Sleep difficulties in children: *Tuberous Sclerosis*

A/ Prof Honey Heussler

Disclosure

- A/Prof Heussler is the principle investigator
- CBD trials- investigator led and sponsored trials for Zynerba and GW Pharma in Epilepsy, Autism, fragile X and 22q11del
- Axial Biotherapeutics- sponsored trials in Autism
- Ovid- sponsored trials in Angelman syndrome
- Anavex- Sponsored trial in Rett syndrome
- ARC funded grant following sleep transitions

Framework

- Impact is clearly important to families and children- impact is wider than just child- often on siblings and parents
- Common presenting difficulties
- An approach to management
- What evidence is there?

What is sleep?

- Opportunity for rest and consolidation:
- **Bodily functions-** immunological, cardiac etc
  - Sleep deficiency is associated with heart disease, high blood pressure, stroke, obesity
  - It affects how your body reacts to insulin and appetite
- **Brain modulation:** memory, architecture,
  - Setting down of pathways to learn and remember- executive function and prefrontal cortex
  - Emotionality – mood and lability

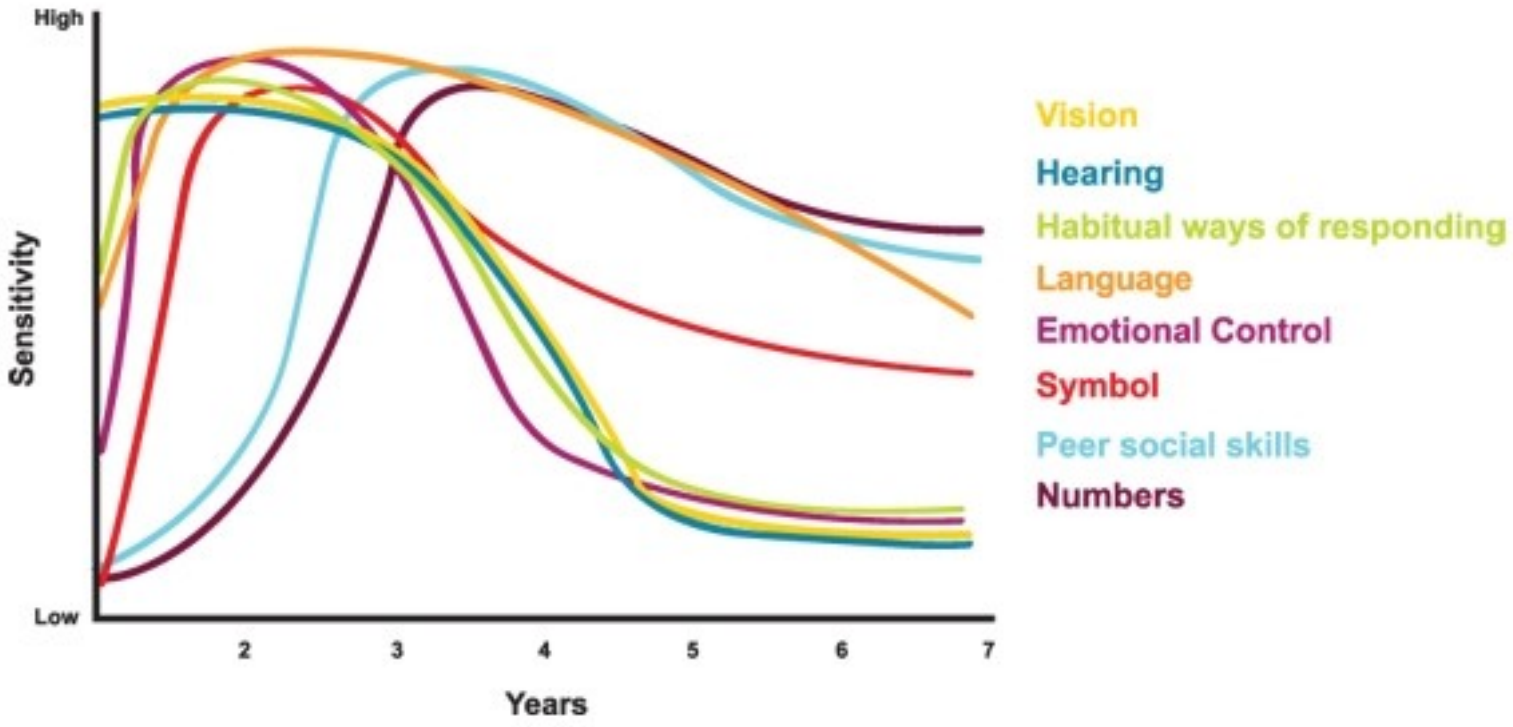
Society- Daytime function in terms of driving and attention critical tasks

Background

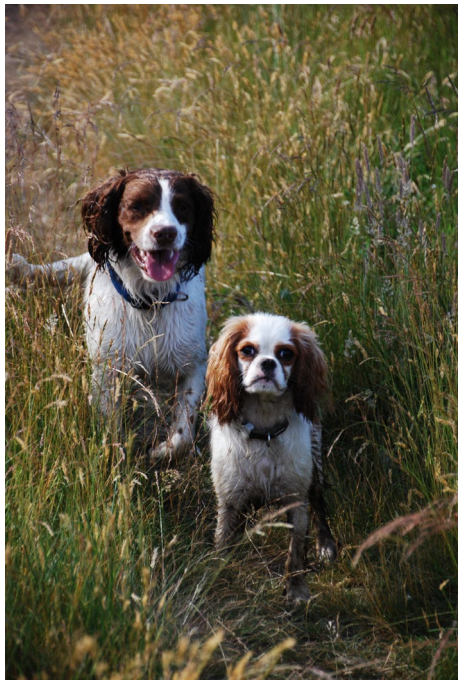
- High proportion of individuals with disabilities have sleep difficulties (80%)at all ages.
- Assessment is difficult and complicated by:
  - Anxiety
  - Aggression
  - Mood
  - Sensory differences
  - Cognitive understanding
  - Communication
  - Difficulty in assessing for medical conditions
- Treatment is also difficult for the same reasons
- Is the effect of hypoxaemia and sleep fragmentation the same for Children with Developmental disability vs TD?
- Remember family emotions and dynamics and management abilities to function

When this starts in infancy?

- Critical periods of child development- relates to stages of brain growth



Developmental trajectories



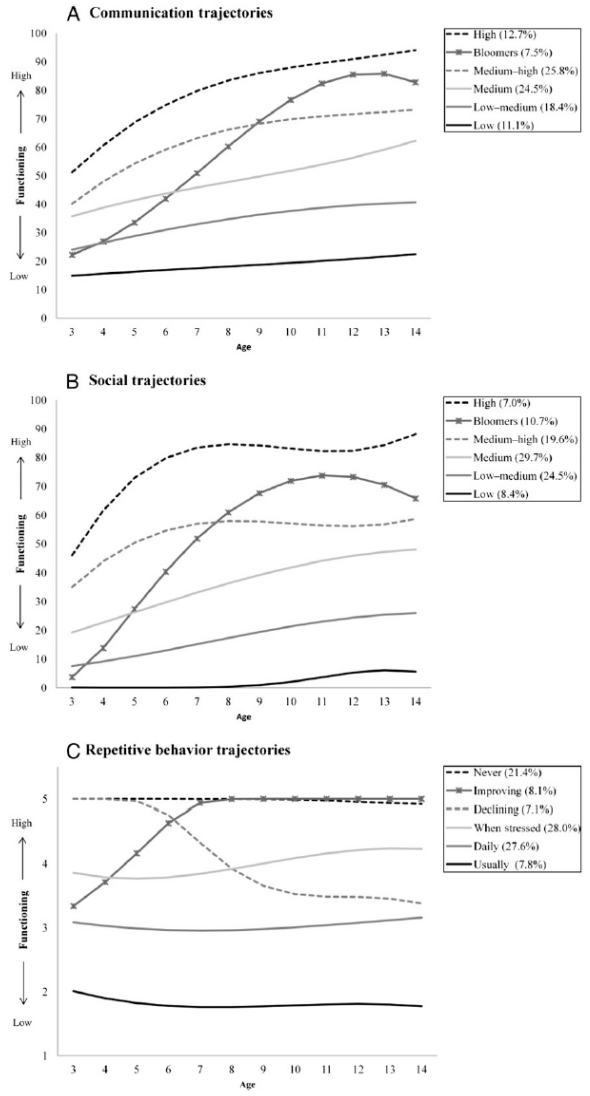


FIGURE 1
(A) Modeled communication, (B) social, and (C) repetitive behavior symptom trajectories based on CDER scores by age.

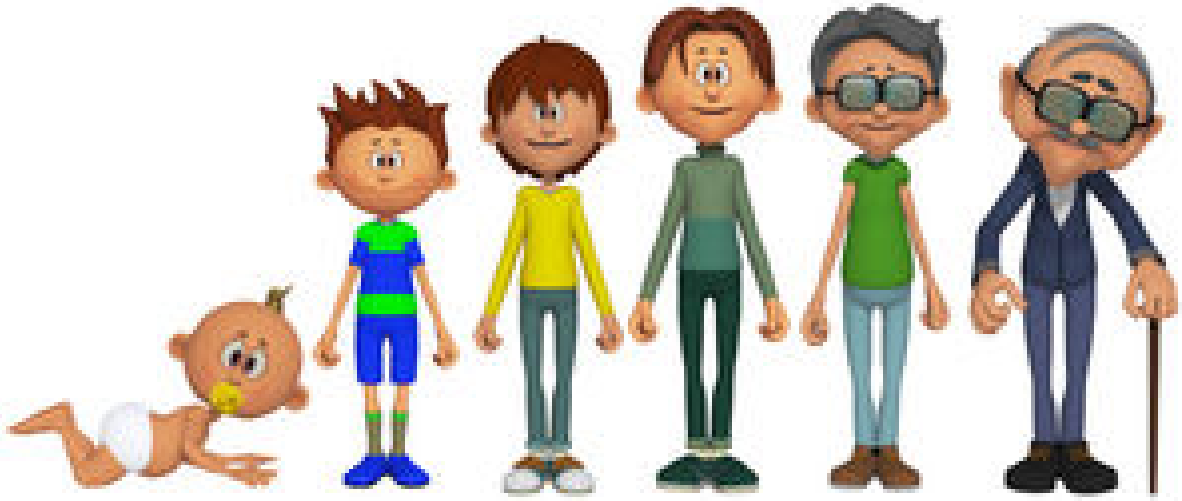
Fountain et al Pediatrics 2012

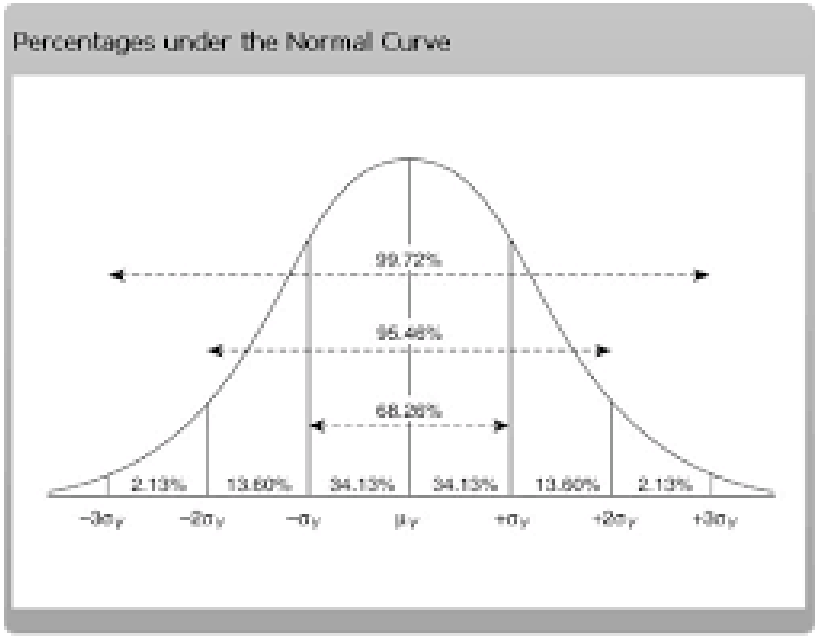
Sleep Disorders

Restriction vs interruption

- **Mood** → Increased irritability, decreased positive mood, poor affect modulation
- **Behavioral manifestations** → Increased impulsivity, hyperactivity, mood lability, inattentiveness
- **Neurocognitive performance** → Decreased cognitive flexibility, impaired motor skills, decreased attention
- **Other Effects** → Deleterious effect on cardiovascular, immune and metabolic systems; increased accidental injuries; affect family

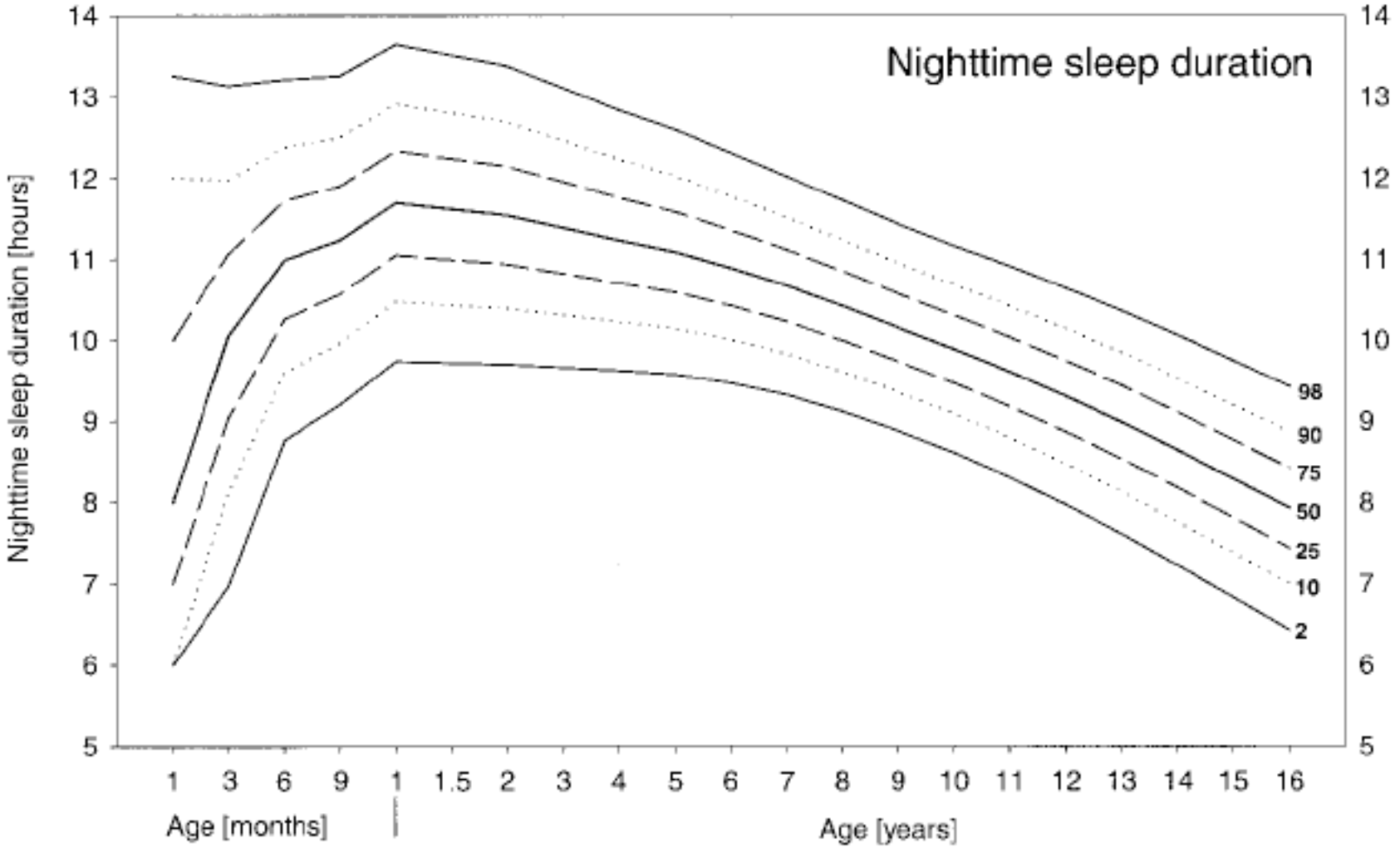
So- what is Normal?





Normal sleep development

How sleep changes with age



Iglowstein et al. (2003)

Normal sleep development

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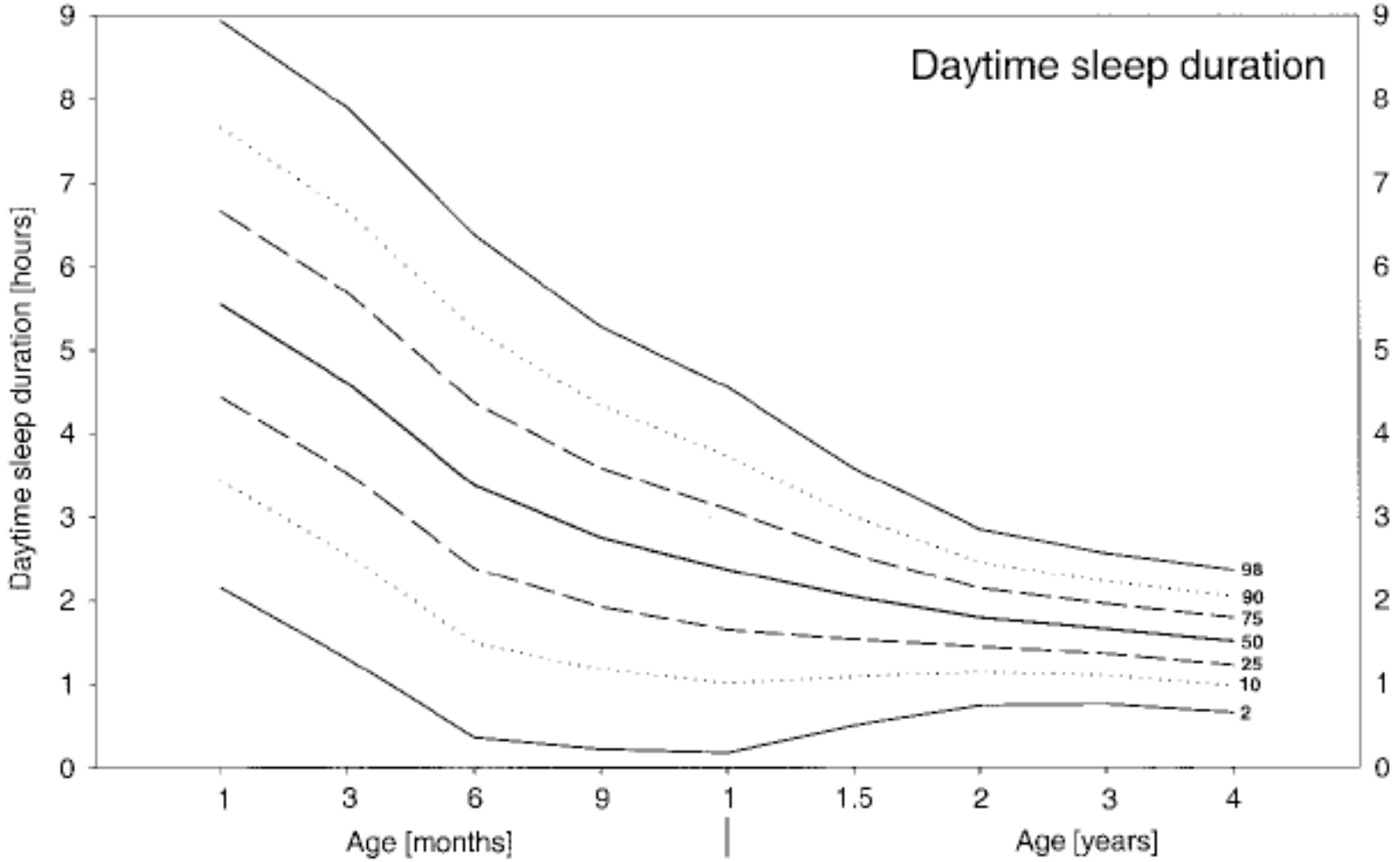


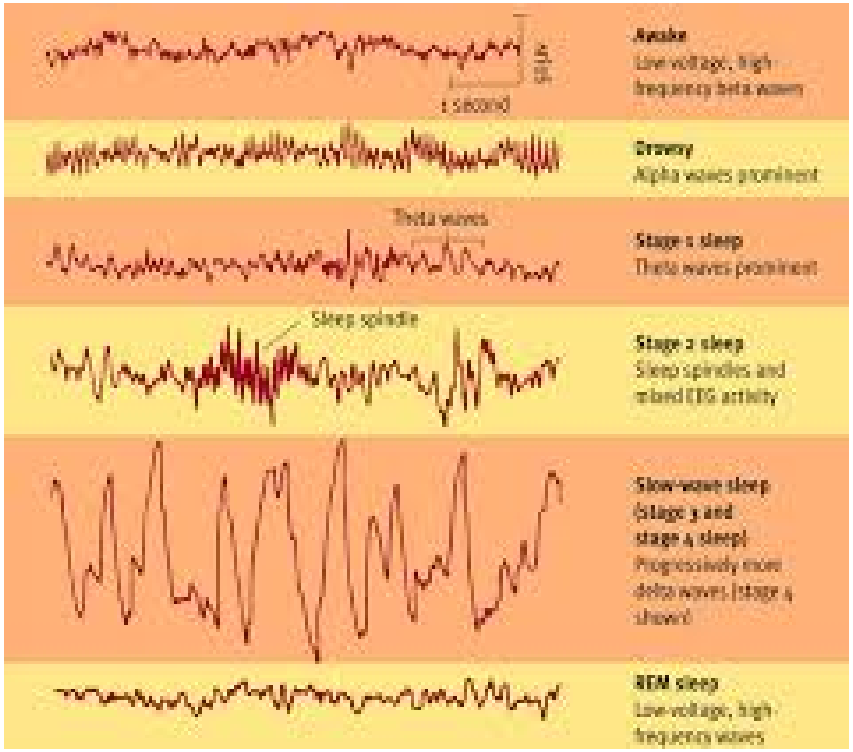
Iglowstein et al. (2003)

Sleep matures with Age

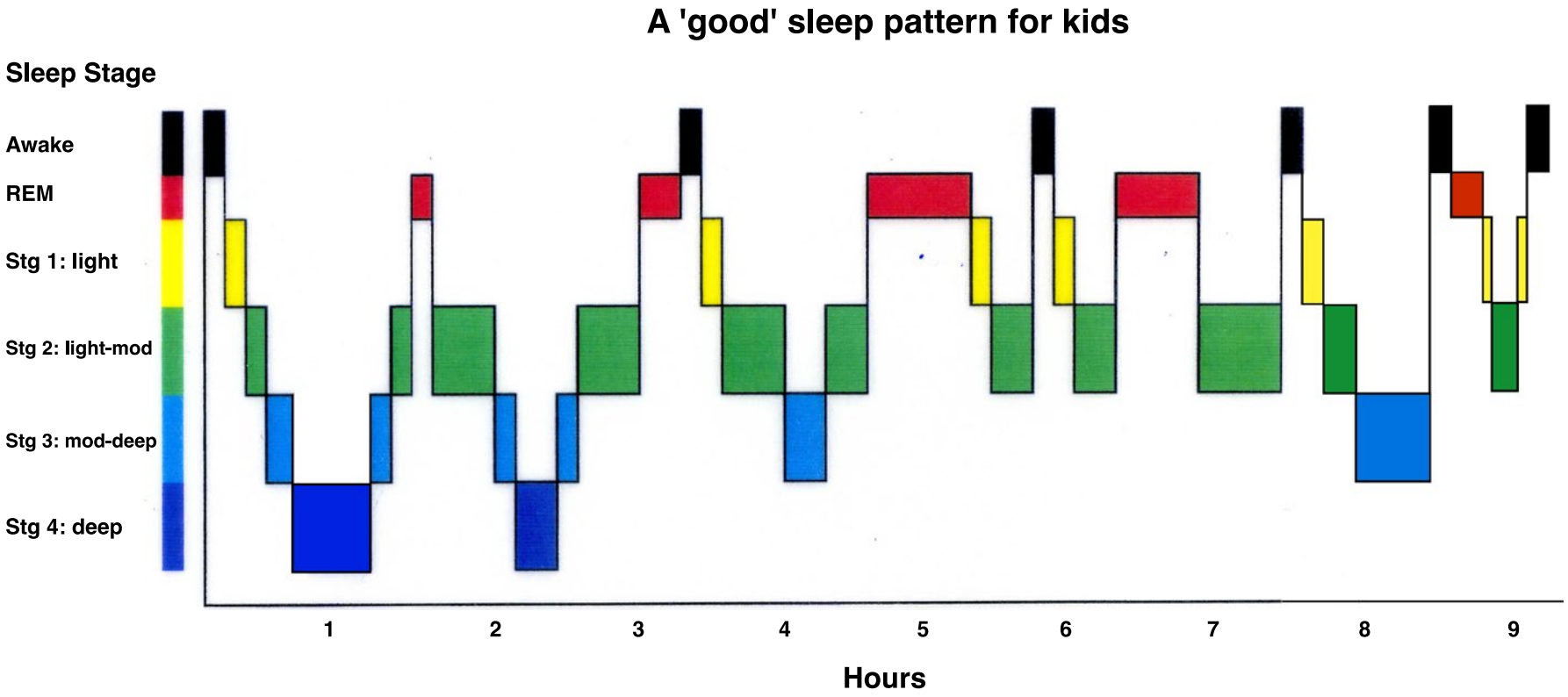
- Likely related to brain maturation
- We see changes in EEG development particularly in the first 2 years
- Various studies have identified development of sleep spindles in sleep to be related to speech and language development
- Maturity of EEG in sleep has been related to general developmental outcomes at 2 years

- It is normal for infantile patterns of breathing and EEG to persist in children with developmental delays and delayed myelination
- In first 3 months periods of mild desaturation are within normal limits in REM with central events. Periodic breathing is not uncomon

Sleep stages are defined by EEG



Typical sleep pattern



Autism and Sleep

- Prevalence- up to 80% of children have a sleep problem in Autistic population
- 50% of ADHD
- Variety of disorders

Normal sleep drivers

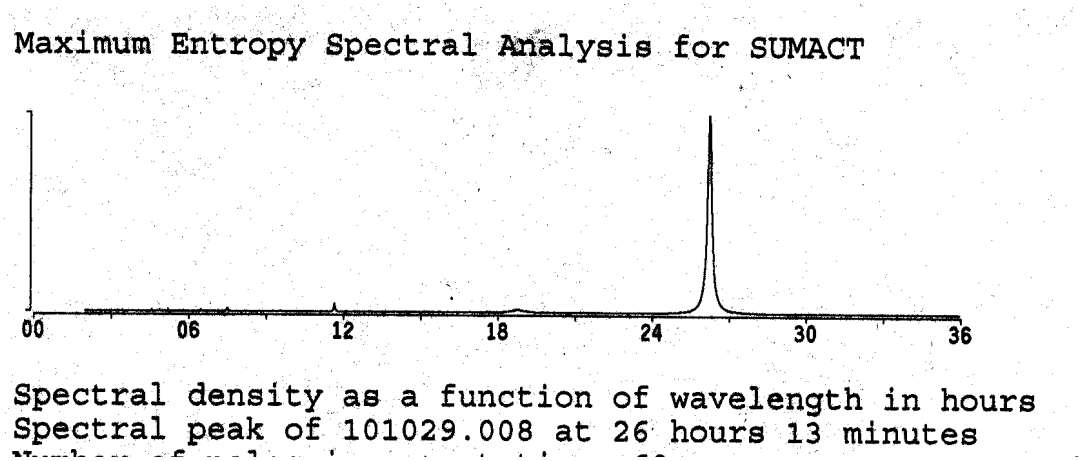
Circadian scheduling- daily cycle

Sleep pressure- time since last had deep sleep ie the longer you stay awake the tireder you will feel

Ultradian rhythm- approx. 90 minute cycle of feeling more and less alert

Circadian scheduling

- Circa -around and dies- day
- Supra chiasmatic nucleus of the anterior hypothalamus
- Small nucleus in which experimental and pathological lesions can block the ability to express circadian rhythms.
- Entrainment factors important in maintaining cycle



Circadian Cycle

Circadian cycle:
Genetic control
Light controlling melatonin release
Behavioural entrainment
Ultradian cycles

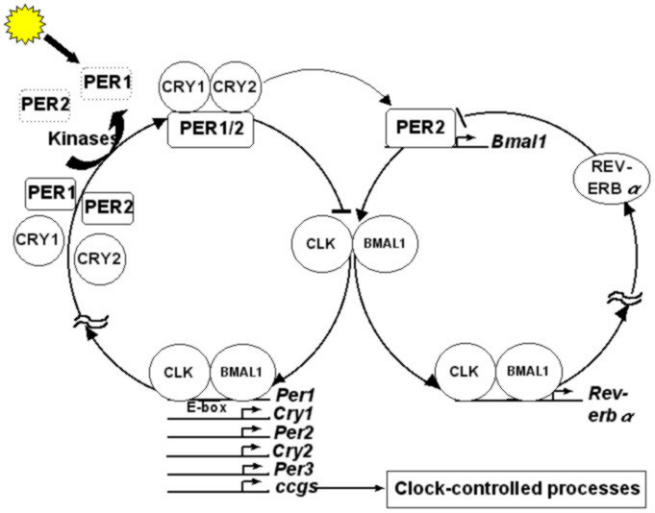
Hormonal + others:
Cortisol
Growth hormone
Immune function
Pubertal and sex hormones

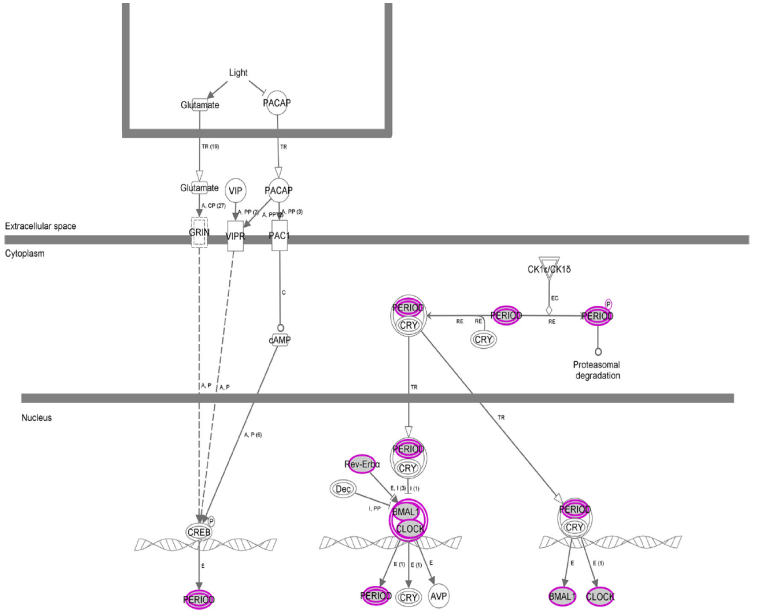
It is hard to know how this sits with an atypical brain
In some dysregulated cycles
Possibly longer cycles
Visually impaired

Regulators

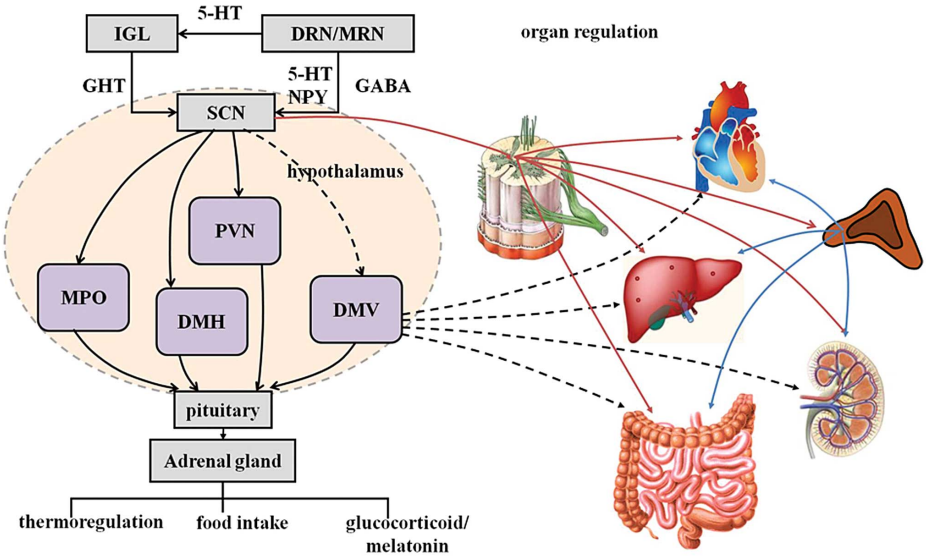
- Light
- Behavioural entrainment
- Food
- Temperature
- Genetics
- Age
- Seizures and EEG

Genetics of sleep





. Network of circadian core clock genes. Network of the core clock genes identified as circadian oscillating genes in our microarray analysis ghted in pink). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



J. Renaud et al. / Neuroscience 308 (2015)

Sleep in general

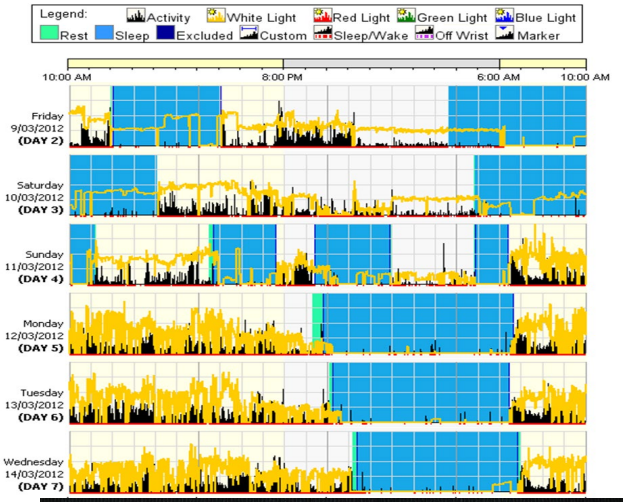
- Difficulty in initiating sleep
- Difficulty in maintaining sleep
- Disorders of hypersomnolence
- Medical issues
  - Epilepsy
  - Abnormal EEGs
  - Asthma
  - Ezcema
- Differences in parental interactions
- High risk of sleep disordered breathing
  - OSA
  - Obesity hypoventilation
  - Central dysregulation

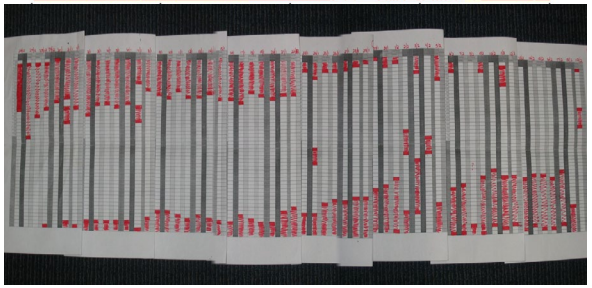
Susceptable groups

- ADHD
- Autism
- Developmentally delayed
  - Visually impaired- e.g. Septo- optic dysplasia
  - Physically impaired e.g. Cerebral palsy/ Myotonic/ neuromuscular
  - Seizures
  - Behaviourally difficult
- Special circumstances- multiple syndromes
  - Smith Magenis
  - Rett
  - Angelman's
  - CHARGE
  - Down syndrome
  - TSC

Generic Tips

- Good detailed history
  - Consider medical causes of sleep disruption – not always evident
  - Epilepsy
  - Exczema
  - Gastro oesophageal reflux **
- Parental Questionnaire
- Observation- YEAH.. the age of the smart phone
- Actigraphy
- Portable assessments ??
- In hospital observation…
- Oximetry
- PSG-
- MSLTs- almost impossible (need a cognitive level of at least 8 years of age)
- Think about behavioural and developmental profile





Sleep in Tuberous sclerosis

Sleep problems in TSC associated with **current Epilepsy** and high levels of behaviorual disturbance but pervasive developmental delays and parental stress were not

Autism/ sensory issues/ dysregulation

Study done several years ago demonstrated that there was reduced total sleep time, more difficulty in transitioning between sleep stages, more wakings, more time in light sleep and less in stage 2 and less in REM sleep with a longer time to get into REM and that this was much worse when seizures were active. *Bruni et al 1994*

Sleep alterations were more obvious when there was a large bilateral tuber load in frontal and temporal areas of the brain as opposed to cortical and posterior *Hunt, Stores et al 1994*

MELATONIN improved total sleep time (30 mins or so) but no change in wake after going to sleep *FJK O' Callaghan et al 1999*

Using a sleep questionnaire 1.4% had a total score of sleep disturbance and about 45 had problems in one area as opposed to total score in control groups of around 4% and 20%. Sleep disorders are more frequent in TSC than in the general population and correlate with behavior especially hyperactivity and dysregulation *Zambrelli et al 2021*

Sleep hygiene

- Establishment of good sleep habits
  - Ability to calm
  - Feel safe
  - Habits-sleep entrainment
    - Day different to night
      - Light
      - Activity
      - Noise
    - Routine
    - Consistent associations with sleep
    - Calming activities

Reasonable evidence that sleep hygiene alone will improve sleep initiation in children with ADHD/ ASD by as much as 30%

Understanding

Limit setting

1. Child has difficulty falling/staying asleep
2. Child stalls/refuses to go to bed at appropriate bedtime or return to bed during the night
3. Caregiver shows insufficient/inappropriate limit setting – pattern often ticky for kids with disabilities or illness

Sleep association disorders

1. Falling asleep is an extended process requiring special conditions
2. Sleep-onset associations are problematic/demanding
3. Special conditions not present, sleep onset delayed/sleep disrupted
4. Night-time awakenings require caregiver intervention

Behavioural Insomnia of Childhood (Sleep-onset association)

Very similar to Separation Anxiety Disorder (separation from caregiver at night), though OK to go to school, etc.

Nighttime fears are prevalent (up to 73%) and peak in middle childhood (Muris et al., 2000)

Include fears of:

- Dark, Noises, Shadows, Intruders
- Threat to self/family, Monsters, Insects
- Bad dreams/nightmares
- Worries about the day's events

(Gordon & King, 2002; Gordon et al., 2007)

Children may have difficulty on sleep-overs/school camps.

These need exploring in the populations with developmental disability or autism as they may occur at a later chronological age

Behavioural Insomnia of Childhood - Treatment

CBT for sleep-onset association types *(Paine & Gradisar, 2011)*

Cognitive restructuring	(eg, addressing nighttime fears)
Sleep hygiene	(eg, reducing stimulating activities)
Bedtime fading	(eg, gradually decreasing time in bed)
Graduated Extinction	(eg, separating from parents)

Findings

Improvements in sleep latency, wake after sleep onset, and sleep efficiency (diary-reported; large effects [~0.80-1.10]). No change in total sleep time (effect = 0.01).

Improvements in frequency and severity of children's sleep-associations. No change in bedtime resistance.

Behavioural Insomnia of Childhood – Treatment

Bedtime fading (SOL> 30 up 15 mins later if< 15 mins to bed 15 mins earlier)

- (eg, gradually decreasing time in bed; later bedtime)

Sleep hygiene

- (eg, reducing stimulating nighttime activities; dim light conditions)

Positive bedroom associations

- (eg, quiet activities with parent in bedroom, then alone in bedroom, then alone in bed)

Positive reinforcement for positive bedtime behaviours

- (eg, praise, tangible rewards [eg, activities])

Parent training

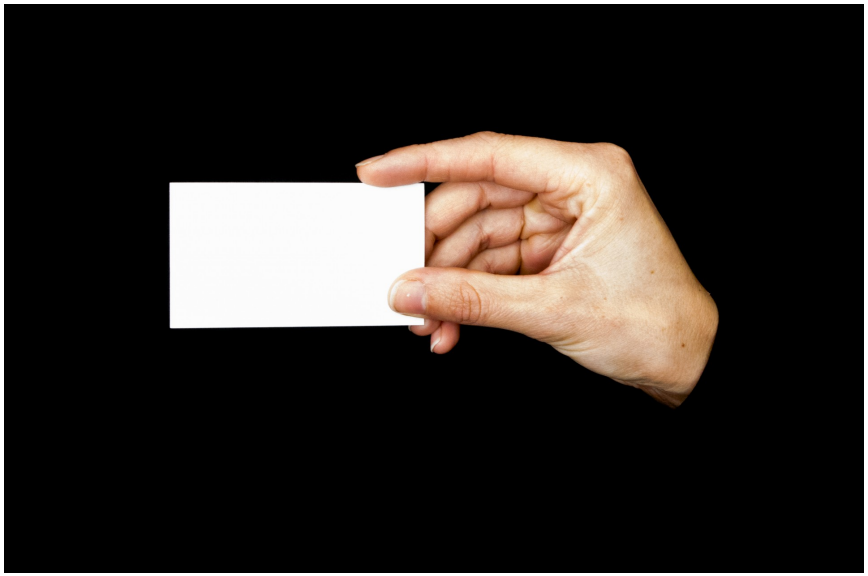
- (eg, providing clear, simple instructions; gently, physically assisting kids to bedroom)

Camping out techniques

1. Camping out techniques can be used
2. Parent sleeps in room with child and gradually withdraws
3. Can use this coupled with coming and going- going to check on something for a few seconds and just asking child to lie quietly
4. Rewards should be for feasible things
5. This child unlikely to get to sleep because his phase has shifted and thus should be rewarded for lying quietly

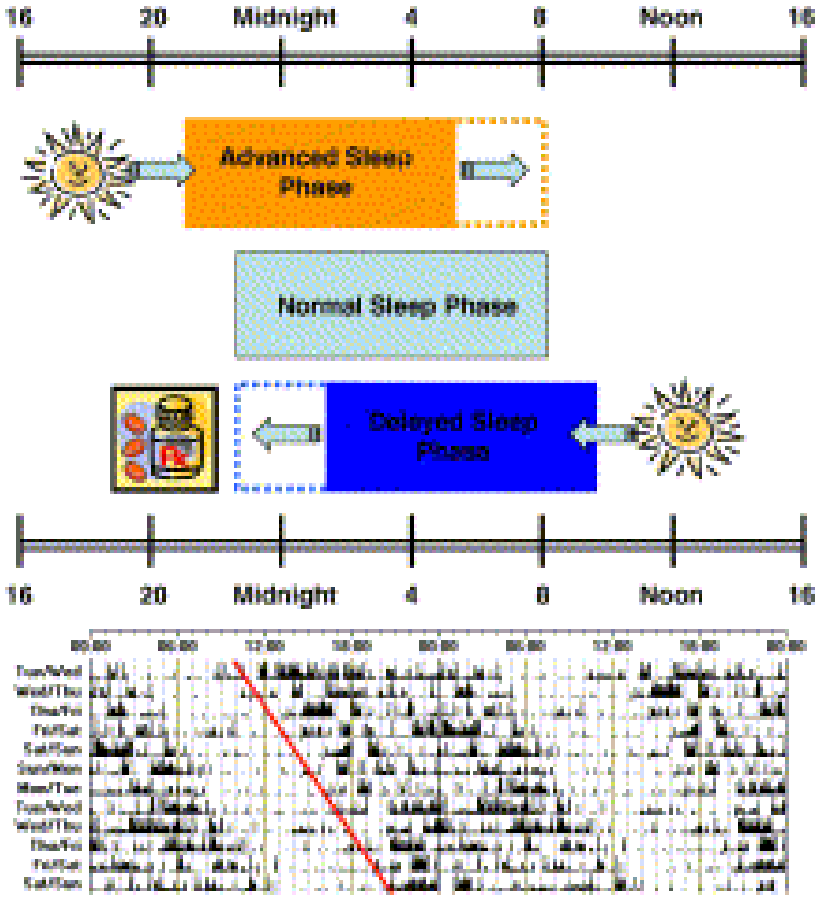
Other techniques

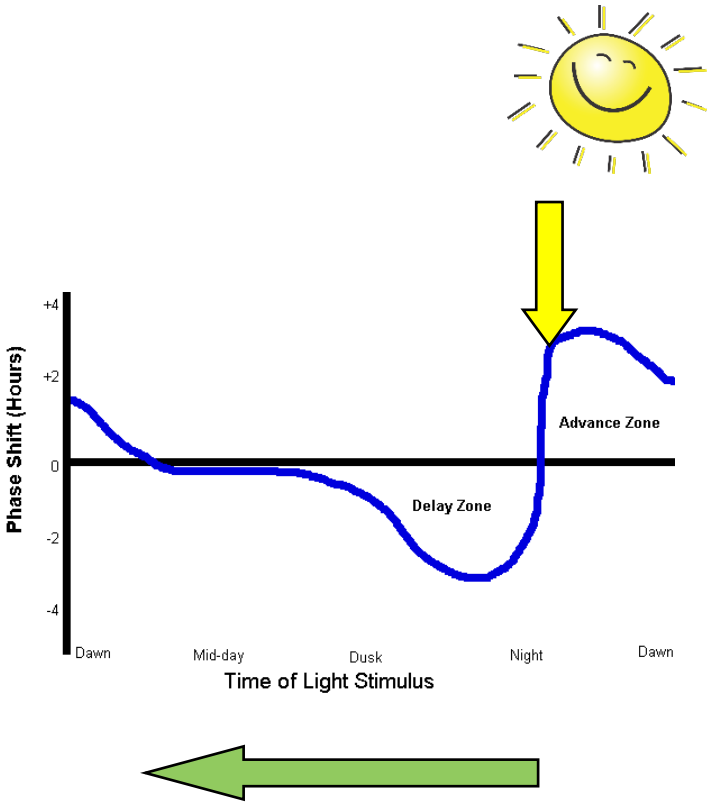
- Get out of bed card



- Checking method

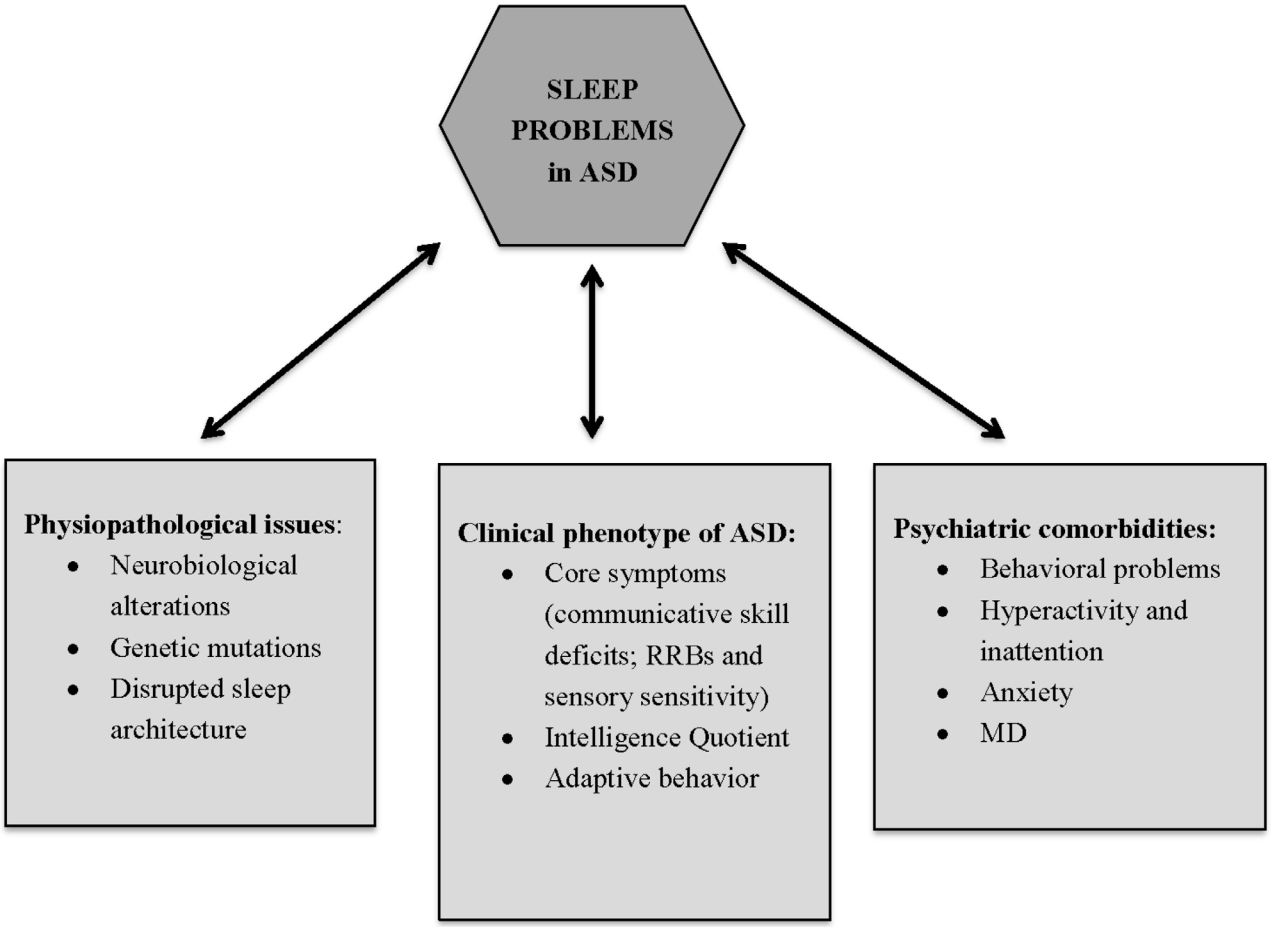
How to use light





Barion A, Zee P-Sleep Medicine 8(6) 2007

Sleep problems



Mazzone, L.; Postorino, V.; Siracusano, M.; Riccioni, A.; Curatolo, P. The Relationship between Sleep Problems, Neurobiological Alterations, Core Symptoms of Autism Spectrum Disorder, and Psychiatric Comorbidities. J. Clin. Med. ***2018****, 7, 102.*

Sleep Problems

- Predisposing factors to problematic sleep
- Medical concerns- Seizures, Eczema, Asthma etc
- Disorders of sleep related breathing-Obstructive sleep apnoea

- Sleep study

Autism and sleep

- Disorders of Initiating and Maintaining Sleep
  - Limit setting
  - Anxiety – threat
  - Reviewing- rigidity
  - Sensory- hypersensitivity to touch 24% of variance
  - Sleep association

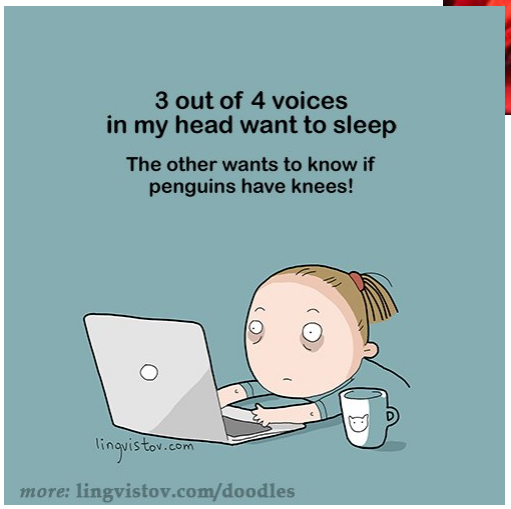
Sleep

- What to do about it?
- Sleep hygiene works in at least 20-30%
  - Dark
  - Light and bright in am
  - Quiet
  - Bed and self settle in beginning of night like later in night
  - Routine
  - Bed for sleeping
  - Calming activities (might look different in this population)
- Behavioural strategies
- Are no different to general population?
- BUT with modifications..

Strategies

- Limit setting- good routines clear communication, social stories
- Rewards for staying in bed- appropriate
- Calming activities preferably with low light- dim screens
- Work through some of sensory things – e.g. touch
- Teach to stay in bed

- Camping out
- Checking in & out
- Out of bed card



Why is it so?

- Melatonin
- ¼ have different genes that make us high or low metabolisers of melatonin
- Some recent interest in maternal melatonin and effect on fetus
- Melatonin follows the circadian rhythm
- If given is at very high doses so if it works for a short time then it doesn't may need to stop and restart
- REMEMBER bright light

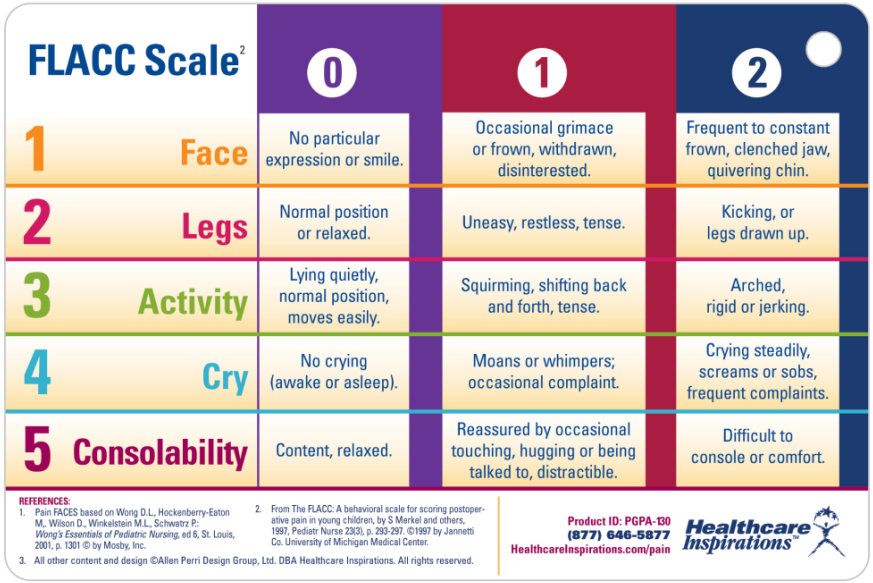
in morning and dim light in ev

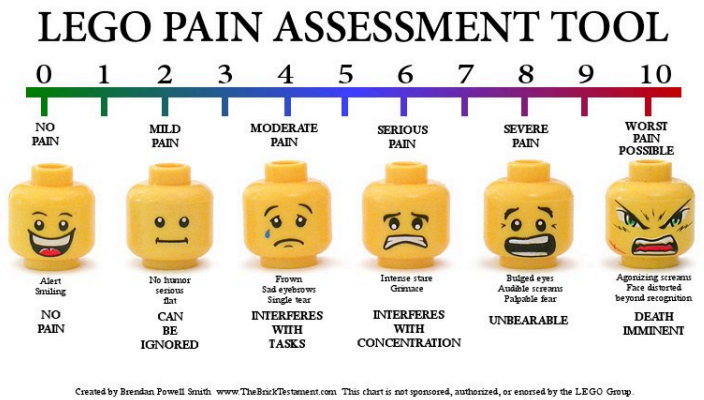
Pain

- Prevalence.. Unknown but in some developmental disorders with ASD up to 80% of behavioural presentations with pain
- **VARIES in all people** as to how people interpret Pain
- **Change** in demeanour
- More or less Irritable
- Quieter or louder
- Moving more or less
- Wearing clothes differently
- Letting you touch in some places but not others
- Eating patterns changing
- Sleep changing

How do we know

- They tell us
- Pain scales
- Observation of protection of limb etc
- Facial features- FLACC scale



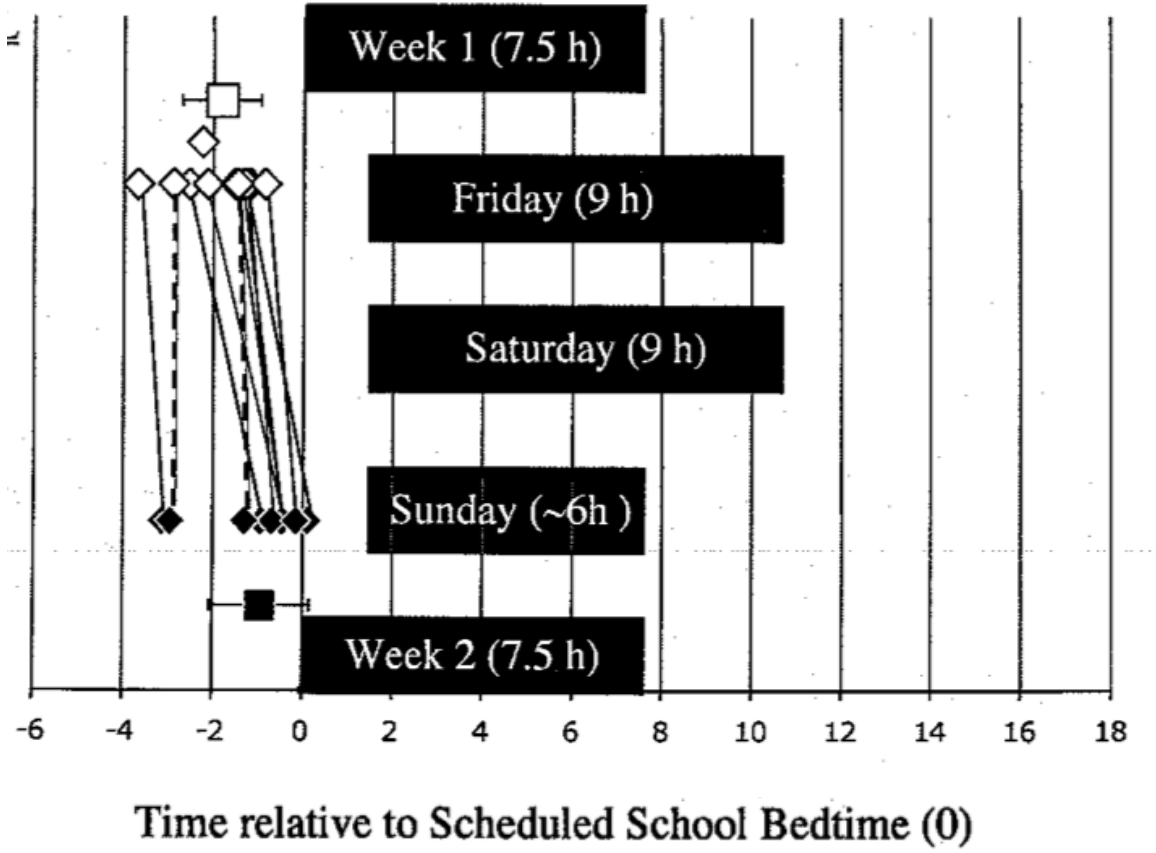


Pain

- What might it be?
- Gastro-oesophageal Reflux (C Oliver et al)
- Fractures
- Gut pain
- Headaches/ migraines
- Leg pains
- Hip pains
- Teeth
- Ears

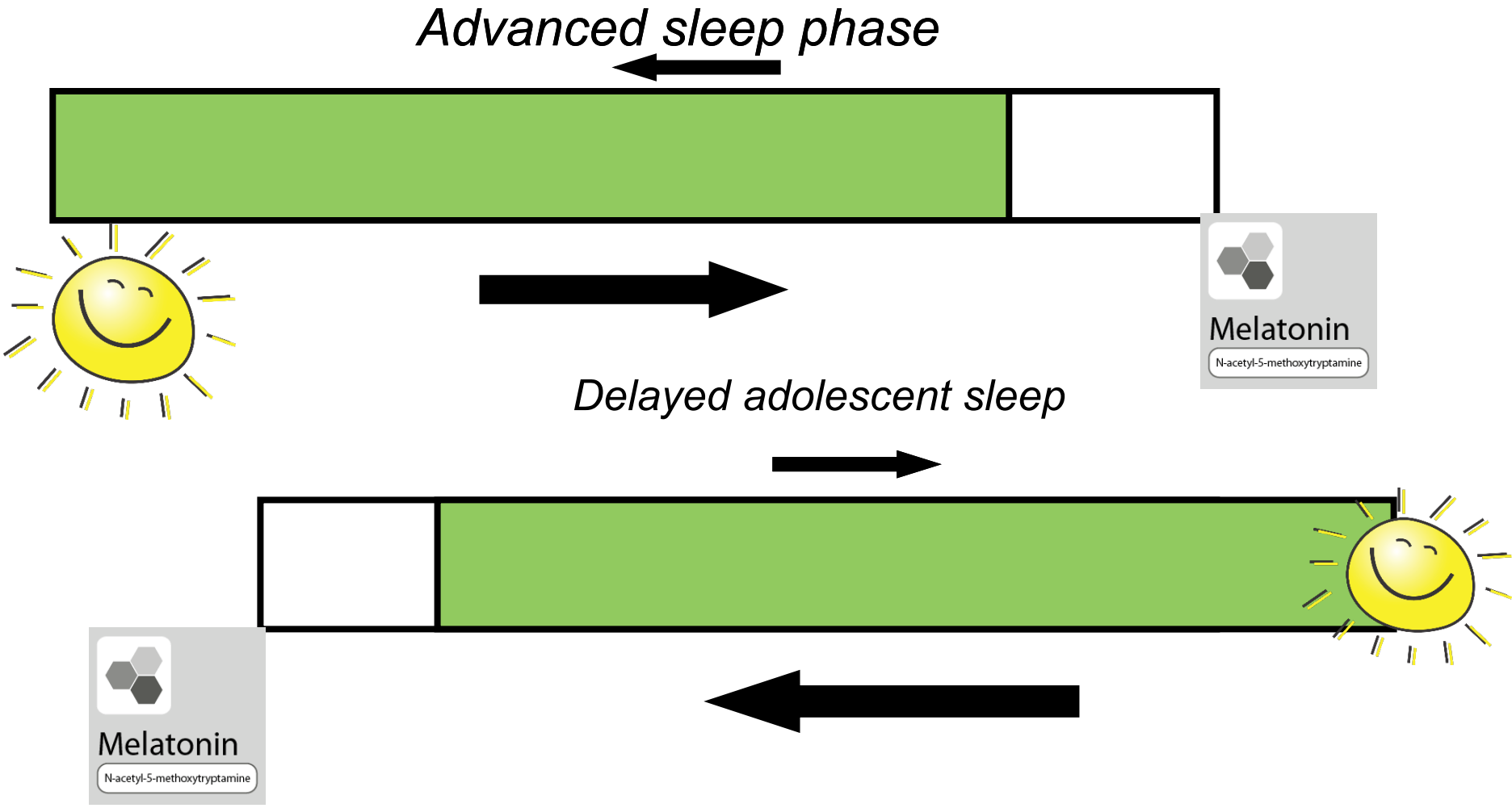
Adolescence

When provided a simulated weekend sleep-in, teens 24-hr circadian rhythm (aka 'body clock') shows a delay dim light melatonin onset (DLMO) of ~45 min



(Crowley, 2009, unpublished thesis)

Melatonin


Advanced sleep phase
Melatonin
N-acetyl-5-methoxytryptamine
Delayed adolescent sleep
Melatonin
N-acetyl-5-methoxytryptamine

Parasomnias (para = alongside of, somnus = sleep)

A collection of sleep disorders occurring during sleep, or the transition from wake-to-sleep. Common theme is central nervous system activation resulting in sleep-related movements / emotions.

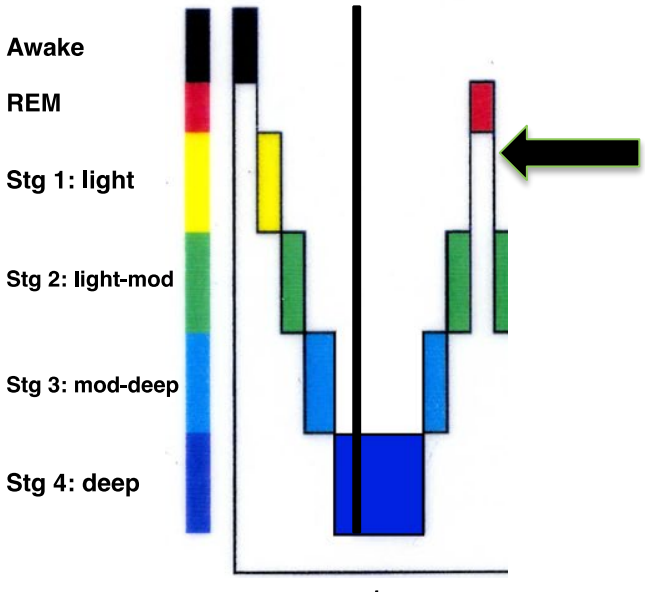
Although infrequent clinically, common NREM parasomnias include:

- Sleepwalking
- Sleep terrors / Confusional arousals
- Sleep enuresis
- Sleep-related Body rocking / Head-bangi

(AASM, 2005; Sadeh, 2005)

Can be dangerous, hence their inclusion as a clinical disorder.

Typically a result of brief awakening from 'Deep Sleep' – thus not recalled by child.

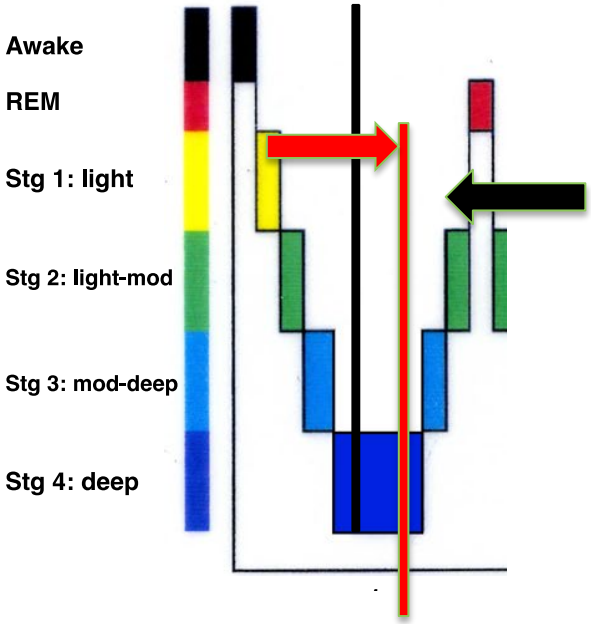


Treatment options for Parasomnias

Scheduled awakenings are currently recommended for treatment of many NREM parasomnias (Sadeh, 2005).

Need to wake child 15-30 mins prior to anticipated parasomnia.

Continue this for 5-7 nights (Sadeh, 2005)



For sleep-related rhythmic movement disorder, these can occur during wake/sleep, NREM, or REM.
For wake/sleep transitions, a combination of hypnotics and bedtime fading have produced positive results (Etzioni et al., 2005)

Any Questions?