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 ½ - 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 (20-60% slow waves)
Stage 3 = < 50% delta waves
Stage 4 = > 50% delta waves

Stage 4 (over 60% 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. Huntington's chorea, Rett's syndrome)
- dementia
  - sleep becomes fragmented with both initial insomnia and early morning waking
  - 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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total Sleep time</th>
<th>REM</th>
<th>Light sleep Stages 1 &amp; 2</th>
<th>Deep sleep Stages 3 &amp; 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioids</td>
<td>↓</td>
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<td>↓</td>
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<tr>
<td>Caffeine</td>
<td>↓</td>
<td>↓ REM latency ↑ REM sleep</td>
<td></td>
<td>slightly ↓</td>
</tr>
<tr>
<td>Amphetamines, cocaine</td>
<td>initial insomnia and reduced TST</td>
<td>↑ REM latency ↓ REM sleep</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**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 ½ 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