asked specifically about any history of nasal problems in the past and concurrent nasal symptoms. No subject reported concurrent or recent (preceding one month) nasal symptoms such as nasal blockage, rhinorrhea or change in sense of smell. This was checked a second time on the test day to ensure no subject had a concurrent or recent history of rhinitis that had developed between the screening and test days. Anterior rhinoscopy was performed on all subjects during screening, and those with significant septal deviation (n=2) or signs of rhinitis (n=1) were excluded. No other nasal pathology was detected during screening.

The majority of subjects (20/29) reported no significant previous medical history. Two subjects had a history of seasonal rhinitis however they were both tested during the autumn period and denied any recent nasal symptoms. They did not have signs of rhinitis on anterior rhinoscopy. Three subjects reported mild asthma during childhood however they had been asymptomatic and had not required any treatment for at least four years. Two subjects had previously required abdominal surgery in the form of an appendicectomy (n=1) and a cholecystectomy (n=1) however they had fully recovered from these procedures. One male subject reported a history of mild depression and another reported a history of migraines, both of which were deemed unlikely to affect the results of the study.

Nine subjects were taking prescribed medication at the time of the study. The majority of these subjects were females taking contraception in the form of the combined oral contraceptive pill (n=5), the progesterone implant (n=2) and the progesterone-only contraceptive pill (n=1). One subject was taking sertraline, a selective-serotonin reuptake inhibitor used to treat depression.

4.4: Discussion

During screening and testing, efforts were made to minimise factors that could influence nasal airflow. Potential influencing factors are discussed below, with references to evidence from the relevant literature. The demographics of the left- and right-handed groups were similar.

Subject factors

The average age of this cohort was 20.8 years, with a range of 18 – 30 years. The average age of right-handed subjects was slightly higher at 21.9 years, compared to 19.8 years in left-handed subjects. Studies have suggested that advancing age can affect patterns of nasal airflow, however changes seem to be more likely in individuals aged over 50 years (74, 75) and therefore the age range in this group is unlikely to be a potential confounding factor.

Although BMI was not measured specifically, none of the recruited subjects were overweight.

Both male and female subjects were included in the study. Searleman et al. (2005) only included males due to concerns that changes in female sex hormone levels as part of the menstrual cycle could affect nasal airflow (113). However conflicting results have been published regarding this theory, with one study reporting nasal congestion during menstruation (92) and another reporting no difference in nasal airflow throughout different phases of the menstrual cycle (93). Perhaps more importantly, two other studies that measured nasal airflow over several hours using different methods found that gender did not significantly affect nasal airflow (29, 74). Enquiring about phase of the menstrual cycle in female subjects was therefore considered unnecessary. Female subjects were asked whether they were pregnant, however formal testing was not carried out as the study did not involve any risks to pregnant women (such as might be the case with a drug trial). Whilst pregnancy-induced rhinitis is relatively common, it predominantly occurs in the latter stages of

pregnancy and is associated with symptoms such as nasal stuffiness (88, 89). All subjects were asked specifically about nasal symptoms and examined by anterior rhinoscopy to exclude those with rhinitis.

Most subjects had no significant past medical history. Of note, three subjects reported mild childhood asthma but had been asymptomatic for at least four years and were not taking any inhalers. Their respiratory function therefore was assumed to be normal. Two patients reported seasonal rhinitis, however they were tested during the autumn and were asymptomatic with normal anterior nasal examinations.

Anterior rhinoscopy was performed on each subject in order to exclude those with nasal pathology such as nasal polyps or septal deviation, which can affect nasal airflow (28, 54, 107). A more detailed nasal examination in the form of nasal endoscopy was deemed unnecessary as it is an invasive procedure and only subjects with no history of nasal problems or concurrent nasal symptoms were recruited into the study.

Eight out of fifteen female subjects were taking some form of contraception, either progesterone-only (n=3) or combined oestrogen and progesterone (n=5). Although there have been concerns that oestrogens can cause nasal congestion (92, 97), a study on the effect of the modern combined contraceptive pill failed to show that it altered nasal airflow (99). Therefore it was deemed unlikely that contraception of any kind would influence the results of this study. All other subjects denied taking any regular prescribed or over-the-counter medication, apart from one male subject who was taking sertraline, a selective-serotonin reuptake inhibitor used to treat depression, which has no nasal side effects listed in the British National Formulary (173).

Positional factors

Changes in posture are known to affect nasal airflow. Sometimes referred to as the corporo-nasal reflex, stimulation of pressure sensors in the thorax, pectoral and

pelvic girdles leads to ipsilateral nasal congestion and contralateral nasal decongestion (78-80). Changing from a sitting to a supine position will increase nasal airway resistance via an increased blood flow to the nasal vessels (76, 77). In order to avoid these effects, subjects were not permitted to lie down during the measurement period. Positional factors can also affect the reliability of measurements obtained using the modified GM (66) and therefore care was taken to ensure that each subject sat up straight with their head in a neutral position during measurements. To ensure continuity in the measurement technique, all measurements were performed by one investigator, and anatomical landmarks (columella and upper lip) were used to maintain the same positioning of the plate at each measurement.

Environmental factors

Recruitment and testing took place in two groups, 15 subjects were tested in November and December 2015, and 14 were tested in April and May 2016. Testing was performed in a laboratory, and all subjects spent the 6-hour measurement period in the same room, with allowances for toilet breaks as required. Although the exact temperature and humidity level in the laboratory were not recorded, it was always kept at a comfortable level. Room temperature differences were not shown to affect nasal airflow when acoustic rhinometry was performed at room temperatures of 18-22°C and 30-33°C (86). During the first test period, the average maximum outdoor temperature was 12°C, the average minimum temperature was 10°C and the average humidity was 88% (174). During the second test period, the average maximum outdoor temperature was 12°C, the average minimum temperature was 8°C and the average humidity was 77% (174). Whilst the outdoor environment was slightly different for each subject, importantly they were given a 30-minute rest period in the test environment prior to starting any measurements, allowing acclimatisation to the indoor environment, as suggested in a previous study using the modified GM (55). As ingestion of hot water has been shown to increase nasal congestion (87), subjects were not permitted to drink hot drinks or eat hot food during the test period. No such effect was found with cold drinks (87) and

therefore subjects were permitted bottled water throughout the day and were given a standardised cold meal at midday.

Temperature and humidity changes also have the potential to reduce the reliability of the modified GM (55, 66). In order to prevent heating of the plate, excessive handling was avoided and a different plate was used for each of three measurements performed at each time point. This also ensured that there were no remaining condensation areas left from the previous measurement and allowed all three measurements to be performed in quick succession. The plates were kept in the same room as the subject during the testing period and cleaned at the end of each test day.

Other factors

Sleep was not permitted during the test period as sleep has been shown to affect nasal airflow patterns, irrespective of posture in some instances (27, 28). During the test period, subjects were asked to remain at rest but were permitted to study, read or watch television. Subjects were asked to avoid strenuous exercise, for example swimming, cycling or running in the three hours prior to the start of the study. This was necessary as studies have shown that exercising abolishes the asymmetry of airflow between the nasal passages, increasing the overall nasal airflow to meet the increased metabolic demand (84, 85). Subjects were asked not to consume more than four units of alcohol in the 12 hours prior to the test period due to the risks of increasing nasal congestion (100, 101). As cigarette smoking can damage the nasal mucosa (102), only non-smokers were recruited into the study.

Chapter 5: Nasal airflow patterns

5.1: Introduction

Multiple observational studies of nasal airflow patterns have been published over the last century e.g. (3, 5, 8-11, 13). What is clear from these studies is that a great deal of variability exists amongst nasal airflow patterns, not only between but also within individuals (8-11). This has led to controversy over the use of the term "nasal cycle", as the key features of regularity and reciprocity have not been consistently demonstrated (13).

Nevertheless, some similarities in patterns of nasal airflow have been observed. For example, several studies have noted some degree of reciprocity between the nasal passages, defined as congestion on one side with accompanying decongestion on the other without a change in the overall nasal airway volume (13, 15). Others have observed a parallel or in-phase relationship, with fluctuations in nasal airflow occurring in both nasal passages with no reversal of nasal airflow dominance (9, 15). In some individuals, fluctuations in nasal airflow have been observed but without any discernable pattern (8, 15). Kern (1981) used the term "non-cycle nose" to describe individuals without the classical features of a nasal cycle (9). He suggested three categories; no change in nasal resistance, changes in one nasal passage but not in the other, and an in-phase or parallel relationship (9).

This section discusses the nasal airflow patterns observed in this cohort of healthy individuals.

5.2: Methods

In order to obtain an overall description of the nasal airflow patterns for each subject, the nasal airflow patterns were put into different categories according to the definitions listed below. This part of the data analysis was done prior to unblinding to hand preference.

Category 1:

Subjects with definite changes in nasal airflow dominance that were sustained, i.e. a change in the dominance of nasal airflow from the left to the right nasal passage or *vice versa*. A sustained change was defined as at least four consecutive measurements of dominance in one side, which then switched to become at least four consecutive measurements of dominance in the contralateral side (see Figure 8). A period of uncertainty between the change was allowed, specifically no more than two equal measurements (see Figure 9). Although the time period of four measurements was chosen arbitrarily, it was thought to be reasonable as it reflected a one hour period out of the six hour total measurement period.

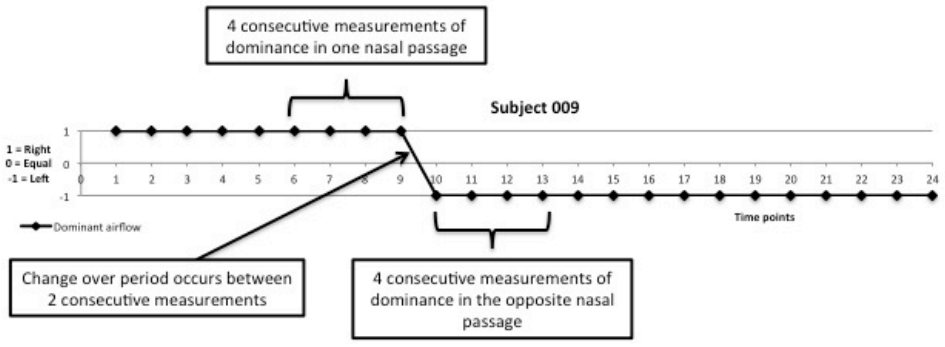

Figure 8: An example of a subject whose nasal airflow pattern fits into Category 1.

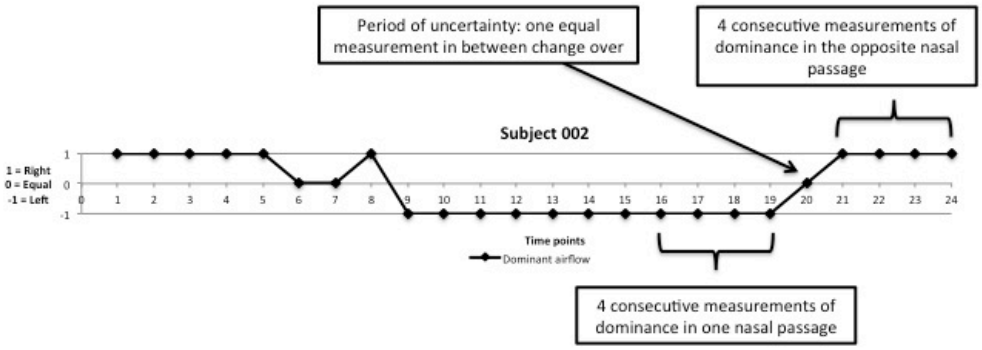

Figure 9: A second example of a subject whose nasal airflow patterns fit in to Category 1.

Category 2:

Subjects with little or no change in nasal airflow dominance, defined as consecutive readings of dominance in one nasal passage throughout the measurement period (see Figure 10) with the exception of no more than three readings that indicate dominance in the contralateral nasal passage (see Figure 11). Equal readings were disregarded in this group.

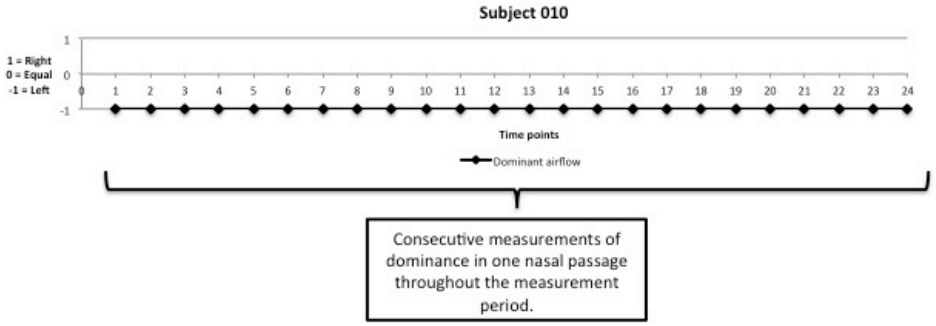

Figure 10: An example of a subject whose nasal airflow pattern fits into Category 2.

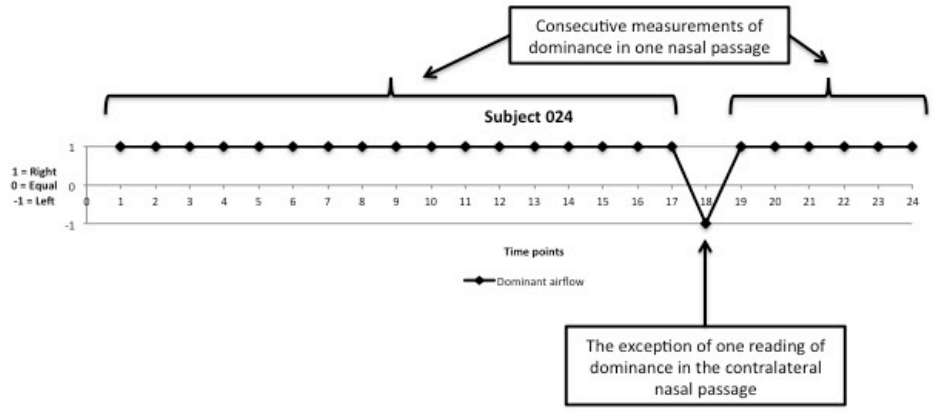

Figure 11: A second example of a subject whose nasal airflow pattern fits into Category 2.

Category 3:

Subjects with variations in the patterns of nasal airflow dominance that did not fit in with either of the above two categories (see Figure 12).

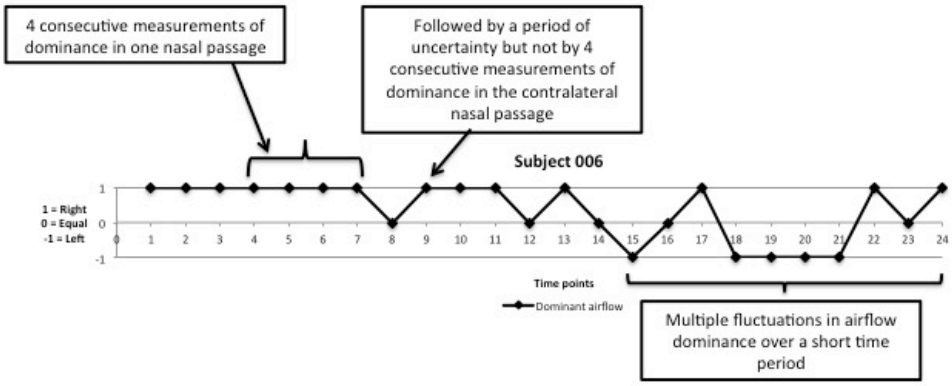

Figure 12: An example of a subject whose nasal airflow pattern fits into Category 3.

5.3: Results

Table 7 shows the categorisation of subjects into the groups described above. Sixteen subjects (55%) exhibited at least one definite and sustained reversal of nasal airflow dominance during the 6-hour measurement period and could therefore be described as in Category 1 (see Figures 13-15). Eight subjects (28%) had little or no change in nasal passage dominance (see Figures 16 and 17). Only five subjects (17%)

had nasal airflow patterns that were highly variable and therefore could not be grouped into Category 1 or 2 (see Figure 18).

Table 7: Subjects grouped into categories according to their patterns of nasal airflow.

Category 1		**Category 2**	**Category 3**
002	022	005	003
004	023	007	006
009	025	008	015
012	028	010	027
013	031	011	030
018	032	024	
019	034	033	
020	035	036	

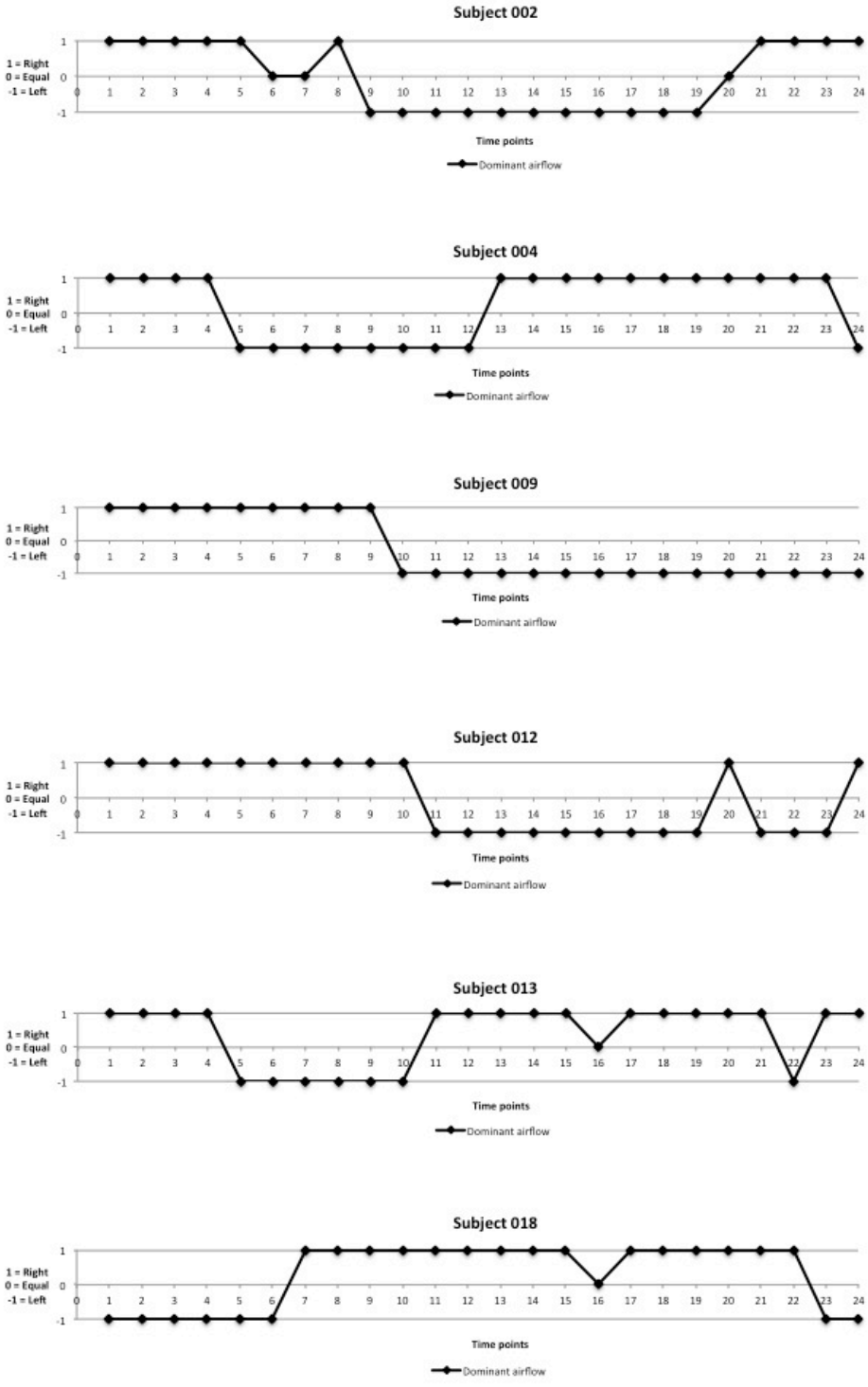

Figure 13: Nasal airflow patterns of subjects in Category 1.

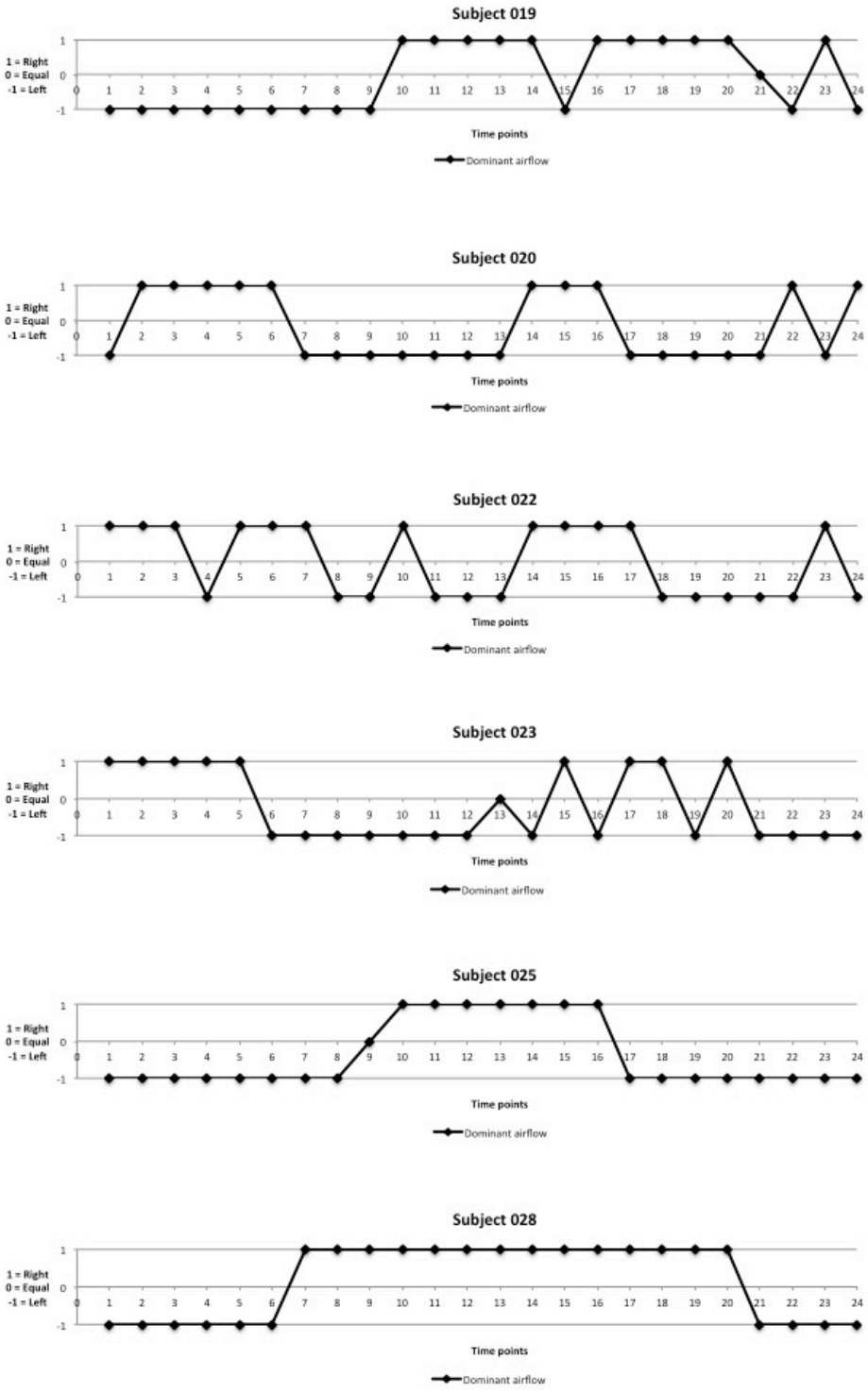

Figure 14: Nasal airflow patterns of subjects in Category 1, continued.

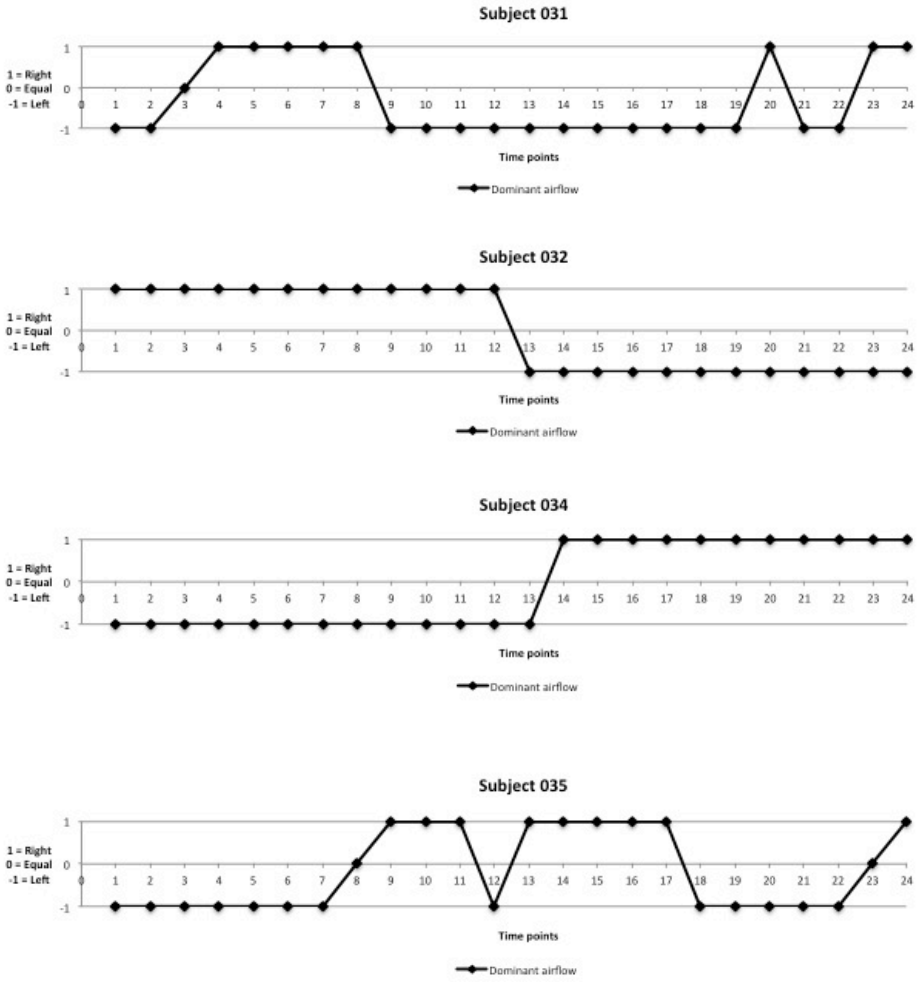

Figure 15: Nasal airflow patterns of subjects in Category 1, continued.

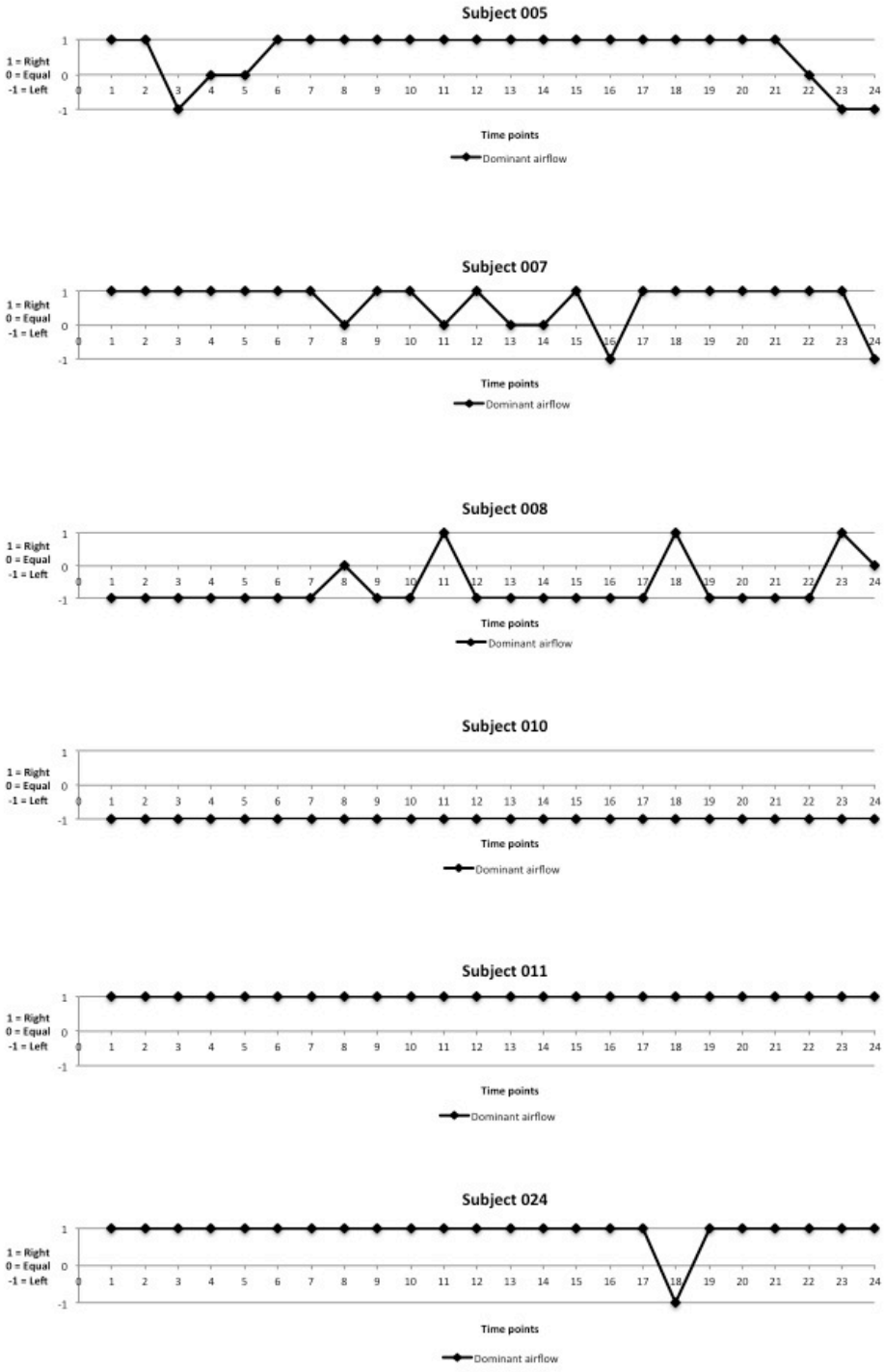

Figure 16: Nasal airflow patterns of subjects in Category 2.

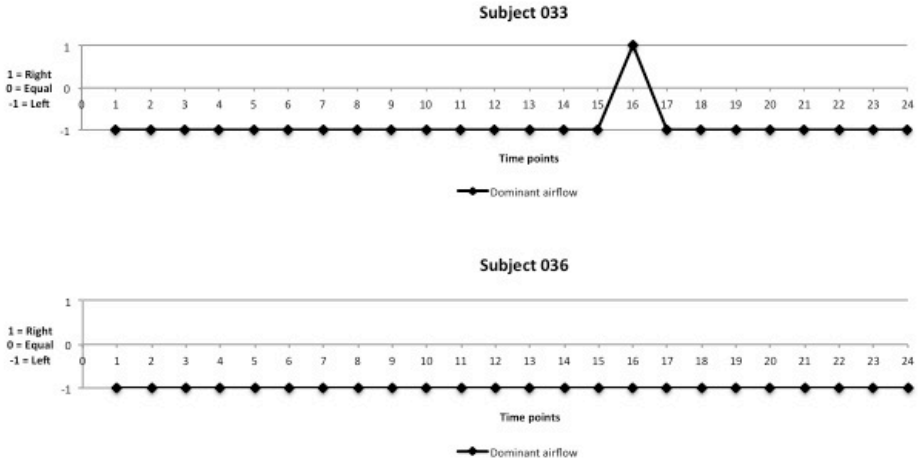

Figure 17: Nasal airflow patterns of subjects in Category 2, continued.

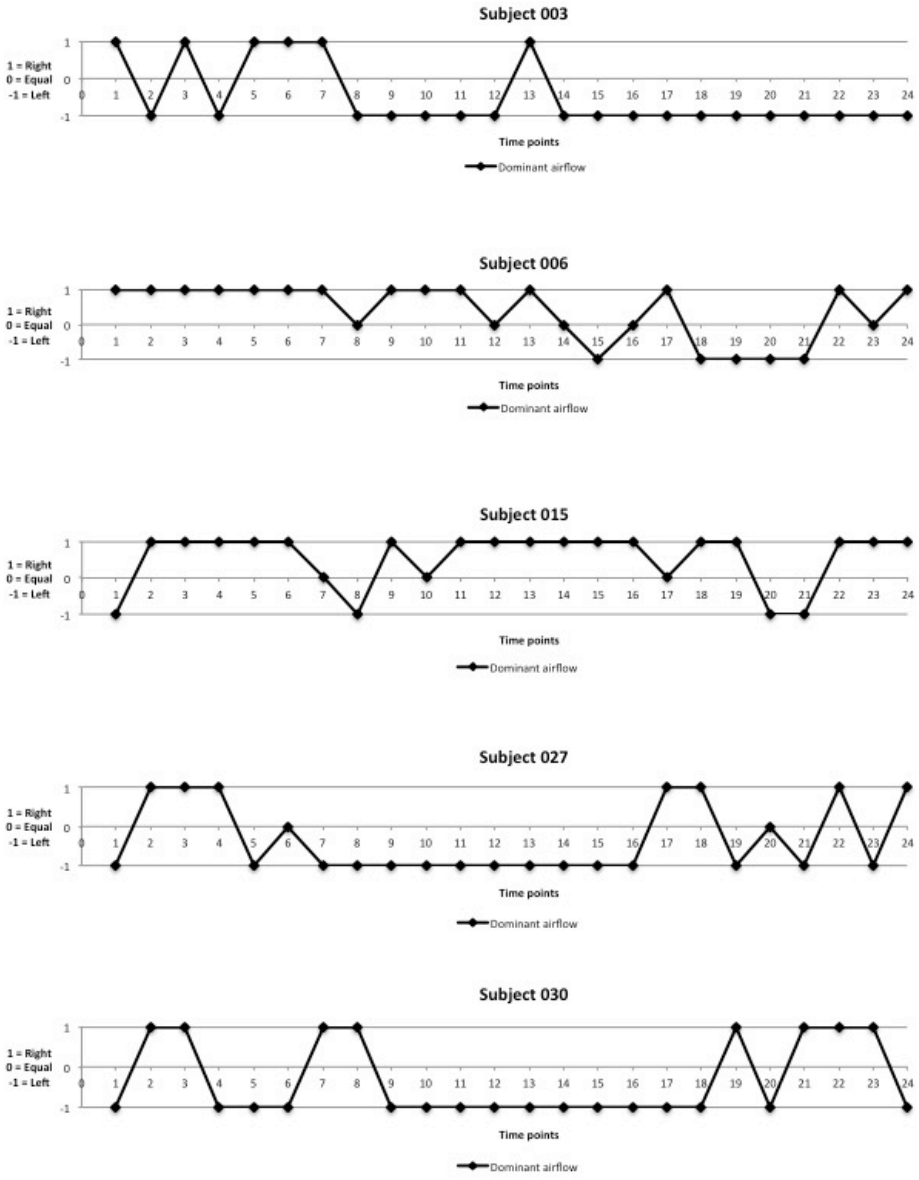

Figure 18: Nasal airflow patterns of subjects in Category 3.

To interpret this data, one must consider the physiological basis for these patterns. In each figure, the nasal passage with the dominant i.e. the greatest nasal airflow is represented by a diamond at each time point. This is equivalent to whichever nasal passage produced the greatest condensation area on the modified GM, and in most cases was judged to be either the left or the right nasal passage. The degree of difference between the condensation areas was not recorded, only whether one was larger than the other, and therefore this is a crude method of evaluating nasal passage dominance.

When a nasal passage is dominant, it receives the greatest sympathetic output from the brainstem, leading to vasoconstriction of the nasal veins, reduced nasal congestion and therefore greater nasal airflow (38). At the same time, the non-dominant nasal passage receives less sympathetic output, resulting in dilation of the nasal veins, increased nasal congestion and therefore reduced nasal airflow. A change in nasal passage dominance from one side to the other indicates that the balance of sympathetic output has shifted from one side of the brainstem to the other. In most subjects, it is likely that changes in sympathetic output occurred frequently throughout the day, leading to changes in nasal airflow. However if this change was not large enough to cause a complete reversal of nasal passage dominance, it would not have been detected.

In some instances, it was not possible to decide whether the left or right nasal passage had produced the greatest condensation area as they appeared to be equal, for example measurements 8, 12, 14, 16 and 23 in Subject 006 (see Figure 12). There are two possible explanations for this finding. First, it could be due to the method used. The modified GM did not provide quantitative values for the amount of nasal airflow in each nasal passage. Instead, the dominant nasal passage was decided subjectively by the investigator by observing the differences in the condensation areas produced by each side. It is possible therefore that subtle differences could have been missed, preventing the investigator from making a judgment on which nasal passage was dominant and leading to a recording of "Equal" for that time point. Alternatively, it could be that sympathetic output from the brainstem was divided equally between the nasal passages, leading to equal venous congestion and therefore equal nasal airflow.

At each 15-minute time interval, three measurements of nasal airflow were taken in quick succession, as taking an average of three measurements has been recommended to improve reliability (55). If there was uncertainty as to which nasal passage had produced the largest condensation area, this measurement was recorded as "Equal". Therefore there were three possible outcomes at each measurement; "Left", "Right" or "Equal". The majority result at each time point was

taken to be the correct measurement. For example, if two or more measurements were “Left”, the result at that time point was recorded as “Left”. If two or more measurements were “Equal”, the result at that time point was recorded as “Equal”. If one measurement was “Left”, one was “Right”, and the other was “Equal”, the result was recorded as “Equal”.

Table 8: Summary of measurements throughout the 6-hour time period for each subject.

Subject number	Time points when all 3 readings the same		Time points when 2/3 readings the same		Time points when all 3 readings different		Total number of “Equal” readings throughout measurement period	
	/24	%	/24	%	/24	%	/72	%
002	20	83	3	13	1	4	6	8
003	21	88	3	13	0	0	0	0
004	22	92	2	8	0	0	2	3
005	16	67	7	29	1	4	7	10
006	12	50	11	46	1	4	14	19
007	12	50	11	46	1	4	12	17
008	16	67	7	29	1	4	5	7
009	24	100	0	0	0	0	0	0
010	17	71	7	29	0	0	5	7
011	24	100	0	0	0	0	0	0
012	22	92	2	8	0	0	1	1
013	18	75	6	25	0	0	5	7
015	16	67	6	25	2	8	4	6
018	22	92	1	4	1	4	1	1
019	22	92	1	4	1	4	2	3
020	17	71	7	29	0	0	1	1
022	18	75	6	25	0	0	3	4
023	19	79	4	17	1	4	4	6
024	20	83	4	17	0	0	3	3
025	18	75	6	25	0	0	6	8
027	19	79	3	13	2	8	3	4
028	23	96	1	4	0	0	1	1
030	20	83	4	17	0	0	0	0
031	20	83	4	17	0	0	4	6
032	24	100	0	0	0	0	0	0
033	24	100	0	0	0	0	0	0
034	24	100	0	0	0	0	0	0
035	20	83	3	13	1	4	6	8
036	23	96	1	4	0	0	1	1

On average, all three measurements gave the same result at each specific time point 82% of the time (20/24). Two out of three measurements gave the same result 16% (4/24) of the time on average, whereas all three measurements were different an average of 2% (0.5/24) of the time. Across all measurements for the entire 6-hour

period, the average number of equal readings recorded was 3/72 (4.5%). There was however a lot of variability seen here, with two subjects recording 12 and 14 equal readings and seven subjects recording none. In general however, the investigator was able to make a judgment as to whether the left or right nasal passage was dominant. Considering all 29 subjects had three measurements taken 24 times, giving a total of 72 measurements for each subject and 2,088 measurements altogether, a dominant nasal passage was recorded 1,992 times i.e. in 95% of measurements. This suggests that the modified GM was an appropriate method for measuring nasal passage dominance.

5.4: Discussion

Considering evidence from previous studies, it is clear that the data presented above is consistent with findings in the literature. There is considerable variability in the nasal airflow patterns observed. Over half of the subjects demonstrated at least one definite and sustained reversal of nasal airflow dominance, indicating some degree of reciprocity. Those who did not exhibit a definite and sustained reversal of nasal airflow dominance either had no reversal of nasal passage dominance or had fluctuations in nasal passage dominance without any obvious pattern, i.e. without clear reciprocity or regularity.

Unlike other methods of measuring nasal airflow such as rhinomanometry, the modified GM method used in this study did not provide quantitative values. It is possible therefore that some reversals of nasal passage dominance could have been missed if the difference between nasal airflow on each side was small. In addition, it is difficult to know exactly what was happening with regard to nasal airflow fluctuations for subjects in Category 2, i.e. with no reversal of nasal passage dominance during the measurement period. There are several possibilities here. The measurement period of 6 hours could have been too short to capture a reversal of nasal passage dominance, as there is some evidence from the literature that the

duration of the nasal cycle can be as long as 6 or 7 hours (8, 10). Alternatively, there may have been no fluctuations in nasal airflow, as suggested by Kern (1981) (9). The most likely explanation however, given that in most studies fluctuations in nasal airflow over a period of hours have been observed to some degree, is that changes in nasal airflow did occur, but that these changes were not large enough to cause reversal of nasal passage dominance.

The patterns of nasal airflow obtained in this study have been compared with those from a previous study of a different group of subjects in which nasal airflow was measured hourly over an 8-hour period using anterior rhinomanometry (175). As shown in Figures 19-22, very similar patterns can be seen. This demonstrates that whilst there is clear inter-individual variation, some consistent patterns in nasal airflow can be found when comparing different subjects. In addition, the modified GM has successfully detected these patterns.

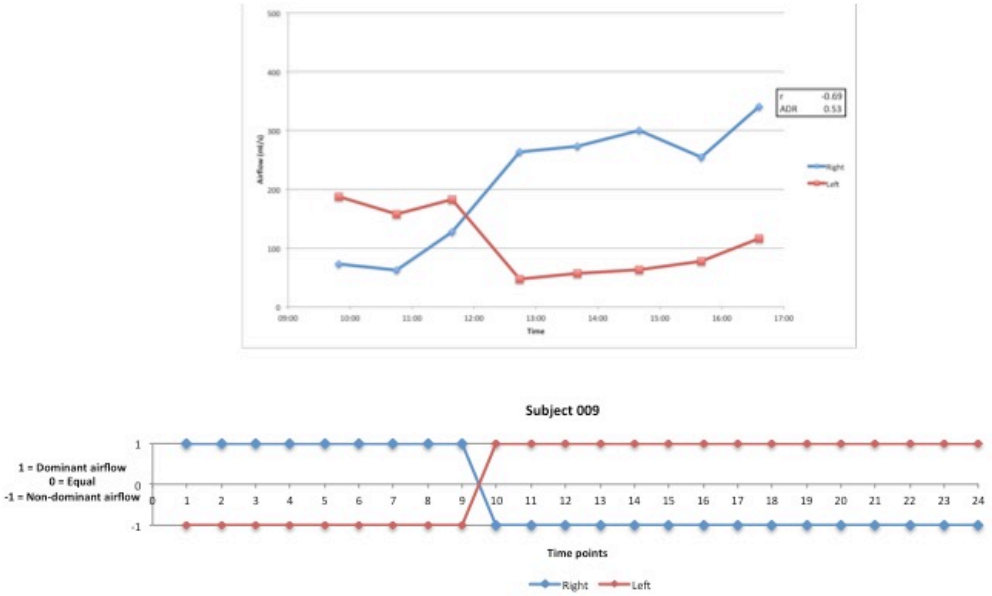

Figure 19: Comparison of nasal airflow patterns. Top graph: hourly measurements of nasal airflow obtained using anterior rhinomanometry from one subject over 8 hours (175). Bottom graph: 15-minute measurements of nasal airflow obtained using the modified GM in a different subject over 6 hours. The right nasal passage is represented by the blue line, the left nasal passage is represented by the red line. The pattern observed is almost identical in that there is one reversal of nasal passage dominance, this occurs from left to right in the top graph and from right to left in the bottom graph. Using rhinomanometry (top graph), fluctuations in nasal airflow are demonstrated at each time point, however it is only on one occasion that the fluctuation is great enough to cause reversal of nasal passage dominance. Fluctuations that did not lead to a reversal of nasal passage dominance are not demonstrated by the modified GM (bottom graph), as quantitative values were not obtained.

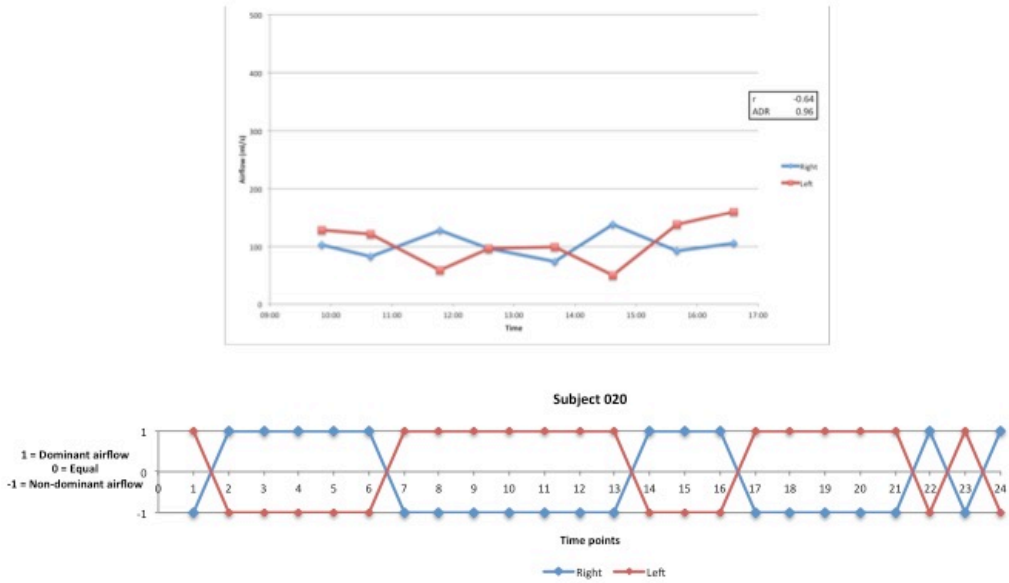

Figure 20: Comparison of nasal airflow patterns. Top graph: hourly measurements of nasal airflow obtained using anterior rhinomanometry from one subject over 8 hours (175). Bottom graph: 15-minute measurements of nasal airflow obtained using the modified GM in a different subject over 6 hours. The right nasal passage is represented by the blue line, the left nasal passage is represented by the red line. The patterns observed are similar, in that fluctuations in nasal airflow occur throughout the measurement period leading to several reversals of nasal passage dominance.

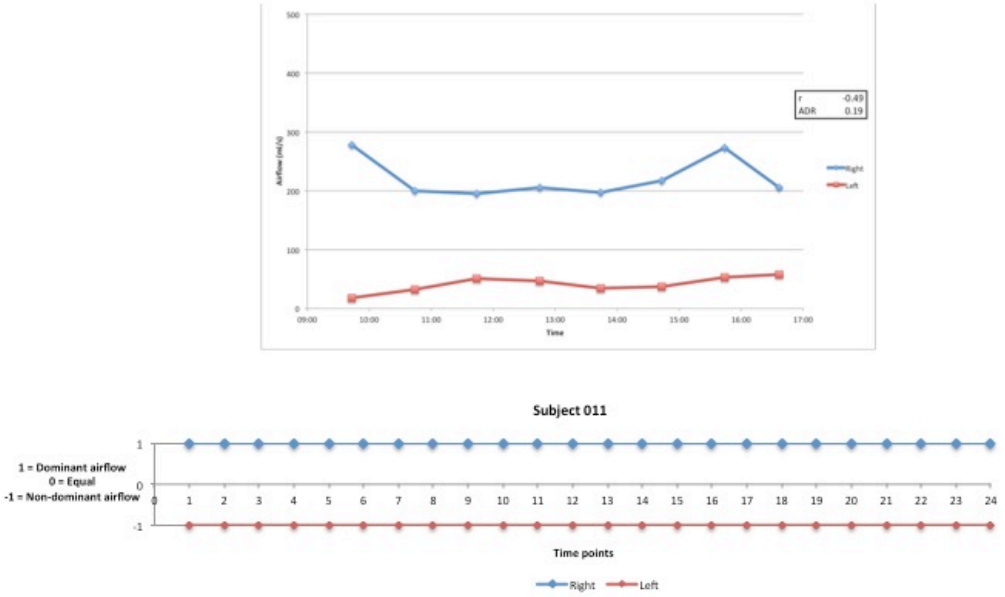

Figure 21: Comparison of nasal airflow patterns. Top graph: hourly measurements of nasal airflow obtained using anterior rhinomanometry from one subject over 8 hours (175). Bottom graph: 15-minute measurements of nasal airflow obtained using the modified GM in a different subject over 6 hours. The right nasal passage is represented by the blue line, the left nasal passage is represented by the red line. Once again, the nasal airflow patterns are very similar. In both subjects, the right nasal passage has remained dominant throughout the measurement period. Using anterior rhinomanometry, small fluctuations in nasal airflow were detected, whereas this was not possible with the modified GM. However none of these fluctuations were great enough as to result in reversal of nasal passage dominance.

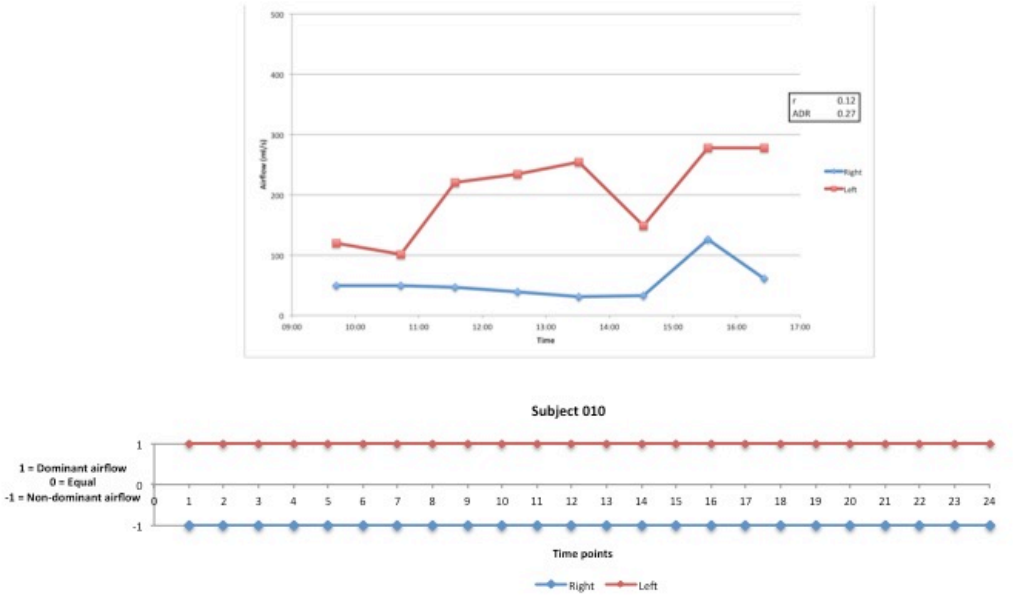

Figure 22: Comparison of nasal airflow patterns. Top graph: hourly measurements of nasal airflow obtained using anterior rhinomanometry from one subject over 8 hours (175). Bottom graph: 15-minute measurements of nasal airflow obtained using the modified GM in a different subject over 6 hours. The right nasal passage is represented by the blue line, the left nasal passage is represented by the red line. Again, the nasal airflow patterns are very similar. In both subjects, the left nasal passage has remained dominant throughout the measurement period, with small fluctuations detected by anterior rhinomanometry but not by the modified GM.

Chapter 6: Nasal airflow and hand preference

6.1: Introduction

The principle aim of this study was to look for any correlation between nasal passage dominance and hand preference. The existing literature in this field is very limited, with only one published study specifically designed to answer this research question in healthy individuals.

The very notion of this relationship may seem unusual, as one could question how and why nasal airflow would be related to handedness. However humans have a tendency for lateral preferences (113), and the nose is considered to be two separate passages rather than a single entity. Therefore if people can be left-handed and left-eyed, could they also be left-nosed?

Searleman et al. (2005) reported that healthy individuals did exhibit nasal passage dominance, just as they exhibit hand and eye dominance, and that this dominance did correlate with hand dominance (113). However, the reliability of this finding is questionable (see section 1.9 for more detail).

The following sections present new evidence and discuss these findings in relation to the previously proposed link between hand preference and nasal passage dominance.

6.2: Methods

As part of the screening process, the hand preference of each subject was ascertained by observation of handwriting and completion of the Edinburgh Handedness Inventory (Short Form).

The dominant nasal passage was recorded using the modified GM at 15-minute intervals over a 6-hour period on one day (see Chapter 3 for detailed methodology).

Once all data had been collected, it was analysed in order to look for a correlation between hand preference and nasal passage dominance. Several methods of analysis were used. Similarly to Searleman et al. (2005) (113), the percentage of time each nasal passage was dominant was calculated for each subject and this was compared in left- and right-handed subjects. Next, left-handed and right-handed subjects were compared according to their nasal airflow patterns, which were categorised as described in Chapter 5. The results were then compared directly with those presented by Searleman et al. (2005) (113). A different method of determining overall nasal passage dominance was used and following classification of subjects as either left- or right-nasal passage dominant, a chi-square test was used to look for a correlation between nasal passage dominance and hand preference.

6.3: Results

Nasal airflow patterns were analysed in 14 right-handed subjects and 15 left-handed subjects. Tables 9 and 10 show the percentage of time each nasal passage was dominant in left-handed and right-handed subjects respectively. As shown, there was considerable variability within each group of subjects. In left-handers, the percentage of time that the left nasal passage was dominant ranged from 0% to 100%. Likewise in right-handers, the percentage of time that the right nasal passage was dominant ranged from 4.2% to 95.8%.

Table 9: Nasal passage dominance in left-handed subjects. The percentage of time each nasal passage was dominant for each left-handed subject is shown. Note that the percentages do not always add up to 100%, this is because in some subjects (e.g. Subject 005) there were time points when nasal airflow was recorded as being equally divided between the nasal passages and therefore a dominant nasal passage could not be determined at that time point.

Subject number	% of time right nasal passage dominant	% of time left nasal passage dominant
003	25.0	75.0
004	58.3	41.7
005	75.0	12.5
006	58.3	20.8
007	75.0	8.3
008	12.5	79.2
009	37.5	62.5
010	0.0	100.0
011	100.0	0.0
012	50.0	50.0
015	70.8	16.7
032	50.0	50.0
034	45.8	54.2
035	37.5	54.2
036	0.0	100.0

Table 10: Nasal passage dominance in right-handed subjects. The percentage of time each nasal passage was dominant for each right-handed subject is shown. As above, the percentages do not always add up to 100% for the same reason.

Subject number	% of time right nasal passage dominant	% of time left nasal passage dominant
002	41.7	45.8
013	66.7	29.2
018	62.5	33.3
019	45.8	50
020	41.7	58.3
022	50	50
023	37.5	58.3
024	95.8	4.2
025	29.2	66.7
027	29.2	62.5
028	58.3	41.7
030	33.3	66.7
031	33.3	62.5
033	4.2	95.8

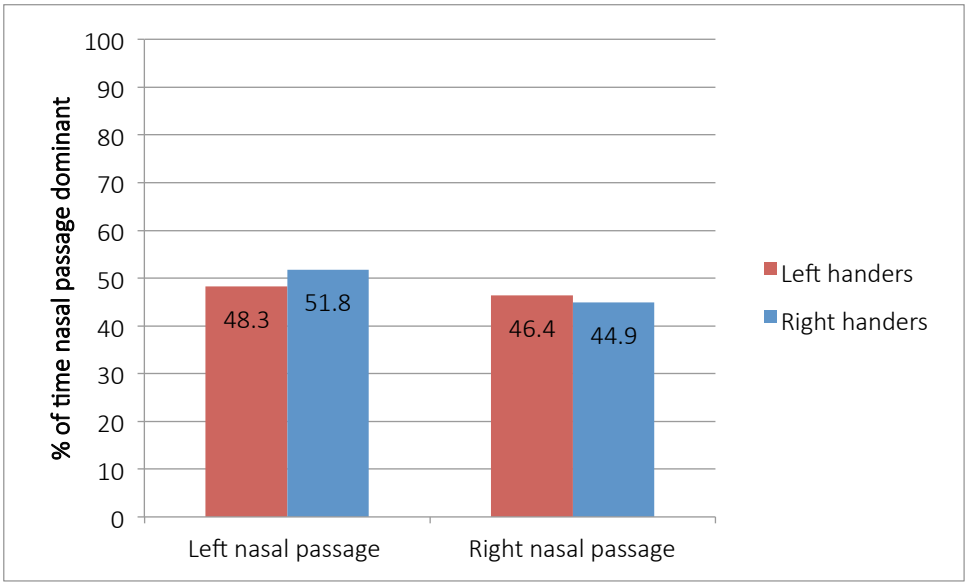

Figure 23: Nasal passage dominance in left- and right-handers. Graph demonstrates the average percentage of time each nasal passage was dominant in left-handed and right-handed subjects. The reason that the percentages displayed do not total 100% is that in some subjects, nasal passage dominance was divided equally (50% and 50%) between both sides.

In left-handers, the left nasal passage was dominant for more 50% of the measurement period in 7 out of 15 subjects (47%). In right-handers, the right nasal passage was dominant for more than 50% of the measurement period in 7 out of 14 subjects (50%). In left-handers, the left nasal passage was dominant an average of 11.6 times out of 24, or 48.3% of the time, whereas the right nasal passage was dominant for 46.4% of the time (see Figure 23). In right-handers, the right nasal passage was dominant an average of 10.8 times out of 24, or 44.9% of the time, whereas the left nasal passage was dominant for 51.8% of the time (see Figure 23). Just from this simple analysis, no clear correlation between nasal passage dominance and hand preference can be demonstrated.

Next, left- and right-handed subjects were compared according to the categorisation of their nasal airflow patterns (see Table 7). Of the 15 left-handers, 6 were in Category 1, 6 were in Category 2 and 3 were in Category 3. Of the 14 right-handers, 10 were grouped to Category 1, 2 were in Category 2 and 2 were in Category 3 (see Figure 24). There appears to be a trend towards right-handers having definite changes in nasal passage dominance with more variability of nasal airflow patterns

seen in left-handers. However, using the chi-square test, no statistically significant correlation between hand preference and categories of nasal airflow patterns was found (p = 0.21).

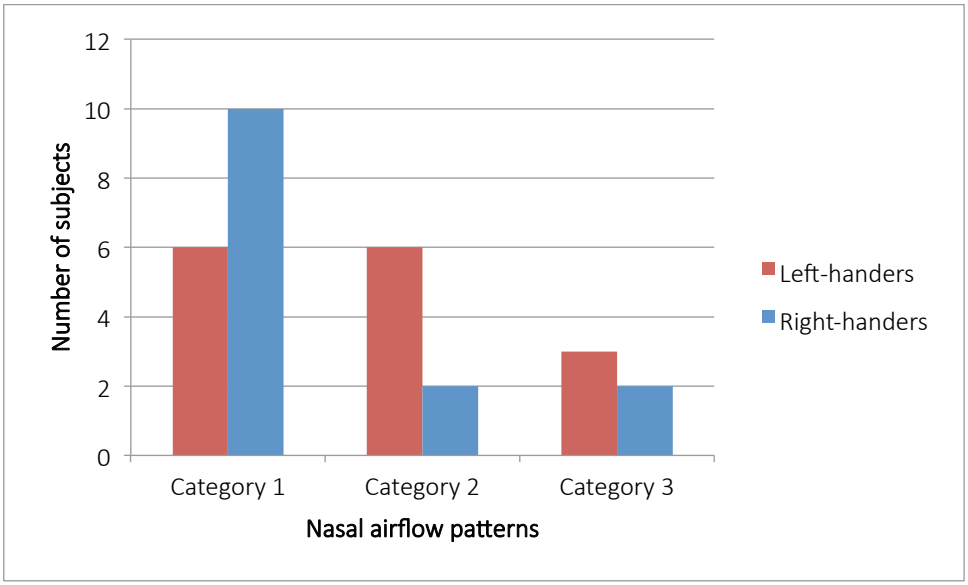

Figure 24: Graph to demonstrate the categorisation of left- and right-handers according to their nasal airflow patterns. Category 1: Subjects with definite changes in nasal airflow dominance that were sustained, i.e. a change in the dominance of nasal airflow from the left to the right nasal passage or *vice versa*. Category 2: Subjects with little or no change in nasal airflow dominance, defined as consecutive readings of dominance in one nasal passage throughout the measurement period. Category 3: Subjects with variations in the patterns of nasal airflow dominance that did not fit in with Category 1 or Category 2.

Comparison with Searleman et al. (2005)

The above analysis using the percentage of time each nasal passage was dominant (calculated from the number of readings) is similar to that reported by Searleman et al. (2005), the only published study to describe the possible relationship between hand preference and nasal airflow in healthy subjects (113). They state (p. 117):

"During 24 trials of the 6-hour testing period, the left-handed males were significantly more likely than chance (50%) to have their left nostril, rather than their right, be the dominant one (59.3%, Z=2.73, p<.01). By an almost identical percentage (59.5%), right-handers show the reverse pattern: the right nostril is the dominant one in airflow (Z=3.09, p<.01)." (113)

Figures 25 and 26 demonstrate the differences between the current data and the results presented by Searleman et al. (2005) (113). There is an obvious difference between the current study results and those published by Searleman et al. (2005) (113). In Searleman et al.'s (2005) study, nasal airflow was divided roughly 60:40 with overall nasal passage dominance positively correlating to hand preference (113). This finding was reported to be significant, with a *p* value of less than 0.01, however the statistical methods used were not specified. In the current study, the division of nasal airflow was closer to 50:50, with no clear correlation between nasal passage dominance and hand preference.

There is a significant issue with the above description of the data analysis. From the information provided in the article, which is quite limited, it appears that Searleman et al. (2005) have used the average percentage of time one nasal passage was dominant to categorise subjects as either right- or left-nasal passage dominant and then attempted to correlate this with hand preference (113). They have used 50% as the cut off value, so that left nasal passage dominance is defined as greater airflow through the left nasal passage for more than 50% of the 24 readings taken over a 6-hour period, and *vice versa* for right nasal passage dominance (113). However, given the known variability of nasal airflow patterns and the relatively short measurement period of 6 hours on one day, it seems that having left or right nasal passage dominance for an average of 50-60% of the readings could easily happen by chance. If the measurement period were to be extended by an hour, potentially this figure and even the overall nasal passage dominance in one subject could change. Therefore, a more robust method for determining nasal passage dominance was used for this study, and this is explained below.

This figure has been removed by the author for copyright reasons.

Figure 25: Graph from Searleman et al. 2005 (113). The graph compares the percentage of time each nasal passage (or nostril) was dominant based on the maximum airflow rate.

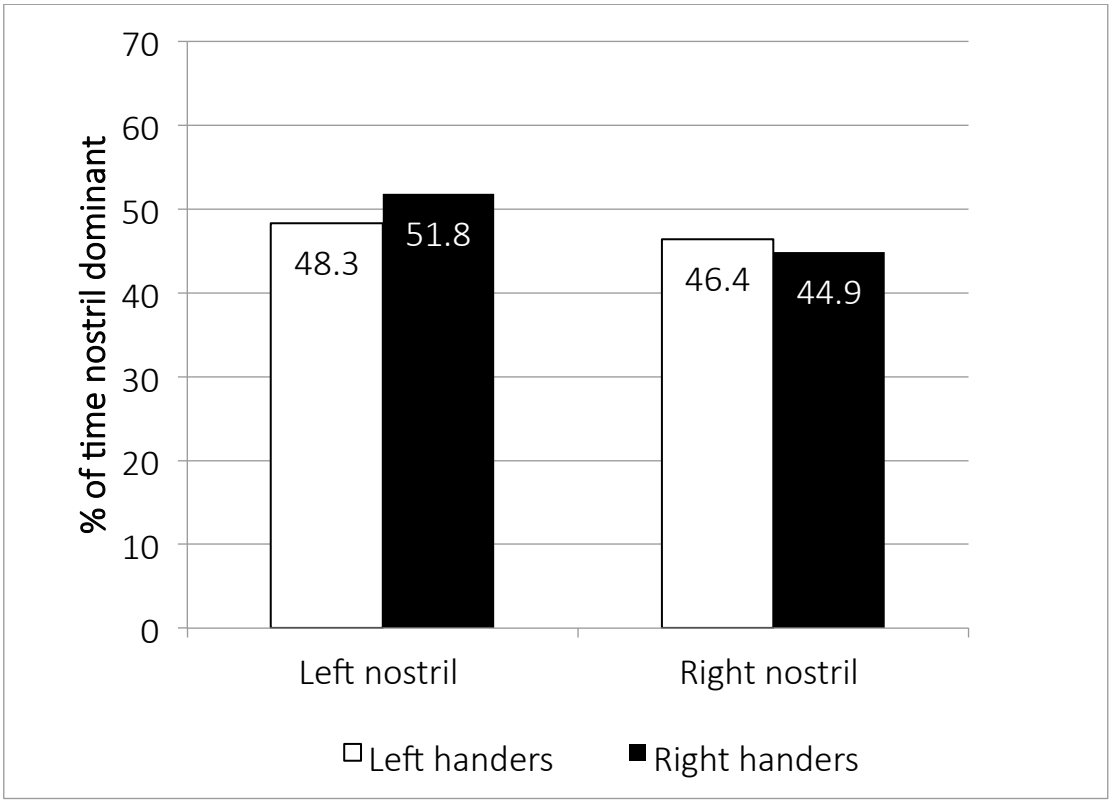

Figure 26: Graph using the data from this study formatted to reflect the format of the graph published by Searleman et al. (2005) (113). The percentage of time each nasal passage was dominant in left-handers and right-handers is shown.

Determining nasal passage dominance

The sampling distribution of the data can be described as binomial, as it has a fixed number of observations (n=24), each observation is independent, each observation represents one of two outcomes (nasal passage dominance or no difference between the nasal passages) and the probability of success is the same for each observation. The binomial distribution could therefore be used to determine the number of successes i.e. dominant nasal passage readings occurring with a specific probability (*p*). This is shown in Table 11. In some subjects, some of the readings were "Equal", in other words, a dominant nasal passage could not be determined. As these readings are essentially unknowns, they had to be excluded in order to use the binomial distribution, and this was taken into account when calculating the probability of successes (see Table 11).

In this case, the null hypothesis is that there is no overall nasal passage dominance, and the alternative hypothesis is that a subject has a dominant nasal passage, which is either the left or the right. For a *p* value of 0.1, when all of the 24 readings are known values, 7 non-dominant readings were permitted to allow a subject to be categorised as being nasal passage dominant. For example, if a subject had 18 readings that were left and 6 readings that were right, they were categorised as left nasal passage dominant. However if they had 16 readings that were right and 8 readings that were left, they were categorised as unclear, meaning that there was no clear overall nasal passage dominance and that the findings were more likely due to chance. Figures 27 and 28 are representative (not actual) graphs of the data, used to illustrate the differences between this method of determining nasal passage dominance and, from the information provided in their article, what was presumably used by Searleman et al. (2005) (113).

Table 11: Using binomial distribution to determine how to categorise each subject as either left- or right-nasal passage dominant.

Number of readings where a nasal passage is dominant	Number of non-dominant readings allowed in order to categorise a subject as left- or right-nasal passage dominant		
	***p*=0.1**	***p*=0.2**	***p*=0.4**
24	7	8	9
23	7	7	9
22	6	7	8
21	6	7	8
20	5	6	7
19	5	6	7

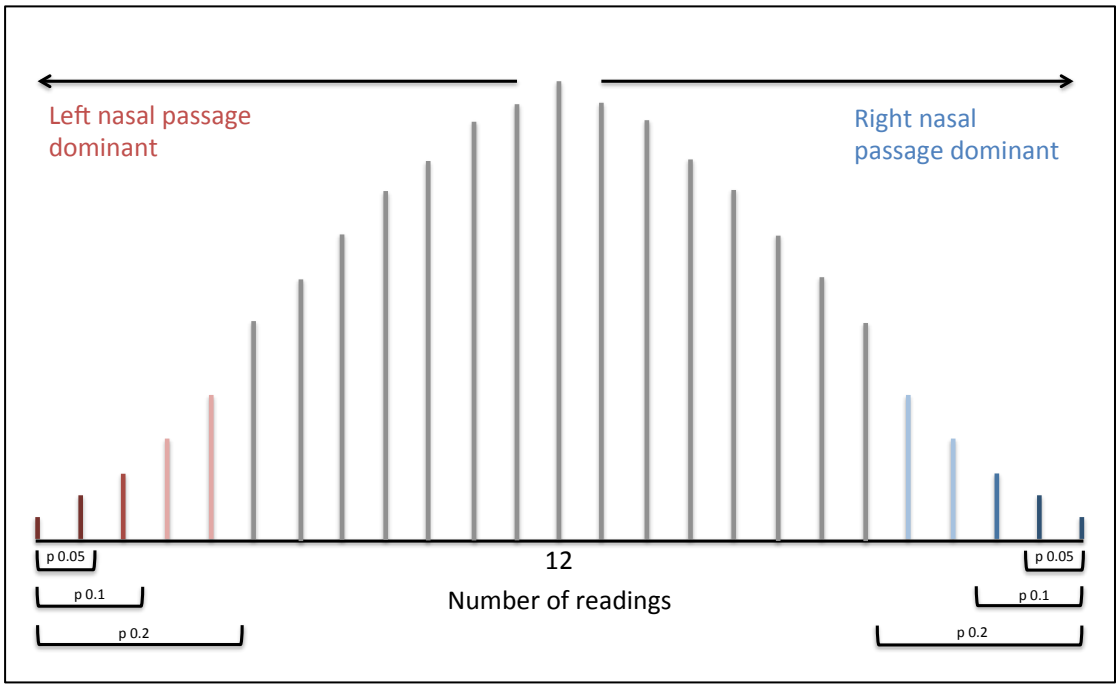

Figure 27: A normal distribution curve is represented by the vertical lines. The null hypothesis is that subjects do not exhibit any nasal passage dominance, i.e. nasal airflow is divided roughly equally between the nasal passages. The alternative hypothesis is that subjects have a dominant nasal passage, which is either left or right. At the extremes of both ends of the curve, subjects can be categorised as left (shown in red) or right (shown in blue) nasal passage dominant, i.e. the null hypothesis is rejected. The cut-off point in the number of readings required to categorise a subject as either left or right nasal passage dominant is dependent on the *p* value used for this purpose and this is shown for *p* values of 0.05, 0.1 and 0.2 at each extreme, which would equate to 0.1, 0.2 and 0.4 when considering all of the readings. The lines shown in grey represent those where nasal passage dominance cannot be assigned, i.e. the null hypothesis is accepted.

The *p* values used may seem relatively high, however even at a *p* value of 0.4, the null hypothesis is not outside the extreme quartiles, as at this level 20% would be left-nasal passage dominant, 20% would be right-nasal passage dominant and 60% would have no overall dominance.

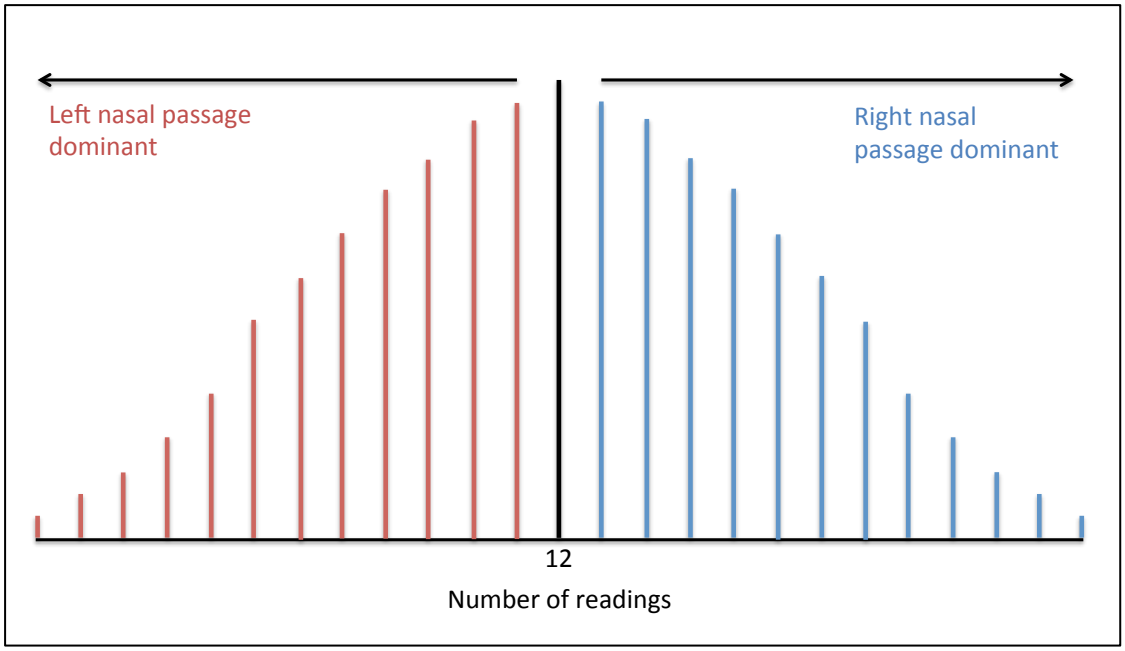

Figure 28: This figure demonstrates the method possibly used by Searleman et al. (2005) (113). A normal distribution curve is represented by the vertical lines. A cut-off of 50% was used, i.e. if more than 50% of readings (n=12) were left nasal passage dominant, the subject was categorised as being left nasal passage dominant (shown in red), and *vice versa* for the right nasal passage (shown in blue).

Table 12: Nasal passage dominance in each subject calculated using binomial distribution. The number of known values indicates the number of readings at which a dominant nasal passage could be allocated, or those where airflow was not classified as being "Equal" between the nasal passages. The fourth column under overall nasal passage dominance indicates the nasal passage dominance if the cut off used is 50% i.e. if more than half of the readings were either right or left nasal passage dominant.

Subject number	No.of known values	No. of times right nasal passage dominant	No. of times left nasal passage dominant	Overall nasal passage dominance				Hand preference
				p=0.1	p=0.2	p=0.4	50% cut off	
002	21	10	11	Unclear	Unclear	Unclear	Left	Right
003	24	6	18	Left	Left	Left	Left	Left
004	24	14	10	Unclear	Unclear	Unclear	Right	Left
005	21	18	3	Right	Right	Right	Right	Left
006	19	14	5	Right	Right	Right	Right	Left
007	20	18	2	Right	Right	Right	Right	Left
008	22	3	19	Left	Left	Left	Left	Left
009	24	9	15	Unclear	Unclear	Left	Left	Left
010	24	0	24	Left	Left	Left	Left	Left
011	24	24	0	Right	Right	Right	Right	Left
012	24	12	12	Unclear	Unclear	Unclear	Unclear	Left
013	23	16	7	Right	Right	Right	Right	Right
015	21	17	4	Right	Right	Right	Right	Left
018	23	15	8	Unclear	Unclear	Right	Right	Right
019	23	11	12	Unclear	Unclear	Unclear	Left	Right
020	24	10	14	Unclear	Unclear	Unclear	Left	Right
022	24	12	12	Unclear	Unclear	Unclear	Unclear	Right
023	23	9	14	Unclear	Unclear	Left	Left	Right
024	24	23	1	Right	Right	Right	Right	Right
025	23	7	16	Left	Left	Left	Left	Right
027	22	7	15	Unclear	Left	Left	Left	Right
028	24	14	10	Unclear	Unclear	Unclear	Right	Right
030	24	8	16	Unclear	Left	Left	Left	Right
031	23	8	15	Unclear	Unclear	Left	Left	Right
032	24	12	12	Unclear	Unclear	Unclear	Unclear	Left
033	24	1	23	Left	Left	Left	Left	Right
034	24	11	13	Unclear	Unclear	Unclear	Left	Left
035	22	9	13	Unclear	Unclear	Unclear	Left	Left
036	24	0	24	Left	Left	Left	Left	Left

Table 13: Summary of the number of subjects categorised as unclear, right or left nasal passage dominant at different probability levels.

Nasal passage dominance	**Number of subjects**			
	***p*=0.1**	***p*=0.2**	***p*=0.4**	**50% cut off**
Unclear	16	14	10	3
Right	7	7	8	10
Left	6	8	11	16
Total	29	29	29	29

Table 14: Nasal passage dominance as determined using binomial distribution in the left-handed and right-handed groups.

Nasal passage dominance at different probability levels		**Number of subjects**	
		Right-handers	**Left-handers**
p=0.1	Unclear	10	6
	Right	2	5
	Left	2	4
p=0.2	Unclear	8	6
	Right	2	5
	Left	4	4
p=0.4	Unclear	5	5
	Right	3	5
	Left	6	5
50% cut off	Unclear	1	2
	Right	4	6
	Left	9	7

Just from looking at the numbers in Table 14, there does not seem to be an obvious correlation between hand preference and nasal airflow dominance. Even using 50% of readings as the cut-off to define a nasal passage as dominant, more right-handers had left nasal passage dominance and more left-handers had right nasal passage dominance, although the numbers were very similar.

The disadvantage of using the binomial distribution to determine whether a subject can be classified as having a dominant nasal passage is that of 29 subjects tested, the final number used for analysis has been reduced, as some subjects did not exhibit a dominant nasal passage. In an attempt to counteract this, analysis of the data was done using increasing probability levels in order to increase the number of included subjects. However, even at the highest *p* value of 0.4, 10 subjects (5 right-handers and 5 left-handers) could not be classified as having a dominant nasal passage as the division of airflow between the right and left nasal passages was not significantly different. Searleman et al. (2005) did not state that nasal passage dominance could not be ascertained in any of their subjects (113). Conversely in this study, 3 subjects had 12 readings of left nasal passage dominance and 12 readings of right nasal passage dominance out of a total of 24 readings, meaning that the division of airflow between the nasal passages was exactly equal throughout the measurement period.

Determining whether a correlation between hand preference and nasal passage dominance exists.

A chi-square test was used to look for a statistically significant correlation between hand preference and nasal passage dominance. This was done for each of the different probability levels used to determine nasal passage dominance (p=0.1, p=0.2, p=0.4) and also using the 50% cut off, and is shown in Tables 15 – 18.

Table 15: Chi-square table using *p* value of 0.1 to categorise nasal passage dominance.

	Right-handers	**Left-handers**	**Total**
Right nasal passage dominant	2	5	7
Left nasal passage dominant	2	4	6
Total	4	9	13
***p* = 0.85**			

Table 16: Chi-square table using *p* value of 0.2 to categorise nasal passage dominance.

	Right-handers	Left-handers	Total
Right nasal passage dominant	2	5	7
Left nasal passage dominant	4	4	8
Total	6	9	15
***p* = 0.40**			

Table 17: Chi-square table using *p* value of 0.4 to categorise nasal passage dominance.

	Right-handers	Left-handers	Total
Right nasal passage dominant	3	5	8
Left nasal passage dominant	6	5	11
Total	9	10	19
***p* = 0.46**			

Table 18: Chi-square table using 50% as the cut off to categorise nasal passage dominance.

	Right-handers	Left-handers	Total
Right nasal passage dominant	4	6	10
Left nasal passage dominant	9	7	16
Total	13	13	26
***p* = 0.42**			

A statistically significant correlation between hand preference and nasal airflow was not identified in this data set. This is not surprising as no trend towards a correlation was seen earlier in the data analysis (see Figure 23). Unfortunately the subject numbers in the data set were reduced because in some subjects it was not clear whether they had any overall nasal passage dominance, rather, it appeared that nasal airflow was divided roughly equally between both nasal passages. Even when nasal passage dominance was defined by having either right or left nasal passage dominance for over 50% of the measurement period, the *p* value remained non-significant at 0.42 (see Table 18), however due to the variability in nasal airflow patterns this method of defining nasal passage dominance should be considered unreliable.

6.4: Discussion

The findings of this study directly contradict those published by Searleman et al. in 2005 (113). Some of the potential issues with the methods and findings described by Searleman et al. (2005) have already been highlighted, for example the methods used to measure nasal airflow, determine hand preference and analyse the data (113).

In order to look for disparities in the data analysis, the theoretical results needed to produce a significance level of less than 0.01, as obtained by Searleman et al. (2005) (113), were ascertained. Their study had a total of 20 subjects, with 9 left-handers and 11 right-handers. This information was used to populate a chi-square table with the numbers for left-handed, left-nasal passage dominant subjects and right-handed, right-nasal passage dominant subjects. These numbers were then altered to look at the different levels of significance that could be achieved. The total number of subjects in the nasal passage dominance groups was changed as this was unknown, whereas the known values for the number of left-handers and right-handers was kept the same. Unfortunately this is speculation, as although contacted several times by email to request further detail about the data collected and its analysis, there was no reply from the lead author. Table 19 demonstrates the most extreme results that could have been found by Searleman et al. (2005) (113), that is all (n=11/11) right-handers being right nasal passage dominant and all (n=9/9) left-handers being left nasal passage dominant. In this case, the *p* value would have been 0.000007, in other words a highly significant finding.

Table 19: Chi-square table using the most extreme possible values in Searleman et al.'s (2005) (113) data i.e. all the right-handers were right nasal passage dominant and all the left-handers were left nasal passage dominant.

	Right-handers	**Left-handers**	**Total**
Right nasal passage dominant	11	0	11
Left nasal passage dominant	0	9	9
Total	11	9	20
***p* value = 0.000007**			

Table 20: Chi-square table using the least extreme values required to produce a *p* value of less than 0.01.

	Right-handers	**Left-handers**	**Total**
Right nasal passage dominant	8	1	9
Left nasal passage dominant	3	8	11
Total	11	9	20
***p* value = 0.006**			

Table 21: Chi-square table using another possible combination of the least extreme values required to produce a *p* value of less than 0.01.

	Right-handers	**Left-handers**	**Total**
Right nasal passage dominant	9	2	11
Left nasal passage dominant	2	7	9
Total	11	9	20
***p* value = 0.008**			

Tables 20 and 21 show two different combinations of values that would be the least extreme values required to produce a *p* value of less than 0.01. These values should still be considered as extreme and the correlation is immediately obvious since 73 – 82% of right-handers would have been right-nasal passage dominant and 78% of left-handers would have been left-nasal passage dominant. Tables 22 and 23 show two different combinations of values that would be the most extreme values resulting in a *p* value of greater than 0.01. Again, although the *p* value is higher than that reported by Searleman et al. (2005) (113), the results required to produce these *p* values are still extreme, with high percentages of subjects having positively correlated hand preference and nasal passage dominance. If any of the above

results or similar ones were actually obtained, surely they would have been clearly reported in this fashion by Searleman et al. (2005) (113), instead of the percentage of time values that were published.

Table 22: Chi-square table demonstrates the results required to produce a *p* value of over 0.01, the significance level found by Searleman et al. (2005) (113).

	Right-handers	**Left-handers**	**Total**
Right nasal passage dominant	8	2	10
Left nasal passage dominant	3	7	10
Total	11	9	20
***p* value = 0.02**			

Table 23: Chi-square table using another possible combination the results required to produce a *p* value of over 0.01.

	Right-handers	**Left-handers**	**Total**
Right nasal passage dominant	9	3	12
Left nasal passage dominant	2	6	8
Total	11	9	20
***p* value = 0.03**			

Considering the results that were published by Searleman et al. (2005) (113), specifically that left-handers had left nasal passage dominance for almost 60% of the time and *vice versa* for right-handers, a chi-square test was then performed using 60% to determine the number of right-handed, right-nasal passage dominant subjects and the number of left-handed, left-nasal passage dominant subjects (see Table 24). Using these numbers, the *p* value was 0.4. This is interesting as the *p* value obtained in this study was 0.4 to 0.86 depending on the categorisation of subjects' nasal passage dominance.

Table 24: Chi-square table using 60% to calculate the presumptive value for right-handed, right-nasal passage dominant subjects and left-handed, left-nasal passage dominant subjects.

	Right-handers	**Left-handers**	**Total**
Right nasal passage dominant	7	4	11
Left nasal passage dominant	4	5	9
Total	11	9	20
***p* value = 0.4**			

Chapter 7: Final Discussion and Conclusions

The aims of this study were:

1. To summarise the literature concerning nasal airflow and brain activity, focusing on a possible correlation between cerebral asymmetries and asymmetries in nasal airflow patterns.
2. To look specifically for a correlation between hand preference and nasal airflow in human subjects by measuring nasal airflow patterns over a period of hours, and compare these findings to the available literature.

7.1: Nasal airflow asymmetry and cerebral asymmetry

Correlations between nasal airflow and cerebral asymmetry have been suggested, however unfortunately the literature base concerning this topic is hugely varied making it difficult to construct firm conclusions. The asymmetry in nasal airflow is controlled by asymmetrical sympathetic output from collections of sympathetic neurons in the brainstem (38). The role of higher cortical centres in this pathway however is not clear, and the potential influences of handedness (113), ultradian rhythms in cerebral activity (128) and disease (70, 108) have all been suggested. Conversely, there is also some evidence to suggest that asymmetrical nasal airflow can affect the brain. In patients with certain types of epilepsy, nasal hyperventilation has been shown to activate epileptic foci in the brain (140). Further to this, some researchers have postulated that unilateral forced nostril breathing can affect brain activity and cognitive functions (142, 156), although the evidence for this is weak and has been contested by other studies (136, 158).

7.2: Hand preference and nasal passage dominance

This study did not identify a relationship between hand preference and nasal passage dominance, and in fact in a relatively high proportion of subjects a dominant nasal passage could not be ascertained (although the exact figure depends on the method of classifying nasal passage dominance – see section 6.3).

The following are the possible reasons for not identifying an association between hand preference and nasal airflow:

1. Lack of statistical power. It remains possible that there is a relationship between nasal airflow and hand preference however the effect was too small to be detected in this sample. Conducting the same analysis in a much larger sample could possibly detect an effect. It should be noted however that a smaller sample size was used in the study by Searleman et al. (2005), in which statistical significance was reported (113).

2. The measurement period was too short. Alternation of nasal passage dominance, sometimes referred to as the nasal cycle, has been reported to occur up to 8-hourly (8). Therefore, with a measurement period of 6 hours, it is possible that in some subjects the alternation of nasal passage dominance was missed. In three subjects, one nasal passage remained dominant for the entire measurement period, and it is possible that they will have had alternation in nasal passage dominance that either occurred just before the first measurement or after the last one. Also, in subjects who did demonstrate alternations in nasal passage dominance, some could have been missed by the 6-hour measurement period, which could have affected the results. For example, if the next few readings after the 6-hour period had demonstrated another switch in nasal passage dominance, the percentage of time each nasal passage was dominant would have changed, which could have altered the classification of the subject as left- or right-nasal passage dominant.

3. There is no relationship between hand preference and nasal airflow and the results reported by Searleman et al. (2005) (113) occurred by chance.

It is the opinion of this author that the 3rd option is the most likely. There are three reasons for reaching this conclusion. First, the physiological reasoning underlying this relationship is implausible. Handedness has been shown to correlate with other behavioural lateral preferences, for example eye preference, hand clasping and leg crossing, however the correlations are small and these measures cannot be reliably used to determine handedness (118). Nasal airflow is controlled by the autonomic nervous system and is dissimilar to behavioural lateral preferences such as hand clasping and leg crossing. Since there isn't a consistent relationship between handedness and these behaviours, it doesn't seem logical to have a consistent relationship between handedness and nasal airflow.

Although not fully understood, it is likely that the purpose of having fluctuations in nasal passage dominance is related to the air-conditioning (26) and immune defence functions of the nose (18). Therefore, equal or roughly equal division of labour between the two nasal passages would be required. The division of labour may not occur hourly or even daily, which is why it could be missed in some studies. In fact, studies have shown that nasal airflow patterns vary when measured in the same individual on different days (11). Bearing this in mind, it would be possible for the findings by Searleman et al. (2005) (113) to have occurred by chance, and had the experiment been repeated on a different day, the opposite relationship may have been discovered.

In addition, there is no obvious reason why the air-conditioning and immune functions of the nose would be related to cerebral organisation. Hand preference may be related to speech development which usually occurs in the left hemisphere (121), and the lateralisation of speech may confer advantages for speech development (125). When a complex action originates in the brain, there may be

advantages to having it arise in only one hemisphere (119). The conductance of air through the nasal passages is not a complex action such as speech or hand movements and therefore having a dominant nasal passage would not be advantageous in this respect.

Secondly, a relationship between nasal airflow and hand preference is not supported by the other literature concerning nasal airflow. In the wealth of observational studies performed over the last century looking at nasal airflow patterns in healthy individuals, none have reported an incidental finding of overall right nasal passage dominance. If Searleman et al.'s (2005) (113) findings were correct, this would be extremely surprising given the overwhelming majority of right-handers in the general population. In a study comparing nasal airflow patterns of schizophrenic vs. healthy individuals, 53.1% of the healthy cohort had no overall lateralisation of nasal airflow, meaning that the left and right nasal passages were dominant for roughly equal amounts of time (108). The rate of left nasal passage dominance was 25%, and the rate of right nasal passage dominance was 21.9% (108). This was a larger study with 64 healthy control subjects who were all right-handed, conducted over a longer period of 12 hours (108). This finding is conducive with the theories on the function of the alternations in nasal passage dominance, as explained above.

Thirdly, reproduction of Searleman et al.'s 2005 study using similar methods failed to identify a relationship between hand preference and nasal airflow (113). In recent years, there have been concerns amongst the scientific community that many published study findings are not reproducible. In his 2005 paper, Ioannidis states:

> "It can be proven that most claimed research findings are false" (176).

Colquhoun (2014) described the misuse and misinterpretation of *p* values as a major contributor to this, as there is a lack of understanding when it comes to significance testing (177). It is generally accepted that a *p* value of less than 0.05 confers statistical significance, however this is commonly misinterpreted as the error rate. In fact, a *p* value of less than 0.05 suggests that the test sample provides enough evidence to reject the null hypothesis, however it does not prove that the alternative

hypothesis is true. With a *p* value of 0.05, there is a 5% chance that the alternative hypothesis has occurred by chance alone. Colquhoun (2014) argues that a 5% chance is actually quite high in itself, but due to the misinterpretation and lack of power in many published studies, this figure is actually a lot higher (177). The error rate, or false discovery rate, is equivalent to the false positive rate, i.e. incorrectly accepting the alternative hypothesis (177). Sellke et al. (2001) estimated that the error rate for a *p* value of 0.05 was over 29%, and for a *p* value of 0.01 was typically close to 15% (178).

Searleman et al. (2005) stated that they obtained a *p* value of less than 0.01 for their results, although the statistical methods used to calculate this have not been described (113). This equates to a less than 1% chance that the alternative hypothesis (in this case a positive correlation between nasal airflow and hand preference) has occurred by chance alone, however how much less than 1% this is cannot be known. The error rate or false discovery rate, on the other hand, is likely to be much higher (see Sellke et al. 2001 (178) and Colquhoun 2014 (177)). This may be compounded by the fact that the sample size was small meaning the study was probably underpowered, and there was a risk of bias, for example as participants were not randomised and there was no blinding. It has been suggested that even a well-powered epidemiological study may only have a one in five chance of being true (176). Colquhoun (2014) suggests that a *p* value of less than 0.001 should be required to demonstrate a positive finding.

Another major issue is the general reluctance to report negative findings (177). It is therefore impossible to know whether other research groups have conducted similar studies on hand preference and nasal airflow, but not reported their findings if they were not positive or significant. As discussed previously, Searleman et al.'s 2005 study is the only published report of a correlation between nasal airflow and hand preference (113), and so presumably the scientific community has accepted this finding. It has in fact been cited on 12 occasions. Accepting and re-iterating the

results obtained by a single research team, even if they were statistically significant, can be misleading (176). This is particularly true for small studies with small effect sizes where there may be differences in definitions, study design, methodology and outcomes (176). In the relatively small field of nasal airflow research, there is a high degree of variability in the methods and outcome measures used (see sections 1.2 and 1.7 on the nasal cycle and methods of measuring nasal airflow), and many studies have small numbers of participants. One could argue that accepting the findings of Searleman et al. (2005) (113) as true is not a disaster, as it is unlikely to have affected clinical practice or patient safety. However, understanding physiology is the basis for understanding pathology, and currently the physiological factors that influence nasal airflow and the nasal cycle are not fully understood.

As discussed in the Chapter 2, conflicting theories have been suggested for cortical influence on nasal airflow. Nasal blockage is a common presentation to Ear, Nose and Throat surgeons, and at times there is no pathology detected. In these cases, there may be a physiological explanation for the patient's symptoms. The results presented here, along with evidence from other studies, do not suggest that hand preference is a factor.

7.3: Limitations of this study

The sample size of 29 subjects may have been too small to detect a relationship between nasal airflow and hand preference. Unfortunately the study by Searleman et al. (2005) did not provide enough information for power calculations to be performed (113), and therefore this was a pilot study. Measuring nasal airflow patterns and how they alter over time is, by definition, time consuming, and therefore many studies that have looked at nasal airflow have involved small numbers of participants. It is also possible that the measurement period of 6 hours was too short, however this was chosen to reflect the methods used by Searleman et al. (2005) (113).

The method chosen to measure nasal airflow was the modified GM, which does not provide quantitative values. Instead, the investigator made a judgement as to which nasal passage was dominant at each time point by looking at the condensation areas produced by each nasal passage. Therefore, it is possible that human error and bias may have occurred. The investigator was blinded to hand preference where possible in an attempt to minimise the risk of bias.

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Appendix 1: Inclusion and Exclusion Criteria

Inclusion criteria:

1. Aged 18 or over
2. Have given written informed consent

Exclusion criteria:

1. Any history of chronic nasal conditions
2. Active nasal disease e.g. current upper respiratory tract infection
3. Any history of trauma (including surgery) to nose, sinuses or central nervous system
4. Any significant septal abnormality
5. Any disease or medical or surgical history that the investigator deems may affect nasal physiology and influence the results of the study e.g. chronic respiratory disease or intake of medicines known to affect the nose such as topical corticosteroids or decongestants
6. Known allergy to aluminium
7. Member of study staff or partner or relative of study staff
8. Intake of more than 4 units of alcohol within 12 hours of measurement of nasal airflow
9. Performance of vigorous exercise within 3 hours of measurement of nasal airflow
10. Current smoker, defined by a daily use of any tobacco product
11. Pregnant or lactating women
12. Mixed or unclear handedness

Appendix 2: Participant Information Sheet

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Appendix 3: Consent Form

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Appendix 4: Edinburgh Handedness Inventory – Short Form. Adapted from Veale (2014) (172).

Please indicate your preferences in the use of hands in the following activities or objects:

	Always right	**Usually right**	**Both equally**	**Usually left**	**Always left**
Writing					
Throwing					
Toothbrush					
Spoon					

Scoring

For each item:

Always right = 100; Usually right = 50; Both equally = 0; Usually left = -50; Always left = -100

To calculate the Laterality Quotient add the scores then divide by four:

Writing score

Throwing score

Toothbrush score

Spoon score

Total

Lateral quotient score (total / 4)

Classification	**Laterality Quotient Score**
Left handers	-100 to -61
Mixed handers	-60 to 60
Right handers	61-100