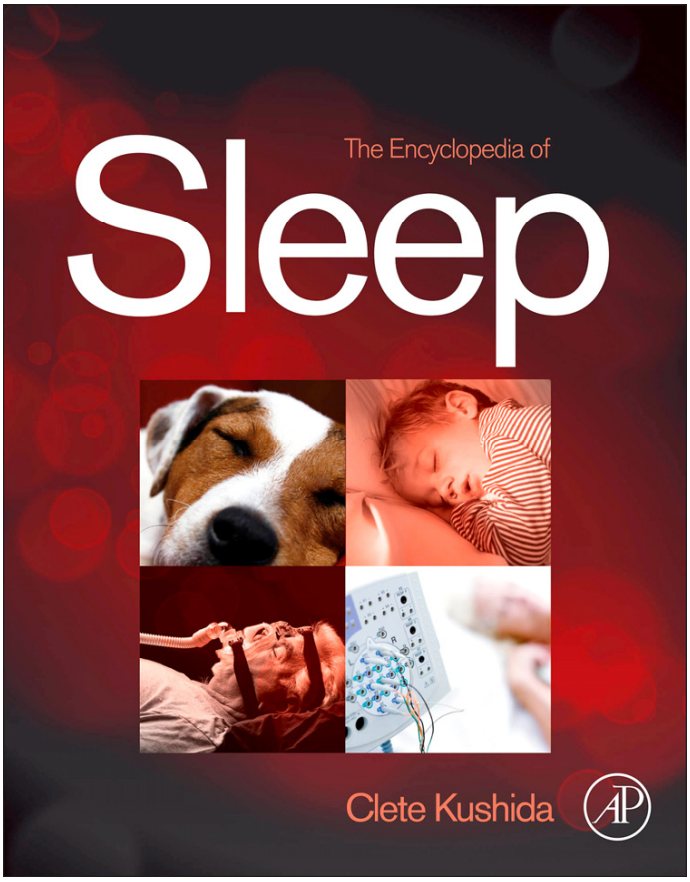

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Ontogeny of Sleep

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Glossary

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.

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.

To 'sleep like a baby' is to sleep soundly and deeply. But does this phrase accurately capture the quality of infant sleep? For new parents this issue is of great interest, if only because the amount of sleep parents get is so intimately tied to the sleep patterns of their infants. But the science behind infant sleep is just as interesting, as it touches on many of the issues that are central to the understanding of the organization, neural control, and functions of sleep across the life span.

The study of sleep in developing animals, including humans, presents a variety of conceptual and methodological challenges. Some of these challenges arise because infants are small, often fragile creatures, at a period in their lives when they resemble – but are not identical to – their future adult forms. These challenges are made even greater because the infant's body and brain are changing rapidly.

Another challenge is to guard against assessing infant sleep through the prism of adult sleep. Although infants grow up to become adults, one must seek to understand them – and their sleeping habits – on their own terms. Only when the unique and shared sleep characteristics of infants and adults in a diversity of species have been successfully explained will the mysteries of sleep be solved.

Humans Sleep Most When They Are Young

Perhaps the most conspicuous feature of sleep in early infancy is its sheer quantity. Although some early reports indicated that human newborns sleep more than 20 h each day, subsequent investigators using increasingly sophisticated methods provided more accurate estimates. In 1953, the pioneering sleep researcher Nathaniel Kleitman, who reported the discovery of rapid eye movement (REM) sleep with Eugene Aserinsky that same year, improved upon previous estimates by recording the activity patterns of human infants in the home environment from the 3rd to the 26th postnatal week. In this study, infants were found to sleep an average of 14–15 h each day, ranging from a low of 12 h to a high of 17 h. In addition, this high quantity of sleep diminished by only 1 h over the first 6 postnatal months.

As in Kleitman's study, estimates of the duration of wakefulness can be ascertained by monitoring such high-amplitude, coordinated movements as kicking, stretching, and reaching. During sleep – particularly during REM sleep (hereafter referred to as active sleep) – jerky movements or twitches of the limbs also occur. These *myoclonic twitches* are a ubiquitous feature of infant sleep. Moreover, these movements do not begin at birth, but are rather a prominent feature of embryonic behavior in mammals and birds. Indeed, as the behavioral embryologist Michael Corner has noted, the familiar movements that are observed in newborns during sleep are "nothing less than the continued postnatal expression of primordial nervous functional processes."

Similar to the results reported in the Kleitman study, high quantities of postnatal sleep have been recorded using behavioral measures alone in nonhuman species, including rats. Nonetheless, as reliable as behavior can be in estimating sleep–wake activity, electrographic measures are often preferred because they provide sensitive, quantifiable information regarding brain activity (i.e., electroencephalogram or EEG), eye movements (i.e., electrooculogram or EOG), and muscle tone (i.e., electromyogram or EMG).

In 1966, Howard Roffwarg and his colleagues published a seminal paper documenting electrographic features of sleep in 14 human newborns. Consistent with the findings of others from around this same time, these newborns exhibited features characteristic of the three primary behavioral states: (1) *wakefulness*, characterized by an activated EEG, high muscle tone, and gross body movements; (2) *quiet sleep*, characterized by EEG delta waves (also called slow waves), decreased muscle tone, and behavioral quiescence; and (3) *active sleep*, characterized by an activated EEG, absence of muscle tone, REMs, and myoclonic twitches. Subsequent work has made it clear that REMs during active sleep are produced by twitches of the eye muscles.

Roffwarg and colleagues combined their own data with that of other investigators to produce **Figure 1**, which has become the iconic depiction of human sleep and wakefulness across the life span. As the figure illustrates, active and quiet sleep at birth each occupy ~8 h of the day. Also, as active sleep declines with age, the amount of time spent waking increases.

Associated with the high quantities of sleep in newborns is a strong drive to sleep, or sleep pressure. In other words, it is very difficult to keep an infant awake for long periods of time. For example, it is initially very easy to arouse a sleeping infant rat. However, over time, the pup falls back to sleep more

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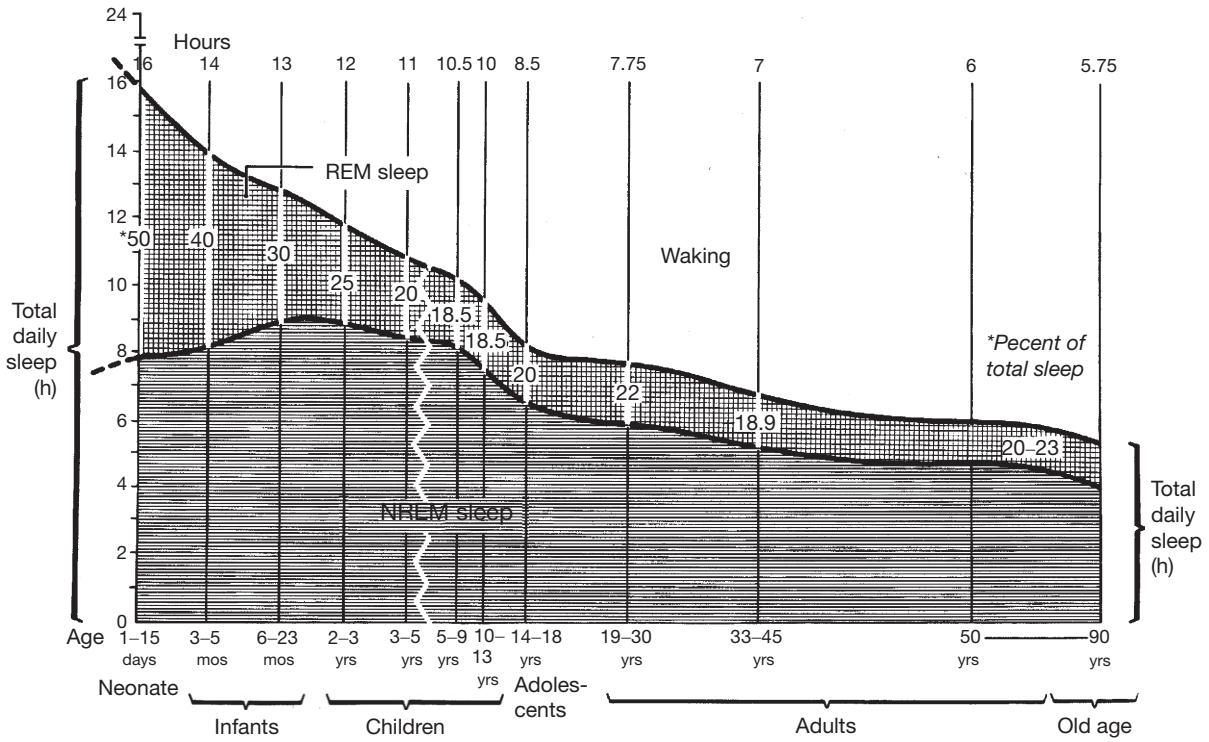

Figure 1 Humans sleep most when they are young. Relative rates of waking, REM (or active) sleep, and non-REM (NREM, or quiet) sleep in humans across the life span. Revised from Roffwarg HP, Muzio JN, and Dement WC (1966) Ontogenetic development of the human sleep-dream cycle. *Science* 152: 604–619, with permission from Howard P. Roffwarg.

quickly after each arousing stimulus and so, to maintain wakefulness, the arousing stimulus must be applied more and more often. After only 30 min, the arousing stimulus must be applied nearly continuously to keep the pup awake. In contrast, sleep pressure in adult rats increases 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, it is said that humans have consolidated bouts of sleep and wakefulness. But in humans with the sleep disorder narcolepsy, this consolidated sleep–wake pattern is disrupted. Individuals with narcolepsy have fragmented bouts of sleep and wakefulness such that they are more likely to fall asleep during the day and more likely to wake up at night. Interestingly, all human infants exhibit a fragmented pattern of sleep and wakefulness. Indeed, this characteristic of infant sleep perhaps captures best what it means to sleep like a baby.

The fragmented sleep–wake pattern of human newborns is easily observed. Sleeping newborns can wake up suddenly and fall back to sleep just as fast. Such rapid transitions between states occur similarly during the day and night; in other words, there is initially no clear circadian rhythm. As weeks go by, bouts of sleep and wake gradually consolidate, becoming longer and longer. Importantly, even as this consolidation takes place, the total amount of sleep accumulated during the day and night does not change. By the age of 3–4 months, further consolidation of sleep and wake bouts has occurred and the total amount of sleep accumulated each day has not changed substantially. But now, sleep is concentrated largely at night, thus marking the beginning of the diurnal activity pattern that characterizes the human species.

In infant rats, the same basic developmental pattern is observed. As shown in Figure 2, alternations between sleep and wake occur very rapidly at 2 days of postnatal age (P2). In contrast, by P21, sleep and wake bouts have consolidated significantly, resulting in many fewer transitions in a given period of time. (Although consolidation occurs postnatally in rats and humans, it occurs prenatally in sheep, whose offspring are born in a relatively mature state.) Furthermore, it appears that the consolidation of sleep and wake bouts develops as hypothalamic structures come to modulate the activity of brainstem structures. One such hypothalamic structure is the suprachiasmatic nucleus (SCN); when the SCN of adult rats is destroyed, fragmented sleep and wake bouts result, reminiscent of the infantile pattern.

Even more can be gleaned from these data through separate statistical analyses of sleep and wake bouts. For example, if all the sleep bouts from P2 rats are extracted and their statistical structure analyzed, it is found that they follow a so-called exponential distribution; the same is true of wake bouts at this age. This means that the probability that a sleep or wake bout will terminate at any given moment is constant across time. Accordingly, cycling between sleep and wake states at this age is a Markov process, that is, a process that is unaffected by how long the pup has been asleep or awake in the immediate past.

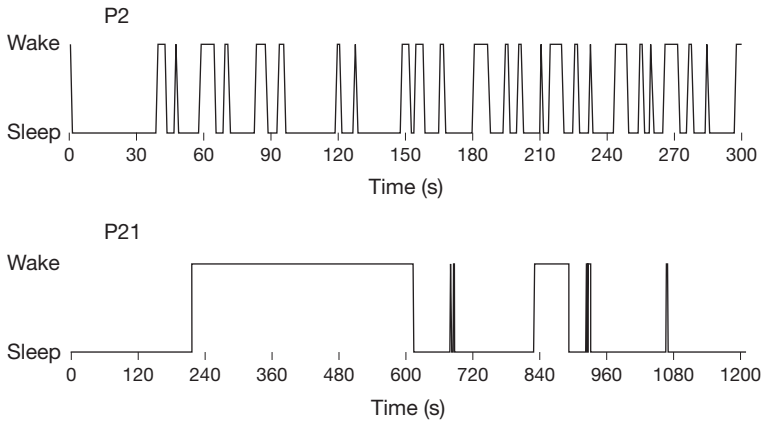

Figure 2 Infant sleep and wake bouts are fragmented. Sleep–wake cycles in a 2-day-old rat (P2; upper trace) and a 21-day-old rat (P21; lower trace). Note the different time scales in the two traces. Sleep and wake bouts at P2 are highly fragmented in relation to those at P21. From Blumberg MS, Seelke AM, Lowen SB, and Karlsson KA (2005) Dynamics of sleep-wake cyclicity in developing rats. *Proceedings of the National Academy of Sciences* 102: 14860–14864. Copyright by the National Academy of Sciences.

By P21, rats exhibit more consolidated sleep bouts, but they retain the exponential distribution exhibited at P2. However, by P21, wake bouts exhibit a qualitative shift in their statistical properties. Specifically, rather than follow an exponential distribution, they now follow a power-law distribution. For power-law distributions, the probability that a bout will terminate at any given moment decreases as the wake bout increases; in other words, 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). It is as if the system has a memory for how long it has been awake in the immediate past. Exponential sleep bout distributions and power-law wake bout distributions have also been observed in adult humans, cats, and mice.

Precise analyses of the statistical properties of sleep and wake bouts are helping to better understand the biological mechanisms responsible for consolidation during normal development and fragmentation when things go wrong (as in narcolepsy). For example, such analyses can be used to generate and test computational models of sleep–wake processes, thereby helping to understand the kinds of neural mechanisms required to produce bout consolidation and circadian rhythmicity. In addition, neuroscience methods can be used to probe the neural circuits that are responsible for the various features of sleep–wake organization. For example, destruction of one component of the system known to be important for arousal – a brainstem nucleus called the locus coeruleus – has been shown to prevent the emergence of power-law wake behavior in rats without disrupting sleep. Further dissection of this brain circuit (which includes the SCN) at different ages, coupled with computational modeling, may soon provide a fuller description of the ontogeny of ultradian sleep–wake processes.

Circadian sleep–wake rhythms arise through the developmental modification of the ultradian sleep–wake rhythm. Based on what is known about the regulation of circadian rhythms, it can be inferred that, across development, the SCN – which in all mammals is metabolically active during the day and inactive at night – gradually gains influence over the neural mechanisms that produce ultradian sleep–wake rhythms. For example, in a diurnal species such as humans, the ultradian rhythm is increasingly modulated by the SCN so that, between the third and fourth postnatal months, sleep predominates at night even as the total daily quantity of sleep remains largely unchanged. Similarly, in a nocturnal species like the Norway rat, the ultradian rhythm is increasingly modulated by the SCN so that, by the end of the second postnatal week, sleep predominates during the day. And because the pattern of SCN activity is identical in diurnal and nocturnal species – that is, the SCN is always more active during the day than during the night – the evolution of diurnality and nocturnality in various species must have arisen through developmental modifications of the neural connections between the SCN and other structures.

Developmental Changes in Sleep Structure Build on a Basic Foundation

For an adult animal to be considered in quiet or active sleep, it is generally demanded that certain requirements be met. Accordingly, the requirements of quiet sleep are met when an animal is lying still and relaxed in a characteristic posture, with the eyelids shut and the eyes unmoving, and exhibiting cortical delta waves in the EEG. The requirements of active sleep are met when an animal's muscle tone is completely suppressed, when it exhibits phasic motor activity (i.e., myoclonic twitching) of the limbs and eyes (i.e., REMs), and when it exhibits an activated EEG devoid of delta waves. Although there are other characteristics of each sleep state, the focus here is on muscle tone, behavior, and cortical EEG.

Depending on the age and species of the infant subject under study, one or more of the standard electrographic criteria of sleep may be absent. This simple observation presents a conundrum that can inspire a variety of responses. For example, if infant sleep states do not conform to criteria established in adults, one might conclude that the adult forms of sleep differentiate from poorly organized infant sleep states or from a single amalgamated 'protostate.' Although such accounts continue to be favored by some investigators, a different

account emerges when the process by which sleep states are constructed throughout early development are carefully documented.

Figure 3 depicts schematically the development of sleep–wake states across the early postnatal period in rats. Because rats are altricial (i.e., born in a relatively immature state), many important developmental milestones can be observed postnatally that occur prenatally in other species, such as humans or sheep. For example, as will be discussed further later on, delta activity – the EEG signature of quiet sleep in adults – does not develop until P11 in rats. In contrast, delta activity develops by 32 weeks postconception in humans (average gestation length: 40 weeks), 115–120 days postconception in sheep (average gestation length: 147 days), and 50 days postconception in guinea pigs (average gestation length: 65 days).

In rats, the foundational structure of a sleep–wake cycle is seen as early as 2 days after birth (P2 in Figure 3). The cycle begins with a period of wakefulness characterized by high muscle tone. It is during this period that a pup exhibits such wake-related movements as kicking, yawning, 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, and head. Within a single period of sleep, these bursts of twitching can be interrupted by brief bouts of behavioral quiescence. The pattern just described at P2 is similar to that observed through P9; however, with age, sleep and wake bouts become longer, as do the periods of quiescence between bursts of twitching.

The eyelids of infant rats are initially sealed shut and they do not open until P15. Also, the eyes are not fully mobile during the early postnatal period, so REMs cannot be used as a criterion of active sleep. However, because REMs are produced by twitches of the muscles that control the eyes, it is possible to relate extraocular muscle twitching to other forms of twitching throughout the body. When this was done in infant rats, it was found that the extraocular muscles twitch along with the other skeletal muscles of the body. Thus, the absence of REMs early in the development of rats and other species does not indicate that active sleep is disorganized at these ages.

Figure 3 indicates that, by P9, the period of quiescence between wakefulness and the first bout of active sleep has become more pronounced. But because 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 (depicted as sinusoidal waves in Figure 3) now occurs exactly during this initial period of quiescence. By P13, delta power has increased and is also more reliably expressed during periods of quiescence between bursts of twitching. Altogether, these observations support the notion that although delta activity aids in the identification of quiet sleep at P11 and beyond, its absence at younger ages is not an indication that quiet sleep does not yet exist. Rather, with age, sleep components are added to and integrated with an already existing, organizational structure.

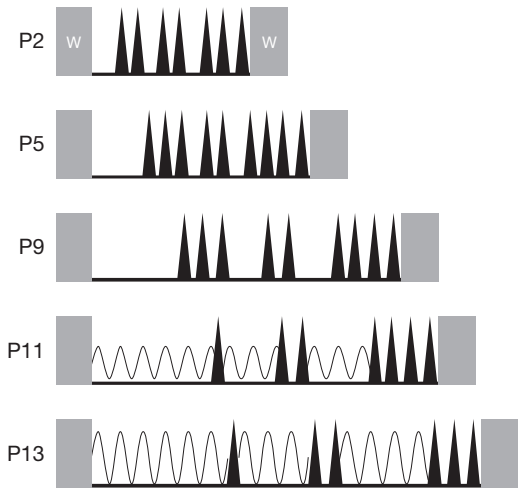

Figure 3 Developmental changes in sleep structure build on a basic foundation. Schematic depiction of developmental changes in sleep and wakefulness and the emergence of delta activity in infant rats. Gray rectangles represent periods of high muscle tone and high-amplitude movements (e.g., kicking, stretching), indicative of wakefulness (W). Interposed periods of sleep are defined by suppressed muscle tone (horizontal black lines). Phasic bursts of myoclonic twitching, indicative of active sleep, are depicted as black triangles. Delta activity, indicative of quiet sleep, is depicted as sinusoidal waves. With age, delta power, indicated as increased amplitude of the sinusoidal waves, increases. Adapted from Seelke AMH and Blumberg MS (2008) The microstructure of active and quiet sleep as cortical delta activity emerges in infant rats. *Sleep* 31: 691–699. This copyrighted material is used with permission granted by the Associated Professional Sleep Societies – Darien, Illinois.

The Neural Control of Infant Sleep

Because the brain contains the neural circuitry that controls and modulates sleep–wake processes, a full understanding of the ontogeny of sleep requires a fuller understanding of how developmental changes in brain circuitry are related to developmental changes in sleep expression. Fortunately, work in adult animals has progressed to a point where many of the basic neural elements that contribute to sleep have been identified. This information can now be used to investigate these elements in developing animals.

Given similarities in the basic organizational structure of sleep in infants and adults, it is not surprising that at least some of the neural substrates of infant sleep are similar to those of adults. This conclusion emerged from work using infant rats. Specifically, there exists a region within the medulla that, when activated, suppresses muscle tone during sleep. This medullary region receives neural projections from mesopontine brainstem areas, including the subcoeruleus, pontis oralis, and dorsolateral pontine tegmentum. Neurons in these areas exhibit firing properties that suggest they play a role in the modulation of muscle tone and the production of twitches.

By cutting off the mesopontine region from more rostral structures, including such forebrain structures as the hypothalamus and cerebral cortex, it is seen that the brainstem alone contains circuitry sufficient to produce the basic features of the infant's sleep–wake cycle – including fluctuations in muscle tone and behavior. However, as already mentioned, the sleep and wake bouts produced by this brainstem circuit are

fragmented, suggesting that developing interactions with forebrain structures, including the SCN, contribute to the consolidation of sleep and wake bouts across development.

As described earlier, when infant rats are deprived of sleep over a 30-min period, they exhibit rapid increases in sleep pressure. Sleep pressure comprises one of two compensatory or 'homeostatic' responses to sleep deprivation; the other response, sleep rebound, refers to the increased sleep that occurs when a sleep-deprived animal is allowed to sleep. Thus, when a newborn rat is allowed to sleep after a 30-min sleep-deprivation period, it exhibits an immediate increase in sleep that partially makes up for the sleep lost during the deprivation period. Interestingly, while the brainstem alone is sufficient to support the accumulation of sleep pressure in newborn rats, sleep rebound appears to depend on the same hypothalamic nuclei that support sleep rebound in adults. These findings further solidify the notion that sleep–wake processes in newborns reflect a foundational structure on which adult processes are built.

Why Do Infants Sleep So Much?

Noting the striking 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 development." Accordingly, they put forward the *ontogenetic hypothesis*, which emphasized how the brainstem mechanisms that produce active sleep provide direct ascending stimulation to the forebrain, thereby promoting brain development at those ages when wake-related stimulation is low. Consistent with this hypothesis, subsequent work has indicated that active sleep plays a regulatory role in the modulation of visual cortical plasticity early in development.

The concept of activity-dependent development is a cornerstone of contemporary neuroscience; 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 that concept. In subsequent decades, researchers have come to believe that, in general, the infant and also the juvenile brain is highly plastic and that active sleep – as well as quiet sleep – contributes to that plasticity. For example, research indicates that naps aid language learning in human infants, that quiet sleep enhances cortical plasticity in juvenile rats, and that juvenile songbirds need sleep in order to learn and remember their song. Recently, researchers found that human infants are able to learn even while they sleep, a capacity that the authors of the study suggested may be unique to infants due to their enhanced brain plasticity. 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 to elucidate the functions of sleep in adults.

Why Do Infants Twitch So Much During Sleep?

Conventional wisdom has long held that the twitches of sleeping infants and adults are the outward manifestation of dreams. For example, George Romanes, comparative psychologist and protégé of Charles Darwin, wrote in 1883 that "ferrets dream, as I have frequently seen them when fast asleep moving their noses and twitching their claws as if in pursuit of rabbits." But as conspicuous as the twitches of adults may be, they are exceedingly more conspicuous in infants. In fact, in terms of intensity and frequency, twitching is among the most prominent of infantile behaviors. However, in light of the conventional wisdom, it could be that all of these twitches are mere functionless by-products of a dreaming brain.

Based on recordings in infant rats from the nuchal muscle (i.e., the muscle at the back of the neck that holds up the head) – estimates indicate that this muscle twitches over 38 000 times each day. In light of such extraordinary levels of activity, it is difficult to imagine that twitches are mere functionless by-products.

The first strong evidence in favor of a functional role for twitches came when investigators, using experimental and computational approaches, showed that tactile feedback from a twitching limb, produced when the limb touches a nearby object, guides the organization of spinal sensorimotor circuits. The next breakthrough came when investigators, recording from somatosensory cortex in neonatal rats during periods of twitching, discovered a new cortical event – they called it a spindle burst – comprising a brief wavelike burst of activity (a typical spindle burst might oscillate at 15 Hz for 1 s). Importantly, these spindle bursts appeared to be triggered by twitches during sleep such that forelimb twitches triggered spindle bursts in the forelimb region of somatosensory cortex, hindlimb twitches triggered spindle bursts in the hindlimb region, etc. Subsequent work suggested that spindle bursts are triggered specifically by the proprioceptive feedback generated by a twitching limb. Figure 4 summarizes the path from twitch production to forebrain activation.

All together, these recent findings are helping to dispel the notion that twitches are functionless by-products of the

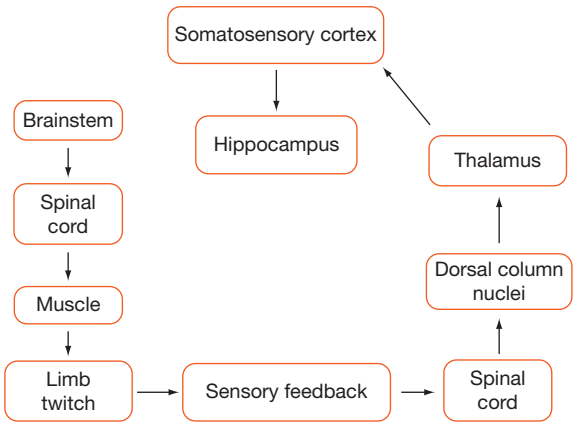

Figure 4 Sensory feedback from sleep-related limb movements activates the central nervous system. The likely neural pathway from the triggering of a twitch to the processing of twitch-related sensory feedback in the forebrain. Neurons within the brainstem trigger a limb twitch, whereupon sensory feedback is generated. In particular, proprioceptive feedback is communicated through the spinal cord, dorsal column nuclei, and thalamus before generating a spindle burst in primary somatosensory cortex. From the cortex, activation is communicated to the hippocampus and, perhaps, to other structures.

dreaming brain. On the contrary, these findings are suggesting that twitches are active contributors to the establishment, refinement, and maintenance of neural circuits linking muscle, spinal cord, and brain.

Finally, this developing story about the functional consequences of twitching does not end with the cortex. The hippocampus, a subcortical structure that is important for learning and memory, also exhibits activity patterns that are strongly linked with twitching in infant rats. Specifically, it appears that twitches initially trigger spindle bursts in cortex, and this cortical activity subsequently activates the hippocampus (see **Figure 4**). It is not yet known whether this cascade of activation triggered by twitching continues beyond the hippocampus to other brain structures.

Conclusion

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 prominent in early development, some believe that an understanding of the ontogeny of sleep is critical to understanding its functions. In addition, because evolutionary change occurs through modifications of developmental processes, the study of sleep ontogeny across a diversity of species will also inform human understanding of sleep phylogeny, as well as the neural mechanisms underlying species differences. In sum, there are few areas of sleep investigation where increased attention to developmental processes will fail to yield important insights.

See also: **Background:** Chemical Neuroanatomy of Sleep–Wake Systems; Evolution of Sleep (Sleep Phylogeny); Mammalian Sleep; **Chronobiology of Sleep:** Sleep Homeostasis; **Critical Theoretical and Practical Issues:** The Function of Sleep; **Dreaming:** Neurobiology of Dreaming; **Intrinsic Factors Affecting Sleep Loss/Deprivation:** Homeostatic and Circadian Influences; **Pediatric Sleep:** Neonates and Infants; **Sleep and the Nervous System:** Basic Sleep–Wake Mechanisms; **Sleep Deprivation/Fragmentation Paradigms:** Sleep Fragmentation.

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