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# BARRY UNIVERSITY

# INFANT SLEEP PATTERNS AND LEARNING PROCESSES: EXPANDING RESEARCH ON THE FUNCTION OF SLEEP IN EARLY LIFE

by

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## A THESIS

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Infant Sleep Patterns and Learning Processes: Expanding Research on the Function of Sleep in Early Life

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### Abstract

Using Mismatch Negativity (MMN) as a measure of learning, an emerging body of infant research is challenging the consensus that the sleeping brain prohibits the complete transfer and retention of meaningful information during sleep. Physiological evidence suggests that the developing brain may allow adequate conditions for passive learning during sleep, where mechanisms readily available for inducing long-lasting plastic changes may serve to efficiently enhance the effects of linguistic experience.

Until recently, there has been little empirical evidence to help explain how it is that human infants learn acoustic and linguistic information so rapidly, despite spending so much time in sleep. Consider the fact that intrauterine recordings of fetal cardiac reactions have demonstrated that the human fetus, at approximately 25 to 28 weeks gestational age, is capable of hearing, processing, retaining, and responding to a variety of acoustic information such as its mother's heartbeat and speech (Descasper & Spence, 1986; Krueger, Holditch-Davis, Quint, & DeCasper, 2004; Yoshinaga-Itano, 1998). At birth, neonates are able to discriminate their mother's voice from other voices (Sai, 2005) and appear to demonstrate acoustic preferences based upon prenatal auditory experiences (DeCasper, & Spence). Shortly after birth, infants are able to extract a variety of regularities from acoustic stimuli and are able to discriminate among several aspects of speech (e.g., frequency, intensity, and duration) without any explicit learning (Carral et al., 2005; Sakai, 2005). Within the first 2 months of life, while much of the time is still spent in sleep, infants demonstrate progressively increased linguistic ability, as they begin to distinguish between different phonemes and more complex sounds (Cheour-Luhtanen et al., 1995; Cheour et al., 1998; Cheour, Kushnerenko, Čeponienė, Fellman, & Näätänen, 2002a).

An emerging body of infant research <u>suggests</u> that some form of learning is possible during sleep. <u>This</u> challenges the consensus that the sleeping brain prohibits the complete transfer and retention of meaningful information. In fact, in contrast to findings derived from studies investigating adult humans and other animals' capacity to learn complex information during sleep, recent physiological findings suggest that the newborn infant brain utilizes time spent in sleep to process and encode new information regarding

language (Cheour et al., 2002b). These findings may contribute to developmental knowledge and may have implications for early intervention; specifically for those at risk of having an auditory processing disorder or other medical conditions that increase the risk for auditory problems. Although the picture remains quite complex due to an incomplete understanding of either sleep or language acquisition alone, examination of research in both areas helps elucidate the possible mechanisms behind this ability and a new function of sleep for an early epoch in development.

In order to address the assumptions underlying this area of research, this review will begin with a review of the literature on sleep. Next, it will report what is currently known about learning and memory processes as they relate to sleep including the physiological measure currently being used in this research area in order to <u>illustrate its</u> potential relevance and contribution to research in this area.

#### Sleep

Until recently, sleep generally has been viewed as a sedentary state wherein the brain remains largely inactive. Based on the findings from current sleep research, sleep is now widely recognized as a state of dynamic brain reorganization at the anatomical, neurobiological, and physiological levels (Izac, 2006). Of particular interest is the conceptualization of sleep as representing a continuum of consciousness as well as the presumed function of each level of sleep (Coenen & Drinkenburg, 2002; Gottselig, et al., 2004).

It is important to recognize that the vast majority of references to sleep denote the characteristics of sleep of the developed brain (i.e., adult sleep). Similarly, the bulk of research on learning and memory processes occurring during sleep refers to adult sleep.

Therefore, as will be noted in a later section, although infant sleep appears to be remarkably different <u>from</u> adult sleep, it necessary first <u>to</u> discuss what is known about adult sleep. <u>Thus</u> the relevance of differentiated sleep patterns in infants may be best understood as relevant to this current research area. Mindful of this fact, the mature sleep pattern is first discussed, followed by the infant sleep pattern.

#### Adult Sleep

Adult sleep is physiologically defined by five stages of sleep that are broadly categorized in terms of two major types of sleep: non-rapid eye movement sleep (n-REM) (stages 1-4) and rapid-eye-movement sleep (REM) (stage 5). This classification is rooted in physiological observation of electrical activity that manifests on measures such as electroencephalography (EEG) in terms frequency waves and rhythms. These EEG patterns have been suggested by many to reflect, in part, precisely timed neuronal firing that promotes specific memory-related processes by way of manipulation of the amount of information from the outside world successfully transferred to the cortex for processing. Possible reasons for this activity will be discussed shortly. (Axmacher, Mormann, Fernandez, Elger, & Fell, 2006 Coenen & Drinkenburg, 2002; see also Izac, 2006)

		Total Percentage of Sleep Time Spent in Each State	
State	Hz	Adult/Mature	Infant
NREM (Stages 1-4)		75 percent	50 percent
Stage 1	9-11Hz. – 4-7 Hz.		
Stage 2	12-14 Hz.		
Stages 3 an	d 4 .5-4 Hz.		
REM	15-30 Hz.	25 percent	50 percent

Table 1. Adult and Infant Patterns

N-REM sleep is broadly associated with the presence of slow, high-amplitude, synchronous (EEG) activity (see Table 1). However, there is notable variation in electrical brain activity as sleep progresses through all four stages of n-REM sleep, as each subsequent sleep stage represents deeper sleep or a reduced degree of interaction with the outside world. In a normal healthy adult, sleep commences with Stage 1 sleep, which is associated with the disappearance of alpha waves (approximately 9-11 Hz. and characteristic of relaxed wakefulness), and the emergence of theta waves ranging from approximately 4-7 Hz. Stage 2 is defined by unique 12-14 Hz. sleep spindles and high amplitude K-complexes, both of which appear to reflect an increased inhibition so as to

promote deeper sleep by way of the attenuation of synaptic information being transmitted afferently from the thalamus (which receives external information and relays it to the cortex). This pattern of activity is reportedly rooted in sleep-induced release of inhibitory (GABA-ergic) transmitters that decrease thalamo-cortical relay to the cortex by way of hyperpolarization of thalamocortical neurons. Thus, as compared to the waking state and Stage 1 of sleep, there is a reduced transfer ratio of sensory input to acutal processing by the brain (i.e., reduced consciousness) (Hennevin, Huetz, & Edeline, 2007; McCormick & Bal, 1994). Stages 3 and 4 are often referred to as slow-wave-sleep or deep sleep since they are characterized by slow, high amplitude, delta waves of approximately .5-4 Hz. Initiated by the same processes described above, it is within these final stages of n-REM sleep that consciousness is most reduced as the cortex receives little external input. (Axmacher et al., 2006; Coenen & Drinkenburg, 2002; Izac, 2006; Siegel, 2004; Steriade, 2000)

REM sleep, also referred to as paradoxical sleep (PS) in nonhuman <u>subjects</u>, is strikingly unique compared to the four other sleep stages. Accordingly, it is classified alone as a type of sleep. Unlike n-REM sleep, REM sleep is characterized by lowamplitude, high-frequency, dynsynchronous EEG activity that typically ranges between 15-30 Hz. This pattern of activity is comparable to that observed in the awake state and, as in the awake state, reflects a high amount of cortical arousal (Rechtschaffen & Siegel, 2000). Several physiological events that take place both in anticipation of and during REM suggest that the brain is preparing itself for the processing of incoming information (viz., depolarization of cells in several neural areas). Oddly enough, the opposite seems to be true. The onset of REM sleep is accompanied by a further increase in the activation of inhibitory neuromodulators that decrease thalamo-cortical relay resulting in an extremely low transfer ratio. Although some external stimuli are still available for cortical processing, only stimuli that are either relevant or intense enough (e.g., one's name being called or an alarm clock going off) are able to pass the thalamo-cortical activation threshold (Perrin, Garcia-Larrea, Mauguière, & Bastuji, 1999; see also Coenen & Drinkenberg, 2002). Despite the near absence of external stimulation, the brain remains actively attuned to internal sources of stimulation (Coenen & Drinkenberg; Izac, 2006; Siegel, 2004).

#### Infant Sleep

Human infant sleep, which is remarkably unique compared to adult sleep, may deserve to be viewed as a less restrictive continuum of consciousness that serves different functions. The general pattern of infant sleep is divided into active sleep (AS), which resembles REM, and quiet sleep (QS), which resembles n-REM. Unlike the normal healthy adult who generally experiences all five sequential sleep stages at 85<sub>2</sub> to 100<sub>2</sub> minute intervals approximately four to six times per night (8 to 9 hours total), infants spend the first few months of life moving through three to four sleep cycles per day and most of the day is spent in sleep. Importantly, there are two notable differences between infant and adult sleep: first, whereas adults spend approximately 25% of total nightly sleep in REM, infant sleep appears to be more evenly distributed (i.e., 50% of total time is in REM-like AS). Second, unlike adult sleep, the onset of infant sleep is accompanied by REM-like AS (Dang-Vu , Desseilles, Peigneux, & Maquet, 2006; Izac, 2006; Middlemiss, 2004). The development of the mature sleep cycle is a progressive process that extends through early childhood (Rechtschaffen & Siegel, 2000); however,

pronounced milestones are observed during the first few months of life, where sleep spindles and K-complexes begin to emerge on the EEG, signaling the beginning of effective inhibition of thalamo-cortical transmission (Kinsley, Polk, Ross, Levisohn, & Freedman, 2003). Accordingly, a more mature five-stage sleep sequence begins to emerge, where sleep commences with n-REM and discrete stages are more identifiable (Dan & Boyd, 2006; Dang-Vu et al., 2006; Middlemiss, 2004; Peirano, Algarin, & Uauy, 2003).

#### Functional Activity: Leaning and Memory

Due to the dynamic processes that occur simply for inhibitory purposes and the pronounced activity demonstrated in the brain thereafter, many have questioned the functional role of these activities and have attempted to link them to learning and memory processes. Although caution must be used when generalizing the findings to infants, past research sheds some light onto the possible role of the infant sleep pattern when considering the state of the developing brain.

Despite much research, there is currently no compelling empirical evidence to indicate that adults are capable of learning complex information presented during sleep. In fact, the inhibitory processes discussed above would argue against complex learning occurring during sleep (see Coenen & Drinkenberg, 2002). Nonetheless, many studies illustrate the contribution of sleep in learning and memory processes. Studies of both animals and humans have demonstrated the facilitative effect of sleep on recently acquired memories, that is, new information acquired prior to going to sleep (Backhaus & Junghanns, 2006; De Knoinck, Lorrain, Christ, Proulx, & Coulombe, 1989; Ellenbogen, Hulbert, Stickgold, Dinges, & Thompson-Shill, 2006; Mednick et al., 2002; Walker,

Brakefield, Morgan, Hobson, & Stickgold, 2002). Investigators have also identified multiple alterations in the sleep cycle induced by learning prior to sleep and exposure to enriched environments prior to sleep (Cantero, Atienza, & Salas, 2002; Gutwein & Fishbein, 1979; De Koninck et al.; Lecas, 1976; Leconte, Hennevin, & Bloch, 1974; Smith & Lapp, 1986). Sleep deprivation studies further illustrate the impact of sleep on acquisition (Palchykova, Winsky-Sommerer, Meerlo, Dürr, & Tobler, 2006; Smith & Kelly, 1988).

Despite ample evidence that sleep, in general, plays a large role in enhancing the effects of learning, the relative contribution of states or stages of sleep to the process of learning and memory remains unclear. Still, it appears that REM (or PS) is particularly implicated in these effects, as learning prior to sleep has been shown to prolong PS episode duration, decrease the latency of PS onset, and lengthen total PS sleep (Lecas, 1976; Smith & Lapp, 1986). Similarly, sleep deprivation studies suggest the existence of critical windows of information consolidation after learning, where PS must occur in order for the brain to reorganize itself, or make plastic change, that allow longer lasting memories to be formed (Smith & Butler, 1982; Smith & Kelly, 1988; for a review see Smith, 1995, 1996; see also Hennevin, Hars, Maho, & Bloch, 1995).

To date, the majority of research on adults suggests that n-REM and REM sleep serve different functions in memory consolidation effects for experiences that occur during the waking state. Specifically, n-REM sleep is believed to play a more prominent role in the consolidation of hippocampus-dependent *explicit*, or *declarative*, memory (i.e., memory that is consciously learned and recalled) (Daurat, Terrier, Foret, & Tiberge, 2007; Tucker et al., 2006; for a physiological view see Axmacher et al., 2006; see also Marshall & Borne, 2007), while REM is believed to play a larger role in the consolidation of *implicit* and emotionally-charged memory (i.e., memory that is not explicitly learned, but can be unconsciously recalled) that is not as dependent on hippocampal function (Smith, 1995). However, interference effects, <u>in which</u> one type of learning <u>interferes</u> with another, suggest that these relationships are not straightforward (Brown & Robertson, 2007; Fogel, Smith, & Cote, 2007; Mednick et al., 2002). The degree to which different types of memories are supported by separate systems remains to be elucidated (Stickgold & Walker, 2007).

At the neurotransmitter level, a body of research evidence suggests that the differential release of the cholinergic neurotransmitter acetylcholine (Ach) may account for these n-REM-REM differences in memory consolidation discussed above and may also shed some light on the relative complementary roles of both types of sleep. In the waking state, Ach is associated with increased arousal, learning, and the promotion of neural plasticity. Again, however, studies have found preferential memory effects, such that Ach appears to favor the consolidation of one kind of memory. For example, it has been reported that experimentally blocking cholinergic activity seems to enhance consolidation of declarative memory during the waking state (Rasch, Born, & Gais, 2006) while enhancing cholinergic activity during n-REM is associated with reduced declarative memory consolidation (Gais & Born, 2004). Ach levels are typically low during adult n-REM sleep, although they are comparable to those observed in the waking state during REM. Some investigators have suggested that the discrepant levels of Ach is a necessary condition for state-specific processes; namely, that the low cholinergic tone characteristic of n-REM promotes reactivation of hippocampal neurons and

consolidation of memory by reducing input interference from new learning. In contrast, the high cholinergic activity during REM sleep suppresses reactivation of previously acquired memories, thereby providing more efficient conditions for inducing neural modification associated with newly acquired memories (Hasselmo, 1999; Hasselmo & Brower, 1993; Rasch et al.).

Even though the relationship between sleep and memory processes are not fully understood, there is ample evidence that one purpose of sleep is to consolidate memories and promote neural changes associated with newly encoded information. As many sleep researchers have suggested, REM sleep appears to be especially implicated in the latter, where physiological activity and biological changes during this stage seem to favor implicit learning (Frank, Issa, & Stryker, 2001; Dang-Vu et al., 2006; Marks, Shaffery, Oksenberg, Speciale, & Roffward, 1995).

In general, the body of research supports a functional role of REM-like sleep in early brain development since REM is similarly evident during early development in several nonhuman species (Meier & Berger, 1965; Shimizu & Himwich, 1968) and, in nonhuman infants, has been linked to the formation and strengthening of early sensory pathways (Frank et al., 2001; Marks et al., 1995). Some studies even suggest even that sleep mechanisms may provide the means to reactivate and "replay" sensory memories during sleep in order reprocess them, thus strengthening effects of initial experiences in both humans and other animals (Dave & Margoliash, 2000; Walker, Stickgold, Alsop, Gaab, & Schlaug, 2005).

The fact that the developing infant brain is not capable of effective cortical inhibition until after the first few months suggests that sleep in early life serves a

somewhat different function. Namely, it would seem that uninhibited pathways may allow for passive learning during sleep, where mechanisms readily available for inducing long-lasting plastic changes may serve to enhance the effects of experience more efficiently. Through the new use of long-used measures, this new area of research seems to be validating this contention.

Mismatch Negativity (MMN): A Component of the Evoked Potential (EP)

Researchers have long found the task of studying infant learning to be encumbering for methodological reasons. Fortunately, this area of research has the advantage of using data derived from the EEG in order to directly observe learning that the developing infant cannot directly express. For years EEG has been used to investigate adult responses and, as of now, appears to be a promising method to investigate auditory learning in young infants. This is especially true when investigating responses occurring during sleep.

EEG consists of the use of scalp electrodes for the purpose of receiving the summation of electrical activity occurring in different brain areas. This electrical information is amplified and recorded in terms of patterned "brain waves". One kind of wave is called an evoked potential (EP), which is the averaged brain response to the repeated presentation of a specific stimulus. Since the electrical activity is derived from neuronal events, several distinct components of the recorded activity can be analyzed and interpreted; for example, how the brain responds to the physical characteristics of a stimulus and, inferentially, how much cognitive significance is attributed to a stimulus (Hillyard & Picton, 1987). For the purpose of exploring the learning process, researchers in this area often focus on one component of the EP: mismatch negativity (MMN). The

use of this measure for the purpose of researching infant learning appears to be especially attractive since the characteristics of MMN allow for infants to be studied during sleep and offers a relatively objective measure of neural processing.

Figure 1. Example Representation of MMN<sup>1</sup>



<sup>1</sup>From "Frontal mismatch negativity (MMN) related to Toronto Alexithymia Scale (TAS) Factors," by Starratt, G., Starratt, C., Berger, C. & Abrams, G. (2004, May). American Psychology Society, Chicago, IL. Adapted with permission of the author.

According to Näätänen, MMN is a negative deflection of the auditory evoked potential that represents the outcome of an automatic change-detection mechanism (Näätänen, Gaillard, & Mäntysalo, 1978; Näätänen, Simpson, & Loveless, 1982). This is depicted in Figure 1 as the negative (upward) deflection at about 200 milliseconds after stimulus onset (arrow). Its utility in investigating auditory processing lies in the fact that it can be elicited in several different conditions, is sensitive to very small deviations in physical properties of stimuli, has been found to be congruent with behavioral measures of learning, and has been shown to be elicited during sleep in infants (Näätänen, 2000, 2001, 2002). MMN is believed to be associated with the process of stimulus comparison. More specifically, it is elicited by the recognition that an incoming ("deviant") stimulus differs in one or more physical properties from a preceding sequence of same ("standard") stimuli (Näätänen, Paavilainen, & Reinikainen, 1989; Näätänen, 1997). For example, MMN has been shown to be elicited by simple physical stimulus deviations, such as duration (Näätänen et al., 1989) frequency (Schröger, Näätänen, & Paavilainen, 1992), and pitch (Kropotov et al., 2000), as well as by more complex acoustic deviations (Paavilainen, Jaramillo, Näätänen, & Winkler, 1999; Tervaniemi, Ilvonen, Karma, Alho, & Näätänen, 1997). Therefore, the use of MMN in infant learning research allows for researchers to examine very specific areas of learning.

The fact that MMN elicitation is produced in response to a pre-attentive perceived change (i.e., that the brain recognizes a change before one is consciously aware of a change) has been suggested to reflect a functional biological change-detection mechanism that is necessary for monitoring and switching attention to certain aspects of the environment. According to prevailing theory, MMN is believed to be elicited when change is detected due to short-lived memory traces (i.e., precise representations of the physical features of the standard stimuli) that appear to be formed by the standard sequence and provide a basis for comparison. (Näätänen et al., 1989). Importantly, the physical characteristics of MMN provide information concerning the facility by which the comparison is made, since more permanent memory traces (i.e., those formed by prior experiences) are activated by the standard sequence and contribute to the comparison process. Thus much information is provided regarding how much permanent learning has occurred. For example, a deviant stimulus that is easily detected to be different from the

standard sequence elicits more prominent MMN as compared to a deviant that is harder to discriminate from the standard (<u>Pakarinen</u>, Tekegata, Rinne, Hutoilainen, & Näätänen, <u>2007</u>; Schröger et al., 1992).

Several previous studies have utilized this measure for the purpose of gaining information regarding how acoustic information is processed. For example, studies investigating the impact of musical experience on attentional processing among adults have found that musicians demonstrate a more prominent MMN in response to deviations in the temporal order of tones (Tervaniemi et al., 1997) and the numerical regularity of tones, as compared to non-musicians (Zuijen, Sussman, Winkler, Näätänen, & Tervaniemi, 2005). Linguistic studies have demonstrated that the MMN can be used to gather information regarding the processing of linguistic information since languagespecific memory traces appear to be reflected in the response. For example, it has been shown that more prominent MMN is elicited in response to native-language speech sounds, as compared to non-native speech sounds (Cheour et al., 1998; Näätänen et al., 1997, Tervaniemi et al., 2006), and that individuals exposed to a non-native (foreign) language develop sensory memory traces that are reflected in the MMN response (Cheour, Shestakova, Alku, Čeponiene, & Näätänen, 2002c; Shestakova, Huotilainen, Ceponiené, & Cheour, 2003; Winkler et al., 1999). Further illustrating the reflection of memory traces in the MMN response are studies examining the changes in MMN as a result of auditory training. For example, one study found that auditory listening training over a five-day period resulted in several progressive changes in the MMN response as compared to that at baseline (viz., decreased onset latency, increased duration, and increased area), which were consistent with behavioral measures (Tremblay, Kraus,

Carrell, & McGee, 1997). In a subsequent study, similar results were found; specifically, MMN response showed progressive change in latency, duration, and area over the course of the training, and these manifestations of change in the MMN response preceded behavioral change at all testing points (Tremblay, Kraus, & McGee, 1998). Another study, which investigated the impact of audiovisual training in a group of children identified as reading impaired, found a posttraining increase in MMN amplitude which corresponded to significantly enhanced performance on reading measures (Kujala et al., 2001). These few examples demonstrate the sensitivity of MMN to electrophysiological changes resulting from experience.

As alluded to above, MMN is especially useful for studying infants since it is developmentally stable, does not require attention and, perhaps due to the decreased inhibitory processes exhibited by the infant brain during sleep, does not appear to be constrained by sleep states. In fact, a prominent MMN response has been demonstrated during both AS and QS in infants (Alho, Sainio, Sajeniemi, Reinikainen, & Näätänen, 1990; Cheour-Luhtanen et al., 1995; Hirasawa, Kurihara, & Konishi, 2002), even though it seems to be somewhat constrained by sleep states in adults (Atienza & Cantero, 2001; Atienza, Cantero, & Escara, 2001; Atienza, Cantero, & Gómez, 1997; Nielsen-Bohlman, Knight, Woods, & Woodward, 1991). Taken together, these studies suggest that the MMN response may be a particularly useful index for studying sleep-based language learning, or acquisition among infants.

#### Summary

Recent research is beginning to demonstrate that the early infant brain has an impressive ability to learn linguistic information despite prolonged sleep. This finding has led researchers to revisit the possibility that the infant brain utilizes time spent in sleep in order to encode and consolidate new information. Although current knowledge does not support such a role in adults, research using the MMN as a measure of learning suggests that the infant brain may allow the conditions to do so.

Although the practical utility of such findings is currently unknown, it is possible that auditory training during sleep may provide an early intervention for at-risk populations. Taken together, these studies suggest that the MMN response may be a particularly useful index for studying sleep-based language learning, or acquisition among infants. In light of the fact that early life reflects a critical period for language development (Liu, Kuhl, & Tsao, 2003) that has been demonstrated to be related to linguistic ability in later life (Mayberry, Lock, & Kazmi, 2002), these findings may prove clinically useful. Future research <u>may</u> lead to a better understanding of the precise mechanisms behind this function, as well as the developmental limitations on this capacity.

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