Lecture 4.2 – Function of Sleep II

1. Sleep and Physical Body Restoration

A. Physical Exercise and Sleep Architecture

- **Theoretical Expectation:** Because physical exertion accelerates ATP consumption and generates adenosine, it was historically hypothesized that strenuous exercise would dramatically increase subsequent sleep duration and slow-wave sleep (SWS) via Process S.
- **Empirical Findings:** Comprehensive meta-analyses demonstrate that acute, moderate exercise exerts minimal objective effects on sleep architecture (e.g., total sleep time, awakenings, SWS, or REM sleep duration remain largely unchanged).
- **Fit vs. Unfit Individuals (Trinder Study, University of Melbourne):**
    - *Trained/Fit Cohort:* Completing a 21 km treadmill run produced only a minor, statistically non-significant increase in slow-wave sleep compared to non-exercise baseline sessions.
    - *Untrained/Unfit Cohort:* Unaccustomed severe exercise reduced slow-wave sleep and caused poor subjective sleep ratings due to muscle soreness and somatic discomfort.
- **Subjective vs. Objective Dissociation:** Regular, moderate exercise consistently improves subjective sleep quality ratings, even when objective polysomnographic sleep metrics show negligible alterations.

B. Physical Injury, Illness, and Immune Cross-Talk

- **Somnolence Following Physical Trauma:** Skeletal fractures and soft-tissue injuries induce sleepiness through both centrally sedating analgesics and the systemic release of inflammatory mediators.
- **Infection-Induced Hypersomnia:** Viral and bacterial infections elicit marked increases in daytime sleepiness and total sleep duration, mediated by pro-inflammatory cytokines acting as somnogenic Process S signaling molecules.
- **Thermoregulation and Fever:** Sleep deprivation impairs the host's capacity to mount an adaptive fever response, compromising immune defense and prolonging recovery timelines.
- **Rhinovirus Inoculation Study:**
    - Healthy adults wore actigraphy monitors for seven days to quantify habitual sleep duration prior to nasal inoculation with rhinovirus.
    - *Infection Rates by Sleep Duration:* Individuals sleeping > 7 hours had a 17.2% infection rate; 6–7 hours had 22.7%; 5–6 hours had 30.0%; and < 5 hours had a 45.2% infection rate.
    - *Controlled Validation:* Laboratory sleep-restriction experiments confirmed that sleep debt directly reduces host resistance to viral exposure.

Practice Multiple-Choice Questions

Question 1

A stroke patient can reach out and use a spoon during a meal, but cannot demonstrate holding a spoon when asked to pantomime the motion. What condition does this represent?

A) Parkinsonian motor freezing

B) Cerebellar dysdiadochokinesia

C) Constructional apraxia

D) Ideomotor limb apraxia

Question 2

What neuroanatomical site is most frequently damaged in individuals who present with severe constructional apraxia?

A) The primary motor cortex paracentral lobule

B) The right posterior parietal cortex

C) The internal globus pallidus

D) The anterior medullary pyramid

Question 3

Which physical examination finding is characteristic of a patient with acquired cerebellar ataxia?

A) Tremor that increases in amplitude as the finger reaches a target

B) Severe lead-pipe rigidity felt throughout passive movement

C) Flaccid paralysis of the face with loss of the corneal blink reflex

D) An extensor plantar response upon stroking the lateral foot

Question 7

In sensorimotor control, how does corollary discharge influence perception during self-generated physical actions?

A) It amplifies sensory feedback from the limb, increasing attention to self-generated movements.

B) It slows conduction velocity along primary motor pathways, preventing sudden muscle contractions.

C) It attenuates predictable sensory inputs, helping the brain detect unexpected external events.

D) It triggers rapid desensitization of muscle spindles, which reduces resting muscle tone.

Question 8

Why are individuals unable to produce a typical tickle response when applying light mechanical stimulation to their own skin?

A) The density of Merkel discs is too low to detect movements generated by one's own hands.

B) Mechanoreceptors in the skin become refractory when touching another part of the same body.

C) Proprioceptive signals from the arm fatigue the ascending tracts within the dorsal columns.

D) An internal efference copy predicts the sensory consequences, cancelling the tactile response.

Question 9

What electrophysiological abnormality supports the hypothesis that schizophrenia involves an impaired internal forward model?

A) A failure to attenuate auditory evoked potentials during self-generated vocalizations

B) Excessive suppression of visual signals during voluntary saccadic eye movements

C) A loss of somatosensory evoked potentials when receiving unexpected tactile taps

D) Increased motor nerve conduction velocities along peripheral alpha motor axons

Answer Key & Detailed Explanations

1. **A** — In obstructive sleep apnea (OSA), respiratory efforts by the diaphragm and intercostal muscles continue against an occluded upper airway; in central sleep apnea (CSA), central respiratory drive ceases entirely, so no thoracoabdominal movements occur.
2. **C** — In congestive heart failure, reduced cardiac output prolongs circulation transit time, creating a phase lag between pulmonary blood gas changes and central/peripheral chemoreceptor sensing. This delay drives an unstable "overshoot and undershoot" cycle of hyperventilation and central apnea.
3. **B** — CCHS is a genetic disorder affecting development of the retrotrapezoid nucleus (RTN). Patients lose autonomic chemosensory drive to CO_2, causing severe hypoventilation or apnea during sleep when voluntary cortical breathing drive is absent.
4. **D** — Intramuscular single motor unit recordings demonstrate that phasic inspiratory units of the genioglossus stop firing at sleep onset (as EEG shifts to theta activity), removing active dilation and predisposing the airway to collapse.
5. **B** — An apnea is a complete or near-complete cessation of airflow lasting at least 10 seconds; a hypopnea is a partial reduction in airflow (typically $\geq 50\%$) lasting at least 10 seconds that is accompanied by an EEG arousal or an oxyhemoglobin desaturation.
6. **C** — Severe OSA causes profound sleep fragmentation: repetitive obstructive events and associated arousals prevent patients from reaching or maintaining Stage 3/4 slow-wave sleep, yielding an architecture dominated by light sleep and recurrent awakenings.
7. **C** — Van Dongen et al. demonstrated that subjective ratings of sleepiness do not reliably predict objective performance on the Psychomotor Vigilance Task (PVT); some individuals feel relatively alert despite high error rates, while others feel exhausted but perform well.
8. **A** — Patients with PTSD experience heightened hyperarousal and fragmented sleep; recurrent awakenings prevent stable sleep architecture, denying the upper airway the stable conditions needed to build up chemoreceptive drive and recruit pharyngeal dilator muscles.
9. **B** — CPAP delivers a continuous column of pressurized air via a mask interface, acting as a physical "pneumatic splint" that pushes the collapsible soft palate and tongue away from the posterior pharyngeal wall.
10. **D** — Opioids depress respiration through multiple pathways: they blunt chemosensitivity to CO_2 in the RTN and peripheral carotid bodies, while directly suppressing pacemaker activity in the pre-Bötzinger complex, reducing tidal volume and respiratory rate.

2. Brain Restoration: The Glymphatic Waste-Clearance System

A. Discovery and Structural Overview

- **Discovery:** Identified by Jeffrey Iliff and Maiken Nedergaard, the glymphatic system is a glial-dependent perivascular fluid-transport network that clears metabolic waste and distributes nutrients (glucose, lipids, amino acids) across the brain.
- **Fluid Compartments of the Brain:**
  - 10% in the intravascular space (blood vessels).
  - 10% to 15% in cerebrospinal fluid (ventricles and subarachnoid space).
  - 20% in intracellular compartments.
  - ~50% in interstitial fluid (ISF) within porous extracellular matrix channels.

B. Convective Fluid Dynamics

- **Periarterial Inflow:** Cerebrospinal fluid (CSF) travels in a ring-shaped conduit (Virchow-Robin space) surrounding cerebral arteries, bounded internally by vascular endothelium and externally by the vascular end-feet of astrocytes.
- **Arterial Pulsatility:** Rhythmic expansion of the arterial wall driven by cardiac systole propels CSF forward through periarterial channels.
- **Interstitial Transvective Flow:** CSF exits through astrocytic end-foot gaps into the interstitial parenchyma, mixing with ISF and sweeping metabolic byproducts toward perivenous pathways for systemic dural/venous drainage.

C. Sleep-Dependent Gating and Neurodegenerative Clearance

- **Astrocytic Volume Shifts:** During wakefulness, astrocytic cell bodies and end-feet are hydrated and swollen, restricting interstitial space. During sleep, astrocytes shrink, expanding interstitial space volume by approximately 60%.
- **Augmented Waste Clearance:** Expanded interstitial pathways dramatically accelerate convective fluid exchange during sleep.
- **Beta-Amyloid Dynamics:** Approximately 65% of cerebral β-amyloid clearance occurs via glymphatic flow during sleep. Chronic sleep disruption promotes amyloid plaque accumulation, elevating long-term Alzheimer's disease risk in genetically susceptible populations.

3. Sleep, Learning, and Memory Consolidation

A. Motor and Visual Skill Consolidation

- **Behavioral Testing (Walker Studies):** Procedural motor tasks (such as finger-tapping sequences) and visual texture discrimination skills show marked performance gains following sleep compared to equivalent intervals of wakefulness.
- **Stage-Specific Correlates:** Performance enhancements on procedural motor tasks correlate with the density and duration of sleep spindles during Stage 2 (N2) NREM sleep.

Lecture 5.1 – Sleep and Memory

1. Classification of Memory Systems

- **Historical Perspective:** Historically, sleep was viewed as a passive, dormant state akin to "nothingness" or near-death. Modern neuroscience recognizes sleep as an active, dynamically organized biological state critical for neural plasticity and memory processing.
- **Declarative (Explicit) Memory:** Conscious recollection of factual information and events.
    - *Episodic Memory:* Memory for personally experienced events defined by specific contextual parameters ("what, where, and when").
    - *Semantic Memory:* Decontextualized general world knowledge, facts, and conceptual definitions.
- **Non-Declarative (Implicit / Automatic) Memory:** Unconscious behavioral adaptations and procedural skills that do not require conscious retrieval.
    - *Procedural Memory:* Motor sequence learning and automated behavioral routines (e.g., motor tapping, instrument playing, riding a bicycle, mirror tracing).
    - *Associative Learning / Conditioning:* Classical conditioning paradigms where neutral stimuli acquire predictive value (e.g., Pavlovian conditioning).
    - *Non-Associative Learning:* Behavioral changes following repeated exposure to a single stimulus, such as habituation (diminishing response to a repetitive, harmless auditory alarm).
    - *Priming:* Enhanced speed or probability of identifying a stimulus following prior sub-threshold exposure (e.g., semantic or perceptual cues altering word-stem completions).
- **Neuroanatomical Dissociation:** Distinct memory subtypes rely on separate neural circuits. Clinical populations with localized cerebral damage or neurodegenerative pathologies (e.g., Alzheimer's disease) often show selective loss of recent episodic encoding while retaining distant autobiographical traces and procedural motor abilities.

2. Stages of Memory Processing

- **Encoding (Acquisition):** The initial perceptual registration and neural representation of incoming information into short-term working memory.
    - *Working Memory Capacity:* Historically described as holding 7 ± 2 items, modern cognitive estimates suggest a capacity limit of roughly 4 to 5 distinct informational chunks.
    - *Chunking Strategies:* Grouping continuous data streams into structured clusters (e.g., grouping telephone digits into three- or four-digit blocks) optimizes short-term retention.
- **Consolidation:** The time-dependent biological stabilization process where labile, transient memory traces are reorganized and transferred from temporary storage into stable, long-term cortical networks.

5. The NREM–REM Ultradian Flip-Flop Circuit

A. The Basic Rest-Activity Cycle (BRAC)

- Sleep architecture in humans alternates between NREM and REM stages across regular ~90-minute ultradian cycles.
- This rhythm reflects an underlying 90-minute ultradian periodicity present during daytime wakefulness (fluctuations in sustained vigilance and attention), termed the Basic Rest-Activity Cycle.

B. Mutual Inhibition in the Brainstem REM Switch

A secondary brainstem flip-flop switch regulates the transition between NREM and REM states:

- **REM-On Center:**
  - *Sublaterodorsal Nucleus (SLD):* Located in the dorsal pons. Contains GABAergic neurons that fire selectively during REM sleep, directly inhibiting the REM-off center.
- **REM-Off Center:**
  - *Ventrolateral Periaqueductal Gray (vlPAG) & Lateral Pontine Tegmentum (LPT):* GABAergic neurons that fire during wakefulness and NREM sleep to inhibit the SLD.
- **Modulatory Inputs on the REM Switch:**
  - *Cholinergic Drive (LDT/PPT):* Active during wakefulness, quiescent during NREM, and active during REM; provides excitatory input to the REM-on SLD.
  - *Orexinergic & Monoaminergic Restraint:* Orexin neurons excite the REM-off neurons (vlPAG/LPT) both directly and via excitatory projections through the LC and Raphe. High orexinergic and monoaminergic tone acts as a functional gate, preventing REM entry during wakefulness. A drop in orexin and monoaminergic firing is permissive for REM onset.

C. Generation of REM Sleep Phenomena

- **Cortical Desynchronization (Wake-Like EEG):** Driven by reactivation of ascending cholinergic projections from the LDT and PPT to the thalamus and cortex.
- **Somatic Muscle Atonia:** Activated SLD glutamatergic/GABAergic projections descend to the medulla and spinal cord to drive glycinergic and GABAergic inhibitory interneurons, hyperpolarizing somatic α-motor neurons.
  - *Sparing:* Somatic motor inhibition spares the extraocular motor neurons (permitting rapid eye movements) and phrenic/intercostal motor pools (maintaining respiration).
- **Phasic Rapid Eye Movements:** Generated by ascending projections from the pontine reticular formation to the midbrain tectum and forebrain oculomotor circuits.

Lecture 10.2: Sleep Apnea

1. Diagnostic Definitions and Polysomnographic Metrics

- **Core Nomenclature:**
  - **Apnea:** Derived from the Greek/Latin roots (*a-* meaning "without" or "no", and *-pnea* meaning "breathing"); clinically defined as the complete or near-complete cessation of airflow lasting for at least 10 seconds.
  - **Hypopnea:** (*hypo-* meaning "low" or "reduced"); defined as a discernable reduction in airflow (typically $\geq 50\%$ drop) lasting at least 10 seconds, associated with physiological consequences such as an electroencephalographic (EEG) arousal from sleep or systemic arterial blood oxygen desaturation.
- **Polysomnography (Sleep Study Instrumentation):**
  - Diagnostic gold standard incorporating comprehensive physiological monitoring:
    - *Electroencephalogram (EEG):* Tracks sleep architecture, identifying transitions from wakefulness (alpha rhythm: 8–12 Hz) to light sleep (theta waves: 3–7 Hz in Stage 1/2), sleep spindles and K-complexes (Stage 2), delta slow waves (Stage 3/4 slow-wave sleep), and rapid eye movement (REM) sleep.
    - *Electromyogram (EMG):* Monitors chin and limb muscle tone.
    - *Electrooculogram (EOG):* Captures slow rolling eye movements at sleep onset and rapid eye movements during REM sleep.
    - *Airflow Channels:* Monitored via nasal pressure prongs (cannula) and thermal or thermistor sensors positioned over the mouth.
    - *Respiratory Effort Bands:* Inductive plethysmography bands positioned around the thorax and abdomen to distinguish obstructive respiratory efforts from central absence of neuromuscular drive.
    - *Pulse Oximetry (SpO_2):* Continuous transcutaneous measurement of arterial oxyhemoglobin saturation.
- **Apnea-Hypopnea Index (AHI):**
  - Calculated as the total number of apneas and hypopneas per hour of objective sleep.
  - *Normal:* Fewer than 5 events per hour (occasional breathing irregularities due to nasal congestion or position changes are physiologically normal).
  - *Mild:* 5 to 14.9 events per hour (diagnosed as a clinical disorder only if accompanied by daytime sleepiness or daytime symptoms).
  - *Moderate:* 15 to 30 events per hour (treated as a clinical disorder regardless of whether the patient reports subjective symptoms).
  - *Severe:* Greater than 30 events per hour (some clinical sleep studies record AHIs of 120–130, meaning breathing stops more than twice per minute across the night).