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Fetal Yawning

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Abstract

Fetal neurobehavioral patterns have been considered as indicators of nervous system development. Moreover, the capacity of 4-dimensional sonography to evaluate complex facial expressions allows recognition of common behaviors with which one can appreciate the prenatal functional development of the central nervous system. Using yawning as an example, we review this interpretation on the basis of knowledge derived from phylogeny and ontogeny. As a flip-flop switch, the reciprocal interactions between sleep- and wake-promoting brain regions allow the emergence of distinct states of arousal. By its ontogenic links with REM sleep, yawning appears to be a behavior which causes arousal reinforcement through the powerful stretching and the neuromuscular connections induced. Yawning indicates a harmonious progress in the development of both the brainstem and the peripheral neuromuscular function, testifying to the induction of an ultradian rhythm of vigilance. The lack of fetal yawn, frequently associated with lack of swallowing (associated or not with retrognathia), may be a key to predicting brainstem dysfunction after birth.

General movements are part of the repertoire of spontaneous movement, and are present from early fetal life. Prior to the 1970s, self-perception by mothers was the only testimony of this fetal motor activity. The advent of ultrasound technology in the 1970s enabled live unobtrusive observations of fetal behaviors in humans, vastly increasing our knowledge of many other types of more subtle motor activity (swallowing, respiratory movements, smiling, hiccups) and thus human fetal development. Our understanding of the developmental order and sequence of fetal behavior increased substantially, leading to a greater appreciation of embryologic and developmental anatomy. The introduction of 4-dimensional ultrasound (4D-US) has led to very important conclusions concerning fetal behavior milestones [1]. The development of oral sensorimotor function and swallowing (essential for survival) from the fetal period through early infancy indicates normal or abnormal neurobehavioral development. While the appreciation of these functions takes a long time, another daily behavior will can be detected: yawning [2]. Curiously, little data has been

published over the last 25 years, since the following was written: 'yawning is a universally well known, but poorly understood' [3] or 'a rudimentary reflex' and 'appears to have at best an obscure purpose, if any' [4]. Although remarkably little interest has been paid to yawning in research (despite the fact it is an everyday phenomenon), we will discuss the meaning of this behavior and how its characterization can enhance neurobehavioral understanding.

First however, it must be specified that human research on prenatal programming of behavior is intrinsically correlational, never manipulatively experimental, and frequently based upon homologies with others vertebrates.

A popular saying states that 'the organ generates the function'. However, embryology instructs us that body movement in a fetus is required for maturation of motor function and is involved in the development of other organs, such as the lung. Furthermore, body movement indicates an harmonious progression in the development of both the central motor system and peripheral neuromuscular function [5]. All the movements that a newborn is able to produce originate during the fetal life and are performed throughout the life span. Behaviors observed in utero – including breathing, yawning and others – are a part of the continuum of activity shown in a newborn infant and undergo neuromuscular rewiring. The onset and developmental course of fetal motility have been studied since ultrasound technology appeared; however, the evaluation of facial expressions was impossible using real-time 2D-US. In particular, it was the capacity of 4D-US to evaluate complex facial expressions that allowed recognition of yawning [2, 6, 7].

What Is a Yawn?

de Vries et al. [8] have proposed a classification of fetal movement patterns studied longitudinally: the first movement is observable during the 7th postconceptional week; generalized trunk and limb movements by the 9th week; movements of the fetal jaw and face observed around the 11th week. Yawning is recognized as one of the movement patterns consistently present from the end of the first trimester until delivery.

A yawn is a paroxysmic cycle characterized by a standard cascade of movements over a 5- to 10-second period. The 4D-US differentiates this typical development: the fetal mouth, previously closed, opens widely for 4–6 s with simultaneous retraction of the tongue, followed by a quick closure, and usually combined with retroflexion of the head and sometimes elevation of the arms (pandiculation) [9]. This harmonious sequence is markedly different than a brief swallowing episode. Using a color Doppler technique, it is possible to observe the flow of amniotic fluid through the fetal mouth, oropharynx, pharynx and trachea to the lungs [10]. This movement pattern is nonrepetitive in the fetus, contrarily to adults. Yawning appears to be clearly not just a matter of opening one's mouth, but a generalized stretching of muscles, especially

those of the respiratory tract (diaphragm, intercostals), face and neck. Thus, it can be inferred that yawning is a part of the generalized stretch with which it is generally accompanied [11].

Embryology and Mechanisms

In 1973, T. Dobzhansky remarked: 'nothing in biology makes sense except in the light of evolution.' Ernst von Haeckel (1834–1919) stated that: 'ontogenesis is a brief and rapid recapitulation of phylogenesis, determined by the physiological functions of heredity (generation) and adaptation (maintenance).' The truth of these quotations is illustrated by yawning. Indeed, the ultrasound investigation reveals an ontogenic onset between 12 and 15 weeks of gestation [2]. Indeed, yawning is a phylogenetically old and stereotyped phenomena that occurs in a huge variety of species, from reptiles and fish to birds and mammals. Its survival without evolutionary variations postulates a particular importance in terms of developmental need [9]. The strong muscular contraction that represents a yawn has a metabolically expensive cost. If we agree with the terms of the Darwin's evolutionary propositions, the cost in brain activity must be outweighed by the advantages gained in terms of developmental fitness. Thus, a structural hypothesis suggests an activation in the synthesis of neurotrophins which leads to a cascade of both new synapse formation or recruitment and activation through the diencephalon, brainstem and spinal cord. The phenomenon of activity-dependent development has been clearly shown to be one mechanism by which early sensory or motor experience can affect the course of neural development. Activity-dependent development may be a ubiquitous process in brain maturation by which activity in one brain region can influence the developmental course of other regions [12].

A wealth of data has been accumulated on genes that are expressed in the embryo and govern the hindbrain segmentation. Hox homeobox genes form 4 conserved clusters encoding transcription factors that orchestrate ontogenesis along the rostro-caudal axis of the body, including hindbrain segmentation and limb formation. The facial bone structure and the brain differentiate from a common embryonic structure, the ectoblast. The cephalic pole comprises an original embryological encephalo-facial and encephalo-cervical segmentation with a strict topographical correspondence: the naso-frontal and premaxillary structures are joined to the forebrain; the maxillo-mandibular and anterior cervical structures are joined to the brainstem and its nerves [13–15]. The human brainstem is fashioned around the 6th–7th week of gestation and matures in a caudal to rostral arc, thereby forming the medulla, pons and midbrain. The medulla mediates arousal, breathing, heart rate, and gross movements of the body and head, and medullary functions appear prior to those of the pons, which precede those of the midbrain [16]. The ability to produce motor behavior generated centrally and linked to arousal and respiratory function

is a property of the brainstem reticular formation, which has been remarkably conserved during the phylogeny of vertebrates including agnathans, fishes, amphibians, reptiles and birds. Therefore, conservative developmental mechanisms orchestrating the organogenesis of the brainstem in all vertebrates are probably crucial for arousal and breathing [17]. At the beginning of the 3rd month, the embryo becomes a fetus with the occurrence of the first oral and pharyngeal motor sequences under the control of the neurological development of the brainstem, such as suction-deglutition and yawning activity. Therefore, suction and yawning have the same embryological origin, which shows the importance of the brainstem in the neurophysiological development of the oropharyngeal activity coordinated with the respiratory, cardiac and digestive regulations that have the same neuroanatomical localization. Its occurrence marks the developmental stage when the brainstem is already individualized and the pituitary gland has become functional, whereas the extension of the temporal and frontal neocortex takes up to 22–24 weeks to reach completion [18–20]. Movements of the tongue or jaw assist the development of the palate by promoting horizontal elevation of vertically orientated palatal shelves. Activity of neck and tongue muscles are always accompanied by mouth-tongue movement [21]. The relationship or connection between the neural network of mouth-tongue movement and respiratory activities are not perfectly understood. It seems that information about central respiratory and locomotor rhythms, necessary for cerebellum control of the coordination between respiration and locomotion, converges at the level of the lateral reticular nucleus [22]. It is probable that the explanation for craniofacial congenital developmental abnormalities, which ultrasound investigation helps to reveal, lies here. As the saying goes: 'the face predicts the brain.'

Why Does Yawning Share a Link with Arousal?

The phylogenetic appearance of sleep suggests that the nocturnal rest of poikilotherms most probably becomes in mammals a form of REM sleep or paradoxical sleep, which is characterized by peripheral muscular atonia originating in the dorsal part of the brainstem, rostral to the pons [23].

Based on numerous studies of fetuses and infants in a variety of mammalian species, it is widely believed that the earliest form of sleep is properly characterized as active sleep, which is an immature form of REM sleep and preponderant at birth. Accordingly, it is thought that quiet sleep, an immature form of slow-wave sleep, emerges as the predominance of REM sleep diminishes during ontogeny [24].

In early intrauterine life, a diffuse collection of phasic and cyclic motor events occur, and these gradually coalesce. For the fetus, sleep and wakefulness are reliably characterized, respectively, by periods of myoclonic twitching expressed against a background of muscle atonia and high-amplitude behaviors (e.g. locomotion or

stretching-yawning) expressed against a background of high muscle tone. Movements of the limbs, such as stretching, yawning and kicking, are typically considered to indicate periods of wakefulness. Periods of twitching are almost always followed by the abrupt onset of high-amplitude awake behaviors, thus completing the cycle. Although myoclonic twitching during active sleep in infants is more prevalent and more intense than that seen during REM sleep in adults, its similarities to adult behavior and its linkage to periods of atonia suggest developmental continuity between the infant and adult sleep states. The maturation of the central nervous system, based on the myelinization, starts in the spinal cord then proceeds to the brainstem and forebrain. So, paradoxical sleep mechanisms located in the brainstem are the first to mature and the only ones to function. Then, the slow-wave sleep and waking structures become mature. Namely, the widespread control of neuronal activity exerted by specific REM sleep processes help to direct brain maturation through activity-dependent developmental mechanisms. It may be inferred that REM sleep (and possibly yawning) directs the course of brain maturation in early life through the control of neural activity [25, 26].

Behavioral pattern continuity from prenatal to postnatal life shows a strict parallelism between the ontogeny of REM sleep and yawning. Basically, REM sleep in the human declines from 50% of total sleep time (8 h) and a frequency of 30–50 yawns per day in the newborn to 15% of total sleep time (1 h) and less than 20 yawns per day in the adult. This decrease takes place mainly between birth and the end of puberty [27].

The emergence of distinct states is followed by dramatic changes in the amount, duration and cyclicity of rest and activity. An ultradian rhythm may be seen: in a period of 50–60 minutes there appears to be an alternation of moments characterized by motor activity and moments characterized by rest, as in the newborn [28]. Each period of rest switches over to a period of activity by a yawn. Thus, a periodicity of 1–2 yawns per hour can be noticed. Yawning appears 2 weeks before discernable sleep-wake states, and its expression gradually becomes linked. No changes in the incidence of yawns between 20 and 36 weeks of gestational age were observed in the fetus by P.J. Roodenburg [29]. In full-term infants, yawns are frequently observed on the first day of life. The embryo and the fetus are exposed to 24-hour periodicity in mothers' parameters of the circadian cycle that may play a role in the normal development of the fetus pacemaker. No data are available on how fetal yawning links up fetal rhythm with maternal rhythm.

C. Saper [30] proposed a model for reciprocal interactions between sleep- and wake-promoting brain regions, which produces a flip-flop switch. This model could explain the rapid transitions from awaking in sleep and from REM sleep to awaking. It is a survival necessity to ensure a repairing sleep while having the capacity to flee a predator (arousal). The transition is controlled by integrative autonomic structures that encompass regulated changes occurring in anticipation of the event. Yawning (a stretch syndrome) can be seen as a behavior for testing

this switch/transition, like a reinforcement of muscle tone. Awakening is controlled by around 4 different and redundant circuits mainly located in the reticular formation of the pons (adrenergic), the peduncle (dopaminergic), the hypothalamus (histaminergic) and the Meynert basifrontal region (cholinergic). The permissive networks controlling awakening must be tonically reinforced by the hypocretin system originating in the lateral hypothalamus. Next, the neuron's activation of the ventrolateral preoptic nucleus (VLPO) is correlated with the amount of sleep. The powerful muscular contraction caused by yawning releases arousal by activation of the reticular formation (locus coeruleus), to which the cranial nerves send retroprojections. On becoming aware, the yawning and stretching reverse the muscular atonia which characterizes REM sleep. When the pressure of sleep increases, it is supposed that the firing of the GABA and galanin VLPO neurons reduce the muscular tone of antigravitational muscles, notably those of the neck and masseters. Thus, yawning seems to be averse to this pressure. F. Giganti et al. [32] observed yawning in premature infants in all behavioral states, except during quiet sleep, and viewed it as a transitional state, suggesting a spreading activation of facial motor patterning. Thus, yawning may be seen as a nervous reflex loop which occurs as arousal reinforcement [31–33].

Yawning or Not: A Pathology?

Yawning occurs regularly, at a rate of about 1 or 2 per hour. When a yawn is observed during a 4D-US examination, it is obviously by chance or after very long investigation. Yawning generally appears after a period of rest, and indicates awakening. If normal swallowing is seen (much more frequent), yawning seems to offer no additional interest as an indication of harmonious brainstem maturation. Conversely, the lack of or a dysfunction in swallowing requires spending time on the collection of phasic and cyclic motor events that characterizes the ultradian fetal rhythm; thus, increasing the opportunity to notice a yawn. If the ultrasound examination suggests the absence of yawn and deglutition, it is imperative to search for mandibular hypoplasia and glossoptosis often associated with cleft palate [34].

Petrikovsky et al. [35] reported that clusters of yawning activity were observed in a series of anemic fetuses, and proposed that yawning repetitiveness helps track the fetus's anemia.

Diseases without Any Data Collected

Infants must develop safe and effective respiration and oral feeding skills soon after birth if they are to survive. For this to occur, infants must have the necessary anatomical structures and adequate central control to coordinate swallowing,

ventilation, sleep and arousal. Yawning is associated with all of these behaviors [34]. Although no data have actually been collected, we have built a non-exhaustive inventory of congenital pathologies in which the research of yawning is of interest: congenital central hypoventilation syndrome (also known as Ondine's curse, after a figure from Germanic mythology) which results in hypoventilation, most pronounced during sleep, with relative insensitivity to hypercarbia and a lesser insensitivity to hypoxia, in the absence of other abnormalities of the cardiorespiratory system. Congenital central hypoventilation syndrome can be associated with Hirschsprung's disease. Abnormalities in swallowing or esophageal motility were identified in newborns with facial dysmorphism and hypotonia. This suggests a generalized abnormality of gastrointestinal motility and brainstem functioning [36, 37].

Mandibular hypoplasia is a frequently encountered craniofacial difference, and can be classified into congenital and developmental:

- Mandibulofacial dysostosis with a variety of limb abnormalities.
- Pierre Robin sequence is characterized by a posterior U-shaped cleft palate, retrognatia and glossoptosis. Several arguments favor an embryonic origin consisting of an anomaly in caudal hind brain development. Feeding disorders are the most important functional symptom. Maternal testimonies, which one of us received, seem to agree with the lack of yawning at birth and a parallel progress across the first year of life for swallowing and yawning. Also, Pierre Robin syndrome can be seen as prenatal a brainstem dysfunction responsible of the oro-facial maldevelopment that can be diagnosed at 23 weeks' gestation during a 4D-US [38, 39].
- Any syndrome (primary bilateral or unilateral growth anomalies) associated or not with temporo/mandibular joint ankylosis or aglossia/microglossia, i.e. Franceschetti syndrome, Goldenhar syndrome, Richner-Hanhart syndrome.

Moebius syndrome comprises a congenital facial diplegia and bilateral abducens nerve palsies by degenerative and involved nuclei of the VI, VII and XII nerves. Simultaneous occurrence of limb malformations with cranial nerve dysfunction suggests a disruption in normal morphogenesis during a critical period in the development of the embryonic brainstem, most likely 4–7 weeks of gestation. Instances of bilateral paresis of the soft palate and scattered instances of dysphagia (some of which resolve in infancy) have been reported. Inability to close the mouth is the norm [40, 41].

Watershed infarcts in the fetal and neonatal brainstem are clinically expressed as multiple cranial neuropathies, failure of the central respiratory drive, or dysphagia [42].

Goldenhar syndrome includes malformations primarily involving the jaw, mouth and ears and, in most cases, affects one side of the body. It represents defects in the embryonic first and second brachial arches, the first pharyngeal pouch and brachial cleft, and the primordia of the temporal bone [43].

Joubert syndrome is a rare genetic disorder characterized by the absence or underdevelopment the cerebellar vermis and a malformed brainstem. The most common features include ataxia, an abnormal breathing pattern, sleep apnea, abnormal eye and tongue movements, and hypotonia [44].

It is possible to complete this catalog by adding congenital trismus, Crisponi syndrome, Stüve-Wiedemann syndrome, and other similar disorders.

Conclusion

A popular belief states that yawning is a response to elevated CO_2 or depressed O_2 levels in the blood. Provine and Tate [45] found no support for this hypothesis. Fetal yawning in amniotic fluid (like a fish's yawn in water) also show data against any association between oxygenation capacity and yawning.

With the significant advances in the image quality and resolution of ultrasound, and now 3D and 4D technology, the practice of ultrasound examination during pregnancy has moved forward from an anatomical examination to a functional evaluation. Recognition of fetal yawning helps to verify the harmonious progress of brainstem maturation and to appreciate the neural underpinnings of the sleep and arousal systems. Abnormalities in yawning foster intensive research of anemic fetuses (frequency amplified) or brainstem dysfunction with or without mandibular hypoplasia (frequency sparse or null) [34]. We hope and expect that upcoming research completes the data currently available.

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