Ontogeny of sleep

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Glossary

Active sleep One of several alternative names for REM sleep, along with paradoxical sleep, desynchronized sleep, etc. Although some restrict its use to developing animals, others prefer it more generally as a less biased descriptor of the state.

Altricial Animals that are born in a state of relative immaturity. Such offspring are typically born without fur or down, their eyes are sealed, they are relatively immobile, and they are dependent on maternal care for nourishment, warmth, and protection. Dogs, rats, and hawks are examples of altricial species.

Myoclonic twitches Brief, jerky movements of the limbs and other appendages (e.g., whiskers, eyes) that occur predominantly during REM sleep. They are produced by activation of skeletal muscle.

Precocial Animals that are born in a state of relative maturity. Such offspring are typically born with fur or down, their eyes are open, they are relatively mobile, and they are not as dependent as altricial species on maternal care for nourishment, warmth, and protection. Sheep, horses, and ducks are examples of precocial species.

Quiet sleep One of several alternative names for non-REM sleep, along with slow-wave sleep, synchronized sleep, etc. Although some restrict its use to developing animals, others prefer it more generally as a less biased descriptor of the state.

Introduction

To "sleep like a baby" is to sleep soundly, deeply, and for long stretches of time. But, as any new parent knows, this phrase doesn't accurately capture how babies really sleep. Nor does it provide insight into the developmental journey toward adult sleep and the changes within the brain that make that journey possible. Thus, to fully describe and explain the unique features of infant sleep, we must address a myriad of issues, including its basic behavioral organization, its neural control, and its functions.

Infant animals are not simply small versions of adults, but rather are qualitatively different creatures that must continually adapt to the needs of a rapidly changing body. For this reason, we must guard against the temptation to assess infant sleep from an adult-centered perspective. Instead, we should seek to understand infant sleep on its own terms (Blumberg and Seelke, 2010). Ultimately, any complete resolution to the mysteries of sleep will have to account for its early expression and transformation across the lifespan as well as its expression in a diversity of species (Blumberg and Rattenborg, 2017; Blumberg et al., 2020).

We sleep most when we are young

Perhaps the most conspicuous feature of sleep in early infancy is its sheer quantity. In 1953, the pioneering sleep researcher Nathaniel Kleitman documented this feature by recording the behavioral patterns of human infants in the home environment from the 3rd to the 26th postnatal week (Kleitman and Engelmann, 1953). In this study, newborns slept 14 to 15 h each day, with this high quantity of sleep decreasing by only 1 h by the 26th week.

As Kleitman's study illustrates, sleep and wake periods can be identified using behavioral measures alone (Thoman et al., 1987; Blumberg and Seelke, 2010). Most of us are familiar with these behaviors: For example, an awake baby is often kicking or stretching with eyes wide open. When asleep, the baby becomes still with eyes shut, as breathing becomes regular and slow. Such periods of stillness are indicative of quiet sleep and contrast with periods of active sleep, when one observes bursts of rapid eye movements, myoclonic twitches of the limbs, and irregular breathing.

As reliable as behavior can be in estimating sleep-wake activity, electrographic measures are valued because they provide more detailed information for distinguishing sleep and wake states. Electrographic measures include measures of cortical activity (i.e., electroencephalogram or EEG), eye movements (i.e., electrooculogram or EOG), and muscle tone (i.e., electromyogram or EMG). Using these electrographic measures, investigators in the 1960s began carefully describing the organization of sleep-wake states in premature and full-term human neonates (e.g., Parmelee et al., 1967; Dreyfus-Brisac and Monod, 1965; Roffwarg et al., 1966).

Roffwarg and colleagues combined their own data with that of other investigators to produce **Fig. 1**, which has become the iconic depiction of human sleep and wakefulness across the lifespan (Roffwarg et al., 1966). As the figure illustrates, active and quiet sleep at birth each occupy approximately 8 h of the day. Whereas the amount of time spent in quiet sleep decreases only slightly with age, the amount of time spent in active sleep declines dramatically and is accompanied by an increase in the amount of time spent awake.

Accompanying the long durations of sleep in newborns, there is also a strong drive to sleep. This drive—referred to as sleep pressure—can be demonstrated in infant rats using a sleep-deprivation procedure in which a pup is awakened as soon as it falls asleep (Todd et al., 2010). Initially, it is very easy to keep the pup awake. However, over time, it falls back to sleep more and more quickly after each arousing stimulus. Within only 30 min, the arousing stimulus must be applied nearly continuously to keep the pup awake. In contrast, sleep pressure in sleep-deprived adult rats increases much more slowly over the course of several days.

Infant sleep and wake bouts are fragmented

As adults, humans stay awake most of the day and sleep most of the night. Accordingly, we say that adults have consolidated bouts of sleep and wakefulness. In contrast, infants exhibit a fragmented pattern of sleep and wake, transitioning rapidly between the two states across the day and night. Indeed, this characteristic of infant sleep perhaps best captures what it really means to "sleep like a baby."

In **Fig. 2**A, the fragmented sleep-wake pattern of human infants is easily observed, as is the decrease in the frequency of sleep-wake transitions between two weeks and five months of age (Sokoloff et al., 2020). Not shown in the figure is how these rapid transitions between states occur similarly during the day and night (i.e., there is initially no clear circadian rhythm). As weeks go by, bouts of sleep and wake gradually consolidate, becoming longer and longer. By three to four months of age, further consolidation of sleep and wake bouts has occurred; but now, sleep is concentrated largely at night and wake concentrated during the day, thus marking the beginning of the diurnal activity pattern that characterizes the human species (Kleitman and Engelmann, 1953).

In infant rats, the same basic pattern of bout consolidation is observed. As shown in **Fig. 2**B, alternations between sleep and wake occur very rapidly at two days of postnatal age (P2). In contrast, by P21, sleep and wake bouts have consolidated significantly,

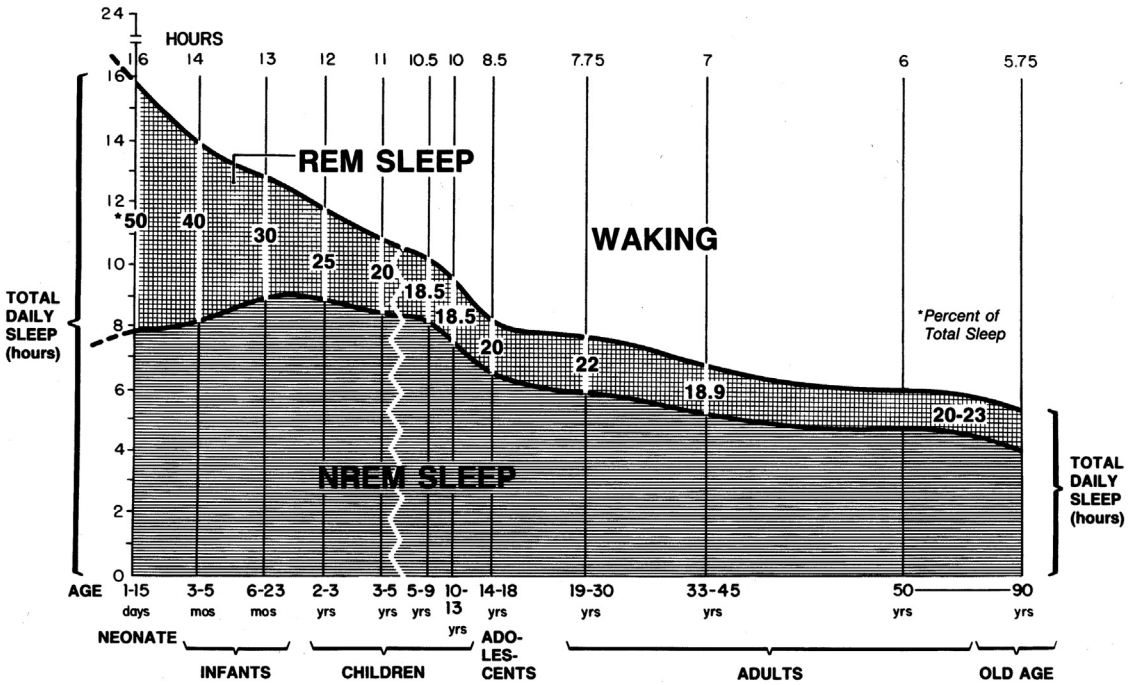

Fig. 1 We sleep most when we are young. Relative rates of waking, REM (or active) sleep, and non-REM (NREM, or quiet) sleep in humans across the lifespan. Revised from Roffwarg, H. P., Muzio, J. N., Dement, W. C., 1966. Ontogenetic development of the human sleep-dream cycle. Science 152, 604–619. Used with permission of Howard P. Roffwarg.

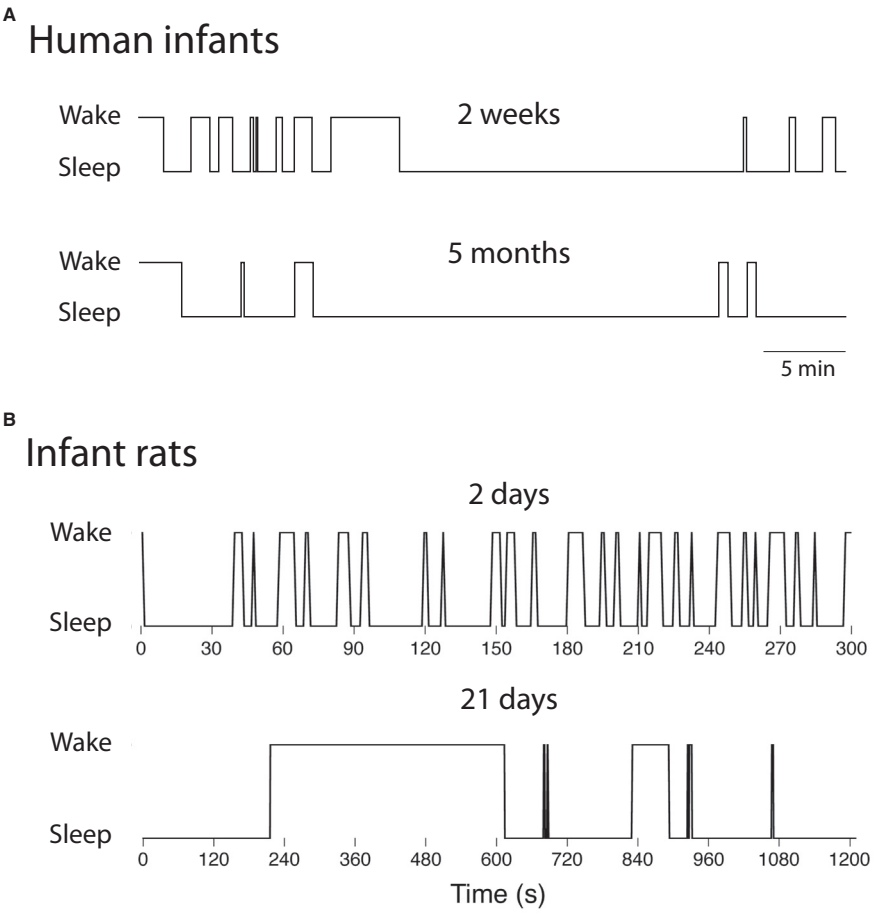

Fig. 2 Consolidation of sleep and wake bouts with age. (A) Sleep and wake bout durations for a representative human infant at two weeks and five months of age. (B) Sleep-wake cycles in a P2 and a P21 rat. Note the different time scales in the two traces. Sleep and wake bouts at P2 are highly fragmented in relation to those at P21. In both humans and rats, note the age-related reductions in the number of state transitions, indicative of bout consolidation. (A) Adapted from Sokoloff, G., Hickerson, M., Wen, R., Tobias, M., McMurray, B., Blumberg, M. S., 2020. Spatiotemporal organization of myoclonic twitching in sleeping human infants. Dev. Psychobiol. 62, 697–710. Copyright © John Wiley & Sons, Inc. (B) Adapted from Blumberg, M. S., Seelke, A. M., Lowen, S. B., Karlsson, K. A., 2005. Dynamics of sleep-wake cyclicity in developing rats. Proc. Natl. Acad. Sci. 102, 14860–14864. Copyright © by the National Academy of Sciences.

resulting in far fewer transitions over a given period of time. In altricial species like rats, the process of sleep consolidation largely occurs postnatally. However, in a precocial species like sheep, sleep consolidation occurs prenatally (Karlsson et al., 2010).

Infant sleep and wake bouts exhibit distinct statistical properties

The rapid oscillations between sleep and wake in both newborn humans and rats can be likened to a seesaw moving up and down. In early development, this simple oscillator, illustrated in Fig. 3A, appears to be controlled entirely by structures within the brainstem as the sleep-wake oscillations continue even after surgical disconnection of the brainstem from the forebrain. Moreover, by looking at the statistical properties of the sleep and wake bouts, we can glean much more about the functional properties of the oscillator. Specifically, when analyzed separately, sleep and wake bouts in P2 rats occur randomly over time; when we say "random," we mean that we cannot predict how long a sleep (or wake) bout will be by looking at the duration of previous bouts (Blumberg et al., 2005). Stated differently, the system has no memory for the durations of previous sleep bouts. Between P2 and P21, as sleep bouts gradually consolidate, they continue to occur randomly.

Wake bouts also occur randomly in the youngest pups. However, by P21 they exhibit a qualitative shift in their statistical properties. Specifically, they now exhibit a statistical structure such that the probability that a wake bout will terminate at any given moment decreases as the wake bout increases: The longer an animal has been awake, the more likely it will remain awake in the immediate future (of course, this is only a probabilistic statement; a return to sleep is inevitable). In this case, the system seems to have a memory for how long it has been awake in the immediate past. The statistical properties of sleep and wake bouts in rats at P21 are also observed in adult humans, cats, and mice (Lo et al., 2004).

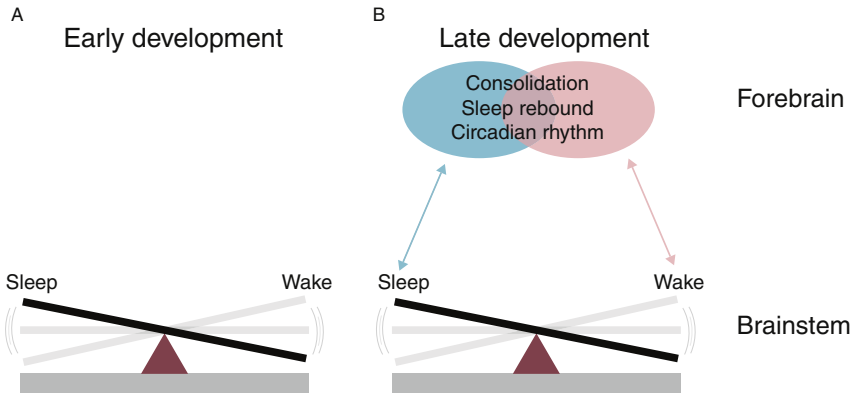

Fig. 3 Sleep-wake rhythms are initially produced by an oscillator in the brainstem. (A) In early development, the brainstem oscillator functions independently of the hypothalamus and other forebrain structures. (B) Later in development, the brainstem oscillator interacts increasingly with forebrain structures to enable the consolidation of sleep and wake bouts, expression of sleep rebound after deprivation, and circadian rhythmicity. Adapted from Blumberg, M. S., Gall, A. J., Todd, W. D., 2014. The development of sleep-wake rhythms and the search for elemental circuits in the infant brain. Behav. Neurosci. 128, 250–263. Copyright © American Psychological Association.

Developmental changes in sleep-wake organization reflect increases in neural connectivity

By understanding the statistical properties of sleep and wake bouts across early development, we can more easily reveal the neural contributions to sleep-wake organization. For example, in rats, damage to one neural component of the system—a brainstem nucleus called the locus coeruleus (LC)—prevents the developmental transition in the statistical structure of wake bouts described above (Gall et al., 2009). In addition, as illustrated in **Fig. 3**B, the consolidation of sleep and wake bouts with age depends on the developmental strengthening of functional connections between the basic oscillator in the brainstem and several forebrain structures (Blumberg et al., 2014). These forebrain structures include the dorsomedial hypothalamus and the suprachiasmatic nucleus (SCN). When these structures or their connectivity are damaged, sleep and/or wake bouts revert to a fragmented state.

Thus far, we have focused on the ultradian sleep-wake rhythm that is defined as repeated oscillations over a 24 h period. But there is also the circadian sleep-wake rhythm that expresses itself as a bias toward being awake during the day (diurnality, as in humans) or at night (nocturnality, as in rats). Circadian rhythms are largely (though not exclusively) governed by activity in the SCN, which functions as a biological clock. As noted above, the circadian sleep-wake rhythm emerges developmentally as the SCN gradually gains influence over the brainstem mechanisms that produce ultradian sleep-wake rhythms (see **Fig. 3**B). For example, as noted earlier for human infants, this process occurs around the third to fourth postnatal month as bouts of consolidated wakefulness are increasingly more likely to occur during the day. It is as if the SCN places its thumb on the seesaw in **Fig. 3**B to bias it toward sleep during the night and wake during the day (or vice versa for a nocturnal species).

In the nocturnal Norway rat, the ultradian rhythm is increasingly modulated by the SCN so that, by the end of the second postnatal week, the ultradian sleep-wake rhythm is biased to have longer sleep bouts during the day. In the diurnal Nile grass rat, the ultradian rhythm is similarly modulated, but the bias is for longer sleep bouts at night (Todd et al., 2012). Importantly, because the circadian pattern of SCN activity is identical in diurnal and nocturnal species—that is, the SCN is more active during the day than during the night in all mammalian species studied thus far—the evolution of diurnality and nocturnality cannot be due to evolutionary changes in the SCN per se. Accordingly, diurnality and nocturnality must have arisen through developmental modifications of the neural connections between the SCN and other structures (Todd et al., 2012).

Thus far, as illustrated in **Fig. 3**B, structures in the forebrain are increasingly able to modify the brainstem oscillator, resulting in (a) the consolidation of sleep and wake bouts and (b) the emergence of circadian rhythmicity as connections are formed and strengthened with the SCN and related structures. But there is also a third feature of sleep-wake regulation—sleep rebound—that relies on functional connections between the brainstem and the forebrain.

As described earlier, when infant rats are deprived of sleep over a 30 min period, they exhibit rapid increases in sleep pressure. This response is supported by brainstem mechanisms alone: When the brainstem is disconnected from the forebrain, the sleep-pressure response is unaffected (Todd et al., 2010).

Now let's consider sleep rebound which, along with sleep pressure, comprise the two recognized compensatory or "homeostatic" responses to sleep deprivation. Sleep rebound refers to the increased sleep that occurs when a sleep-deprived animal is allowed to sleep. For example, when a rat as young as P2 is allowed to sleep after a 30 min sleep deprivation period, it exhibits an immediate increase in sleep that partially compensates for the sleep lost during the deprivation period. Interestingly, in contrast with sleep pressure, disconnecting the brainstem from the forebrain in P2 rats eliminates deprivation-induced sleep rebound (Todd et al., 2010). It is not yet clear when the forebrain establishes connections with the brainstem to support sleep rebound. But, what is clear is that only one of the two components of sleep homeostasis, beginning very early in development, depends upon the forebrain for its expression.

Developmental changes in active and quiet sleep

As noted earlier, we judge an adult animal to be in active or quiet sleep when certain behavioral and electrographic requirements are met. But how do we make these judgments when, for a given species, certain "essential" criteria are not met? For example, if rapid eye movements are judged to be an "essential" feature of REM sleep, how do we assess REM sleep in a blind mole rat that lacks eyes or an owl whose eyes do not move in their sockets (Blumberg et al., 2020)? These kinds of challenges to our definitions of sleep states are even more vexing when we consider the gradual developmental emergence of the various components of sleep.

Because rats are altricial, we can observe many important developmental milestones postnatally that occur prenatally in precocial species, such as sheep. For example, as will be discussed further below, cortical delta activity—one of the most distinctive components of quiet sleep in adults—does not develop until P11 in rats. In human infants, which are neither entirely altricial or precocial, delta activity emerges and strengthens in power gradually over the first several postnatal months (Jenni et al., 2004). In contrast, delta waves develop by 115–120 days postconception in sheep (gestation length ~147 days; Szeto and Hinman, 1985) and 50 days postconception in guinea pigs (gestation length ~65 days; Umans et al., 1985).

Returning to infant rats, we can learn a lot about the development of sleep states by closely observing the structure of sleep when delta waves are first expressed (Seelke and Blumberg, 2008). We can begin at P2 and the basic structure of the sleep-wake cycle: The cycle begins with a period of wakefulness, characterized by high muscle tone and such wake movements as kicking and stretching. Thereafter, muscle tone decreases and the pup becomes behaviorally quiescent, indicative of quiet sleep. Active sleep begins with the expression of bursts of muscle twitching—resulting in jerky movements of the limbs, tail, whiskers, and head—interspersed with brief periods of behavioral quiescence. This basic pattern continues through P9, with one major developmental change being the consolidation of sleep and wake bouts.

In addition, by P9, the period of quiescence that separates the end of a bout of wakefulness and the first instance of twitching (and thus the onset of active sleep) becomes more pronounced. But because, as already noted, quiet sleep is typically defined based on the presence of delta waves in the EEG, one might doubt that this initial period of quiescence qualifies as "true" quiet sleep. However, only 2 days later on P11, delta activity suddenly emerges—and it occurs exactly where you would expect it to occur if that initial period of post-wake and pre-twitch quiescence at P9 were indeed quiet sleep (Seelke and Blumberg, 2008). Thus, although delta activity is undoubtedly a key component of quiet sleep at P11 and beyond, its absence at younger ages does not necessarily imply that quiet sleep does not yet exist. Rather, with age, we see that sleep components can be added to and integrated with an already-existing sleep structure.

The developmental emergence of individual sleep components is even more compelling for active sleep (Blumberg et al., 2020). Fig. 4 illustrates this process metaphorically, in infant rats, as individual strands of a rope coming together. We see that muscle atonia and twitching are the first components of active sleep to emerge, followed sequentially by the theta (4–8 Hz) rhythm in the hippocampus, rapid eye movements, and an activated EEG rhythm (the last component mirroring the emergence of delta activity in the EEG during quiet sleep).

Why do developing animals sleep so much?

Noting the dominance of active sleep at birth, Roffwarg and colleagues asserted in 1966 that "any hypothesis which purports to account for the regulation of REM sleep will eventually have to explain the great quantities of [active] sleep during early

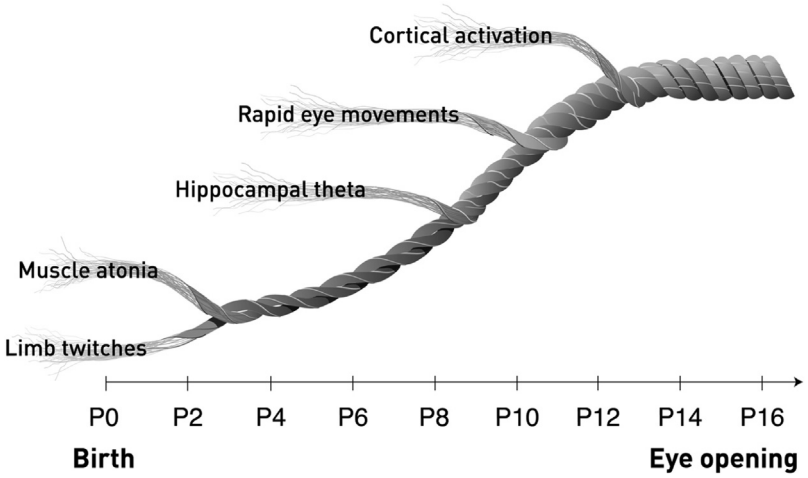

Fig. 4 Developmental coalescence of REM sleep components in infant rats. The various components of REM (active) sleep emerge sequentially and coalesce over developmental time. P, postnatal day. From Blumberg, M. S., Lesku, J. A., Libourel, P. A., Schmidt, M. H., Rattenborg, N. C., 2020. What is REM sleep? Curr. Biol. 30, R38–R49. Copyright © Cell Press.

development" (Roffwarg et al., 1966). Accordingly, they put forward the ontogenetic hypothesis, which emphasized how the brainstem mechanisms that produce active sleep also provide direct ascending stimulation to the forebrain, thereby promoting brain development. Recently, researchers working from first principles and with archival human data—incorporating such variables as sleep time, brain size, and brain metabolic rate—theorized that active sleep plays a functional role in neural reorganization through 2–3 years of age, consistent with the ontogenetic hypothesis (Cao et al., 2020). But beyond humans and mammals—from birds to fish to invertebrates—sleep and sleep-like behavior are more prevalent early in life, suggesting a universal role for sleep in basic developmental processes (Lesku and Rattenborg, 2014; Corner, 2013; Kayser and Biron, 2016).

The ontogenetic hypothesis, with its view of active sleep as a period of vigorous brain stimulation, is an early example of a hypothesis that rests on the concept of activity-dependent development. In subsequent decades, researchers have come to believe that the infant and juvenile brain is highly plastic and that active and quiet sleep contribute to that plasticity (for review, see Rasch and Born, 2013). For example, research indicates that naps aid memory and language learning in human infants (Kurdziel et al., 2013; Friedrich et al., 2015; Hupbach et al., 2009), that active sleep promotes plasticity in developing visual cortex (Dumoulin Bridi et al., 2015; Renouard et al., 2018), that active sleep modifies dendritic spines in the motor cortex of young mice (Li et al., 2017), that sleep affects the learning of song in juvenile songbirds (Shank and Margoliash, 2009; Deregnaucourt et al., 2005), and that sleep contributes to the proliferation of neurons in larval flies (Szuperak et al., 2018). Researchers have even found that human infants are able to learn while they sleep, a capacity that the authors of the study suggest may be unique to infants due to their enhanced brain plasticity (Fifer et al., 2010). These and many other findings suggest that sleep plays a complex role in the development of the nervous system and in basic processes of learning and memory. Ultimately, understanding the functional aspects of sleep in early development can help us better understand the functions of sleep in adults.

What is the significance of twitching for the developing brain?

Conventional wisdom has long held that the twitches of active sleep are mere by-products of dreams—simply the outward manifestation of an internal process. However, research over the past 15 years has argued against this notion by providing ample evidence that twitch-related sensory feedback robustly activates the infant brain. Indeed, this research shows that twitches are even more effective than wake movements in triggering brain activation (Blumberg et al., 2020).

The first study to record twitching and cortical activity in neonatal rats led to the discovery of "spindle bursts" in somatosensory cortex (Khazipov et al., 2004). Spindle bursts—which are brief oscillatory bursts with an average frequency of 15 Hz—have since been documented in other primary sensory cortical areas (e.g., visual cortex in response to retinal waves; Hanganu et al., 2006). That spindle bursts occur in a somatotopically precise fashion and are thought to contribute in a variety of ways to cortical development (Luhmann et al., 2016) suggests that twitches contribute to the activity-dependent development of sensorimotor cortex. But it should be stressed that the functional importance of twitches likely extends to the entire sensorimotor system, beginning with the shaping of spinal circuits (Petersson et al., 2003; Inácio et al., 2016; Blumberg et al., 2015).

As summarized in **Fig. 5**, we now have a fuller picture of the causes and consequences of twitching for the infant brain. First, as shown in the inset, we can categorize neural spiking activity within a brain structure as to whether it precedes (red) or follows (green) the production of a twitch (in this case, a twitch of the forelimb). If the former, we infer that the neural activity is part of a motor circuit that produces a twitch; if the latter, we infer that the neural activity is part of a sensory circuit that is triggered by a twitch. It is also possible that the neural activity coincides with the production of the twitch (blue), which suggests that the neural activity is a corollary discharge (or motor copy) of the motor system that produced the twitch (corollary discharges help animals keep track of movements that are self-generated versus those that are other-generated; Crapse and Sommer, 2008). Using the iconography established in the inset, the main part of **Fig. 5** presents how a forelimb twitch is produced by neural structures in and adjacent to a midbrain motor structure called the red nucleus, how sensory feedback from a forelimb twitch cascades through sensorimotor structures in the brain, and how corollary discharge signals are conveyed to the cerebellum. Overall, the complexity and ubiquity of twitch-related neural activity suggests that twitches are active contributors to the establishment, refinement, and maintenance of neural circuits linking muscle, spinal cord, and brain.

Active sleep and twitching promote functional connectivity in the developing brain

Thus far, we have seen that sensory feedback arising from twitches during active sleep triggers two forms of activity: cortical spindle bursts in sensorimotor cortex and neural spiking activity throughout the sensorimotor system. Spindle bursts comprise one form of local field potential (LFP); the EEG, measured at the surface of the brain, is another one. LFPs reflect the synchronized fluctuations in electrical activity across many neurons: When a population of neurons repeatedly fire together and then go silent together, the LFP reflects this synchronized activity as neural oscillations or rhythms. When the activity of neurons in two distant and distinct neural structures fluctuate together, we say that the two LFPs are coherent. When two structures are coherent, we say that they are functionally connected. In developing animals, we can track the emergence of functional connectivity and thus glimpse the conditions under which two or more structures begin to communicate with each other.

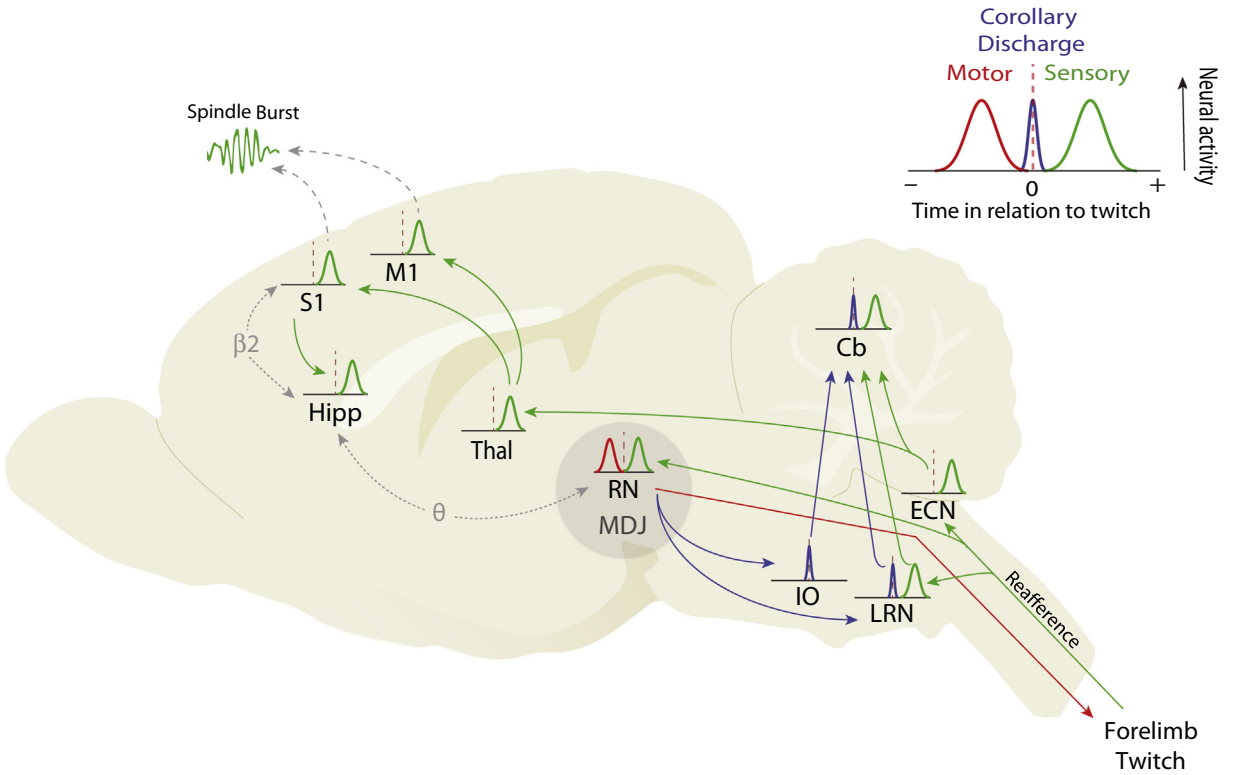

Fig. 5 Neural structures associated with twitching during active sleep in infant rats. Inset: Cartoon depiction of three categories of neural spiking activity in the vicinity of a twitch: (1) activity that precedes a twitch is indicative of motor outflow (red), (2) activity that follows a twitch is indicative of sensory feedback (or reafference; green), and (3) activity that is nearly simultaneous with a twitch is indicative of a corollary discharge signal (or motor copy; blue). Main figure: Against a background image of a sagittal section of an infant rat brain, the three iconic representations of motor, sensory, and corollary discharge signals are used to illustrate twitch-related activity during active sleep. The production of a forelimb twitch begins in midbrain structures, including the red nucleus (RN) and surrounding areas in the mesodiencephalic junction (MDJ). When a forelimb twitch is produced, reafferent signals are conveyed to the spinal cord, the external cuneate nucleus (ECN), and the RN. From the ECN, reafferent signals flow to the cerebellum (Cb) as well as the thalamus, arriving next in primary somatosensory (S1) and motor (M1) cortex. Along with spiking activity in S1 and M1, thalamocortically generated spindle bursts are detected in the LFP. From S1, reafference is conveyed to the hippocampus. Corollary discharge signals, generated by the RN and adjacent structures, are conveyed separately to the inferior olive (IO) and lateral reticular nucleus (LRN), before projecting to the cerebellum. Finally, also detected using LFP recordings is the occurrence of twitch-triggered bursts of coherent rhythmic activity in the RN and hippocampus in the theta band (θ; 4–7 Hz) and in S1 and hippocampus in the beta2 band (β2; 20–30 Hz). From Blumberg, M. S., Dooley, J. C., Sokoloff, G., 2020. The developing brain revealed during sleep. Curr. Opin. Physiol. 15, 14–22. Copyright © Elsevier.

As shown in **Fig. 5**, forelimb twitches are produced by neural activation in the red nucleus and sensory feedback from twitches cascades through the sensorimotor system, including the hippocampus. One of the characteristic features of the adult hippocampus is that its LFP exhibits, during active sleep and other conditions, a prominent oscillation known as the theta rhythm. In infant rats, this rhythm is first detectable around P8 (Del Rio-Bermudez et al., 2017). At this age, theta is expressed as brief rhythmic bursts immediately after a twitch; by P12, theta is expressed continually during active sleep and is amplified after a twitch. Surprisingly, theta also occurs in the red nucleus, exhibits a similar developmental pattern as that found in the hippocampus, and the theta recorded in both structures is highly coherent; when pups are not in active sleep, this coherent theta activity disappears. In other words, when the red nucleus and hippocampus first begin to communicate with each other, they seem to do so exclusively during active sleep.

The hippocampus of P8 rats also exhibits twitch-dependent activity that is coherent with activity in primary somatosensory cortex; in this case, the coherence is found not with theta, but with the higher-frequency beta2 rhythm (20–30 Hz; Del Rio-Bermudez et al., 2020). All together, these findings suggest that twitching—and active sleep more generally—provides a critical context for synchronizing neural activity across distant and developing brain areas that are just beginning to communicate with one another.

Conclusions

Niko Tinbergen, one of the founders of ethology, identified four questions that should be asked about any behavior: what causes it (mechanism), how did it evolve (phylogeny), why does it occur (function), and how does it develop (ontogeny). Because sleep is so prominently expressed in early development, it can reasonably be argued that an understanding of the development of sleep—including the development of its separable components—is critical to understanding its functions (Blumberg and

Rattenborg, 2017). In addition, because evolutionary change occurs through modifications of developmental processes, the study of sleep ontogeny across a diversity of species will also inform our understanding of sleep phylogeny, as well as the neural mechanisms that underlie species differences. Thus, from this perspective, a fuller understanding of sleep ontogeny is necessary for answering all four of Tinbergen's questions regarding sleep.

If active sleep provides a critical context for sensorimotor development and early functional connectivity, then it follows that disruptions of sleep in early development, especially during sensitive periods, could guide the infant down atypical developmental trajectories, with cascading negative consequences across the lifespan (Del Rio-Bermudez and Blumberg, 2018). In fact, accumulating evidence indicates that many neurodevelopmental disorders, including autism spectrum disorder and schizophrenia, are characterized by abnormal sleep (Picchioni et al., 2014; Kamara and Beauchaine, 2019; Robinson-Shelton and Malow, 2015; Barone et al., 2019), sensorimotor impairments (Green et al., 2009; Mittal and Walker, 2007), and altered functional connectivity and neural communication (Hartung et al., 2016; Whitfield-Gabrieli et al., 2009; Baran et al., 2019). Untangling these complex developmental relationships remains an important focus for future research.

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