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## **ABSTRACT**

### **Objective:**

The propensity to arouse from sleep is an integrative part of the sleep structure and can have direct implications in various clinical conditions. This study was conducted to evaluate the maturation of spontaneous arousals during the first year of life in healthy infants.

### **Design:**

Nineteen infants were studied with night-time polysomnography on 3 occasions: 2-3 months, 5-6 months and 8-9 months. Ten infants with a median age of 3 weeks were added to the main study to assess the maturation of arousals from birth. The infants were born full-term, were healthy at the time of study, had no history of apnea. Sleep state and cardiorespiratory parameters were scored according to recommended criteria. Arousals were differentiated into subcortical activations or cortical arousals, according to the presence of autonomic and/or EEG changes. Frequencies of subcortical activations and cortical arousals were studied at different ages in both REM and NREM sleep.

### **Results:**

During sleep time, the frequency of total arousals, cortical arousals and subcortical activations decreased with age. The maturation of the arousal events differed according to sleep states and types of arousals. With age, cortical arousals increased in REM sleep ( $p=.006$ ) and decreased in NREM sleep ( $p=.01$ ). Subcortical activations decreased with age in REM ( $p<.001$ ) and NREM sleep ( $p<.001$ ).

## **Conclusions:**

During total sleep time, the frequency of cortical arousals and subcortical activations decreased with maturation. However, the maturation process was different between cortical arousals and subcortical activations. This finding suggests a difference in the maturational sequence of the different brain centers regulating arousals.

## **INTRODUCTION**

The sudden and unexplained death of sleeping infants aged less than one year, the sudden infant death syndrome (SIDS), is still the principal cause of postneonatal mortality in many industrialized countries. The mechanisms responsible for SIDS are still largely unknown. Failure to arouse from sleep may play a role in SIDS (1). An insufficient propensity to arouse could lower the chance of infants to survive when exposed to noxious conditions during sleep. Arousals reflect a progressive activation of various structures, from subcortical to cortical areas (2,3). Following CO<sub>2</sub> exposure, infants always showed a specific sequence of stereotyped behaviors before awakenings, from a sigh (i.e., an augmented breath) coupled with a startle, followed by thrashing movements and full arousal (3). Autonomic and brainstem arousals can occur without changes in cortical activity (4). We have previously shown that future SIDS victims had more subcortical activations and fewer cortical arousals than the control infants, suggesting an incomplete arousal process in infants who eventually died of SIDS (5). Few deaths from SIDS occur before 2 months of age. Most deaths from SIDS occur in the first 6 months of life, with a specific peak between 2 and 4 months of age (6). The present study was undertaken to evaluate the maturation of spontaneous arousals during the first year of life in healthy infants.

## **METHOD**

**SUBJECTS** Main Study: From January 2003 to March 2004, nineteen healthy infants were studied polygraphically during one night at 2-3 months, 5-6 months and 8-9 months.

Complementary study: From July 2004 to March 2006, ten newborns were added to the

main study to study the maturation from the first weeks of life. All infants were healthy and were admitted to join a sleep research program on sleep-related behavior. The infants were eligible for the study if they met the following criteria: they were born full term, from non-smoking parents who used no alcohol or drugs, and they were put to sleep in supine position. This position was their usual sleeping position. They had no family or personal history of apnea or SIDS. At the time of the study, all infants were healthy, not sleep deprived, and receiving no medication. The aim and the methodology of the study were approved by the University Ethical Committee and were explained to the parents, who gave their informed consent.

## POLYGRAPHIC STUDIES

The infants were admitted to the sleep laboratory for a 9-hour, night-time monitoring session. Monitoring was performed in a quiet and darkened room at an ambient temperature ranging from 20 to 23°C. The infants were laid on a hard mattress covered by a single-layer sheet, without any pillow, and allowed to fall asleep in their usual supine position. Recording began at about 9:00 P.M. The infants were observed continuously by a technician during their recordings. Careful attention was paid to avoid changes in sleep position during the night. They were fed on demand, and their behavior and any nursing intervention were charted. The following variables were recorded simultaneously: two scalp EEGs with central and occipital leads, two electrooculograms, digastric electromyogram (EMG) and electrocardiogram (ECG). Respiratory movements were measured with the use of thoracic and abdominal strain gauges, and airflow by oral and nasal thermistors. Oxygen saturation was recorded continuously from a pulse oximetry sensor (Nelcor, Hayward, CA). Gross body movements were measured with an actigraph placed on one arm. The data was collected with a computerized infant sleep recorder (Alice Recording System III; Respironics, Murrysville, PA). During the recording sessions, care was taken to control the stability of the infant's environments and to exclude

inadvertent arousals induced by stimuli such as noise, light, touch, nursing intervention, or room drafts.

## DATA ANALYSIS

The polygraphic recordings were analysed at 30-second intervals. From birth to 2 months, sleep state was identified according to the criteria of Anders et al (7). After two months of age, sleep state was defined according to the criteria of Guilleminault and Souquet (8). To simplify the results, sleep stages were presented as NREM (QS) sleep, REM (AS) sleep, indeterminate sleep, or wakefulness. Indeterminate sleep was scored together with REM sleep. Sleep efficiency was defined as the ratio of the total sleep time divided by the total recording time, expressed as percent. Gross body movements were measured from the actigraphs and confirmed visually. Sleep apneas were scored only if they lasted 3 seconds or more (9). Central apneas were defined as the simultaneous recording of flat tracings by both the thoracic and abdominal movements and the thermistors. Obstructive apneas were defined when continuous deflections were shown on the thoracic and abdominal channels while a flat tracing was recorded by the thermistor. Mixed apnea was recorded if a central apnea was directly followed by an obstructive episode, and were scored together with obstructive apneas. The frequencies of apneas were measured by dividing the total number of apneas by the total sleep time in minutes and multiplying by 60. Mean values for oxygen saturation and heart rate were calculated during the night according to the sleep stages. Drops in heart rate (HR) and in oxygen saturation referred to changes greater than 10% and 3% of basal values, respectively.

## CORTICAL AROUSAL AND SUBCORTICAL ACTIVATION Arousals were

subdivided into subcortical activations or cortical arousals, according to the consensus on arousal scoring in healthy infants under 6 months (10). A subcortical activation was scored if no change in EEG was seen, while at least two of the following changes occurred: a gross body movement detected by movement sensors or seen as an artefact movement in the somatic channels (ECG, EEG, respiratory parameters) or by

direct observation; changes in heart rate (at least 10% higher than baseline values); changes in breathing pattern (frequency and/or amplitude) in NREM sleep or increase in chin EMG tonus in REM sleep. A cortical arousal was scored using the above criteria, with the addition of the occurrence of an abrupt change in EEG background frequency of at least 1 Hz, for a minimum of 3 seconds. Total arousals corresponded to the sum of cortical arousal and subcortical activation. Baseline sleep states that preceded arousal or subcortical activation were established during 30-sec time periods. At least 10 seconds of uninterrupted sleep were required between arousals. Cortical arousals and subcortical activations were subdivided into spontaneous and respiratory induced events. Spontaneous cortical arousals or subcortical activations occurred for no detected cause. Respiratory arousals corresponded to respiratory related subcortical activations or cortical arousals, associated with central, mixed or obstructive apnea. Awakening was defined as a cortical arousal (as defined above) lasting 1 minute or more or a cortical arousal (as defined above) directly followed by an epoch meeting the Anders/ Rechtschaffen and Kales criteria for wakefulness (7, 10). Two independent scorers analysed the sleep recordings to ensure reliability. Scoring discrepancies were discussed and codes thus agreed on were used in the data analysis.

## STATISTICAL ANALYSIS

For the main study, statistical significance was performed with the use of an analysis of variance for repeated measures for age. Wilcoxon matched-pairs test was used to compare the values obtained during REM and NREM sleep. To compare the results of the newborns with those of the infants from the main study, the Kruskal-Wallis test was used. Mann-Whitney tests were performed to compare the newborn group with each infant group. Statistical significance was defined with a level of  $p < \leq .05$ . Values were expressed as

mean and standard deviation.

## RESULTS

The general characteristics of the 19 infants and 10 newborns are shown in table 1. While the frequency of breastfeeding decreased with age, there was no statistical difference between breastfeed infants (complete or mixed breastfeeding) and bottle-feed infants across the different ages. With maturation, there was a significant increase in total sleep time ( $p < .001$ ) and in % of NREM sleep ( $p < .001$ ) and a decrease in % of REM sleep ( $p = .002$ ) (Table 2, Fig.1). Sleep efficiency and % of wake time during sleep did not show significant changes. The same significant trend was found with newborns (table 2, Fig.1). Moreover, newborns had less sleep efficiency ( $p < .001$ ) and more awake time (%) ( $p = .002$ ) than the infants.

The frequency of central and obstructive apneas decreased with age ( $p = .016$  and  $p = .05$ , respectively) (Table 3). For central apneas, this change was seen in both sleep stages but especially during REM sleep ( $p < .001$ ). Differences were found for obstructive apneas only during NREM sleep ( $p = .045$ ). No differences were found in the duration of central and obstructive apneas. The same significant results were found in newborns for the frequency of central and obstructive apneas ( $p < .001$  and  $p = .011$  respectively). The obstructive apneas were longer in newborns compared to infants ( $p = .029$ ) (Table 3).

Maturation was characterized by significantly lower basal heart rate with age in REM ( $p < .001$ ) and NREM sleep ( $p < .001$ ) (Table 3). Newborns had a higher basal heart rate in REM ( $p < .001$ ) and NREM sleep ( $p < .001$ ) than infants. Basal oxygen saturation with age ( $p < .001$ ). The same significant difference was found when newborns were studied ( $p = .001$ ). The frequency of heart rate and saturation drops following central apneas decreased from 2-3 months to 8-9 months of age ( $p = .02$  and  $p = .03$ , respectively).

Significant differences after the obstructive apneas were only seen for the saturation drops



( $p=.02$ ). The same statistical trend for the frequency of saturation drops after central apnea was found in newborns ( $p=.034$ ), especially when newborns were compared to 8-9 months-old infants ( $p=.015$ ).

During total sleep time, the frequency of total arousals ( $p<.001$ ), cortical arousals ( $p<.001$ ) and subcortical activations ( $p<.001$ ) decreased with age (Table 4, Fig 2). With maturation, the frequency of cortical arousals decreased in total sleep ( $p<.001$ ) and in NREM sleep ( $p=.01$ ) but increased in REM sleep ( $p=.006$ ) (Table 4, Fig 3). The same trend was seen when newborns were taken into account, especially when newborns were compared to 8-9 months. Subcortical activations decreased continuously from 2-3 months to 8-9 months in total sleep ( $p<.001$ ), NREM ( $p<.001$ ) and REM sleep ( $p<.001$ ). The same results were found when newborns were considered with the infants (Table 4, Fig 4). The ratio of cortical arousal to subcortical activation increased significantly with age in total sleep ( $p<.001$ ) and REM sleep ( $p < .001$ ). No significant difference was seen during NREM sleep. We found the same results when newborns were evaluated with the infants. The frequencies of arousals induced by apneas ( $p=.011$ ) and the frequency of spontaneous arousals ( $p=.009$ ) decreased with age. The same trend was found when newborns were considered but reached statistical significance only with spontaneous arousals ( $p=.048$ ). The % of apneas followed by arousals decreased with age ( 26.11+/-20.58 at 2-3 months, 19.36+/-16.07 at 5-6 months and 10.10+/-13.73 at 8-9 months, respectively) ( $p=.02$ ).

In both REM and NREM sleep, there were more frequent cortical arousals than subcortical activations across the different ages ( $p\leq 001$ ). At different ages, total arousals and cortical arousals were more frequent in REM than in NREM sleep ( $p<.001$ ) (Table 4). There were significant differences in the frequency of subcortical activations between REM and NREM sleep at 5-6 months of age and 8-9 months of age, however not at 2-3 months of age. For newborns, there were more total arousals ( $p=.007$ ), cortical arousals ( $p=.007$ ) and

subcortical activations ( $p=.009$ ) in REM than in NREM sleep.

**DISCUSSION** During sleep time, total arousals, cortical arousals and subcortical activations decreased with age. Moreover, the maturation of the arousal events differed according to sleep stages and types of arousals. While subcortical activations decreased with maturation in the different sleep stages, cortical arousals increased in REM sleep and decreased in NREM sleep. As all infants were recorded under similar controlled conditions, the observed differences according to age could not be related to experimental factors that modify arousal thresholds in infants, such as previous sleep deprivation (11), exposure to sedative drugs (12), type of feeding (13), or high environmental temperatures (14).

As previously reported, we found that the frequency of sleep apneas decreased with age, especially in REM sleep (9, 15). The heart rate values also decreased with maturation in REM and NREM sleep (16). However, due to the schedule of our study, it was not possible to see the specific pattern described by Harper consisting of an increase in heart rate from birth to 1 month of life (16). Like Poets et al., we saw a rise in the saturation values during the first months of life (17).

We must admit several limitations of this study. First, the limited number of infants studied may prevent reaching significance in some analyses. Second, the infants of 3 weeks of age were different from the infants followed longitudinally. However, the results were similar to the other longitudinal studies from birth to 6 or 12 months of age (18, 19). Third, as our work was focused on the arousal events, to simplify the results, sleep stages analysis was reported into wakefulness, NREM (QS) sleep and REM (AS) sleep, combining REM and

indeterminate sleep. Fourth, the scoring of cortical arousals and subcortical activations depended on the combination of autonomic and electroencephalographic changes (10). Scoring was based on the evidence that arousal is a continuous process that includes subcortical structure-induced autonomic changes, and cortical activation (2-3). The visual scoring of cortical arousals corresponded to complete arousals, that included both autonomic and cortical activations. Arousal reactions that only included autonomic but no cortical changes, were scored as subcortical activation. As scoring was done visually, it cannot be excluded that spectral or other automatic techniques might lead to a different outcome (20). Fifth, because of the limited number of subjects available for analysis, this report was limited to the description of arousal characteristics. No multiple analyses were done on various infant characteristics that could lead to an identification of determinant factors in the arousal processes. Finally, gross body movements were only measured with one actigraph instead of 2 as recommended by the consensus on arousals (10). However, the study on the frequency of arousals in SIDS victims was published with one actigraph as well. We compared conditions of recordings and analyses between SIDS and healthy infants in the same way.

As already well described before, we found that during the first year of life, there was a continuous decrease in total sleep time and REM sleep along with a concomitant increase in sleep efficiency and NREM sleep (18, 19, 21-23). During the first six months of life, spontaneous mobility during sleep, defined by the number of movements and the % of the time spent in movements, decreased (21-23). Although the analysed parameters were different, we found in the same way that subcortical activations decreased with maturation in REM and NREM sleep. This could reflect the developmental neurophysiological changes that occur within the central nervous system's structure responsible for sleep mechanisms. Sleep and waking states are produced by the activity of excitatory and

inhibitory neurons located in several brainstem and forebrain centers. The regions that mature earliest are usually the medulla and pons, followed by the midbrain, thalamus and hypothalamus, and then by the cerebral cortex and striatum (24). The primitive motor reflexes during the first few months of life originate in and are mediated by subcortical structures since the corticospinal tracts are not yet myelinated. During sleep, the newborn exhibits a considerable amount of neuromuscular activity that continues until he is about 3 months of age. The response and adaptation to various environmental and internal stimuli during the neonatal stage are simple and stereotyped. These reflexes responses decreased progressively with age. In response to nasal occlusion, 83% of newborns were able to establish an oral airway compared to only 54% of 6-week-old infants (25). This effect could be responsible for the decrease in the frequency of arousals induced by apnea in our study. As there were few arousals induced by apneas, cortical arousals and subcortical activations were considered together. The appearance of spindles during the first 3 months of infancy reflects developmental changes in thalamo-cortical structures (26) and also in dendrite myelination and growth (27, 28). The disappearance of the transient reflexes generally parallels anatomical and functional maturation of those parts of the cerebral cortex that inhibit and control the activity of the corresponding lower centers.

In our study, we observed that the frequency of cortical arousals increased in REM sleep and decreased in NREM sleep. As reported before, we know that the probability of spontaneous arousals from sleep was significantly higher in REM sleep than in NREM sleep across the different ages (29). The excitatory processes that elicit the brainstem and cortical responses during sleep are possibly enhanced during REM sleep (30). The level of cortical activity during REM sleep is more closely related to the activity in wakefulness than to the activity during NREM sleep. In NREM sleep, the inhibitory influence that prevents the spread of arousal activity along the pathways from the brainstem to the cortex

is more prominent than in REM sleep (31). This NREM property could explain the increase in cortical arousals with age found only in REM sleep. The arousal structures and mechanisms are different in REM and NREM sleep (31). NREM sleep involves the thalamic reticular nucleus and the cortex. REM sleep includes executive REM-on neurons such as the pedunculopontine nucleus (PPT) and the laterodorsal nucleus (LDT), and permissive REM-off systems in the pons and in the basal forebrain. During the first weeks of life, different postnatal development occurs in PPT and LDT nuclei in their membrane properties (32) as well as in the distribution of terminals to the thalamus nuclei (33). There are also significant postnatal changes occurring in the synaptology of corticothalamic fibers in the thalamus nuclei (34). All these structures are implicated in the control of arousal,

i.e. waking and REM sleep. From childhood to old age, the frequency of spontaneous arousals during sleep increases with age (35). Consistent with this higher arousability, the stimulus intensity required to induce the awakenings decreases (35). Children have higher arousal threshold than adults; the younger the child, the higher the arousal threshold. Studying electroencephalographic arousals after obstructive apneas in infants and in children, McNamara et al found fewer cortical arousals in infants than in children (36).

Maturation and structural dysfunction could be implicated within the infants' arousal system in future SIDS victims. Future SIDS victims, aged 2 months of life, had a similar frequency of subcortical activations as healthy 3 weeks-old infants, suggesting a delay in maturation (7). However, the frequency of cortical arousals was lower in SIDS victims than in healthy infants of both 3 weeks and 3 months. Pathological and immunological findings in SIDS victims were in favor of structural (37-39) or functional changes (40-43), especially at the brainstem level. Delayed central nervous system myelination has also been described in SIDS victims (37) and could be implicated in the reduced propagation of

subcortical to cortical arousals. Compared to control infants, future SIDS victims have been reported to have more and longer obstructive apneas (44-46), higher basal heart rate and reduced heart rate (47) compatible with a decrease in parasympathetic tonus, an increase in sympathetic activity, or a combination of both conditions (48,49). These alterations in breathing and cardiac controls found in SIDS victims could also result from the changes within their central nervous system. The simultaneous presence of obstructive breathing, imbalance of autonomic nervous system and decrease in arousability could then become a potential risk condition for SIDS.

In conclusion, during the first months of life, the frequency of cortical arousals and subcortical activations decreased in healthy infants. However the maturation of the arousal events differed according to sleep states and types of arousals. These results could contribute to our understanding of maturation of the brain structures implicated in sleep-wake behaviours and the mechanisms responsible for the sudden and unexpected death of an apparently healthy infant.

## REFERENCES

1. Newman NM, Trindler JA, Phillips KA, Jordan K, Cruickshank J. Arousal deficit: mechanisms of the sudden infant death syndrome ? *Aust Paediatr J* 1989;25:196-201.
- 1 Moruzzi G, Magoun HW. 1995. Brain stem reticular formation and activation of the EEG. *J Neuropsychiatry* 7:251-267.
- 2 Lijowska, A.S., Reed, N.W., Chiodini, B.A.M. and Thach, B.T. 1997. Sequential arousal and airway-defensive behavior of infants in asphyxial sleep environments. *J Appl Physiol* 83:219-228.
- 3 Rees K, Spence DPS, Earis JE, Calverley PMA. 1995. Arousal responses from apneic events during non-rapid-eye-movement sleep. *Am J Respir Crit Care Med* 152:1016-1021.
- 4 Kato I, Franco P, Groswasser J, Scaillet S, Kelmanson I, Togari H, Kahn A. Incomplete arousal processes in infants who were victims of sudden death. *Am J Respir Crit Care Med* 2003;168:1298-1303.
- 5 Krous HF, Beckwith JB, Byard RW, et al. Sudden Infant Death Syndrome and Unclassified Sudden Infant Deaths: A Definitional and Diagnostic Approach. *Pediatrics*

2004;114:234-238.

7. Anders T, Emde E, Parmelee A, eds. A manual of standardized terminology, techniques and criteria for scoring of states of sleep and wakefulness in newborn infants. UCLA Brain information service/BRI: Los Angeles, California; 1971:p.111.

6 Guilleminault C, Souquet M. Sleep states and related pathology. In: Korobkin R, Guilleminault C, eds. *Advances in Perinatal Neurology*. New-York: Spectrum Publications, 1979:225-47.

7 Kato I, Franco P, Groswasser J, Kelmanson I, Togari H, Kahn A. Prevalence of obstructive and mixed sleep apneas in 1023 infants. *Sleep* 2000;23:487-492.

10. The International Paediatric North Group on Arousals. The scoring of arousals in healthy term infants (between the ages of 1 and 6 months). *J Sleep Res* 2005; 14:3741.

8 Franco P, Seret N, Van Hees JN, Vermeulen F, Scaillet S, Kahn A. Decreased arousals in healthy infants following short-term sleep deprivation. *Pediatrics* 2004;114:e192-197.

9 Kahn A, Hasaerts D, Blum D. 1985. Phenothiazine-induced sleep apneas in normal infants. *Pediatrics* 75:844-847.

13. Horne RS, Parslow PM, Ferens D, Watts AM, Adamson TM. Comparison of evoked arousability in breast and formula fed infants. *Arch Dis Child* 2004; 89:225.

10 Franco P, Scaillet S, Valente F, Chabanski S, Groswasser J, Kahn A. Ambient temperature is associated with changes in infants' arousability from sleep. *Sleep* 2001; 24:325-329.

11 Gaultier C. Sleep Apnea in infants. Review article. *Sleep Medicine Reviews*. 1999;4:303-312.

12 Harper RM, Hoppenbrowers T, Sterman MB, McGinty DJ, Hodgman J. Polygraphic studies of normal infants during the first six months of life. Heart rate and variability as a function of state. *Pediatr Res* 1976; 10:945-947.

13 Poets CF, Stebbens VA, Southall DP. Arterial oxygen saturation and breathing movements during the first year of life. *J Dev Physiol* 1991;15:341-5.

14 Hoppenbrouwers T, Hodgman J, Harper R, Sterman M. Temporal distribution of sleep states, somatic activity, and autonomic activity during the first year of life. *Sleep* 1982; 5:131-144.

15 Peirano P, Algarin C, Uauy R. Sleep-wake states and their regulatory mechanics throughout early human development. *J Pediatr* 2003 ;143 :S70-79.

16 Black JE, Guilleminault C, Colrain IM, Carrillo O. Upper airway resistance syndrome. Central electroencephalographic power and changes in breathing effort. *Am J Respir Care Med* 2000; 162:406-11

17 Louis J, Cannard C, Bastuji H, Challamel MJ. Sleep ontogenesis revisited: A Longitudinal 24-Hour Home Polygraphic Study on 15 Normal Infants During the First Two Years of Life. *Sleep* 1997;20:323-333.

18 Coons S, Guilleminault C. Development of Sleep-Wake Patterns and Non-rapid Movement Sleep Stages during the First Six months of life in Normal Infants. *Pediatrics* 1982; 69:793-798.

19 Vecchierini-Blineau MF, Nogues B, Louvet S, Desfontaines O. Maturation de la motricité généralisée, spontanée au cours du sommeil, de la naissance à terme à l'âge de 6 mois *Neurophysiol Clin* 1994 ;24 :141-154.

20 Yakovlev PI, Lecours AR: The myelogenetic cycles of regional maturation of the brain. In Minlowski A, ed: *Regional development of the brain in early life*. Philadelphia, 1967, FA Davis.

21 Swift PG, Emery JL. Clinical observations on responses to nasal occlusion in infancy. *Arch Dis Child* 1973, 48: 947-951.

- 22 Steriade M, Deschênes M, Domich L, Mulle C. Abolition of spindle oscillation in thalamic neurons disconnected from nucleus reticularis thalami. *J Neurophysiol* 1985;54:1473-97.
- 23 Schadé JP, Meeter K. Neuronal and dendritic patterns in the uncinate area of the human hippocampus. *Prog Brain Res* 1963;3:89-110.
- 24 Van der Knapp MS, Valk J. MR imaging of the various stages of normal myelination during the first year of life. *Neuroradiology* 1990;459-70.
- 25 Horne R, Franco P, Adamson T, Groswasser J, Kahn A. Effects of body position on sleep and arousal characteristics in infants. *Early Hum Dev* 2002; 69:25-33 (Review).
- 26 Hess C, Mills K, Murray N, Schriefer T. Excitability of the human motor cortex is enhanced during REM sleep. *Neurosci Letters* 1987; 82:47-52.
- 27 Steriade M. Brain electrical activity and sensory processing during waking and sleep states. In: Kryger MH, Roth T, Dement WC, eds. *Principles and practice of sleep medicine*. Philadelphia, 2005, 93-112.
- 28 Kobayashi T, Good C, Biedermann J, Barnes C, Skinner RD, Garcia-Rill E. Developmental changes in pedunculopontine nucleus neurons. *J Neurophysiol* 2004; 91:1470-1481.
- 29 Hoshino K, Katoh YY, Bai W, Kaiya T, Norita M. Distribution of terminals from pedunculopontine tegmental nucleus and synaptic organization in lateralis medialis-suprageniculate nucleus of cat's thalamus: anterograde tracing, immunohistochemical studies, and quantitative analysis. 2000; 17:893-904.
- 30 Matsumoto S, Hoshino K, Kobayashi K, Norita M. Postnatal development of the corticothalamic projections from the visual association cortex to the lateralis posterior complex in the cat. *Acta Physiol Hung*. 2006;93:79-90.
- 31 Busby KA, Mercier L, Pivik RT. Ontogenetic variations in auditory arousal threshold during sleep. *Psychophysiology* 1994; 31:182-188.
- 32 McNamara F, Issa FG, Sullivan CE. Arousal Pattern following central and obstructive breathing abnormalities in infants and children. *J Appl Physiol* 1996; 81:2651-7.
- 33 Kinney HC, Brody BA, Finkelstein DM, et al. Delayed central nervous system myelination in the sudden infant death syndrome. *J Neuropathol Exp Neurol* 1991;50:29-48.
- 34 Filiano JJ, Kinney HC. Arcuate nucleus hypoplasia in the sudden infant death syndrome. *J. Neuropath. Exp. Neurol.* 1992; 51:394-403.
- 35 Waters K, Meehan B, Huang J, Gravel R, Michaud J, Côté A. Neuronal apoptosis in sudden infant death syndrome. *Pediatr Res* 1999; 45:166-172.
- 36 Carpentier V, Vaudry H, Mallet E, Laquerriere A, Leroux P. Increased density of somatostatin bindings sites in respiratory nuclei of the brainstem in sudden infant death syndrome. *Neuroscience* 1998;86:159-66.
- 37 Kinney HC, Filiano JJ, White WF. Medullary serotonergic network deficiency in the Sudden Infant Death Syndrome: Review of a 15-year study of a single dataset. *J Neuropathol Exp Neurol* 2001;60:228-47.
42. Paterson DS, Trachtenberg FL, Thompson EG, et al. Multiple serotonergic brainstem abnormalities in sudden infant death syndrome. *JAMA* 2006; 296:2124-32.
- 38 Kinney HC, Randall LL, Sleeper LA, et al. Serotonergic brainstem abnormalities in Northern Plains Indians with the sudden infant death syndrome. *J Neuropathol Exp Neurol.* 2003; 62:1178-91.
- 39 Guillemainault C, Ariagno RL, Forno LS, Baldwin R, Owen M. Obstructive sleep apneas and near miss SIDS: I. Report of an infant with sudden death. *Pediatrics* 1979; 63:837-843.
- 40 Kahn A, Groswasser J, Rebuffat E, Sottiaux M, Blum D, Foerster M, Franco P, Bochner A, Alexander M, Bachy A, Richard P, Verghote M, Le Polain D, Wayenberg JL.



Sleep and cardiorespiratory characteristics of infant victims of sudden death: a prospective case-control study. *Sleep* 1992;15:287-292.

41 Kato I, Groswasser J, Franco P, Scaillet S, Kelmanson I, Togari H, Kahn A. Developmental characteristics of apnea in infants who succumb to sudden infant death syndrome. *Am J Respir Crit Care Med* 2001;164:1464-1469.

42 Schechtman VL, Harper RM, Kluge KA, Wilson AJ, Hoffman HJ, Southall DP. Cardiac and respiratory patterns in normal infants and victims of the sudden infant death syndrome. *Sleep* 1988;11:413-424.

43 Kluge AK, Harper RM, Schechtman VL, Wilson AJ, Hoffman HJ, Southall DP. Spectral analysis assessment of respiratory sinus arrhythmia in normal infants and infants who subsequently died of sudden infant death syndrome. *Pediatr Res* 1988; 24:677-682.

44 Franco P, Szliwowski H, Dramaix M, Kahn A. Polysomnographic study of the autonomic nervous system in potential victims of sudden infant death syndrome. *Clin Auton Research* 1998b;8:243-249.

**TABLE 1: Demographic characteristics of the studied infants.**

| <b>MAIN STUDY GROUP</b>                                    |                      | <b>NEWBORN GROUP</b> |
|--|----------------------|----------------------|
| <b>No. Infants</b>   | 19                   | 10                   |
| <b>Gender (M/F)</b>  | 9/10                 | 5/5                  |
| <b>Gestational age (weeks)</b>                             | 40 (38-41)           | 40 (37-40)           |
| <b>Birth weight (g)</b>                                    | 3318<br>(2440-4400)  | 3835<br>(3400-4170)  |
| <b>Age at first sleep study (weeks)</b>                    | 8 (7-13)             | 3 (0-5)              |
| <b>Weight at the first study (g)</b>                       | 4600<br>(3270-7200)  | 4509<br>(3670-5020)  |
| <b>Breastfed/Bottle-fed/mixed<br/>at first sleep study</b> | 12/4/3               | 6/2/2                |
| <b>Age at the second sleep study (weeks)</b>               | 19 (13-26)           |                      |
| <b>Weight at the second study (g)</b>                      | 6490<br>(5040-8250)  |                      |
| <b>Breastfed/Bottle-fed/mixed<br/>at the second study</b>  | 9/7/3                |                      |
| <b>Age at the third sleep study (weeks)</b>                | 30 (22-42)           |                      |
| <b>Weight at the third study (g)</b>                       | 8000<br>(6600-10400) |                      |
| <b>Breastfed/Bottle-fed/mixed<br/>at the third study</b>   | 6/8/5                |                      |

The values represent absolute, median, and range values.

**TABLE 2: Sleep Characteristics of studied infants**

|                                   | <b>NEWBORN<br/>GROUP 0-1<br/>MONTH</b> | <b>MAIN STUDY GROUP 2-3 MONTHS 5-6<br/>MONTHS 8-9 MONTHS</b> |          |          | ANOVA | KW    |
|-----------------------------------|--|--|----------|----------|-------|-------|
| <b>Total Recording Time (min)</b> | 547+/-38                               | 537 +/-9   | 538+/-23 | 554+/-42 | NS    | NS    |
| <b>Total Sleep Time (min)</b>     | 418+/-42                               | 470+/-18   | 475+/-35 | 552+/-55 | <.001 | <.001 |
| <b>Sleep Efficiency (%)</b>       | 78+/-9                                 | 90+/-3   | 63+/-11  | 91+/-4   | NS    | <.001 |
| <b>NREM sleep (%)</b>             | 59+/-11                                | 30+/-6   | 54+/-12  | 42+/-10  | <.001 | <.001 |
| <b>REM sleep (%)</b>              | 22+/-9                                 | 57+/-8   | 12+/-6   | 46+/-9   | .002  | .001  |
| <b>Awake (%)</b>                  |  | 13+/-3   |          | 11+/-5   | NS    | .002  |

For the main study, statistical significance was assessed-with the use of an analysis of variance for repeated measures for age. Kruskal-Wallis tests (KW) were performed between newborn group and main group study The values represent mean +/- standard deviation.

**TABLE 3: Cardio-respiratory Characteristics of studied infants**

|   | <b>NEWBORN<br/>GROUP 0-1<br/>MONTH</b> | <b>MAIN STUDY GROUP 2-3 MONTHS 5-6<br/>MONTHS 8-9 MONTHS</b>                          |  |  | Anova  | KW                                       |
|---|--|---|--|--|--|--|
| <b>CENTRAL APNEA Frequency<br/>(/h sleep) (/h REM sleep)<br/>(/hNREM sleep) Duration<br/>Mean +/- DS (sec)<br/>Range (min-max) (sec) % of<br/>heart drops after central apnea<br/>% of saturation drops after<br/>central apnea</b> | 4.8+/-3 5.3+/-2.9                      | 1.8+/-0.9<br>1.9+/-1.1<br>7+/-1.3<br>10.1+/-2.2<br>(3-16)<br>47.4+/-22.6<br>35+/-26.0 | 1.6+/-0.6<br>1.9+/-1.0<br>1.3+/-1.0<br>9.5+/-2.2<br>(3-16.5)<br>36.9+/-18.1<br>29.6+/-23.9 | 1.1+/-0.6<br>0.4+/-0.5<br>0.6+/-0.6<br>9.4+/-1.4<br>(3-12)<br>29.2+/-13.1<br>14.5+/-18.2 | .016<br><.001<br>.011<br>NS<br>.003<br>.0024 | <.001<br><.001<br><.001<br>NS NS<br>.034 |

### OBSTRUCTIVE APNEA

|                                   |            |           |           |           |     |      |
|-----------------------------------|------------|-----------|-----------|-----------|-----|------|
| <b>Frequency (/h sleep)</b>       | 1.0+/-0.8  | 0.6+/-0.6 | 0.6+/-0.6 | 0.2+/-0.3 | .05 | .011 |
| <b>Duration Mean +/- DS (sec)</b> | 10.2+/-3.8 | 6.4+/-5.1 | 8+/-4.2   | 4.9+/-3.9 | NS  | .029 |
| <b>Range (min-max) (sec)</b>      | (3-16)     | (3-15.5)  | (3-15.5)  | (4-10.5)  |     |      |

### HEART RATE

|                          |              |             |             |             |       |       |
|--------------------------|--------------|-------------|-------------|-------------|-------|-------|
| <b>REM (bpm)</b>         | 129.7+/-10.9 | 133.1+/-9.8 | 127.7+/-8.6 | 120.9+/-4.8 | <.001 | <.001 |
| <b>NREM (bpm)</b>        | 129.7+/-10.8 | 127.3+/-8.8 | 122.3+/-9.7 | 115.6+/-5.6 | <.001 | <.001 |
| <b>OXYGEN SATURATION</b> | 96.5+/-0.6   | 96.8+/-1.7  | 97.4+/-1.1  | 98.7+/-1.0  | <.001 | <.001 |

The values represent mean +/-standard deviation. For the main study, statistical significance was assessed with the use of an analysis of variance for repeated measures for age. Kruskal-Wallis tests (KW) were performed between newborn group and main study group.

**TABLE 4: Arousal characteristics of the infants studied**

| NEWBORN GROUP   | MAIN STUDY GROUP |             |             |            | ANOVA | KW                              |
|---|------------------|-------------|-------------|------------|-------|---------------------------------|
|   | 0-1 MONTH        | 2-3 MONTHS  | 5-6 MONTHS  | 8-9 MONTHS |       |                                 |
| <b>Frequency of Total Arousals (/h of sleep)</b>                |                  |             |             |            |       |                                 |
| Total sleep   | 20.5+/-3.5       | 16.9+/-2.9  | 17.1+/-1.6  | 13.1+/-1.8 | <.001 | <.001                           |
| REM sleep   | 24.0+/-6.6       | 21.7+/-5.1  | 26.2+/-5.9  | 25.3+/-6.1 | 0.04  | NS<.001                         |
| NREM sleep  | 8.6+/-5.2        | 8.2+/-3.3   | 4.9+/-2.8   | 4.5+/-2.4  | <.001 |                                 |
| P (REM vs NREM)   | .007             | <.001       | <.001       | <.001      |       |                                 |
| <b>Frequency of Cortical Arousals (h of sleep)/ Total sleep</b> |                  |             |             |            |       |                                 |
| Total sleep   | 16.1+/-3.0       | 15.1+/-2.8  | 16.1+/-1.7  | 12.7+/-1.8 | <.001 | .021                            |
| REM sleep   | 18.7+/-4.9       | 20.7+/-4.3  | 24.5+/-5.2  | 26.4+/-6.2 | .006  | .001<.001<.001<.001<.001<.001NS |
| NREM sleep  | 7.3+/-4.0        | 4.8+/-3.0   | 5.1+/-3.9   | 2.4+/-1.1  | .01   |                                 |
| P (REM vs NREM)   | .007             | <.001       | <.001       | <.001      | <.001 |                                 |
| <b>Frequency of Subcortical arousals /h of sleep)</b>           |                  |             |             |            |       |                                 |
| Total sleep   | 4.4+/-1.6        | 2.3+/-1.4   | 1.0+/-0.6   | 0.4+/-0.2  | <.001 |                                 |
| REM sleep   | 4.9+/-2.0        | 9.8+/-4.1   | 0.6+/-1.3   | 0.6+/-0.9  | <.001 |                                 |
| NREM sleep  | 2.2+/-1.3        | 14.6+/-5.9  | 0.9+/-0.6   | 0.5+/-0.2  | NS    |                                 |
| P(REM vs NREM)  | .009             | 3.1+/-2.6   | 0.5 .003    | 0.2 .002   |       |                                 |
| <b>Cortical/Subcortical</b>                                     |                  |             |             |            |       |                                 |
| Total sleep   | 4.4+/-2.5        | 24.2+/-17.7 | 51.5+/-35.0 | 17.9       |       |                                 |
| REM sleep   | 4.7+/-2.9        | 27.5+/-17.9 | 59.1+/-32.8 | 6.5+/-7.1  |       |                                 |
| NREM sleep  | 3.3+/-2.0        | 27.5+/-17.9 | 59.1+/-32.8 | 3.2+/-4.3  |       |                                 |

The values represent mean +/- standard deviation. For the main study, statistical significance was assessed with the use of an analysis of variance for repeated measures for age. Kruskal-Wallis tests (KW) were performed between newborn group and main study group Figure 1: Maturation of sleep efficiency (%), NREM Sleep (%), REM sleep (%) and awake time after sleep (%) from 0-1 month to 8-9 months of age.

Figure 1 Figure 2: Maturation of total arousals, cortical arousals, subcortical activations during total sleep time from 0-1 month to 8-9 months of age. The frequency of arousals is given as an index (number of arousals/h of sleep).

Figure 1

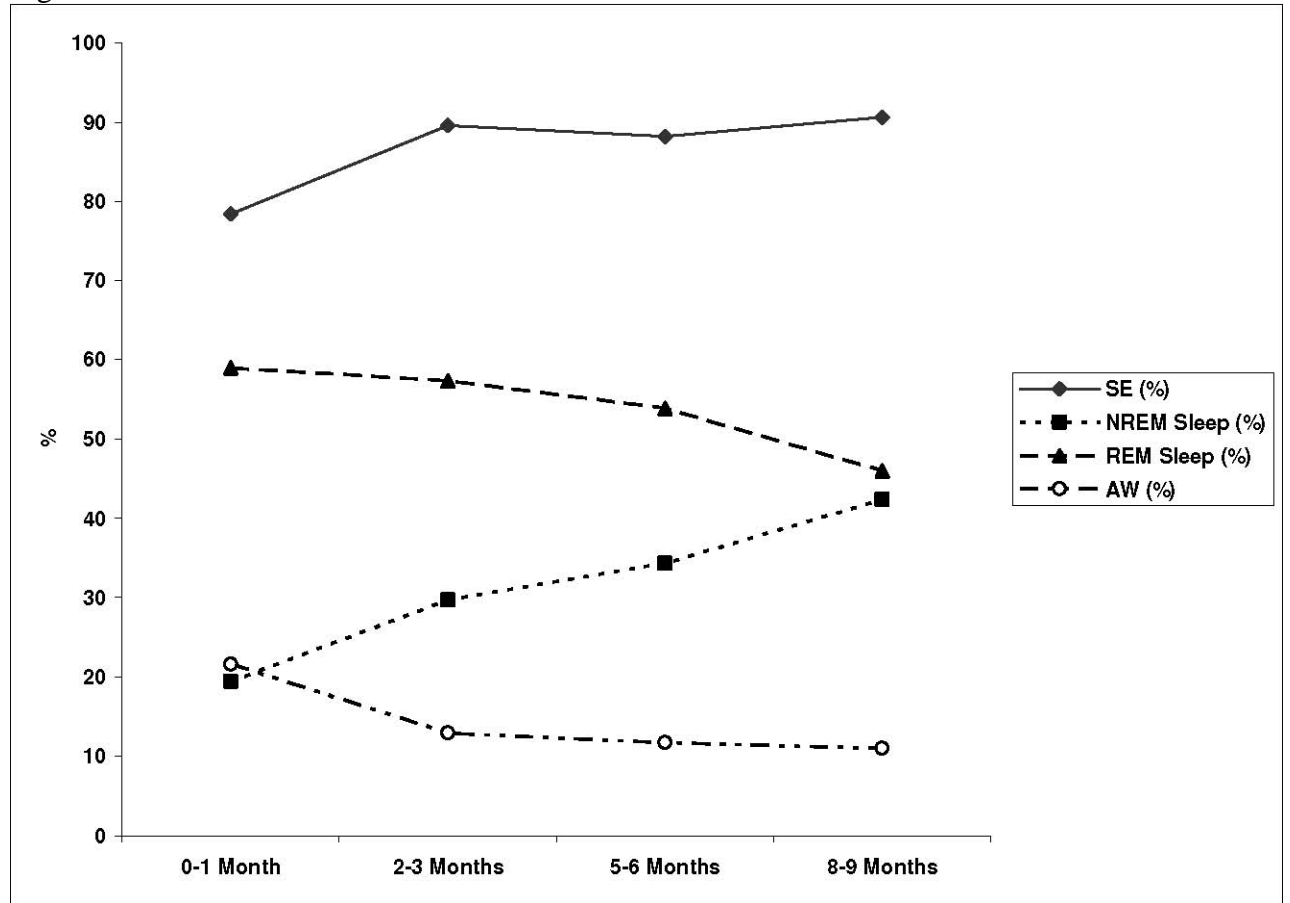


Figure 2

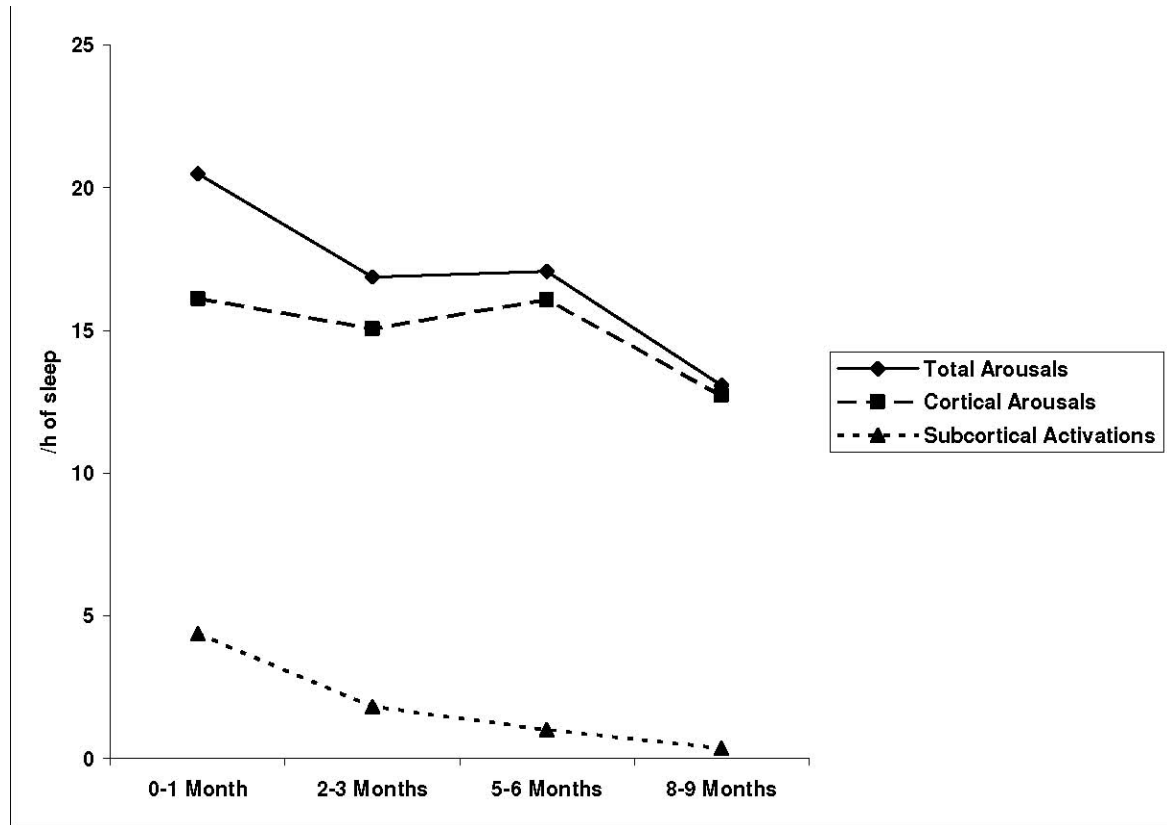


Figure 3: Maturation of cortical arousals from 0-1 month to 8-9 months of age in total sleep, REM sleep and NREM sleep. The frequency of cortical arousals is given as an index (number of arousals/h of sleep).

Figure 3

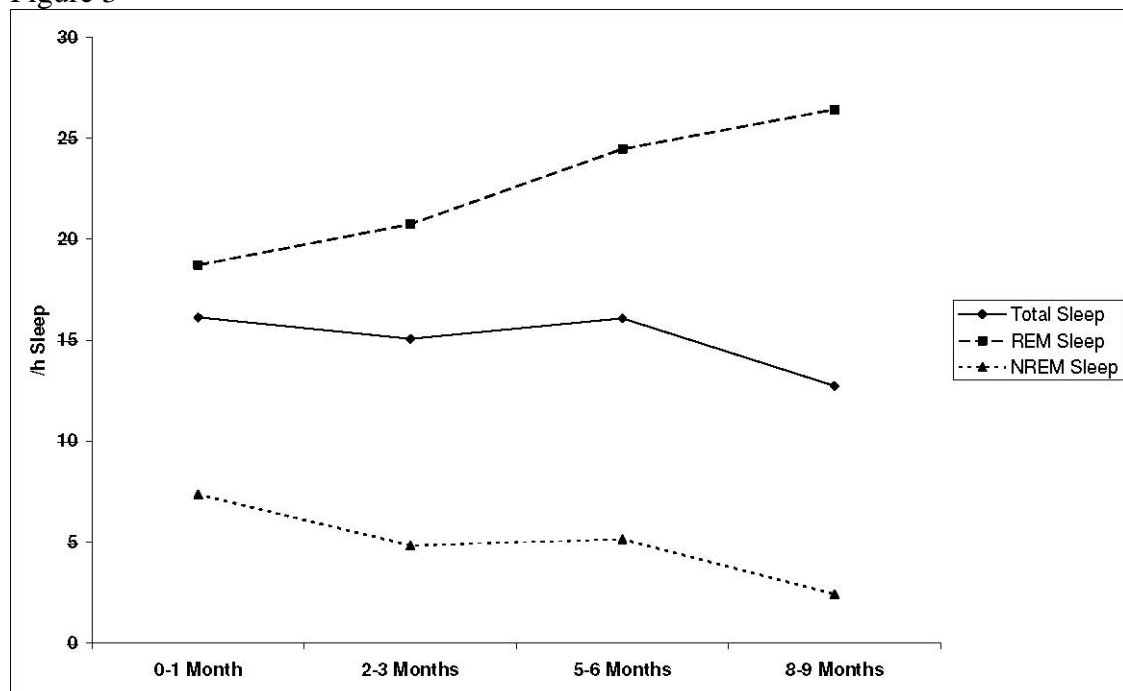




Figure 4: Maturation of subcortical activations from 0-1 month to 8-9 months of age in total sleep, REM sleep and NREM sleep. The frequency of subcortical activations is given as an index (number of arousals/h of sleep).

Figure 4

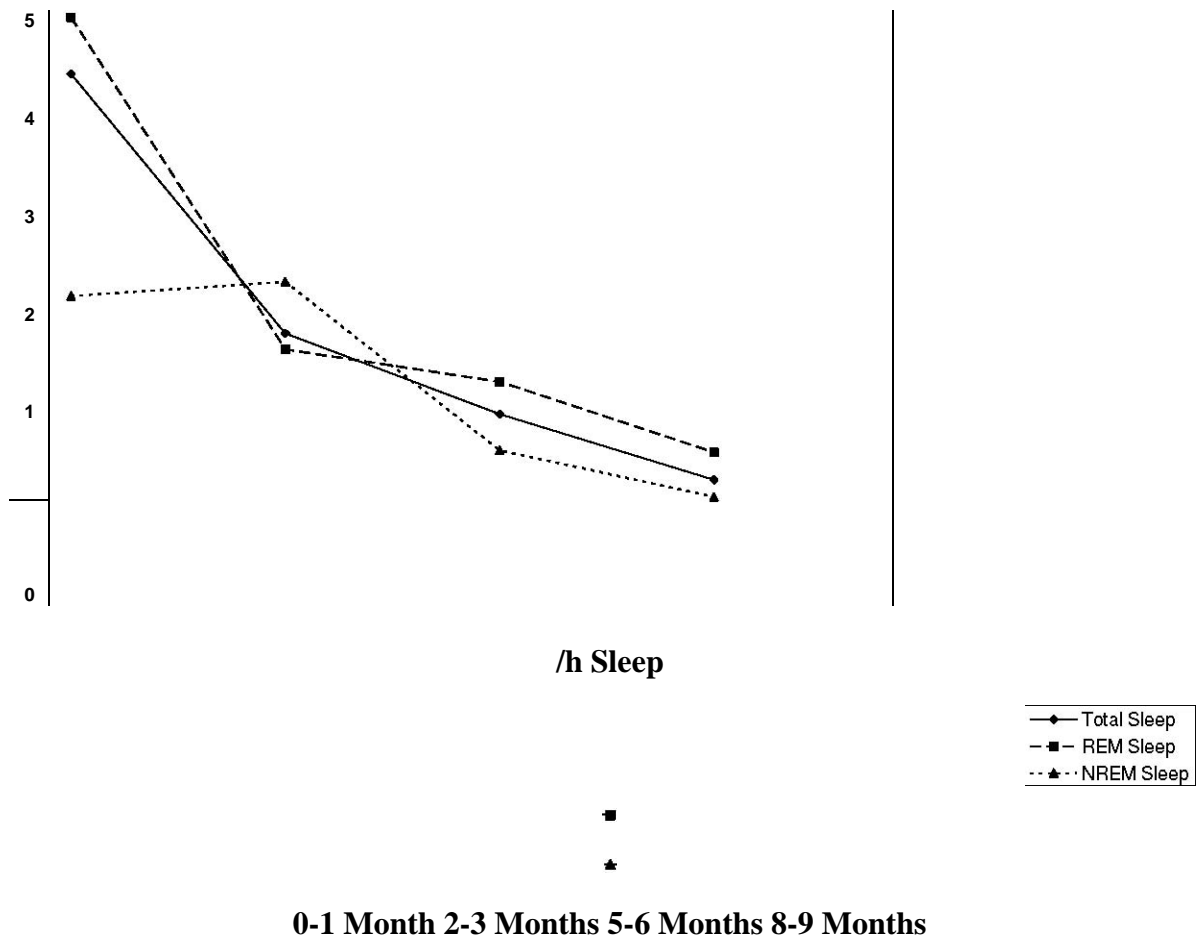


Figure 5: Evolution with age of cortical on subcortical ratio in total sleep, REM sleep and NREM sleep. The cortical on subcortical ratio represents the ratio between cortical arousals on subcortical activations.

Figure 5

