

# Arousal has no effect on non-nutritive breathing–swallowing coordination during the first year of human life

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## Abstract

Although the brainstem plays an important role in breathing–swallowing coordination (BSC), the role of suprabulbar structures is ill defined. Given the known decrease in global cerebral activity during sleep, the sleep–wake paradigm was used to elucidate suprabulbar influences. Non-nutritive BSC of 10 healthy human infants was monitored longitudinally during wakefulness and sleep from birth to 1 year of age. Time-locked recordings of submental muscle activity, nasal airflow, and thyroid acoustics enabled the categorization of swallows depending on the preceding and following respiratory phase. In contrast to the change in the overall pattern of BSC with age, and despite well-known marked postnatal cortical development over this time, no arousal-related differences were seen during the first year of life. This most likely reflects complete brainstem control of non-nutritive BSC in infants.

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## 1. Introduction

Breathing and swallowing are intricately coordinated, life-sustaining functions that share several anatomical structures and cranial nerves. Non-nutritive breathing–swallowing coordination (BSC) is considered to be an important feature of the laryngeal chemoreflex, since non-nutritive swallows occur in response to peripheral sensory stimulation (Praud and Reix, 2005). Given the importance of coordinating these two functions, clarification of central control is imperative. The brainstem is recognized as providing the primary role in the control of BSC (Miller and Sherrington, 1916; Smith et al., 1989; Lewis et al., 1990; Dick et al., 1993; Feroah et al., 2002; Saito et al., 2002) but given the cortical involvement in the control of both breathing (Davenport and Reep, 1995) and swallowing (Martin and Sessle, 1993), it would seem likely that

the cerebral cortex would also play a substantial role in BSC. Recent research indicates that the developing cerebral cortex may have increasing control over infant *nutritive* BSC during the first year of life (Kelly et al., 2007c), but whether the same applies to *non-nutritive* BSC remains to be seen.

The comparison of non-nutritive BSC during wakefulness and sleep provides a suitable paradigm in which cortical influence over non-nutritive BSC may emerge (Kelly et al., 2007a). Evidence from positron emission tomography and functional magnetic resonance imaging studies indicates relative cortical quiescence during sleep; “Widespread deactivation characterizes the wake-to-NREM-sleep transition, whereas selective activation is seen in REM sleep” during which “. . .the dorsolateral prefrontal cortex remains conspicuously deactivated” (review by Hobson and Pace-Schott, 2002, p. 691). During sleep, particularly non-rapid eye movement sleep, respiration is under automatic control, whereas during wakefulness, cortical activation can supersede this automatic control (Moss, 2005). Thus, sleep provides a condition in which cortical activity is minimal and its comparison to wakefulness provides the opportunity for

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potential cortical non-nutritive BSC influence to be elucidated. A difference in non-nutritive BSC between wakefulness and sleep could therefore be attributed to differing degrees of cortical input, thereby highlighting cortical control. Using a similar paradigm in adults, a recent pilot study reported that the pattern of BSC during volitional awake swallowing differs from that during reflexive sleep swallowing (Kelly et al., 2006a). Similarly, in newborn lambs, BSC during quiet sleep differs to that of active sleep and wakefulness suggesting level of arousal and therefore the centres controlling sleep have some impact on those centres that are responsible for BSC (Reix et al., 2003).

The difference in non-nutritive BSC between wakefulness and sleep may be evident even as early as the first few days of human life despite cortical immaturity. This argument is strengthened by early cortical influence over respiration and swallowing. Lesion studies in newborn animals support suprabulbar influence of respiration (review by Neubauer et al., 1990) and suprabulbar damage in human neonates may result in feeding and/or swallowing disorders (Sarnat, 1989). Thus, despite being undeveloped, the cortex may exert notable influence over breathing and swallowing, and therefore non-nutritive BSC as well. It might also be expected that differences between sleep and wake conditions would become increasingly apparent as a result of cortical maturation. During postnatal development of the central nervous system, there is substantial synaptogenesis (Huttenlocher and Dabholkar, 1997) and myelination of the cortex (Gibson, 1991) and corticobulbar tracts (Sarnat, 1989), thus descending suprabulbar (including cortical) input, particularly during wakefulness, is likely to increase.

We hypothesized that non-nutritive BSC during wakefulness would differ from that during sleep in newborns, and that this difference would become increasingly apparent as the infants matured. Given that the firing patterns of specialized neurons in the brainstem may account for the preferential swallow–respiratory pattern of BSC in humans (Saito et al., 2003), it is expected that under conditions of heightened cortical activity that this pattern is altered. The present study is the first to compare BSC under non-nutritive swallowing conditions of sleep and wakefulness to examine the potential role of the cortex in the BSC of human infants born at term. Wilson et al. (1981) monitored breathing and non-nutritive swallowing during sleep and wake conditions in preterm infants and reported that more swallows occurred during respiratory pauses than during regular breathing. Unfortunately, they did not provide an analysis of the proportional distribution of swallows occurring before or after expiration or inspiration and nor did they differentiate between sleep and wake conditions. Similarly, Don and Waters (2003) monitored the breathing and swallowing of sleeping infants but did not specifically address the coordination of inspiration and expiration with swallowing but rather reported on the interaction and incidence of apnea, arousal, and swallowing. They found that swallows occurred with approximately one third of arousals and apneas. Nixon et al. (2008) investigated breathing–swallowing patterns of preterm infants at term age during sleep and wakefulness and found their patterns were remarkably consistent across the two

conditions. Whether the same applies to term infants has yet to be established. The primary aim of the present study was to compare BSC during wakefulness (Kelly et al., 2007b) to that of sleep in healthy term infants. We also wished to determine whether BSC changes as infants mature and whether the changes are dependent on level of arousal.

## 2. Methods

This longitudinal study was approved by the Canterbury Regional Health Ethics Committee.

### 2.1. Subjects

Ten healthy term neonates were recruited into the study via written consent from their parents. The eight female and two male neonates did not meet any of the predetermined exclusion criteria: born to mothers with prenatal maternal complications, were born at or below 37 weeks gestational age, presented with Apgar scores at or below ‘6’ at 5 min after birth (i.e., outside of normal limits, Francis et al., 1987), reported medical complications at birth (e.g., signs of neurological or cardio-respiratory disorders or disease). Throughout the duration of the study, the infants’ development was monitored (and deemed within normal limits) via parental reports of good general health at each visit, measures of weight, head circumference, the presence and/or absence of certain age-appropriate reflexes and, from 1 month of age, the completion of the Denver Developmental Screening Test II. This latter test is a reliable and valid standardized tool (Frankenburg and Dodds, 1992) and is the tool of choice for pediatricians who routinely use formal screening assessments of development (Sand et al., 2005).

### 2.2. Equipment

Time-locked recordings of submental muscle activity (via submental surface electromyography, SEMG), nasal airflow (via a nasal cannula), and thyroid acoustics (via a laryngeal microphone) (Kelly et al., 2006b, 2007b,c) were captured by the Kay Elemetrics Swallowing Workstation (Model 7100, Kay-PENTAX™, Lincoln Park, NJ); equipment used in other swallow–respiratory studies (e.g., Butler et al., 2004; Kelly et al., 2006a). The bipolar submental SEMG was recorded from two electrodes. (Thought Technology Triode™, Thought Technology, Montreal, Canada) positioned over the submental muscles with the reference electrode positioned on the forehead. The SEMG signal was amplified, bandpass filtered (50–220 Hz), rectified, low-pass filtered at 3 Hz, and, along with nasal airflow, digitized at 250 Hz. Following the performance of recommended calibration procedures, infant-size nasal prongs were situated and secured at the nares. The laryngeal microphone was positioned lateral to the thyroid, and held or taped in position with surgical tape. The microphone was a modified omnidirectional condenser microphone (bandwidth 50–12,500 Hz) connected to a preamplifier (Rolls mini-mic MP13). The acoustics signal was sampled at 4000 Hz.

### 2.3. Procedure

Breathing–swallowing coordination was monitored under two conditions determined by the investigator’s subjective observations: wakefulness and daytime sleep. In the former condition, the infants were deemed fully alert as per investigator observations of intermittent or continuous body movements while eyes were open and the infants were reacting to visual, auditory, and/or tactile stimuli during interaction with the caregiver or investigator. Recording continued for as long as the infant tolerated the procedure or parental time permitted. Recording was temporarily stopped when pacifiers were required or if mouth-breathing (during mouth-opening in the absence of a respiratory waveform) was suspected based on the investigator’s observation. Given that the effect of body position on infant BSC is unknown, attempts were made to keep the infants in a supine body position in both conditions and across assessment ages; this proved somewhat difficult from 9 months of age as infants became more mobile and less tolerant of equipment placement. Sleep,

characterized by closed eyes in the presence or absence of regular breathing and small body movements (Precht, 1974) was subjectively monitored by the investigator and confirmed by failure of the infant to respond to auditory stimuli. Recordings were made at the following times: within 48 h after birth, at 1, 2, 3, and 4 weeks, 2, 3, 6, 9, and 12 months of age. Early recording sessions took place at a regional birthing unit while later sessions were carried out at the Institute. Each recording session involved the assessment of BSC during both sleep and wakefulness (not necessarily in that order) and lasted approximately 5 h in total, although occasionally infants had to return to the birthing unit or Institute the following day if both conditions could not be assessed within parental time constraints. The number of swallows attained in each session was governed by three phenomena: infant 'cooperation', duration of sleep, and, to a lesser extent, parental availability constraints.

#### 2.4. Data analysis

Swallows were distinguished by characteristic simultaneous bursts of SEMG and acoustic activity in the absence of nasal airflow. Each swallow was classified according to the phase of respiration preceding and following swallowing apnea: inspiration–inspiration (II), inspiration–expiration (IE), expiration–expiration (EE), expiration–inspiration (EI), and mid-pause (P). Swallows executed during respiratory pauses and consecutive swallows, between which no respiration occurred, were classified as 'mid-pause'. The number of swallows in each respiratory-phase category was divided by the total number of swallows obtained for each infant for each condition at each age, and entered into the database.

#### 2.5. Data processing and preparation

On three occasions, behavioral constraints (such as lack of cooperation, decreased tolerance of equipment placement, or failure to sleep) of three infants at different ages made recording impractical; twice during wakefulness and once during sleep. Hence, these infants were allocated the percentage frequency of occurrence for all respiratory-phase categories for the relevant condition and at the relevant age from another infant that was deemed to be their 'closest match' (Elliott and Hawthorne, 2005). Also, few swallows were obtained in each respiratory-phase category in the latter age groups, particularly for the sleep condition. This could be attributed to reduced duration of day-time sleep and possibly a reduction in the frequency of swallows with increasing age, although these were not specifically examined. Thus, for more robust statistical analysis, data from consecutive ages were amalgamated (regrouped). The amalgamation process involved calculating the mean percentage frequency across two or more age groups for each respiratory-phase category. Thus, the amalgamation created four new age-groups:  $\geq 48$  h, 1–4 weeks (mean of 1, 2, 3, and 4 weeks), 2–3 months (mean of 2 and 3 months), and 6–12 months (mean of 6, 9, and 12 months).

All statistical analyses were performed on the four new age-groups using the Statistical Package for the Social Sciences (SPSS, version 11.5, 2002) and a  $p$ -value  $< 0.05$  was adopted. A random 18 assessments (17% of all sleep and wake swallows) were reanalyzed in order to determine intra- and inter-rater reliability. Given that the data consisted of repeated samples of the BSC of the same individuals, repeated-measures ANOVA was chosen to determine whether BSC was influenced by condition and whether this influence changed as the infants matured. The effects of level of arousal (condition) and age on BSC (proportional distribution of swallows within the 5 respiratory-phase categories) were tested using repeated-measures ANOVA. Condition, age, and respiratory-phase category were entered as within-subject effects. The sphericity assumption for repeated-measures was tested using Mauchly's test (Mauchly, 1940) and, when not met, the Greenhouse-Geisser correction was applied. Significant main or interaction effects were further explored via Fisher's Least Significance Difference (LSD) tests (Fisher, 1935).

### 3. Results

Intra-class correlation coefficients identified satisfactory inter- and intra-rater reliability for respiratory-phase categorization (ICC = 0.949 and 0.977, respectively).

A total of 7597 non-nutritive swallows were identified and included in the analysis: 4094 wake (Kelly et al., 2007b) and 3503 sleep. Amalgamation achieved a minimum of 10 swallows in each respiratory-phase category for both conditions.

Repeated-measures ANOVA revealed no main effect of age or level of arousal but there was a respiratory-phase category effect [ $F(4, 36) = 46.1, p < 0.001$ ]. The proportional distribution of swallows in each respiratory-phase category was as follows: EE ( $M = 33.3\%$ , S.E. = 2.1%), P ( $M = 25.0\%$ , S.E. = 1.5%), IE ( $M = 23.0\%$ , S.E. = 1.2%), EI ( $M = 13.4\%$ , S.E. = 1.5%), and II ( $M = 2.4\%$ , S.E. = 0.7%). Further exploration of the respiratory-phase category effect using Fisher's LSD testing revealed significant differences between: II and IE, II and EE, II and P, and EE and EI (Fig. 1).

Repeated-measures ANOVA revealed no interactions between respiratory-phase category and level of arousal, or age and level of arousal and, more importantly, no interaction of age, condition, and respiratory-phase category [ $F(3.62, 32.6) = 1.35, p = 0.272$ ]. As there was no overall age effect, the means and standard error scores of the each respiratory-phase category during wakefulness and sleep across all ages are presented in Table 1.

There was an interaction between age and respiratory-phase category [ $F(3.65, 32.8) = 9.39, p < 0.001$ ]. In order to further assess changes as a function of age within each respiratory-

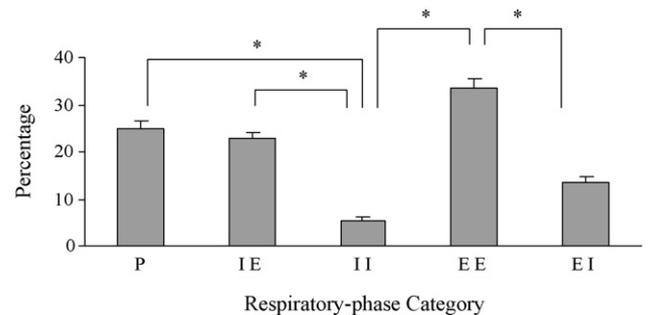


Fig. 1. Proportional distribution of swallows (mean percentage and standard error score) in each respiratory-phase category. Note: \* = significant effect ( $p < 0.05$ ) determined by Fisher's LSD testing, II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration, P = mid-pause.

Table 1

Proportional distribution (mean percentage and standard error score) of swallows in each respiratory-phase category for both conditions across all ages

Respiratory-phase category	Swallowing condition			
	Wake		Sleep	
	<i>M</i>	S.E.	<i>M</i>	S.E.
II	5.4	0.6	5.4	0.9
IE	23.8	1.5	22.2	1.9
EE	34.8	2.6	31.8	2.3
EI	12.6	1.2	14.3	1.9
P	23.5	2.2	26.5	1.3

Note: Results based on amalgamated data, *M* = mean, S.E. = standard error, II = inspiration-SA-inspiration, IE = inspiration-SA-expiration, EE = expiration-SA-expiration, EI = expiration-SA-inspiration, P = mid-pause.

phase category, five separate repeated-measures ANOVAs were conducted for each respiratory-phase category. Age effects were found only for II [ $F(3, 27) = 4.0, p = 0.018$ ], IE [ $F(3, 27) = 4.87, p = 0.008$ ], EI [ $F(3, 27) = 6.38, p = 0.002$ ], and P swallow proportions [ $F(3, 27) = 23.5, p < 0.001$ ]. The LSD test was applied to data on consecutive ages to explore the nature of these age effects. This revealed a decrease in P swallows between the 1–4 weeks and 2–3 months. There were no differences between consecutive ages for II, IE, or EI proportions and, hence, the age effect is due to the gradual increases in proportional distribution of these categories.

## 4. Discussion

### 4.1. Main findings

This is the first longitudinal study to investigate the impact of arousal on the coordination of breathing and non-nutritive swallowing in healthy infants up to the age of 12 months. Non-nutritive breathing–swallowing coordination during sleep and wakefulness did not differ at any point in the first year of life. Thus, our hypotheses that non-nutritive BSC during wakefulness would differ from that during sleep in newborns, and that this difference would become increasingly apparent as the infants matured were rejected. As wakefulness is associated with heightened cortical activity this suggests that, at least in the first 12 months, the cortex has limited or no influence on non-nutritive BSC. The presumed corollary of this is that the brainstem exerts essentially full control over the coordination of breathing and non-nutritive swallowing during the first year of life.

The similarities of the means and standard error scores between conditions suggest that suprabulbar input into non-nutritive BSC is completely absent or, at most, minimal and/or inconsistent. It is possible that with age the developing cortex increases its contribution to BSC and that sometime beyond the first year this becomes evident. This would be supported by prior research that suggests level of arousal influences BSC in adults (Nishino and Hiraga, 1991; Kelly et al., 2006a). Thus, the absent condition effect in the present study may reflect immature infant cortices and/or corticobulbar tracts. Small increases in infant cortical activity during wakefulness might therefore be insufficient to alter BSC. As substantial cortical myelination (Sarnat, 1989; Sowell et al., 2003; Nagy et al., 2004) and organization (Brown et al., 2005; Casey et al., 2005) continues beyond the first year of human life it is likely that descending input increases after 1 year of age, beyond the observation period of this study.

Alternatively, it is also possible that the degrees of cortical activity between wakefulness and sleep were similar and since both sleep and wake swallows were spontaneously performed, the degree of cortical input into the initiation of swallowing may have been similar. Prior research indicates that in adult humans the degree of cortical input into governing a volitional swallow is greater than that required during spontaneous/reflexive swallows in awake individuals (Kern et al., 2001). More recent research has revealed that adult BSC differs

between volitional and non-volitional (awake and sleep) swallowing conditions (Kelly et al., 2007a). Thus, further research comparing BSC under volitional and reflexive swallowing conditions using objective quantification of the degree of cortical activity is required, such as by electroencephalography (review by Grigg-Damberger et al., 2007).

The argument for essentially full control of non-nutritive BSC by the brainstem during the first year of life is strengthened by the pattern of maturation of BSC seen in the present study which can be largely attributed to changes in the brainstem. The present study demonstrates that changes in non-nutritive BSC during the first year are primarily the result of a gradual decrease in the proportion of P swallows. The findings of three earlier studies suggest that brainstem maturation plays a key role in the maturation of respiratory and swallowing-related phenomena in the human or animal model. First, brainstem maturation coincides with a decrease in the frequency of prolonged respiratory pauses in preterm infants, suggesting a strong relationship between the two (Henderson-Smart et al., 1983). Second, the firing patterns of respiratory and swallowing nerves during reflexive swallowing in decerebrate animals differs between kittens and adult cats suggesting that postnatal maturation involves increasing central differentiation of the brainstem control of breathing and swallowing (Sumi, 1967). Third, elicited pharyngeal swallows may result in a prolonged cessation of respiration in newborn animals, a phenomenon that declines with age such that swallowing and inhalation or exhalation are alternated (Harned et al., 1978). This, too, may explain the increasing fusion of respiration and swallowing and subsequent decline in multiple swallows performed in quick succession (P swallow category) with age in the present study. Thus, the decline of P swallow proportions in the present study may reflect the substantial brainstem contribution to BSC. In combination with the absent effect of increased level of arousal and subsequent heightened cortical input, this provides support for isolated brainstem control of non-nutritive BSC.

### 4.2. Clinical implications and future research

Given that non-nutritive swallowing may be an essential component of infant airway protection (Thach, 2001), describing its coordination with breathing is imperative. Our data are the first to provide this description in healthy term infants between the ages of 0–12 months and, as a result, indirect comparison to patient populations can be made. Prior research suggested that preterm infant non-nutritive BSC is largely characterized by a tight association between swallowing and respiratory pauses or apneas (Wilson et al., 1981; Menon et al., 1984). In contrast, while swallows occur during respiratory pauses at term age in preterms (Nixon et al., 2008) and even less often in term infants (present study), it is not the predominant feature of BSC in either group. Specifically, our data demonstrate that the majority of non-nutritive swallows of term infants occur immediately prior to expiration (IE and EE categories). Future research is encouraged to make direct comparisons between patient groups

and normal controls in order to also establish the definitive characteristics and potential implications of ‘disordered’ non-nutritive BSC.

The results from our study suggest that the cortex has limited influence on non-nutritive BSC. Future research should aim to confirm these findings in a larger cohort of infants and to target night-time sleep so as to obtain a larger number of swallows from each infant. This might identify further sleep–wake differences, particularly in the older age-groups where data from our study were sparse. Furthermore, a larger cohort and increased duration of recordings to obtain a greater number of swallows would also eliminate the need to amalgamate the data from certain age-groups, as in the present study. Research incorporating objective quantification of cortical activity (e.g., EEG, EPs, fMRI) during wakefulness and sleep would also help confirm our findings. Similarly, comparison of the BSC of infants with isolated brainstem or cortical lesions to healthy controls should confirm that the brainstem does indeed play a much greater role than the cortex in non-nutritive BSC. Also, a more detailed analysis of respiratory function such as tidal volume and rate may determine to the extent to which the maturation of the respiratory system contributes to the maturation of infant non-nutritive BSC. Finally, although rates of swallowing were not quantified in our study, it was clear that these declined dramatically with age. Quantification of declining rate of swallowing and its impact on BSC deserves investigation.

#### 4.3. Conclusions

Our study is the first to demonstrate that during the first year of human life non-nutritive BSC changes but at no point is there a difference between sleep and wakefulness. Given the considerable cortical activity associated with wakefulness, the similarity in the pattern of BSC between these two conditions suggests absent or limited cortical influence over BSC and, therefore, essentially complete brainstem control.

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