A decorative graphic consisting of several paper airplanes of varying sizes and colors (white and red) flying upwards and to the right. Each airplane is connected to a dotted line that trails behind it, suggesting a path or trajectory. The background is a light blue gradient.

Development and Maturation of Sleep: Understanding Bidirectional Relationships

Madeleine Grigg-Damberger MD

Professor of Neurology, University of New Mexico

Presented New Jersey Sleep Society, November 14, 2020, 10-11 AM (EST)

Talk Objectives

- Learn that sleep in early life plays crucial roles in optimal neural and cognitive brain development, cortical maturation, and brain connectivity.
- Know that twitching during REM sleep in fetus and premature infants stimulates mapping of sensorimotor, visual and auditory neuronal networks.
- Understand sleep restriction in adolescence can alter the developmental trajectory of brain and behavior.

Sleep Vital to Human Health, Necessary for Life and Serves Critical Roles in Brain Function

Brain Development and Synaptic Efficiency

Attention, Memory Consolidation, and Learning

Emotion, Pain and Motivation Regulation

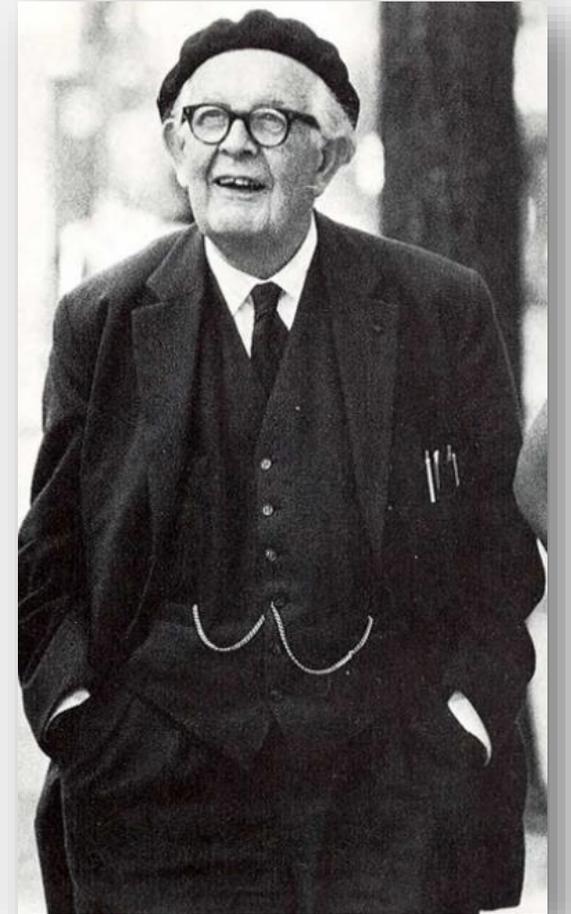
Metabolism and Appetite Regulation

Immune and Hormone function

Cardiovascular Function

Sleep is the Principal Behavior State of Infancy and Early Childhood

- Piaget thought play was the major 'work' of children, but it is sleep for neonates and young infants.
 - At term, infants spend 14 to 18 hours per 24 sleeping, 50% of it in REM sleep; premature infants 80%;
 - By age 2, average child has spent 10,000 hours asleep compared to 7,500 hours awake;
- **Why do infants spend so much time in sleep?**

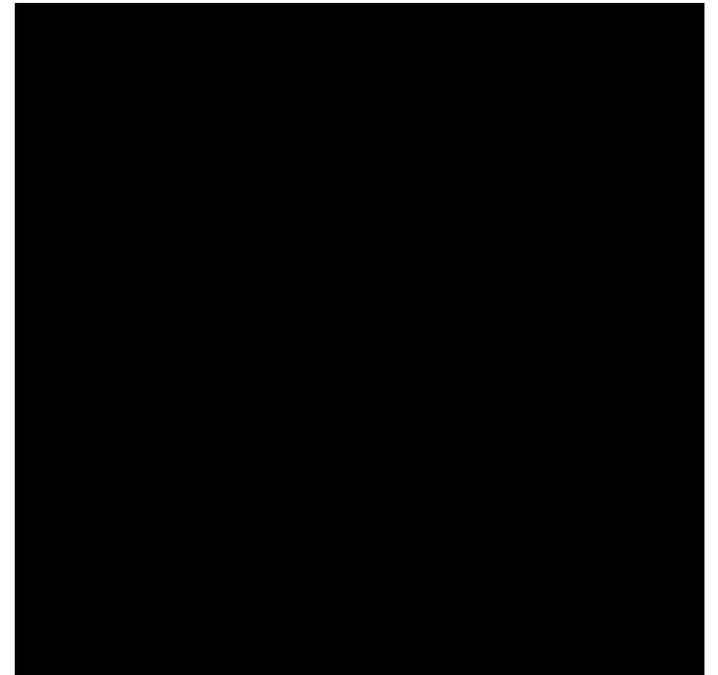




Sleep in Fetus
and Premature
Infants Fosters
Neural Networks

Not Enough Going On in Womb to Foster Brain Development and Connectivity

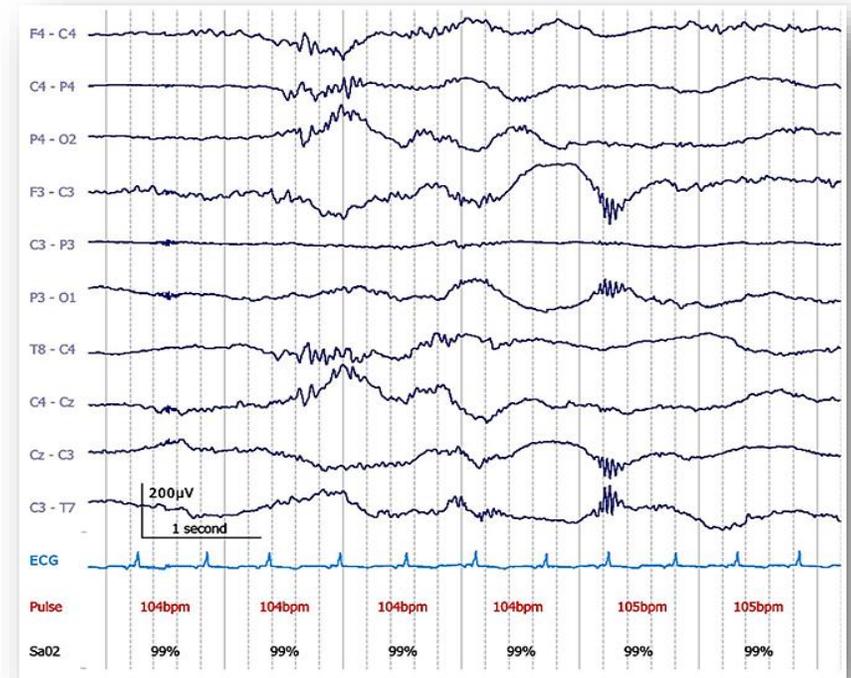
- Ascending stimulation to forebrain from brain stem during REM sleep promotes fetal and early infant brain development when wake-related stimulation is low
 - Ten thousands of twitches which induce jerky movements of limbs during REM sleep have been shown to map sensorimotor, auditory, visual, tactile and pain systems.
 - Twitching during brief periods of W no such effect.
 - Decreased startles and twitches in human neonates associated with poor behavioral and neurological outcomes at later age.



Fetal MRI of Infant 20 weeks GA moving in womb

Limb Twitching During REM Sleep in Premature Infants Triggers Delta Brush Activity in EEG: Mapping Cortex

- Mapping of auditory, touch, pain, and smell in early development shown to correlate with delta brush activity in premature infants;
- Sporadic hand and foot movements infants 29-31wGA herald appearance of **delta brushes** in respective lateral and medial contralateral central cortex.
- Direct hand and foot stimulation reliably provoked delta brushes in same regions.



- Delta brushes observed 26 to 44 weeks, maximal 34 weeks.



**Rest-activity Cycles First Appear
20 Weeks Gestational Age (wGA)**

Behavior Correlates Better Identify Sleep/Wake States in Premature and Term Infants

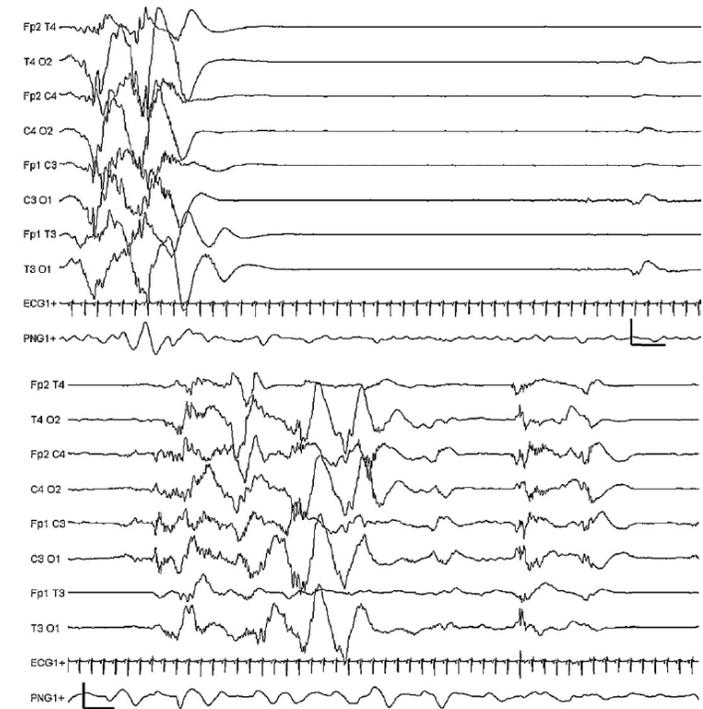
REMs first seen 18-20 wGA

Respiration as a marker of NREM (regular) REM (irregular)
first seen 32 wGA

Chin EMG last to develop: increased NREM 34 wGA, then less reliable 37-40 wGA, 80-85% reliable 40+ wGA.

24-25 Weeks PMA

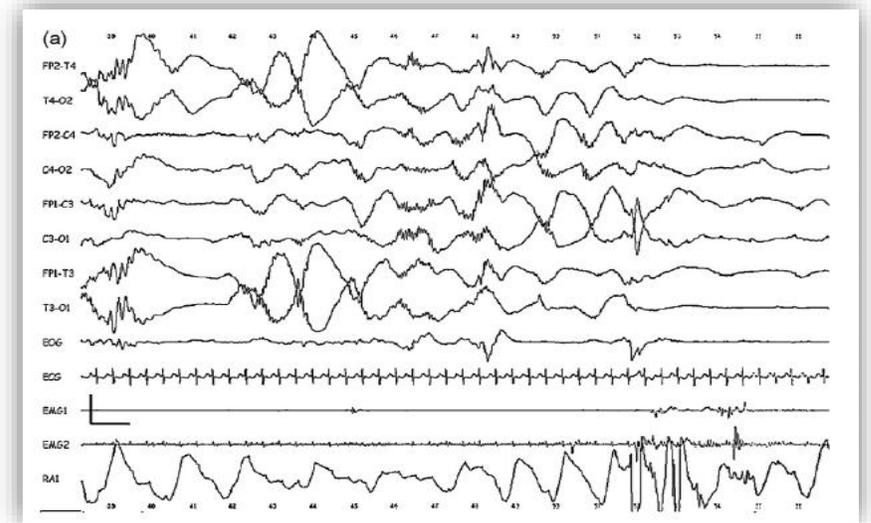
- Rest/activity cycles observed but behaviors inconsistently associated with EEG;
- EEG shows “trace discontinu” = runs of high amplitude ($>300 \mu\text{V}$) 0.3-1 Hz delta with superimposed theta and sharp waves lasting < 60 s and inter-burst intervals (IBIs) 20-25 s
- No visible change in EEG even if painful stimuli handling provokes limb withdrawal movement.



EEG pattern called trace discontinu

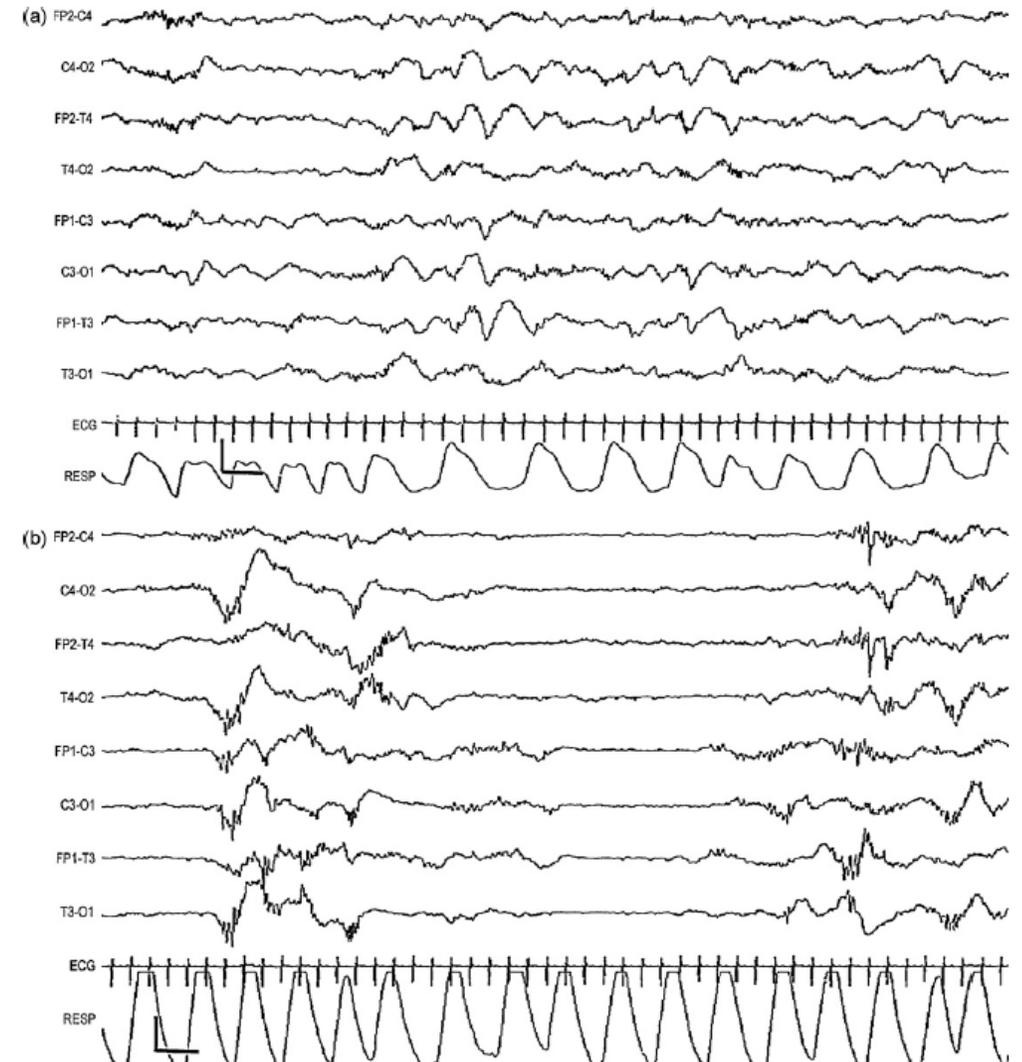
28-29 Weeks wGA

- 3 behavioral states identifiable: Wakefulness (W), active/REM (R) and quiet/NREM (N) sleep;
- Very little W; mostly REM sleep;
- EEG **more continuous** (runs lasting up to 160 s) with IBIs ≤ 30 s;
- Reactivity of EEG to stimuli now seen.



32-35 Weeks PMA

- Behavioral correlates of W, R and N present;
- EEG in REM and W continuous need behavioral correlates to distinguish;
- EEG discontinuous NREM with IBIs ≤ 20 s;
- W best recognized by eyes open and movement artifacts.

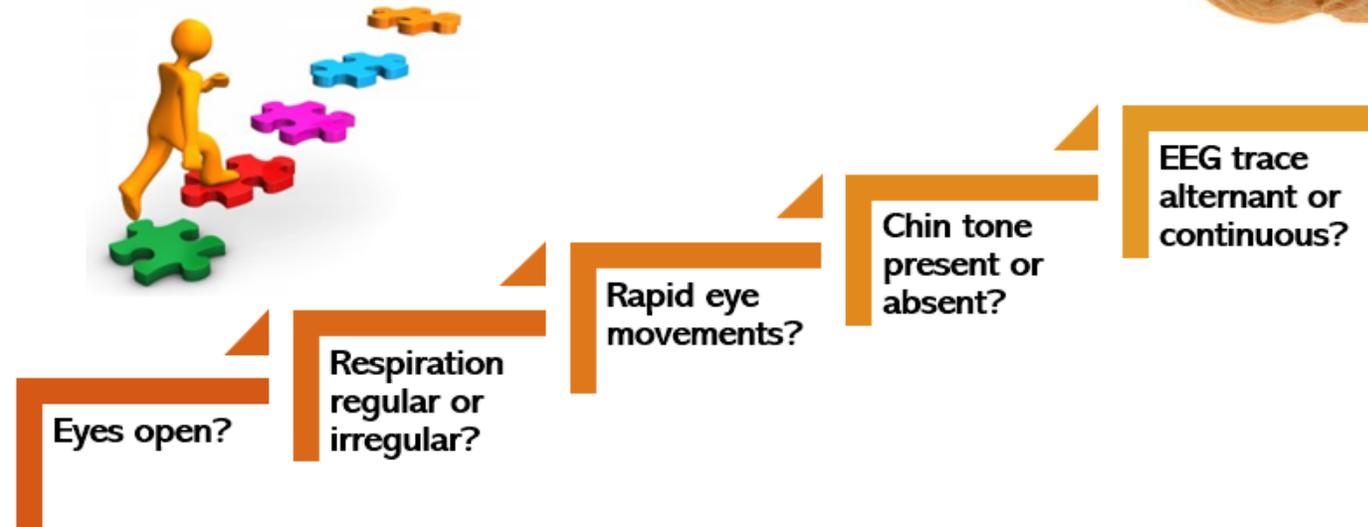


34 weeks CA: REM continuous, NREM discontinuous; respiration regular NREM, irregular REM.

Scoring Sleep/Wake in Infants 0-2 Months Using AASM Scoring Rules in Nutshell



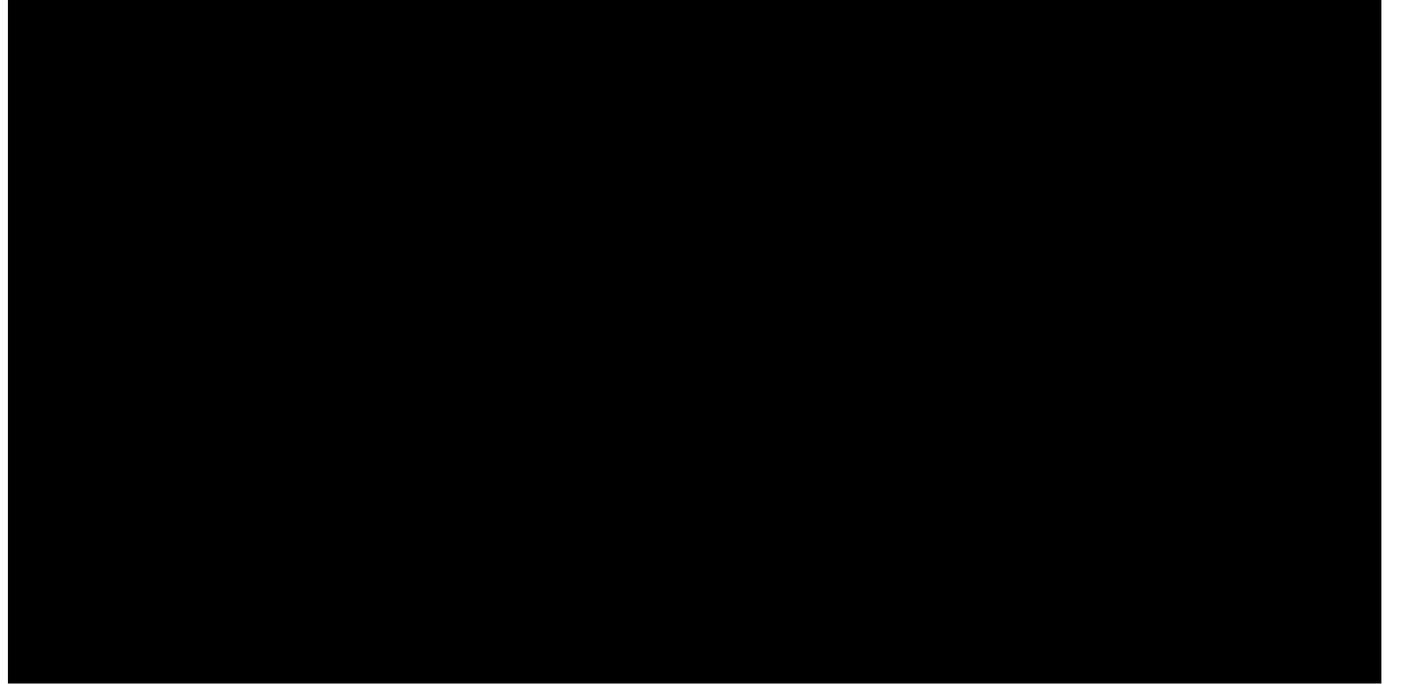
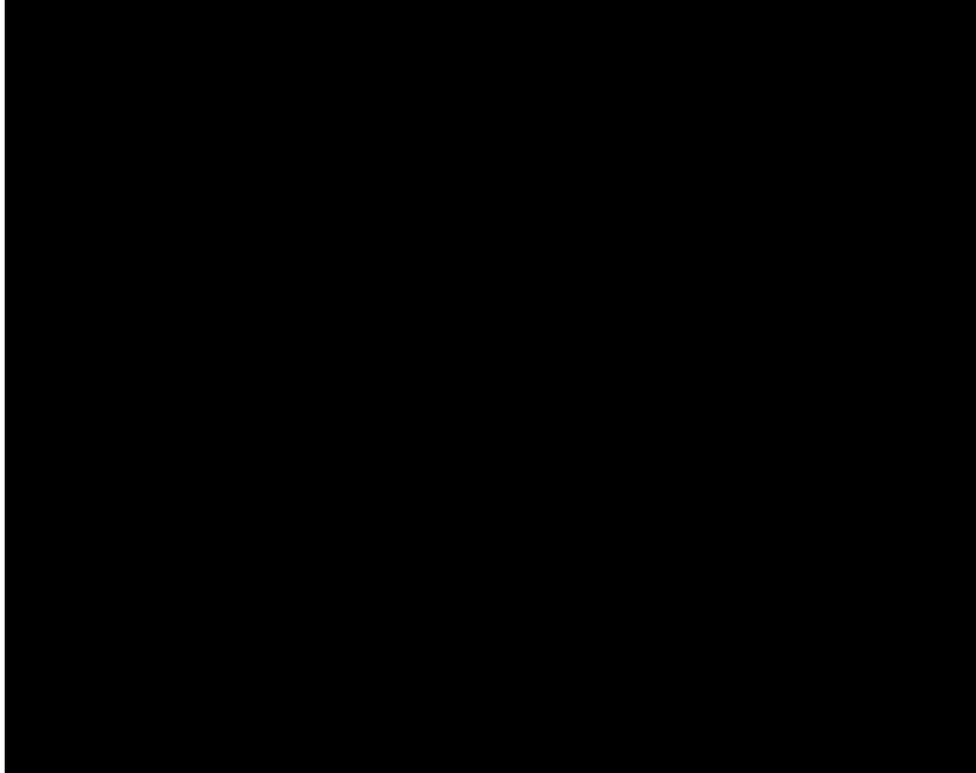
- Wakefulness (W)
- REM Sleep (R)
- NREM Sleep (N)
- Transitional Sleep (T)



Important concepts:

- 1) Regularity or irregularity of respiration single most reliable PSG characteristic when scoring infant PSGs;
- 2) Eyes open best determinant of Wakefulness;
- 3) Sleep onsets more often REM sleep till 2-3 months post-term;
- 4) Chin EMG often unreliable marker REM sleep
- 5) Infant behaviors more important for identifying sleep/wake states than EEG.

Behavioral Correlates of REM Sleep



Rapid eye movements; Irregular respiration
Atonic chin EMG; Eyes closed, slight opening and closing;
blinks; Smiles, frowns, grimaces; Bursts of sucking, small
twitches, sighs and sobs

Premature Infants Sleep Better in Womb Than Neonatal ICU

- Infants in NICU born preterm (<37 wGA) compared fetuses of similar age in womb less TST and more NREM sleep;¹
 - Premature born had more immature sleep patterns, stage shifts and transitional sleep (and associated with poorer developmental outcomes on Bayley II at 6 months):
 - Those with longer periods of sustained sleep, more REM sleep time had better cognitive outcomes.



- Prospective longitudinal study of 142 infants born mean 32 wGA:³
 - W from quiet sleep → better neonatal neuromaturation, less negative emotionality and better verbal symbolic, and executive competencies age 5
 - Shorter episodes of active/REM and quiet/NREM → poorer outcome.

Getting Older: 41-45+ Weeks PMA

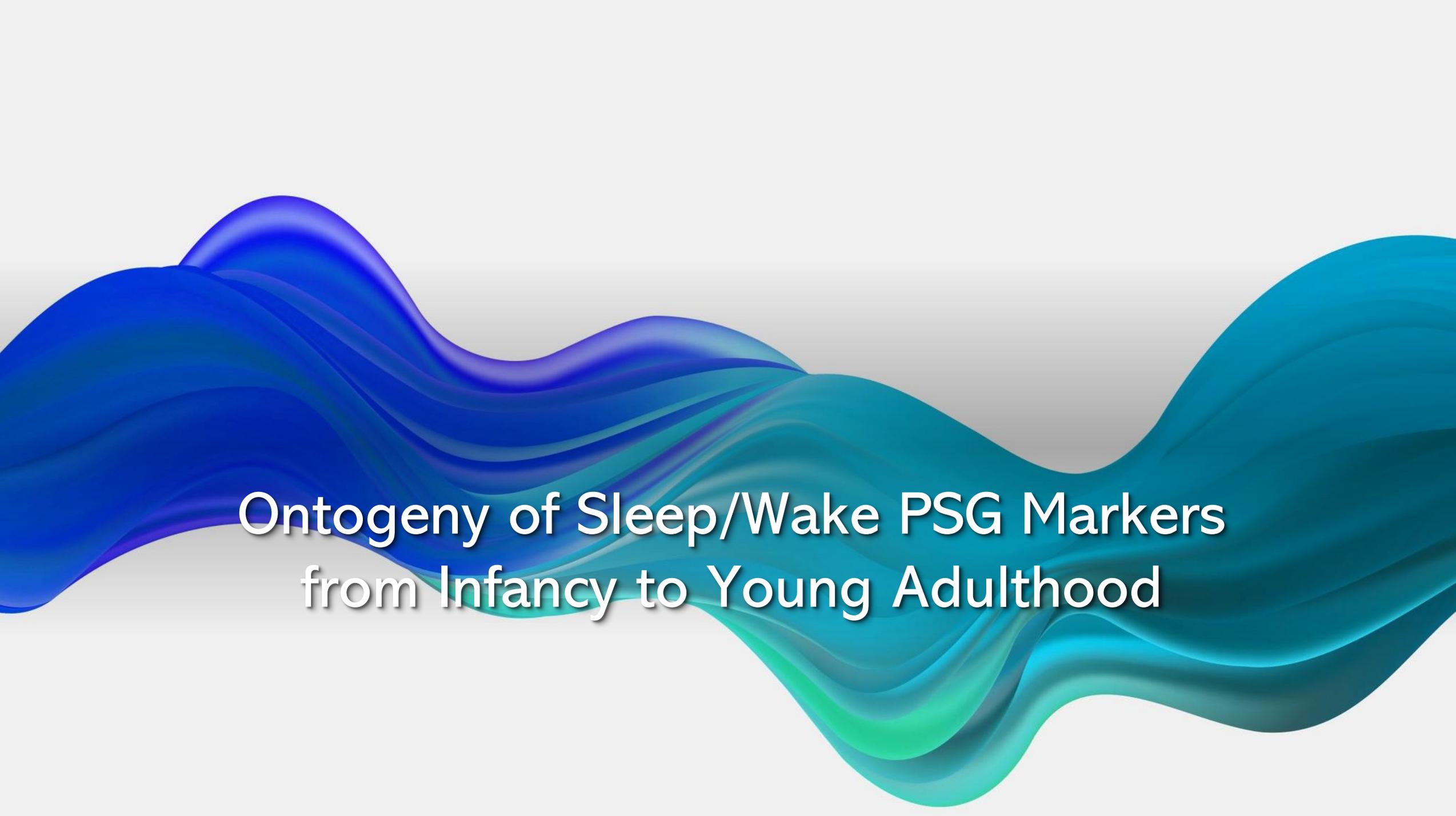
- **41-44 weeks PMA:**

- Delta brushes gradually disappear by 44 weeks PMA;
- IBIs brief (typically 2-4 sec) and IBI amplitudes $>50 \mu\text{V}$; by 44 weeks IBIs have “filled in”, trace alternant replaced by CSWS.

- **45+ weeks PMA:**

- First major EEG feature of mature sleep to appear after birth are sleep spindles.
- Sometimes seen 43-44 weeks PMA, often present 46-48 weeks, should be present 3 months term.

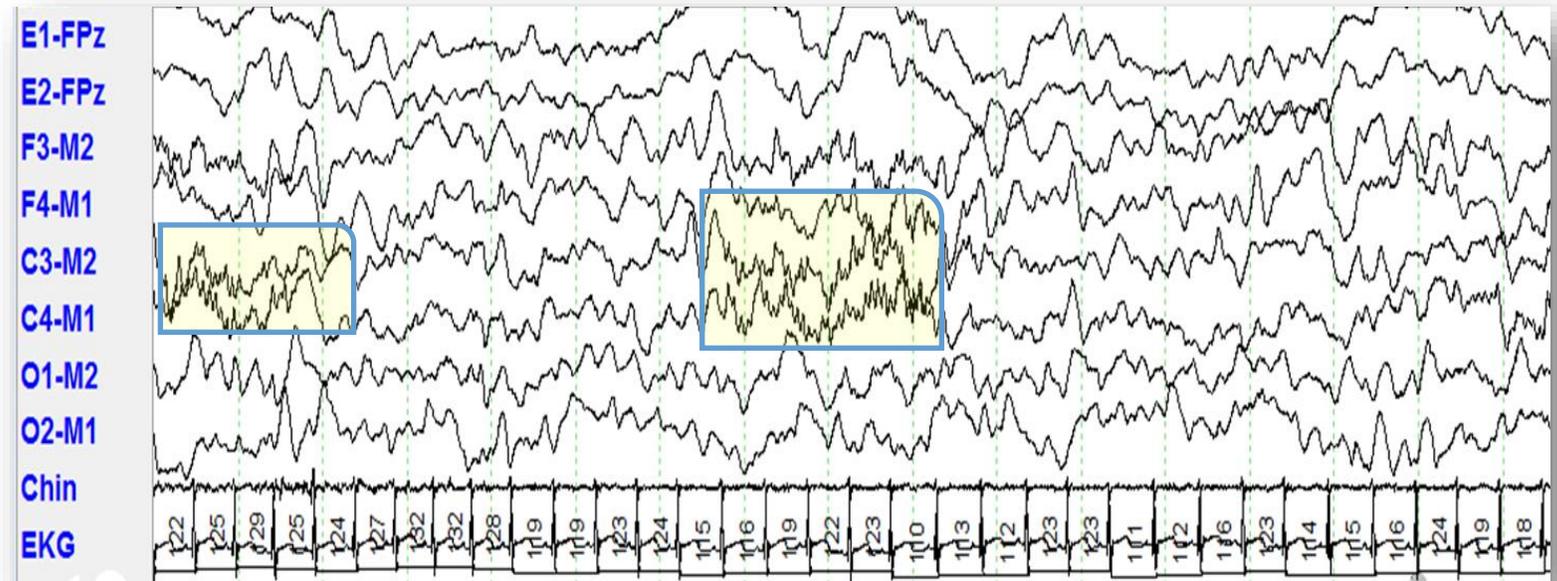
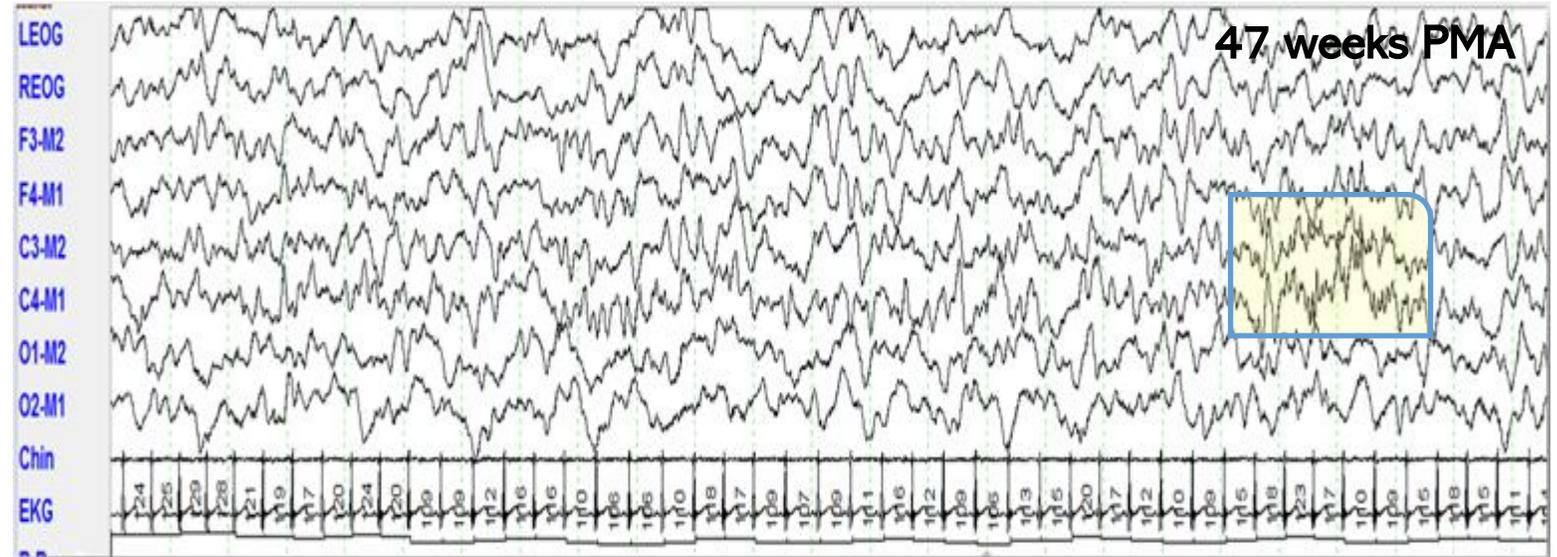


The background features a series of overlapping, wavy bands in shades of blue and teal, creating a sense of movement and depth. The colors transition from a deep blue on the left to a lighter teal on the right. The text is centered over this graphic.

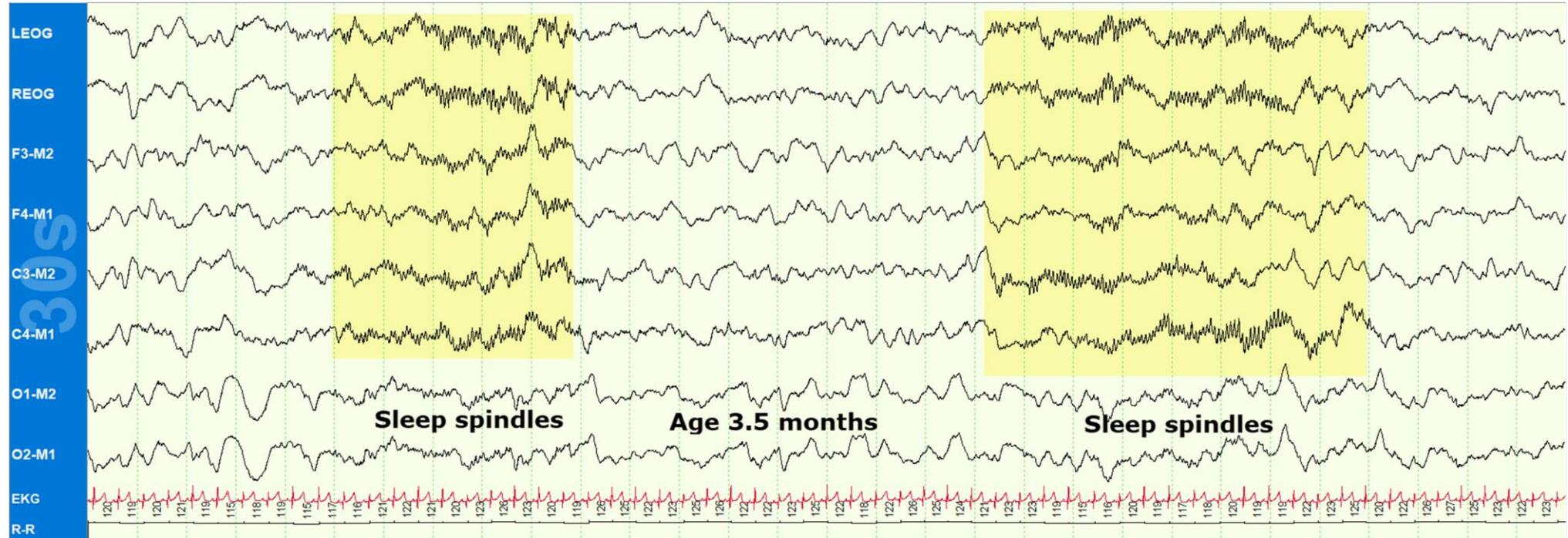
Ontogeny of Sleep/Wake PSG Markers from Infancy to Young Adulthood

Sleep Spindles First Major Feature of Mature Sleep After Birth

- Sleep spindles (12-14 Hz) first appear Cz;
- 50% of sleep spindles synchronous 6 and 9 months; 70% 12 months; synchronous by 2 years;



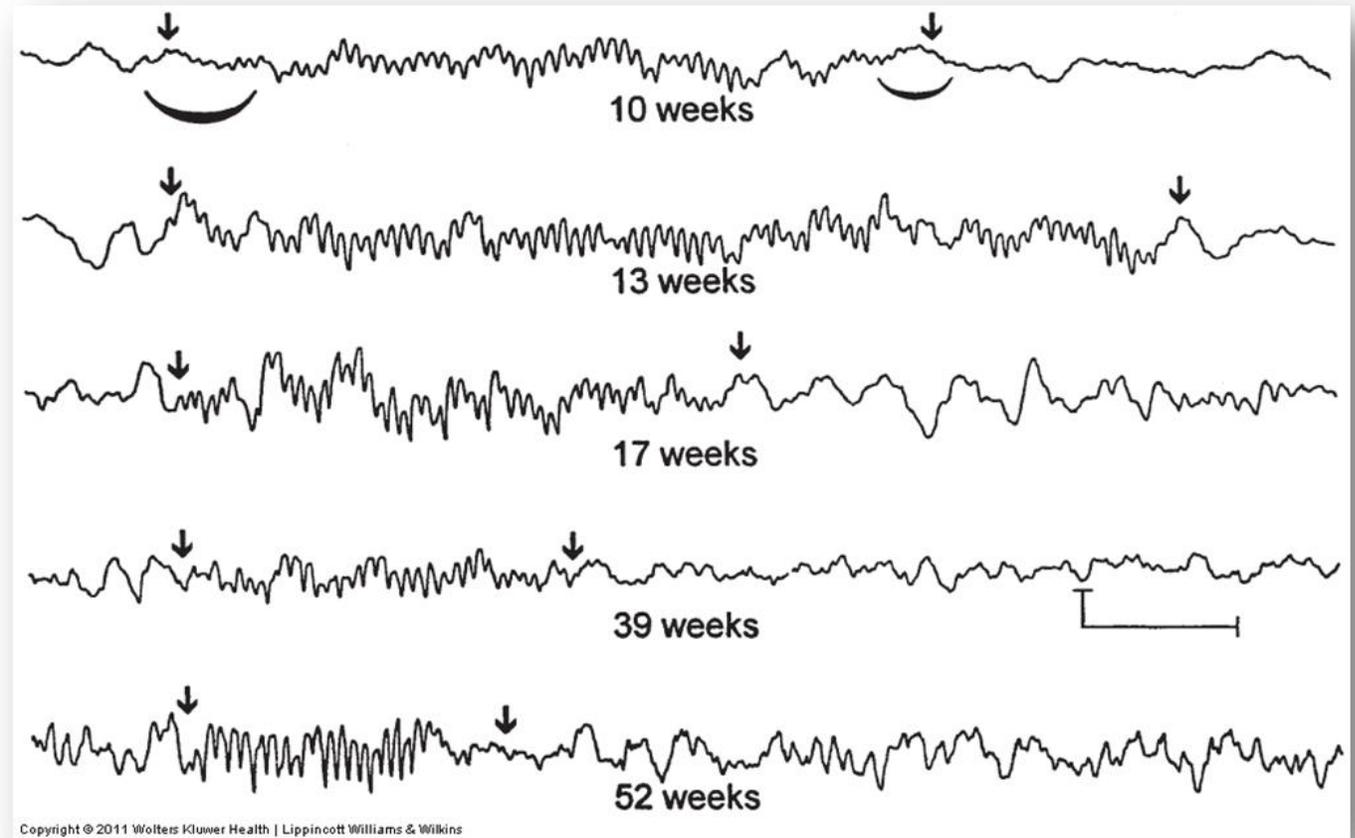
Long-Lasting Sleep Spindles Ages 3-6 Months



Sleep spindles often last 3-8 seconds (up to 10-15 s) ages 3-6 months (especially 3-4 months)

Shape and Duration of Sleep Spindles Change with Age 10 to 52 Weeks

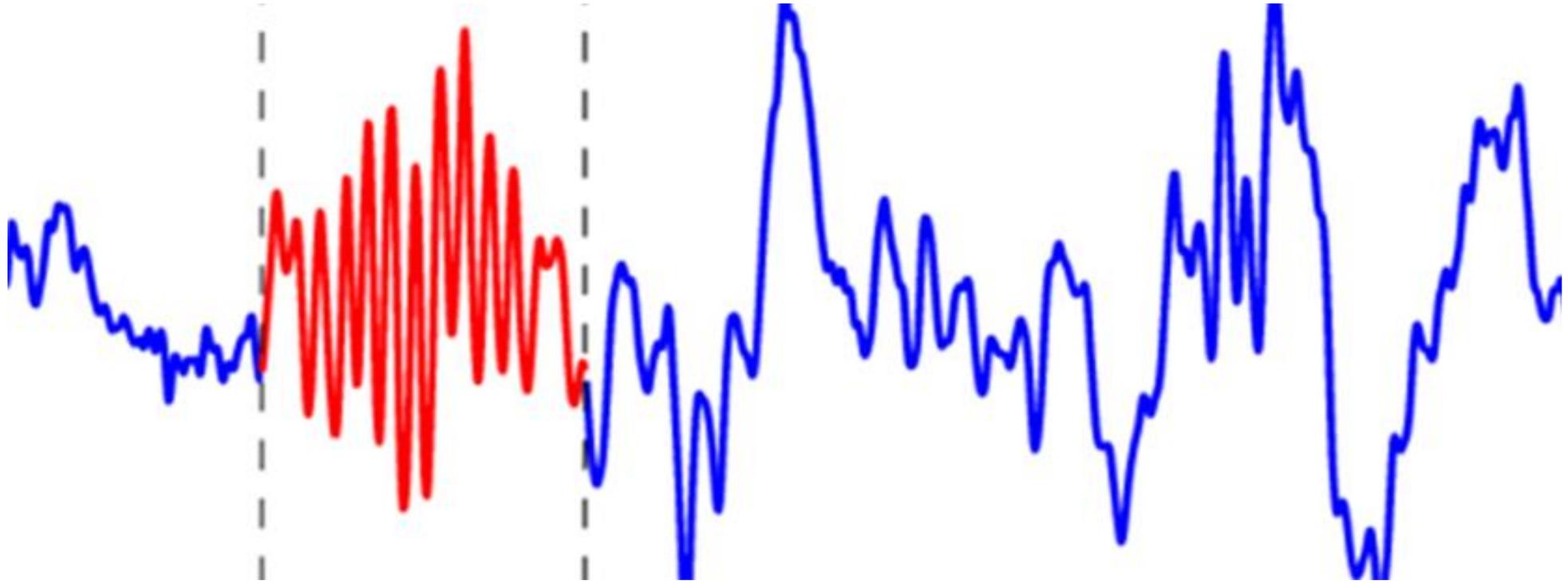
- Spindles of infancy usually show a sharp configuration, comb-like runs, note the rounded surface negative top and spiky surface positive component.



Frontal Sleep Spindles Common Children < 13 Years



Sleep spindles children often two different frequencies: 11-12.75 Hz frontal; 12-14.75 Hz centroparietal; frontal spindles less after age 13.



Sleep spindles play important role in memory consolidation during NREM 3 sleep

Memory processing during NREM 3 sleep works best if sleep spindles are coupled to slow oscillations and coupling improves from childhood to adolescence.

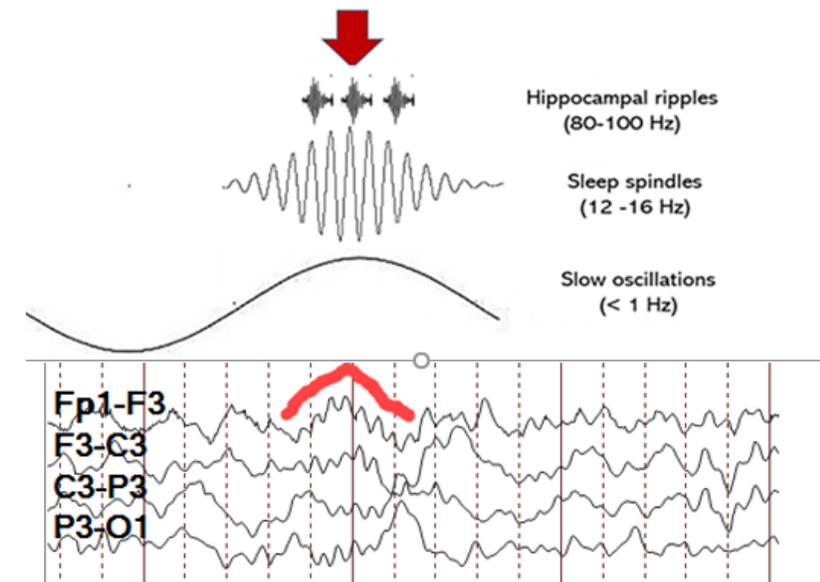
Sleep Spindles and Slow Wave Activity Important in Learning in Toddlers and Children

- Schoolchildren who spent more time in NREM 3 during afternoon naps were able to learn a particular motor sequence better than adults and showed stronger hippocampal activation at explicit knowledge retrieval.
- Experimental study: sleep spindles, slow wave activity, and NREM 3 after learning a novel task positively affect memory reorganization in toddlers.

REFs: 1) Friedreich M et al. Nat Commun 2015;6:1-9; 2) Wilhelm I et al. Nat Neurosci 2013;16:391-3; 3) Urbain C et al. Neuroimage 2013; 134:213-22.

Memory Processing NREM 3 Depends Upon Slow Oscillation-Spindle-Ripple Coupling

- Sleep spindles play important roles in memory processing and consolidation including for children.
- Transfer of memory traces acquired awake are temporarily stored in the hippocampus.
- Depolarizing up state of slow oscillations (generated in prefrontal cortex) facilitate transfer of memory engrams in hippocampal ripples nested in troughs of sleep spindles.
- Phase-coupling of slow oscillation-spindle-ripples provide the neurobiological scaffold for moving newly acquired memories to long-term storage in neocortex.

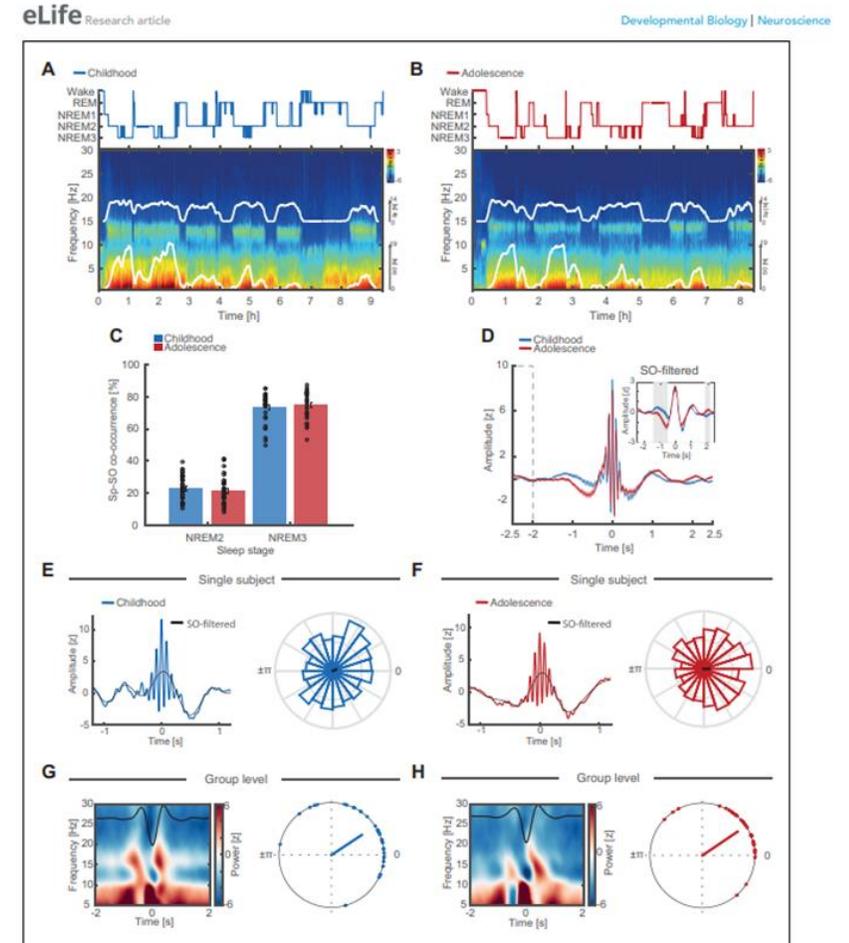


Coupling of hippocampal ripples, sleep spindles to slow oscillation up state.

REFs: Helfrich RF et al. Nat Commun 2019;10(1):3572; 2) Antony JW. Trends Neurosci 2019;42(1):

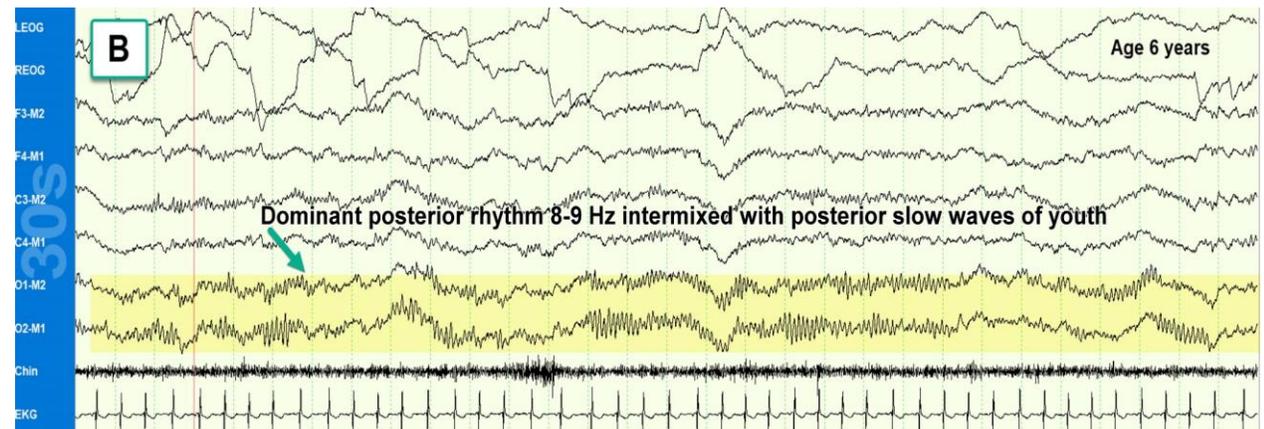
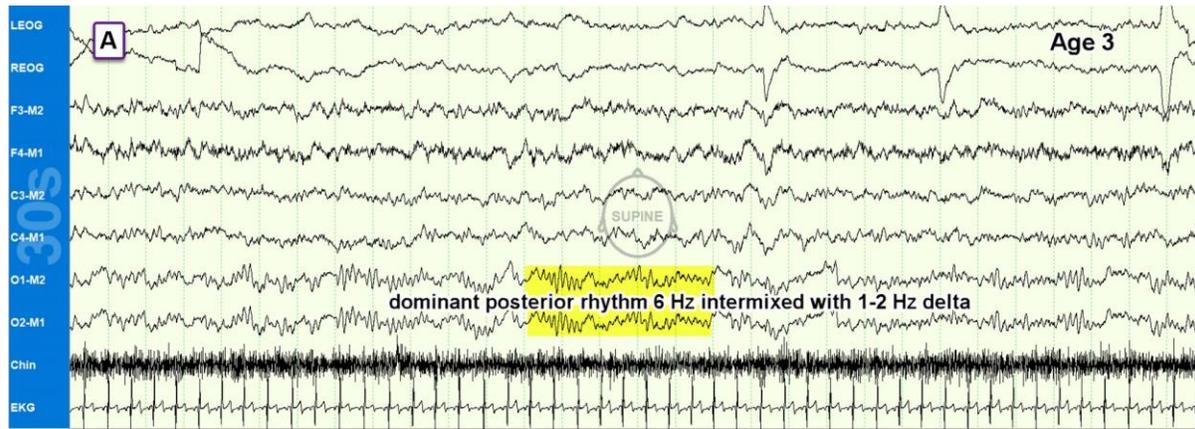
SO-Spindling Coupling Increases Childhood to Adolescence and Enhances Memory Formation

- Hahn et al. (2019) tested ability of children to store memories, retesting them later as adolescents.
 - Ability to recall a set of words was better after a full night's sleep;
 - Memory recall was best when phase coupling of slow oscillations-spindles were observed.
 - Children with better spindle-SO coupling have improved memory formation once they became teenagers.
- Hahn et al. (2020) found SO-spindle coupling strength increases during maturation and increases in coupling enhance memory formation from childhood to adolescence.

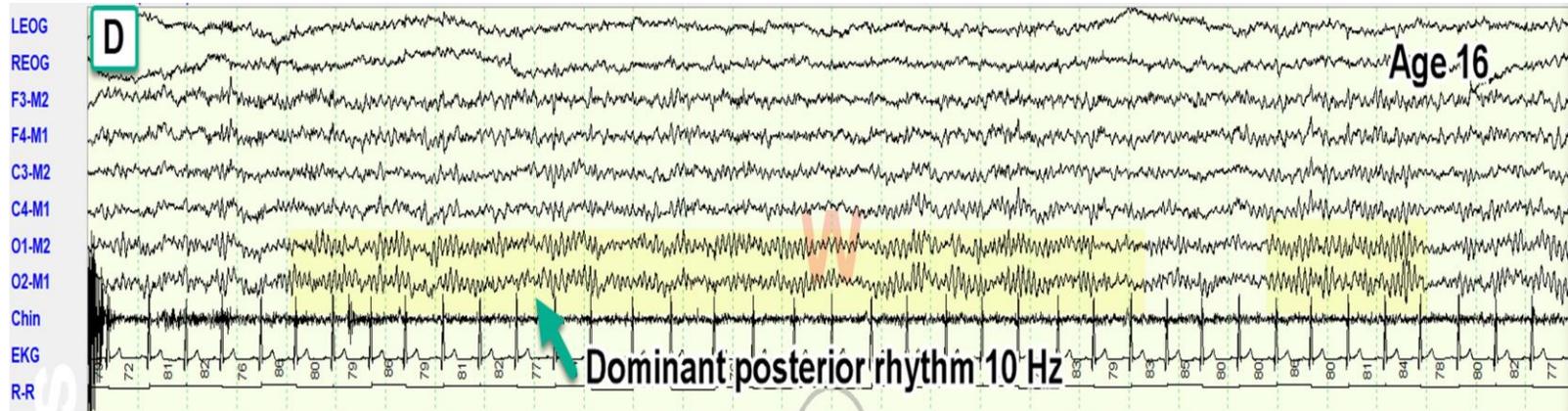
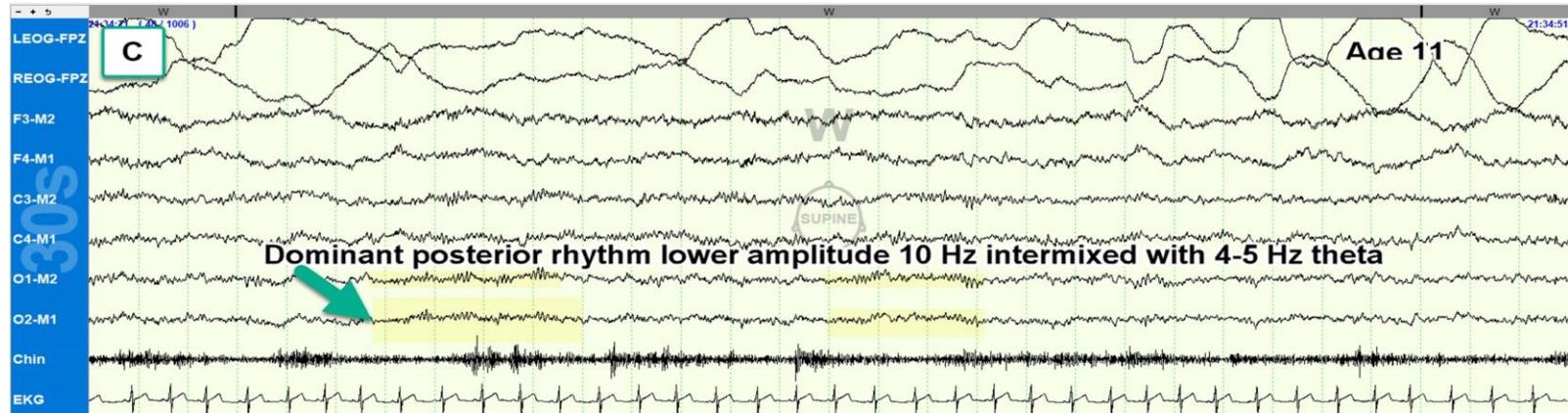


Further Development and Maturation of Polysomnographic Markers of Sleep/Wake

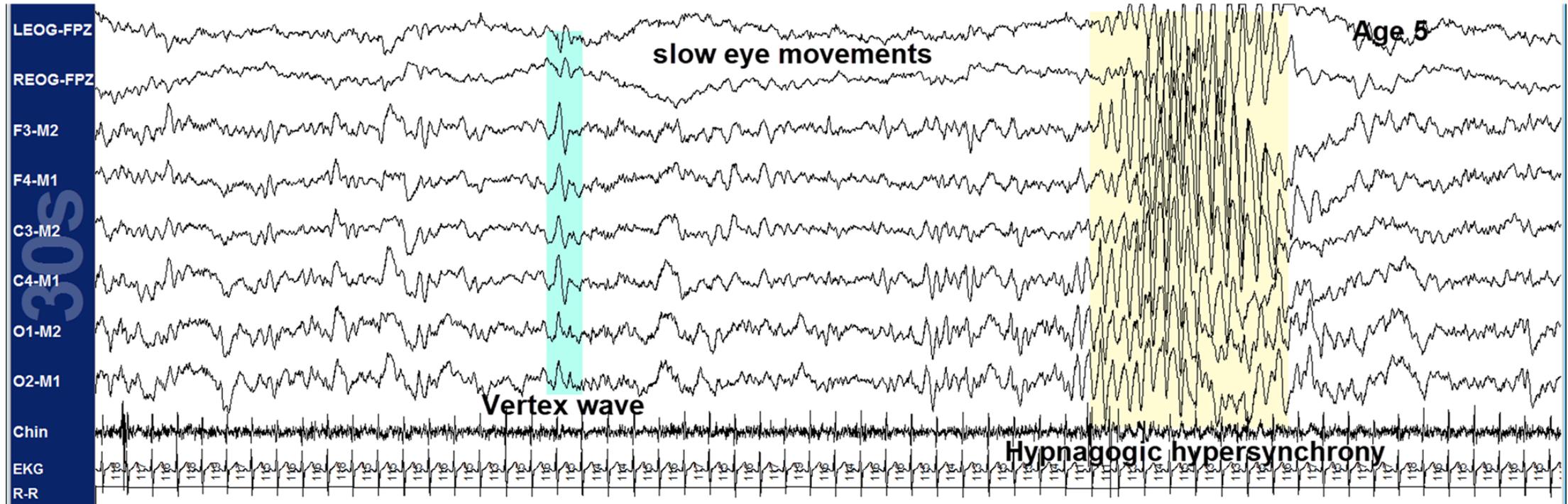




- Dominant posterior rhythm (DPR) next EEG marker to develop;
 - First seen 3.5-4.5 Hz 3-4 months;
 - 5-6 Hz 5-6 months;
 - 8 Hz by age 3;
 - 9 by age 9;
 - 10 by age 15.
- Abnormally slow DPR for age:
 - 1 y: < 5 Hz
 - 4 y: < 6 Hz
 - 5 y: < 7 Hz
 - ≥ 8 y < 8 Hz.



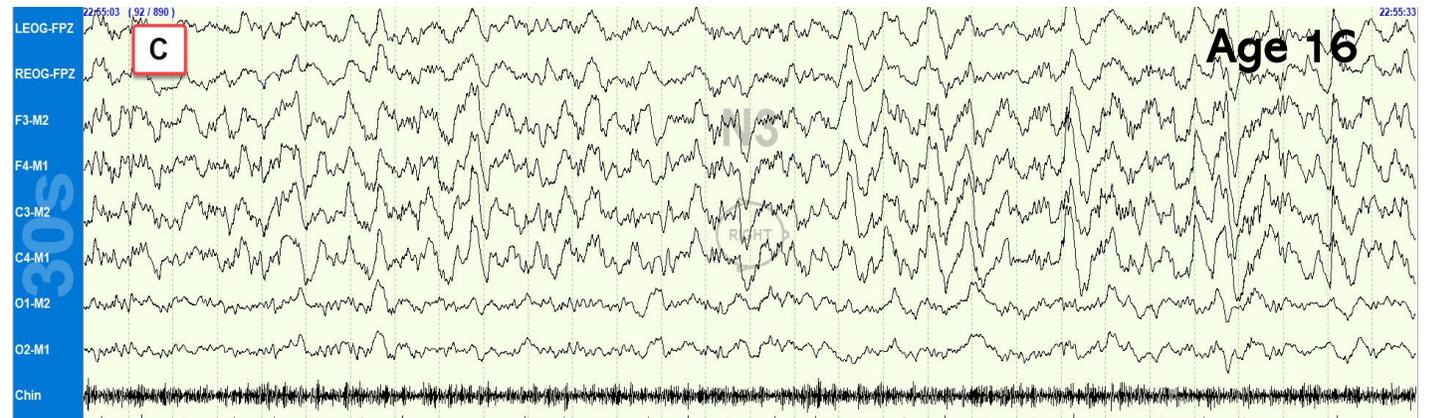
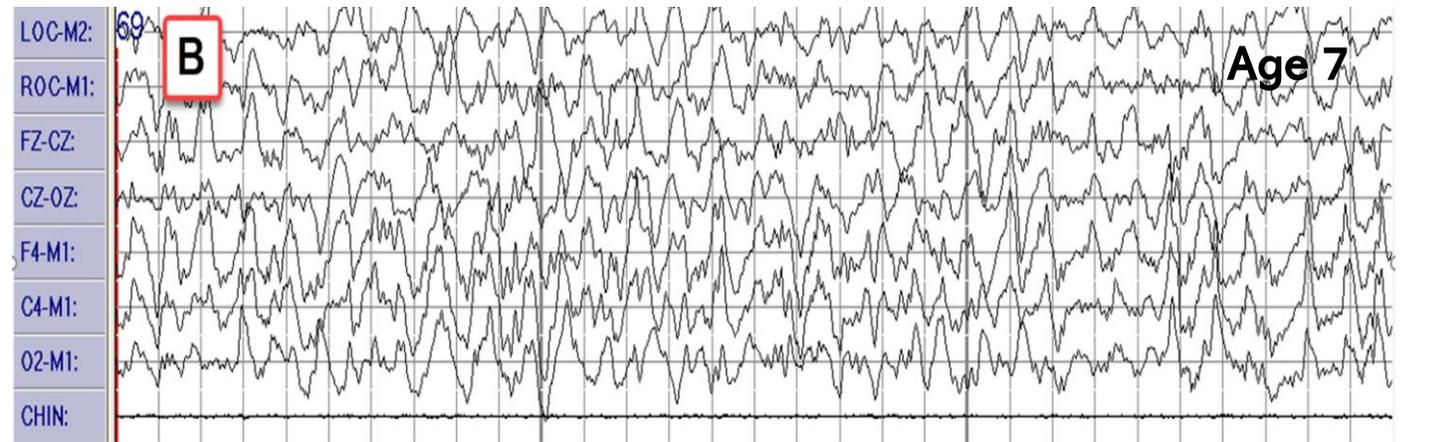
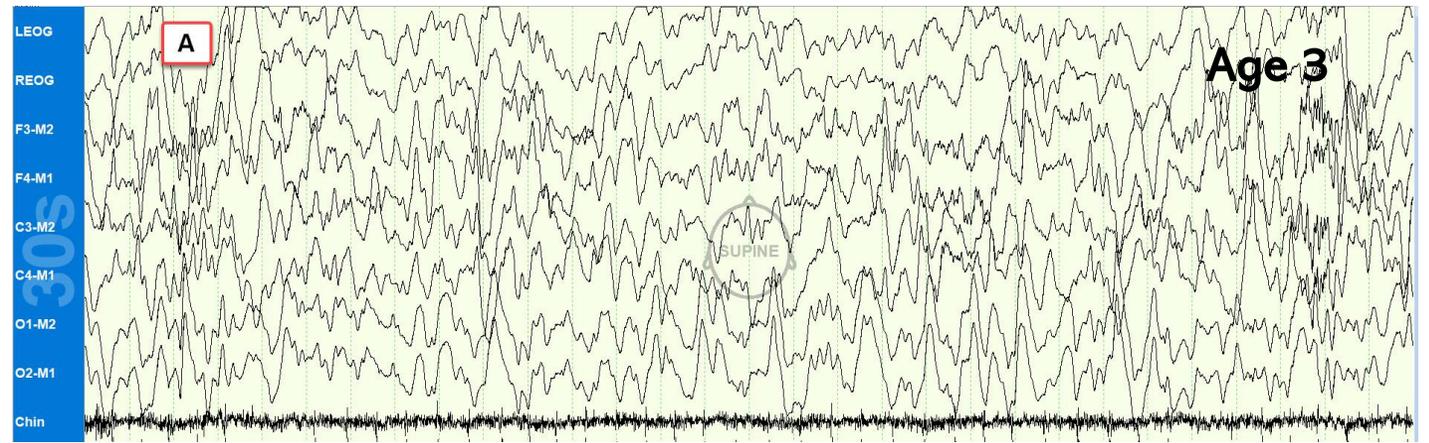
Hypnagogic Hypersynchrony (HH) Signals Drowsiness and NREM 1 Sleep



- Hypnagogic hypersynchrony are paroxysmal bursts or runs of diffuse bilaterally synchronous rhythmic high amplitude 75-350 μV waves which begin abruptly and can occur intermittently or continuously for several minutes; 3-4 Hz at age 2-3 months; 4-5 Hz older children.
- First appears age 3 months term (seen 30% of them then); most prominent 3 to 11 months (95% between 6-9 months and 2-4 y) gradually disappear (10% of 11-year-olds, rare after 12-13 y).

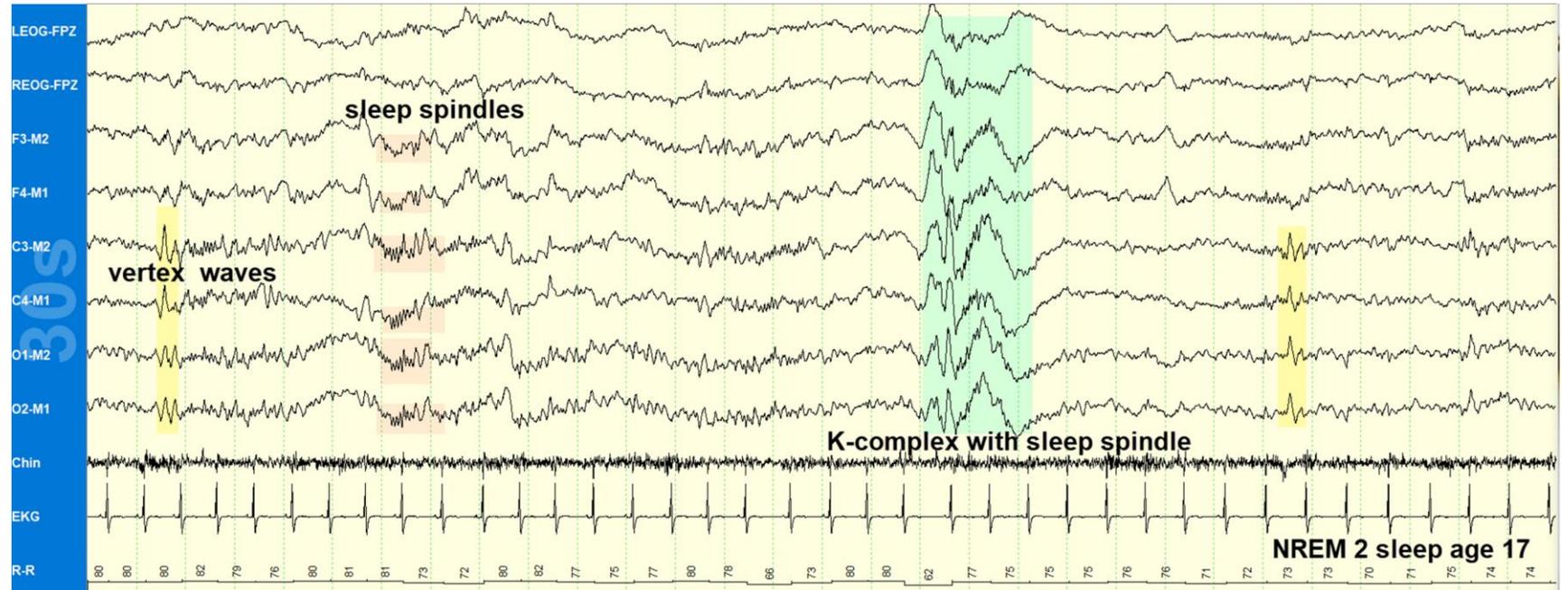
NREM 3 sleep

- NREM 3 in infants and children usually $> 150 \mu\text{V}$; often $\geq 300 \mu\text{V}$ young children;
- Scored when $> 50\%$ of epoch contains $0.5\text{-}2\text{Hz} \geq 75 \mu\text{V}$;
- Slow wave activity (SWA) of N3 can be scored in a PSG as early as 3 months months, most often 4-4.5 months, and usually present by 5-6 months of age.



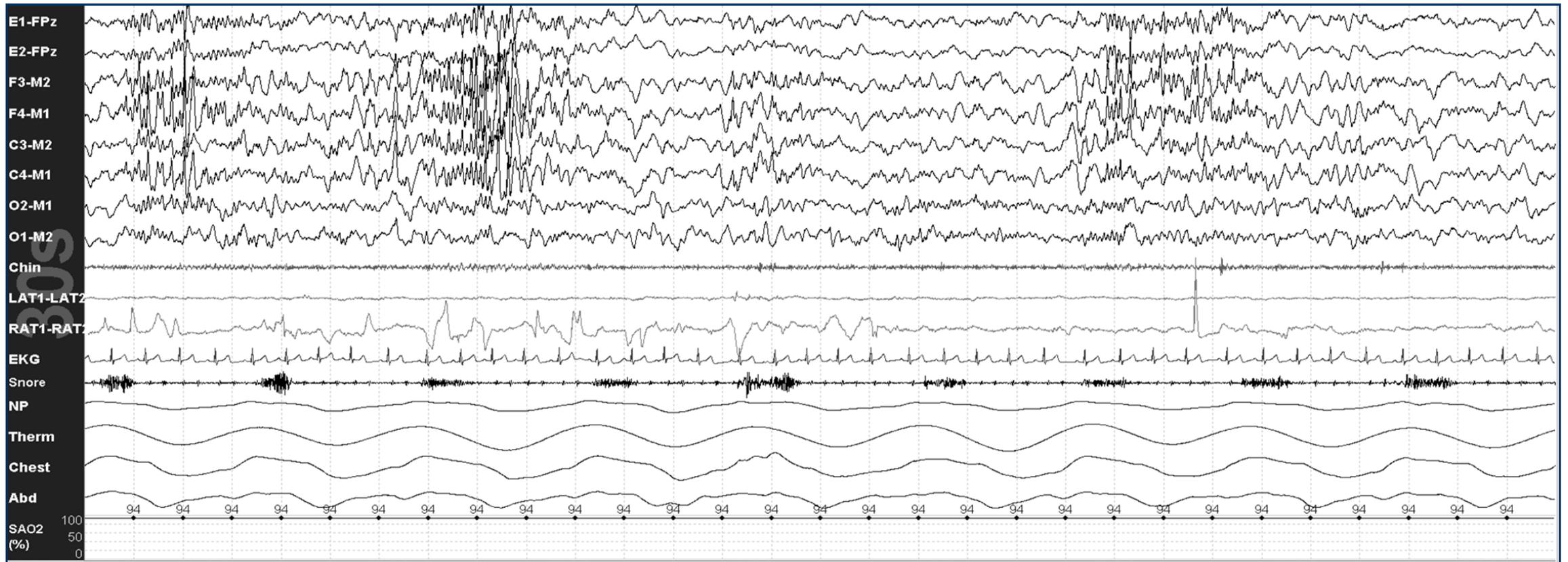
Vertex Waves and K-Complexes

- Vertex waves first appear as early as age 6 months; resemble older children and adults age 30 months.
- Maximal central seen late N1 and N2; surface electronegative.



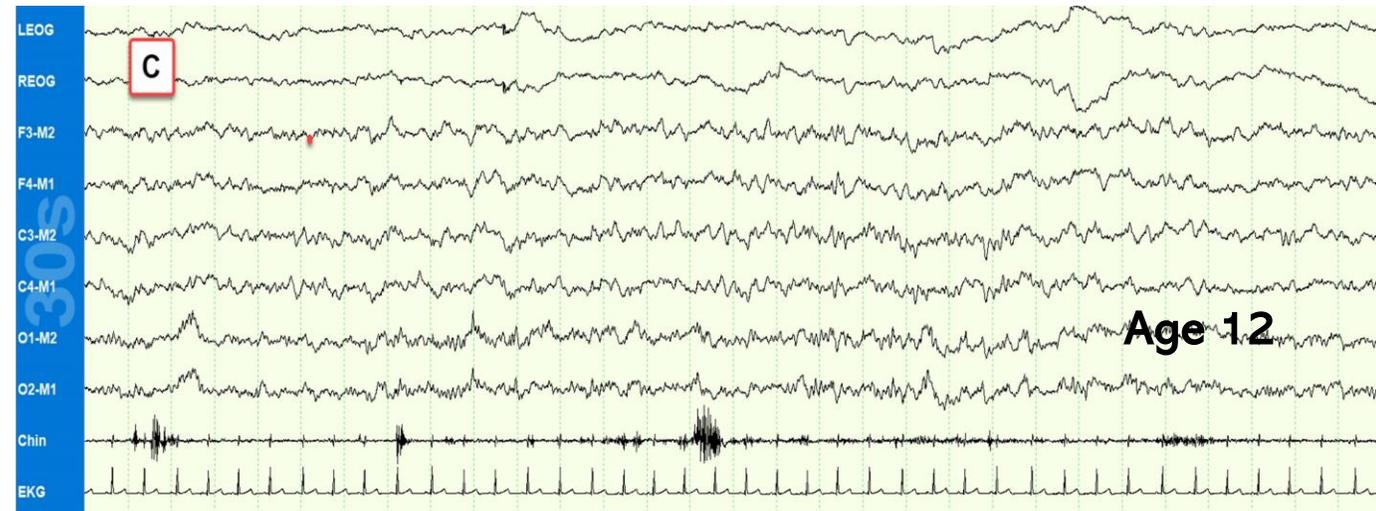
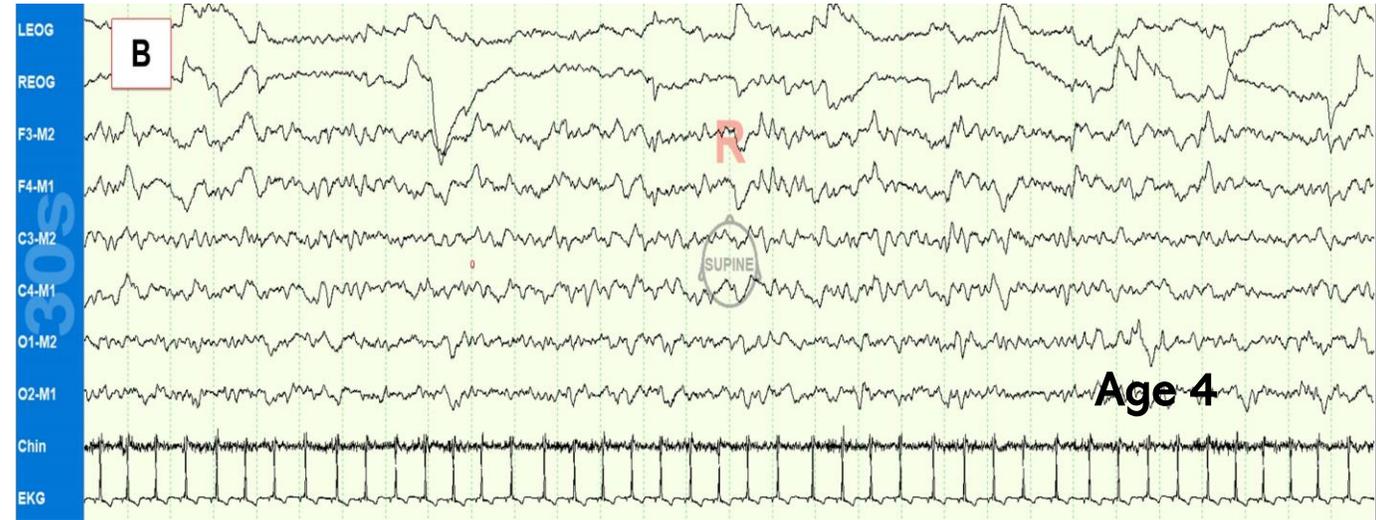
K-complexes: 1) typically first 5-6 months post-term; 2) Surface negative 50-100 μV wave lasting 200 ms followed by surface positive 30-50 μV 300-500 ms maximal frontal; 3) well-established by 18 months.

Vertex Waves Often Repetitive Runs and Sharply Contoured



- Vertex waves in young children (beginning ~30 months) often occur in repetitive runs; Around 36 mo, vertex waves often $>250 \mu\text{V}$ sharply peaked sometimes misidentified as epileptiform; Between ages 3-13 vertex waves evolved to those seen in adults.

REM Sleep Easiest to Recognize in PSG Any Age



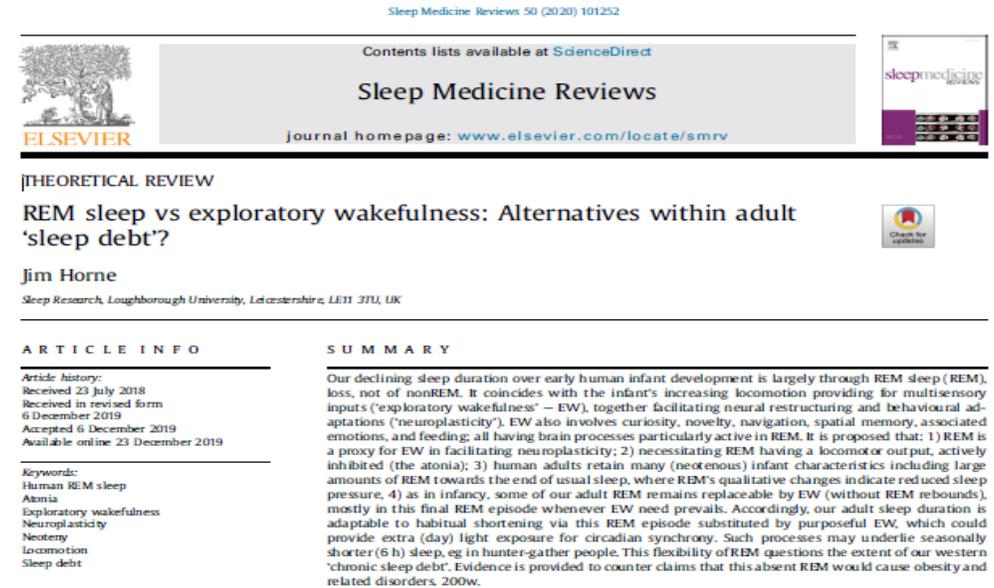
- All the REM sleep generator mechanisms and connections are present in rates equivalent to development age of human infants 32 weeks PMA and similar to those seen in adult cats.



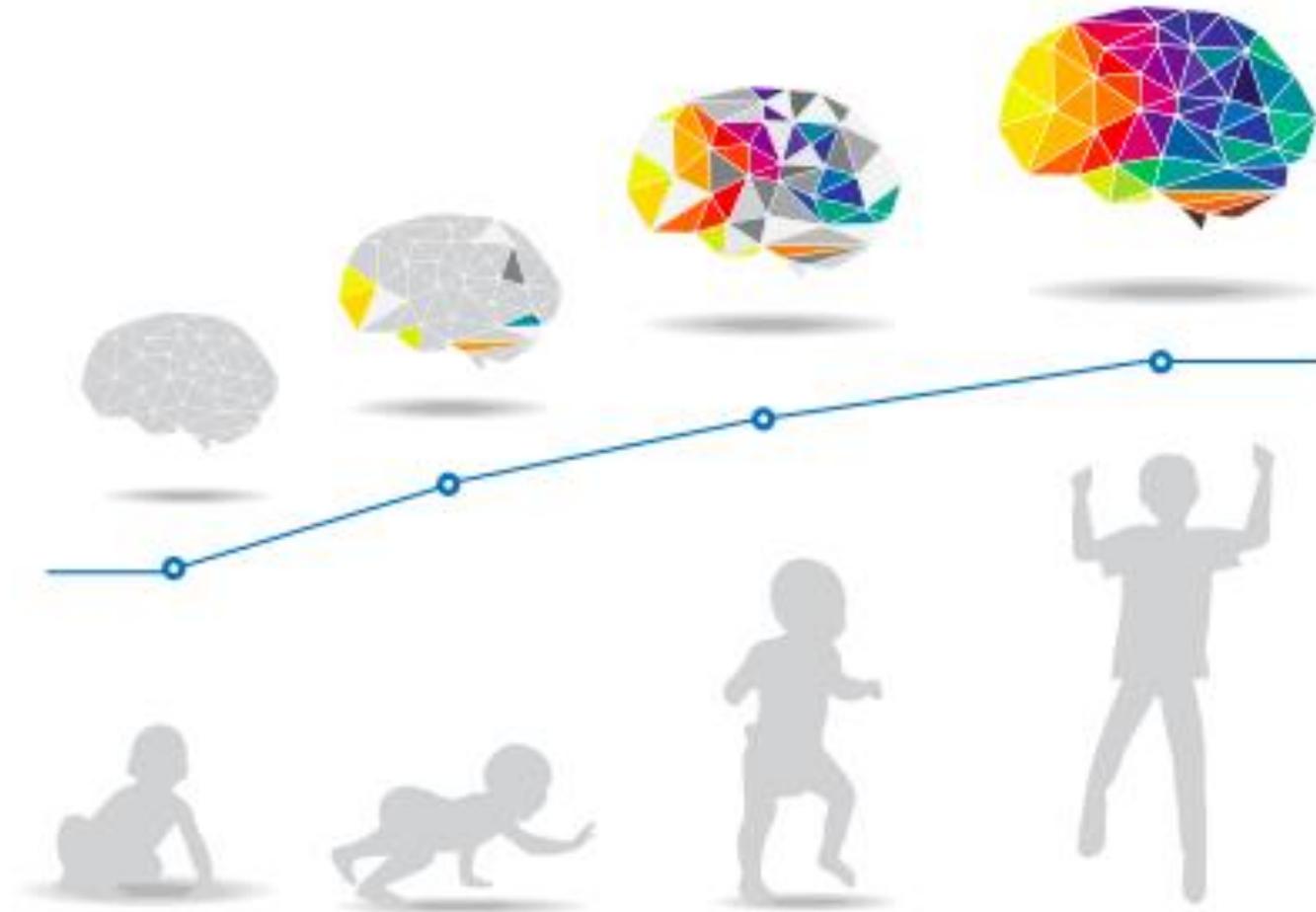
Roles of REM Sleep in Development and Maturation

REM Sleep vs. Exploratory Wakefulness

- Horne (2020) argues decline in sleep duration during early infancy largely due to decreased time spent in REM sleep:
 - Decreased REM sleep time coincides with increased time infant spend “exploring”;
 - Locomotion fosters change within higher visual and motor brain areas; exploration when moving more likely to encounter new complex events which facilitates neuroplasticity;
 - As adults we may not need the last REM cycle (after obtaining > 6 h of sleep) replaced by wakefulness.



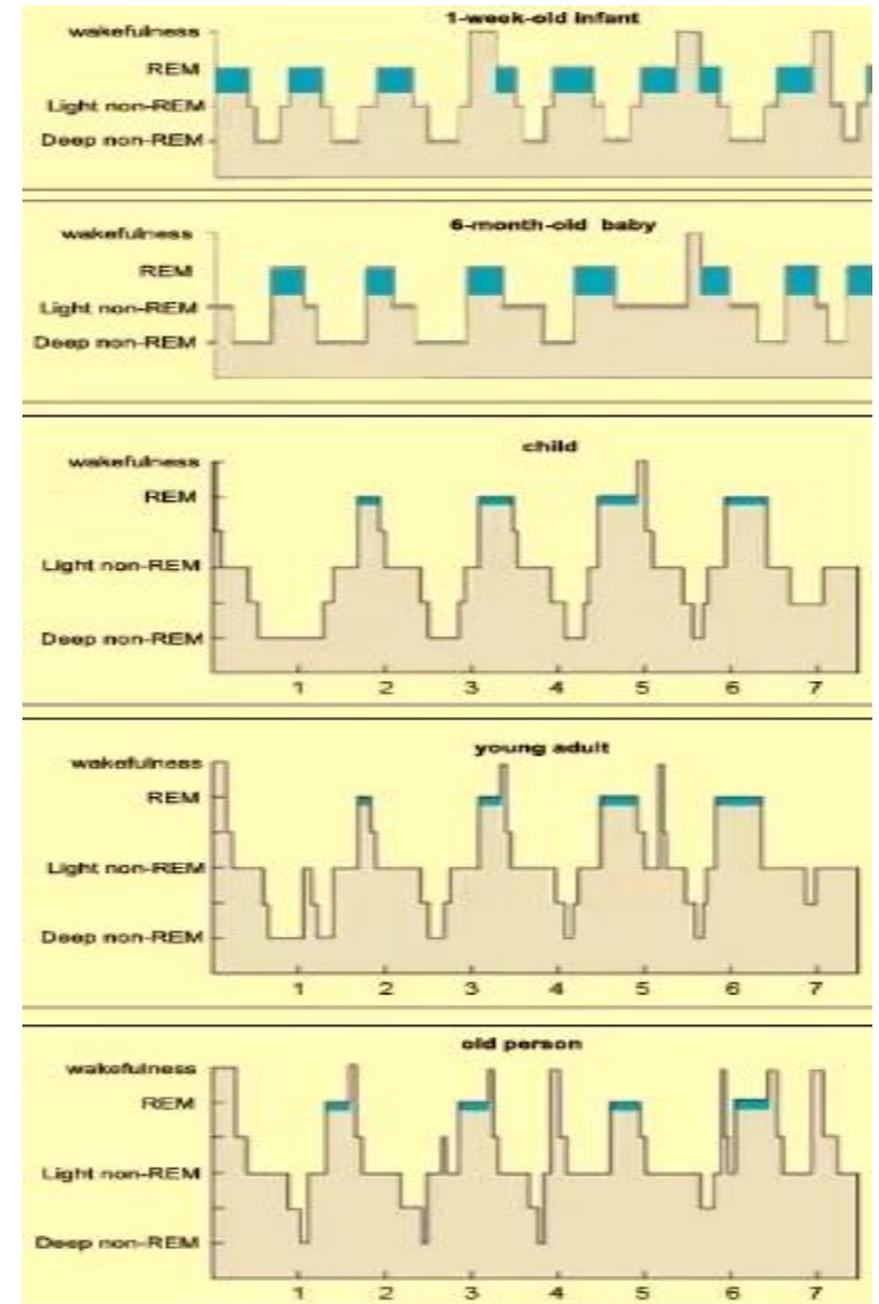
- Anterior cingulate, amygdala and hippocampus active especially during REM sleep and W;
- Immobility during R sleep prevents locomotion;
- Ability to live without last REM cycle may explain little/no REM sleep in foraging elephants and marine mammals and seasonal changes in sleep duration in native peoples.



Maturation of Sleep Architecture Across Childhood

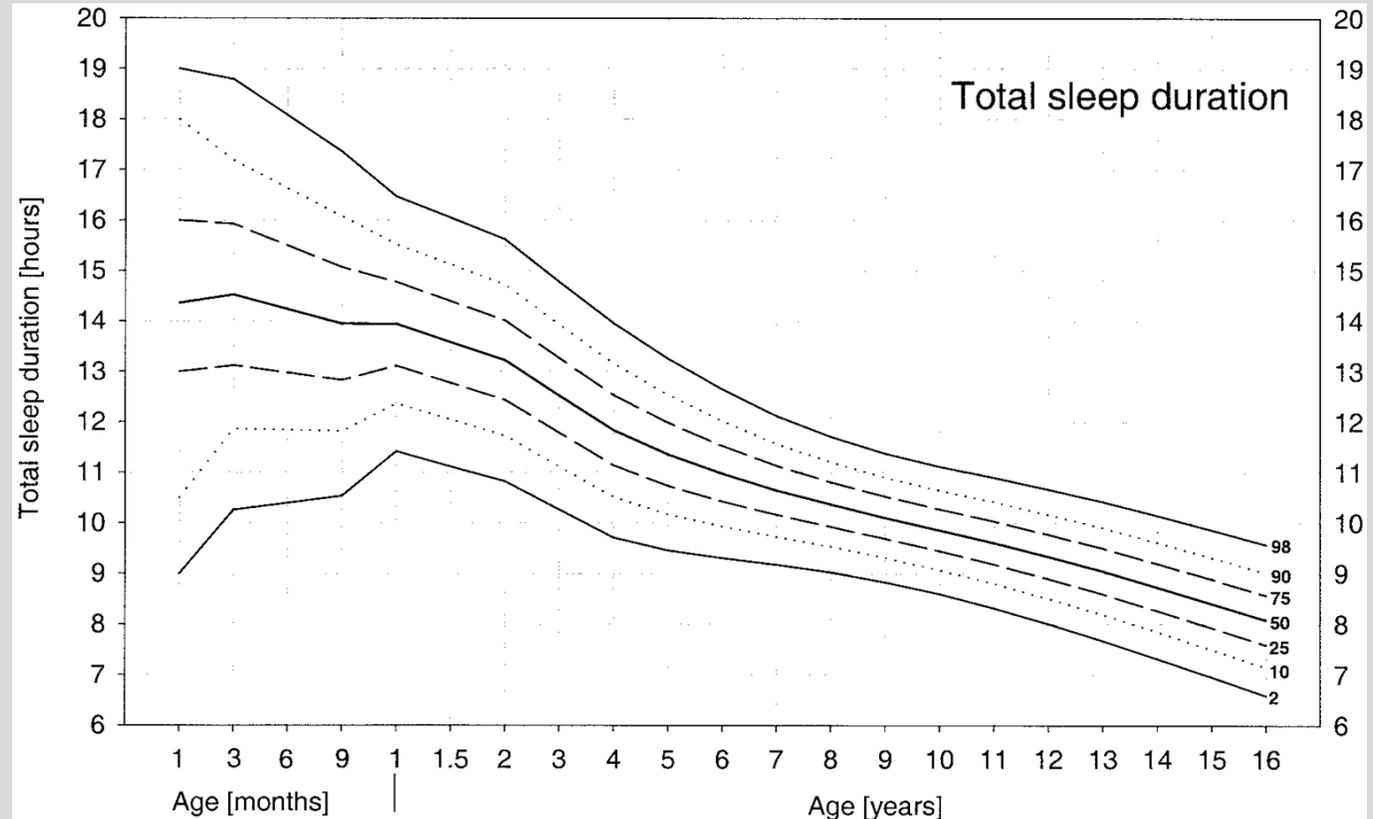
Most Conspicuous Changes in Sleep Architecture Across Infancy to Adolescence

- 1) Decrease in total sleep time;
- 2) Gradual consolidation of sleep at night, wakefulness in day;
- 3) Decrease in intensity of NREM 3 SWA;
- 4) Steady decline in percentage of time spent in REM sleep with compensatory increase in Wakefulness.



Longitudinal Study of How Sleep Duration Changes with Age (n = 493 from birth to age 16)

- Total sleep duration decreased from average 14.2 (\pm 1.9) h at age 6 months to 8.1 \pm 0.8 h at age 16:
- Great variability of sleep duration when younger: 96% of all children slept 10.8-15.6 hours compared to 8-10.7 hours at age 12.
- Most prominent decline in napping occurred between age 1.5 (96%) and 4 (35%).



- Consolidation of nocturnal sleep during first 12 months after birth with a decreasing trend of daytime sleep.

How Sleep Architecture Changes with Age

Sleep characteristic	Change with age
NREM and REM distribution	<ul style="list-style-type: none"> • Evenly distributed during night < age 3 months and sleep polyphasic; • By age 6 months N3 preferentially beginning of night; R later night;
REM latencies	<ul style="list-style-type: none"> • 2/3 of sleep onsets are REM sleep 3 weeks term, 18% age 6 mo; • REM latencies 20-40 min age 3-12 months; 15 ± 20 min age 3 mo; • 70 ± 29 at age 2; sleep latencies average 116 min ages 1-10, 136 min 11-18
Sleep cycle length	<ul style="list-style-type: none"> • Average 50-70 min term infants; 85-115 min ages 8-12, 90-100 min adults
Sleep stage distribution	<ul style="list-style-type: none"> • REM sleep time: 80% preterm; 50% term; 30% age 1; adult range of 20-25% reached age 5; • Ages 5-19 REM sleep time stable, NREM 2 increases, NREM 3 increases. • NREM 3 delta power begins to decrease age 11.5, reduced 60% by age 16



**Maturation of Sleep
Across Adolescence More
About Connectivity than
Synaptic Pruning**

Physiologic and Behavioral Forces Impact Upon Adolescence Sleep Development

Slowed rise of sleep pressure

Lengthening of circadian clock day (phase delay)

Early school start times and homework

Bedtime autonomy

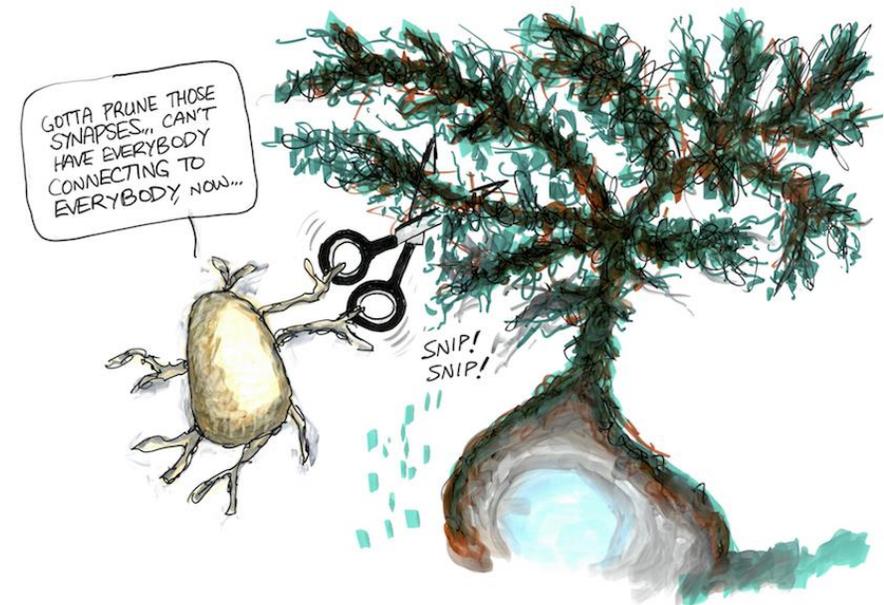
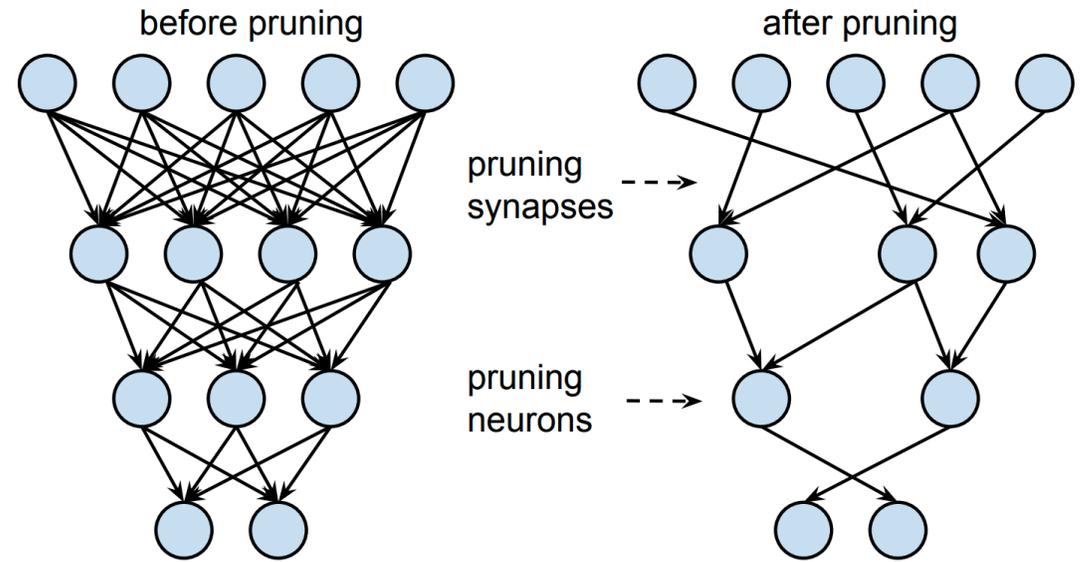
Screen time

- Later bedtimes in teens due to circadian clock which runs a bit longer, a slower rise of process S homeostatic drive, and lots of psychosocial pressures (autonomy, screen time, social networking, academic performance).

Caffeine, sports, social networking, academic pressure, new loves and lost loves, jobs.

Pruning Synapses Optimizes Their Efficiency

- Sleep enhances synaptic strength, efficiency and plasticity;
- Infant brain at birth 100 billion neurons and 2500 synapses per neuron; 15,000 synapses per neuron by age 2-3;
- Synaptic pruning begins age 8 months in visual cortex, age 2 in frontal cortex and usually complete by age 11 removing 40%.



60% Decline in NREM 3 Slow Wave Activity (SWA)

- Absolute values of SWA (EEG power between 0.5 to 4 Hz during NREM sleep):
 - Follow inverted U curve in human development:
 - Progressive increase ages 6-8, peak age 8, progressive decline greatest ages 12-16.5 years (but continues in 2nd and 3rd decade)



Believed to reflect number of cortical neurons that participate and number and strength of synaptic connections between them.

Final Stages of Adolescent Brain Development: Strengthening of White Matter Connections Between Critical Brain Regions

- Synaptic pruning already done (over-emphasized);
- Final developments are increases in brain size (mostly cortical white matter), synaptic strength and brain connectivity,.
- Prefrontal cortex (PFC) and anterior cingulate last to develop; PFC part of brain most vulnerable to sleep loss.
- Late Bedtimes, phase delay and sleep restriction in them can impact final remodeling of cortical circuitry for adult decision-making, cognition and social interaction.



- Sleep restriction in adolescence can alter the developmental trajectory of brain and behavior.

- Crossover within-subjects design using 7 Tesla brain fMRI in 8 healthy adolescents after 4 h vs. 8 h of night sleep:
 - 8-h night increased global and local efficiency of bilateral amygdala and less efficiency in posterior cingulate;
 - 4-h night → Aberrant functional connectivity patterns in key frontal limbic circuitry

Neurophysiological differences in the adolescent brain following a single night of restricted sleep – A 7T fMRI study

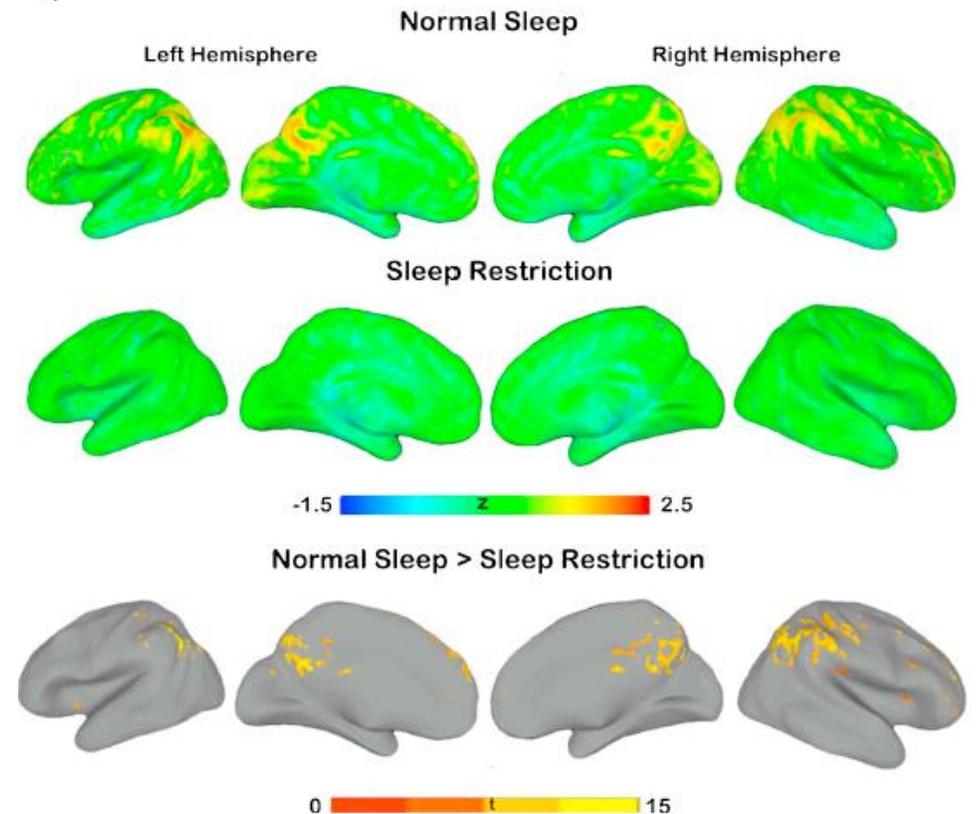
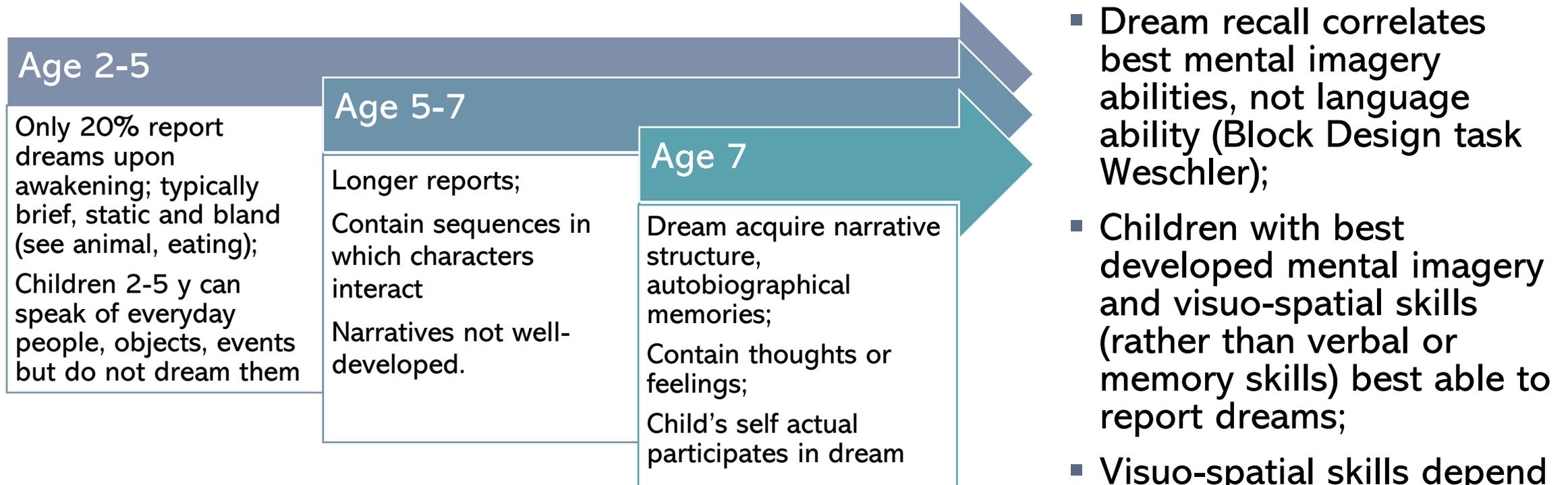


Fig. 3. Regional homogeneity (ReHo) differences between normal sleep and sleep restriction.

Dreaming Develops in Children in Parallel With Visuospatial Skills Develop (and Parietal Lobes Myelinate)



- Children blinded after age 5-7 have visual imagination, and dream with visual imagery throughout life.

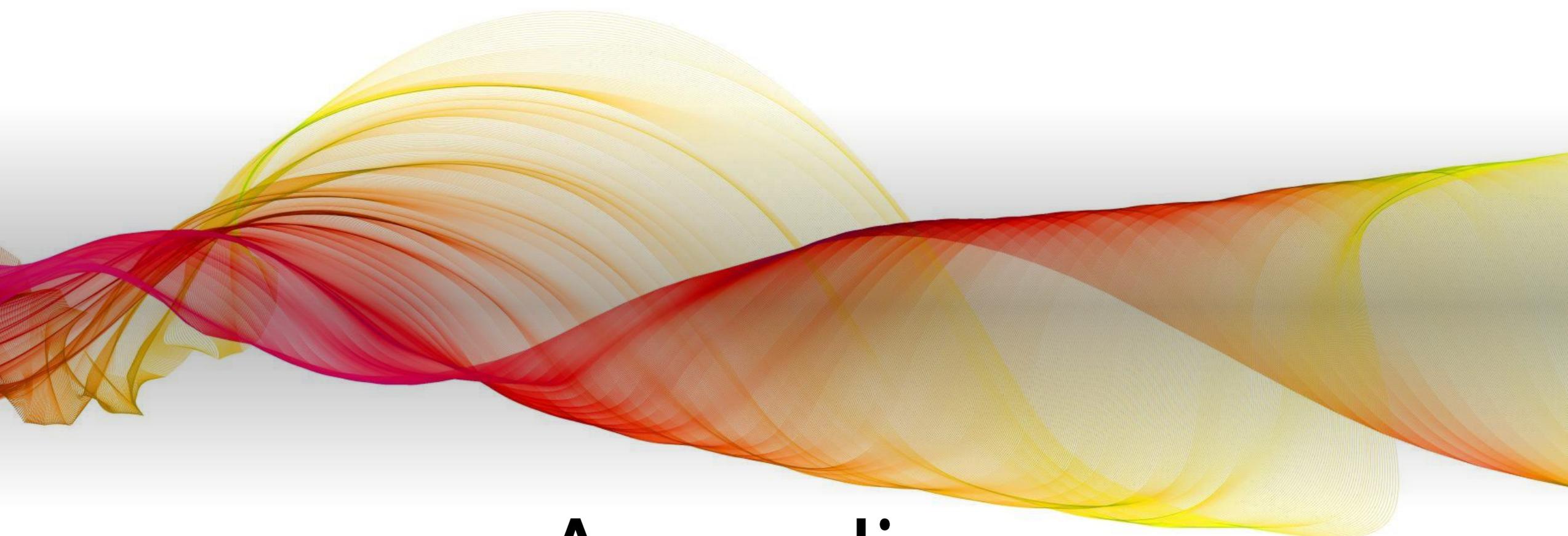
- Dream recall correlates best mental imagery abilities, not language ability (Block Design task Weschler);
- Children with best developed mental imagery and visuo-spatial skills (rather than verbal or memory skills) best able to report dreams;
- Visuo-spatial skills depend on parietal lobes are not fully myelinated till age 7.

Ontogeny of Circadian Rhythms

- Last 10 weeks gestation circadian rhythm of fetus synchronized with mother's rest-activity cycle, heart rate, cortisol, melatonin and body rhythms;
- Newborn infants no rest-activity circadian rhythm before one month of age;
- Age 5-6 weeks (after birth): sleep more concentrated during night and W more prevalent during day;
- Age 12-14 weeks: long nocturnal sleep period, shorter daytime naps and 1-3 hours of W preceding nocturnal sleep period .
- Age 6 months: infants display a circadian pattern with period, amplitude, and phase activity similar to adult.



Thanks for your attention and questions?



Appendix



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REVIEW/MISE AU POINT

Electroencephalography in premature and full-term infants. Developmental features and glossary

Électroencéphalographie du nouveau-né prématuré et à terme. Aspects maturatifs et glossaire

M. André^{a,*}, M.-D. Lamblin^{b,*}, A.M. d'Allest^c, L. Curzi-Dascalova^d,
F. Moussalli-Salefranque^e, S. Nguyen The Tich^f, M.-F. Vecchierini-Blineau^g,
F. Wallois^h, E. Walls-Esquivelⁱ, P. Plouin^e

^a Service de médecine et réanimation néonatales, maternité universitaire, 10, rue Heydenreich, 54042 Nancy, France

^b Service de neurophysiologie clinique, CHRU Roger-Salengro, 59037 Lille cedex, France

^c Explorations fonctionnelles et réanimation néonatale, CHU Antoine-Becière, 157, avenue de Trivaux, 92141 Clamart cedex, France

^d Inserm U676, hôpital Robert-Debré, 48, boulevard Sérurier, 75019 Paris, France

^e Explorations fonctionnelles du système nerveux, CHU Necker-Enfants Malades, 149, rue de Sèvres, 75015 Paris, France

^f Service de neurologie pédiatrique, CHU d'Angers, 4, rue Larrey, 49933 Angers cedex 9, France

^g Centre du sommeil, CHU de l'Hôtel-Dieu, 1, place du Parvis-Notre-Dame, 75181 Paris cedex 04, France

^h Explorations fonctionnelles du système nerveux pédiatrique, CHU d'Amiens-Nord, place Victor-Pauchet, 80054 Amiens, France

ⁱ Unité d'EEG, service de pédiatrie, CHI André-Grégoire, 56, boulevard de la Boissière, 93105 Montreuil-Sous-Bois, France

- In 2010, French published updated atlas for identifying sleep/wake states in premature and term infants using digital techniques.
- Rest-activity cycles first appear 20-21 weeks gestational age (wGA).
- Brain only matures so fast, inside/outside womb, so wGA and postmenstrual age (PMA) time points essentially “interchangeable”.

Sleep in Full-Term Newborns

- 5-6 sleep episodes which last 50-300 minutes then awake 90-180 minutes;
- Bottle-fed sleep longer (3-5 h) than breast-fed (2-3 h);
- Hunger and satiety drive when newborn sleeps and wakes;
- Day/night reversal common first few weeks following term birth;
- Beginning 1st month of life, sleep periods begin to adapt to a day-night cycle and other environmental clues: Increasing infant's daytime activity and dim lights at night can help align sleep with night.

REF: Sadeh A. Maturation of normal sleep patterns from childhood to adolescence. In: Loughlin GM, Carroll JL, Marcus CL (eds). Sleep and Breathing in Children: A Developmental Approach. Marcel Dekker, New York, 2000:63-78.

Strategies to Improve Sleep/Wake Cycling Neonatal Intensive Care Unit

- **Train** staff and parents to differentiate REM sleep from wakefulness;
- **Skin-to-skin contact** (kangaroo care):
 - Infants who received it had better organization of sleep/wake states, increased alertness, less crying;
- **Lights out** 7 pm to 7 am:
 - Infants spend less time W (especially less time crying);
- **Massage therapy:**
 - Improved organization of sleep/wake state days 1 to 5 compared to controls.



- Decrease light and noise;
- Use cue-based oral feeding;
- Minimize hands-on care;
- Promote self-regulatory behavior (sucking, grasping).



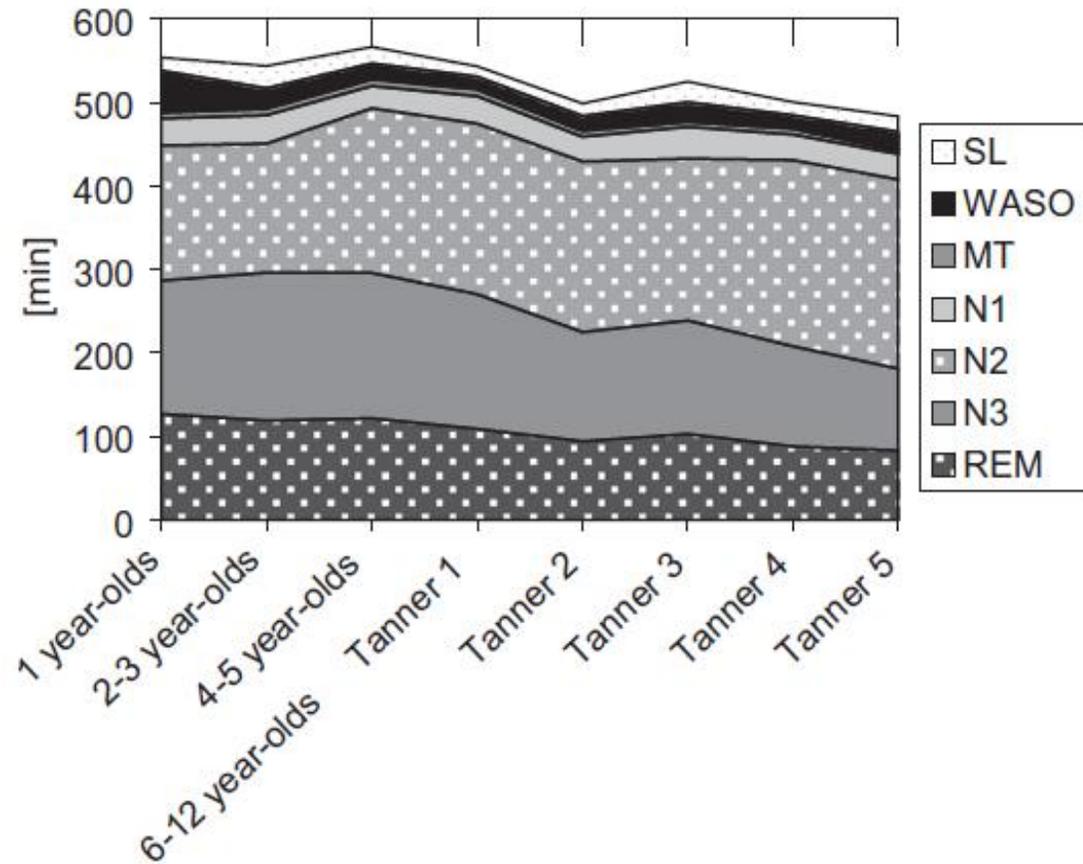
Original Article

Normative values of polysomnographic parameters in childhood and adolescence: Quantitative sleep parameters

Sabine Scholle^{a,*}, Uta Beyer^b, Michael Bernhard^c, Stephan Eichholz^d, Thomas Erler^e, Petra Graneß^f, Barbara Goldmann-Schnalke^g, Katharina Heisch^h, Frank Kirchoffⁱ, Karsten Klementz^j, Gerhard Koch^k, Annmarie Kramer^l, Christoph Schmidlein^m, Barbara Schneiderⁿ, Birgit Walther^o, Alfred Wiater^p, Hans Christoph Scholle^q

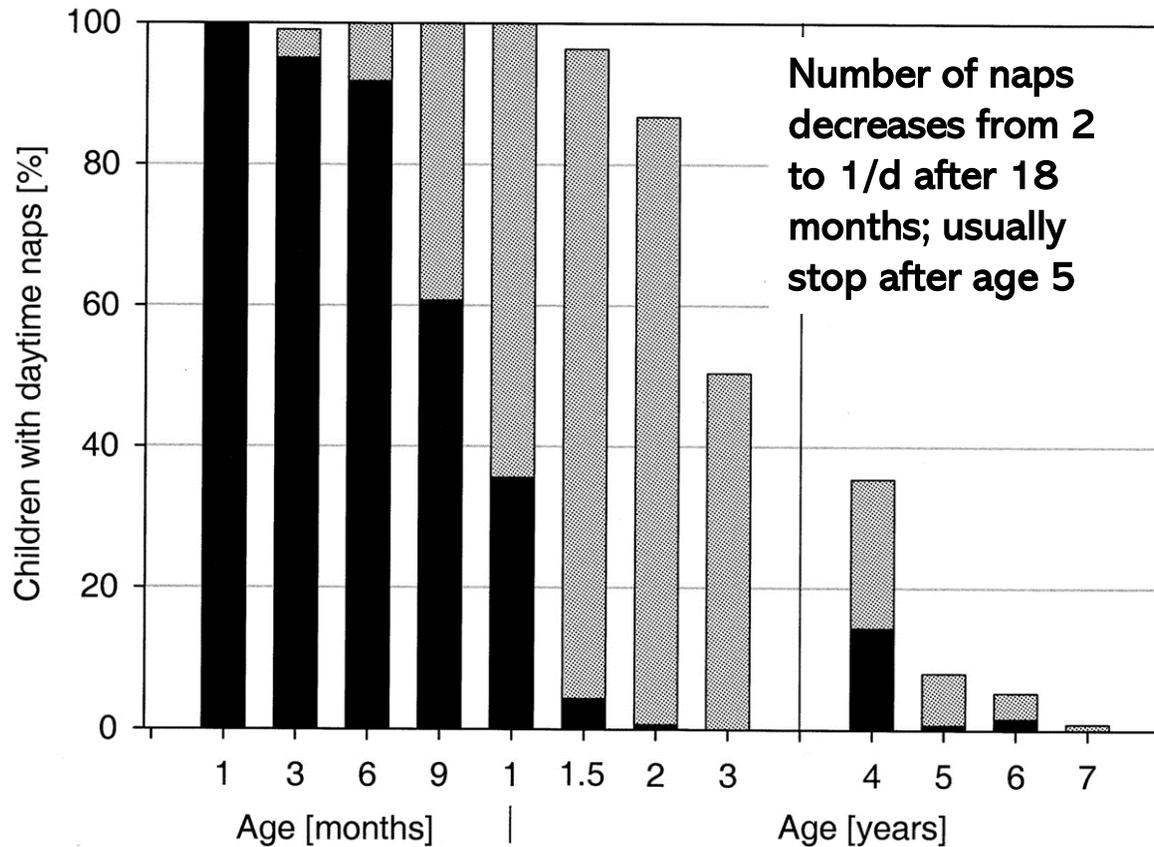
^aZentrum für Schlaf- und Beatmungsmedizin, Robert-Koch-Krankenhaus Anstalt GmbH, Anstalt, Germany

- Scholle et al. (2011) published normative values for first night single PSG parameters ages 1-18 y;
 - REM latency, awakening index, sleep efficiency, mean sleep cycle duration, and number of sleep stage shifts ↑ with age;
 - TST, WASO, movement time, number of sleep cycles, NREM 3 and REM sleep ↓ with age.

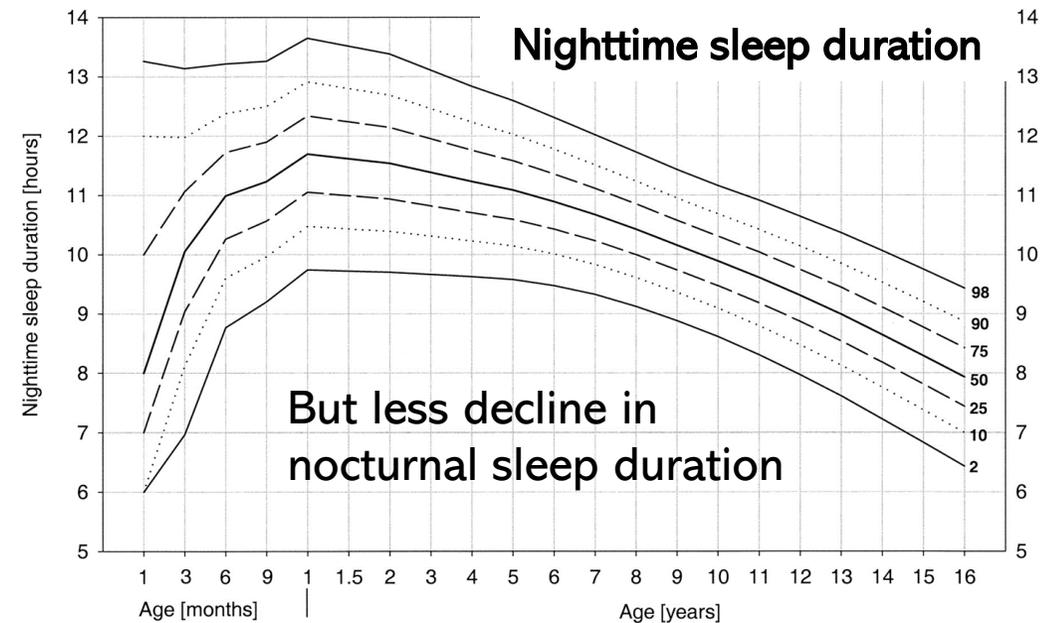
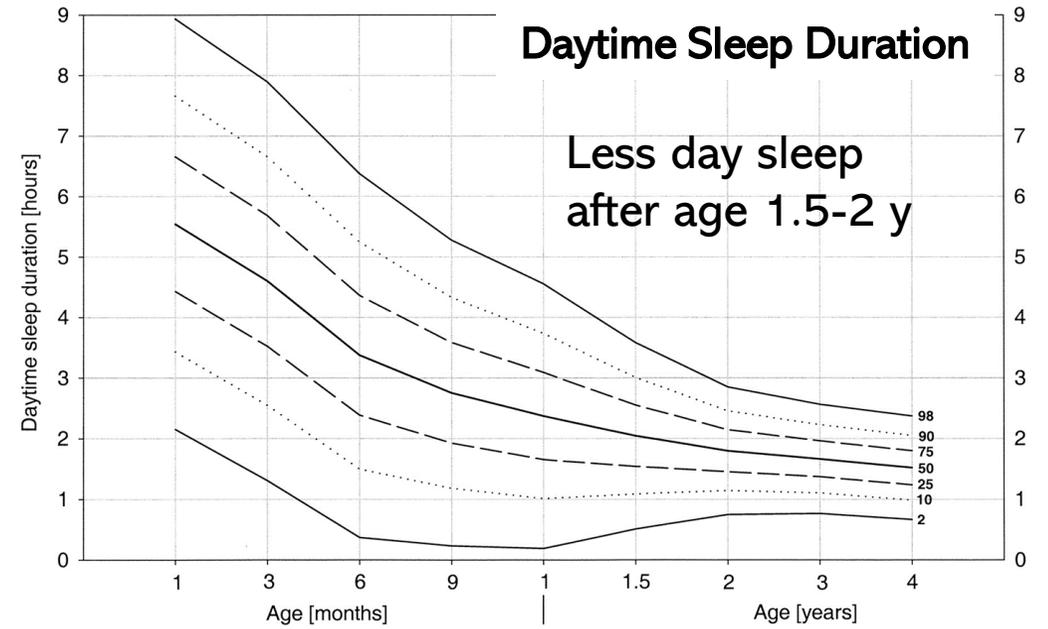


- Cycle duration shorter in youngest children (65 ± 7 min) vs. adolescents (91 ± 11 min/Tanner 5) → number of N-R cycles per night decreases with age;
- REM latency increases ages 3-5 y.

Most Prominent Decline in Napping Occurred Between age 1.5 (96%) and 4 (35%)

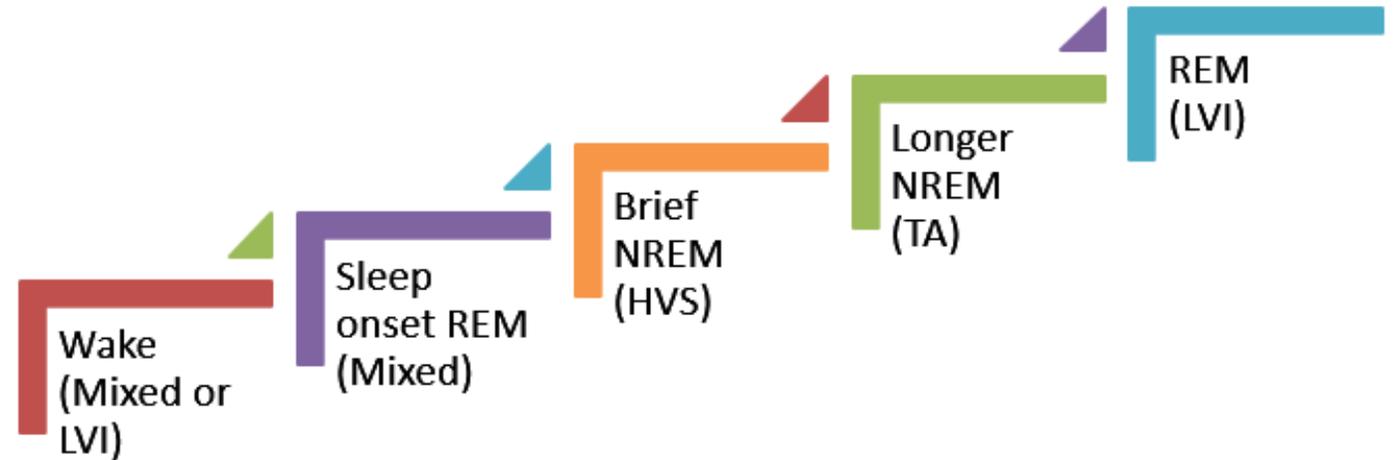


Percentage of children who napped during the first 7 y after birth; For 1 month to 3 y: dark bars \geq 2 naps/d; light bars 1 nap/d; For 4-7 y: dark bars daily napping; light bars occasional naps.



Neonatal Sleep Cycling

- Sleep cycles 50-60 min interrupted by wake for feeding and care every 3-4 h;
- In a cycle of REM-NREM-REM sleep:
 - R sleep lasts 10-45 (mean 25) min;
 - N 20 min;
 - T sleep 10 min.



- Stage N after first period of stage R often begins with HVS for 3-5% of cycle, then a longer period of TA for 25%;
- Stage T (10-15% of TST on good day) most often at sleep onset, stage shifts especially from R to N and following arousals.