A phylogenetic hypothesis for the origin of hiccough

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Summary

The occurrence of hiccoughs (hiccups) is very widespread and yet their neuronal origin and physiological significance are still unresolved. Several hypotheses have been proposed. Here we consider a phylogenetic perspective, starting from the concept that the ventilatory central pattern generator of lower vertebrates provides the base upon which central pattern generators of higher vertebrates develop. Hiccoughs are characterized by glottal closure during inspiration and by early development in relation to lung ventilation. They are inhibited when the concentration of inhaled CO_2 is increased and they can be abolished by the drug baclofen (an agonist of the $GABA_B$ receptor). These properties are shared by ventilatory motor patterns of lower vertebrates, leading to the hypothesis that hiccough is the expression of archaic motor patterns and particularly the motor pattern of gill ventilation in bimodal breathers such as most frogs. A circuit that can generate hiccoughs may persist in mammals because it has permitted the development of pattern generators for other useful functions of the pharynx and chest wall muscles, such as suckling or eupneic breathing. ***BioEssays*** **25:182–188, 2003.**

Introduction

Hiccoughs (or hiccups), combining a sudden inspiration immediately followed by an active closure of the glottis responsible for a peculiar sound, are a common phenomenon. They are experienced by nearly everyone, yet their origin and significance remain elusive and hence debated.[1,2] Several hypotheses have been proposed. Hiccoughs could result from the activation of a reflex arc of which the afferent limb would comprise the phrenic and vagus nerves plus the sympathetic chain. The central link of this arc would be located within the spinal cord, the brainstem and the hypothalamus, and the cerebellum and cerebral hemispheres would possibly be involved.[3,4] Hiccough could also represent a form of epilepsy, although most patients with chronic hiccough do not have any cerebral dysfunction and although diazepam, a major anticonvulsant drug, can trigger or worsen hiccough (see the review in Ref. 1). It has also been suggested, from observations made in patients with multiple sclerosis, that hiccough could be caused by the suppression of supraspinal inhibitory influences.[5] Another hypothesis is that hiccough could result from a dysfunction of the reciprocal inhibition of an ''inspiratory complex'' related to breathing and a ''glottis closure complex'' related to swallowing.[3] Some authors believe that hiccough represents the persistence of a fetal digestive reflex preventing amniotic fluid aspiration.[6] For others, fetal hiccough may prepare respiratory muscles for their postnatal breathing function after birth.[7,8]

We have taken a fresh look at hiccoughs by considering their past. We present here a phylogenetic hypothesis for their origin. It is based on the principle that neural mechanisms for rhythm generation in the brainstem are preserved through evolution and on the observation of numerous similarities between hiccoughs and ventilation in lower vertebrates such as the frogs. We begin by summing up the main characteristics of normal breathing at rest, eupnea, in humans and by reviewing what is known about hiccoughs, then discuss the phylogenetic origin of respiration and the likelihood that hiccoughs are a by-product of earlier, but conserved, respiratory behaviours.

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Eupneic breathing in mammals

Pulmonary gas exchanges in mammals depend upon the continuous renewal of the alveolar gas by a cyclical process called ventilation. This includes an inspiratory phase during which pulmonary inflation results from the contraction of inspiratory muscles. This contraction generates a negative intrathoracic pressure, aspiration, which pumps air into the lung.

The main inspiratory muscles are the diaphragm, the parasternal intercostal muscles and the external intercostal muscles; several neck muscles including the scalene musles and the sternomastoid muscles can serve as accessory inspiratory muscles. The entry of air in the airways when inspiratory muscles contract is facilitated by the coordinated activation of muscles that dilate the upper airway and the glottis.[9] After inspiration comes expiration, pulmonary deflation, which, in some species such as man during resting conditions, is due to the elastic recoil of the lungs and the chest wall toward their position of equilibrium. During the initial phase of expiration, lung deflation is slowed down by a persistent activity of the inspiratory muscles, the postinspiratory activity.[10] In some species (e.g. horses), expiration is extended beyond the point of equilibrium of the relaxed respiratory system by a cyclical contraction of expiratory muscles. The main expiratory muscles are the abdominal muscles.

The automatic, phasic and continuous contraction of the respiratory muscles results from the output of neuronal networks located in the brainstem.[11] Several experimental arguments suggest that pacemaker neurones located in the Pre-Bötzinger complex, just caudal to the retrofacial nucleus and ventral to the nucleus ambiguous, are essential for generating the respiratory rhythm (see for example Refs. 12–15). This remains however controversial since other works suggest that the respiratory rhythm results from emergent properties of the neuronal networks (see for example Refs. 16,17).

Clinical nature of hiccough

In contrast to eupneic breathing, hiccoughs combine a sudden powerful coordinated burst of inspiratory muscles of the thorax, the diaphragm, neck accessory and external intercostal muscles, with brief inhibition of expiratory muscles, active movement of the tongue toward the roof of the mouth (personal observations) and active adduction of the vocal cords, i.e. glottal closure, which occurs after the beginning of inspiratory flow and is responsible for the peculiar sound.[1,18,20] (Fig. 1). Hiccoughs often occur in runs, when they have a more or less regular rhythm with a frequency up to the same order as respiration. They can be entrained by the respiratory rhythm but persist during voluntary apneas[18] or

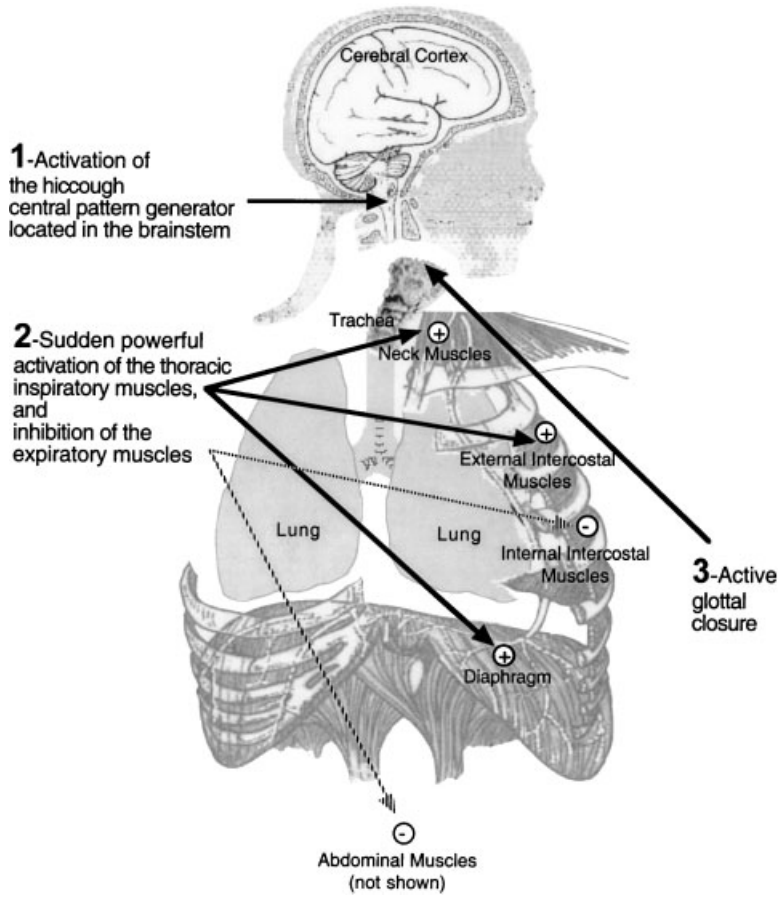

Figure 1. Schematic summary of the events occurring during hiccough. Hiccough starts with activation of a putative hiccough central pattern generator, located in the brainstem (1). Then, hiccoughs combine a sudden powerful coordinated burst of inspiratory muscles of the thorax—diaphragm, neck accessory and external intercostal muscles—with brief inhibition of expiratory muscles (2) and active adduction of the vocal cords leading to glottal closure. This occurs about 35 ms after the beginning of inspiratory flow and is responsible for the peculiar sound (3).

the apneas of the central sleep apnea syndrome.[21] These data are best explained by postulating that there is a rhythm generator responsible for generating hiccoughs that is separate from the adult mammalian eupnoeic rhythm generator but may interact with it.[18] This interaction is suggested by the recruitment of inspiratory muscles in both cases and by the fact that hiccoughs occur preferentially during inspiration.[18,22] The neuronal circuit producing hiccoughs is probably located in the brainstem (Fig. 2) because hiccoughs can be produced in the cat by electrical stimulation in a small area between the nucleus ambiguous and the lateral reticular nucleus.[23] In addition, hiccoughs in humans are not associated with premotor cortical potentials, an electroencephalographic activity that originates in the cerebral cortex and precedes voluntary movements, as opposed to voluntary inspiratory efforts of roughly comparable dynamics, such as maximal sniffs.[24]

Hiccoughs have been monitored in many mammalian species. In cats, rats and rabbits, hiccoughs are defined by a brief powerful inspiratory effort accompanied by the glottal closure that is the unique feature of hiccough separating it from many other aspirative behaviours such as aspiration reflex, gasp, sniff and sigh.[19,20,25]

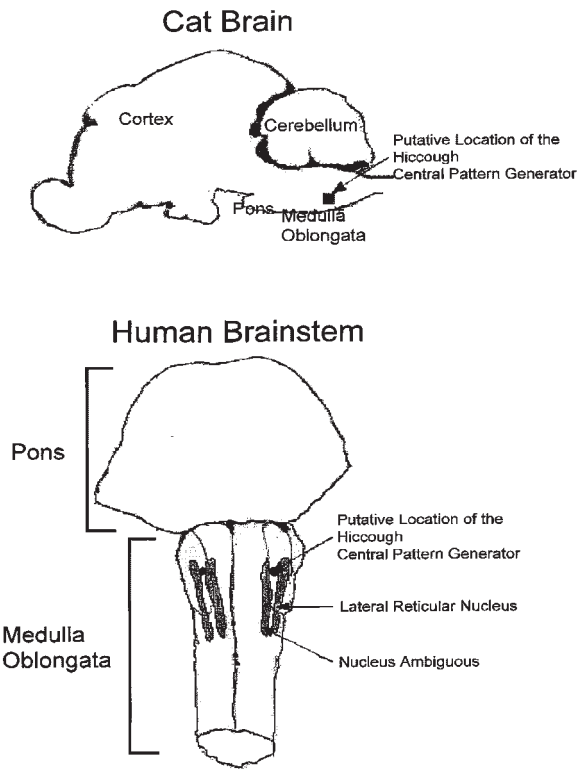

Figure 2. Putative location of the hiccough central pattern generator. The location in the cat brain is shown according to the data of Arita et al.[23] The hypothetical location in the human brainstem is derived from these data obtained in the cat.

Hiccoughs occur in the human fetus. They are defined by jerky contractions of the diaphragm with abrupt displacements of the thorax and the abdomen that can be seen on ultrasound scan imaging. Hiccoughs frequently follow each other in regular succession.[26] Hiccoughs appear before breathing movements and, through the latter part of gestation, occur in runs that may be separate from runs of fetal breathing movements or may run concurrently.[26] They are common in newborn babies, disappear in infancy, but reappear occasionally, briefly, in most people throughout life. In healthy adults and children, acute bouts of hiccoughs are often triggered by an oesophageal or a gastric aggression like gastric distension following overeating, eating too quickly or drinking carbonated beverages. Emotional factors can also induce a hiccough bout.[1] A host of conditions, at times intermingled, can be associated with persistent or chronic hiccough. They include almost all causes of cerebral damage (e.g. encephalitis, brain tumors, multiple sclerosis . . .), various brainstem lesions, metabolic or toxicologic factors (e.g. dysnatremia, alcohol consumption, or the use of opioids . . .) (see review in Ref. 1). They also include disorders likely to be associated with the strong stimulation of phrenic afferents (e.g. mediastinal tumors or pericarditis) or vagal afferents (esophageal diseases have been reported to cause as many as 75% of chronic hiccoughs, Ref. 27). Unexplained hiccoughs lasting several years without clear explanation have been reported (see review in Ref. 1).

Ancestral ventilation

The diaphragm evolved long after our ancestors invaded land.[28] Early air-breathers were aquatic and their ventilation was likely similar to that of extant but primitive air-breathers such as gar, lungfish and amphibians.[29] These animals use buccal muscles to pump either water over their gills or air into their primitive sack-like lungs with positive pressure. Therefore, in these animals, buccal muscles have an inspiratory action, but inspiration is not due to aspiration. During gill ventilation, coordinated rhythmic contractions of pharyngeal muscles continually push water from the buccal cavity over the gills while the glottis is closed to prevent flooding the lung[30] (Fig. 3). Filter feeders, which include the tadpole, use a very similar motor pattern for feeding, suggesting that these behaviors share similar neuronal circuits and a common evolution. The same muscles are also involved in air-ventilation, but the sequence of muscle activation depends on the lower vertebrate in question.

Research, most notably in frog and gar,[29,31] has demonstrated that air-breathing and gill ventilation in our ancestors was probably orchestrated by brainstem central pattern generators (CPG): neural networks with an oscillator function and

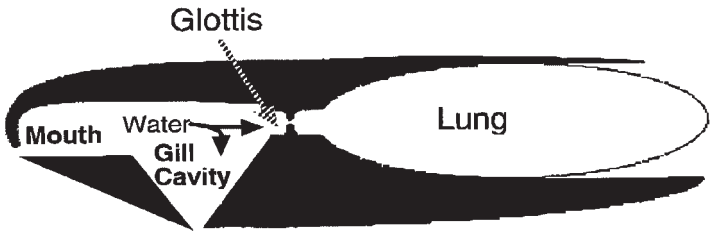

Figure 3. Schematic diagram of the rostral part of a tadpole body. During gill ventilation, coordinated rhythmic contractions of buccal muscles continually push water from the mouth over the gills. If the glottis was not closed the lung would be flooded.

a motor pattern function that can generate rhythmic motor activity in the absence of phasic input. While the detailed neuronal mechanisms underlying gill and lung ventilation in lower vertebrates have yet to be worked out, a growing body of evidence suggests that these highly coordinated behaviors are generated by distinct mechanisms. In premetamorphic tadpoles displaying only gill ventilation, lung ventilation is inhibited by a $GABA_B$-dependent pathway that does not affect the gill CPG.[32] In metamorphic tadpoles, the gill CPG depends upon chloride-dependent post-synaptic inhibition in contrast to the lung CPG.[33,34] In isolated brainstem of postmetamorphic tadpoles, lung ventilation is inhibited by concentrations of baclofen (an agonist of the $GABA_B$ receptor) lower than those that inhibit gill ventilation.[35] Consistent with a functional difference between gill and lung CPGs, microinjections of AMPA and GABA in the tadpole brainstem identified two distinct neuronal oscillators[36] that were anatomically separable.[36,37]

Phylogenetic conservation of respiratory rhythm generators

Following metamorphosis in tadpoles, the gills degenerate and the frog breathes air exclusively. However, a gill ventilation-like rhythm persists in the adult as oscillations of the buccal cavity that go on between runs of lung breaths. If the gill CPG persists in the adult,[38–40] could not similar conservation occur through evolution? Could not the ventilatory CPG in lower vertebrates constitute a scaffold upon which the CPG for mammalian ventilation evolved through modification of ancestral components and addition of new ones?[41–43]

This paradigm of conservation of rhythm generation and pattern formation properties of the brainstem provides the conceptual basis for many physiological studies of the generation of ventilation[29,40,44–46] and is supported by many observations. All air-breathing tetrapods show a three-phase neural respiratory cycle of expiration, inspiration and post-inspiration—postinspiratory apnea or slowing down of expiration.[10] The region of the brainstem responsible for lung ventilation in postmetamorphic tadpoles may be homologous to the pre-Bötzinger complex,[37] the brainstem structure possibly responsible for the eupneic rhythm in mammals.[12,13,15] Primitive air-breathing fish, amphibians and reptiles breathe intermittently by using the buccal muscles innervated by cranial nerves to push air into lungs[47–50] and embryos of mice and chicks show intermittent respiratory activity in cranial nerves.[41,51] In adult mammals, respiratory activity persists in cranial nerves driving pharyngeal, laryngeal and neck accessory muscles.[52–55] Conservation of the respiratory controller is further illustrated by the fact that the Hering-Breuer inspiratory-inhibiting reflex has been found in all air-breathing vertebrates.[40] This reflex consists of an early cut-off of inspiration and a prolongation of expiratory time that result from lung inflation.

Conservation of circuits for hiccoughs

A central pattern generator in non-mammalian life forms that might be the precursor of the hiccough oscillator should show similar temporal behavior and generate a similar motor pattern. Based on the feature of rhythmic bursting of inspiratory muscles, candidates include the generators responsible for sigh, gasp, aspiration reflex, primitive air-breathing, and gill ventilation. However, a salient feature of hiccoughs is glottal closure during neural inspiration,[25] which leads to a unique dissociation between neural activation of the inspiratory muscles and actual inspiration. Only gill ventilation (and, similarly, the first buccal elevation during two-cycle air-breathing in ray-finned fish such as the gar) demonstrate activation of inspiratory muscles during glottal closure.

Gill ventilation shows additional similarities to the hiccoughs. For example, in the tadpole, gill ventilation appears before lung ventilation[38,39] and hiccoughs are one of the first respiratory-like movements produced by mammalian fetuses.[26] The frequency of gill ventilation in the intact tadpole is decreased by severe hypercapnia—augmentation of inhaled CO_2 concentration, either in water or in air—as is the frequency of hiccoughs.[18,56] Both hiccoughs and gill ventilation produce contraction of inspiratory muscles, comprising elevation of the floor of the mouth in both cases, but contraction of thoracic muscles as well in the case of hiccoughs. Furthermore, lung inflation inhibits both hiccoughs[57] and gill ventilation in the tadpole.[58,59]

In lower vertebrates, lung inflation also inhibits air-breathing and, although hypercapnia increases the frequency of air-breathing (opposite to its effect on hiccoughs), the sudden contraction of inspiratory muscles during hiccoughs resembles the sudden onset of the neural output of the air-breathing CPG in premetamorphic tadpoles.[60] In addition, a low dose of baclofen, the $GABA_B$ receptor agonist[61,62] is sufficient to abolish the air-breathing motor pattern of the isolated brainstem of the tadpole. At much higher concentrations, the gill ventilatory motor pattern is also abolished.[35] Remarkably, the same drug is also used to cure intractable hiccoughs.[27,63,64] Although $GABA_B$ receptors are widely distributed in the human body,[61] experimental results plead for a central action of baclofen on the hiccough CPG. Indeed, the hiccough-like reflex induced in the cat by electrical stimlulation of the medulla is abolished by microinjection of baclofen into the same site[65] and the effect of intravenously administrated baclofen is inhibited by intracisternal administration of a $GABA_B$ receptor antagonist.[66]

These similarities are consistent with the hypothesis that the CPG responsible for hiccough in humans is a phylogenetic relic of the circuits used to produce ventilation in lower vertebrates (Table 1).

Phylogenetic models of hiccoughs

We propose that an archaic ventilatory CPG persists in the mammalian brainstem. We assume that, normally in mammals, the ancient output of this archaic CPG—activation of inspiratory muscles during glottal closure—is suppressed during eupnea by more recently evolved circuits. Why should the archaic CPG not disappear altogether?

One hypothesis that glottal closure naturally brings to mind is that of a protective mechanism against inappropriate aspiration of liquids or solids rather than air. The fact that the human airway and foodway cross above the glottis makes such mistakes a significant risk, particularly in infants because of the immature state of the nervous system. However, a protective mechanism of this kind would not be expected to reinforce inspiration as hiccough does, but rather to have an expulsive effect. This function is that of cough, which consistently occurs when food enters the airway. Hiccough is not known to arise from such mistakes, occurring independently.

Table 1. Similarities between hiccough and tadpole gill ventilation

- Automatic motor pattern
- Central pattern generator in the brainstem
- Early developmental behaviour
- Respiratory-related behaviour
- Glottal closure
- Contraction of inspiratory muscles
- Inhibition by lung inflation
- Inhibition by hypercapnia

In fact, hiccough is often related to stimulations of the esophagus (see above) that occur only after a successful passage into the foodway. In addition, hiccough does exist in non-human mammalian species in whom the larynx is positioned high in the neck, with an intranarial portion that creates largely separate respiratory and digestive routes (see Ref. 67). This minimizes the risk of food misdirection towards the airway and makes hiccup in these species unlikely to have a protective anti-aspiration function.

Another possibility is that more modern circuitry for eupnea includes elements of the archaic CPG, which now play a role in rhythm generation and in elaborating the pattern of inspiratory motor output to cranial motor neurons, while newer elements command glottal opening and motor output to chest wall muscles. This model accounts for the occurrence of hiccough during circumstances such as brainstem lesions that damage the source of the suppressive influence, stimulation of esophageal afferents powerful enough to oppose the suppressive input, or during development when the suppressive input is not fully established.[1] Executing its original motor pattern, the relical CPG closes the glottis and activates inspiratory muscles, raising the base of the tongue to compress the buccal cavity, contracting the diaphragm and generating a hiccough. A testable prediction of this model is that most neurones active in the generation of the eupneic rhythm, except those responsible for glottal opening during inspiration, should also be active during hiccoughs. Furthermore, if our hypothesis is true, the spatiotemporal sequence of neuronal activation responsible for inspiratory muscle contraction and for glottal closure during hiccoughs in mammals should resemble the spatiotemporal sequence of neuronal activation responsible for buccal muscle contraction and for glottal closure during gill ventilation in bimodal breathers.

Alternatively, the archaic ventilatory CPG may not participate in eupnea but instead may play a role in other normal behaviors requiring buccal compression and glottal closure. In this view, suckling, which involves rapid rhythmic buccal aspiration combined with closure of the glottis, seems by far and away the most-likely mammalian manifestation of a preserved central pattern generator responsible for gill ventilation.[68] Important features differentiate suckling and hiccough. Hiccough relates to breathing and involves the activation of inspiratory muscles, not seen during suckling. Suckling is associated with oropharyngeal peristalsis[69,70] and swallowing whereas hiccough is associated with the cessation of peristalsis in the oesophagus[71] and favours acid gastro-esophageal reflux. Airway closure in suckling depends mainly on a passive movement of the larynx toward the epiglottis[68] whereas it results from active adduction of the vocal cords in hiccough as in gill ventilation.[18,20,49,60] These differences imply that, if our hypothesis about the phylogenetic origin of hiccough is correct, suckling depends on a central pattern generator that uses only the part of the

archaic gill central pattern generator that govern buccal movements. According to this model, hiccough would occur through a malfunction in which spinal motor neurones controlling the inspiratory muscles are activated in addition to cranial "inspiratory" motor neurones required for the ingestive behaviour of suckling. Hiccough may thus be the evolutionary price to pay for the development of suckling. The ontogenetic sequence of expression of the two motor behaviours is compatible with this contention. Hiccough can indeed be identified in the fetus by ultrasound scan imaging not only before breathing movements (see above), but before suckling patterns, identified by rhythmical bursts of regular jaw opening and closing followed by swallowing.[26,68] Of note, the hypothesis of the conservation of the archaic gill CPG to permit suckling would also fit well with the more frequent occurrence of hiccoughs in neonates and the decrease of this occurrence with age.

Another testable prediction of our model is therefore that the majority of neurones involved in suckling will also be activated during hiccoughs. The spatiotemporal sequence of activation of neurones responsible for buccal muscle contraction and for glottal closure may also be similar during hiccoughs in mammals and during gill ventilation in bimodal breathers. This could also be tested by simple clinical studies trying to establish a link between feeding modalities and hiccoughs in mammals.

Conclusion

The exact origin and physiological significance of hiccoughs are unknown. Here we propose a phylogenetic perspective that sheds a new light on this annoying affliction which, at first sight, would appear to have no physiological advantage. This approach results from the concept that the ventilatory central pattern generator of lower vertebrates provides the base upon which central pattern generators of higher vertebrates develop.

Hiccoughs are characterized by glottal closure during neuronal inspiration, and by early development in relation to lung ventilation. They are inhibited during hypercapnia and by lung inflation. They can be abolished by baclofen. These properties are shared by ventilatory motor patterns of lower vertebrates, leading to the hypothesis that hiccough is the resurgence of archaic motor patterns and particularly of the motor pattern of gill ventilation in bimodal breathers such as most frogs, at the tadpole stage. A circuit that can generate hiccoughs may persist in mammals because it has permitted the development of pattern generators for other useful functions such as modern eupnea or suckling. Neurone recordings may permit testing of these models by comparing the pattern of neuronal activation during hiccoughs in mammals and during gill ventilation in bimodal breathers.

The merits of these models have to be considered against the documented complexities of even the simplest of neuronal circuits, which can operate in several different modes and interact with other networks to generate multiple motor patterns as well as undergo extensive modification in the course of development and evolution. While neither model has experimental proof, we believe that they provide a novel framework for the study of hiccough, generate testable predictions and should provoke new discussion on this fascinating, common but little understood ailment.

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