

Part 2: Development of the Resting Membrane Potential

1. Equilibrium Potential and the Nernst Equation

- **Equilibrium:** Reached when the driving forces of a concentration (chemical) gradient and an electrical gradient balance each other out, resulting in **no net flux** of that specific ion across the membrane.
- **Goldman-Hodgkin-Katz (GHK) Equation:** Predicts the net membrane potential based on the relative permeabilities and concentration gradients of multiple ions (K^+ , Na^+ , Cl^-).
- **Nernst Equation (Single-Ion Equilibrium Potential):**

$$E_{ion} = \frac{RT}{zF} \ln \left(\frac{[ion]_{out}}{[ion]_{in}} \right) \approx 61 \log_{10} \left(\frac{[ion]_{out}}{[ion]_{in}} \right) \quad (\text{at } 37^\circ\text{C})$$

- **Potassium (K^+) Equilibrium Potential (E_K):** Given typical physiological concentrations ($[K^+]_{out} \approx 5 \text{ mM}$, $[K^+]_{in} \approx 140 \text{ mM}$), E_K is approximately -88.3 mV .
 - **Sodium (Na^+) Equilibrium Potential (E_{Na}):** Given high extracellular and low intracellular sodium, E_{Na} is approximately $+59 \text{ mV}$.
- **Why Resting Potential Differs from E_K :** The resting membrane potential (-65 mV) is close to, but slightly more positive than, E_K because resting membranes possess a small, steady resting permeability to sodium (Na^+) and other ions.

2. Energy Stores and Cellular Respiration

- Neurons store immense potential energy across their cell membranes in the form of steep electrochemical gradients.
- Maintaining these ion gradients consumes a massive fraction of total brain energy expenditure (**50% to 60% of total brain metabolic energy**) dedicated solely to operating active ion pumps like the Na^+/K^+ -ATPase.

Part 3: Ion Channels

1. General Properties of Ion Channels

- Ion channels are specialized transmembrane proteins that create hydrophilic pores across the hydrophobic lipid bilayer, enabling passive ion diffusion down electrochemical gradients.
- **Gating Mechanisms (Opening and Closing):**
 - **Voltage-Gated Channels:** Opened or closed by shifts in the transmembrane voltage difference.
 - **Ligand-Gated Channels:** Opened by the binding of specific chemical molecules (neurotransmitters like glutamate, or ions like calcium).
 - **Mechanically Gated Channels:** Opened by physical deformation or mechanical stress (e.g., *Piezo2* touch receptors).
 - **Leak / Two-Pore Channels:** Constitutively open, maintaining baseline resting permeability (especially for K^+).

Question 9

During the dissolution of sodium chloride ($NaCl$) crystals in water, how do water molecules orient themselves around the dissociated sodium cations (Na^+)?

- A) The partially positive hydrogen atoms point outward away from the ion.
- B) The partially negative oxygen poles of water molecules orient tightly around the positively charged sodium ion.
- C) Water molecules form an uncharged lipid micelle around the salt crystal.
- D) Hydroxyl radicals displace the sodium ion entirely.

Question 10

What stoichiometric ratio characterizes ion transport by the primary active Na^+/K^+ -ATPase pump during each ATP hydrolysis cycle?

- A) 1 intracellular Na^+ pumped out for 1 extracellular K^+ pumped in
- B) 2 intracellular Na^+ pumped out for 3 extracellular K^+ pumped in
- C) 3 intracellular Na^+ pumped out for 2 extracellular K^+ pumped in
- D) 4 intracellular Na^+ pumped out for 1 extracellular K^+ pumped in

Question 11

Why is maintaining extremely low intracellular free calcium (Ca^{2+}) concentrations critical for neuronal function?

- A) Calcium ions act as potent intracellular second messengers that trigger downstream ~~signaling~~ cascades when allowed to rush in.
- B) High intracellular calcium causes immediate crystallization of the axonal cytoplasm.
- C) Calcium ions poison the active sites of all known RNA polymerases.
- D) Free calcium ions prevent the assembly of myelin sheaths by oligodendrocytes.

Question 4

What physiological consequence occurs when the intracellular transmembrane potential reaches the critical threshold level (e.g., -55 mV)?

- A) All potassium leak channels undergo permanent denaturation.
- B) Voltage-gated sodium channels rapidly open, initiating the regenerative influx of sodium.
- C) The cell membrane seals itself shut to halt all metabolic activity.
- D) Sodium-potassium pumps reverse their stoichiometric ratio to pump sodium inward.

Question 5

What is the primary cellular function of the refractory period immediately following an action potential?

- A) To stimulate local dendritic protein synthesis
- B) To ensure unidirectional propagation and prevent backward resetting of the impulse
- C) To permanently lock the membrane potential at $+30$ mV
- D) To accelerate the metabolic decay of intracellular ATP stores

Question 6

Which glial cell type is responsible for depositing the insulating myelin sheath around axons within the peripheral nervous system (PNS)?

- A) Astrocytes
- B) Schwann cells
- C) Microglia
- D) Ependymal cells

Answer Key & Detailed Explanations

1. **C** — Maguire and colleagues found that London taxi drivers developed larger posterior hippocampi because their occupation requires acquiring "The Knowledge"—internalizing complex, dynamic spatial routes across 25,000 streets—whereas bus drivers follow fixed, repetitive paths.
2. **A** — Synaptic facilitation occurs when a second action potential arrives before residual calcium from the first spike has been cleared; this residual calcium binds to low-affinity sensors like Synaptotagmin-7, increasing release probability.
3. **B** — Short-term sensitization decays as free serotonin is cleared and cAMP levels fall, allowing cellular phosphatases to dephosphorylate voltage-gated potassium channels, which restores normal action potential duration and baseline calcium influx.
4. **D** — In the hippocampal trisynaptic circuit: the perforant path connects the entorhinal cortex to the dentate gyrus, mossy fibers connect the dentate gyrus to CA3, and Schaffer collaterals connect CA3 pyramidal neurons to CA1 pyramidal neurons.
5. **C** — Early-LTP relies on phosphorylating pre-existing AMPA receptors and inserting them from local submembrane pools (protein-synthesis independent), whereas Late-LTP requires transcription (via CREB) and de novo protein synthesis to alter spine architecture.
6. **A** — At resting potentials, extracellular Mg^{2+} is drawn into the NMDA receptor pore by the negative intracellular potential, blocking ion flux; postsynaptic depolarization expels the Mg^{2+} ion, allowing Ca^{2+} entry when glutamate is bound.
7. **B** — Silent synapses possess NMDA receptors but lack functional surface AMPA receptors; at resting potentials, NMDA channels remain blocked by Mg^{2+} , preventing baseline EPSPs until LTP recruits AMPA receptors to the membrane.
8. **A** — The bidirectional calcium hypothesis states that large, rapid calcium influxes activate protein kinases (CaMKII, PKC) that promote AMPA receptor insertion (LTP), whereas small, prolonged calcium rises activate protein phosphatases (calcineurin, PP1) that trigger AMPA receptor endocytosis (LTD).
9. **B** — Under STDP rules, if the postsynaptic neuron fires *before* the presynaptic spike ($t_{post} < t_{pre}$), the postsynaptic membrane is already repolarizing when glutamate binds, resulting in small, subthreshold calcium influx that selectively recruits phosphatases to drive LTD.
10. **B** — Sustained PKA signaling causes catalytic subunits to translocate into the nucleus and phosphorylate CREB, activating the transcription of ubiquitin hydrolase (which sustains PKA activity) and structural proteins that expand synaptic contacts.

Lecture 9.1 - Control of Movement I

1. Overview of the Motor Control Hierarchy

- **Core Function:** Motor control coordinates voluntary and involuntary contractions of skeletal muscles. Patterns of electrical activity within the cerebral cortex, brainstem centers, and local spinal circuits orchestrate motor outputs.
- **Conceptual Divisions of the Motor Hierarchy:**
 - **Upper Motor Neurons (UMNs):** Neuronal cell bodies located entirely within the central nervous system (cerebral cortex and specific brainstem nuclei) whose descending axons project down to influence lower motor circuits.
 - **Lower Motor Neurons (LMNs):** Neuronal cell bodies located in the brainstem motor nuclei and the ventral (anterior) horn of the spinal cord. Their peripheral axons project through cranial nerves or ventral spinal roots directly to innervate skeletal muscle fibers.
 - **The "Final Common Pathway":** Term coined by Sir Charles Sherrington to indicate that all descending commands, sensory reflex loops, and interneuronal programs must converge onto lower motor neurons to produce force and movement.

2. Anatomy and Physiology of Upper Motor Neurons

A. Cortical Motor Regions and Laminar Cytoarchitecture

- **Primary Motor Cortex (M1):**
 - Anatomically situated in the precentral gyrus and the anterior paracentral lobule of the frontal lobe, immediately rostral to the central sulcus.
 - Functionally distinguished from premotor areas because it requires a significantly lower electrical threshold to evoke discrete muscular twitches.
- **Premotor Cortex:** Positioned anterior to M1; coordinates motor planning, posture, orientation toward sensory targets, and complex temporal movement sequences.
- **Six-Layered Neocortex and Betz Cells:**
 - The motor cortex is organized into six horizontal cytoarchitectonic laminae.
 - **Layer V (Internal Pyramidal Layer):** Houses the primary projection neurons, including giant pyramidal **Betz cells** (discovered in the 1870s by Vladimir Betz).
 - Betz cells possess exceptionally large cell bodies and thick myelinated axons, but constitute only about 5% of the total pyramidal projection population in the motor cortex. They project to lower motor pools dedicated to specific, highly demanding motor groups rather than innervating all skeletal muscles.

Practice Multiple-Choice Questions

Question 1

What structural characteristic distinguishes Betz cells within the primary motor cortex?

- A) They occupy layer IV of the neocortex and project directly to sensory thalamic relay nuclei.
- B) They are giant pyramidal neurons residing in layer V that make up roughly 5% of projection cells.
- C) They represent the primary population of inhibitory interneurons regulating motor strip excitability.
- D) They synthesize myelin sheaths around descending axons within the subcortical corona radiata.

Question 2

What symptom profile distinguishes a lower motor neuron lesion from an upper motor neuron lesion?

- A) Spasticity with hyperreflexia and a positive Babinski sign
- B) Flaccid paralysis with hyporeflexia and pronounced muscle atrophy
- C) Severe muscle hypertrophy accompanied by velocity-dependent rigidity
- D) Loss of fine touch sensation with preserved voluntary motor control

Question 3

Following a spinal cord ~~hemisection~~ injuring the lateral corticospinal tract in the cervical spine, on which side will distal extremity weakness manifest?

- A) Contralateral to the lesion because axons decussate in the spinal segment of termination
- B) Bilaterally due to extensive proprietary axonal branching through the anterior white commissure
- C) Ipsilateral to the lesion because the tract has already crossed at the medullary pyramids
- D) Contralateral to the lesion because corticospinal ~~fibers~~ cross within the cerebral peduncles

Answer Key & Detailed Explanations

1. **A** — Direct pathway striatal MSNs release GABA onto GPI neurons, transiently pausing their tonic inhibitory discharge; this disinhibits the VA/VL motor thalamus and increases excitatory drive to the cortex.
2. **B** — Dopamine binding to D1 receptors couples to G_{as} , which stimulates adenylyl cyclase, elevates intracellular cAMP, and activates PKA to phosphorylate cation channels and depolarize direct-pathway MSNs.
3. **C** — The lateral cerebrocerebellar cortex projects topographically to the dentate nucleus (the largest deep cerebellar nucleus), which relays motor planning signals to the contralateral premotor and motor cortices via the VL thalamus.
4. **D** — Cerebellar pathways double-cross: descending cortico-ponto-cerebellar fibers cross the midline in the pons, and ascending dentatothalamic outputs cross in the midbrain to the contralateral motor cortex, whose descending corticospinal tracts cross back at the pyramidal decussation.
5. **A** — The middle cerebellar peduncle is purely an afferent pathway, composed of roughly 20 million transverse pontocerebellar fibers that cross from the contralateral pontine nuclei to enter the cerebellar hemisphere.
6. **B** — Purkinje cells represent the sole projection neurons leaving the cerebellar cortex; their axons use GABA to deliver inhibitory control over neurons within the deep cerebellar nuclei and vestibular complex.
7. **C** — Chorea consists of brief, rapid, random, involuntary movements that flow unpredictably between muscle groups; early Huntington's disease impairs striatal indirect-pathway neurons, provoking these hyperkinetic symptoms.
8. **D** — Climbing fibers originate exclusively from the contralateral inferior olivary nucleus, ascending through the inferior cerebellar peduncle to wrap directly around the dendritic tree of a single Purkinje cell and evoke powerful complex spikes.
9. **A** — Cerebellar ataxia reflects the loss of real-time motor error detection and adjustment, turning smooth multi-joint motor execution into disjointed, dysmetric, and tremulous movements.
10. **C** — Hemiballismus typically results from stroke or focal damage to the contralateral subthalamic nucleus; loss of STN excitatory output to the GPI disinhibits the motor thalamus, resulting in unconstrained, violent proximal limb movements.

Answer Key & Detailed Explanations

1. **A** — Salt transduction occurs through apical epithelial sodium channels (ENaC); sodium ions pass directly into the taste receptor cell down their chemical and electrical gradient, depolarizing the membrane without requiring second-messenger cascades.
2. **B** — Taste buds across the posterior third of the tongue (associated with circumvallate and foliate papillae) are innervated by the glossopharyngeal nerve (CN IX), whereas the anterior two-thirds are supplied by the facial nerve (CN VII) and the epiglottis/pharynx by the vagus nerve (CN X).
3. **C** — The sweet taste receptor is an obligate heterodimer of T1R2 and T1R3 (T1R2 + T1R3). In contrast, the umami receptor is composed of T1R1 + T1R3, and bitter tastes are detected by diverse monomeric T2R GPCRs.
4. **C** — Primary taste afferents from cranial nerves VII, IX, and X enter the solitary tract and terminate within the rostral (gustatory) division of the nucleus of the solitary tract (NTS) in the medulla oblongata.
5. **B** — Third-order gustatory neurons in the ventral posteromedial nucleus of the thalamus (parvocellular part, VPMpc) project to the primary gustatory cortex, situated in the anterior insula and the adjacent frontal operculum (hidden within the lateral fissure).
6. **B** — Olfactory receptor neurons are authentic bipolar neurons that project a peripheral ciliated dendrite to the surface and send an axon directly through the cribriform plate into the brain, unlike photoreceptors, hair cells, or taste receptor cells, which are specialized neuroepithelial cells.
7. **B** — In the ciliary membrane, cAMP directly gates CNG cation channels to permit Na^+ and Ca^{2+} entry; the resulting rise in intracellular calcium opens Anoctamin-2 (calcium-activated chloride channels), driving Cl^- efflux into the mucosal fluid and amplifying membrane depolarization.
8. **A** — Each olfactory receptor neuron expresses only one receptor gene, and all axons expressing that same receptor converge precisely onto the same pair of glomeruli within the olfactory bulb, creating a functional spatial odor map.
9. **A** — Olfactory tract axons project directly from mitral and tufted cells to primary olfactory cortical regions (such as the piriform cortex, amygdala, and entorhinal cortex) without first passing through a thalamic relay.
10. **D** — The facial nerve (CN VII) supplies special sensory taste innervation to the anterior two-thirds of the tongue via the chorda tympani; damage in Bell's palsy causes loss of taste across the ipsilateral anterior two-thirds of the tongue.

Lecture 11.1 – Association Cortex and Cognition I

1. Overview of Cortical Processing and Cognition

- **The Sensorimotor Converter:** The brain functions as a sensorimotor converter, receiving sensory inputs from the external environment and producing adaptive behavioral and motor outputs essential for survival.
- **Definition of Cognitive Functions:** The internal processing steps occurring between primary sensation and motor output constitute cognitive functions. These mental processes include perception, attention, decision-making, planning, problem-solving, learning, and memory.
- **Primary vs. Association Cortices:**
 - **Primary Sensory and Motor Cortices:** Include the primary motor cortex (controls voluntary movement), primary somatosensory cortex (processes touch and temperature), primary auditory cortex (located within the temporal lobe), and primary visual cortex (occipital lobe). These regions directly receive peripheral sensory signals via first-order thalamic relays or directly project motor execution commands.
 - **Association Cortices:** Comprise the remaining regions of the neocortex within the parietal, temporal, and frontal lobes. Their principal inputs derive from regions that have already processed information. They mediate higher-order cognitive functions.

2. Cytoarchitecture and Laminar Circuitry of the Neocortex

A. Evolutionary Classification of Cortical Types

- **Neocortex (Isocortex):** Evolutionarily the newest cortex, possessing six distinct histological layers, present across all mammalian species.
- **Paleocortex:** Evolutionarily older 3-layered cortex, represented by the olfactory cortex.
- **Archicortex:** Four-layered evolutionary structure, represented by hippocampal formations.

B. Laminar Organization and Regional Variations

- **Layer IV (Granular Layer):** Serves as the primary recipient of afferent thalamic inputs.
- **Layer V (Infragranular Output Layer):** Serves as the primary source of descending projections to subcortical structures.
- **Heterotypical Granular Cortex:** Typical of primary sensory cortices; displays a prominent, thick Layer IV and a reduced Layer V.