

Sleep and Infant Learning

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Human neonates spend the majority of their time sleeping. Despite the limited waking hours available for environmental exploration, the first few months of life are a time of rapid learning about the environment. The organization of neonate sleep differs qualitatively from adult sleep, and the unique characteristics of neonatal sleep may promote learning. Sleep contributes to infant learning in multiple ways. First, sleep facilitates neural maturation, thereby preparing the infants to process and explore the environment in increasingly sophisticated ways. Second, sleep plays a role in memory consolidation of material presented while the infant was awake. Finally, emerging evidence indicates that infants process sensory stimuli and learn about contingencies in their environment even while asleep. As infants make the transition from reflexive to cortically mediated control, learned responses to physiological challenges during sleep may be critical adaptations to promote infant survival. Copyright © 2010 John Wiley & Sons, Ltd.

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CHARACTERISTICS OF INFANT SLEEP

Neonates sleep at least 16–18 h per day, and their sleep patterns are markedly different from the sleep patterns of older infants and adults (Anders, Sadeh, & Appareddy, 1995; Gertner *et al.*, 2002). Neonatal behavioural states are not limited simply to wakefulness versus sleep: within sleep epochs, distinct states also can be observed, which have characteristic patterns of respiration, heart rate, electroencephalographic (EEG) activity, eye movements, and muscle activity (Prechtl, 1977). In seminal work, Prechtl (1974) described behavioural states in the

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newborn. State 1 by Prechtl's designation, quiet sleep, is characterized by regular respiration, slow and regular heart rate, and the absence of eye movements and gross muscle movements, with the exception of transient movements and heart rate increases if the infant startles (Prechtl, 1974). Neonates in quiet sleep show an EEG pattern known as *tracé alternant*, defined by bursts of high-amplitude slow-wave activity interspersed with low-voltage activity (Prechtl, 1974). While older infants also exhibit a quiet sleep state, the *tracé alternant* disappears by 46–48 weeks postconceptional age (PCA; Mirmiran, Maas, & Ariagno, 2003). Prechtl's State 2, active sleep, is characterized by variable respiration and heart rate and the presence of both slow and rapid eye movements (REM), along with continuous EEG activity of mixed amplitude (Mirmiran *et al.*, 2003; Prechtl, 1974). To meet criteria, a behavioural state must persist for several minutes without interruption (Prechtl & O'Brien, 1982). When sleeping infants do not show the sustained, specific pattern of physiological and behavioural activity characteristic of either quiet or active sleep, they are said to be in indeterminate sleep. Quiet and active sleep states can be distinguished by 30 weeks PCA in both foetuses and preterm infants although indeterminate sleep predominates during this developmental period (Czikk, Sweeley, Homan, Milley, & Richardson, 2002; Mirmiran *et al.*, 2003; Richardson, Caetano, Homan, & Carmichael, 1994). The emergence of quiet and active sleep states provides an early indication of neural maturation (Mirmiran *et al.*, 2003). Compared with adults and older infants, newborns spend much more time in active sleep, amounting to over half of their total sleep time (Anders *et al.*, 1995).

The first year of life is characterized by a number of developmental changes in sleep patterns, including an increase in quiet sleep (Fagioli & Salzarulo, 1982; Ficca, Fagioli & Salzarulo, 2000; Louis, Cannard, Bastuji, & Challamel, 1997; Mirmiran *et al.*, 2003); increase in the number of sleep cycles and total sleep cycle length (Ficca *et al.*, 2000); decrease in active sleep (Coons & Guilleminault, 1982; Fagioli & Salzarulo, 1982; Louis *et al.*, 1997; Mirmiran *et al.*, 2003); decrease in indeterminate sleep (Fagioli & Salzarulo, 1982; Ficca *et al.*, 2000; Louis *et al.*, 1997; Mirmiran *et al.*, 2003); decrease in total sleep time (Louis *et al.*, 1997); development of a clear circadian rhythm (Coons & Guilleminault, 1982; Louis *et al.*, 1997; Mirmiran *et al.*, 2003); and a changeover to the adult-like pattern of quiet sleep being more prevalent at the beginning of nighttime sleep (Fagioli & Salzarulo, 1982; Hoppenbrouwers, Hodgman, Harper, & Serman, 1982). Sleep patterns are initially fragmented in human neonates, with frequent transitions not only among sleep states but also between sleeping and waking. In the first few months after birth, as the forebrain matures and exerts greater control over the brainstem and cortical regions to organize sleep–wake rhythms, sleep episodes become longer and more continuous (Mirmiran *et al.*, 2003). This developmental pattern of the consolidation of sleep episodes, first described by Coons and Guilleminault (1982), has also been observed in rats (Blumberg, Seelke, Lowen, & Karlsson, 2005). In humans, sleep spindle activity, which is thought to be related to the development of thalamocortical circuits, increases dramatically in early infancy and by 6 months of age it comes to resemble adult sleep spindle activity (Louis, Zhang, Revol, Debilly, & Challamel, 1992). Sleep spindle activity is associated with hyperpolarization and synchronization of thalamocortical neurons (Dijk, 1995), and it has been suggested that the increase in sleep spindle activity in the first few months of life reflects the development of these thalamocortical circuits (Louis *et al.*, 1992). These changes in sleep patterns from the foetal period through late infancy have been attributed to maturation of multiple neural networks (Scher, Steppe, Dahl, Asthana, & Guthrie, 1992).

Sleep Promotes Brain Development

Sleep also may play a dynamic role in brain development. Active sleep may facilitate neural processes, such as synapse formation and pruning, by providing endogenous stimulation to the brain (Denenberg & Thoman, 1981; Mirmiran & Ariagno, 2003; Roffwarg, Muzio, & Dement, 1966). The high prevalence of active sleep in early infancy, a period of rapid brain development, seems to be consistent with this hypothesis. Evidence that active sleep is important for brain development comes from the animal literature, in which rats deprived of REM sleep during the neonatal period had reduced cerebral cortex and brainstem volume and alterations in neurotransmitter sensitivity compared with typically developing rats (Mirmiran, Feenstra, Dijcks, Bos, & Van Haaren, 1988; Mirmiran, Scholtens, Van de Poll, Uylings, Van der Gugten, & Boer, 1983; Mirmiran, Uylings, & Corner, 1983). Comparative phylogenetic research indicates that across mammalian species, REM sleep duration was associated with brain volume relative to body mass, which can be taken as a very rough indicator of cognitive complexity (Lesku, Roth, Amlaner, & Lima, 2006). Extrapolating from these findings at the species level, it is possible that REM sleep duration also could contribute to neurodevelopmental differences between individuals of the same species.

REM sleep in infancy appears to set the stage for later learning. Rats deprived of REM sleep during the neonatal period showed no neural plasticity when placed in an enriched environment as adults (Mirmiran, Scholtens, *et al.*, 1983). In humans, this early influence of sleep patterns on brain development may predict individual differences in later cognitive function. For example, infants who had more mature patterns of sleep in the neonatal period, including higher nighttime activity level and lower total sleep time, obtained higher scores on the Bayley Mental Development Index when tested at 6 months of age (Gertner *et al.*, 2002).

ROLE OF SLEEP IN PLASTICITY, LEARNING, AND MEMORY CONSOLIDATION

Sleep deprivation studies provide evidence that both REM and non-REM (NREM) sleep influence experience-dependent neural plasticity mechanisms. REM sleep deprivation prolongs the critical period of synaptic plasticity in the rat visual cortex and delays the development of synaptic plasticity in the lateral geniculate nucleus of the hypothalamus (Shaffery, Lopez, Bisette, & Roffwarg, 2006; Hogan, Howard, Roffwarg, & Shaffery, 2001). Thus, REM sleep is not only involved in neural maturation but also influences synaptic plasticity in response to visual input. While this phenomenon has been studied most thoroughly in the developing visual system, REM sleep has excitatory inputs throughout the brain; hence, it may influence plasticity in other brain regions as well (Peirano & Algarin, 2007). NREM sleep also is thought to play a role in synaptic remodelling, specifically through reactivation of neural activity patterns that occurred during wakefulness (Bear & Malenka, 1994; Kavanau, 1994; Kudrimoti, Barnes, & McNaughton, 1999; Peirano & Algarin, 2007). Synaptic remodelling of the visual cortex in response to monocular deprivation was enhanced by NREM sleep (Frank, Issa, Stryker, & Keck, 2001).

Sleep plays an important role in memory consolidation processes, both in developing animals (e.g. Deregnacourt, Mitra, Feher, Pytte, & Tchernichovski, 2005) and in adult humans (Fenn, Nusbaum, & Margoliash, 2003; Stickgold & Walker, 2005; Wagner, Gais, Haider, Verleger, & Born, 2004; Walker, Brakefield,

Hobson, & Stickgold, 2003). Adults tested after an intervening period of sleep had enhanced ability to abstract a rule from previously learned materials, leading Wagner *et al.* (2004) to suggest that neural restructuring that occurs during sleep could facilitate insight. In adults, the effective consolidation of different types of memory may be sleep state dependent. Plihal and Born (1999) found that REM sleep and slow-wave sleep were associated with the consolidation of non-declarative and declarative memory, respectively. Visual memory consolidation appears to be dependent both on REM sleep (Karni, Tanne, Rubenstein, Askenasy, & Sagi, 1994) and on slow-wave sleep (Gais, Plihal, Wagner, & Born, 2000). Stage 2 NREM sleep has been specifically identified as important in the consolidation of motor memory (Smith & MacNeill, 1994; Walker, Brakefield, Morgan, Hobson, & Stickgold, 2002). Sleep spindle activity originating in the hippocampus during slow-wave sleep may serve the function of memory consolidation by transmitting information from the hippocampus to the neocortex (Buzsaki, 1996; Gais, Molle, Helms, & Born, 2002; Sirota, Csicsvari, Buhl, & Buzsaki, 2003). Capellini, McNamara, Preston, Nunn, and Barton (2009) further posit that following the transfer of information from the hippocampus and amygdala to the neocortex during NREM sleep, this information then is integrated into neocortical networks during REM sleep. Relatedly, in adults, consolidation of declarative memory was related to the duration of NREM-REM sleep cycles (Mazzoni, Gori, Formicola, Gneri, Massetani, Murri, *et al.*, 1999) and was impaired when sleep cycles were interrupted (Ficca, Lombardo, Rossi, & Salzarulo, 2000). While conclusions about infant sleep cannot be extrapolated from adult studies, it would be an interesting research question to examine whether the normative developmental increase during infancy in the number and duration of sleep cycles (Ficca *et al.*, 2000) corresponds to improved consolidation of different types of memories during sleep.

The role of sleep in infant memory consolidation has yet to be comprehensively examined. A recent study exposed 15-month-old infants to an artificial language and manipulated whether or not they napped between the learning phase and the test phase (Gomez, Bootzin, & Nadel, 2006). Infants in both groups demonstrated memory for word pairs identical to those presented in the learning phase, but only infants who napped showed that they had learned the grammatical rules of the language and could recognize those rules in novel word strings. Therefore, sleep appeared to facilitate abstracting knowledge about environmental contingencies from stimuli presented during wakefulness (Gomez *et al.*, 2006).

LEARNING, MEMORY, AND NEONATAL SLEEP PATTERNS

Newborn infants spend up to 70% their time asleep (So, Adamson, & Horne, 2007) and are able to maintain wakefulness only for brief intervals (Anders & Roffwarg, 1973; Peirano & Algarin, 2007). One consequence of this fact is that most awake experiences will be followed shortly thereafter by a period of sleep, so any learning that takes place while awake is likely to benefit from the memory facilitation produced by sleep. Perhaps even more intriguing is the possibility that infants have the capacity to learn new information while asleep. Notably, in adults, there have been no conclusive demonstrations of an ability to learn during sleep. Two studies with small samples of adults have reported some indication of classical conditioning during sleep (Beh & Barratt, 1965; Ikeda & Morotomi, 1996). However, research on adult learning during sleep is scant, and other

researchers have contended that adults are not capable of learning during sleep (Aarons, 1976). In any event, it is problematic to compare 'learning during sleep' for neonates versus adults because of the qualitative differences between neonate and adult sleep. The greater plasticity of the neonate brain may enable learning in circumstances that would not suffice for adult learning (Hensch, 2004).

Even while asleep, infants are surrounded by environmental contingencies, often spanning multiple sensory modalities. For example, a decrease in warmth reliably follows the removal of a swaddling blanket. Might neonates be able to learn about the environmental contingencies they experience during sleep, in addition to those experienced during their fleeting periods of wakefulness? This question is of great interest to Sudden Infant Death Syndrome (SIDS) researchers because of its implications for infant survival. Some of the situations that infants encounter during sleep, such as respiratory occlusion and thermal challenges, require a response on the part of the infant, and infants already at risk for SIDS who have difficulty learning to respond adaptively may be especially vulnerable. Before exploring whether infants are capable of learning an association between two sensory stimuli during sleep, it is necessary to establish (1) that newborns are capable of learning and (2) that they are capable of processing new information during sleep.

Neonatal Learning

From the first days of life, awake infants are capable of classical conditioning and operant learning (Lipsitt, 1998; Rovee-Collier & Lipsitt, 1982; Sullivan, Taborsky-Barba, Mendoza, Itano, Leon, *et al.*, 1991; Watson & Rayner, 1920). It is possible to condition both positive-approach behaviours (e.g. rooting, sucking, or smiling) and avoidance/escape behaviours by selectively reinforcing existing reflexes in waking neonates (Lipsitt, 1998). For example, awake human neonates can learn to alter sucking behaviour to obtain a variety of reinforcers, including milk (Papousek, 1961), a sweet-tasting solution (Siqueland & Lipsitt, 1966), and the sound of their mothers' voice (DeCasper & Fifer, 1980). In another example of cross-sensory associative learning in awake neonates, Sullivan *et al.* (1991) paired a citrus odour with tactile stimulation. The following day, the neonates produced the conditioned response—a head turn—in response to the citrus odor. This learned response was observed regardless of whether the neonates were awake or asleep at the time of testing (Sullivan *et al.*, 1991). This study demonstrates a number of impressive competencies in the human neonate: to learn an association between two stimuli across sensory modalities, remember that association over a 24-h period, and generalize the learned response to occur during sleep and wakefulness. It is easy to see how such competencies might be adaptive—such as learning to recognize and orient toward the mother's odour to facilitate suckling.

Neonates Process Information While Asleep

Newborn infants are in fact capable of processing information during sleep. For example, they actively process auditory stimuli while asleep (Cheour, Martynova, Naatanen, Erkkola, Sillanpaa, Kero, *et al.*, 2002; deRegnier, Nelson, Thomas, Wewerka, & Georgieff, 2000; Sambeth, Ruohio, Alku, Fellman, & Huotilainen, 2008). Neonate event-related potentials (ERPs) differed in response to their mother's voice versus a stranger's voice, with the ERP to the stranger's voice showing the negative slow wave that is a characteristic response to novelty

(deRegnier *et al.*, 2000). Thus, the infants were able to recognize a familiar stimulus, their mother's voice, and to differentiate it from a novel stimulus. Neonates also are able to learn to recognize an auditory stimulus during sleep in a mismatched negativity paradigm, in which a deviant tone is occasionally interspersed with a repeated standard tone (Cheour *et al.*, 2002). Their ERPs to the deviant tone resemble the response observed in waking adults, indicating that they have learned during sleep to habituate to the standard tone and to distinguish it from the deviant tone. Thus, even during sleep, neonates are processing sensory inputs and representing specific aspects of their environments.

Neonates Can Learn During Sleep

A recent study demonstrated learning in neonates when information was presented only during sleep (Fifer, Byrd, Kaku, Eigsti, Isler, Grose-Fifer, *et al.*, in press). Sleeping neonates were presented with a delay eyelid conditioning paradigm pairing a tone with an air puff, and responses were assessed using EEG recordings. The neonates increased their rate of conditioned eye movements in response to the tone alone, providing evidence of their capacity to learn associations while asleep. Moreover, in the frontal brain regions, there was a change in evoked response potentials (ERPs) to the tone over the course of the conditioning session, with an increasingly positive slow-wave response, suggesting an adaptation in cognitive processing of the conditioned stimulus.

SLEEP STATE MAY INFLUENCE LEARNING

Several studies of classical conditioning in sleeping rats suggest that the efficacy of associative learning paradigms may vary according to the sleep state. Rats that underwent a classical conditioning paradigm during REM sleep were able to learn a conditioned response, as assessed by neural responding in the hippocampus and amygdala to the conditioned stimulus (Hennevin, Hars, Maho, & Block, 1995). They also transferred the conditioned response to the awake state, engaging in avoidance behaviours in response to the conditioned stimulus. Interestingly, this learning was state dependent—while associative learning occurred in both awake and REM sleep states and generalized between these two states, no new associative learning occurred during NREM sleep nor did previously acquired conditioned responses transfer to the NREM sleep state (Hennevin *et al.*, 1995; Maho & Bloch, 1992). The findings from the animal literature raise the possibility that associative learning during sleep could be state dependent for human infants as well.

It will be important for future studies of infant associative learning during sleep to classify sleep states and the levels within them more thoroughly using cardiorespiratory, electroencephalographic, and myographic measures together. Neonates often alternate between sleep states fairly frequently, and a significant portion of their sleep is still of indeterminate state (not classifiable as either quiet or active sleep). Thus, it is likely that in one conditioning session a given infant might spend time in quiet, active, and indeterminate sleep. Nonetheless, identifying the predominant sleep state may help to account for individual differences in learning among infants of the same PCA. If human neonates are found to learn associations more readily in active as opposed to quiet sleep state, that would suggest an additional evolutionary function of the predominance of active

sleep in early infancy. Spending more time in active sleep not only provides sources of endogenous stimulation to facilitate neural maturation but also might benefit the neonates by offering more opportunities to master environmental contingencies and to develop adaptive responses to those contingencies.

LEARNING DURING SLEEP: IMPORTANCE FOR SURVIVAL

Regardless of underlying mechanisms, there is a clear adaptive value to learning during sleep. Infant survival is threatened during sleep, and the ability to learn escape behaviours or postural adjustments rapidly in response to cardiorespiratory challenges may be critically important (Mitchell, Williams, & Taylor, 1999). Neonates necessarily are inexperienced with prone sleep, as there is no opportunity for this behaviour in the womb. Reliable contingencies are present in the sleep environment: certain sleep positions and tactile cues can co-occur with respiratory and thermal challenges. Relief from these conditions can be associated with adaptive postural adjustments or arousal (Lipsitt, 1982; Paluszynska, Harris, & Thach, 2004). For example, the neonate is aided by an innate, brainstem-mediated sleep startle reflex of head lifting in reaction to respiratory occlusion (McGraw, 1963; Paluszynska *et al.*, 2004). Gunther (1955) characterized the neonate response to respiratory occlusion as a fixed action pattern. The reflexive head movements would lead to increased air flow, so that they would be reinforced, thereby increasing the probability that this behaviour would be repeated promptly in the future, even in response to milder respiratory occlusion (Gunther, 1955, Lipsitt, 1998). Infants born with a weaker or deficient respiratory occlusion reflex, or those with deficits in the neural pathways required for associative learning of an adaptive arousal response, may be particularly susceptible during this already vulnerable period (Burns & Lipsitt, 1991; Lipsitt, 1998). Recent SIDS research suggests that respiratory-related challenges are only one of many requiring physiological responses during infant sleep (Sahni, Schulze, Kashyap, Ohira-Kist, Fifer, & Myers, 2005). Changes in temperature, blood pressure, and heart rate constantly require adjustments during sleep and transitions to different states.

Consistent with the view that learning plays a key role in adjustment to challenges, developing rat pups exposed to brief episodes of hypoxia during quiet sleep had increased latency to arousal over repeated trials, indicating habituation (Darnall, Williams, & Schneider, 2008). When arousal was rewarded with increased air flow, simulating the result of an adaptive response, habituation to hypoxia was no longer evident. Thus, the association of an infant response with escape from hypoxia not only reinforces that response but also prevents habituation to hypoxia. Neonatal rats exposed to repeated episodes of hypoxia during sleep exhibit a persistent increase in the rate of sleep apneas, indicating an experience-dependent effect on respiratory control mechanisms during sleep (Thomas, Friedman, MacKenzie, & Strohl, 1995). Human infants who, like Darnall *et al.*'s rat pups, have previously experienced intermittent hypoxia and have failed to mount an effective response may be more vulnerable to arousal failure.

Although there are myriad risk factors associated with the incidence of SIDS, age dependency is the hallmark of the syndrome. Converging data from a number of related fields support the characterization of the high risk period as one of marked homeostatic instability (Kinney, Filiano, Sleeper, Mandell, Valdes-Dapena, & White, 1995). Complex sleep-dependent developmental changes are evident in a wide range of systems including control of respiration

(Haddad & Donnelly, 1988; Hoppenbrouwers, Hodgman, Harper, & Sterman, 1980), periodic breathing (Kelly, Carley, & Shannon, 1988), and thermal regulation (Azaz, Fleming, Levine, McCabe, Stewart, & Johnson, 1992). During this same period of vulnerability, infants have difficulty mounting a robust response to postural challenge, showing no increase in heart rate and only a weak electrocortical response to a head-up tilt while asleep (Myers, Gomez-Gribben, Smith, Tseng, & Fifer, 2006). SIDS can result from a deficit in autonomic control, in which cerebellar and vestibular structures fail to mount compensatory somatomotor and cardiorespiratory responses to a drop in blood pressure (Harper, 2001). During this time, there is also an abrupt shift in the pattern of sleep-wake states with a marked decline in REM sleep as well as an attenuation of ability to respond to hypoxia (Kemp & Thach, 1993; Trinder, Newman, Le Grande, Whitworth, Kay, Pirkis, *et al.*, 1990). In addition, circadian rhythms become more firmly established (Lodemore, Peterson, & Wailoo, 1992). Interestingly, through this time period, EEG activity and behavioural arousal during quiet sleep are diminished, whereas in active sleep arousability is increased (Trinder *et al.*, 1990).

CONCLUSIONS

The unique characteristics of infant sleep, including a preponderance of active sleep and frequent transitions between states, may be particularly well suited for timely learning about the extrauterine environment. Optimal sleep prepares the infant to learn when awake, and after learning has occurred during wakefulness, critical memory consolidation processes follow during sleep. Emerging evidence suggests that neonates also can process sensory input and learn while sleeping. A more thorough understanding of sleep state processes during stimulation is needed to address possible evolutionary implications of infant learning in different states as well as developmental changes in learning capacities. The ability to learn adaptive responses to physiological challenges in the sleeping environment has crucial implications for infant survival. Future research also should examine individual differences in infants who are in the developmental window of the greatest SIDS vulnerability to better understand the role of learning during sleep in promoting infant survival.

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