Sleep Disorders
A Physiological and Behavioral Description of Sleep
What is EEG?
(electroencephalogram)

- EEG results from the combined activity of a large number of similarly oriented pyramidal neurons.
- Requires synchronous activity across groups of cells.
- EEG reflects summed post synaptic activity of large cell ensembles.
Sleep: Electrical Signs

I. beta activity
   A. ~20 Hz
   B. desynchronized, LVF
   C. awake and alert

II. alpha activity
   A. ~10 Hz
   B. synchronized, HVS
   C. resting, inattentive, eyes closed

III. theta activity (from the cortex)
   A. ~5 Hz
   B. synchronized, HVS
   C. light sleep, extreme boredom

IV. delta activity
   A. ~2.5 Hz
   B. synchronized, HVS
   C. deep slow-wave sleep (SWS)
Sleep: Electrical Signs

EEG Patterns: Measuring Brain Activity

Awake
- Alpha activity
- Beta activity

Stage 1 sleep
- Theta activity

Stage 2 sleep
- Sleep spindle
- K complex
- Seconds

Stage 3 sleep

Stage 4 sleep
- Delta activity

Relaxed wakefulness
- Alpha waves

Stage 1
- Theta waves

Stage 2
- Sleep spindles

Stages 3 and 4
- Delta waves

REM or dreaming sleep
- Theta activity
- Beta activity
REM Sleep: Electrical Signs

I. the EEG - synchronized during SWS; desynchronized during REM

II. the EOG - slow and drifting during SWS; shows rapid eye movements during REM

III. the EMG - reduced activity during SWS; very much reduced or absent activity during REM

IV. PGO waves (recorded from the LGN) - absent during SWS, appear just before the onset of REM
A Typical Night’s Sleep

Normal sleep hypnogram

<table>
<thead>
<tr>
<th>Sleep Stages</th>
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<tbody>
<tr>
<td>Wake</td>
</tr>
<tr>
<td>REM</td>
</tr>
<tr>
<td>Stage 1</td>
</tr>
<tr>
<td>Stage 2</td>
</tr>
<tr>
<td>Stage 3</td>
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<tr>
<td>Stage 4</td>
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</tbody>
</table>

- Deep Sleep (SWS)
- Dreaming (REM)

1. first cycle
2. second cycle
3. third cycle
4. fourth cycle
5. fifth cycle
The Sleep Cycle

- wakefulness - alert and vigilant (beta) or resting with eyes closed (alpha)
- stage 1 - theta begins to appear in EEG
  - a transitional state - eyes may flutter open occasionally
  - there may be sensory shocks such as falling sensations
  - thinking becomes distorted with bizarre associations
  - hypnagogic hallucinations
- stage 2 - light sleep (more theta)
  - sleep spindles - short bursts of alpha that may play a role in memory consolidation (can occur during any stage of non-REM sleep, but occur primarily during stage 2)
  - K-complexes - may be the brain attempting to “kick start” delta activity or to prevent awakening due to external disturbances during light sleep (normally occur only during stage 2 sleep)
- stages 3 and 4 - delta begins to appear in the EEG and eventually comes to predominate (American Academy of Sleep Medicine has combined these into a single stage called stage 3)
  - most restful stage of sleep
  - sleeper most difficult to awaken, acts groggy and unresponsive
  - typically occurs mostly during the first half of the night
  - sleepwalking and sleep talking occur during this stage (not REM)
- REM - rapid eye movement sleep; this is when dreaming occurs
The Sleep Cycle

- REM sleep - in humans, detected by a sudden decrease in muscle tension, the appearance of REMS, and a shift to desynchronized EEG
  - this is when dreaming occurs
- first episode may last 10 min., but episodes become progressively longer during the night
- in an average night there will be 4-5 REM periods - we all dream every night, but some of us don’t remember it
- also called paradoxical sleep (because of the desynchronized EEG)
- the flaccid paralysis of muscles is only partial in humans, but is more complete in animals, which can become quite floppy
- sexual arousal - penile erection and vaginal moistening occur
The Basic Rest-Activity Cycle

- Nathaniel Kleitman (discovered that REM is associated with dreaming)

- the 90 min. cycles seen in SWS/REM alternation is also seen throughout the day in activities like eating, drinking, smoking, performance on cognitive tasks, etc.

(Mammoth Cave, KY, 1938)
Sleep is Not a State of Brain Shutdown
Changes in Sleep During the Lifespan

- During certain periods of gestation, the brain is in REM 24 hrs/day.
- This may be in the service of brain development, or...
- It may be because the incompletely developed brain is not fully capable of SWS.
Effect of Aging on Sleep Cycles

- Young adult
  - Sleep stages: REM, 1, 2, 3, 4
- Elderly person
  - Sleep stages: REM, 1, 2, 3, 4
Patterns of the stages of sleep of a normal subject and of a patient with major depression. Note the reduced sleep latency, reduced REM latency, reduction in slow-wave sleep (stages 3 and 4), and general fragmentation of sleep (arrows) in the depressed patient.

Effect of Depression on Sleep Cycles

Mental Activity During Sleep

• during REM sleep
  • blood flow is high in the visual association cortex
  • low in the primary visual cortex (no direct visual input)
  • lots of activity in motor areas as if the person were actually moving - but these impulses are prevented from reaching the muscles
  • brain mechanisms active during a dream are those that would be active if the events of the dream were actually occurring
  • except activity in the prefrontal areas is low - the planning, organizing area of the brain
  • night terrors, as well as sleepwalking and sleeptalking, typically occur during SWS
Mental Activity During Sleep

- Motor (and premotor) cortex
- Inferior parietal
- Occipito-temporal visual cortex
- Post. cingulate
- Precuneus
- Ant. cingulate, medial prefrontal
- Basal forebrain
- Orbitofrontal
- Amygdala
- Hippocampus
- Thalamus
- Midbrain; pontine tegmentum
Is the Content of Dreams Symbolic?

- latent vs. manifest content (Freud)
- or is it inherently meaningless random brain activity that the brain then attempts to give some meaning to
  - Hobson’s activation-synthesis theory
  - the brainstem reticular formation bombards the cortex with impulses, and the cortex does what it does (attempts to make sense of it all)
- the content of most dreams is mundane
The Functions of Sleep

- All vertebrates sleep or become quiescent (enter a sleep-like state).

- All warm-blooded vertebrates (birds and mammals) cycle between SWS and REM - which means REM does not have any uniquely human significance.

  - Question: What do all birds and mammals have that no other animal has?

  - Answer: A neocortex.

- Some marine mammals (bottlenose dolphins and porpoises) sleep one brain hemisphere at a time.
Functions of REM Sleep

- Does REM have something to do with brain development?

- Animals born with mature brains spend less time in REM than animals born with immature brains.

- There has been long-standing speculation that REM sleep has something to do with memory consolidation.

- The default theory of REM (Horne) - REM has no useful function other than to be the easiest state of the body to maintain. When wakefulness or SWS is needed, it is produced instead.

<table>
<thead>
<tr>
<th>animal</th>
<th>% REM sleep</th>
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<tbody>
<tr>
<td>guinea pigs</td>
<td>5.3%</td>
</tr>
<tr>
<td>rats</td>
<td>15%</td>
</tr>
<tr>
<td>cats</td>
<td>23%</td>
</tr>
<tr>
<td>premature infants</td>
<td>75%</td>
</tr>
<tr>
<td>full-term infants</td>
<td>50%</td>
</tr>
<tr>
<td>adult humans</td>
<td>15-25%</td>
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</tbody>
</table>
Sleep and Learning

- Evidence is now mounting that sleep plays a role in long-term memory consolidation, and the role of REM and SWS may be different.

- explicit (declarative) vs. implicit (nondeclarative or procedural) memory

  - REM seems to be involved in consolidation of implicit memories.
  
  - SWS seems to be involved in consolidation of explicit memories.
What Are The Effects of Too Little Sleep
Sleep Deprivation Experiments

- some early experiments on sleep deprivation (esp. REM deprivation) suggested that prolonged wakefulness could make you psychotic
- this doesn’t actually seem to be the case
1959

Pete Tripp, a dj at WMGM radio in NY, agreed to stay awake for 201 hrs. to raise money for the March of Dimes. He ended up hallucinating and delusional.

But Pete is reported to have taken amphetamine to help keep himself awake during the ordeal!

67 hrs. in

199 hrs. 50 mins.

being walked by a nurse to keep him awake

being put to bed afterwards
1964

Randy Gardner, a 17-yr-old high school student in San Diego, CA, stayed awake for 264 hrs. (11 days) with the help of friends, TV reporters, and a basketball, in an attempt to get into the Guinness Book of World Record. He suffered no permanent ill effects. He did experience a little “paranoia”, blurred vision, and slurred speech after several days of wakefulness.

Note: to discourage people from harming themselves, the Guinness Book no longer publishes this record.
The REM Rebound

REM deprivation results in a "pressure to dream"

An increasing number of awakenings are required to keep the subject deprived...

and when allowed to sleep normally, the subject shows a rebound in REM...

however, SWS is recovered first!
Sleep Deprivation (cont.)

• after 11 days awake, Randy Gardner was allowed to sleep as much as he wanted
  
  • the 1st day he slept almost 15 hrs.
  
  • the 2nd day he slept a little more than 10 hrs.
  
  • he did not make up all his lost sleep time - in 11 days he would have slept about 88 hrs., and only about 20 hrs. of that “were made up”
  
  • about 7% of light sleep (stages 1 and 2) were made up
  
  • about 68% of slow-wave sleep (stages 3 and 4) were made up
  
  • about 53% of REM sleep was made up
Sleep Deprivation (cont.)

• more recent studies have suggested that the primary effect of sleep deprivation is profound sleepiness

• visual effects - visual distortions and “hallucinations” (fog, cobwebs, etc.)

• failure of concentration

• no serious deterioration in simple mental capabilities - highly motivated subjects do as well as non-sleep-deprived subjects

• when people are aroused from SWS, they act groggy and confused, as if the cortex had been shut down and was taking some time to start up again - maybe the function of SWS is to allow the cortex to rest after mental exertion (this seems to be the case)

• there is a direct relationship between how much beta an area of cortex displays during wakefulness and how much delta it displays during SWS - “the harder it works, the harder it rests”
Sleep Deprivation (cont.)

72 Hours of Total Sleep Deprivation: Effect on Arithmetic Task Performance

Some Effects of Sleep Deprivation

Turner-Fairbank HYSIM Driving Simulator Performance under Sleep Deprivation

Fig 2. Localization of epileptiform graphoelements on EEG 1 (routine EEG) and 2 (sleep-deprived EEG). GBD, generalized bilateral discharges; GBD>R, generalized bilateral discharges, predominant to the right; GBD>L, generalized bilateral discharges, predominant to the left; LF, left frontal; RF, right frontal; LT/RT, left/right temporal; MRF, median right frontal.
Changes in Brain Activity After Sleep Deprivation

**FIG1:** Activation during the arithmetic task after a normal night of sleep (top) and following sleep deprivation (bottom). Significant activation in color is overlaid onto the mean Talairach anatomical image averaged across all 13 subjects. Yellow represents the most intense activation, red the least intense. Slices are the following distances from the center point: 41 mm superior (axial), 25 mm right (sagitta) and 29 mm anterior (coronal). Axial and coronal slices are in radiological orientation (left and right are reversed). From the December 1999 issue of *NeuroReport*.
PHYSIOLOGY
OF
SLEEP
Chemical Control of Sleep

• If there is a sleep-promoting substance, it must be restricted to the brain.
  • Adenosine is a prime candidate.
  • It is produced in areas of the brain that consume energy very rapidly.
  • Adenosine may promote delta activity in the EEG.
  • Adenosine antagonists (e.g., caffeine) promote wakefulness.
Neural Control of Arousal

- the reticular formation and ascending reticular activating system (ARAS)
The Five Arousal Systems

- five systems of arousal neurons
  - acetylcholine - dorsal pons and basal forebrain
  - norepinephrine - locus coeruleus
  - serotonin - raphe nuclei of the pons and medulla
  - histamine - tuberomammillary nucleus of the hypothalamus
  - orexin - lateral hypothalamus

- a high level of activity in these neurons keeps us awake, while a low level puts us to sleep

- drugs have predictable effects
The Biological Clock

Figure 9.27
Melatonin
Melatonin
In Case You Haven’t Had Enough on Melatonin

Sleep efficiency - percent of time spent asleep while in bed (85% considered normal)

Sleep Disorders
How Much Sleep is Enough

- there are large individual differences
  - a few people do fine with 5 hrs. (rarely less)
  - other people need 9 or even 10 hrs.
- people who get about 7 hrs/night live the longest - does this mean we should all force ourselves to get 7 hrs/night?

- signs of insufficient of poor quality sleep
  - difficulty waking up
  - poor concentration and attention
  - urge to sleep during the day
  - feelings of moodiness or depression
Insomnia

• incidence: 25% occasionally and 9% regularly

• forms of insomnia
  • sleep onset insomnia
  • sleep maintenance insomnia
  • early awakening insomnia
  • pseudoinomnia
  • sleep apnea
  • fatal familial insomnia - a rare genetic disorder
Fatal Familial Insomnia

- autosomal dominant gene
- found in probably less than 100 families worldwide
- it’s a prion disease related to CJD
- average age of onset of symptoms is 50 yrs.
- always progresses to a fatal outcome in 1-2 yrs.
Causes of Insomnia

• irregular sleeping habits - sleep is a rhythm!
• stress, worry
• psychological disorders such as depression and anxiety disorders
• pain, discomfort, physical ailments
• drug dependency insomnia - withdrawal from sleeping medications (iatrogenic)
• sleep apnea - throat muscle atonia or obstruction of the throat (usually)
Insomnia and Body Temperature

Figure 2. Circadian rhythm of gastrointestinal temperature. Mean values (black line) recorded every 60 s during 24-h period are shown. The mean best-fit curve (red line) between the experimental data and the cosine curve of the 20 participants is shown ($r=0.97$). Red vertical arrow illustrates the beginning of the three morning test sessions.
Insomnia and Body Temperature

Figure 9.15 Insomnia and circadian rhythms. A delay in the circadian rhythm of body temperature is associated with onset insomnia; an advance is associated with termination insomnia.
This may be a case of common cause rather than cause and effect.
Narcolepsy

• diagnosed incidence - 1 in 1500-2000 people (maybe 3X that many cases are undiagnosed)
• usually first diagnosed during adolescence
• a neurological disorder characterized by sleep, or some of its phenomena, intruding into wakefulness
• sleep attacks - an overwhelming urge to sleep, usually in monotonous situations
• cataplexy - person collapses into a flaccid paralysis, usually during emotionally arousing situations, but remains awake and aware of his surroundings
• sleep paralysis - intrusion of REM paralysis into wakefulness just before or after sleep
• hypnagogic hallucinations - intrusion of visual dreaming into wakefulness (often during periods of sleep paralysis)
During the intensely hot summer of 1825, I experienced an attack of this affection. Immediately after dining, I threw myself on my back upon a sofa, and, before I was aware, was seized with difficult respiration, extreme dread, and utter incapability of motion or speech. I could neither move nor cry, while the breath came from my chest in broken and suffocating paroxysms. During all this time I was perfectly awake; I saw the light glaring in at the windows in broad sultry streams; I felt the intense heat of the day pervading my frame; and heard distinctly the different noises in the street, and even the ticking of my own watch, which I had placed on the cushion beside me; I had, at the same time, the consciousness of flies buzzing around, and settling with annoying pertinacity on my face. During the whole fit, judgment was never for a moment suspended. I felt assured that I labored under incubus. I even endeavored to reason myself out of the feeling of dread which filled my mind, and longed, with insufferable ardour, for some one to open the door, and dissolve the spell which bound me in its fetters. The fit did not continue above five minutes: by degrees I recovered the use of sense and motion; and, as soon as they were so far restored as to enable me to call out and move my limbs, it wore insensibly away. (Binns, 1852, p. 156)

from Carlson, 2e, p.467
Causes of Narcolepsy

• in the lateral hypothalamus there is a nucleus of neurons that use a peptide neurotransmitter called hypocretin or orexin

• these cells are activated by environmental events and psychological factors that motivate wakefulness

• they activate brainstem areas that maintain wakefulness

• narcolepsy is due to a deficiency of orexin receptors or of orexin-secreting neurons - probably due to a genetic disorder, perhaps autoimmune

• onset is usually during adolescence, which is when the immune system begins attacking these cells
Narcolepsy and Hypocretin (Orexin)

A schematic diagram of the effect of activation of the hypocretinergic system of neurons of the lateral hypothalamus on the sleep/waking flip-flop. Motivation to remain awake or events that disturb sleep activate the hypocretinergic neurons.

- Inhibited
- Mutual inhibition
- Activated
- Brain stem and forebrain arousal systems
- ACh NE 5-HT Histamine
- Alert waking state

Motivation to remain awake
- Activation holds flip-flop "on"

Hypocretin Neurons (controls vs narcoleptics)

Structure of hypocretin

Thannickal et al. (2000)
Neuron, v. 27, p. 469

Narcoleptic
Control

Treatment

• Ritalin or similar stimulants for sleep attacks

• antidepressants that are both 5-HT and NE agonists are used to treat the REM sleep symptoms (and ACh antagonists)

• activity in 5-HT and NE systems suppress REM sleep

• REM sleep is triggered by ACh neurons arising in the pons
Other Sleep Disorders: REM

- REM sleep behavior disorder - aka REM without atonia
  - results in dreams being acted out
  - presumably due to disruption of functioning of a nucleus in the medulla called the nucleus magnocellularis - associated with neurodegenerative disorders like Parkinson's disease
  - this is the nucleus that keeps the muscles turned off during REM sleep
  - so now all that motor activity visible on the scans can be expressed in behavior!
  - similar disorders can be produced in experimental animals by lesioning this nucleus

- absence of REM sleep - at least one person has been discovered who has no REM sleep (doesn't seem to have any ill effects)
Other Sleep Disorders: SWS

- disorders associated with SWS
- sleepwalking and sleep-talking
- night (sleep) terrors
- bed wetting
- sleep-related bruxism
- sleep-related eating disorder
- restless legs syndrome (Willis-Ekborn disease)
Biological Rhythms

Sleep part 3
Here's basically how it works...
Zeitgebers
Circadian Rhythms

- circadian = “about a day”

- the primary (but not the only) clock for circadian rhythms is in the suprachiasmatic nucleus of the hypothalamus

- the SCN receives input from a special light-sensitive ganglion cell in the retina, which contains a photopigment called melanopsin
Circadian Rhythms

- Free-running rhythms - in the absence of environmental cues, most circadian rhythms tend to run a little longer than 24 hrs.

  (Illustrated on the next slide)

- In nature circadian rhythms are "entrained" to environmental cues that have a 24-hr. period.
Wheel-running activity of a rat. Note that the animal's activity occurs at "night" (that is, during the 12 hours the light is off) and that the active period is reset when the light period is changed. When the animal is maintained in constant dim illumination, it displays a free-running activity cycle of approximately 25 hours.


Actogram.

Sensors in the floor of his cage measure the activity of a lab animal. After 22 days the lighting was made continuous. The animal still has a regular activity and resting rhythm, but based on his biological clock which does not work exactly in 24 hours: a circadian rhythm.
The Interpretation of Dreams

- Eugene Aserinsky / Nathaniel Kleitman’s "Rapid Eye Movement" sleep (1953)
  - A low level of brain activity
  - Inhibition of muscle tone
  - Waves of excitation from the pons
  - Rapid eye movement
    - A brain enters REM sleep 4 or 5 times per night, at approximately 90 minute intervals, and each period lasts about 20 minutes
- William Dement (1954)
  - Sleep consists of cycles of different stages of sleep, repeated four or five times a night

- Nathaniel Kleitman, (1938) : physiology of sleep and circadian rhythm

Kleitman at work in Mammoth Cave, Kentucky (150 feet underground).
It ain’t easy being a circadian rhythm these days
It ain’t easy being a circadian rhythm these days.
It ain’t easy being a circadian rhythm these days

Common Negative Effects of Shift Work

- Lack of Communication between staff on different shifts.
- Lack of “Teamwork”.
- Lack of concentration while on duty.
- Potential Unsafe Conditions.
- Stress/fatigue.
- SHIFT LAG.
Seasonal Rhythms

* the pineal gland and melatonin
* melatonin is secreted from the pineal gland during the night
* regulated by input from the SCN via
  * paraventricular nuc. of the hypothalamus
  * sympathetic nervous system
Seasonal Rhythms

- During winter months when the nights are longer, more melatonin is secreted, and animals go into their winter phase of the behavioral cycle.

- Something similar may happen in humans, resulting in:
  - Weight gain during the winter
  - Seasonal affective disorder
The End of Sleep