EEG, Sleep and sleep disorders

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EEG
<table>
<thead>
<tr>
<th>Type</th>
<th>Frequency (Hz)</th>
<th>Location</th>
<th>Normally</th>
<th>Pathologically</th>
</tr>
</thead>
</table>
| Alpha | 8 – 13         | posterior regions of head, higher in amplitude on non-dominant side. Central sites at rest | • relaxed/reflecting  
   • closing the eyes  
   • Also associated with inhibition control, seemingly with the purpose of timing inhibitory activity in different locations across the brain. | • coma |
| Beta  | 13 – 30        | symmetrical distribution, most evident frontally; low amplitude waves | • alert/working  
   • active, busy or anxious thinking, active concentration | • benzodiazepines |
| Gamma | 30 – 100+      | Somatosensory cortex | • Displays during cross-modal sensory processing  
   • Also is shown during short term memory | • A decrease in gamma band activity may be associated with cognitive decline, |
<table>
<thead>
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<th>Normally</th>
<th>Pathologically</th>
</tr>
</thead>
</table>
| **Delta** | up to 4 | frontally in adults, posteriorly in children; high amplitude waves | • adults slow wave sleep  
• in babies  
• Has been found during some continuous attention tasks | • subcortical lesions  
• diffuse lesions  
• metabolic encephalopathy  
• hydrocephalus  
• deep midline lesions |
| **Theta** | 4 – 8 | Found in locations not related to task at hand | • young children  
• drowsiness or arousal in older children and adults  
• idling  
• Associated with inhibition of elicited responses (has been found to spike in situations where a person is actively trying to repress a response or action) | • focal subcortical lesions  
• metabolic encephalopathy  
• deep midline disorders  
• some instances of hydrocephalus |
EEG: Fast Fourier transformation (FFT) analysis
Clinical uses of the EEG

• Detection (and localisation) of seizure activity
• To detect encephalopathy
• To determine depth of anaesthesia
• Adjunct test of brain death
EEG – spikes and waves

BRE with left contemporal spikes
Figure 1. Routine awake EEG recordings. (A) On hospital day 3, EEG showed a mild excess of background slow activities in the bilateral centroparietal region. An elevated serum lithium level of 1.78 mEq/l was detected. (B) EEG on hospital day 8 demonstrated high amplitude triphasic waves with intermixed theta activities in the parieto-occipital region. However, the serum lithium level was reduced to 0.55 mEq/l. (C) On hospital day 17, EEG recovered to normal alpha activity.
EEG electrode placements
Sleep
Underlying physiology and pharmacology of sleep

- Normal sleep
- Measurement of sleep and sleep architecture
- Structures and neurotransmitters involved in sleep regulation
How much sleep do we need?

we need as much as is necessary

• to stop us feeling fatigued or sleepy the next day

• to enable us to perform our daily routine adequately
How much sleep do we need?

• Very variable from person to person, but 7-8 hrs common

• Less than 5 hours causes problems with performance in normal young volunteers in a lab*

• More than 10 hours sometimes causes ‘sleep drunkenness’

• Many people prefer 2 sleep periods (siesta)

• Some people use naps to catch up

• Many normal people have shorter sleep on weekdays and make up the ‘sleep debt’ at weekends

Why do we sleep when we do?

Coincidence of 3 processes

• Circadian process (‘body clock’) 🕒
• Time since last sleep (wake-dependent drive, homeostasis) 🥇
• Low arousal (relaxing, winding down) 😊
Circadian and homeostatic drives to sleep interact
Sleep: arousal / alertness / worry

- High arousal can overcome other drives to sleep
  - Worry, stimulants

- Low arousal can overcome other drives to be awake
  - Boredom, sedating drugs
Measuring sleep

Subjective measures

Ask the patient (include evening, bedtime, night, next day)
Questionnaires
Diary

Objective measures

Actigraphy – wrist-worn, measures movement
Measuring sleep

Polysomnography - measures continuous brain activity, eye movement, muscle activity (+ respiratory variables if required)

Waveforms interpreted visually to produce hypnogram of sleep stages
Idealized normal hypnogram: first sleep cycle

Stage 1
- ‘drowsy’ state, not perceived as fully asleep
- sounds seem far away
- eyes roll from side to side
- happens in front of TV, in lectures etc

11.30pm 7.30am

0 1 2 3 4 5 6 7 8 hours
Idealized normal hypnogram: first sleep cycle

- Stage 2
  - light sleep, ~50% of night
  - breathing & heart slower, muscles more relaxed
  - ‘falling’ sensations and sleep jerks happen
  - some imagery

- REM
- stage 1
- stage 3
- stage 4

K complex
sleep spindle

0 1 2 3 4 5 6 7 8
hours

7.30am
11.30pm - 7.30am

Stages 3,4 (Slow wave sleep)

- ‘restorative’ stage of sleep, if deprived will always be made up
- deep sleep, 20% of night in young adults
- slower heart / breathing, muscles relaxed, pale
- confused on waking straight from this stage
- some imagery

• awake
• REM
• stage 1
• stage 2
• stage 3
• stage 4
Idealized normal hypnogram: first sleep cycle

REM (rapid eye movement sleep)
- cortex active (‘paradoxical sleep’)
- muscles paralysed
- eyes move rapidly from side to side
- heart rate, breathing, autonomic function as awake
- most dreaming (bizarre, storylike)
Idealized normal hypnogram

- awake
- REM
- stage 1
- stage 2
- stage 3
- stage 4

11.30pm to 7.30am
Normal hypnogram

REM latency
70-90 min

awake
movement
REM
stage 1
stage 2
stage 3
stage 4

Sleep efficiency
Time asleep/time in bed
96%
Ascending arousal system

- Raphe, 5HT
- Hypothalamus, histamine, orexin
- Basal forebrain, ACh
- Locus coeruleus, NA
- VTA dopamine
- Pontine nuclei, ACh
- Locus coeruleus, NA
- Raphe, 5HT
Ascending arousal system
During sleep, projections from the VLPO nucleus in the hypothalamus (GABA, galanin) inhibit the main components of the arousal system.
# Neurotransmitters and sleep in humans

<table>
<thead>
<tr>
<th>Endogenous transmitter</th>
<th>Maintains wakefulness</th>
<th>Promotes sleep</th>
<th>Agents promoting wakefulness</th>
<th>Agents promoting sleep</th>
<th>Agents causing sedation</th>
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<tbody>
<tr>
<td>GABA</td>
<td>✓</td>
<td>✓</td>
<td>agonists, positive allosteric modulators</td>
<td>agonists, positive allosteric modulators</td>
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<td>M1 and M2 agonists</td>
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<td>✓</td>
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<td>α1 antagonists</td>
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<tr>
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<td>✓</td>
<td>uptake blockers releasers (stimulants)</td>
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<td>uptake blockers</td>
<td>5HT&lt;sub&gt;2&lt;/sub&gt; antagonists, 5HTP</td>
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<tr>
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<td>✓</td>
<td></td>
<td>H1 antagonists</td>
<td></td>
</tr>
<tr>
<td>acetylcholine</td>
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<td>✓</td>
<td></td>
<td>muscarinic antagonists</td>
<td></td>
</tr>
<tr>
<td>orexin</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>antagonists</td>
<td></td>
</tr>
</tbody>
</table>
Sleep Disorders and their treatment

Original Paper

British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias and circadian rhythm disorders

SJ Wilson¹, DJ Nutt², C Alford³, SV Argyropoulos⁴, DS Baldwin⁵, AN Bateson⁶, TC Britton⁷, C Crowe⁸, D-J Dijk⁹, CA Espie¹⁰, P Gringras¹¹, G Hajak¹², C Idzikowski¹³, AD Krystal¹⁴, JR Nash¹⁵, H Selsick¹⁶, AL Sharpley¹⁷ and AG Wade¹⁸
Sleeping and waking – what goes wrong

- **insomnia**
  not enough sleep or sleep of poor quality

- **hypersomnia**
  excessive daytime sleepiness

- **parasomnia**
  unusual happenings in the night

- **other, eg:**
  circadian rhythm disorders
  restless legs syndrome

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What is insomnia?

A
Difficulty
- initiating sleep,
- maintaining sleep,
- waking up too early
or
- sleep is chronically non-restorative or poor in quality

B
Occurs despite adequate opportunity and circumstances for sleep

C
At least one form of daytime impairment
i. Fatigue or malaise
ii. Attention, concentration, or memory impairment
iii. Social or vocational dysfunction or poor school performance
iv. Mood disturbance or irritability
v. Daytime sleepiness
vi. Motivation, energy, or initiative reduction
vii. Proneness for errors or accidents at work or while driving
viii. Tension, headaches, or gastrointestinal symptoms in response to sleep loss
ix. Concerns or worries about sleep

Severity and duration criteria in DSM IV, ICD-10, ICSD

International Classification of Sleep Disorders (ICSD)
Diagnosing insomnia:

Preliminary questions for eliminating other sleep disorder as primary

• Are you a very heavy snorer? Does your partner say that you sometimes stop breathing at night? (obstructive sleep apnoea syndrome (OSAS))

• Do your legs often twitch and can’t keep still in bed? Do you wake from sleep with jerky leg movements? (restless legs syndrome - RLS, periodic limb movements in sleep - PMLS)

• Do you sometimes fall asleep in the daytime completely without warning? Do you have collapses or extreme muscle weakness triggered by emotion, for instance when you’re laughing? (narcolepsy)

• Do you tend to sleep well but just at the “wrong times”; and are these sleeping and waking times regular? (circadian rhythm sleep disorder; evidence also from sleep diary)

• Do you have unusual behaviours associated with your sleep that trouble you or that are dangerous? (parasomnias)
Why treat insomnia?

- Impaired quality of life
- Impaired daytime performance (objectively measured), accidents at work, road accidents
- ↑ absenteeism (associated with 13.6% of DOR - Hajak et al, 2011)
- ↑ risk of hypertension
- ↑ risk of first episode/relapse of depression
Algorithm for treatment of insomnia:

Wilson et al. 2010
BAP Guidelines
# Individual hypnotic drugs (efficacy)

<table>
<thead>
<tr>
<th>Significantly different from placebo</th>
<th>Sleep onset latency</th>
<th>Total sleep time</th>
<th>Wake time after sleep onset</th>
<th>Sleep quality</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Self-rated</td>
<td>PSG</td>
<td>Self-rated</td>
<td>PSG</td>
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<tr>
<td>temazepam</td>
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<td>(✓)*</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>lormetazepam</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>zopiclone</td>
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<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>zolpidem</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>No</td>
</tr>
<tr>
<td>zaleplon</td>
<td>✓</td>
<td>✓</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>eszopiclone</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>ramelteon</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>(week 1 only)</td>
</tr>
<tr>
<td>PR melatonin</td>
<td>✓</td>
<td>✓</td>
<td>Not measured</td>
<td>No</td>
</tr>
</tbody>
</table>

PSG = polysomnography

* formulation changed since studies, longer absorption time with current tablet cf gel capsule previous formulation
Safety of hypnotics

• ADVERSE EVENTS/SIDE EFFECTS
  ▪ taking all benzodiazepines and all 3 Z drugs together, less common for Z drugs

• NEXT-DAY DRIVING
  ▪ Epidemiology studies show that road accidents increase with benzos and zopiclone
  ▪ deficits in driving simulator performance with benzos and zopiclone
  ▪ no reported effects of zolpidem, zaleplon, PR melatonin

• REBOUND (worsening of sleep after stopping)
  ▪ except zaleplon, melatonin, ramelteon
Hypnotics & excess mortality

• Prospective study (20y) in Sweden
  - regular hypnotic use ↑ all-cause mortality risk
  - hazard ratios: men 4.54 (2.47-8.37) / women 2.03 (1.07-3.86)
  - high association with suicide

• Retrospective study in US
  - prescription of hypnotic increased hazard ratio > threefold
  - even if < 18 pills prescribed p.y. (dose response association)
  - applied to several common hypnotics incl. antihistamines
  - for high users: ↑ incident cancer, RR: 1.35 (1.18-1.55)
  - not attributable to previous diseases

Hypnotics – duration of treatment

Recommendation

• Use as clinically indicated (A)
• To stop medication try intermittent use at first if it makes sense, then try to stop at regular intervals – say every 3-6 months depending on ongoing life circumstances and with patient’s consent (D)
• CBT during taper improves outcome (A)
Cognitive-behavioural therapy works in chronic insomnia

Suggested behaviors
• No clock-watching
• Bedroom for sleeping
• Scheduling time for planning, worrying etc early evening

Cognitions
• Working on attitudes and beliefs about sleep
• Changing negative automatic thoughts re:
  ▪ not falling asleep now
  ▪ dire consequences

Behavioral techniques
• Sleep restriction
• Paradoxical intent

Sleep remained improved 1y later & 84% of patients were drug free

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Hypersomnia - excessive daytime sleepiness

Common causes

lack of sleep without any underlying disease (insufficient sleep syndrome)

depression, neurological disorders, drug effects

Caused by primary sleep disorder

- fragmentation of nocturnal sleep
  (e.g. by breathing related disorders such as obstructive sleep apnea, movement disorders or parasomnias)
- intrusion of sleep phenomena into the awake state (e.g. in narcolepsy)
- disturbances of circadian rhythms (e.g. in delayed sleep phase syndrome, shift work sleep disorder).
Treatment of hypersomnia: Modafinil

- wakefulness-promoting drug used to reduce excessive daytime sleepiness in narcolepsy
- does not affect cataplexy (unlike sodium oxybate)
- restores alertness only moderately
- mode of action
  - reduces cortical GABA (catecholamine-dependent)
  - increases histamine in TMN (indirectly)
  - increases extracellular glutamate (also indirectly)

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Parasomnias

Non-REM sleep
- Night terrors
- Sleepwalking
- Confusional arousals
- Bruxism
- Enuresis
- Sleep starts
- Sleep talking
- Head-banging

REM sleep
- REM sleep behaviour disorder (RBD)
- Sleep paralysis
- Nightmares
Night terrors and sleepwalking

Usually strong family and childhood history

Night terrors

- recurrent episodes of abrupt awakening, usually in first third of night, usually with a scream
- intense fear and signs of autonomic arousal
- unresponsiveness to comforting
- no detailed recall
- cause significant distress
- incidence ~ 2% adults

Sleep walking

- rare to present for treatment unless injured self or others
- similar course to night terrors, often both in same subject
Nightmares associated with psychototropic medications

- cholinesterase inhibitors
- beta-blockers
- SSRIs esp paroxetine
- levodopa
- GHB
Treatment of nightmares

• Psychological treatments effective (1b)
  • focus on guided imagery, pleasant images
  • exposure - writing down dreams
  • changing the ‘ending’

• A few case series show beneficial effects of the alpha-1 adrenergic blocker prazosin in reducing nightmares related to PTSD in both military and civilian settings ¹

Raskind et al, Biol Psychiatry. 2007; 61(8):928-34
REM behaviour disorder

• Violent complex behaviour at night
• Subject recall 80-90%
• 2 abnormalities
  ▪ lack of atonia during REM sleep
  ▪ increased vividness and/or nasty content of dreams
REM behaviour disorder

- Incidence unknown (prob <1%), identified in 1980s, increasingly recognised
- Older age group, steady rise after 55
- Idiopathic or associated with Parkinson’s disease (~50% of PD pts), Lewy body dementia (~70%), multiple system atrophy (>90%)
- RBD may be the first manifestation of these disorders, antedating the onset of parkinsonism, cerebellar syndrome, dysautonomia, and dementia by several years.
- M >> F (80-90% male except for those with MSA)
Drugs which probably provoke symptoms of RBD

- all SSRIs
- venlafaxine
- mirtazapine
- imipramine, clomipramine
  - (only reported in narcoleptic patients with RBD)
- bisoprolol
- tramadol
Drugs that relieve symptoms of RBD

- No prospective or controlled studies
- Evidence based on case series (level IV)

<table>
<thead>
<tr>
<th>drug</th>
<th>No of patients</th>
<th>Very effective</th>
<th>Partially effective</th>
<th>No effect</th>
<th>Side effects</th>
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<tr>
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<td>79%</td>
<td>11%</td>
<td>10%</td>
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<tr>
<td></td>
<td>38</td>
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<td>32%</td>
<td>13%</td>
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<td>110</td>
<td>82%</td>
<td>17%</td>
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<td>14</td>
<td>N=6</td>
<td>N=6</td>
<td>N=4</td>
<td>N=5</td>
</tr>
</tbody>
</table>
Sleep paralysis

• Intrusion of REM atonia (and sometimes dream imagery) into awake state
• Isolated prevalence ~3% (?) lifetime, unknown current, 20% in panic disorder and GAD
• May be genetically determined
• Exacerbated by
  ▪ irregular sleep routine /sleep deprivation
  ▪ alcohol
  ▪ anxiety / tension
Treatment of sleep paralysis

• No proven treatment

• Clinical experience: improved by
  ▪ better sleep hygiene (inc. ↓ alcohol)
  ▪ reduced anxiety
  ▪ practical strategies for signalling to partner - sensory input stops it