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Potential Evolutionary, Neurophysiological, and Developmental Origins of Sudden Infant Death Syndrome and Inconsolable Crying (Colic): Is It About Controlling Breath?

ABSTRACT

The authors develop a conceptual, testable model suggesting lack of developmental synchrony between cortical and subcortical neural tracts necessary for breathing control underlying human vocalization (speech breathing), potentially leaving infants vulnerable to inconsolable crying. They propose that this lack of developmental synchrony also helps explain the human susceptibility to sudden infant death syndrome. Beginning around 1 month, during sleep and awake periods, infants gradually learn to shift between volitional and autonomic breathing control based on developing functional interconnections between cortical and subcortical neural networks. The existence of sudden infant death syndrome and inconsolable crying may reflect adaptive failures exacerbated by prolonged parent–infant separation, whether night or day, due to one or the other subsystem of neural networks and/or their functioning nuclei not being equally mature or able to sufficiently send, detect, or respond to signals provided by the other. Implications of these proposed models for family practice and family science research are examined.

In this article we address what neurological and physiological components sudden infant death syndrome (SIDS) and inconsolable crying have in common and how each may share, at least conceptually, the same biological origins. The hypotheses we develop to support this model and the types of research findings that lead us to make these conceptual bridges emerge from an expansion of an earlier model developed by McKenna (McKenna 1986, 1990a, 1990b; McKenna & Mosko, 1990). This model addressed potential origins of SIDS from a comparative, evolutionary, species-wide perspective. Working from human evolutionary data, including psychobiological and neurophysiological studies, McKenna proposed that the infants' emerging speech breathing skills represent a transition from

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one to two neural-breathing (and vocalizing) control subsystems (one supporting volitional and one supporting nonvolitional respiration; see Figure 1). Over the first 7 months these subsystems become fully integrated into a "supersystem." In this supersystem, each subsystem, while functionally *inter*dependent, still maintains its original separate function that accommodates maintenance breathing (i.e., quiet breathing) and more episodic purposeful, volitional breathing during sleep stage transitions, in addition to purposeful voice while awake (see Figure 1). In other words, and in addition to chemoreceptor neural networks, this shifting between subsystems and recurrent integrations is completed by way of processes that depend on both ponto–medullary (subcortical) structures developing in relationship to increasing cortical interconnectivity, eventually facilitating seemingly effortless communication between these supportive structures (see Figure 1).

We propose that glitches in these developing systems create altogether a unique, species-wide potential susceptibility by infants to either SIDS or inconsolable crying based on the neurophysiological process by which human infants learn to speech-breathe. Although development of language is critical to humankind's evolution, we suggest that, for a brief period, the adaptations underlying the need to willfully control breath as required for speech makes infants susceptible to at least these two kinds of breathing control errors. Risk of these breathing control errors is increased, we suggest, when and if environmental factors—namely, prolonged separation from the caregiver—coincide with the peak time in which a transition from strict subcortical-controlled breathing to a system in which cortical nuclei and their neuro-networks during both awake and sleep periods are becoming integrated, producing shared dual control.

The infantile breathing control "glitches" we propose as occurring during these periods of instability are characterized by a delay in development of, or a lack of developmental synchrony between, cortical and subcortical neural circuits necessary for breathing control underlying both sleep stage transitions and human vocalization. This lack of synchrony, we hypothesize, compromises the unique, human developmental process whereby infants, through practice and learning, acquire the capacity to shift between

volitional and nonvolitional breathing control. We hypothesize that outcomes of this lack of synchrony help explain the human susceptibility to SIDS, a sleep-related, tragic infant death that still resists a full explanation of its biological origins. At the same time, this lack of synchrony potentially leaves human infants vulnerable to inconsolable crying because it leaves infants unable, while crying, to disassociate their voice from their breath, leading the two temporarily to become functionally bound. On the basis of this foundation we examine these proposed hypotheses and examine their implications for family science.

The authors present this work with full understanding that the ideas presented simplify functionally interrelated, complex neurobiological systems, some of which are not yet completely understood. There are some conceptual risks here in describing the evolution of primate–mammalian vocalization research (see Brudzynski, 2010) alongside and in relationship to language and the development of human respiration in the context of both infant sleep and awake periods. Though the model proposed is empirically based, it is incomplete. The goal of the material presented is to provoke a more integrative dialogue between fields—a new mindset, perhaps, for further inquiry, future corrections, and intellectual refinement.

Establishing a Biocultural Model

Normative Patterns of Development of Respiratory Control, Vocalization, and Emotional Response

We begin with the observation that the eventual capacity to control breath underlying vocalizations, referred to as *speech breathing*, begins to develop after the first month or two of an infant's life, but is not completely developed until around 7 months of age (Hollien, 1980; Langlois, Baken, & Wilder, 1980; Laufer, 1980; McKenna, 1986; McKenna et al., 2007). At this time of maturation, speech breathing becomes marked by prelinguistic sequences that are gradually calibrated by cortical nuclei to coordinate and sustain just the right amount of exhaled air, released at the right speed and with retention of enough residual air in the lungs (and behind the glottis) to support both speech fluidity and metabolic needs (Whitehead, 1983). Collectively, these
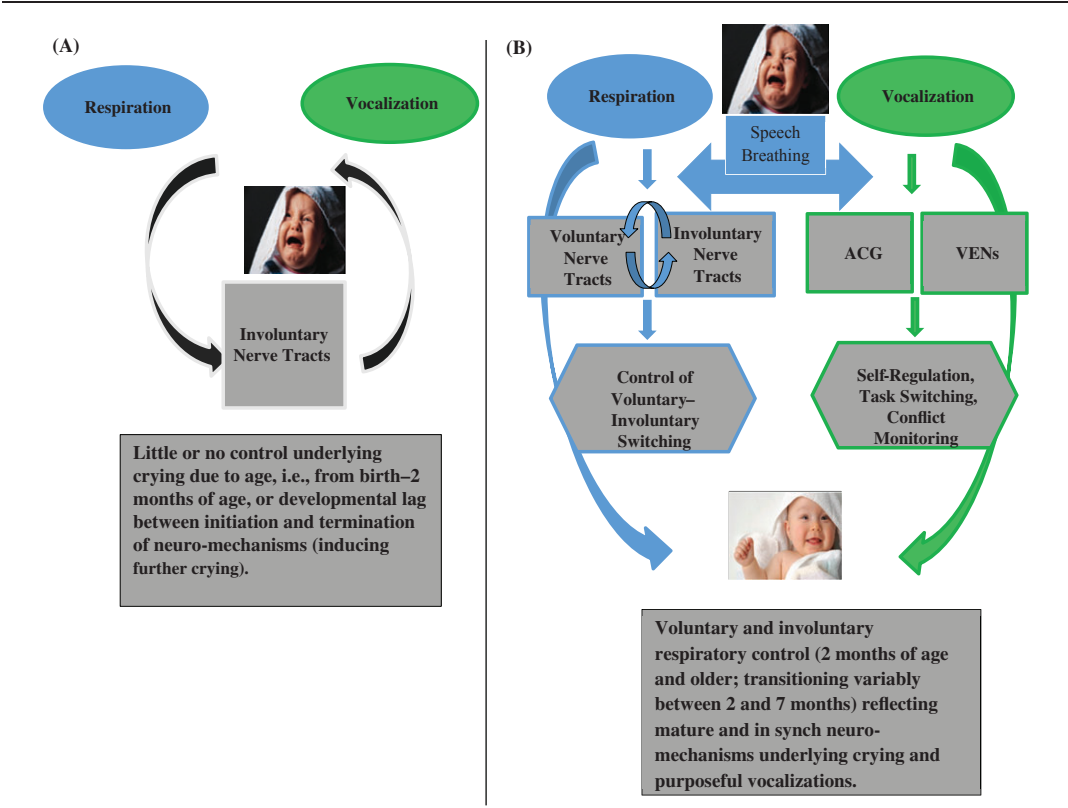
Note. ACG, anterior cingulate gyrus; VENs, von Economo neurons.

skills and their underlying neurological bases provide for a labile, multisensory, highly integrated, dual-control breathing system that ties together the autonomic system functioning subcortically with cortical nuclei orchestrating volitional control of breath. These developing networks occur in relation to left hemispheric language centers (i.e., Wernicke's area), functioning to hear and store words and promoting comprehension; Broca's area, conducting motor control of lips, tongue, and other laryngeal and oropharyngeal muscles; and the arcuate fasciculus that bridges these critical language nuclei across its physiological production.

In addition to these developmental trajectories is the role of the anterior cingulate gyrus (ACG), which contributes to the vocalization system of diverse animals, including humans (Jürgens, 2002; Ludlow, 2005), and to human infants' capacity for controlling emotions, emotional–cognitive interfacing, and self-regulation (Newman, 2007; Posner, Rothbard, & Sheese, 2007; Yeung, Nystrom, Aronson, & Cohen, 2006). Ludlow (2005) and Jürgens (2002) have identified the ACG's role in supporting emotional expression found when we laugh and cry. These researchers concluded that the ACG and related structures are more imperative for normal emotional expressions than for volitional-based vocalizations including speech. This distinction is evident in spasmodic dysphonia, a laryngeal dystonia in which a person has abnormal muscle tone and can cry, laugh, and

shout in a normal manner, but has difficulties with speech communication (Brin, Blitzer, & Stewart, 1998; Izdebski, Dedo, & Boles, 1984). Thus, Ludlow (2005) suggested that emotional expression uses the older vocalization system (i.e., cingulate cortex, periaquaductal grey, retroambiguus, and ambiguus) that is found in other species, whereas speech expression depends on cortical control (i.e., more direct control by the laryngeal motoneurons of the laryngeal motor cortex at the inferolateral end of the primary motor cortex adjacent to the sylvian fissure) (Simonyan & Jürgens, 2003).

Two Breathing Control Glitches as Related to SIDS and Inconsolable Crying?

A Conceptual Beginning Point Regarding SIDS

We propose two possible types of glitches, or nonnormative outcomes, associated with infants' inability to switch between volitional and nonvolitional control of respiration resulting from, we suggest, a mismatch of sorts (or lack of developmental synchrony) in the maturational timing of the critical neural networks that promote continuous, fluid breathing across different infant sleep and wake states. The first nonnormative outcome potentially related to SIDS risk is represented in a physiological pathway that, because of some kind of developmental mismatch, fails to switch either into or out of volitional or nonvolitional control of respiration during sleep, compromising sufficient oxygen saturation levels and leading to hypoxia and infant death. Neurobiological studies conducted by Baba and colleagues (1983), Haddad and colleagues (Haddad & Mellins, 1983; Haddad, Leistner, Lai, & Mellins, 1981), Quattrocchi and colleagues (Quattrochi, Baba, Liss, & Adrion, 1980), and, independently, by Kahn and colleagues (2000) suggest that these glitches could find expression during infant transitions from one sleep stage to another, interrupting continuous breathing signals required to assure effective respiratory continuity.

In the case of SIDS, we posit that the cortex fails to receive a signal, or at least a sufficient signal, from ponto–medullatory structures, including from immature chemoreceptors needed to awaken or arouse the infant (by way of cortical activation), so that the infant can willfully control the taking of a breath to terminate the ongoing apnea. Infants are especially vulnerable to this kind of signal insufficiency after the gasping reflex, which protects infants from prolonged apneas, is lost after a month or so following birth (Hollien, 1981; Plum & Leigh, 1981; Remmers, 1981). Infants are made further vulnerable from this adaptive failure, it has been argued (see McKenna, Ball, & Gettler, 2007), when they sleep alone, without breast milk and breastfeeding, devoid of extrasomatic stimulation that can rely on other neurologically integrated sensory streams or subsystems that can provide supplemental (back-up) stimuli to arouse the infant to take a breath, such as touch, movement, inhalation of parental CO_2, or sounds from the caregiver, all of which have physiological effects on breathing, as we describe next.

A Conceptual Beginning Point Regarding Inconsolable Crying

In regard to inconsolable crying, we posit a second type of glitch in which the infant is, to an extent, not *under*aroused, as is the case for SIDS, but over- or hyperaroused whereby both volitional and nonvolitional subsystems, during this period of becoming integrated, fail to give way to the other. With this glitch, both subsystems are stimulated and functioning simultaneously, essentially not permitting the infant to disassociate his or her crying from breath (i.e., to stop crying). Furthermore, sensing this lack of control, the infant participates by willfully crying more, thereby essentially prolonging the crying the infant could not stop in the first place.

A Conceptual Beginning Point Regarding the ACG

Aside from both glitches theoretically representing an error in which both subsystems of breathing control fail, or miscommunicate, across neural networks, the problem is compounded by a lower number of neural nuclei and/or axons and dendrites present during this developmental stage than with later maturation. These neural nuclei include the large spindle-shaped neurons called *von Economo neurons* (VENs), which play a regulatory role in the ACG as regard task switching (Conor et al., 2006), and a developmental lag in their development further places infants at risk of breathing problems. These proliferating cells do not reach their highest density until about 4 months of age, after which the infant has already passed through the time

he or she is most vulnerable to either SIDS or inconsolable crying. The point is that, though multifunctional (and complex), the ACG and its supportive neurons potentially play a critical role in stopping and starting motor activities, including both emotional and non-emotional communicative expressions, including crying (Allman, Hakeem, Erwin, Nimchinsky, & Hof, 2001).

In What Ways Is the Human Respiratory System Different from Other Mammals?

To illustrate further just how unique this development of human respiratory control and vocalization is that helps explain the timing of peak risk of SIDS and inconsolable crying, we highlight the distinctiveness of this development in humans as compared with the respiratory control systems characteristic of other mammals. In the past 50 years, research has revealed that for the first month of life human respiration is mostly controlled by means of the central autonomic nervous system, wherein infants' vocalizations are mostly involuntary (McKenna, 1986; Mitchell & Berger, 1981; Remmers, 1981; see Figure 1, Panel A). Neonatal breathing is shallow and depends mostly on diaphragm movements rather than rib muscle (intercostal) movements. Respiratory behavior is primarily reflexive and based not on the infant's volitional efforts but primarily driven by chemoreceptors sensitive to $CO_2:O_2$ ratios in the blood, the neuronal centers in the infants' brain stem's reticular formation, and possibly the nuclei in the spinal cord itself (Harper, 1984; Mitchell & Berger, 1981). Progression to a more volitional control of respiration in relationship to vocalizations is gradual and begins variably around 2 to 3 months of age. This development is marked by noticeable (and measureable) acoustic changes in infants' vocalizations explained by increasingly more precise control by the infant of its underlying breath.

Specific to human breathing and vocalizing, and in addition to innervation of the phrenic nerve that drives the diaphragm to maintain proper $CO_2:O_2$ ratios, are three primary neural tracts that transact to make possible this voluntary–involuntary, dual-control breathing control system. These tracts—corticobulbar, corticospinal, and reticulospinal (see Figure 2; Garcia-Campmany, Stam, & Goulding, 2010; McKenna, 1986; McKenna et al., 1993, 1994; Moss, 2005)—

elaborately and diffusely project into the neocortex (i.e., the newer part of the human brain) via the thalamus from ponto–medullary structures in the lower brain stem (see Figure 2) and, in at least one case, descend into the spinal cord itself (Kim et al., 2008). While volitional respiration is developing, and while awake, infants essentially practice and learn how to assert and integrate breath units with sound units vis-à-vis these three nerve tracts and their neural support structures. During this particular developmental period infants continually and rapidly shift, and/or attempt to shift, between involuntary (subcortical) and voluntary (cortically based) control networks (Harper, 1984; McGinty, 1984; Mitchell & Berger, 1981; Plum & Leigh, 1981).

Kuypers's (1958a, 1958b) work is consonant with the importance we place here on what is unique about human respiration and the developing neuro-architecture and physiology that make human infants, but not other species, vulnerable to breathing-related syndromes. Kuypers (1958a) conducted anatomical studies of the corticobulbar pathways in humans and the rhesus macaque monkey and found that only humans have direct corticobulbar projections from the motor cortex to the laryngeal motor neurons in the nucleus ambiguous. More recent research examining other primate species with which humans share a great number of evolutionary commonalities likewise has revealed that only humans house direct corticobulbar projections to the nucleus ambiguus (Ludlow, 2005; Simonyan & Jürgens, 2003). Ludlow (2005) described research among primates in which coughing, swallowing, and laryngeal muscle control in general are exclusively associated with subcortical nuclei rather than cortical nuclei as found in humans. These findings are also consonant with other findings on volitional breathing involving the corticobulbar track by Boliek and colleagues (Boliek, Hixon, Watson, & Morgan, 1996), who reported that, among humans, tumors on the corticobulbar tract eliminate voluntary breathing, whereas damage to the automatic brain stem structures does not have similar effects. This research helps document that the forebrain cortical projections near the motor area influence human breathing (particularly in relationship to vocalizing in the context of crying initially) and then later influence speech itself.

FIGURE 2. AT BIRTH, BREATHING AND CRYING ARE CONTROLLED FROM THE BRAINSTEM BY MEANS OF AUTONOMIC FUNCTIONING. BETWEEN 2 TO 4 MONTHS OF AGE, THE INFANT GAINS INCREASING CORTICO-VOLUNTARY CONTROL OF BREATHING AND CRYING UTILIZING THREE TRACTS: CORTICOBULBAR, CORTICOSPINAL, AND RETICULOSPINAL. WITH PERMISSION, ADAPTED FROM MCKENNA (1986).

At Birth

From Brainstem-Reflective Breathing and Crying

At 2-4 Months

Increasing Cortico-Voluntary Control
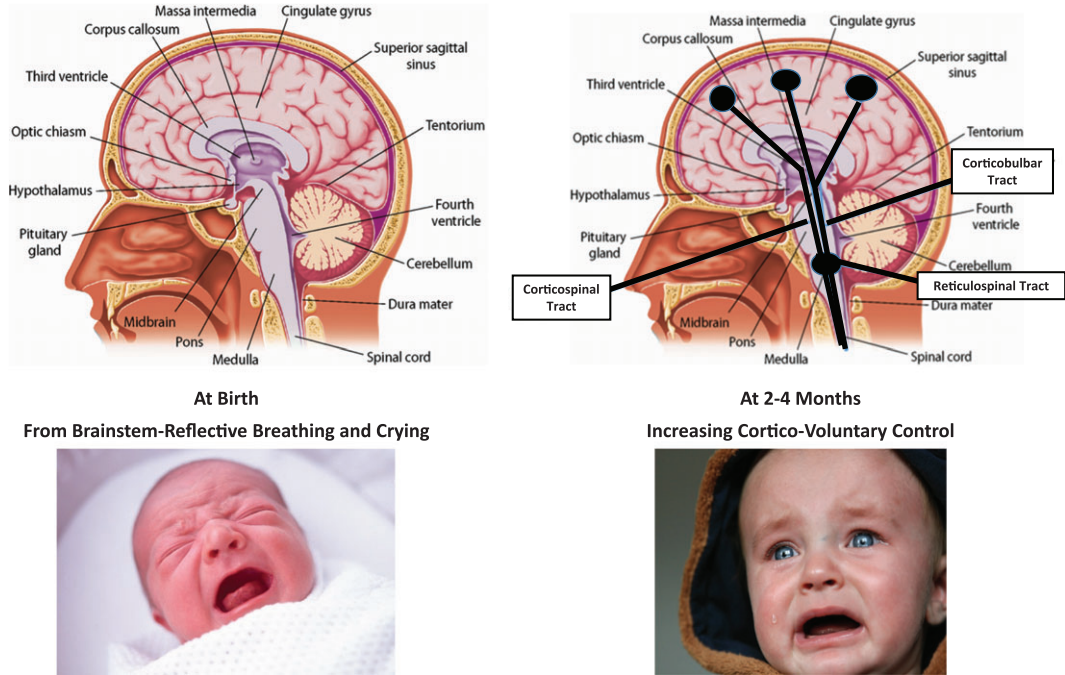
BREATHING CONTROL: WHAT IS LEARNED, AND TO WHAT EXTENT DOES EXPERIENCE PLAY A ROLE?

There is no doubt but that language is one of humankind's most remarkable sets of adaptations that required the evolution of critical anatomical, neurobiological, and physiological changes to accommodate it. An important period in this evolution occurs between 2 and 4 months of age, during what is often called infants' *first developmental shift*. Just as infants learn how to reach intentionally for objects during this time, they also learn how to assert increasingly more precise control over the laryngeal muscles by the manipulation of air flow, volume, and subglottal pressure, aided by control of the muscles of the tongue, lip, and intercostal muscles driven by episodic, infant-directed, willful behaviors (Dezateux & Stocks, 1997; McKenna, 1986). Indeed, as others have shown, specific breathing patterns underlying crying and attempts to initiate purposeful or willful voice precedes speech and, indeed, is practice for it, both in a behavioral

and physiological sense (Hollien, 1980; Wilder, 1972). For example, like speech breathing, cry breathing occurs by way of the infant purposefully prolonging exhalation while quickening inspiratory flow (all mediated by the cortex) to permit communicative (voice) fluidity (Langlois et al., 1980; Laufer, 1980).

With the development of control of respiration during this developmental shift, the infant begins to express intentional presyllabic and later syllabic vocalizations, mimicking sounds in the environment. With this, infants can—through their own intentions and efforts, and supported by the expanding cortical neural pathways—sustain more melodic cries (Hollien, 1980; Wilder, 1972). It is interesting, and perhaps not coincidental, that at or around 7 months of age, when speech breathing is mastered, parents express an ability to acoustically identify the relative meaning of their infant's cries, differentiating between, for example, hunger, discomfort, or desires to be held, and so on, reflecting the infant's own intents and emotional

status (Hollien, 1982; also see Wilder, 1972; Laufer, 1980; Langlois et al., 1980). It is the purposeful pulmonic manipulations that change the acoustic properties of infants' cries (pitch, tempo, volume) that, even before language, permit infants to practice producing specific sounds they wish to make. Indeed, infants' presyllabic and crying behavior use the exact same underlying proximate neurobiological and physiological mechanisms as does mature speech.

However, specifically we acknowledge that what might happen to make human infants vulnerable to breathing control errors must be analyzed critically and comparatively against the background provided by Carrol (2003), who stated that

> Rhythmic activity in spinal motoneurons innervating the respiratory muscles is produced by a neural network located in the ventrolateral region of the brain stem. This network consists of three interconnected groups of neurons: the ventral respiratory group (VRG) in the ventrolateral medulla, the dorsal respiratory group (DRG) in the nucleus tractus solitarius (NTS) of the medulla, and the pontine respiratory group (PRG) in the dorsolateral pons. In addition, a group of neurons in the pre-Bötzinger complex (PBC), within the VRG, is essential for respiratory rhythm generation. The respiratory rhythm generated by this network is not simply repetitive inspiratory bursts but consists of alternating bursts of neural activity controlling separate inspiratory, postinspiratory, and expiratory phases of the respiratory cycles. (p. 389)

That said, infants' developing volitional control over voice and the respiration underlying it depend on practice and the building of coordination between higher and lower brain structures and their mediating neural networks. For example, speech breathing requires a larger residual volume (i.e., amount of air remaining in the lungs after expiration or vocalization; Forner & Hixon, 1977; Whitehead, 1983) and, unlike nonvolitional or maintenance breathing, requires fewer breaths per minute, from an average of 18 to approximately 10 to 14 breaths per minute, respectively (see Figure 3; see also Whitehead, 1983). Similarly, unlike vegetative breathing or maintenance (quiet) breathing, speech breathing essentially limits inspiratory interruptions to ensure the maximum use of air for phonation or vocalization as air is expired (Langlois et al., 1980; Lauffer et al. 1980).

With this in mind, we speculate that infants' control of respiration and vocalization is learned,
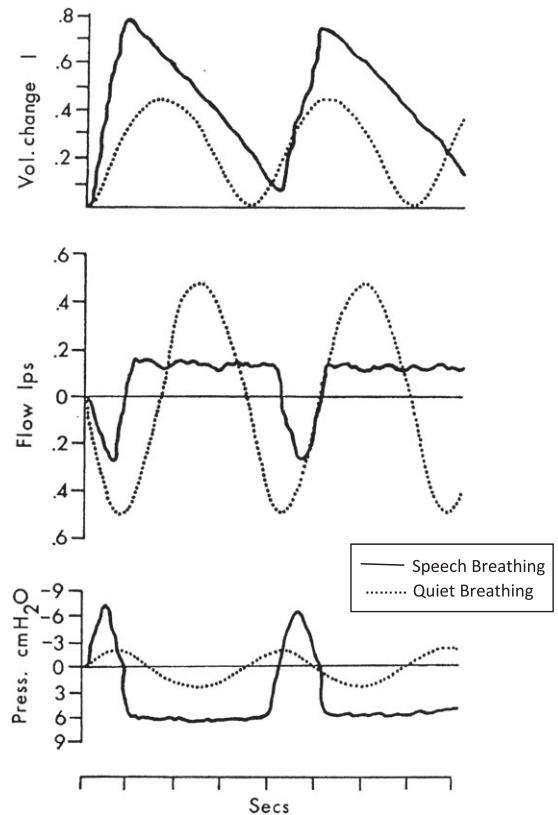
or experiential. This learning is based not only on infants' hearing voice and sensing breath (i.e., breathing stimuli from others), but also through proprioceptive auditory processes that permit the infant to correct mistakes (Burnett, Freedland, Larson, & Hain, 1998). Through this experience infants gradually perfect the temporal correspondences between initiation of purposeful sound and breathing needed for communicative fluidity.

HOW DO WE KNOW LARYNGEAL MUSCULAR CONTROL OVER BREATH IS EXPERIENTIALLY BASED?

Support for the importance of learning, experience, and proprioceptive infant feedback in acquiring speech breathing skills is found in

the research that has addressed the relationship between laryngeal muscular control, breathing, and vocalizing. This research also illuminates how engagement with external, somatosensory stimuli is specifically required as infants essentially practice laryngeal fold movements when developing control over vocalizations as preparation for speech (Kattwinkel, 1977; Ludlow, 2005).

Evidence from Speech Deficiencies of Persons with Hearing Impairment

Critical to these insights are studies that have examined the breathing and vocalizing of infants and children with hearing impairment. This work shows that the degree of speech intelligibility (i.e., how much of what a person says can be understood by others) depends on the child's level of hearing impairment. Children with hearing impairment not only lose excess air per any given syllable—at least three times as much compared to children with normal hearing—but in general face experientially based lifetime difficulties controlling both loudness and pitch, as well as an inability generally to learn the activities required for proper speech articulation. For example, in children with impaired hearing the timing of linguistic breaks relative to expiration duration may not be timed efficiently to permit speech fluidity (Laufer, 1980).

Further support regarding the importance of experience comes from Whitehead's (1983) experimental data, which indicated that persons with hearing impairment initiate speech at much-too-low lung volumes and generally while speaking maintain lower-than-required functional residual capacities (the total amount of air remaining in the lungs after expiration). Because speakers with hearing impairment maintain only half the amount of air in their lungs as do speakers who are not hearing impaired, the individuals with hearing impairment must apply greater muscular pressure. Whitehead pointed out that this works against respiratory (lung) recoil forces. Thus, the speech of the person with hearing impairment continues beyond the functional residual capacity of the lungs that support the vocalization (Forner & Hixon, 1977; Whitehead, 1983).

Presuming that otherwise-normal, auditory-based proprioceptive learning processes are hindered in infants and children with hearing impairment, this rich body of research suggests that the limitations and difficulties of deaf infants and children learning to speech breathe is due to infants' inability to hear themselves (or those close to them) vocalize following attempts at breath manipulations. This results in difficulty getting sounds right as well as difficulty in producing sounds at the moment desired, which lends additional support to the role of basic learning by way of self-correction and interaction with others in the gradual development of speech breathing over time.

Supporting the cortical nature of learning speech, Simonyan and Ludlow (2003) suggested that speech expression very likely reflects direct control of the laryngeal motor neurons by the laryngeal motor cortex, located at the inferolateral end of the primary motor cortex adjacent to the sylvian fissure. Even more relevant to our overall proposal is Burnett and colleagues' (1998) conclusion that, indeed, the cortically controlled speech system is highly dependent on close interactions with what they call "auditory targets" facilitating active corrections in speech production when errors occur.

THROUGH WHAT EXTRASOMATIC CHANNELS MIGHT INFANTS BEST LEARN HOW TO SPEECH BREATHE?

Are Human Infants Presensitized to Detect and Respond to External Respiratory Signals/Cues?

These data point clearly to the importance of learning through auditory input from self and others, which both depend on cortical mediation. However, on a related note, these data underscore the added importance of *access* to external parental breathing cues, which is made possible by prolonged sensory engagement (including hearing, smelling, and feeling breath) sustained by proximity and contact, as, for example, by way of infant-carrying behaviors on the part of the caregiver, cosleeping, and breastfeeding (see McKenna et al., 1993; McKenna & Mosko, 1990). These interactions provide the opportunity for intimate sensory exchanges between infants and their caregivers that, in any number of ways, help regulate overall the infant's physiology, including respiration (McKenna & Mosko, 1990; McKenna et al., 2007).

The potential importance of social proximity to others for optimal development is evidenced

in research showing that infants are presensitized to respond to breathing and auditory vesicular sounds and are sensitive to their caregivers' breath, usually, but not exclusively, the mother's (Reite & Field, 1985). When in close contact, the caregivers' breath gently falls against the infant's cheeks, stimulating the infant's subdermal cells. These external breathing signals are augmented by vestibular movement, such as stimulation of the caregivers' chest, with its rising and falling acting as a *zeitgeber* (rhythm giver), very likely promoting the infant's breathing stability when close enough to exchange such signals.

Rhythmic (or arrhythmic) sound may act as a signal that influences breathing cycle rates among mammals in general. This is suggested by a number of studies. Stewart and Stewart (1991) found that brief, quiet, repetitive auditory stimuli affected the respiratory behavior of sleeping puppies. Specifically, they found that the stimulus presentation was associated with an increase in the sleep respiration rate irrespective of the stimulus presentation rate being faster or slower than the baseline respiratory rate and irrespective of the pattern of presentation being regular or random. Verification of this sensitivity among human infants is found in the work of Thoman and Graham (1986), who showed how much and in what ways human neonates are born presensitized to breathing sounds and movements. In their research with seriously apnea-prone newborns they showed how sleep contact with a "breathing teddy bear" reduced the infants' apneas by as much as 60%. The experimental protocol involved inserting small mechanical air pumps into the belly of the teddy bear that caused the teddy bear's belly to move up and down at a speed set for each individual infant's "best" breathing frequency. We discuss this further in the Summary and Implications for Family Science section.

Human Neurophysiology of Respiratory Control and SIDS: What Goes Wrong?

We propose that the presence of either (a) a lack of synchrony in physiological pathways or (b) missed signals that occur as autonomic (i.e., subcortical) and volitional (i.e., cortical) neural networks come to function as one system. These two elements contribute to infants' risk of SIDS or expression of inconsolable crying. In regard to the outcome of SIDS, the potential that a developmental lag exists that either impedes,

limits, or altogether prevents developing volitional and nonvolitional breathing systems to sufficiently integrate is suggested in the work of several research outlined herein (e.g., Baba et al., 1983; Haddad et al., 1981; Quattrochi et al., 1980). Support for the potential of such a developmental glitch being associated with infants' risk of SIDS is found in Haddad and colleagues' (1981) research, which showed that the rate of brain maturity of near-miss SIDS infants was slower than that of infants in a control group, as indicated by delayed reorganization of REM and NREM sleep patterns. This same research team suggested that there may be a *functional imbalance* between the maturity of two types of intercellular connections involving the dendritic spine synapse (the more common) and the electronic spineless connections *between* the dendrites that permit, and in some cases may interfere with, intercellular communication between these three nerve tracts (Quadrocchi et al., 1980).

Indeed, the work by Baba and colleagues (1983) and Quattrochi and colleagues (1980), as well as that of Haddad et al. (1981), is potentially central to our conceptual model proposed for both SIDS and inconsolable crying. Together, their findings make it reasonable to suggest that if one kind of neural track connection is mature (as regards neuronal communication) while the other is not, then this lack of synchrony in function may "compromise the synchronous synaptic capabilities of the reticular network" altogether (Baba et al., 1983, p. 2791). This thereby impedes the transfer of information and/or signals related to respiratory control during sleep, especially during and before REM to NREM transitions.

The work of Kahn and colleagues (2000) further supports this thesis. These researchers reported that most obstructive and central apneas for infants between 8 and 15 weeks of age (the SIDS and inconsolable-crying window of vulnerability) occurred during REM sleep, the sleep stage in which infants begin to exhibit off-and-on, willful volitional breathing participation. This, then, makes it possible that the apnea occurs at the moment infants need to shift to autonomic breathing.

In a large polysomnographic study of infants during sleep, Kahn and colleagues reported that of 2,300 infants studied (involving 20,750 polysomnographs), 30 later died from SIDS. The polysomnographs of these 30 SIDS victims

were subsequently compared with those of a control group matched for sex, age, gestational age, and birth age. The total number of obstructive and mixed apneas were significantly higher in the 30 infants who died of a SIDS event compared to those in the control group. In fact, apneas were seen in 63% (19 of the future 30) of SIDS infants; only 10% (six of the 60) control infants exhibited any apneas at all. This suggests the existence of problems with the breathing control among SIDS victims compared with surviving infants. It also would support the general acceptance that it is not so much that apneas are the cause of SIDS, per se, so much as the inability to arouse to terminate the apneas; that is, that an arousal deficiency remains the problem. Such a condition is itself potentially due to a relatively low-density of acetylcholine nerve sites documented by Kinney et al. (2003), which, at normal densities, function in critical ways to help infants successfully reinitiate breathing following a normal, sleep-related apnea or extended breathing pause (see McKenna et al., 2007, for a thorough review).

As to how this might apply to helping to understand inconsolable crying, Kahn and his colleagues (2000) reported that, while awake, SIDS victims showed difficulties coordinating swallowing with respiration and experienced *breath holding spells*, reflecting difficulties in fully controlling their breath cycles. With this, then, we propose that the same set of preconditions—that is, a lack of maturational synchrony effecting control of breath and, in this case, termination capacities—is consistent with our proposal about inconsolable crying. We propose that, while awake, infants with these preconditions may have no problem initiating a cry, but might not have equal capacities to end it. Alternatively, after starting to cry, infants with these preconditions fail to exhibit commensurate capacities to disassociate their vocalizing from the breathing cycle that sustains crying. If this is the case, as postulated previously, infants can quickly realize their inability to stop crying. This realization, we contend, given the role of the ACG in crying and emotional response, would therein cause the infant to respond with continued crying, thereby doing more of what the infant was attempting to reverse—thus resulting in a cruel negative loop.

## SWITCHING THE SUBJECT: TASK SWITCHING, WHAT IS THE CONNECTION?

Normative Patterns of Neural Development as They Support Crying

In his extensive research on the neurobiology of the mammalian cry circuit, Newman (2007) identified the ACG as a key contributor to crying based on its role in regulation of emotional and adaptive responses. In his work, Newman (2004) tentatively supported the possibility of a neuronal developmental lag serving as the causal explanation of colic. He argued that, given the complex interactions between the structures belonging to the mammalian cry circuit, it is reasonable to conclude that variability in the timing of the maturation of these structures could affect the nature of infants' crying behavior. In this article we move this possibility forward to conceptualize very specifically what structures and conduits may be involved.

We begin with an examination of the VENs as related to infants' response control and social behavior (see Figure 4). VENs are most abundant in the frontoinsular cortex (area FI) and at lower density in the ACG. They are unique in structure, being four times larger than the normal pyramidal neurons and having long-distance projections into other areas of the cortex and brain regions (Allman et al., 2001). VENs have been found only in higher functioning mammals, (e.g., great apes, whales, and elephants), with humans having the largest number at maturation (Cauda, Geminiani, & Vercelli, 2014; Hakeem et al., 2009). On the basis of these characteristics of VENs, Hakeem and colleagues (2009) suggested that the size and nature of VENs facilitate rapid communication of social information in the larger brains of these mammals, thus functioning to support regulatory behavior (Hakeem et al., 2009).

In humans, VENs first appear in utero at 36 weeks postconception and are present in small numbers through infants' first month of life (Allman et al., 2001). During this period of development only, VENs are symmetrically located in the right and left hemisphere. The majority of VENs emerge at 4 months of age, either through differentiation or postnatal neurogenesis. At this time, VENs begin to bear the hallmarks of migratory neurons; that is, they become elongated, have undulating leading and trailing processes, and continue to significantly increase in number from 4 to 8 months of age.

FIGURE 4. TRAJECTORY OF DEVELOPMENT OF THE INCREASING DENSITY OF VON ECONOMO NEURONS (VENs) IN THE ANTERIOR CINGULATE GYRUS (ACG; REGULATING TASK SWITCHING NECESSARY FOR CRYING TERMINATION) IN RELATIONSHIP TO SUSCEPTIBILITY TO EITHER INCONSOLABLE CRYING OR "AROUSING" TO TERMINATE APNEAS AS REGARDS COLIC BY THE ACG, OR APNEAS RELATED TO THE EXPRESSION OF SUDDEN INFANT DEATH SYNDROME (SIDS). INFERENCE DRAWN FROM ALLMAN, HAKEEM, ERWIN, NIMCHINSKY, AND HOF (2001).
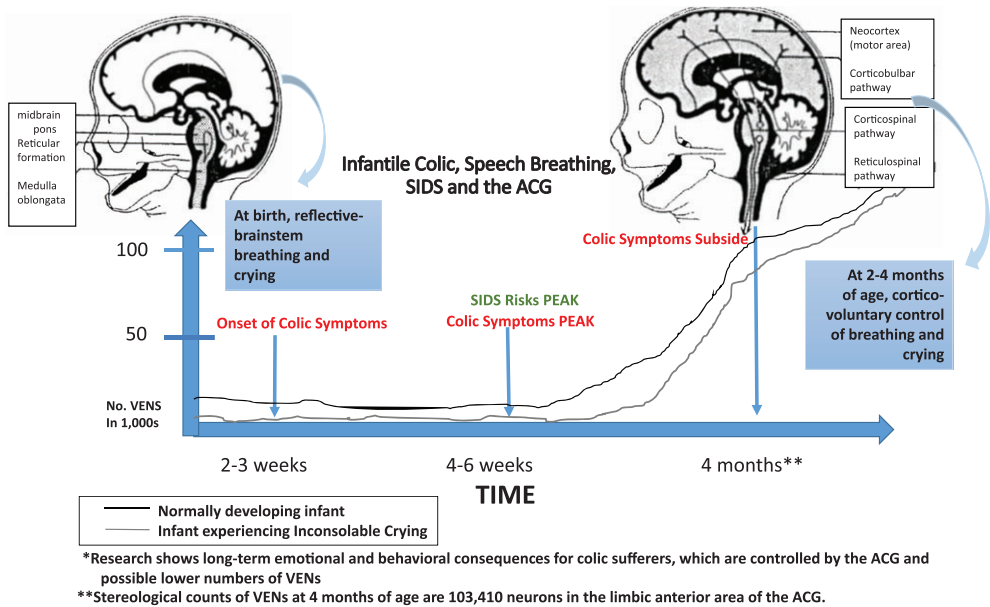
From this period and throughout adulthood VENs are predominantly located in the right hemisphere. Scholars have proposed that the prevalence of VENs in the right hemisphere supports the right hemisphere's involvement in the negative feedback and error correction associated with sympathetic activation that supports determining a response (Allman et al., 2001; Allman, Hakeem, & Watson, 2002). This was evidenced in the work of Houdé and colleagues (Houdé, Rossi, Lubin, & Joliot, 2010), who reported greater activation of the right hemisphere in adolescents, compared to younger children, when faced with a go versus no-go decision-making task that required self-control and the determination of correct and incorrect response actions.

The developmental time frame of the increase in number of VENs at 4 months (see Figure 4) is consistent with other developmental changes connected with ACG function. These include infants' demonstration of greater control of emotional states and regulatory control associated with changes in wake–sleep cycles (Rothbart, Sheese, Rueda, & Posner, 2011) as well as

their ability to hold their heads steady, smile spontaneously, and visually track and reach for an object (Allman et al., 2001). The VENs play a major role in both social error signaling and prosocial signals (Allman et al., 2010). This is supported by analysis of fronto-temporal dementia, which is characterized by a loss of social awareness and the capacity to self-monitor in social situations (Seeley et al., 2006).

Nonnormative Patterns as Related to Inconsolable Crying

We propose that delays in development of the neural networks associated with the ACG, particularly in relation to the presence of VENs, contribute to infants' inability to terminate crying episodes. Based on the contribution of the ACG and VENs to task-switching and emotional response (Botvinick, Cohen, & Carter, 2004), we propose that glitches in the normative development of these neural circuits are associated with infants' inability to adequately evaluate the cost–benefit analysis of ceasing to cry,

and thus be unable to overcome the task inertia of crying. This is further affected by the role of the ACG in infants' developing capacity for volitional control of breath and speech breathing because the role of the ACG in task switching would contribute to infants' capacity to switch between volitional and autonomic control of breath (Frysinger & Harper, 1986). Underdevelopment of these neural circuits may potentially result in infants' experiencing difficulties in overcoming the task inertia of switching between the two breathing systems. This immaturity of the control mechanisms may contribute also to infants' inability to terminate crying.

Supporting an association between infants' experience of inconsolable crying and infants' regulatory capacity is research that has identified a greater likelihood that infants who experience inconsolable crying also exhibit disorganization between sleep–wake regulation and a more general, transient self-regulatory dysfunction of their behavioral–emotional states (DeGangi, Laurie, Castellan, & Craft, 1991; Maldonado-Duran & Sauceda-Garcia, 1996; Papousek & Papousek, 1996). In further support of this potential association, Neu (1997) found no differences in intelligence between 6- to 8-year-old children who had or had not experienced infantile colic, but did find that children who had experienced colic crying demonstrated more impulsive behavior, were significantly more active, demonstrated a lower threshold to sensory stimuli, and experienced more negative moods. He also noted that colic-prone infants had significantly more sleeping problems at this later age and were more likely to be diagnosed with attention-deficit/hyperactivity disorder.

If Arousals Are Protective, Shouldn't Colicky Babies Be at Less Risk for SIDS?

Although in a rather circumspect way, a final potential support for the connection between SIDS and colic and impaired respiratory control among infants can be drawn from a connection proposed by Weissbluth (1981). Starting from the observation that frequent infant awakenings "occur in infantile colic, acid [reflux] sleep-related respiratory control disorders" (p. 1193), Weissbluth proposed the novel idea that these colic-related night wakings could "represent," or at least inadvertently function as, "an alternative and protective behavioral arousal

mechanism amongst near-miss SIDS infants" (p. 1193). Especially fascinating is the idea of colic functioning as potential protection from SIDS, which is, in fact, oddly complementary to the ideas expressed here, and vice versa. This is especially true as regards the SIDS research neurobiology we report in support of our own model (see also Mosko, Richard, McKenna, & Drummond, 1996, 1997).

In our model we highlight and pinpoint specifically the functional interrelationships of physiological subsystems, both cortical and subcortical, that likely are involved in Weissbluth's (1981) model. Both models require reference to neural network flow and effectiveness being possibly thwarted by a deficiency or underdevelopment in breathing control signaling stimuli, in particular those stimuli that are dependent on cortically based arousal capacities that are important during infant sleep. Assuming the potential for both approaches to have merit, it is fascinating to think that the less severe outcome of inconsolable crying, as we have argued, could also be due (ultimately) to the same developmental, breathing control dyssymmetry. But here, in regard to inconsolable crying, we describe a vulnerability to situations in which infants' voice (crying) and breath can become temporarily bound (while infants are awake) during which period a form of hyperarousal that is out of infants' control prevents the infant from disassociating breathing from voice in order to stop the crying. Yet, perhaps inadvertently, and at the same time, according to Weissbluth (1981), this deficiency, or what we are calling herein a *breathing control glitch*, could be helping these same SIDS-prone infants from sleeping in a sustained, more consolidated sleep form wherein transitions from one stage of sleep (and breathing control) to another could place them at higher risk for SIDS. In this group of infants the initiation capacities for crying (*arousing*, using Weissbluth's perspective) are not matched with the capacity to terminate crying. Yet, in this form of expression, crying can act to reduce the chances of the infant suffering from a more catastrophic event: SIDS.

Voluntary Versus Involuntary Breathing Research: Does It Lead to "A Platonic Search for Reality Behind the Shadows"?

We are not unmindful of Remmers's (1981) apropos comment that trying to separate

voluntary from involuntary breathing control "leads to a platonic search for reality behind the shadows" (p. 1199). Such an effort requires as strict an adherence to what is empirically established as is possible. But, however inexact and missing in details or inadequately conceptualized the proposed origins of SIDS and inconsolable crying proposed here might be, we think that the integration of research summarized herein and forward, using evolutionary-based characteristics of our species and an examination of related neural regulatory systems, offers a new mindset that, at the very least, could produce the kind and level of research that is necessary to determine whether there is any merit to our way of thinking. We are not unmindful of the risky, larger-than-life, conceptual leaps we are making.

That said, we feel confident in the implications drawn from the excellent studies of speech breathing and how human infants eventually master control over speech breathing in part by hearing themselves and others speech breathe. The research supports the importance of practice and rehearsal in mastering speech breathing, a process that, although perhaps developmentally risky, is still crucial in learning to speak. The fact that SIDS appears to be, as we have mentioned, a unique human syndrome that has never been seen or experimentally induced in other animals gives us a powerful beginning point to posit that as long as one of the negative trade-offs is nonfatal (inconsolable crying) and the other affects relatively so few infants (SIDS), surely it is the case that the adaptive benefits of speech far outweighs the costs in infant lives lost (however tragic).

To further develop this model we submit an additional set of factors that help us understand, from an evolutionary point of view, the potential biologically based "safeguards" of this species-wide developmental progression of breathing control involving the role that parents play in regulating human infants' physiology, including respiration (McKenna & Gettler, 2016; McKenna & Mosko, 1990; McKenna et al., 2007). McKenna (1986) started with the observation that the human neonate is born neurologically the least mature primate mammal of all (with only 25% of its adult brain volume) and thus is highly dependent on the caregiver for external physiological regulation and support for the longest period of time. Until very recent historical periods—largely the last century, when SIDS first was named as a syndrome—infants' survival relied on constant carrying by mothers or other caregivers and mother–infant cosleeping with breastfeeding. McKenna and colleagues have explored what role the behavioral and physiological effects of nighttime sleep isolation from the parent and lack of breastfeeding might play in relationship to SIDS etiology. Through empirical studies, McKenna has highlighted the specific ways a sensory-rich microenvironment could buffer infants during this relatively short-lived, less stable period in which these neonates make this neurobiologically based transition to speech breathing.

Indeed, McKenna and colleagues' decade-long polysomnographic studies of bedsharing and breastfeeding mother–infant dyads (sleeping alone and together) have documented just how much and in what ways mothers regulate their infant's sleep architecture, breathing, heart rate, blood pressures, hormonal status, feeding patterns, arousals, and temperature, specifically during infants' first critical developmental shift between 2 and 4 months of age (McKenna et al., 2007), all of which is relevant to understanding, perhaps, why SIDS has, for the most part, been associated with Western industrialized societies, where separate sleep and bottle feeding have been favored. Take, for example, McKenna and Mosko's (1990) study of the apparent physiological coregulation of mother–infant respiratory signals while mothers and infants bed-shared. In this research, mother–infant bed-sharing dyads could be differentiated from other mother–infant dyads by the complementarity of each partner's breathing cycles. Infants clearly breathe much faster than their mothers, and yet, both from infrared videotapes and polysomnographic respiratory recordings, McKenna and Mosko determined that each partner's total breaths per minute was influenced by the other, especially by partner-induced arousals that often precipitated brief, overlapping apneas, altogether changing oxygen saturation levels that would have been different had each partner slept alone. They found that the apneas were much shorter in the deepest stage of sleep, when arousing them to terminate the apnea could be a more serious challenge, especially for arousal-deficient infants.

Thus, we contend that when human infant hearing is normal, engaging in humankind's default, oldest, and most successful sleeping and

feeding practices—that is, safe cosleeping with breastfeeding (*breastsleeping*; McKenna & Gettler, 2016)—would provide just the right context for the human infant's transition to dual-control respiratory behavior. We contend that this context provides a microenvironment in which the infant can observe, hear, detect, smell, and feel the breathing movements, sounds, gases, and general airflow emitted by their mothers or other caregivers. This includes infants' gaining access to exhaled maternal CO_2 that is smelled and processed by the infants' chemoreceptors, potentially helping to drive the infants' phrenic nerve at some point during the breathing cycle (Mosko et al., 1998).

Are Long-Term Consequences of Inconsolable Crying Associated with ACG Functioning?

An additional question to ask is whether these convergent deficiencies in neural structures place infants at greater risk of exhibiting emotional and behavioral problems at later ages. Toward that end, we note that Milidou, Henriksen, Jensen, Olsen, and Søndergaard (2012) found that children with a history of infantile colic had a slightly increased probability of exhibiting emotional and conduct problems, attention-deficit/hyperactivity disorder, and difficult relations with peers in comparison to children who did not have a history of colic. That adolescents who had infantile colic demonstrate greater problems controlling and integrating emotions, attention, and self-regulation could reflect a continuing decrement in functionality at the ACG level although, given the maturity of chemoreceptors as a backup for the reinitiation of breathing, the consequences would no longer be life threatening (SIDS) but find expression in different ways. Furthermore, it may be that the number of VENs housed in the ACG remains lower in adolescents who had infantile colic than in adolescents who did not have a history of colic crying.

Testing This Model

To test this neurobiological and developmental approach toward understanding infantile colic, or inconsolable crying, we turn to previous neuroscientific research that has identified neuroanatomical structures of the developing brain and cerebral connections based on functional connectivity as illuminated by

magnetic resonance imaging (MRI) using spontaneous, low-frequency coherent fluctuation in blood-oxygen-level-dependent signals (Damaraju et al., 2010; Fransson et al., 2007; Smyser, Snyder, & Neil, 2011). Although one challenge regarding neuroimaging of infants is the certainty of patient safety, the safety of performing MRI investigations in infants has been established, including higher field strengths and, specifically, 3T MRI is increasingly being used to study pediatric patients (Dagia & Ditchfield, 2008; Raschle et al., 2012; Smyser et al., 2011). Thus, the first steps of investigating this theory would include performing functional connectivity MRI on infants who have colic between the ages of 2 and 5 months and analyzing differences found between subjects of varying ages and between control groups.

Summary and Implications for Family Science

In Relation to Parent Presence and SIDS

Indeed, as mentioned, it was in the context of identifying the possible reasons why human infants are the only species to die from SIDS that normative patterns of developing human respiratory control (speech breathing) were first examined. It was in addressing this question that the role of breast milk, breastfeeding, and cosleeping (i.e., parental proximity and sensory exchanges) gained attention as the safest context in which to support the complex developmental respiratory "switch" that occurs as infants gain control of voice and the breathing skills necessary to support it.

As mentioned, at birth human infants are the least neurologically mature primate and enjoy no opportunities or abilities to control specific sounds and/or underlying breathing, at least in any voluntary way. This time period is short in duration, as the infant does not for very long stay a passive recipient of its limited capacities. Beginning at birth through 3 months, the neocortex and its ascending tracts (see Figure 2) begin increasingly to integrate with the reticular activating system and ponto–medullary structures, eventually giving the infant the developing neuronal capacities needed to intentionally shape types of vocalizations, well before language and the breathing control required to do so. As outlined in the research discussed earlier, it is infants' engagements with their mothers (or other caregivers) that are important in

the process of infants successfully and safely gaining at least partial control over voice and breath. We have argued here and elsewhere that maternal–infant contact, and in particular infants' sensory–bodily exchanges with their mothers (McKenna et al., 2007), can externally compensate for, buffer, or make less likely the breathing control glitches about which we have posited this theory.

We acknowledge that in Western industrial societies the overall importance of nighttime proximity in the form of bedsharing rather than being protective is controversial, primarily because safety can be compromised by specific independent risk factors such as maternal smoking and/or bedsharing while desensitized by drugs or alcohol (and other modifiable risks) that increase the chances of infant suffocation, or SIDS/SUDI (sudden unexpected death in infants). But we also acknowledge that the field of SIDS research is marked by a clear lack of consensus as to whether bedsharing itself is the risk factor or, as many argue, that the specific dangerous conditions and the circumstances within which bedsharing is practiced is the problem, and not bedsharing itself (McKenna et al., 2007). In support of the role of the context of bedsharing and risk, we do know that, across cultures, where modern urban problems such as maternal smoking, drug and alcohol use, and absence of breastfeeding are not characteristic, we find the lowest SIDS rates, with some cultures where bedsharing and breastfeeding is the norm never experiencing or hearing about such tragic infant deaths (Nelson, Taylor, Jenik, & The ICCPS Study Group, 2000).

Given this context, the breastsleeping mothers' closeness (night and day) to her infant not only supports this developmental progression of respiration control that is important to both SIDS and inconsolable crying in the best possible way, but also acts as a *zeitgeber*, just as it did throughout prenatal amniotic breathing during the last trimester and, for about 45% of the time (see McKenna, 1986), through placental–umbilical generated maternal signals and cues that influence amniotic prenatal breathing.

In regard to inconsolable crying, the array of supplementary sensory subsystems that can find their way into respiratory neural networks (i.e., subsystems involving auditory, touch, and movement–vestibular stimuli) all assert important effects on breathing through contact with mothers or care providers and may lessen the intensity and duration of the crying (Barr et al., 1993). In addition, these sensory events can neurologically support the likelihood the crying comes to a conclusion sooner.

These postnatal signals and cues mimic those the infant experienced prenatally and involve auditory and vestibular cues by way of both vesicular breathing sounds and sensations of the mothers' breath on the infant's skin. The mother's rocking of the infant can change the breathing patterns, even, as studies have shown, synchronizing the baby's breathing (McKenna & Mosko, 1990). Also involved is another type of breathing cue emitted by the caregiver: the inhalation by the infant of the caregiver's expelled CO_2 gases that stimulate the phrenic nerve to drive the infant's diaphragm (McKenna, 1996; McKenna & Mosko, 1990; Mosko et al., 1998; Mosko, McKenna, Dickel, & Hunt, 1993; Mosko, Richard, & McKenna, 1997; Mosko, Richard, McKenna, Drummond, & Mukai, 1997; Richard, Mosko, McKenna, & Drummond, 1996; McKenna & Richard, 1994).

In Relation to Inconsolable Crying

The applied implication of the model we have proposed here is that the presence and responsiveness of the parent remain essential to the resolution of the neurological issues underlying inconsolable crying (i.e., colic), even if the presence of a glitch in infants' capacity to control breathing or to engage in task-switching leaves the infant unable, in the first months of development, to volitionally control crying or crying cessation. Within the framework of this model the presence of the parent and the sensory engagement provided would contribute to the development of the immature neural networks involved.

Important to share with parents as well is research showing that parental factors and quality of maternal care are not the cause of infant colic, although these factors may exacerbate and possibly prolong colic symptoms (Papousek & Papousek, 1996; Papousek & von Hofacker, 1998; St. James-Roberts, Conroy, & Wilsher, 1998). Not surprising is research showing that parents of infants experiencing inconsolable crying report increased parental anxiety and conflict; decreased energy, vitality, and ability to handle daily life events; less flexibility in daily communication; and, among mothers, increased chances of maternal depression,

reduced mother–infant face-to-face interaction, and increasing conflict with partners (Barr, 1995; Papousek & von Hofacker, 1998; Vik et al., 2009; Bond, Prager, Tiggemann, & Tao, 2001). While offering the infant contact during inconsolable crying bouts may lessen intensity and duration, Barr (2012) suggests if the parent can no longer tolerate the stress to the point where they may hurt the infant, the parent should put the infant down in a safe place, walk away temporarily and seek a partner, friend, or other relative to respond with the care he or she is no longer able to provide.

If the model herein is supported by future research, practitioners can help parents understand that, like themselves, the baby is temporarily a victim of the crying episode and not a willful participant. From this perspective parents can see episodes of inconsolable crying as an outcome of the infants' current developmental trajectory and an occurrence that is transitory (Barr, Paterson, MacMartin, Lehtonen & Young, 2005). Being able to identify that they and their infants are both part of a crisis that is not of their own making should provide parents support during this stressful period and help parents be empathic regarding their infants' lack of volitional control to terminate crying episodes.

The research conducted by Salisbury and colleagues (2012) underscores the importance of providing parents support in managing the distress associated with prolonged crying, information about the normative nature of colic episodes, and help in avoiding self-criticism.

Finally, Barr (2006) forwarded an innovative speculation that crying is a phylogenetically old, neurologically based behavior that occurs across a number of mammal species and is expressed in diverse developmental patterns. An important outcome of this research is the idea that colic (or inconsolable crying) may be best conceptualized as if on a continuum of expression and as differing from parent to parent. As such, inconsolable crying should be represented as a variant of normative human infant development that differentiates human babies not so much in kind but in degree (Barr, 2012). Moreover, Barr (2006) pointed to the past 30 years of research in this area as establishing the existence of a pattern of excessive crying in the first months of life as typical across differing cultures. This led him to propose that colic is a clinically useless concept given that colic, or inconsolable crying, is something that babies do and not something that

babies have, as in a disease (Barr, 1993). He identified this phenomenon of inconsolable crying, however, as especially prevalent in infants in Western cultures wherein care providers limit or refrain from responding to their infants by the increased contact, retrieval, and/or carrying or licking common among other mammals. After all, as Barr et al. (1993) found, increasing infant carrying (and general infant contact) from 3 to more than 4 hours a day (at least as found in one study) can reduce the duration of crying/fussing behavior by 43% at about 6 weeks of age. This demonstrates that even if infants "do" colic, to use Barr's word for it, it is not the case that its severity (and overall duration) is immutable, and this is important news for weary parents.

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