

## RESEARCH PAPER

# Effect of spontaneous movement on respiration in preterm infants

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## Abstract

A common condition in preterm infants (<37 weeks' gestational age) is apnoea resulting from immaturity and instability of the respiratory system. As apnoeas are implicated in several acute and long-term complications, prediction of apnoeas may preempt their onset and subsequent complications. This study tests the hypothesis that infant movements are a predictive marker for apnoeic episodes and examines the relation between movement and respiration. Movement was detected using a wavelet algorithm applied to the photoplethysmographic signal. Respiratory activity was measured in nine infants using respiratory inductance plethysmography; in an additional eight infants, respiration and partial pressure of airway carbon dioxide ( $P_{CO_2}$ ) were measured by a nasal cannula with side-stream capnometry. In the first cohort, the distribution of movements before and after the onset of 370 apnoeic events was compared. Results showed that apnoeic events were associated with longer movement duration occurring before apnoea onsets compared to after. In the second cohort, respiration was analysed in relation to movement, comparing standard deviation of inter-breath intervals (IBI) before and after apnoeas. Poincaré maps of the respiratory activity quantified variability of airway  $P_{CO_2}$  in phase space. Movement significantly increased the variability of IBI and  $P_{CO_2}$ . Moreover, destabilization of respiration was dependent on the duration of movement. These findings support that bodily movements of the infants precede respiratory instability. Further research is warranted to explore the predictive value of movement for life-threatening events, useful for clinical management and risk stratification.

## KEYWORDS

apnoea, breathing, movement, Poincaré map, preterm infants, respiration, respiratory stability

## 1 | INTRODUCTION

About 10% of infants are born preterm (<37 weeks' gestational age) and may face a number of complications including sepsis, intraventricular haemorrhage and respiratory problems, such as bronchopulmonary dysplasia. Immature respiratory control can lead to apnoeas of prematurity that then further cause intermittent hypoxia and bradycardia (Poets et al., 1993; Schindler et al., 2017). Severe apnoeic

and intermittent hypoxic events have been associated with multiple morbidities (Di Fiore et al., 2019; Poets, 2020) such as retinopathy of prematurity (Di Fiore et al., 2010; Di Fiore et al., 2012), neurodevelopmental impairment (Janvier et al., 2004) and death (Poets et al., 2015).

Respiration is functionally linked to motor activity by both central and peripheral mechanisms (for review see Shevtsova et al., 2019). Central mechanisms of interaction include direct signals between

pontomedullary respiratory circuits and the locomotor regions in the mesencephalic areas and the spinal cord. Peripheral mechanisms of interaction include entrainment of respiratory rhythm to movement generated by afferent inputs. An important example of the vital linkage between movement and ventilation is exercise hyperpnoea characterized by an increased frequency of breathing and tidal volume. Body movements stimulate these proprioceptors sending an excitatory neural signal to the respiratory centre fine-tuning its activation (Amann et al., 2010). This increases the ventilation rate which aids in expelling  $\text{CO}_2$  produced during the increased metabolism thus maintaining relatively constant levels of arterial partial pressure of  $\text{CO}_2$  ( $P_{\text{aCO}_2}$ ). In neonates, the eupnoeic  $P_{\text{aCO}_2}$  threshold, ensuring normal breathing, is very close to the apnoeic  $P_{\text{aCO}_2}$ , likely leading to both periodic breathing and apnoeas (Khan et al., 2005). While these interactions are established, it is unclear which of these mechanisms dominate during spontaneous movements in preterm infants and, more importantly, how movement is related to respiratory instability and apnoea.

Many studies on preterm infants have identified a link between apnoea and the immaturity of chemoreceptors (Di Fiore et al., 2013; Gauda et al., 2013). However, bodily movements may also affect respiration through the activation of peripheral proprioceptors or through other coupling mechanisms. These connections have received relatively little attention to date and only a few studies have quantified the incidences of movement in connection with an apnoea. For example, Curzi-Dascalova & Christova-Guéorguieva (1983) showed that 17% of respiratory pauses were preceded by gross body movements. Respiration during squirming movements showed a variable and slow respiratory rate leading to cessation of breathing and a decrease in minute volume (Abu-Osba et al., 1982). Mathew and colleagues found that motor activity preceded apnoeic episodes in 202 of 352 recorded events, and movements tended to continue during these events (Mathew et al., 1991). Similar results were found by (Weintraub et al., 1994) where the number of occurrences of respiratory pauses (3–10 s long) per hour was correlated with the number of body movements. Although these studies have examined the relative number of movements associated with apnoeas, they have not quantified the influence of movements around apnoeas, nor have they quantified the changes in respiration following the movements.

The stability of the preterm respiratory system has been categorized into at least four states ranging from very stable, with an average lifetime of 12 h, to very unstable with an average lifetime of 10 s (Clark et al., 2016). From the perspective of non-linear dynamics, the most stable rhythmic state could be considered a limit-cycle attractor with a characteristic frequency regulated by the central respiratory oscillator (Paydarfar & Buerkel, 1995; Paydarfar & Eldridge, 1987). However, the system is continuously perturbed off this attractor by intrinsic fluctuations in central neural excitation, spontaneous physiological events such as muscle twitches, and extrinsic events such as ambient sounds or postural adjustments by caregivers. Preterm newborns appear to be more vulnerable to these perturbations and may easily transition to less stable states. Such unstable states may

## New Findings

### • What is the central question of this study?

The respiratory centres in the brainstem that control respiration receive inputs from various sources, including proprioceptors in muscles and joints and suprapontine centres, which all affect limb movements. What is the effect of spontaneous movement on respiration in preterm infants?

### • What is the main finding and its importance?

Apnoeic events tend to be preceded by movements. These activity bursts can cause respiratory instability that leads to an apnoeic event. These findings show promise that infant movements might serve as potential predictors of life-threatening apnoeic episodes, but more research is required.

include or cause apnoeic episodes. A movement can be considered as a disturbance to the respiratory control system and therefore its response could provide information about the stability of the respiratory system.

The hypothesis of this study is that respiratory stability and apnoeic events in preterm infants are associated with movement events. More specifically, we hypothesize that movements can reduce the stability of their breathing pattern. To test this hypothesis, the duration of movements was examined with reference to the onset of apnoeas in nine infants. The results provided evidence of the association between the two. In a second cohort of eight preterm infants, the stability of respiration was examined by quantifying the variability of inter-breath intervals (IBI) and Poincaré maps obtained from the continuous respiratory signal. Both measures of variability increased following movement onset. Moreover, the degree of respiratory destabilization was dependent on the duration of movement. These findings provide new information on how movement and respiration are coupled in preterm infants.

## 2 | METHODS

### 2.1 | Ethical approval

The study protocol was approved by the Institutional Review Board of the University of Massachusetts Medical School (approval no. 13413) and conformed with the *Declaration of Helsinki*, except for registration in a database. The attending physician identified eligible infants, and written informed consent was obtained from the infant's mother or legal guardian.

**TABLE 1** Infant demographics and recording times

Subject ID	GA (weeks)	PMA (weeks)	Birth weight (g)	Study weight (g)	Sex	Study duration (h)	Analysable duration (h)
1	27.29	29.43	1045	1220	M	45.62	39.60
2	30.57	30.71	1785	1755	M	43.84	36.38
3	30.14	30.71	1710	1710	M	43.71	37.86
4	29.43	30.14	925	843	F	46.78	41.03
5	31.29	32.29	1868	1674	M	49.75	36.91
6	28.86	30.14	1115	1140	F	48.61	39.91
7	28.57	30.14	1050	1110	M	20.34	17.29
8	30.29	30.57	1225	1230	F	70.32	53.43
9	33.86	34.29	1860	1900	M	47.27	36.74
10	29.71	33.29	1150	1680	F	7.24	4.69
11	32.86	33.57	1570	1442	F	3.37	1.64
12	29.29	30.29	1190	1040	F	6.58	5.01
13	27.71	28.86	1105	1030	M	7.11	5.73
14	32.57	33.43	2295	2009	M	7.41	6.18
15	32.14	33.29	1330	1350	M	5.97	4.98
16	31.14	32.00	1565	1377	M	6.81	4.70
17	28.43	30.43	1378	1360	M	3.71	3.32

GA, gestational age; PMA, postmenstrual age.

## 2.2 | Subjects

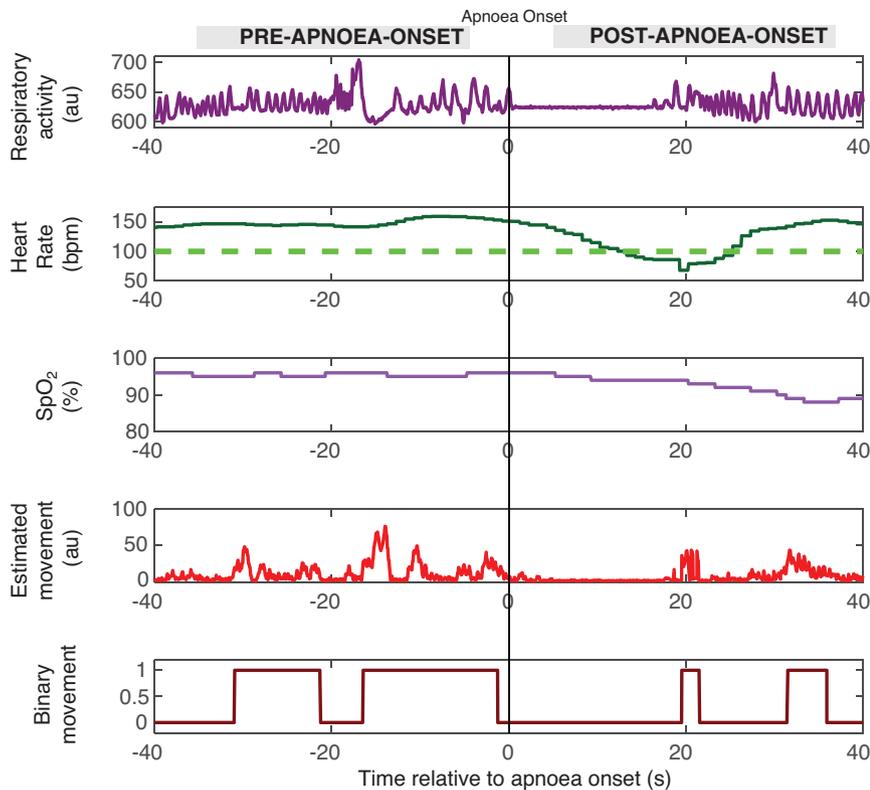
The prospective study was performed at the Neonatal Intensive Care Unit (NICU) at the University of Massachusetts Memorial Healthcare. Data were collected from a total of 17 preterm infants, separated into two cohorts. Cohort 1 comprised nine infants (three females and six males;  $30 \pm 1.9$  weeks' gestational age;  $30.9 \pm 1.5$  weeks' postmenstrual age), and Cohort 2 comprised eight infants (three females and five males;  $30.5 \pm 2$  weeks' gestational age;  $31.9 \pm 1.8$  weeks' postmenstrual age). While the infants in Cohort 1 were recorded for longer durations, for the infants in Cohort 2 additional respiratory measurements were available via side-stream capnography. Infants were excluded if they had intraventricular haemorrhage higher than grade 2, hydrocephalus, a congenital anomaly that complicated the infant's cardio-pulmonary status, or any pulmonary disease that required the infants to receive supplemental oxygen, continuous positive airway pressure therapy or mechanical ventilatory support during the study. All infants were spontaneously breathing room air. Table 1 lists subject characteristics and the duration of obtained measurements per infant.

## 2.3 | Data acquisition

All infants were studied in their NICU incubator, which provided a thermoregulated environment. A bedside monitor (IntelliVue MP70, Philips Medical Systems, Andover, MA, USA) displayed electro-

cardiogram (ECG) and photoplethysmography (PPG) signals, blood oxygen saturation ( $S_{pO_2}\%$ ), heart rate (HR) and respiration rate. Breathing activity (pneumogram) was recorded using respiratory inductance plethysmography (Somnostar PT, Viasys Healthcare, Yorbalinda, CA, USA) sensing movement of the upper abdomen. IBIs were extracted from the pneumogram using automated peak-detection software (LabChart 7, ADInstruments, Colorado Springs, CO, USA). A pulse-oximeter probe attached to the infant's hand or foot captured the PPG and  $S_{pO_2}$  signals. The PPG signal was used to estimate bodily movements based on the disruptions that the signal experienced during movements (Zuzarte et al., 2019). A wavelet-based algorithm developed previously identified the onset and offset of these disruptions, that is, artifactual events in the PPG signal, which are distinct from the pulsatile signal related to perfusion. These events afforded the calculation of the durations that movement was present in a binary 'on-off' fashion. Data from all periods of feeding (bottle and gavage) and nursing assessments were excluded from analysis. Periods during kangaroo care when the infant was taken out of the incubator were also excluded until the baby was placed back in the incubator and settled down. Due to the long data acquisition duration, infant position was not controlled. Each nurse repositioned the infants between prone and supine following the routine care procedures.

Data were recorded using the Vuelogger Patient Monitoring System (Wyss Institute, Boston, MA, USA), which retrieved physiological information from the bedside monitor and time-synced them with the pneumogram. The signals were sampled at the following rates: ECG: 500 Hz; pneumogram: 200 Hz; PPG: 125 Hz; movement duration:



**FIGURE 1** Time series of respiratory activity (from pneumogram), heart rate,  $S_{pO_2}$  and movement, before (PRE-APNOEA-ONSET) and after (POST-APNOEA-ONSET) the onset of apnoea, defined as time = 0 (Comparison 1). Bradycardia threshold is indicated by the green dashed line. Movement was estimated using a wavelet-based algorithm on the photoplethysmogram. Total movement durations in the PRE-APNOEA-ONSET and POST-APNOEA-ONSET conditions were computed from the binary movement time series

25 Hz. The data were streamed to the Vuelogger's hard disk at the bedside and then exported for analysis.

In addition to these data, infants in Cohort 2 wore nasal cannulas that measured respiratory activity with side-stream capnometry, which facilitated continuous measurement of partial pressure of carbon dioxide ( $P_{CO_2}$ ) (M2741A, Philips Medical Systems, Andover, MA, USA). As these measurements eliminated mechanical artifacts generated by movement and provided a more reliable continuous signal, it afforded to study the effects of movement on the stability of respiration.

## 2.4 | Movement with respect to onset of apnoeas

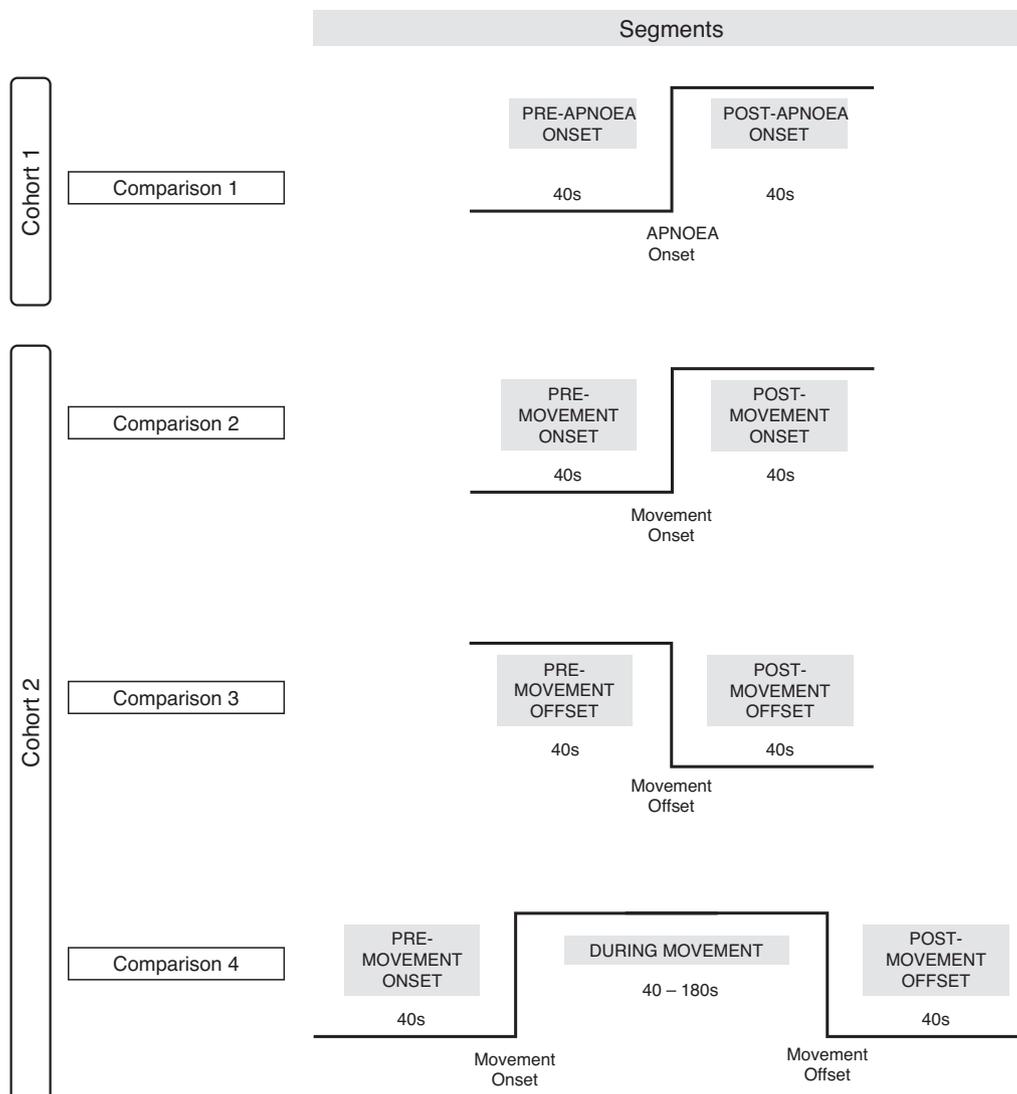
The first cohort (infants no. 1–9) was studied to explore the movements and their durations before and after the onset of apnoeas. In accordance with clinical practice, apnoeas were defined as: (1) a cessation of breathing longer than 10 s, if accompanied by bradycardia (HR <100 bpm) and oxygen desaturation ( $S_{pO_2}$  <88%), (2) a cessation of breathing longer than 20 s, regardless of bradycardia or desaturation, or (3) co-occurrence of a bradycardia and oxygen desaturation, independent from a cessation of breathing (Darnall et al., 1997; Delivoria-Papadopoulos & McGowan, 1998; Deulofeut et al., 2006). For apnoeas that were clustered in time, only the first apnoea in the cluster was included in the analysis; apnoeas occurring within 60 s from the offset of its preceding apnoea were excluded to avoid the immediate effects of any apnoea on subsequent apnoeas.

Mean recording time for the infants in Cohort 1 was  $46.2 \pm 12.7$  h resulting in a total of 370 apnoeic events following the above criteria. Subjects from Cohort 2 were not included in this analysis since the mean recording duration was much shorter ( $6 \pm 1.6$  h) and contained only relatively few apnoeic events. For each subject, the mean and standard deviation of the IBI in the 40 s PRE-APNOEA-ONSET and 40s POST-APNOEA-ONSET segments were computed (Comparison 1). The movement durations in these paired segments were also compared. Furthermore, this comparison of movement duration was also applied to a subset of apnoeic events, defined as pathological apnoeic pauses that had either bradycardia or oxygen desaturation associated with it. Figure 1 shows a representative segment of the respiratory activity and heart rate together with the binary movement signal with reference to an apnoeic onset.

Apnoeic events that generated an alarm on the bedside monitors alerted NICU nurses to manually stimulate and in some cases reposition the infant to terminate the apnoea. Therefore, the segments following APNOEA-OFFSET were not analysed, since it was difficult to distinguish between spontaneous or nurse-induced movements.

## 2.5 | Respiratory activity following movement onset and offset

While examining the occurrence of movement before and after an apnoea documents their association, it does not allow conclusions about any causal effect of movement on respiratory activity. Therefore, in the second cohort of infants a more reliable signal of continuous



**FIGURE 2** Schematic representation of all segments compared

respiratory activity was collected to study the effect of movement on respiration more directly. The  $P_{\text{CO}_2}$  signal served as a continuous measurement of respiratory activity with its peak defining the end-tidal  $P_{\text{CO}_2}$  ( $P_{\text{ETCO}_2}$ ).  $P_{\text{ETCO}_2}$  served as a non-invasive surrogate for the arterial partial pressure of  $\text{CO}_2$  ( $P_{\text{aCO}_2}$ ) that can otherwise only be obtained invasively by sampling arterial blood gas.  $P_{\text{CO}_2}$  was sampled through a nasal cannula that limited any direct mechanical transfer from movement to respiration (Iwasaki et al., 1989). Cohort 1 could not be considered for this analysis since their respiratory activity was recorded only with respiratory inductance plethysmography, which is affected by a variety of non-respiratory movements through direct mechanical coupling. To evaluate the effect of movement on the stability of respiration, measures were obtained from the continuous respiratory time series at three different instances and compared. A schematic representation of three different comparisons is illustrated in Figure 2.

Comparison 2: respiratory activity 40 s pre and 40 s post the onset of movements. For each subject, multiple paired segments of

respiratory data were compared: PRE-MOVEMENT-ONSET versus POST-MOVEMENT-ONSET. To avoid confounding, the 40 s-long segment before the onset had to be free of other movements to minimize after-effects of a previous movement activity on the analysed segment.

Comparison 3: to focus on the effects after the offset of movement, respiratory activity from paired segments 40 s before movement offset (PRE-MOVEMENT-OFFSET) and 40 s after movement offset (POST-MOVEMENT-OFFSET) were selected. Only those paired segments that had no movement for at least 40 s after the offset of movement were included.

Comparison 4: a smaller subset of data from Cohort 2 was used to compare paired respiratory segments before and after movement bursts. The data selected before movement onset (PRE-MOVEMENT-ONSET) and after movement offset (POST-MOVEMENT-OFFSET) were 40 s long without any movement activity. The interval of the movement (DURING-MOVEMENT) typically comprised several movement bursts of varying duration that were at least 40 s

long, but no longer than 180 s. This ensured that comparisons between PRE-MOVEMENT-ONSET and POST-MOVEMENT-OFFSET were temporally neither too close nor too far from each other. Paired segments were compared using the following dependent measures.

### 2.5.1 | Variability of IBI

For each infant, the IBIs were determined from the peaks of the  $P_{CO_2}$  using an automated peak-detection algorithm (LabChart 7, ADInstruments). Mean and standard deviation of IBIs were used as a measure of respiratory stability in each of the 40-s segments.

### 2.5.2 | Respiratory variability from Poincaré maps

Respiratory stability was also analysed in phase space. Even though the phase space of the respiratory attractor is likely to be high-dimensional, its stability can be examined in a lower-dimensional projection. To this end, the experimentally measured time series of  $P_{CO_2}$  were mapped into a two-dimensional phase space spanned by the measured  $P_{CO_2}$  and its first time derivative  $dP_{CO_2}$ , obtained by numerical differentiation. Since differentiation is a high-pass operation that amplifies any high frequency components and noise in the signal, the derivative was subsequently low-pass filtered using a fourth-order zero-lag Butterworth filter. Figure 3a shows the PRE- and POST-MOVEMENT-ONSET segments (Comparison 2) of the estimated movement signal and the  $P_{CO_2}$  signal and its time derivative  $dP_{CO_2}$ .

The phase portraits obtained from these time series are shown in Figure 3b. The upper branch of the phase portrait denotes expiration and the lower branch denotes inspiration as the trajectory traverses in clockwise direction.

Poincaré sections from these two-dimensional phase portraits were obtained to assess changes in respiratory stability. A Poincaré section is an  $(n - 1)$ -dimensional surface that is transverse to the flow of an  $n$ -dimensional dynamic system (Rasband, 2015; Strogatz, 2018). The Poincaré section and the topology of the Poincaré map have been previously used to quantify the stability of physiological data, such as cardiac signals (Glass & Mackey, 1988; Honerkamp, 1983), respiratory signals (Del Negro et al., 2002) and also rhythmic human movements (Dingwell & Kang, 2007; Hurmuzlu et al., 1994; Zhang & Sternad, 2019). Figure 3b illustrates the Poincaré section as a green line passing through the origin of the phase space during the expiration phase. The origin of the Poincaré section was determined for each subject separately as the mean of  $P_{CO_2}$  and  $dP_{CO_2}$  from the entire recording. The second point defining the section was selected as the 97.5th percentile of the distributions of the respiratory signal. Other phases in a given limit cycle are possible and should theoretically give the same results.

The points of intersection of the trajectories with the Poincaré section rendered the Poincaré map with coordinates  $\mathbf{p} = [p_1, p_2, \dots, p_n]$ . If the system is stable, the successive intersections show convergence to a single reference point on the limit-cycle attractor. For

an unstable system, the discrete points diverge over successive cycles. While the Poincaré analysis theoretically assumes a reference point, this reference point is not known in the measured data. For analysis purposes, the coordinates for the reference point  $\mathbf{p}^*$  were obtained from the average of all  $\mathbf{p}$  at the section of an entire recording session (Figure 3c). The deviations of each  $\mathbf{p}_i$  from  $\mathbf{p}^*$  were then obtained as  $d = [d_1, d_2, \dots, d_n]$ . This distance along the Poincaré section is measured in arbitrary units (au).

The degree of stability for the respective segments was quantified as the mean and standard deviation of  $d$ , denoted by Mean- $d$  and SD- $d$ , respectively. For the empirical analysis two additional Poincaré sections were chosen: one during the inspiration phase and one at end of expiration ( $dP_{CO_2} = 0$ , thus  $P_{CO_2} = P_{ETCO_2}$ ). Figure 4 illustrates these three Poincaré sections. For the end-expiratory section, the mean and standard deviation of the  $P_{ETCO_2}$  were also obtained.

### 2.5.3 | Change in respiratory variability as a function of movement duration

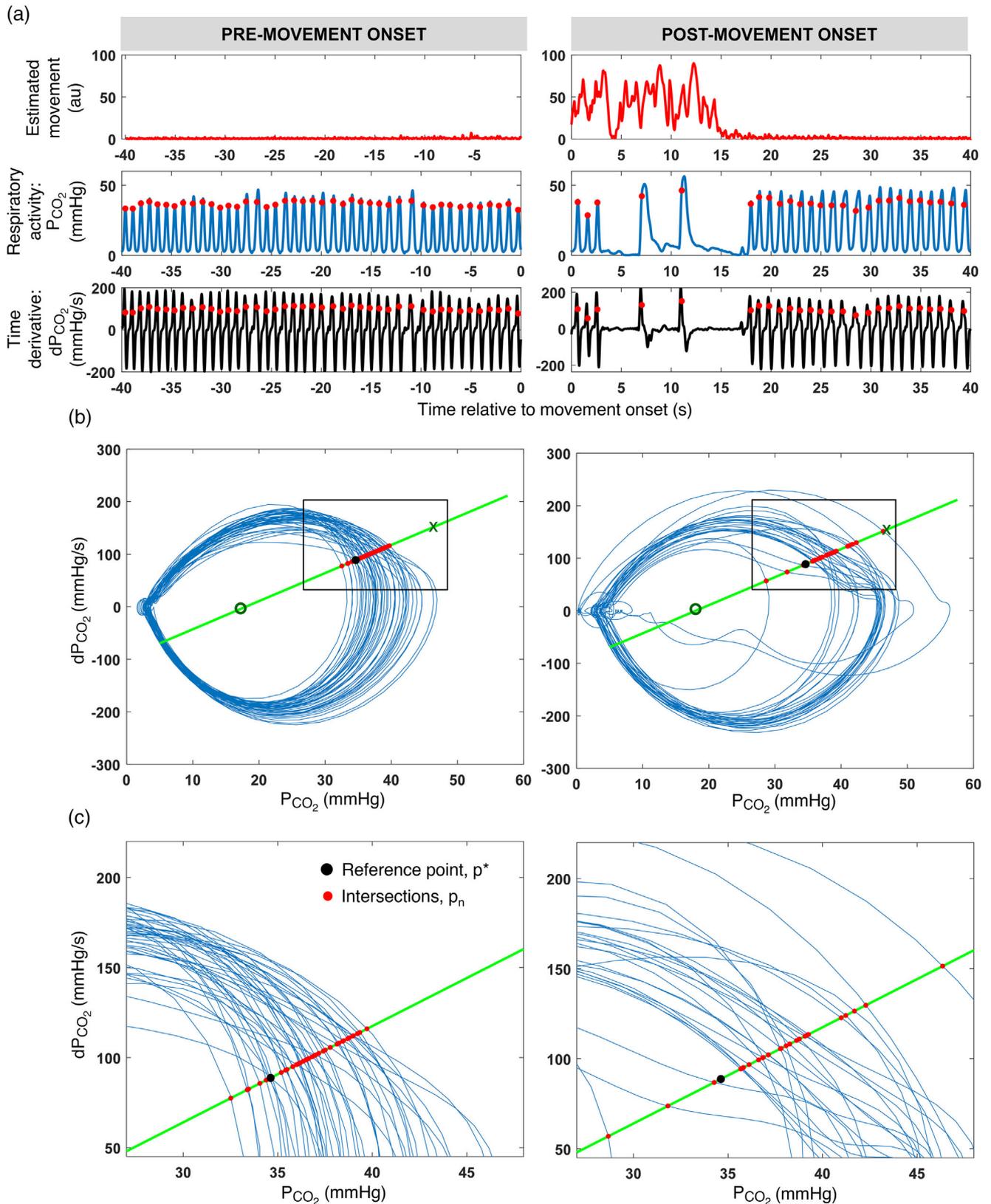
If movement disrupts the stability of the limit cycle, then this effect should scale with the amount or duration of movement. To test this hypothesis, the variability measure SD- $d$  after the transition (movement onset or offset) was analysed with respect to movement duration.

## 2.6 | Statistical analyses

To test for differences in the dependent measures before and after the apnoea and before and after the onsets and offsets of movement, a linear mixed-effects model (LME) was used. LME models allow modelling both fixed effects (before and after movement onset) and random effects (inter-subject variability), that is, account for both within- and across-subject variance. Since there were repeated observations within each subject, subject ID was included as a random effect.

The following dependent measures were analysed for Cohort 1: total movement duration, mean and standard deviation of IBI. The dependent measures in Cohort 2 were: mean and standard deviation of IBI; for each Poincaré section: Mean- $d$  and SD- $d$ ; additionally, for the Poincaré section at the end of expiration: the mean and standard deviation of  $P_{ETCO_2}$ . These measures are summarized in Table 2.

For all dependent variables, separate linear mixed-effects models were implemented. For Cohort 1, one fixed effect was tested: Comparison 1: PRE-APNOEA-ONSET and POST-APNOEA-ONSET. For Cohort 2, three different sets of analyses were conducted: Comparison 2: PRE-MOVEMENT-ONSET and POST-MOVEMENT-ONSET; Comparison 3: PRE-MOVEMENT-OFFSET and POST-MOVEMENT-OFFSET; and Comparison 4: PRE-MOVEMENT-ONSET, DURING-MOVEMENT and POST-MOVEMENT-OFFSET. A random slope was included in the model to allow each subject to have a different slope for the compared segments.

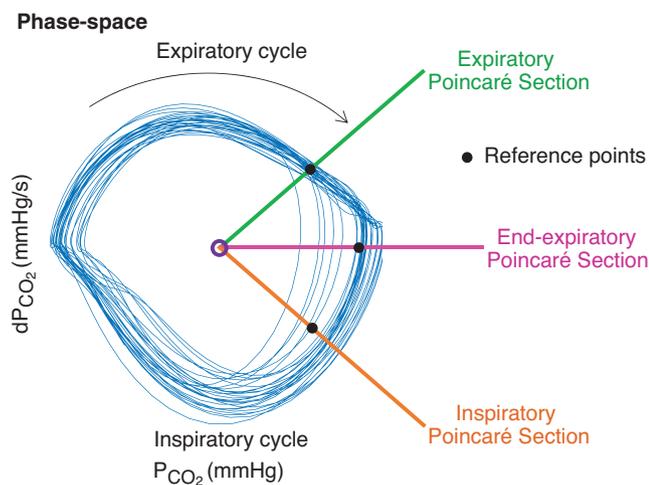


**FIGURE 3** (a) Time series of movement, respiratory activity ( $P_{CO_2}$ ) and its first derivative ( $dP_{CO_2}$ ), from Comparison 2: before (PRE-MOVEMENT-ONSET: left) and after (POST-MOVEMENT-ONSET) the onset of movement. (b) Phase portrait of the same time series of  $P_{CO_2}$  with a Poincaré section in the expiratory phase (green line). Markers 'o' and 'x' represent the two points used to define the Poincaré section. The red points indicate the intersections of the trajectories with the Poincaré section. These locations are projected onto the time series in (a) (red points). (c) Zoomed versions of the orbits in the rectangles in (b). For this subject (no. 14), the reference point ( $p^*$ ) on the Poincaré section is denoted by the black point. The distance of each intersection  $p_n$  from the reference point  $p^*$  are denoted by  $d_n$

**TABLE 2** Measurements and comparisons

	Poincaré section			Other measures
	Expiratory	End-expiratory	Inspiratory	
Comparison 2	Mean- <i>d</i>	Mean- <i>d</i>	Mean- <i>d</i>	Mean-IBI
	SD- <i>d</i>	SD- <i>d</i>	SD- <i>d</i>	SD-IBI
		Mean- $P_{\text{ETCO}_2}$		SD- <i>d</i> $\propto$ Mov_dur
		SD- $P_{\text{ETCO}_2}$		
Comparison 3	Mean- <i>d</i>	Mean- <i>d</i>	Mean- <i>d</i>	Mean-IBI
	SD- <i>d</i>	SD- <i>d</i>	SD- <i>d</i>	SD-IBI
		Mean- $P_{\text{ETCO}_2}$		SD- <i>d</i> $\propto$ Mov_dur
		SD- $P_{\text{ETCO}_2}$		
Comparison 4	SD- <i>d</i>	SD- <i>d</i>	SD- <i>d</i>	
			SD- $P_{\text{ETCO}_2}$	

*d*, distance from reference point; Mov\_dur, movement duration in the movement segments;  $P_{\text{ETCO}_2}$ , end-tidal  $\text{CO}_2$ ; SD, standard deviation.



**FIGURE 4** Example phase space with three Poincaré sections: expiratory (green), end-expiratory (pink) and inspiratory (orange)

The relation between respiratory variability of the Poincaré map (SD-*d*) with movement duration was analysed using the same linear mixed-effects model. SD-*d* post-transition was taken as the dependent variable with movement duration as the independent variable and SD-*d* pre-transition as a covariate.

All statistical analyses were conducted using RStudio statistical software version 1.2.5019 (RStudio, Inc., Boston, MA, USA). The model was implemented using the 'lmer' function from the lme4 package (Bates et al., 2015). The average difference of the measures between the compared segments, 95% confidence intervals and *P*-values were estimated from the fitted model using the lmerTest package (Kuznetsova et al., 2017). For the three segments of Comparison 4, multiple pairwise Tukey tests were performed with Bonferroni correction using the 'glht' function from the 'multcomp' package

(Hothorn et al., 2008). Results were considered statistically significant when  $P < 0.05$ .

### 3 | RESULTS

#### 3.1 | Comparison 1: movements before and after apnoeic onset

In Cohort 1 (infants nos 1–9), a total of 370 apnoeic events were identified. Table 3 lists the number of these apnoeic events for each subject along with the baseline  $S_{\text{pO}_2}$  and heart rate values. In addition, the table also lists the infants' feeding schedule and whether they were given caffeine.

The onset of each apnoea served as reference for comparing the IBI and movement before and after the apnoea. As expected, the mean IBI in the POST-APNOEA segments was longer by 2.3 s (95% CI: 1.2–3.2; POST:  $3.8 \pm 1.6$  s; PRE:  $1.5 \pm 0.4$  s;  $P = 0.003$ ). The standard deviation of IBI was also higher in the POST-APNOEA segments by 3.7 s (95% CI: 2.5–4.8; POST:  $5.0 \pm 1.9$  s; PRE:  $1.3 \pm 0.5$  s;  $P = 0.0003$ ). Of the 370 apnoeic events, 250 had more movement in the PRE-APNOEA-ONSET segments when compared to the POST-APNOEA-ONSET segments. Applying the mixed-model analysis, total movement duration in the PRE-APNOEA-ONSET segments ( $15.5 \pm 4.1$  s) was significantly longer than in the POST-APNOEA-ONSET segments ( $10.8 \pm 4.3$  s;  $F_{(1,6,73)} = 16.9$ ;  $P = 0.005$ ; 95% CI: 3.19–8.61). Of the 370 apnoeic events, 219 were pathological apnoeas since they were associated with bradycardia and/or oxygen desaturations. Of these pathological apnoeic events, the total movement duration in the PRE-APNOEA-ONSET segments ( $14.8 \pm 4.1$  s) was still significantly longer than in the POST-APNOEA-ONSET segments ( $11.1 \pm 4.9$  s;  $F_{(1,7,16)} = 6.8$ ;  $P = 0.033$ ; 95% CI: 1.26–8.13). Figure 5 summarizes the results showing that seven of the nine subjects showed this increase. Hence, it can be concluded that when longer movements

**TABLE 3** Number of apnoeic events with the baseline oxygenation and heart rate values. Mean oxygenation and heart rate for pathological apnoeic events before after apnoea onset are also shown

Subject ID	Feeding schedule	Caffeine	All apnoeic events			Pathological apnoeic events				
			Baseline values		Count	S <sub>pO<sub>2</sub></sub> (%)		HR (bpm)		Count
			S <sub>pO<sub>2</sub></sub> (%)	HR (bpm)		Pre-apnoea-onset	Post-apnoea-onset	Pre-apnoea-onset	Post-apnoea-onset	
1	Q3	y	95.3 ± 2.5	156.4 ± 8.2	96	41	92.2 ± 4.2	77.8 ± 5.5	139.7 ± 12.4	89.0 ± 16.6
2	Q4	n/a	99.3 ± 1.5	133.3 ± 13.3	66	41	97.7 ± 3.5	94.8 ± 5.1	110.3 ± 19.3	72.5 ± 12.6
3	Q4	n/a	99.1 ± 1.2	133.4 ± 11.9	69	39	97.4 ± 8.0	92.0 ± 11.4	114.2 ± 19.7	76.1 ± 15.9
4	Q3	y	99.5 ± 0.6	166.1 ± 6.7	6	6	99.2 ± 1.0	98.3 ± 1.2	147.2 ± 34.0	50.4 ± 12.0
5	Q4	y	97.1 ± 9.8	140.8 ± 10.7	41	18	91.2 ± 18.1	79.4 ± 18.2	124.0 ± 16.9	115.9 ± 27.3
6	Q3	n/a	91.8 ± 4.2	134.4 ± 3.2	14	8	87.1 ± 5.6	85.4 ± 5.8	124.7 ± 3.6	75.5 ± 16.2
7	Q3	y	98.6 ± 1.2	155.3 ± 6.0	21	20	97.3 ± 2.4	89.7 ± 4.5	143.3 ± 14.4	68.9 ± 13.7
8	Q3	n/a	97.0 ± 1.5	145.6 ± 6.1	49	38	96.4 ± 1.7	90.2 ± 8.2	130.2 ± 15.7	47.4 ± 24.6
9	Q4	n/a	90.5 ± 15.8	157.3 ± 15.6	8	8	88.1 ± 15.3	77.1 ± 11.3	130.4 ± 19.6	77.1 ± 5.4
Mean			96.5 ± 4.3	147.0 ± 9.1			94.1 ± 6.6	87.2 ± 7.9	129.3 ± 17.3	74.7 ± 16.0
Total					370	219				

Values are means ± SD. Feeding schedule: Q3, feeds every 3 h; Q4, feeds every 4 h. Caffeine: y, infant was on caffeine during study; n/a, information about caffeine unknown.

occurred, apnoeas, including pathological apnoeas, were more likely to appear.

### 3.2 | Comparison 2: respiratory measures upon onset of movement

Using the onset of movements for reference, respiratory variables before and after the movement onset were compared in Cohort 2. The mean IBI increased upon movement onset by 0.28 s ( $F_{(1,6,6)} = 10.3$ ;  $P = 0.0161$ ; 95% CI: 0.11–0.45). The standard deviation of the IBIs also showed a significant increase following the onset of movement by 0.33 s ( $F_{(1,5,4)} = 24.3$ ;  $P = 0.0035$ ; 95% CI: 0.21–0.46). Figure 6 summarizes this increase in mean and variability showing that each of the nine individuals displayed this trend.

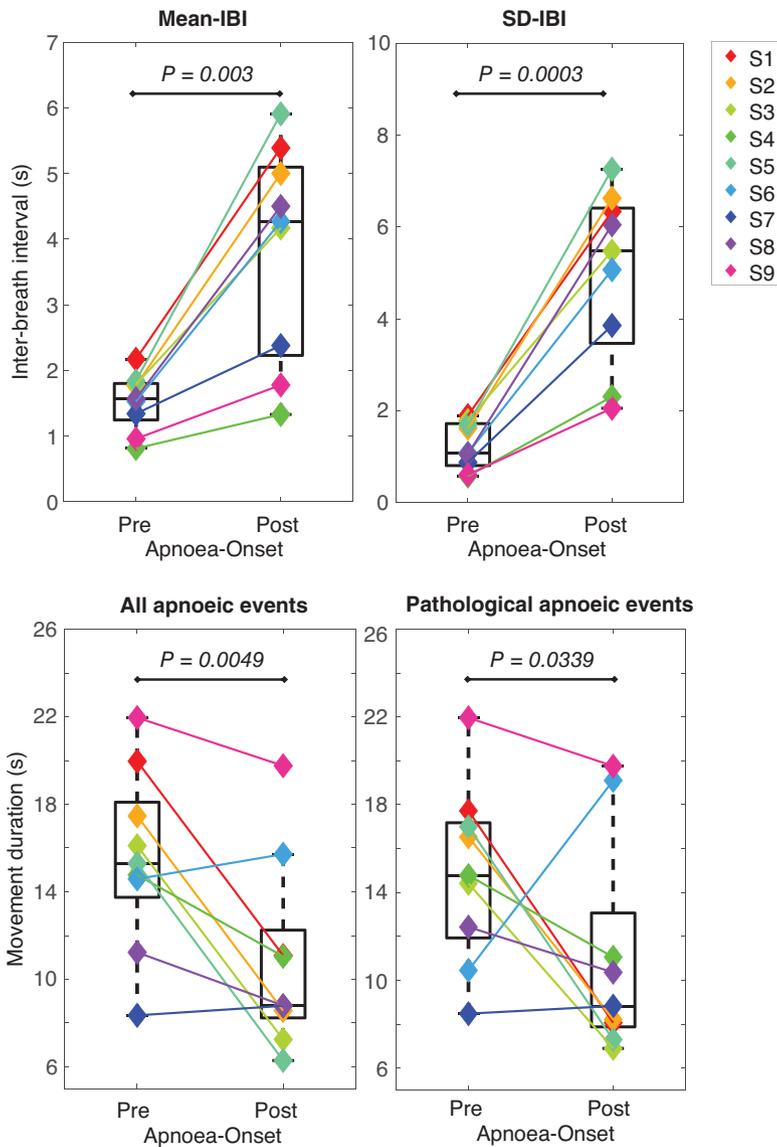
To further probe into the potential effect of movement as perturbation to the respiratory rhythm, the continuous  $P_{CO_2}$  signals were compared before and after movement onset. The 2D phase portrait was reconstructed for each segment and Poincaré sections were applied. To identify potential differences in respiration before and after movement onset, the Poincaré section was applied at the expiration phase, at the end of expiration, and at the inspiration phase. For the expiratory Poincaré section, the onset of movement significantly increased the Mean- $d$  ( $F_{(1,5,3)} = 7.01$ ;  $P = 0.0428$ ) and its variability SD- $d$  ( $F_{(1,6,3)} = 16.65$ ;  $P = 0.0059$ ) (Figure 7a). Note that subject 10 had a lower  $P_{ETCO_2}$  value due to the use of a non-standard nasal cannula and was an outlier in this and subsequent analyses. The subject was not excluded from analysis, but excluding the subject would have yielded stronger significance. This indicates that upon movement onset, the intersections with the Poincaré section were further away from the reference point and also more variable, suggesting less

stability in the respiratory activity. The same comparison at the end of expiration showed that while the Mean- $P_{ETCO_2}$  did not change, SD- $P_{ETCO_2}$  increased significantly after movement onset by 1.07 mmHg ( $F_{(1,5,3)} = 51.88$ ;  $P = 0.0006$ ; 95% CI: 0.8–1.34) (Figure 7b). Additional results from the end-expiratory and the inspiratory Poincaré sections have been summarized in Table 4.

### 3.3 | Comparison 3: respiratory measures upon offset of movement

The preceding analyses of changes in the respiratory measures used the onset of movement as reference. The aftereffects of movement on respiratory activity were also analysed by using movement offset as the demarcation. The first set of analyses on the IBI showed that the mean IBI did not show any significant change after movement offset ( $F_{(1,6,83)} = 4.04$ ;  $P = 0.0852$ ). However, the standard deviation of the IBI decreased significantly following the offset of movement ( $F_{(1,5,93)} = 18.62$ ;  $P = 0.0051$ ) by 0.3 s (95% CI: 0.17–0.43; Figure 8).

Respiratory measures obtained from the Poincaré section were also compared before and after movement offset. In the expiratory Poincaré section, there was no difference in Mean- $d$  across segments ( $F_{(1,6,2)} = 3.15$ ;  $P = 0.1245$ ); however, SD- $d$  was significantly lower in the segment after the movement offset ( $F_{(1,6,5)} = 12.28$ ;  $P = 0.0112$ ; Figure 9a). Similar results were obtained in the end-expiratory and inspiratory Poincaré sections (Table 5). This indicates that after movement offset, the intersections of the phase space with the Poincaré section were less variable, suggesting higher stability in the respiratory activity. In the end-expiratory Poincaré section, there was no difference in Mean- $P_{ETCO_2}$  across segments ( $F_{(1,6,5)} = 2.42$ ;  $P = 0.1668$ ). However, SD- $P_{ETCO_2}$  was significantly lower in the



**FIGURE 5** Changes in mean and standard deviation of inter-breath intervals (IBIs) and movement duration from PRE-APNOEA-ONSET to POST-APNOEA-ONSET segments (Comparison 1) in Cohort 1 (subject nos 1–9). Movement duration in PRE-APNOEA-ONSET to POST-APNOEA-ONSET segments was also calculated for a subset of apnoeas that were classified as pathological. Each coloured marker represents a single subject

**TABLE 4** Summary statistics of respiratory measures at the Poincaré sections at the onset of movement. Comparison 2: PRE-MOVEMENT-ONSET versus POST-MOVEMENT-ONSET segments

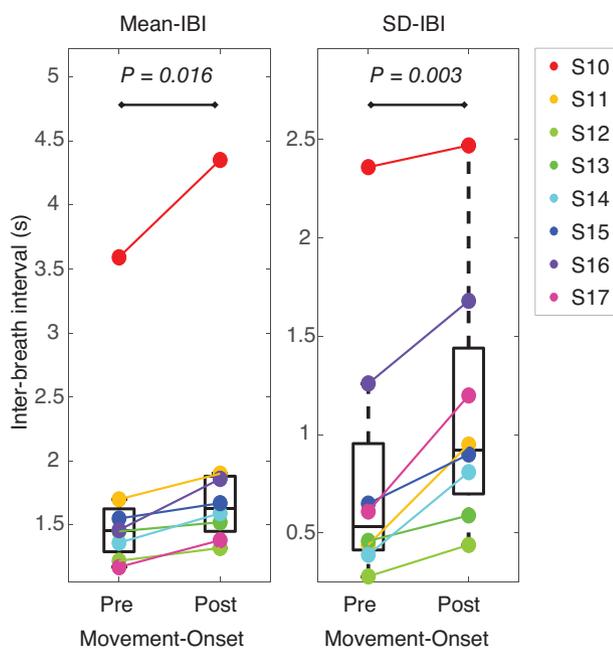
Poincaré section	Measures	PRE	POST	Diff (95% CI)	P
Expiratory	Mean- <i>d</i> (au)	19.1 ± 5.6	20.4 ± 4.9	1.2 (0.4 to 2.1)	<b>0.0428</b>
	SD- <i>d</i> (au)	9.3 ± 2.3	11.2 ± 2.9	1.7 (0.9 to 2.5)	<b>0.0059</b>
End-expiratory	Mean- <i>d</i> (au)	5.8 ± 1.1	6.2 ± 1.1	0.5 (0.3 to 0.7)	<b>0.0120</b>
	SD- <i>d</i> (au)	3.2 ± 0.6	3.6 ± 0.5	0.4 (0.3 to 0.6)	<b>0.0040</b>
	Mean- $P_{\text{ETCO}_2}$ (mmHg)	35.5 ± 5.2	35.1 ± 4.6	-0.2 (-1.0 to 0.5)	0.5934
	SD- $P_{\text{ETCO}_2}$ (mmHg)	5.0 ± 1.1	6.1 ± 1.0	1.1 (0.8 to 1.3)	<b>0.0006</b>
	Mean-IBI (s)	1.7 ± 0.8	2.0 ± 1.0	0.3 (0.1 to 0.5)	<b>0.0161</b>
	SD-IBI (s)	0.8 ± 0.7	1.1 ± 0.7	0.3 (0.2 to 0.5)	<b>0.0035</b>
Inspiratory	Mean- <i>d</i> (au)	23.0 ± 3.7	24.3 ± 3.6	1.4 (0.6 to 2.3)	<b>0.0296</b>
	SD- <i>d</i> (au)	10.7 ± 2.5	12.4 ± 2.7	1.5 (1.0 to 2.0)	<b>0.0026</b>

Values are means ± SD. *P*, overall effect as estimated by a linear mixed model. Values in bold are significant at  $P < 0.05$ . CI, confidence interval for average difference; Diff., average difference between POST and PRE segments; IBI, inter-breath interval; Mean-*d*, mean distance from reference point;  $P_{\text{ETCO}_2}$ , end-tidal  $\text{CO}_2$ ; SD-*d*, standard deviation of distance from reference point.

**TABLE 5** Summary statistics of respiratory measures at the Poincaré sections at the offset of movement. Comparison 3: PRE-MOVEMENT-OFFSET versus POST-MOVEMENT-OFFSET segments

Poincaré section	Measures	PRE	POST	Diff (95% CI)	P
Expiratory	Mean- <i>d</i> (au)	20.9 ± 3.9	19.3 ± 5.4	-1.1 (-2.3 to 0.1)	0.1245
	SD- <i>d</i> (au)	11.1 ± 2.7	9.4 ± 2.2	-1.7 (-2.6 to -0.8)	<b>0.0112</b>
End-expiratory	Mean- <i>d</i> (au)	6.3 ± 0.9	5.9 ± 1.0	-0.3 (-0.5 to -0.1)	<b>0.0440</b>
	SD- <i>d</i> (au)	3.7 ± 0.5	3.2 ± 0.6	-0.5 (-0.7 to -0.3)	<b>0.0031</b>
	Mean- $P_{\text{ETCO}_2}$ (mmHg)	35.1 ± 4.6	36.0 ± 5.5	0.7 (-0.2 to 1.6)	0.1668
	SD- $P_{\text{ETCO}_2}$ (mmHg)	6.0 ± 1.1	5.0 ± 1.3	-1.1 (-1.4 to -0.7)	<b>0.0014</b>
	Mean-IBI (s)	2.0 ± 1.3	1.8 ± 0.9	0.1 (-0.1 to 0.3)	0.0852
	SD-IBI (s)	1.2 ± 0.9	0.9 ± 0.8	0.2 (0.03 to 0.4)	<b>0.0051</b>
Inspiratory	Mean- <i>d</i> (au)	24.5 ± 2.9	23.9 ± 3.3	-0.6 (-1.4 to 0.2)	0.2573
	SD- <i>d</i> (au)	12.5 ± 2.8	10.9 ± 2.5	-1.5 (-2.3 to -0.8)	<b>0.0081</b>

Values are means ± SD. *P*, overall effect as estimated by a linear mixed model. Values in bold are significant at  $P < 0.05$ . CI, confidence interval for average difference; Diff., average difference between POST and PRE segments; IBI, inter-breath interval; Mean-*d*, mean distance from reference point;  $P_{\text{ETCO}_2}$ , end-tidal  $\text{CO}_2$ ; SD-*d*, standard deviation of distance from reference point.

**FIGURE 6** Differences in mean and standard deviation of inter-breath intervals in Comparison 2: PRE-MOVEMENT-ONSET versus POST-MOVEMENT-ONSET segments in Cohort 2 (subject nos 10–17). Each coloured marker represents a single subject

segment after the movement offset ( $F_{(1,6,19)} = 30.18$ ;  $P = 0.0014$ ; Figure 9b).

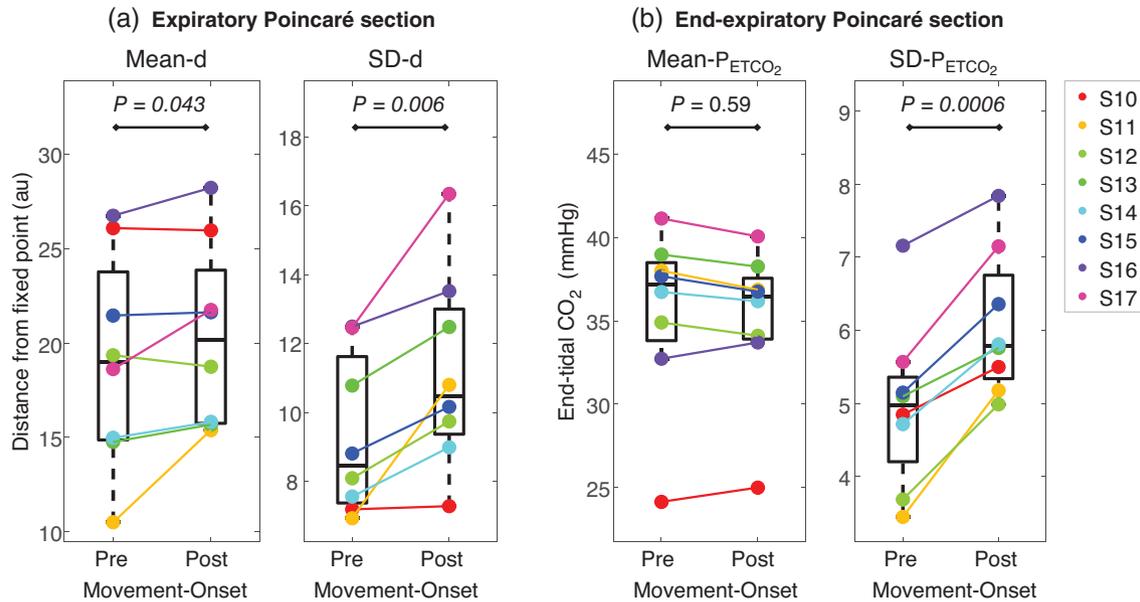
### 3.4 | Respiratory variability as a function of movement duration

Given the significant changes in respiratory variability induced by movement, we also evaluated if longer durations of movements had

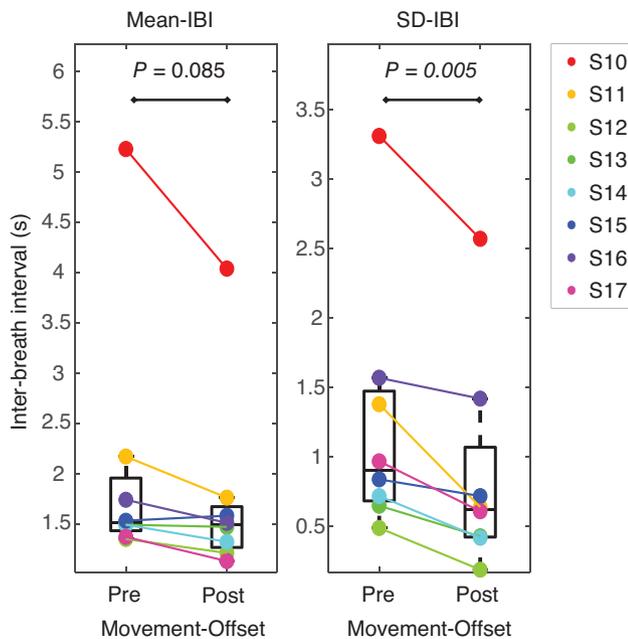
a larger effect. To quantify this effect, movement duration after onset was included in the linear mixed-effects model. The POST-MOVEMENT-ONSET variability (SD-*d*) increased significantly with increasing movement duration in all three sections. The slopes of the regressions were: expiratory Poincaré section:  $\beta = 0.12$ ; 95% CI: 0.07–0.16;  $P = 0.0028$ ; end-expiratory section:  $\beta = 0.03$ ; 95% CI: 0.01–0.04;  $P = 0.0062$ ; and the inspiratory section:  $\beta = 0.12$ ; 95% CI: 0.05–0.14;  $P = 0.0045$ . This indicates that for every 1 s increase in movement duration, variability increased by 0.12 au in the inspiratory and expiratory Poincaré sections. Respiratory variability was also analysed as a function of movement duration with movement offset as demarcation. The linear mixed-effects model showed that overall movement duration before its offset had a significant effect on the POST-MOVEMENT-OFFSET respiratory variability measure (SD-*d*) in all three Poincaré sections: expiratory ( $\beta = -0.08$ ; 95% CI: -0.13 to -0.02;  $P = 0.038$ ), end-expiratory ( $\beta = -0.02$ ; 95% CI: -0.03 to -0.005;  $P = 0.0391$ ), and inspiratory Poincaré section ( $\beta = -0.08$ ; 95% CI: -0.14 to -0.02;  $P = 0.0413$ ).

### 3.5 | Comparison 4: respiratory variability before, during and after the movement

A final analysis focused on comparing respiratory activity in segments before the onset, during and after the offset of movement. In the expiratory Poincaré section a significant difference in SD-*d* was seen across the three segments ( $F_{(2,4,94)} = 7.19$ ;  $P = 0.0344$ ; Figure 10a). *Post hoc* Tukey tests revealed that SD-*d* values increased after movement onset by 2.66 au ( $z = 4.31$ ;  $P < 0.0001$ ; 95% CI: 1.24–4.08). SD-*d* decreased again after movement had terminated by 2.89 au ( $z = -3.48$ ;  $P = 0.0015$ ; 95% CI: 0.98–4.8). Importantly, there was no difference between the PRE-ONSET and POST-OFFSET segments ( $z = 0.49$ ;  $P = 1$ ). Similar results for SD-*d* were obtained from the end-expiratory and inspiratory Poincaré sections.



**FIGURE 7** Differences in respiratory stability in Comparison 2: PRE-MOVEMENT-ONSET versus POST-MOVEMENT-ONSET segments in Cohort 2 (subject nos 10–17). Each coloured marker represents a single subject. (a) Mean (Mean- $d$ ) and standard deviation (SD- $d$ ) of the distance from reference point using Poincaré sections taken at the expiratory Poincaré section. (b) Mean and standard deviation of end-tidal  $\text{CO}_2$  obtained at the end-expiration Poincaré section. Note: subject denoted by red had lower  $P_{\text{ETCO}_2}$  values due to the use of a non-standard nasal canula for sampling of  $\text{CO}_2$ . The subject was not excluded from analysis; excluding the subject would have yielded stronger significance



**FIGURE 8** Differences in mean and standard deviation of inter-breath intervals in Comparison 3: PRE-MOVEMENT-OFFSET versus POST-MOVEMENT-OFFSET segments in Cohort 2 (subject nos 10–17). Each coloured marker represents a single subject

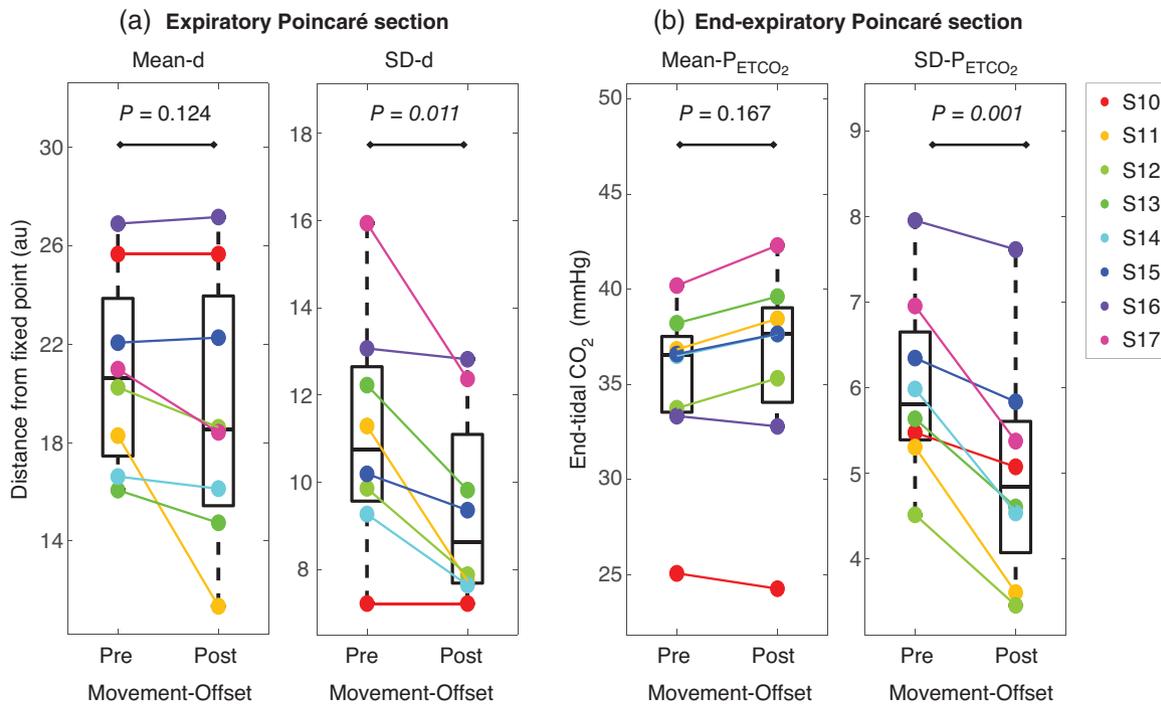
Additionally,  $\text{SD-}P_{\text{ETCO}_2}$  from the end-expiratory Poincaré section showed a significant difference was seen across the three segments ( $F_{(2,4.7)} = 19.3$ ;  $P = 0.0053$ ). *Post hoc* Tukey tests revealed that  $\text{SD-}P_{\text{ETCO}_2}$  values increased after movement onset by 1.60 mmHg ( $z = 7.23$ ;

$P < 0.0001$ ; 95% CI: 1.09–2.12).  $\text{SD-}P_{\text{ETCO}_2}$  decreased again after movement had terminated by 1.58 mmHg ( $z = -5.44$ ;  $P = 0.0015$ ; 95% CI: 0.91–2.26). Again, there was no difference between the PRE-ONSET and POST-OFFSET segments ( $z = 0.09$ ;  $P = 1$ ; Figure 10b). These findings indicate that respiratory variability measures increased with the onset of movement but returned to pre-movement onset values following the offset of movement.

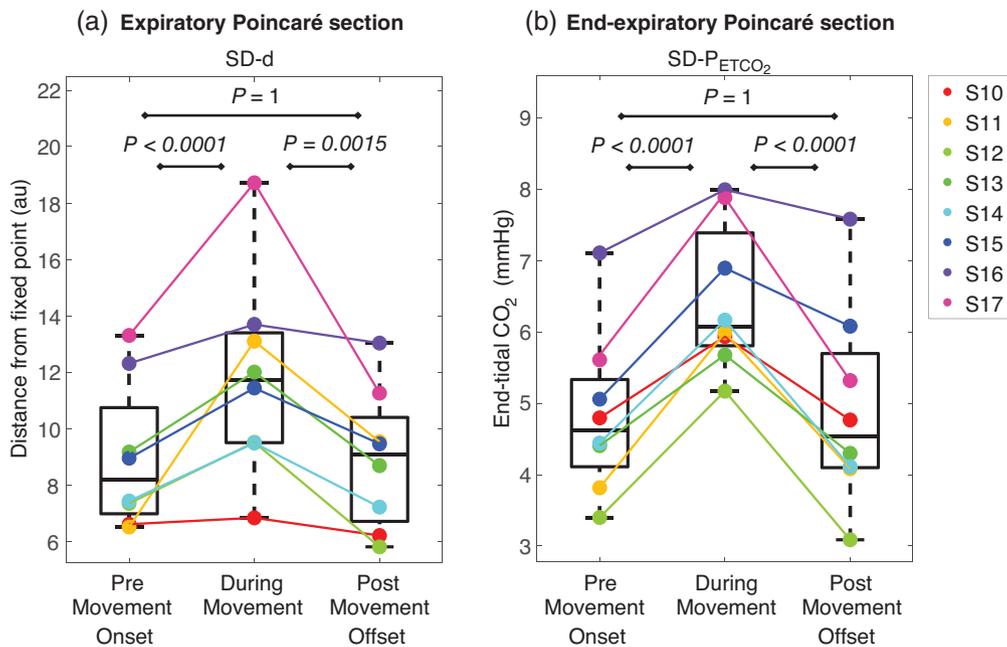
## 4 | DISCUSSION

### 4.1 | Sensory influences to the control of breathing

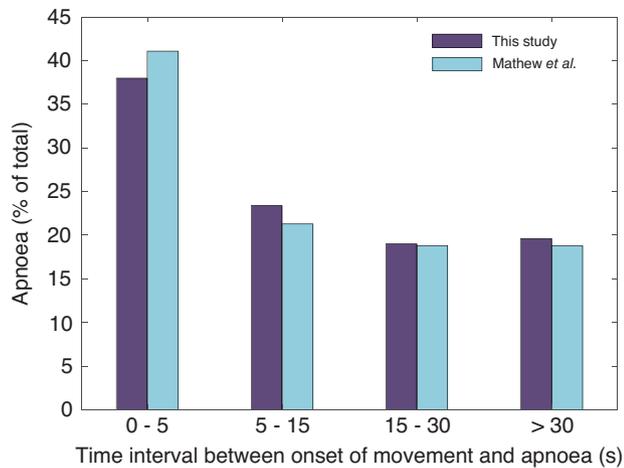
Respiratory rhythms are generated and regulated by neural circuitry distributed throughout the pons and medulla. This respiratory control network generates automatic breathing under normal conditions, but it may fail in preterm infants (Martin & Wilson, 2012). Central and peripheral chemosensitivity is a major chemical driver of respiratory neural output. Feedforward central commands from the supra-pontine regions to the locomotor and respiratory rhythm generators are also a driver of the intensity and patterns of inspiratory and expiratory activities in response to changing metabolic conditions (Eldridge et al., 1981). Feedback from peripheral sensory inputs such as mechanoreceptors in the lungs and airways as well as from proprioceptors in muscles and joints are also known to influence respiratory activity (Shevtsova et al., 2019). These feedback input signals are generated or modified by movements related to both respiration and limb movements. Therefore, this study aimed to analyse the effect of gross body movements on respiratory rhythm.



**FIGURE 9** Differences in respiratory stability for Comparison 3 (PRE-MOVEMENT-OFFSET and POST-MOVEMENT-OFFSET segments) in Cohort 2 (subject nos 10–17). Each coloured marker represents a single subject. (a) Mean (Mean- $d$ ) and standard deviation (SD- $d$ ) of the distance from reference point at the expiratory Poincaré sections. (b) Mean and standard deviation of end-tidal  $CO_2$  obtained at the end-expiratory Poincaré section



**FIGURE 10** Variability measures for Comparison 4 (PRE-MOVEMENT-ONSET, DURING-MOVEMENT and POST-MOVEMENT-OFFSET segments) in Cohort 2 (subject nos 10–17). Each coloured marker represents a single subject. (a) Standard deviation (SD- $d$ ) of the distance from reference point at the expiratory Poincaré sections. (b) Standard deviation of end-tidal  $CO_2$  obtained at the end-expiratory Poincaré section



**FIGURE 11** Time interval between onset of movements and onset of apnoeas

## 4.2 | Onset of apnoea relative to movement

The association of movement with respiratory pauses in preterm infants has previously been reported, noting a relative increase in the number of apnoeas associated with bouts of movement (Abu-Osba et al., 1982; Curzi-Dascalova & Christova-Guéorguiéva, 1983; Weintraub et al., 1994). Mathew and colleagues analysed the timing of the onsets of movements and of apnoeas in 10 preterm infants and found that 202 of 352 apnoeic events were preceded by motor activity that continued through the onset of apnoea (Mathew et al., 1991). About 41% of the 202 apnoeic episodes were preceded by movements that started 5 s or less before the apnoea. In 21% of the 202 episodes, movement began between 5 and 15 s before the onset of apnoeas. For the remaining 38% of apnoeas, movement activity started 15 s and longer before the apnoea.

To compare our data with Mathew et al.'s results, we replicated their method for Cohort 1. First, all apnoeic episodes from infants 1–9 were identified. As in Mathew et al., we limited the analysis to only those apnoeas that had movement activity preceding the apnoeic onset and continuing with it. We then computed the time intervals between the onsets of apnoeas and the movement that preceded and continued during the apnoeic event, at least until the apnoea began. These time intervals were classified into bins of 0–5 s, 5–15 s, 15–30 s and >30 s. We found that 158 of the 370 apnoeic events were concomitant with movement activity; 60 (38%) of those 158 events began within 5 s of movement onset; 37 (23%) of the 158 events occurred between 5 and 15 s of movement onset (Figure 11).

Although our results replicated those of Mathew and colleagues, their analysis provided a limited picture of the impact of movement on breathing because it excluded apnoeas that were not concomitant with movement. Also, while the analysis considered the temporal relation between the onsets of movements and the concomitant apnoeas, it omitted the effects of any preceding movement segments. These criteria constitute a selection bias and might have skewed their results. Our analysis considered all 370 apnoeic events, irrespective

of their temporal association with movement. The findings of our study revealed longer movement durations before apnoeic events, including pathological apnoeas, and therefore suggests that movement and apnoeas are not only closely associated, but also causally related. To further scrutinize this association, subsequent analyses investigated the changes in respiratory activity around an isolated movement activity.

## 4.3 | Changes in respiratory features following onset and offset of movement

The timing of breaths often exhibits wide variations that are of clinical importance when associated with prolonged apnoeas and hypoxia. Our findings suggest that movement causes both prolongation and increased variability of IBI, suggesting a destabilizing effect of movement on respiratory rhythm. Experimental and computational studies support the idea that non-linear input–output properties at many levels of organization could destabilize breathing in preterm infants (Khoo, 2000). Possible factors are an increased loop gain of chemical feedback (Carley & Shannon, 1988), unstable interactions with the neural systems underlying sleep and arousal (Lehtonen & Martin, 2004), and intrinsic properties of the immature central respiratory oscillator (Del Negro et al., 2002; Frey et al., 1998; Paydarfar & Buerkel, 1995). Changes in the variability of respiration induced by movement likely reflect its maturity and functional integrity (Khoo, 2000), related to both central interactions with the brainstem respiratory network and feedback effects from mechanoreceptors, for example Type III and IV afferent inputs from limb muscles activated during movement (Amann et al., 2010).

Linear signal processing methods only provide limited information since they ignore any non-stationarities and other dynamics of the time series. Non-linear methods that allow analysis of the dynamic characteristics of the respiratory drive are likely to uncover more information. Studies in deafferented neonatal and adult animals support that the neural respiratory rhythm is generated by a non-linear limit cycle oscillator, subject to noisy perturbations arising within or impinging upon the oscillator (Paydarfar & Buerkel, 1995). In infants, the dynamics of breathing during quiet sleep can best be described as a noise-driven non-linear system with a two-dimensional periodic orbit (Small et al., 1999). Several previous studies have applied non-linear methods such as calculating the Lyapunov exponent, correlation dynamics and Poincaré maps to study the dynamics of the respiratory system (Donaldson, 1992; Ruan et al., 2009; Small et al., 1999). We applied Poincaré sections that quantified the variability of the signal in a reconstructed phase space to assess the role of movements for the neuro-respiratory controller.

Upon the onset of movement, the Poincaré section revealed a significant increase in both deviation and variability around the reference point. This marked change was similarly present in the expiratory, end-expiratory and inspiratory Poincaré sections. After the end of the movement, the variability indices returned to the pre-movement values, thus indicating the presence of a stable attractor

at baseline. Furthermore, the increase in variability depended on the duration of the movement. This change in variability suggests that a negative feedback loop was responsive to movement perturbations and scaled with movement duration to stabilize the system. Previous research demonstrated that preterm infants have an elevated loop gain due to the immaturity of the controller compared to healthy controls (Carley & Shannon, 1988; Edwards et al., 2018; Terrill et al., 2015). It is possible that a higher gain in the feedback loop may cause higher variability that can in some cases lead to apnoeas. This elevated loop gain along with increasing variability and decreasing levels of carbon dioxide introduces non-linearities in the feedback, making non-linear methods more appropriate for the analysis of the respiratory system (Khoa, 2000).

Besides the feedback mechanism, there is also evidence of feedforward control of respiration during movement. This is based on observations of increases in respiratory activity in decorticate cats when feedback mechanisms were eliminated (Eldridge et al., 1985; Eldridge et al., 1981). In adults the feedforward central mechanism plays an important role in the increase in ventilation during exercise and is known as exercise hyperpnoea. These descending central commands are responsible for a parallel drive from the hypothalamic (Eldridge et al., 1981), mesencephalic (Gariépy et al., 2012), or pontomedullary (Romaniuk et al., 1994) locomotor region to the respiratory and locomotion controllers. Although these commands increase ventilation in adults during movement, our results show a drop in the respiratory rate following the onset of an isolated movement activity (Figure 5b). We speculate that in preterm infants this effect could be a result of the underdeveloped neural substrates from the supra-pontine regions to the respiratory controller. White matter development and myelination in these regions is not complete during the preterm period (Dubois et al., 2014). An alternative source of central inhibition of breathing by movement could be the neural circuits that are associated with the oxygen conserving response (Panneton, 2013). Of note, inhibition of breathing in exercising adults and in infants can conserve cerebral and cardiac  $O_2$  by elevating flow to these organs while reducing blood perfusion in the viscera and muscles (Lindholm et al., 1999; Lobban, 1995). The same neural circuits that mediate the dive reflex have also been hypothesized to cause sudden infant death syndrome as they can trigger apnoeas and bradycardias (Lobban, 1991; Maturri et al., 2005). The dive reflex is typically elicited by trigeminal stimulation; however, we speculate that movement might activate a component of the underlying central neural circuitry causing an inhibition in breathing.

Another factor that could cause respiratory instability is a smaller  $CO_2$  reserve, defined as the difference between the eupnoeic and apnoeic arterial  $P_{CO_2}$  threshold ( $P_{aCO_2}$ ) (Katayama et al., 2007). The  $CO_2$  reserve is known to be around 1.3 mmHg in preterm infants, which is small relative to adults (Khan et al., 2005). Therefore, the relative proximity of the eupnoeic and apnoeic threshold could easily lead to unstable breathing. When this is combined with higher non-linear feedback gains, it is conceivable that apnoeas are elicited. Even though our study did not have access to the arterial blood gases, the end-tidal partial pressure of carbon dioxide ( $P_{ETCO_2}$ ) obtained from

the peak of the exhaled  $P_{CO_2}$  waveform is well correlated with the arterial partial pressure of carbon dioxide,  $P_{aCO_2}$  (Wu et al., 2003). Results showed that at the end of expiration, there was a significant increase in the variability of  $P_{ETCO_2}$ , including  $P_{CO_2}$  following the onset of movement. A higher feedback gain combined with an increased occurrence of hypoventilation or hyperventilation (increased IBI) could cause a higher variability in  $P_{CO_2}$ . Persistent fluctuations of  $P_{aCO_2}$  may cause central apnoeas in preterm infants given their narrow  $CO_2$  reserve if  $P_{aCO_2}$  falls below the apnoeic threshold. After the end of movement, variability of the distance from the reference point ( $SD-d$ ) and  $P_{ETCO_2}$  variability were significantly lower than during movement. Yet, they were higher than the pre-movement values, although this difference was not significant, potentially suggesting that there is a delay to return to the baseline values. However, we were unable to quantify this delay with the metrics from the available non-invasive data.

In summary, our findings indicate that after a period of rest, an onset of movement induced a significant increase in variability of IBIs,  $P_{ETCO_2}$  and the dynamic measures of the respiratory controller. The system returned to a baseline level of variability after the end of the movement. However, it is important to note that movement is not the sole source of respiratory variability, since there are bouts of increased variability without a preceding movement.

#### 4.4 | Questions for future research

This study explored the relation between spontaneous movement activity and ventilatory instability. Infant movement was measured using a wavelet-based algorithm that quantified the movement-induced distortions in the PPG signal (Zuzarte et al., 2019). While the algorithm obtained a reliable estimation of movement duration, it was unable to capture any qualitative features, such as how forceful or how slow movements were, or which limb was moving. Note though that small limb movements even when remote from the sensor were measured. Classification of certain types of activity, specifically sighs which could change breathing patterns, was also not available. Any movement detected by the wavelet PPG algorithm was included in all analyses.

Aside from bodily movements, there are also other factors that could have induced unstable breathing and apnoea. Examples are fluctuations in peripheral chemoreceptor sensitivity, obstruction of upper airways and transitions between different sleep stages, including interaction of all these during arousal. Differences between stages of sleep and transitions from sleep to wakefulness could have a disruptive effect on breathing. However, this study did not use a full polysomnography to assess sources of variability arising from different sleep states. Although video recording was available, the video camera was oriented to optimize viewing of the limbs and trunk of the infant. The face was not a part of the video's field of view and therefore did not allow reliable behavioural scoring of sleep and wake states.

Another factor for respiratory instability are interindividual differences in ventilatory response to arousal during sleep-wake

transitions (Horner et al., 2001). A greater ventilatory response in some subjects could lower  $P_{aCO_2}$  below the apnoeic threshold and thereby cause periodic breathing by an increase the frequency of occurrence of central apnoeas (Xie et al., 1994). More information about whether an apnoea was terminated by a caregiver or self-resolved by the infant without any external stimulation would be of benefit in studying the role of movement on periodic breathing and recurrent apnoeas.

Incidences of apnoeas in preterm infants also decline by gestational age, as the infants mature and gain in body weight. In the NICU, preterm infants are often administered methylxanthines, such as caffeine, which reduce the frequency of apnoea. Incidences of apnoeas also vary relative to position of the infant and towards the end of feeds. Our previous work continuously quantified infant movement in the NICU and revealed that the distribution of movement duration in preterm infants changes as they get older (Zuzarte et al., 2020).

Hence, given these additional considerations, caution should be exercised when directly extrapolating these findings to apnoeas of prematurity in clinical practice. Future longitudinal studies with a larger number of preterm infants could help corroborate the present findings as well as study apnoeas as a result of the combined effect of post-menstrual age, body weight, sleep state, caffeine, feeds, infant position and spontaneous movement.

Finally, the finding that spontaneous bodily movement precedes apnoeic episodes suggests that movement features could predict subsequent apnoeic events in individual infants using a statistical machine learning framework, which was previously supported in a preliminary study (Williamson et al., 2013). We speculate that movement-induced respiratory variability is an important physiological feature that precedes apnoeic episodes, and inclusion of measures related to respiratory variability will enhance the accuracy of predictive algorithms.

## 5 | CONCLUSION

Spontaneous movements in preterm infants can influence the activity of the respiratory centre. Our findings suggest that the degree of perturbation from movement to respiration can indicate the maturity of the neuro-respiratory system. These findings could be used for a novel index of maturation, where the interaction between movement and respiration could be analysed over several weeks of prematurity. Furthermore, movement could be used as a window for risk-stratification and as a predictive measure of apnoeas and bradycardias.

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## COMPETING INTERESTS

The authors declare that they have no competing interests.

## AUTHOR CONTRIBUTIONS

Data collection was conducted at the University of Massachusetts Memorial Healthcare, Worcester, MA. I.Z. and D.P. conceptualized and designed the work. I.Z. collected the data. I.Z., D.P. and D.S. analysed and interpreted the data. I.Z., D.P. and D.S. drafted and revised the manuscript critically for important intellectual content. All authors approved the final version of the manuscript, and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

## DATA AVAILABILITY STATEMENT

All data points are plotted within the figures of the manuscript. Any additional data that support the findings of this study are available from the corresponding author upon request.

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