核心課程編號：B19

睡眠 障礙

學習目標

一年期醫師畢業後一般醫學訓練(PGY)	畢業前一般醫學訓練(UGY)
知識 1.睡眠的分期 2.常見睡眠疾病的種類與治療	**知識** 1.睡眠的分期與常見的腦波圖形 2.睡眠疾病的種類: 猝睡症、異睡症、失眠、睡眠呼吸終止症候群 3.睡眠疾病的診斷流程 4.睡眠疾病常作檢查結果的判讀 **技能** 1.睡眠疾病相關的病史詢問 2.睡眠疾病相關的身體檢查

ITE

- 請說明睡眠的分期
- 各種睡眠疾患的簡介
- Narcolepsy的診斷和治療

睡眠醫學

- 目前已成為新興的綜合性科學
  - 1970年代以後睡眠呼吸中止症受到重視，吸引胸腔科、喉科、口腔外科、心臟科、內分泌科等學者參與研究。
  - 1990年，ASDA歸納出國際睡眠疾病分類(ICSD)。
  - 1993年，美國成立國家睡眠障礙研究中心(NCSDR)。
  - 1998年，美國國家睡眠基金會(NSF)和一些睡眠障礙患者的照護學會相繼成立。
  - 2002年，台灣睡眠醫學學會(TSSM)成立。2010年開始**睡眠醫學專科醫師認證**
  - 2005年，美國醫學專業委員會(ABMS)正式認可睡眠醫學為獨立的次專科(Subspecialty)學門。

快速動眼期(REM)

- 正常人由入睡到第一次REM的時間(REM latency) 通常為80 - 90分鐘。
- 正常睡眠， REM期約佔20% - 25% 。
- 據估計，若由REM期喚醒，約有84%的人會說他們正在做夢。
- REM期中的EEG與清醒時的EEG極為相似，需配合EMG觀察。

EEG: Electroencephalogram
REM: Rapid eye movement

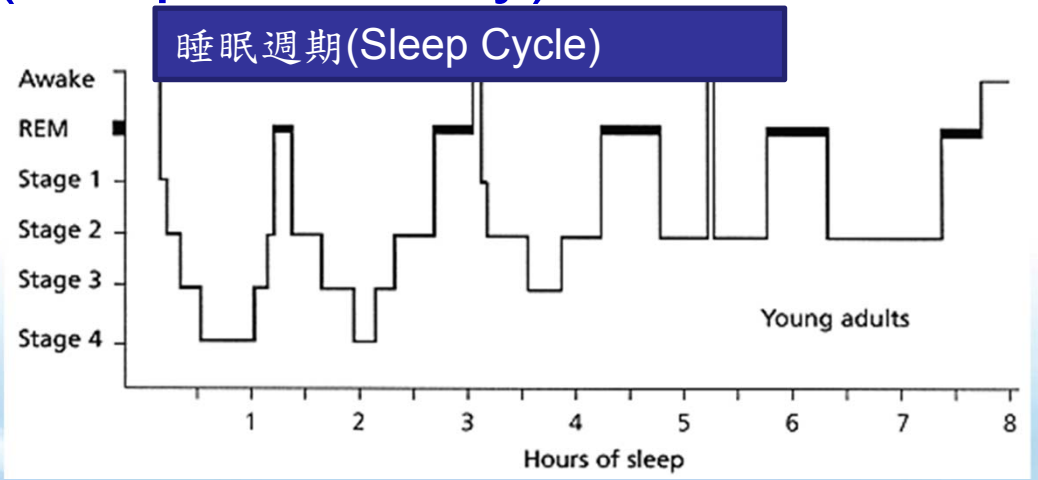
非快速動眼期(NREM)

- NREM期又可分為第一、第二、第三及第四期。(AASM 改成N1，N2，N3)
- Light Sleep
  - 第一期約佔全部睡眠的5% 。
  - 第二期約佔全部睡眠的45%-55% 。
- Deep Sleep
  - 第三及第四期約佔全部睡眠的20%-25%
  - 於2008年AASM併成N3

NREM: non-rapid eye movement
AASM: American Academy of Sleep Medicine

睡眠期

- 睡眠主要分為非快速眼動期及快速眼動期。
- 睡眠週期(Sleep Cycle)是指非快速動眼期(NREM)與隨後發生的快速動眼期(REM)。通常為期90分鐘，整夜有4～6個周期。
- 正常人的入眠期(sleep latency)通常低於15分鐘。
- 正常人的睡眠效率(sleep efficiency)應高於85%。



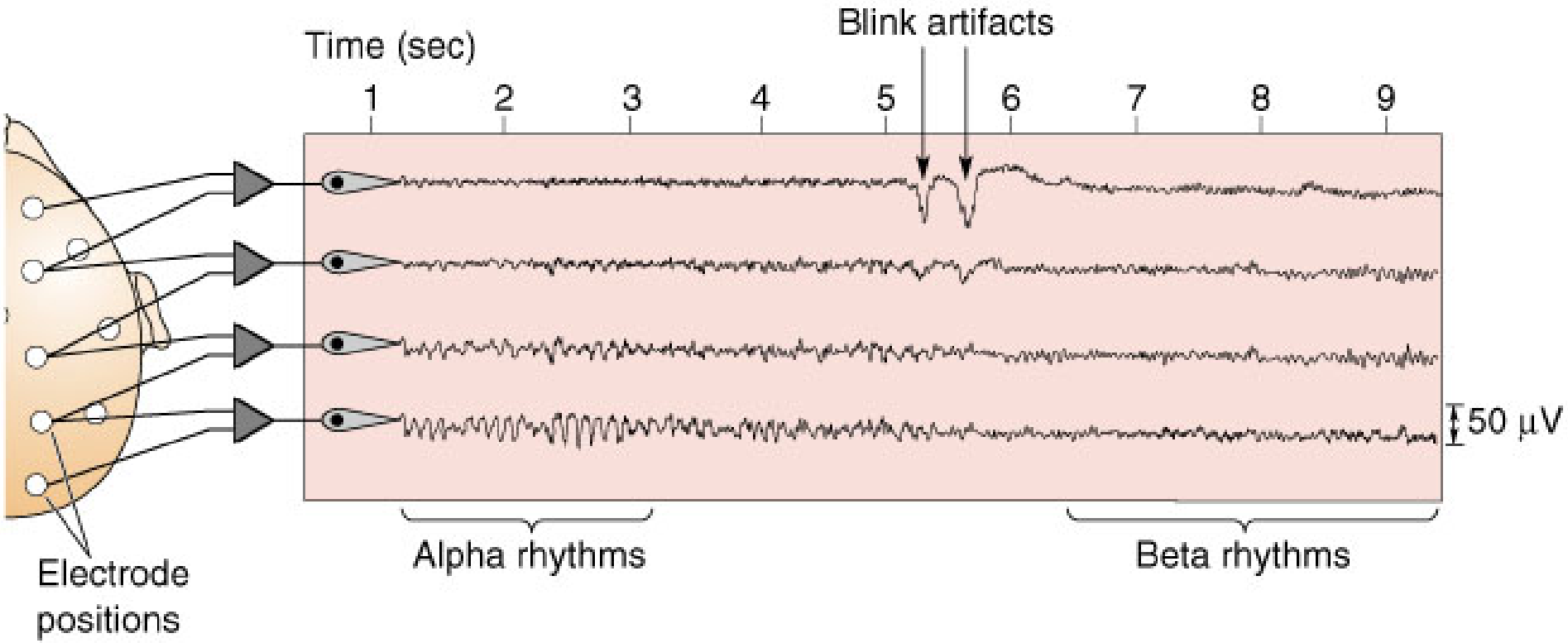
Sleep Physiology

- Adults require 7-8 hours sleep/night
- Sleep is active and complex
- Stages of sleep:
  - 4 stages of non-REM sleep
  - Rapid eye movement (REM)
  - Categorization based on degree of synchrony as measured by polysomnography
  - The stages of sleep cycle over 90 minutes-REM becoming progressively longer

EEG

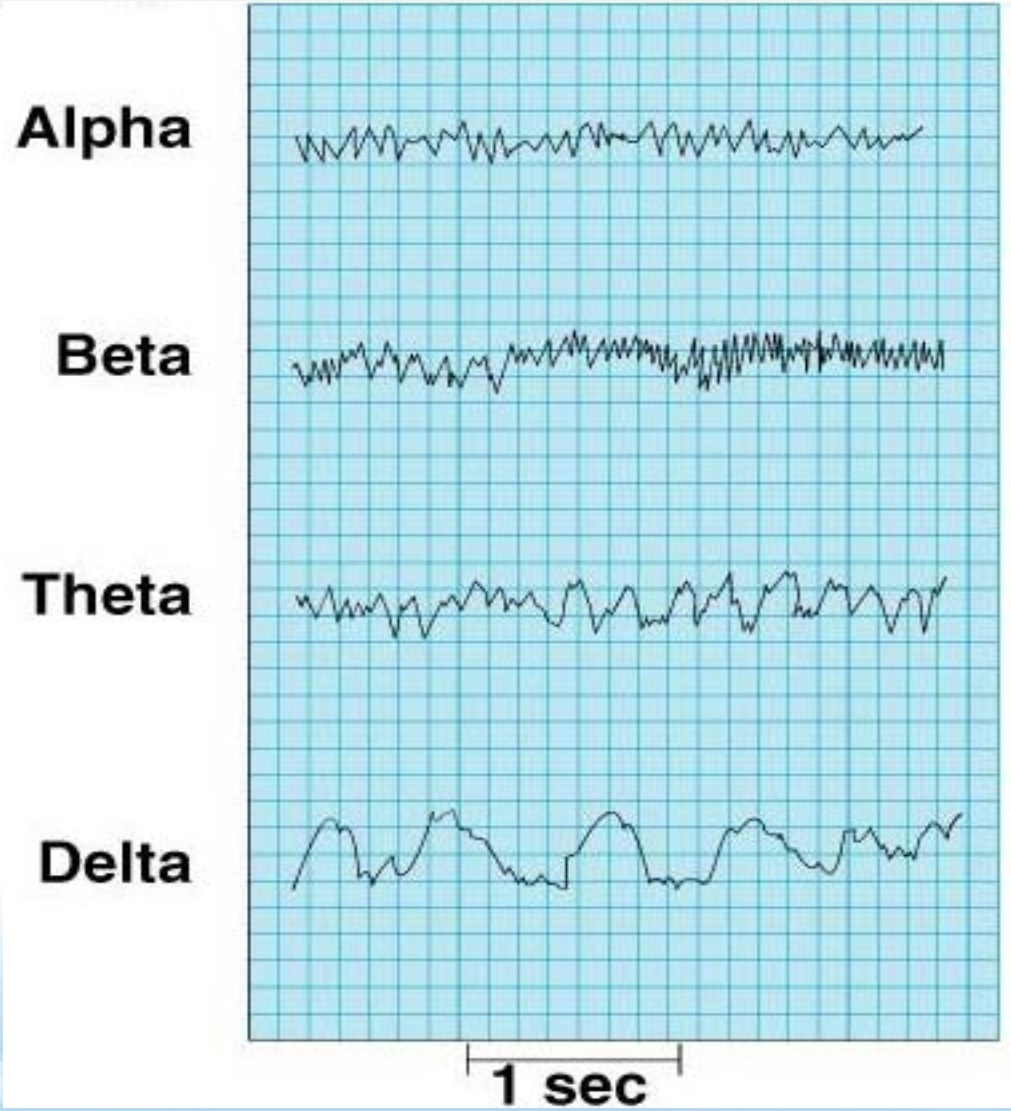
Electroencephalogram (EEG)

The EEG be recorded with Scalp electrodes through the unopened skull or with electrodes on or in the brain



Electroencephalogram (EEG)

- Measures synaptic potentials produced at cell bodies and dendrites.
- Used clinically diagnose epilepsy and brain death.
- 腦波是醒及睡眠分期的基礎要件

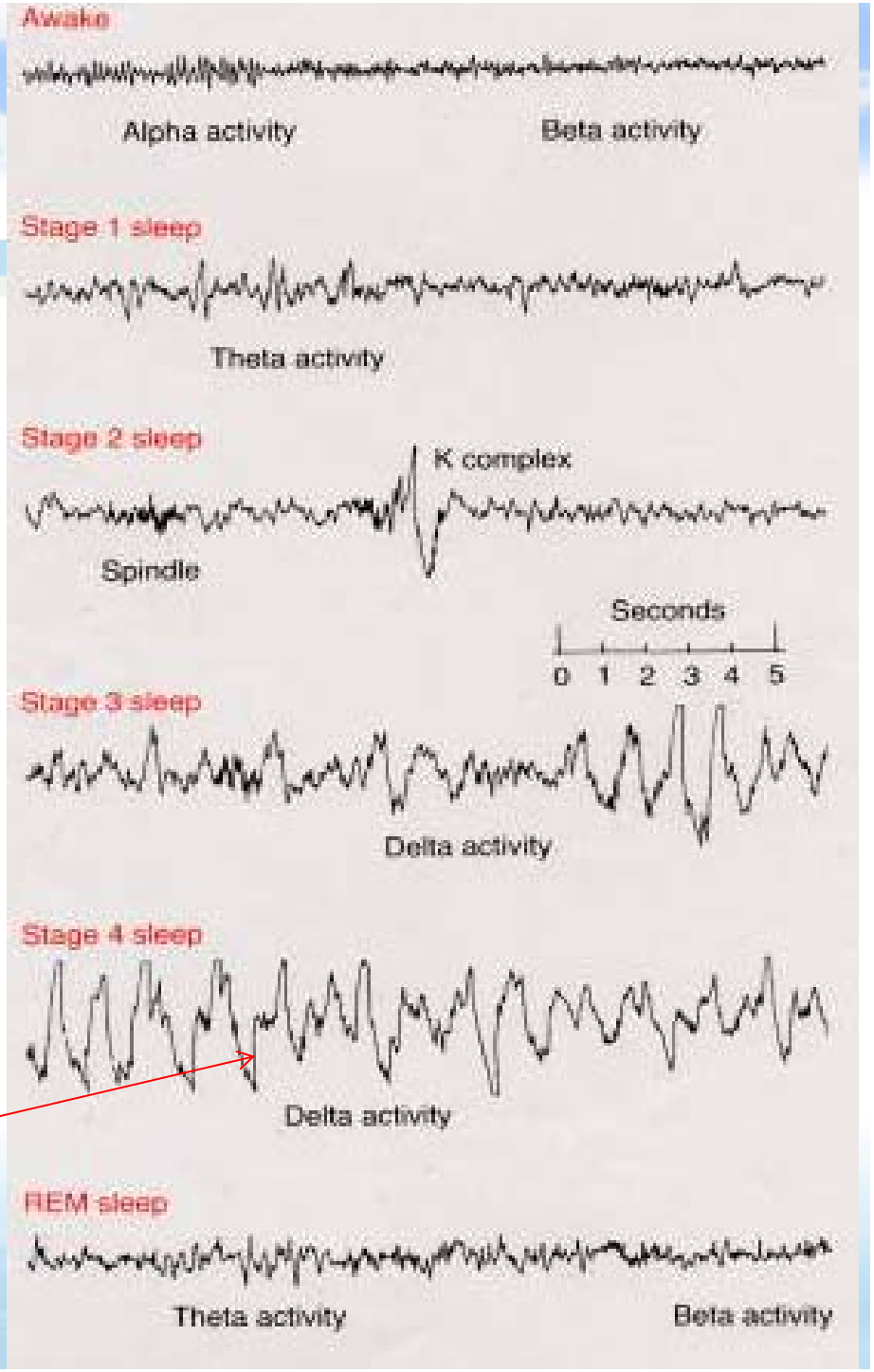


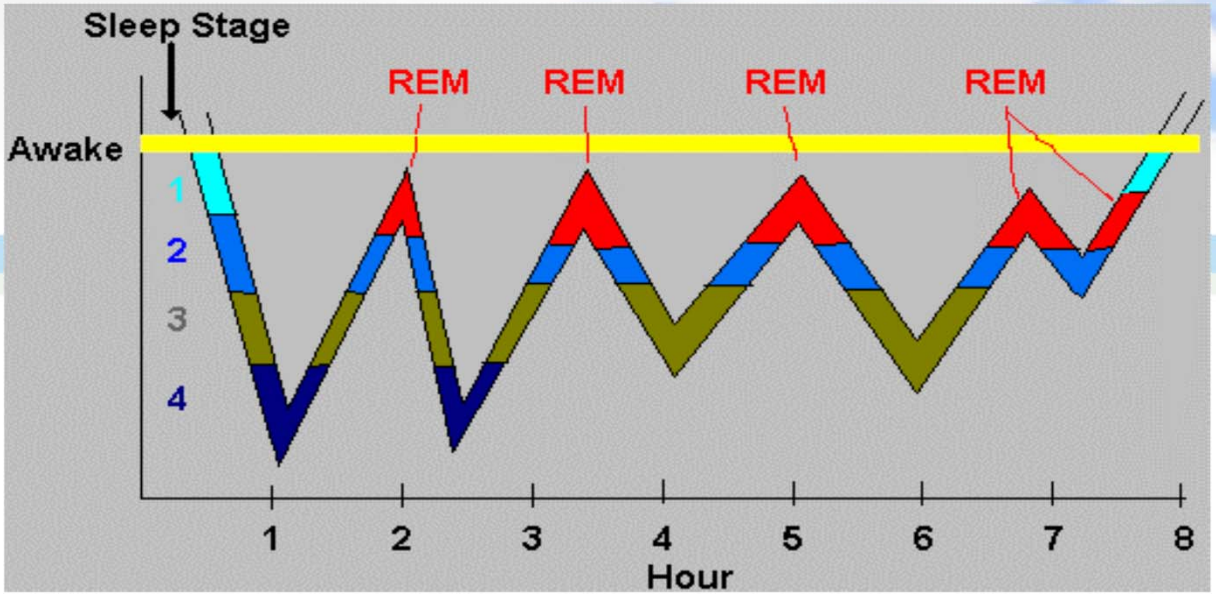
Diagnostic Tests In Sleep

- Polysomnography: 睡眠生理檢查的黃金準則
  - Electroencephalogram (EEG)
  - Electrooculogram (EOG)
  - Mentalis Electromyogram (EMG)
  - Surface EMG of tibialis anterior
  - ECG, nasal and oral airflow, respiratory effort, oxygen saturation

睡眠分期

- Stage 1
  - eyes are closed and relaxation begins;
  - the EEG shows alpha waves; one can be easily aroused
- Stage 2
  - EEG pattern is irregular with sleep spindles (high-voltage wave bursts)
  - arousal is more difficult
- Stage 3 and 4=current N3
- >20% (6-15 sec) of each epoch and must contain Delta activity





- 睡眠圖 (sleep histogram)
- A typical sleep pattern alternates between REM and NREM sleep
- SWS precedes REM sleep
- REM sleep lengthens over the night (睡得越久REM的持續時間越長)
- Basic sleep cycle = 90 minutes (人類)
- The suprachiasmatic and preoptic nuclei of the hypothalamus regulate the sleep cycle

Sleep disorders(睡眠疾患)

- The International classification of sleep disorders (ICSD-3) , 2014
- Categories:
  - Insomnias
  - Sleep related breathing disorders
  - Central disorders of Hypersomnias
  - Circadian rhythm sleep-wake disorders
  - Parasomnias
  - Sleep-related movement disorders

Insomnia

- Difficulty initiating sleep, difficulty maintaining sleep, or early morning awakenings
- Distress or impairment that is caused by the insomnia
- Frequency of at least three nights per week for at least 3 months' duration
- Duration of at least 3 months
- Adequate opportunity for sleep
- Insomnia that is not better explained by another disorder or a substance
- 可分為Chronic Insomnia Disorder and Short-Term Insomnia Disorder (<3 months)

Principles of Sleep Hygiene for insomnias

- sleep in cool, quiet, comfortable place.
- keep regular sleep-wake schedule
- when having trouble sleeping at night, avoid daytime naps.
- Exercise during the day.
- avoid caffeine, food close to bedtime
- make bed a restful haven for sleep
- don’t worry about not getting enough sleep
- changes sleeping place, if unable to sleep, get up

Idiopathic Hypersomnia

- Excessive daytime sleepiness but without clearly defined sleep attacks.
- Lifelong with worsening in old age.
- Begin in adolescence- middle age.
- MSLT: excessive sleepiness, no sleep onset REM
- CT/MRI : R/O third ventrical tumor

多次入睡潛伏時間測試（Multiple sleep latency test , MSLT)

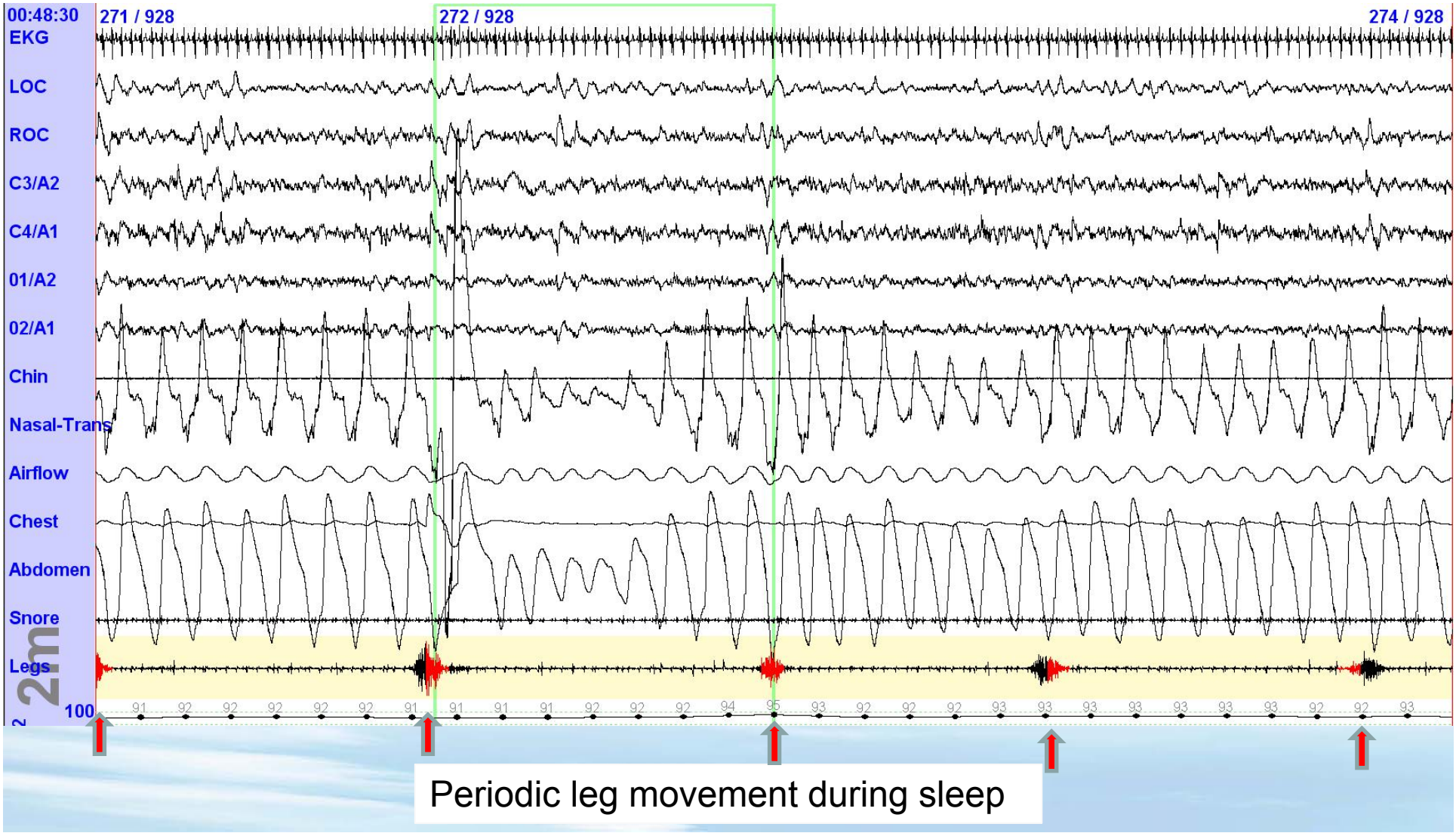
Kleine- Levin Syndrome

- Recurrent episodes of hypersomnia and behavioral abnormalities:
  - hyperphagia
  - sexual disinhibition
- The patient is apathetic, irritable in between
- CT/MRI is appropriate.
- Spontaneous remission is typical

Periodic leg movement

- Stereotyped, periodic movement of the legs
- occurs every 20-30 seconds, leads to arousal
- present with excessive wake time sleepiness or insomnia
- may be associated with restless leg syndrome, sleep apnea or narcolepsy
- Treatment : levo-dopa, clonazepam

Periodic leg movement during sleep



Periodic leg movement during sleep

Restless Leg Syndrome

- Disagreeable leg sensation, usually prior to sleep onset causes irresistable urge to move the legs.
- >80% with PLMS.
- Idiopathic or secondary to uremia, Iron deficiency anemia or pregnancy
- Treatment: dopamine agonist, L-dopa, clonazepam,

Parasomnias: Night Terror

- Occurs primarily in children
- Sudden arousal from slow wave sleep :
  - piercing scream or cry
  - automatic and behavioral manifestation of intense fear (marked tachycardia, mydriasis sweating). The child is agitated and confused.
  - lasts for few minutes, sleep resumes. Amnesia +
  - Treatment: Reassurence, diazepam, imipramine, SSRI

Parasomnias: Sleepwalking

- May overlap with night terror (non-REM)
- Involves complex behavior:
  - sitting up in bed, walking, dressing, eating, voiding and even driving a car.
  - can avoid objects but incoordinated
  - lasts few minutes mostly in 25% children (11-12)
- Treatment: reassurance, safety restraints and if frequent consider diazepam

Parasomnias: Sleep Enuresis

- Involuntary micturation during sleep following attainment of control while awake
- usually idiopathic
- may be caused by urogenital disease, or other medical problem
- it may represent delayed micturation
- Treatment: bladder training, Imipramin

Parasomnias: REM behavior sleep disorder (RBD)

- Lack of REM atonia allows patient to enact his dreams.
- Motor activity may be harmful
- most patients are elderly
- The condition usually idiopathic
- Neurological cause in 1/3rd.
- Treatment: sleep study. clonazepam

REM 睡眠行為異常

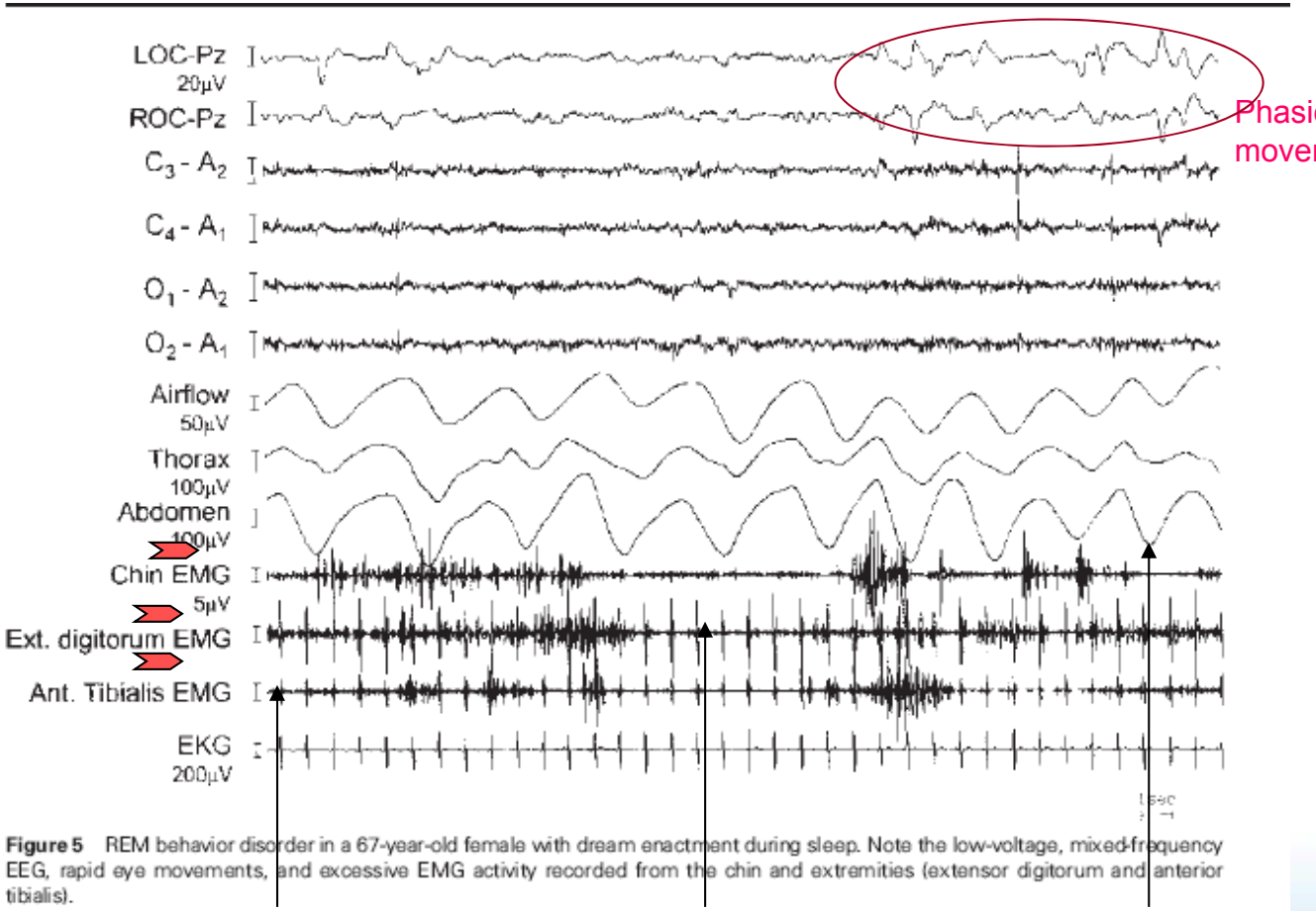
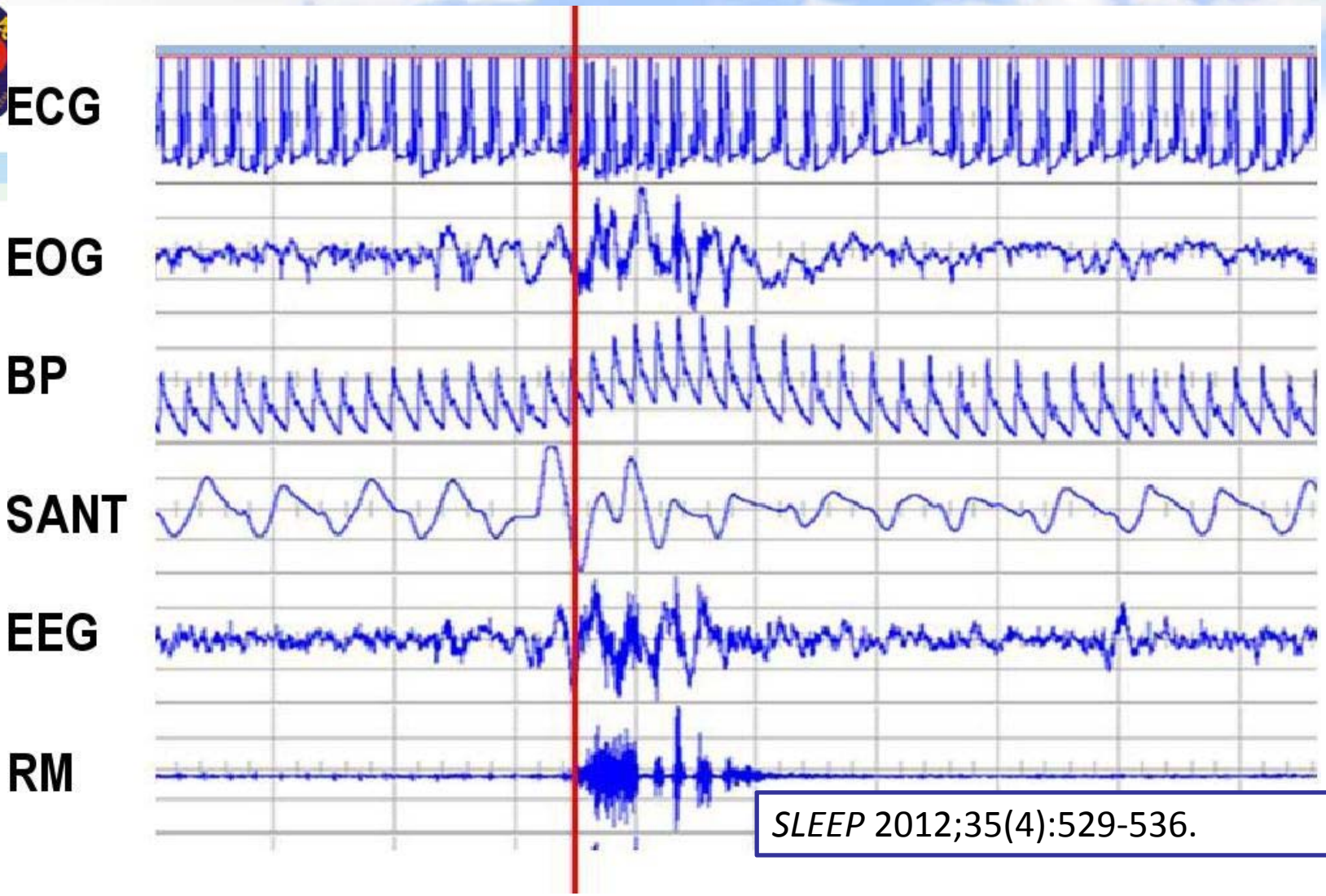


Figure 5 REM behavior disorder in a 67-year-old female with dream enactment during sleep. Note the low-voltage, mixed-frequency EEG, rapid eye movements, and excessive EMG activity recorded from the chin and extremities (extensor digitorum and anterior tibialis).

Increased chin and limb EMG activity during REM sleep

Parasomnias: Miscellaneous

- Sleep Bruxism: grinding or clenching of teeth during sleep. It disturb nocturnal sleep and may cause morning headache
- Head banging:
  - more common in girls
  - no apparent family stress
  - Short lived
  - usually no specific treatment is necessary.



SLEEP 2012;35(4):529-536.

Rhythmic masticatory muscle activity/sleep bruxism (RMMA/SB) is associated with blood pressure fluctuations during sleep. Arousals and body movements often occur with RMMA/SB and can impact the magnitude of this BP surge.

Narcolepsy

- A syndrome consisting of excessive daytime sleepiness and disordered regulation of REM sleep
- Prevalence : 2-16/10,000
- males = females
- positive family history in 1/3 of patients
- Age of onset : 15-35

Historical aspects

- 1862 Caffe first describe cases of hypersomnia, subsequently called “narcolepsy”
- 1880 Gelineau first applied term “narcolepsy” and described the tetrad
- 1931, 1935 use CNS stimulant medications to control sleepiness of narcolepsy
- 1941 EEG study
- 1963 first described the sleep onset REM period of narcolepsy
- 1978 first applied the MSLT to narcolepsy
- 1984 Honda et al. documented the association of HLA DR-2 and narcolepsy
- 1999 Mignot et al. discovered a mutation of the hypocretin Receptor 2 gene of canine narcolepsy
- 2000 Hypocretin 1 is reduced or absent in the CSF in narcolepsy patients

ETIOLOGY

- Hypocretin cells are absent in deceased narcoleptic patients
- Animal model: Canine due to hypocretin-2 receptor gene mutation
- Hypocretin
  - 33 and 28 amino-acids of hypocretin 1 and 2 (orexin A and B) discovered in lateral hypothalamus in 1998
  - Located in synaptic vesicles with neuroexcitatory effect widely projecting in CNS (olfactory bulb cerebral cortex, thalamus, hypothalamus, brainstem)
  - Ventro-lateral pre-optic area (VLPO) and tubero-mammillary nucleus
  - They have wake promoting and REM sleep suppressant effects

Narcolepsy symptoms

- Excessive waketime sleepiness: sleep attacks
  - sleepiness in inappropriate situations
  - irresistable ,brief (5-10 minutes) sleep attacks
  - abrupt or gradual, dreaming is common,
  - refreshing
- **Cataplexy:** sudden, usually brief loss of muscle tone induced by emotions.

Narcolepsy symptoms

- Consciousness is preserved in cataplexy
- results in buckle of the knee, ptosis, jaw or head droop or complete collapse.
- **Sleep paralysis** :inability to move skeletal muscles voluntarily during sleep-wake transition, usually at sleep onset
  - the patient is conscious but unable to move.

Narcolepsy symptoms

- Hypnagogic Hallucination: vivid auditory or visual dream-like experiences that occur at the onset of sleep or awakening
- Automatic behaviour: complex, often routine activities, during which the patient is inattentive. There is partial amnesia
- Decreased quality and quantity of nocturnal sleep: frequent awakening, vivid dreams

Narcolepsy :Diagnosis

- History ESS>10
- Multiple Sleep Latency Test (MSLT)
  - excessive daytime sleepiness
  - mean sleep latency less than 8 minutes
  - >2 times Sleep onset REM period(SOREMPs)
- HLA typing :HLA DQB1* 0602 (Dr/DQw1)
- CSF Hypocretin-1 level

Epworth sleepiness scale

嗜睡量表

嗜睡問卷調查表

請選出在以下不同情況中，你打瞌睡的頻率：

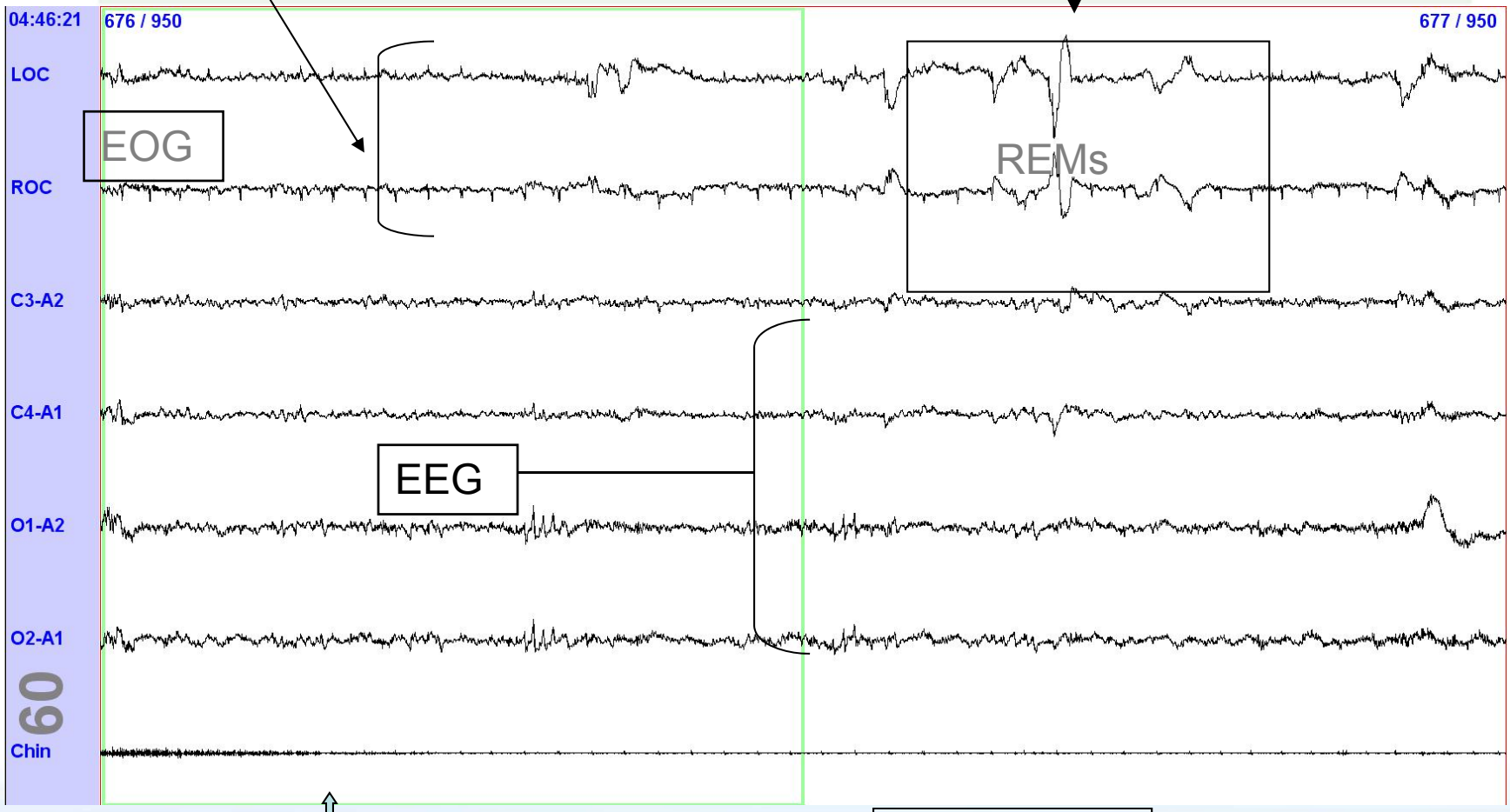
0：從未　1：很少　2：一半以上　3：幾乎都會

1.	坐著閱讀時	0	1	2	3
2.	看電視時	0	1	2	3
3.	在公眾場合安靜坐著(如在戲院或會議中)	0	1	2	3
4.	坐車連續超過一小時(不包括自己開車)	0	1	2	3
5.	在下午躺下休息時	0	1	2	3
6.	坐著與人交談時	0	1	2	3
7.	沒有喝酒情況下，在午餐後安靜坐著時	0	1	2	3
8.	開車中遇到交通問題而停下數分鐘時間	0	1	2	3

Multiple Sleep Latency Test

- Mean sleep latency of less than 8 minutes
- 2 or more sleep onset REM periods
- No other sleep disorder that accounts for the findings(MSLT should be performed following an overnight PSG)
- Limitation
  - MSLT negative finding could not exclude case of Narcolepsy/cataplexy- (15% false negative in n+/c+)
  - Very young child
  - Poor interruptive if patient with prior disruptive sleep
  - Expensive

猝睡症患者在MSLT檢查時出現的sleep onset of REM periods(SOREMPs)



Narcolepsy: Treatment

- Narcolepsy: Stimulants
  - Modafinil: α1adrenergic stimulant
  - Dextroamphetamine
  - methyphenidate
  - Pemoline-hepatotoxic
- Cataplexy:
  - Tricyclic Anti-depressant :clomipramine, imipramine, protriptyline
  - Flouxetine, clonidine, γ hydroxybutyrate

Drugs Used in the Treatment of Narcolepsy

Table 2. Drugs Used in the Treatment of Narcolepsy.

Drug	Dose in Adults*	Common Side Effects	Serious Risks and Side Effects	Relative Cost†
For excessive daytime sleepiness				
Modafinil	100–400 mg every morning, or 200 mg twice daily	Headache, anxiety, nausea, insomnia	Severe rash	Moderate
Armodafinil	150–250 mg every morning, or 125 mg (half of a 250-mg tablet) twice daily	Headache, anxiety, nausea, insomnia	Severe rash	Moderate
Methylphenidate	10–30 mg twice daily, or 20 mg sustained-release formulation every morning with an additional 10–20 mg every afternoon	Reduced appetite, nausea, headache, insomnia	Potential for abuse; psychosis, mania, seizures, cardiovascular effects	Low
Dextroamphetamine	5–30 mg twice daily, or 10 mg of a sustained-release formulation every morning with an additional 10–20 mg every afternoon	Reduced appetite, nausea, headache, insomnia	High potential for abuse; psychosis, mania, seizures, cardiovascular effects	Low
Amphetamine–dextroamphetamine	10–30 mg twice daily, or 20 mg of a sustained-release formulation twice daily	Reduced appetite, nausea, headache, insomnia	High potential for abuse; psychosis, mania, seizures, cardiovascular effects	Low
Sodium oxybate (sodium salt of γ-hydroxybutyrate)	2.25–4.5 g at bedtime and an additional 2.25–4.5 g given 2.5 to 4 hr later	Nausea, dizziness, urinary incontinence, sleepwalking, morning sedation, anxiety	Potential for abuse; confusion, psychosis, severe sedation or coma with overdose	High
For cataplexy				
Venlafaxine	37.5–75 mg twice daily, or 37.5–150 mg of an extended-release formulation every morning	Transient nausea, headache, insomnia; increase in blood pressure when administered in higher doses	None	Low
Fluoxetine	20–80 mg every morning	Nausea, dry mouth, insomnia	None	Low
Clomipramine	10–150 mg at bedtime or each morning	Dry mouth, constipation, sweating, dizziness, somnolence, weight gain, orthostatic hypotension	Cardiotoxicity, hypotension, seizures	Low
Sodium oxybate (sodium salt of γ-hydroxybutyrate)	2.25–4.5 g at bedtime and an additional 2.25–4.5 g given 2.5–4 hr later	Nausea, dizziness, urinary incontinence, sleepwalking, morning sedation, anxiety	Potential for abuse; confusion, psychosis, severe sedation or coma with overdose	High

* Wakefulness-promoting medications are usually taken in the morning; if necessary, additional doses can be taken at midday or in the early afternoon, 30 to 60 minutes before the morning dose wears off. The second dose should not be given late in the afternoon, because such late doses can cause insomnia. Sodium oxybate should not be combined with alcohol or sedatives. Adapted from Scammell.[45]

† Relative costs range from low to high.

Scammell TE. N Engl J Med 2015;373:2654-2662.

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