

Effect of sighs on breathing memory and dynamics in healthy infants

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Running Head

Breathing memory and dynamics after sighs

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ABSTRACT

Deep inspirations (sighs) play a significant role in altering lung mechanical and airway wall function however their role in respiratory control remains unclear. We examined whether sighs act via a resetting mechanism to improve control of the respiratory regulatory system. Effects of sighs on system variability, short-range and long-range memory and stability were assessed in 25 healthy term infants at 1 month of age (mean 36 days, range: 28-57 days) during quiet sleep. Variability was examined using moving window coefficient of variation (CV), short-range memory with autocorrelation function and long-range memory using detrended fluctuation analysis. Stability was examined by studying the behaviour of the attractor using phase-space plots. Variability of tidal volume (V_T) and minute ventilation (V'_E) increased during the initial 15 breaths post-sigh. Short-range memory of V_T decreased during the 50 breaths preceding sigh, becoming uncorrelated (random) during the 10 breath pre-sigh window. Short-range memory increased post-sigh for the entire 50 breaths when compared to the randomised dataset and for 20 breaths when compared to the pre-sigh window. Similar but shorter lasting changes were noted in V'_E . No change in long-range memory was seen after sigh. CV and range of points located within a defined attractor segment increased after sigh. Thus, control of breathing in healthy infants shows long-range stability and improvement in short-range memory and variability after sigh. These results add new evidence that the role of sighs is not purely mechanical.

INTRODUCTION

Infants demonstrate dynamic regulation of lung function over time. Lung volume is actively elevated above that determined by tissue elastic properties and a compliant chest wall (26). Recent studies have suggested that dynamic regulation of airway tone is particularly important in infants (16). It is likely that this dynamic regulatory process represents a tightly controlled negative feedback system, whereby information from peripheral and central chemo-receptors as well as pulmonary stretch receptors is provided to respiratory regulatory neurons in the brainstem, with continuously variable output to the respiratory system musculature (43, 44).

Biological feedback systems such as those utilised for (e.g.) respiratory control are reflective of engineering control systems and may be modelled using similar mathematical concepts (9, 35). From an engineering point of view, a control system requires an appropriate balance between system *stability* and *sensitivity*, permitting responsiveness to fluctuations whilst maintaining function within tightly regulated limits. Excess sensitivity of such a system may lead to dramatic ‘overshoot’ type responses, instability and positive feedback (24). Reduction in sensitivity and excessive stability may result in diminished capacity for response to environmental change and poor feedback control. On the other hand, a certain amount of stability is required in order for the biological system to return to a steady state following a perturbation. Variability observed in the output parameters of a system is often the result of these two competing mechanisms. Long-range and short-range memory within such a dynamical system are responsible for maintaining this delicate equilibrium by incorporating information from previous events into the current system state. An ideal error tolerant system returns

quickly to a steady state whereby long-range memory is not altered. Long-range memory may therefore be considered a feature of stability.

From engineering systems it is known that many control loop feedback systems incorporate a resetting mechanism. There is evidence that spontaneous deep inspirations (sighs) play an important role in resetting the mechanical properties of the lung tissue (10, 12) and airway walls (7), however there is little information in the literature as to whether sighs also act as a 'resetting' mechanism for the loop control system. In adults, sighs during sleep are associated with increased inspiratory and expiratory flows and increased inspiratory time as a fraction of respiratory cycle time ($t_I:t_{TOT}$), indicating they may play an important role in the control process (31). Sighs are a more frequently observed phenomenon in infant breathing than in adults (19, 31) and given the increased contribution of dynamic processes to respiratory control in this age group, may make a major contribution to homeokinesis. Fleming et al (13) used a linear approach to investigate the developmental changes in oscillatory responses of breath-to-breath minute ventilation (V'_E) after sigh in infants aged up to 7 months. Newborn infants had a stable system with delayed responses to the sigh stimulus that evolved with age to exhibit a stable but more responsive system suggestive of improvement in feedback control. Animal studies demonstrate no difference in respiratory pattern following sigh in rapid eye movement (REM) versus NREM sleep, however a smaller tidal volume (V_T) and longer expiratory time is evident, resolving on most occasions by the third post-sigh breath (20). The factors responsible for inducing the sigh and the effects of this event on the stability of the system remain unclear.

We hypothesised that sighs may play a crucial role not only for lung mechanics but also as a resetting mechanism for the negative feedback control system. To examine whether term healthy infants demonstrate alterations in regulation of breathing following sighs during quiet natural sleep, we analysed the effect of sighs on tidal breathing indices in terms of respiratory variability, short-range and long-range memory and stability.

METHODS

Study design

This cross-sectional observational study examined the regulation of breathing in relation to sighs in healthy infants during quiet natural sleep. Breath-by-breath V_T , V'_E , minimum exhaled O_2 and end-tidal CO_2 as well as the classical parameters of respiratory drive (t_I : t_{TOT} , V_T/t_I , t_{PTEF}/t_E , t_I , t_E , $V'_{max,insp}$ – see ABBREVIATIONS) were examined for 50 breaths preceding and following a spontaneous sigh. Data analysis was performed in terms of variability, short-range and long-range memory and stability of V_T and V'_E . Variability was examined using moving window coefficient of variation (CV). Short-range memory was assessed for data sets of 50 breaths using an autocorrelation function (20). Detrended fluctuation analysis (28) examined long-range memory over 100 breaths. Stability of the system was assessed using phase-space plots (23).

Subjects

Data used in this study were obtained from a subgroup of 25 infants from a total cohort of 80 healthy term infants recruited antenatally to a separate large epidemiological study. Data from each infant were visually examined for presence of a sigh. A sigh was defined as a tidal breath at least double the mean V_T of the preceding 10 breaths (10, 40). A sigh breath was identified in 40 infants however 15 were excluded due to absence of NREM sleep state, insufficient data adjacent to sigh (<50 breaths), significant data artefact or when a change in sleep state, movement or arousal occurred during the study. This left data from 25 infants that were suitable for analysis. Demographic data are provided in Table 1. All infants had an unremarkable pregnancy and normal delivery. None of the

infants had respiratory infections in the period between birth and date of study. The study was approved by the ethics committee of the University Hospital of Berne. Written informed parental consent was obtained prior to study and parents were most often present at the time of measurement.

Measurements

The technique for measurement of tidal breathing parameters in spontaneously sleeping infants has been published in detail previously (8). Briefly, infants were studied in the supine position in a cot or mother's arms during quiet natural sleep. Sleep state was defined clinically using the criteria of Precht (33) with closed eyes, absence of gross body or limb movements and regular respiratory pattern. Heart rate and oxygen saturation were monitored continuously for the duration of study (Biox 3700, Datex-Ohmeda, Helsinki, Finland). Measurements were made over periods of up to 10 minutes duration using methodology and equipment compliant with recently published international standards for the measurement of lung function in infancy (5, 17, 18).

Tidal breathing was measured by applying a compliant silicon facemask to the infant's mouth and nose (size 1, Homedica, Cham, Switzerland) after warming to skin temperature (17). The mask was connected in series with a CO₂ analyser, combined nitric oxide (NO) and O₂ sensor (Exhalyser, EcoMedics, Duernten, Switzerland) and prototype ultrasonic flowmeter (Spiroson model M30.8001, EcoMedics, Duernten, Switzerland) containing a bacterial filter (Spirette™) surrounding a deadspace reduction apparatus (Size 1). The measurement setup was connected to a bias flow of 14 L/min.

Combined instrumental dead-space without the face mask was 3 mL. Total dead-space of the silicon mask was 15 mL. The effective total measurement dead-space was 10.5 mL,

with 50% of the mask space assumed to be occupied by the infant's face. This gives a mean dead-space V_D /kg body weight of ~ 2.2 mL, which is at the upper limit of current recommendations (17) for short range measurements. End-tidal CO_2 was monitored for the entire test procedure and did not increase during the measurements. Signals were 12-bit analogue-to-digital converted and sampled at 200 Hz using a custom designed data acquisition and analysis package (WBreath v3.7.6.0, Firmware v3.06, EcoMedics, Duernten, Switzerland). The sampling time delay was corrected for each signal.

Data Analysis

Data analysis was performed using custom software written in Matlab (Matlab 6 v12, Mathworks, Inc). V_T was integrated from the flow signal after correction for any technical signal drift. V'_E was calculated by multiplying V_T by the respiratory frequency (f_{resp}) on a breath-by-breath basis. A representative example of V_T and associated sigh used for analysis is shown as a function of time in Figure 1a. Breath-to-breath V_T was plotted as a function of breath number for a 10 minute time series (Figure 1b). The sigh breath itself was excluded from the analysis.

Classical tidal breathing parameters associated with respiratory drive

We analysed the mean (95% confidence interval (95%CI)) of $t_I:t_{\text{TOT}}$, V_T/t_I , t_{PTEF}/t_E , t_I , t_E and $V'_{\text{max,insp}}$ (31, 41) for 50 breaths before and after the sigh event and compared them using paired t-tests. Moving window CV analysis was used to determine whether these parameters were predictive for the sigh event or changed after the sigh (see below).

Change in minimum exhaled O₂ and end-tidal CO₂ in response to sigh

In order to examine the possible influence of alterations in O₂ and CO₂ on the sigh event and the post-sigh control of breathing, breath-to-breath changes in minimum exhaled O₂ and end-tidal CO₂ were investigated in 18/25 and 25/25 infants respectively. In 7 cases O₂ was not measured as an analyser was not present within our equipment setup. Mean (95% CI) minimum exhaled O₂ and end-tidal CO₂ values were calculated for the 10 breath period immediately preceding the sigh and compared with values for each breath following the sigh for a period of 20 breaths.

Variability of V_T and V_E

Variability was examined using an established moving window algorithm whereby CV was obtained by dividing the SD by the mean for repeated windows of 10 breaths (23, 29). A 50% window overlap was used for each subsequent measurement until the end of the 50 breath series. This technique provided 8 windows of 10 breath periods for each of the 50 breath pre- and post-sigh data series. Comparisons were made between changes of CV in the period leading up to sigh, alteration of CV in response to sigh, and the period required for return to the baseline level of CV after the sigh event. Results for all 25 infants were pooled and mean (95% CI) CV for each window displayed as a function of window number before and following the sigh event.

Short-range memory

Within each analysis window containing 10 breaths as described above, the breath-to-breath autocorrelation function (c) (Matlab 6 v12, Mathworks, Inc, International) was also calculated with a lag of 1 breath ($c(1)$) which represents the correlation coefficient

between 2 consecutive breaths. $c(1)=1$ indicates a 100% correlation between adjacent breaths whereas $c(1) = 0$ indicates they are totally uncorrelated or random. Statistical analysis was performed for the entire group (N=25).

To test whether correlations represented the presence of true memory, data within an individual window were shuffled 10 times (i.e. the order of the data points within the window were randomised), with the autocorrelation calculation repeated on each occasion. The average $c(1)$ for the 10 shuffles was then obtained for each window. By definition, a randomised data set such as this is uncorrelated and $c(1)$ should approximate 0. The existence of a significant difference in $c(1)$ for the whole group of infants before and after shuffling indicated the presence of true short-range memory.

Long-range memory

In a subgroup of 12 infants, 100 tidal breaths were available either side of the sigh such that long-range correlations could be examined using a modified form of detrended fluctuation analysis (28). The calculation of correlation exponent (α) with this algorithm uses a modified root mean square analysis, a detailed description of which has been reported previously (8, 28, 30). Briefly, the breath-by-breath V_T and V_E time series preceding and following sigh were analysed as follows. The breath-to-breath series ($x_i = x_1, x_2 \dots x_N$) was first integrated ($y(k)$).

$$y(k) = \sum_{i=1}^k [x_i - x_{avg}]$$

The series was then divided into equally sized non-overlapping windows of length (n) and a linear regression line was fit through the data in each window, giving the local

trend of the data $y(k)$. The fluctuation function $F(n)$ of the time series corresponding to each window length (n) was calculated following detrending of data within each window by subtracting the local trend ($y_n(k)$).

$$F(n) = \frac{1}{N} \sum_{k=1}^N \sqrt{[y(k) - y_n(k)]^2}$$

If the functional form of $F(n)$ follows a power law, $F(n) \sim n^\alpha$, the process is said to exhibit long-range correlation. The exponent α can be obtained as the slope of a straight line fit to $F(n)$ vs. n on a log-log plot (see Figure 2). A value of α of 0.5 represents a random process with uncorrelated data. A positively correlated signal occurs when $\alpha > 0.5$.

Stability

The dynamics of a system can be characterised by its attraction towards a steady state within a setting of continuously occurring intrinsic and extrinsic fluctuations which tend to perturb it away from this stable state or ‘basin’ of attraction. We consider a sigh as a local non-stationarity within the respiratory control system and observe the return of the system to a steady state in response to this transient stimulus. We used phase space plots of raw tidal flow data to assess the changes in system stability after a sigh (23, 37). In order to undertake such an analysis the scalar data series must first be converted into a geometric reconstruction of the system dynamics. A graphical representation of this form is known as an embedding within phase space. The plotted variables constitute the trajectory of the system behaviour as it evolves in time. Consequently, the points within

the phase space represent all possible states of the system for the period of observation and comprise the *attractor* (4).

Reconstruction of the attractor was performed using the technique of time delay embedding (39). For a given time series $s_i=(s_1, s_2, \dots, s_N)$ of N measurements sampled at a fixed rate, a data point s_i within the scalar time series is plotted against a point $s_{i+\xi}$ that is ‘delayed’ in time within the series by a given value ξ called the embedding delay. The appropriate embedding of the vector time series S_i is given by the relationship $\xi = m\tau$, whereby m represents the number of dimensions in which the data is to be embedded and τ is the time lag. The dimension is therefore represented by the number of delayed points used in the reconstruction of the attractor. Each time a point within the scalar series is related to another point located a given delayed time distant, a dimension is added to the reconstruction. Hence a reconstruction in 3-dimensions relates a given reference point with 2 other points located at specified (and different) delays from the point of interest.

$$S_i = (s_{i+\xi}, s_{i+2\xi}, \dots, s_{i+(m-1)\xi}) \quad \text{where } i = 1, 2, \dots, N-(m-1)\xi$$

In each infant, 50 breaths of raw tidal flow data (sampled every 5 msec) were examined visually within a 2- or 3-dimensional embedded phase space. Each pre- and post-sigh plot therefore comprised 15,000-18,000 data points. Different embedding time delays were systematically examined in order to obtain the best unfolding of the attractor dynamics in phase space. In most instances the embedding delay was similar between infants, and in each infant the same embedding delay was used to examine pre- and post-sigh data. As would be expected from a periodic or quasi-periodic signal, the embedding delay was related to the breathing frequency, in most cases in the order of 400 msec. This delay is

of similar magnitude to that reported previously for respiratory data embedding (37) and is representative of the dominant period relationship observable in low-dimensional attractor systems in which a self-excited or forced periodic behaviour is present. Within such systems, a useful starting point for identification of the time delay is around one quarter of the dominant period (1). We have selected an embedding delay of ~ 0.25 of normal respiratory cycle period in order to provide an acceptable unfolding of the attractor dynamics.

To quantify the dynamics before and after a sigh, we examined the variability between cycles of the attractor within phase space plotted in 2 dimensions. A small region of one limb of the attractor cycles was selected in order to obtain at least one point from each embedded cycle. Data from the selected region were normally distributed in each infant and variability of the cycles around the mean was assessed in terms of CV and range.

Statistical Analysis

Comparisons of indices of variability, autocorrelation and detrended fluctuation analysis as well as pre- and post-sigh attractor dynamics were made for the grouped data using paired t-test. Data are presented as mean \pm 95% CI unless otherwise stated. Results were considered statistically significant when $p < 0.05$.

RESULTS

Classical tidal breathing parameters associated with respiratory drive.

When examined over the 50 breath period, mean V_T , t_I and $t_I:t_{TOT}$ decreased following the sigh (Table 2). Other parameters of respiratory drive (t_E , V_T/t_I , t_{PTEF}/t_E , $V'_{max,insp}$) were unchanged. More detailed analysis using a moving window CV algorithm showed most of the observed alteration in t_I and $t_I:t_{TOT}$ to be occurring during the first 1-2 windows (10-15 breaths) post-sigh.

Change in minimum exhaled O_2 and end-tidal CO_2 in response to sigh

The minimum exhaled O_2 and end-tidal CO_2 concentration data demonstrated a high level of stability during the 50 breath period leading up to sigh. Consequently, the mean (95% CI) value for the 10 breaths immediately preceding sigh was used to compare data following the sigh event (Figure 3). A significant increase in minimum exhaled O_2 was evident for the first 2 breaths post-sigh compared with the pre-sigh values when examined for the entire group. Changes in end-tidal CO_2 lasted slightly longer with a significant reduction noted to the 5th post-sigh breath.

Variability of V_T and V'_E

CV of V_T increased in 23 of 25 infants following the sigh when examined over the entire 50 breath period. For the moving window analysis, cross-sectional data were normally distributed allowing the use of mean (95% CI) for presentation of data. Individual V_T variability data for each analysis window were grouped for all 25 infants and are presented in Figure 4a. Baseline V_T variability was not significantly different between measurement windows during the pre-sigh period ($p=0.22$) implying that no indication of

the approaching sigh was evident in the pre-sigh variability. Compared to the 10 breath window immediately prior to the sigh, there was a significant increase in variability during the first 2 analysis windows post-sigh, representing a period of 15 breaths. Similar changes in variability were observed in V'_E (Figure 4b).

Short-range memory

Comparison of auto-correlation data for windows located at an increasing distance after the sigh with the window immediately preceding sigh is presented in Figure 5a. Grouped mean CV of $c(1)$ for V_T was significantly increased during the first 3 post-sigh windows, representing a period of 20 breaths (Figure 5a). In contrast, $c(1)$ of V'_E was significantly higher for the first post-sigh window only, the second window having a borderline significance of $p=0.05$ (Figure 5b).

Linear regression analysis through the group means for each analysis window pre-sigh showed a significant decrease of correlation of V_T ($r^2 = 0.59$, $p = 0.02$) and V'_E ($r^2 = 0.53$, $p = 0.04$) in comparison to a randomised series during the period leading up to the sigh (Figure 6). Both the V_T and V'_E series demonstrated a weak breath-to-breath correlation that was significantly different from a randomised series but became less significant as the sigh event approached. In the case of the V_T series the original and randomised data were not significantly different for the pre-sigh window ($p=0.08$) indicating a loss of deterministic correlation. Following the sigh, both V_T and V'_E showed a significant increase in correlation in comparison to their respective randomised series that persisted for the duration of 8 post-sigh analysis windows (i.e. the full 50 breaths).

Long-range memory

The exponent α characterising the long-range correlation of V_T and V'_E was unchanged in response to sigh as shown in Table 3. The observed trend ($p=0.06$) towards change in long-range correlation (over 100 breaths) of V_T is consistent with a contribution from short-range correlations observed over 50 breaths.

Stability

An example of a typical phase space embedding in 2- and 3-dimensions from a single infant is shown in Figure 7. The significant alteration in attractor dynamics following the sigh event is clearly evident. Similar visual changes were observed in all infants. CV of data points within the analysed attractor region increased significantly after sigh in 18/25 infants (pre-sigh: 0.18 (0.09, 0.27), post-sigh: 0.37 (0.22, 0.52), $p<0.001$). The range increased in 22/25 infants (pre-sigh: 0.03 (0.02, 0.04) post-sigh: 0.05 (0.04, 0.06), $p<0.02$). Importantly, on each occasion the respiratory behaviour returned to the same position within phase space post-sigh, indicating overall stability of the system.

DISCUSSION

Sighs play an important role in altering the mechanical properties of the lungs and airway walls. In bronchoconstricted adults sighs lead to an increase in specific airway conductance and bronchodilatation secondary to an increase in transpulmonary pressure that is not related to change in lung volume (11). In preterm infants mechanical effects of sighs include maintenance of lung volume (32), increased dynamic lung compliance and reduced lung resistance (10), confirming their role in altering lung mechanics.

The exact origin of spontaneous sighs remains controversial. They may result from activation of lung and chest wall receptors in response to reduced pulmonary compliance associated with alveolar atelectasis (6). Animal studies have demonstrated increasing sigh frequency in response to hypoxia (3) and hypercapnia (34) whilst interruption of vagal pathways leads to loss of these feedback responses (3). Vagal neural feedback to the brainstem respiratory centre plays a significant role within the reflex pathway responsible for mediating sigh activity (25). For example, the increase in neurally mediated end-expiratory volume and respiratory frequency following sighs in cats is not observed after passive inflation manoeuvres (38). The shorter time required for end-expiratory volume to return to baseline in comparison to lung compliance in these cats is further evidence of dissociation between neural and mechanical effects of sighs. The increased sigh frequency reported in infants with an immature breathing control system (e.g. preterm infants) (2, 19) highlights the likely importance of sighs within the neuro-regulatory feedback loop.

Recently, regulatory properties of the respiratory negative feedback loop have been analysed using mathematical techniques derived from engineering systems control theory

(24, 35). The behaviour of the control loop after a sigh may be reflective of the maturity and functional integrity of neuro-respiratory feedback control. Using these techniques, we investigated whether or not sighs are important for the regulation and resetting of the neuro-respiratory controller. Our data showed that a highly regulated and stable negative feedback loop system exists in healthy infants and that sighs represent a mechanism for improving the memory associated with neuro-respiratory control of breathing within this system.

Classical tidal breathing parameters associated with respiratory drive. This study suggests that established indices of respiratory drive and control such as $t_I:t_{TOT}$, V_T/t_I , t_{PTEF}/t_E , t_I , t_E , $V'_{max,insp}$ are not predictive of an impending sigh event. Most of these parameters remained unchanged during the 50 breath post-sigh period although a small but statistically significant decrease in t_I and $t_I:t_{TOT}$ occurred during the 2 window periods immediately after sigh in comparison to the pre-sigh window. Ueda et al showed t_{PTEF} to be one factor that identified reduced respiratory drive in infants of smoking mothers (41), suggesting its potential usefulness for the examination of control. The reason for the insensitivity of most of the classical drive parameters to changes in respiratory control induced by a sigh in this study is unclear. Whilst t_I/t_{TOT} and t_I are higher during pre-sigh breaths in adults than immediately post-sigh (31), physiological differences make comparisons between infants and adults particularly difficult. Techniques permitting analysis of the dynamic characteristics of respiratory drive, such as those derived from system control theory may reveal more information about the continually changing behaviour of this control system than is provided by standard linear methods.

Change in minimum exhaled O₂ and end-tidal CO₂ in response to sigh. The correlation between arterial O₂ and CO₂ values and exhaled gas concentrations is known to be limited (42), however due to the non-invasive nature of this study we were unable to analyse blood gases. We did however, monitor O₂ and CO₂ in exhaled gas continuously. Breath-to-breath minimum exhaled O₂ and end-tidal CO₂ revealed highly stable values over 50 breaths pre- and post-sigh, with alterations in both exhaled concentrations of both gases returning to pre-sigh values within 6 breaths (Figure 3). These changes were of a shorter duration than those observed in variability or short-range memory of V_T and V'_E after sigh. Since changes in flow and volume occur during these first few breaths after sigh this may impact upon the concentrations of exhaled gases. When examined over a longer period the mean minimum O₂ and end-tidal CO₂ were not different from pre-sigh values.

Variability of V_T and V'_E . A typical feature of an adaptive control system operating in a noisy environment is variability. A system locked into a steady state is likely to be insensitive to small perturbations within its external environment. Reduction of physiological variability has been associated with morbidity and mortality, for example in the reduced heart rate variability observed with age (22, 30), heart disease (29) and in extreme cases preceding life threatening arrhythmias (27, 36). In the absence of changes in external noise, changes in the variability of breathing induced by a sigh may be considered an indicator of changes in neuro-respiratory feedback control. It is interesting to note that variability in V_T or V'_E does not predict the occurrence of a sigh. In contrast, the sigh itself introduces a significant increase in variability of both V_T and V'_E for a

period of 15 breaths (Figure 4) after which time the system returns rapidly to a baseline level of fluctuation.

Memory in respiratory control. The existence of memory within a feedback system allows the recent history (or state) to play a role in the response to a transient perturbation, thus assisting with return to steady state behaviour. Many biological systems exhibit long-range memory characterised by a power law in which decay of correlations slowly fade away with time. These systems may be said to demonstrate scale invariant or fractal characteristics. While this has been shown for heart rate (29) and breathing (30) in adults, we have recently demonstrated such long-range memory in infant breathing (8). Detrended fluctuation analysis (28) performed on V'_E during this study identified no change of long-range correlation after sigh in healthy infants. A trend towards an increase in α of V_T after sigh might be related to the observed changes in short-range memory described below. The presence of a power law memory is likely to be beneficial for the long-range stability of the control system. However, such analysis does not reveal the rapid dynamics following a perturbation of the system.

The analysis techniques used in this study allowed us to follow rapid changes in system dynamics. In the context of an engineering control system, the presence of short-range memory may act like a low pass filter for a sudden perturbation, allowing a smoother response to the stimulus. The loss of short-range memory (decrease in $c(1)$) as the sigh event approached and apparent random behaviour of V_T immediately pre-sigh suggests that the complete loss of correlations in V_T may predict the next sigh. Post sigh, $c(1)$ was significantly increased in comparison to the randomised series for the 50 breaths post-

sigh but steadily decreased probably towards the onset of the next sigh. These data are compatible with a recovery of short-range memory of the respiratory control system following the sigh, which is consistent with the hypothesis that sighs may act as a resetting mechanism for the control loop. Our findings are supported by the data of Franco et al (15) who recently demonstrated differences in the response to sigh between healthy infants and those who later succumbed to sudden infant death syndrome (SIDS). Together, these two studies show that sighs may play an important role in resetting autonomic tone in NREM sleep.

Stability of the control system. In order to characterise the clear increase in fluctuations of the attractor after a sigh, we analysed a segment of the attractor path within a predetermined region of 2-dimensional phase space (Figure 7). Compared to the locked in and unresponsive behaviour of the pre-sigh attractor (Figure 7a), there was a clear increase in fluctuations of the attractor following a sigh (Figure 7b). The comparatively low variability indices observed pre-sigh occurred alongside a gradual reduction in short-range memory of the system and we speculate that this reduced memory and apparent reduction in system responsiveness are intimately related. The significant increase in path fluctuation suggests that the attractor was less ‘locked-in’ and more responsive to perturbations (Figure 7b). This marked increase in cycle fluctuation within phase space is confirmed by the significant increases in both the range and variability of data points obtained from the attractor segments. Importantly, the breathing control system returned to the same ‘basin’ of attraction during the period after sigh in all infants as indicated by the unchanged position of the attractor within the phase space plot. Thus while the system

is more variable and perhaps better regulated, it remains stable. It is worth noting that stability and variability represent different phenomena in system behaviour and often coexist together. Furthermore, an increase in variability (e.g. CV) does not necessarily imply an alteration of correlation properties. Consequently, a system may be intrinsically stable whilst demonstrating significant variability in response to (e.g.) extrinsic fluctuations (24).

Technical issues and limitations of the study. As the aim of this study was to assess the alterations in neuroregulatory control occurring after sigh we examined the output parameters of this complex system in terms of tidal breathing indices. The techniques employed during this study allowed us to investigate the *global* properties of this feedback system. A limitation of these methods was the inability to separate and define the contributions of the various input parameters into this regulatory system, for example those from chemoreceptors and pulmonary stretch receptors.

From a physiological point of view, the conditions under which measurements are made are important. Measurement conditions were standardised as far as possible whilst maintaining the non-invasive nature of this study. Nevertheless, even the pressure and temperature of the face mask can influence control of breathing (14). The mask was warmed to skin temperature prior to application and infants were given time to adapt to the new facemask conditions before commencing measurements. Whilst infants were studied in a cot or in arms, in all cases the body and head position were standardised. A major strength of this study lies in the homogeneous population of healthy infants, all of whom were measured under conditions of quiet unседated sleep. Such studies must be

performed carefully, since sigh behaviour of infants during different sleep stages may vary (19). In this study we undertook careful prospective evaluation of behaviourally defined sleep patterns (33) to avoid the possibility of observing alterations in sleep state after sigh.

Sighing occurs about every 50 to 100 breaths in healthy infants. Thus, the information on long range correlations is limited to a maximum of approximately 100 breaths. Detrended fluctuation analysis was designed for much longer datasets and a limited number of data points can introduce bias. We have tested the effect of reducing the number of data points from 1000 to 100 using a correlated noise signal with a known α value of 1.0. Using a data set size of 100 values the difference in α was not more than 15% when compared to the larger series. To partly overcome this limitation of data set size we always compared the same number of data points before and after the sigh. Phase space plot analysis is dependent on the correct choice of raw data, the embedding dimension and time delay. We used raw tidal flow time series data, as this represents the most basic form of information obtained from the respiratory system using our equipment. Consequently, the attractor may be visualised in phase space in its 'original' form, prior to data manipulations such as integration. In addition, the accuracy of the reconstruction of the attractor is dependant upon the amount of data included. Attractor reconstructions normally incorporate at least several thousand points (1, 21, 23, 37) and hence short data series of 50-100 breaths (e.g. V_T) are insufficient. For our purposes, a time series of 50 breaths consisted of approximately 15,000-18,000 data points, hence providing much clearer information regarding the attractor behaviour and therefore also about the global system dynamics.

Reconstruction of the attractor in phase space is dependant upon the nature of the individual signal under study. Numerous techniques have been developed to assist with accurately representing the intrinsic dynamics of the system graphically. It is possible to obtain a suitable value of the embedding delay (ξ) in several ways (1, 23). In this study the embedding delay was increased systematically and the attractor trajectories viewed visually for consistency of appearance at different delays. That is, the unfolding of the attractor trajectories was examined at many delays, with an appropriate delay being that which provided best visual representation of the system dynamics.

SUMMARY

We found an increased variability of tidal breathing following a sigh in healthy infants during quiet sleep. Short-range breath-to-breath memory of the neuro-respiratory control system decreased towards the sigh event. After the sigh this memory was recovered before steadily returning to pre-sigh conditions. Both long-range memory and the location of the system attractor within phase space were unchanged after sigh, consistent with the presence of long-range stability. Attractor dynamics were observed to be markedly different with a relatively fixed, 'locked-in' behaviour pre-sigh changing to a more adaptive pattern with increased fluctuation post-sigh. These findings support the hypothesis that sighs in infants not only act to reset mechanics, but also change the properties of the neuro-respiratory control system. Finally, an intriguing finding was the observation that loss of short-range memory appeared to be a predictor of a sigh.

The ability to sigh may be an important mechanism of control of breathing. The response to a sigh may be different in various groups of infants at risk for inadequate control of breathing such as premature infants, those with neurological impairment or infants at risk for SIDS. Further studies should investigate sigh behaviour during maturation and in disease in order to develop a new sensitive marker of control of breathing in these infants at risk.

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ABBREVIATIONS

f_{resp}	Breathing frequency
t_{E}	Expiratory time
t_{I}	Inspiratory time
t_{PTEF}	Time to peak tidal expiratory flow
t_{TOT}	Duration of total breath cycle
V'_{E}	Breath-to-breath minute ventilation
$V'_{\text{max,insp}}$	Maximum inspiratory flow
V_{T}	Breath-to-breath tidal volume

FIGURE LEGENDS

Figure 1. Example sigh data from a representative infant. a) Raw tidal flow data. b) Breath-by-breath tidal volume (V_T).

Figure 2. Detrended fluctuation analysis from a representative infant (pre-sigh V_T). Fluctuation function ($F(n)$) was calculated at increasing window sizes (n) after local detrending was performed within each window. Correlation exponent α is the gradient on a log-log plot and represents the long-range memory of the system. 100 breaths pre- and post-sigh data were examined and α values compared for the entire group ($N=12$) before and after sigh using paired t-test.

Figure 3. Response of minimum exhaled O_2 and end-tidal CO_2 to sigh. Data are group mean (95%CI). Post-sigh breaths were compared with the mean of 10 breaths immediately preceding sigh. Minimum exhaled O_2 increased significantly from pre-sigh for the first 2 post-sigh breaths (* $p<0.05$). The fourth post-sigh breath achieved marginal significance ($^{\S}p=0.05$). End-tidal CO_2 returned to pre-sigh levels within 6 breaths after sigh.

Figure 4. Change in variability (CV) of V_T and V'_E in response to sigh. Data are group ($N=25$) mean (95% CI) for each analysis window pre- and post-sigh. Each analysis window examined 10 breaths with a 50% overlap between windows. a) In comparison to the pre-sigh window, variability of V_T increased for the first 2 post-sigh windows

(15 breaths). b) Variability of V'_E also increased for a period of 2 analysis windows (15 breaths) post-sigh, before returning to baseline levels. * $p < 0.05$, ** $p < 0.001$.

Figure 5. Change in autocorrelation ($c(1)$) of V_T and V'_E with sigh. Data are group (N=25) mean (95% CI) for each analysis window pre- and post-sigh. Each analysis window examined 10 breaths with a 50% overlap between windows. a) $c(1)$ of V_T increased during the first 3 post-sigh windows in comparison to the pre-sigh window. This represents a period of 20 breaths over which breath-to-breath short-range memory was increased after the sigh event. After this period memory properties returned to values not significantly different from pre-sigh. b) $c(1)$ of V'_E also increased post-sigh, however changes were shorter lasting, being significantly different for the first post-sigh window only (10 breaths). The second post-sigh window achieved marginal significance ($p = 0.05$) when compared to the pre-sigh window. * $p < 0.05$, ** $p < 0.001$.

Figure 6. Linear regressions for group mean $c(1)$ values for V_T and V'_E at each pre-sigh analysis window. Linear regressions through the grouped mean $c(1)$ for V_T and V'_E demonstrated a decrease in correlation towards the impending sigh. Regression for V_T (—): $c(1) = -0.0123x + 0.155$, $r^2 = 0.59$. Regression for V'_E (---): $c(1) = -0.0132x + 0.192$, $r^2 = 0.53$. Data from each infant were shuffled within each analysis window in order to remove any correlation properties associated with short-range memory in the dataset. When compared to the randomised, uncorrelated data series, regression slopes were significantly different for both V_T ($p = 0.02$) and V'_E ($p = 0.04$).

Figure 7. Phase space embedded plots from a representative infant. a) Pre-sigh and b) post-sigh embeddings in 3-dimensions. Each embedding comprises approx. 15,000 data points from the raw tidal flow signal. A given point within the series is plotted against points with delays of 100 points (500 msec) and 120 (600 msec) points. The same delays were used before and after sigh. Whilst the location of the attractor within the phase space is unchanged after sigh, the dynamics of the system are visually markedly different. Phase space embeddings in 2-dimensions were used to quantify changes in dynamics c) pre-sigh and d) post-sigh. In this case, the appropriate delay was 80 points (400 msec). Variability of the post-sigh attractor was significantly higher than pre-sigh when examined in terms of CV ($p < 0.001$) and range ($p < 0.02$).

Table 1. Demographic Data

<i>Infant</i>	<i>BW</i>	<i>GA</i>	<i>PNA</i>	<i>SW</i>	<i>Pre-sigh</i>		<i>Post-sigh</i>	
					V_T	V'_E	V_T	V'_E
1	3.43	40.7	38	4.60	33.4	1055	33.9	1028
2*	3.57	39.4	37	5.45	28.2	1755	24.4	1444
3	3.61	40.9	31	4.19	36.7	1308	32.4	1208
4*	4.15	42.3	30	5.51	37.8	1349	35.2	1318
5	3.58	40.6	32	4.32	33.4	1402	29.8	1314
6	4.82	40.6	37	6.30	38.9	1304	41.1	1299
7	2.53	36.1	37	3.60	24.8	1258	25.1	1344
8*	2.83	40.6	33	3.52	29.0	1610	26.6	1472
9*	3.84	40.6	38	4.70	39.1	1267	38.4	1269
10	2.75	35.3	57	4.70	34.5	1182	29.3	1262
11	3.48	39.3	43	5.07	29.4	876	25.9	858
12*	2.97	40.7	41	3.76	29.7	1148	26.5	1176
13	3.03	37.7	36	4.06	35.9	2558	30.9	1923
14	3.92	41.1	32	5.10	33.2	1835	28.3	1827
15*	2.66	38.9	36	3.48	23.6	726	21.5	800
16	3.67	40.0	37	4.76	31.3	1208	28.5	1320
17*	4.60	37.1	37	5.20	28.6	1434	27.9	1317
18	3.39	38.1	28	4.43	31.6	1077	28.4	1050
19*	4.25	41.9	29	5.65	27.7	2173	28.3	1837
20*	3.30	41.0	39	3.84	40.1	1149	38.1	1132
21*	3.06	41.4	33	3.95	31.7	1256	33.1	1385
22*	3.97	41.1	38	5.72	37.3	1179	37.9	1223
23	2.80	39.6	37	4.35	33.5	1280	34.3	1228
24	3.55	39.3	37	4.16	36.2	1196	34.8	1161
25*	3.02	39.1	36	3.87	22.7	979	22.5	1045
<i>Maximum</i>	4.82	42.3	57	6.30	40.1	2558	41.1	1923
<i>Mean</i>	3.47	39.7	36	4.57	32.3	1342	30.5	1290
<i>Minimum</i>	2.53	35.3	28	3.48	22.6	726	21.5	800

BW; birthweight (kg), GA; Gestational age (weeks), PNA; Post-natal age (days) SW; weight at time of study (kg), V_T ; tidal volume (mL), V'_E ; minute ventilation (mL/min). * Infant data used for 100 breath analysis.

Table 2. Classical indices of respiratory drive.

		<i>Pre-sigh mean</i>		<i>Post-sigh mean</i>		<i>p value</i> [§]
f_{resp}	(/min)	42.4	(36.8, 48.0)	44.1	(39.3, 48.9)	0.08
V_{T}	(mL)	32.3	(30.3, 34.3)	30.5	(28.3, 32.7)	0.0001*
V'_{E}	(mL/min)	1342	(1179, 1505)	1290	(1179, 1401)	0.12
t_{I}	(sec)	0.64	(0.59, 0.74)	0.59	(0.55, 0.63)	0.0005*
t_{E}	(sec)	0.90	(0.79, 1.01)	0.88	(0.77, 0.99)	0.27
$t_{\text{I}}:t_{\text{TOT}}$	(%)	42.5	(40.3, 44.7)	41.1	(39.2, 43.0)	0.001*
$V_{\text{T}}:t_{\text{I}}$	(mL/sec)	52.5	(47.6, 57.4)	52.2	(49.1, 55.3)	0.83
$t_{\text{PTEF}}:t_{\text{E}}$	(%)	39.3	(33.1, 45.5)	35.0	(29.7, 40.3)	0.11
$V'_{\text{max,insp}}$	(mL/s)	72.8	(66.4, 79.2)	73.3	(69, 77.6)	0.76

Grouped mean (mean - 95% C.I, mean + 95% CI) of all 25 infants for mean of 50

breaths pre- and post-sigh in each infant. [§] Paired t-test. * $p < 0.05$.

Table 3. Long-range regulation of V_T and V'_E pre- and post-sigh

	<i>Pre-Sigh α</i>	<i>Post-Sigh α</i>	<i>p value</i> [§]
V_T	0.72 (0.63, 0.81)	0.83 (0.71, 0.95)	0.06
V'_E	0.88 (0.78, 0.98)	0.85 (0.72, 0.98)	0.71

N=12. Mean (mean - 95% C.I, mean + 95% CI). α ; correlation coefficient.

[§] Paired t-test.

Figure 1a)

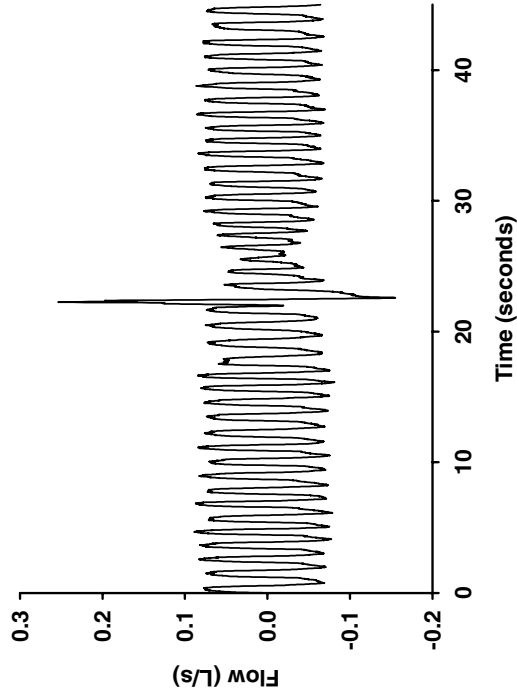
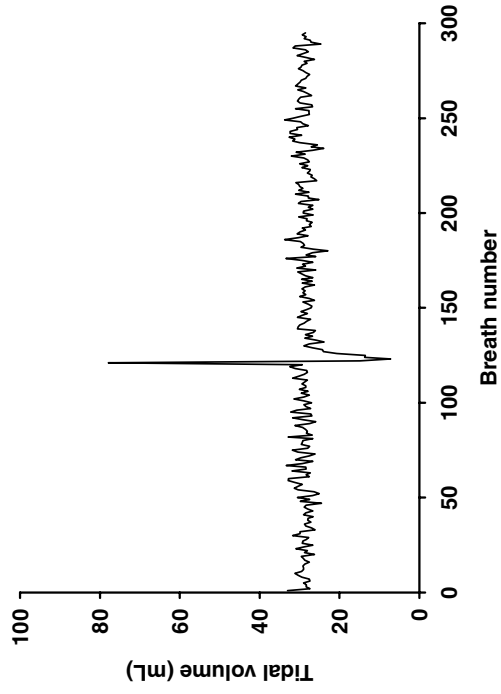


Figure 1b)



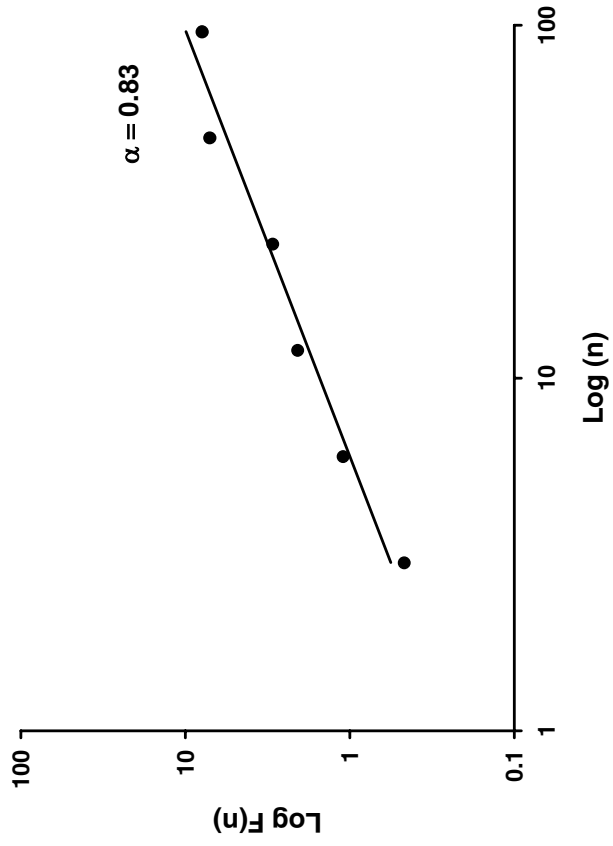


Figure 2

Figure 3

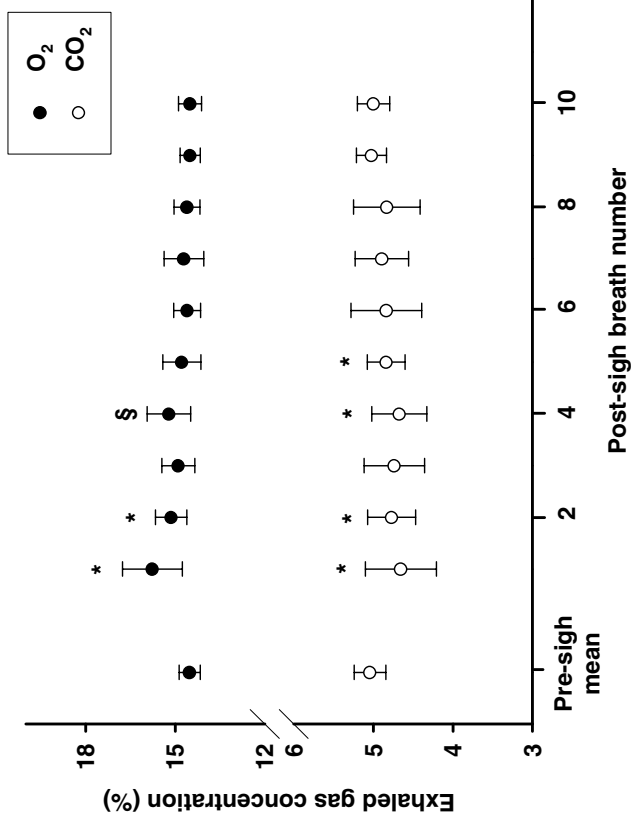


Figure 4a) V_T

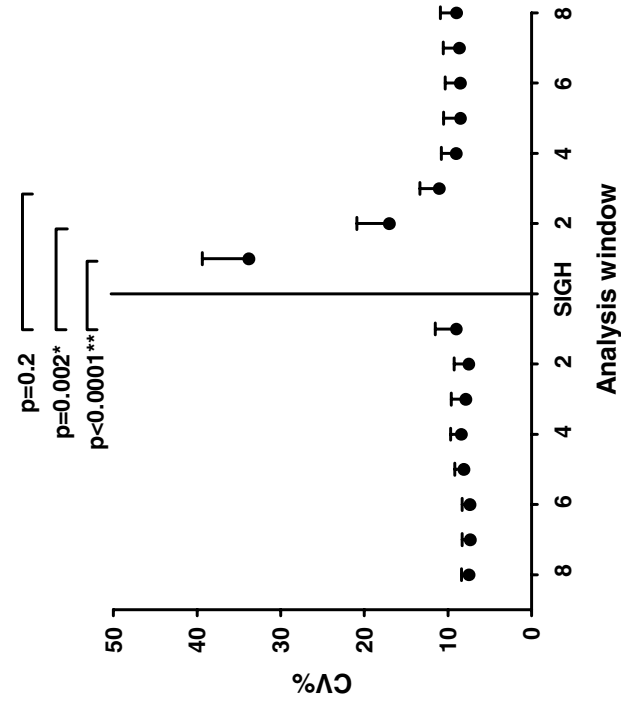


Figure 4b) V_E

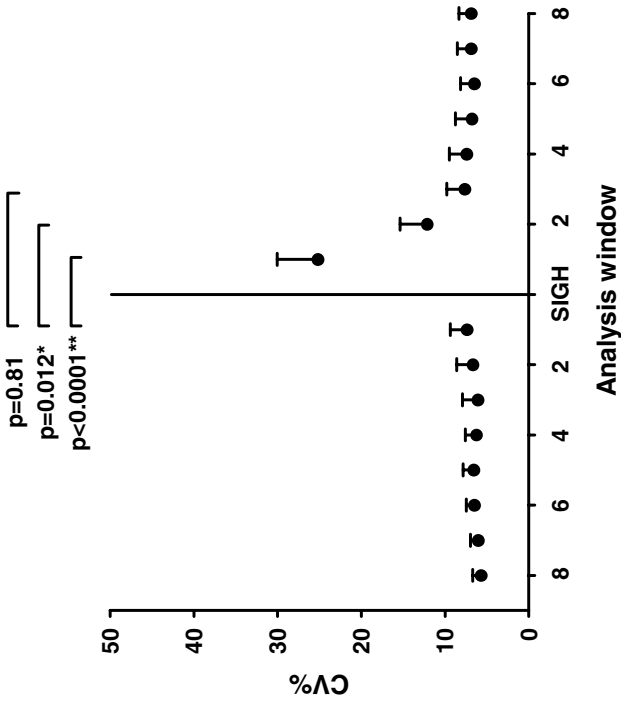


Figure 5a) V_T

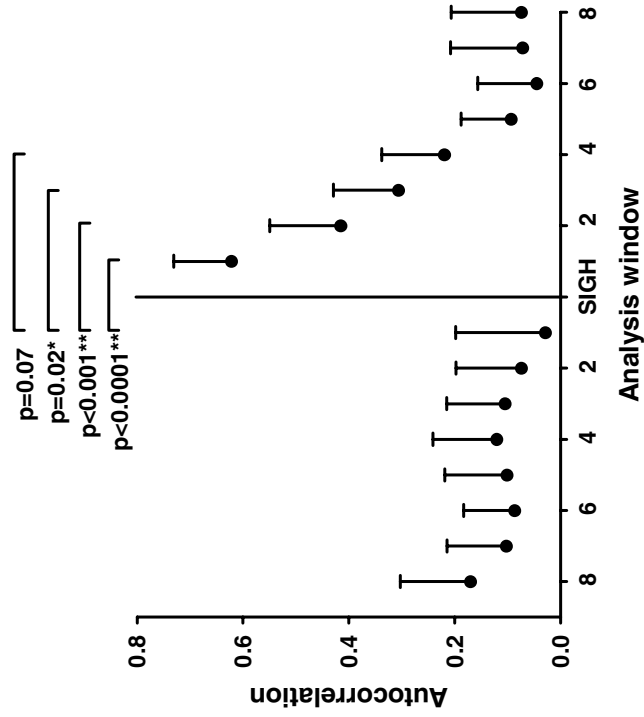
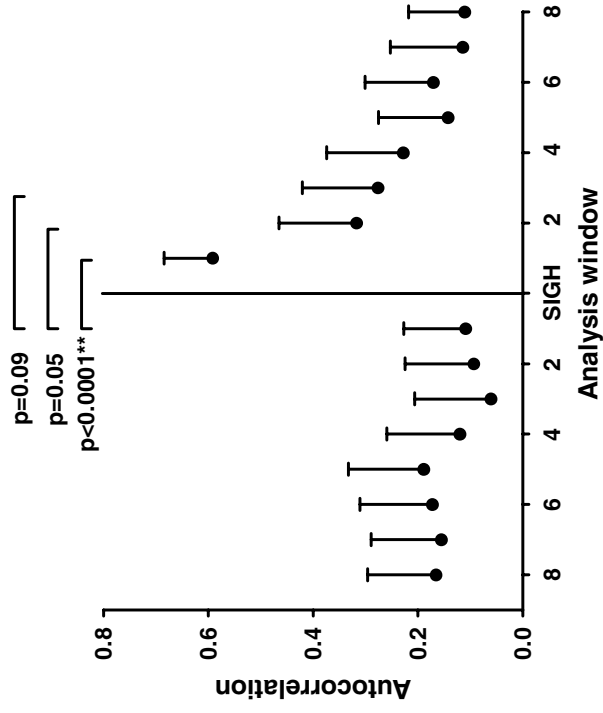


Figure 5b) V'_E



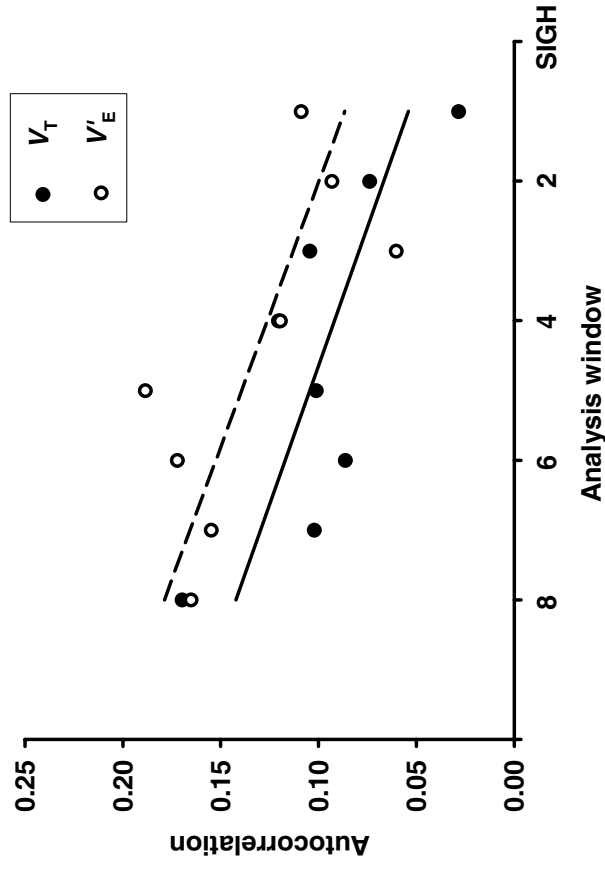


Figure 6

Figure 7a)

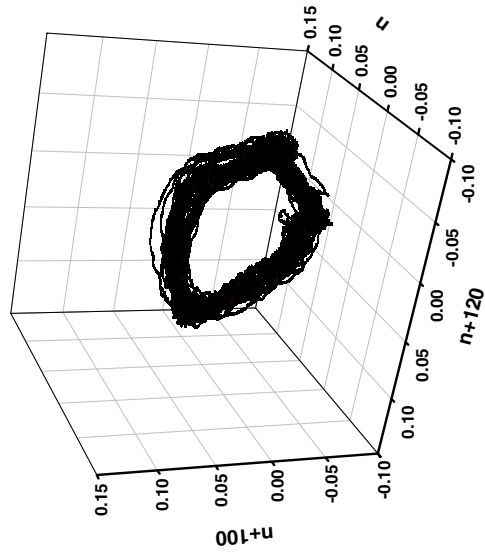


Figure 7b)

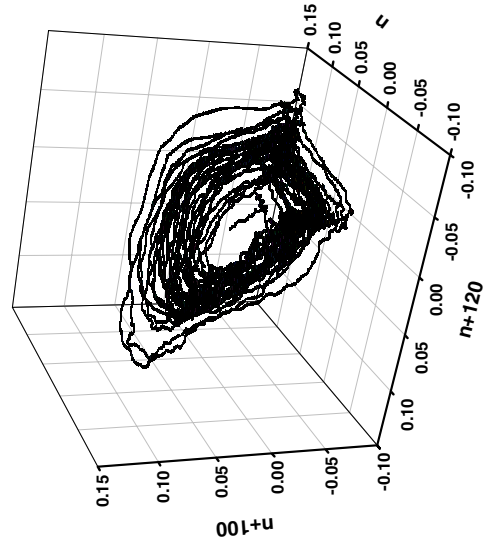


Figure 7c)

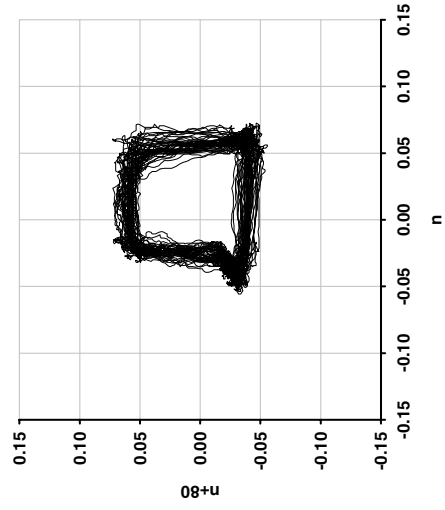


Figure 7d)

