

Sleep and Disorders of Sleep

Neuroanatomy and neurophysiology

1. **wakefulness:**
 - a) reticular formation
 - b) intra-laminar and midline medial thalamic nuclei
 - c) posterior subthalamus
 - d) hypothalamus
 - e) basal foramen
2. **slow wave sleep:**
 - a) raphe nuclei of the brainstem
 - i) involved in sleep promotion
 - b) non-specific thalamic nuclei
 - c) anterior hypothalamus (preoptic region)
3. **neurotransmitters associated with wakefulness:**
 - a) acetylcholine - in cortex
 - b) noradrenaline - in cortex
 - c) peptides such as P
 - d) histamine in hypothalamus
 - e) corticotrophin releasing hormone
 - f) thyrotrophin releasing hormone
 - g) vasoactive intestinal polypeptide
 - h) ACTH and TRH
4. **neurotransmitters associated with slow wave sleep:**
 - a) GABA
 - b) 5-HT
 - i) 5-HT acts to reduce sensory input to inhibit motor activity
 - c) alpha-melanocyte secreting hormone
 - d) somatostatin

The sleep wake cycle

- During sleep :
 - GH and prolactin are released
 - corticosteroids tend to fall
 - catecholamines are usually low, but become raised in the first REM period in patients waking with migraine
 - airways reflexes are reduced
 - cardiac output falls
 - peripheral blood pressure falls but pulmonary arterial BP increases
 - gastric acid secretion decreases
 - metabolic rate, heart rate, and BP are lowest in delta, or slow wave sleep
 - respiratory rate is reduced
 - cerebral blood flow, brain temperature and metabolism all fall
- During REM sleep :

- there is near paralysis of many muscles
- cerebral blood flow increases, as does brain temperature
- thermoregulation stops and there is no shivering or sweating
- the intercostal muscles and muscles of the upper airways become hypotonic
- penile erection occurs

The monoaminergic model of the sleep-wake cycle

- nREM sleep is associated with serotonergic neuronal activity, originating in the raphe complex
- REM sleep is associated with noradrenergic neuronal activity, originating in the locus coeruleus

The cellular model of the sleep-wake cycle

- **pontine gigantocellular tegmental fields** (nucleus reticularis pontis caudalis) – acetylcholine – is responsible for causing the onset of REM sleep; these are known as the ‘on cells’
- these cells are inhibited by the **dorsal raphe nuclei** (5-HT) and the **locus coeruleus** (NA); known as the ‘off cells’

Sleep architecture

- divided into:
 - a) D (Desynchronized) sleep = REM
 - b) S (Synchronized) sleep = NREM
 - time from stage 1 to stage 4 is approximately 20 minutes
1. Stage 1
 - transitional stage between sleep and wakefulness
 - decreased reactivity to external stimuli, thoughts drift and subject is no longer reality oriented
 - waves have frequency of 3 – 7 Hz
 2. Stage 2
 - thought processes become further fragmented
 - *sleep spindles* and *K complexes* occur in the EEG
 3. Stages 3 & 4
 - nocturnal enuresis is most likely to occur
 - known as deep or slow wave sleep
 - wave frequencies decrease to $\frac{1}{2}$ 1 Hz (delta waves)
 - when delta waves appear more than 50 % of the time, then the person is in stage 4 sleep
 4. REM sleep
 - occurs at about 90 minute intervals throughout the night
 - EEG pattern shows :
 - mixed frequency, low voltage waves
 - *sawtooth waves*
 - subject displays *rapid eye movements* and low amplitude on the EMG

- dreams in NREM sleep are:
 - less easily recalled
 - less vivid
 - less visual
 - less emotional
 - more pleasant

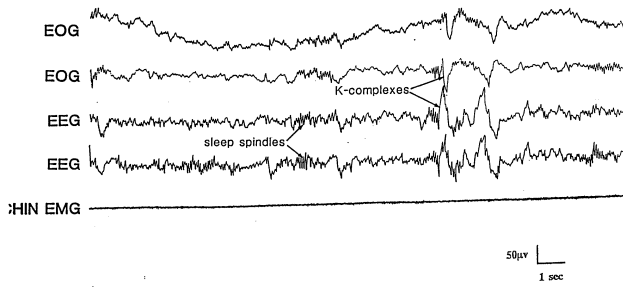
Features of REM sleep

- increased recall of dreams if woken
- increased complexity of dreams
- increased sympathetic activity
- transient runs of conjugate eye movements
- maximal loss of muscle tone
- increased heart rate
- increased systolic blood pressure
- increased respiratory rate
- increased cerebral blood flow
- occasional myoclonic jerks
- penile erection or increased vaginal blood flow
- increased protein synthesis (in rat brains)

Features of non-REM sleep

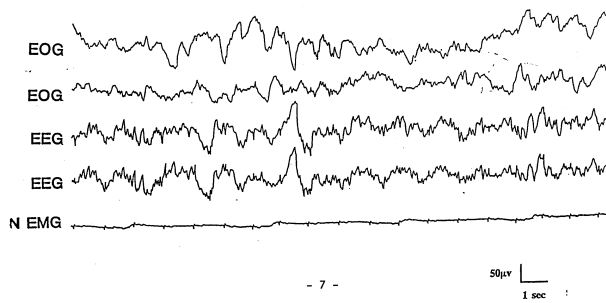
- reduced recall of dreaming if woken
- reduced complexity of dreams
- increased parasympathetic activity
- upward ocular deviation with few or no eye movements
- abolition of tendon reflexes
- decreased heart rate
- decreased systolic blood pressure
- decreased respiratory rate
- decreased cerebral blood flow
- penis not usually erect

Stage 2



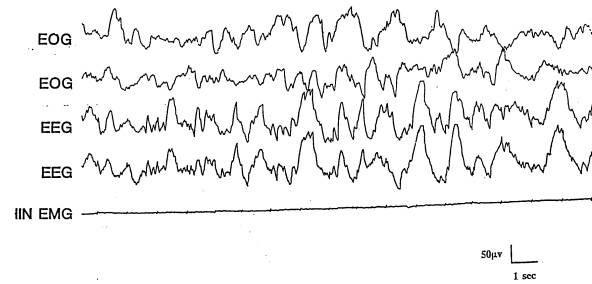
Stage 3 (20-50% slow waves)

Stage 3 = < 50 % delta waves
Stage 4 = > 50 % delta waves

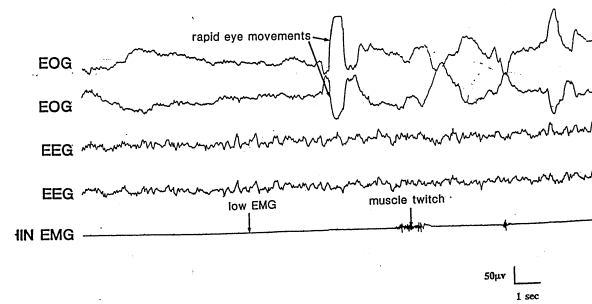


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Stage 4 (over 50% slow waves)



Stage REM



Classification of sleep disorders

1. **DIMS - disorders of initiating and maintaining sleep**
 - a) Psychophysiological insomnia - transient and persistent
 - b) DIMS associated with psychiatric disorder
 - c) DIMS associated with drug and alcohol abuse
 - d) Other conditions:
 - i) restless leg syndrome
2. **DOES - disorders of excessive somnolence**
 - a) Psychophysiological DOES - transient and persistent
 - b) DOES associated with psychiatric disorder
 - c) DOES associated with drug and alcohol abuse
 - d) Sleep apnoea
 - e) Narcolepsy
 - f) Idiopathic CNS Hypersomnia
 - g) Other medical conditions
3. **Disorders of the sleep-wake cycle**
 - a) transient - jet lag or shift work
 - b) persistent - people who frequently change their cycle e.g. MPs and business men
4. **Dysfunction associated with sleep, the sleep stages, and partial arousals (the PARASOMNIAS)**
 - a) Sleep walking
 - b) Night terrors
 - c) Sleep related enuresis
 - d) Dream anxiety attacks (nightmares)
 - e) Sleep-related epilepsy
 - f) Bruxism
 - g) Head banging (a.k.a. *jacatio capitis nocturnis*)
 - h) Body rocking
 - i) Sleep paralysis
 - j) Painful nocturnal penile erections

Excessive daytime sleepiness

Aetiology

1. Insufficient night-time sleep
 - a) unsatisfactory irregular sleep routines
 - b) circadian rhythm sleep disorders
 - c) frequent parasomnias
 - d) chronic physical illness

- e) psychiatric disorders
- 2. Pathological sleep
 - a) obstructive sleep apnoea
 - b) narcolepsy
 - c) other CNS disease
 - d) drug effects
 - e) Kleine-Levin syndrome
 - f) depressive illness

Insomnia

Epidemiology

- 50 % lifetime prevalence
- more common in:
 - females
 - the elderly
 - unemployed
 - separated
 - lower socioeconomic class

Neurological causes

- cerebral degenerative disorders (e.g. Huntingtons's chorea, Rett's syndrome)
- dementia
 - sleep becomes fragmented with both initial insomnia and early morning wakening
 - there may be nocturnal wandering and confusion in the early part of the evening
 - there may be reversal of the day/ night pattern
- Parkinsonism
 - fragmented sleep
 - daytime somnolence
 - sleep-wake cycle disturbance
- Fatal familial insomnia
- sleep-related epilepsy
 - about 25 % of patients have predominantly sleep-related epilepsy
- Electrical Status Epilepticus of sleep
- sleep related headaches

Psychiatric Illness

- 40 % have a concurrent psychiatric disorder

(Obstructive) Sleep apnoea syndrome

- affects 2 % of the population
- majority of patients are male

- at least a third are obese, with a large collar size due to excess fat
- most common from late middle age

Aetiology

- due to airways being obstructed by fatty tissue, resulting in the cessation of breathing 100's of times per night

Clinical features

- loud snoring (95 %)
- daytime sleepiness (90 %)
- unrefreshed or disturbed sleep
- morning headache and confusion
- nocturnal choking
- enuresis
- swelling of the ankles

Complications

- death
- pulmonary hypertension
- cor pulmonale

Treatment

- continuous positive airways pressure (CPAP)
- surgery - uvulopalatopharyngoplasty (UPPP)
 - only 60 - 70 % respond to this operation
 - non-responders are more likely to be obese

Narcolepsy

- characterized by excessive sleepiness associated with REM sleep phenomena such as:
 1. Cataplexy
 - a) sudden temporary episodes of paralysis with muscle tone, precipitated by strong emotion
 - b) occurs in most cases
 2. Sleep paralysis
 - a) a transient and generalized inability to move or speak during the transition between sleep and wakefulness
 - b) typically occur while falling asleep
 - c) the paralysis is flaccid, and usually complete
 - d) episodes usually last only a few seconds, and less than one minute
 3. Hypnagogic hallucinations
 - a) occur while falling asleep

Epidemiology

- usually begins between the ages of 10 and 20 years

- onset is rare after middle age

Aetiology

- family history of narcolepsy in a third of cases
- HLA blood typing almost always shows HLA-DR2 and HLA-DQw1, compared with a quarter of the general population - points to a genetic origin and links it with chromosome 6

Sleep abnormalities

- show a reduced sleep latency during the day
- greatly reduced REM latency at night - the patient may show REM at sleep onset

Psychiatric aspects

- schizophrenia-like mental disorders have been reported to occur more frequently in patients with narcolepsy than in the general population

Treatment

- regular dosage with AMPHETAMINE or METHYLPHENIDATE has some effect in reducing narcoleptic attack but little effect on cataplexy
- tricyclic antidepressants do not affect the sleep disorder but may reduce the frequency of cataplexy
- MIDAFENIL affects the sleep-wake switch in the brain

The Kleine-Levin syndrome

- rare secondary sleep disorder
- most cases are in young men with onset in early adolescence

Clinical features

- episodes of somnolence and increased appetite, often lasting for days or weeks and with long intervals of normality between them
- patients can always be roused from the daytime sleep, but are irritable and occasionally aggressive on waking
- the patient only rouses to eat or empty bladder and bowels
- incontinence does not occur
- when awake, he eats voraciously, typically eating any food in sight, although the patient rarely complains of hunger
- mental symptoms:
 - some are muddled and experience depression, and disorientation
 - vivid imagery may be prominent, with waking fantasies which are difficult to disentangle from vivid dreams
 - visual and auditory hallucinations may occur
 - hypersexuality occurs in around 25 % of cases
- few physical signs:
 - pulse and temperature usually normal

- pupils may be unequal
- plantar reflexes may be upgoing
- CSF is normal
- EEG shows the usual changes of drowsiness or sleep
- frequency of attacks varies from one to twelve per year, with an average of two per year

Parasomnias

Nightmares

- an awakening from REM sleep to full consciousness with detailed dream recall
- usually occur in the 1st third of nocturnal sleep
- causes:
 - frightening experiences during the day
 - PTSD
 - fever
 - psychotropic drugs
 - alcohol detoxification

Night terror disorder

- sometimes familial
- begins and ends in childhood
- child awakes terrified and may scream, and usually appears confused
- occurs in stage 3-4 sleep
- usually occur in the 1st third of nocturnal sleep
- there is little or no dream recall

Sleep-walking disorder (Somnambulism)

- an automatism occurring during deep non-REM sleep (stages 3 and 4), usually in the early part of the night
- affects 1 % of the population
- M>F
- associated with enuresis
- most common between the ages of 5 and 12 years
 - 15 % of this age group sleepwalk at least once
- may be familial
- possibly due to an abnormality of deep sleep – subject goes from deep sleep to wakefulness

The effects of drugs on sleep

Alcohol

- biphasic action
- in the first half of the night :

- decreasing sleep onset latency (promotes sleep initially)
- deep sleep increased
- REM sleep decreases
- in the 2nd half of the night :
 - rebound increase in REM sleep
- the sleep promotion associated with small doses of alcohol may be related to prior sleep deprivation
- alcohol exacerbates sleep-related breathing disorders, sleep apnoea, and sleep walking
- chronic use of excessive amounts of alcohol is disruptive to all stages of sleep
- during withdrawal, the total sleep time is reduced and non-REM sleep is particularly affected

Drug	Total Sleep time	REM	Light sleep Stages 1 & 2	Deep sleep Stages 3 & 4
<i>Opioids</i>	↓	↓	↓	↓
<i>Caffeine</i>	↓	↓ REM latency ↑ REM sleep		slightly ↓
<i>Amphetamines, cocaine</i>	initial insomnia and reduced TST	↑ REM latency ↓ REM sleep		

Insomnia and depression

- disturbance of sleep continuity
 - more time awake
 - increased sleep fragmentation
 - early morning wakening
- disturbance in the sleep architecture
 - decreased slow wave sleep
- disturbance in REM sleep
 - shortened REM latency
 - more REM activity (higher % in first 1/2 of the night)
 - higher REM density
- sleep deprivation (esp. deprivation of REM sleep) has a beneficial effect on mood in depressed patients
- antidepressants destroy REM sleep - there is a rebound of REM sleep on discontinuation

Sleep and psychiatric illness

1. *Depression*
 - a) reduced stage 3 and 4
 - b) reduced REM latency
 - c) REM occurs earlier in night

2. *Schizophrenia*
 - a) reduced slow wave sleep
 - b) reduced REM
3. *Anxiety*
 - a) increased stage 1 and 2
 - b) reduced efficacy of sleep
4. *Panic disorder*
 - a) increased sleep latency
5. *Alcoholism*
 - a) increased delta
 - b) increased REM sleep
 - c) increased alpha activity
6. *Alzheimer's disease*
 - a) increased sleep
 - b) fragmentation
 - c) reduced sleep efficiency