

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.

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.

Lecture 5.2 – PTSD: Is Dysfunction of Sleep and Memory to Blame

1. Clinical Diagnostic Criteria and Epidemiology of PTSD

Diagnostic Timeline

- **Acute Stress Disorder vs. PTSD:** Trauma-related symptoms occurring within the initial days and weeks following exposure are classified as Acute Stress Disorder. A formal diagnosis of Post-Traumatic Stress Disorder (PTSD) requires symptoms to persist for a minimum duration of at least one month.
- **Delayed Expression:** Symptoms do not always manifest immediately following trauma exposure; clinical onset may occur months or years post-event.

Diagnostic Framework (Five Core Criteria)

- **Criterion A (Trauma Exposure):** Exposure to actual or threatened death, serious injury, or sexual violence via direct experience, witnessing the event, or learning of traumatic events affecting close family/associates.
- **Criterion B (Intrusive Symptoms):** At least one symptom required (e.g., recurrent involuntary intrusive memories, distressing nightmares, dissociative flashbacks, intense physiological reactivity to trauma cues).
- **Criterion C (Persistent Avoidance):** At least one symptom required (e.g., deliberate avoidance of trauma-related internal thoughts/feelings or external reminders such as specific locations, routes, or people).
- **Criterion D (Negative Alterations in Cognition and Mood):** At least two symptoms required (e.g., dissociative amnesia regarding event aspects, pervasive negative self/world beliefs, distorted blame, chronic negative emotional states, diminished interest in significant activities, feelings of detachment).
- **Criterion E (Alterations in Arousal and Reactivity):** Marked hyperarousal symptoms (e.g., irritable outbursts, reckless behavior, hypervigilance, exaggerated startle response, concentration difficulties, sleep disturbances).
- **General Diagnostic Requirements:** Symptoms must cause clinically significant distress or functional impairment and must not be attributable to the direct physiological effects of a substance or another medical condition.

Epidemiology and Economic Impact

- **Lifetime Trauma Prevalence:** Approximately 70% of the general population encounters at least one Criterion A traumatic event across their lifespan.
- **Conditional PTSD Risk:** Roughly 7% to 10% of trauma-exposed individuals develop clinical PTSD.
- **Australian Context:** Affects approximately 1 million Australians annually, generating an estimated economic burden of \$17 billion per year in lost productivity and healthcare costs.

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 (vIPAG) & 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 (vIPAG/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 (SpO₂):* 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).

4. Polysomnographic Hypnogram Architecture in Severe OSA

A standard overnight hypnogram from a patient with untreated severe OSA displays marked disruption of normal sleep architecture:

- **Absence of Slow-Wave Sleep (SWS):** Stage 3/4 non-REM deep restorative sleep is virtually absent or severely reduced across the early cycles of the night because recurring obstructive events terminate in arousals before deep sleep can be established.
- **Delayed and Fragmented REM Sleep:** Entry into REM sleep is delayed, and REM episodes are truncated rather than lengthening across the night.
- **Severe Sleep Fragmentation:** The sleep hypnogram shows hundreds of abrupt transitions from light sleep stages into brief awakenings or arousals across the night.
- **Sawtooth Oxyhemoglobin Desaturation:** Continuous pulse oximetry reveals deep desaturation dips (often dropping from 98% down into the 60% range) matching each obstructive apnea, interspersed with recovery spikes during post-arousal hyperventilation.

5. Systemic and Neurocognitive Consequences

- **Pathophysiological Drivers:** Clinical complications stem from two distinct physiological insults: **sleep fragmentation** (loss of slow-wave sleep, fragmented REM) and **intermittent hypoxia** (repeated cycles of desaturation followed by re-oxygenation).
- **Cardiovascular and Metabolic Morbidities:**
 - Intermittent hypoxia and recurrent arousals trigger sympathetic hyperactivation, endothelial dysfunction, systemic oxidative stress, and vascular inflammation.
 - Markedly elevates the risk of treatment-resistant systemic hypertension, ischemic stroke, myocardial infarction, congestive heart failure, and insulin resistance/type 2 diabetes.
- **Neurocognitive and Psychomotor Impairments:**
 - Patients develop daytime sleepiness, cognitive fatigue ("brain fog"), executive dysfunction, and deficits in working memory and consolidation.
 - *Psychomotor Vigilance Task (PVT):* Sustained 10-minute reaction-time testing shows that chronic sleep fragmentation causes frequent **lapses of attention** (reaction times exceeding 500 ms) due to microsleeps and attentional instability.
 - *Trait Discordance (Van Dongen et al. Findings):* Experimental sleep deprivation paradigms reveal that subjective ratings of sleepiness do not correlate with objective neurocognitive performance. Some individuals report feeling alert while demonstrating severe attentional lapses on the PVT, whereas others report extreme subjective sleepiness while maintaining intact objective performance.