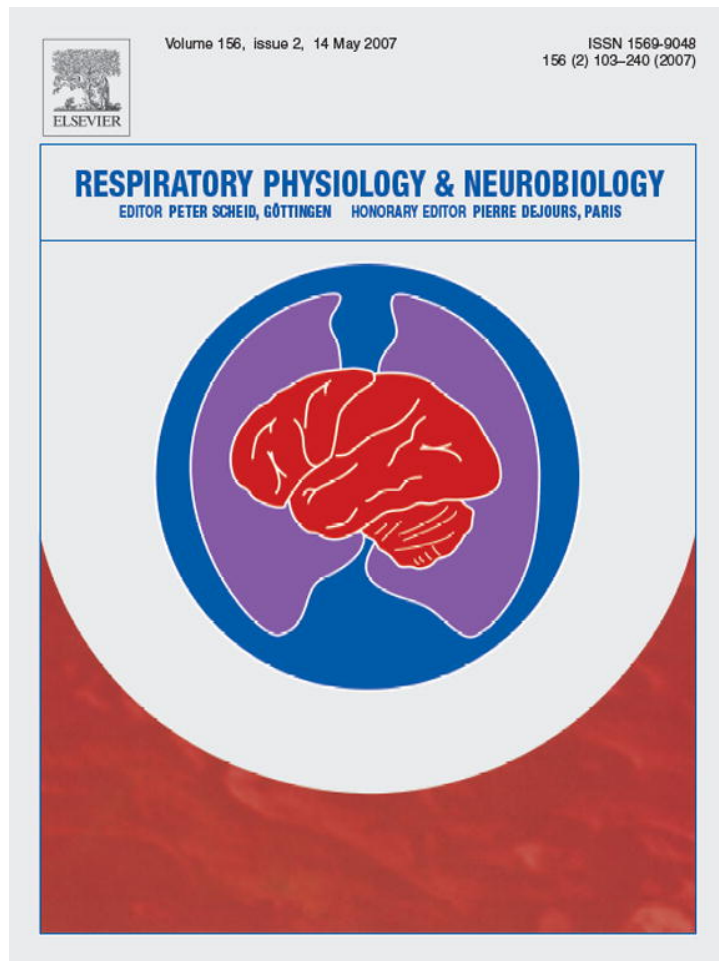


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The early impact of feeding on infant breathing–swallowing coordination

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Abstract

This longitudinal study assessed the coordination of nutritive and non-nutritive swallowing with breathing in 10 healthy term infants from birth to 1 year of age. Swallows were classified into five respiratory-phase categories: mid-inspiration (II), mid-expiration (EE), inspiratory–expiratory cusp (IE), expiratory–inspiratory cusp (EI), and mid-pause (P). Breathing–swallowing coordination differed markedly between the two swallowing conditions, especially between 2 weeks and 2 months. Significant condition effects were found in up to four respiratory-phase categories (II, IE, EI, and P). The condition effect was minimal from 9 months with only IE swallow proportions differing between conditions. These data suggest a ‘critical period’ in infantile neural response to oropharyngeal stimulation during feeding and that the impact of this on infants with neurological and/or respiratory disorders should be further investigated.

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1. Introduction

Breathing–swallowing coordination during feeding matures in early infancy in both term and preterm infants (Lau et al., 2003; Mizuno and Ueda, 2003). In animals, infant (Reix et al., 2003; Reix et al., 2004) and adult patterns (Feroah et al., 2002) of non-nutritive breathing–swallowing coordination are very similar, suggesting that this behaviour is adult-like at birth (Reix et al., 2004). However, there are no published data on whether this is true for humans (Praud and Reix, 2005), nor are there comparisons of nutritive and non-nutritive swallowing conditions in human infants.

It is likely that feeding has an impact on breathing–swallowing coordination given reports of the dramatic effect on the cardiovascular system of healthy neonates (Cohen et al., 1998) and the effect of sensory input on other aspects of infant feeding such as suck motor patterns (Finan and Barlow, 1998), sucking rate (Burke, 1977), and the ratio of sucks to

swallows (Burke, 1977). There is also a close association of apnoea and bradycardia with post-swallow pharyngeal residue (Itani et al., 1988), which highlights the impact of pharyngeal stimulation on the respiration of premature infants. Laryngeal sensory stimulation in infant animals typically evokes prolonged apnoea (Marchal et al., 1982; Lawson et al., 1991). Oropharyngeal stimulation provided by gastroesophageal reflux may stimulate an exaggerated LCR with subsequent prolongation of apnoea (Thach, 1997), thus the impact of pharyngeal stimulation on the breathing–swallowing coordination of infants warrants further investigation.

The neural networks that organize swallowing, respiration, mastication (Miller, 1999), and sucking (Finan and Barlow, 1998) are found in the brainstem and are influenced by sensory feedback (Miller, 1999). This is supported by evidence that the activity of brainstem respiratory neurones and respiration are altered during laryngeal stimulation in piglets (Lawson et al., 1991). Although the precise mechanisms governing breathing–swallowing coordination and the maturation thereof in human infants are unclear, evidence from decerebrate animals suggests that the brainstem is heavily involved (Wallois et al., 1993). Since cranial nerves involved in respiration and swallowing (Marlot and Duron, 1979) and suprabulbar structures

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(Gibson, 1991) mature postnatally in mammals, these structures may also play a role in the maturation of breathing–swallowing coordination in human infants. Maturation of the nervous system is likely to result in reduced response to sensory stimulation. This is supported by animal research that documents a more dramatic effect of oral electrical stimulation on breathing and swallowing in the young than in the adult animal (Wallois et al., 1993). Furthermore, the elicitation of swallowing results in complete cessation of respiration in mammalian infants (Harned et al., 1978; Lucier et al., 1979), but at 2–3 months of age, the elicitation results in an alternation of respiration and swallowing (Harned et al., 1978).

In order to determine the effects of increased oropharyngeal stimulation on the breathing–swallowing coordination of healthy neonates under natural conditions, the breathing–swallowing coordination of nutritive swallows (recently reported in Kelly et al., *in press*) were compared to non-nutritive swallows recorded during wakefulness. Given existing evidence of the effect of sensory stimulation on neonatal physiology, it was hypothesized that the impact of feeding-associated sensory stimulation on breathing–swallowing coordination would be obvious in the neonatal period. It was further hypothesized that this impact would diminish with age since some authors report no obvious impact on adult breathing–swallowing coordination (Nishino et al., 1985). Thus, breathing–swallowing coordination was assessed during wakeful nutritive and non-nutritive swallowing conditions soon after birth and a further nine times until the infants reached 1 year of age.

2. Methods

2.1. Participants

Eight healthy female and two male neonates, born at or above 38 weeks gestational age, were recruited with the approval of the Canterbury Regional Health Ethics Committee. Written consent was obtained from a parent of each neonate. The neonates were born to mothers without prenatal maternal complications and presented with Apgar scores at or above ‘7’ at 5 min after birth. The neonates had no reported medical complications at birth, nor did they have nervous system or upper-body structural abnormalities. Participants were also deemed healthy at the time of assessment (e.g. free of upper respiratory tract infection). At each assessment, measures of normal development were documented: weight, head circumference, and the presence (or absence) of reflexes appropriate for chronological age (rooting, walking, grasp, Moro, Babinski, and tonic neck reflexes). From 1 month of age the Denver Developmental Screening Test II (DDST II) was also completed during each visit. All infants were found to be within normal limits on these measures.

2.2. Procedure and equipment

Breathing–swallowing coordination was monitored during wakefulness for as long as the infant tolerated the procedure and during breast or bottle feeding in a reclined position. Attempts

to keep a supine body position consistent across both conditions and across assessment ages were made given the known physiological effects of altered body position in infants (Chen et al., 1995). However, due to behavioural constraints this was not always possible, particularly during wakefulness at 9 months and 1 year of age. Recording was momentarily halted if mouth-breathing was suspected (mouth opening). Assessments were made during the day within the first 48 h, at 1, 2, 3, and 4 weeks, 2, 3, 6, 9, and 12 months of age using simultaneous time-locked recordings of submental muscle activity, nasal airflow and thyroid acoustics, as previously described (Kelly et al., *in press*, 2006). All recordings were captured by an integrated hardware–software system (Kay Elemetrics Swallowing Workstation). The collective submental muscle group was located by palpation and bipolar surface EMG electrodes (Thought Technology Triode™) were positioned over this muscle group with a reference electrode on the forehead. The rectified and averaged submental surface electromyography (SEMG) signals were sampled at 250 Hz. An infant nasal cannula was used to measure airflow. Nasal prongs were situated at the entrance to each nostril and secured firmly around the head. Thyroid acoustics were measured by a laryngeal microphone and were used to rule out submental EMG artifact and confirm swallowing onset. The laryngeal microphone was a modified omnidirectional condenser microphone with a sensitivity of -62 ± 3 dB, an impedance of <2.0 k Ω , and a frequency response of 50–12,500 Hz. The microphone was connected to a preamplifier (Rolls mini-mic preamplifier MP13, gain of 6–50 dB). The signal from the preamplifier was sampled at 4000 Hz. The microphone was positioned lateral to the thyroid, which was located by palpation and held or taped in position. Body position was monitored using custom-made mercury switch position monitor secured to a soft elasticized band fitted around the chest with Velcro® at the level of the xiphisternum from 9 months of age. A change in body position resulted in a change in the output voltage which correlated to one of four body positions: side-lying (left = 1.02 V, right = 0.69 V), upright (1.55 V), supine (0.35 V), and prone (1.33 V). The mercury switch position monitor was connected to a custom-made sensor box (which also acted as an external battery-operated power source) and the output fed into the auxiliary channel of the Kay Elemetrics Swallowing Workstation. The signal was sampled at 250 Hz.

2.3. Data analysis, processing and preparation

Swallows (identified by concurrent bursts of SEMG activity and thyroid acoustics and absent nasal airflow) were assigned to one of five categories based on the phase of respiration preceding and following the swallow (Kelly et al., *in press*): inspiration-SA-inspiration (II), inspiration-SA-expiration (IE), expiration-SA-expiration (EE), expiration-SA-inspiration (EI), and mid-pause (P). ‘Mid-pause’ swallows included those swallows performed during periods of absent nasal airflow of 2 s or longer and consecutive swallows between which no respiration occurred. Given that the number of swallows performed in each condition could not be controlled for between or within individuals, the proportion of swallows in each respiratory-phase

Table 1
Number of wake and feeding swallows at each assessment age

Age	Wake	Feeding
48 h	712	1479
1 week	377	1777
2 weeks	449	1778
3 weeks	491	1722
4 weeks	366	1508
2 months	467	1369
3 months	437	1533
6 months	388	1415
9 months	250	1221
1 year	157	1271

category for each condition for each individual was calculated and expressed as a percentage and entered into the database.

Poor infant cooperation prevented the collection of data during wakefulness on one occasion for two infants. These infants were allocated the percentage frequency of occurrence for all respiratory-phase categories for the relevant condition at the relevant age from another infant determined to be their 'closest match' (Elliott and Hawthorne, 2005). The Statistical Package for the Social Sciences (SPSS, version 11.5, 2002) was used for statistical analyses and a p -value < 0.05 was taken to indicate statistical significance. A random 18 assessments (approximately 18% of all wake and feeding swallows) were reanalysed by

the primary and independent raters in order to determine intraclass correlation coefficients for intra- and inter-rater reliability, respectively. The effects of respiratory-phase category, age, and condition on coordination were tested using repeated-measures analysis of variance (ANOVA). Respiratory-phase category, age, and condition were entered as within subject effects. Mauchly's test (Mauchly, 1940) was used to test the sphericity assumption for repeated-measures and when this assumption was not met the Greenhouse–Geisser correction was applied to the significance tests. Fisher's least significance difference (LSD) tests were used to further explore significant main or interaction effects.

3. Results

A total of 19,167 swallows (4094 non-nutritive and 15,073 nutritive) were analysed (Table 1). Intraclass correlation coefficients demonstrated satisfactory inter- and intra-rater reliability for swallow categorization ($r = .946$ and $.962$, respectively).

A repeated-measures ANOVA comparing non-nutritive and nutritive conditions revealed an overall respiratory-phase category effect [$F = 44.0$, d.f. = 4, 36, and $p < 0.001$]. Fisher's LSD testing revealed that the proportion of II swallows was lower than that of EE swallows, irrespective of age and condition (Table 2). The repeated-measures ANOVA revealed no overall age or condition effect.

Table 2
Proportional distribution (mean percentage and standard deviation) of swallows in each respiratory-phase category

Respiratory-phase category	Age									
	48 h	1 week	2 weeks	3 weeks	4 weeks	2 months	3 months	6 months	9 months	1 year
II										
<i>M</i>	7.8	7.7	9.2	6.6	10.2	11.8	10.4	7.2	8.8	11.6
S.D.	7.9	8.9	10.1	5.9	8.7	11.4	12.3	7.8	8.8	10.0
Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	33.3	34.5	33.3	19.2	26.2	35.7	45.4	32.6	29.2	31.3
IE										
<i>M</i>	24.2	27.5	25.0	28.4	27.7	25.9	29.0	33.0	29.0	41.4
S.D.	12.5	11.0	13.8	14.3	11.7	8.7	11.5	16.1	14.7	21.7
Minimum	0.0	10.0	5.3	5.6	4.0	5.6	6.5	8.7	0.0	10.2
Maximum	55.8	51.2	57.7	52.6	53.0	41.8	52.3	59.2	61.0	100.0
EE										
<i>M</i>	37.6	31.1	31.5	33.8	29.7	34.1	30.9	31.7	39.8	27.6
S.D.	19.0	14.6	13.0	10.9	12.0	15.8	12.6	12.9	15.4	11.4
Minimum	10.3	7.1	12.6	12.5	13.6	8.4	10.2	6.5	18.4	0.0
Maximum	80.0	51.9	63.3	52.8	57.9	65.2	61.7	51.8	66.7	48.3
EI										
<i>M</i>	11.6	13.8	11.7	9.9	11.4	14.9	17.8	13.6	17.0	19.2
S.D.	8.4	8.0	7.2	7.7	9.5	10.5	8.8	9.3	11.6	11.0
Minimum	0.0	3.0	0.0	0.0	0.0	0.0	2.0	0.7	0.5	0.0
Maximum	26.7	28.6	27.8	27.4	35.0	44.1	36.8	48.9	33.3	38.9
P										
<i>M</i>	18.7	19.9	23.1	21.2	20.9	13.4	11.9	14.4	5.4	0.2
S.D.	16.6	15.9	15.8	14.6	18.0	11.2	10.7	16.5	8.3	0.6
Minimum	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Maximum	53.8	58.0	53.5	41.0	64.0	34.6	34.7	46.4	31.0	1.8

Note—*M*: mean, S.D.: standard deviation, II: inspiration-SA-inspiration, IE: inspiration-SA-expiration, EE: expiration-SA-expiration, EI: expiration-SA-inspiration, P: mid-pause.

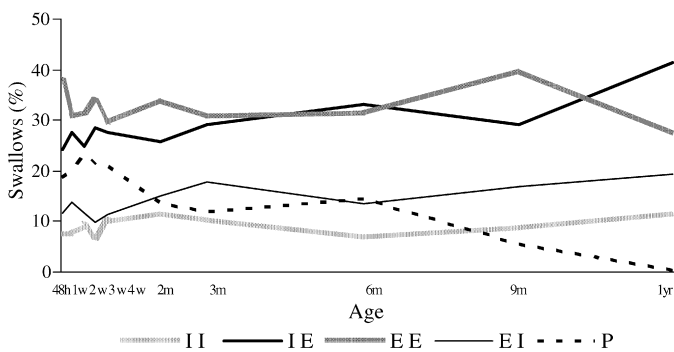


Fig. 1. Proportional distribution of all swallows in each respiratory-phase category at each age. *Note:* these data are not continuous, but were obtained at discrete ages and only displayed in this manner for ease of reference. II: inspiration-SA-inspiration, IE: inspiration-SA-expiration, EE: expiration-SA-expiration, EI: expiration-SA-inspiration, P: mid-pause, h: hours, w: week, m: months, yr: year.

The repeated-measures ANOVA revealed an interaction of respiratory-phase category and age [$F=4.59$, d.f. = 6.03, 54.3, and $p=0.001$]. Fisher's LSD testing revealed that the interaction was primarily characterized by a higher proportion of EE than II (at all ages), EI (at all ages except at 1 year), and P (at all ages except at 2 and 4 weeks). There was also a higher proportion of IE than II (at all ages), EI (at all ages), and P (between 2 months and 1 year) (Table 2 and Fig. 1).

The repeated-measures ANOVA also revealed a respiratory-phase category by condition interaction [$F=29.8$, d.f. = 4, 36, and $p<0.001$]. Fisher's LSD test showed a lower proportion of P swallows during nutritive than during non-nutritive swallowing conditions.

Finally, the repeated-measures ANOVA revealed a respiratory-phase category by condition by age interaction [$F=3.02$, d.f. = 6.47, 58.2, and $p=0.010$]. Fisher's LSD tests showed that this interaction was characterized by three phenomena. First, at certain ages, there were higher proportions of II, IE, and EI swallows during nutritive than during non-nutritive swallowing conditions (Fig. 2A–E). Second, EE swallow proportions were higher in the non-nutritive than nutritive swallowing condition at two ages, but the reverse was true at 48 h. Third, there were consistently lower P swallow proportions during nutritive than during non-nutritive swallowing throughout the first 6 months of life but not beyond. In summary, the number of respiratory-phase categories subject to a condition effect was low initially, but peaked between 2 weeks and 2 months with the majority of categories affected, and then declined until only one category was affected from 6 months (bottom graph, Fig. 2F).

4. Discussion

Breathing–swallowing coordination differed between nutritive and non-nutritive swallowing conditions throughout the first year of life in healthy term infants. In particular, the most striking finding was the considerable impact of nutritive swallowing on breathing–swallowing coordination between the ages of 2 weeks and 2 months (Fig. 2F). However, the impact of

a substantially greater number of feeding swallows than wake swallows, particularly at these ages, on this effect is unknown (Table 1). Nonetheless, these results suggest that there may be a 'critical period' during which infants exhibit a greater respiratory response to oropharyngeal stimulation. Similar research in adults has shown no obvious effect of nutritive swallowing on breathing–swallowing coordination (Nishino et al., 1985) suggesting that the substantial, but diminishing effect of nutritive swallowing on breathing–swallowing coordination in maturing infants is a feature of infant neurophysiology. The present results also indicate that throughout the first year of life the majority of nutritive and non-nutritive swallows are followed by expiration. Post-swallow expiration is also dominant in adults (Preiksaitis et al., 1992; Klahn and Perlman, 1999; Hiss et al., 2001) and, thus, these infants exhibit an adult-like feature of breathing–swallowing coordination even from birth.

The dominant pattern of post-swallow expiration observed in humans is unlike that of animals. During non-nutritive swallowing, animals (infants and adults alike) typically swallow in the II respiratory-phase (37–45%, Feroah et al., 2002; Reix et al., 2003; Reix et al., 2004), a rare occurrence in human infant swallowing (2.3–12.8%, in the present study). It appears that humans and animals also differ in terms of the maturation of breathing–swallowing coordination. According to Reix et al. (2004), the similarity of the pattern of breathing–swallowing coordination between lambs and adult goats suggests that little or no maturation occurs postnatally. Although the direct comparison between human infant and adult non-nutritive breathing–swallowing coordination has yet to be reported, infant nutritive swallowing has been shown to mature postnatally (Kelly et al., in press). It is possible that postnatal anatomical maturation characterized by the descent of the larynx and epiglottis in humans, that does not occur in other mammals, may account for this maturation difference between the species.

The maturation of human infant breathing–swallowing coordination is also characterized by a decline in the incidence of 'mid-pause' swallows (those occurring consecutively or during prolonged respiratory pauses). The proportion of 'mid-pause' swallows, although much lower during nutritive than non-nutritive swallowing conditions in the first 6 months, declined gradually with age such that there were virtually none in either condition by 9 months. Although the early and substantial impact of feeding on breathing–swallowing coordination was expected, a higher proportion of 'mid-pause' swallows during nutritive than non-nutritive swallowing was anticipated. It was anticipated because respiration may cease, albeit temporarily, following sensory stimulation in mammalian infants (Harned et al., 1978; Thach, 1997), thus it seems likely that swallowing would occur during respiratory pauses more often during feeding. However, this was not the case for the infants in the present study and could reflect a fusion of *continuous* breathing with nutritive sucking and swallowing. This is supported by evidence that preterm infants swallow mainly during respiratory pauses (Mizuno and Ueda, 2003) or frequently in succession without breathing between swallows (Hanlon et al., 1997); both phenomena decline with age. The overall decline in 'mid-pause' swallows with age may also reflect the declining occurrence of

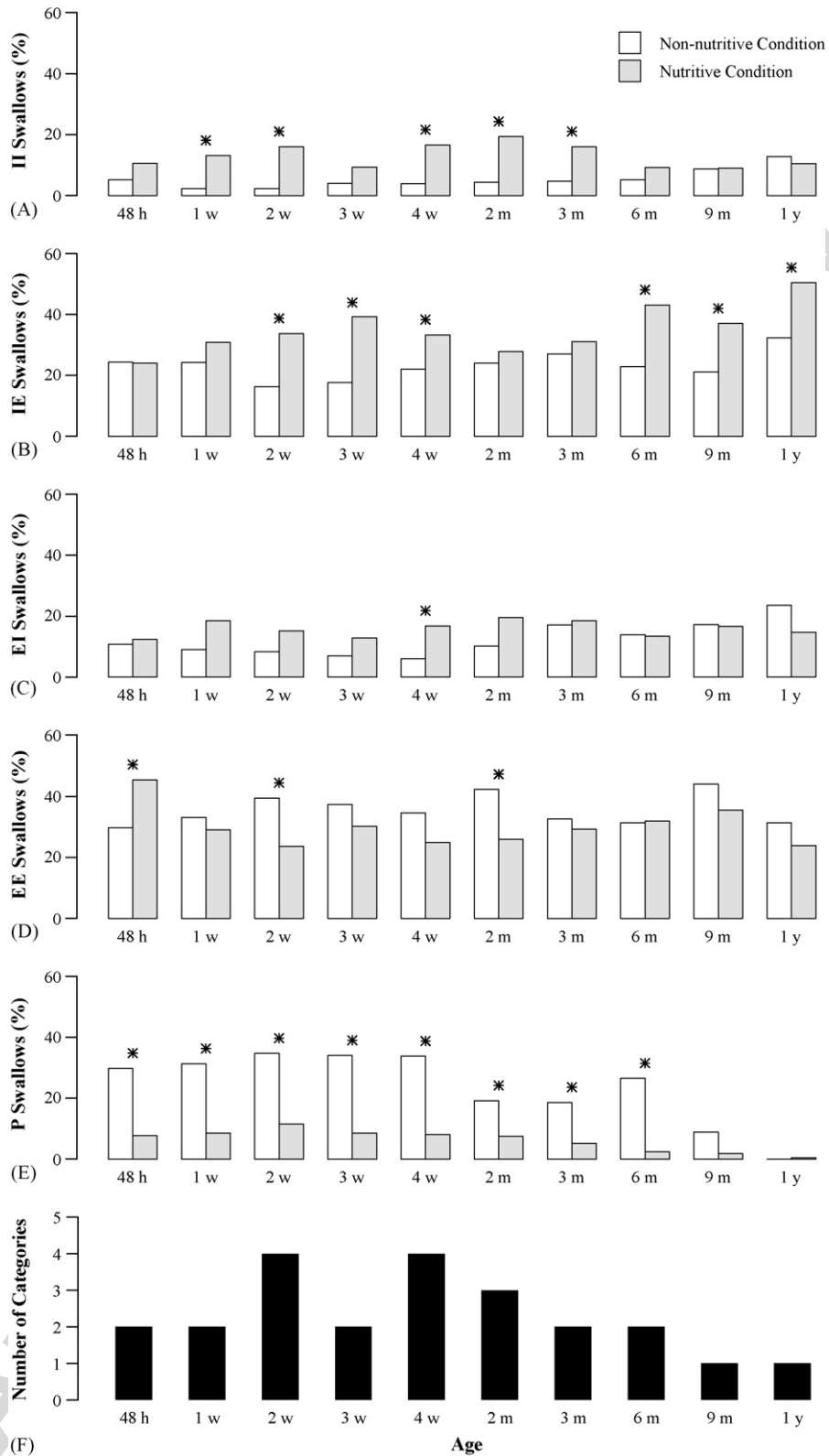


Fig. 2. Percentage frequency of swallows in each respiratory-phase category during wakefulness (non-nutritive) and feeding (A–E) and the total number of respiratory-phase categories altered by feeding (F). Note: * significant condition effect ($p < 0.05$) determined by Fisher's LSD testing. II: inspiration-SA-inspiration, IE: inspiration-SA-expiration, EE: expiration-SA-expiration, EI: expiration-SA-inspiration, P: mid-pause, h: hours, w: week, m: months, y: year.

respiratory pauses associated with the maturing respiratory system (Richards et al., 1984). With reference to the incidence of respiratory pauses, future research should determine the extent to which respiratory maturation alone accounts for the maturation of breathing–swallowing coordination. This would require measurements of respiratory function, such as tidal volume and rate, which cannot be calculated by the recording techniques adopted by the present study.

The early impact of nutritive swallowing on breathing–swallowing coordination suggests that the infant nervous system responds dramatically to the presence of the liquid bolus, particularly between 2 weeks and 2 months. Overall, the proportions of all respiratory-phase categories were subject to a condition effect at one point or another during the first year. The number of categories subject to this condition effect was maximal during the first month and diminished beyond 6 months. In other words, breathing–swallowing coordination was most altered by oropharyngeal sensory stimulation associated with bolus ingestion between 2 weeks and 2 months of life. These findings suggest that there might be a ‘critical period’ in the neural development during which otherwise healthy infants may have an exaggerated response to oropharyngeal stimulation.

The present study is behavioural in nature, thus identifying the central nervous system structures that are responsible to the maturation of the impact of feeding on breathing–swallowing coordination is not possible. However, inferences made from the literature suggest that global maturation may facilitate this process. Brainstem maturation may account for the declining impact of nutritive swallowing on breathing–swallowing coordination in the latter stages of the first year, in the present study. This is supported by a review that concluded that postnatal maturation of a brainstem respiratory centre, the Kolliker-Fuse nucleus, may be the source of more flexible adaptation of sensory processing in the mature individual (Dutschmann et al., 2004). Thus, it is possible that maturation of the Kolliker-Fuse nucleus results in improved sensory processing during feeding, thereby minimizing the impact of feeding on breathing–swallowing coordination in the more mature infant.

Furthermore, brainstem maturation is involved in the maturation of some of the constituents of breathing–swallowing coordination, thus it is feasible that brainstem maturation may, too, contribute to the changes in the patterns of breathing–swallowing coordination observed in the present study. For instance, postnatal brainstem maturation may be at least partially responsible for developmental changes in human respiration (Denavit-Saubie et al., 1997) and feeding-related reflexes in mammals (Thexton and Griffiths, 1979). In addition, 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).

Age-related changes in the interaction between bulbar and suprabulbar networks may also be responsible for the maturation of the impact of feeding on breathing–swallowing coordination. Adult brainstem CPGs are influenced by suprabulbar regions (review by Miller, 1999). This is demonstrated by cortical activation of volitional swallowing and cortical influence over the degree of swallowing-related neuromuscular activity (Miller et

al., 1997). Similarly, suprapontine structures (above the pons), such as the midbrain and hypothalamus, which are densely connected to the cortex, can also influence respiration (review by Horn and Waldrop, 1998). It is possible that these higher centres are responsible for the integration of afferent information and the ensuing ventilatory adaptation (Horn and Waldrop, 1998). Thus, it is also feasible that pharyngeal sensory stimulation may result in the suprabulbar modulation of respiration. In the developing neonate, higher brain regions may become increasingly active in the modulation of CPGs as a result of the myelination of the corticobulbar tract. This tract begins myelinating in the latter stages of gestation and is only well myelinated by the age of 2 years (Sarnat, 1989). Bosma (1986) suggested that in young infants feeding behaviour is primarily brainstem mediated with escalating engagement of suprabulbar structures with increasing age. Thus, increasing suprabulbar regulation of the CPGs controlling breathing–swallowing coordination may have accounted, at least in part, for the declining impact of nutritive swallowing on breathing–swallowing coordination in the present study.

5. Conclusions

Although future research using a greater number of infants should aim to confirm these findings, these results suggest that the breathing–swallowing coordination of human infants is altered by feeding, particularly between 2 weeks and 2 months of age. This indicates a possible ‘critical period’ in normal infant neural development during which immature sensorimotor integration can result in an exaggerated efferent response to feeding-related oropharyngeal stimulation. The impact of this exaggerated response on the success of feeding in infants with neurological and/or respiratory disorders should therefore be further investigated. The magnified neonatal respiratory response to feeding declined with age possibly due to the protracted increase in descending suprabulbar inhibition but more likely due to brainstem maturation.

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